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Organometallic Additions to β-substituted *N*-Boc-β-aminoaldehydes: a New Synthesis of Enantiomerically Pure 1,3-disubstituted *N*-Boc-1,3-aminoalcohols

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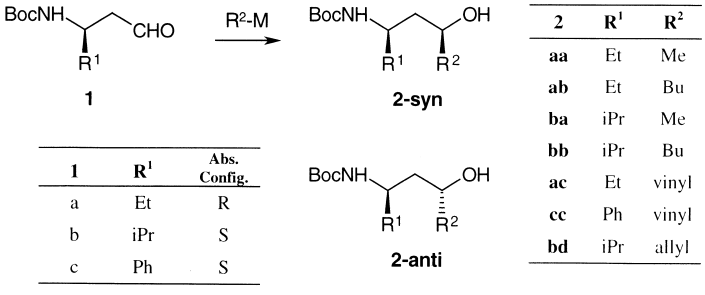
Abstract—1,2-addition of organolithium and organomagnesium derivatives to β-substituted (*N*-Boc)-β-aminoaldehydes gave access to enantiomerically pure, 1,3-disubstituted, 1,3-aminoalcohols. A diastereoselective version of this addition was also investigated and Gilman cuprates were found to add onto aldehydes **1a**–**b** with notable diastereoselectivity (up to 70% *de*) in favour of the *anti* isomer. The absolute configuration of each obtained 1,3-aminoalcohol was determined.

Introduction

Chiral 1,3-aminoalcohol sequences are found in compounds of biological interest such as nucleoside antibiotics[1] (sperabilines A–D, negamicine) or in alkaloids.[2] Various methodologies are already available to design such chiral sequences. Among them, the cycloaddition of olefins to nitrones[3] and nitrile oxides,[2,3a,4] the addition reaction to β-alkoxyimines[5] or the more specific intramolecular rearrangement of β-silyloxyiminium salts,[6] the reduction of β-hydroxyoximes[1b,7] and β-aminoketones,[8] the double reduction of enaminones,[9] the addition of azaenolates to aldehydes,[10] and finally the cyclofunctionalisation of homoallylic alcohols[11] or amines[1a] bearing, respectively, at the oxygen a carbamid group or at the nitrogen a carboxyl group, are the most well known. Some of these methodologies have also been used relevantly in non-racemic synthesis.[1a,1b,2,5,8]

Surprisingly, the simple addition of an organometallic reagent to the β-aminoaldehydes **1**, which would lead to the *N*-protected β-aminoalcohols **2** has been scarcely examined. Only recently, Evans et al. mentioned the non-diastereoselective addition of vinylmagnesium bromide to the racemic (*N*-Boc)-3-aminopropanal.[12] Since non-racemic *N*-Boc protected β-aminoaldehydes of type **1** are readily obtained from the corresponding α-aminoacids, either through an Arndt–Eistert homologation step followed by the reduction to the aldehyde[13] or by a chain elongation via a nitrile and subsequent partial reduction[14], we decided to investigate this reaction (Scheme 1).



1	R^1	Abs. Config.
a	Et	R
b	iPr	S
c	Ph	S

2	R^1	R^2
aa	Et	Me
ab	Et	Bu
ba	iPr	Me
bb	iPr	Bu
ac	Et	vinyl
cc	Ph	vinyl
bd	iPr	allyl

Scheme 1.

Keywords: organolithium; organomagnesium; β-aminoaldehydes; diastereoselective addition; cuprates; 1,3-aminoalcohols; enantiomers.

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Optically pure *N*-Boc protected β-aminoaldehydes **1** (ee up to 99% depending on the starting α-aminoacid) used in this study were prepared according to this latter methodology. In this paper, we wish to describe the synthesis of non-racemic *N*-Boc protected β-amino alcohols **2** from β-amino-aldehydes of type **1** through the addition of various organo-metallic reagents.

Results and Discussion

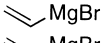
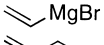
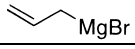
The addition of organolithium and Grignard reagents was first tested on the aldehydes **1a** (ee=97%) and **1b–c** (ee=99%); 2.5 equiv. of methyl or butyllithium were added to a diethyl ether solution of the aldehyde at −80°C. After 1 h, during which the reaction temperature was raised from −80 to −40°C, the reaction mixture was hydrolysed and then analysed by GC. The results are given in Table 1. The same procedure was used for the addition of diethyl ether solutions of methylmagnesium iodide and butylmagnesium bromide. Only 70–80% of the starting aldehyde reacted even in the presence of a large excess of the nucleophilic reagent; 6–10% of the starting aldehyde was found in each crude reaction mixture. Using 10 equiv. of methyllithium did not increase the conversion percentage. The most likely reason we can foresee to explain this lack of completion of the addition is a partial enolisation of the aldehyde, giving back **1** after hydrolysis of the reaction mixture. The diastereoselectivity was very poor whatever reagent used, slightly favouring the *syn* alcohol in the case of MeLi, BuLi and BuMgBr. Not surprisingly, this selectivity is not explained by the Felkin's derived model for the addition of nucleophiles to β-chiral carbonyl compounds.[15] Indeed this model which predicts the favoured formation of the *anti* diastereoisomer does not take into account polar or Lewis basic substituents such as the Boc group.

The vinylic and allylic magnesium bromides were also tested with aldehydes **1** since they give access to the synthetically interesting allylic and homoallylic alcohols **2ac**, **2cc** and **2bd**. The additions were conducted in diethyl ether or in a diethyl ether/THF mixture. Once again, the corresponding alcohols were obtained without significant diastereoselectivity in 61–63% combined yields after chromatographic separation and purification; 3.5 equiv. of reagents (see Experimental) were found in this case to be the optimum stoechiometry in order to obtain the best yields. All diastereoisomeric alcohols **2** were readily separated and purified by flash chromatography. Most of the compounds obtained are solids and they appeared stable toward usual purification methods (low-pressure distillation, or silica gel chromatography).

After these preliminary results, the diastereoselective synthesis of one or the other of the two possible diastereoisomeric alcohols **2** was investigated. A literature survey shows that cases of good 1,3 inductions in organometallic addition reactions to β-chiral, β-hetero-substituted aldehydes or ketones are observed only when using particularly chelating organometallics, such as methyl titanium chloride reagents, leading to chelation controlled additions.[16] In this regard, the low diastereoselectivity that we observed with organolithium and Grignard reagents was expected. These latter reagents have been proved in general to be inefficient in chelation controlled additions with substrates bearing heterosubstituent in β or further positions. Unfortunately, in our hands, the utilisation of $(Me)_nTiCl_{(4-n)}$ in reaction with aldehyde **1a** was not satisfactory as we encountered unsolvable difficulties in reproducibility and completion of the reaction which may be due to the presence of the Boc group. Gilman cuprates are another important class of reagents used for chelation controlled additions to hetero-substituted carbonyl compounds.[16] Particularly they have shown good 1,2 inductions in chelation controlled additions (formation of the *Anti*-Cram product) to α-chiral β-alkoxy-aldehydes[17] and, noteworthy, to *N*-Boc-α-aminoaldehydes.[18] We were curious about the stereochemical outcome of the addition of Gilman cuprates to the aldehydes **1**. We therefore examined the addition of methyl and butyl cuprates (4 mol equiv.), prepared from copper iodide (I) and a solution of methyl and butyllithium, respectively, to the aldehydes **1a** and **1b**, in diethyl ether at −90°C. After 15 min at this temperature the aldehydes were fully consumed (GC analysis) and the hydrolysis gave a mixture of the expected diastereoisomeric alcohols **2a–d**. Diastereoselectivities were determined by GC analysis. Results are reported in the Table 2.

Moderate to good 1,3 inductions in favour of the *anti* isomer, with a maximum of 70% de observed in the case of the addition of dimethylcuprate on the aldehyde **2a** (entry 1) were obtained. The combined yields determined after purification and separation of the diastereoisomers by column chromatography were satisfactory, notably better

Table 1. Addition of organolithium and Grignard reagents to aldehydes **1** (reactions were carried out in diethyl ether from −80 to −20°C)

Entry	Aldehyde	R^2-M	Amino alcohols	Diastereomeric ratios (*anti*/*syn*)[a]	Yields[b] [%]
1	**1a**	MeLi	**2aa**	48/52	(78)
2	**1a**	BuLi	**2ab**	46/54	(72)
3	**1a**	MeMgI	**2aa**	53/47	66
4	**1a**	BuMgBr	**2ab**	44/56	62
5	**1b**	MeLi	**2ba**	48/52	(80)
6	**1b**	BuLi	**2bb**	49/51	(74)
7	**1a**		**2ac**	52/48	63
8	**1c**		**2cc**	56/44	61
9	**1b**		**2bd**	52/48	62

[a] Diastereomeric ratios were determined by GC analysis and ^{1}H NMR spectroscopy.
[b] Yields in brackets are conversion percentages measured by GC analysis; others are isolated yields.

Table 2. Addition of organo copper reagents to the aldehydes **1**

Entry	Aldehyde **1**	Copper reagent	Solvent	Temperature (°C)	β-Amino alcohol 2	*anti*/*syn* (%)[a]	Yields[b] [%]
1	**1a**	$Me_2CuLi{\cdot}LiI$	Et_2O	−90	**2aa**	85/15	74
2	**1a**	$Bu_2CuLi{\cdot}LiI$	Et_2O	−90	**2ab**	75/25	59
3	**1b**	$Me_2CuLi{\cdot}LiI$	Et_2O	−90	**2ba**	82/18	76
4	**1b**	$Bu_2CuLi{\cdot}LiI$	Et_2O	−90	**2bb**	61/39	68
5	**1a**	$Me_2CuLi{\cdot}LiI$	Heptane	−85	**2aa**	70/30	–
6	**1a**	$Me_2CuLi{\cdot}LiI$	Toluene	−85	**2aa**	76/24	–
7	**1a**	$Me_2CuLi{\cdot}LiI$	THF	−85 to 0	**2aa**	53/47	–
8	**1a**	$MeCu(CN){\cdot}Li$	Et_2O	−80	**2aa**	83/17	(44)
9	**1a**	$MeCu(CN){\cdot}Li{\cdot}BF_3$	THF	−80	**2aa**	50/50	–
10	**1a**	$MeCu{\cdot}MgBr_I{\cdot}SMe_2$	Et_2O/SMe_2	−80	**2aa**	51/49	(74)
11	**1a**	$MeCu(CN)ZnI{\cdot}2LiCl{\cdot}BF_3{\cdot}OEt_2$	THF	−80	**2aa**	52/48	(90)

[a] Diastereomeric ratios were determined by GC analysis and ^{1}H NMR spectroscopy.
[b] Yields in brackets are obtained from GC analysis; others are isolated yields.

than when organolithium and Grignard reagents were used. In contrast with the latter, no trace of the starting aldehyde was observed at the end of the reaction, which indicates that no enolisation and subsequent side reactions compete with the expected 1,2 addition. Reaction temperatures between −70 and −20°C and different solvents (heptane, toluene or THF) were tested in order to optimise this reaction. However, the addition at −90°C in diethyl ether remained the best one in terms of diastereoselectivity and yield; 4–5 equiv. of cuprate were necessary to obtain maximum completion of the reaction and optimum diastereoselectivity. This is a well-known drawback of the use of cuprates. To obviate this, we tested the lower order cyanocuprate $MeCu(CN){\cdot}Li$[19] which requires only 1 equiv. of MeLi for its preparation. With this reagent, the selectivity is still good in favour of the *anti* isomer (*de*=66%). However, the addition of 5 equiv. of $MeCu(CN){\cdot}Li$ in diethyl ether at −90°C to the aldehyde **1a** led only to ca. 50% completion of the reaction (Table 2, entry 8). The use of the more economical Grignards and lithium reagents remains therefore a worthy alternative, particularly if the two diastereoisomers are needed. Other copper-based organometallic reagents were tested: $MeCu{\cdot}MgBrI{\cdot}SMe_2$ in OEt_2/SMe_2 solution,[20] $MeCu(CN)Li{\cdot}BF_3{\cdot}OEt_2$,[21] and the Knochel reagent $MeCu(CN)ZnI{\cdot}2LiCl{\cdot}BF_3{\cdot}OEt_2$.[22] With these latter reagents only poor diastereoselectivity was observed (Table 2, entries 9–11).

In the light of the literature data,[16–18] a chelation controlled addition seems the most likely reason for the notable 1,3 induction observed with the cuprates. The existence of a chelated transition state is also supported by the sharp contrast with the diastereoselectivities obtained with all other tested (known as non-chelating) reagents and by the fact that when using a more Lewis basic solvent like THF, the diastereoselectivity of the addition of Me_2CuLi to **1a** dramatically dropped (Table 2, entry 7).

In order to establish the relative configuration of the alcohols **2** (*syn* or *anti*), the structure of the alcohol **2ab-*anti*** was resolved by single crystal X-ray analysis; **2ab-*anti*** adopts a cyclic conformation in crystalline form due to a hydrogen bonding between hydrogen of the OH function and oxo oxygen of the carbamate moiety (1.9 Å) (Fig. 1).

The relative configuration of all compounds **2** were established according to an early work by Jacques et al.[8d] by IR-spectral data analysis of the two diastereoisomers. All IR spectra of the alcohols **2**, recorded in a non-protic solvent (dichloromethane), showed two characteristic absorption

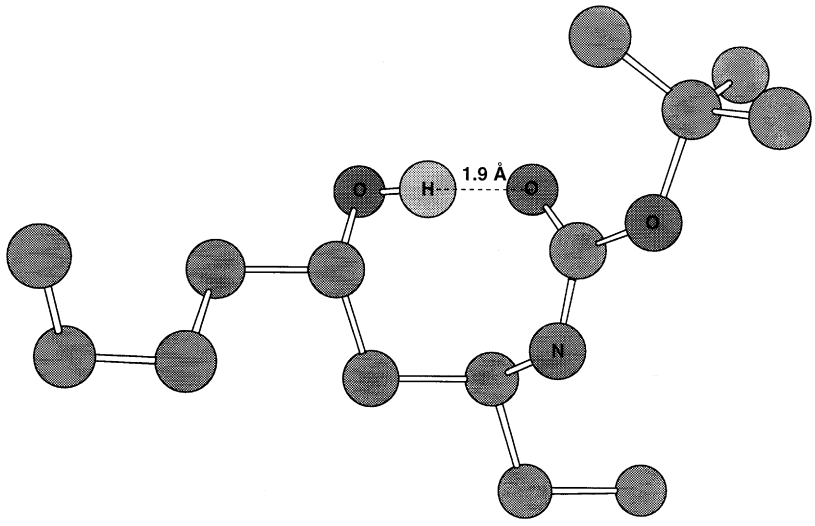


Figure 1. View of **2ab-*anti*** in crystalline form; for more convenience, C–H hydrogens are not represented.

Table 3. Free and associated OH frequencies of **2-*anti*** and **2-*syn*** in CH_2Cl_2

1,3-Aminoalcohols		TLC R_f[a]	Infrared		
	Relative configuration		O–H (free) ν (cm^-)	O–H (associated) ν (cm^{-1})	$(\epsilon_{OH\ ass.}+\epsilon_{NH})/\epsilon_{OH}$ free
2aa	*anti*	0.40	3603	3455	33
	syn	0.19	3609	3435	4.0
2ab	*anti*	0.50	3621	3433	14
	syn	0.33	3610	3436	3.4
2ba	*anti*	0.59	3607	3439	16
	syn	0.49	3607	3440	4.4
2bb	*anti*	0.58	3608	3439	25
	syn	0.40	3610	3440	4.8
2ac	*anti*	0.50	3602	3433	7.0
	syn	0.34	3602	3435	1.2
2cc	*anti*	0.31	3601	3436	7.8
	syn	0.19	3609	3440	2.4
2bd	*anti*	0.75	3600	3439	18
	syn	0.62	3596	3440	3.5

[a] Thin layer chromatography: AcOEt/Heptane=1/2; except for alcohol **2bd** (AcOEt/Heptane=1/1).

peaks. The first peak at ca. 3600 cm^{-1} corresponded to a free O–H bond absorption and the second at ca. 3430 cm^{-1} corresponded to an associated O–H, this latter sometimes overlapping with the N–H absorption (Table 3).

The absorption around 3440 cm^{-1} has been attributed to the associated O–H bond since no variation of its intensity could be observed when varying the concentration of the samples. Assuming that all *anti* diastereoisomers behave similarly to **2b** *anti*, the *anti* configuration was attributed to all diastereoisomers which display the highest ratio $(\epsilon_{OH\ ass}+\epsilon_{NH})/\epsilon_{OH}$ free) and the lowest polarity, and therefore highest R_f in TLC analysis. The X-ray structure of **2ab-*anti*** showed that the chelated conformer of the alcohols **2** are 8-membered rings which formally possess the 6,8-disubstituted cyclooct-1-en-3-one structure. Further examination of this model indicates that the pseudo-equatorial position of the two substituents R^1 and R^2 is much more favourable for the **2-*anti*** than for the **2-*syn*** alcohols. This is in agreement with the IR observations mentioned above. The systematic downfield chemical shift of the OH proton in the *anti* diastereoisomers (3.60–4.20 ppm), as compared to the *syn* ones (2.17–2.97 ppm), confirmed the favoured intramolecular chelation in the former.[12]

All alcohols, **2**, were synthesised from optically active aldehydes **1** of known absolute configuration (chiral carbon α to the nitrogen). Hence, having established the relative configuration of the two asymmetric centres, it was possible to determine the absolute configuration of all the diastereoisomeric alcohols.

Conclusion

In summary, synthesis of optically active, *N*-Boc protected, 1,3-disubstituted 1,3-aminoalcohols **2,** by addition of various organometallic reagents to β-aminoaldehydes **1**, has been studied. It has been observed that organolithium and Grignards reagents led to the 3-alkyl, allyl or homoallyl alcohols **2** in satisfactory yields but without diastereoselectivity. The ease of separation of each diastereoisomer by column chromatography made this synthesis convenient for synthetic purposes. Relative, then absolute configurations of all synthesised alcohols were determined. In our attempts to find a reagent for the diastereoselective addition to aldehydes **1**, we discovered that Gilman cuprates give the 1,3-aminoalcohols **2** with moderate to good diastereoselectivity (up to 70% de) in favour of the *anti* diastereoisomer.

Experimental

General

Melting points were determined with an Electrothermal IA9300 apparatus and are uncorrected. Thin layer chromatography analysis was performed on aluminum precoated plates (silica gel 60, 0.2 mm) purchased from Merck; eluant: ethyl acetate/heptane=1/2 unless other solvent mixture was specified). For preparative flash-chromatography, Geduran SI 60 (Merck, 0.040–0.063 mm) silica gel was used. Gas Chromatography analysis was 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 100–240 at a rate of 10°C/min. Optical rotation measurements were performed on a Perkin–Elmer 241C polarimeter (concentrations in g/100 mL). IR spectra were recorded on a Fourrier transform apparatus BioRad FTS 175C. ^1H 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 1). Microanalysis was performed at the Central Laboratory for Analysis, CNRS, Lyon (France). Single-crystal X-ray determination of the structure of **2ab-*anti*** was resolved by Dr Loïc Toupet of the 'Groupe de Matière Condensée et Matériaux', University of Rennes 1, Rennes (France).

All reaction solvents were dried before use using standard procedures and reactions requiring inert atmosphere were carried out under nitrogen atmosphere in flame dried glassware. Enantiomerically enriched aldehydes **1a–c** were prepared according to a previously published procedure:[14] **1a**, R configuration ee=97%, **1b**, R configuration, ee=99%,

and **1c**, S configuration, ee=99%. Copper(I) iodide and cyanide were purchased from Aldrich. They were dried in situ before use by repeated heating with a heat gun (~200°C) under vacuum (0.1 mmHg). Methyl and butyllithium, 1.6 M in hexane solution, were purchased from Acros and contain LiCl residues. All Grignard reagents used, MeMgI (1.65 M in diethyl ether), BuMgBr, (1.4 M in diethyl ether), vinylMgBr (0.95 M in THF) and allylMgBr (0.34 M in THF) were prepared according to classical procedures.

General procedure (A) for the addition of organolithium or organomagnesium derivatives to the aldehydes 1a–c

To a stirred and cooled to −80°C 0.2 M solution of the aldehyde **1** in diethyl ether or THF (used in the case of vinyl and allyl magnesium bromides), were added dropwise, along the surface of the flask, 2.5 M equiv. of the solution of the organometallic derivative. The mixture was stirred and allowed to warm up slowly to −20°C over an approximate 1 h period. The hydrolysis was achieved by cautious addition of a saturated solution of ammonium chloride. After returning to ambient temperature, the two phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic phases were combined, washed twice with brine and dried over magnesium sulphate. Removal of the solvents under reduced pressure gave a yellowish oil which was analysed by GC and ^{1}H NMR spectroscopy to determine the diastereoisomeric ratio of the *syn* and *anti* alcohols and to evaluate the completion of the reaction by comparison with an internal standard. The two diastereoisomers were eventually separated and isolated by flash chromatography.

General procedure (B) for the addition of methyl and butyl cuprates to the aldehydes 1a–b

To a suspension of dry copper (I) iodide in diethyl ether (0.5 M) cooled at −20°C was slowly added, under stirring, a 1.6 M solution in hexane of methyllithium (1.9 M equiv.). The transmetallation reaction was immediately observed and the yellow solution of $Me_2CuLi{\cdot}LiCl$ was then cooled at −90°C. A ca. 1 M solution in diethyl ether of the aldehyde **1** (0.25 M equiv.) was added dropwise, along the surface of the flask, over 20 min. After 1 h stirring at this same temperature, the hydrolysis was done by cautious addition of methanol (ca. 3 M equiv.). After a few minutes, the cold mixture was poured in a separatory funnel containing a solution of saturated ammonium chloride and shaken. After returning to room temperature, the aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed twice with brine and dried over magnesium sulphate. After removal of the solvents under vacuum, a crude oil was obtained which was analysed by GC and ^{1}H NMR spectroscopy. Flash chromatography (ethyl acetate/heptane 1/9–1/2) afforded the analytically pure *syn* and *anti* alcohols **1**.

Tests for the addition of methyl cuprates to aldehyde **1a** in diethyl ether at different temperatures ranging from −70 to −20°C and in toluene, heptane, THF at the temperatures mentioned in Table 2 were conducted using the same experimental conditions as described above except for solvent and reaction temperature. The crude reaction mixtures were analysed by GC and ^{1}H NMR spectroscopy after hydrolysis and work-up.

General procedure for the addition of the other methyl copper complexes listed in Table 2

A molar solution of aldehyde **1** in diethyl ether was added to 5 M equiv. of the organometallic reagent in the solvent, or the mixture of solvents (~0.5 M), and at the temperature mentioned in Table 2. MeCu(CN)Li in diethyl ether,[19] $MeCu{\cdot}MgIBr{\cdot}SMe_2$ in a OEt_2/SMe_2 solvent mixture,[20] $MeCu(CN){\cdot}Li{\cdot}BF_3{\cdot}OEt_2$ in THF,[21] $MeCu(CN)ZnI{\cdot}2LiCl{\cdot}BF_3{\cdot}OEt_2$[22] were prepared in situ according to the literature procedures. Hydrolysis and work-up were conducted as previously described and crude reaction mixtures analysed by GC and ^{1}H NMR spectroscopy.

Synthesis of the *syn* and *anti* 4-(*N*-tertiobutyloxycarbonyl)-aminohexan-2-ol (2aa) *(Procedure B):* Starting from 2.28 g (12.0 mmol) of copper iodide, 14.2 mL (22.8 mmol) of methyllithium solution (1.6 M in hexane) and 603 mg (3.00 mmol) of aldehyde **1a**, 407 mg (1.88 mmol, 63%) of **2aa-*anti*** and 72 mg (0.33 mmol, 11%) of **2aa-*syn*** were obtained after flash chromatography of the crude oily residue.

(2*S*,4*R*)-4-(*N*-Tertiobutyloxycarbonyl)-aminohexan-2-ol (2aa-*syn*). Colourless solid: mp≤40°C. R_f=0.19. $[\alpha]_D^{25}$=+14.7 (c=0.3, $CHCl_3$). IR (CH_2Cl_2): 1708 cm^{-1} (C=O), 3435 (NH, O–$H_{associated}$), 3609 (O–H_{free}). ^{1}H NMR ($CDCl_3$): δ=0.92 (t, 3 H, J=7.4 Hz, CH_3CH$_2$), 1.22 (d, 3 H, J=6.3 Hz, CH_3CHOH), 1.49–1.59 (m, 4 H, CH$_3$CH_2, CHCH_2CH), 1.44 (s, 9 H, (CH_3)$_3$C), 2.30 (br s, 1 H, OH), 3.55–3.60 (m, 1 H, C*H*NH), 3.91 (m, 1 H, C*H*OH), 4.64 (br d, 1 H, J=8.1 Hz, NH), ^{13}C NMR ($CDCl_3$) δ: (10.2 (*C*H$_3$CH$_2$), 23.7 (*C*H$_3$CHOH), 28.4 ((*C*H$_3$)$_3$C), 28.9 (CH$_3$*C*H$_2$), 44.9 (CH*C*H$_2$CH), 50.5 (CHNH), 66.4 (CHOH), 79.5 ((CH$_3$)$_3$*C*), 156.2 (C=O). HRMS (EI, 70 eV): $C_{11}H_{23}NO_3$ ($M^{+\cdot}$); calcd=217.1678, found=217.1658.

(2*R*,4*R*)-4-(*N*-Tertiobutyloxycarbonyl)-aminohexan-2-ol (2aa-*anti*). Colourless solid: mp≤40°C. R_f=0.40. $[\alpha]_D^{25}$=0.0 (c=0.5, $CHCl_3$). IR (CH_2Cl_2): 1687 cm^{-1} (C=O), 3455 (NH+O–$H_{associated}$), 3603 (O–H_{free}). ^{1}H NMR ($CDCl_3$): δ=0.95 (t, 3 H, J=7.4 Hz, CH_3CH$_2$), 1.19 (d, 3 H, J=6.3 Hz, CH_3CHOH), 1.23–1.58 (m, 4 H, CH$_3$CH_2, CHCH_2CH), 1.45 (s, 9 H, (CH_3)$_3$C), 3.62–3.73 (m, 1 H, C*H*NH), 3.79 (m, 1 H, C*H*OH), 3.97 (br s, 1 H, OH), 4.39 (d, 1 H, J=8.3 Hz, NH), ^{13}C NMR ($CDCl_3$) δ: (10.7 (*C*H$_3$CH$_2$), 22.6 (*C*H$_3$CHOH), 28.3 ((*C*H$_3$)$_3$C), 28.7 (CH$_3$*C*H$_2$), 46.1 (CH*C*H$_2$CH), 49.1 (CHNH), 63.5 (CHOH), 79.9 ((CH$_3$)$_3$*C*), 157.5 (C=O). HRMS (EI, 70 eV): $C_{11}H_{23}NO_3$ ($M^{+\cdot}$); (m/z) calcd=217.1678, found=217.1672.

Synthesis of the *syn* and *anti* 3-(*N*-tertiobutyloxycarbonyl)-aminononan-5-ol (2ab) *(Procedure B):* Starting from 762 mg (4.0 mmol) of copper iodide, 4.6 mL (7.8 mmol) of butyllithium solution (1.7 M in hexane) and 201 mg (1.0 mmol) of aldehyde **1a**, 116 mg (0.44 mmol, 44%) of **2ab-*anti*** and 38 mg (0.15 mmol, 15%) of

2ab-*syn* were obtained after flash chromatography of the crude oily residue.

(3*R*,5*S*)-3-(*N*-Tertiobutyloxycarbonyl)-aminononan-5-ol (2ab-*syn*). Colourless solid: mp=57°C (pentane). R_f=0.33. $[\alpha]_D^{25}$=+9.4 (*c*=0.5, $CHCl_3$). IR (CH_2Cl_2): 1708 (C=O), 3436 (NH, O–$H_{associated}$), 3610 (O–H_{free}). ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, *J*=7.5 Hz, CH_3CH$_2$CH$_2$), 0.95 (t, 3 H, *J*=6.9 Hz, CH_3CH$_2$CH), 1.23–1.75 (m, 10 H, all CH_2), 1.44 (s, 9 H, (CH_3)$_3$C), 2.46 (br s, 1 H, OH), 3.53–3.63 (m, 1 H, C*H*NH), 3.66–3.74 (m, 1 H, C*H*OH), 4.50 (d, 1 H, *J*=7.5 Hz, NH). ^{13}C NMR ($CDCl_3$) δ: (10.1 (*C*H$_3$CH$_2$CH), 14.1 (*C*H$_3$CH$_2$CH$_2$), 22.7 (CH$_3$*C*H$_2$CH), 27.8 28.9 (CH$_3$*C*H$_2$*C*H$_2$), 28.4 ((*C*H$_3$)$_3$C), 37.4 (C$_3$H$_7$*C*H$_2$), 43.1 (CH*C*H$_2$CH), 50.8 (CHNH), 70.4 (CHOH), 79.4 ((CH$_3$)$_3$*C*), 156.2 (C=O). HRMS (EI, 70 eV): $C_{12}H_{24}NO_3$ ([M−˙C$_2$H$_5$]$^+$); calcd=230.1756, found=230.1754.

(3*R*,5*R*)-3-(*N*-Tertiobutyloxycarbonyl)-aminononan-5-ol (2ab-*anti*). Colourless solid: mp=45°C (pentane). R_f=0.50 $[\alpha]_D^{25}$=+10.0 (*c*=0.25, $CHCl_3$). IR (CH_2Cl_2): 1687 (C=O), 3433 (NH, O–$H_{associated}$), 3621 (O–H_{free}). ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, *J*=7.5 Hz, CH_3CH$_2$CH$_2$), 0.95 (t, 3 H, *J*=7.5 Hz, CH_3CH$_2$CH), 1.27–1.56 (m, 10 H, all CH_2), 1.45 (s, 9 H, (CH_3)$_3$C), 3.51–3.59 (m, 1 H, C*H*OH), 3.62–3.78 (m, 1 H, C*H*NH), 3.92 (br s, 1 H, OH), 4.37 (d, 1 H, *J*=8.8 Hz, NH). ^{13}C NMR ($CDCl_3$) δ: (10.7 (*C*H$_3$CH$_2$CH), 14.1 (*C*H$_3$CH$_2$CH$_2$), 22.7 (CH$_3$*C*H$_2$CH), 28.2 28.7 (CH$_3$*C*H$_2$*C*H$_2$), 28.3, (*C*H$_3$)$_3$C), 36.6 (C$_3$H$_7$*C*H$_2$), 44.3 (CH*C*H$_2$CH), 49.1 (CHNH), 67.5 (CHOH), 79.8 (CH$_3$)$_3$*C*), 157.4 (C=O). HRMS (EI, 70 eV): $C_{12}H_{24}NO_3$ ([M−˙C$_2$H$_5$]$^+$); calcd=230.1756, found=230.1777.

Synthesis of the *syn* and *anti* 5-methyl-4-(*N*-tertiobutyloxycarbonyl)-aminohexan-2-ol (2ba) *(Procedure B):* Starting from 2.28 g (12.0 mmol) of copper iodide, 14.2 mL (22.7 mmol) of methyllithium solution (1.6 M in hexane) and 646 mg (3.00 mmol) of aldehyde **1b**, 440 mg (1.90 mmol, 63%) of **2ba-*anti*** and 60 mg (0.26 mmol, 9%) of **2ba-*syn*** were obtained after flash chromatography of the crude oily residue.

(2*R*,4*R*)-5-Methyl-4-(*N*-tertiobutyloxycarbonyl)-aminohexan-2-ol (2ba-*syn*). Colourless solid: mp≤40°C. R_f=0.49. $[\alpha]_D^{25}$=−9.4 (*c*=0.8, $CHCl_3$). IR (CH_2Cl_2): 1709 (C=O), 3440 (NH, O–$H_{associated}$), 3607 (O–H_{free}). ^{1}H NMR ($CDCl_3$): 0.88 (d, 3 H, *J*=7.0 Hz, (CH_3)(CH$_3$)CH), 0.91 (d, 3 H, *J*=6.8 Hz, (CH$_3$)(*C*H$_3$)CH), 1.27 (d, 3 H, *J*=6.2 Hz, CH_3CHOH), 1.45 (s, 9 H, (CH_3)$_3$C), 1.48 (ddd, 1 H, *J*=14.3, 9.0, 7.0 Hz, CHC*H*HCH), 1.58 (dt-like, 1 H, *J*=14.3, 4.5 Hz, CHCH*H*CH), 1.76 (dhept, 1 H, *J*=6.7, 5.0 Hz, (CH$_3$)$_2$C*H*), 2.42 (br s, 1 H, OH), 3.47–3.55 (m, 1 H, C*H*NH), 3.90 (sext-like, 1 H, *J*=6.3 Hz, C*H*OH), 4.56 (d, 1 H, *J*=8.5 Hz, NH). ^{13}C NMR ($CDCl_3$) δ: (17.5 ((*C*H$_3$)(CH$_3$)CH), 18.8 ((CH$_3$)(*C*H$_3$)CH), 23.6 (*C*H$_3$CHOH), 28.4 ((*C*H$_3$)$_3$C), 32.7 ((CH$_3$)$_2$*C*H), 42.3 (CH*C*H$_2$CH), 54.0 (CHNH), 66.9 (CHOH), 79.4 ((CH$_3$)$_3$*C*), 156.3 (C=O). HRMS (EI, 70 eV): $C_9H_{18}NO_3$ ([M−˙C$_3$H$_7$]$^+$); calcd=188.1287, found=188.1294.

(2*S*,4*R*)-5-Methyl-4-(*N*-tertiobutyloxycarbonyl)-aminohexan-2-ol (2ba-*anti*). Colourless oil: R_f=0.59. $[\alpha]_D^{25}$=−4.4 (*c*=0.7, $CHCl_3$). IR (CH_2Cl_2): 1688 (C=O), 1708 (C=O), 3439 (NH, O–$H_{associated}$), 3607 (O–H_{free}). ^{1}H NMR ($CDCl_3$): δ=0.92 (d, 3 H, *J*=6.2 Hz, (CH_3)(CH$_3$)CH), 0.94 (d, 3 H, *J*=6.5 Hz, (CH$_3$)(CH_3)CH), 1.20 (d, 3 H, *J*=6.4 Hz, CH_3CHOH), 1.31 (ddd, 1 H, *J*=13.8, 11.9, 2.3 Hz, CHC*H*HCH), 1.45 (s, 9 H, (CH_3)$_3$C), 1.51 (ddd, 1 H, *J*=13.8, 10.6, 2.9 Hz, CHCH*H*CH), 1.69 (dhept, 1 H, *J*=6.7, 5.5 Hz, (CH$_3$)$_2$C*H*), 3.62 (dddd, 1 H, *J*=11.9, 9.7, 5.5, 2.9 Hz, C*H*NH), 3.78 (m, 1 H, *J*=2.3 Hz, C*H*OH), 3.92 (br s, 1 H, OH), 4.47 (d, 1 H, *J*=9.7 Hz, NH). ^{13}C NMR ($CDCl_3$) δ: (18.2 ((*C*H$_3$)(CH$_3$)CH), 19.4 ((CH$_3$)(*C*H$_3$)CH), 22.7 (*C*H$_3$CHOH), 28.4 ((*C*H$_3$)$_3$C), 32.2 ((CH$_3$)$_2$*C*H), 43.1 (CH*C*H$_2$CH), 52.5 (CHNH), 63.7 (CHOH), 79.8 ((CH$_3$)$_3$*C*), 157.6 (C=O). HRMS (EI, 70 eV): $C_9H_{18}NO_3$ ([M−˙C$_3$H$_7$]$^+$); calcd=188.1287, found=188.1313.

Synthesis of the *syn* and *anti* 2-methyl-3-(*N*-tertiobutyloxycarbonyl)-aminononan-5-ol (2bb) *(Procedure B):* Starting from 762 mg (4.0 mmol) of copper iodide, 4.6 mL (7.8 mmol) of butyllithium solution (1.7 M in hexane) and 215 mg (1.0 mmol) of aldehyde **1b**, 123 mg (0.45 mmol, 66%) of **2bb-*anti*** and 63 mg (0.23 mmol, 23%) of **2bb-*syn*** were obtained after flash chromatography of the crude oily residue.

(3*R*,5*R*)-2-Methyl-3-(*N*-Tertiobutyloxycarbonyl)-aminononan-5-ol (2bb-*syn*). Colourless oil: R_f=0.40. IR (CH_2Cl_2): 1709 (C=O), 3440 (NH, O–$H_{associated}$), 3610 (O–H_{free}). ^{1}H NMR ($CDCl_3$) δ: 0.87 (d, 3 H, *J*=6.6 Hz, (CH_3)(CH$_3$)CH), 0.90 (t, 3 H, *J*=7.0 Hz, CH_3CH$_2$), 0.91 (d, 3 H, *J*=6.7 Hz, (CH$_3$)(CH_3)CH), 1.28–1.52 (m, 7 H, CHC*H*HCH, CH$_3$CH_2CH_2CH_2), 1.44 (s, 9 H, (CH_3)$_3$C),), 1.64 (dt-like, 1 H, *J*=14.0, 4.1 Hz, CHCH*H*CH), 1.78 (dhept, 1 H, *J*=6.6, 5.0 Hz, (CH$_3$)$_2$C*H*), 2.76 (br s, 1 H, OH), 3.49–3.58 (m, 1 H, C*H*NH), 3.63–75 (m, 1 H, C*H*OH), 4.55 (d, 1 H, *J*=9.8 Hz, NH). ^{13}C NMR ($CDCl_3$) δ: (14.1 (*C*H$_3$CH$_2$), 17.5 ((*C*H$_3$)(CH$_3$)CH), 18.8 ((CH$_3$)(*C*H$_3$)CH), 22.7 (CH$_3$*C*H$_2$), 27.8 (CH$_3$CH$_2$*C*H$_2$), 28.4 ((*C*H$_3$)$_3$C), 32.5 ((CH$_3$)$_2$*C*H), 37.2 (C$_3$H$_7$*C*H$_2$), 40.5 (CH*C*H$_2$CH), 54.1 (CHNH), 70.8 (CHOH), 79.4 ((CH$_3$)$_3$*C*), 156.4 (C=O). HRMS (EI, 70 eV): $C_{12}H_{24}NO_3$ ([M−˙C$_3$H$_7$]$^+$); calcd=230.1756, found=230.1777.

(3*R*,5*S*)-2-Methyl-3-(*N*-tertiobutyloxycarbonyl)-aminononan-5-ol (2bb-*anti*). Colourless solid: mp=62°C. R_f=0.58. $[\alpha]_D^{25}$=−9.2 (*c*=0.8, $CHCl_3$) IR (CH_2Cl_2): 1687 (C=O), 3439 (NH, O–$H_{associated}$), 3608 (O–H_{free}). ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, *J*=7.3 Hz, CH_3CH$_2$), 0.92 (d, 3 H, *J*=6.2 Hz, (CH_3)(CH$_3$)CH), 0.94 (d, 3 H, *J*=6.2 Hz, (CH$_3$)(CH_3)CH), 1.24–1.54 (m, 8 H, all CH_2), 1.45 (s, 9 H, (CH_3)$_3$C), 1.69 (dhept, 1 H, *J*=6.2, 5.6 Hz, (CH$_3$)$_2$C*H*), 3.50–3.59 (m, 1 H, C*H*OH), 3.65 (dddd, 1 H, *J*=12.0, 9.8, 5.6, 2.9 Hz, C*H*NH), 3.86 (s, 1 H, OH), 4.43 (d, 1 H, *J*=9.8 Hz, NH). ^{13}C NMR ($CDCl_3$) δ: (14.1 (*C*H$_3$CH$_2$), 18.3 ((*C*H$_3$)(CH$_3$)CH), 19.4 ((CH$_3$)(*C*H$_3$)CH), 22.7 (CH$_3$*C*H$_2$), 28.3 (CH$_3$CH$_2$*C*H$_2$), 28.4 ((*C*H$_3$)$_3$C), 32.3 ((CH$_3$)$_2$*C*H), 36.7 (C$_3$H$_7$*C*H$_2$), 41.4 (CH*C*H$_2$CH), 52.4 (CHNH), 67.6 (CHOH), 79.8 ((CH$_3$)$_3$*C*), 157.6 (C=O). HRMS (EI, 70 eV): $C_{12}H_{24}NO_3$ ([M−˙C$_3$H$_7$]$^+$); calcd=230.1756, found=230.1754.

Synthesis of the *syn* and *anti* 5-(*N*-tertiobutyloxycarbonyl)-aminohept-1-en-3-ol (2ac) *(Procedure A):* Starting from 1.51 g (7.50 mmol) of **1a** and 27.5 mL (26.1 mmol,

3.3 equiv.) of vinyl magnesium bromide solution (0.95 M in THF), 558 mg (2.43 mmol, 33%) of **2ac-*anti*** and 532 mg (2.32 mmol, 30%) of **2ac-*syn*** were obtained after flash chromatography of the crude oily residue.

(3*R*,5*R*)-5-(*N*-Tertiobutyloxycarbonyl)-aminohept-1-en-3-ol (2ac-*syn*). Colourless oil. R_f=0.34. $[\alpha]_D^{25}$=+8.6 (c=0.9, $CHCl_3$). IR (CH_2Cl_2): 1710 (C=O), 3435 (NH, O–$H_{associated}$), 3602 (O–H_{free}). ^{1}H NMR ($CDCl_3$): 0.92 (t, 3 H, J=7.4 Hz, CH_3CH$_2$), 1.44 (s, 9 H, (CH_3)$_3$C), 1.17–1.74 (m, 4 H, all CH_2), 2.97 (br s, 1 H, OH), 3.37–3.73 (m, 1 H, C*H*NH), 4.22 (dt-like, 1 H, J=6.2 Hz, C*H*OH), 4.57 (d, 1 H, J=8.0 Hz, NH), 5.10 (d, 1 H, J=10.3 Hz, CH=CH*H*), 5.25 (dt-like, 1 H, J=16.5, 1.3 Hz, CH=CH*H*), 5.89 (ddd, 1 H, J=17.0, 10.6, 5.7 Hz, C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$) δ: (10.1 (*C*H$_3$CH$_2$), 28.4 ((*C*H$_3$)$_3$C), 28.8 (CH$_3$*C*H$_2$), 42.6 (CH*C*H$_2$CH), 49.8 (CHNH), 71.0 CHOH), 79.3 ((CH$_3$)$_3$*C*), 114.5 (CH=*C*H$_2$), 140.9 (*C*H=CH$_2$), 156.1 (C=O). Elemental analysis: $C_{12}H_{23}NO_3$ (229.32): calcd C 62.85 H 10.10; found C 62.32 H 10.13.

(3*S*,5*R*)-5-(*N*-Tertiobutyloxycarbonyl)-aminohept-1-en-3-ol (2ac-*anti*). Colourless solid: mp=69°C. R_f=0.50, $[\alpha]_D^{25}$=+23.2 (c=0.8, $CHCl_3$). IR (CH_2Cl_2): 1688 (C=O), 3433 (NH, O–$H_{associated}$), 3602 (O–H_{free}). ^{1}H NMR ($CDCl_3$) δ: 0.96 (t, 3 H, J=7.4 Hz, CH_3CH$_2$), 1.45 (s, 9 H, (CH_3)$_3$C), 1.26–1.77 (m, 4 H, all CH_2), 3.61–3.81 (m, 1 H, C*H*NH), 4.09–4.21 (m, 1 H, C*H*OH), 4.11 (s, 1 H, OH), 4.84 (d, 1 H, J=8.8 Hz, NH), 5.09 (dt-like, 1 H, J=10.4, 1.6 Hz, CH=CH*H*), 5.27 (dt-like, 1 H, J=17.2, 1.6 Hz, CH=CH*H*), 5.89 (ddd, 1 H, J=17.2, 10.4, 5.3 Hz, CHC*H*=CH$_2$). ^{13}C NMR ($CDCl_3$) δ: (10.7 (*C*H$_3$CH$_2$), 28.4 ((*C*H$_3$)$_3$C), 28.5 (CH$_3$*C*H$_2$), 43.8 (CH*C*H$_2$CH),), 49.1 (CHNH), 68.6 (CHOH), 79.8 ((CH$_3$)$_3$*C*), 113.7 (CH=*C*H$_2$), 140.4 (*C*H=CH$_2$), 157.3 (C=O). Elemental analysis: $C_{12}H_{23}NO_3$ (229.32): calcd C 62.85 H 10.11; found C 62.62 H 9.93.

Synthesis of the *syn* and *anti* 5-phenyl-5-(*N*-tertiobutyloxycarbonyl)-aminopent-1-en-3-ol (2cc) *(Procedure A):* Starting from 1.07 g (4.29 mmol) of **1c** and 15.8 mL (15.0 mmol, 3.5 equiv.) of vinyl magnesium bromide solution (0.95 M in THF), 404 mg (1.46 mmol, 34%) of **2cc-*anti*** and 321 mg (1.16 mmol, 27%) of **2cc-*syn*** were obtained after flash chromatography of the crude oily residue.

(3*R*,5*S*)-5-Phenyl-5-(*N*-tertiobutyloxycarbonyl)-aminopent-1-en-3-ol (2cc-*syn*). Colourless oil: R_f=0.19. IR (CH_2Cl_2): 1712 (C=O), 3440 (NH, O–$H_{associated}$), 3609 (O–H_{free}). ^{1}H NMR ($CDCl_3$) δ: 1.33 (s, 9 H, (CH_3)$_3$C), 1.87–2.09 (m, 3 H, CH_2, OH), 4.11 (q-like, 1 H, J=5.9 Hz, C*H*OH), 4.71–4.89 (m, 1 H, C*H*NH), 5.05–5.11 (m, 1 H, NH), 5.04 (dt-like, 1 H, J=10.3, 1.4 Hz, CH=CH*H*), 5.16 (dt-like, 1 H, J=17.2, 1.3 Hz, =CH*H*), 5.88 (ddd, 1 H, J=17.2, 10.4, 5.8 Hz, CHC*H*=CH$_2$), 7.19–7.31 (m, 5 H, H arom.). ^{13}C NMR ($CDCl_3$) δ: (28.3 ((*C*H$_3$)$_3$C), 44.0 (CH_2), 52.9 (CHNH), 70.8 (CHOH), 79.7 ((CH$_3$)$_3$*C*), 114.8 (CH=*C*H$_2$), 126.4 127.4 128.7 ($C_{arom.}$), 140.7 (*C*H=CH$_2$), 142.6 ($C_{arom.,\ quat.}$), 155.4 (C=O). HRMS (EI, 70 eV): $C_{12}H_{15}NO_3$ ([M−CH$_2$=C(CH$_3$)$_2$]$^+$); calcd=221.1051, found=221.1045.

(3*S*,5*S*)-5-Phenyl-5-(*N*-tertiobutyloxycarbonyl)-aminopent-1-en-3-ol (2cc-*anti*). Colourless solid: mp≤40°C. R_f=0.31. IR (CH_2Cl_2): 1712 (C=O), 3436 (NH, O–$H_{associated}$), 3601 (O–H_{free}). ^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 9 H, (CH_3)$_3$C), 1.82 (dd, 2 H, J=6.9, 6.6 Hz, CHCH_2CH), 3.62 (br s, 1 H, OH), 4.13 (dt-like, 1 H, J=6.3 Hz, CHOH), 4,88 (q-like, 1 H, J=7.5 Hz, C*H*NH), 5.04 (dt-like, 1 H, J=10.3, 1.4 Hz, CHCH=CH*H*), 5.10 (broad s, 1 H, NH), 5.20 (d, 1 H, J=17.4 Hz, CH=CH*H*), 5.84 (ddd, 1 H, J=17.0, 10.6, 5.7 Hz, CHC*H*=CH$_2$), 7.16–7.33 (m, 5 H, H arom.). ^{13}C NMR ($CDCl_3$) δ: (29.7 ((*C*H$_3$)$_3$C), 44.3 (*C*H$_2$), 51.7 (CHNH), 68.9 (CHOH), 80.1 ((CH$_3$)$_3$*C*), 114.4 (CH=*C*H$_2$), 126.4, 127.5, 128.8 ($C_{arom.}$), 140.1 (*C*H=CH$_2$), 141.8 ($C_{arom.,\ quat.}$), 156.5 (C=O). HRMS (EI, 70 eV): $C_{16}H_{23}NO_3$ ($M^{+\cdot}$); calcd=277.1678, found=277.1686.

Synthesis of the *syn* and *anti* 2-methyl-3-(*N*-tertiobutyloxycarbonyl)-aminooct-7-en-5-ol (2bd) *(Procedure A):* Starting from 215 mg (1.00 mmol) of **1b** and 12 mL (4.0 mmol, 4.0 equiv.) of allyl magnesium bromide solution (0.34 M in THF), 77 mg (0.30 mmol, 30%) of **2bd-*anti*** and 83 mg (0.32 mmol, 32%) of **2bd-*syn*** were obtained after flash chromatography of the crude oily residue.

(3*R*,5*R*)-2-Methyl-3-(*N*-tertiobutyloxycarbonyl)-aminooct-7-en-5-ol (2bd-*syn*). Colourless oil: R_f=0.62 (ethyl acetate/Heptane=1/1). $[\alpha]_D^{25}$=−8.6 (c=0.4, $CHCl_3$). IR (CH_2Cl_2): 1709 (C=O), 3440 (NH, O–$H_{associated}$), 3596 (O–H_{free}). ^{1}H NMR ($CDCl_3$): 0.87 (d, 3 H, J=7.0 Hz, (CH_3)(CH$_3$)CH), 0.91 (d, 3 H, J=6.7 Hz, (CH$_3$)(CH_3)CH), 1.47 (ddd, 1 H, J=14.0, 9.4, 7.0 Hz, NHCHC*H*HCH), 1.65 (dt-like, 1 H, J=14.0, 4.6 Hz, NHCHCH*H*CH), 1.44 (s, 9 H, (CH_3)$_3$C),), 1.77 (oct-like, 1 H, J=6.9 Hz, (CH$_3$)$_2$C*H*CH), 2.19 (dt-like, 1 H, J=13.8, 7.3 Hz, C*H*HCH=CH$_2$), 2.35 (dt-like, 1 H, J=13.8, 6.8 Hz, CH*H*CH=CH$_2$), 2.79 (br s, 1 H, OH), 3.49–3.56 (m, 1 H, C*H*NH), 3.71–3.79 (m, 1 H, C*H*OH), 4.60 (d, 1 H, J=8.9 Hz, NH), 5.12 (d, 1 H, J=11.1 Hz, CH=CH*H*), 5.13 (d, 1 H, J=16.1 Hz, CH=CH*H*), 5.75–5.89 (m, 1 H, C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$) δ: (17.6 ((*C*H$_3$)(CH$_3$)CH),), 18.8 ((CH$_3$)(*C*H$_3$)CH), 28.4 ((*C*H$_3$)$_3$C), 32.5 ((CH$_3$)$_2$*C*H), 39.6 (*C*H$_2$CH=CH$_2$), 41.8 (NHCH*C*H$_2$CH), 53.7 (CHNH), 69.5 (CHOH), 79.4 ((CH$_3$)$_3$*C*), 117.9 (CH=*C*H$_2$), 134.8 (*C*H=CH$_2$), 156.3 (C=O). HRMS (EI, 70 eV): $C_{11}H_{20}NO_3$ ([M−$\dot{C}_3H_7$]$^+$); calcd=214.1443, found=214.1452.

(3*R*,5*S*)-2-Methyl-3-(*N*-tertiobutyloxycarbonyl)-aminooct-7-en-5-ol (2bd-*anti*). Colourless solid: mp=59°C (pentane). R_f=0.75 (ethyl acetate/Heptane=1/1). $[\alpha]_D^{25}$=−13.3 (c=0.7, $CHCl_3$). IR (CH_2Cl_2): 1687 (C=O), 3439 (NH, O–$H_{associated}$), 3600 (O–H_{free}). ^{1}H NMR ($CDCl_3$): 0.92 (d, 3 H, J=6.7 Hz, (CH_3)(CH$_3$)CH), 0.94 (d, 3 H, J=6.2 Hz, (CH$_3$)(CH_3)CH), 1.30–1.56 (m, 2 H, NHCHCH_2CH), 1.45 (s, 9 H, (CH_3)$_3$C), 1.70 (oct-like, 1 H, J=6.6 Hz, (CH$_3$)$_2$C*H*CH), 2.21 (dddt-like, 1 H, J=13.8, 7.0, 1.5, 1.2 Hz, CH$_2$=CHC*H*HCH), 2.30 (dt-like-t-like, 1 H, J=13.8, 7.0, 1.2 Hz, CH$_2$=CHCH*H*CH), 3.60–3.70 (m, 2 H, C*H*OH, C*H*NH), 3.77 (br s, 1 H, OH), 4.45 (d, 1 H, J=10.0 Hz, NH), 5.06 (ddt, 1 H, J=10.3, 2.0, 1.2 Hz, CH$_2$CH=CH*H*), 5.09 (ddt, 1 H, J=17.3, 2.0, 1.5 Hz, CH$_2$CH=CH*H*), 5.87 (ddt, 1 H, J=17.2, 10.2, 7.0 Hz, CH$_2$C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$) δ: (18.2 ((*C*H$_3$)(CH$_3$)CH), 19.4 ((CH$_3$)(*C*H$_3$)CH), 28.4 ((*C*H$_3$)$_3$C),

32.3 ($(CH_3)_2CH$), 40.7 ($CH_2CH{=}CH_2$), 41.5 ($NHCHCH_2CH$), 52.4 (CHNH), 67.2 (CHOH), 79.8 ($(CH_3)_3C$), 116.8 ($CH{=}CH_2$), 135.5 ($CH{=}CH_2$), 157.5 (C=O). HRMS (EI, 70 eV): $C_{11}H_{20}NO_3$ ($[M-{}^{\cdot}C_3H_7]^+$); calcd=214.1443, found=214.1438.

References

1. (a) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465–6466. (b) Hashiguchi, S.; Kawada, A.; Natsugari, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2435–2444. (c) Knapp, S.; *Chem. Rev.* **1995**, *95* (6), 1859–1876. (d) Shibahara, S.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1972**, *94* (12), 4353–4354.

2. Kozikowski, A. P.; Chen, Y.-Y. *J. Org. Chem.* **1981**, *46*, 5248–5250.

3. (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Naturel Products Synthesis Through Pericyclic Reactions*; ACS monograph, 1983. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines and Synthetic Applications*; VCH, 1995.

4. (a) Kosikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265–4267. (b) Jaeger, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3133–3136. (c) Jaeger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601–603. (d) Jaeger, V.; Grund, H.; Buss, V.; Schwab, W.; Mueller, I. *Bull. Soc. Chim. Belg.* **1983**, *92* (11/12), 1039–1054.

5. Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814–815.

6. (a) Hioki, H.; Okuda, M.; Miyagi, W.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 6131–6134. (b) Hioki, H.; Isawa, T.; Yoshizuka, M.; Kunitake, R.; Itô, S. *Tetrahedron Lett.* **1995**, *36*, 2289–2292.

7. (a) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1984**, 147–150. (b) Narasaka, K.; Yamazaki, U.; Ukaji, Y. *Chem. Lett.* **1984**, 2065–2068.

8. (a) Mukaiyama, T. *Organic Reactions*; Wiley: New York, 1982; Vol. 28, Chapter 3. (b) Wanner, K. T.; Höfner, G. *Tetrahedron* **1991**, *47* (10), 1895–1910. (c) Tramontini, M. *Synthesis* **1982**, 605–644. (d) Brienne, M.-J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1969**, *106*, 2395–2407.

9. (a) Maroni, P.; Cazaux, L.; Tisnes, P.; Zambeti, M. *Bull. Soc. Chim. Fr.* **1980**, *117*, 179–186. (b) Matsumura, Y.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 6312–6314.

10. Tirel, P.-J.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30* (15), 1947–1950.

11. Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Itô, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797–1798.

12. Evans, P. A.; Holmes, A. B.; MacGeary, R. P.; Russel, K.; O'Hanlon, P. J.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 123–138.

13. (a) Rodriguez, M.; Aumelas, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 5153–5156. (b) Rodriguez, M.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 7319–7322. (c) Greenlee, W. J.; Alliborn, P. L.; Perlow, D. S.; Paqtchet, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem.* **1985**, *28*, 434–442. (d) Johnson, R. L.; Verschoor, K. *J. Med. Chem.* **1983**, *26*, 1457–1462. (e) McIntosh, J. O.; Acquaah, S. O. *Can. J. Chem.* **1988**, *66*, 1752–1756.

14. Toujas, J.-L.; Jost, E.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 713–718.

15. Brienne, M.-J.; Ouannès, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, *105*, 1036–1047.

16. (a) Devant, R. M.; Radung, H.-E. In *Stereoselective Synthesis* (Houben-Weyl), Georg Thieme: Stuttgart, 1996; Vol. 2, Part D.1.3. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.

17. Stil, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035–1038.

18. Reetz, M. T.; Röefling, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35* (13), 1969–1972.

19. (a) Hamon, L.; Levisalles, J. *Tetrahedron* **1989**, *45*, 489–494. (b) Hamon, L.; Levisalles, J. *J. Organomet. Chem.* **1983**, *253*, 259–272.

20. House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460–1469.

21. Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370–4382.

22. (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1993**, *53* (10), 2390–2392. (b) Knochel, P.; Xiao, C.; Yeh, M. C. P. *Tetrahedron Lett.* **1988**, *29* (51), 6697–6700.