Enantioselective Synthesis of *β*-Dibenzylamino Alcohols via a Dynamic Kinetic Resolution of α-Halo Acids

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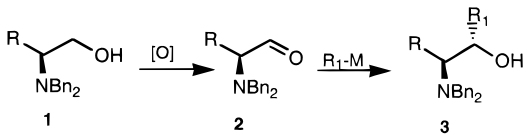
Chiral, nonracemic *β*-amino alcohols are the key precursors to the synthetically important α-amino aldehydes. Particularly valuable are the *β*-dibenzylamino alcohols since these are readily oxidized to α-dibenzylamino aldehydes, also known as Reetz aldehydes. The latter compounds have been shown to be configurationally quite stable and to react with organometallics with high diastereoselectivity (Scheme 1).[1] The relative stereochemistry of the new *β*-amino alcohols thus generated is predicted on the basis of nonchelation-controlled addition of the organometallic to the aldehyde carbonyl group.[1,2]

Reetz aldehydes are usually prepared from α-amino acids via *N*,*N*-dibenzylation, reduction with $LiAlH_4$, and subsequent oxidation. This is an efficient route to nonracemic compounds when the precursor α-amino acid is available in enatiomerically pure form as is the case with the natural α-amino acids. With side chains not found in the natural α-amino acids, the additional steps required to prepare such compounds make the access to compounds such as **1** and **2** a somewhat lengthy and inefficient procedure.

We have recently reported that the reaction of (*R*)-pantolactone esters of racemic α-bromo acids **4** with primary amines in THF at room temperature affords α-amino esters in a highly diastereomeric manner in greater than 50% yield.[3] The greater than 50% yield of one diastereomer was attributed to a dynamic kinetic resolution process in which the (*R*,*R*) isomer of **4** reacted more quickly with the amine than the (*S*,*R*) isomer and the released bromide or the added iodide served to isomerize the slower to the faster reacting isomer.

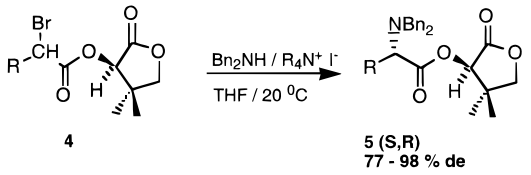
When these conditions were applied to the reaction of **4**, R = CH_2alkyl, or aryl, with dibenzylamine in THF containing 20 mol % of tetra-*n*-butylammonium iodide, the (*S*,*R*)-α-amino esters **5** were obtained with good to excellent de's (77−98%) and in acceptable yields (60−85%) (Scheme 2). The products **5** were subsequently reduced with $LiAlH_4$ to give the enantiomerically enriched *β*-dibenzylamino alcohols **1** without loss of stereochemical integrity[4] (Table 1). The 500 MHz proton NMR showed the diastereotopic benzylic hydrogens as an AB quartet (J_{AB} = 13−14 Hz), with one doublet typically near δ = 3.3 and the other near δ = 3.8. The oxidation of these alcohols to the Reetz aldehydes **2** has been described.[1,5]

Scheme 1



1 **2** **3**

Scheme 2



4 **5 (S,R)** **77 - 98 % de**

Table 1. Preparation of α-Dibenzylamino Alcohols via the Sequence 4, 5, 3[a]

	compound **5**		
R	yield (%)	de (%)[a]	compound **3**, yield (%)
C_2H_5	66	86	76
Ph	70	>98	87
$pBrC_6H_4$	76	>98	76
$Ph(CH_2)_2$	56	82	76
$C_6H_{11}(CH_2)_2$	82	88	78

[a] Determined by 500 MHz NMR integration of the signals of the pantolactone methine hydrogen of the two diastereomers.

We have also investigated the use of *tert*-butyl (4*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate as the chiral auxiliary in the above process.[6] This compound had been shown to be superior to (*R*)-pantolactone as an auxiliary in the dynamic kinetic resolution process. For example, reaction of the diastereomeric mixture of **6** (R = C_2H_5) with benzylamine afforded excellent yields of the aminoimide **7** in essentially enatiomerically pure form. Unfortunately the reaction of **6** with dibenzylamine was quite slow and thus the desired adduct **8** was not obtained directly from **6** but was best prepared via N-benzylation of **7** with K_2CO_3 and benzyl bromide. Fortunately, the two-step sequence was efficient and gave **8** from **6** in approximately 70% yield. The chiral auxiliary was removed by treatment with sodium methoxide in methanol to yield the ester **9** which is a suitable precursor to **1** and **2**. In the earlier publication[6] we had shown that compounds of the type **6** (R = CH_2alkyl, aryl) react with benzylamine to give **7** in good chemical yield (60−85%) and excellent enantiomeric purity (>98% ee). The conversion of these derivatives of **7** into **9**, and eventually the dibenzylamino aldehydes, should be analogous to that described above (Scheme 3).

The absolute stereochemistry at the α-carbon of the major isomer is (*S*) when (*R*)-pantolactone is used and (*R*) when the imidazolidinone is used as the chiral auxiliary. Thus these auxiliaries, when used in conjunc-

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(1) For an excellent review, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, **30**, 1531.

(2) (a) Hanessian, S.; Devasthale, P. V. *Tetrahedron Lett.* **1996**, **37**, 987. (b) For use of these aldeydes in hetero Diels−Alder reactions: (i) Grieco, P. Moher, E. D. *Tetrahedron Lett.* **1993**, *34*, 5567. (ii) Jucak, J.; Golebiowski, A.; Raczko, J. *J. Org. Chem.* **1989**, *54*, 2496. Midland, M. M.; Afonso, M. M. *J. Am. Chem Soc.* **1989**, *111*, 4368.

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(4) The enantiomeric purity of several of the alcohols **4** was determined by 500 MHz analysis of the Mosher esters [Dale, J.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543]. The results were as expected on the basis of the de of the precursor ester **5**.

(5) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (b) Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, **29**, 3295.

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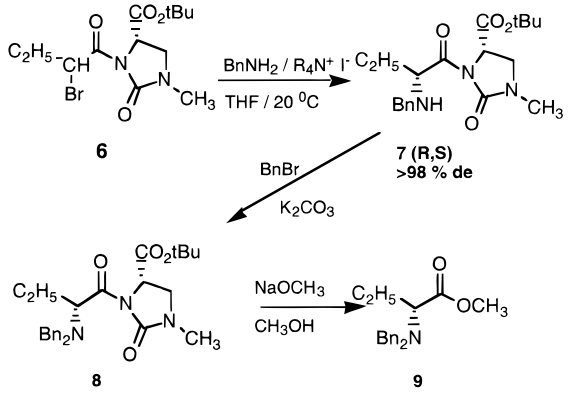
Scheme 3



tion with racemic α-halo acids, can provide a variety of *β*-dibenzylamino alcohols **1** and the derived Reetz aldehydes **2** in either enantiomeric form.

Experimental Section

General Procedure for the Preparation of the (*R*)-Pantolactone Esters 4. Procedure A. A solution of the appropriate acid chloride, commercially available or prepared via the procedure of Harpp et al.,[7] in dry THF was added to a solution of THF containing *(R)*-pantolactone (1.0 equiv) and triethylamine (2.1 equiv) at 0 °C. The reaction mixture was stirred for 1 h and then diluted with water. Usual workup and silica gel chromatography afforded the desired esters **4**.

Procedure B. The appropriate α-halo acid (1.0 equiv), DCC (1.0 equiv), and DMAP (0.1 equiv) were dissolved in dry CH_2Cl_2 and stirred under nitrogen until TLC indicated that the starting alcohol had been consumed.[8] The mixture was filtered, and the filtrate was washed three times with water and once with 10% HCl. The crude product was purified via silica gel chromatography.

Compound 4 (R = Ph): prepared in 72% yield via method B; colorless solid, mp 143−144 °C; IR (film) 1800, 1762 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 0.88, 1.10, 1.15, 1.23 (4 s, total 6H) 3.98, 4.05 (2 s, 2H), 5.34, 5.36 (2 s, 1H), 5.48, 5.51 (both s, 1H) 7−25−7.60 (m,5H). Anal. Calcd for $C_{14}H_{15}BrO_4$: C, 51.40; H 4.62. Found: C, 51.61; H, 4.70.

Compound 4 (R = *p*-BrC$_6$H$_4$): obtained as a yellowish oil in 76% yield via method A; IR (film) 1782, 1740 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$) *δ* 1.20 and 1.23 (2 s, 6H) 3.92 (s, 2H), 5.23, 5.27 (both s, 1H), 5.32, 5.37 (both s, 1H), 7.24−7−53 (m, 4H); HRMS calcd for *m/z* $C_{14}H_{14}Br_2O_4$ 325.0022, found 325.0048.

Compound 4 (R = C$_6$H$_{11}$(CH$_2$)$_2$, Br = I): prepared via method A in 82% yield; colorless oil; IR (film) 1782, 1740 cm^{-1}; ^1H NMR (200 MHz) *δ* 0.75 (m, 2H), 1.06, 1.08, 1.13, 1.14 (all s, total 6H), 1.03−1.36 (m, 6H), 1.55 (m, 5H), 1.82−1.97 (m, 2H), 3.93 (s, 2H), 4.21, 4.32 (2 t, *J* = 7.6 Hz, 2H), 5.24, 5.28 (2,s, 1H); MS (CI) *m/z* (relative intensity) 409 (100, M + 1).

Compounds **4** (R = C_2H_5 and Ph$(CH_2)_2$), see ref 3.

Preparation of α-Dibenzylamino Derivatives 5. General Procedure. (R)-Pantolactone esters **4** (1.0 equiv), Bu_4N^+ I^- or Hex_4N^+ I^- (0.2 equiv), triethylamine (2.0 equiv), and dibenzylamine (1.05 equiv) were dissolved in sufficient dry THF to form approximately a 0.2 M solution of the α-halo ester. The mixture was stirred at approximately 20 °C until TLC indicated the absence of starting halo ester, diluted with ether and washed with water. The aqueous phase was re-extracted with ether. The combined organic fractions were dried, and the solvent was evaporated. The crude product was examined by 500 MHz ^1H NMR to determine the diastereomer ratio. Purification was done via silica gel chromatography using hexane:ethyl acetate mixtures as eluents.

Compound 5 (R = C$_2$H$_5$): obtained in 66% yield as a yellowish oil; IR (film) 1782, 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 0.95 (t, *J* = 7 Hz, 3H), 1.13 (s, 3H), 1.20 (s, 3H), 1.76−1.83 (m, 2H), 3.33−3.36 (m, 1H), 3.78 (AB, *J* = 14.0 Hz, 4H), 4.06−4.08 (m, 2H), 5.47 and 5.45 (2 s, 14:1 ratio, 1H) 7.2−7.3 (m, 10 H); ^{13}C NMR *δ* 10.9, 20.2 22.9, 23.0 40.4, 54.2, 62.2, 74.8, 76.2, 127.0 (2X), 128.2, 128.5, 128.8, 139.6, 171.6, 172.3. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.88; H, 7.39. Found: C, 72.92; H, 7.32.

Compound 5 (R = Ph(CH$_2$)$_2$): obtained in 56% yield as a slightly yellowish oil; IR (film) 1795, 1766 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 1.12 (s, 3H), 1.21 (s, 3H), 2.77−2.81 (m, 4H), 3.50 (t, *J* = 7.7 Hz, 1H), 3.97 and 3.67 (2 d, *J* = 13.8 Hz, 4H), 4.03 (s, 2H), 5.46 and 5.48 (2 s, 10:1 ratio, 1H), 7.07−7.39 (m, 15H); ^{13}C NMR *δ* 20.4, 23.0, 31.7, 32.4, 40.1, 54.4, 60.2, 75.0, 76.2, 126.0, 127.1, 128.3, 129.0, 139.4, 171.4, 172.3; HRMS calcd for $C_{30}H_{33}NO_4$ 471.2417, found 471.2409.

Compound 4 (R = Ph): obtained as a single isomer, mp 83−84 °C, in 70% yield; IR (KBr) 1794, 1748 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 0.95 (s, 3H), 1.27 (s, 3H), 3.78 (AB, *J* = 13.6 Hz, 4H), 4.05 (s, 2H), 4.70 (s, 1H), 5.60 (s,1H), 7.2−7.4 (m, 15H); ^{13}C NMR *δ* 19.6, 22.0.7, 39.6, 53.7, 65.2, 74.7, 75.9, 127.7, 128.0, 128.2, 128.3, 128.4, 128.7, 135.9, 138.9, 170.5, 171.7. Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 65.9. Found: C, 75.42, H 6.58.

Compound 4 (R = *p*-BrC6H4): beige solid, mp 145−146 °C; yield 76%; IR (KBr) 1792, 1745 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 0.99 (s, 3H), 1.18 (s, 3H), 3.81 (AB, *J* = 13.9 Hz, 4H), 4.05 (s, 2H), 4.66 (s, 1H), 5.54 (s, 1H), 7.2−7.35 (m, 12H), 7.46−7.48 (m, 2H); ^{13}C NMR *δ* 20.1, 23.0, 40.1, 54.0, 64.9, 75.2, 76.2, 122.2, 127.2, 128.4, 128.9, 130.4, 131.6, 135.3, 138.9, 170.4, 171.9. Anal. Calcd for $C_{28}H_{28}BrNO_4$: C, 64.36; H, 5.41; N, 2.68. Found: C, 64.35; H, 5.59; N, 2.43.

Compound 4 (R = C$_6$H$_{11}$(CH$_2$)$_2$). This compound was obtained in about 70% yield as a pale yellowish oil; it was contaminated with about 5% of the α,*β*-unsaturated ester resulting from HBr elimination. These two materials were not separable by silica gel chromatography. The mixture was not further characterized except to determine the diastereomer ratio in the usual manner (*SR:RR* = 10:1). The material was reduced as is, and the reduction product was characterized.

Reduction of the α-Dibenzylamino esters 4 to α-Dibenzylamino Alcohols 3. General Procedure. The α-dibenzylamino-(*R*)-pantolactone ester (1 equiv) was dissolved in dry THF to make approximately a 0.1 M solution. To this was added 4 equiv of powdered $LiAlH_4$ over a period of about 30 min. The reaction mixture was stirred at room temperature for 16 h and quenched carefully with a sodium potassium tartrate solution. The resultant solution was stirred for 16 h and then extracted several times with ethyl acetate. The crude product was purified by silica gel chromatography using hexane:ethyl acetate (3:1) as eluent.

(*S*)-2-(*N*,*N*-Dibenzylamino)butane: yield 76%; $[\alpha]^{23}_D$ = 42.6° (CH_2Cl_2, *c* = 1.16); IR (film) 3434 cm^{-1}; ^{13}C NMR *δ* 11.8, 17.9, 53.2, 60.5, 60.7, 127.2, 128.5, 129.1, 139.4. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.23; H, 8.62; N, 5.20. Found: C, 79>84; H, 8.86; N, 4.89.

(*S*)-2-(*N*,*N*-Dibenzylamino)-4-phenylbutanol: yield 76%. $[\alpha]^{23}_D$ = −28.2° (*c* = 1.08, CH_2Cl_2); IR (film) 3611, 3440 cm^{-1}; ^1H NMR (500 MHz) *δ* 1.52−1.60 (m, 1H), 1.98−2.07 (m, 1H), 2.43−2.50 (m, 1H), 2.62−2.68 (m, 1H), 2.78−2.82 (m, 1H), 3.05 (bs, 1H), 3.34 (d, *J* = 13.2 Hz, 2H), 3.46 (dd, *J* = 10.5, 10.3 Hz, 1H), 3.57 (dd, *J* = 10.5, 4.9 Hz, 2H), 3.77 (d, *J* = 13.2 Hz, 2H), 7.13−7.30 (m 15 H); ^{13}C NMR *δ* 27.1, 33.2, 53.1, 58.1, 60.6, 126.0, 127.1, 128.3, 128.4, 128.5, 129.0, 139.1, 141.7. Anal. Calcd for $C_{24}H_{27}NO$: C, 83.42; H, 7.89; N, 4.06. Found: C, 83.08; H, 7.74; N, 4.24.

(*S*)-2-(*N*,*N*-Dibenzylamino)-2-phenylethanol: yield 89%; $[\alpha]^{17}_D$ = +17.3° (*c* = 1.8, CH_2Cl_2); IR (film) 3459 cm^{-1}; ^1H NMR (500 MHz) *δ* 2.98 (bs, 1H), 3.13 (d, *J* = 13.2 Hz, 2H), 3.60 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.90−3.94 (m, 3H) 4.12 (t, *J* = 10.6 Hz, 1H) 7.22−7−42 (m, 15H); ^{13}C NMR *δ* 53.6, 60.5, 63.1, 128.1, 128.4, 128.6, 129.0, 129.3, 135.0, 139.1. Anal. Calcd for $C_{22}H_{23}$-NO: C, 83.24; H, 7.32; N, 4.41. Found: C, 83.19; H, 7.14, N, 4.72.

(*S*)-2-(*N*,*N*-Dibenzylamino)-2(4-bromophenyl)ethanol: yield 64%; white solid mp = 104−105 °C; $[\alpha]^{23}_D$ = +168° (*c* = 1.0, CH_2Cl_2); IR (KBr) 3468 cm^{-1}; ^1H NMR (500 MHz) *δ* 3.13 (d, *J* = 13.5 Hz, 2H), 3.60 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.88−3.91 (m,

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3H), 4.08 (t, J = 10.6 Hz), 7.13,(m, 2H), 7.23−7.38 (m, 10H), 7.51−7.55 (m, 2H); ^{13}C NMR δ 53.5, 60.4, 62.5, 122.0, 127.4, 128.6, 128.9, 130.8, 131.5, 134.2, 138.8. Anal. Calcd for $C_{22}H_{22}BrNO$: C, 66.67; H, 5.61; N, 3.53. Found: C, 66.71; H, 5.64; N, 3.46.

(*S*)-2-(*N*,*N*-Dibenzylamino)-4-cyclohexylbutanol: yield 76%, based on crude **4**; $[\alpha]^{23}_D = -15.6°$ (c = 1.06, CH_2Cl_2); IR 3468 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (m, 2H) 1.17 (m, 6H), 1.57 (bs), 1.54−1.69 (m, 5H), 2.72 (t, J = 4.5 Hz, 2H), 3.16 (m, 1H), 3.39 (d, J = 13.2 Hz, 2H), 3.47 (dd, J = 10.2, 4.5 Hz, 1 H), 3.80 (d, J = 13.2 Hz, 2H), 7.21−7.31 (m, 10 H); ^{13}C NMR δ 21.9, 126.3, 26.4, 33.1, 33.5, 34.7, 37.7, 53.2, 59.2, 60.8, 127.2, 128.5, 129.1, 139.4. Anal. Calcd for $C_{24}H_{31}NO$: C, 81.85; H, 9.26. Found: C, 81.64; H, 9.38.

Preparation of 7. The diastereomeric mixture **6**[6] was subjected to the kinetic dynamic resolution conditions described above but using benzylamine as nucleophile. **7:** yield 92%; mp = 88−90 °C; $[\alpha]^{23}_D = -19.5°$ (c = 2.6, CH_3OH); IR (KBr) 3425, 1738, 1677 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 3H), 1.48 (s, 9H), 1.40−1.70 (m, 2H), 2,85 (s, 3H), 3.28 (dd, J = 9.7, 4.0 Hz, 1H), 3.64 (t, J = 9.9 Hz, 1H), 3.67 (AB, J = 12.4 Hz, 2H), 4.53 (dd, J = 10.3, 4.0 Hz, 1H), 4.57 (dd, J = 7.2, 5.4 Hz, 1H), 7.29, (m, 5H); ^{13}C NMR δ 10.3, 26.7, 27.9, 30.6, 46.7, 52.0, 53.2, 60.7, 82.9, 126.9, 128.3, 128.5, 140.1, 153.7, 168.8, 176.4. Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.98; H, 7.99. Found: C, 64.16, H 7.84.

Preparation of 8 via Benzylation of 7. Compound **7** (0.93 g, 2.5 mmol) was dissolved in 10 mL of dry THF, and benzyl bromide (0.47 g, 2.75 mmol), potassium carbonate (0.76 g, 7.5 mmol), and $Bu_4N^+ I^-$ (0.1 g) were added. The reaction mixture was stirred for 48 h and then diluted with 75 mL of ether and washed with water. The crude product was purified by silica gel chromatography to afford 1.0 g, 86%, of **8** as a colorless oil: IR (film) 1739, 1697 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.98 (t, 7.3 Hz, 3H), 1.55 (s, 9H), 1.71 (m, 2H), 2.79 (s, 3H), 3.29 (dd, J = 9.6, 4.7 Hz, 1H), 3.60 (t, J = 9.6 Hz, 1H), 3.87 (AB quartet, J = 14.5 Hz, 4H), 4.62, (dd, J = 10.3, 4.7 Hz, 1H), 4.72 (t, J = 7.6 Hz, 1H), 7.17−7.41 (m, 10H); MS (CI) m/z (relative intensity) 466 (M + 1, 55), 410 (11), 238 (100), 91 (100).

Methyl (*R*)-2-(*N*,*N*-Dibenzylamino)butanoate, (9). Compound **8** (2 mmol) was allowed to react with 1 equiv of a 2.4 M solution of $NaOCH_3$ in methanol at room temperature until TLC indicated the absence of **8** (approximately 3 h). The reaction mixture was neutralized with a 1% HCl solution, and the methanol was removed under reduced pressure. The remaining aqueous phase was extracted with ether. Further workup afforded a crude product. Purification by silica gel chromatography afforded **9** as a colorless oil in 94% yield: $[\alpha]^{23}_D = +51.5°$ (c =1.1, CH_2Cl_2); IR (film) 1728 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (s, 3H), 1.76 (m, 2H), 3.24 (t, J = 7.8 Hz, 1H), 3.72 (AB quartet, J = 13.8 Hz, 4H), 3.75 (s, 3H), 7.35 (m, 10H); ^{13}C NMR δ 11.6, 23.4, 51.6, 55.1, 63.1, 127.5, 128.8, 129.3, 129.4, 140.3, 174.1; HRMS calcd for m/z $C_{19}H_{23}NO_2$ 297.1735, found 297.1740.

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