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1,3-Benzyl Migration in Iminium Ions: Evidence for a Fast Free-Radical Chain Reaction

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Dedicated to Professor Paul Margaretha on the occasion of his retirement

Keywords: Rearrangement / Density functional calculations / Heterocycles / Alkaloids / Radical reactions

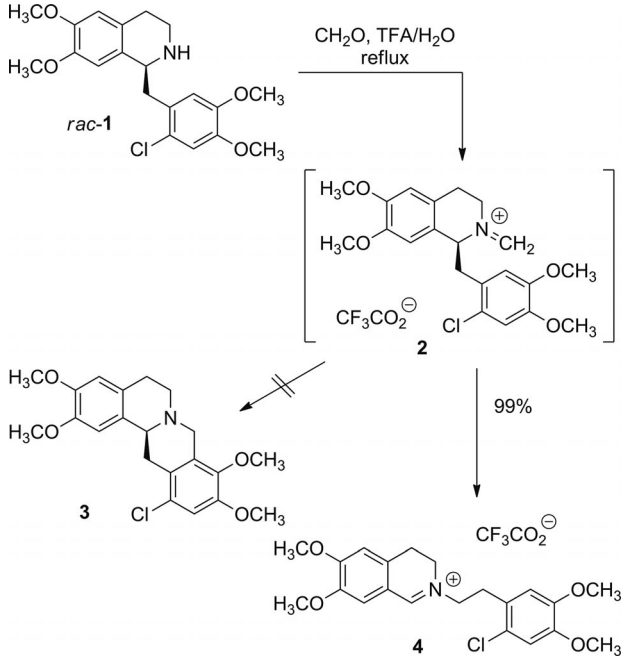
The "exocyclic" 1,3-benzyl shift observed in iminium salts derived from 1-benzyl-1,2,3,4-tetrahydroisoquinolines is related to the "endocyclic" Knabe rearrangement. A crossover experiment, isotopic labelling, the study of initiators and inhibitors as well as DFT calculations of gas-phase model structures provide evidence for a free-radical pathway under kinetic entropy control that is not affected by "slow" radical traps.

Introduction

During an attempted synthesis of the tetrahydroprotoberberine alkaloid tetrahydropalmatine[1] by Pictet–Spengler reaction of the chlorinated benzyltetrahydroisoquinoline **1** with formaldehyde in aqueous trifluoroacetic acid and subsequent dechlorination of the anticipated cyclization product **3**,[2] the rearranged iminium salt **4** was obtained in high yield (Scheme 1).

A related process with similar characteristics is the acid-promoted rearrangement of 1,2-disubstituted dihydroisoquinolines reported by Knabe and co-workers (Scheme 2).[3]

These authors at first suggested a chain reaction involving benzyl anions. This hypothesis was supported by the detection of toluene derivatives. A radical hypothesis was discarded based on the negative results of EPR and CIDNP experiments and the preference of the reaction for polar solvents.[4] However, kinetic studies by Rüchardt and co-workers provided solid evidence for a radical chain mechanism for the Knabe rearrangement.[5] Remarkably, in contrast to the Knabe reaction, the homologating rearrangement described herein is not inhibited by dioxygen.



Scheme 1. Unexpected benzyl migration instead of the attempted Pictet–Spengler cyclization.

Results and Discussion

When isoquinoline **1** was treated with deuterated paraformaldehyde, the exocyclic NCH_2 group carried the label whereas the use of deuterated trifluoroacetic acid as solvent did not lead to the incorporation of deuterium into the product. To rule out pathways involving free benzyl cations, thioanisole (2 equiv., 0.46 M) was added as a scavenger but this did not diminish the reaction rate. Thus, the initially assumed fragmentation of the methyleneiminium ion **2** to form an intermediate resonance-stabilized azomethine ylide appeared less likely. On the other hand, iodine in amounts as small as 1 mol-% (2.3 mM) was found to be an effective inhibitor of the rearrangement, the same being true of cu-

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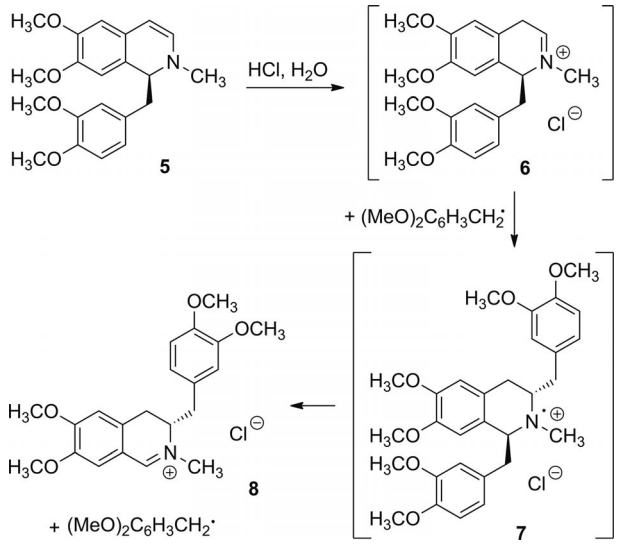
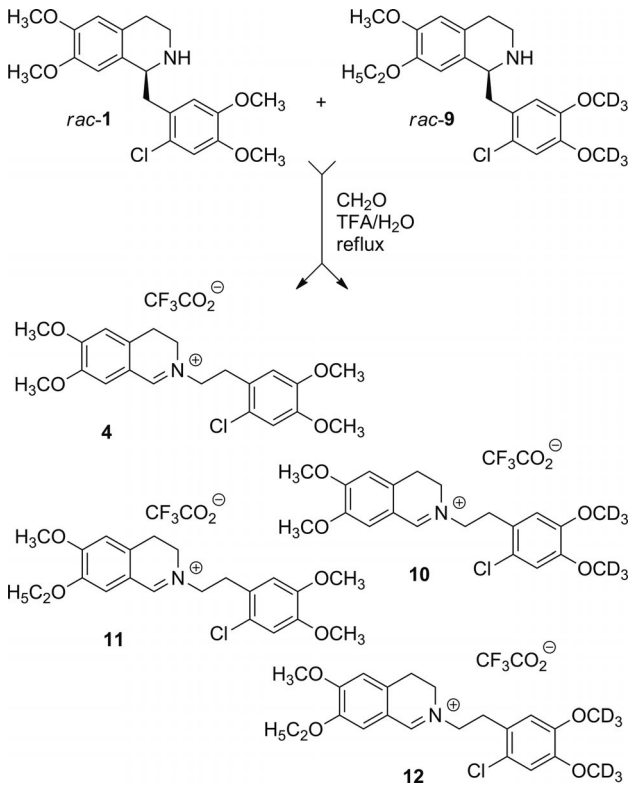


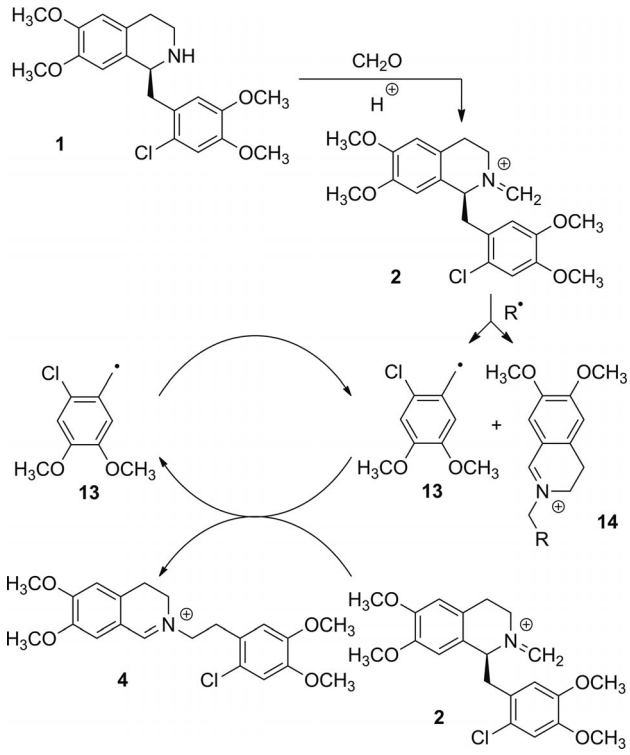
Scheme 2. Radical mechanism of the Knabe rearrangement postulated by Rüchardt and co-workers.

prous chloride (20 mol-%, 46 mM) and TEMPO (2 equiv., 0.46 M), whereas the addition of dibenzoyl peroxide led to an accelerated reaction. The intermolecular nature of the rearrangement could be proven in a crossover experiment: an equimolar mixture of **1** and its hexadeuterated 7-ethyl analogue **9** was subjected to the reaction and resulted in the formation of all four possible reaction products in equal amounts as judged by mass spectrometry (Scheme 3).



Scheme 3. Statistical fragment exchange in a crossover experiment.

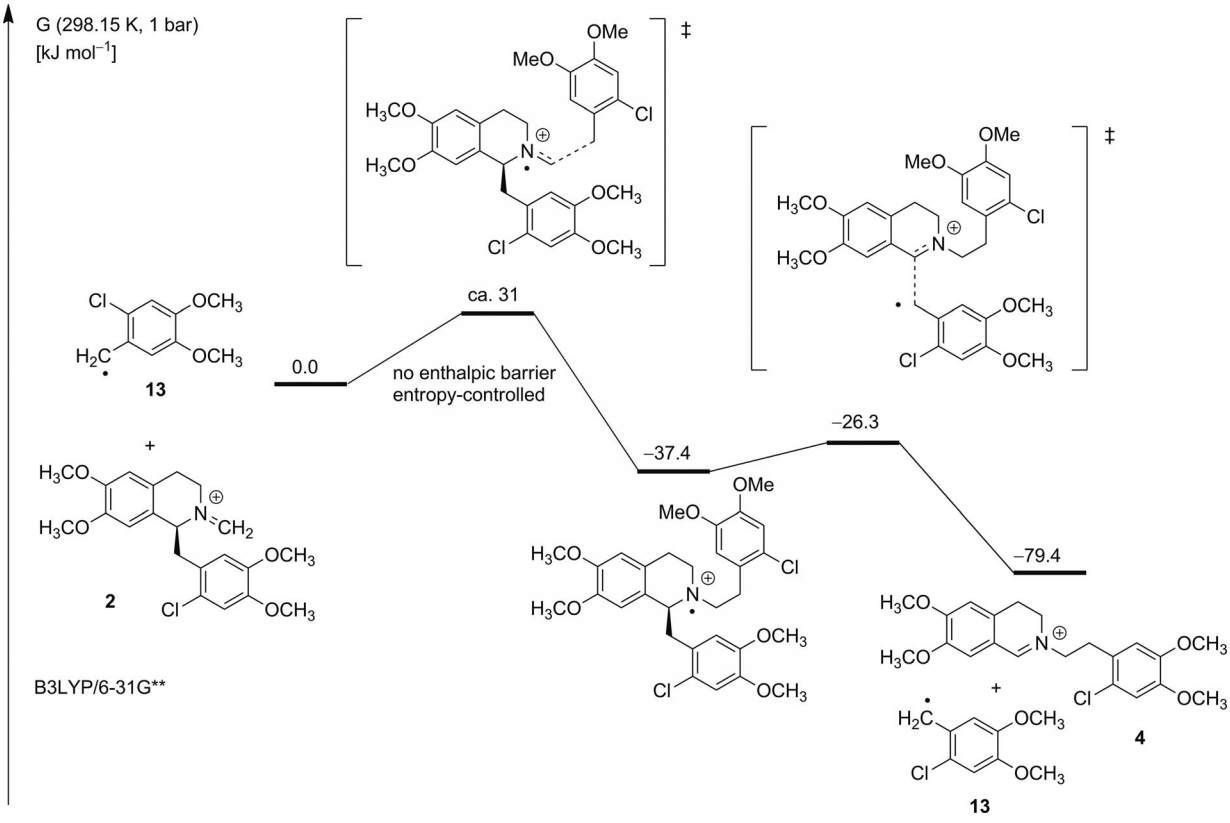
It was concluded that the reaction of **1** with an initiator radical may lead to the scission of the exocyclic C–C bond, producing a benzylic radical that attacks the next molecule of **1** in a chain reaction with the formation of the rearranged product **4** (Scheme 4). As expected for an intermolecular reaction, high yields of **4** were only obtained in reaction mixtures with high concentrations of amine **1**. DFT calculations at the UB3LYP/6-31G** level of theory were performed for gas phase model structures to test this hypothesis.[6] While closed-shell pathways are predicted to involve prohibitive barriers, the results for the free-radical mechanism are depicted in Scheme 4. The C–C bond-forming reaction between the benzyl radical **13** and the iminium ion **2** has no enthalpic barrier and is thus expected to be kinetically entropy-controlled.[7]



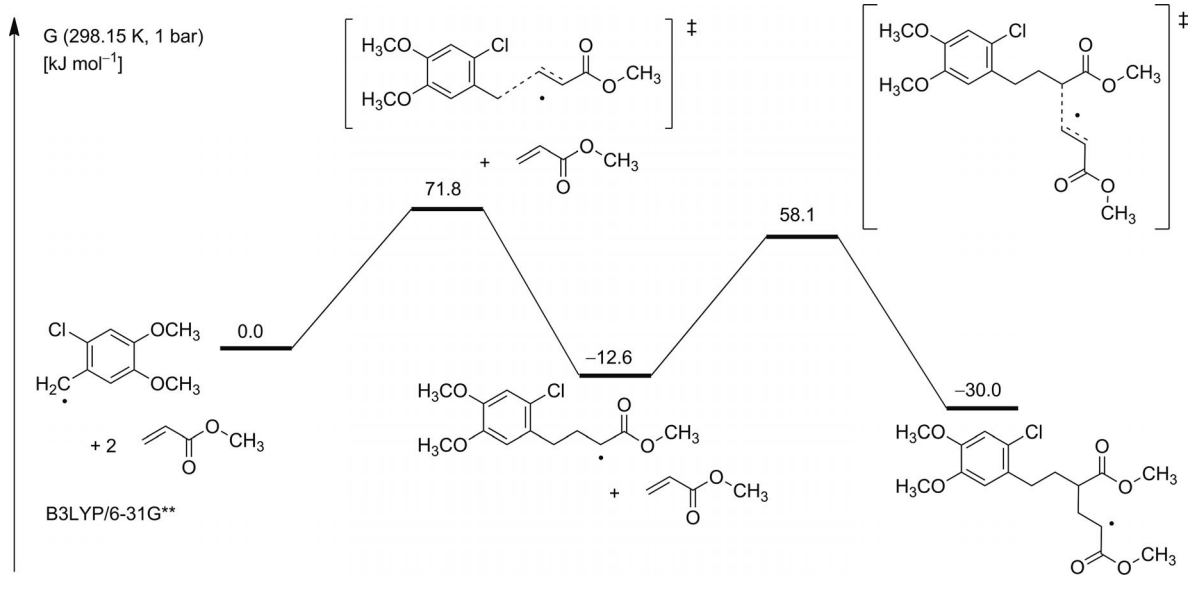
Scheme 4. Proposed reaction mechanism.

The Gibbs free energy of the transition state was computed to have an approximate barrier of 31 kJ mol^{-1} by a structure optimization–frequency calculation scan of distances of the newly formed C–C bond. Apparently, the electron-rich benzyl radical **13** with its high-energy SOMO is ideally suited to react with the electron-deficient iminium cation **2** with its low-energy LUMO. In the next step, an exergonic C–C bond cleavage in the tertiary aminyl radical cation intermediate[8] proceeds rapidly with a predicted Gibbs free-energy barrier of only 11.1 kJ mol^{-1}. The product **4** and benzyl radical **13** are formed, thereby completing one cycle in the radical chain reaction (Scheme 5). Attempts to detect the proposed radicals by EPR spectroscopy were unsuccessful. Surprisingly, the addition of methyl acrylate (2 equiv., 0.46 M) did not lead to a reaction with the olefin

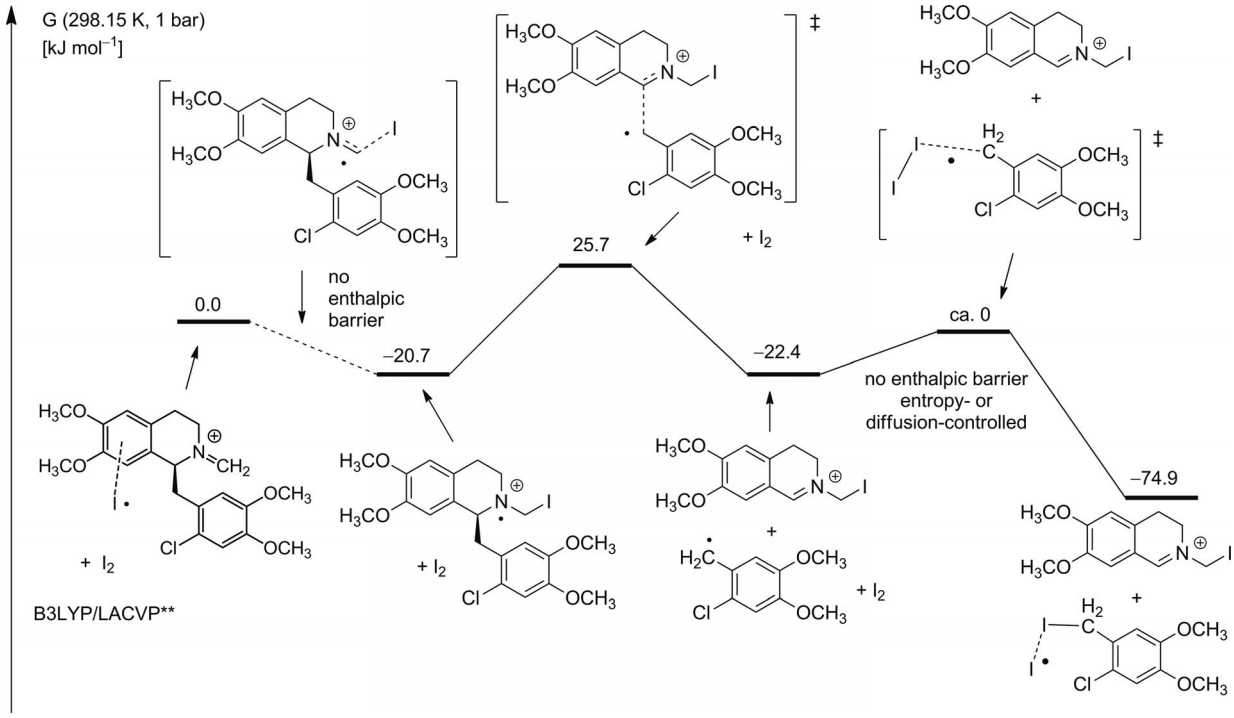
but instead resulted in the same rearrangement product with even higher purity. Moreover, replacement of argon by air did not lead to a diminished yield either. Thus, the postulated propagation step has to proceed faster than the reaction of the benzyl radical **9** with dioxygen or methyl acrylate. The lower reactivity of the proposed intermediates towards methyl acrylate is again consistent with the results of quantum chemical model calculations. The activation free energies $\Delta G^{\neq}$ for both the addition of the initial benzyl radical **13** to methyl acrylate as well as the propagation steps of the radical polymerization of methyl acrylate are predicted to be $>70\ kJ\,mol^{-1}$, therefore clearly proceeding more slowly than diffusion or entropy control. The activation energy E_a (60 °C) for the chain propagation step in methyl acrylate polymerization has been determined experimentally by Matheson et al. to be $6.3\ kcal\,mol^{-1}$



Scheme 5. Gibbs free-energy diagram for the computed radical chain propagation step.



Scheme 6. Gibbs free-energy diagram for the computed trapping experiment with methyl acrylate.



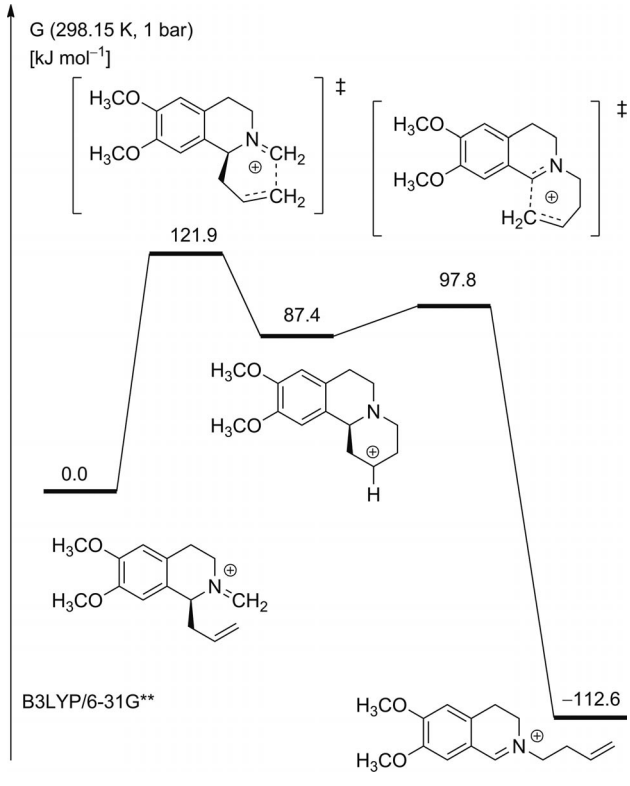
Scheme 7. Gibbs free-energy diagram for the computed radical trapping reaction with iodine.

(26.4 kJ mol^{-1}),[9] in reasonable accord with the computed $\Delta H^{\neq}$ (25 °C) = 4.5 kcal mol^{-1} (18.7 kJ mol^{-1}, Scheme 6, see also the Supporting Information). The difference between this activation enthalpy and the Gibbs activation energy displayed in Scheme 6 arises from entropic contributions caused by the reduced number of molecules.

In contrast to the slow reaction of acrylate esters with alkyl radicals, our DFT calculations predict that an iodine atom reacts with the iminium ion **2** under entropic or even diffusion control (Scheme 7). In addition, the benzyl radical **13** is very efficiently trapped by an iodine molecule. Here, the predicted Gibbs free activation energy of less than 23 kJ mol^{-1} highlights the unsurpassed role of iodine as a radical trap.[10] Several other 1-substituted 1,2,3,4-tetrahydroisoquinolines were subjected to the same reaction conditions, but only in some cases could the rearranged products be identified by HRMS as well as by their characteristic ^{1}H NMR resonances (Table 1).

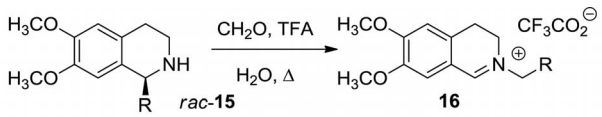
None of these substrates underwent the homologating rearrangement more efficiently than compound **1**. The same holds true for the allyl-substituted compound **15b**. The reaction of its iminium derivative could involve a [3,3] sigmatropic rearrangement with a Gibbs free activation energy of more than 120 kJ mol^{-1} according to our model calculations (Scheme 8).

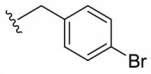
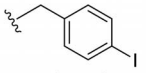
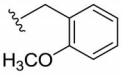
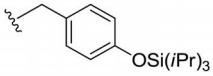
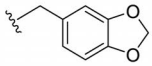
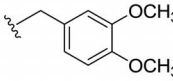
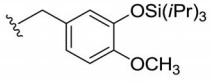
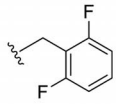
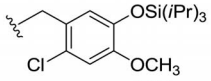
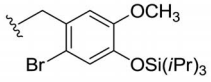
Interestingly, this 2-azonia-Cope rearrangement[11] does not proceed by a concerted C–C bond formation/C–C bond cleavage reaction, but involves a high-energy carbocationic intermediate. To the best of our knowledge, only theoretical



Scheme 8. Gibbs free-energy diagram for the computed stepwise [3,3] sigmatropic rearrangement.

Table 1. Suitability of other substrates for benzyl migration.



Reactant	R	Rearranged product detected[a]
15a	Me	–
15b	allyl	+
15c		+[b]
15d		+[b]
15e		+[c]
15f		–[d]
15g		–[b]
15h		–[b]
15i		–[b,d]
15j		–
15k		+[b,d]
15l		+

[a] Detected by ^{1}H NMR spectroscopy and HRMS. [b] Pictet–Spengler reaction occurred. [c] Addition of dibenzoyl peroxide was necessary. [d] TIPS ether was partially cleaved under these conditions.

calculations of 3-azonia-Cope and anionic 1-aza-Cope rearrangements have been reported in the literature so far.[12]

Conclusions

We have extended the Knabe rearrangement with its formal 1,3-migration of benzyl substituents in 1,4-dihydroisoquinolinium salts to exocyclic derivatives. Experimental data combined with theoretical model calculations provide evidence for an extremely fast radical chain reaction that operates under kinetic entropy control. We have demonstrated that the absence of an effect of "slow" radical traps does not rule out radical reactions altogether, but only of even slower radical chain reactions.

Experimental Section

Materials and Methods: All reactions were carried out under argon. Solvents were dried and distilled before use: THF was distilled from potassium/benzophenone, Et_2O from sodium/benzophenone and CH_2Cl_2 from calcium hydride. Ethyl acetate was distilled from potassium carbonate. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC was performed on TLC aluminium sheets (silica gel 60 F_{254}). Flash chromatography was carried out on silica gel (35–70 μm). ^{1}H and ^{13}C NMR spectra were recorded by using standard pulse sequences on high-resolution FT NMR spectrometers equipped with inverse or direct observe probes and gradient shim units. Chemical shifts are referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.0 ppm). IR spectra were recorded with routine FTIR spectrometers in transmission mode or by using a diamond ATR unit. Melting points were measured with a Dr. Tottoli apparatus or a digital melting-point apparatus with electric heating and are uncorrected. MS spectra were recorded with double-focusing spectrometers (FD-MS, FAB-MS, EI-MS) or with a linear ion trap LC/MSD detector (ESI-MS). ESI-HRMS spectra were recorded with a high-resolution Q-TOF spectrometer with a dual source and a suitable external calibrant. The 1-substituted 1,2,3,4-tetrahydroisoquinolines **15a**,[13] **15b**[14] and **15h**[13] shown in Table 1 were prepared according to known procedures.

1-(2-Chloro-4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1): A solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile[13,15] (797 mg, 3.65 mmol) in dry THF (12 mL) was cooled to –78 °C. A solution of KHMDS (1.46 g, 7.31 mmol) in dry THF (20 mL) was added slowly. The mixture was stirred for 5 min and 2-chloro-4,5-dimethoxybenzyl bromide[16] (1.02 g, 3.94 mmol) in dry THF (15 mL) was added. After stirring for 110 min at –78 °C, the reaction mixture was gradually warmed to ambient temperature. After the addition of 1 N NaOH (60 mL), the mixture was extracted with ethyl acetate (5 × 15 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to yield the dihydroisoquinoline as a viscous pale-yellow oil (1.66 g). Due to the sensitivity of the product to air, this material was not further purified.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98, 6.85, 6.80, 6.65 (4 s, 4 H, 5-H, 8-H, 3′-H, 6′-H), 4.09 (s, 2 H, Ar-CH_2), 3.87 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.72 (m, 2 H, 3-H_2), 2.65 (m, 2 H, 4-H_2) ppm. Sodium borohydride (346 mg, 9.14 mmol) was added to a cooled solution of the dihydroisoquinoline in a mixture of MeOH (5 mL) and THF (20 mL). The reaction mixture was stirred at ambient temperature for 14 h. After addition of 1 N NaOH (50 mL), the mixture was extracted with ethyl acetate (5 × 15 mL) and the combined organic layers were dried with Na_2SO_4. Removal of the solvent in vacuo gave the crude product (1.44 g) as a yellowish oil. This material was purified by column chromatography (silica, cyclohexane/EtOAc/Et_2NH, 6:1:1, R_f = 0.1) to give **1** as a light-yellow oil (932.4 mg, 67.5%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 6.90 (s, 1 H, 3′-H), 6.76 (s, 1 H, 6′-H), 6.69 (s, 1 H, 8-H), 6.60 (s, 1 H, 5-H), 4.22 (dd, J = 9.5, J = 4.0 Hz, 1 H, 1-H), 3.87 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.31 (dd, J = 13.8, J = 4.0 Hz, 1 H, Ar-CH_b), 3.25 (ddd, J = 12, J = 6.7, J = 5.2 Hz, 1 H, 3-H_b), 2.99–2.87 (m, 2 H, 3-H_a, Ar-CH_a), 2.78–2.71 (m, 2 H, 4-H_2), 1.67 (br. s, 1 H, NH) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 148.5 (C-5′), 147.9 (C-4′), 147.8 (C-7), 147.4 (C-6), 130.8 (C-4a), 129.1 (C-2′), 127.6 (C-8a), 125.5 (C-1′), 114.5 (C-6′), 113.0 (C-3′), 112.1 (C-5), 110.0 (C-8), 56.4, 56.3, 56.2, 56.1

($4 \times OCH_3$), 55.5 (C-1), 40.7 (Ar-CH_2), 40.6 (C-3), 29.7 (C-4) ppm. IR (NaCl): $\tilde{\nu}$ = 3401, 3058, 2935, 2823, 1608, 1510, 1354, 1261, 1221, 1167, 1112, 1033, 969, 859, 732 cm^{-1}. MS (FAB): *m*/*z* (%) = 378.2 (30) $[M + H]^+$, 192.1 (100) $[M - C_9H_{10}ClO_2]^+$. HRMS (FAB): calcd. for $[C_{20}H_{24}ClNO_4 + H]^+$ 378.1472; found 378.1472.

3,4-Bis(trideuteriomethoxy)benzaldehyde: A solution of KOH (9.90 g, 176 mmol) in MeOH (150 mL) was degassed by ultrasonication under a slow stream of argon. After addition of protocatechualdehyde (10.0 g, 72.4 mmol) and [$^2H_3$]methyl *p*-toluenesulfonate[18] (32.9 g, 173 mmol), the reaction mixture was heated at reflux for 90 min. The mixture was poured into water (600 mL) and extracted with diethyl ether (6×75 mL). The combined organic layers were washed twice with KOH (5% in water, 100 mL), water (150 mL) and dried with Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica, cyclohexane/EtOAc, 1:1, R_f = 0.68) to give the title compound as colourless crystals (4.38 g, 35.1%). M.p. 43–44 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.86 (s, 1 H, CHO), 7.46 (dd, ^3J = 8.2, ^2J = 1.9 Hz, 1 H, 6-H), 7.41 (d, ^2J = 1.9 Hz, 1 H, 2-H), 6.98 (d, ^3J = 8.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 191.2 (CHO), 127.1 (C-2), 110.5 (C-6), 109.0 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 3076, 2849, 2253, 2073, 1690, 1589, 1510, 1441, 1290, 1145, 989, 802 cm^{-1}. MS (ESI): *m*/*z* (%) = 173.11 (23.8) $[M + H]^+$, 145.11 (100) $[M - CHO]^{+}$. HRMS (ESI): calcd. for $[C_9H_4D_6O_3 + H]^+$ 173.1079; found 173.1076.

2-Chloro-4,5-bis(trideuteriomethoxy)benzaldehyde: 3,4-Bis(trideuteriomethoxy)benzaldehyde (300 mg, 1.73 mmol) was dissolved in $CHCl_3$ (0.4 mL) and sulfuryl chloride (393 μL, 4.87 mmol) was added at 0 °C. The reaction mixture was stirred overnight. The resulting yellow solution was quenched by the addition of saturated aq. $NaHCO_3$ (25 mL) and the crude product was extracted with ethyl acetate (3×5 mL). Concentration of the organic layer afforded a yellow oil that was recrystallized from *tert*-butyl methyl ether to give the title compound as colourless crystals (91.2 mg, 25.5%). M.p. 137–138 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.32 (s, 1 H, CHO), 7.39 (s, 1 H, 3-H), 6.89 (s, 1 H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.8 (CHO), 132.2 (C-1), 125.5 (C-2), 112.6 (C-6), 110.0 (C-3) ppm. IR (NaCl): $\tilde{\nu}$ = 3074, 2874, 2238, 2076, 1672, 1594, 1508, 1406, 1290, 1228, 980, 868 cm^{-1}. MS (ESI): *m*/*z* (%) = 207.07 (100) $[M + H]^+$. HRMS (ESI): calcd. for $[C_9H_3D_6ClO_3 + H]^+$ 207.0690; found 207.0688.

2-Chloro-4,5-bis(trideuteriomethoxy)benzyl Alcohol: Sodium borohydride (13.6 mg, 368 μmol) was added to solution of 2-chloro-4,5-bis(trideuteriomethoxy)benzaldehyde (152 mg, 736 μmol) in a mixture of MeOH (5 mL) and THF (5 mL). The reaction mixture was stirred at ambient temperature for 40 min. The solvent was removed in vacuo and 1 N HCl (5 mL) was added. This mixture was extracted with dichloromethane (4×5 mL) and the combined organic layers were dried with Na_2SO_4. Removal of the solvent in vacuo gave the title compound (154 mg, quant.) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1 H, 3-H), 6.86 (s, 1 H, 6-H), 4.72 (d, J = 6.3 Hz, 2 H, Ar-CH_2), 1.84 (t, J = 6.3 Hz, 1 H, OH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 130.5 (C-1), 123.7 (C-6), 112.6, 111.8 (C-2, C-5), 62.9 (Ar-CH_2) ppm. IR (NaCl): $\tilde{\nu}$ = 3400, 2954, 2881, 2254, 2073, 1646, 1503, 1402, 1280, 1228, 1178, 1103, 995, 862 cm^{-1}. MS (ESI): *m*/*z* (%) = 191.07 (100) $[M - OH]^+$. HRMS (ESI): calcd. for $[C_9H_4D_6ClO_2]^+$ 191.0740; found 191.0742.

2-Chloro-4,5-bis(trideuteriomethoxy)benzyl Bromide: Pyridine (14.7 μL, 180 μmol) and PBr_3 (26.9 μL, 286 μmol) were added to a solution of 2-chloro-4,5-bis(trideuteriomethoxy)benzyl alcohol (150 mg, 719 μmol) in dry THF (3 mL) at 0 °C. After stirring for 10 min at 0 °C, the mixture was warmed to ambient temperature and a small amount of ice was added. The mixture was extracted with diethyl ether (3×5 mL), the combined organic layers were washed with brine, then with saturated aq. $NaHCO_3$ and dried with Na_2SO_4. The solvent was removed in vacuo to yield the title compound (175 mg, 89.6%) as a colourless oil. The product was stored in dry THF (2 mL) with a small amount of $CaCO_3$ to avoid decomposition. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 1 H, 3-H), 6.86 (s, 1 H, 6-H), 4.58 (s, 2 H, Ar-CH_2) ppm. MS (ESI): *m*/*z* (%) = 270.00 (100) $[M]^+$.

7-Ethoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile: A solution of KCN (198 mg, 1.81 mmol) in water (1.04 mL) was added to a solution of 7-ethoxy-6-methoxy-3,4-dihydroisoquinoline[19] (198 mg, 964 μmol) in MeOH (253 μL). The mixture was cooled to 0 °C and concentrated hydrochloric acid (1.01 mL) was added slowly. The reaction mixture was stirred for 6 h at ambient temperature. HCN vapour was removed by using a slow stream of argon (CAUTION!). The mixture was carefully poured into saturated aq. $NaHCO_3$ (10 mL) and the resulting solution was extracted with ethyl acetate (3×5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The product crystallized upon addition of diethyl ether to give the title compound (169 mg, 75.3%) as light-red crystals. M.p. 129–130 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.67, 6.61 (2 s, 2 H, 5-H, 8-H), 4.95 (s, 1 H, 1-H), 4.14–4.04 (m, 2 H, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 3.30–3.23 (m, 2 H, 3-H_2), 2.90–2.82 (m, 1 H, 2-H_b), 2.71–2.65 (m, 1 H, 2-H_a), 2.10 (br. s, 1 H, NH), 1.46 (t, ^3J = 7 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 149.7 (C-7), 147.4 (C-6), 127.1 (C-8a), 121.2 (C-4a), 120.4 (CN), 112.5 (C-8), 111.1 (C-5), 64.8 (OCH_2CH_3), 56.1 (OCH_3), 48.2 (C-1), 41.0 (C-3), 28.0 (C-3), 14.9 (OCH_2CH_3) ppm. IR (NaCl): $\tilde{\nu}$ = 3385, 3055, 2983, 2208, 1677, 1608, 1518, 1465, 1266, 1223, 1120, 1040, 736 cm^{-1}. MS (ESI): *m*/*z* (%) = 233.13 (100) $[M + H]^+$. HRMS (ESI): calcd. for $[C_{13}H_{16}N_2O_2 + H]^+$ 233.1285; found 233.1281.

1-[2-Chloro-4,5-bis(trideuteriomethoxy)benzyl]-7-ethoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (9): A solution of 7-ethoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (160 mg, 688 μmol) in dry THF (4 mL) was cooled to –78 °C. KHMDS (274 mg, 1.37 mmol) in dry THF (4 mL) was added slowly. The mixture was stirred for 5 min and 2-chloro-4,5-bis(trideuteriomethoxy)benzyl bromide (187 mg, 688 μmol) in dry THF (2 mL) was added. After stirring for 2 h, the reaction mixture was gradually warmed to ambient temperature. After the addition of 1 N NaOH (10 mL), the mixture was extracted with ethyl acetate (4×5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to yield the dihydroisoquinoline as a viscous yellow oil (279.5 mg). Due to its instability against aerial oxidation, this material was used without further purification.[17] ^1H NMR (400 MHz, $CDCl_3$): δ = 6.97, 6.84, 6.79, 6.65 (4 s, 4 H, 5-H, 8-H, 3′-H, 6′-H), 4.13–4.01 (m, 4 H, Ar-CH_2, OCH_2CH_3), 3.87 (s, 3 H, OCH_3), 3.72 (t, ^3J = 7.5 Hz, 2 H, 3-H_2), 2.65 (t, ^3J = 7.5 Hz, 2 H, 4-H_2), 1.39 (t, ^3J = 7.0 Hz, 2 H, OCH_2CH_3) ppm. Sodium borohydride (65.2 mg, 1.72 mmol) was added to a solution of the dihydroisoquinoline in MeOH (2.5 mL) and THF (2.5 mL). The reaction mixture was stirred at ambient temperature for 16 h. After the addition of 1 N NaOH (5 mL), the mixture was extracted with ethyl acetate (4×5 mL). The combined organic layers were dried with Na_2SO_4. Removal of the solvent in vacuo gave the crude product (265.6 mg) as a yellowish oil. This material was purified by column chromatography (silica, cyclohexane/EtOAc/Et_2NH, 7:1:0.5, R_f = 0.1) to give **9** as a light-yellow oil (222.7 mg, 81.3%). ^1H NMR, COSY (400 MHz, $CDCl_3$): δ = 6.89 (s, 1 H, 3′-H), 6.75

(s, 1 H, 6′-H), 6.72 (s, 1 H, 8-H), 6.60 (s, 1 H, 5-H), 4.23–4.20 (m, 1 H, 1-H), 4.07–4.02 (q, ^3J = 13.8 Hz, 2 H, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 3.33–3.23 (m, 2 H, 3-H_b, Ar-CH_b), 2.98–2.86 (m, 2 H, 3-H_a, Ar-CH_a), 2.81–2.68 (m, 2 H, 4-H_2), 1.92 (br. s, 1 H, NH), 1.44 (t, ^3J = 13.8 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 148.4, 148.2 (C-4′, C-5′), 147.9 (C-6), 146.6 (C-7), 130.6 (C-8a), 128.9 (C-2′), 127.6 (C-4a), 125.4 (C-1′), 114.4 (C-8), 112.9 (C-3′), 112.2 (C-5), 111.6 (C-6′), 64.8 (OCH_2CH_3), 56.1 (C-1), 55.5 (OCH_3), 40.7 (C-3), 40.4 (Ar-CH_2), 29.6 (C-4), 15.0 (OCH_2CH_3) ppm. IR (NaCl): $\tilde{\nu}$ = 3345, 3047, 2926, 2831, 2218, 2070, 1608, 1505, 1394, 1263, 1225, 1109, 1036, 968, 860, 732 cm^{-1}. MS (ESI): *m*/*z* (%) = 398.20 (100) [M + H]$^+$. HRMS (ESI): calcd. for [$C_{21}H_{20}D_6NO_4$ + H]$^+$ 398.2000; found 398.1997.

General Procedure for the Preparation of the Tetrahydroisoquinolines 15: A solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile[13,15] (797 mg, 3.65 mmol) in dry THF (12 mL) was cooled to –78 °C. A solution of KHMDS (1.46 g, 7.31 mmol) in dry THF (20 mL) was added slowly. The mixture was stirred for 5 min and the benzyl bromide (3.94 mmol) in dry THF (15 mL) was added. After stirring for 3–4 h at –78 °C, the reaction mixture was gradually warmed to ambient temperature. After the addition of 1 N NaOH (60 mL), the mixture was extracted with ethyl acetate (5 × 15 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to give the crude imine. Due to the sensitivity of the product to air, this material was not further purified.[17] Sodium borohydride (346 mg, 9.14 mmol) was added to a cooled solution of the 1-benzyl-3,4-dihydroisoquninoline in a mixture of MeOH (5 mL) and THF (20 mL). The reaction mixture was stirred at ambient temperature overnight. After the addition of 1 N NaOH (50 mL), the mixture was extracted with ethyl acetate (5 × 15 mL) and the combined organic layers were dried with Na_2SO_4. Removal the solvent in vacuo gave the crude product, which was purified by column chromatography.

1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15c): The reaction was conducted according to the general procedure. Reagents: KHMDS (910 mg, 4.56 mmol) in THF (10 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (500 mg, 2.29 mmol) in THF (10 mL), 4-bromobenzyl bromide (510 mg, 2.40 mmol) in THF (10 mL), MeOH (10 mL), THF (10 mL) and $NaBH_4$ (216 mg, 5.71 mmol). The reaction yielded a yellow oil (981 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 7:1:0.5, R_f = 0.1) gave **15c** as a light-yellow oil (551 mg, 66%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.44 (d, ^3J = 8 Hz, 2 H, 2′-H, 6′-H), 7.12 (d, ^3J = 8 Hz, 2 H, 3′-H, 5′-H), 6.58 (s, 1 H, 5-H), 6.51 (s, 1 H, 8-H), 4.19 (dd, J = 8.6, J = 5 Hz, 1 H, 1-H), 3.85 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.23–3.12 (m, 2 H, Ar-CH_b, 3-H_b), 3.00–2.94 (m, 2 H, Ar-CH_a, 3-H_a), 2.77–2.73 (m, 2 H, 4-H_2) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 148.16 (C-7), 147.52 (C-6), 138.12 (C-1′), 131.99 (C-3′, C-5′), 131.60 (C-2′, C-6′), 129.6 (C-4_a), 127.3 (C-8_a), 120.8 (C-4′), 112.3 (C-5), 109.9 (C-8), 56.9 56.3, 56.2 (C-1, 2 × OCH_3), 42.4 (Ar-CH_2), 40.8 (C-3), 29.3 (C-4) ppm. IR (NaCl): $\tilde{\nu}$ = 2999, 2931, 2831, 1609, 1510, 1487, 1463, 1324, 1259, 1221, 1111, 1011, 857, 801, 781 cm^{-1}. MS (ESI): *m*/*z* (%) = 362.07 (100) [M + H]$^+$. HRMS (ESI): calcd. for [$C_{18}H_{20}BrNO_2$ + H]$^+$ 362.0750; found 362.0747.

6,7-Dimethoxy-1-(4-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline (15d): The reaction was conducted according to the general procedure. Reagents: KHMDS (670 mg, 3.35 mmol) in THF (10 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (360 mg, 1.64 mmol) in THF (10 mL), 4-iodobenzyl bromide (510 mg, 1.72 mmol) in THF (5 mL), MeOH (10 mL), THF (10 mL) and $NaBH_4$ (160 mg, 4.17 mmol). The reaction yielded a yellow oil (1041 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 7:1:0.5, R_f = 0.1) gave **15d** as a light-yellow oil (568 mg, 84.6%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.65–7.63 (d, ^3J = 8.4 Hz, 2 H, 2′-H, 6′-H), 7.02–6.70 (d, ^3J = 8.4 Hz, 2 H, 3′-H, 5′-H), 6.59 (s, 1 H, 5-H), 6.55 (s, 1 H, 8-H), 4.15 (dd, J = 14, J = 4.4 Hz, 1 H, 1-H), 3.86 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.22–3.11 (m, 2 H, Ar-CH_b, 3-H_b), 2.97–2.87 (m, 2 H, Ar-CH_a, 3-H_a), 2.80–2.67 (m, 2 H, 4-H_2), 2.23 (br. s, 1 H, NH) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 148.02, 147.45 (C-6, C-7), 139.03 (C-1′), 137.96 (C-2′, C-6′), 131.88 (C-3′, C-5′), 130.14 (C-4_a), 127.57 (C-8_a), 112.26 (C-5), 109.81 (C-8), 92.07 (C-4′), 56.97 (C-1), 56.32, 56.20 (2 OCH_3), 42.60 (Ar-CH_2), 40.93 (C-3), 29.58 (C-4) ppm. IR (NaCl): $\tilde{\nu}$ = 2994, 2932, 2831, 1609, 1510, 1463, 1353, 1257, 1220, 1111, 1006, 909, 726 cm^{-1}. MS (ESI): *m*/*z* (%) = 410.06 (100) [M + H]$^+$. HRMS (ESI): calcd. for [$C_{18}H_{20}INO_2$ + H]$^+$ 410.0611; found 410.0612.

1-(2-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15e): The reaction was conducted according to the general procedure. Reagents: KHMDS (365 mg, 1.83 mmol) in THF (5 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (200 mg, 916 μmol) in THF (5 mL), 2-methoxybenzyl bromide (194 mg, 962 μmol) in THF (5 mL), MeOH (5 mL) and $NaBH_4$ (86.6 mg, 2.29 mmol). The reaction yielded a yellow oil (355 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 8:1:0.5, R_f = 0.1) gave **15e** as a pale-yellow oil (261 mg, 91.0%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 1 H, 4′-H), 7.20–7.19 (m, 1 H, 6′-H), 6.96–6.92 (m, 2 H, 3′-H, 5′-H), 6.70 (s, 1 H, 5-H), 6.61 (s, 1 H, 8-H), 4.19 (dd, J = 9.4, J = 3.5 Hz, 1 H, 1-H), 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.30–3.24 (m, 2 H, 3-H_b, Ar-CH_b), 2.97–2.85 (m, 2 H, 3-H_a, 4-H_b), 2.78–2.75 (m, 2 H, 4-H_2), 1.75 (br. s, 1 H, NH) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 157.9 (C-2′), 147.4, 146.1 (C-6, C-7), 131.5 (C-1′), 131.4 (C-6′), 128.0 (C-8_a), 127.9 (C-4′), 127.3 (C-4_a), 120.6 (C-5′), 111.8 (C-8), 110.6 (C-3′), 110.0 (C-5), 56.1 (OCH_3), 56.0 (OCH_3), 55.5 (OCH_3), 55.2 (C-1), 40.3 (C-4), 38.0 (Ar-CH_2), 29.7 (C-4) ppm. IR (NaCl): $\tilde{\nu}$ = 3006, 2931, 2832, 1601, 1511, 1492, 1462, 1241, 1222, 1112, 1028, 909, 727 cm^{-1}. MS (FAB): *m*/*z* (%) = 314.2 (61) [M + H]$^+$, 192.1 (100) [M – C_8H_9O]$^+$. HRMS (FAB): calcd. for [$C_{19}H_{23}NO_3$ + H]$^+$ 314.1756; found 314.1759.

1-[4-(Triisopropylsilyloxy)benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15f): The reaction was conducted according to the general procedure. Reagents: KHMDS (78.6 mg, 394 μmol) in THF (1.5 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (39.5 mg, 182 μmol) in THF (2 mL), 4-triisopropylsilyloxybenzyl bromide[20] (67.9 mg, 198 μmol) in THF (1.5 mL), MeOH (10 mL) and $NaBH_4$ (24.7 mg, 653 μmol). The reaction yielded a light-yellow oil (122.4 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 8:1:0.5, R_f = 0.15) gave **15f** as a light-yellow oil (75.9 mg, 92.2%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.08 (d, ^3J = 8.0 Hz, 2 H, 2′-H, 6′-H), 6.83 (d, ^3J = 8.0 Hz, 2 H, 3′-H, 6′-H), 6.82 (s, 1 H, 8-H), 6.58 (s, 1 H, 5-H), 4.12 (dd, J = 12, J = 4 Hz, 1 H, 1-H), 3.86 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.23–3.17 (m, 1 H, 3-H_b), 3.13 (dd, J = 12, J = 4 Hz, 1 H, Ar-CH_b), 2.91–2.85 (m, 2 H, Ar-CH_a, 3-H_a), 2.75–2.71 (m, 2 H, 4-H_2), 2.08 (br. s, 1 H, NH), 1.29–1.20 (m, 3 H, CH), 1.11–1.09 (d, J = 7.1 Hz, 18 H, CH_3) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 155.1 (C-4′), 147.8 (C-6), 147.3 (C-7), 131.5 (C-1′), 130.6 (C-2′, C-6′), 129.6 (C-4_a), 127.6 (C-8_a), 120.3 (C-2′, C-5′), 112.1 (C-5), 109.9 (C-8), 57.2 (C-1), 56.3, 56.2 (2 OCH_3), 42.2 (Ar-CH_2), 41.0 (C-3), 29.7 (C-4),

18.3 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 2944, 2866, 1608, 1508, 1464, 1260, 1226, 1114, 1012, 883, 854 cm^{-1}. MS (ESI): *m/z* (%) = 456.29 (100) $[M + H]^+$. HRMS (ESI): calcd. for $[C_{27}H_{41}NO_3Si + H]^+$ 456.2928; found 456.2928.

6,7-Dimethoxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (15g): The reaction was conducted according to the general procedure. Reagents: KHMDS (53.4 mg, 268 μmol) in THF (1.5 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (29.3 mg, 134 μmol) in THF (1 mL), 3,4-methylenedioxybenzyl bromide (30.4 mg, 141 μmol) in THF (1.5 mL), MeOH (2 mL) and $NaBH_4$ (14.3 mg, 378 μmol). The reaction yielded a brown oil (122.4 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 8:1:0.5, R_f = 0.1) gave **15g** as a light-brown oil (30.6 mg, 69.8%). ^1H NMR, COSY (400 MHz, $CDCl_3$): δ = 6.77 (d, J = 7.9 Hz, 1 H, 5′-H), 6.75 (d, J = 1.8 Hz, 1 H, 2′-H), 6.70 (dd, J = 7.9, J = 1.8 Hz, 1 H, 6′-H), 6.63 (s, 1 H, 8-H), 6.59 (s, 1 H, 5-H), 5.94 (m, 2 H, OCH_2O), 4.10 (dd, J = 9.0, J = 4.2 Hz, 1 H, 1-H), 3.86 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.23–3.17 (m, 1 H, 3-H_b), 3.12 (dd, J = 13.8, J = 4.4 Hz, 1 H, Ar-CH_b), 2.96–2.90 (m, 1 H, 3-H_a), 2.84 (dd, J = 13.8, J = 9.5 Hz, 1 H, Ar-CH_a), 2.78–2.69 (m, 2 H, 4-H_2), 2.04 (br. s, 1 H, NH) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 147.9 (C-3′), 147.7 (C-6), 147.3 (C-7), 146.3 (C-4′), 132.9 (C-1′), 130.5 (C-4_a), 127.5 (C-8_a), 122.5 (C-6′), 112.1 (C-5), 109.7 (C-8), 109.7 (C-2′), 108.5 (C-5′), 101.0 (OCH_2O), 57.1 (C-1), 56.2, 56.0 (2 OCH_3), 42.5 (Ar-CH_2), 40.8 (C-3), 29.6 (C-4) ppm. IR (NaCl): $\tilde{\nu}$ = 3000, 2939, 2838, 1609, 1503, 1488, 1441, 1247, 1223, 1112, 1038, 929, 860, 811 cm^{-1}. MS (ESI): *m/z* (%) = 192.1 (27) $[M - C_8H_7O_2]^+$, 328.2 (100) $[M + H]^+$. HRMS (ESI): calcd. for $[C_{19}H_{21}NO_4 + H]^+$ 328.1543; found 328.1541.

4-Methoxy-3-(triisopropylsilyloxy)benzyl Alcohol: Sodium borohydride (1.44 g, 38.6 mmol) was dissolved in dry EtOH (5 mL) and cooled to 0 °C. A solution of 4-methoxy-3-(triisopropylsilyloxy)-benzaldehyde[21] (9.93 g, 32.2 mmol) in dry EtOH (15 mL) was added slowly. The resulting mixture was stirred for 2 h at room temperature and the solvents evaporated to dryness. Water (50 mL) was added to the residue and the mixture extracted with EtOAc (4 × 80 mL). The combined organic layers were washed with sat. aq. NH_4Cl (100 mL), water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered and evaporated to give the title compound (9.74 g, 96.0%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.89–6.85 (m, 2 H, 2-H, 6-H), 6.80 (d, ^3J = 8.0 Hz, 1 H, 5-H), 4.53 (s, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 2.00 (br. s, 1 H, OH), 1.30–1.21 (m, 3 H, CH), 1.10 (d, ^3J = 7.6 Hz, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.5 (C-4), 145.6 (C-3), 133.7 (C-1), 120.2, 119.7 (C-2, C-6), 112.1 (C-5), 65.1 (Ar-CH_2), 55.6 (OCH_3), 18.0 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 3332, 2944, 2867, 1513, 1464, 1427, 1289, 1136, 883, 832 cm^{-1}. MS (FD): *m/z* (%) = 310.0 (52) $[M]^+$, 311.3 (100) $[M + H]^+$. HRMS (ESI): calcd. for $[C_{17}H_{30}O_3Si + Na]^+$ 333.1862; found 333.1853.

4-Methoxy-3-(triisopropylsilyloxy)benzyl Bromide: PPh_3 (847 mg, 3.24 mmol) and NBS (573 mg, 3.24 mmol) were added to a stirred solution of 4-methoxy-3-(triisopropylsilyloxy)benzyl alcohol (672 mg, 217 mmol) in dry CH_2Cl_2 (5 mL) cooled to 0 °C. The reaction mixture was warmed up to room temperature, stirred for an additional 20 min and poured into water (10 mL). The product was extracted with Et_2O (3 × 20 mL), washed with NaOH (1 M, 20 mL) and brine (20 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to give the title compound (768 mg, 94.8%) as a colourless oil. The product was stored in dry THF (10 mL) with a small amount of $CaCO_3$ to avoid decomposition. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.93–6.90 (m, 2 H, 2-H, 6-H), 6.77 (d, ^3J = 8.8 Hz, 1 H, 5-H), 4.44 (s, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 1.29–1.22 (m, 3 H, CH), 1.10–1.05 (m, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.4 (C-4), 145.8 (C-3), 130.4 (C-1), 122.3, 121.5 (C-2, C-6), 112.0 (C-5), 55.6 (OCH_3), 34.4 (Ar-CH_2), 18.1 (6 CH_3), 13.1 (3 CH) ppm.

1-(4-Methoxy-3-triisopropylsilyloxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15i): The reaction was conducted according to the general procedure. Reagents: KHMDS (910 mg, 4.58 mmol) in THF (10 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (500 mg, 2.29 mmol) in THF (10 mL), 4-methoxy-3-(triisopropylsilyloxy)benzyl bromide (900 mg, 2.41 mmol) in THF (8.6 mL), MeOH (10 mL) and $NaBH_4$ (220 mg, 5.73 mmol). The reaction yielded a yellow oil (958 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 8:1:1, R_f = 0.1) gave **15i** as a light-yellow oil (774 mg, 69.5%). ^1H NMR, COSY (500 MHz, $CDCl_3$): δ = 6.79–6.74 (m, 3 H, 2′-H, 5′-H, 6′-H), 6.67 (s, 1 H, 5-H), 6.57 (s, 1 H, 8-H), 4.08 (dd, J = 8.8, J = 4.4 Hz, 1 H, 1-H), 3.87 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.20–3.15 (m, 1 H, 3-H_b), 3.10–3.07 (dd, J = 17.0, ^4J = 4.4 Hz, 1 H, Ar-CH_b), 2.90–2.84 (m, 2 H, Ar-CH_a, 3-H_a), 2.71–2.67 (m, 2 H, 4-H_2), 1.80 (br. s, 1 H, NH), 1.24–1.17 (m, 3 H, CH), 1.08–1.06 (d, J = 7.5 Hz, 18 H, CH_3) ppm. ^{13}C NMR, HSQC, HMBC (125.8 MHz, $CDCl_3$): δ = 149.7, 147.5, 147.2, 145.6 (C-6, C-7, C 3′, C-4′), 131.3 (C-1′), 130.6 (C-8a), 127.6 (C-4a), 122.5 (C-2′), 121.5 (C-6′), 112.3 (C-5), 111.9 (C-5′), 109.5 (C-8), 56.9 (C-1), 56.1, 55.9, 55.7 (3 OCH_3), 41.6, 41.1 (Ar-CH_2, C-3), 29.7 (C-4), 18.1 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 2942, 2865, 1509, 1463, 1269, 1225, 1111, 1032, 994, 882, 834 cm^{-1}. MS (ESI): *m/z* (%) = 486.4 (86) $[M + H]^+$, 971.7 (100) $[2M]^+$. HRMS (ESI): calcd. for $[C_{28}H_{43}NO_4Si + H]^+$ 486.3032; found 486.3032.

1-(2,6-Difluorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15j): The reaction was conducted according to the general procedure. Reagents: KHMDS (730 mg, 3.66 mmol) in THF (10 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (400 mg, 1.83 mmol) in THF (10 mL), 2,6-difluorobenzyl bromide (408 mg, 1.97 mmol) in THF (8 mL), MeOH (10 mL) and $NaBH_4$ (173 mg, 4.58 mmol). The reaction yielded a colourless oil (600 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 8:1:0.5, R_f = 0.15) gave **15j** as a colourless solid (419 mg, 71.7%). M.p. 77–79 °C. ^1H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.24–7.16 (A part of ABB′XX′ system, m, 1 H, 4′-H), 6.92–6.89 (BB′ part of ABB′XX′ system, m, 2 H, 3′-H, 5′-H), 6.63 (s, 1 H, 5-H), 6.60 (s, 1 H, 8-H), 4.17 (t, J = 7.0 Hz, 1 H, 1-H), 3.86 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.32–3.26 (m, 1 H, 3-H_b), 3.10 (d, J = 7.0 Hz, 2 H, Ar-CH_2), 3.01–2.95 (m, 1 H, 3-H_a), 2.75–2.71 (m, 2 H, 4-H_2), 1.64 (br. s, 1 H, NH) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 164.1, 160.9 (C-2′, C-6′), 147.7, 147.3 (C-6, C-7), 130.7 (C-8a), 128.1 (C-4′), 127.3 (C-4a), 115.7 (C-1′), 111.9 (C-8), 111.5, 111.2 (C-3′, C-5′), 109.8 (C-5), 56.1, 56.0 (2 OCH_3), 55.4 (C-1), 39.5 (C-3), 30.0 (Ar-CH_2), 29.4 (C-4) ppm. IR (NaCl): $\tilde{\nu}$ = 3006, 3003, 2935, 2907, 2833, 1623, 1590, 1510, 1467, 1353, 1262, 1223, 1110, 1012, 937, 856, 778 cm^{-1}. MS (FAB): *m/z* (%) = 320.2 (44) $[M + H]^+$, 192.1 (100) $[M - C_7H_5F_2]^+$. HRMS (FAB): calcd. for $[C_{18}H_{19}F_2NO_2 + H]^+$ 320.1462; found 320.1473.

2-Chloro-4-methoxy-5-(triisopropylsilyloxy)benzyl Alcohol: 4-Methoxy-3-(triisopropylsilyloxy)benzyl alcohol (see above, 1.00 g, 3.22 mmol) was dissolved in $CHCl_3$ (1 mL) and sulfuryl chloride (280 μL, 3.54 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature overnight. The resulting yellow solution was quenched by the addition of sat. aq. $NaHCO_3$ (15 mL)

and the crude product was extracted with ethyl acetate (3 × 10 mL). Concentration of the organic layer afforded the title compound as a colourless oil (1.01 g, 90.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1 H, 3-H), 6.82 (s, 1 H, 6-H), 4.64 (s, 2 H, Ar-CH_2), 3.79 (s, 3 H, OCH_3), 1.89 (br. s, 1 H, OH), 1.28–1.19 (m, 3 H, CH), 1.08 (d, ^3J = 7.5 Hz, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.9 (C-4), 144.6 (C-5), 130.2 (C-1), 127.4 (C-2), 120.9 (C-6), 113.2 (C-3), 62.7 (Ar-CH_2), 56.0 (OCH_3), 17.9 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 3381, 2943, 2866, 1501, 1463, 1440, 1270, 1160, 880, 856, 680 cm^{-1}. MS (FAB): *m*/*z* (%) = 344.3 (100) $[M]^+$.

2-Chloro-4-methoxy-5-(triisopropylsilyloxy)benzyl Bromide: Pyridine (28.2 μL, 346 μmol) and PBr_3 (54 μL, 579 μmol) were added to a solution of 2-chloro-4-methoxy-5-(triisopropylsilyloxy)benzyl alcohol (500 mg, 1.45 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. After stirring for 10 min at 0 °C, the mixture was warmed to ambient temperature and a small amount of ice was added. The mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine and sat. aq. $NaHCO_3$ and dried with Na_2SO_4. The solvent was removed in vacuo to yield the title compound (533 mg, 90.1%) as a colourless oil. The product was stored in dry THF (10 mL) with a small amount of $CaCO_3$ to avoid decomposition. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1 H, 3-H), 6.82 (s, 1 H, 6-H), 4.52 (s, 2 H, Ar-CH_2), 3.80 (s, 3 H, OCH_3), 1.28–1.19 (m, 3 H, CH), 1.09 (d, ^3J = 7.2 Hz, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.0 (C-4), 144.8 (C-5), 127.2 (C-1), 126.1 (C-2), 122.6 (C-6), 113.4 (C-3), 55.8 (OCH_3), 31.3 (Ar-CH_2), 18.0 (6 CH_3), 13.0 (3 CH) ppm.

1-[2-Chloro-4-methoxy-5-(triisopropylsilyloxy)benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15k): The reaction was conducted according to the general procedure. Reagents: KHMDS (487 mg, 2.44 mmol) in THF (10 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (266 mg, 1.22 mmol) in THF (8 mL), 2-chloro-4-methoxy-5-(triisopropylsilyloxy)benzyl bromide (522 mg, 1.28 mmol) in THF (10 mL), MeOH (10 mL), THF (10 mL) and $NaBH_4$ (115 mg, 3.05 mmol). The reaction yielded a yellow oil (788 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 8:1:0.5, R_f = 0.15) gave **15k** as a colourless oil (524 mg, 82.7%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 6.87 (s, 1 H, 3′-H), 6.78 (s, 1 H, 6′-H), 6.71 (s, 1 H, 8-H), 6.59 (s, 1 H, 5-H), 4.18 (dd, J = 9.5, J = 3.8 Hz, 1 H, 1-H), 3.86 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.79 (s, 3 H, 4′-OCH_3), 3.22–3.19 (m, 2 H, Ar-CH_b, 3-H_b), 2.96–2.87 (m, 2 H, Ar-CH_a, 3-H_a), 2.74 (t, J = 6.0 Hz, 2 H, 4-H_2), 1.63 (br. s, 1 H, NH), 1.28–1.19 (m, 3 H, CH), 1.09–1.05 (m, 18 H, CH_3) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 150.3 (C-4′), 147.8, 147.4 (C-6, C-7), 144.4 (C-5′), 130.9 (C-4a), 129.0 (C-1′), 127.5 (C-8a), 125.5 (C-2′), 123.1 (C-6′), 113.6 (C-3′), 112.0 (C-5), 109.9 (C-8), 56.2, 56.0, 55.9 (3 OCH_3), 55.4 (C-1), 40.2 (C-3), 39.7 (Ar-CH_2), 29.7 (C-4), 18.0 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 2939, 2861, 1608, 1499, 1460, 1325, 1265, 1227, 1114, 1014, 880, 851 cm^{-1}. MS (ESI): *m*/*z* (%) = 520.3 (100) $[M + H]^+$. HRMS (ESI): calcd. for $[C_{28}H_{42}ClNO_4Si + H]^+$ 520.2644; found 520.2645.

2-Bromo-5-methoxy-4-(triisopropylsilyloxy)benzaldehyde: Imidazole (413 mg, 6.06 mmol) and TIPSCl (334 mg, 1.73 mmol) were added to a stirred solution of 2-bromo-4-hydroxy-5-methoxybenzaldehyde[22] (400 mg, 1.73 mmol) in dry DMF (5 mL). The reaction mixture was stirred for 15 min at room temperature and poured into water (50 mL). The product was extracted with *n*-hexane (3 × 10 mL), washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to afford the title compound (606 mg, 92.8%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 1 H, CHO), 7.41 (s, 1 H, 6-H), 7.08 (s, 1 H, 3-H), 3.84 (s, 3 H, OCH_3), 1.32–1.22 (m, 3 H, CH), 1.10 (d, ^3J = 7.2 Hz, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 191.2 (CHO), 152.2 (C-5), 150.9 (C-4), 127.1 (C-1), 124.6 (C-3), 111.2 (C-6), 110.7 (C-2), 55.7 (OCH_3), 17.9 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 2941, 2867, 1690, 1584, 1495, 1463, 1389, 1290, 1212, 1159, 993, 880, 749 cm^{-1}. MS (FAB): *m*/*z* (%) = 387.1 (100) $[M]^+$.

2-Bromo-5-methoxy-4-(triisopropylsilyloxy)benzyl Alcohol: The title compound was prepared from 2-bromo-5-methoxy-4-(triisopropylsilyloxy)benzaldehyde (583 mg, 1.51 mmol) and $NaBH_4$ (28.5 mg, 7.52 mmol) according to the procedure used for the preparation of 4-methoxy-3-(triisopropylsilyloxy)benzyl alcohol. The title compound (550 mg, 93.8%.) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03, 6.96 (s, 2 H, 3-H, 6-H), 4.67 (d, J = 6.2 Hz, 2 H, Ar-CH_2), 3.81 (s, 3 H, OCH_3), 1.93 (t, J = 6.2 Hz, 1 H, OH), 1.28–1.19 (m, 3 H, CH), 1.09 (d, ^3J = 7.4 Hz, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.6 (C-5), 146.0 (C-4), 132.4 (C-1), 124.3 (C-3), 112.6 (C-6), 112.1 (C-2), 65.2 (Ar-CH_2), 55.7 (OCH_3), 18.0 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 3363, 2942, 2868, 1601, 1468, 1382, 1311, 1205, 1156, 901, 883 cm^{-1}. MS (FAB): *m*/*z* (%) = 389.1 (100) $[M]^+$.

2-Bromo-5-methoxy-4-(triisopropylsilyloxy)benzyl Bromide: The title compound was prepared from 2-bromo-5-methoxy-4-(triisopropylsilyloxy)benzyl alcohol (550 mg, 1.41 mmol), pyridine (27.5 μL, 337 μmol) and PBr_3 (53 μL, 565 μmol) according to the procedure used for the preparation of 2-chloro-4-methoxy-5-(triisopropylsilyloxy)benzyl bromide. The title compound (589 mg, 92.2%) was obtained as a colourless oil. The product was stored in dry THF (10 mL) with a small amount of $CaCO_3$ to avoid decomposition. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (s, 1 H, 3-H), 6.90 (s, 1 H, 6-H), 4.57 (s, 2 H, Ar-CH_2), 3.80 (s, 3 H, OCH_3), 1.28–1.20 (m, 3 H, CH), 1.09 (d, ^3J = 7.5 Hz, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.7 (C-5), 147.0 (C-4), 129.4 (C-1), 124.6 (C-3), 114.6 (C-2), 114.3 (C-6), 55.8 (OCH_3), 34.4 (Ar-CH_2), 18.0 (6 CH_3), 13.0 (3 CH) ppm.

1-[2-Bromo-5-methoxy-4-(triisopropylsilyloxy)benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15l): The reaction was conducted according to the general procedure. Reagents: KHMDS (487 mg, 2.44 mmol) in THF (8 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (266 mg, 1.22 mmol) in THF (8 mL), 2-bromo-5-methoxy-4-(triisopropylsilyloxy)benzyl bromide (580 mg, 1.28 mmol) in THF (10 mL), MeOH (10 mL), THF (10 mL) and $NaBH_4$ (115 mg, 3.05 mmol). The reaction yielded a yellow oil (788 mg). Purification of the crude product by flash chromatography (silica, cyclohexane/EtOAc/Et_2NH, 7:1:0.5, R_f = 0.2) gave **15l** as a colourless oil (380 mg, 55.1%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.08 (s, 1 H, 3′-H), 6.72 (s, 2 H, 6′-H, 8-H), 6.60 (s, 1 H, 5-H), 4.24 (dd, J = 9.4, J = 3.8 Hz, 1 H, 1-H), 3.86 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.30 (dd, J = 13.8, J = 4.2 Hz, 1 H, 3-H_b), 3.26–3.22 (m, 1 H, Ar-CH_b), 2.99–2.87 (m, 2 H, Ar-CH_a, 3-H_a), 2.78–2.73 (m, 2 H, 4-H_2), 1.86 (br. s, 1 H, NH), 1.29–1.22 (m, 3 H, CH), 1.09 (d, J = 7.5 Hz, 18 H, CH_3) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 150.3 (C-5′), 147.8, 147.3 (C-6, C-7), 145.2 (C-4′), 131.1 (C-1′), 130.6 (C-4a), 127.5 (C-8a), 124.5 (C-3′), 115.1 (C-6′), 112.0 (C-5), 110.0 (C-8), 56.2, 56.0, 55.9 (3 OCH_3), 55.4 (C-1), 42.9 (C-3), 40.7 (Ar-CH_2), 29.7 (C-4), 18.1 (6 CH_3), 13.0 (3 CH) ppm. IR (NaCl): $\tilde{\nu}$ = 2950, 2971, 1602, 1496, 1463, 1386, 1255, 1216, 1106, 1014, 908, 876, 734 cm^{-1}. MS (ESI): *m*/*z* (%) = 564.2 (100) $[M + H]^+$. HRMS (ESI): calcd. for $[C_{28}H_{42}BrNO_4Si + H]^+$ 564.2139; found 564.2127.

General Procedure for the Rearrangement: The 1-substituted 1,2,3,4-tetrahydroisoquinoline (52.9 μmol) was dissolved in trifluoroacetic acid (84 μL, 211 mg, 1.85 mmol) and formalin (37% in H_2O, 147 μL) was added. The mixture was stirred at 80 °C for 2.5 h. The solution was made alkaline with sat. aq. $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. Due to the limited stability of the products, no further purification was undertaken in most cases. The 3,4-dihydroisoquinolinium salts produced were characterized by HRMS and the ^1H NMR spectra.

2-[2-(2-Chloro-4,5-dimethoxyphenyl)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Trifluoroacetate (4): The title compound was prepared from **1** (20.0 mg, 53.0 μmol) following the procedure for the rearrangement: 26.4 mg, 99%, yellow wax. ^1H NMR, COSY (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H, 1-H), 7.53 (s, 1 H, 8-H), 7.10 (s, 1 H, 6′-H), 6.80 (s, 1 H, 3′-H), 6.75 (s, 1 H, 5-H), 4.36 (t, ^3J = 7.5 Hz, 2 H, N-CH_2), 3.99 (s, 3 H, 7-OCH_3), 3.93 (s, 3 H, 6-OCH_3), 3.88 (s, 3 H, 5′-OCH_3), 3.84 (s, 3 H, 4′-OCH_3), 3.86–3.82 (m, 2 H, 3-H_2), 3.31 (t, ^3J = 7.5 Hz, 2 H, Ar-CH_2), 3.11 (t, ^3J = 8.0 Hz, 2 H, 4-H_2) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 167.7 (C-1), 161.9 [q, ^2J(C,F) = 33.2 Hz, C=O], 158.4 (C-7), 149.2 (C-6), 148.4 (C-5′), 148.1 (C-4′), 131.2 (C-8a), 125.3 (C-2′), 124.6 (C-1′), 117.8 (C-4a), 116.3 (C-8), 114.1 (C-6′), 112.6 (C-3′), 110.6 (C-5), 59.6 (N-CH_2), 57.0 (7-OCH_3), 56.9 (6-OCH_3), 56.7 (5′-OCH_3), 56.5 (4′-OCH_3), 48.4 (C-3), 32.3 (Ar-CH_2), 26.0 (C-4) ppm. The CF_3 resonance was not found. IR (NaCl): $\tilde{\nu}$ = 2970, 2840, 1651, 1609, 1510, 1465, 1345, 1263, 1203, 1138, 1045, 801 cm^{-1}. MS (FAB): *m*/*z* (%) = 390.2 (100) $[M]^+$, 206.1 (41) [M + H – $C_9H_{10}ClO_2$]$^+$. HRMS (FAB): calcd. for $[C_{21}H_{25}ClNO_4]^+$ 390.1472; found 390.1463.

2-[2-(2-Chloro-4,5-dimethoxyphenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline: Crude **4** (27.4 μmol) was dissolved in MeOH (1 mL) and $NaBH_4$ (68.5 mg) was added. After stirring for 1 h at room temperature, the reaction mixture was quenched with NaOH (1 M, 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The resulting material was purified by column chromatography (silica, toluene/ethanol, 8:1, R_f = 0.1) to give the title compound as a light-yellow oil (8.5 mg, 82%). ^1H NMR, COSY (400 MHz, CD_3OD): δ = 6.95 (s, 1 H, 6′-H), 6.94 (s, 1 H, 3′-H), 6.71 (s, 1 H, 5-H), 6.67 (s, 1 H, 8-H), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.70 (s, 2 H, 1-H), 3.01–2.96 (m, 2 H, Ar-CH_2), 2.90–2.84 (m, 4 H, 3-H_2, 4-H_2), 2.75–2.71 (m, 2 H, N-CH_2) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, CD_3OD): δ = 149.9, 149.7 (C-4′, C-5′), 149.30 (C-7), 148.9 (C-6), 130.6 (C-1′), 127.3, 127.2 (C-4_a, C-8_a), 125.9 (C-2′), 115.2 (C-6′), 114.2 (C-3′), 112.9 (C-5), 111.2 (C-8), 59.1 (N-CH_2), 56.7 (OCH_3), 56.6 (OCH_3), 56.5 (OCH_3), 56.4 (OCH_3, C-1), 52.0 (C-3), 31.5 (Ar-CH_2), 29.1 (C-4) ppm. IR (NaCl): $\tilde{\nu}$ = 2926, 2850, 1609, 1515, 1464, 1260, 1220, 1167, 1123 cm^{-1}. MS (ESI): *m*/*z* (%) = 392.1 (100) [M + H]$^+$. HRMS (ESI): calcd. for $[C_{21}H_{27}ClNO_4 + H]^+$ 392.1629; found 392.1623.

2-[2-(2-Chloro-4,5-dimethoxyphenyl)[1-$^2H_2$]ethyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Trifluoroacetate: Tetrahydroisoquinoline **1** (52.9 μmol) was dissolved in a mixture of trifluoroacetic acid (84 μL, 211 mg, 1.85 mmol), water (90.8 μL) and MeOH (12.8 μL). [D_2]Paraformaldehyde (59.3 mg) was added and the mixture was stirred at 80 °C for 2.5 h. The solution was made alkaline with sat. aq. $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo to afford the title compound (18.2 mg, 87%) as a yellow wax. ^1H NMR, COSY (200 MHz, $CDCl_3$): δ = 9.85 (s, 1 H, 1-H), 7.56 (s, 1 H, 8-H), 7.14 (s, 1 H, 6′-H), 6.80 (s, 1 H, 3′-H), 6.75 (s, 1 H, 5-H), 3.99 (s, 3 H, 7-OCH_3), 3.96 (s, 3 H, 6-OCH_3), 3.88 (s, 3 H, 5′-OCH_3), 3.83 (s, 3 H, 4′-OCH_3), 3.88–3.83 (m, 2 H, 3-H_2), 3.31 (s, 2 H, Ar-CH_2), 3.10 (t, ^3J = 8.1 Hz, 2 H, 4-H_2) ppm. MS (FAB): *m*/*z* (%) = 392 (19) $[M]^+$, 208 (100) [M + H – $C_9H_{10}ClO_2$]$^+$. HRMS (FAB): calcd. for $[C_{21}H_{23}D_2ClNO_4 + H]^+$ 392.1598; found 392.1601.

Crossover Experiment: Tetrahydrosioquinolines **1** (15.39 mg, 38.7 μmol) and **9** (14.63 mg, 38.7 μmol) were stirred with trifluoroacetic acid (122.6 μL) and formalin (37% in H_2O, 214.6 μL) at 80 °C for 2.5 h. The solution was made alkaline with sat. aq. $NaHCO_3$ and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The products were detected by ESI-HRMS. **4**: calcd. for $[C_{21}H_{25}ClNO_4]^+$ 390.1467; found 390.1468; **10**: calcd. for $[C_{21}H_{19}D_6ClNO_4]^+$ 396.1843; found 396.1840; **11**: calcd. for $[C_{22}H_{27}ClNO_4]^+$ 404.1623; found 404.1624; **12**: calcd. for $[C_{22}H_{21}D_6ClNO_4]^+$ 410.2000; found 410.2001.

2-(But-3-enyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Trifluoroacetate (16b): Prepared following the procedure for the rearrangement starting from 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**15b**; 12.4 mg, 53.0 μmol), trifluoroacetic acid (84 μL) and formalin (147 μL). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1 H, 1-H) ppm. MS (ESI): *m*/*z* (%) = 246.15 (100) $[M]^+$. HRMS (ESI): calcd. for $[C_{15}H_{20}NO_2]^+$ 246.1489; found 246.1487.

2-[2-(4-Bromophenyl)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Trifluoroacetate (16c): Prepared following the procedure for the rearrangement starting from **15c** (10.0 mg, 2.76 μmol), trifluoroacetic acid (43.7 μL) and formalin (78.4 μL). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1 H, 1-H) ppm. MS (ESI): *m*/*z* (%) = 374.37/376.42 (60/55) $[M]^+$. HRMS (ESI): calcd. for $[C_{19}H_{21}{}^{79}BrNO_2]^+$ 374.0756; found 374.0741.

2-[2-(4-Iodophenyl)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Trifluoroacetate (16d): Prepared following the procedure for the rearrangement starting from **15d** (10.0 mg, 2.44 μmol), trifluoroacetic acid (38.9 μL) and formalin (68.1 μL). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1 H, 1-H) ppm. MS (ESI): *m*/*z* (%) = 422.45 (77) $[M]^+$. HRMS (ESI): calcd. for $[C_{19}H_{21}INO_2]^+$ 422.0617; found 422.0609.

6,7-Dimethoxy-2-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroisoquinolinium Trifluoroacetate (16e): Prepared following the procedure for the rearrangement starting from **15e** (10.0 mg, 31.9 μmol), trifluoroacetic acid (50.4 μL), formalin (88.2 μL) and dibenzoyl peroxide (0.77 mg, 3.19 μmol). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.50 (s, 1 H, 1-H) ppm. MS (ESI): *m*/*z* (%) = 326.17 (100) $[M]^+$. HRMS (ESI): calcd. for $[C_{20}H_{24}NO_3]^+$ 326.1751; found 326.1749.

2-{2-[2-Chloro-4-methoxy-5-(triisopropylsilyloxy)phenyl]ethyl}-6,7-dimethoxy-3,4-dihydroisoquinolinium Trifluoroacetate (16k): Prepared following the procedure for the rearrangement starting from **15k** (10.0 mg, 19.2 μmol), trifluoroacetic acid (30.5 μL) and formalin (53.3 μL). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H, 1-H) ppm. MS (ESI): *m*/*z* (%) = 532.26 (100) $[M]^+$, 376.13 (27) [M – TIPS + H]$^+$. HRMS (ESI): calcd. for $[C_{29}H_{43}ClNO_4Si]^+$ 532.2644; found 532.2638.

2-{2-[2-Bromo-5-methoxy-4-(triisopropylsilyloxy)phenyl]ethyl}-6,7-dimethoxy-3,4-dihydroisoquinolinium Trifluoroacetate (16l): Prepared following the procedure for the rearrangement starting from **15l** (10.0 mg, 17.7 μmol), trifluoroacetic acid (28 μL) and formalin (49.1 μL). ^1H NMR, (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H, 1-

H) ppm. MS (ESI): *m*/*z* (%) = 576.21/578.21 (100) $[M]^+$. HRMS (ESI): calcd. for $[C_{29}H_{43}{}^{79}BrNO_4Si]^+$ 576.2139; found 576.2113.

Supporting Information (see footnote on the first page of this article): Spectra, Cartesian coordinates and energies of the computed structures.

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