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An Enantiospecific Synthesis of β-Amino Acids

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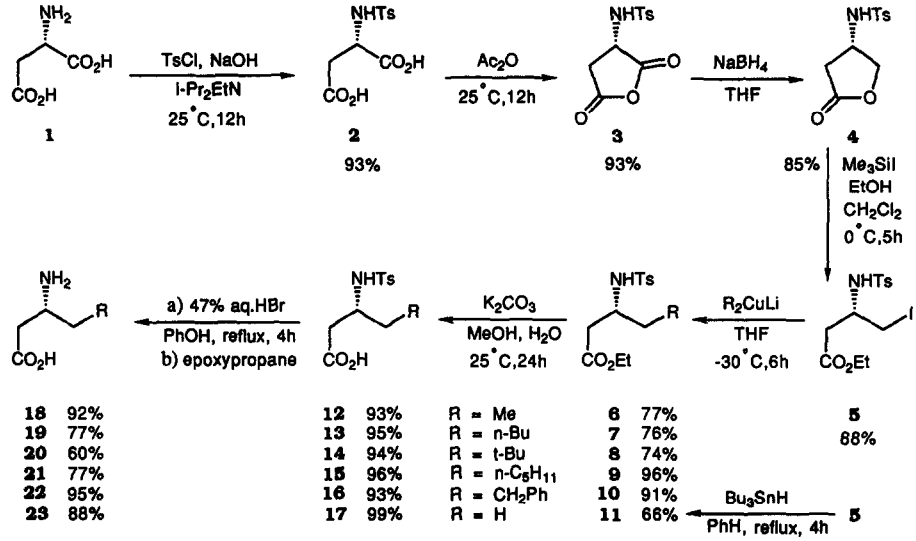
Abstract. *L-Aspartic acid by regioselective modification of the α-carboxylic acid group, namely N-tosylation, anhydride formation, reduction, iodo-esterification, alkylation, and deprotection afforded a series of γ-alkyl β-aminobutyric acids of the R configuration (ee>99%).*

β-Amino acids have attracted particular attention on account of their occurrence in natural products such as alkaloids and antibiotics,[1] as well as their utility as intermediates for preparing β-lactams[2] and therapeutically enhanced peptides.[3] Consequently, considerable efforts have been expended to devise methods for their synthesis. In most cases, enantioselectivity is conferred by an external chiral agent.[4] However, two interesting exceptions make use of the innate chirality of α-amino acids. One involves homologation by the Arndt-Eistert procedure[5]. The other relies on the differential chemical modification of the acid and amide groups of L-asparagine.[6] It occurred to us that aspartic acid, provided the correct sequence of reactions were followed, would offer certain operational advantages. We now report a new procedure whereby a range of homochiral γ-substituted β-amino acids is readily obtainable by reaction of a pivotal β-homoserine derivative.

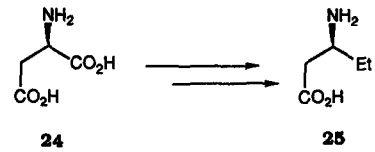
L-Aspartic acid (**1**), taken as starting material, serves as an illustration. First, the amino group was protected by converting **1** into N-tosyl-L-aspartic acid (**2**) (Scheme 1). Treatment of **2** with acetic anhydride formed the succinic anhydride **3** which by selective reduction[7] with sodium borohydride gave the lactone **4**. Next, submission of **4** to trimethylsilyl iodide[8] and ethanol in methylene chloride at 0°C under nitrogen furnished the key chiral intermediate,[9] the ethyl ester **5**, in an overall yield of 65% from **1**. Nucleophilic substitution in **5** was effected by reaction with various lithium organocuprates[10] in THF at -30°. The methyl, *n*-butyl, *t*-butyl, *n*-pentyl and benzyl groups were all successfully introduced in high yield (74-96%) to give the corresponding β-(N-tosyl)amino ethyl esters (**6-10**). In contrast, attempts with lithium diphenylcuprate were unsuccessful and led to β-elimination or recovery of **5**. However, reductive de-iodination of **5** with tributyltin hydride gave the parent ester **11** in 66% yield.[11] Lastly, alkaline hydrolysis of the esters **6-11** with potassium carbonate in aqueous methanol liberated the respective 2R-β-(N-tosyl)amino acids (**12-17**). Subsequently, the tosyl group was removed by heating in a mixture of aqueous hydrobromic acid and phenol,[12] followed by treatment with 1,2-epoxypropane in ethanol.[13] The β-amino acids **18-23** were obtained in yields of 27-52% from L-aspartic acid.[14]

In order to verify that the integrity of the initial chiral center had been preserved, especially after exposure to the conditions of saponification and deprotection, a pair of β-amino acids was tested for enantiomeric purity. By way of comparison, D-aspartic acid (**24**) was subjected to the above sequence of reactions and con-

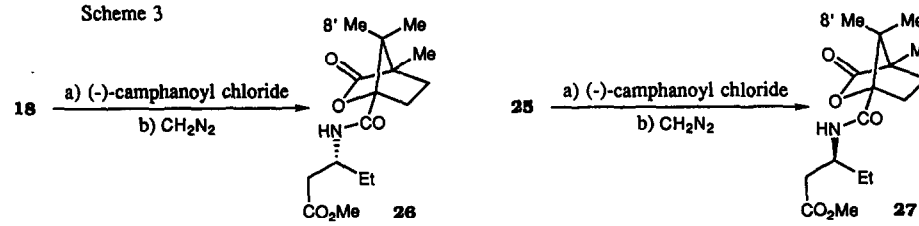
Scheme 1



Scheme 2



Scheme 3



verted to 3S-aminopentanoic acid (**25**) (Scheme 2). It was gratifying to note that its optical rotation ($[\alpha]_D^{20}$ + 38.5°, c = 0.28, H_2O) mirrored that[14] of its 3R isomer **18**. Nonetheless, to be absolutely sure, both **18** and **25** were derivatized as their N-camphanoyl methyl esters, **26** and **27** respectively (Scheme 3).[15] Careful examination of the ^{1}H-NMR spectra (400 MHz) revealed that **26** and **27** and therefore the related synthetic β-amino acids were enantiomerically pure (ee>99%).[16] Gas chromatographic analysis of **26** and **27** further confirmed that neither diastereomer was contaminated by the other.

The present examples demonstrate that the transformation of L-aspartic acid into R-γ-alkyl β-aminobutyric acids is chemically and enantiomerically efficient and works equally well for the D-isomer thereby providing access to the S series of β-amino acids. The procedure is simple to perform, requires only a few steps, including one chromatographic separation, and delivers product on the gram scale. Applications to the synthesis of indolizidine alkaloids as well as further elaboration of the iodo-β-homoserine ester **5** are under study and the results will be reported in due course.

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References and Notes

1. C.N.C. Drey, in *Chemistry and Biochemistry of the Amino Acids*, Ed. G.C. Barrett, Chapman and Hall, New York, 1985, chapter 3; O.W. Griffith, *Ann. Rev. Biochem.* **1986**, *55*, 855.
2. T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen, F.A. Bouffard, *J. Am. Chem. Soc.* **1980**, *102*, 6161; K. Okano, T. Izawa, M. Ohno, *Tetrahedron Lett.* **1983**, *24*, 217; H. Huang, N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1984**, 1465; S. Kim, S.B. Chang, P.H. Lee, *Tetrahedron Lett.* **1987**, *28*, 2735; S. Kim, P.H. Lee, T.A. Lee, *J. Chem. Soc., Chem. Commun.* **1988**, 1242.
3. A.F. Spatola, in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, B. Weinstein, Ed., Marcel Dekker, New York, 1983, Vol. 7, pp. 331-333, and references cited therein.
4. a) J. d'Angelo, J. Maddaluno, *J. Am. Chem. Soc.* **1986**, *108*, 8112; H. Estermann, D. Seebach, *Helv. Chim. Acta* **1988**, *71*, 1824; H. Kunz, D. Schanzenbach, *Angew. Chem.* **1989**, *101*, 1042; J.M. Brown, A.P. James, L.M. Prior, *Tetrahedron Lett.* **1987**, *28*, 2179; D. Keirs, D. Moffat, K. Overton, R. Tomanek, *J. Chem. Soc., Perkin Trans.* **1991**, 1041; W.D. Cabell, M. Kitamura, R. Noyori, *Tetrahedron Asymmetry* **1991**, *2*, 543. b) S.G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1991**, *2*, 183.
5. K. Balenovic, D. Cerar, Z. Fuks, *J. Chem. Soc.* **1952**, 3316; C.W. Jefford, Q. Tang, A. Zaslona, *J. Am. Chem. Soc.* **1991**, *113*, 3513.
6. P. Gmeiner, *Arch. Pharm.* **1991**, *324*, 551.
7. D.M. Bailey, R.E. Johnson, *J. Org. Chem.* **1970**, *35*, 3574; D.H.R. Barton, M. Bénéchie, F. Khoung-Huu, P. Potier, V. Reyna-Pinedo, *Tetrahedron Lett.* **1982**, *23*, 651; G.J. McGarvey, R.N. Hiner, Y. Matsubara, T. Oh, *Tetrahedron Lett.* **1983**, *24*, 2733; G.J. McGarvey, J.M. Williams, R.N. Hiner, Y. Matsubara, T. Oh, *J. Am. Chem. Soc.* **1986**, *108*, 4943.
8. M. Kolb, J. Barth, *Synth. Commun.* **1981**, *11*, 763; M. Larchevêque, S. Henrot, *Tetrahedron Lett.* **1987**, *28*, 1781.
9. The iodo-β-homoserine ester **5** was obtained as colorless crystals (ether-hexane), m.p. 59.0-60.0°C; $[\alpha]_D^{20}$ = -7.59° (c 0.87, $CHCl_3$). ^{1}H-NMR (400 MHz): 1.23 (t, *J* = 7.1 Hz, 3H), 2.43 (s, 3H), 2.55 (dd, *J* = 16.6, 6.1 Hz, 1H), 2.69 (dd, *J* = 16.6, 5.2 Hz, 1H), 3.22 (dd, *J* = 10.3, 6.6 Hz, 1H), 3.32 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.56 (m, 1H), 4.06 (qd, *J* = 7.1, 2.4 Hz, 2H), 5.43 (d, *J* = 8.9 Hz), 7.32 (d, *J* = 8.3 Hz,

2H), 7.77 (d, J = 8.3 Hz, 2H). ^{13}C-NMR (100 MHz): 10.53, 13.98, 21.50, 38.90, 50.47, 61.04, 127.04, 129.76, 137.40, 143.75, 170.31. MS M/z: 412 (M^+, 0.88), 284 [(M-HI)$^+$, 14.5], 91 (100%). Anal. calcd for $C_{13}H_{18}SO_4NI$: C, 37.97; H, 4.41; N, 3.41; Found C, 38.00; H, 4.36; N, 3.49.

10. Me_2CuLi and $(C_5H_{11})_2CuLi$ were prepared from CuI; $(n\text{-}Bu)_4CuLi$ from CuBr, while $(t\text{-}Bu)_2CuLi$ and $(PhCH_2)_2CuLi$ were prepared from CuBr•Me_2S. As the reaction was too slow in Et_2O as solvent, THF was used instead.
11. The β-(N-tosyl)amino esters **6-11** were obtained as oils which were purified by column chromatography over SiO_2 (hexane:ethyl acetate, 3:2). Optical rotations ($[\alpha]_D^{20}$) were determined in $CHCl_3$ and had the following values: **6**, +36.5° (c 1.6); **7**, +23.3° (c 1.35); **8**, +33.6° (c 1.15); **9**, +21.0° (c 1.6); **10**, (not done, owing to trace contaminant); **11**, +28.1° (c 1.05). ^{1}H-NMR (200 MHz, $CDCl_3$): **6**, δ 0.76 (t, J = 7.5 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.46 (dt, J = 14.4, 7.2 Hz, 2H), 2.35 (dd, J = 5.6, 1.4 Hz, 2H), 2.40 (s, 3H), 3.45 (m, 1H), 4.03 (qd, J = 7.1, 1.5 Hz, 2H), 5.35 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H). **7**, δ 0.77 (t, J = 6.4 Hz, 3H), 1.19 (t, J = 7.1 Hz), 1.08-1.48 (m, 8H), 2.36 (dd, J = 5.8, 3.2 Hz, 2H), 2.39 (s, 3H), 3.49 (m, 1H), 4.03 (q, J = 7.1 Hz, 2H), 5.28 (d, J = 9.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H). **8**, δ 0.84 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H), 1.26 (dd, J = 3.5, 13.0 Hz, 1H), 1.47 (dd, J = 7.6, 13.0 Hz, 1H), 2.34 (d, J = 4.6 Hz, 2H), 2.42 (s, 3H), 3.71 (m, 1H), 4.10 (q, J = 7.2 Hz), 5.31 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H). **9**, 0.81 (t, J = 6.3 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.05-1.50 (m, 10H), 2.36 (d, J = 2.7 Hz, 1H), 2.39 (d, J = 2.7 Hz, 1H), 2.40 (s, 3H), 3.48 (m, 1H), 4.04 (qd, J = 1.1, 7.1 Hz, 2H), 5.25 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H). **10**, not done, owing to impurity. **11**, δ 1.12 (d, J = 6.7 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 2.39 (dd, J = 5.1, 0.89 Hz, 2H), 2.40 (s, 3H), 3.67 (m, 1H), 4.05 (qd, J = 7.1, 1.4 Hz, 2H), 5.28 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H).
12. H.R. Snyder, R.E. Hecker, *J. Am. Chem. Soc.* **1952**, *74*, 2006.
13. U. Schöllkopf, J. Nozulak, U. Groth, *Synthesis* **1982**, 868.
14. The β-amino acids gave correct elemental analyses, were formed as solids from **1** in the overall yields indicated and had the following values for $[\alpha]_D^{20}$ determined in H_2O except where noted: **18**, 43%; -38.6° (c 1.1); lit.[6] -37.0° (c 0.7); **19**, 36%; -33.8° (c 0.36); lit.[6] -22.0° (c 0.5, H_2O:MeOH, 1:1); **20**, 27%; -32.5° (c 1.2); **21**, 46%; -26.8° (c 0.33); **22**, 52%; -28.4° (c 0.56); **23**, 37%; -39.6° (c 0.53); lit.[4b] -39.8° (c 0.47). ^{1}H-NMR (200 MHz, D_2O): **18**, δ 0.78 (t, J = 7.4 Hz, 3H), 1.48 (m, 2H), 2.22 (dd, J = 8.1, 16.6 Hz, 1H), 2.38 (dd, J = 5.1, 16.6 Hz, 1H), 3.23 (m, 1H). **19**, δ 0.65 (t, J = 7.0 Hz, 3H), 1.01-1.26 (m, 6H), 1.42 (m, 2H), 2.18 (dd, J = 8.1, 16.5 Hz, 1H), 2.33 (dd, J = 4.9, 16.5 Hz, 1H), 3.25 (m, 1H). **20**, δ 0.77 (s, 9H), 1.38 (t, J = 4.6 Hz, 2H), 2.26 (dd, J = 8.3, 16.9 Hz, 1H), 2.42 (dd, J = 4.3, 16.9 Hz, 1H), 3.38 (m, 1H). **21**, δ 0.66 (t, J = 6.8 Hz, 3H), 1.05-1.28 (m, 8H), 1.43 (m, 2H), 2.21 (dd, J = 8.1, 16.6 Hz, 1H), 2.37 (dd, J = 4.9, 16.6 Hz, 1H), 3.27 (m, 1H). **22**, δ 1.92 (m, 2H), 2.40 (dd, J = 8.9, 16.8 Hz, 1H), 2.60 (dd, J = 4.1, 16.8 Hz, 1H), 2.72 (t, J = 8.1 Hz, 2H), 3.42 (m, 1H), 7.15-7.38 (m, 5H). **23**, δ 1.09 (d, J = 6.7 Hz, 3H), 2.25 (d, J = 1.4 Hz, 1H), 2.28 (d, J = 0.4 Hz, 1H), 3.37 (m, 1H).
15. L.D. Arnold, J.C.G. Driver, J.C. Vederas, *J. Am. Chem. Soc.* **1987**, *109*, 4649.
16. The C8'-methyl group of the 3R isomer (**26**) displayed a proton resonance upfield (Δ 0.03 ppm) from that of the 3S isomer (**27**).

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