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Ready Access to 6-Alkyl, 6-Phenyl, 5,6-Dialkyl, and 5-Alkyl-6-phenyl Substituted 1,2,3,4-Tetrahydroisoquinolines

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Summary. Readily available bicyclic enone precursors were used in a novel strategy for the synthesis of 6-mono- and 5,6-disubstituted tetrahydroisoquinolines (alkyl and phenyl in position 6, hydrogen and methyl in position 5). After 1,2-addition of the respective organometallic reagents to the enones, the crude intermediate alcohols were subjected to a dehydratization/aromatization procedure using the *in situ* generated triphenylmethyl cation. Overall yields obtained by this procedure were between 27 and 86%. Whereas the synthesis of N-benzyl protected 6-*t*-butyl-tetrahydroisoquinoline was successful, partial dealkylation occurred in the 5-methyl-6-*t*-butyl analogue. Some of the new N-benzyl tetrahydroisoquinolines were transformed into the corresponding unprotected heterocycles.

Keywords. Aromatization; Enones; Heterocycles; Organometallics; Tetrahydroisoquinolines.

Introduction

In the field of medicinal chemistry, semi-rigid analogues of biologically interesting compounds, synthesized by incorporating conformationally flexible structures in different ring systems, are frequently used for the elucidation of the most active conformation. This method has also been applied successfully to the antimycotic naftifine [1], the first representative of the allylamine class of selective inhibitors of the fungal squalene epoxidase [2, 3]. Extensive structure-activity relationship studies within this class of antifungal agents [1, 4–9] yielded – among many other potent compounds – the highly active benzylamine derivative **1** [10, 11]. In the course of exploring the active conformation of **1** we anticipated the synthesis of its semi-rigid analogue **2** (Fig. 1). A literature search on potential intermediates revealed only one hit, *i.e.* the reported procedure for the synthesis of 6-*t*-butyl-isoquinoline [12]. Although the authors investigated various methods for the *Pomerantz-Fritsch* cyclization, they obtained a maximum yield of only 4% for this step. The attempt to cyclize the corresponding benzylaminoacetaldehyde diethyl acetal has been described to produce only unstable oils. In the present

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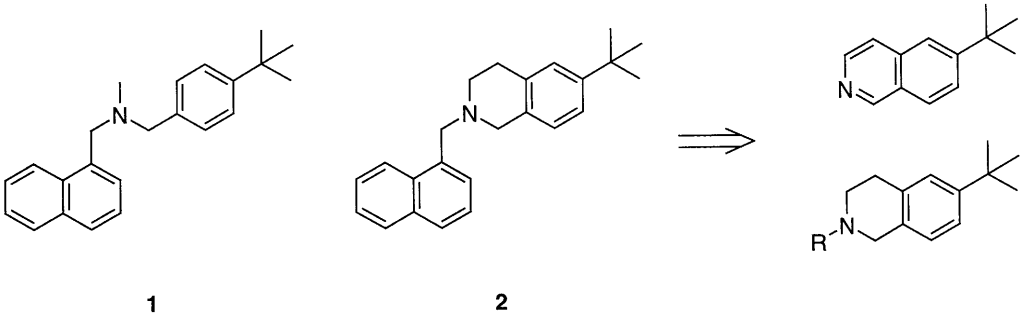


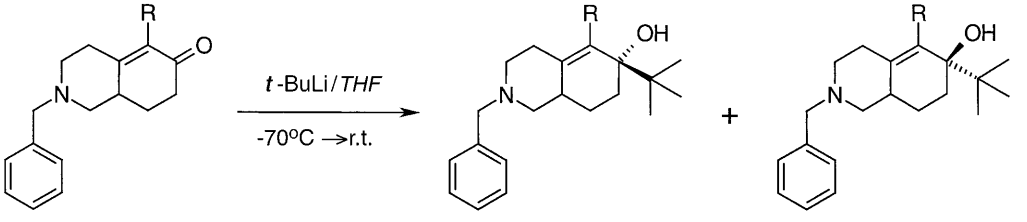
Fig. 1. Antifungal benzylamine **1**, its conformationally restricted analogue **2**, and potential key intermediates for the synthesis of **2**

communication, we report on a new strategy which provides ready access to 6-substituted 1,2,3,4-tetrahydroisoquinolines.

Results and Discussion

Ring closure reactions to isoquinoline derivatives usually require strongly acidic conditions. To circumvent potential instability of the product and/or possible dealkylation by a reversed *Friedel-Crafts* reaction, we envisaged to start the synthesis from a bicyclic precursor. Thus, we reacted N-protected hexahydroisoquinolin-6-one **3** [13], easily accessible from N-benzyl-4-piperidone, with *t*-butyllithium (Scheme 1).

The two isomers of alcohol **4a** were the main products and the only compounds which could be isolated in pure form from the product mixture, in addition to some recovered starting material. When the reaction mixture was allowed to stand at room temperature for a longer period of time, *e.g.* overnight, the formation of minor by-products, presumably derived from dehydratization (compounds with the same chromatographic properties were formed upon treatment of **4a** with 6 *N* HCl at ambient temperature), was observed by TLC. The product resulting from 1,4-addition of the organometallic reagent was not detected under the conditions used. The yields of the isolated alcohols, however, were quite moderate, partially due to losses during the chromatographic purification: 39% for **4aa** (OH equitorial, *t*-butyl axial), 12% for **4ab** (OH axial, *t*-butyl equitorial), and 12% of recovered starting



3: *R* = H
5: *R* = methyl

4aa: *R* = H, OH equitorial
4ba: *R* = methyl, OH equitorial

4ab: *R* = H, OH axial
4bb: *R* = methyl, OH axial

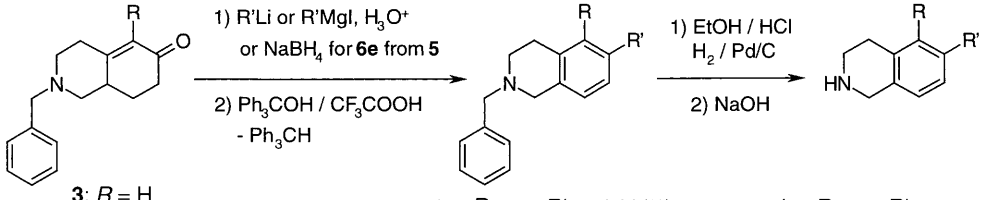
Scheme 1. Reaction of enones **3** and **5** with *t*-butyllithium

material **3**. As a consequence of the labour-intensive chromatography step and the moderate yields, the crude product mixture obtained by the addition of *t*-butyllithium to enone **3** was subjected to treatment with triphenylmethanol in boiling trifluoroacetic acid (Scheme 2). Under these conditions, the desired tetrahydroisoquinoline derivative **6a** was formed by elimination of water and subsequent aromatization using the ability of the *in situ* generated triphenylmethyl cation to abstract hydride from the intermediate cylohexadiene system [14, 5]. Following this procedure, compound **6a** was obtained in 65% overall yield starting from **3**, which is a higher conversion than the combined yields of the isolated alcohols **4aa** and **4ab** from the first step. When these purified alcohols **4aa** and **4ab** were used as starting material for the dehydratization/aromatization reaction, **6a** was obtained in more than 90% yield. These findings confirmed that one of the limiting factors for a high-yield conversion of **3** into **6a** was the isolation and purification of the intermediate alcohol **4a**.

In the next step (Scheme 2), **6a** was hydrogenated over Pd/C in ethanol to produce the corresponding deprotected tetrahydroisoquinoline **7a**. Target compound **2**, the desired conformationally restricted analogue of **1**, was then readily prepared from **7a** by alkylation with 1-chloromethylnaphthalene (see Ref. [9]; details are not described here).

In order to demonstrate a more general applicability of the method, we employed several different organometallic reagents (Scheme 1). Since the aim of the study was to develop an easy and straightforward method, the intermediate alcohols produced in the addition reaction were not isolated, and the crude product mixtures were used in the following reaction. The yields of compounds **6b–d** are listed in Scheme 2. Whereas aliphatic organometallic reagents gave overall yields between 51 and 65%, the use of phenyllithium afforded **6d** in 86% yield.

For further evaluation of scope and limitation of the strategy, the 5-methyl substituted enone derivative **5** [15] was reacted with selected oganometallic reagents (Scheme 2). Again, the crude product mixture was heated with triphenyl-



3: *R* = H
5: *R* = methyl

	R	*R'*	yield (%)
6a	H	*t*-butyl	65
6b	H	ethyl	53
6c	H	*n*-butyl	51
6d	H	phenyl	86
6e	methyl	H	27
6f	methyl	*t*-butyl	-
6g	methyl	ethyl	34
6h	methyl	*n*-butyl	46
6i	methyl	phenyl	49

	R	*R'*	yield (%)
7a	H	*t*-butyl	76
7b	H	ethyl	83
7c	H	*n*-butyl	75
7d	H	phenyl	76
7e	methyl	ethyl	73
7f	methyl	phenyl	75

Scheme 2. Synthesis of tetrahydroisoquinolines **6** and **7** from enones **3** and **5**

methanol in trifluoroacetic acid as solvent. Following this procedure, the corresponding 6-substituted 5-methyl-1,2,3,4-tetrahydroisoquinolines **6g–i** (R = ethyl, *n*-butyl, phenyl) were prepared. The yields of isolated products were generally moderate (Scheme 2). When *t*-butyllithium was reacted with **5** and the crude product subsequently heated with triphenylmethanol in trifluoroacetic acid, we isolated a non-separable mixture of the desired compound **6f** ($R = t$-butyl) and the monosubstituted analogue **6e** in a ratio of 1:2. The addition reaction of *t*-butyllithium with enone **5** was repeated, and both isomers of alcohol **4b** were isolated by chromatography (48% for **4ba** (OH equitorial, *t*-butyl axial), 18% for **4bb** (OH axial, *t*-butyl equitorial)). Treatment of both pure isomers of **4b** as well as of their crude product mixture before with triphenylmethanol in boiling trifluoroacetic acid in separate experiments gave almost identical results, *i.e.* a low yield of a mixture of **6f** and **6e** in a ratio of approximately 1:2. Shortening of the reaction time did not significantly alter this ratio (determined by ^{1}H NMR spectroscopy of the isolated products), and the consumption of the starting material **4b** was not complete. These findings indicated that the *t*-butyl group was partially lost during the dehydratization/aromatization procedure. Generation of reactive species in the dealkylation process might also explain the low yield of products **6f** and **6e**. So far, we have no sound explanation why the *t*-butyl group in **6a** as well as in the intermediates of its synthesis is stable towards the recation conditions, whereas in the corresponding 5-methyltetrahydroisoquinoline series partial dealkylation is observed. For confirmation of the structure of the by-product, we prepared pure **6e** by reduction of enone **5** using sodium borohydride followed by the same dehydratization/aromatization procedure (Scheme 2). The yield of isolated **6e** was unexpectedly low (27%). When compared to the yields of 6-monosubstituted tetrahydroisoquinolines **6a–d**, those obtained for all studied 5-methyl analogues **6e–i** were considerably lower. Whereas steric factors might be responsible in all steps, more detailed investigations are required to clarify this issue.

Finally, some of the N-benzyl protected tetrahydroisoquinolines **6** were successfully converted into the corresponding deprotected analogues **7** (Scheme 2) by catalytic hydrogenation.

In summary, we have developed a procedure for the synthesis of some 6-substituted and 5-methyl-6-substituted 1,2,3,4-tetrahydroisoquinolines starting from readily available bicyclic precursors. Further studies are required to explore the full scope of the sequence, in particular for the introduction of functional groups in position 5 and/or 6 of 1,2,3,4-tetrahydroisoquinolines.

Experimental

Melting points were determined on a Reichert Thermovar microscope and are not corrected. The temperature is given in °C. Thin-layer chromatography was performed using silica gel F_{254} plates (Merck), and bands were visualized with UV, iodine vapour, or potassium permanganate. Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck), pressure 3–5 bar. ^{1}H NMR spectra were routinely recorded at 250 MHz (Bruker WM 250), for compound **4** at 500 MHz (Bruker AMX 500), usually in $CDCl_3$ with *TMS* as internal standard. Chemical shifts are given as δ units. Elemental analyses were performed by Mag. *J. Theiner*, Microanalytical Laboratory at the University of Vienna, Institute of Physical Chemistry. *n*-Butyllithium (1.6 *M* solution in hexane), *t*-butyllithium (1.5 *M* in pentane), and phenyllithium (1.6 *M* in cyclohexane/ether) were

purchased from Fluka. Ethylmagnesium iodide was freshly prepared from ethyl iodide and magnesium in Et_2O and used immediately.

2-Benzyl-6-t-butyl-1,2,3,4,6,7,8,8a-octahydro-6-isoquinolinol (**4aa, 4ab**; $C_{20}H_{29}NO$)

A solution of 3.4 g (14.1 mmol) of enone **3** in dry *THF* (35 cm^3) was cooled to −70°C and treated with 11 cm^3 (16.5 mmol, 1.5 *M* solution in pentane) of *t*-butyllithium under argon. After stirring for 1 h at −70°C, the mixture was allowed to warm to room temperature. Then the mixture was poured onto ice/aqueous NH_4Cl solution (150 cm^3), diluted with Et_2O (40 cm^3), and stirred vigorously. The aqueous layer was separated and extracted with Et_2O (2×40 cm^3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give crude **4a** (mixture of stereoisomers). The crude product thus obtained was used in the subsequent dehydratization/aromatization reaction without further purification or chromatographed (SiO_2, ethyl acetate:toluene = 1:1; additional TLC detection using CH_2Cl_2:MeOH = 9:1 allows ready discrimination between **4ab** and starting material **3**) to obtain the pure isomers **4aa** (OH in equitorial, *t*-butyl in axial position) and **4ab** (OH in axial, *t*-butyl in equitorial position) in 39 and 12% yield, respectively.

4aa: Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.20$–7.35 (m, 5H), 5.58 (q, $J = 2$ Hz, 1H, H-5), 3.50 (s, 2H), 2.96 (ddd, $J = 2.0 + 5.5 + 11$ Hz, 1H, H-1_{eq}), 2.92 (dddd, $J = 2 + 2.5 + 5 + 10.5$ Hz, 1H, H-3_{eq}), 2.37 (dddd, $J = 2 + 5 + 12 + 14$, 1H, H-4_{ax}), 2.15–2.23 (m, 1H, H-8a), 2.12 (dt, $J = 2.5 + 14$ Hz, 1H, H-4_{eq}), 1.92 (ddd, $J = 3 + 10.5 + 12$, 1H, H-3_{ax}), 1.53–1.70 (m, 4H, H-1_{ax}, H-7_{ax}, H-7_{eq}, H-8), 1.32–1.42 (m, 1H, H-8), 0.93 (s, 9H) ppm.

4ab: Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$–7.35 (m, 5H), 5.59 (dd, $J = 2 + 2.6$ Hz, 1H, H-5), 3.50 (s, 2H), 2.99 (dddd, $J = 2 + 2.5 + 4.5 + 10.5$ Hz, 1H, H-3_{eq}), 2.81 (ddd, $J = 2.0 + 4.5 + 10.5$ Hz, 1H, H-1_{eq}), 2.34 (dddd, $J = 2.6 + 4.5 + 12.5 + 13$, 1H, H-$4_{ax}$), 2.25–2.29 (m, 1H, H-8a), 2.07 (dt, $J = 2.5 + 13$ Hz, 1H, H-4_{eq}), 1.98 (dddd, $J = 4 + 7 + 12 + 14$ Hz, 1H, H-8_{ax}), 1.87 (ddd, $J = 2.5 + 10.5 + 12.5$, 1H, H-3_{ax}), 1.79 (dd, $J = 10.5 + 11.5$ Hz, 1H, H-1_{ax}), 1.69 (ddd, $J = 4 + 12 + 13.5$ Hz, 1H, H-7_{ax}), 1.52 (ddd, $J = 4 + 5.5 + 13.5$ Hz, 1H, H-7_{eq}), 1.34 (dddd, $J = 3 + 4 + 5.5 + 14$ Hz, 1H, H-8_{eq}), 0.97 (s, 9H) ppm; NOEs observed from *t*-butyl to H-7_{ax}, H-7_{eq}, and H-5: 9.4, 5.5, and 17%.

2-Benzyl-6-t-butyl-5-methyl-1,2,3,4,6,7,8,8a-octahydro-6-isoquinolinol (**4ba, 4bb**; $C_{21}H_{31}NO$)

Following the procedure described for the synthesis of **4a**, reaction of enone **5** with *t*-butyllithium gave two isomeric alcohols as yellowish oils after silica gel chromatography (toluene:ethylacetate = 2:1).

4ba (OH in equitorial, *t*-butyl in axial position): 48% yield; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$–7.35 (m, 5H), 3.50 (d, $J = 13.1$ Hz, 1H, Ph-CH_2N), 3.46 (d, $J = 13.1$ Hz, 1H, Ph-CH_2N), 2.84–2.93 (m, 2H, H-3_{eq}, H-1_{eq}), 2.63 (dt, $J = 2.5 + 14.5$ Hz, 1H, H-4_{eq}), 2.13–2.20 (m, 1H, H-8a), 1.99–2.08 (m, 1H, H-4_{ax}), 1.89 (ddd, $J = 2.5 + 10.6 + 13.4$ Hz, 1H, H-3_{ax}), 1.78–1.84 (m, 1H, H-7_{ax}), 1.77 (t, $J = 1.8$ Hz, 3H, CH_3), 1.59–1.70 (m, 3H, H-1_{ax}, H-7_{eq}, H-8_{eq}), 1.10–1.17 (m, 1H, H-8_{ax}), 0.98 (s, 9H) ppm.

4bb (OH in axial, *t*-butyl in equitorial position): 18% yield; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.23$–7.36 (m, 5H), 3.50 (d, $J = 13.1$ Hz, 1H, Ph-CH_2N), 3.46 (d, $J = 13.1$ Hz, 1H, Ph-CH_2N), 2.97 (dddd, $J = 2.1 + 2.5 + 4.7 + 10.8$ Hz, 1H, H-3_{eq}), 2.83 (ddd, $J = 2.1 + 4.5 + 10.6$ Hz, 1H, H-1_{eq}), 2.55 (dt, $J = 2.5 + 13.9$ Hz, 1H, H-4_{eq}), 2.26–2.34 (m, 1H, H-8a), 2.20–2.24 (m, 1H, H-7_{eq} or H-8_{eq}), 2.02–2.09 (m, 1H, H-4_{ax}), 1.88 (ddd, $J = 2.5 + 10.8 + 13.4$, 1H, H-3_{ax}), 1.76 (dd, $J = 1.3 + 2.1$ Hz, 3H, CH_3), 1.57–1.68 (m, 2H, H-7_{eq} or H-8_{eq}, H-1_{ax}), 1.32–1.46 (m, H-7_{ax}, H-8_{ax}), 1.01 (s, 9H) ppm.

2-Benzyl-6-t-butyl-1,2,3,4-tetrahydroisoquinoline (**6a**; $C_{20}H_{25}N$)

A mixture of 1.4 g (4.7 mmol) of crude **4a**, 1.35 g (5.17 mmol) of triphenylmethanol, and 12 cm^3 trifluoroacetic acid was heated to reflux for 6 h, cooled, and poured onto ice/water (100 cm^3). The

aqueous phase was adjusted to *pH* 9 by cautious addition of solid Na_2CO_3 and extracted with Et_2O ($3\times30\,cm^3$). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. Purification by column chromatography on silica gel (toluene:ethyl acetate = 9:1) afforded 847 mg (65%) of **6a**. When pure **4aa** or **4ab** was subjected to the same conditions, **6a** was obtained in 94% yield.

6a: Yellowish crystals; m.p.: 49–51°C; ^1H NMR ($CDCl_3$): $\delta = 7.15$–7.44 (m, 5H), 7.11–7.19 (m, 2H), 6.94 (d, $J = 7.9$ Hz, 1H), 3.69 (s, 2H), 3.62 (s, 2H), 2.91 (t, $J = 5.8$ Hz, 2H), 2.76 (t, $J = 5.8$ Hz, 2H), 1.28 (s, 9H) ppm; calc.: C 85.97, H 9.02, N 5.01; found: C 86.00, H 8.80, N 4.80.

2-Benzyl-6-ethyl-1,2,3,4-tetrahydroisoquinoline (**6b**; $C_{18}H_{21}N$)

The *Grignard* reagent, prepared from 151 mg (6.21 mmol) of Mg and 970 mg (6.22 mmol) of ethyl iodide in dry Et_2O, was cooled to −15°C and treated slowly with 500 mg (2.07 mmol) of enone **3** dissolved in Et_2O/*THF* (1/1). The mixture was stirred overnight at room temperature and then poured onto ice/aqueous NH_4Cl solution ($50\,cm^3$). The aqueous layer was separated and extracted with Et_2O ($3\times25\,cm^3$). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was taken up in trifluoroacetic acid ($6\,cm^3$), and 293 mg (2.28 mmol) of triphenylmethanol were added. The mixture was heated to reflux for 2 h, cooled, and poured onto ice/water ($50\,cm^3$). The aqueous phase was adjusted to *pH* 9 by cautious addition of solid Na_2CO_3 and extracted with Et_2O ($3\times25\,cm^3$). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. Purification by column chromatography on silica gel (toluene: ethyl acetate = 9:1) afforded 275 mg (53%) of **6b**.

6b: Oil; ^1H NMR ($CDCl_3$): $\delta = 7.21$–7.45 (m, 5H), 6.83–7.02 (m, 3H), 3.68 (s, 2H), 3.60 (s, 2H), 2.87 (t, $J = 5.8$ Hz, 2H), 2.73 (t, $J = 5.8$ Hz, 2H), 2.58 (q, $J = 7.6$ Hz, 2H), 1.20 (t, $J = 7.6$ Hz, 3H) ppm; calc.: C 86.01, H 8.42, N 5.57; found: C 86.10, H 8.20, N 5.40.

2-Benzyl-6-n-butyl-1,2,3,4-tetrahydroisoquinoline (**6c**; $C_{20}H_{25}N$)

6c was obtained in 51% yield starting from enone **3** and *n*-butyllithium following the procedures described for the synthesis of crude **4a** and the subsequent transformation into **6a** without purification of the intermediate alcohol.

6c: Oil; ^1H NMR ($CDCl_3$): $\delta = 7.23$–7.46 (m, 5H), 6.86–6.98 (m, 3H), 3.70 (s, 2H), 3.62 (s, 2H), 2.88 (t, $J = 5.9$ Hz, 2H), 2.75 (t, $J = 5.9$ Hz, 2H), 2.55 (t, $J = 7.7$ Hz, 2H), 1.53–1.67 (m, 2H), 1.35 (sex, $J = 7.1$ Hz, 2H), 0.93 (t, $J = 7.1$ Hz, 3H) ppm; calc.: C 85.97, H 9.02, N 5.01; found: C 85.90, H 9.00, N 4.80.

2-Benzyl-6-phenyl-1,2,3,4-tetrahydroisoquinoline (**6d**; $C_{22}H_{21}N$)

86% yield; yellowish crystals; m.p.: 92–96°C; ^1H NMR ($CDCl_3$): $\delta = 7.53$–7.66 (m, 2H), 7.26–7.49 (m, 10H), 7.03–7.12 (m, 1H), 3.71 (s, 2H), 3.67 (s, 2H), 2.97 (t, $J = 5.7$ Hz, 2H), 2.80 (t, $J = 5.7$ Hz, 2H) ppm; calc.: C 88.25, H 7.07, N 4.68; found: C 88.30, H 7.10, N 4.50.

2-Benzyl-5-methyl-1,2,3,4-tetrahydroisoquinoline (**6e**; $C_{17}H_{19}N$)

A solution of 1.5 g (5.88 mmol) of **5** in MeOH ($15\,cm^3$) was treated with 110 mg (2.93 mmol) of $NaBH_4$ and stirred for 1.5 h at room temperature. The mixture was poured into H_2O ($250\,cm^3$) and extracted with Et_2O ($3\times40\,cm^3$). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue (1.25 g) was taken up in trifluoroacetic acid ($15\,cm^3$), and 1.4 g (5.38 mmol) of triphenylmethanol were added. The mixture was heated to reflux for 4 h, cooled, and poured onto ice/water ($300\,cm^3$). The aqueous phase was adjusted to *pH* 9 by cautious addition of

solid Na_2CO_3 and extracted with Et_2O ($3 \times 50\,cm^3$). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was partitioned between 2 *N* aqueous HCl and Et_2O by vigorous stirring for 30 min to remove triphenylmethane and excess triphenylmethanol. The aqueous layer was separated, washed with Et_2O, adjusted to *pH* 9 by cautious treatment with solid Na_2CO_3, and extracted with Et_2O ($3 \times 40\,cm^3$). The combined organic layers were dried over $MgSO_4$, and evaporated *in vacuo*. Purification by column chromatography on silica gel (toluene:ethyl acetate = 9:1) afforded 376 mg (27%) of **6e** as yellowish oil.

^{1}H NMR ($CDCl_3$): $\delta = 7.23$–7.48 (m, 5H), 6.96–7.09 (m, 2H), 6.86 (dd, $J = 2.2 + 6.5$ Hz, 1H), 3.69 (s, 2H), 3.64 (s, 2H), 2.78 (s, 4H), 2.22 (s, 3H) ppm; calc.: C 86.03, H 8.07, N 5.90; found: C 85.80, H 8.20, N 5.65.

Attempted synthesis of 2-benzyl-6-t-butyl-5-methyl-1,2,3,4-tetrahydroisoquinoline (**6f**; $C_{21}H_{27}N$)

Enone **5** was reacted with *t*-butyllithium and the crude product treated with triphenylmethanol in trifluoroacetic acid as described for the synthesis of **6a**. However, the isolated product (SiO_2 chromatography, toluene:ethyl acetate = 9:1, ~19% yield) was a mixture of **6e** and **6f** (ratio *ca.* 2:1). The same product mixture was obtained when intermediates **4ba** and **4bb** were isolated, purified, and used in the next step. Reduction of the reaction time of the dehydratization/aromatization step to *e.g.* 1 h did not significantly improve the product ratio in favour of **6f**, and the conversion was not complete as observed by TLC.

Characteristic signals of **6f**: ^{1}H NMR ($CDCl_3$): $\delta = 3.67$ (s, $-CH_2-$), 3.61 (s, $-CH_2-$), 2.36 (s, $-CH_3$), 1.42 (s, $-C(CH_3)_3$) ppm.

2-Benzyl-5-methyl-6-ethyl-1,2,3,4-tetrahydroisoquinoline (**6g**; $C_{19}H_{23}N$)

6g was obtained in 34% yield starting from **5** following the procedure described for the synthesis of **6b**.

Oil; ^{1}H NMR ($CDCl_3$): $\delta = 7.23$–7.49 (m, 5H), 6.96 (d, $J = 7.8$ Hz, 1H), 6.81 (d, $J = 7.8$ Hz, 1H), 3.68 (s, 2H), 3.61 (s, 2H), 2.78 (s, 4H), 2.64 (q, $J = 7.5$ Hz, 2H), 2.16 (s, 3H), 1.18 (t, $J = 7.5$ Hz, 3H) ppm; calc.: C 85.99, H 8.74, N 5.28; C 85.73, H 8.93, N 5.08.

2-Benzyl-6-n-butyl-5-methyl-1,2,3,4-tetrahydroisoquinoline (**6h**; $C_{21}H_{27}N$)

Yield: 46%; oil; ^{1}H NMR ($CDCl_3$): $\delta = 7.23$–7.43 (m, 5H), 6.92 (d, $J = 7.8$ Hz, 1H), 6.78 (d, $J = 7.8$ Hz, 1H), 3.66 (s, 2H), 3.59 (s, 2H), 2.76 (s, 4H), 2.58 (t, $J = 7.7$ Hz, 2H), 2.15 (s, 3H), 1.30–1.58 (m, 4H), 0.94 (t, $J = 7.1$ Hz, 3H) ppm; calc.: C 85.95, H 9.27, N 4.77; found: C 85.70, H 9.35, N 4.58.

2-Benzyl-5-methyl-6-phenyl-1,2,3,4-tetrahydroisoquinoline (**6i**; $C_{23}H_{23}N$)

Yield: 49%; yellowish crystals; m.p.: 104–106°C; ^{1}H NMR ($CDCl_3$): $\delta = 7.16$–7.47 (m, 10H), 7.04 (d, $J = 7.9$ Hz, 1H), 6.92 (d, $J = 7.9$ Hz, 1H), 3.72 (s, 2H), 3.68 (s, 2H), 2.83 (s, 4H), 2.12 (s, 3H) ppm; calc.: C 88.14, H 7.40, N 4.47; found: C 87.89, H 7.62, N 4.36.

6-t-Butyl-1,2,3,4-tetrahydroisoquinoline (**7a**; $C_{13}H_{19}N$)

A solution of 1.15 g (4.1 mmol) of **6a** in MeOH was treated with excess methanolic HCl and subsequently evaporated *in vacuo*. The hydrochloride salt of **6a** thus obtained was dissolved in EtOH ($15\,cm^3$), and the solution was charged with 100 mg of 10% Pd/C and stirred for 4 h at 50°C under an atmosphere of hydrogen. The warm mixture was filtered over celite and the catalyst washed with hot ethanol. The filtrate and the washing were combined, and most of the solvent was distilled off

in vacuo. The residue was warmed up to achieve a clear solution (addition of a few drops of EtOH might be required) and treated with ethyl acetate (10 cm^3). Upon cooling, the hydrochloride salt of **7a** precipitated; filtration and washing with ethyl acetate yielded 700 mg (76%) of **7a**·HCl as colourless crystals. The free base was obtained by treatment of the salt with 1 *N* aqueous NaOH and extraction with ethyl acetate.

7a·HCl: M.p.: 219–223°C; calc.: C 69.16, H 8.93, N 6.20, Cl 15.70; found: C 69.35, H 9.10, N 6.05, Cl 15.40.

7a: Oil; ^{1}H NMR ($CDCl_3$): $\delta = 7.19$ (dd, $J = 2 + 8$ Hz, 1H), 7.12 (d, $J = 2$ Hz, 1H), 6.96 (d, $J = 8$ Hz, 1H), 4.05 (s, 2H), 3.18 (t, $J = 6$ Hz, 2H), 2.82 (t, $J = 6$ Hz, 2H), 2.37 (br, s, 1H), 1.30 (s, 9H) ppm.

6-Ethyl-1,2,3,4-tetrahydroisoquinoline (**7b**; $C_{11}H_{15}N$)

7b·HCl: Yield: 83%; colourless crystals; m.p.: 246–248°C; calc.: C 66.83, H 8.16, N 7.08, Cl 17.93; found: C 66.58, H 8.24, N 6.86, Cl 17.75.

7b: Oil; ^{1}H NMR ($CDCl_3$): $\delta = 6.88$–7.05 (m, 3H), 3.98 (s, 2H), 3.14 (t, $J = 6$ Hz, 2H), 2.78 (t, $J = 6$ Hz, 2H), 2.60 (q, $J = 7.5$ Hz, 2H), 1.90 (br, s, 1H), 1.23 (t, $J = 7.5$ Hz, 3H) ppm.

6-n-Butyl-1,2,3,4-tetrahydroisoquinoline (**7c**; $C_{13}H_{19}N$)

7c·HCl: Yield: 75%; colourless crystals; m.p.: 181–184°C; calc.: C 69.16, H 8.93, N 6.20, Cl 15.70; found: C 69.04, H 8.97, N 6.06, Cl 15.63.

7c: Oil; ^{1}H NMR ($CDCl_3$): $\delta = 6.85$–7.04 (m, 3H), 3.99 (s, 2H), 3,14 (t, $J = 6$ Hz, 2H), 2.78 (t, $J = 6$ Hz, 2H), 2.56 (t, $J = 7.5$ Hz, 2H), 2.01 (br, s, 1H), 1.49–1.68 (m, 2H), 1.25–1.46 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H) ppm.

6-Phenyl-1,2,3,4-tetrahydroisoquinoline (**7d**; $C_{15}H_{15}N$)

7d·HCl: Yield: 76%; colourless crystals; m.p.: 230–233°C; calc.: C 73.31, H 6.56, N 5.70, Cl 14.43; found: C 73.21, H 6.47, N 5.40, Cl 14.32.

7d: Oil; ^{1}H NMR ($CDCl_3$): $\delta = 7.60$ (d, $J = 8$ Hz, 2H), 7.20–7.50 (m, 5H), 7.08 (d, $J = 8$ Hz, 1H), 4.04 (s, 2H), 3.19 (t, $J = 6$ Hz, 2H), 2.88 (t, $J = 6$ Hz, 2H), 1.82 (br, s, 1H) ppm.

6-Ethyl-5-methyl-1,2,3,4-tetrahydroisoquinoline (**7e**; $C_{12}H_{17}N$)

7e·HCl: Yield: 73%; colourless crystals; m.p.: 223–225°C; calc.: C 68.07, H 8.57, N 6.62, Cl 16.74; found: C 67.85, H 8.64, N 6.60, Cl 16.36.

7e: Oil; ^{1}H NMR ($CDCl_3$): $\delta = 6.92$ (d, $J = 7.8$ Hz, 1H), 6.79 (d, $J = 7.8$ Hz, 1H), 3.89 (s, 2H), 3.09 (t, $J = 6.1$ Hz, 2H), 2.69 (t, $J = 6.1$ Hz, 2H), 2.62 (q, $J = 7.5$ Hz, 2H), 2.15 (s, 3H), 1.14 (t, $J = 7.5$ Hz, 3H) ppm.

5-Methyl-6-phenyl-1,2,3,4-tetrahydroisoquinoline (**7f**; $C_{16}H_{17}N$)

Yield: 75%; yellowish crystals; m.p.: 53–56°C; ^{1}H NMR ($CDCl_3$): $\delta = 7.26$–7.46 (m, 5H), 7.07 (d, $J = 7.8$ Hz, 1H), 6.95 (d, $J = 7.8$ Hz, 1H), 4.08 (s, 2H), 3.24 (t, $J = 6$ Hz, 2H), 2.72 (t, $J = 6$ Hz, 2H), 2.13 (s, 3H), 1.86 (br, s, 1H) ppm; calc.: C 86.05, H 7.67, N 6.27; found: C 85.88, H 7.77, N 5.99.

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