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A Concise Diastereospecific Synthesis of 3-Amino-2-hydroxy Acids

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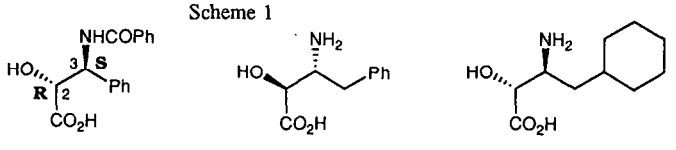
Abstract. L-Aspartic acid by N-tosylation, anhydride formation, reduction, α-hydroxylation, iodo esterification and alkylation followed by saponification and deprotection afforded a series of 4-alkyl-3-amino-2-hydroxybutyric acids having the 2S,3R configuration (de>95%).

Homochiral 3-amino-2-hydroxy acids are of considerable importance because they are the crucial components of medicinally useful molecules such as taxol,[1] an anti-tumor agent, bestatin, an immunological response modifier[2] and certain small peptides possessing antihypertensive activity.[3,4] Consequently, much attention has been devoted to the synthesis of the C13 side-chain of taxol (**1**),[5,6] the non-leucine part of bestatin (**2**)[7-12] and cyclohexylnorstatine (**3**)[4,13-16] (Scheme 1). The essential problem has been the construction of the desired diastereomeric C2,C3 portion. A remarkable variety of solutions has been devised, among which may be noted the hydroxamination of cinnamic ester,[6] the Curtius rearrangement of an azide derivative of L-malic acid,[7] the formation of cyanohydrins from α-amino aldehydes,[8,9] the condensation of a 1,3-dioxolan-4-one with phenylacetaldehyde followed by azidation,[10] the cyclo-addition of an imine and benzoylketene,[11,15] the iodocyclocarbamation of an allylamine,[12] the azidation of a D-glucose derivative[14] and the aldol condensation of an α-amido aldehyde.[16]

Scheme 1



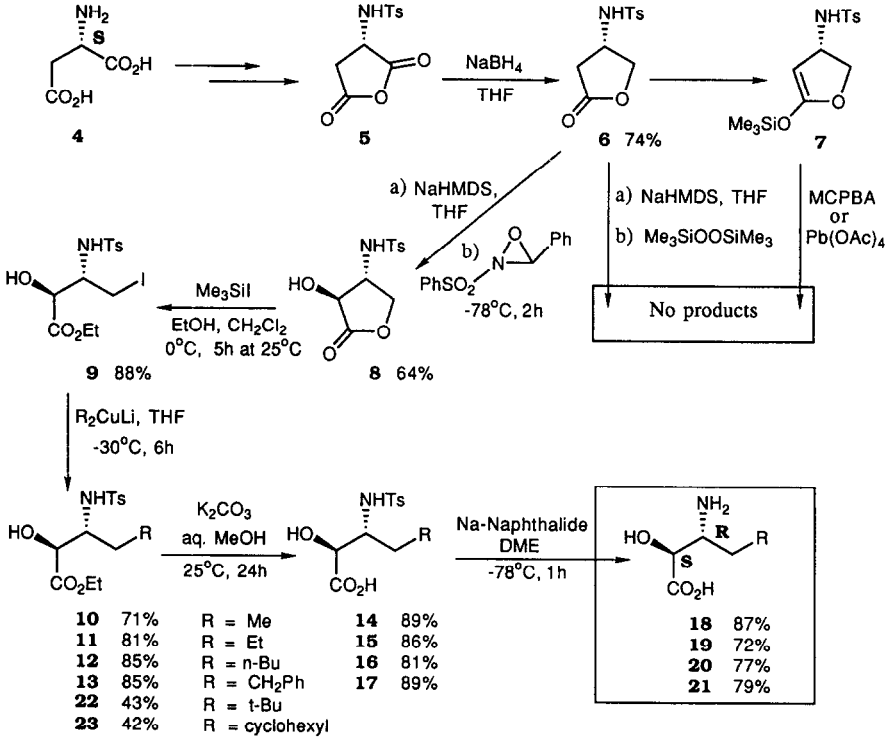
1 **2** **3**

Notwithstanding this plethora of methods, we thought that homochiral 3-amino-2-hydroxy acids might be generally accessible by a modification of our procedure for preparing β-amino acids from aspartic acid.[17] We now describe a new, practical synthesis of some representative examples which relies on the diastereoselective hydroxylation of 3S-(N-tosylamino)butyrolactone (**6**) as the key step.

L-Aspartic acid (**4**) was first converted into N-tosylaspartic anhydride (**5**) and then selectively reduced to **6** (Scheme 2). Next, several conventional reagents for hydroxylation were tried out on **6**. Disappointingly, submission of the enol ether **7** in THF to *m*-chloroperbenzoic acid (MCPBA)[18] or lead tetraacetate[19] gave no reaction or led to complex mixtures, respectively.[20] Similarly, treatment of **6** in THF at -78°C with sodium hexamethyldisilazide (NaHMDS) and bis-(trimethylsilyl)peroxide[21] was equally without effect. Fortunately, replacement of the peroxide by racemic 2-phenylsulfonyl-3-phenyloxaziridine[22] resulted in the formation of a single product, the *trans*-hydroxy-N-tosylamino lactone **8**, in 64% yield.[23] Opening of **8** by exposure to trimethylsilyl iodide and ethanol in methylene chloride under nitrogen at 0°C proceeded smoothly to form the

pivotal chiral intermediate, the hydroxyiodo-homoserine ester **9** in 88% yield.[24] Nucleophilic substitution on **9** with the usual lithium organocuprates in THF at -30°C worked well and permitted the introduction of the methyl, ethyl, *n*-butyl and benzyl groups so giving the corresponding 2-hydroxy-3-(N-tosylamino) ethyl esters (**10-13**) in 71 to 85% yield.[25] Saponification with potassium carbonate in aqueous methanol delivered the respective 2-hydroxy-3-(N-tosylamino) acids (**14-17**)[26] which were subsequently deprotected by the action of sodium naphthalide in dimethoxyethane (DME). The 4-alkyl-3-amino-2-hydroxybutyric acids (**18-21**) were obtained in yields of 21 to 25% from L-aspartic acid.[27]

Scheme 2



As far as we can judge by careful scrutiny of the NMR spectra of the products, hydroxylation had occurred in a diastereospecific manner. No signal corresponding to the other diastereomer was seen. In other words, not only is the original chiral center wholly conserved, but it has effectively controlled the creation of the new chiral center at the C2 position. Clearly, the N-tosylamino grouping is sufficiently large to prevent any *cis* attack by the oxaziridine on the carbanion derived from **6**.

Attempts to prepare the bestatin component **2** proved fruitless. The reaction of lithium diphenylcuprate with **9** invariably led to β-elimination. However, the action of the bulkier reagents, lithium di-*t*-butyl- and dicyclohexylcuprates, on **9** was moderately successful in that the 4-*t*-butyl- and 4-cyclohexylbutyric esters **22** and **23** were produced in 43 and 42% yield. Therefore, repetition of the sequence with D-aspartic acid as the starting material would afford cyclohexylnorstatine **3** *via* the enantiomer of **23**.

These examples amply demonstrate that L-aspartic acid can be efficiently transformed into 2S,3R-4-alkyl-3-amino-2-hydroxybutyric acids. Although some chromatography is necessary, the procedure is operationally simple and requires only five steps from the intermediate lactone **6**. The preparation of other acids should be feasible, especially those of the 2R,3S series if D-aspartic acid were used as the homochiral educt.

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References and Notes

1. D. Guénard, F. Guéritte-Voegelein, P. Potier, *Acc. Chem. Res.* **1993**, *26*, 160.
2. H. Umezawa (Ed.), "Small Molecular Immunomodifiers of Microbial Origin. Fundamental & Clinical Studies of Bestatin", Pergamon Press, Oxford, **1981**; H. Suda, T. Takita, T. Aoyagi, H. Umezawa, *J. Antibiotics* **1976**, *26*, 100.
3. Microginin is a pentapeptide which inhibits angiotensin-converting enzyme (T. Okino, H. Matsuda, M. Murakami, K. Yamaguchi, *Tetrahedron Lett.* **1993**, *34*, 501).
4. A tripeptide, coded as KRI 1314, and containing isopropyl cyclohexylnorstatine at the C-terminal, powerfully inhibits human renin (K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, H. Umeyama, Y. Kiso, *J. Chem. Soc., Chem. Commun.* **1989**, 1678.
5. A.M. Kanazawa, A. Correa, J.-N. Denis, M.-J. Luche, A.E. Greene, *J. Org. Chem.* **1993**, *58*, 255.
6. M.E. Bunnage, S.G. Davies, C.J. Goodwin, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375; L. Deng, E.N. Jacobsen, *J. Org. Chem.* **1992**, *57*, 4320.
7. B.H. Norman, M.L. Morris, *Tetrahedron Lett.* **1992**, *33*, 6803.
8. R. Herranz, J. Castro-Pichel, S. Vinuesa, M.T. Garcia-López, *J. Org. Chem.* **1990**, *55*, 2232.
9. F. Matsuda, T. Matsumoto, M. Ohsaki, Y. Ito, S. Terashima, *Chemistry Lett.* **1990**, 723.
10. W.H. Pearson, J.V. Hines, *J. Org. Chem.* **1989**, *54*, 4235.
11. Y. Kobayashi, Y. Takemoto, Y. Ito, S. Terashima, *Tetrahedron Lett.* **1990**, *31*, 3031; C. Palomo, A. Arrieta, F.P. Cossio, J.M. Aizpurua, A. Mielgo, N. Aurrekoetxea, *Tetrahedron Lett.* **1990**, *31*, 6429.
12. S. Kobayashi, T. Osobe, M. Ohno, *Tetrahedron Lett.* **1984**, *25*, 5079.
13. R.W. Dugger, J.L. Ralbovsky, D. Bryant, J. Commander, S.S. Massett, N.A. Sage, J.R. Selvidio, *Tetrahedron Lett.* **1992**, *33*, 6763; T. Matsumoto, Y. Kobayashi, Y. Takemoto, Y. Ito, T. Kamijo, H. Harada, S. Terashima, *Tetrahedron Lett.* **1990**, *31*, 4175.
14. T. Inokuchi, S. Tanigawa, M. Kanazaki, S. Torii, *Synlett* **1991**, 707.
15. Y. Ito, T. Kamijo, H. Harada, S. Terashima, *Heterocycles* **1990**, *30*, 299.
16. Y. Takemoto, T. Matsumoto, Y. Ito, S. Terashima, *Tetrahedron Lett.* **1990**, *31*, 217.
17. C.W. Jefford, J.B. Wang, *Tetrahedron Lett.* **1993**, *34*, 1111.
18. G.M. Rubottom, R. Marrero, *Synthetic Commun.* **1981**, *11*, 505.
19. G.M. Rubottom, J.M. Gruber, R. Marrero, H.D. Juve, Jr., C.W. Kim, *J. Org. Chem.* **1983**, *48*, 4940.
20. The silyl ether **7** was prepared *in situ* from **6** by successive treatment with lithium diisopropylamide and trimethylsilyl chloride in THF at -78°C.

21. M. Pohmakotr, C. Winotai, *Synthetic Commun.* **1988**, *18*, 2141.

22. F.A. Davis, B.C. Chen, *Chem. Rev.* **1992**, *92*, 919.

23. (2S,3R)-2-Hydroxy-3-(N-tosylamino)-4-butanolide (**8**) was obtained pure as a colorless oil by column chromatography over silica (CH_2Cl_2: hexane:EtOAc; 2:1:1); $[\alpha]_D^{25}$ = -23.4° (c 3.7, EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.67 (d, *J* = 8, 2H), 7.20 (d, *J* = 8, 2H), 6.41 (d, *J* = 4, 1H), 4.50 (d, *J* = 8.8, 1H), 4.15 (s, 1H), 3.85 (m, *J* = 3.3, 2H), 2.31 (s, 3H); MS: 271 (M^+, 2.8), 214 (3.7), 197 (7.0), 155 (19.8), 116 (8.4), 91 (100); HRMS: calcd for $C_{11}H_{13}NSO_5$ 271.0514, found 271.0501.

24. (2S,3S)-Ethyl 2-hydroxy-3-(N-tosylamino)-4-iodobutyrate (**9**), after chromatography over silica (EtOAc: hexane, 5:3), was obtained as colorless crystals, m.p. 88.5-90°C; $[\alpha]_D^{25}$ = +43.2° (c 1.9, EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$: 7.66 (d, *J* = 8, 2H), 7.25 (d, *J* = 8, 2H), 5.14 (d, *J* = 12, 1H), 4.57 (s, 1H), 4.06 (qd, *J* = 4, 1H), 3.84 (m, 1H), 3.74 (qd, *J* = 8, 1H), 3.23 (m, 1H), 3.19 (m, 2H), 2.36 (s, 3H), 1.11 (t, *J* = 8, 3H); MS: 428 (M^++1, 3.3), 354 (0.60), 3.24 (23), 155(59), 91 (100); HRMS; calcd for $C_{13}H_{18}NSO_5I$ 426.9950, found: 426.9903.

25. The 2-hydroxy-3-(N-tosylamino) esters **10-13** were obtained pure as colorless solids by column chromatography over silica (EtOAc: hexane, 2:3), except **12**, which was an oil; m.p. **10**, 75-76.5°; **11**, 113-114°; **13**, 110-111°C. Optical rotations ($[\alpha]_D^{25}$) were determined in EtOAc and had the following values: **10**, +35.2° (c 8.25); **11**, +32.0° (c 0.7); **12**, 25.9° (c 1.86); **13**, +18.5° (c 7.5). ^{1}H-NMR (400 MHz, $CDCl_3$): **10**, δ 7.67 (d, *J* = 8, 2H), 7.21 (d, *J* = 8, 2H), 5.13 (d, *J* = 9.6, 1H), 4.10 (m, 1H), 4.07 (d, *J* = 1.2, 1H), 3.94 (qd, *J* = 7.2, 1H), 3.50 (q, *J* = 7.6, 1H), 3.37 (d, *J* = 5.2, 1H), 2.34 (s, 3H), 1.55 (qd, *J* = 7, 1H), 1.33 (qd, *J* = 7, 1H), 1.19 (t, *J* = 7.2, 3H), 0.71 (t, *J* = 7.4, 3H). **11** (not reported). **12**, δ 7.67 (d, *J* = 8.4, 2H), 7.20 (d, *J* = 8.4, 2H), 5.23 (br, 1H), 4.14 (m, 1H), 4.05 (m, 1H), 4.01 (m, 1H), 3.54 (m, *J* = 7.6, 1H), 3.44 (br, 1H), 2.34 (s, 3H), 1.47 (m, 1H), 0.7-1.2 (br, 13H). **13**, δ 7.69 (d, *J* = 8.4, 2H), 7.25 (m, 5H), 7.03 (d, *J* = 8.4, 2H), 4.95 (d, *J* = 10, 1H), 4.20 (m, 2H), 4.03 (m, 1H), 3.72 (m, *J* = 8, 1H), 3.22 (d, *J* = 4.4, 1H), 2.54 (t, *J* = 6.8, 2H), 2.43 (s, 3H), 1.93 (m, 1H), 1.62 (m, 1H), 1.27 (t, *J* = 6.8, 3H).

26. The 2-hydroxy-3-(N-tosylamino) acids **14-17** were obtained as colorless solids; m.p. **14**, 179-180°; **15**, 115-117°; **16**, 107-109°; **17**, 166-168°C. Optical rotations ($[\alpha]_D^{25}$) were determined in acetone and had the following values: **14**, +32.9° (c 4.3); **15**, +27.5° (c 2.0); **16**, +22.0° (c 6.5); **17**, +19.1° (c 3.8). ^{1}H-NMR (400 MHz, CD_3COCD_3): **14**, δ 7.75 (d, *J* = 8.4, 2H), 7.34 (d, *J* = 8.4, 2H), 6.18 (d, *J* = 7, 1H), 4.16 (d, *J* = 2.4, 2H), 3.53 (m, 1H), 2.40 (s, 3H), 1.61 (m, 1H), 1.34 (m, 1H), 0.75 (t, *J* = 7.2, 3H). **15** (not reported). **16**, δ 7.75 (d, *J* = 8.4, 2H), 7.35 (d, *J* = 8.4, 2H), 6.17 (d, *J* = 9.2, 1H), 4.15(br, 2H),3.59 (q, *J* = 7.2, 1H), 2.40 (s, 3H), 1.60 (m, 1H), 1.28 (m, 6H), 1.10 (m, 1H), 0.78 (t, *J* = 7.2, 3H). **17**, δ 7.73 (d, *J* = 6.6, 2H), 7.35 (d, *J* = 8, 2H), 7.23 (m, 2H), 7.13 (m, 1H), 7.02 (d, *J* = 8, 2H), 6.33 (d, *J* = 12, 1H), 4.25 (s, 1H), 3.70 (m, 1H), 2.45 (m, 2H), 2.40 (s, 3H), 1.94 (m, 1H), 1.55 (m, 1H).

27. The 3-amino-2-hydroxy acids **18-21** were solids and had the following $[\alpha]_D^{25}$ values (determined in H_2O:MeOH, 1:1, except where noted): **18**, -13.4° (c 1.2, H_2O); **19**, -9.8° (c 1.1); **20**, -5.0° (c 0.85); **21**, -3.5° (c 0.66, H_2O:MeOH, 2:1). ^{1}H-NMR (400 MHz, D_2O, dioxane as internal standard): **18**, δ 3.93 (d, *J* = 4, 1H), 3.20 (m, 1H), 1.59 (m, 1H), 1.48 (m, 1H), 0.83 (t, *J* = 7.2, 3H). **19** (not reported). **20**, δ 3.92 (d, *J* = 3.6, 1H), 3.25 (m, 1H), 1.55 (m, 1H), 1.43 (m, 1H), 1.26 (m, 2H), 1.15 (m, 4H), 0.71 (t, *J* = 7.2, 3H). **21**, δ 7.18 (br, 5H), 3.83 (s, 1H), 2.90 (m, 1H), 2.58 (m, 2H), 1.69 (m, 1H), 1.58 (m, 1H).

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