Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3759–3768

TETRAHEDRON: *ASYMMETRY*

A new approach to non racemic saturated and unsaturated 5-aminoalkyl methyl ketones

Gianna Reginato,* Alessandro Mordini, Marinella Verrucci, Alessandro Degl'Innocenti and Antonella Capperucci

Centro CNR Composti Eterociclici, Dipartimento di Chimica Organica 'U. Schiff', via G. Capponi 9, I-50121 Florence, Italy

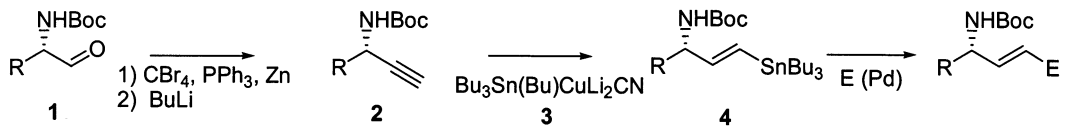
Received 28 July 2000; accepted 23 August 2000

Abstract

Non racemic *t*-Boc protected aminoalkyl ketones have been obtained starting from γ-stannylated (*E*)-allylamines through a high yielding two step procedure consisting of a Stille coupling and a subsequent Wacker oxidation. These compounds are useful intermediates for obtaining 2,6-disubstituted piperidines.

1. Introduction

The construction of versatile non racemic building blocks provides us with powerful tools for efficient syntheses of biological compounds. We have already shown in previous works our efforts in this area[1–5] and in particular we have recently reported a procedure for preparing non racemic stannylated allylamines **4**,[6] which were obtained with high enantiomeric purity starting from amino aldehydes **1**, easily derived from naturally occurring amino acids (Scheme 1).

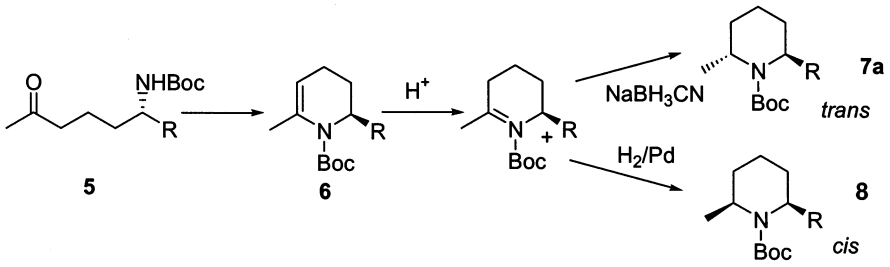


Scheme 1.

* Corresponding author. Tel: +39 55 2757609; fax: +39 55 2476964; e-mail: reginato@cesce.fi.cnr.it

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00335-9

These compounds have proved to be useful three-carbon homologating reagents, the vinyl-tin moiety being able to react with electrophiles via palladium-catalyzed coupling (Scheme 2)[7,8] and have been employed for obtaining enantiomerically enriched allylamines[6] or aminoalcohols.[3]

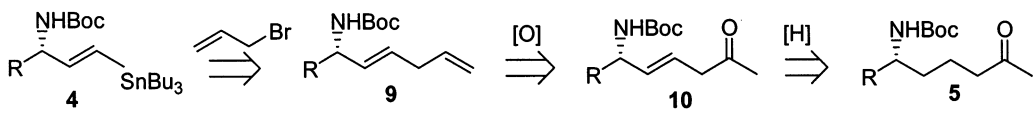


Scheme 2.

In consideration of these premises we envisaged that non racemic vinylstannanes **4** could be also exploited for developing a general method for the preparation of enantiomerically enriched aminoketones of type **5**. These are a very interesting class of compounds, being, for instance, useful precursors of the corresponding tetrahydropyridines **6**, which have been shown[9] to be an efficient entry to piperidines **7** or **8**.

The piperidine ring is a common structural feature of many synthetic pharmaceuticals. Alkaloids containing 2,6-disubstituted piperidines are abundant in nature and many of them, having a methyl substituent in the 6 position, exhibit significant biological activity.[10,11] They have been found for example in the skin secretion of tropical frogs of the family of *Dendrobatidae*[12] and in some species of pines[13] and fire ants.[14] For this reason this kind of compound has been the object of intensive synthetic efforts, resulting in a variety of racemic and asymmetric synthesis.[15–17] In many instances aminoalkyl ketones **5** have been employed as key intermediates for the synthesis of some of these naturally occurring compounds[18–20,21,22] such as solenopsin A[23] or some indolizidine alkaloids.[24,25]

Despite these features no general methods to prepare this class of compounds has been reported, therefore we reasoned that easily achievable allylation of **4** and subsequent oxidation would provide a simple and mild method for obtaining a new family of enantiomerically enriched unsaturated amino ketones **10**, in which the R lateral chain and the absolute configuration of the C_2 stereocenter are derived from the starting amino acid. Reduction of compounds **10** would give the target compounds **5** (Scheme 3).



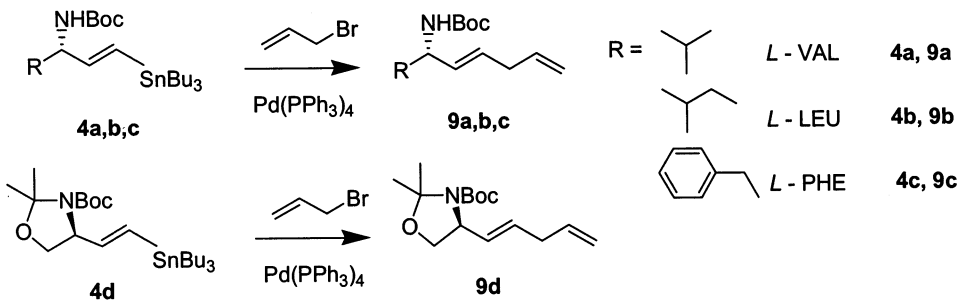
Scheme 3.

Herein we wish to report our results on the stereoselective synthesis of a new range of non racemic unsaturated (**10**) and saturated (**5**) 5-aminoalkyl methyl ketones. Both the enantiomeric forms could be selectively obtained, as they are derived from easily available D- or L-amino acids.

2. Results and discussions

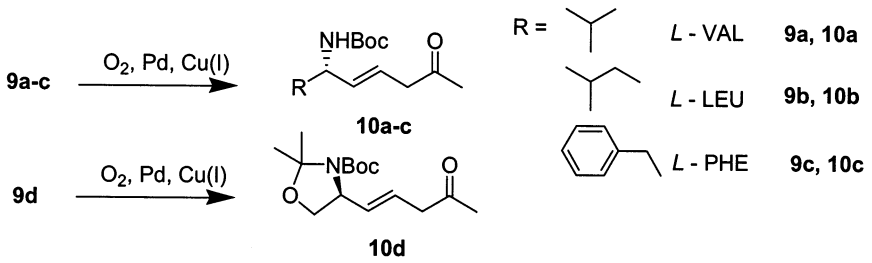
The transformation of naturally occurring amino acids to the corresponding aldehydes is a very well known procedure, and these compounds are useful intermediates in organic synthesis.[26,27] In particular they have been efficiently used for preparing the corresponding propargylamines[28,6] **2a**,**b**,**c** or the corresponding oxazolidine derivative **2d**.[29,3] In addition, stannylallyl derivatives **4** have been efficiently prepared using alkynes **2** through the addition of a mixed stannylcuprate **3**.

Following this protocol,[6] non racemic stannylated amines **4a**,**b**,**c** and oxazolidine **4d** were prepared starting from the corresponding L-amino acids and from D-serine, respectively. According to the well known Stille procedure,[30] compounds **4** were reacted with an excess of allyl bromide in the presence of $Pd(PPh_3)(CH_2Ph)Cl_2$ complex as catalyst and the corresponding coupled compounds **9a–d** were obtained in good yields after washing of the reaction mixture with aqueous NaOH solution and filtration through silica gel[31] (Scheme 4). As expected, in all the cases we examined, the reaction proceeded with retention of configuration with respect to the vinyl–tin bond, as it was confirmed by ^1H NMR analysis. Therefore, as Stille coupling conditions have already been proved[6,32] not to alter the enantiomeric excesses in non racemic compounds, we could conclude that this can be an efficient and mild method for obtaining non racemic dienamines **9a–d** with a predictable (*E*)-geometry.



Scheme 4.

The next step was the oxidation of the terminal double bond to the corresponding carbonyl compounds. This transformation can be easily achieved using $PdCl_2$ in the presence of a cooxidant, and O_2 and we decided to attempt the $PdCl_2$/CuCl system under oxygen atmosphere, using DMF as solvent (Scheme 5).[33]



Scheme 5.

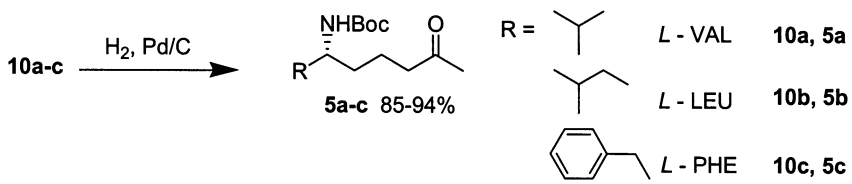
The reaction proceeded smoothly and unsaturated amino ketones **10a–d** were obtained in high yields and purified by flash chromatography. Experimental details are shown in Table 1.

Table 1
Yields and $[\alpha]_D$ values determined for compounds **9a–d** and **10a–d**

Starting materials	**9**[a]	Exp. details	$[\alpha]_D$	**10**[a]	$[\alpha]_D$
4a	**9a** 60% (>95%)	72 h 45°C $CHCl_3$	$[\alpha]_D^{21} = -4.4$ $c = 1.16$, $CHCl_3$	**10a** 60% (>95%)	$[\alpha]_D^{21} = -20.2$ $c = 1.06$, $CHCl_3$
4b	**9b** 77% (>95%)	72 h 45°C $CHCl_3$	$[\alpha]_D^{21} = -11.4$ $c = 1.26$, $CHCl_3$	**10b** 57% (>95%)	$[\alpha]_D^{20} = -13.6$ $c = 1.16$, $CHCl_3$
4c	**9c** 74% (>95%)	48 h 45°C $CHCl_3$	$[\alpha]_D^{24} = +3.9$ $c = 1.04$, $CHCl_3$	**10c** 49% (>95%)[c]	$[\alpha]_D^{22} = +6.2$ $c = 0.90$, $CHCl_3$
4d	**9d** 84% (>95%)	72 h 45°C $CHCl_3$	+9.0 $c = 1.53$, $CHCl_3$	**10d** 82% (>95%)	+25.3 $c = 1.12$, $CHCl_3$

[a] Yield of isolated compounds. Conversions (calculated on the crude by ^1H NMR analysis) are reported in parenthesis.

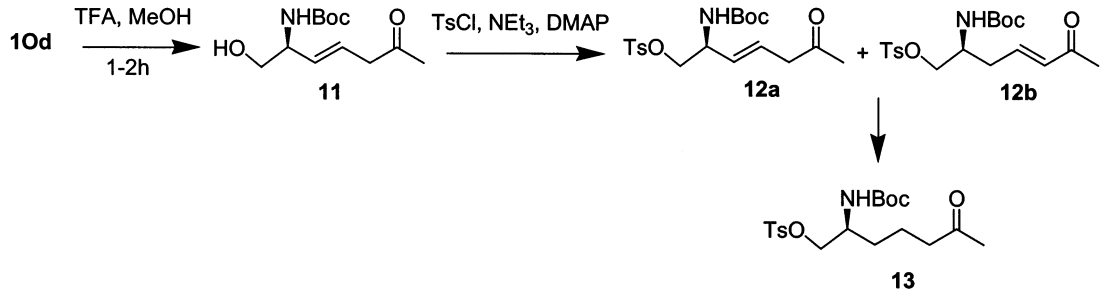
This is a new family of non racemic compounds with interesting features. The presence of the double bond should allow further functionalizations of positions 2 and 3 of the molecular backbone, which are currently under investigation. Remarkably, double bond migration to the corresponding α,β-unsaturated ketones has never been observed under our reaction conditions. Finally, pure compounds **10a–c** were hydrogenated with Pd catalysis to quantitatively obtain the target compounds **5a–c** (Scheme 6).



Scheme 6.

Unfortunately, hydrogenation of compound **10d** was found to be more difficult, as an inseparable mixture of at least three different compounds was recovered after treatment with H_2 under Pd/C catalysis. Such behavior has been observed previously in similar compounds,[34] and to circumvent this problem we decided to hydrolyze the acetonide and protect the hydroxyl group as its tosylate derivative, prior to performing the reduction. TFA/MeOH reagent was used for the oxazolidine ring opening. As we have already observed in the case of other substrates,[5] *t*-Boc protecting group was not removed in these conditions. Crude **11** was then reacted with PTSA-Cl and Et_3N/imidazole in order to obtain the corresponding tosylate **12a**, a useful precursor for introducing different lateral chains by nucleophilic substitution. In this case the result was also not straightforward, as a variable amount of the conjugated isomer **12b** was recovered in the reaction mixture. Purification by chromatography did not allow recovery of pure **12a.** Although

hydrogenation of the mixture under usual conditions afforded the reduced compound **13**, it was not isolated leading to a rapid decomposition. We concluded therefore, that introduction of different lateral chains on the backbone of 5-aminoalkyl methyl ketones must be performed at an earlier stage of the reaction sequence (Scheme 7).



Scheme 7.

Amino alcohol **11** has also been transformed to prove that the enantiomeric purity of the starting material was maintained through the whole reaction sequence. Diastereomeric Mosher esters were prepared by reaction with both (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPACl). ^{1}H NMR analysis of the two diastereomers were found to be clearly distinguishable and showed no contamination from racemized material.

3. Experimental

3.1. General methods and materials

All reactions were carried out under a positive pressure of dry nitrogen. Ether extracts were dried with Na_2SO_4. Reactions were monitored by TLC on SiO_2; detection was carried out using a $KMnO_4$ basic solution. Flash column chromatography[35] was performed using glass columns (10–50 mm wide) and SiO_2 230–400 mesh. ^{1}H NMR spectra of hydrogen nuclei were recorded at 200 or 300 MHz. ^{13}C NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$ δ 7.26 for ^{1}H NMR; $CHCl_3$ δ 77.0 for ^{13}C NMR). Coupling constants (J) are reported in hertz (Hz). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet) and bs (broad singlet). Mass spectra were obtained at a 70 eV ionization potential and are reported in the form m/z (intensity relative to base = 100). Polarimetric measurements were performed in $CHCl_3$ solution at $\lambda = 589$ nm, and the temperature is specified case by case.

Stannylated amines **4a–c** and oxazolidine **4d** were prepared according to the literature.[6] THF was dried by distillation over sodium benzophenone ketyl. CH_2Cl_2 was purified by the standard procedure, dried over $CaCl_2$ and stored over 4 Å molecular sieves. DMF was distilled over calcium hydride and stored over 4 Å molecular sieves. Petroleum ether, unless specified, is the 40–70°C boiling fraction.

3.2. Coupling with allylbromide. General procedure

Stannylamines **4** were dissolved in $CHCl_3$ together with allylbromide (2 equiv.) and $Pd(CH_2Ph)(PPh_3)Cl_2$ (10%). The reaction was stirred for 24 h or more depending on the

substrate, then more allylbromide (1–1.5 equiv.) was added and allowed to react for a further 24 h. After completion the solvent was evaporated, the residue was diluted with ether, treated with a 1 M NaOH solution and stirred for 1 h. After extraction with ether the organic phase was washed with brine and dried. Evaporation afforded a crude mixture that, after filtration on SiO_2, yielded pure compounds **9**.

3.2.1. N-*[(2*E*),(1*S*)-1-(Methylethyl)hexa-2,5-dienyl](tert-butoxy)carboxamide* ***9a***

Amine **4a** (1200 mg, 2.5 mmol) was reacted according to the general procedure. After purification (eluent: petroleum ether/ethyl acetate = 8/1) 360 mg of **9a** (60%) were obtained: ^{1}H NMR (200 MHz) δ: 5.81 [ddt, 1H, *J*app = 17.2, 10.2 Hz, 7.0 Hz]; 5.57 [m, 1H, ABX_2, J_{AB} = 15.4, J_{Ax} = 7.7 Hz]; 5.34 [m, 1H, ABY, J_{AB} = 15.4, J_{BY} = 6.2 Hz]; 5.09–4.97 [m, 2H]; 4.46 [bs, 1H]; 3.91 [m, 1H]; 2.77 [m, 1H]; 1.82–1.63 [m, 1H]; 1.43 [s, 9H]; 0.88 [d, 3H, *J* = 7.0 Hz]; 0.87 [d, 3H, *J* = 7.0 Hz]. ^{13}C NMR (50.3 MHz) δ: 155.58; 136.73; 130.22; 129.12; 115.32; 79.13; 57.52; 36.33; 32.50; 28.39; 18.59; 18.19. MS *m*/*e*: 196 (4); 57 (100). $[\alpha]_D^{23}$ = −4.4 (*c* = 1.16, $CHCl_3$). Anal. calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.46; H, 10.62; N, 5.88.

3.2.2. N-*[(2*E*),(1*S*)-1-(3-Methylpropyl)hexa-2,5-dienyl](tert-butoxy)carboxamide* ***9b***

Amine **4b** (905 mg, 1.8 mmol) was reacted according to the general procedure. After purification (eluent: petroleum ether/ethyl acetate = 10/1) 345 mg of **9b** (77%) were obtained: ^{1}H NMR (200 MHz) δ: 5.80 [ddt, 1H, *J* = 16.9 Hz, 10.3 Hz, 6.4 Hz]; 5.59 [m, 1H, ABX_2, J_{AB} = 15.4, J_{BX} = 6.4 Hz]; 5.33 [m, 1H, ABY, J_{AB} = 15.4, J_{AY} = 6.2 Hz]; 5.07–4.97 [m, 2H]; 4.33 [bs, 1H]; 4.09 [m, 1H]; 2.75 [m, 2H]; 1.74–1.50 [m, 1H]; 1.43 [s, 9H]; 1.35–1.25 [m, 2H]; 0.91 [d, 3H, *J* = 6.6 Hz]; 0.89 [d, 3H, 6.6 Hz]. ^{13}C NMR (50.3 MHz) δ: 155.20; 136.59; 132.37; 128.11; 115.27; 79.11; 50.69; 44.97; 36.29; 28.48; 24.78; 22.63. MS *m*/*e*: 196 (6); 57 (100). $[\alpha]_D^{23}$ = −11.4 (*c* = 1.26, $CHCl_3$). Anal. calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53; Found: C, 71.12; H, 10.72; N, 5.58.

3.2.3. N-*[(2*E*),(1*S*)-1-Benzylhexa-2,5-dienyl](*tert*-butoxy)carboxamide* ***9c***

Amine **4c** (410 mg, 0.75 mmol) was reacted according to the general procedure. After purification (eluent: petroleum ether/ethyl acetate = 10/1) 166 mg of **9c** (74%) were obtained: ^{1}H NMR (200 MHz) δ: 7.32–7.09 [m, 5H]; 5.75 [ddt, 1H, *J* = 18.3 Hz, 9.1 Hz, 6.4 Hz]; 5.52 [m, 1H, ABX_2, J_{AB} = 15.6, J_{BX} = 5.9 Hz]; 5.39 [m, 1H, ABY, J_{AB} = 15.6, J_{AY} = 5.2 Hz]; 5.05–4.90[m, 2H]; 4.54–4.24 [m, 1H+1H]; 2.86–2.76 [m, 2H]; 2.72 [m, 2H]; 1.39 [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 155.07; 137.60; 136.36; 130.95; 129.58; 128.78; 128.20; 126.32; 115.38; 79.33; 53.24; 41.97; 36.27; 28.42. MS *m*/*e*: 196 (4); 91 (27); 57 (100). $[\alpha]_D^{20}$ = +3.9 (*c* = 1.04, $CHCl_3$). Anal. calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.43; H, 8.72; N, 4.88.

3.2.4. tert-*Butyl 4-[(1*E*)-penta-1,4-dienyl](4*S*)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate* ***9d***

Oxazolidine **4d** (3.6 g, 7.0 mmol) was reacted according to the general procedure. After purification (eluent: petroleum ether/ethyl acetate = 10/1) 1.56 mg of **9d** (84%) were obtained: ^{1}H NMR (200 MHz) δ: 5.79 [ddt, 1H, *J* = 16.9 Hz, 10.3 Hz, 6.6 Hz]; 5.56 [m, 1H]; 5.43 [m, 1H, ABY, J_{AB} = 15.4 Hz, J_{AY} = 7.4 Hz]; 5.08–4.96 [m, 2H]; 4.38–4.14 [m, 1H]; 3.99 [dd, 1H, *J* = 8.8, 5.8 Hz]; 3.69 [dd, 1H, *J* = 8.8, 2.2 Hz]; 2.77 [m, 2H]; 1.57 [bs, 6H]; 1.48–1.42 [m, 9H]. ^{13}C NMR (50.3 MHz) δ: 151.97; 136.41; 130.16; 129.96; 115.50; 93.73; 79.53; 68.39; 59.05; 36.14; 28.39; 26.12; 23.22. MS *m*/*e*: 252 (2); 196 (29); 57 (100). $[\alpha]_D^{24}$ = +9.0 (*c* = 1.53, $CHCl_3$). Anal. calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.53; H, 9.36; N, 5.28.

3.3. Oxidation to methylketones. General procedure

CuCl (1 equiv.) and $PdCl_2$ (0.2 equiv.) were dissolved into a 10/1 DMF/H_2O solution and stirred under O_2 atmosphere at room temperature for 2 h. Dienamines **9** (1 equiv.) were then added and left to react overnight. After this time the mixture was diluted with ether and treated with an NH_4Cl saturated solution. The organic layer was washed with water (three times) and with brine and then dried. After evaporation of the solvent pure compounds **10** were obtained after column chromatography.

3.3.1. N-*[(2*E*)(1*S*)-1-(Methylethyl)-5-oxohex-2-enyl](*tert-*butoxy)carboxamide* ***10a***

Amine **9a** (308 mg, 1.29 mmol) was reacted according to the general procedure. After purification (eluent: petroleum ether/ethyl acetate = 2/1) 200 mg of **10a** (60%) were obtained: ^{1}H NMR (200 MHz) δ: 5.67 [m, 1H; ABMXX′, J_{AB} = 15.5 Hz, J_{BX} = 7.3 Hz, J_{BM} = 1.2 Hz]; 5.45 [m, 1H, ABM, J_{AB} = 15.5, J_{AM} = 5.9 Hz]; 4.51 [bs, 1H]; 4.01–3.84 [m, 1H]; 3.15 [d, 2H, J = 6.6 Hz]; 2.14 [s, 3H]; 1.71 [sest, 1H, J = 7.0 Hz]; 1.43 [s, 9H]; 0.88 [d, 3H, J = 7.0 Hz]; 0.87 [d, 3H, J = 7.0 Hz]. ^{13}C NMR (50.3 MHz) δ: 206.87; 155.54; 133.78; 123.12; 79.27; 57.32; 47.23; 32.37; 29.66; 28.37; 18.66; 18.14. MS m/e: 212 (2); 83 (29); 57 (100). $[\alpha]_D^{27} = -20.2$ (c = 1.06, $CHCl_3$). Anal. calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.79; H, 9.82; N, 5.44.

3.3.2. N-*[(2*E*)(1*S*)-1-(2-Methylpropyl)-5-oxohex-2-enyl](*tert-*butoxy)carboxamide* ***10b***

Amine **9b** (350 mg, 1.4 mmol) was reacted according to the general procedure. After purification (eluent: petroleum ether/ethyl acetate = 3/1) 215 mg of **10b** (57%) were obtained: ^{1}H NMR (200 MHz) δ: 5.70 [dt, 1H, Japp = 15.6, 7.6 Hz]; 5.45 [dd, 1H, Japp = 15.6, 6.0 Hz]; 4.36 [bs, 1H]; 4.12 [m, 1H]; 3.13 [d, 2H, Japp = 7.0 Hz]; 2.14 [s, 3H]; 1.76–1.51 [m, 1H]; 1.37–1.24 [m, 2H]; 1.43 [s, 9H]; 0.91 [d, 2H, Japp = 6.2 Hz]. ^{13}C NMR (50.3 MHz) δ: 206.85; 155.17; 135.80; 122.16; 79.25; 50.34; 47.15; 44.57; 29.39, 28.40; 24.73; 22.64; 22.42. MS m/e: 186 (2); 57 (100). $[\alpha]_D^{23} = -13.6$ (c = 1.16, $CHCl_3$). Anal. calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.75; H, 9.98; N, 4.98.

3.3.3. N-*[(2*E*)(1*S*)-5-Oxo-1-benzylhex-2-enyl](*tert-*butoxy)carboxamide* ***10c***

Amine **9c** (135 mg, 0.5 mmol) was reacted according to the general procedure. After purification (eluent: petroleum ether/ethyl acetate = 2/1) 70 mg of **10c** (49%) was obtained: ^{1}H NMR (200 MHz) δ: 7.35–7.10 [m, 5H]; 5.72–5.45 [m, 2H]; 4.48 [bs, 1H]; 4.38 [m, 1H]; 3.11 [d, 2H, J = 6.2 Hz]; 2.82 [m, 2H]; 2.07 [s, 3H]; 1.40 [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 206.46; 155.04; 137.32; 134.26; 129.47; 128.33; 126.47; 122.85; 79.51; 65.86; 47.14; 41.70; 29.75; 28.40. MS m/e: 212 (6); 156 (37); 57 (100). $[\alpha]_D^{22} = +6.2$ (c = 0.90, $CHCl_3$). Anal. calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.35; H, 8.18; N, 4.68.

3.3.4. tert-*Butyl 4-((1*E*)-4-oxopent-1-enyl)(4*S*)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate* ***10d***

Oxazolidine **9d** (1.30 g, 4.9 mmol) was reacted according to the general procedure. After workup 1.14 g of pure **10d** (82%) were obtained. 88 mg of the crude were purified (eluent: petroleum ether/ethyl acetate = 3/1) to afford 50 mg of analytically pure **10d**: ^{1}H NMR (200 MHz) δ: 5.69 [m, 1H]; 5.53 [m, 1H, J_{AB} = 15.2 Hz, J_{BX} = 7.0 Hz]; 4.28 [m, 1H]; 4.02 [dd, 1H, J = 9.0, 6.0 Hz]; 3.72 [dd, 1H, J = 9.0, 2.0 Hz]; 3.15 [d, 2H, J = 7.0 Hz]; 2.14 [s, 3H]; 1.58 [bs, 6H]; 1.48–1.43 [bs, 9H]. ^{13}C NMR (50.3 MHz) δ: 206.36; 151.85; 133.26; 124.16; 93.77; 79.80; 68.17; 58.88; 46.98; 29.48; 28.46; 26.59; 23.69. MS m/e: 268 (1); 168 (30); 57(100). $[\alpha]_D^{23} = +25.3$

($c=1.12$, $CHCl_3$). Anal. calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4,94. Found: C, 63.87; H, 8.82; N, 4.88.

3.4. Hydrogenation of unsaturated amino ketones

Compounds **10a–d** were dissolved in 95% ethanol, and hydrogenated (H_2, 1 atm) over a catalytic amount of Pd on carbon. The reaction was monitored by GC; after completion, the solution was filtered over Celite. Evaporation of the solvent afforded pure compounds **5a–d**.

3.4.1. N-*[(1*R*)-1-(Methylethyl)-5-oxohexyl](*tert-*butoxy)carboxamide* ***5a***

Compound **10a** (200 mg, 0.8 mmol) was reacted according to the general procedure. After workup 186 mg of pure **5a** (93%) were obtained: ^{1}H NMR (200 MHz) δ: 4.26 [bs, 1H]; 3.41 [m, 1H]; 2.50–2.40 [m, 2H]; 2.13 [s, 3H]; 1.76–1.15 [m, 1H+4H] 1.43 [s, 9H]; 0.88 [d, 3H, $J=6.8$ Hz]; 0.85 [d, 3H, $J=6.8$ Hz]. ^{13}C NMR (50.3 MHz) δ: 208.81; 155.94; 78.89; 55.05; 43.26; 32.11; 31.79; 29.71; 28.44; 20.37; 19.17; 17.62. MS m/e: 214 (2); 158 (68); 114 (100); 57(100). $[\alpha]_D^{21}=+9.6$ ($c=0.93$, $CHCl_3$).

3.4.2. N-*[(1*R*)-1-(2-Methylpropyl)-5-oxohexyl](*tert-*butoxy)carboxamide* ***5b***

Compound **10b** (215 mg, 0.8 mmol) was reacted according to the general procedure. After workup 185 mg of pure **5b** (85%) were obtained: ^{1}H NMR (200 MHz) δ: 4.36 [bs, 1H]; 3.60 [m, 1H]; 2.41 [m, 2H]; 2.12 [s, 3H]; 1.70–1.05 [m, 1H+2H+4H]; 1.42 [s, 9H]; 0.89 [d, 3H, $J=6.6$ Hz]; 0.88 [d, 3H, $J=6.6$ Hz]. ^{13}C NMR (50.3 MHz) δ: 208.71; 155.60; 78.89; 48.38; 44.97; 43.33; 35.49; 29.90; 28.44; 24.93; 23.16; 22.25; 19.96. MS m/e: 214 (5); 85 (86); 57 (100). $[\alpha]_D^{21}=-9.6$ ($c=0.96$, $CHCl_3$].

3.4.3. N-*[(1*R*)-5-Oxo-1-benzylhexyl](*tert-*butoxy)carboxamide* ***5c***

Compound **10c** (70 mg, 0.23 mmol) was reacted according to the general procedure. After workup 65 mg of pure **5c** (94%) was obtained: ^{1}H NMR (200 MHz) δ: 7.30–7.10 [m, 5H]; 4.41 [bd, 1H, $J=7.6$ Hz]; 3.80 [m, 1H]; 2.74 [m, 2H]; 2.46–2.35 [m, 2H]; 2.08 [s, 3H]; 1.80–1.20 [m, 4H]; 1.38 [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 208.54; 155.41; 138.02; 129.31; 128.20; 126.18; 79.06; 51.22; 43.06; 41.39; 33.41; 29.86; 28.33; 20.06. MS m/e: 214 (5); 158 (50); 57(100). $[\alpha]_D^{21}=+9.9$ ($c=0.92$, $CHCl_3$).

3.5. *(1*S*)*-N-*[(2*E*)-1-(Hydroxymethyl)-5-oxo-esen-2-enyl](*tert-*butyl)lcarboxamide* ***11***

Compound **10d** (630 mg, 2.2 mmol) was dissolved in MeOH (30 mL) and, after cooling at 0°C, 10 mL of CF_3COOH were added dropwise. After 1 h the reaction was let to reach rt and reacted until the starting material was consumed. Volatiles were evaporated and the residue diluted with ether and washed with a Na_2CO_3 saturated solution and brine. Pure **11** (530 mg, 98%) was obtained after evaporation of the solvent: ^{1}H NMR (200 MHz) δ: 5.79 [m, 1H, $J_{AB}=15.6$ Hz]; 5.52 [m, 1H, $J_{AB}=15.6$ Hz, $J_{BX}=5.7$ Hz]; 4.94 [bd, 1H, $J=6.6$ Hz]; 4.23 [m, 1H]; 3.65 [m, 2H]; 3.20 [d, 2H, $J=6.8$ Hz]; 2.20 [bs, 1H]; 2.16 [s, 3H]; 1.44 [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 206.73; 155.77; 131.90; 124.15; 79.74; 64.96; 54.00; 46.86; 29.60; 28.36. MS m/e: 212 (3); 156 (31); 57 (100).

*3.5.1. (3*E*)(2*S*)-2-[(*t*-butoxy)carbonylamino]-6-oxohepten-3-yl-4-methylbenzensulfonate* ***12a*** *and (4*E*)(2*S*)-2-[(*tert*-butoxy)carbonylamino]-6-oxohept-4-enyl-4-methylbenzenesulfonate* ***12b***

Crude **11** (130 mg, 0.5 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) together with TsCl (125 mg, 0.65 mmol), 0.1 mL of NEt_3 and DMAP. After 24 h the reaction mixture was diluted with CH_2Cl_2 washed with Na_2CO_3 saturated solution and brine. After purification (eluent: petroleum ether/ethyl acetate = 3/2) a 1/1 mixture of **12a** and **12 b** (174 mg, 88%) was obtained. **12a**: ^{1}H NMR (200 MHz) δ: 7.80–7.79 [m, 2H]; 7.42–7.39 [m, 2H]; 5.87 [m, 1H, J_{AB} = 15.8 Hz, J_{BX} = 6.8 Hz]; 5.50 [m, 1H, J_{AB} = 15.8 Hz]; 4.68 [m, 1H]; 4.55 [m, 1H]; 4.39 [m, 2H]; 3.21 [d, 2H, J_{bX} = 6.8 Hz]; 2.48 [s, 3H]; 2.15 [s, 3H]; 1.43 [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 206.36; 151.85; 133.26; 124.16; 93.77; 79.80; 68.17; 58.88; 46.98; 29.48; 28.46; 26.59; 23.69. **12b**: ^{1}H NMR (200 MHz) δ: 7.76–7.75 [m, 2H]; 7.34–7.33 [m, 2H]; 6.62 [m, 1H, J_{AB} = 16.0 Hz, J_{BX} = 7.2 Hz]; 6.04 [d, 1H, J = 16.0 Hz]; 4.68 [m, 1H]; 4.35 [m, 1H]; 4.09 [m, 2H]; 2.45 [s, 3H]; 2.42 [m, 2H]; 2.13 [s, 3H]; 1.40 [s, 9H].

References

1. Capella, L.; Degl'Innocenti, A.; Reginato, G.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1989**, *54*, 1473.
2. Ricci, A.; Reginato, G.; Degl'Innocenti, A.; Seconi, G. *Pure Appl. Chem.* **1992**, *64*, 439.
3. Reginato, G.; Mordini, A.; Caracciolo, M. *J. Org. Chem.* **1997**, *62*, 6187–6192.
4. Reginato, G.; Mordini, A.; Degl'Innocenti, A.; Manganiello, S.; Capperucci, A.; Poli, G. *Tetrahedron* **1998**, *54*, 10227.
5. Reginato, G.; Mordini, A.; Valacchi, M.; Grandini, E. *J. Org. Chem.* **1999**, *64*, 9545.
6. Reginato, G.; Mordini, A.; Messina, F.; Degl'Innocenti, A.; Poli, G. *Tetrahedron* **1996**, *52*, 10985.
7. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
8. Farina, V.; Krishnamuthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998.
9. Comins, D. L.; Weglarz, M. W. *J. Org. Chem.* **1991**, *56*, 2506.
10. Strunz, G.; Findlay, J. *The Alkaloids*; Academic Press: Orlando, 1985; p. 26.
11. Schneider, M. J. Alkaloids: *Chemical and Biological Perspectives*; Pergamon: Oxford, 1996; p. 10.
12. Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *40*, 3453.
13. Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc.* **1955**, *77*, 631.
14. MacConnell, J. C.; Blum, M. S. *Tetrahedron* **1971**, *27*, 1129.
15. Munchhof, M. J.; Meyers, A. I., *J. Am. Chem. Soc.* **1995**, *117*, 5399 and references therein.
16. Bubnov, Y. N.; Klimkina, E. V.; Ignatenko, A. V.; Gridnev, I. D. *Tetrahedron Lett.* **1997**, *38*, 4631.
17. Ciblat, S.; Besse, P.; Papastergiou, V.; Veschambre, H.; Canet, J.-L.; Troin, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 2221 and references therein.
18. Takahata, H.; Bandoh, H.; Hanayama, M.; Momose, T. *Tetrahedron*: *Asymmetry* **1992**, *3*, 607.
19. Wasserman, H. H.; Rusieki, V. *Tetrahedron Lett.* **1988**, *29*, 4977.
20. Takahata, H.; Bandoh, H.; Takefumi, M. *Tetrahedron* **1993**, *49*, 11205.
21. Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594.
22. Swarbrick, M. E.; Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 1993.
23. Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911.
24. Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.
25. Solladié, G.; Chu, G.-C. *Tetrahedron Lett.* **1996**, *37*, 111.
26. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
27. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
28. Hauske, J. R.; Dorff, P.; Julin, S. M. G.; Bussolari, J. *Tetrahedron Lett.* **1992**, *33*, 3715.
29. Meffre, P.; Gauzy, L.; Branquet, E.; Durand, P.; Goffic, F. L. *Tetrahedron* **1996**, *52*, 11215.
30. Sheffry, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833.

31. Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Lett*. **1998**, *39*, 2123.
32. Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *59*, 3213.
33. Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett*. **1976**, *34*, 2975.
34. Kumar, K. K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899.
35. Still, W. C.; Kahn, M. K.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 293.