Pictet-Spengler Cyclization *vs.* Aminal Formation: Competing Reaction Pathways of Benzo[*b*][1,7]naphthyridines Controlled by the Configuration

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Dedicated to Professor *Burchard Franck* on the occasion of his 75th birthday

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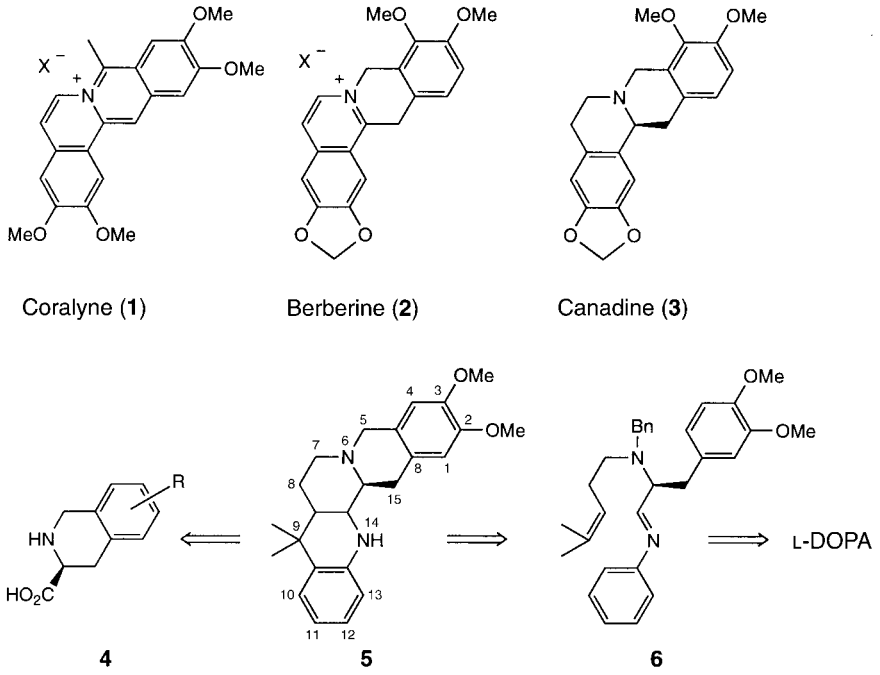
Diastereoisomeric benzo[*b*][1,7]naphthyridines **13a**,**b** were synthesized in nine steps from L-DOPA employing a *Lewis* acid-catalyzed cyclization of *N*-(4-methylpent-3-enyl)-α-amino aldehydes as the key step. Under aprotic *Pictet-Spengler* conditions, compounds **13a**,**b** undergo different reaction pathways depending on the relative configuration. Whereas *trans,cis*-diastereoisomer **13a** yielded the desired *Pictet-Spengler* cyclization product albeit in very low yield, the corresponding concave-shaped all-*cis*-diastereoisomer **13b** undergoes intramolecular aminal formation.

Introduction. – There has been considerable interest in protoberberine alkaloids, such as coralyne (**1**), berberine (**2**), and canadine (**3**) (*Scheme 1*), due to their important pharmacological activities [1]. We considered that the structurally related benz[*b*]isoquinolino[2,3-*h*]naphthyridine **5** might be potentially useful as a protoberberine mimic. During earlier studies, we observed that analogues of **5** display promising *in vitro* cytotoxicity against human-brain-tumor cell lines [2]. Regarding the synthesis of **5**, we decided to apply a sequence of *Lewis* acid-catalyzed cyclization [3] of L-DOPA-derived precursor **6**, followed by *Pictet-Spengler* reaction [4] as the key steps. It was anticipated that this route should be more amenable to variations of the substitution pattern than the previously employed route with tetrahydroisoquinolinic acid **4** as the precursor [2]. However, during our investigations we discovered that the benzo[*b*][1,7]naphthyridines **13** obtained from the *Lewis* acid-catalyzed cyclization of **6** underwent different reaction pathways depending on the relative configuration. In other words, either stereospecific aminal formation or *Pictet-Spengler* reaction was observed. The results of this study are reported below.

Results and Discussion. – To prepare the desired cyclization precursor **6**, L-DOPA was first converted to (*S*)-3-(3,4-dimethoxyphenyl)alanine (**7**) in 57% yield according to the procedure of *Tsuda et al.* (*Scheme 2*) [5]. *N*-Alkylation of **7** was effected with 5-bromo-2-methylpent-2-ene and CaO in DMF to give the amino acid derivative **8** in 57% yield. Further *N*-benzylation was achieved in the presence of K_2CO_3 and Bu_4NI in DMF in 93% yield. The resulting fully protected ester **9** was then reduced with $LiAlH_4$ to give the alcohol **10**. *Swern* oxidation of **10** proceeded without any event to give the aldehyde **11** [6]. To prevent racemization, compound **11** was immediately submitted to

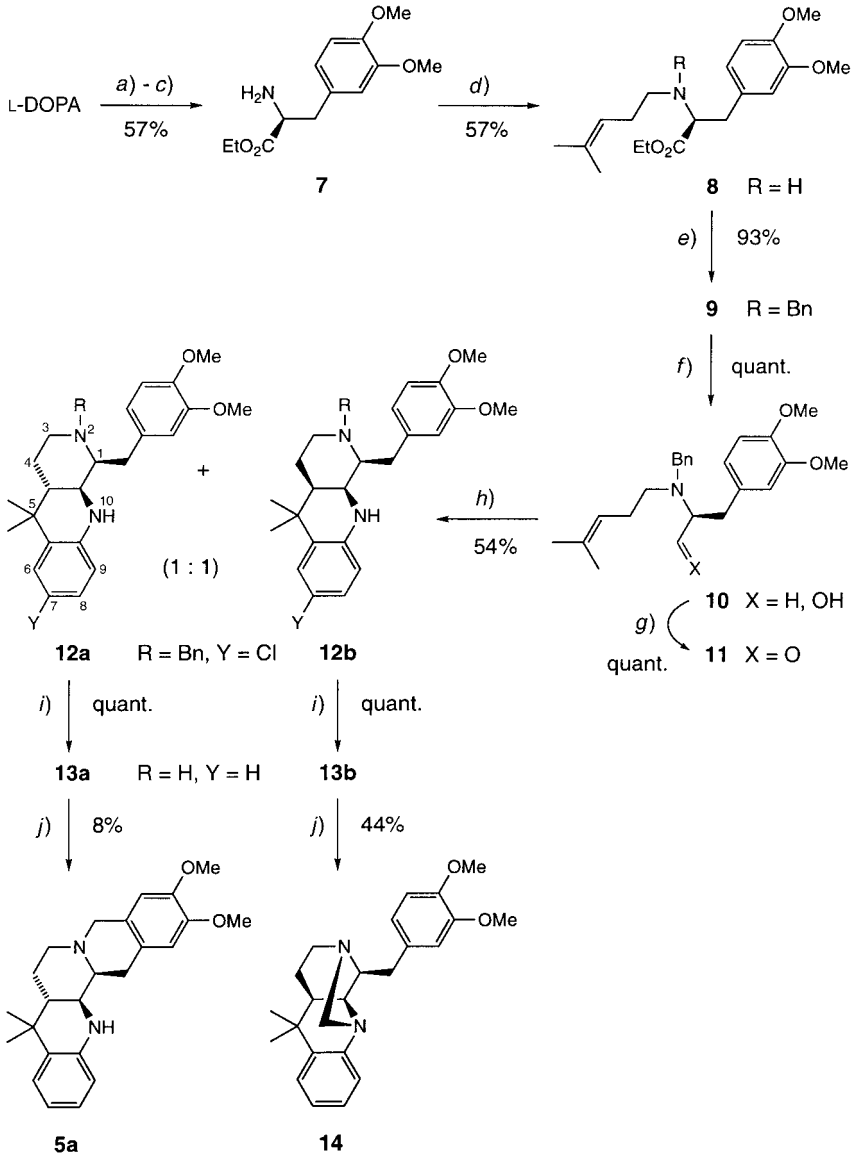
Scheme 1



the one-pot imine formation/cyclization conditions. Thus, imine **6** was generated *in situ* from **11** and 4-chloroaniline in the presence of 4-Å molecular sieves. After removal of the molecular sieves, the mixture was treated with $EtAlCl_2$ to induce the cyclization. Unfortunately, poor stereoselectivity was observed, and the diastereoisomers **12a** and **12b** were obtained in 28 and 26% yield, respectively. 4-Chloroaniline was used instead of aniline, because the 7-Cl-substituted benzo[*b*][1,7]naphthyridines **12a**,**b** could be separated more easily by flash chromatography than the corresponding 7-H derivatives. Debenzylation of the diastereoisomeric products **12a**,**b** was achieved by catalytic hydrogenation at elevated pressure according to a modified procedure by *Jung et al.* [7]. Under these conditions, the Cl substituents were also removed [8], and the desired compounds **13a**,**b** were isolated in almost quantitative yield.

Our first attempts to perform the *Pictet-Spengler* cyclization under classical conditions employing aqueous HCHO solution and HCOOH (or HCl) were unsuccessful [4][9]. Only decomposition of starting material was observed. We assumed that, at least partially, the trouble was caused by the secondary arylamine, although it should be less basic and thus less nucleophilic. However, *Cook* and co-workers reported the successful preparation of β-carbolines under aprotic conditions employing *N*-benzyltryptophane derivatives with an unprotected indole N-atom [10]. Encouraged by these results, the diastereoisomeric benzo[*b*][1,7]naphthyridines **13a**,**b** were treated separately with paraformaldehyde and toluene at 110°. Remarkably, the course of the reaction depended on the configuration. The *cis*,*trans*-configured diastereomer **13a** gave indeed the desired pentacyclic *Pictet-Spengler* adduct **5a**,

Scheme 2



a) Ac_2O, HCO_2H. *b*) Me_2SO_4, NaOH, H_2O. *c*) AcCl, EtOH. *d*) $BrCH_2CH_2CH{=}C(CH_3)_2$, CaO, DMF, r.t., 6 d. *e*) BnBr, TBAI, K_2CO_3, DMF, 100°, 2 d. *f*) $LiAlH_4$, Et_2O, r.t., 12 h. *g*) $(COCl)_2$, DMSO, CH_2Cl_2, –45°, Et_3N, 6 h. *h*) Mol. sieves (4 Å), 4-chloroaniline, CH_2Cl_2, r.t., 2 d; $EtAlCl_2$, –78° → r.t., 2 d. *i*) H_2 (10 atm), Pd/C, EtOH, 60°, 12 h. *j*) $(CH_2O)_n$, toluene, 110°, 15 h.

however, with a very low yield. Evidently, *Pictet-Spengler* cyclization was accompanied by massive decomposition of the starting material. In contrast, similar treatment of the all-*cis*-diastereoisomer **13b** yielded the bridged aminal **14** in 44% yield. No trace of the

corresponding *Pictet-Spengler* product was found in this case. Despite the presence of an activated aromatic system, the initially formed iminium ion is exclusively attacked by the aryl amine. Aminal formation and *N*-chloromethylation are common problems in alkaloid chemistry, which usually occur during isolation and extraction from natural sources [3a][11]. However, the above mentioned case seems to be the first example where aminal formation competes with *Pictet-Spengler* cyclization. The configuration dictates the pathway. In diastereoisomer **13a**, the two N-atoms are *antiperiplanarly* oriented, thus making the intramolecular aminal formation impossible. In contrast, in diastereoisomer **13b**, the N-atoms are oriented in a *gauche* position with respect to each other, thus favoring the formation of the diazabicyclo[3.2.1]octane subunit.

In conclusion, despite suitable activation by two MeO groups aprotic *Pictet-Spengler* cyclization of benzo[*b*][1,7]naphthyridines **13a**,**b** is strongly retarded. Depending on the relative configuration of **13**, different pathways were observed. The *cis*,*trans*-configured diastereoisomer **13a** yielded the desired pentacyclic protoberberine analogue **5a** only in small amounts. In contrast, under similar conditions the corresponding all-*cis*-configured precursor **13b** undergoes exclusively aminal formation to the brigded compound **14**.

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Experimental Part

General. All reactions were performed under N_2 according to the standard *Schlenk* technique. 5-Bromo-2-methylpent-2-ene was prepared according to [12]. M.p.: obtained by differential scanning calorimetry; *Rheometric Scientific DSC SP*, heating rate: 10 K min^{-1}. IR Spectra: *Nicolet 320* FT-IR spectrometer. NMR Spectra: *Bruker AM-400*; δ in ppm and *J* in Hz. Configurational assignments are based on 2D NMR (COSY, CH correlation) and 1D-NOE experiments. MS: *Finnigan MAT 8430* (EI, 70 eV).

*(*S*)-3-(3,4-Dimethoxyphenyl)alanine Ethyl Ester* (**7**). To a soln. of L-DOPA (10.0 g, 50.0 mmol) in HCOOH (90 ml, 90 wt%) was added Ac_2O (30 ml), and the mixture was stirred for 3 h at r.t. The mixture was evaporated to dryness, redissolved in H_2O (50 ml), and the evaporation/solution procedure was repeated 7 ×. The residue was dissolved in 10N NaOH (15 ml), and freshly dest. Me_2SO_4 (9.50 ml, 0.10 mol) was added dropwise under ice-cooling, while adjusting pH to 5–9 by simultaneous addition of 10N NaOH. After stirring for 30 min, Me_2SO_4 (28.5 ml, 0.30 mol) was added, and stirring was continued for 1.5 h. Then, the pH was adjusted to 2 by careful addition of 8N H_2SO_4 (10 ml), the mixture was extracted with AcOEt (3 × 200 ml) and evaporated. The residue was dissolved in EtOH (130 ml). After addition of AcCl (28 ml), the mixture was stirred for 3 h at r.t. and then evaporated. The residue was redissolved in H_2O (50 ml), and the aq. layer was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give **7** (7.23 g, 57%). Pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.82–6.73 (*m*, 3 H); 4.17 (*q*, *J* = 7.4, 2 H); 3.87 (*s*, 3 H); 3.85 (*s*, 3 H); 3.73 (*dd*, *J* = 7.4, 5.4, 1 H); 3.05 (*dd*, *J* = 13.3, 5.4, 1 H); 2.86 (*dd*, *J* = 13.3, 7.4, 1 H); 2.14 (*s*, 2 H); 1.26 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 174.6; 148.9; 147.9; 129.4; 121.4; 112.4; 111.2; 61.0; 55.9; 55.8; 55.7; 40.2; 14.1.

*(*S*)-N-(4-Methylpent-3-enyl)-3-(3,4-dimethoxyphenyl)alanine Ethyl Ester* (**8**). To a soln. of **7** (6.32 g, 25.0 mmol) in DMF (25 ml) were added CaO (3.50 g, 62.5 mmol) and 5-bromo-2-methylpent-2-ene (4.48 g, 27.5 mmol), and the resulting mixture was stirred for 6 d at r.t. After filtration *via Celite*, the solvent was evaporated and the crude product was purified by flash chromatography (FC) (SiO_2; hexanes/AcOEt 5:1, then 7:3) to give **8** (4.79 g, 57%). Colorless oil. IR (film) 3320, 1732. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.80–6.71 (*m*, 3 H); 5.02 (*tq*, *J* = 7.1, 1.4, 1 H); 4.11 (*dq*, *J* = 7.2, 2 H); 3.86 (*s*, 3 H); 3.85 (*s*, 3 H); 3.48 (*t*, *J* = 6.9, 1 H); 2.89 (*d*, *J* = 6.9, 2 H); 2.60 (*dt*, *J* = 10.9, 7.3, 1 H); 2.47 (*dt*, *J* = 10.9, 7.0, 1 H); 2.14 (*ddd*, *J* = 7.0, 7.0, 7.0, 2 H); 1.66 (br. *s*, 1 H); 1.66, 1.59 (*s*, 6 H); 1.19 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 174.5; 148.7; 147.7; 133.5; 129.8; 121.5; 121.2; 112.3; 111.1; 63.2; 60.5; 55.8; 55.7; 47.9; 39.2; 28.7; 25.6; 17.7; 14.2. EI-MS: 335 (1, M^+), 266 (100), 262 (20), 192 (44), 184 (56), 151 (31), 110 (30), 83 (17). EI-HR-MS: 335.2097 (calc. for $C_{19}H_{29}NO_4$; found: 335.2088).

*(*S*)*-N-*Benzyl*-N-*(4-methylpent-3-enyl)-3-(3,4-dimethoxyphenyl)alanine Ethyl Ester* (**9**). To a soln. of **8** (1.68 g, 5.00 mmol) in DMF (5 ml) were added K_2CO_3 (0.69 g, 5.00 mmol), Bu_4NI (1.81 g, 5.00 mmol) and BnBr (0.86 g, 5.00 mmol), and the mixture was stirred for 4 h at r.t. and then heated for 2 d at 100°. After cooling to r.t., toluene (25 ml) was added, and the solvent was azeotropically destilled *in vacuo* (3×). The remaining residue was dissolved in pentane (20 ml) and purified by FC (SiO_2; pentane/AcOEt 30:1) to give **3** (1.97 g, 93%). Pale yellow amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.25–7.16 (*m*, 5 H); 6.75 (*d*, *J* = 8.3, 1 H); 6.67 (*dd*, *J* = 8.3, 2.0, 1 H); 6.58 (*d*, *J* = 2.0, 1 H); 5.04 (*tq*, *J* = 7.1, 1.5, 1 H); 4.15 (*dq*, *J* = 10.8, 7.2, 1 H); 4.11 (*dq*, *J* = 10.8, 7.2, 1 H); 3.98 (*d*, *J* = 14.3, 1 H); 3.86, 3.76 (2*s*, 6 H); 3.60 (*d*, *J* = 14.3, 1 H); 3.57 (*t*, *J* = 7.4, 1 H); 3.02 (*dd*, *J* = 13.8, 7.4, 1 H); 2.84 (*dd*, *J* = 13.8, 7.4, 1 H); 2.68 (*ddd*, *J* = 13.0, 9.4, 6.9, 1 H); 2.50 (*ddd*, *J* = 13.0, 9.1, 5.2, 1 H); 2.20–2.00 (*m*, 2 H); 1.66 (*s*, 3 H); 1.55 (*s*, 3 H); 1.26 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.6; 148.5; 147.4; 139.9; 132.4; 131.2; 128.6; 128.0; 126.7; 122.0; 121.4; 112.4; 110.9; 64.1; 60.1; 55.9; 55.6; 55.1; 50.5; 35.7; 27.3; 25.7; 17.7; 14.5. EI-MS: 356 (100, $M - C_5H_9]^+$), 274 (42), 264 (8), 246 (3), 236 (7), 200 (11), 192 (14), 165 (4), 151 (38), 149 (2), 107 (4), 91 (82), 83 (9).

*(*S*)*-N-*Benzyl-3-(3,4-dimethoxyphenyl)*-N-*(4-methylpent-3-enyl)alaninol* (**10**). To a suspension of $LiAlH_4$ (667 mg, 17.5 mmol) in Et_2O (50 ml) was added dropwise a soln. of **9** (2.16 g, 5.00 mmol) in Et_2O (5 ml) under ice-cooling, and the resulting mixture was stirred at r.t. overnight. After careful hydrolysis with H_2O (0.67 ml), 15% NaOH (0.67 ml), and H_2O (2.0 ml), the soln. was filtered, dried ($MgSO_4$), and concentrated *in vacuo* to yield **10** (1.87 g, 98%). Colorless highly viscous oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.32–7.24 (*m*, 5 H); 6.77 (*d*, *J* = 8.0, 1 H); 6.64 (*dd*, *J* = 8.0, 2.0, 1 H); 6.58 (*d*, *J* = 2.0, 1 H); 5.05 (*tq*, *J* = 7.1, 1.5, 1 H); 3.95 (*d*, *J* = 13.3, 1 H); 3.85 (*s*, 3 H); 3.83 (*s*, 3 H); 3.46 (*d*, *J* = 13.3, 1 H); 3.39 (*dd*, *J* = 10.6, 10.4, 1 H); 3.33 (*dd*, *J* = 10.6, 4.8, 1 H); 3.06–2.98 (*m*, 1 H); 2.94 (*dd*, *J* = 13.4, 4.3, 1 H); 2.68 (*dt*, *J* = 12.9, 8.2, 1 H); 2.52 (*dt*, *J* = 12.9, 6.0, 1 H); 2.30 (*dd*, *J* = 13.4, 9.6, 1 H); 2.17 (*ddd*, *J* = 8.2, 7.1, 6.0, 2 H); 1.70 (*d*, *J* = 1.3, 3 H); 1.59 (*d*, *J* = 1.3, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.9; 147.4; 139.4; 133.4; 131.8; 128.9; 128.4; 127.1; 121.9; 120.8; 111.9; 111.3; 62.1; 60.5; 55.9; 55.8; 54.1; 48.6; 31.4; 27.4; 25.7; 17.8. EI-MS: 352 (8, M^+), 314 (88), 284 (2), 270 (2), 241 (3), 232 (100), 223 (3), 200 (2), 177 (4), 165 (6), 151 (54), 137 (2), 107 (4), 91 (72), 83 (16).

*(*S*)*-N-*Benzyl-3-(3,4-dimethoxyphenyl)*-N-*(4-methylpent-3-enyl)alaninal* (**11**). To a soln. of oxalyl chloride (0.51 g, 4.00 mmol) in CH_2Cl_2 (15 ml) were added dropwise DMSO (0.63 g, 8.00 mmol) in CH_2Cl_2 (5 ml) at −45°. After stirring for 10 min, **10** (778 mg, 2.00 mmol) was added dropwise, and the resulting soln. was stirred for 6 h at −45°. The mixture was hydrolyzed by addition of Et_3N (1.50 ml), warmed to r.t. and washed with H_2O (3 × 20 ml). The org. layer was dried ($MgSO_4$) and evaporated to give **11** as a brown oil (775 mg, quant.), which was immediately used for the imine condensation. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.61 (*s*, 1 H); 7.30–7.11 (*m*, 5 H); 6.77–6.50 (*m*, 3 H); 5.00 (*tq*, *J* = 7.1, 1.5, 1 H); 3.77 (*d*, *J* = 14.0, 1 H); 3.76 (*s*, 3 H); 3.72 (*s*, 3 H); 3.55 (*d*, *J* = 14.0, 1 H); 3.39 (*t*, *J* = 6.8, 1 H); 2.95 (*dd*, *J* = 13.9, 7.2, 1 H); 2.72 (*dd*, *J* = 13.9, 5.8, 1 H); 2.64–2.50 (*m*, 2 H); 2.09 (*ddd*, *J* = 7.2, 7.2, 7.2, 2 H); 1.61 (*s*, 3 H); 1.49 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 202.7; 148.8; 147.4; 139.3; 132.9; 131.9; 128.7; 128.3; 127.2; 121.7; 121.3; 112.4; 111.2; 70.0; 55.9; 55.7; 55.5; 50.8; 29.9; 27.7; 25.7; 17.8.

*2-Benzyl-7-chloro-1-(3,4-dimethoxybenzyl)-1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethylbenzo[*b*][1,7]naphthyridine* (**12a**,**b**). To a mixture of **11** (388 mg, 1.00 mmol) and molecular sieves (4 Å) (1 g) in CH_2Cl_2 (10 ml) was added 4-chloroaniline (128 mg, 1.00 mmol), and the mixture was stirred for 2 d at r.t. After removal of the molecular sieves by filtration *via Celite*, the filtrate was cooled to −78° and treated with $EtAlCl_2$ (2.6 ml, 2.6 mmol, 1M soln. in hexane) at −78°. After warming to r.t. stirring was continued for 2 d. Then, the mixture was poured onto ice-cold 2M NH_4F (50 ml), and the aq. layer was separated with CH_2Cl_2 (3 × 50 ml). The combined org. layers were dried ($MgSO_4$), concentrated, and purified by FC (SiO_2; hexanes/$CHCl_3$/Et_3N 10:1:1) to give diastereoisomer **12b** as the first fraction (127 mg, 26%) and diastereoisomer **12a** as the second fraction (139 mg, 28%).

*(1*S*,4a*R*,10a*S*)-Diastereoisomer* (**12a**): yellow solid. M.p. >250° (dec.). $[\alpha]_D^{22} = -81.2$ (*c* = 0.50, CH_2Cl_2). IR (film): 3396, 3391. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.40–7.32 (*m*, 4 H); 7.29–7.26 (*m*, 1 H); 7.07 (*d*, *J* = 2.3, 1 H); 6.91 (*dd*, *J* = 8.4, 2.3, 1 H); 6.72 (*d*, *J* = 8.3, 1 H); 6.58 (*dd*, *J* = 8.3, 2.0, 1 H); 6.46 (*d*, *J* = 2.0, 1 H); 6.44 (*d*, *J* = 8.4, 1 H); 3.82 (*s*, 3 H); 3.76 (*s*, 3 H); 3.81 (*s*, 2 H); 3.37 (*m*, 1 H); 2.98 (*dd*, *J* = 13.1, 3.5, 1 H); 2.90 (*ddd*, *J* = 10.6, 3.0, 3.0, 1 H); 2.74–2.70 (*m*, 1 H); 2.70–2.63 (*m*, 2 H); 1.72–1.66 (*m*, 1 H); 1.55–1.48 (*m*, 1 H); 1.33 (*s*, 3 H); 1.15 (*s*, 3 H); 1.27–1.22 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.9; 147.3; 141.9; 139.2; 132.3; 130.5; 128.6; 128.4; 127.2; 126.4; 126.1; 121.5; 121.0; 116.0; 112.0; 111.3; 62.9; 58.7; 55.9; 55.7; 46.8; 46.1; 37.4; 35.6; 32.8; 25.9; 27.7; 22.8. EI-MS: 490 (4, M^+), 339 (100), 233 (11), 220 (10), 192 (4), 178 (12), 172 (4), 151 (17), 120 (14), 91 (34). EI-HR-MS: 490.2387 (calc. for $C_{30}H_{35}N_2O_2Cl$; found: 490.2379).

*(1*S*,4a*S*,10a*S*)-Diastereoisomer* (**12b**): yellow solid. M.p. >250° (dec.). $[\alpha]_D^{20} = +40.4$ (*c* = 0.50; CH_2Cl_2). IR (film): 3404; 3373. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.25–7.19 (*m*, 4 H); 7.16–7.12 (*m*, 1 H); 6.97 (*d*, *J* = 2.5, 1 H);

6.97 (*dd*, *J* = 8.6, 2.5, 1 H); 6.75–6.69 (*m*, 2 H); 6.68 (*dd*, *J* = 7.3, 1.3, 1 H); 6.52 (*d*, *J* = 8.6, 1 H); 4.08 (*d*, *J* = 13.9, 1 H); 3.74 (*s*, 4 H); 3.72 (*s*, 3 H); 3.26 (*d*, *J* = 13.9, 1 H); 3.37 (*s*, 1 H); 3.16 (*dd*, *J* = 13.9, 5.1, 1 H); 2.80–2.72 (*m*, 1 H); 2.68 (*dd*, *J* = 13.9, 9.9, 1 H); 2.52 (*ddd*, *J* = 9.9, 5.1, 1.6, 1 H); 2.03–1.97 (*m*, 1 H); 1.32–1.27 (*m*, 1 H); 1.11 (*s*, 3 H); 0.93 (*s*, 3 H); 1.13–1.05 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.3; 147.1; 141.0; 139.0; 130.8; 130.6; 128.2; 127.8; 126.5; 125.9; 125.7; 121.4; 120.9; 116.3; 112.0; 110.7; 65.5; 56.7; 55.4; 55.3; 52.9; 47.0; 43.4; 35.4; 35.2; 32.4; 25.5; 21.8. EI-MS: 490 (5, M^+), 339 (100), 233 (7), 220 (16), 206 (3), 178 (6), 151 (6), 120 (12), 91 (14). EI-HR-MS: 490.2387 (calc. for $C_{30}H_{35}N_2O_2Cl$; found: 490.2379).

*(1*S*,4a*R*,10a*S*)-1-(3,4-Dimethoxybenzyl)-1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethylbenzo[*b*][1,7]naphthyridine* (**13a**). A soln. of **12a** (490 mg, 1.00 mmol) in EtOH (10 ml) was treated with Pd/C (100 mg, 10 wt-%) and hydrogenated at 10 atm and 60° for 12 h. Then, the catalyst was removed by filtration, and the mixture was evaporated to give **13a** (365 mg, quant.). Colorless solid. M.p. >250° (dec.). $[\alpha]_D^{22} = -32.6°$ ($c = 1.00$, CH_2Cl_2). IR (KBr): 3411, 3400. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.06 (*dd*, *J* = 7.8, 1.3, 1 H); 6.93 (*dd*, *J* = 7.8, 7.8, 1 H); 6.85 (*s*, 1 H); 6.78 (*d*, *J* = 8.1, 1 H); 6.75 (*d*, *J* = 8.1, 1 H); 6.65–6.59 (*m*, 2 H); 4.83 (br. *s*, 1 H); 4.04–4.00 (*m*, 1 H); 3.84 (*s*, 3 H); 3.82 (*s*, 3 H); 3.66 (*s*, 1 H); 3.57–3.50 (*m*, 1 H); 3.40–3.32 (*m*, 1 H); 3.13–2.96 (*m*, 2 H); 1.84–1.78 (*m*, 1 H); 1.71–1.63 (*m*, 1 H); 1.58–1.46 (*m*, 1 H); 1.33 (*s*, 3 H); 1.16 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 149.2; 148.2; 141.4; 128.0; 126.9; 126.8; 125.9; 121.2; 117.6; 114.6; 112.3; 111.4; 57.3; 55.9; 55.8; 45.1; 38.7; 36.8; 35.1; 33.5; 32.4; 25.6; 19.7. EI-MS: 366 (32, M^+), 351 (15), 215 (100), 194 (9), 186 (41), 170 (14), 151 (48), 144 (66), 130 (15), 106 (9), 91 (10). HR-MS: 366.2300 (calc. for $C_{23}H_{30}N_2O_2$; found: 366.2299).

*(1*S*,4a*S*,10a*S*)-1-(3,4-Dimethoxybenzyl)-1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethylbenzo[*b*][1,7]naphthyridine* (**13b**). According to the same procedure as described for **13a**, hydrogenation of **12b** yielded **13b** (366 mg, quant.). Colorless solid. M.p. 254°. $[\alpha]_D^{22} = +58.6$ ($c = 1.00$; CH_2Cl_2). IR (KBr): 3408, 3400. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.08 (*dd*, *J* = 7.8, 1.5, 1 H); 7.03 (*ddd*, *J* = 7.8, 7.4, 1.5, 1 H); 6.92 (*dd*, *J* = 7.8, 1.2, 1 H); 6.88 (*d*, *J* = 1.8, 1 H); 6.82 (*dd*, *J* = 8.1, 1.8, 1 H); 6.73 (*d*, *J* = 8.1, 1 H); 6.68 (*ddd*, *J* = 7.4, 7.4, 1.2, 1 H); 4.87 (br. *s*, 1 H); 3.84 (*s*, 3 H); 3.83 (*s*, 3 H); 3.59 (br. *s*, 1 H); 3.51–3.44 (*m*, 2 H); 3.33–3.27 (*m*, 2 H); 2.92 (*ddd*, *J* = 13.1, 13.1, 3.5, 1 H); 1.68–1.60 (*m*, 1 H); 1.50–1.44 (*m*, 1 H); 1.40–1.34 (*m*, 1 H); 1.26 (*s*, 3 H); 1.08 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 149.1; 148.1; 140.9; 127.5; 127.2; 127.0; 125.9; 121.5; 118.0; 115.4; 112.2; 111.4; 60.8; 56.0; 55.8; 44.5; 44.3; 43.1; 35.4; 34.4; 33.3; 25.6; 19.7. EI-MS: 366 (32, M^+), 351 (14), 243 (5), 215 (100), 194 (8), 186 (49), 170 (11), 158 (26), 151 (22), 144 (32), 130 (9), 121 (3), 106 (3), 91 (5). EI-HR-MS: 366.2300 (calc. for $C_{23}H_{30}N_2O_2$; found: 366.2299).

*(8a*R*,14a*S*,14b*S*)-5,6,7,8,8a,9,14,14a,14b,15-Decahydro-2,3-dimethoxy-9,9-dimethylbenz[*b*]isoquinolino[2,3-*h*]naphthyridine* (**5a**). A mixture of **13a** (183 mg, 0.50 mmol) and paraformaldehyde (150 mg) in toluene (30 ml) was refluxed in a *Dean-Stark* trap filled with molecular sieves (4 Å) for 15 h. Then, the solvent was removed *in vacuo*, and the crude product was purified by FC (SiO_2; hexanes/$CHCl_3$/Et_3N 10:1:1) to give **5a** (15 mg, 8%). Colorless solid. M.p. >200° (dec.). $[\alpha]_D^{22} = -106.8$ ($c = 0.50$, CH_2Cl_2). IR (KBr): 3419. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (*dd*, *J* = 7.8, 1.5, 1 H); 7.04 (*ddd*, *J* = 7.8, 7.8, 1.5, 1 H); 6.67–6.63 (*m*, 2 H); 6.62 (*s*, 1 H); 6.55 (*s*, 1 H); 4.38 (br. *s*, 1 H); 3.86 (*s*, 6 H); 3.80–3.68 (*m*, 2 H); 3.56–3.50 (*m*, 1 H); 3.13–3.04 (*m*, 2 H); 2.83–2.72 (*m*, 2 H); 2.64–2.57 (*m*, 2 H); 1.70–1.58 (*m*, 3 H); 1.34 (*s*, 3 H); 1.27 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.0; 147.9; 142.4; 127.9; 127.6; 126.7; 125.9; 123.5; 117.2; 114.7; 111.4; 109.4; 57.6; 55.9; 55.9; 55.8; 49.9; 46.3; 37.9; 35.0; 33.7; 25.9; 24.4; 22.8. EI-MS: 378 (24, M^+), 345 (7), 244 (7), 229 (4), 218 (10), 206 (100), 191 (8), 164 (13), 149 (7), 144 (12), 121 (4), 110 (4), 97 (4). EI-HR-MS: 378.2307 (calc. for $C_{24}H_{30}N_2O_2$; found: 378.2300).

*(1*S*,4a*S*,10a*S*)-1-(3,4-Dimethoxybenzyl)-1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethyl-2,10-methanobenzo[*b*][1,7]naphthyridine* (**14**). A mixture of **13b** (183 mg, 0.50 mmol) and paraformaldehyde (150 mg) in toluene (30 ml) was refluxed in a *Dean-Stark* trap filled with molecular sieves (4 Å) for 15 h. Then, the solvent was removed *in vacuo*, and the crude product was purified by FC (SiO_2; hexanes/$CHCl_3$/Et_3N 20:1:1) to give **14** (85 mg, 44%). Colorless solid. M.p. >200° (dec.). $[\alpha]_D^{22} = +69.4$ ($c = 0.50$, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (*dd*, *J* = 7.6, 1.3, 1 H); 7.04 (*ddd*, *J* = 7.6, 7.6, 1.5, 1 H); 6.76 (*ddd*, *J* = 7.6, 7.6, 1.3, 1 H); 6.75–6.70 (*m*, 3 H); 6.68 (*dd*, *J* = 7.6, 1.5, 1 H); 4.72 (*d*, *J* = 8.6, 1 H); 3.79 (*s*, 3 H); 3.77 (*s*, 3 H); 3.71 (*d*, *J* = 8.6, 1 H); 3.32 (*s*, 1 H); 3.06 (*dd*, *J* = 7.3. 7.3, 1 H); 2.90–2.82 (*m*, 2 H); 2.76–2.70 (*m*, 2 H); 1.49 (*dd*, *J* = 10.5, 6.4, 1 H); 1.36–1.28 (*m*, 1 H); 1.14 (*s*, 3 H); 1.11 (*s*, 3 H); 0.84–0.77 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.7; 147.3; 145.3; 132.2; 131.9; 126.6; 126.4; 121.0; 119.8; 119.5; 112.2; 111.2; 75.2; 72.2; 55.9; 55.8; 55.5; 53.9; 43.0; 37.5; 37.0; 31.2; 26.0; 21.7. EI-MS: 378 (100, M^+), 363 (29), 345 (9), 334 (11), 306 (8), 290 (6), 227 (23), 206 (90), 199 (10), 186 (17), 170 (25), 151 (66), 144 (34), 115 (10), 107 (8), 91 (10). EI-HR-MS: 378.2307 (calc. for $C_{24}H_{30}N_2O_2$; found: 378.2300).

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