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ALKALI METAL-MEDIATED SYNTHESIS OF 1- AND 4-SUBSTITUTED *N*-ALKYL-1,2,3,4-TETRAHYDROISOQUINOLINES

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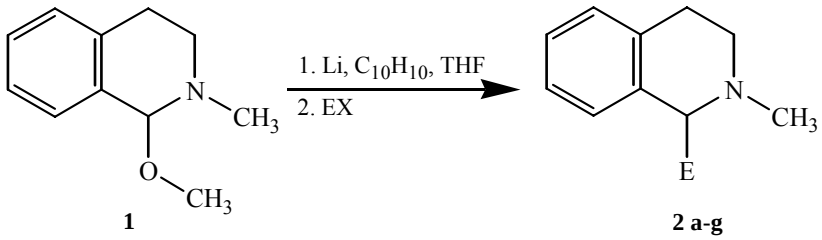
Abstract – Reductive cleavage by electron transfer from Li or K metal of 1-alkoxy-substituted *N*-alkyltetrahydroisoquinolines led to the formation of organometallic derivatives. Quenching of these intermediates with electrophilic reagents afforded 1- or 4-substituted *N*-alkyl-1,2,3,4-tetrahydroisoquinolines, depending upon the nature of the metal.

INTRODUCTION

Generation of α-*N*,*N*-dialkylamino-substituted benzyllithium derivatives is a topic of current interest in synthetic organic chemistry. Indeed, besides their potential synthetic utility, there is an increasing interest in the reactivity and structural features of α-tertiary amino-substituted alkali metal organometallics.[1-3] Following our interest in the reductive metalation of benzyl alkyl ethers derivatives,[4] we demonstrated that reductive cleavage of open chain and cyclic α-*N*,*N*-dialkylamino-substituted benzyl alkyl ethers, by electron trasfer from alkali metals in THF, is a highly regioselective reaction, resulting in the exclusive cleavage of the benzylic carbon – oxygen bond, and disclosing an original approach to the generation of α-*N*,*N*-dialkylamino-substituted arylmethyllithium reagents.[5,6]



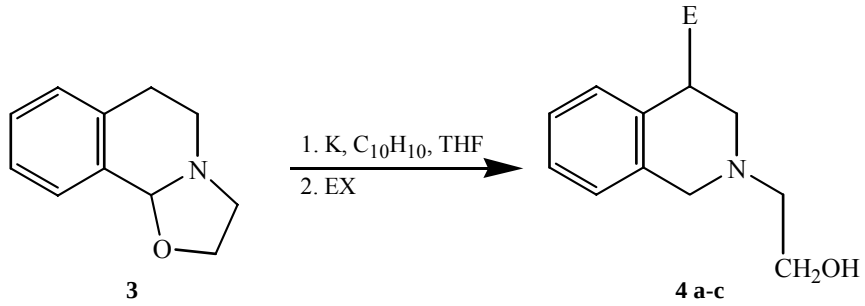
1 **2 a-g**

Scheme 1. Reductive metalation and reaction with electrophiles of tetrahydroisoquinoline (**1**). **2a**, E = H; **2b**, E = D; **2c**, E = CH_2Ph; **2d**, E = C_6H_{13}; **2e**, E = $(CH_3)_2COH$; **2f**, E = $(\underline{CH_2})_5COH$; **2g**, E = $(\underline{CH_2})_4COH$.

We wish now to report an extension of this procedure to the regioselective synthesis of substituted 1,2,3,4-tetrahydroisoquinoilines.

Indeed, application of this procedure to 1-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1**), allows the generation of the corresponding organolithium derivative, which can be trapped with different electrophiles, leading to the synthesis of 1-substituted 2-methyl-1,2,3,4-tetrahydroisoquinolines (**2**) (Scheme 1).

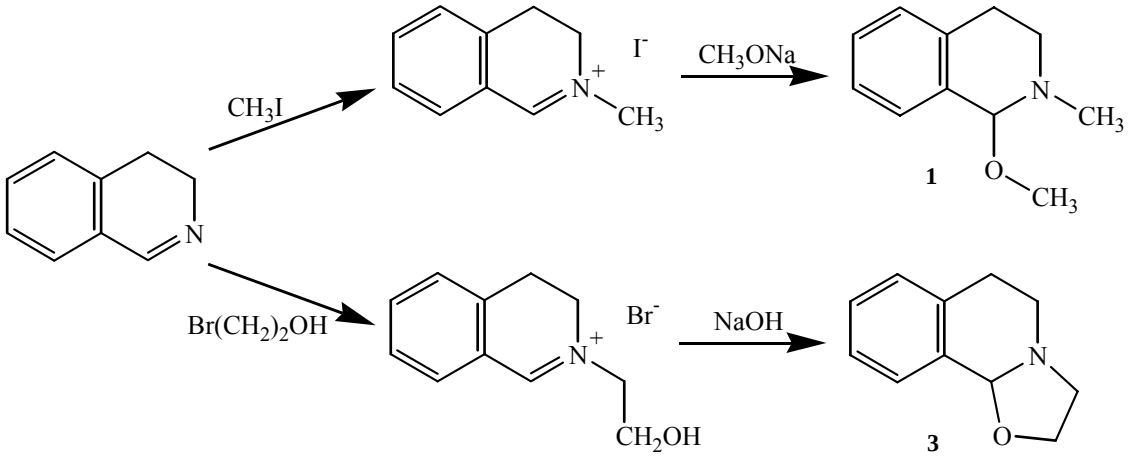
Potassium-mediated reduction of 2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (**3**), led to benzylic carbon – oxygen bond cleavage; however, quenching this reaction mixture with different electrophiles led to the recovery of 4-substituted 2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)ethanols (**4**), *via* an unprecedented prototropic rearrangement (Scheme 2).



Scheme 2. Reductive metalation and reaction with electrophiles of tetrahydroisoquinoline (**3**). **4a**, E = H; **4b**, E = D; **4c**, E = C_4H_9.

RESULTS AND DISCUSSION

Tetrahydroisoquinoline (**1**) was obtained in 56% overall yield by reacting 3,4-dihydroisoquinoline with CH_3I,[7,8] followed by reaction of the resulting dihydroisoquinolinium iodide with CH_3ONa. Tetrahydroisoquinoline (**3**) was obtained according to a literature procedure,[9] in 76% overall yield, by the reaction of 3,4-dihydroisoquinoline with 2-bromoethanol, followed by reaction with aqueous NaOH (Scheme 3).



Scheme 3. Synthesis of tetrahydroisoquinolines (**1**) and (**3**).

Reductive cleavage reactions of compounds (**1**) and (**3**) were carried out under Ar with an excess of alkali metal in the presence of a catalytic amount of naphthalene[10] in tetrahydrofuran (THF).

Selected results obtained in the reductive metalation of tetrahydroisoquinoline (**1**) are reported in Table 1 (Scheme 1). Reduction of tetrahydroisoquinoline (**1**) with 10 equivalents of Li metal in the presence of 20 mol% of naphthalene in THF at –30 °C for 2 h quantitatively afforded, after aqueous work up, tetrahydroisoquinoline (**2a**) (Entry 1). Formation of an intermediate organolithium derivative was evidenced quenching the reduction mixture with D_2O. Under this conditions, 61% deuterium incorporation at C-1 was detected by ^1H NMR spectroscopy of the crude reaction mixture (Table 1, Entry 2). It is worth noting that the intermediate organometal is stable under the reaction conditions, as demonstrated by quenching the reduction mixture with D_2O, after 7 h stirring at –30 °C (Table 1, Entry 3). However, a relatively better result can be obtained running the reduction at –60 °C; under these conditions, deuterium incorporation increased to 69% (Table 1, Entry 4). We were unable to further improve this result, either increasing the relative amount of the metal (up to 20 equivalents, not reported in Table 1), or the relative amount of the catalyst (up to 1 equivalent, not reported in the Table).

Table 1. Reductive lithiation of tetrahydroisoquinoline (**1**) and reaction with electrophiles[a]

Entry	T (°C)	t (h)	EX	Product, E =	Yield (%)[b]
1	-30	2	H_2O	**2a**, H	>95[c]
2	-30	2	D_2O	**2b**, D	61[d]
3	-30	7	D_2O	**2b**, D	59[d]
4	-60	2.5	D_2O	**2b**, D	69[d]
5	-30	2	$PhCH_2Cl$	**2c**, $PhCH_2$	40
6	-30	2	$C_6H_{13}Br$	**2d**, C_6H_{13}	36
7	-60	2.5	$(CH_3)_2CO$	**2e**, $(CH_3)_2COH$	45
8	-60	2.5	$(\underline{CH_2)_5}CO$	**2f**, E = $(\underline{CH_2)_5}COH$	44
9	-60	2.5	$(\underline{CH_2)_4}CO$	**2g**, E = $(\underline{CH_2)_4}COH$	52

[a]All reactions were run in the presence of 10 equivalents of Li metal and in the presence of 20 mol% of $C_{10}H_{10}$. [b]Isolated yield, unless otherwise indicated. [c]As determined by ^1H NMR spectroscopy. [d]Deuterium content, as determined by ^1H NMR spectroscopy (see EXPERIMENTAL).

The organolithium intermediate, obtained as described above, was trapped with different electrophiles, including alkyl halides (Table 1, Entries 5 and 6) and enolizable ketones (Table 1, Entries 7-9). The

corresponding 1-substituted tetrahydroisoquinolines (**2c-g**) were obtained in 36-52% yields. Taking into account the relative amount of the organolithium derivative formed in the reductive cleavage step, these results can be considered as satisfactory.

It is worth noting that our procedure represents an umpolung of the known reactivity of 1-alkoxy-substituted tetrahydroisoquinolines towards nucleophilic reagents,[11-13] thus allowing the coupling of the 1-tetrahydroisoquinolyl skeleton with alkyl halides, as well as its addition to carbonyl derivatives.

As a further extension of this procedure, we investigated the reductive cleavage of the polycyclic tetrahydroisoquinoline (**3**). Selected results are reported in Table 2 (Scheme 2).

Table 2. Reductive lithiation of tetrahydroisoquinoline (**3**) and reaction with electrophiles[a]

Entry	Metal	T (°C)	t (h)	EX	Product, E =	Yield (%)
1	Li	-30	4	H_2O	**3** + **4a**, H	n.d.[b]
2	Li	-20	4	H_2O	**3** + **4a**, H	n.d.[b]
3	Li	0	5	H_2O	**4a**, H	n.d.[b]
4	K	-30	5	H_2O	**4a**, H	50[c]
5	K	-30	5	D_2O	**4b**, D	75[d]
6	K	-30	5	C_4H_9Br	**4c**, C_4H_9	33[c]

[a]All reactions were run in the presence of 10 equivalents of metal and in the presence of 20 mol% of $C_{10}H_{10}$. [b]n.d. = not determined, several unidentified products also formed; see text. [c]Isolated yield. [d]Deuterium content, as determined by ^1H NMR spectroscopy (see EXPERIMENTAL).

Attemps to obtain selective reductive cleavage of tetrahydroisoquinoline (**3**) under the reaction conditions reported above, were unsuccessful. Indeed, reduction of tetrahydroisoquinoline (**3**) with Li metal and a catalytic amount of naphthalene (20 mol%), between –30 and –20 °C, led to relative complex reaction mixtures containing, besides the desired alcohol (**4a**) unreacted starting material as well as several unindentified reaction products (Table 2, Entries 1 and 2). A reaction run at 0 °C, under otherwise identical conditions, led to complete conversion of the starting material, but afforded an intractable reaction mixture (Table 2, Entry 3).

Better results were obtained employing, as a reducing agent, K in the presence of a catalytic amount of naphthalene (20 mol%), at –30 °C. Under the new conditions, aqueous work up allowed the recovery of tetrahydroisoquinoline (**4a**) in 50% isolated yield (Table 2, Entry 4). Under similar conditions, D_2O quenching evidenced the formation of an intermediate organometal derivative. To our surprise, however, the resulting tetrahydroisoquinoline (**4b**) incorporated deuterium at C-4, not at C-1 (Table 2, Entry 5).

Furthemore, quenching a similar reduction mixture with C_4H_9Br, led to the formation of the 4-alkyl-substituted tetrahydroisoquinoline (**4c**) in 33% isolated yield (Table 2, Entry 6).

Structures of tetrahydroisoquinolines (**4b**) and (**4c**) were unambiguously determined by means of their NMR spectra (see EXPERIMENTAL). Indeed, the ^{1}H NMR spectrum of compound (**4b**) showed a 2 H's singlet at 3.71, assigned to protons at C-1, and a multiplet at 2.88-2.95, assigned at C-4, with an integration corresponding to 1.25 protons. The last resonance has to be compared with a 2 H's multiplet (2.92-2.98), assigned to protons at C-4 in the ^{1}H NMR spectrum of non-deuterated tetrahydroisoquinoline (**4a**).

Accordingly, the ^{1}H NMR spectrum of the 4-butyl-substituted tetrahydroisoquinoline (**4c**) showed two doublets corresponding to 1 H each, at δ 3.62 and 3.83 (J = 15.2 Hz), assigned to diastereotopic protons at C-1. Finally, its off-resonance decoupled ^{13}C NMR spectrum exhibits a doublet at δ 38.0, in agreement with the chemical shift of a benzylic carbon, not substituted with a nitrogen atom.

These results represents a strong evidence that reductive metalation of tetrahydroisoquinoline (**3**) occurs with generation of a carbanionic center at C-1 which, successively, rearranges to the corresponding C-4 carbanion. To the best of our knowledge, such a prototropic rearrangement is without precedent, and it has no similarities with the results observed in the reductive lithiation of tetrahydroisoquinoline (**1**).

To rationalize these results, we assume that the carbanionic center at C-4 is less basic than the carbanionic center at C-1, due to the presence of the nitrogen atom. Furthermore, K as a counter ion enhances this difference, as compared with Li, thus promoting the prototropic rearrangement. From this point of view, it is worth noting that metalation of tetrahydroisoquinolines occurs selectively at C-4,[2] whilst the higher basicity of potassium organometals, with respect to lithium organometals, is well documented.[14,15]

Although unexpected, these findings disclose a new approach to 4-substituted *N*-alkyltetrahydro-isoquinilines.

EXPERIMENTAL

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation immediately prior to use. Li wire, 99.9 % purity, was 3.2 mm diam., and D_2O was 99.8% isotopic purity. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ (unless otherwise indicated), with $SiMe_4$ as internal standard, on a Varian VXR 300. Deuterium incorporation was calculated by monitoring the ^{1}H NMR spectra of crude reaction mixtures, and by comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. IR spectra were obtained on thin films with a Perkin Elmer 1310 spectrophotometer. Flash chromatography were performed on Merck silica gel 60 (40-63 μm), and TLC analyses on Macherey-Nagel silica gel pre-coated plastic sheets (0.20

mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

1-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1): Methyl iodide (12.83 g, 90.4 mmol) was added, under dry N_2, to a well stirred suspension of 3,4-dihydroisoquinoline[7] (5.93 g, 45.2 mmol) in 70 mL of dry acetone. The resulting mixture was stirred at rt overnight, during which time a yellow solid separated. The yellow solid was filtered off, washed with cold acetone and dried, to afford 2-methyl-3,4-dihydroisochinolinium iodide (9.87 g, 80%), mp 127-128 °C (lit.,[8] mp 127-128 °C), which was not further characterized.

Na metal (0.84 g, 36.5 mg atom) was dissolved, under N_2, in dry CH_3OH (60 mL). The solution was chilled to 0 °C, and the yellow solid was added in small portions. The resulting mixture was stirred for 20 min, then allowed to warm to rt, filtered and the solvent evaporated in vacuo.

The residue was dissolved in Et_2O (100 mL), filtered again, and the solvent evaporated to afford a residue which, distilled in vacuo, afforded a colourless oil (4.50 g, 56% overall), characterized as follows: bp 65 °C/1 mmHg ; ^{1}H NMR (CD_3OD) δ 2.57 (3H, s, NCH_3), 2.64-3.36 (4H, m, 2 x CH_2), 3.39 (3H, s, OCH_3), 4.82 (1H, s, CH), 7.14-7.33 (4H, m, 4 x ArH); ^{13}C NMR (CD_3OD) δ 28.5, 41.5, 47.4, 49.8, 93.7, 126.9, 128.9, 129.1, 129.6, 135.6, 136.3; Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.37; H, 8.65; N, 8.15.

2,3,6,10b-Tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (3): Compound (**3**) was synthesized according to a literature procedure,[9] in 76% overall yield, and was characterized as follows: mp 48-50 °C (lit.,[9] mp 50 °C); R_f = 0.35 (petroleum ether/AcOEt/Et_3N = 4:6:1); ^{1}H NMR (DMSO-d_6) δ 2.56-2.88 (4H, m, 2 x CH_2), 3.08-3.18 (1H, m, CH) 3.23-3-31 (1H, m, CH), 3.60-3.67 (1H, m, CHO), 3.72-3.80 (1H, m, CHO), 5.06 (1H, s, ArCHO), 7.15-7.32 (4H, m, 4 x ArH); ^{13}C NMR (DMSO-d_6) δ 29.1, 44.7, 54.1, 61.4, 89.6, 125.9, 127.9, 128.0, 128.8, 132.3, 135.0.

Reductive cleavage of tetrahydroisoquinolines (1) and (3) and reaction with electrophiles. General procedure: Li wire (210 mg, 30 g atom) was placed under Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in dry THF (15 mL). A catalytic amount of naphthalene (77 mg, 0.6 mmol) was added to the suspended metal, each metal piece was cut into 2-3 smaller pieces with a spatula, and the mixture stirred until a dark green colour appeared.

Alternatively, K dispersion was prepared in a similar apparatus by vigorously stirring the freshly cut metal (1.17 g, 30 g atom) in dry THF (15 mL) at reflux temperature for 10 min; the metal suspension was allowed

to cool to rt without stirring. A catalytic amount of naphthalene (77 mg, 0.6 mmol) was added to the suspended metal, and the mixture stirred until a dark green colour appeared.

The mixture was chilled to the reported temperature (Tables) and a solution of the appropriate tetrahydoisoquinoline (3 mmol), dissolved in 5 mL of dry THF, was added dropwise. The mixture was stirred for the reported time (Tables), and a solution of the appropriate electrophile (1.2 equiv) in THF (2 mL) was slowly added. After stirring for 30 min, the mixture was quenched by slow dropwise addition of H_2O (10 mL, *caution*), the cold bath removed, and the resulting mixture extracted with Et_2O (3 x 10 mL). The organic phase was washed with brine (10 mL), dried (K_2CO_3) and the solvent evaporated.

Reaction products were characterized as follows.

2-Methyl-1,2,3,4-tetrahydroisoquinoline (2a): Purified by flash chromatography (petroleum ether/AcOEt/Et_3N = 6:4:1), R_f = 0.50; bp 102 °C/20 mmHg (lit.,[16] bp 50-52/0.1 mm/Hg); ^{1}H NMR δ 2.45 (3H, s, NCH_3), 2.68 (2H, t, *J* = 6.0 Hz, CH_2), 2.92 (2H, t, *J* = 6.0 Hz, CH_2), 3.58 (2H, s, CH_2), 6.98-7.04 (1H, m, ArH), 7.06-7.18 (3H, m, 3 x ArH); ^{13}C NMR δ 29.2, 46.0, 52.8, 57.9, 125.5, 126.1, 126.4, 126.6, 133.8, 134.7.

1-Deutero-2-methyl-1,2,3,4-tetrahydroisoquinoline (2b): Purified by flash chromatography (petroleum ether/AcOEt/Et_3N = 6:4:1), R_f = 0.50; ^{1}H NMR δ 2.45 (3H, s, NCH_3), 2.64-2.74 (2H, m, CH_2), 2.92 (2H, t, CH_2, *J* = 6.0 Hz), 3.54 (1.4 H, br s, CHD, 60% D content), 6.98-7.04 (1H, m, ArH), 7.06-7.18 (3H, m, 3 x ArH); ^{13}C NMR δ 29.0, 45.9, 52,8, 57.4 (t, *J* = 21 Hz), 125.5, 126.1, 126.3, 127.6, 133.6, 134.3.

1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (2c): Purified by flash chromatography (petroleum ether/Et_3N = 10:1), R_f = 0.37; bp 95-100 °C/1 mmHg (lit.,[17] 177-180 °C/12 mmHg); ^{1}H NMR δ 2.50 (3H, s, NCH_3), 2.65 (1H, dt, *J* = 15.9, 4.8 Hz, CH), 2.76 (1H, dt, *J* = 12.0, 4.8 Hz, CH), 2.81-2.95 (2H, m, CH_2), 3.12-3.26 (2H, m, CH_2), 3.81 (1H, t, *J* = 6.3 Hz, ArH), 6.75 (1H, d, *J* = 7.8 Hz, ArH), 6.98-7.14 (5H, m, 5 x ArH), 7.15-7.29 (3H, m, 3 x ArH); ^{13}C NMR δ 25.9, 41.5, 42.8, 47.0, 65.0, 125.3, 125.9, 125.9, 127.9, 128.0, 128.7, 129.6, 134.3, 137.8, 140.0.

1-Hexyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (2d): Purified by flash chromatography (petroleum ether/AcOEt/Et_3N = 9.5:0.5:1), R_f = 0.53; bp 90-95 °C/1 mmHg; ^{1}H NMR δ 0.82-0.91 (3H, m, CH_3), 1.16-1.45 (8H, m, 4 x CH_2), 1.64-1.84 (2H, m, CH_2), 2.45 (3H, s, NCH_3), 2.62-2.74 (1H, m, CH), 2.76-2.88 (2H, m, CH_2), 3.08-3.17 (1H, m, CH), 3.43 (1H, t, *J* = 5.4 Hz, CH), 6.98-7.20 (4H, m, 4 x ArH); ^{13}C NMR δ 14.1, 22.7, 25.5, 26.2, 29.7, 31.8, 34.9, 42.9, 48.4, 63.8, 125.6, 125.6, 127.1, 128.6, 134.6, 138.6; Anal. Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 82.91; H, 11.02; N, 6.07.

2-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-ol (2e): Purified by flash chromatography (AcOEt/MeOH/Et_3N = 10:0.1:1), R_f = 0.61; bp 65-70 °C/1 mmHg; ν_{max}/ cm^{-1} 3440; ^1H NMR δ 0.89 (3H, s, CH_3), 1.34 (3H, s, CH_3), 2.52-2.60 (1H, m, CH), 2.60 (3H, s, NCH_3), 2.70-2.78 (1H, m, CH), 2.79-2.87 (1H, m, CH), 3.34 (1H, quint, *J* = 5.6 Hz, CH), 3.48 (1H, s, CH), 4.25 (1H, br s, OH), 7.10-7.20 (4H, m, 4 x ArH); ^{13}C NMR δ 25.8, 27.5, 29.0, 46.9, 50.6, 72.5, 73.3, 125.5, 126.5, 128.1, 129.0, 134.1, 136.2; Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.95; H, 9.42; N, 6.75.

1-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexan-1-ol (2f): Purified by flash chromatography (petroleum ether/AcOEt/Et_3N = 6:4:1), R_f = 0.66; bp 90-95 °C/1 mmHg; ν_{max}/ cm^{-1} 3460; ^1H NMR δ 0.84 (1H, td, *J* = 13.2, 4.4 Hz, CH), 0.92-1.06 (1H, m, CH), 1.32-1.44 (2H, m, CH_2), 1.50-1.75 (6H, m, 3 x CH_2), 2.50 (1H, td, *J* = 10.4, 4.0 Hz, CH), 2.58 (3H, s, NCH_3), 2.67 (1H, dt, *J* = 16.0, 4.8 Hz, CH), 2.68 (1H, dt, *J* = 16.0, 4.8 Hz, CH), 3.28-3.40 (2H, m, CH_2), 3.84 (1H, br s, OH), 7.08-7.20 (4H, m, 4 x ArH). ^{13}C NMR δ 21.8, 22.3, 25.7, 28.1, 33.5, 36.8, 47.2, 51.3, 73.3, 74.1, 125.4, 126.4, 127.9, 129.4, 134.3, 136.8; Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.21; H, 9.73; N, 5.60.

1-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclopentan-1-ol (2g): Purified by flash chromatography (petroleum ether/AcOEt/Et_3N = 6:4:1), R_f = 0.63; bp 85-90 °C/1 mmHg; ν_{max}/ cm^{-1} 3440; ^1H NMR δ 1.18-1.88 (8H, m, 4 x CH_2), 2.59 (3H, s, NCH_3), 2.68-2.92 (4H, m, 2 x CH_2), 3.32-3.46 (1H, m, CH), 3.72 (1H, br s, OH), 7.11-7.21 (4H, m, 4 x ArH); ^{13}C NMR δ 22.9, 23.9, 25.2, 36.3, 39.5, 44.5, 48.1, 69.8, 83.4, 125.6, 126.8, 128.6, 129.2, 134.5, 136.8; Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.73; H, 9.38; N, 5.94.

2-(1,2,3,4-Tetrahydroisoquinolin-2-yl)ethanol (4a): Purified by flash chromatography (AcOEt/MeOH/Et_3N = 9:3:1); R_f = 0.43; bp 140-145 °C/1 mmHg (lit.,[18] 164-166 °C/12 mmHg); ν_{max}/ cm^{-1} 3410; ^1H NMR δ 2.75-2.80 (2H, m, CH_2), 2.84-2.91 (2H, m, CH_2), 2.92-2.98 (2H, m, CH_2), 3.17 (1H, br s, OH), 3.72-3.76 (2H, m, CH_2O), 3.78 (2H, s, $ArCH_2N$), 7.00-7.06 (1H, m, ArH), 7.10-7.19 (3H, m, 3 x ArH); ^{13}C NMR δ 28.8, 50.5, 55.5, 57.9, 58.9, 125.7, 126.3, 126.5, 128.6, 133.9, 134.8.

2-(4-Deutero-1,2,3,4-tetrahydroisoquinolin-2-yl)ethanol (4b): Purified by flash chromatography (AcOEt/MeOH/Et_3N = 9:3:1); R_f = 0.43; ^1H NMR δ 2.70-2.74 (2H, m, CH_2), 2.79-2.84 (2H, m, CH_2), 2.88-2.95 (1.25 H, m, CHD, 75% D content), 3.21 (1H, br s, OH), 3.68-3.74 (2H, m, CH_2O), 3.71 (2H, s, $ArCH_2N$) 7.00-7.06 (1H, m, ArH), 7.10-7.19 (3H, m, 3 x ArH).

2-(4-Butyl-1,2,3,4-tetrahydroisoquinolin-2-yl)ethanol (4c): Purified by flash chromatography (petroleum ether/AcOEt/Et_3N = 4:6:1); R_f = 0.43; bp 105-110 °C/0.1 mmHg; ν_{max}/ cm^{-1} 3380; ^1H NMR δ 0.83-0.96 (3H, m, CH_3), 1.28-1.46 (4H, m, 2 x CH_2), 1.66-1.76 (2H, m, CH_2), 2.66-2.90 (5H, m, 2 x CH_2, CH), 3.08 (1H, br s, OH), 3.62 (1H, d, *J*=15.2 Hz, CH_2), 3.72 (2H, t, CH_2, *J*=5.6 Hz), 3.83 (1H, d, *J*=15.2 Hz, CH_2), 7.01-7.04 (1H, d, *J* = 6.8 Hz, ArH), 7.11-7.23 (3H, m, 3 x ArH); ^{13}C NMR δ 14.0 (q), 22.8 (t), 29.5 (t), 35.5 (t), 38.0 (d), 54.6 (t), 56.2 (t), 57.9 (t), 59.1 (t), 125.7 (d), 126.4 (d), 126.4 (d), 128.1 (d), 133.7 (s), 138.7 (s) ; Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.04; H, 10.12; N, 6.13.

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