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Synthesis of homochiral *N*-Boc-β-aminoaldehydes from *N*-Boc-β-aminonitriles

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Summary — Enantiopure *N*-Boc-β-aminoaldehydes are efficiently prepared in good yields from *N*-Boc-β-aminonitriles by reduction of the nitrile function with diisobutylaluminum hydride (DIBAL-H).

β-aminoaldehyde / β-aminonitrile / α-aminoacid / homochiral / enantiomeric excess / reduction / DIBAL-H

Résumé — Synthèse de *N*-Boc-β-aminoaldéhydes homochiraux à partir des *N*-Boc-β-aminonitriles. Les *N*-Boc-β-aminoaldehydes énantiomériquement purs sont préparés de façon simple et avec de bons rendements à partir des β-aminonitriles par réduction avec l'hydrure de diisobutylaluminium (DIBAL-H).

β-aminoaldéhyde / β-aminonitrile / α-aminoacide / homochiral / excès énantiomérique / réduction / DIBAL-H

Introduction

α-aminoacids, protected at nitrogen in various ways, can be transformed without racemization into the corresponding α-aminoaldehydes. Then, provided one chooses the right protective groups, it is possible to transform these aldehydes into a wealth of very useful synthetic intermediates [1]. The situation is completely different with the homologous homochiral β-aminoaldehydes which have found little use in organic synthesis due to the lack of general methods for their preparation and their instability. Few efficient methods are described in the literature for the preparation of protected non-chiral or racemic β-aminoaldehydes including ozonolysis of homoallylic amines [2], nucleophilic substitution on β-chloro or bromo acetals with primary or secondary amines [3] and conjugate addition of amines or imides to α,β-unsaturated aldehydes [4, 5]. Other routes, such as the reduction of β-aminoimides [6], the oxidation of γ-aminoalcohols [7], the reductive ring opening of 5-alkoxyisoxazolidines [8], the Mannich reaction [9] or the hydroboration of propargylic amines [10] also lead more or less efficiently to β-aminoaldehydes. Serious problems were encountered as to the stability of free β-aminoaldehydes such as condensation reactions [3] and facile β-elimination of the amino group [4, 9]. However, β-aminoaldehydes show excellent stabilities when masked as acetals, oxalates or hydrazones. Usually, the free β-aminoaldehydes may be isolated when protected at nitrogen as an amide, carbamate, imide, sulfonamide or phosphonamide [10]. Nevertheless, some non-protected β-aminoaldehydes could be prepared in solution and used as such [4, 5].

Homochiral β-aminoaldehydes **1** protected at nitrogen (scheme 1) should be very versatile intermediates but no general and simple access to these compounds exists. The aldehyde **2** derived from aspartic acid has been described as a naturally occurring molecule and found important synthetic applications [11]. Optically pure β-aminoacetal **3** [12] and α-hydroxy-β-aminoaldehyde **4** [13] were used in the synthesis of taxol side chains. β-aminoaldehydes of type **5** were prepared from α-aminoacids through an Arndt–Eistert reaction involving the use of diazomethane and were utilized for the synthesis of pseudopeptides [14] and enzyme inhibitors [15].

An asymmetric synthesis of the aldehydes **6** was recently proposed and involves the 1,4-addition of an homochiral lithium amide to α,β-unsaturated *N*-methoxyamides followed by a diisobutylaluminum hydride (DIBAL-H) reduction of the obtained *N*-methoxyamides [16]. Other syntheses of non-racemic β-aminoaldehydes were reported, including the ozonolysis of dihydropyrroles [17] or the opening *N*-tosylaziridines by dithiane anion [18]. In this paper, we describe a simple synthesis of homochiral *N*-Boc-β-aminoaldehydes from the corresponding optically pure β-aminonitriles.

Results and discussion

Our synthesis is based on the partial reduction of the nitrile function of β-aminonitriles. Such an approach

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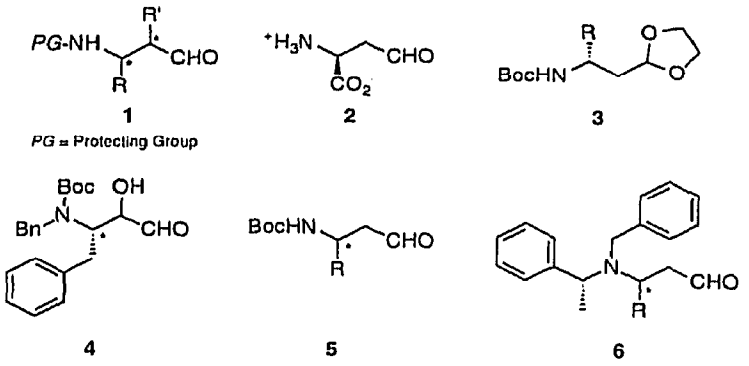


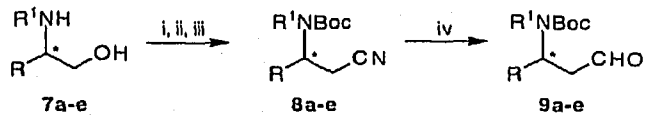
Scheme 1. Known homochiral β-aminoaldehydes.

Table I. Synthesis of *N*-Boc-β-aminoaldehydes **9**.

Compound	R_1	R	*Abs config of* **7**	**7** → **8** *Yield (%)*[a]	**8** → **9** *Yield (%)*[a]	*Abs config of* **9**	**7** → **9** *Yield (%)*[a]
a	H	Et	R	56	66	R	37
b	H	*i*Pr	S	67	73	R	49
c	H	Bn	S	68	72	S	49
d	H	Ph	R	79	68	S	54
e	$-(CH_2)_3-$		S	47	44	S	21

[a] Isolated yields of analytically pure products.

was already attempted by Marko et al [4] and reported to lead only to decomposition products and polymers. We suspected that the reason for such a failure was the basicity of the nitrogen of the tertiary amino groups in the examined β-aminonitriles. Therefore, we adressed to the reduction of *N*-Boc-β-aminonitriles **8a–e** (scheme 2). Recently, **8** has been prepared by Caputo et al from the β-aminoalcohol **7** via the corresponding *N*-Boc-β-aminoiodides and nucleophilic displacement of the iodide by tetraethylammonium cyanide in dichloromethane [19]. Although giving good yields, we did not use this method, instead we have followed a more conventional and convenient line, as far as scale-up is concerned, previously developed in our laboratory for the synthesis of 1,3-diamines [20]. Thus, the sequence described in scheme 2 allows the preparation of multigram quantities of pure β-aminoaldehydes **9**.

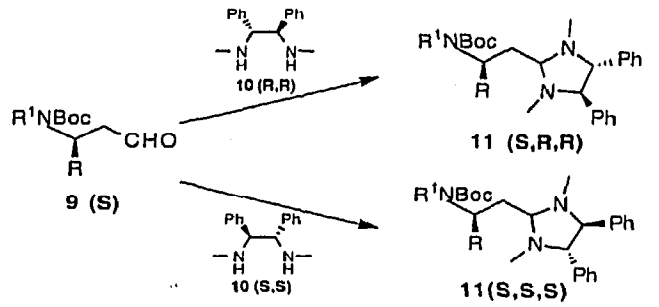


Scheme 2. i: $(Boc)_2O$, THF, RT. ii: MesCl, 1.5 equiv TEA, CH_2Cl_2, RT. iii: NaCN, DMSO, 45 °C. iv: DIBAL-H (for addition mode, see experimental part), toluene/ether.

According to this scheme and after optimization, the obtained results are reported in table I.

Commercially available aminoalcohols **7a–e** were *N*-Boc protected at nitrogen under standard conditions; mesylation with methanesulfonyl chloride in the presence of triethylamine at room temperature led quantitatively to mesylates [21]; nucleophilic substitution with sodium cyanide in DMSO at 45 °C for 15–18 h gave the nitriles **8a–e** in 47–79% isolated yields from the β-aminoalcohols. The reduction of the nitrile function is commonly performed with DIBAL-H and usually leads to good results [22]. Under standard conditions, we could not get yields better than 20%. Nevertheless, under optimized experimental conditions, the addition of an excess of DIBAL-H led to pure **9** with good yields. Ether or toluene were found to be better solvents than heptane or THF for this reduction. Addition rates of the reductive agent also played an important role (see experimental section).

Purification of aldehydes **9a–e** was easily performed by bulb-to-bulb distillation under vacuum, provided that the crude reaction mixtures were thoroughly washed with dilute aqueous HCl and then $NaHCO_3$. If not, complete degradation may be observed. Flash chromatography was also adapted to the purification of **9a–e** with yields comparable to those obtained by distillation, except for **9d** which is unstable on silica gel. Enantiomeric excesses were determined by using Alexakis and Mangeney's method [23]. Aldehydes **9a–e** were reacted with both enantiomers of the *N*,*N*′-dimethyl-1,2-diphenylethane-1,2-diamine **10** optically pure. The corresponding 10 aminals **11** were obtained according to scheme 3. So, starting from an aldehyde **9** (*S*), we can obtain two diastereomers **11** (*S*,*S*,*S*) and **11** (*S*,*R*,*R*). If we would react a mixture of **9** (*S*) + **9** (*R*) with one enantiomer of the diamine (**10** (*S*,*S*) for example), we would obtain **11** (*S*,*S*,*S*) + **11** (*R*,*S*,*S*). **11** (*R*,*S*,*S*) is enantiomer of **11** (*S*,*R*,*R*) and would not be distinguishable by NMR in the absence of a chiral shift reagent.



Scheme 3. Determination of the optical purity of the obtained aldehydes.

Reacting **9** (*R* or (and) *S*) with both enantiomers **10** allows the determination of the enantiomeric excesses simply by ^{1}H NMR spectroscopy since, as in Alexakis and Mangeney's [23] examples, every pair of diastereoisomeric aminals had very distinct chemical shifts, in particular for the protons on the carbon α to the phenyl rings. The enantiomeric excesses were found to be equal to or better than 99% in all the cases reported here, except for **9a** (97% ee measured) obtained from starting aminoalcohol **7a** purchased with 97% optical purity.

In conclusion, we have described an efficient and simple access to enantiomerically pure *N*-Boc-β-aminoaldehydes which offers a profitable alternative to the Arndt–Eistert homologation and the subsequent use of diazomethane. The development of the chemistry of these interesting homochiral building blocks is under active investigation in this laboratory.

Experimental section

General

Melting points were determined with an Electrothermal IA9300 apparatus and are uncorrected. Thin-layer chromatography (TLC) analysis were performed on aluminum-precoated plates (silica gel 60, 0.2 mm) purchased from Merck. For preparative chromatography, Geduran SI 60 (Merck, 0.040–0.063 mm) silica gel was used. Gas chromatography (GC) analyses were conducted on a Fisons 8000 instrument equipped with a DB-17 Megabore column from J&W Scientific. Oven program for all products: 100 °C during 2 min, then 100 to 240 °C at a rate of 10 °C/min. Optical rotation measurements were performed on a Perkin–Elmer 241C polarimeter (concentrations in g/100 mL). ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker AC-300 in $CDCl_3$ with TMS as internal standard. High-resolution mass spectra were obtained on a Varian MAT 311 (CRMPO, University of Rennes I). Microanalyses were performed at the Central Laboratory for Analysis, CNRS, Lyon, France.

All solvents were dried before use [24] and reactions requiring a neutral atmosphere were carried out under nitrogen in flame-dried glassware. DIBAL-H (1.0 M solution in toluene) was purchased from Aldrich. **7a** (97% ee) was purchased from Accros; all other β-aminoalcohols were prepared on a 30 g scale from the corresponding α-aminoacids in their purest enantiomeric form by reduction with LAH [25]. The *N*-Boc-β-aminonitriles **8a–e** have already been prepared in our labotratory [20]. The diastereoisomeric aminals (imidazolidines) **11a–e** were obtained in good yields following the procedure of Alexakis and Mangeney [23] in sufficient amount to record a ^{1}H NMR spectrum. No kinetic resolution was allowed, since the completion of the reaction was evidenced by the absence of the starting aldehyde in the crude reaction mixture as observed by NMR spectroscopy. The optically pure diamines **10** (*R*,*R*) and **10** (*S*,*S*) were readily prepared at the laboratory on a 5 g scale [26].

Reduction of the β-aminonitriles 8a–c; procedure A

In a typical procedure, 5.20 g (20.0 mmol) of the pure nitrile **8c** were partially solubilized in a 250 mL round bottom flask in 100 mL of dry ether and cooled at −60 °C. While vigorously stirred, 24 mL (24 mmol, 1.2 equiv) of DIBAL-H (1.0 M in toluene) was added to the suspension of the nitrile via a syringe pump within 4 h. Another 1.2 equiv of DIBAL-H was added at this same temperature within 2 h and a last 1.6 equiv in 1 h. After stirring for additional 30 min, the clear solution was quenched by cautious addition of 5 mL of methanol and then immediatly poured on 100 mL of a saturated ammonium chloride solution in a separatory funnel. The mixture was shaken and left until it reached room temperature. A thick white gel appeared. The gel was then progressively destroyed by the addition, in small portions, of 100 mL of 0.1 M HCl, 100 mL of 1 M HCl, and as much of 3 M HCl as necessary to reach a pH of 2–3. The solution was then extracted twice with 100 mL ethyl acetate and the organic phases were washed with 100 mL of a 1 M HCl/brine (1:1) solution, twice with 100 mL of a saturated $NaHCO_3$/brine (1:1) solution and dried over K_2CO_3. After removal of the solvents, 4.38 g of the crude **9c** were obtained as a yellowish solid wich was purified by prompt bulb-to-bulb distillation (110–130 °C; 0.01 mm Hg) to give, after recrystallisation in the minimum of a 2:1 hexane/diisopropyl ether mixture, 3.82 g (14.5 mmol, 72%) of the pure product.

Reduction of the β-aminonitriles 8d,e; procedure B

For **9d**, 4.0 equiv of DIBAL-H were added within 15 min at −40 °C. For **9e**, 3.0 equiv of DIBAL-H were added within 1 h at −80 °C. The work-up remains the same. **9d** was obtained as a solid and, after bulb-to-bulb distillation, recrystallized from a 1:4 diisopropyl ether/hexane solution. **9e** is an oil and was purified by flash chromatography (ethyl acetate/heptane, 1:6) instead of being distilled.

- *(3R)-3-[(tert-butoxycarbonyl)amino]pentanal* **9a**

White solid after recrystallisation from petroleum ether; yield: 68%; Mp = 67–68 °C; $Bp_{(0.01\ mm\ Hg)}$ = 60–80 °C; R_f = 0.65 (ethyl acetate/heptane, 1:1); GC = 5.95 min; $[\alpha]_D^{25}$ = 49.6 (c = 1.3, $CHCl_3$).

^{1}H NMR: δ = 0.95 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.49–1.59 (m, 2H, CH_2CH_3), 2.56 (ddd, 1H, J = 16.5 Hz, J = 7.0 Hz, J = 2.6 Hz, CHCHO), 2.62 (ddd, 1H, J = 16.5 Hz, J = 5.7 Hz, J = 1.2 Hz, CHHCHO), 3.85–4.00 (m, 1H, CHNH), 4.62 (broad s, 1H, NH), 9.74 (dd, 1H, J = 2.6 Hz, J = 1.7 Hz, CHO).

^{13}C NMR: δ = 10.4 (CH_2CH_3), 28.0 (CH_2CH_3), 28.3 ($C(CH_3)_3$), 47.9 (CHNH), 48.8 (CH_2CHO), 79.4 ($C(CH_3)_3$), 155.3 (C(O)NH), 201.3 (CHO).

Anal calc for $C_{10}H_{19}NO_3$: C = 59.68, H = 9.52; found C = 59.68, H = 9.56.

• *(3R)-3-[(tert-butoxycarbonyl)amino]-4-methylpentanal (L-Boc-homovalinal)* **9b**

White solid obtained in 73% yield after recrystallisation from petroleum ether; Mp = 74 °C; $Bp_{(0.01\ mm\ Hg)}$ = 70–90 °C; R_f = 0.63 (ethyl acetate/heptane, 1:1); GC = 6.22 min; $[\alpha]_D^{25}$ = −61.0 (c = 1.2, $CHCl_3$).

^1H NMR: δ = 0.93 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.83 (oct, 1H, J = 6.6 Hz, $CH(CH_3)_2$), 2.48 (ddd, 1H, J = 13.7 Hz, J = 8.4 Hz, J = 3.2 Hz, $CHHCHO$), 2.59 (dd, 1H, J = 13.7 Hz, J = 4.9 Hz, $CHHCHO$), 3.87–4.01 (m, 1H, $CHNH$), 4.75 (d, 1H, J = 9.1 Hz, NH), 9.75 (dd, 1H, J = 3.2 Hz, J = 1.5 Hz, CHO).

^{13}C NMR: δ = 18.3 ($CHCH_3$), 19.1 ($CHCH_3$), 28.3 ($C(CH_3)_3$), 32.5 ($CH(CH_3)_2$), 46.7 (CH_2CHO), 51.5 (CHNH), 79.5 ($C(CH_3)_3$), 155.6 (C(O)NH), 201.5 (CHO).

Anal calc for $C_{11}H_{21}NO_3$: C = 61.37, H = 9.83; found: C = 61.48, H = 9.81.

• *(3S)-3-[(tert-butoxycarbonyl)amino]-4-phenylbutanal (L-Boc-homophenylalaninal)* **9c**

White solid obtained in 72% yield; Mp = 92 °C; $Bp_{(0.01\ mm\ Hg)}$ = 110–130 °C; R_f = 0.57 (ethyl acetate/heptane, 1:1); GC = 9.55 min; $[\alpha]_D^{25}$ = −23.8 (c = 1.2, $CHCl_3$).

^1H NMR: δ = 1.43 (s, 9H, $C(CH_3)_3$), 2.53 (ddd, 1H, J = 16.8 Hz, J = 7.0 Hz, J = 2.3 Hz, $CHHCHO$), 2.59 (ddd, 1H, J = 16.8 Hz, J = 5.1 Hz, J = 1.2 Hz, $CHHCHO$), 2.80 (dd, 1H, J = 13.4 Hz, J = 7.6 Hz, $CHHC_6H_5$), 2.94 (dd, 1H, J = 13.4 Hz, J = 6.2 Hz, $CHHC_6H_5$), 4.20–4.33 (m, 1H, $CHNH$), 4.89 (broad d, 1H, J = 8.8 Hz, NH), 7.12–7.34 (m, 5H, H arom), 9.75 (dd, 1H, J = 2.1 Hz, J = 1.2 Hz, CHO).

^{13}C NMR: δ = 28.3 ($C(CH_3)_3$), 40.7 ($CH_2C_6H_5$), 47.5 (CH_2CHO), 47.7 (CHNH), 79.6 ($C(CH_3)_3$), 126.8, 128.6, 129.3 (C arom), 137.2 (C quat arom), 155.2 (C(O)NH), 201.1 (CHO).

Anal calc for $C_{15}H_{21}NO_3$: C = 68.42, H = 8.04; found: C = 68.12, H = 7.83.

• *(3S)-3-[(tert-butoxycarbonyl)amino]-3-phenylpropanal (D-Boc-homophenylglycinal)* **9d**

White solid obtained in 69% yield; Mp = 91–93 °C; $Bp_{(0.01\ mm\ Hg)}$ = 80–100 °C; R_f = 0.65 (ethyl acetate/heptane, 1:1); $[\alpha]_D^{25}$ = −30.1 (c = 1.5, $CHCl_3$).

^1H NMR: δ = 1.41 (s, 9H, $C(CH_3)_3$), 2.89 (dd, 1H, J = 16.7 Hz, J = 4.7 Hz, $CHHCHO$), 2.96 (dd, 1H, J = 16.7 Hz, J = 6.9 Hz, $CHHCHO$), 5.12–5.33 (m, 2H, $CHNH$, NH), 7.23–7.32 (m, 5H, Harom), 9.72 (dd, 1H, J = 2.6 Hz, J = 1.8 Hz, CHO).

^{13}C NMR: δ = 28.3 ($C(CH_3)_3$), 49.9 (CH_2CHO), 50.1 (CHNH), 80.0 ($C(CH_3)_3$), 126.3, 127.7, 128.9 (C arom), 141.0 (C quat arom), 155.0 (C(O)NH), 200.2 (CHO).

Anal calc for $C_{14}H_{19}NO_3$: C = 67.45, H = 7.68, N = 5.62; found: C = 67.48, H = 7.65, N = 5.81.

• *(2S)-1-(tert-butoxycarbonyl)pyrrolidine-2-acetaldehyde (L-Boc-homoprolinal)* **9e**

Colorless oil obtained in 44% yield; $Bp_{(0.01\ mm\ Hg)}$ = 60–80 °C; R_f = 0.46 (ethyl acetate/heptane, 1:1); GC = 6.93 min, $[\alpha]_D^{25}$ = −46.5 (c = 1.5, $CHCl_3$).

^1H NMR (2 rotamers A, 55% and B, 45% are observed at room temperature): δ = 1.45 (s, 9H, $C(CH_3)_3$), 1.59–1.71 (m, 1H, $CHCH_2CH_2$), 1.85 (quint, 2H, J = 7.1, $CHCH_2CH_2$), 2.03–2.19 (m, 1H, $CHCH_2CH_2$), 2.48 (dd, 1H, J = 15.5 Hz, J = 6.9 Hz, $CHHCHO$), 2.79 (B, broad d, 0.45H, J = 15.6 Hz, $CHHCHO$), 2.91 (A, broad d, 0.55H, J = 16.2 Hz, $CHHCHO$), 3.30–3.47 (m, 2H, CH_2N), 4.18–4.30 (m, 1H, CHN), 9.77 (t, 1H, J = 2.1 Hz, CHO).

^{13}C NMR: δ = 22.9 (B, $CHCH_2CH_2$), 23.7 (A, $CHCH_2CH_2$), 28.3 ($C(CH_3)_3$), 31.1 (A, $CHCH_2CH_2$), 32.1 (B, $CHCH_2CH_2$), 46.2 (B, CH_2N), 46.5 (A, CH_2N), 48.9 (A, CH_2CHO), 49.5 (B, CH_2CHO), 52.3 (CHN), 79.5 (A, $C(CH_3)_3$), 80.0 (B, $C(CH_3)_3$), 154.0 (C(O)NH), 201.0 (CHO).

HRMS: calc for $C_{10}H_{19}NO_2$ ($M^{+\bullet}$ − CO) 185.1407, found 185.1416.

Diastereoisomeric aminals **11a–e** *from the β-aminoaldehydes* **9a–e**

In a typical procedure, 20.15 mg (0.1 mmol) of **9a** was reacted with 24.05 mg of the diamine **10** (*R,R*) (0.1 mmol), in 5 mL of ether, in the presence of molecular sieves (4 Å, about 100 mg), within 1 h. The mixture was then thoroughly filtered on silica gel (5 g), the residual molecular sieves being washed several times with ether. The solution was concentrated under vacuum, and a ^1H NMR spectrum of the crude white solid obtained was recorded.

• *Imidazolidine* **11a** *(R,R,R)*

White solid; Mp = 126 °C.

^1H NMR: δ = 1.00 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 1.60–1.77 (m, 4H, CH_2CH_3 + $NHCHCH_2CHN_2$), 2.16 (s, 3H, NCH_3), 2.46 (s, 3H, NCH_3), 3.55 (d, 1H, J = 8.5 Hz, CHC_6H_5), 3.63 (d, 1H, J = 8.5 Hz, CHC_6H_5), 3.87–3.99 (m, 1H, $NHCH$), 3.99 (t, 1H, J = 5.7 Hz, CHN_2), 5.25 (broad s, 1H, NH), 7.11–7.31 (m, 10H, H arom).

• *Imidazolidine* **11a** *(R,S,S)*

Colorless oil.

^1H NMR: δ = 0.97 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.47 (s, 9H, $C(CH_3)_3$), 1.61–1.71 (m, 3H, CH_2CH_3 + $NHCHCH_2CHN_2$), 1.93 (dt, 1H, J = 14.3 Hz, J = 4.8 Hz, $NHCHCH_2CHN_2$), 2.20 (s, 3H, NCH_3), 2.32 (s, 3H, NCH_3), 3.54 (d, 1H, J = 8.8 Hz, CHC_6H_5), 3.76 (d, 1H, J = 8.8 Hz, CHC_6H_5), 3.73–3.86 (m, 1H, $NHCH$), 3.81 (t, 1H, J = 5.7 Hz, CHN_2), 5.64 (broad s, 1H, NH), 7.14–7.29 (m, 10H, H arom).

• *Imidazolidine* **11b** *(R,R,R)*

Colorless oil.

^1H NMR: δ = 0.94 (d, 3H, J = 7.5 Hz, $CH(CH_3)_2$), 0.96 (d, 3H, J = 7.5 Hz, $CH(CH_3)_2$), 1.47 (s, 9H, $C(CH_3)_3$), 1.56 (ddd, 1H, J = 14.6 Hz, J = 10.1 Hz, J = 4.7 Hz, $NHCHCH_2CHN_2$), 1.93 (ddd, 1H, J = 14.5 Hz, J = 5.7 Hz, J = 10.1 Hz, $NHCHCH_2CHN_2$), 1.95–2.07 (m, 1H, $CH(CH_3)_2$), 2.23 (s, 3H, NCH_3), 2.30 (s, 3H, NCH_3), 3.50 (d, 1H, J = 8.5 Hz, CHC_6H_5), 3.76 (d, 1H, J = 8.5 Hz, CHC_6H_5), 3.77–3.87 (m, 2H, $NHCH$, CHN_2), 5.35 (broad s, 1H, NH), 7.19–7.29 (m, 10H, H arom).

• *Imidazolidine* **11b** *(R,S,S)*

Colorless oil.

^1H NMR: δ = 0.98 (d, 3H, J = 7.0 Hz, $CH(CH_3)_2$), 0.99 (d, 3H, J = 6.7 Hz, $CH(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$), 1.59–1.97 (m, 3H, $NHCHCH_2CHN_2$ + $CH(CH_3)_2$), 2.14 (s, 3H, NCH_3), 2.50 (s, 3H, NCH_3), 3.58 (s, 2H, CHC_6H_5), 3.87–3.99 (m, 1H, $NHCH$), 3.99 (dd, 1H, J = 8.5 Hz, J = 2.6 Hz, CHN_2), 4.90 (broad s, 1H, NH), 7.10–7.21 (m, 10H, H arom).

• *Imidazolidine* **11c** *(S,R,R)*

Colorless oil.

^{1}H NMR: δ = 1.43 (s, 9H, C(CH$_3$)$_3$), 1.86 (ddd, 1H, J = 14.7 Hz, J = 9.7 Hz, J = 5.0 Hz, NHCHCH_2CHN$_2$), 1.91 (dt, 1H, J = 14.5 Hz, J = 4.6 Hz, NHCHCH_2CHN$_2$), 2.07 (s, 3H, NCH$_3$), 2.24 (s, 3H, NCH$_3$), 2.82 (dd, 1H, J = 13.5 Hz, J = 7.6 Hz, CH_2C$_6$H$_5$), 3.14 (broad d, 1H, J = 8.1 Hz, CH_2C$_6$H$_5$), 3.52 (d, 1H, J = 8.8 Hz, CHC$_6$H$_5$), 3.78 (d, 1H, J = 8.7 Hz, CHC$_6$H$_5$), 4.05–4.17 (m, 1H, NHCH), 4.25 (t, 1H, J = 4.7 Hz, CHN$_2$), 6.03 (broad s, 1H, NH), 7.26–7.34 (m, 15H, H arom).

• *Imidazolidine* **11c** *(S,S,S)*

Colorless oil.

^{1}H NMR: δ = 1.44 (s, 9H, C(CH$_3$)$_3$), 1.76–1.90 (m, 2H, NHCHCH_2CHN$_2$), 2.05 (s, 3H, NCH$_3$), 2.42 (s, 3H, NCH$_3$), 2.79 (dd, 1H, J = 13.1 Hz, J = 8.1 Hz, CH_2C$_6$H$_5$), 3.09 (broad d, 1H, J = 12.6 Hz, CH_2C$_6$H$_5$), 3.73 (broad s, 2H, CHC$_6$H$_5$), 4.03–4.13 (m, 1H, NHCH), 4.15–4.27 (m, 1H, J = 4.7 Hz, CHN$_2$), 5.47 (broad s, 1H, NH), 7.06–7.42 (m, 15H, H arom).

• *Imidazolidine* **11d** *(S,S,S)*

Colorless oil.

^{1}H NMR: δ = 1.45 (s, 9H, C(CH$_3$)$_3$), 1.76–1.90 (m, 2H, NHCHCH_2CHN$_2$), 2.05 (s, 3H, NCH$_3$), 2.42 (s, 3H, NCH$_3$), 2.79 (dd, 1H, J = 13.1 Hz, J = 8.1 Hz, CH_2C$_6$H$_5$), 3.09 (broad d, 1H, J = 12.6 Hz, CH_2C$_6$H$_5$), 3.73 (broad s, 2H, CHC$_6$H$_5$), 4.03–4.13 (m, 1H, NHCH), 4.15–4.27 (m, 1H, CHN$_2$), 5.47 (broad s, 1H, NH), 7.06–7.42 (m, 15H, H arom).

• *Imidazolidine* **11e** *(S,R,R)*

Colorless oil.

^{1}H NMR: (two rotamers, A 52% and B 48%, are visible on one signal at room temperature) δ = 1.53 (s, 9H, C(CH$_3$)$_3$), 1.60–2.29 (m, 6H, all CH$_2$ but CH$_2$N), 2.20 (s, 3H, NCH$_3$), 2.36 (s, 3H, NCH$_3$), 3.38 (broad s, 2H, CH$_2$N), 3.50 (d, 1H, J = 8.5 Hz, CHC$_6$H$_5$), 3.67 (broad s, 1H, CHNBoc), 3.87 (rotamer B, d, 0.48H, J = 7.9 Hz, CHC$_6$H$_5$), 3.88 (rotamer A, d, 0.52H, J = 8.1 Hz, CHC$_6$H$_5$), 4.24 (broad s, 1H, CHN$_2$), 7.17–7.27 (m, 10H, H arom).

• *Imidazolidine* **11e** *(S,S,S)*

Colorless oil.

^{1}H NMR: (two rotamers, A 65% and B 35%, are visible on one signal at room temperature) δ = 1.49 (s, 9H, C(CH$_3$)$_3$), 1.51–2.44 (m, 6H, all CH$_2$ but CH$_2$N), 2.27 (s, 3H, NCH$_3$), 2.37 (s, 3H, NCH$_3$), 3.38 (d, 1H, J = 8.2 Hz, CHC$_6$H$_5$), 3.40 (broad s, 2H, CH$_2$N), 3.67 (d, 1H, J = 8.2 Hz, CHC$_6$H$_5$), 3.77 (broad s, 1H, CHNBoc), 4.05 (rotamer A, broad s, 0.65H, CHN$_2$), 4.13 (rotamer B, broad s, 0.35H, CHN$_2$), 7.11–7.27 (m, 10H, H arom).

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