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Article

The Addition of Allyltrimethylsilane to Cyclic *N*-Acyliminium Ions Derived from (*S*)-(+)-Mandelic Acid and Cyclohexyl-Based Chiral Auxiliaries

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A adição de aliltrimetilsilano, promovida por $TiCl_4$, a íons *N*-aciliminios cíclicos de 5- e 6-membros derivados do ácido (*S*)-(+)-mandélico, (*1R,2S*)-*trans*-2-fenil-1-cicloexanol e (*1R,2S,5R*)-8-fenilmentol ocorreu com baixas a moderadas razões diastereoisoméricas (1:1-6:1) e forneceu as respectivas amidas e carbamatos em bons rendimentos. A melhor diastereosseleção facial foi observada com o uso de (*1R,2S,5R*)-8-fenilmentol como auxiliar quiral. As amidas e carbamatos 2-substituídos foram convertidos nos alcalóides (*S*)- e (*R*)-propil pirrolidina e coniina com eficiente recuperação dos auxiliares quirais.

The $TiCl_4^-$ promoted addition of allyltrimethylsilane to chiral 5- and 6-membered *N*-acyliminium ions employing (*S*)-(+)-mandelic acid, (*1R,2S*)-*trans*-2-phenyl-1-cyclohexanol and (*1R,2S,5R*)-8-phenylmenthol derivatives as chiral auxiliaries occurred with low to moderate diastereoisomeric ratios (1:1-6:1) to afford 2-substituted amides and carbamates in good yields. The best diastereoselection was observed with (*1R,2S,5R*)-8-phenylmenthol as the chiral auxiliary. The 2-substituted amides and carbamates were converted to the corresponding alkaloids (*S*)- and (*R*)-propyl pyrrolidine and coniine with efficient recovery of the chiral auxiliaries.

Keywords: (*S*)-(+)-Mandelic acid, cyclohexyl-based chiral auxiliaries, *N*-acyliminium ions, pyrrolidine and piperidine derivatives

Introduction

The introduction of cyclohexyl-based chiral auxiliaries by Corey[1] in 1975 and mandelic acid by Trost[2] in 1980 stirred the interest for the development of new methodologies for asymmetric carbon-carbon bond formation. Despite that, few asymmetric routes are now available for the regioselective introduction of alkyl groups in the α-nitrogen position of *N*-acyliminium ions[3] employing recoverable chiral auxiliaries[4].

We were attracted by the possibility of using (*S*)-(+)-mandelic acid, (*1R,2S*)-*trans*-2-phenyl-1-cyclohexanol and (*1R,2S,5R*)-8-phenylmenthol as chiral auxiliaries during the addition of allyltrimethylsilane to chiral 5- and 6-membered *N*-acyliminium ions formed *in situ* from the corresponding 2-methoxy amides and carbamates prepared through anodic oxidation[5] (Scheme 1).

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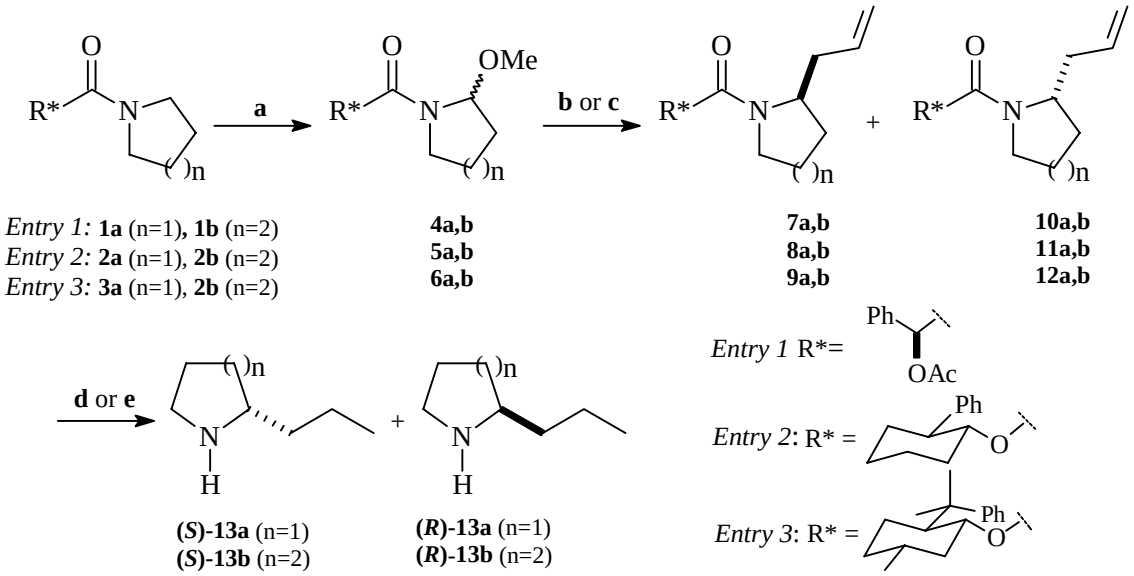
Results and Discussion

The electrochemical oxidation of chiral amides **1a,b** and chiral carbamates **2a,b** and **3a,b**, derived from (*S*)-(+)-mandelic acid, (*1R,2S*)-*trans*-2-phenyl-1-cyclohexanol and (*1R,2S,5R*)-8-phenylmenthol, respectively, was performed in an undivided cell equipped with a platinum plate anode and a tungsten wire cathode (MeOH, i = 100 mA, J = 25 mA cm^{-1}) to afford the corresponding 2-methoxy mandelic amides **4a,b** and 2-methoxy carbamates **5a,b** and **6a,b** in 62-78% yield, as epimeric mixtures at the α-nitrogen position. The carbon-carbon bond formation step was achieved by treatment of a CH_2Cl_2 soln. of **4a,b**, **5a,b** and **6a,b** with $TiCl_4$ at -78ºC and addition of allyltrimethyl-silane (Scheme 1).

Dichloromethane solutions of the epimeric mixtures (**4a-b**, **5a-b,** and **6a-b**) were treated with $TiCl_4$ at –78 ºC (Scheme 1) to generate the corresponding *N*-acyliminium ions, followed by the addition of allyltrimehtylsilane. In the case of the reactions employing **4a** and **4b**, hydrolysis



a) –2e$^-$, MeOH, Pt anode, i=100 mA. b) i.$TiCl_4$, allyltrimethylsilane, -78ºC-1.5 h, r.t-2.0 h, CH_2Cl_2; ii. K_2CO_3, MeOH, 12 h; c) $TiCl_4$, allyltrimethylsilane, -78ºC, 3.5 h, CH_2Cl_2 d) i. H_2, Pd-C, overnight, r.t; ii. 3 mol dm^{-3} HCl, dioxane, reflux, 120 h. e) i. H_2, Pd-C, overnight, r.t; ii. Method A: 4.7 mol dm^{-3} NaOMe, MeOH, 110ºC, sealed ampoule, Method B: 1 mol dm^{-3} MeLi, THF/cumene, 0ºC-r.t.

Scheme 1.

Table 1. The addition of allytrimethylsilane to α-OMe derivatives 4-6a,b promoted by TiCl4

Entry	n	α-OMe derivatives	R* (Chiral Auxiliaries)	Product	d.r[a]	Yield %
1	1	**4a**	(*S*)-*N*-(*O*-acetyl)-mandeloyl	**7a:10a**	2:1	71
2	2	**4b**	(*S*)-*N*-(*O*-acetyl)-mandeloyl	**7b:10b**	2:1	60
3	1	**5a**	(*1R*,*2S*)-*trans*-2-phenyl-1-cyclohexyl	**8a:11a**	1:1	75
4	2	**5b**	(*1R*,*2S*)-*trans*-2-phenyl-1-cyclohexyl	**8b:11b**	1:2	68
5	1	**6a**	(*1R*,*2S*,*5R*)-8-phenylmenthyl	**9a:12a**	6:1[b]	70
6	2	**6b**	(*1R*,*2S*,*5R*)-8-phenylmenthyl	**9b:12b**	3:1	65

[a]Diastereoisomeric ratios determined by GC-MS analyses; [b]Diastereoisomeric ratio determined by chiral GC analyses.

of the acetyl group (K_2CO_3, MeOH) of the products afforded *N*-mandeloyl 2-allyl pyrrolidines **7a/10a** (71% yield) and *N*-mandeloyl 2-allyl piperidines **7b/10b** (60% yield), respectively. The unambiguous assignment of the NMR spectra was precluded by the presence of rotational isomers around the amide bond. The diastereoisomeric ratio was determined to be 2:1 for both 2-allyl amides **7a/10a** and **7b/10b** by GC-MS analyses (Table 1). The absolute configuration at the newly formed stereogenic center was assigned after catalytic hydrogenation followed by hydrolysis (3 mol dm^{-3} HCl, dioxane, reflux) of the 2-allyl amides **7a** and **10a** (separated by flash chromatography on silica gel) to provide (*S*)- and (*R*)-2-propyl pyrrolidine (**13a**) {[α]$_D$ -1.94 (*c* 1.3, 2.0 mol dm^{-3} HCl) and +2.0 (*c* 1.5, 2.0 mol dm^{-3} HCl), respectively; lit.[6] (*R*)-**13a**, [α]$_D$ +2.0 (*c* 1.5, 2 mol dm^{-3} HCl)} in 57% yield. When the same protocol was applied to the 2:1 mixture of **7b/10b**, a 2:1 mixture of (*S*)- and (*R*)-coniine (**13b**) enriched in the *S* isomer {(*S/R*)-**13b**.HCl, [α]$_D$ +4.2 (*c 1*.0, EtOH); lit.[7] (*R*)-**13b**, [α]$_D$ -9.2 (*c* 0.8, EtOH)} was obtained in 50% yield (Scheme 1).

Low diastereofacial preference was also observed in the addition of allyltrimethylsilane to 2-methoxy carbamates **5a,b** derived from (*1R*,*2S*)-*trans*-2-phenyl-1-cyclohexanol.The 1:1 and 1:2 diastereoisomeric ratios were assigned to the ratios of 2-allyl carbamates **8a/11a** (75% yield) and **8b/11b** (68% yield), respectively, by GC-MS analyses. Catalytic hydrogenation followed by methanolysis (Method A: NaOMe, MeOH, 110 ºC, sealed ampoule)[4d] of **8a/11a** allowed the recovery of (*1R*,*2S*)-*trans*-2-phenyl-1-cyclohexanol (95% yield) and afforded racemic 2-propyl pyrrolidine (**13a**) in 91% yield. The same protocol was applied to 2-allyl carbamates **8b/11b** to afford a levorotatory mixture (1:2 ratio) enriched in (*R*)-coniine (**13b**) {(*S/R*)-**13b**.HCl, [α]$_D$ -4.2 (*c* 1.0, EtOH); lit.[7] (*R*)-**13b,** [α]$_D$ -9.2 (*c* 0.8, EtOH)} in 86% yield.

Better facial discrimination was observed when 8-phenylmenthol derivatives were employed. The $TiCl_4$ promoted addition of allyltrimethylsilane to **6a** and **6b** afforded the corresponding 2-allyl carbamates **9a/12a** and **9b/12b** in 70% and 65% yield, respectively. The diastereoisomeric ratio of **9b/12b** (3:1) was determined by

GC-MS analysis. Enantiomerically enriched (*S*)-coniine (**13b**) {(*S/R*)-**13b**.HCl, $[\alpha]_D$ +5.4 (*c* 1.0, EtOH)} was obtained in 78% yield after catalytic hydrogenation and recovery of (*1R,2S,5R*)-8-phenylmenthol (Method B: 1 mol dm^{-3} MeLi, THF/cumene, 0ºC-r.t, 85% yield).

Unfortunately, baseline resolution was not achieved in the GC-MS analyses of 2-allyl carbamate **9a/12a** derived from **6a** and the determination of the diastereoisomeric ratio had to be postponed to the stage of preparation of 2-propyl pyrrolidine (**13a**) which was derivatized as the corresponding trifluoroacetamide and submitted to chiral GC analyses (6:1 enantiomeric ratio)[8]. The major 2-propyl carbamate derived from **9a** ($[\alpha]_D$ -46.7, *c* 2.0, CH_2Cl_2) was isolated and converted (Method B: 1.0 mol dm^{-3} MeLi, THF/cumene, 0ºC-r.t) to (*S*)-2-propyl pyrrolidine (**13a**) {$[\alpha]_D$ +18.2 (*c* 1.8, MeOH); lit.[6b] (*R*)-**13a**, $[\alpha]_D$ -18.0 (*c* 0.1, MeOH)} in 90% yield after catalytic hydrogenation, followed by flash chromatography on silica gel with efficient recovery of the chiral auxiliary (92% yield).

The $TiCl_4$-promoted reaction of allyltrimethylsilane with chiral cyclic *N*-acyliminium ions derived from 2-methoxy amides **4a,b** and 2-methoxy carbamates **6a,b**, except in the reaction with 2-methoxy carbamate **5b**, resulted from the approach of the nucleophile to the *Si* face of the *N*-acyliminium ions. The better facial discrimination (6:1 d.r) observed with (*1R,2S,5R*)-8-phenylmenthol as the chiral auxiliary was rationalized from the kinetically preferred attack of the nucleophile to the *s-cis* conformation of *N*-acyliminium ions (Figure 1)[9], which might be enforced by π-stacking[10] interactions involving the low-lying LUMO of the carbamoyl group and HOMO of the phenyl substituent. Comins and coworkers[3a,b] (Figure 2) revealed this behavior in the addition of Grignard reagents to chiral *N*-acylpyridinium salts containing cyclohexyl-based chiral auxiliaries such as (*1R,2S,5R*)-8-phenylmenthol and the excellent stereocontrol observed was again assigned to π-stacking interactions between the iminium moiety and the phenyl substituent of the chiral auxiliary.

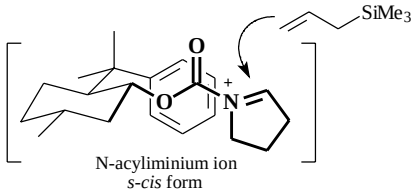


Figure 1. Addition of allyltrimethylsilane to the *s-cis* conformation of *N*-Acyliminium ion derived from **6a**.

Conclusion

Overall, this paper describes an efficient procedure for generating chiral cyclic 5- and 6-membered N-acyliminium ions, followed by in situ addition of allyltrimethylsilane to yield the corresponding 2-allyl pyrrolidines and piperidines. We have shown that the carbon-carbon bond formation in the addition of allyltrimethylsilane to chiral *N*-acyliminium ions occurred with low diastereoselection (1:1-2:1 d.r) employing (*S*)-(+)-mandelic acid and (*1R,2S*)-*trans*-2-phenyl-1-cyclohexanol as chiral auxiliaries. However, moderate diastereoselection (6:1 d.r) was observed with (*1R,2S,5R*)-8-phenylmenthol as the chiral auxiliary. The results describe an attractive route to pyrrolidine and piperidine derivatives, particularly to pure (*S*)-2-propyl pyrrolidine (**13a**) which is present as a structural motif in many naturally occurring and biologically important compounds. The method also allows for an efficient recovery of the chiral auxiliary.

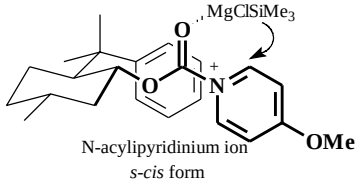


Figure 2. Addition of trimethylsilylmagnesium chloride to the *s-cis* conformation of *N*-acylpyridinium ion.

Experimental

General

(*S*)-Mandelid acid, (*1R,2S*)-*trans*-2-phenyl-1-cyclohexanol and (*1R,2S,5R*)-8-phenylmenthol, allyl-trimethylsilane, solvents and reagents were purchased from commercial sources, unless otherwise noted. Amides **1a,b** were synthesized from (S)-(+)-mandelic acid, pyrrolidine and piperidine in 68% and 66% overall yield, respectively. Carbamates **2a,b** and **3a,b** were synthesized by the reaction of (*1R,2S*)-*trans*-2-phenyl-1-cyclohexylchloroformate and (*1R,2S,5R*)-8-phenymenthyl chloroformate with pyrrolidine and piperidine in 80%, 86%, 95% and 91% yield, respectively. All experiments were carried out under an argon atmosphere except for hydrolyses under acid conditions. Dichloromethane was distilled from CaH_2, methanol and ethanol were distilled from Mg turnings. The titanium (IV) chloride (Aldrich Co.) was distilled from CaH_2 and stored in a Schlenk flask. The normal processing of organic extracts consisted of drying over $MgSO_4$, filtration and concentration under reduced pressure with a rotatory evaporator. The compounds were purified by column chromatography on silica gel (200-400 mesh, 70-230 mesh, 60 Å). The electrochemical oxidation was performed using a Princeton Applied Research potenciostat/galvanostat model 173 equipped with a current

follower, model 176, and Hewlett Packard 6255A (Dual DC Power Supply, 0-40V, 0-1.5A). The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-300/P (7.05T), Varian Gemini (7.05T) and Varian Inova (11.7T) spectrometers. Chemical shifts (δ) are recorded in ppm with the solvent resonance as the internal standard and coupling constants (*J*) recorded in Hz. Signals for rotational and/or configurational isomers are denoted inside brackets. The infrared spectra were recorded as films in KBr cells on a Perkin-Elmer 1600 (FTIR) spectrometer (film and NaCl) and Nicolet Impact 410 (FTIR). Elemental analyses and high resolution mass spectroscopy (HRMS) were performed on a 2400 CHN-Perkin Elmer instrument and Autoespec-Micromass-EBE, respectively. Optical rotations were measure on a polarimeter Polamat A Carl Zeiss Jena using a quartz cell and a mercury or sodium lamp. The melting points were measured on an Electrothermal 9100 apparatus. The gas chromatography analyses (FID detector) were performed using a HP-5890-II equipment. Gas chromatography-mass spectrometry (GC/MS) analyses were performed on a Hewlett Packard 5890/Hewlett Packard 5970 MSD.

*General procedure for the electrochemical oxidation and preparation of 2-methoxy amides **4a,b** and carbamates **5a,b and 6a,b***. A solution of amides **1a,b** or carbamates **2-3a,b** (2.4 mmol) and tetraethylammonium *p*-toluene-sulfonate (Et_4NOTs, 1.2 mmol) in methanol (12 cm^3) was added into an undivided glass cell, equipped with a platinum plate anode (2.0 x 2.0 cm^2) and a tungsten wire cathode. The substrate was electrolyzed at constant current (100 mA, J = 25 mA.cm^{-2}) under magnetic stirring and the reaction temperature was maintained between 15-20^{o}C with external water bath. After the passage of 8.0 F.mol^{-1}, the solvent was removed under reduced pressure, the residue was dissolved in water (20 cm^3) and extracted with CH_2Cl_2 (3 x 20 cm^3). The product was separated by column chromatography on silica gel.

*N-[(O-acetyl)-mandeloyl]-2-methoxy pyrrolidine (**4a**)*: 50% diethyl ether/hexane as eluent (78% yield). White solid. IR (film): $\nu_{max.}$/cm^{-1} 2940, 1739, 1670, 1420 and 1234.^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.30-7.60 (m, 5H), [6.45, 6.35, 6.10, 6.00 (s, 1H)], [5.50, 5.57, 5.49, 4.80 (d, *J* 6.0, 1H)], 3.80-3.50 (m, 2H), [3.40, 3.39, 3.30, 3.20 (s, 3H)], 2.20 (s, 3H), 2.00-1.50 (m, 4H). ^{13}C-NMR (75 MHz, CDCl3): δ 170.5, 168.7, 133.0, 129.7, 129.2, 129.1, 128.4, [89.1, 88.0], [74.0, 56.0, 54.0], [46.0, 45.0], 31.0, 23.0, 21.0. Elemental analysis- Found: C, 64.87, H, 7.13, N, 4.72; Calc. for $C_{15}H_{19}O_4N$: C, 64.90, H, 6.85, N, 5.00%.

*N-[(O-acetyl)mandeloyl]-2-methoxy piperidine (**4b**):* 25% hexane/diethyl ether as eluent (71% yield). White solid. IR: $\nu_{max.}$/cm^{-1} 3055, 2946, 1739, 1663, 1438 and 1371. ^{1}H-NMR (300 MHz, CD_3CN): δ 7.45 (m, 5H), [6.30, 6.20, 6.15 (s, 1H)], [5.70, 5.00 (s, 1H)], [4.30, 3.65, 3.55 (d, *J* 10, 1H)], [3.40, 3.20, 3.00 (s, 3H)], 2.80 (m, 1H), 2.15 (s, 3H), 1.90-1.10 (m, 5H), 0.70 (m, 1H). ^{13}C-NMR (75 MHz, CD_3CN): δ 172.0, 167.5, 135.0, 129.4, 129.3, 129.2, 84.0, 80.0, 74.0, 55.0, 41.0, 37.0, 30.0, 25.0, 21.0, 18.0. Elemental Analysis- Found: C, 65.58, H, 7.42, N, 4.66; Calc. for $C_{16}H_{21}O_4N$: C, 65.90, H, 7.20, N, 4.80%.

*N-[(1R,2S)-trans-2-phenyl-1-cyclohexyloxycarbonyl]-2-methoxy pyrrolidine (**5a**):* 70% hexane/ethyl acetate as eluent (76% yield). Pale yellow oil. IR: $\nu_{max.}$/cm^{-1} 3060, 3028, 2933, 2858, 2831, 1705, 1450, 1402, 1356, 1327, 1182, 1084, 1012, 756, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.32-7.11 (m, 5H), [5.06, 4.96, 4.62 (s, 1H)], 4.83-4.74 (m, 1H), [3.30, 3.00, 2.50 (s, 3H)], 3.20-3.10 (m, 2H), 2.78-2.61 (m, 1H), 2.28-2.10 (m, 1H). 1.95-1.28 (m, 11H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ156.0, 154.8, 143.8, 143.5, 129.1, 128.4, 128.3, 128.2, 127.7, 127.6, 127.4, 127.1, 126.5, 126.4, 126.3, 126.2, 88.7, 88.2, 87.6, 77.2, 76.6, 55.5, 55.1, 54.1, 50.2, 49.9, 45.5, 45.2, 44.8, 35.3, 33.9, 33.6, 33.5, 32.8, 32.6, 32.5, 32.1, 31.8, 25.6, 25.2, 24.5, 24.4, 22.2, 21.5.

*N-[(1R,2S)-trans-2-phenyl-1-cyclohexyloxycarbonyl]-2-methoxy piperidine (**5b**):* 70% hexane/ethyl acetate as eluent (71% yield). Pale yellow oil. *IR* $\nu_{max.}$/cm^{-1} 3025, 2933, 2854, 1700, 1417, 1356, 1263, 1081, 1033, 755, 700.^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.30-7.11 (m, 5H), [5.10, 4.98, 4.62 (s, 1H)], 4.83-4.74 (m, 1H), 3.90-3.20 (m, 2H), [3.15, 2.25 (s, 3H)], 2.80-2.60 (m, 2H), 1.95-1.70 (m, 4H), 1.70-1.20 (m, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 155.9, 155.0, 143.0, 142.5, 128.3, 127.9, 126.0, 86.0, 84.2, 77.5, 57.8, 57.1, 50.1, 47.8, 47.0, 46.2, 44.8, 35.8, 33.8, 33.0, 32.5, 26.1, 25.9, 24.5, 24.0, 23.5.

*N-[(1R,2S,5R)-8-phenylmenthyloxycarbonyl]-2-methoxy pyrrolidine (**6a**): 65%* hexane/ethyl acetate as eluent (62% yield). Pale yellow oil. IR: $\nu_{max.}$/cm^{-1} 3056, 2952, 2925, 2869, 1708, 1600, 1509, 1454, 1363, 1205, 1122, 1031, 769, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.32-7.07 (m, 5H), [5.16, 5.08, 3.40, 3.24 (d, 3J = 4.3, 1H)], [3.39, 3.32, 3.04 (s, 3H)], 2.96-2.78 (m, 1H), 2.20-1.40 (m, 12H), [1.32, 1.35, 1.75 (s, 3H)], [1.24, 1.22, 1.20, 1.18 (s, 3H)], 1.12-0.90 (m, 2H), [0.88, 0.84 (d, 3H)]. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 155.3, 154.7, 153.1, 152.5, 128.0, 127.9, 127.7, 125.4, 124.7, 88.7, 88.2, 87.2, 74.9, 74.5, 55.6, 55.3. 50.1, 45.2, 44.7, 44.6, 43.9, 42.5, 42.3, 34.3, 31.0, 29.9, 28.8, 23.3, 22.1, 21.5. HRMS- Found: 359.23963; Calc. for $C_{22}H_{33}O_3N$: 359.24605.

*N-[(1R,2S,5R)-8-phenylmenthyloxycarbonyl]-2-methoxy piperidine (**6b**):* 65% hexane/ethyl acetate as eluent (71% yield). Pale yellow oil. IR (film): ν_{max}/cm^{-1}

3023, 2917, 2952, 2829, 1702, 1602, 1402, 1180, 1083, 755, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.31-7.22 (m, 4H), 7.16-7.11 (m, 1H), [5.39, 5.35, 4.46, 3.95 (m, 1H)], 4.90-4.70 (m, 1H), [3.49, 3.25, 3.19, 3.09 (s, 3H)], [2.95, 2.82, 2.72, 2.44, 2.38 (m, 1H)], 2.09-2.00 (m, 2H), 1.94 (m, 1H), 1.80-1.40 (m, 9H), 1.39 (s, 3H), [1.20, 1.21 (s, 3H)], 1.19-0.90 (m, 2H), 0.85 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 155.0, 152.2, 152.3, 128.2, 125.6, 125.3, 96.0, 95.0, 82.0, 81.0, 87.2, 75.0, 76.0, 54.9, 50.8, 42.7, 41.0, 40.0, 38.5, 35.0, 32.0, 30.5, 27.9, 25.9, 24.5, 21.9, 19.0. HRMS-Found: 373.26011; Calc. for $C_{23}H_{35}O_3N$: 373.26169.

*General procedure for the preparation of 2-allyl amides **7/10a,b**:* To a stirred solution of 2-methoxy amides **4a,b** (3.7 mmol) in dry CH_2Cl_2 (5 cm^3) at -78ºC, under an argon atmosphere, $TiCl_4$ (3.7 mmol) was added. After 0.5 h, allytrimethylsilane (7.5 mmol) was added and the reaction mixture was stirred for 1 h. The temperature was raised to room temperature and the mixture was stirred for 2 h. The reaction was quenched by the addition of water (5 cm^3) and extracted with CH_2Cl_2 (2 x 15 cm^3). After evaporation under reduced pressure, a solution of methanol (5 cm^3), K_2CO_3 (100 mg) was added to the pale yellow oil and the mixture was stirred 12 h at room temperature. After removal of methanol *in vacuo*, the diastereoisomeric mixture was purified by flash column chromatography on silica gel.

*N-mandeloyl-2-(1-propenyl) pyrrolidine (**7/10a**):* 70% hexane/ethyl acetate as eluent (71% yield). Pale yellow oil. IR: $\nu_{max.}$/cm^{-1} 3405, 2971, 2924, 1638, 1449, 1381, 735, 701.Elemental Analysis: Found - C, 72.96, H, 7.97, N, 5.54; calc for $C_{15}H_{19}O_2N$ C, 73.00, H, 7.75, N, 5.71. Data for the major isomer **7a**: $[\alpha]^{23}_D$ +4.8 (*c* 3.0, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ *7.*35 (m, 5H), 5.63 (m, 1H), 5.05 (d, *J* 6.0, 1H), 5.01 (s, 1H), 4.99 (s, 1H), 4.80 (d, 3 *J* 6.0, 1H), 4.30 (m, 1H), 3.40 (m, 1H), 2.90 (m, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 2.00-1.80 (m, 3H), 1.60 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.0, 140.0, 134.0, 129.2, 128.7, 127.9, 118.0, 73.0, 58.0, 46.0, 38.0, 28.0, 24.0. Data for the minor isomer **10a**: $[\alpha]^{23}_D$ +47.3 (*c* 3.0, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.80 (m, 1H), 5.15 (m, 2H), 5.05 (d, *J* 6.0, 1H), 4.70 (d, *J* 6.0, 1H), 4.20 (m, 1H), 3.40 (m, 1H), 2.90 (m, 1H), 2.70 (m, 1H), 2.20 (m, 1H), 2.00-1.60 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.0, 139.0, 135.0, 129.1, 128.6, 128.0, 127.6, 118.0, 73.0, 58.0, 46.0, 37.0, 28.0, 24.0.

*N-mandeloyl-2-(1-propenyl) piperidine (**7/10b**):* 50 % ethyl acetate/hexane as eluent (90 % yield). Pale yellow oil. IR: $\nu_{max.}$/cm^{-1} 3406, 2940, 2855, 1634, 1452, 1397, 1266, 1064, 1012, 764, 701. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.70 (m, 1H), 5.20-5.00 (m, 2H), 4.95-4.80 (m, 2H), [4.55, 3.75, 3.40 (m, 1H)], 2.90-2.15 (m, 3H), 1.75-1.15 (m, 7H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.0, 140.0, 134.0, 128.9, 128.7, 128.5, 128.3, 127.5, 118.0, 72.0, [52.0, 49.0], [41.0, 38.0], 34.0, 27.0, [26.0, 24.0], 19.0. Elemental Analysis- Found: C, 73.89, H, 7.98, N, 5.05; Calc. for $C_{16}H_{21}O_2N$: C, 74.00, H, 8.10, N, 5.40%.

*General procedure for the preparation of 2-allyl carbamates **8/11a,b** and **9/12a,b**:* To a stirred solution of 2-methoxy carbamates **5/6a,b** (1.32 mmol) in dry CH_2Cl_2 (3 cm^3) at -78ºC, under an argon atmosphere, $TiCl_4$ (1.5 mmol) was added. After 0.5 h, allyltrimethylsilane (2.64 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was quenched by the addition of water (5 cm^3) and extracted with CH_2Cl_2 (3 x 10 cm^3). The products were purified by flash column chromatography on silica gel.

*N-[(1R,2S)-trans-2-phenyl-1-cyclohexyloxycarbonyl]-2-(1-propenyl) pyrrolidine (**8/11a**):* 70% hexane/ethyl acetate as eluent (75% yield). Colorless oil. IR: $\nu_{max.}$/cm^{-1} 3062, 3027, 2931, 2857, 1698, 1639, 1602, 1448, 1407, 1355, 1184, 1105, 1033, 755, 700. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26-7.14 (m, 5H), 5.60-5.30 (m, 1H), 5.10-4.75 (m, 3H), [3.66-3.61, 3.33-3.18, 3.00-2.81 (m, 3H)], [2.67-2.61, 2.50-2.05 (m, 3H)], 1.92-1.25 (m, 12H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.5, 143.5, 135.1, 128.3, 128.0, 127.6, 127.3, 126.1, 76.7, 56.1, 56.9, 50.4, 46.4, 39.0, 38.0, 35.1, 33.7, 33.1, 25.7, 24.7. HRMS Found: 314.21257; Calc. for $C_{20}H_{27}O_2N$ (M+1): 314.21200.

*N-[(1R,2S)-trans-2-phenyl-1-cyclohexyloxycarbonyl]-2-(1-propenyl) piperidine (**8/11b**):* 70% hexane/ethyl acetate as eluent (68% yield). Colorless oil. IR: $\nu_{max.}$/cm^{-1} 3025, 2929, 2857, 1698, 1417, 1101, 755, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28-7.13 (m, 5H), [5.56, 4.95-4.78 (m, 4H)], 4.05 (s, 1H), 3.78 (d, *J* 13.0, 1H), 2.70-2.52 (m, 2H), 2.23-2.05 (m, 2H), 1.94-1.75 (m, 2H), 1.64-1.21 (m, 12H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 155.3, 143.6, 135.4, 128.3, 128.1, 127.7, 127.5, 126.2, 116.5, 77.0, 50.3, 49.9, 49.7, 38.8, 38.7, 33.9, 33.7, 32.8, 27.1, 25.8, 25.1, 25.0, 24.7, 24.6, 18,5; 18,4. HRMS- Found: 328.22760; Calc. for $C_{21}H_{29}O_2N$ (M+1): 328.22765;.

*N-[(1R,2S,5R)-8-phenylmenthyloxycarbonyl]-2-(1-propenyl) pyrrolidine (**9/12a**):* 65% hexane/ethyl acetate as eluent (70% yield). Colorless oil. IR: $\nu_{max.}$/cm^{-1} 2954, 2921, 2869, 1693, 1641, 1407, 1330, 1184, 1108, 992, 910, 755, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28-7.20 (m, 4H), 7.10 (m, 1H), [5.79, 5.50 (m, 1H)], 5.14-4.90 (m, 2H), 4.78 (m, 1H), [3.80, 2.60 (m, 1H)], 3.22 (m, 1H), [2.80, 2.38 (m, 1H)], 2.19-1.99 (m, 2H), 1.85-1.40 (m, 9H), [1.35, 1.21 (s, 3H)], 1.18 (s, 3H), [1.30-1.20 (m, 1H)], 0.90-1.00 (m, 2H), 0.86 (d, *J* 7,0 3H) ^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.0, 153.0, 152.7, 135.9, 127.9, 125.4, 124.7, 117.0, 77.2, 74.1, 56.7, 54.7, 50.8, 46.0, 45.5, 42.5, 42.2, 39.2, 38.4, 38.0, 34.5, 31.1, 29.3, 28.7, 27.9, 26.2, 24.6, 23.2, 22.8, 21.6. HRMS- Found: 370.26754; Calc. for $C_{24}H_{35}O_{2N}$ (M+1): 370.26935;.

*N-[(1R,2S,5R)-8-phenylmenthyloxycarbonyl]-2-(1-propenyl) piperidine (**9/12b**):* 65% hexane/ethyl acetate as

eluent (65% yield). Colorless oil. IR: $\nu_{max.}$/cm^{-1} 3091, 3061, 2954, 2930, 2866, 1687, 1641, 1423, 1369, 1259, 1149, 1093, 1034, 700. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.32-7.20 (m, 4H), 7.10 (m, 1H), [5.80, 5.60 (m, 1H)], 5.10-4.90 (m, 2H), 4.80 (m, 1H), [4.38, 4.00 (m, 1H)], [3.40, 3.25, 3.19 (m, 1H)], [2.75, 2.60, 2.10 (m, 1H)], 2.40-2.20 (m, 2H), 2.00-1.90 (m, 2H), 1.68-1.20 (m, 16H), 1.10 (m, 1H), 0.98-0.80 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 155.0, 152.0, 135.9, 128.0, 125.6, 125.1, 116.5, 75.4, 51.0, 50.5, 49.8, 42.5, 40.2, 39.0, 35.0, 34.4, 31.8, 27.9, 25.7, 25.9, 26.2, 22.0, 18.8. HRMS-Found: 383.28420; Calc. for $C_{25}H_{37}O_2N$: 383.28242;.

*General procedure for the preparation of 2-propyl pyrrolidine (**13a**) and coniine (**13b**) derived from amides **7/10a,b**:* A solution of 2-allyl amides **7/10a,b** (1.7 mmol) in ethanol (5 cm^3) containing 10% Pd-C was stirred overnight at room temperature under hydrogen atmosphere (H_2, 1 atm). The catalyst was removed by filtration through Celite®, and the filter pad was washed with diethyl ether (3 x 30 cm^3). The combined filtrates were concentrated under reduced pressure and a solution of 3 mol dm^{-3} HCl:dioxane (1:1, 2.0 cm^3) was added to the oily residue. The reaction mixture was refluxed 120 h, the solvent was removed *in vacuo* and the residue was extracted with diethyl ether (3 x 30 cm^3). The product was purified by column chromatography on silica gel.

*General procedure for the preparation of 2-propyl pyrrolidine (**13a**) and coniine (**13b**) from carbamates **8/11a,b** and **9/12a,b:*** A solution of 2-allyl carbamates **8/11a,b** or **9/12a,b** (0.91 mmol) in ethanol (2 cm^3) containing 10% Pd-C was stirred overnight at room temperature under hydrogen atmosphere (H_2, 1 atm). The catalyst was removed by filtration through Celite®, and the filter pad was washed with diethyl ether (3 x 10 cm^3). The combined filtrates were concentrated under reduced pressure. *Method A:* To a solution of 2-propyl carbamates derived from **8/11a,b** in methanol (2 cm^3) was added a 4.7 mol.dm^{-3} solution of NaOMe in methanol (2 cm^3) and the reaction mixture was stirred 30 h (n=1) or 36 h (n=2) in a sealed ampoule at 110ºC. After filtration through silica gel with methanol (20 cm^3) the combined filtrates were acidified (pH 1.0) with methanolic 10% HCl. Methanol was removed *in vacuo* and the residue was purified by column chromatography on silica gel. *Method B:* To a solution of 2-propyl carbamates derived from **9/12a,b** in THF (2.0 cm^3) was added, at 0ºC, a 1.0 mol.dm^{-3} solution of MeLi in THF/cumene (2.0 mmol). The reaction mixture was stirred 36 h (n=1) or 48 h (n=2) at room temperature. The reaction was quenched by the addition of water (3 cm^3) and extracted with diethyl ether (3 x 5 cm^3). The combined filtrates were acidified (pH 1.0) with methanolic 10% HCl and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel.

*Propyl pyrrolidine (**13a**):* $CHCl_3$:MeOH:NH_4OH (90:9:1) as eluent. Yellow oil. IR: $\nu_{max.}$/cm^{-1} 3396, 2960, 2931, 2873, 2744, 2532, 2466, 1593, 1462, 1414, 1385, 1078, 1018, 943. (*S*)-**13a**, $[\alpha]^{23}_D$ -1.94 (*c* 1.3, 2 mol dm^{-3} HCl) and $[\alpha]^{23}_D$ +18.2 (*c* 1.8, MeOH); (*R*)-**13a,** $[\alpha]^{23}_D$ +2.0 (*c* 1.5, 2.0 mol dm^{-3} HCl), lit.[6] (*R*)-**13a**, $[\alpha]^{23}_D$+2.0 (*c* 1.5, 2.0 mol dm^{-3} HCl) and $[\alpha]^{23}_D$ +18.0 (*c* 0.1, MeOH). ^{1}H-NMR (300 MHz, D_2O): δ 3.45 (qt, *J* 7.69, 1H), 3.15 (m, 2H), 2.10 (m, 1H), 1.80 (m, 2H), 1.55 (m, 3H), 1.28 (sext., *J* 7.3, 2H), 0,79 (t, *J* 7.3, 3H). ^{13}C-NMR (75 MHz, D_2O): δ 60.3, 44.6, 33.2, 29.3, 22.6, 19.0, 12.5. Coniine (***13b***): $CHCl_3$:MeOH:NH_4OH (90:9:1) as eluent. Yellow oil. IR: $\nu_{max.}$/cm^{-1} 3417, 2954, 2933, 2738, 2573, 2532, 2507, 2451, 2403, 1591, 1456, 1387, 1215, 1036, 754. (*S/R*)- and (*R/S*)-**13b**.HCl (2:1 mixture): $[\alpha]^{23}_D$ +4.2 and –4.2, respectively (*c* 1.0, EtOH); (*S/R*)- **13b**. HCl (3:1mixture): $[\alpha]^{23}_D$ +5.4 (*c* 2.4, EtOH); lit.[7]: (*R*)-**13b**.HCl, $[\alpha]^{20}_D$ -9.2 (*c* 0.8, EtOH). ^{1}H-NMR (300 MHz, D_2O): δ 3.29 (d, *J* 14.0, 1H), 3.05 (m, 1H), 2.87 (t, *J* 12.9, 1H), 1.90 (d, *J* 12.9, 1H), 1.78-1.65 (m, 2H), 1.50 (m, 3H), 1.30 (m, 4H), 0.82 (t, *J* 7.4, 3H). ^{13}C-NMR (75 MHz, D_2O): δ 56.7, 44.7, 35.2, 28.2, 22.0, 21.5, 17.7, 13.0.

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