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CHIRAL SYNTHESIS OF D- AND L-3,3-DIPHENYLALANINE (DIP), UNUSUAL α-AMINO ACIDS FOR PEPTIDES OF BIOLOGICAL INTEREST

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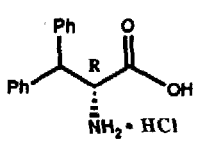
Abstract: The asymmetric syntheses of D-(R)-(-)- and L-(S)-(+)-3,3-diphenylalanine (Dip) are described.

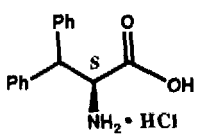
Currently, there is great interest in the design and synthesis of unusual α-amino acids which may provide specific conformational restraint, and also biostability to degradation by peptidases to small peptides/peptidomimetics as potential therapeutic agents.[1] In this regard, we undertook the preparation of multigram quantities of D- and L-3,3-diphenylalanine (Dip). Although these compounds have been incorporated into peptides as a racemate, and then separated as diastereoisomers,[2,3] attempts at resolution by the action of enzymes such as hog kidney acylase, or carboxypeptidase on N-acetyl Dip are reported to be unsuccessful.[2] Our experiments at resolution using other commercial acylases also failed. However, we were able to obtain large quantities of D- and L-Dip by conventional resolution method using cinchona alkaloids.[4] The absolute configuration of the resolved isomers (**1a**), ($[\alpha]_D^{23}$ = -64.5° (c=1.0, MeOH)) as D-Dip hydrochloride and (**1b**), ($[\alpha]_D^{23}$ = +63.9° (c=1.0, MeOH)) as L-Dip hydrochloride were tentatively assigned on the basis of the order of elution on a Diacel Crownpack HPLC column,[5,6,7,8] This assignment of absolute configuration could not be confirmed by a single crystal x-ray



(**1a**)

D-Dip HCl

$[\alpha]_D$ = -63.7° (chiral syn.)
$[\alpha]_D$ = -64.5° (resolution)
(c=1.0, MeOH)



(**1b**)

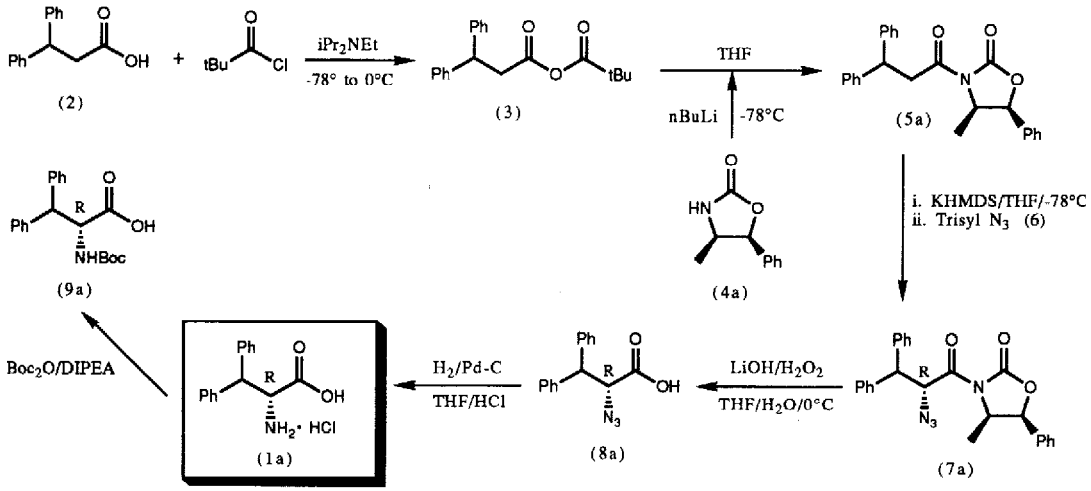
L-Dip HCl

$[\alpha]_D$ = +63.8° (chiral syn.)
$[\alpha]_D$ = +63.9° (resolution)
(c=1.0, MeOH)

analysis,[9] since a single crystal of the compound or a derivative thereof could not be obtained. In order to confirm the assigned configurations, we undertook the chiral synthesis of D- and L-Dip using Evans methodology,[10] which confirmed our original assignment of configuration. A recent report by Chassaing *et. al.*,[11] on the asymmetric synthesis of these same amino acids via an alternative sultam derived chiral auxiliary methodology (4 steps, 46% overall yield, 95% d.e., long reaction times),

prompted us to report our facile on large scale, chiral synthesis of D-(R)-(-)-Dip hydrochloride (**1a**)[11] as shown in Scheme I.

Scheme I

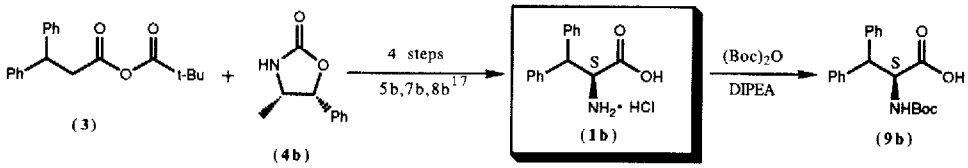


The conversion of 3,3-diphenylpropionic acid (**2**) (1.1 equiv.), to the mixed anhydride (**3**) was accomplished by the treatment of the acid (**2**) with DIPEA (1.2 equiv.) and pivaloyl chloride (1.05 equiv.) in THF at -78°C. The milky mixture was warmed to 0°C over 60 min. The solid was filtered and the filtrate was added to the lithiated oxazolidinone solution at -78°C, which was prepared by the addition of n-BuLi (1.0 equiv.) to the solution of (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (**4a**), (1.0 equiv.) in dry THF. The yellow solution was warmed to 0°C, and quenched with water. The residue, after standard work-up, was flash chromatographed (silica gel, hexane:AcOEt/4 : 1) to yield the acyloxazolidinone (**5a**),[12] 82% yield, mp 106°C, $[\alpha]_D^{23}$ = -13.5° (c=1.0, MeOH). Deprotonation of (**5a**) by the addition of KHMDS (1.05 equiv.) in THF at -78°C, followed by the addition of a solution of trisyl azide (**6**)[10](1.25 equiv.) in THF, rapidly quenching with AcOH (4.6 equiv.) after 2 min at -78°C, and warming quickly to 30°C gave a light yellow solution, which was diluted with CH_2Cl_2, washed with brine, $NaHCO_3$ (sat.), and dried ($MgSO_4$). The concentrated yellow oil was flash chromatographed (silica gel, hexane:AcOEt/8 : 1) to give the azido oxazolidinone (**7a**), 94% yield, mp 90 - 91°C, $[\alpha]_D^{23}$ = -206.2° (c=1.0, MeOH). HPLC[13] showed a single diastereoisomer indicating complete stereocontrol during azide entry onto the potassium enolate template of (**5a**). The azide (**7a**) in 4 : 1 THF-H_2O at 0°C, was hydrolyzed with a solution of LiOH-H_2O (2.0 equiv.) in H_2O_2 (5.0 equiv., 30% aqueous). After 1 hr., aqueous Na_2SO_3 (1 M) was added. THF was removed in vacuo, and the aqueous was acidified to pH 1 with 6 N HCl at 0°C. The product was extracted with CH_2Cl_2, and dried ($MgSO_4$). The azido acid (**8a**) was obtained by flash chromatography (silica gel, hexane:AcOEt:AcOH/50 : 50 : 2), 99% yield, mp 108 - 109.5°C, $[\alpha]_D^{23}$ = -54.2° (c=1.0, MeOH). The chiral auxiliary (**4a**) was recovered (96%, mp 120 - 121°C). The azido acid (**8a**) in THF-HCl (1 N), (4 : 1), was hydrogenated at 50 psi, over 10% Pd-C, for 20 hrs. The solvent was removed, and the residue was recrystallized from 2N HCl

to give a white solid, as D-(R)-(-)-Dip hydrochloride (**1a**), 77% yield, mp 248 - 253°C (dec.), $[\alpha]_D^{23}$ = -63.7° (c=1.0, MeOH).-[14] Chiral HPLC[15] indicated a >99% enantiomeric purity. Further treatment of (**1a**) with $(Boc)_2O$ (2.0 equiv.) and DIPEA (2.5 equiv.) in methanol gave N-Boc-D-Dip (**9a**), 81% yield, mp 153 - 154°C (dec.), $[\alpha]_D^{23}$ = -35.7° (c=1.0 MeOH).

The L-(S)-(+)-DIP hydrochloride (**1b**) (mp 247 - 250°C (dec.), $[\alpha]_D^{23}$ = +63.8° (c=1.0, MeOH)) and N-Boc-L-Dip (**9b**)[16] (mp 152 - 153°C (dec.), $[\alpha]_D^{23}$ = +32.2° (c=1.0, MeOH)) were similarly synthesized using (4S,5R)-4-methyl-5-phenyl-2-oxazolidinone (**4b**)[17] as the chiral auxiliary (Scheme II).

Scheme II



In conclusion, the synthetically useful D-(R)-(-)-Dip and L-(S)-(+)-Dip can be enantioselectively prepared in good yield using Evans methodology. The predictable stereochemistry of the α-amino acids obtained from this methodology confirmed the absolute configuration assigned to the enantiomers, obtained by conventional resolution, using fast and easily available chiral HPLC techniques.

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8. The absolute configuration of the resolved Dip was assigned by chiral HPLC with the same conditions as described in note 15, the isomer with t_R (retention time) = 80.76 min assigned as D-(-)-Dip and t_R = 89.75 min as L-(+)-Dip.
9. We thank Professor A. T. McPhail (Duke University) for this effort.
10. a) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L.; *J. Am. Chem. Soc.*, **1990**, *112*, 4011. b) Evans, D. A.; Ellman, J. A.; *J. Am. Chem. Soc.*, **1989**, *111*, 1063.
11. a) Josien, H.; Martin, A.; Chassaing, G.; *Tetrahedron Lett.*, **1991**, *32*, 6547. b) The rotation and mp of D- and L-Dip we found are significantly higher than those reported by Chassaing. The enantiomeric purity of our D- and L-Dip is confirmed by chiral HPLC analysis (see note 8 and 15).
12. The acyloxazolidinone (**5a**) was also prepared using 3,3-diphenylpropionyl chloride, (mp 41 - 43°C), instead of the mixed anhydride which gave (**5a**) in 80% yield, mp 106°C, recrystallized from hexane-AcOEt (4 : 1).

13. Analytical reverse-phase HPLC was performed with a 4.6 x 250 mm, 5 μM, C-18, Beckman Ultrasphere column, solvent A: 0.05 M $NH_4H_2PO_4$ in water; solvent B: acetonitrile, A:B/45:55, to give one peak, t_R = 11.73 min.

14. Spectral data for: (**5a**): IR(KBr): 1784.0, 1764.5, 1494.6, 1454.1, 1350.2 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.40-7.13 (m, 15H), 5.46 (d, J=8.76 Hz, 1H), 4.68 (t, J_1=J_2=9.39 Hz, 1H), 4.64-4.53 (m, 1H), 3.78 (d, J=8.61 Hz, 2H), 0.71 (d, J=7.92 Hz, 3H). ^{13}C NMR($CDCl_3$): δ 171.16, 153.00, 143.43, 143.34, 133.19, 128.71, 128.64, 128.52, 127.90, 127.78, 126.55, 126.50, 125.59, 78.89, 54.70, 46.77, 40.92, 14.29. MS(CI): m/z 386 (M^++1), 385 (M^+), 222, 167 (base), 165, 77. Anal.: Calcd. for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.86; H, 6.11; N, 3.63. (**7a**): IR(KBr): 2109.7, 1783.6, 1734.1 cm^{-1}. ^1H NMR(CD_3OD): δ 7.49-7.24 (m, 15H), 6.04 (d, J=13.26 Hz, 1H), 5.03 (d, J=8.55 Hz, 1H), 4.55 (d, J=13.32 Hz, 1H), 4.45-4.34 (m, 1H), 0.81 (d, J=7.98 Hz, 3H). ^{13}C NMR(CD_3OD): δ 171.36, 153.97, 141.06, 134.37, 129.93, 129.90, 129.73, 129.63, 129.50, 128.66, 128.49, 128.29, 127.18, 126.89, 80.70, 62.38, 56.44, 54.96, 14.48. MS(FAB): m/z 427 (M^++1), 401 (base), 386. Anal.: Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14. Found: C, 70.06; H, 5.22; N, 12.79. (**8a**): IR(KBr): 3416.5-3303.9(br), 2121.9, 1739.4 cm^{-1}. ^1H NMR(CD_3OD): δ 7.41-7.14 (m, 10H), 4.65 (d, J=11.16 Hz, 1H), 4.50 (d, J=11.37 Hz, 1H). ^{13}C NMR(CD_3OD): δ 172.69, 141.86, 141.51, 129.75, 129.64, 129.49, 128.17, 66.62, 53.97. MS(CI): m/z 222 (M^+-45), 196, 195, 194, 167 (base). Anal.: Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found; C, 67.31; H, 4.90, N, 15.03. (**1a**): IR(KBr): 3508.9-3373.7(br), 3361.9-3268.0(br), 1757.5 cm^{-1}. ^1H NMR(CD_3OD): δ 7.52-7.17 (m, 10H), 4.85 (d, J=12.66 Hz, 1H), 4.43 (d, J=12.63 Hz, 1H). ^{13}C NMR(CD_3OD): δ 171.04, 140.24, 139.65, 130.50, 129.81, 129.52, 129.41, 129.17, 128.70, 57.41, 54.84. MS(CI): m/z 242 (M^++1), 196, 167 (base). (**9a**): IR(KBr): 3386.6-3372.1(br), 1716.9, 1700.4 cm^{-1}. ^1H NMR(CD_3OD): δ 7.34-7.15 (m, 10H), 4.97 (d, J=13.29 Hz, 1H), 4.34 (d, J=13.20 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR(CD_3OD): δ 176.27, 155.53, 140.11, 139.40, 128.78, 128.71, 128.60, 128.26, 127.28, 127.12, 80.59, 56.60, 52.63, 28.20. MS(CI): m/z 342 (M^++1), 286, 242, 196, 167 (base). Anal: Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.31; H, 6.86; N, 3.94.

15. The chiral HPLC was performed with 4.0 x 150 mm chiral crown ether column, Daicel Crownpak CR(+) and Varian Star HPLC System, solvent A: $HClO_4$ in H_2O, pH 1.0, solvent B: MeOH, A:B/86:14, flow rate 0.6 mL/min., to give (**1a**) t_R = 80.86 min., purity 99.9% by peak area normalization, (**1b**) t_R = 86.30 min., purity 99.3% by peak area normalization.

16. Spectral data for: (**1b**): IR(KBr): 3450-3321 (br), 3090.7-2830.6 (br), 1757.4 cm^{-1}. ^1H NMR(CD_3OD): δ 7.52-7.19 (m, 10H), 4.86 (d, J=12.54 Hz, 1H), 4.43 (d, J=12.54 Hz, 1H). ^{13}C NMR(CD_3OD): δ 171.05, 140.25, 139.66, 130.52, 129.83, 129.55, 129.44, 129.17, 128.71, 57.44, 54.83. MS(CI): m/z 242 (M^++1), 196, 167 (base). (**9b**): IR(KBr): 3388.2(br), 3380.5(br), 1700.1, 1695.8 cm^{-1}. ^1H NMR(CD_3OD): δ 7.35-7.17 (m, 10H), 4.97 (d, J=10.92 Hz, 1H), 4.36 (d, J=10.68 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR($CDCl_3$): δ 176.79, 155.55, 140.30, 139.60, 128.77, 128.60, 128.33, 127.21, 127.07, 80.55, 56.81, 52.73, 28.24. MS(FAB): m/z 342 (M^++1), 286, 242 (base). Anal: Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.98; H, 6.95; N, 3.87.

17. Compounds (**4b**), (**5b**), (**7b**), (**8b**) are enantiomers of (**4a**), (**5a**), (**7a**), (**8a**) respectively.

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