Iodocyclisation of 1,4-Dihydropyridines; Synthesis and Reactivity of 1-Iodoindolo[2,3-*a*]quinolizidines[1]

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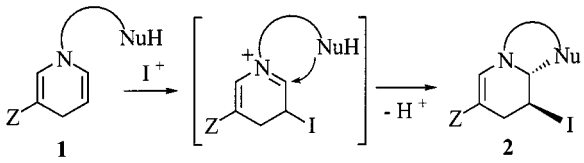
The addition of iodine (or related species) to β-acyl-*N*-alkyl-1,4-dihydropyridines **1**, which possess an *N*-substituent with an appropriate nucleophile moiety, leads to the corresponding 3-iododihydropyridinium ions, which undergo an internal nucleophilic attack to give, regio- and stereoselectively, the iodobi(poly)heterocyclic ring systems **2a–f** in good yields. Reactivity studies on the iodoindoloquinolizidines **2e,f** lead to the pentacyclic cyclopropane systems **4a,b**, azides **5** and **6**, norderivative **9** and, by a base-induced elimination, dihydropyridine **10**, a precursor of the zwitterionic alkaloids flavopereirine and 6,7-dihydroflavopereirine.

Introduction

The rich reactivity of β-acyl-1,4-dihydropyridines[2–7] make these compounds valuable synthetic intermediates, especially in the fields of natural product synthesis and medicinal chemistry.[8–10] The major drawback of the synthetic manipulation of these compounds is that they are easily oxidised to the corresponding pyridinium salts. In fact, this reactivity plays an important role in nature, where NADH is converted into NAD^+ in many metabolic reductions. Recently we have accomplished "nonbiomimetic" oxidations of *N*-alkyl-1,4-dihydropyridines, including formal epoxidations,[11] diaminations,[12] and alcoxyhalogenations,[13] in simple experimental procedures that avoid the natural oxidation route. Herein we report the extension of this methodology to the preparation of polycyclic 3-iodo-1,2,3,4-tetrahydropyridines through an intramolecular nucleophilic attack upon the iminium ions initially generated by reaction of a variety of 1,4-dihydropyridines with iodonium ions (Scheme 1). The possibility of further conversion of these heterocyclic systems using radical chemistry makes them potentially interesting for the synthesis of a broad variety of alkaloids and other bioactive substances.



Scheme 1. Iodocyclisation of 1,4-Dihydropyridines

Results and Discussion

The required 1,4-dihydropyridines **1** were prepared by reduction of the corresponding pyridinium salts with sodium dithionite.[14] Treatment of the *N*-(hydroxyethyl) derivative **1a**[15][16] with NIS (1.1 equiv.) in THF solution stereoselectively afforded the *trans* iodooxazolidine **2a** (Scheme 2) in 30% yield. The stereoelectronic factors behind the process, involving an electrophilic addition to an activated carbon–carbon double bond followed by a nucleophilic trapping of the formed iminium ion, are well-known, and favour the *trans* stereochemistry observed, arising from an *anti* addition.[17] This was confirmed by NMR spectroscopic analysis (coupling constants of the diagnostic signals, COSY and NOESY spectra). Analogously, when **1b** was treated with iodine (1 equiv.), the expected *trans* iodooxazine **2b** (22%) was obtained, together with **3** (33%), the latter coming from the acid-promoted cyclisation of the starting material. In order to avoid this undesired by-product formation, the reaction was run in the presence of excess $NaHCO_3$ or Na_2CO_3 (to scavenge the protons produced in the cyclisation step); under these conditions, no **3** was detected and the yield of **2b** increased to 67% (Scheme 2).

The use of chiral dihydropyridines has recently become a powerful methodology in alkaloid synthesis.[18][19] In order to exploit the iodocyclisation reaction and have access to enantiomerically pure compounds, we decided to test this methodology upon substrates, such as **1c**, bearing a chiral auxiliary on the heterocyclic nitrogen. Taking into account the good levels of stereocontrol achieved using this oxazolidine precursor[20] and the convenient transformation and/or removal procedures that enables it to be used, we prepared **1c** using Marazano's synthesis, which involves the reaction of the Zincke salt (obtained through the alkylation of 3-acetylpyridine ethylene acetal with 1-chloro-2,4-dinitrobenzene) with (*R*)-(−)-phenylglycinol, followed by reduction of the chiral pyridinium salt.[16] Knowing the instability of this type of dihydropyridine (which lacks the electron-withdrawing group at the β-position), a series of experiments was performed to try to obtain an analogue of **1c** bearing the stabilising acetyl residue instead of the elec-

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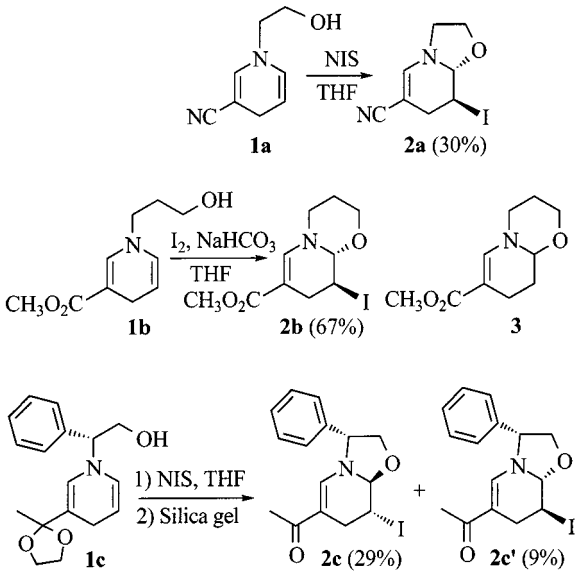


Scheme 2. Iodocyclisation of 1,4-Dihydropyridines **1a−c**

tron-donating acetal. Attempts to hydrolyse the acetal moiety at the pyridinium salt stage with aqueous HCl or $FeCl_3$/SiO_2 did not prove successful, and only treatment with $CeCl_3 \cdot 7H_2O$/NaI in acetonitrile[21] afforded mixtures of the starting material together with some of the expected ketone. However, the process was slow and the resulting compounds were difficult to purify so we returned to the original procedure. Reaction of **1c** (immediately after its preparation) with NIS in THF solution gave a crude product, which was subjected to a mild hydrolysis by stirring a CH_2Cl_2 solution over silica gel to afford a mixture of the iodotetrahydropyridines **2c** (29%) and **2c′** (9%). Modification of the experimental conditions did not improve the low overall yield nor the moderate stereoselection; it should be considered, however, that this two-step/one-pot process involves a double asymmetric induction, in which the first stereogenic centre to be created is located in a somewhat remote position with respect to the chiral auxilliary. Nevertheless, the protocol stereospecifically forms highly functionalised, chiral oxazolotetrahydropyridines, which may become valuable synthetic intermediates. The absolute stereochemistry was assigned from one- and two-dimensional NMR spectroscopy, including COSY, NOE, ROESY, and HMQC experiments, and showed a (3*R*, 8*R*, 8a*S*) configuration for the major stereoisomer and (3*R*, 8*S*, 8a*R*) for the minor isomer. The stereochemical outcome of this process is similar to that observed in related additions[16][22] (see Figure 1).

To broaden the scope of this general approach, we explored the possibility of forming C−C bonds by the *nonbiomimetic* oxidation of dihydropyridines. It was envisaged that a suitable C-nucleophile (i.e., an electron-rich olefin or an activated aromatic ring) would trap the oxidatively generated α-iodo iminium salt. After several unsuccessful attempts to cyclise 1-allyl-1,4-dihydropyridines,[23] the homoallyl derivative **1d** was found to undergo a smooth iodocyclisation with iodine in THF solution[24] to afford the di-

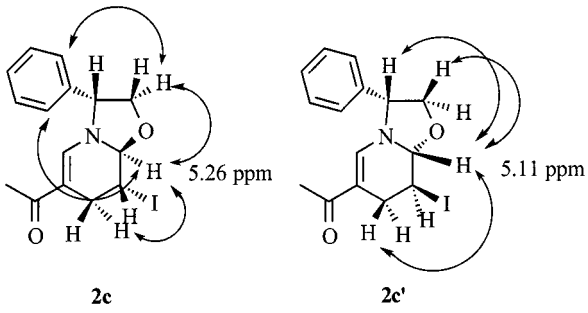
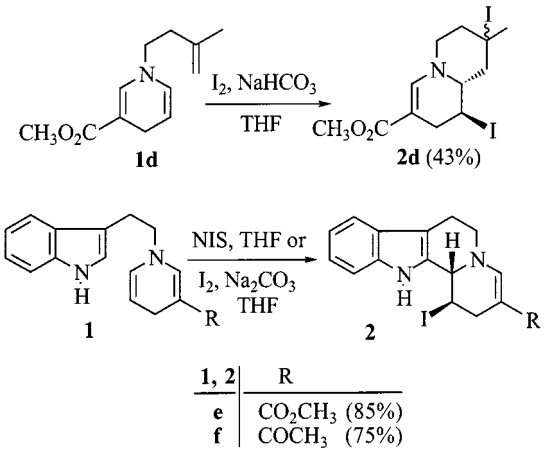


Figure 1. Diagnostic NOE′s and chemical shifts of **2c** and **2c′**

iodide **2d** (43% isolated yield; partial decomposition took place during the purification by column chromatography) as an epimeric mixture at the tetrasubstituted sp^3 carbon atom. The overall transformation probably involves a stereocontrolled (*anti*) addition of the double bond to the initially formed iminium ion, followed by a nonstereospecific trapping of the resulting tertiary carbocation by an iodide. This would explain the high chemoselectivity of the process, which allows the distinction of the enamine moiety (more reactive towards the electrophilic iodine) from the olefinic portion (acting in the second phase to capture the iminium ion); the third double bond (part of a vinylogous urethane) is totally inert under these reaction conditions. With respect to the aromatic ring trapping, no halocyclisations were observed with different substituted 1-phenethyl-1,4-dihydropyridines (only alkoxyhalogenation-type products were detected).[25] However, with the *N*-tryptophyl derivatives **1e**,**f**, the situation changed dramatically and, on reaction with NIS (**1e**) or I_2 (**1f**), the corresponding iodoindoloquinolizidines **2e** (85%) and **2f** (75%) were stereoselectively obtained (Scheme 3).



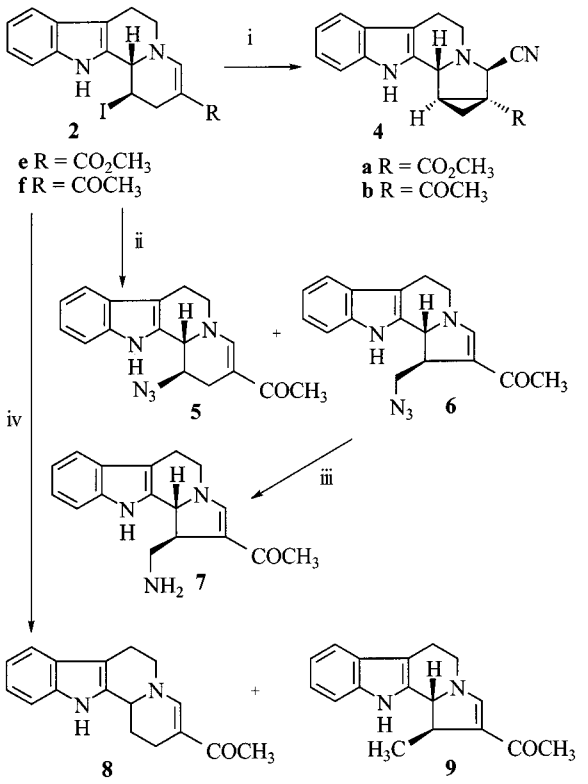
Scheme 3. Iodocyclisation of 1,4-Dihydropyridines **1d−f**

The two latter compounds exhibit a high degree of functionalisation, which deserves further studies. The coexistence of a reactive carbon-iodine bond (suitable for radical and nucleophilic reactions) with a low-basicity nitrogen (connected through a double bond with a carbonyl group) in a tetracyclic framework bearing an indole ring makes this proposal attractive, especially considering the bioactivity

shown by Vinca-Eburna derivatives.[26] First of all, treatment of **2e** with KCN resulted in the stereoselective formation of cyclopropane **4a** (94% of a single stereoisomer, see Scheme 4). This uncommon, but known, transformation[27] probably proceeds through an addition of the nucleophile to the conjugated double bond followed by an intramolecular nucleophilic displacement of the halide by the in-situ-generated enolate. The stereochemistry was unambiguously determined by NMR spectroscopy, including a NOESY spectrum (see Figure 2). In a similar manner, **2f** could be converted into **4b** (93%). On the other hand, the reaction of NaN_3 with **2f** under phase-transfer conditions gave the indoloquinolizidine azide **5** (20%) and the ring-contraction product **6** (37%). A reasonable mechanism to account for these facts invokes a conjugate addition to give an intermediate cyclopropane, which may be attacked at the two less sterically demanding positions (to release the ring strain and to regenerate the vinylogous amide) to form the final reaction products. This would explain the observed retention of configuration of **5** with respect to the starting material. Azide **6** was reduced to the corresponding primary amine **7** (61%) by treatment with PPh_3 in a THF/H_2O mixture. On the other hand, Zn-mediated reduction of **2f** in protic medium[28] afforded a mixture of the indoloquinolizidine **8**[29] (72%) and the indoloindolizidine **9** (23%). Again, this unusual ring contraction may be explained by the intermediacy of a cyclopropyl species, in this case a cyclopropylcarbinyl radical in equilibrium with its homoallyl counterparts.[30] In sharp contrast to the previous ionic process, it should be noted that here the predominant product is the six-membered ring **8**, probably showing a kinetic preference favouring the secondary cyclohexyl-type radical pathway over the primary cyclopentylmethyl pathway.

On treatment of **2f** with morpholine or sodium methanethiolate, no addition products were detected, and small amounts ($\leq$ 10%) of the elimination product **10**[31] were isolated (Scheme 5). Although DBU-promoted elimination did not improve the results, an efficient transformation (79%) was achieved using sodium methoxide as a base in MeOH solution. Aerobic (O_2) oxidation of the dihydropyridine **10** afforded the pyridinium salt **11**[29] (35%, isolated as the perchlorate), whereas treatment with DDQ was faster and more efficient, yielding **11** in 78% yield. This constitutes a formal synthesis of the zwitterionic indole alkaloids flavopereirine and 6,7-dihydroflavopereirine[32][33] because this salt has previously been transformed into 3-(1-hydroxyethyl)hexahydroindolo[2,3-*a*]quinolizine,[29] which, in turn, has been converted into 6,7-dihydroflavopereirine in a two-step procedure[34] and then to flavopereirine by DDQ-oxidation.[33d] Although several previous syntheses of these natural products are clearly more efficient (in terms of overall yield and number of steps), our sequence shows the feasibility of carrying out a *nonbiomimetic oxidation* of dihydropyridine **1f**, followed by a dehydrohalogenation, to furnish a second dihydropyridine **10**, which is oxidised in a *biomimetic* manner to the corresponding pyridinium salt **11**.

In conclusion, a synthetic methodology based on the iodocyclisation of dihydropyridines **1** has been developed,



Scheme 4. Reagents, conditions and yields: (i) KCN, $(Bu)_4N^+I^-$, $CH_2Cl_2-H_2O$, room temp. (**4a**, 94%, **4b**, 93%); (ii) NaN_3, $(Bu)_4N^+I^-$, $CH_2Cl_2-H_2O$, room temp. (**5**, 20%, **6**, 37%); (iii) PPh_3, THF/H_2O, 60°C (61%); (iv) Zn, CuI, $EtOH-H_2O$,))), room temp. (**8**, 72%, **9**, 23%)

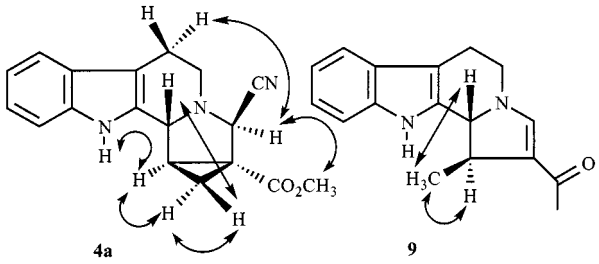
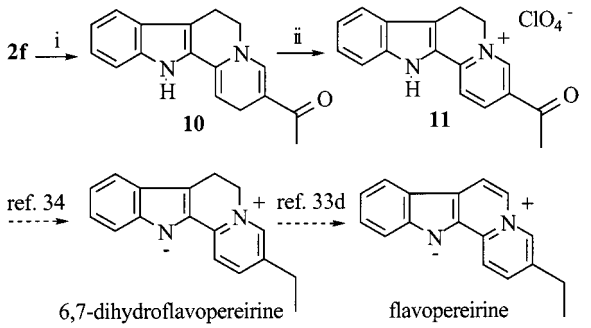


Figure 2. Diagnostic NOE′s of **4a** and **9**



Scheme 5. Reagents, conditions and yields: (i) NaOMe, MeOH, 60°C (79%); (ii) O_2, CH_2Cl_2, room temp. (35%), or DDQ, CH_2Cl_2, room temp., then $HClO_4$ (78%)

and the implementation of this *nonbiomimetic* oxidation procedure to the synthesis of a broad variety of heterocyclic

systems **2**, including alkaloid precursors, has been efficiently performed.

Experimental Section

General: All solvents were dried by standard methods. Reagents were of commercial quality from freshly-opened containers. All reactions were conducted under an atmosphere of dry N_2. Prior to concentration under reduced pressure, all organic extracts were dried with anhydrous Na_2SO_4 powder. Melting points were measured using a Büchi apparatus and are uncorrected. Microanalyses were performed with a Carlo Erba 1106 analyser by Centro de Investigación y Desarrollo (CSIC), Barcelona. All compounds are racemates except dihydropyridine **1c** and oxazolidines **2c** and **2c′**. Optical rotations were measured with a Perkin−Elmer 241 polarimeter using a 1dm cell with a total volume of 1 mL. − NMR: Varian Gemini-200 (200 and 50.3 MHz, for ^1H and ^{13}C, respectively), Varian Gemini-300 (300 and 75.4 MHz), Varian VXR 500 (500 and 125.6 MHz). For ^1H NMR, $CDCl_3$ as solvent, TMS as an internal reference, CD_3OD as solvent, $\delta_H = 3.31$; for ^{13}C, $CDCl_3$ as solvent, $\delta_C = 77.0$. − IR: Perkin−Elmer 1600 series FTIR. − UV: Hitachi U-2000 apparatus in MeOH solution. − MS: Hewlett-Packard 5989A (70 eV, low resolution) and Autospec-EQ (high resolution).

Synthesis of Dihydropyridines 1: Compounds **1a** and **1b** were prepared by $Na_2S_2O_4$ reduction of the corresponding pyridinium salts (prepared by reaction of 3-cyanopyridine with 2-bromoethanol, and methyl nicotinate with 3-bromo-1-propanol, respectively) following the procedure stated in ref.[15] Compound **1c** was synthesised following the reported procedure.[16] Compound **1d** was the product of the standard reduction[14] of the pyridinium salt formed by alkylation of methyl nicotinate with 3-iodo-2-methyl-1-butene (prepared in turn, from the alcohol *via* the tosylate). Compounds **1e**[35] and **1f**[29] were prepared according to published methods.

Iodooxazolidine 2a: A solution of NIS (165 mg, 0.73 mmol) in THF (10 mL) was added dropwise at 0°C under an inert atmosphere to a suspension of dihydropyridine **1a** (100 mg, 0.67 mmol) in anhydrous THF (50 mL), and the resulting mixture was stirred at this temperature for 15 min. Water (200 mL) was added, and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ solution (100 mL, 0.1 M), water (100 mL), and a saturated aqueous Na_2CO_3 solution (100 mL), dried, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexanes/ethyl acetate) to give **2a** (oil, 55 mg, 30%). − IR (KBr): $\tilde{\nu}$ = 2189 (C≡N), 1615 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 270 (4.0). − ^1H NMR ($CDCl_3$): δ = 2.86 (m, 2 H), 3.47 (m, 1 H), 3.66 (m, 1 H), 3.83 (m, 1 H), 3.99 (m, 1 H), 4.16 (m, 1 H), 4.90 (d, *J* = 8.9 Hz), 7.02 (d, *J* = 1.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 19.4 (d), 33.8 (t), 49.1 (t), 62.6 (s), 65.1 (t), 90.5 (d), 119.9 (s), 142.9 (d). − MS (70 eV); *m/z* (%): 276 (59) [M^+], 149 (100) [M^+ − I]. − $C_8H_9IN_2O$: Calcd for [M^+] 275.9760; found 275.9760.

Iodooxazine 2b: An iodine solution (25 mL, 50 mM in THF) was added dropwise at 0°C under an inert atmosphere to a suspension of dihydropyridine **1b** (224 mg, 1.14 mmol) and $NaHCO_3$ (2.5 g) in anhydrous THF (50 mL), and the resulting mixture was stirred at 0°C for 15 min. Water (200 mL) was added, and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ solution (100 mL, 0.1 M), water (100 mL), and a saturated aqueous Na_2CO_3 solution (100 mL), dried, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexanes/ethyl acetate) to give **2b** (oil, 247 mg, 67%). − IR (KBr): $\tilde{\nu}$ = **1**689 (C=O), 1628 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 279 (4.22). − ^1H NMR ($CDCl_3$): δ = 1.49 (d, *J* = 13.4 Hz, 1 H), 1.97 (m, 1 H), 2.80 (dd, *J* = 17.5, 4.1 Hz, 1 H), 2.98 (m, *J* = 17.5, 4.8, 1.5 Hz, 1 H), 3.49 (m, 2 H), 3.70 (s, 3 H), 3.84 (m, 1 H), 4.16 (m, 1 H), 4.29 (m, 1 H), 4.66 (d, *J* = 3.6 Hz, 1 H), 7.23 (d, *J* = 1.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 20.7 (d), 26.5 (t), 28.0 (t), 51.0 (q), 51.7 (t), 67.9 (t), 87.4 (d), 98.1 (s), 142.5 (d), 168.0 (s). − MS (70 eV); *m/z* (%): 323 (22) [M^+], 292 (13) [M^+ − OMe], 196 (100) [M^+ − I]. − $C_{10}H_{14}INO_3$: calcd for [M^+] 323.0018; found 323.0020. When the reaction was performed in the absence of $NaHCO_3$, **2b** (22%) was isolated together with oxazine **3** (33%). − ^1H NMR ($CDCl_3$, data obtained from a mixture with **2b**): δ = 1.49 (d, *J* = 13.4 Hz, 1 H), 2.00 (m, 3 H), 2.32 (m, 2 H), 3.40 (m, 2 H), 3.68 (s, 3 H), 4.12 (m, 2 H), 4.48 (t, *J* = 4.4 Hz, 1 H), 7.17 (s, 1 H). − ^{13}C NMR ($CDCl_3$, data obtained from a mixture with **2b**): δ = 16.4 (t), 26.2 (t), 26.8 (t) , 50.9 (q), 51.2 (t), 67.5 (t), 83.0 (d), 99.4 (s), 144.1 (d), 168.5 (s).

Chiral Iodooxazolidines 2c and 2c′: A solution of NIS (190 mg, 0.84 mmol) in THF (10 mL) was added dropwise at 0°C under an inert atmosphere to a solution of dihydropyridine **1c** (220 mg, 0.77 mmol) in anhydrous THF (50 mL), and the resulting mixture was stirred at 0°C for 15 min. Water (200 mL) was added, and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ solution (100 mL, 0.1 M), water (100 mL), and a saturated aqueous Na_2CO_3 solution (100 mL), dried, filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL). SiO_2 (5 g) was added, and the resulting suspension was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel. Elution with hexanes/ethyl acetate gave **2c** (oil, 82 mg, 29%). IR (KBr): $\tilde{\nu}$ = 1640 (C=O), 1590 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 306 (4.20). − $[\alpha]^{20}_D = -145$ (*c* = 0.6, MeOH). − ^1H NMR ($CDCl_3$): δ = 2.06 (s, 3 H), 2.73 (m, *J* = 16.7, 12.5, and 1.5 Hz, 1 H), 3.43 (dd, *J* = 16.7, and 5.2 Hz, 1 H), 3.81 (m, 1 H), 3.89 (m, 1 H), 4.53 (m, 1 H), 4.69 (m, 1 H), 5.26 (d, *J* = 9 Hz, 1 H), 7.22 (d, *J* = 1.5 Hz, 1 H), 7.33 −7.45 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 21.9 (d), 24.2 (q), 32.0 (t), 64.6 (d), 73.7 (t), 92.8 (d), 111.8 (s), 126.8 (d), 128.9 (d), 129.3 (d), 136.9 (s), 140.8 (d), 192.7 (s). − MS (70 eV); *m/z* (%): 369 (30) [M^+], 242 (100) [M^+ − I]. − $C_{15}H_{16}INO_2$: Calcd. for [M^+] 369.0226; found 369.0226. Further elution afforded **2c′** (25 mg, 9%, slightly contaminated with **2c**). − ^1H NMR ($CDCl_3$): δ = 1.98 (s, 3 H), 2.75 (m, *J* = 17.0, 12.3, and 1.9 Hz, 1 H), 3.43 (dd, *J* = 16.8, and 5.4 Hz, 1 H), 4.05 (m, 1 H), 4.13 (dd, *J* = 9.1 and 2.6 Hz, 1 H), 4.38 (dd, *J* = 9.1 and 6.9 Hz, 1 H), 4.82 (dd, *J* = 7.0 and 2.6 Hz, 1 H), 5.11 (d, *J* = 9.1 Hz, 1 H), 7.09 (d, *J* = 1.6 Hz, 1 H), 7.35 −7.45 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 21.3 (d), 24.0 (q), 32.3 (t), 63.1 (d), 73.2 (t), 92.0 (d), 110.4 (s), 127.1 (d), 128.7 (d), 129.2 (d), 139.9 (s), 140.7 (d), 192.4 (s).

Iodoquinolizidine 2d: An iodine solution (18.5 mL, 50 mM in THF) was added dropwise at 0°C under an inert atmosphere to a suspension of dihydropyridine **1d** (174 mg, 0.84 mmol) and Na_2CO_3 (2.5 g) in anhydrous THF (50 mL), and the resulting mixture was stirred at 0°C for 15 min. Water (200 mL) was added, and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ solution (100 mL, 0.1 M), water (100 mL), and a saturated aqueous Na_2CO_3 solution (100 mL), dried, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexanes/ethyl acetate, partial decomposition) to give **2d** as a mixture of

epimers at the C-methyl stereocentre (167 mg, 43%). − IR (NaCl): $\tilde{\nu}$ = 1683 (C=O), 1622 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 289 (4.22). − ^1H NMR ($CDCl_3$, data for the major epimer): δ = 2.12 (s, 3 H), 3.36−2.31 (m, 8 H), 3.40 (m, 1 H), 3.68 (s, 3 H), 4.16 (dd, *J* = 7.1 and 5.5 Hz, 1 H), 7.28 (s, 1 H). − ^{13}C NMR ($CDCl_3$, data for the major epimer): δ = 24.1 (d), 31.5 (t), 31.7 (q), 41.3 (s), 46.5 (t), 50.2 (t), 50.9 (q), 51.5 (t), 58.5 (d), 95.8 (s), 144.2 (d), 167.6 (s). − MS (70 eV); *m/z* (%): 461 (7) [M^+], 334 (13) [M^+ − I], 206 (100) [M^+ − I_2, H]. − $C_{12}H_{17}I_2NO_2$: calcd for [M^+] 406.9348; found 460.9340.

Iodoindoloquinolizidine 2e: Following the experimental procedure described for **2a**, from dihydropyridine **1e** (250 mg, 0.89 mmol) and NIS (219 mg, 0.97 mmol), **2e** (308 mg, 85%) was obtained after column chromatography (silica gel, hexanes/ethyl acetate). M.p. (acetone/Et_2O) 137−138°C. − IR (KBr): $\tilde{\nu}$ = 3380 (N−H), 1675 (C=O), 1604 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 292 (4.40), 221 (4.69). − ^1H NMR ($CDCl_3$): δ = 2.75−2.97 (m, 2 H), 2.99 (dd, *J* = 16.5 and 8.1 Hz, 1 H), 3.12 (dd, *J* = 16.5 and 5.0 Hz, 1 H), 3.50 (m, 1 H), 3.68 (s, 3 H), 3.74 (m, 1 H), 4.57 (m, 1 H), 4.99 (d, *J* = 7.7 Hz, 1 H), 7.09−7.25 (m, 2 H), 7. 37 (d, *J* = 8.1 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.55 (s, 1 H), 8.80 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.8 (d), 22.6 (t), 30.0 (t), 50.8 (q), 51.4 (t), 60.2 (d), 96.6 (s), 108.9 (s), 111.2 (d), 118.0 (d), 119.3 (d), 121.9 (d), 126.4 (s), 130.7 (s), 135.8 (s), 144.9 (d), 168.5 (s). − MS (70 eV); *m/z* (%): 408 (6) [M^+], 280 (100) [M^+ -IH], 221 (59). $C_{17}H_{17}N_2O_2I$ (408.2): calcd. C 50.01, H 4.20, N 6.86; found C 49.85, H 4.22, N 6.69.

Iodoindoloquinolizidine 2f: Following the experimental procedure described for **2b**, from dihydropyridine **1f** (250 mg, 0.94 mmol), Na_2CO_3 (2.5 g) and iodine (262 mg, 1.03 mmol), **2f** (276 mg, 75%) was obtained after column chromatography (silica gel, hexanes/ethyl acetate). M.p. (acetone/Et_2O) 140−141°C. − IR (KBr): $\tilde{\nu}$ = 3417 (N−H), 1620 (C=O), 1573 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 294 (4.45), 222 (4.70). − ^1H NMR ($CDCl_3$): δ = 2.19 (s, 3 H), 2.80−3.00 (m, 3 H), 3.25 (dd, *J* = 16.5 and 4.9 Hz, 1 H), 3.61 (m, 1 H), 3.76 (dd, *J* = 13.1 and 5.2 Hz, 1 H), 4.54 (m, 1 H), 5.05 (d, *J* = 7.7 Hz, 1 H), 7.10−7.26 (m, 2 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.48 (s, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 8.95 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.5 (t), 22.7 (d), 23.8 (q), 30.9 (t), 52.0 (t), 60.1 (d), 109.2 (s), 111.4 (d), 117.8 (d), 119.6 (d), 122.4 (d), 126.3 (s), 130.7 (s), 135.8 (s), 146.6 (d), 193.2 (s), (one quaternary carbon not seen). − MS (70 eV); *m/z* (%): 392 (1) [M^+], 265 (22) [M^+ -I], 221 (25). $C_{17}H_{17}IN_2O$ (392.2): calcd. C 52.06, H 4.37, N 7.14; found C 52.19, H 4.41, N 7.09.

α-Aminonitriles 4a,b: A solution of KCN (498 mg, 7.65 mmol) in water (10 mL) was added at room temperature to a solution of indoloquinolizidine **2e** or **2f** (2.5 mmol) in CH_2Cl_2 (30 mL). Tetrabutylammonium iodide (471 mg, 1.27 mmol) was added, and the biphasic mixture was stirred at room temperature for 40 h. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic extracts were washed with water (10 × 50 mL), dried and filtered. The solvent was removed under reduced pressure to give a residue, which was chromatographed over silica gel. Elution with hexanes/ethyl acetate afforded the corresponding α-aminonitriles **4**.

4a: (94%), m.p. (acetone/Et_2O) 184−186°C. − IR (KBr): $\tilde{\nu}$ = 3391 (N−H), 2240 (C≡N), 1726 (C=O) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 280 (4.20), 223 (4.69). − ^1H NMR ($CDCl_3$): δ = 1.68 (dd, *J* = 8.0 and 4.5 Hz, 1 H), 1.87 (dd, *J* = 5.2 and 4.5 Hz, 1 H), 2.36 (dd, *J* = 8.0 and 5.2 Hz, 1 H), 2.70 (m, 1 H), 2.92 (m, 1 H), 3.10 (m, 1 H), 3.50 (dd, *J* = 14.0 and 5.0 Hz, 1 H), 3.67 (s, 3 H), 4.27 (s, 1 H), 4.56 (m, *J* = 2.0 Hz, 1 H), 7.13−7.23 (m, 2 H), 7. 36 (d, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 7.5 Hz, 1 H), 7.83 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 16.0 (t), 16.4 (t), 31.8 (d), 33.2 (s), 42.1 (t), 49.6 (d), 52.6 (q), 56.8 (d), 108.0 (s), 111.0 (d), 118.4 (s), 118.5 (d), 120.0 (d), 122.5 (d), 126.9 (s), 131.3 (s), 136.2 (s), 170.4 (s). − MS (70 eV); *m/z* (%): 307 (60) [M^+], 279 (55) [M^+ − CN − 2H], 155 (100). $C_{18}H_{17}N_3O_2$: calcd for [M^+] 307.1321; found 307.1316.

4b: (93%), m.p. (acetone/Et_2O) 180−182°C. − IR (KBr): $\tilde{\nu}$ = 3382 (N−H), 2241 (C≡N), 1673 (C=O) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 289 (4.08), 279 (4.19), 224 (4.80). − ^1H NMR ($CDCl_3$): δ = 1.66 (dd, *J* = 8.4 and 5.2 Hz, 1 H), 1.90 (m, 1 H), 1.92 (s, 3 H), 2.65 (m, 2 H), 2.89 (m, 1 H), 3.08 (m, 1 H), 3.45 (dd, *J* = 14.5 and 5.2 Hz, 1 H), 4.27 (s, 1 H), 4.54 (br. s, 1 H), 7.05−7.20 (m, 2 H), 7. 32 (d, *J* = 7.9 Hz, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H), 9.69 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.7 (t), 16.5 (t), 24.7 (q), 32.0 (d), 41.9 (t), 42.3 (s), 49.0 (d), 57.0 (d), 106.7 (s), 110.9 (d), 118.0 (d), 118.5 (s), 119.0 (d), 121.6 (d), 126.5 (s), 131.4 (s), 136.1 (s), 202.9 (s). − MS (70 eV); *m/z* (%): 291 (60) [M^+], 263 (48), 155 (100). − $C_{18}H_{17}N_3O$·1/4 H_2O (295.8): calcd. C 73.02, H 5.92, N 14.20; found C 73.18, H 5.84, N 13.88.

Azides 5 and 6: A solution of NaN_3 (200 mg, 3 mmol) in water (10 mL) was added at room temperature to a solution of indoloquinolizidine **2f** (200 mg, 0.51 mmol) in CH_2Cl_2 (30 mL). Tetrabutylammonium iodide (95 mg, 0.26 mmol) was added, and the biphasic mixture was stirred at room temperature for 40 h. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic extracts were washed with water (10 × 50 mL), dried and filtered. The solvent was removed under reduced pressure to give a residue, which was chromatographed over silica gel. Elution with hexanes/ethyl acetate (6: 4) afforded azide **6** (58 mg, 37%). M.p. (MeOH-Et_2O) 207−208°C. − IR (KBr): $\tilde{\nu}$ = 3370 (N−H), 2102 (N_3), 1555 (broad, C=O and C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 320 (4.54), 223 (4.70). − ^1H NMR ($CDCl_3$): δ = 2.15 (s, 3 H), 2.90 (m, 2 H), 3.51 (m, 3 H), 3.87 (m, 1 H), 4.22 (dd, *J* = 11.2 and 3.3 Hz, 1 H), 4.98 (m, 1 H), 7.09−7.21 (m, 2 H), 7.26 (s, 1 H), 7.37 (d, *J* = 7.9 Hz, 1 H), 7.45 (d, *J* = 7.7 Hz, 1 H), 8.70 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.5 (t), 25.4 (q), 45.1 (t), 47.4 (d), 53.7 (t), 63.6 (d), 107.2 (s), 111.3 (d), 114.2 (s), 117.9 (d), 119.6 (d), 122.2 (d), 126.6 (s), 132.1 (s), 136.2 (s), 152.9 (d), 190.3 (s). − MS (70 eV); *m/z* (%): 307 (23) [M^+], 250 (94) [M^+ − N_3 − CH_3], 208 (100), [M^+ − CH_2N_3 − $COCH_3$]. − $C_{17}H_{17}N_5O$ (307.1): calcd. C 66.43, H 5.58, N 22.79; found C 66.09, H, 5.51, N 22.39. − Elution with hexanes/ethyl acetate (2:8) afforded azide **5** (31 mg, 20%), m.p. (AcOEt) 219−221°C. − IR (KBr): $\tilde{\nu}$ = 3362 (N−H), 2091 (N_3), 1635 (C=O), 1580 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 305 (4.53), 221 (4.53). − ^1H NMR ($CDCl_3$): δ = 2.23 (s, 3 H), 2.45 (dd, *J* = 15.4 and 10.9 Hz, 1 H), 2.90 (m, 2 H), 3.31 (dd, *J* = 15.4 and 5.3 Hz, 1 H), 3.73 (m, 3 H), 4.35 (d, *J* = 9.9 Hz, 1 H), 7.10−7.27 (m, 2 H), 7.41 (d, *J* = 7.1 Hz, 1 H), 7.43 (s, 1 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 8.85 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.8 (t), 24.0 (q), 25.7 (t), 51.7 (t), 55.3 (d), 59.8 (d), 105.0 (s), 109.1 (s), 111.3 (d), 118.2 (d), 119.8 (d), 122.6 (d), 126.0 (s), 130.1 (s), 136.1 (s), 147.7 (d), 193.0 (s). − MS (70 eV); *m/z* (%): 307 (20) [M^+], 252 (100). − $C_{17}H_{17}N_5O$ (307.1): calcd. C 66.43, H 5.58, N 22.79; found C 66.18, H, 5.49, N 22.83.

Amine 7: Triphenylphosphane (136 mg, 0.52 mmol) was added at room temperature to a solution of azide **6** (80 mg, 0.26 mmol) in THF (3 mL) and H_2O (3 mL), and the resulting mixture was stirred at 60°C for 6 h. Aqueous saturated NaCl solution (100 mL) was added, and the mixture was extracted with ethyl acetate (4 × 30 mL). The organic extracts were dried and filtered. The solvent was removed under reduced pressure to give a residue, which was

chromatographed over silica gel. Elution with CH_2Cl_2/MeOH (95:5) afforded amine **7** (foam, 45 mg, 61%). − IR (KBr): $\tilde{\nu}$ = 3350 (N−H), 3179 (N−H), 1630 (C=O), 1569 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 321 (4.34), 222 (4.50). − ^1H NMR ($CDCl_3$): δ = 2.12 (s, 3 H), 2.85 (m, 3 H), 3.44 (m, 5 H), 3.79 (dd, *J* = 12.9 and 4.1 Hz, 1 H), 4.89 (m, 1 H), 7.02−7.13 (m, 2 H), 7.22 (s, 1 H), 7.35 (d, *J* = 7.5 Hz, 1 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 10.5 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.5 (t), 25.4 (q), 44.6 (t), 45.3 (t), 49.2 (d), 64.7 (d), 106.1 (s), 111.4 (d), 116.0 (s), 117.7 (d), 119.1 (d), 121.5 (d), 126.7 (s), 133.1 (s), 136.3 (s), 153.2 (d), 190.7 (s). − MS (70 eV); *m/z* (%): 281 (11) [M^+], 251 (56) [$M^+ - CH_2NH_2$], 208 (100).

Reduction of Iodoindoloquinolizidine 2f: A suspension of Zn (32 mg, 0.48 mmol) and CuI (27 mg, 0.14 mmol) in a mixture of EtOH/H_2O (3 mL, 7:3, previously degassed) was sonicated (cleaning bath) under inert atmosphere at room temperature for 5 min. A solution of iodoquinolizidine **2f** (70 mg, 0.18 mmol) in THF (2 mL) was added, and the resulting mixture was sonicated for 8 h. Dilution with ethyl acetate (50 mL) and filtration through a short pad of Celite gave a solution which was washed with saturated aqueous NaCl solution (3 × 30 mL), dried, filtered and concentrated under reduced pressure. The residue was chromatographed over silica gel. Elution with hexanes/ethyl acetate (7:3) gave indoloquinolizidine **8**[29] (solid, 34 mg, 72%). − ^1H NMR ($CDCl_3$): δ = 1.89 (m, 2 H), 2.21 (s, 3 H), 2.41 (m, 1 H), 2.85 (m, 3 H), 3.65 (m, 2 H), 4.53 (d, *J* = 11.0 Hz, 1 H), 7.03−7.22 (m, 2 H), 7.37 (d, *J* = 7.5 Hz, 1 H), 7.44 (s, 1 H), 7.54 (d, *J* = 7.2 Hz, 1 H), 8.30 (br. s, 1 H). − MS (70 eV); *m/z* (%): 266 (100) [M^+], 265 (50) [$M^+ - 1$], 251 (16) [$M^+ - CH_3$], 223 (64) [$M^+ - COCH_3$]. − Elution with hexanes/ethyl acetate (6:4) gave indoloindolizidine **9** (foam, 11 mg, 23%). IR (NaCl): $\tilde{\nu}$ = 3272 (N−H), 1663 (C=O), 1549 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 322 (4.18), 223 (4.44). − ^1H NMR ($CDCl_3$): δ = 1.33 (d, *J* = 7.7 Hz, 3 H), 2.18 (s, 3 H), 2.90 (m, 2 H), 3.50 (m, 2 H), 3.86 (dd, *J* = 12.9 and 4.4 Hz, 1 H), 4.69 (d, *J* = 2.0 Hz, 1 H), 7.03−7.15 (m, 2 H), 7.21 (s, 1 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 9.30 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 20.2 (q), 22.5 (t), 25.3 (q), 40.4 (d), 45.2 (t), 67.8 (d), 106.8 (s), 111.2 (s), 111.3 (d), 117.7 (d), 119.3 (d), 121.8 (d), 126.6 (s), 133.1 (s), 136.5 (s), 152.3 (d), 190.4 (s). − MS (70 eV); *m/z* (%): 266 (100) [M^+], 264 (80) [$M^+ - 2H$], 251 (43) [$M^+ - CH_3$], 223 (50) [$M^+ - COCH_3$]. − $C_{17}H_{18}N_2O$: calcd for [M^+] 266.1419; found 266.1409.

Dihydropyridine 10: A solution of indoloquinolizidine **2f** (50 mg, 0.13 mmol) in MeOH (2 mL) was added to a solution of NaOMe (334 mg, 6.18 mmol) in MeOH (15 mL). The resulting solution was stirred at room temperature for 2 h and at reflux temperature for 1 h. The solvent was removed under reduced pressure, water (50 mL) was added to the residue, and the resulting suspension was extracted with ethyl acetate (3 × 30 mL). The organic extracts were dried, filtered, and evaporated under reduced pressure to give a residue, which was chromatographed over silica gel. Elution with hexanes/ethyl acetate (1:1) afforded the somewhat unstable dihydropyridine **10** (foam, 26 mg, 79%). − IR (KBr): $\tilde{\nu}$ = 3225 (N−H), 1682 (C=O), 1552 (C=C) cm^{-1}. − UV (MeOH): λ_{max} (lg ε) = 394 (3.88), 315 (3.96). − ^1H NMR ($CDCl_3$): δ = 2.25 (s, 3 H), 2.99 (t, *J* = 5.8 Hz, 2 H), 3.27 (d, *J* = 3.6 Hz, 2 H), 3.68 (t, *J* = 5.8 Hz, 2 H), 5.21 (t, *J* = 3.6 Hz, 1 H), 7.06−7.23 (m, 2 H), 7.25 (s, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 8.05 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 20.9 (t), 22.2 (t), 24.3 (q), 49.2 (t), 99.3 (d), 107.9 (s), 109.4 (s), 111.4 (d), 118.8 (d), 119.2 (d), 122.7 (d), 126.2 (s), 128.5 (s), 129.2 (s), 137.3 (s), 145.8 (d), 194.2 (s). − MS (70 eV); *m/z* (%): 264 (72) [M^+], 263 (97) [$M^+ - H$], 261 (100) [$M^+ - 3H$], 221 (24) [$M^+ - COCH_3$].

Pyridinium Salt 11: A solution of DDQ (23 mg, 0.11 mmol) in a mixture of CH_2Cl_2/MeOH (5 mL, 4:1) was added to a solution of dihydropyridine **10** (25 mg, 0.09 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was stirred at room temperature for 24 h. Aqueous NaOH (100 mL, 2M) was added, the phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried, filtered and evaporated under reduced pressure. The residue was dissolved in MeOH (3 mL), and $HClO_4$ was added to create an acidic pH (4 drops). Diethyl ether (10 mL) was added, and the precipitate was filtered and dried under vacuum to afford pyridinium perchlorate **11**[29] (solid, 26 mg, 78%). − IR (KBr): $\tilde{\nu}$ = 3440 (N−H), 1704 (C=O), 1620 (C=C) cm^{-1}. − ^1H NMR (CD_3OD): δ = 2.80 (s, 3 H), 3.59 (t, *J* = 7.2 Hz, 2 H), 5.10 (t, *J* = 7.2 Hz, 2 H), 7.10−7.60 (m, 3 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 8.25 (d, *J* = 9.2 Hz, 1 H), 8.93 (dd, *J* = 9.2 and 1.7 Hz, 1 H), 9.45 (d, *J* = 1.7 Hz, 1 H).

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