

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*-acilimínios cíclicos de 5- e 6-membros derivados do ácido (*S*)-(+)-mandélico, (*IR,2S*)-*trans*-2-fenil-1-ciclohexanol e (*IR,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 (*IR,2S,5R*)-8-fenilmentol como auxiliar quirais. 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, (*IR,2S*)-*trans*-2-phenyl-1-cyclohexanol and (*IR,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 (*IR,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 Corey¹ in 1975 and mandelic acid by Trost² 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 ions³ employing recoverable chiral auxiliaries⁴.

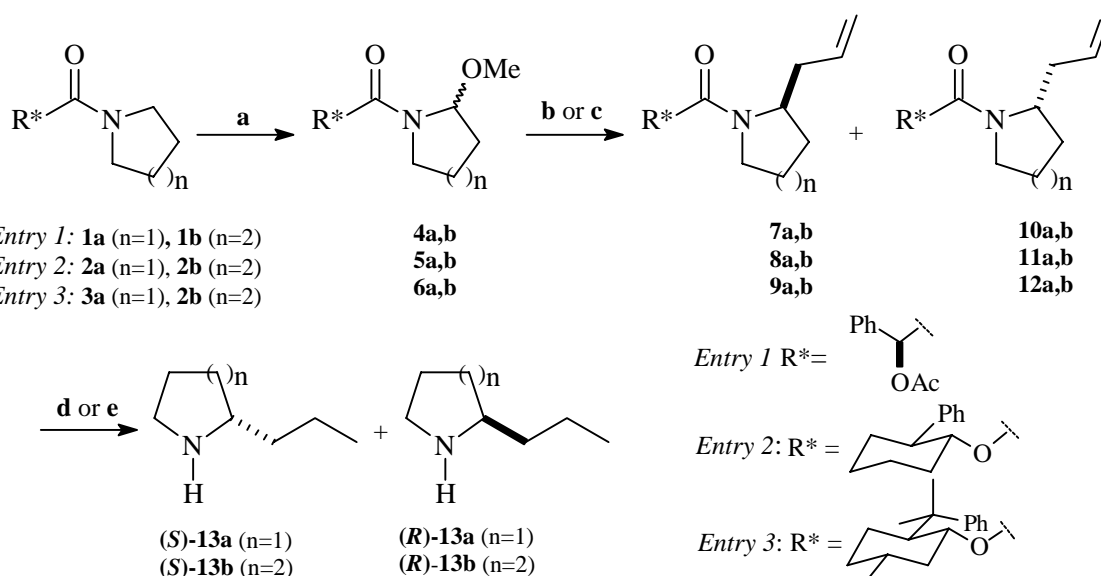
We were attracted by the possibility of using (*S*)-(+)-mandelic acid, (*IR,2S*)-*trans*-2-phenyl-1-cyclohexanol and (*IR,2S,5R*)-8-phenylmenthol as chiral auxiliaries during the addition of allyltrimethylsilane to chiral 5- and 6-membered *N*-acyliminium ions formed *in situ* from the corresponding 2-methoxy amides and carbamates prepared through anodic oxidation⁵ (Scheme 1).

Results and Discussion

The electrochemical oxidation of chiral amides **1a,b** and chiral carbamates **2a,b** and **3a,b**, derived from (*S*)-(+)-mandelic acid, (*IR,2S*)-*trans*-2-phenyl-1-cyclohexanol and (*IR,2S,5R*)-8-phenylmenthol, respectively, was performed in an undivided cell equipped with a platinum plate anode and a tungsten wire cathode (MeOH, $i = 100 \text{ mA}$, $J = 25 \text{ mA cm}^{-1}$) 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 -78°C and addition of allyltrimethylsilane (Scheme 1).

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

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a) $-2e^-$, MeOH, Pt anode, $i=100$ mA. b) i. TiCl_4 , allyltrimethylsilane, -78°C -1.5 h, r.t.-2.0 h, CH_2Cl_2 ; ii. K_2CO_3 , MeOH, 12 h; c) TiCl_4 , allyltrimethylsilane, -78°C , 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, 110°C , sealed ampoule, Method B: 1 mol dm^{-3} MeLi, THF/cumene, 0°C -r.t.

Scheme 1.

Table 1. The addition of allyltrimethylsilane to α -OMe derivatives 4-6a,b promoted by TiCl_4

| 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 |

^aDiastereoisomeric ratios determined by GC-MS analyses; ^bDiastereoisomeric 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**) $\{[\alpha]_{\text{D}} -1.94$ (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**, $[\alpha]_{\text{D}} +2.0$ (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 $\{(\text{S/R})\text{-13b.HCl}$, $[\alpha]_{\text{D}} +4.2$ (c 1.0, EtOH); lit.⁷ (*R*)-**13b**, $[\alpha]_{\text{D}} -9.2$ (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°C , 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**) $\{(\text{S/R})\text{-13b.HCl}$, $[\alpha]_{\text{D}} -4.2$ (c 1.0, EtOH); lit.⁷ (*R*)-**13b**, $[\alpha]_{\text{D}} -9.2$ (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**) $\{([S/R]-\mathbf{13b.HCl}, [\alpha]_D +5.4 (c 1.0, EtOH))\}$ 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, 0°C-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, 0°C-r.t) to (*S*)-2-propyl pyrrolidine (**13a**) $\{([\alpha]_D +18.2 (c 1.8, MeOH); lit.^{6b} (R)-\mathbf{13a}, [\alpha]_D -18.0 (c 0.1, MeOH)\}$ in 90% yield after catalytic hydrogenation, followed by flash chromatography on silica gel with efficient recovery of the chiral auxiliary (92% yield).

The TiCl₄-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 -stacking¹⁰ 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.

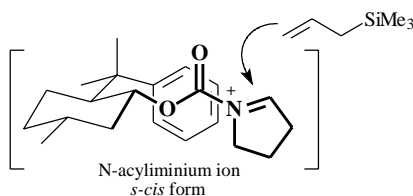


Figure 1. Addition of allyltrimethylsilane to the *s-cis* conformation of *N*-Acyliminium ion derived from **6a**.

Conclusion

Overall, this paper describes an efficient procedure for generating chiral cyclic 5- and 6-membered *N*-acyliminium

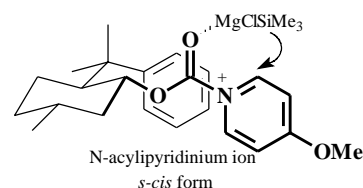


Figure 2. Addition of trimethylsilylmagnesium chloride to the *s-cis* conformation of *N*-acylpyridinium ion.

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.

Experimental

General

(*S*)-Mandelic 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-phenylmenthyl 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 CaH₂, methanol and ethanol were distilled from Mg turnings. The titanium (IV) chloride (Aldrich Co.) was distilled from CaH₂ and stored in a Schlenk flask. The normal processing of organic extracts consisted of drying over MgSO₄, 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 potentiostat/galvanostat model 173 equipped with a current

follower, model 176, and Hewlett Packard 6255A (Dual DC Power Supply, 0-40V, 0-1.5A). The ^1H - 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 measured 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*-toluenesulfonate (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, $J = 25 \text{ mA}\cdot\text{cm}^{-2}$) under magnetic stirring and the reaction temperature was maintained between 15-20°C with external water bath. After the passage of 8.0 $\text{F}\cdot\text{mol}^{-1}$, 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): $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 1739, 1670, 1420 and 1234. ^1H -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, CDCl_3): 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 $\text{C}_{15}\text{H}_{19}\text{O}_4\text{N}$: 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: $\nu_{\text{max}}/\text{cm}^{-1}$ 3055, 2946, 1739, 1663, 1438 and

1371. ^1H -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 $\text{C}_{16}\text{H}_{21}\text{O}_4\text{N}$: 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: $\nu_{\text{max}}/\text{cm}^{-1}$ 3060, 3028, 2933, 2858, 2831, 1705, 1450, 1402, 1356, 1327, 1182, 1084, 1012, 756, 700. ^1H -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): δ 156.0, 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: $\nu_{\text{max}}/\text{cm}^{-1}$ 3025, 2933, 2854, 1700, 1417, 1356, 1263, 1081, 1033, 755, 700. ^1H -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: $\nu_{\text{max}}/\text{cm}^{-1}$ 3056, 2952, 2925, 2869, 1708, 1600, 1509, 1454, 1363, 1205, 1122, 1031, 769, 700. ^1H -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 $\text{C}_{22}\text{H}_{33}\text{O}_3\text{N}$: 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): $\nu_{\text{max}}/\text{cm}^{-1}$

3023, 2917, 2952, 2829, 1702, 1602, 1402, 1180, 1083, 755, 700. ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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 C₂₃H₃₅O₃N: 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 CH₂Cl₂ (5 cm³) at -78°C, under an argon atmosphere, TiCl₄ (3.7 mmol) was added. After 0.5 h, allyltrimethylsilane (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 cm³) and extracted with CH₂Cl₂ (2 x 15 cm³). After evaporation under reduced pressure, a solution of methanol (5 cm³), K₂CO₃ (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: ν_{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 C₁₅H₁₉O₂N C, 73.00, H, 7.75, N, 5.71. Data for the major isomer **7a**: [α]_D²³ +4.8 (c 3.0, EtOH). ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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**: [α]_D²³ +47.3 (c 3.0, EtOH). ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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: ν_{max}/cm⁻¹ 3406, 2940, 2855, 1634, 1452, 1397, 1266, 1064, 1012, 764, 701. ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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 C₁₆H₂₁O₂N: 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 CH₂Cl₂ (3 cm³) at -78°C, under an argon atmosphere, TiCl₄ (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 cm³) and extracted with CH₂Cl₂ (3 x 10 cm³). The products were purified by flash column chromatography on silica gel.

N-[(1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexyloxycarbonyl]-2-(1-propenyl) pyrrolidine (**8/11a**): 70% hexane/ethyl acetate as eluent (75% yield). Colorless oil. IR: ν_{max}/cm⁻¹ 3062, 3027, 2931, 2857, 1698, 1639, 1602, 1448, 1407, 1355, 1184, 1105, 1033, 755, 700. ¹H-NMR (500 MHz, CDCl₃): 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). ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₀H₂₇O₂N (M+1): 314.21200.

N-[(1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexyloxycarbonyl]-2-(1-propenyl) piperidine (**8/11b**): 70% hexane/ethyl acetate as eluent (68% yield). Colorless oil. IR: ν_{max}/cm⁻¹ 3025, 2929, 2857, 1698, 1417, 1101, 755, 700. ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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 C₂₁H₂₉O₂N (M+1): 328.22765;.

N-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl]-2-(1-propenyl) pyrrolidine (**9/12a**): 65% hexane/ethyl acetate as eluent (70% yield). Colorless oil. IR: ν_{max}/cm⁻¹ 2954, 2921, 2869, 1693, 1641, 1407, 1330, 1184, 1108, 992, 910, 755, 700. ¹H-NMR (300 MHz, CDCl₃): 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) ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₄H₃₅O₂N (M+1): 370.26935;.

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

eluent (65% yield). Colorless oil. IR: $\nu_{\max}/\text{cm}^{-1}$ 3091, 3061, 2954, 2930, 2866, 1687, 1641, 1423, 1369, 1259, 1149, 1093, 1034, 700. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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 $\text{C}_{25}\text{H}_{37}\text{O}_2\text{N}$: 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 110°C. 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 0°C, 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: $\nu_{\max}/\text{cm}^{-1}$ 3396, 2960, 2931, 2873, 2744, 2532, 2466, 1593, 1462, 1414, 1385, 1078, 1018, 943. (*S*)-**13a**, $[\alpha]_{\text{D}}^{23}$ -1.94 (*c* 1.3, 2 mol dm^{-3} HCl) and $[\alpha]_{\text{D}}^{23}$ +18.2 (*c* 1.8, MeOH); (*R*)-**13a**, $[\alpha]_{\text{D}}^{23}$ +2.0 (*c* 1.5, 2.0 mol dm^{-3} HCl), lit.⁶ (*R*)-**13a**, $[\alpha]_{\text{D}}^{23}$ +2.0 (*c* 1.5, 2.0 mol dm^{-3} HCl) and $[\alpha]_{\text{D}}^{23}$ +18.0 (*c* 0.1, MeOH). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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: $\nu_{\max}/\text{cm}^{-1}$ 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): $[\alpha]_{\text{D}}^{23}$ +4.2 and -4.2, respectively (*c* 1.0, EtOH); (*S/R*)- **13b**. HCl (3:1 mixture): $[\alpha]_{\text{D}}^{23}$ +5.4 (*c* 2.4, EtOH); lit.⁷: (*R*)-**13b**.HCl, $[\alpha]_{\text{D}}^{20}$ -9.2 (*c* 0.8, EtOH). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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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