Enantioselective Synthesis of β-Substituted Primary and Secondary Amines by Alkylation of (*R*)-Phenylglycinol Amide Enolates

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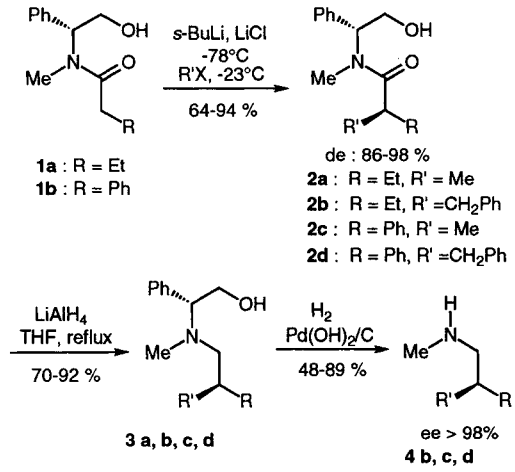
General and convenient syntheses of optically active β-substituted secondary or primary amines **4** and **8** are described. The method is based on diastereoselective alkylation of amides **1** and **5** derived from *R*-(−)-phenylglycinol followed by reduction and removal of the chiral appendage. This procedure has also been applied to the preparation of 1,4-amino alcohols **12** and γ-amino esters **14**.

Optically active amines constitute an important class of compounds which find a wide range of interest as chiral building blocks and as part of many pharmaceutical products. Whereas many reports have been published on the preparation of α-substituted amines, only one general method for the synthesis of β-substituted amines is described.[2] This method includes an application of the SAMP hydrazone strategy and allows the preparation of primary β-substituted amines from the corresponding aldehydes in high yields and total diastereoselectivity. Evans' chiral oxazolidinone alkylation chemistry has also been used for the synthesis of 3-isobutyl-γ-aminobutyric acid (GABA), a potent anticonvulsant.[3] In this example, five steps were necessary to convert the resulting alkylated oxazolidinone to the corresponding amine.

In a recent experiment, we demonstrated that phenylglycinol amides are diastereoselectively alkylated α to the carbonyl group.[4] A mechanism involving a rigid chelated intermediate has been proposed to explain the high level of diastereoselection.[5] At the same time, Myers published the results of the alkylation of pseudoephedrine amides[6] and demonstrated the utility of such intermediates for the preparation of chiral alcohols, aldehydes, ketones and amino acids.[7,8] We now report on the enantioselective synthesis of β-substituted amines, a class of compounds which cannot be obtained directly in pseudoephedrine series due to the non-benzylic character of the amino group.

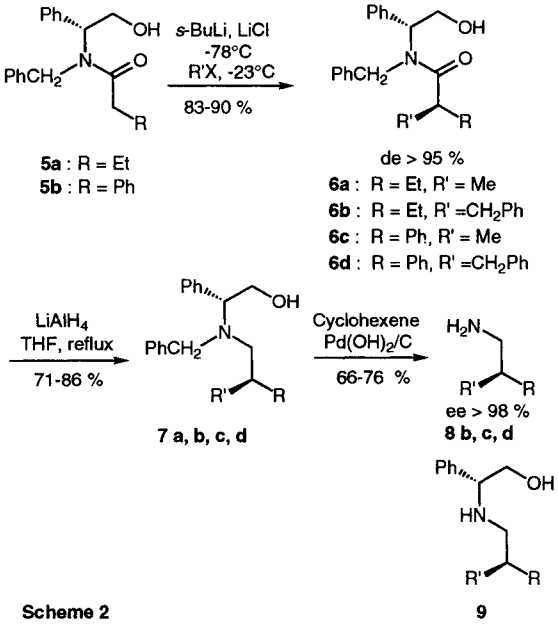
In the first series of experiments we studied the preparation of *N*-methyl-β-substituted amines **4** from *N*-methyl derivatives **1a** and **1b** (Scheme 1), alkylation of which has already been carried out in our laboratory.[4] For phenylacetyl amides **1b** we were able to improve slightly the yields from our first report by using Myers' conditions (*s*-BuLi, LiCl);[6] amides **2c** and **2d** were thus obtained in high yield and good diastereoselectivity. Flash chromatography allowed the isolation of pure compounds (>99% ee, determined by HPLC analysis). Reduction of the carbonyl group ($LiAlH_4$, THF, reflux) occurred without any epimerization of C-3 as observed previously[4] furnishing amino alcohols **3** which were then hydrogenolyzed to lead to *N*-methyl-β-substituted amines **4**.

We then turned our attention to the application of this methodology to the preparation of primary amines (Scheme 2). For this purpose, we needed a *N*-substituted



Scheme 1

derivative of (*R*)-phenylglycinol which could be deprotected after alkylation. The choice of *N*-benzyl group was obvious as it allows the cleavage of the two *N*-benzyl substituents in the same step. Alkylation of *N*-benzyl amides **5a** and **5b** occurred in high de by using previously described conditions. Corresponding amino alcohols **7** were also easily obtained, but we encountered a lot of difficulties to deprotect the amino function. When hydrogenolysis was conducted under standard conditions, a mixture of deprotected amines **8** and monoprotected amine **9** was obtained in poor yield. Neither increase of



Scheme 2

Table. Compounds **2–14** Prepared

Product	Yield (%)	mp (°C) (solvent)	de (%)	IR (KBr/Neat) ν (cm^{-1})	$[\alpha]_D^{25}$ (con., solvent)	^1H NMR (solvent) δ, J (Hz)	^{13}C NMR (solvent) δ
2a	86	106 (EtOAc/ cyclo-hexane)	> 98	3420, 1618	−125 (1.06, $CHCl_3$)	2 rotamers in a 3:1 ratio,[a] ($CDCl_3$): 0.91 (t, 3 H, J = 5.9, CH_2CH_3), 1.12 (d, 3 H, J = 6.5, $CHCH_3$), 1.43–1.72 (m, CH_2CH_3), 2.63 (m, $CHCH_3$), 2.77 (s, NCH_3), 3.98–4.15 (m, CH_2OH), 5.9 (dd, J = 9.4, 5.3, NCHPh), 7.12–7.36 (m, 5 H_{arom})	($CDCl_3$): 12.1, 17.3, 27.1, 30.7, 38.1, 57.6, 61.3, 126.8, 127.6, 128.7, 128.8, 137.6, 178.7
2b	78	67 (EtOAc/ cyclo-hexane)	95	3418, 1619	−2.0 (1.5, $CHCl_3$)	2 rotamers in a 3:1 ratio,[a] ($CDCl_3$): 1.00 (t, J = 7.4, CH_2CH_3), 1.52–1.73 (m, CH_2CH_3), 2.48 (s, NCH_3), 2.70–3.01 (m, CH_2Ph, $CHCH_2Ph$), 3.91 (t, 1 H, J = 10.2, CH_2OH), 4.12 (dd, 1 H, J = 10.2, 5.0, CH_2OH), 5.90 (dd, 1 H, J = 10.2, 5.0, NCHPh), 7.1–7.35 (m, 10 H_{arom})	($CDCl_3$): 12.1, 26.9, 31.0, 39.6, 46.2, 57.6, 61.5, 126.2, 127.3, 127.6, 128.5, 129.1, 129.4, 137.0, 140.0, 177.4
2c	94		86		−140 (0.79, $CHCl_3$)	2 rotamers in a 7:3 ratio,[a] ($CDCl_3$): 1.55 (d, 3 H, J = 6.4, CH_3CHPh), 2.65 (s, 3 H, NCH_3), 3.90–4.15 (m, 3 H, CH_3CHPh and CH_2OH), 5.90 (m, 1 H, NCHPh), 6.40 (d, 1 H, J = 8.0, CH_2OH), 7.0–7.3 (m, 10 H)	($CDCl_3$): 20.7, 28.3, 43.3, 58.7, 60.7, 126.9, 127.3, 127.7, 128.4, 128.7, 129.0, 129.1, 136.4, 137.2, 141.5, 142.7, 175.6
2d	64	124 (EtOAc/ cyclo-hexane)	> 96	3425, 1642	−122 (2.49, $CHCl_3$)	(DMSO-d_6, 135°C): 2.64 (s, 3 H, NCH_3), 2.95 (dd, 1 H, J = 13.8, 6.3, CH_2Ph), 3.42 (dd, 1 H, J = 13.8, 8.2, CH_2Ph), 3.80 (dd, 1 H, J = 12.5, 7.0, CH_2OH), 3.90 (dd, 1 H, J = 12.0, 7.0, CH_2OH), 4.39 (dd, 1 H, J = 8.2, 6.3, $PhCH_2CHPh$), 5.51 (t, 1 H, J = 7.0, $PhCHCH_2OH$), 7.10–7.40 (m, 15 H_{arom})	(DMSO-d_6, 20°C): 2 rotamers in a 1/1 ratio: 28.2, 31.2, 41.8, 42.0, 50.9, 51.8, 58.1, 60.5, 60.6, 61.7, 125.0, 129.0, 137.0, 140.1, 175.0
3a	87	oil	–	–	−37 (1.0, MeOH) (HCl salt)	($CDCl_3$): 0.92 (m, 6 H, CH_3CH, CH_2CH_3), 1.13, 1.41 (2m, 2 H, $CHCH_2CH_3$), 1.61 (m, 1 H, CH_3CHCH_2), 2.12 (m, 5 H, NCH_3, $NCCH_2CH$), 3.20 (br s, 1 H, OH), 3.52 (dd, 1 H, J = 11.6, 5.7, $CHCH_2OH$), 3.67 (dd, 1 H, J = 8.6, 5.7, NCHPh), 3.95 (J = 11.6, 8.6, $CHCH_2OH$), 7.12–7.40 (m, 5 H_{arom})	($CDCl_3$): 11.4, 17.7, 27.6, 32.3, 37.2, 60.1, 60.4, 68.8, 127.8, 128.1, 129.1, 135.4
3b	92	oil	–	–	+7 (0.9, MeOH) (HCl salt)	($CDCl_3$): 0.85 (t, 3 H, J = 7.4, CH_2CH_3), 1.2–2.0 (m, 3 H, $CHCH_2CH_3$), 2.10 (s, 3 H, NCH_3), 2.25 (dd, 1 H, J = 11.3, 6.8, CH_2Ph), 2.35 (dd, 1 H, J = 6.8, 5.6, CH_2CH), 2.45 (dd, 1 H, J = 13.6, 8.5, NCH_2CH), 2.75 (dd, 1 H, J = 13.6, 5.4, NCH_2Ph), 3.60 (dd, 1 H, J = 10.4, 5.0, $CHCH_2OH$), 3.80 (dd, 1 H, J = 10.4, 5.0, $CHCH_2OH$), 4.00 (t, 1 H, J = 10.3, $CHCH_2OH$), 7.10–7.40 (m, 10 H_{arom})	($CDCl_3$): 10.7, 23.9, 36.9, 38.5, 39.2, 57.8, 60.5, 68.7, 125.7, 127.9, 128.2, 129.1, 135.3, 141.1
3c	70	oil	–	–	−2.9 (1.13, $CHCl_3$)	($CDCl_3$): 1.25 (d, 3 H, J = 6.9, CH_2CH_3), 2.10 (s, 3 H, NCH_3), 2.50 (m, 2 H, NCH_2CH), 3.01 (m, 1 H, CH_3CHPh), 3.50 (dd, 1 H, J = 10.3, 4.7, $CHCH_2OH$), 3.72 (dd, 2 H, J = 10.6, 4.7, $CHCH_2OH$), 3.89 (dd, 1 H, J = 10.6, 10.3, $CHCH_2OH$), 7.10–7.40 (m, 10 H_{arom})	($CDCl_3$): 19.7, 35.7, 38.0, 60.3, 62.7, 69.6, 126.4, 127.1, 127.8, 128.2, 128.5, 128.8, 135.6, 145.7
3d	70	oil	–	–	−66 (0.8, MeOH) (HCl salt)	($CDCl_3$): 2.02 (s, 3 H, NCH_3), 2.40–2.70 (m, 2 H, $PhCH_2CH$), 2.83 (dd, 1 H, J = 13.5, 5.7, NCH_2CH), 2.97 (dd, 1 H, J = 13.5, 8.7, NCH_2CH), 3.05 (m, 1 H, $PhCHCH_2Ph$), 3.45 (dd, 1 H, J = 10.3, 5.5, $CHCH_2OH$), 3.65 (dd, 1 H, J = 10.3, 6.6, $CHCH_2OH$), 3.80 (t, 1 H, J = 10.3, $CHCH_2OH$), 7.0–7.40 (m, 15 H_{arom})	($CDCl_3$): 35.2, 41.0, 46.6, 60.2, 61.2, 69.7, 125.9, 126.5, 127.8, 129.0, 135.5, 140.1, 143.4
4b	89	129 (MeOH/ Et_2O)	–	–	+4.1 (0.8, EtOH) (HCl salt)	HCl salt (CD_3OD): 1.04 (t, 3 H, J = 7.3, $CHCH_3$), 1.50 (m, 2 H, CH_2CH_3), 2.10 (m, 1 H, $CHCH_2CH_3$), 2.77 (s, 3 H, NCH), 2.90–3.10 (m, 4 H, NCH_2CHCH_2Ph), 7.2–7.5 (m, 5 H_{arom})	HCl salt (CD_3OD): 10.5, 24.1, 34.4, 38.1, 40.1, 53.5, 127.3, 129.5, 130.1, 140.3

Table. (continued)

Product	Yield (%)	mp (°C) (solvent)	de (%)	IR (KBr/Neat) ν (cm^{-1})	$[\alpha]_D^{25}$ (con., solvent)	^1H NMR (solvent) δ, J (Hz)	^{13}C NMR (solvent) δ
4c	70	138–140 (MeOH/Et_2O)	–	–	+8.6 (0.95, EtOH) (HCl salt)	HCl salt (CD_3OD): 1.40 (d, 3H, J= 6.6, $CHCH_3$), 2.60 (s, 3H, NCH_3), 3.10 (m, 1H, NCH_2CH)), 3.25 (m, 1H, NCH_2CH), 3.54 (m, 1H, CH_3CHPh), 7.2–7.5 (m, 5H_{arom})	HCl salt (CD_3OD): 19.5, 33.7, 37.0, 55.9, 127.0, 127.5, 129.1, 141.4
4d	48	180–182 (MeOH/Et_2O)	–	–	–60 (0.85, MeOH) (HCl salt)	($CDCl_3$): 2.30 (s, 3H, NCH_3), 2.70–3.00 (m, 4H, NCH_2CHCH_2Ph), 3.15 (m, 1H, CH_2CHCH_2), 7.0–7.5 (m, 10H_{arom})	($CDCl_3$): 36.5, 41.4, 47.8, 56.8, 126.0, 126.6, 127.9, 128.2, 128.6, 129.1, 140.1, 143.1
6a	83	oil	–	3420, 1623	–51 (0.97, $CHCl_3$)	2 rotamers in a 7:3 ratio,[a] ($CDCl_3$): 0.81 (m, 3H, CH_2CH_3), 1.02 (d, 3H, J= 6.7, $CHCH_3$), 1.31–1.87 (m, 2H, $CHCH_2CH_3$), 2.47 (m, 1H, CH_3CHCH_2), 3.62 (br s, 1H, OH), 3.80–4.11 (m, 2H, $CHCH_2OH$), 4.33, 4.45 (m, 2H, NCH_2Ph), 5.61 (t, 1H, J= 6.5, $CHCH_2OH$), 7.05–7.40 (m, 10H_{arom})	($CDCl_3$): 12.1, 17.8, 27.4, 38.7, 49.1, 61.2, 62.1, 63.1, 126.0, 127.0, 127.2, 127.3, 127.7, 127.8, 128.1, 128.6, 128.8, 137.5, 137.8, 139.5, 178.9, 179.8
6b	89	80 (MeCN)	>95	3395, 1618	+42 (0.7, $CHCl_3$)	2 rotamers in a 7:3 ratio,[a] ($CDCl_3$): 0.88 (t, 3H, J= 7.4, CH_2CH_3), 1.40–1.76 (m, 2H, $CHCH_2CH_3$), 2.70–2.95 (m, 3H, $PhCH_2CHCH_2$), 3.57 (dd, 1H, J= 7.7, 4.6, $CHCH_2OH$), 4.00 (d, 1H, J= 17.5, NCH_2Ph), 4.01–4.10 (m, 1H, $CHCH_2OH$), 4.31, (d, 1H, J= 17.5, NCH_2Ph), 5.17 (dd, 1H, J= 7.9, 4.6, NCHPh), 6.85–7.44 (m, 10H_{arom})	($CDCl_3$): 11.9, 26.3, 38.8, 47.1, 49.9, 62.9, 63.7, 126.3, 127.3, 128.2, 128.5, 128.6, 128.9, 129.3, 129.5, 137.1, 137.2, 178.4
6c	90	oil	96	3407, 1626	–58 (1.0, $CHCl_3$)	2 rotamers in a 7:3 ratio,[a] ($CDCl_3$): 1.40 (d, 3H, J= 6.9, $CHCH_3$), 3.70–4.20 (m, 3H), 4.60 (d, 1H, J= 17.7, NCH_2Ph), 5.30 (dd, 1H, J= 7.3, 4.3, NCHPh), 7.02 (d, 1H, J= 13.1, OH), 7.1–7.4 (m, 15H_{arom})	($CDCl_3$): 20.9, 43.5, 49.8, 60.7, 63.4, 125.8–129.0, 135.9, 136.7, 136.8, 139.3, 141.0, 142.3, 175.5, 176.6
6d	88		>95		–44 (0.7, $CHCl_3$)	2 rotamers in a 7:3 ratio,[a] ($CDCl_3$): 2.88 (dd, 1H, J= 13.1, 4.6, $PhCH_2CH$), 3.50–4.10 (m, 5H), 4.50 (d, 1H, J= 17.8, NCH_2Ph), 4.75 (dd, 1H, J= 7.7, 4.0, $CHCH_2OH$), 6.81 (d, 1H, J= 7.2, CH_2OH), 7.10–7.50 (m, 20H)	($CDCl_3$): 44.8, 50.6, 53.0, 65.0, 64.0, 125.9–139.9, 176.7, 176.6
7a	71	oil	–	–	–178 (1.4, $CHCl_3$)	($CDCl_3$): 0.85 (t, 3H, J= 7.4, CH_2CH_3), 0.95 (d, 3H, J= 6.5, CH_3CH), 1.0–1.75 (m, 3H, $CH_3CHCH_2CH_3$), 2.15 (dd, 1H, J= 12.6, 4.2, NCH_2CH), 2.25 (dd, 1H, J= 12.6, 10.0, NCH_2CH), 3.00 (d, 1H, J= 13.6, NCH_2Ph), 3.58, (dd, 1H, J= 10.3, 4.9, $CHCH_2OH$), 3.90 (d, 1H, J= 13.6, NCH_2Ph), 3.92 (dd, 1H, J= 10.6, 4.9, $CHCH_2OH$), 4.56 (dd, 1H, J= 10.6, 10.3, $CHCH_2OH$), 7.10–7.50 (m, 10H_{arom})	($CDCl_3$): 11.6, 17.9, 28.1, 32.3, 54.1, 55.7, 60.3, 63.5, 127.0, 127.8, 128.2, 128.5, 129.0, 129.2, 135.2, 139.4
7b	83	oil	–	–	–84 (1.2, $CHCl_3$)	($CDCl_3$): 0.70 (t, 3H, J= 7.4, CH_2CH_3), 1.00–1.90 (m, 3H, CH_3CH_2CH), 2.15 (dd, 1H, J= 13.5, 9.4, NCH_2CH), 2.32 (dd, 1H, J= 13.0, 4.4, $PhCH_2CH$), 2.42 (dd, 1H, J= 13.0, 9.3, $PhCH_2CH$), 2.88 (dd, 1H, J= 13.5, 4.4, NCH_2CH), 2.98 (d, 1H, J= 13.5, NCH_2Ph), 3.62 (dd, 1H, J= 10.1, 4.5, $CHCH_2OH$), 3.9–4.1 (m, 3H, NCH_2Ph, $NCHCH_2OH$), 7.0–7.4 (m, 15H_{arom})	($CDCl_3$): 11.0, 24.2, 38.8, 39.7, 52.6, 54.8, 60.4, 64.5, 125.6, 127.2, 127.9, 128.2, 128.5, 129.1, 135.3, 139.3, 141.2
7c	86	oil	–	–	–101 (1.12, $CHCl_3$)	($CDCl_3$): 1.25 (d, 3H, J= 6.8, CH_3CH), 2.48 (dd, 1H, J= 12.9, 5.3, NCH_2CH), 2.71 (dd, 1H, J= 12.9, 9.5, NCH_2CH), 2.95 (m, 1H, CH_2CHCH_2Ph), 3.15 (d, 1H, J= 13.5, NCH_2Ph), 3.60, 3.80 (2dd, 2H, J= 10.4, 4.7, $CHCH_2OH$), 3.90 (d, 1H, J= 13.5, NCH_2Ph), 4.04 (t, 1H, J= 10.4, $CHCH_2OH$), 7.0–7.5 (m, 15H_{arom})	($CDCl_3$): 19.6, 38.3, 54.6, 58.2, 60.7, 64.7, 126.5, 127.3, 128.0, 128.4, 128.6, 129.2, 135.5, 139.4, 145.7
7d	83	oil	–	–	–105 (1.0, $CHCl_3$)	($CDCl_3$): 2.65–3.05 (m, 5H, NCH_2CHCH_2Ph), 3.20 (d, 1H, J= 13.4, NCH_2Ph), 3.60 (dd, 1H, J= 11.6, 4.7, $CHCH_2OH$), 3.85 (d, 1H, J= 13.4, NCH_2Ph), 3.85 (dd, 1H, J= 10.4, 4.7, $CHCH_2OH$), 4.02 (dd, 1H, J= 11.6, 10.4, $CHCH_2OH$), 6.80–7.40 (m, 20H_{arom})	($CDCl_3$): 40.8, 47.4, 53.4, 55.0, 56.9, 65.8, 125.7–135.6, 139.3, 140.2, 143.4

Table. (continued)

Product	Yield (%)	mp (°C) (solvent)	de (%)	IR (KBr/Neat) ν (cm^{-1})	$[\alpha]_D^{25}$ (con., solvent)	^1H NMR (solvent) δ, J (Hz)	^{13}C NMR (solvent) δ
8b	72	73–75 (MeOH/Et_2O)	–	–	−1.5 (1.0, EtOH) (HCl salt)	(HCl salt, CD_3OD): 1.05 (t, 3H, J= 7.5, CH_2CH_3), 1.50 (m, 2H, CH_2CH_3), 2.04 (m, 1H, CH_2CH), 2.70–3.00 (m, 4H, NCH_2CHCH_2Ph), 7.20–7.40 (m, 5H_{arom})	(CD_3OD): 10.6, 24.1, 38.1, 41.1, 43.2, 127.4, 129.5, 130.1, 130.4, 140.5
8c	66	113 (MeOH/Et_2O)	–	–	+8.8 (0.88, EtOH) (HCl salt)	(HCl salt, CD_3OD): 1.45 (d, 3H, J= 6.5, CH_2CH_3), 3.20 (m, 3H, NCH_2CH), 7.30–7.50 (m, 5H_{arom})	(CD_3OD): 19.6, 39.3, 46.5, 127.9, 128.2, 129.8
8d	76	148–152 (MeOH/Et_2O)	–	–	−58 (1.0, EtOH) (HCl salt)	(HCl salt, CD_3OD): 3.00 (dd, 1H, J= 13.5, 7.8, $PhCH_2CH$), 3.16 (dd, 1H, J= 13.5, 5.9, $PhCH_2CH$), 3.30 (m, 3H, NCH_2CH), 7.10–7.50 (m, 10H_{arom})	(CD_3OD): 41.7, 44.9, 47.6, 127.4, 128.8, 129.2, 129.3, 130.1
10a	67	94 (Et_2O)	75	3422, 1724, 1627	−159 (0.9, $CHCl_3$)	2 rotamers in a 1:1 ratio, ($CDCl_3$): 1.42 (s, 9H, t-C_4H_9), 2.52 (m, 2H, t-BuO_2CCH_2), 2.58, 2.74 (2s, 3H, NCH_3), 3.19 (dd, 1H, J= 16.7, 10.4, t-BuO_2CCH_2), 3.37 (dd, 1H, J= 17.1, 11.1, t-BuO_2CCH_2), 4.05, 4.17 (m, 2H, $CHCH_2OH$), 4.27 [dd, 1H, J= 10.2, 4.6, C(O)CHPh], 4.69 [dd, 1H, J= 11.1, 4.0, C(O)CHPh], 5.35 (dd, 1H, J= 9.4, 4.1, $CHCH_2OH$), 5.66 (dd, 1H, J= 8.4, 5.9, $CHCH_2OH$), 7.0–7.50 (m, 10H_{arom})	($CDCl_3$): 27.9, 28.1, 31.8, 40.8, 40.9, 44.4, 45.8, 59.8, 60.5, 61.2, 61.7, 80.5, 81.1, 127.0–138.3, 171.5, 172.5, 172.9, 173.8
10b	84	oil	96	3434, 1720, 1640	−112 (1.53, $CHCl_3$)	2 rotamers in a 7:3 ratio,[a] ($CDCl_3$): 1.42–1.50 (s, 9H, t-C_4H_9), 2.60 (dd, 1H, J–17.2, 3.5, t-BuO_2CCH_2), 3.42 (m, 2H, t-BuO_2CCH_2, CH_2OH), 3.51 (d, 1H, J= 15.3, NCH_2Ph), 3.90 (m, 2H, $CHCH_2OH$), 4.87 [dd, 1H, J= 11.7, 3.6, C(O)CHPh], 5.05 (d, 1H, J= 15.3, NCH_2Ph), 5.42 (dd, 1H, J= 9.4, 4.2, $CHCH_2OH$), 6.40–7.5 (m, 15H_{arom})	($CDCl_3$): 28.0, 41.2, 41.6, 44.9, 46.7, 45.1, 51.4, 61.6, 62.4, 64.0, 126.8–139.5, 172.0, 172.9, 173.4, 174.2
11a	67	45 (MeOH/Et_2O)	–	–	−37 (1.07, $CHCl_3$)	(CD_3OD): 1.83, 2.11 (2m, 2H, CH_2CH_2OH), 2.26 (s, 3H, NCH_3), 2.63 (dd, 1H, J= 12.6, 7.2, NCH_2CH), 2.73 (dd, 1H, J= 12.6, 7.8, NCH_2CH), 3.10 (m, 1H, CH_2CHCH_2), 3.50 (m, 2H, CH_2CH_2OH), 3.75 (m, 2H, $CHCH_2OH$), 3.98 (m, 1H, $CHCH_2OH$), 7.20–7.50 (m, 10H_{arom})	(CD_3OD): 37.9, 38.4, 42.1, 61.2, 62.7, 62.9, 71.0, 127.3, 128.5, 128.7, 129.1, 129.4, 130.0, 138.6, 145.6
11b	73	oil	–	–	−101 (0.98, $CHCl_3$)	($CDCl_3$): 1.65, 2.01 (2m, 2H, CH_2CH_2OH), 2.50–2.85 (m, 3H, NCH_2CH), 3.12 (d, 1H, J= 13.5, NCH_2Ph), 3.36, 3.48 (2m, 2H, CH_2CH_2OH), 3.65 (dd, 1H, J= 10.8, 4.6, $CHCH_2OH$), 3.92 (d, 1H, J= 13.5, NCH_2Ph), 3.97 (dd, 1H, J= 10.0, 4.6, $CHCH_2OH$), 4.10 (dd, 1H, J= 10.8, 10.0, $CHCH_2OH$), 7.10–7.50 (m, 15H_{arom})	($CDCl_3$): 36.8, 41.0, 54.5, 56.8, 60.3, 60.6, 64.9, 126.1, 126.8, 127.2, 127.4, 127.8, 128.0, 128.2, 128.5, 128.9, 135.0, 138.5, 143.4
12a	73	129–131 MeOH/(Et_2O)	–	–	−11 (1.45, EtOH) (HCl salt)	(HCl salt, CD_3OD): 2.00 (m, 2H, CH_2CH_2OH), 2.74 (s, 3H, NCH_3), 3.30 (m, 1H, CHPh), 3.50 (m, 4H, NCH_2, CH_2OH), 7.30–7.50 (m, 5H_{arom})	(CD_3OD): 34.2, 37.9, 41.3, 55.4, 59.9, 128.8, 128.9, 130.3, 141.1
12b	76	amorphous	–	–	−5.6 (0.5, MeOH)	(HCl salt, CD_3OD): 1.80 (m, 2H, CH_2CH_2OH), 3.50 (m, 5H, $NCH_2CHCH_2CH_2OH$), 7.0–7.5 (m, 5H_{arom})	(CD_3OD): 37.4, 41.6, 45.6, 59.7, 128.2, 128.5, 129.4, 129.7, 140.6
13a	67	85 (EtOAc/cyclohexane)	–	3507, 1723	−3.7 (0.9, $CHCl_3$)	($CDCl_3$): 1.34 (s, 9H, $CO_2C_4H_9$-t), 2.18 (s, 3H, NCH_3), 2.43–2.64 (m, 4H, NCH_2CHCH_2), 3.32 (m, 1H, CH_2CHCH_2), 3.51 (dd, 1H, J= 10.7, 4.6, $CHCH_2OH$), 3.63 (dd, 1H, J= 10.3, 4.5, $CHCH_2OH$), 3.90 (dd, 1H, J= 10.7, 10.3, $CHCH_2OH$), 7.0–7.40 (m, 10H_{arom})	($CDCl_3$): 27.9, 36.9, 40.4, 40.6, 60.3, 60.7, 70.1, 80.6, 126.7, 127.5, 127.8, 128.2, 128.5, 128.6, 135.5, 142.9, 171.6

Table. (continued)

Product	Yield (%)	mp (°C) (solvent)	de (%)	IR (KBr/Neat) ν (cm^{-1})	$[\alpha]_D^{25}$ (con., solvent)	^1H NMR (solvent) δ, J (Hz)	^{13}C NMR (solvent) δ
13b	57	oil	–	3448, 1723	–90 (0.65, $CHCl_3$)	($CDCl_3$): 1.25 (s, 9H, $CO_2C_4H_9$-*t*), 2.35–2.85 (4m, 4H, NCH_2CHCH_2), 2.71 (br s, 1H, CH_2OH), 3.18 (d, 1H, J = 13.5, NCH_2Ph), 3.28 (m, 1H, CH_2CHCH_2), 3.65 (m, 1H, $CHCH_2OH$), 3.90 (d, 1H, J = 13.5, NCH_2Ph), 3.93 (dd, 1H, J = 10.1, 4.8, $CHCH_2OH$), 4.05 (dd, 1H, J = 10.4, 10.1, $CHCH_2OH$), 7.0–7.40 (m, 15 H_{arom})	($CDCl_3$): 27.8, 40.1, 41.1, 54.7, 56.6, 61.0, 65.0, 80.3, 126.7, 127.2, 127.7, 127.8, 128.3, 128.5, 128.9, 129.1, 135.6, 139.1, 142.5, 171.7
14a	93	amorphous	–	3313, 1737	–2.3 (1.0, MeOH) (HCl salt)	(HCl salt, CD_3OD): 2.75 (s, 3H, NCH_3), 2.80 (dd, 1H, J = 16.4, 8.1, $CHCH_2CO_2Me$), 2.95 (dd, 1H, J = 16.4, 6.5, $CHCH_2CO_2Me$), 3.55 (m, 3H, NCH_2CHCH_2), 3.68 (s, 3H, CO_2CH_3), 7.40 (m, 5 H_{arom})	(CD_3OD): 34.3, 39.5, 40.7, 52.3, 54.6, 128.9, 129.1, 130.3, 140.2, 173.0
14b	45	178–180 (MeOH/Et_2O)	–	3320, 1731	–7 (0.5, MeOH) (HCl salt)	(HCl salt, CD_3OD): 2.88 (m, 2H, $CHCH_2CO_2Me$), 3.2–3.6 (m, 3H, NCH_2CH), 3.68 (s, 3H, CO_2CH_3), 7.20–7.50 (m, 5 H_{arom})	(CD_3OD): 34.3, 36.5, 40.0, 47.3, 123.9, 124.7, 125.2, 135.4, 168.1
15a	45	oil	–	3397	–34 (1.1, $CHCl_3$)	($CDCl_3$): 1.08 (s, 9H, OCC_4H_9-*t*), 1.7–1.9 (m, 2H, *t*-$BuOCH_2CH_2$), 2.06 (s, 3H, NCH_3), 2.68 (m, 2H, NCH_2CH), 3.00 (m, 1H, NCH_2CH), 3.12–3.22 (m, 2H, *t*-$BuOCH_2$), 3.45 (dd, 1H, J = 10.3, 4.3, $NCHCH_2OH$), 3.63 (dd, 1H, J = 10.3, 4.3, $NCHCH_2OH$), 3.80 (t, 1H, J = 10.3, $NCHCH_2OH$), 7.0–7.4 (m, 10 H_{arom})	($CDCl_3$): 27.3, 34.7, 34.9, 40.8, 59.0, 60.0, 61.9, 69.7, 72.5, 126.3, 127.7, 128.0, 128.3, 128.5, 135.5, 143.7
15b	50	oil	–	3427	–80 (0.9, $CHCl_3$)	($CDCl_3$): 1.07 (s, 9H, OCC_4H_9-*t*), 1.6–2.0 (m, 2H, *t*-$BuOCH_2CH_2$), 2.53 (m, 1H, NCH_2CH), 2.88 (m, 2H, NCH_2CH), 3.05–3.15 (m, 3H, *t*-$BuOCH_2$, NCH_2Ph), 3.58 (dd, 1H, J = 10.5, 4.6, $NCHCH_2OH$), 3.85 (m, 2H, NCH_2Ph, $NCHCH_2OH$), 4.00 (t, 1H, J = 10.5, $NCHCH_2OH$), 7.0–7.5 (m, 10 H_{arom})	($CDCl_3$): 27.6, 34.8, 41.7, 54.9, 57.8, 59.1, 61.0, 65.5, 72.6, 126.5, 127.2, 127.8, 128.1, 128.3, 128.5, 129.0, 129.3, 136.0, 139.7, 144.0

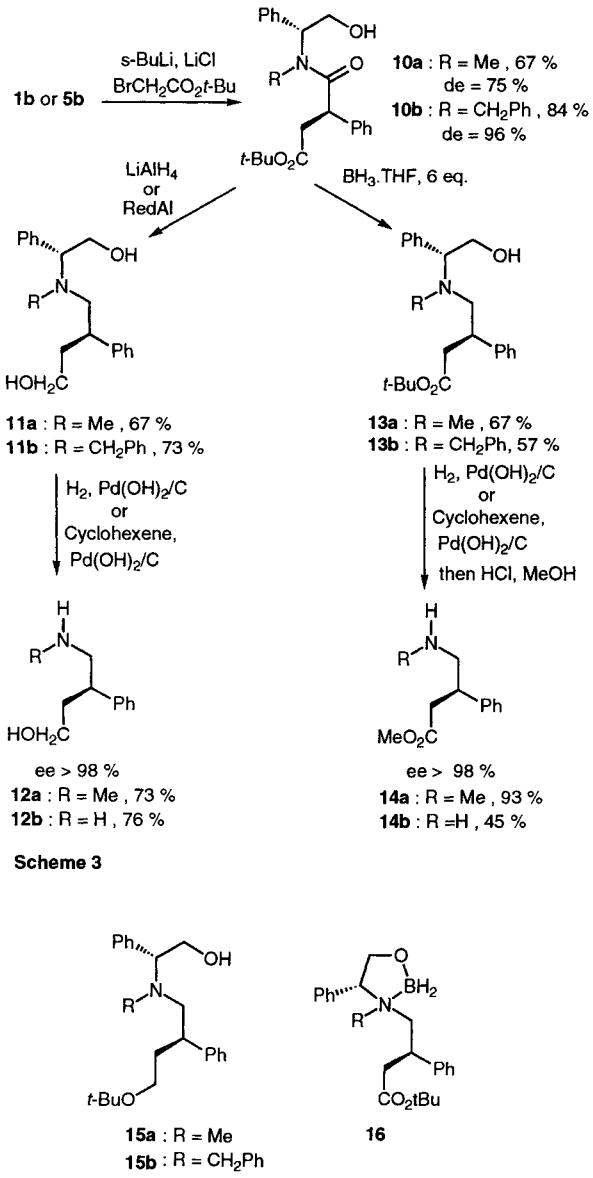
[a] Only the data for major rotamer are given.

H_2 pressure (10 bar) or temperature allowed the complete deprotection. The use of ammonium formate as hydrogen donor was only efficient for amine **7b**. Finally, we obtained good results when deblocking the two *N*-benzyl groups was carried out by transfer hydrogenation using cyclohexene and $Pd(OH)_2/C$. The catalyst was filtered off and any volatile products were removed, after which the residues were treated with a hydrochloric acid solution in MeOH. The desired amines **8** were then obtained by crystallization as hydrochloride salts in good yields.

In order to demonstrate the versatility of our method, we investigated the preparation of functionalized β-substituted amines. For this purpose, amides **1b** and **5b** were alkylated with *tert*-butyl bromoacetate furnishing derivatives **10a** and **10b** in 75 and 96% de, respectively. After separation of the major isomers, $LiAlH_4$ reduction led to amino diols **11a** and **11b** in 67 and 73% yield, respectively. Hydrogenolysis of the chiral appendage required previously reported conditions and allowed the isolation of desired amino alcohols **12a** and **12b**. Amino alcohol **12b** had already been synthesized in a racemic form and used as a precursor in the preparation of 2-phenylpyrrolidine.[9]

In order to prepare 3-aryl GABA derivatives relative to baclofen,[10] we studied the synthesis of amino esters by a selective reduction of the amide carbonyl group with respect to the ester function. This is generally achieved by using borane reagents.[11] When $BH_3 \cdot SMe_2$ was used, the desired amino esters **13** were obtained in poor yield; surprisingly, the major products were the *tert*-butyl ethers **15**, the formation of which is not obvious. Such a reduction has been previously reported in special cases, especially with *tert*-butyl esters.[12,13] In these reports the reducing agent was the $LiAlH_4/BF_3 \cdot OEt_2$ system. In our case, we have some indications for an oxazaborolidine intermediate **16** which could catalyze the reduction of the ester function. Finally, the selective reduction of the amide function was solved by using $BH_3 \cdot THF$ in excess at r.t. The corresponding amino esters **13a** and **13b** were obtained in 67 and 57% yield, respectively. As observed during $LiAlH_4$ reduction, no C-3 epimerization occurred. Hydrogenolysis of these compounds furnished the desired amino esters which were then treated by HCl/MeOH in order to prepare methylamino esters **14a** and **14b** isolated as hydrochloride salts.

In conclusion, an asymmetric synthesis of β-substituted primary and secondary amines has been developed. Our



Scheme 3

strategy allows the preparation of a large variety of functionalized amines. An application to the preparation of β-substituted γ-amino acids was achieved. Particularly attractive is the possibility of obtaining access to polyfunctionalized derivatives which can be considered as starting materials for the elaboration of complex structures. The first applications of this strategy to the preparation of heterocycles will be reported in due course.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker AC 300 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter. Purifications of products were performed by flash chromatography on silica gel (Merck 60). Diastereomeric excesses (de) were determined by HPLC analysis (Millipore, Waters 717+) using a SFCC-Shamdon Column and by ^{1}H and ^{13}C NMR spectroscopy. All new compounds were fully characterized either by elementary analyses (C ± 0.43, H ± 0.38, N ± 0.29) or HRMS. All reactions involving air sensitive materials were carried out under a N_2 atmosphere.

Alkylation of Amides 1 and 5; General Procedure:
A solution of amide **1**, **5** (0.4 mmol) and LiCl (102 mg, 2.4 mmol) in THF (5 mL) was cooled at −78 °C under N_2. A 0.9 M solution of *s*-BuLi (2.5 equiv) in hexane was added dropwise. After stirring for 1 h, electrophile (MeI, $PhCH_2Br$ or *tert*-butyl bromoacetate) (2.5 equiv) was added dropwise at −23 °C. The reaction was followed by TLC. After complete disappearance of starting material (1–4 h), aq NH_4Cl solution (10 mL) was added. The organic and aqueous layers were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with H_2O (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash chromatography with a suitable solvent (EtOAc/cyclohexane) to furnish alkylated products **2**, **6** and **10** (Table).

Reduction of Amides 2, 6 and 10a with $LiAlH_4$; General Procedure:
To a suspension of $LiAlH_4$ (304 mg, 8 mmol) in THF (25 mL) was added a solution of amide **2**, **6** or **10a** (1 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at reflux for 2–3 h, then cooled to 0 °C and treated with H_2O (0.32 mL), 15% aq NaOH (0.32 mL) and H_2O (0.96 mL). The white solid was filtered and the solvent evaporated under reduced pressure to furnish the desired amines **3**, **7** and **11a** (Table).

Reduction of Amide 10b to Aminodiol 11b:
To a solution of amide **10b** (215 mg, 0.47 mmol) in THF (6 ml) was added RedAl® (65 % solution in toluene, 1.8 mmol) at −50 °C. The resulting mixture was stirred at r.t. for 6 h, then cooled to 0 °C and diluted with a 50 % aq solution of KOH (4 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Crude material was purified by chromatography on alumina (CH_2Cl_2/MeOH; 99 : 1) to furnish **11b** as an oil; yield: 130 mg (73 %) (Table).

β-Substituted *N*-Methylamines 4 and 12a; General Procedure:
A solution of amine **3**, **11a** (1 mmol) in MeOH (15 mL) was hydrogenolyzed (H_2, 1 bar) in the presence of $Pd(OH)_2/C$. After filtration, a 2 M solution of HCl in MeOH (5 mL) was added. After stirring for 15 min, the mixture was concentrated under reduced pressure affording a crude material which was washed with Et_2O (2 × 15 mL) to remove phenylethanol. Amines **4** and **12a** were then obtained pure as hydrochloride salts (Table).

Primary β-Substituted Amines 8 and 12b; General Procedure:
To a solution of amine **7**, **11b** (1 mmol) in cyclohexene (30 mL) was added $Pd(OH)_2/C$ (430 mg). The resulting mixture was heated at reflux for 24 h. After filtration, a 2 M solution of HCl in MeOH (5 mL) was added. After stirring for 15 min, the mixture was concentrated under reduced pressure affording a crude material which was washed with Et_2O (2 × 15 mL) to remove phenylethanol. Amines **8** and **12b** were then obtained pure as hydrochloride salts (Table).

Reduction of Amides 10a and 10b with BH_3 · THF; General Procedure:
To a solution of amide **10a**, **10b** (1.3 mmol) in THF (8 mL) under N_2, was added a 1 M THF solution of BH_3 · THF (8.3 mL, 8.3 mmol). The resulting mixture was stirred at r.t. for 4 h, cooled to 0 °C, then carefully treated with a sat. aq solution of Na_2CO_3 (4 mL). The organic and aqueous layers were separated and the aqueous layer extracted with Et_2O (2 × 20 mL) and then with EtOAc (20 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was dissolved in MeOH (10 mL), refluxed for 3 h, and then treated with a sat. aq solution of Na_2CO_3 (4 mL). The organic and aqueous layers were separated and the aqueous layer extracted with Et_2O (2 × 10 mL) and with EtOAc (1 × 10 mL). The combined organic phases were dried ($MgSO_4$), and evaporated under reduced pressure. The crude material was purified either by chromatography on alumina **(13a)** or by flash chromatography on alumina **(13b)** (Table).

(S)-4-(N-Methylamino) and (S)-4-Amino-2-phenylbutyric Acid Methyl Esters **14a** *and* **14b**:

Compunds **14a** and **14b** were obtained from **13a** and **13b** as described for the preparation of **8** and **12b** (Table).

Reduction of Amido Ester 10a and 10b with $BH_3 \cdot SMe_2$ Amino Ethers 15a and 15b; General Procedure:

To a solution of amido ester **10a**, **10b** (1 mmol) in THF under N_2, was added a 2 M solution of $BH_3 \cdot SMe_2$ (1.7 mL, 3.4 mmol). The resulting mixture was stirred at reflux for 1 h and worked up as for the preparation of **13a** and **13b**. Crude materials were purified by flash chromatography on silica gel (EtOAc/cyclohexane, 20:80) (Table).

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