Monatshefte für Chemie 137, 1411–1419 (2006)
DOI 10.1007/s00706-006-0540-y

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Synthesis of *cis*-2,3-Disubstituted Benzo[*a*]quinolizidin-4-ones *via* *Reissert*-Compounds

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Received April 13, 2006; accepted August 15, 2006
Published online October 27, 2006

Summary. Isoquinolin-1-ylmethylfuranones could be readily prepared from certain *Reissert*-compounds and isopilopyl bromide by standard procedures. Their reduction to the desired not isolated 1,2,3,4-tetrahydroisoquinoline intermediates was achieved by chemical and/or catalytical hydrogenation, followed by intramolecular amidation conveniently giving the title compounds in a one-pot synthesis. The structures and the stereochemistry of the target compounds were assigned by ^{13}C NMR spectroscopy and X-ray diffraction analysis.

Keywords. Benzo[*a*]quinolizidinones; Catalytic hydrogenations; Isopilopyl bromide; *Reissert*-compounds; X-Ray structure determination.

Introduction

Benzo[*a*]quinolizidines are key subunits of naturally occurring isoquinoline alkaloids. Well known members of them with a broad spectrum of biological activities are the classical *Ipecacuanha* alkaloids emetine and cephaeline, and the great number of benzo[*a*]quinolizidine-type alkaloids, including tubulosine [1], alancine [2], and the monoterpenoid alangine [3], isolated from the Indian medicinal plant *Alangium lamarckii* (Alangiaceae) [4]. On the other hand benzo[*a*]quinolizidines are important intermediates for the synthesis of the alkaloids mentioned. Furthermore several synthetic active agents possessing the tricyclic core are of general interest, *e.g.*, tetrabenazine (Nitoman®) which exhibits central effects similar to those of reserpine and is therapeutically used for the treatment of hyperkinetic movement disorders. Its dihydro-derivative is believed to be the principle active moiety [5, 6]. Additionally, a number of 2-spiro derivatives of benzo[*a*]quinolizidine have been

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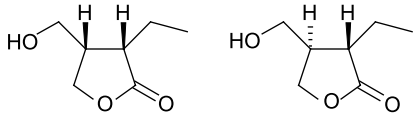
# Part of PhD thesis, LMU München, Germany



A (3*R*,4*R* / 3*S*,4*S*) **1** (3*R*,4*S* / 3*S*,4*R*)

Formula 1. Structures of diastereomeric 3-ethyl-4-hydroxymethyldihydro-furan-2-ones: pilopyl alcohol (**A**) and isopilopyl alcohol (**1**)

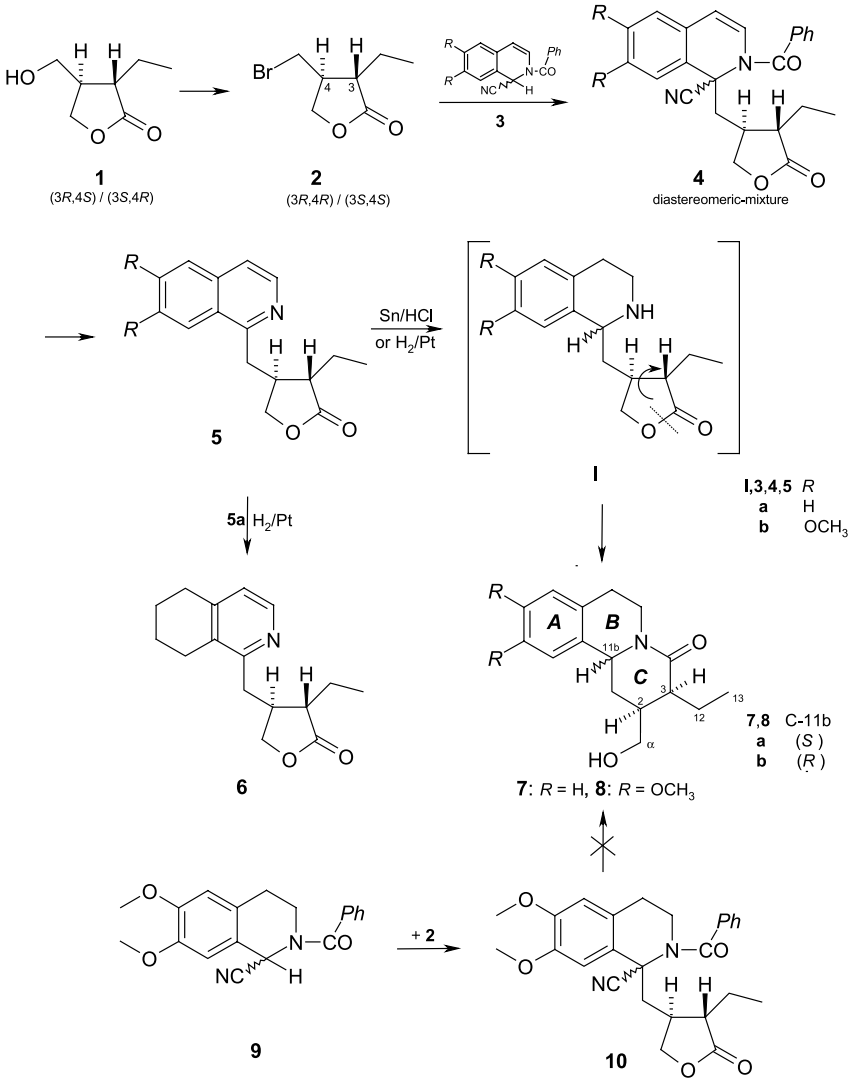
prepared, *e.g.*, pyrrolidine-, imidazolidine-, and oxazolidinediones, which are considered to be potential antihypertensives, anticonvulsants, antidepressants, and hypoglycemics [7].

A number of interesting versatile approaches to benzo[*a*]quinolizidine have been accomplished, mainly in connection with the total synthesis of the *Ipecacuanha* and *Alangium* alkaloids mentioned above [8]. For instance, piperidine derivatives and phenacyl halogenides [9, 10], 2-arylpiperidines and glycidol [11], or lactones and phenethylamines [12] have been reacted to complete the B ring in the last step. On the other hand, tetrahydroisoquinolylacetaldehyde [13] or the corresponding acetic acid [14] are suitable educts to form the C ring in the finishing step. Finally, a biomimetic approach using phenylalanine derivatives and a synthesis equivalent of secologanine has been described [15]. In continuation of our strategy for the synthesis of natural products *via Reissert*-compounds [16] the readily available diastereomeric pilopyl alcohols [17] (see Formula 1) were thought to be very suitable educts for an efficient access to the title compounds.

Results and Discussion

The required 3,4-*trans* configured isopilopyl bromide (**2**) was prepared from the corresponding isopiloyl alcohol (**1**) and reacted with the *Reissert*-compounds **3** giving mixtures of the diastereomers **4** as indicated by double signal sets of the NMR spectra (see Experimental). Compounds **4** were cleaved with methanolic KOH affording the isoquinolinylfuranones **5** as the only products (see Scheme 1). The reaction proceeded with retention of configuration, which could be proved by comparison of the ^{13}C NMR spectrum with, *e.g.*, those of the known stereomeric 4-benzyl-3-ethylfuranones [18]. The methylene groups of the side chaines of **5** resonate in the same range as those of the *trans*-configured reference compound ($\delta = 37.57/37.76$ and $22.25/22.32$ *vs.* 38.6 and 21.9 ppm, see Experimental).

The subsequent catalytic hydrogenation led only in the case of **5b** to the desired, not isolated 1,2,3,4-tetrahydroisoquinoline intermediate **Ib**, whereas **5a** selectively afforded the corresponding 5,6,7,8-hydrogenated derivative **6** in quantitative yield. Its structure could be unambiguously deduced from the NMR spectra (see Experimental and Ref. [19]). However, when Sn/HCl was used, the intended reduction of **5a** to the required intermediate **Ia** occurred. Finally, starting from the isoquinolines **5** the generation of the target compounds **7** and **8** could be achieved in an one-pot reaction without isolation of the intermediates **I** providing separable mixtures of the diastereomers **7a**, **7b** and **8a**, **8b**. Attempts to obtain the quinolizidinone **8** by the



Scheme 1

strategy recently used [16] which starts from dihydro *Reissert*-compounds, *e.g.*, **9** and **10**, and which should avoid the reduction step **5**→**I**, hitherto failed.

The stereochemistry of compounds **7** and **8** was guided by the intramolecular amidation of the intermediate **I**, in the course of which the cleavage of the lactone and a subsequent rotation about 180° around the C-3/C-4 bond had to be assumed leading to a *cis*-substitution at C-2 and C-3 of the products **7** and **8**, which means identical relative configurations (2*R*/3*R* or 2*S*/3*S*) of these atoms. Except for the 2,3-unsubstituted core [20], no ^{13}C NMR data suitable for the elucidation of the stereochemistry of related benzoquinolizidones were available. Therefore, this was performed by X-ray diffraction analysis of the diastereomer **8a** confirming the presumption mentioned, also showing the C-11b atom exhibiting (*S*)-configuration (Fig. 1). Product **8b** was assumed to represent the corresponding diastereomer with the opposite (*R*)-configuration at atom C-11b, which was supported by NMR spec-

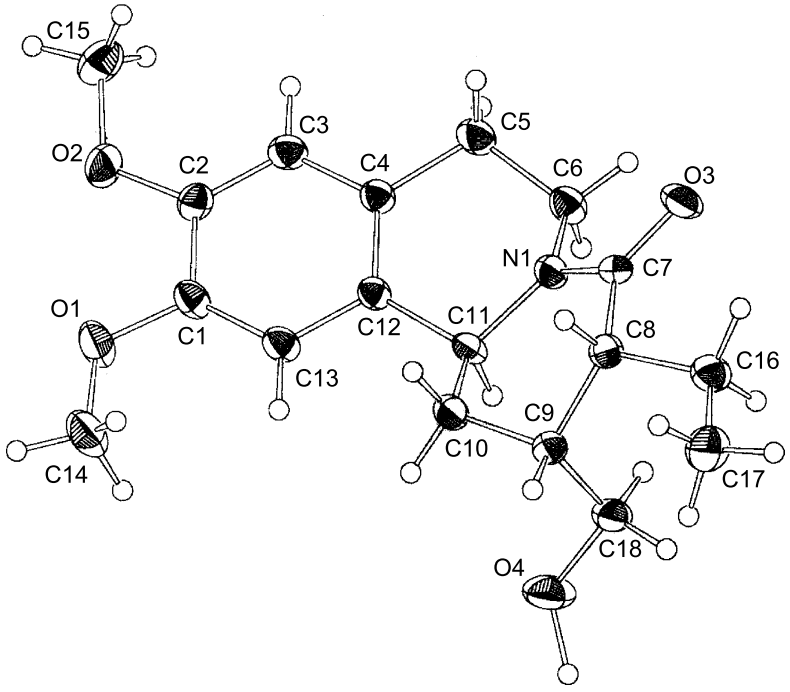


Fig. 1. Crystal structure of **8a**

troscopy. Thus, *e.g.*, irradiation of 2-H gave a positive N*O*E to the protons 11b-H and 3-H, since in **8b** all these protons occupy the same β-side; on the other hand, a similar effect in **8a**, *e.g.*, from 11b-H to 2-H was, as expected, not found. Additionally, the signals of C-11b and of C-α in **8b** occurred about 2–3 ppm at lower field than those of **8a** caused by the change of C-α from the axial into the equatorial position involving therewith the loss of the previous γ-effect. Based on the agreeing ^{13}C NMR shifts with those of **8a** and **8b**, the stereochemistry of the corresponding diastereomeric parent compounds also could be unequivocally assigned as (*2R,3R,11bS*)/(*2S,3S,11bR*)-**7a** and (*2R,3R,11bR*)/(*2S, 3S,11bS*)-**7b**.

In conclusion, we have developed a novel, short approach to the hitherto unknown title compounds based on isopilopyl bromide (**2**) and *Reissert*-compounds. They are regarded to be broadly applicable educts for an efficient approach to pharmacological active compounds of the type already mentioned above. Further studies in this area are in progress.

Experimental

Melting points were measured with a Büchi Melting Point B-545. IR: Perkin Elmer FT-IR Paragon 1000 and Jasco FT-IR 410. NMR: Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz, $CDCl_3$, *TMS* as internal reference); MS (70 eV): Hewlett Packard MS-Engine. X-ray structure determination: Nonius MACH3 diffractometer; crystal dimensions: $0.53 \times 0.33 \times 0.10\,mm^3$, colourless platelets; temperature: 295 K; radiation: MoK_α ($\lambda = 0.71073$ Å); program: SHELXS-86/SHELXL-93; deposition number: CCDC 271669 (12 Union Road, GB Cambridge CB21EZ). Elemental analyses: Heraeus CHN-Rapid; the results are in good agreement with the calculated values. Thin layer chromatography (TLC): aluminum sheets Kieselgel 60 F_{254} (Merck), thickness of layer 0.2 mm. Flash chromatography

(FC): ICN-SiliTech 32–36, 60 A. NaH (60% dispersion in mineral oil); *Reissert*-compounds **3a**, **3b**, and **9** were prepared according to Refs. [16, 21].

(3R,4R)/(3S,4S)-4-Bromomethyl-3-ethyldihydrofuran-2-one (**2**)
To a solution of 6.65 g **1** (46.2 mmol) in 130 cm^3 dry acetonitrile were added 15.3 g tetrabromomethane (46.2 mmol) and 12.2 g triphenylphosphane (46.2 mmol). After stirring the mixture for 15 min at ambient temperature, the solvent was removed *in vacuo*. The residue was dissolved in a small quantity of $CHCl_3$ and purified by FC (column: $d \times h = 6 \times 15\,cm^2$; *n*-hexane:*Et*OA*c* = 4:1). Yield 8.0 g (84%) colourless pure diastereomer **2**; bp 99°C/14 Pa (Ref. [22]: 91°C/6 Pa); TLC (eluent see FC): $R_f = 0.40$ (educt and Ph_3PO: R_f = each 0.0; Ph_3P and CBr_4: R_f = each 0.9; detection: $KMnO_4$ in acetone); IR (film): $\bar{\nu} = 1770$ (lactone), 648 (C–Br) cm^{-1}; MS: a) CI: m/z (%) = 209 ($M^{+\bullet} + 1$, 98), 207 ($M^{+\bullet} + 1$, 100), 85 (36); b) EI: 180 (16), 149 (38), 85 (68), 81 (51), 71 (42), 69 (100), 57 (76), 55 (62); ^{1}H NMR ($CDCl_3$): $\delta = 4.36$ (dd, $J = 9.40/7.52$ Hz, 1H, CH_2O), 3.97 (dd, $J = 9.37/7.68$ Hz, 1H, CH_2O), 3.50 (dd, $J = 10.5/4.8$ Hz, 1H, CH_2Br), 3.37 (dd, $J = 10.6/7.8$ Hz, 1H, CH_2Br), 2.69–2.59 (m, 1H, 4-H), 2.37–2.32 (m, 1H, 3-H), 1.81–1.61 (m, 2H, CH_2C), 0.99 (t, $J = 7.47$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 177.80$ (C=O), 70.00 (CH_2O), 45.48 (C-3), 42.03 (C-4), 33.19 (CH_2Br), 22.57 (CH_2), 10.99 (CH_3) ppm.

(3R,4S/3S,4R)-2-Benzoyl-1-(4-ethyl-5-oxotetrahydrofuran-3-ylmethyl)-1,2-dihydroisoquinoline-1-carbonitrile (**4a**, *diastereomeric mixture*, $C_{24}H_{22}N_2O_3$)
The solution of 6.32 g **3a** (23.9 mmol) in 64 cm^3 dry *DMF* was stirred for 5 min at ambient temperature under Ar. Thereafter 958 mg NaH (23.9 mmol) and 2.48 g **2** (11.9 mmol) were added and stirring was continued for 4 h. The mixture was diluted with 100 cm^3 CH_2Cl_2 and 500 cm^3 ice-cold H_2O and adjusted to $pH = 1$ by dropwise addition of 2 *N* HCl. The aqueous layer was extracted with $3 \times 100\,cm^3$ CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FC. First the excess educt **3a** was separated with *n*-hexane:*Et*OA*c* = 2:1, followed by the product using *n*-hexane:*Et*OA*c* = 1:1. Yield 3.78 g (82%) colourless, glassy foam; TLC (*n*-hexane:*Et*OA*c* = 2:1): $R_f = 0.3$ (educt **3a**: $R_f = 0.6$; isoquinoline-1-carbonitrile: $R_f = 0.5$); IR (KBr): $\bar{\nu} = 2235$ (w, CN), 1773 (CO, lactone), 1675 (CO, amide) cm^{-1}; MS (CI): m/z (%) = 387 ($M^{+\bullet} + 1$, 20), 256 (22), 79 (100); ^{1}H NMR ($CDCl_3$): $\delta = 7.77$–7.70, 7.65–7.55, 7.52–7.46, 7.43–7.38, and 7.17–7.13 (5m, 1, 3, 2, 2, and 1arom H), 6.57, 6.52, 5.83, and 5.78 (4d, each $J = 8.0$ Hz, each 0.5H, 3-H and 4-H), 4.26 and 4.02 (2dd, $J = 9.4/7.2$ and $9.1/7.7$ Hz, each 0.5H), 3.79 and 3.51 (2m, each 0.5H), 2.93 and 2.43 (2d, each $J = 11.6$ Hz, each 0.5H), 2.70–2.59 (m, 1H), 2.47–2.38 (m, 1H), 2.12 and 2.05 (2dt, $J = 10.3/5.7$ and $10.2/5.4$ Hz, each 0.5H), 1.73–1.65 and 1.60–1.52 (2m, each 1H, CH_2), 0.93 and 0.78 (2t, each $J = 7.4$ Hz, each 1.5H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 177.22$, 177.15, 169.54, and 169.48 (CO), 132.72, 132.62, 132.42, 132.34, 130.27, 130.24, 129.50 (2C), 129.35 (2C), 129.03, 128.86 (2C), 128.75 (2C), 128.56, 128.38 (2C), 127.95 (2C), 126.80, 126.72, 126.47, 126.42, 125.75, 125.58, 117.80, 117.26, 107.22, 106.76, 71.81, 71.52, 59.37, 59.00, 45.91, 45.78, 41.63, 41.34, 36.01, 35.74, 21.30, 21.08, 10.50, 10.34 ppm.

(3R,4S/3S,4R)-2-Benzoyl-1-(4-ethyl-5-oxotetrahydrofuran-3-ylmethyl)-6,7-dimethoxy-1,2-dihydroisoquinoline-1-carbonitrile (**4b**, *diastereomeric mixture*, $C_{26}H_{26}N_2O_5$)
The solution of 9.43 g **3b** (29.5 mmol) in 70 cm^3 dry *DMF* was stirred for 30 min at ambient temperature under N_2. Thereafter 1.18 g NaH (29.5 mmol) and the solution of 4.69 g **2** (22.6 mmol) in 5.0 cm^3 *DMF* were added and stirring was continued for 1 h. The reaction mixture was poured into a mixture of 250 cm^3 *Et*OA*c* and 2000 cm^3 H_2O. After adjustment to $pH = 1$ by dropwise addition of 2 *N* HCl the yellowish orange emulsion separated into an orange yellow organic and a greenish blue aqueous layer. The latter was extracted with $3 \times 250\,cm^3$ *Et*OA*c*. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product, *ca.* 13.3 g, was used for the next step without further purification. An analytical sample was obtained by FC (*n*-hexane:*Et*OA*c* = 1:1). [Yield 5.7 g (56%, based on the yield of the product **5b**; see below)] colourless solid; TLC (*n*-hexane:*Et*OA*c* = 1:1):

$R_f = 0.37$ (educt **3b**: $R_f = 0.55$; 6,7-dimethoxyisoquinoline-1-carbonitrile: $R_f = 0.45$, blue fluorescence/UV_{254}); IR (film, $CHCl_3$): $\bar{\nu} = 2255$ (CN), 1770 (CO, lactone), 1673 (CO, amide) cm^{-1}; MS (CI): m/z (%) = 447 ($M^{+\bullet} + 1$, 13), 316 (30), 215 (33), 132 (23), 105 (100); ^1H NMR ($CDCl_3$): $\delta = 7.61–7.45$ (m, 5arom H), 7.22, 7.19, 6.63, and 6.61 (4s, 0.25, 0.75, 0.25, and 0.75H), 6.48 and 6.42 (2d, $J = 8.03$ and 7.85 Hz, 0.75 and 0.25H), 5.74 and 5.68 (2d, $J = 7.74$ and 7.89 Hz, 0.25 and 0.75H), 4.20 and 4.14 (2dd, $J = 9.05/7.72$ and $9.25/7.54$ Hz, 0.25 and 0.75H), 4.09, 4.04, 3.97, and 3.92 (4s, 0.1, 0.1, 2.9, and 2.9H, $2OCH_3$), 3.72–3.65 (m, 1H), 3.03 (dd, $J = 13.8/1.6$ Hz, 0.75H), 2.68–2.35 (m, 2.25H), 2.16–2.04 (m, 1H), 1.68–1.57 (m, 2H), 0.92 and 0.87 (2t, each $J = 7.5$ Hz, 0.75 and 2.25H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 177.16$, 169.55, 150.36, 149.23, 132.96, 132.27, 132.17, 129.37, 129.19, 128.85, 125.24, 124.80, 122.25, 121.93, 120.02, 118.06, 110.11, 108.46, 108.40, 107.25, 106.66, 71.96, 71.60, 59.17, 58.99, 56.50 (2C), 56.16 (2C), 45.89, 45.80, 42.28, 36.23, 36.06, 21.43, 21.26, 10.61, 10.53 ppm.

trans-3-Ethyl-4-isoquinolin-1-ylmethyldihydrofuran-2-one (**5a**, $C_{16}H_{17}NO_2$)
A mixture of 5.2 g **4a** (13.5 mmol), 130 cm^3 *Me*OH, and 12.4 cm^3 12% KOH was refluxed for 1 h. The cooled solution was acidified by introducing gaseous HCl and thereafter concentrated *in vacuo*. The residue was taken up in 100 cm^3 $CHCl_3$ and then solid $NaHCO_3$ was added, until the CO_2 generation stopped. The solid materials were filtered off and consecutively washed with 100 cm^3 $CHCl_3$ and 5 cm^3 saturated solution of $NaHCO_3$. After extraction of the aqueous layer with 2×100 cm^3 $CHCl_3$, the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by FC (*n*-hexane:*Et*OA*c* = 1:1). Yield 2.3 g (72%) pale yellow oil; TLC (eluent see FC): $R_f = 0.40$ (educt **4a**: $R_f = 0.7$); IR (film): $\bar{\nu} = 1770$ (CO, lactone) cm^{-1}; MS (CI): m/z (%) = 256 ($M^{+\bullet} + 1$, 100), 168 (16); ^1H NMR ($CDCl_3$): $\delta = 8.42$ (d, $J = 5.7$ Hz, 3-H), 8.09 (dd, $J = 8.4/0.7$ Hz, 5-H or 8-H), 7.85 (d, $J = 8.0$ Hz, 5-H or 8-H), 7.71 and 7.64 (2ddd, $J = 8.2/7.0/1.2$ and $8.4/7.0/1.3$ Hz, 6-H and 7-H), 7.57 (d, $J = 5.8$ Hz, 4-H), 4.54 and 4.03 (2dd, $J = 9.3/7.6$ and $9.2/7.7$ Hz, each 1H, CH_2O), 3.66 and 3.38 (2dd, $J = 15.3/5.1$ and $15.5/9.5$ Hz, each 1H, CH_2-*isoquin*), 3.17–3.07 (m, 4′-H), 2.46 (dt, $J = 8.8/5.9$ Hz, 3′-H), 1.80–1.69 (m, CH_2), 1.02 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 178.97$ (CO), 157.92 (C-1), 141.65 (C-3), 136.19 (C-4a), 130.18 (C-6 or C-7), 127.67 (C-5 or C-8), 127.59 (C-6 or C-7), 127.05 (C-8a), 124.36 (C-5 or C-8), 119.93 (C-4), 71.90 (C-5′), 46.55 (C-3′), 39.00 (C-4′), 37.57 (CH_2-*isoquin*), 22.25 (CH_2), 11.00 (CH_3) ppm.

trans-4-(6,7-Dimethoxyisoquinolin-1-ylmethyl)-3-ethyldihydrofuran-2-one (**5b**, $C_{18}H_{21}NO_4$)
Preparation according to **5a** from 26.7 g crude **4b** in 350 cm^3 M*e*OH and 78.4 cm^3 12% KOH, time of reflux 15 min. Differing from **5a** the solid materials were exclusively washed with 2×100 cm^3 $CHCl_3$ and then the combined organic extracts were concentrated *in vacuo*. The residue was purified by FC (*Et*OA*c*). Yield 8.0 g (56%) pale yellow oil; TLC (*Et*OA*c*): $R_f = 0.45$; IR (film): $\bar{\nu} = 1769$ (CO, lactone) cm^{-1}; MS (CI): m/z (%) = 316 ($M^{+\bullet} + 1$, 100), 233 (8), 203 (5); ^1H NMR ($CDCl_3$): $\delta = 8.30$ and 7.42 (2d, each $J = 5.6$ Hz, 3-H and 4-H), 7.22 and 7.09 (2s, each 1H, 5-H/8-H), 4.55 (dd, $J = 9.4/7.4$ Hz, 1H, 5′-H), 4.08–4.04 (m, 1H, 5′-H), 4.05 and 4.04 (2s, each OCH_3), 3.53 and 3.27 (2dd, $J = 15.1/4.9$ and $15.1/5.0$ Hz, each 1H, CH_2-*isoquin*), 3.14 (m, 4′-H), 2.45 (dt, $J = 8.2/6.1$ Hz, 3′-H), 1.81–1.74 (m, CH_2), 1.04 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 179.11$, 155.21, 152.71, 150.34, 140.91 (C-3), 133.02, 122.85, 118.74 (C-4), 105.59 and 102.56 (C-5/C-8), 72.04 (C-5′), 56.09 and 56.06 ($2OCH_3$), 46.62 (C-3′), 38.83 (C-4′), 37.76 (CH_2-*isoquin*), 22.32 (CH_2), 11.07 (CH_3) ppm.

trans-3-Ethyl-4-(5,6,7,8-tetrahydroisoquinolin-1-ylmethyl)dihydrofuran-2-one (**6**, $C_{16}H_{21}NO_2$)
A mixture of 113 mg **5a** (0.4 mmol), 3.5 cm^3 *Me*OH saturated with HCl gas, and 22 mg *Adams* catalyst (PtO_2–H_2O) was hydrogenated for 5 h at ambient temperature and 2×10^5 Pa initial pressure of H_2. The catalyst was centrifuged off, and the solvent was removed *in vacuo*. After dissolving the residue in a few cm^3 $CHCl_3$ and adding a small quantity of solid $NaHCO_3$ the mixture was stirred for 5 min, filtered, and evaporated *in vacuo*. Yield 114 mg (100%) colourless oil; TLC (*n*-hexane:*Et*OA*c* = 1:1): $R_f = 0.40$ (educt **5a**: $R_f = 0.34$); IR (film): $\bar{\nu} = 1770$ (CO, lactone) cm^{-1}; MS (CI): m/z (%) = 300 ($M^{+\bullet} + 41$, 2), 288 ($M^{+\bullet} + 29$, 3), 260 ($M^{+\bullet} + 1$, 100), 172 (10), 19 (48); ^1H NMR ($CDCl_3$; most of

the signals appeared as broad unsplitted singlets; 2H belonging to the CH_2-bridge were lacking, whereas the corresponding C-atom appeared in the ^{13}C NMR spectrum, see below): $\delta = 8.25$ and 7.20 (2s, 3-H and 4-H), 4.32 and 4.03 (2s, each 1H, 5′-H), 3.17–2.85 (m, 3H, 4′-H, and CH_2), 2.70 (s, CH_2), 2.38 (s, 3′-H), 1.86–1.80 (weakly splitted s, $2CH_2$), 1.62–1.57 (weakly splitted m, CH_2), 0.92 (s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 178.47$ (CO), 154.03 (C-1), 152.97 (C-4a), 141.08 (C-3), 133.51 (C-8a), 124.52 (C-4), 71.21 (C-5′), 46.41 (C-3′), 39.00 (C-4′), 34.74 (CH_2-*isoquin*), 30.18 (C-8), 25.55 (C-5), 22.31 (C-7), 22.00 (CH_2–*Me*), 21.42 (C-6), 11.03 (CH_3) ppm.

3-Ethyl-2-hydroxymethyl-1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-one
(**7**, *diastereomeric mixture*, $C_{16}H_{21}NO_2$)

To a refluxing mixture of 825 mg **5a** (3.23 mmol), 14 cm^3 *Et*OH, and 21 cm^3 conc. HCl was added portionwise 7.0 g Sn (58.9 mmol). After the metal was completely dissolved, the mixture was cooled to ambient temperature, diluted with 20 cm^3 $CHCl_3$ and adjusted to $pH = 3.5$–4.0 by dropwise addition of 2 *N* NaOH under vigorous stirring. The mixture was again refluxed for 4 h monitoring the *pH* by a glass electrode. The organic layer was evaporated *in vacuo* and the residual diastereomers were separated by FC (*Et*OA*c*).

(*2R,3R,11bS*)/(*2S,3S,11bR*)-**7a**: Yield 199 mg (24%) colourless oil; TLC (*Et*OA*c*): $R_f = 0.44$; IR (film): $\bar{\nu} = 3418$ (OH), 1632 (CO) cm^{-1}; MS (EI): m/z (%) = 259 ($M^{+\bullet}$, 18), 231 (11), 200 (11), 145 (100), 132 (28); ^1H NMR ($CDCl_3$): $\delta =$ 7.24–7.09 (m, 4arom H), 4.83 (dd, $J = 10.5/5.6$ Hz, 11b-H), 4.71 (ddd, $J = 12.3/5.0/3.2$ Hz, 1H, 6-H), 3.80 (dd, $J = 10.8/4.9$ Hz, 1H, CH_2O), 3.66–3.61 (m, 1H, CH_2O), 3.38 (br s, OH), 2.98–2.79 (m, 3H), 2.69 (dt, $J = 15.5/3.3$ Hz, 1H), 2.35 (dquint, $J = 8.7/4.8$ Hz, 2-H), 2.27 (dt, $J = 9.6/5.4$ Hz, 3-H), 2.16–2.06 (m, 1H), 1.80 (ddd, $J = 13.8/10.7/3.4$ Hz, 1H, 1-H), 1.40–1.28 (m, 1H), 0.99 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 171.57$ (CO), 138.02 and 134.93 (C-7a and C-11a), 128.85, 126.61, 126.49, and 124.57 (4arom C), 60.27 (C–OH), 53.17 (C-11b), 45.35 (C-3), 40.24 (C-6), 34.32 (C-2), 31.12 (C-1), 18.84 (C-7), 20.37 (CH_2), 12.32 (CH_3) ppm.

(*2R,3R,11bR*)/(*2S,3S,11bS*)-**7b**: Yield 80 mg (10%) colourless oil; TLC (*Et*OA*c*): $R_f = 0.24$; ^1H NMR ($CDCl_3$): $\delta = 7.23$–7.13 (m, 4arom H), 4.77–4.72 (m, 1H, 6-H), 4.66, 3.66, and 3.56 (3dd, $J = 11.3/5.4$, 10.7/5.7, and 10.7/7.5 Hz, each 1H, CH_2O and 6-H), 2.95–2.84 (m, 7-H and OH), 2.90 (m, 1H, 6-H), 2.76 (m, 1H, 7-H), 2.55–2.50 (m, 2H), 2.40–2.31 (m, 1H, 1-H), 1.68 (dt, $J = 13.5/11.0$ Hz, 1H, 1-H), 1.64–1.51 (m, CH_2), 1.01 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 172.65$ (CO), 137.23 and 134.89 (C-7a and C-11a), 128.85, 126.75, 126.60, and 125.20 (4arom C), 63.53 (C–OH), 55.78 (C-11b), 44.13 (C-3), 39.48 (C-6), 37.18 (C-2), 31.31 (C-1), 29.15 (C-7), 20.61 (CH_2), 13.14 (CH_3) ppm.

3-Ethyl-2-hydroxymethyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-one (**8**, *diastereomeric mixture*, $C_{18}H_{25}NO_4$)

A mixture of 2.29 g **5b** (7.3 mmol), 20 cm^3 glacial acetic acid *pa*, and 211 mg *Adams* catalyst (PtO_2–H_2O) was hydrogenated for 62 h at ambient temperature and 1.1×10^7 Pa initial pressure of H_2. Then further 145 mg catalyst were added and the hydrogenation was continued at the same pressure for 24 h. When the reaction was complete (TLC monitoring: eluent *Et*OA*c*, detection *Dragendorff*'s reagent, $R_f = 0.4$ (educt), 0.1 (product)), the catalyst was filtered off (fritte pore 4) and washed with 10 cm^3 glacial acetic acid. The filtrate was diluted with 60 cm^3 $CHCl_3$ and heated to reflux temperature. Then the mixture was adjusted to $pH = 6$ by cautious addition of *ca.* 37 g triethylamine and refluxed for 3 h. After diluting the cold mixture with 100 cm^3 H_2O and 50 cm^3 $CHCl_3$, the organic layer was consecutively washed with 3×100 cm^3 2 *N* HCl and 3×100 cm^3 2 *N* NaOH, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by FC (*Et*OA*c*:*Me*OH = 1:1) giving the pure diastereomeric products as colourless oils, which on treatment with Et_2O formed colourless amorphous solids.

(*2R,3R,11bS*)/(*2S,3S,11bR*)-**8a**: Yield 530 mg (23%); mp 134.0–134.5°C; TLC (*Et*OA*c*:*Me*OH = 19:1): $R_f = 0.45$; IR (film): $\bar{\nu} = 3407$ (OH), 1614 (CO) cm^{-1}; MS (EI): m/z (%) = 319 ($M^{+\bullet}$, 33), 318 (30), 205 (100), 191 (53); ^1H NMR ($CDCl_3$): $\delta = 6.69$ and 6.58 (2s, 11-H and 8-H), 4.81 (ddd, $J = 12.5/5.1/2.3$ Hz, 6-H), 4.75 (dd, $J = 10.6/5.6$ Hz, 11b-H), 3.84 (s, $2OCH_3$), 3.84–3.80 (m, 1H,

CH_2O), 3.61 (m, 1H, CH_2O), 2.90–2.80 (m, 2H, 7-H and 1-H), 2.75 (dt, $J = 12.1/3.4$ Hz, 1H, 6-H), 2.60 (m, 1H, 7-H), 2.35 and 2.29 (2m, 2-H and 3-H), 2.20–2.08 (m, 1H, CH_2), 1.76 (ddd, $J = 13.8/10.6/3.2$ Hz, 1H, 1-H), 1.38–1.26 (m, 1H, CH_2), 1.00 (t, $J = 7.3$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 171.13$ (CO), 147.76 (C-9), 147.69 (C-10), 129.82 (C-7a), 127.15 (C-11a), 111.55 (C-8), 108.00 (C-11), 60.41 (CH_2O), 56.12 and 55.84 ($2OCH_3$), 52.85 (C-11b), 45.31 (C-3), 40.13 (C-6), 34.28 (C-2), 31.44 (C-1), 28.40 (C-7), 20.36 (CH_2), 12.27 (CH_3) ppm.

(2R,3R,11bR)/*(2S,3S,11bS)*-**8b**: Yield 838 mg (36%); mp 123.5–124.5°C; TLC (*Et*OAc:*Me*OH = 19:1): $R_f = 0.35$; IR (film): $\bar{\nu} = 3397$ (OH), 1620 (CO) cm^{-1}; MS (EI): m/z (%) = 319 ($M^{+\bullet}$, 35), 318 ($M^{+\bullet} - H$, 28), 205 (48), 192 (75), 191 (100), 176 (30); ^{1}H NMR ($CDCl_3$): $\delta = 6.70$ and 6.63 (2s, 11-H and 8-H), 4.80 (m, 6-H), 4.61 (dd, $J = 11.2/5.3$ Hz, 11b-H), 3.87 (s, $2OCH_3$), 3.69 and 3.58 (2dd, $J = 10.6/5.5$ and 10.5/7.9 Hz, each 1H, CH_2O), 2.89–2.81 (2m, each 1H, 6-H and 7-H), 2.70–2.62 (m, 1H, 7-H), 2.55–2.49 (m, 3H, 3-H, 1-H, OH), 2.38–2.30 (m, 2-H), 1.70–1.52 (m, 3H, 1-H and CH_2), 1.02 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 172.43$ (CO), 147.93 (C-9), 147.88 (C-10),

Table 1. Crystallographic data of **8a**[a]

Formula	$C_{18}H_{25}NO_4$
Formula weight	319.39
Temperature (K)	295
Color, shape	colourless platelets
Crystal dimensions (mm^3)	$0.53 \times 0.33 \times 0.10$
Crystal system	triclinic
Space group	*P1*
Cell dimensions:	
a/Å	7.737 (2)
b/Å	8.500 (2)
c/Å	12.907 (3)
α/°	80.30 (2)
β/°	83.86 (2)
γ/°	81.58 (2)
V/Å^3	824.6 (3)
Radiation	MoK_α ($\lambda = 0.71073$ Å)
Θ_{min}–Θ_{max}/°	2.45–23.97
Z	2
$F(000)$	344
μ/mm^{-1}	0.090
Density/g cm^{-3}	1.286
Reflections collected	2780
Independent reflections	2583 ($R_i = 0.0173$)
Observed reflections	1981 ($I > 2\sigma(I)$)
No. of parameters refined	211/0
R-values	
R_1 ($2\sigma(I)$/all data)	0.0408/0.0646
wR_2 ($2\sigma(I)$/all data)	0.1108/0.1247
Goodness of Fit	1.018
Residual electron density (e/Å^3)	0.167/−0.198
System used	SHELXS-86/SHELXL-93 [23]

[a] Further details of the crystal structure determination are available from Cambridge Crystallographic Data Center, 12 Union Road, GB Cambridge CB21EZ quoting the deposition number CCDC 271669 and the complete literature source (e-mail: deposit@ccdc.cam.ac.uk)

129.12 (C-7a), 127.12 (C-11a), 111.61 (C-8), 108.54 (C-11), 63.66 (CH_2O), 56.19 and 55.98 ($2OCH_3$), 55.63 (C-11b), 44.17 (C-3), 39.52 (C-6), 37.25 (C-2), 31–37 (C-1), 28.70 (C-7), 20.68 (CH_2), 13.17 (CH_3) ppm.

(3R,4S)/(3S,4R)-2-Benzoyl-1-(4-ethyl-5-oxotetrahydrofuran-3-ylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**10**, $C_{26}H_{28}N_2O_5$)

The solution of 580 mg **9** (1.8 mmol) in 6 cm^3 dry *DMF* was stirred for 10 min at ambient temperature under Ar. Then 72 mg NaH (1.8 mmol) were added under ice cooling and vigorous stirring followed by 250 mg **2** (1.2 mmol). After stirring for 90 min at ambient temperature the mixture was cautiously poured into a mixture of 100 cm^3 *EtOAc* and 300 cm^3 H_2O, acidified with 2 *N* HCl, and extracted with 3×100 cm^3 *EtOAc*. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated; residual amounts of *DMF* were removed *in vacuo* (oil pump). The crude product was purified by FC (*n*-hexane:*EtOAc* = 1:1). Yield 123 mg (23%) colourless, amorphous solid; mp 234–236°C; TLC (*n*-hexane:*EtOAc* = 1:1): $R_f = 0.30$ (educt **9**: $R_f = 0.40$); IR (KBr): $\bar{\nu} = 2236$ (CN), 1777 (CO, lactone), 1654 (CO, amide) cm^{-1}; MS (EI): m/z (%) = 448 ($M^{+\bullet}$, 1), 321 (20), 308 (32), 105 (100), 77 (25); ^1H NMR ($CDCl_3$): $\delta = 7.56$–7.46 (m, 5arom H), 7.04 and 6.65 (2s, each 1H, 5-H and 8-H), 4.05 (m, 1H), 3.94 and 3.91 (2s, $2OCH_3$), 3.68 (d, $J = 12.8$ Hz, 1H), 3.43 (dd, $J = 9.3/7.2$ Hz, 1H), 3.33 (ddd, $J = 13.4/11.8/2.7$ Hz, 1H), 3.20 (m, 1H), 3.02 (ddd, $J = 15.9/11.7/4.2$ Hz, 1H), 2.71 (m, 1H), 2.32 (d, $J = 13.4$ Hz, 1H), 2.37–2.23 (m, 1H), 2.06 (ddd, $J = 11.0/6.3/4.7$ Hz, 1H), 1.62–1.44 (m, CH_2), 0.83 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 176.99$, 173.15, 149.82, 148.89, 135.12, 131.35, 128.98 (2C), 127.32 (2C), 127.24, 124.50, 119.55 (CN), 111.29, 109.89, 70.81, 56.96, 56.40 (OCH_3), 56.06 (OCH_3), 46.04, 45.50, 42.64, 36.01, 29.35, 20.67, 10.39 ppm.

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