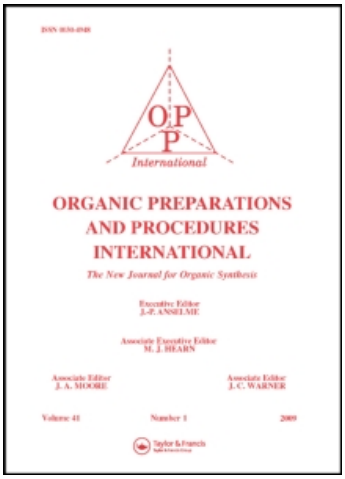

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THE RESOLUTION OF RACEMIC AMINES BY THE FORMATION OF DIASTEREOMERIC AMIDES WITH AMINO ACIDS

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THE RESOLUTION OF RACEMIC AMINES BY THE FORMATION OF DIASTEREOMERIC AMIDES WITH AMINO ACIDS

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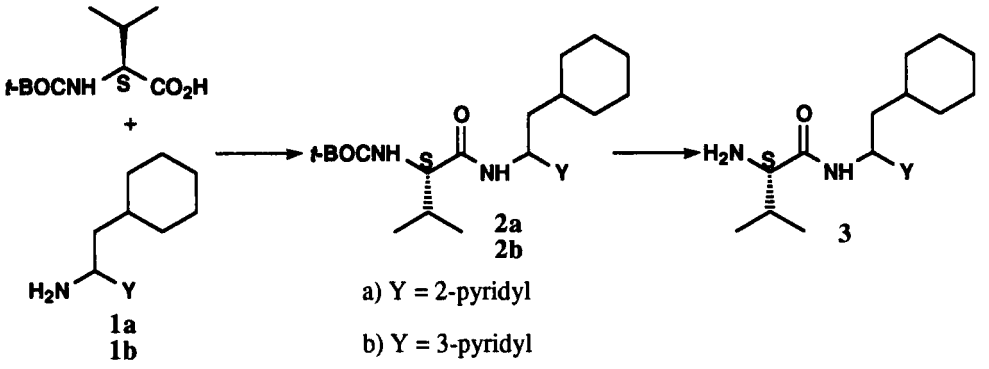
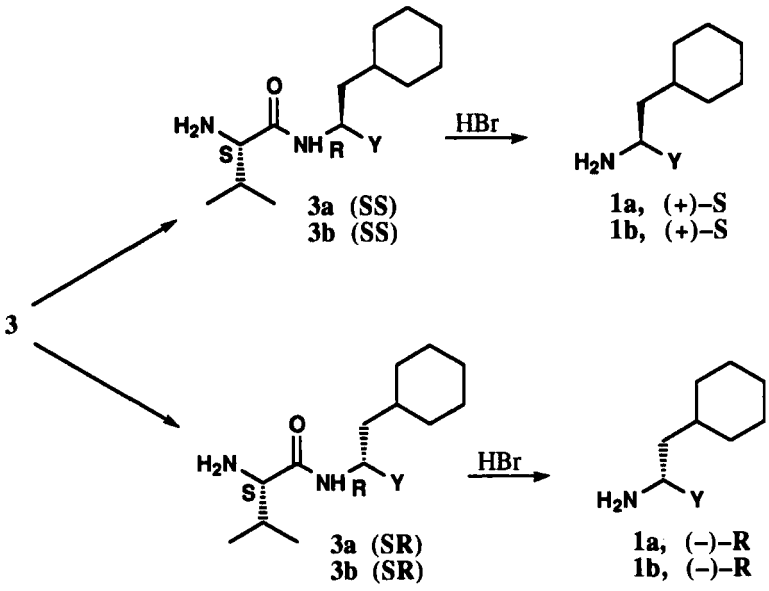
Racemic primary amines (**1a** and **1b**) were needed as intermediates and it was necessary to separate them into their enantiomers on gram scales in good yields and high optical purity. Although there are many acidic resolving agents available,[1] we found that the yields and purities were not satisfactory. We investigated the use of the amino acids, CBz-L-phenylalanine, CBz-L-valine and *t*-Boc-L-valine as chiral auxiliaries. In each case, the amide diastereomers obtained after coupling provided only a small degree of separation on TLC.[2] However, when the N-*t*-butoxycarbonyl group was

removed, a much better separation of the two diastereomers **3a (SS)** and **3a (SR)** was achieved (**Scheme**).[3] The removal of the CBz from the CBz-L-phenylalanine derivative of **1a** to the amino-amide was slightly less satisfactory[4] than for the L-valine derivatives. For the best separation and experimental convenience, the *t*-Boc-L-valine was chosen. The *t*-Boc-L-valine was coupled with the





Compound	Optical Purity % (+)–S	Yield % Overall	Optical Purity % (–)–R	Yield % Overall
2-pyr **1a**	99.8	82	99.9	76
3-pyr **1b**	99.5	52	99.7	48

amines (**1a** and **1b**) to give the diastereomers (**2a** and **2b**). Upon hydrolysis with trifluoroacetic Acid (TFA), the L-valine diastereomers **3** could be readily separated on silica gel chromatography

followed by crystallization as salts to give the **3 (SS)** and **3 (SR).** The **SS** and **SR** diastereomers were hydrolyzed to their pure enantiomers using concentrated HBr.

The purity of the enantiomers was determined by using chiral HPLC. The 2-pyridyl analogue **1a** was separated on a Chiralpak AD[5] column using *n*-hexane-isopropanoldiethylamine (980/20/5) as the mobile phase. However, under the same conditions, no separation was obtained for the 3-pyridyl analogue **1b**. The enantiomers of **1b** were separated on a Chiralpak AS[5] column using *n*-hexane-isopropanol-diethylamine (950/50/10) as the mobile phase. In this fashion, both sets of compounds showed high enantiomeric purity as shown in the Table. The absolute configuration of the (+)-2-pyridyl **1a** enantiomer was determined through X-ray crystallography to have the S-configuration.[6]

EXPERIMENTAL SECTION

The elemental analyses were performed by Midwest Microlab, Indianapolis, IN. The NMR spectra were obtained on Bruker BZH 250 MHz. For the preparation of 1-(2-pyridyl)-2-cyclohexylethylamine **1a**, see ref.7a.

The following procedures were followed, for the resolution of 1-(2-pyridyl)-2-cyclohexylethylamine **1a**.

Coupling[8].- Under argon in an ice bath, 5.56 g (41 mmoles, 1.2 equiv.) of N-hydroxybenzotriazole monohydrate in 50 mL dry THF was added as a slurry to a solution of 8.93 g (41 mmoles, 1.2 equiv.) of N-*t*-Boc-L-valine in 50 mL CH_2Cl_2. After 5 min, 7.88 g (41 mmoles, 1.2 equiv.) of 1-(-3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI) was added. After 0.5 hr. of stirring at 0°, 7.0 g (34.3 mmoles) of **1a** was added. The resulting mixture was stirred at 0° for 1hr and followed by 1hr at RT. The reaction mixture was washed with 2N HCl, then a saturated solution of Na_2CO_3 and the combined aqueous wash was extracted with 100 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and concentrated to give 14.4 g of a foamy residue. Flash column chromatography on silica gel and elution with 10% acetone-pet ether and 50% acetone-pet ether provided 13.4 g (97%) of white foamy solid **2a**.[9]

Anal. Calcd. for $C_{23}H_{37}N_3O_3$: C, 68.45; H, 9.24; N, 10.41. Found: C, 68.22; H, 9.18; N, 10.42

Deprotection.- A solution of 13.3 g (33 mmoles) of **2a** in 25 mL TFA and 25 mL CH_2Cl_2 was stirred for 2hrs under anhydrous conditions. After cooling in an ice bath, a saturated solution of Na_2CO_3 was added until pH 8 was reached. The aqueous phase was exhaustively extracted with CH_2Cl_2 (200-300 mL), dried over $MgSO_4$ and concentrated to afford 10.2 g of a thick syrup. Flash column chromatography over silica gel (elution with 2% and 10% MeOH-CH_2Cl_2) gave 2.4 g pure **3a (SS)**,[9] 4.2 g mixture and 3.3 g pure **3a (SR).**[9] The 4.2g mixture was rechromatographed as above to give pure products. **3a (SS)** was treated with *p*-toluenesulfonic acid to give a crystalline solid. Upon recrystallization from EtOH-ether, 9.7 g (43%) ditosylate[10] was obtained, mp. 254-257° (dec.).

Anal. Calcd. for $C_{32}H_{45}N_3O_7S_2$: C, 59.33; H, 7.00; N, 6.49. Found: C, 59.74; H, 7.15; N, 6.95

3a (SR) was crystallized from ethereal HCl. After recrystallization from EtOH-ether, 5.53 g (45%)

3a (RS) di-hydrochloride salt[10], mp. 206-208°, was obtained.

Anal. Calcd. for $C_{18}H_{29}N_3O{\cdot}2HCl{\cdot}0.5H_2O$: C, 56.10; H, 8.37; N, 10.90; Cl, 18.40

Found: C, 55.63; H, 8.29; N, 10.85; Cl, 18.35

Valine Cleavage.- **3a (SS)** was converted to the free base by extraction of 9.75 g (14.3 mmoles) of the ditosylate into CH_2Cl_2 from aqueous NaOH. The oil was dissolved in 50 mL conc. HBr and refluxed for 40 hrs. The reaction was poured into ice, the pH of the aqueous solution was adjusted to 9 by the addition of 2N NaOH, extracted with CH_2Cl_2, dried and concentrated to give 2.9 g optically pure **1a,(+)-S**[9,11] as an oil. This provided a 99% yield and a 82% overall yield from racemic **1a**.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.12; H, 9.81; N, 13.61

For **3a (SR)**, a solution of 5.50 g (14.6 mmoles) of the di-HCl salt in 50mL conc. HBr was refluxed for 65 hrs. Following the same work up as above, a 2.58 g optically pure **1a,(-)-R**[9,11] was obtained as an oil. This provided an 86% yield and a 76% overall yield from racemic **1a**.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.16; H, 9.84; N, 13.31

Acknowledgement: We thank Scot Campbell and Tracy Saboe for taking the NMR.

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2. e.g. 20% THF-hexane, RF = 0.52 and 0.49 for **2a.**

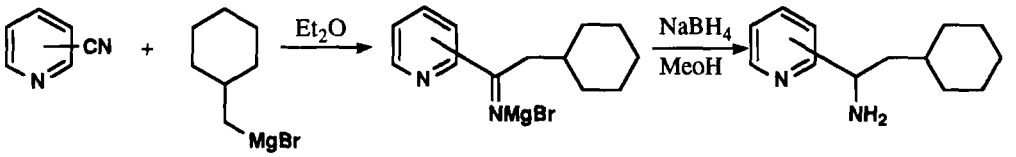
3. 5% MeOH-CH_2Cl_2 RF = 0.34 for **3a (SS)** and RF = 0.17 for **3a (SR).**

4. 5% MEOH-CH_2Cl_2 RF = 0.54 and 0.45 for L-phenylalanine derivatives of **1a.**

5. Chiralpak AD: Amylose-tris[3,5-dimethyl phenyl carbamate] coated on silica gel. Chiralpak AS: Amylose-tris[(S)-α-methyl benzyl carbamate] coated on silica gel.

6. X-ray Crystallography was performed by Dr. Cynthia Day, Crystalytic Company, P. O. Box 82286, Lincoln, NE 68501, on the ditosylate salt of **1a,(+)-S.**

7. a). The amines were prepared by the addition of cyclohexylmethyl-Magnesiumbromide to cyanopyridine[7b] to give the ketimine intermediate. This was followed by *in situ* reduction with $NaBH_4$-methanol.



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9. Compound **2a:** ^{1}H NMR (250 MHz) ($CDCl_3$): δ 0.85 (d, 3H, CH_3), 0.95 (d, 3H, CH_3), 0.95-1.15 (m, 6H, 6ax.cycl), 1.4 (s, 9H, *t*Bu), 1.65 (m, 7H, 5eq.cycl, CH_2), 2.1 (m, 1H, C*H*Me_2), 3.95 (m, 1H, C*H*CO), 5.1 (m, 2H, CH, NH), 6.8 (m, 1H, NH), 7.18 (m, 2H, pyr), 7.6 (m, 1H, pyr), 8.5 (m, 1H, pyr).
Compound **3a (SS):** ^{1}H NMR ($CDCl_3$): δ 0.85 (d, 3H, CH_3), 0.95 (d, 3H, CH_3), 0.9-1.15 (m, 6H, 6ax.cycl), 1.4 (br, 2H, NH_2), 1.7 (m, 7H, 5eq, CH_2), 2.3 (m, 1H, C*H*Me_2), 3.2 (d, 1H, C*H*CO), 5.15 (dd, 1H, CH), 7.15 (m, 1H, pyr), 7.2 (d, 1H, pyr), 7.60 (m, 1H, pyr), 7.95 (br, 1H, NH), 8.55 (d, 1H, pyr).
Compound **3a (SR):** ^{1}H NMR ($CDCl_3$): δ 0.7 (d, 3H, CH_3), 0.92 (d, 3H, CH_3), 0.9-1.15 (m, 6H, 6ax.cycl), 1.5 (s, 2H, NH_2), 1.65 (m, 7H, 5eq, CH_2), 2.2 (m, 1H, C*H*Me_2), 3.2 (d, 1H, C*H*CO), 5.15 (dd, 1H, CH), 7.1 (m, 1H, pyr), 7.2 (m, 1H, pyr), 7.6 (m, 1H, pyr), 7.8 (br, 1H, NH), 8.55 (m, 1H, pyr).
Compound **1a,(+)-S:** ^{1}H NMR ($CDCl_3$): δ 0.95 (m, 3H, 3ax.cycl), 1.5-1.7 (m, 7H, 5eq.cycl, CH_2), 1.72 (br, 2H, NH_2), 4.05 (m, 1H, CH), 7.15 (m, 1H, pyr), 7.25 (m, 1H, pyr), 7.6 (t, 1H, pyr), 8.55 (m, 1H, pyr).
Compound **1a,(-)-R:** Identical NMR spectrum as **1a (S)**.
Data for the 3-pyridyl derivatives: **2b, 3b (SS), 3b (SR),** and **1b (S), 1b (R)**.

10. **3a (SS)** does not crystallize as a dihydrochloride, and **3a (SR)** does not crystallize as the ditosylate.

11. It was slightly less pure chemically, 97% by HPLC, because of incomplete hydrolysis.

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A CONVENIENT METHOD FOR THE GENERATION OF NITRILE OXIDE AND ITS APPLICATION TO THE SYNTHESIS OF 2-ISOXAZOLINES†

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The 1,3-dipolar cycloaddition reaction is one of the most important and versatile methods for the construction of 5-membered heterocycles.[1] Among the various 1,3-dipoles known, nitrile oxides have been used extensively. The usual synthesis of nitrile oxides involves the oxidative dehydrogenation of aldoximes using oxidants such as lead tetraacetate,[2] alkali hypohalites,[3] N-bromosuccinimide in dimethylformamide followed by base treatment,[4] chloramine-T[5] or 1-chlorobenzotriazole[6] as well as the reaction of nitro compounds with an aryl isocyanate.[7] We now report the use of mercuric