Synthesis of Tetrahydro-β-carbolines and Tetrahydroisoquinolines Fused to Pyrrolidines and Solution-Phase Parallel Acylation

Daniel Blanco-Ania,[†] Pedro H. H. Hermkens,[‡] Leo A. J. M. Sliedregt,[§] Hans W. Scheeren,[†] and Floris P. J. T. Rutjes*,[†]

Institute for Molecules and Materials, Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands, Schering-Plough, P.O. Box 20, 5340 BH Oss, The Netherlands, and Solvay Pharmaceuticals, Sector Discovery Weesp, P.O. Box 900, 1380 DA Weesp, The Netherlands

Received November 22, 2008

A structurally diverse library of potentially pharmacologically important compounds employing classical synthesis methods is described. These compounds are synthesized from β-aryl pyrrolidines, providing products with the *2-arylethyl amine* moiety, a structural feature often encountered in compounds active in the central nervous system. Tri- and tetracyclic scaffolds were obtained using the Pictet−Spengler reaction, resulting in hexahydropyrrolo[3,4-*c*]isoquinolines **1**−**3**, an octahydropyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole **4**, and a hexahydrofuro[2,3-*d*]pyrrolo[3,4-*b*]pyridine **5**. These scaffolds were further derivatized in parallel fashion to make a 32-membered amide library with yields from 62 to 100% (90% average) and purities from 63 to 100% (93% average).

Introduction

The Pictet−Spengler reaction[1] has been of vital importance throughout history in the synthesis of numerous pharmacologically important privileged core structures, such as indole alkaloids (with the pyrido[3,4-*b*]indole or β-carboline moiety) and isoquinoline alkaloids.[2] This reaction continues to be important because of the growing interest in the synthesis of biologically active compounds having more complex structures such as manzamine,[3] the *Alstonia*[4] alkaloids, and ecteinascidin 743 derivatives.[5] Herein, we report the synthesis of a series of (hetero)arenopyrrolopyridines **1**−**5** using the Pictet−Spengler reaction (Figure 1).

Compounds **1**−**5** combine a variety of structural motifs possessing different biological properties. First, they all possess the privileged *2-arylethyl amine* moiety, which is encountered in numerous natural and synthetic compounds active in the central nervous system. This moiety is present in some neurotransmitters such as dopamine, epinephrine, norepinephrine, and serotonin.[6] It is also present in several medicines, such as salmeterol[7] and venlafaxine,[8] two of the ten best-selling prescription drugs in 2006.[9] In addition, this feature is also present in many hallucinogenic drugs, such as LSD, MDMA (ecstasy), mescaline, and psilocybin (magic mushrooms).[10] Second, compounds **1**−**5** also possess a tetrahydro(hetero)areno[*c*]pyridine, such as a tetrahydroisoquinoline or a tetrahydro-β-carboline, which are privileged core structures and often show a wide range of pharmacological properties.[11] Compounds with structure **3** have the same core structure as the *amarillidaceae* alkaloids plicamine and obliquine[12] and derivatives of compounds with structure **4** are reported to be tyrosine-kinase receptor inhibitors.[13] Compounds with structure **5** have not been previously synthesized nor have their biological properties been evaluated.

Solution-phase parallel synthesis of single molecule libraries offers many advantages over solid-phase synthesis, such as unlimited scale, easy manipulation, and reduction in validation time. This procedure has received increased attention as a lead discovery and optimization tool for drug discovery.[14] Therefore, we thought to further derivatize compounds **1**−**5** by making a 32-membered amide library[15] using this technique.

Results and Discussion

The basis of this research is the synthesis of substrates **10a**−**e**, which has been described in a previous article.[16] The synthetic approach uses the Knoevenagel condensation of methyl nitroacetate **6** with various aromatic aldehydes to obtain α-nitro acrylates **7a**−**e** as mixtures of diastereoisomers. The choice of the aryl group on the aldehyde is decisive

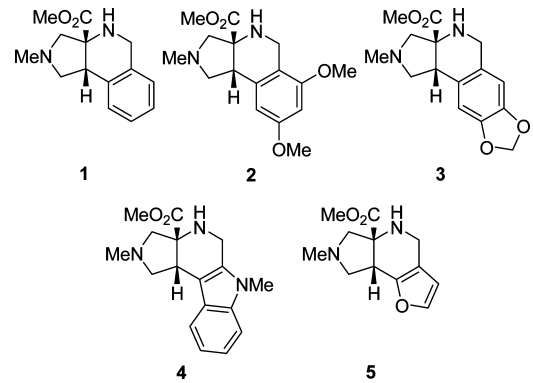
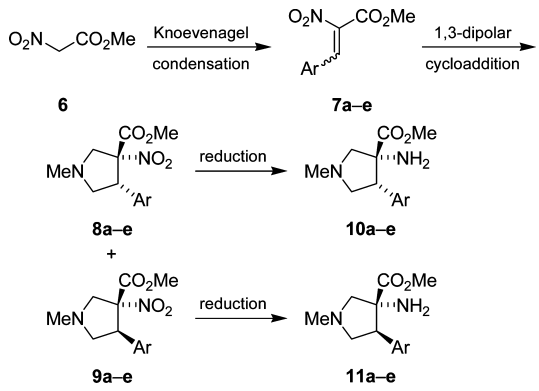


Figure 1. Target products.

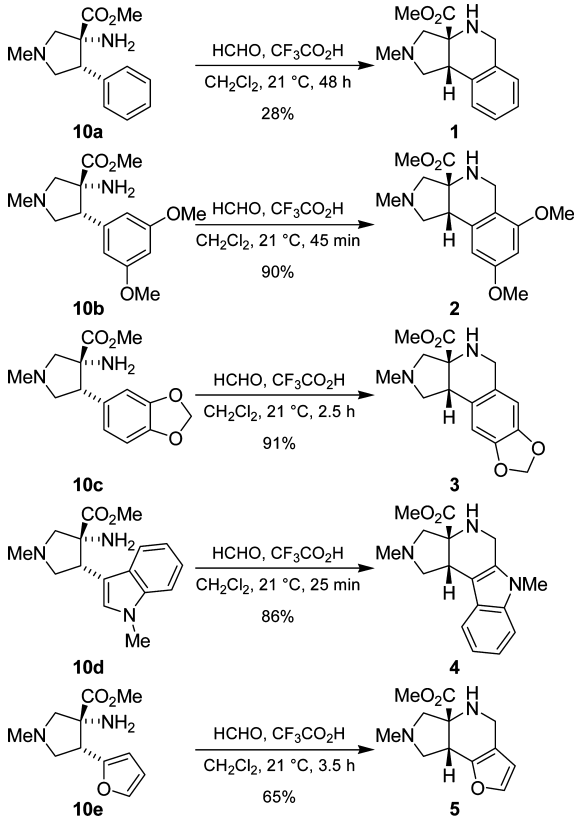
* To whom correspondence should be addressed. E-mail: f.rutjes@science.ru.nl.
† Radboud University Nijmegen.
‡ Schering-Plough.
§ Solvay Pharmaceuticals.

10.1021/cc800191w CCC: $40.75 © 2009 American Chemical Society
Published on Web 05/27/2009

Scheme 1. Formation of Substrates **10a**−**e**

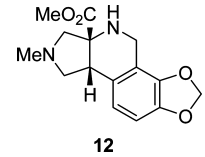


Scheme 2. Pictet−Spengler Reaction of Compounds **10a**−**e**



for the success of the Pictet−Spengler cyclization, since electron-rich aryl groups are needed for successful reactions. Subsequent 1,3-dipolar cycloaddition reactions of **7a**−**e** with the azomethine ylide $CH_2{=}N^+(Me)CH_2^-$ (generated in situ) gave a 1:1 diastereomeric mixture of the racemic pyrrolidine core structures **8a**−**e** and **9a**−**e**. After separation of the diastereoisomers, the reduction of the nitro group to the amine under catalytic hydrogenation conditions furnishes the diamino carboxylates **10a**−**e** and **11a**−**e** (Scheme 1).

Various conditions have been reported in literature for performing a Pictet−Spengler reaction. In our case, we found that addition of trifluoroacetic acid (2 equiv) to a dichloromethane solution[17] of compounds **10a**−**e** and formaldehyde at room temperature gave the desired products **1**−**5** (Scheme 2). The cyclization reaction of the phenyl-substituted pyrrolidine **10a** took place under mild conditions (room temperature), but with a rather low yield (28%). Introduction of electron-donating alkoxy groups on the phenyl ring (compounds **10b** and **c**) or substitution of the phenyl group for electron-rich heteroaryl groups (indolyl **10d** and furyl **10e**) resulted in a faster and cleaner reaction and significantly higher yields, ranging from 65 to 91%. To the best of our knowledge, the cyclization of compound **10e** is the first example of a classical Pictet−Spengler reaction using a nonactivated iminium ion[18] reacting with the 3-position of a furan ring.[19]



12

Figure 2. Possible regioisomer from cyclization of compound **10c**.

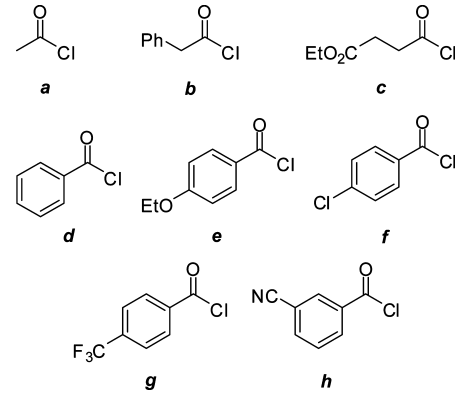


Figure 3. Acyl chlorides **13**{*a*−*h*} used for acylation of substrates **2**−**5**.

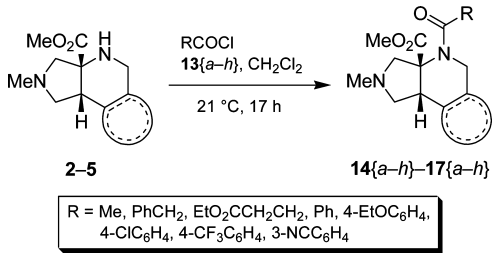
The cyclization with all substrates except for **10c** can result only in one regioisomer.[20] The reaction of compound **10c**, however, gave exclusively the regioisomer shown, whereas the corresponding regioisomer **12** (Figure 2) was not detected.[2b,21]

It is known that the Pictet−Spengler reaction for *trans*-2-arylcyclopentan-1-amines (or other 5-membered cycles, such as tetrahydrofurans and pyrrolidines, e.g., **11a**−**e**) is troublesome.[22] Following the results with substrates **10a**−**e**, we tried the reaction with the two most reactive compounds toward these conditions, the 3,5-dimethoxyphenyl derivative **11b** and the 1-methylindol-3-yl derivative **11d**, but in both cases, there was no trace of product after 48 h. We foresaw a similar result with the least reactive substrates **11a**, **11c**, and **11e**. The strain of the transition state leading to the *trans*-fused bicycle does not allow the reaction to take place.

Compounds **2**−**5** were then derivatized using parallel synthesis by acylation of the free amines to obtain a 32-membered amide library **14**{*a*−*h*}−**17**{*a*−*h*}. Compound **1** was excluded because the yield of its synthesis was low and sufficient material for the parallel synthesis was not obtained. Thus, conversion of compounds **2**−**5** to chemsets **14**−**17** was accomplished using acylation with reagent chemset **13** (Figure 3).

The overnight reaction of substrates **2**−**5** with the eight acyl chlorides **13**{*a*−*h*} (1 equiv) in dichloromethane at room temperature, followed by $NaHCO_3$ (sat.)/CH_2Cl_2 extraction and evaporation of dichloromethane, cleanly yielded 32 new amides **14**{*a*−*h*}−**17**{*a*−*h*} with yields ranging from 62 to

Scheme 3



100% (90% average) and with purities from 63 to 100% (93% average; Scheme 3 and Table 1). By using equimolar amounts of the acyl chlorides and without the addition of an external base (the substrates contain a tertiary amine), the workup did not need the regular thorough repeated extraction or addition of scavengers for the elimination of the residual acyl chlorides.[23]

Conclusions

A reliable method for making an array of potentially pharmaceutically important scaffolds with a (hetero)areno-[*d*]pyrrolo[3,4-*b*]pyridine structure has been presented. We have shown that the (hetero)arene part could be a (substituted) benzene, an indole, and a furan. These scaffolds combine two important privileged structures: the 2-arylethyl amine moiety and the tetrahydro(hetero)areno[*c*]pyridine (e.g., tetrahydroisoquinoline, tetrahydro-β-carboline, and tetrahydrofuro[3,2-*c*]pyridine, a potentially privileged structure). In addition, parallel acylation of these compounds in solution phase resulted in a 32-compound library with excellent yields and high purities, demonstrating the potential for further diversification.

Experimental Section

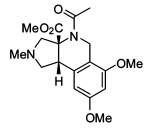
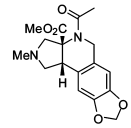
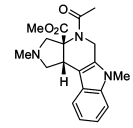
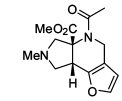
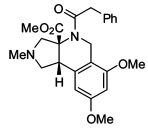
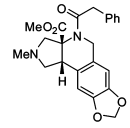
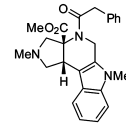
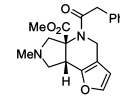
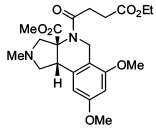
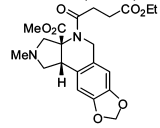
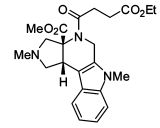
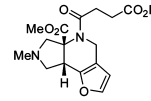
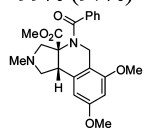
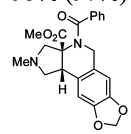
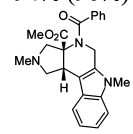
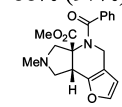
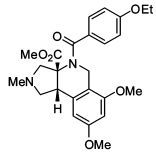
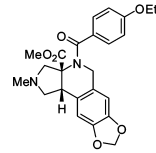
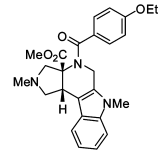
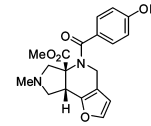
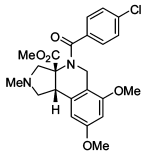
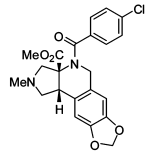
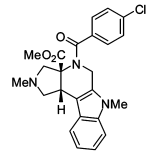
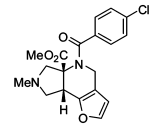
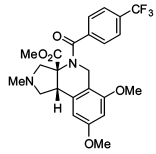
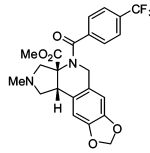
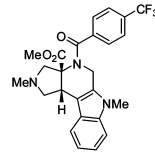
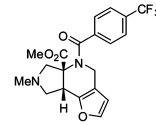
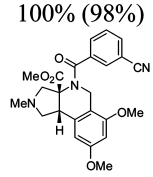
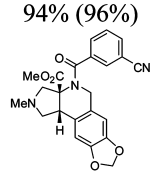
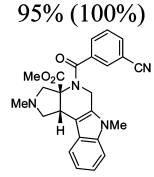
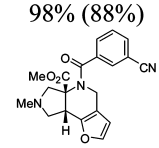
Reagents were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from CaH_2 under nitrogen immediately before use. Reactions were followed, and R_F values were obtained, using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV light and/or by charring at ca. 150 °C after dipping into a solution of $KMnO_4$. Column or flash chromatography was carried out using ACROS silica gel (0.035−0.070 mm, pore diameter ∼6 nm). ISOLUTE SCX-2 columns (propylsulfonic acid functionalized silica)[24] were used for filtration of Pictet−Spengler products. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. NMR spectra were recorded on a Bruker DMX 300 (300 MHz) and a Varian 400 (400 MHz) spectrometer in $CDCl_3$ solutions. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (0.00 ppm) as internal standard. Coupling constants are reported as *J* values in hertz (Hz). Multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and b (broad). Peak assignment in ^{13}C spectra are based on 2D gHSQC and gHMBC spectra, and DEPT 135 when needed. Chain numbering corresponds to IUPAC name, so unprimed atoms belong to the principal chain, primed atoms belong to the first named substituent, doubled-primed atoms to the second named substituent, etc. LC-MS measurements were run on a Shimadzu LC-10A VP series liquid chromatography system, equipped with an SPD-10A VP UV−vis detector and a LCMS-2010A mass spectrometer. The column used for the LC analysis was an Agilent Zorbax Extend C_{18} (3.5 μm, 4.6 × 150 mm), and it was eluted at 1 mL/min with a gradient made up of two solvent mixtures. Solvent A consisted of 0.1% trifluoroacetic acid in water and solvent B consisted of 0.1% trifluoroacetic acid in acetonitrile. The gradient was run as follows: $t = 0$ min, 50% A; $t = 5$ min, 5% A; $t = 10$ min, 5% A; $t = 12.5$ min, 50% A; $t = 20$ min, 50% A. A wavelength of 215 nm was selected for the analysis of purity.

General Procedure for Pictet−Spengler Reaction. To a solution of the amine (**10a**−**e**, 1 mmol) in dichloromethane (12 mL) was added formaldehyde (30 mg, 1 mmol, from a 37 wt % in H_2O solution). Trifluoroacetic acid (228 mg, 2 mmol) was slowly added, and the resulting reaction mixture was stirred at room temperature for the time indicated in each case. Saturated aqueous sodium hydrogen carbonate (2 mL) was added and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 × 12 mL), and the organic extracts were combined, washed with brine (6 mL), and dried over magnesium sulfate. Removal of the solvent under reduced pressure left a residue, which was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:19 → 1:9). An alternative workup, generally giving better yields, involved the immediate filtration of the reaction mixture through an ISOLUTE SCX-2 column before purification.

(±)-Methyl (3a*R*,9b*R*)-2-Methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]isoquinoline-3a-carboxylate 1. According to the general procedure, the reaction of amine **10a** (234 mg, 1.0 mmol) with formaldehyde (30 mg, 1.0 mmol) over 48 h afforded **1** (69 mg, 28%) as a colorless oil. ^1H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.22−7.05 (m, 4 ^1H, 6-C*H* + 7-C*H* + 8-C*H* + 9-C*H*), 3.91 (d, $J = 15.8$ Hz, 1 ^1H, 5-CH*H*), 3.86 (d, $J = 15.8$ Hz, 1 ^1H, 5-C*H*H), 3.81 (t, $J = 8.2$ Hz, 1 ^1H, 9b-C*H*), 3.76 (s, 3 ^1H, OCH_3), 3.34 (d, $J = 10.1$ Hz, 1 ^1H, 3-CH*H*), 3.28 (t, $J = 8.4$ Hz, 1 ^1H, 1-CH*H*), 2.58 (d, $J = 10.1$ Hz, 1 ^1H, 3-C*H*H), 2.54 (t, $J = 8.9$ Hz, 1 ^1H, 1-C*H*H), 2.38 (s, 3 ^1H, NCH_3), 2.23 (bs, 1 ^1H, N*H*). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.0 (CO_2), 135.4 (5a-*C*), 134.5 (9a-*C*), 129.0 (9-*C*), 126.9, 126.4, 126.1, 67.3 (3-*C*), 67.2 (3a-*C*), 63.7 (1-*C*), 52.8 (OCH_3), 44.9 (5-*C*), 43.7 (9b-*C*), 42.2 (NCH_3). FTIR [ν^- (cm^{-1}), neat]: 3334, 2949, 2840, 2789, 1727, 1452, 1240, 760. MS [ESI (*m*/*z*)] calcd. for $(C_{14}H_{18}N_2O_2 + H)^+ = 247$, found 247. R_F: 0.41 ($MeOH/CH_2Cl_2$, 1:8).

(±)-Methyl (3a*R*,9b*R*)-6,8-Dimethoxy-2-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo [3,4-*c*]isoquinoline-3a-carboxylate 2. According to the general procedure, the reaction of amine **10b** (294 mg, 1.0 mmol) with formaldehyde (30 mg, 1.0 mmol) over 45 min afforded **2** (276 mg, 90%) as a colorless oil. ^1H NMR [400 MHz, δ (ppm), $CDCl_3$]: 6.29 (d, $J = 2.2$ Hz, 1 ^1H, 7-C*H*), 6.26 (d, $J = 2.2$ Hz, 1 ^1H, 9-C*H*), 3.89 (d, $J = 16.1$ Hz, 1 ^1H, 5-CH*H*), 3.78 (s, 3 ^1H, OCH_3), 3.77 (s, 3 ^1H, OCH_3), 3.74 (s, 3 ^1H, CO_2CH_3), 3.76−3.70 (m, 2 ^1H, 5-C*H*H + 9b-C*H*), 3.31 (d,

Table 1. Solution-Phase Synthesis of a 32-Membered Amide Library **14**{*a*−*h*}−**17**{*a*−*h*}[a,b]

Reagent	Substrate 2	3	4	5
	Product			
MeCOCl **13a**	 **14a** 80% (100%)	 **15a** 67% (100%)	 **16a** 62% (100%)	 **17a** 62% (88%)
$PhCH_2COCl$ **13b**	 **14b** 98% (88%)	 **15b** 92% (96%)	 **16b** 97% (100%)	 **17b** 89% (96%)
$EtO_2CCH_2CH_2COCl$ **13c**	 **14c** 99% (97%)	 **15c** 95% (97%)	 **16c** 94% (96%)	 **17c** 88% (97%)
PhCOCl **13d**	 **14d** 92% (96%)	 **15d** 86% (88%)	 **16d** 81% (95%)	 **17d** 95% (70%)
$4\text{-}EtOC_6H_4COCl$ **13e**	 **14e** 94% (95%)	 **15e** 94% (96%)	 **16e** 95% (90%)	 **17e** 92% (92%)
$4\text{-}ClC_6H_4COCl$ **13f**	 **14f** 96% (91%)	 **15f** 90% (81%)	 **16f** 99% (88%)	 **17f** 95% (63%)
$4\text{-}CF_3C_6H_4COCl$ **13g**	 **14g** 100% (98%)	 **15g** 94% (96%)	 **16g** 95% (100%)	 **17g** 98% (88%)
$3\text{-}NCC_6H_4COCl$ **13h**	 **14h** 90% (98%)	 **15h** 96% (98%)	 **16h** 92% (100%)	 **17h** 91% (89%)

[a] % = Crude yield based on mass recovery. [b] (%) = Purity determined by LC-MS at 215 nm.

J = 10.3 Hz, 1 ^{1}H, 3-CH*H*), 3.26 (t, J = 8.4 Hz, 1 ^{1}H, 1-CH*H*), 2.60 (t, J = 8.9 Hz, 1 ^{1}H, 1-C*H*H), 2.57 (d, J = 10.0 Hz, 1 ^{1}H, 3-C*H*H), 2.38 (s, 3 ^{1}H, NCH_3), 2.28 (bs, 1 ^{1}H, N*H*). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.2 (CO_2), 159.1 (6-*C*), 156.6 (8-*C*), 136.4 (9a-*C*), 116.8 (5a-*C*), 104.4 (9-*C*), 96.3 (7-*C*), 67.7 (3-*C*), 66.8 (3a-*C*), 63.3 (1-*C*), 55.4 (OCH_3), 55.3 (OCH_3), 52.6 (CO_2CH_3), 43.8 (9b-*C*), 42.1 (NCH_3), 39.0 (5-*C*). FTIR [ν^- (cm^{-1}), neat]: 3330, 2941,

2836, 2784, 1725, 1606, 1454, 1236, 1151, 830. HRMS [EI (*m*/*z*)] calcd. for $C_{16}H_{22}N_2O_4$ = 306.1580, found for [$M^{+\bullet}$] = 306.1566 (Δ = 4.4 ppm), peaks at (relative intensity): 306 (7), 248 (81), 204 (17), 188 (43), 84 (23), 57 (100), 42 (56). R_F: 0.45 ($MeOH/CH_2Cl_2$, 1:8).

(±)-Methyl (3a*R*,10b*R*)-2-Methyl-2,3,3a,4,5,10b-hexahydro-1*H*,8*H*-[1,3]dioxolo[4,5-*g*] pyrrolo[3,4-*c*]isoquinoline-3a-carboxylate 3. According to the general procedure, the reaction of amine **10c** (278 mg, 1.0 mmol) with formaldehyde (30 mg, 1.0 mmol) over 2.5 h afforded **3** (264 mg, 91%) as a yellow oil. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 6.59 (s, 1 ^{1}H, 10-C*H*), 6.54 (s, 1 ^{1}H, 6-C*H*), 5.89 (d, *J* = 1.2 Hz, 1 ^{1}H, 8-CH*H*), 5.89 (d, *J* = 1.2 Hz, 1 ^{1}H, 8-C*H*H), 3.80 (d, *J* = 15.6 Hz, 1 ^{1}H, 5-CH*H*), 3.76 (s, 3 ^{1}H, OCH_3), 3.74 (d, *J* = 15.6 Hz, 1 ^{1}H, 5-C*H*H), 3.68 (t, *J* = 8.3 Hz, 1 ^{1}H, 10b-C*H*), 3.32 (d, *J* = 10.2 Hz, 1 ^{1}H, 3-CH*H*), 3.22 (t, *J* = 8.4 Hz, 1 ^{1}H, 1-CH*H*), 2.56 (d, *J* = 10.2 Hz, 1 ^{1}H, 3-C*H*H), 2.48 (t, *J* = 8.8 Hz, 1 ^{1}H, 1-C*H*H), 2.37 (s, 3 ^{1}H, NCH_3), 2.32 (bs, 1 ^{1}H, N*H*). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.3 (*C*O_2), 146.5 (9a-*C*), 146.0 (6a-*C*), 129.0 (5a-*C*), 127.9 (10a-*C*), 108.8 (10-*C*), 106.2 (6-*C*), 100.8 (8-*C*), 67.4 (3-*C*), 67.1 (3a-*C*), 63.9 (1-*C*), 52.8 (O*C*H_3), 44.9 (5-*C*), 43.8 (10b-*C*), 42.0 (N*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 3323, 2948, 2839, 2785, 1728, 1486, 1240, 1038, 935, 862. HRMS [ESI (*m*/*z*)] calcd. for ($C_{15}H_{18}N_2O_4$ + H)$^+$ = 291.13393, found 291.13458 (|Δ| = 0.4 ppm) R_F: 0.43 ($MeOH/CH_2Cl_2$, 1:8).

(±)-Methyl (3a*R*,10c*R*)-2,6-Dimethyl-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3′,4′:5,6] pyrido[3,4-*b*]indole-3a-carboxylate 4. According to the general procedure, the reaction of amine **10d** (287 mg, 1.0 mmol) with formaldehyde (30 mg, 1.0 mmol) over 25 min afforded **4** (257 mg, 86%) as a light yellow solid. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.46 (d, *J* = 7.8 Hz, 1 ^{1}H, 10-C*H*), 7.26 (d, *J* = 8.3 Hz, 1 ^{1}H, 7-C*H*), 7.18−7.15 (m, 1 ^{1}H, 8-C*H*), 7.11−7.06 (m, 1 ^{1}H, 9-C*H*), 4.14 (dd; *J* = 15.9, 1.7 Hz; 1 ^{1}H, 5-CH*H*), 3.99 (d, *J* = 15.9 Hz, 1 ^{1}H, 5-C*H*H), 3.98 (dt; *J* = 1.7, 8.0 Hz; 1 ^{1}H, 10c-C*H*), 3.72 (s, 3 ^{1}H, OCH_3), 3.58 (s, 3 ^{1}H, 6-NCH_3), 3.30 (t, *J* = 8.3 Hz, 1 ^{1}H, 1-CH*H*), 3.24 (d, *J* = 10.0 Hz, 1 ^{1}H, 3-CH*H*), 2.75 (t, *J* = 8.2 Hz, 1 ^{1}H, 1-C*H*H), 2.64 (d, *J* = 10.0 Hz, 1 ^{1}H, 3-C*H*H), 2.41 (s, 3 ^{1}H, 2-NCH_3), 2.17 (bs, 1 ^{1}H, N*H*). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.9 (*C*O_2), 137.1 (6a-*C*), 133.9 (5a-*C*), 126.9 (10a-*C*), 121.2 (8-*C*), 119.2 (9-*C*), 118.1 (10-*C*), 108.9 (7-*C*), 107.5 (10b-*C*), 67.5 (3-*C*), 67.2 (3a-*C*), 61.9 (1-*C*), 52.6 (O*C*H_3), 42.1 (2-N*C*H_3), 39.9 (10c-*C*), 39.2 (5-*C*), 29.4 (6-N*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 3325, 2935, 2835, 2783, 1731, 1470, 1231, 739. HRMS [EI (*m*/*z*)] calcd. for $C_{17}H_{21}N_3O_2$ = 299.1634, found for [$M^{+\bullet}$] = 299.1633 (Δ = 0.3 ppm), peaks at (relative intensity): 299 (65), 241 (100), 209 (59), 181 (42), 58 (54), 57 (26), 42 (11). R_F: 0.32 ($MeOH/CH_2Cl_2$, 1:8) mp: 149−151 °C.

(±)-Methyl (5a*R*,8a*R*)-7-Methyl-5,5a,6,7,8,8a-hexahydro-4*H*-furo[2,3-*d*]pyrrolo[3,4-*b*]pyridine-5a-carboxylate 5. According to the general procedure, the reaction of amine **10e** (224 mg, 1.0 mmol) with formaldehyde (30.0 mg, 1.0 mmol) over 3.5 h afforded **5** (154 mg, 65%) as a yellow oil. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.26 (d, *J* = 2.0 Hz, 1 ^{1}H, 2-C*H*), 6.19 (d, *J* = 1.9 Hz, 1 ^{1}H, 3-C*H*), 3.80 (d, *J* = 15.6 Hz, 1 ^{1}H, 4-CH*H*), 3.76 (d, *J* = 15.6 Hz, 1 ^{1}H, 4-C*H*H), 3.75 (s, 3 ^{1}H, OCH_3), 3.72 (t, *J* = 6.6 Hz, 1 ^{1}H, 8a-C*H*), 2.99 (d, *J* = 9.8 Hz, 1 ^{1}H, 6-CH*H*), 2.95 (t, *J* = 8.5 Hz, 1 ^{1}H, 8-CH*H*), 2.85 (dd; *J* = 9.0, 6.1 Hz; 1 ^{1}H, 8-C*H*H), 2.72 (d, *J* = 9.8 Hz, 1 ^{1}H, 6-C*H*H), 2.36 (s, 3 ^{1}H, NCH_3), 2.32 (bs, 1 ^{1}H, N*H*). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.0 (*C*O_2), 149.2 (8b-*C*), 141.2 (2-*C*), 116.5 (3a-*C*), 108.0 (3-*C*), 68.6 (5a-*C*), 66.8 (6-*C*), 59.8 (8-*C*), 52.7 (O*C*H_3), 41.7 (N*C*H_3), 40.1 (4-*C* + 8a-*C*). FTIR [ν^- (cm^{-1}), neat]: 3329, 2947, 2838, 2785, 1727, 1233, 728. HRMS [EI (*m*/*z*)] calcd. for $C_{12}H_{16}N_2O_3$ = 236.1161, found for [$M^{+\bullet}$] = 236.1156 (Δ = 1.3 ppm), peaks at (relative intensity): 236 (15), 178 (25), 57 (100), 42 (16). R_F: 0.36 ($MeOH/CH_2Cl_2$, 1:8).

General Procedure for Acylation Reaction. Solutions of **13**{*a*−*h*} (0.1 mmol) from a 0.3 M stock solution in dichloromethane were added to eight separate solutions of **2** (0.1 mmol) in dichloromethane (1.5 mL). The resulting reaction mixture was stirred at room temperature for 17 h. After that time, a saturated solution of $NaHCO_3$ (1.5 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 1.5 mL), and the combined organic layers were evaporated to dryness under vacuum.

(±)-Methyl (3a*R*,9b*R*)-4-Acetyl-6,8-dimethoxy-2-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]isoquinoline-3a-carboxylate 14a. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 6.37 (d, *J* = 2.4 Hz, 1 ^{1}H, 7-C*H*), 6.29 (d, *J* = 2.4 Hz, 1 ^{1}H, 9-C*H*), 4.94 (d, *J* = 15.3 Hz, 1 ^{1}H, 5-CH*H*), 4.20 (d, *J* = 10.8 Hz, 1 ^{1}H, 3-CH*H*), 4.17 (d, *J* = 15.3 Hz, 1 ^{1}H, 5-C*H*H), 3.84 (s, 3 ^{1}H, 6-OCH_3), 3.79 (s, 3 ^{1}H, 8-OCH_3), 3.66 (s, 3 ^{1}H, CO_2CH_3), 3.46 (dd; *J* = 9.6, 7.5 Hz; 1 ^{1}H, 9b-C*H*), 3.15 (dd; *J* = 9.0, 7.5 Hz; 1 ^{1}H, 1-CH*H*), 2.47 (d, *J* = 10.8 Hz, 1 ^{1}H, 3-C*H*H), 2.36 (s, 3 ^{1}H, NCH_3), 2.31 (t, *J* = 9.3 Hz, 1 ^{1}H, 1-C*H*H), 2.23 (s, 3 ^{1}H, COCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.2 (*C*O_2), 171.0 (*C*ON), 160.0 (8-*C*), 156.2 (6-*C*), 135.1 (9a-*C*), 113.5 (5a-*C*), 104.2 (9-*C*), 97.1 (7-*C*), 67.8 (3a-*C*), 66.8 (3-*C*), 63.2 (1-*C*), 55.6 (6-O*C*H_3), 55.5 (8-O*C*H_3), 52.7 (CO_2CH_3), 48.4 (9b-*C*), 41.8 (N*C*H_3), 40.1 (5-*C*), 22.8 (COCH_3). FTIR [ν^- (cm^{-1}), neat]: 2940, 2838, 2781, 1737, 1643, 1605, 1242, 1149, 728. MS [APCI (*m*/*z*)] calcd for ($C_{18}H_{24}N_2O_5$ + H)$^+$ = 349, found 349.

(±)-Methyl (3a*R*,9b*R*)-4-Benzoyl-6,8-dimethoxy-2-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]isoquinoline-3a-carboxylate 14d. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.54−7.35 (m, 5 ^{1}H, Ph), 6.39 (d, *J* = 2.1 Hz, 1 ^{1}H, 9-C*H*), 6.37 (d, *J* = 2.1 Hz, 1 ^{1}H, 7-C*H*), 4.97 (d, *J* = 15.6 Hz, 1 ^{1}H, 5-CH*H*), 4.39 (d, *J* = 11.4 Hz, 1 ^{1}H, 3-CH*H*), 4.17 (d, *J* = 15.6 Hz, 1 ^{1}H, 5-C*H*H), 3.79 (s, 3 ^{1}H, 8-OCH_3), 3.72 (s, 3 ^{1}H, 6-OCH_3), 3.71−3.64 (m, 1 ^{1}H, 9b-C*H*), 3.68 (s, 3 ^{1}H, CO_2CH_3), 3.38 (dd; *J* = 9.9, 7.8 Hz; 1 ^{1}H, 1-CH*H*), 2.98 (d, *J* = 11.4 Hz, 1 ^{1}H, 3-C*H*H), 2.76 (t, *J* = 9.9 Hz, 1 ^{1}H, 1-C*H*H), 2.57 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 172.6 (*C*O_2), 171.8 (*C*ON), 160.2 (8-*C*), 156.0 (6-*C*), 135.3 (1′-*C*), 135.1 (9a-*C*), 130.5 (4′-*C*), 128.4 (2′-*C* + 6′-*C*), 127.8 (3′-*C* + 5′-*C*), 114.4 (5a-*C*), 104.5 (9-*C*), 97.6 (7-*C*), 68.3 (3a-*C*), 64.8 (3-*C*), 61.5 (1-*C*), 55.5 (6-O*C*H_3 + 8-O*C*H_3), 52.9 (CO_2CH_3), 48.1 (9b-*C*), 41.9 (N*C*H_3), 41.3 (5-*C*). FTIR [ν^- (cm^{-1}), neat]: 2949, 2839, 2783, 1738, 1628, 1601, 1211, 1150, 726, 703. MS [APCI (*m*/*z*)] calcd for ($C_{23}H_{26}N_2O_5$ + H)$^+$ = 411, found 411.

(±)-Methyl(3a*R*,9b*R*)-4-(4-Chlorobenzoyl)-6,8-dimethoxy-2-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]isoquinoline-3a-carboxylate 14f. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.45−7.35 (m, 4 ^{1}H, C_6H_4), 6.39 (d, J = 2.1 Hz, 1 ^{1}H, 7-C*H*), 6.35 (d, J = 2.1 Hz, 1 ^{1}H, 9-C*H*), 4.95 (d, J = 15.6 Hz, 1 ^{1}H, 5-CH*H*), 4.28 (d, J = 10.8 Hz, 1 ^{1}H, 3-CH*H*), 4.06 (d, J = 15.6 Hz, 1 ^{1}H, 5-C*H*H), 3.81 (s, 3 ^{1}H, 8-OCH_3), 3.77 (s, 3 ^{1}H, 6-OCH_3), 3.68 (s, 3 ^{1}H, CO_2CH_3), 3.56 (dd; J = 9.6, 7.8 Hz; 1 ^{1}H, 9b-C*H*), 3.21 (dd; J = 9.0, 7.8 Hz; 1 ^{1}H, 1-CH*H*), 2.65 (d, J = 10.8 Hz, 1 ^{1}H, 3-C*H*H), 2.42 (s, 3 ^{1}H, NCH_3), 2.38 (t, J = 9.6 Hz, 1 ^{1}H, 1-C*H*H). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 172.8 (*C*O_2), 170.5 (*C*ON), 160.3 (8-*C*), 156.0 (6-*C*), 136.6 (4′-*C*), 136.3 (9a-*C*), 133.9 (1′-*C*), 129.5 (3′-*C* + 5′-*C*), 128.7 (2′-*C* + 6′-*C*), 114.3 (5a-*C*), 104.8 (9-*C*), 97.3 (7-*C*), 68.3 (3a-*C*), 65.4 (3-*C*), 62.9 (1-*C*), 55.62 (6-O*C*H_3), 55.57 (8-O*C*H_3), 52.9 ($CO_2C$$H_3$), 48.8 (9b-*C*), 41.9 (N*C*H_3), 41.2 (5-*C*). FTIR [ν^- (cm^{-1}), neat]: 2950, 2839, 2783, 1739, 1633, 1603, 1213, 1151, 835, 613. MS [APCI (*m*/*z*)] calcd for $(C_{23}H_{25}ClN_2O_5 + H)^+$ = 445, found 445.

(±)-Methyl (3a*R*,10b*R*)-4-(4-Ethoxybenzoyl)-2-methyl-2,3,3a,4,5,10b-hexahydro-1*H*,8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*c*]isoquinoline-3a-carboxylate 15e. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.44−7.38 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 6.94−6.88 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 6.71 (s, 1 ^{1}H, 10-C*H*), 6.58 (s, 1 ^{1}H, 6-C*H*), 5.97 (d, J = 1.5 Hz, 1 ^{1}H, 8-CH*H*), 5.95 (d, J = 1.5 Hz, 1 ^{1}H, 8-C*H*H), 4.58 (d, J = 15.3 Hz, 1 ^{1}H, 5-CH*H*), 4.31 (d, J = 15.3 Hz, 1 ^{1}H, 5-C*H*H), 4.25 (d, J = 10.8 Hz, 1 ^{1}H, 3-CH*H*), 4.10 (q, J = 6.9 Hz, 2 ^{1}H, C$H_2$$CH_3$), 3.68 (s, 3 ^{1}H, OC$H_3$), 3.52 (dd; J = 9.3, 7.5 Hz; 1 ^{1}H, 10b-C*H*), 3.18 (dd; J = 9.0, 7.5 Hz; 1 ^{1}H, 1-CH*H*), 2.63 (d, J = 10.8 Hz, 1 ^{1}H, 3-C*H*H), 2.41 (s, 3 ^{1}H, NCH_3), 2.35 (t, J = 9.3 Hz, 1 ^{1}H, 1-C*H*H), 1.44 (t, J = 6.9 Hz, 3 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.0 (*C*O_2), 171.2 (*C*ON), 160.9 (4′-*C*), 147.4 (9a-*C*), 146.7 (6a-*C*), 129.7 (2′-*C* + 6′-*C*), 128.0 (10a-*C*), 127.4 (1′-*C*), 127.2 (5a-*C*), 114.4 (3′-*C* + 5′-*C*), 109.1 (10-*C*), 106.5 (6-*C*), 101.2 (8-*C*), 68.1 (3a-*C*), 65.3 (3-*C*), 63.7 (*C*$H_2$$CH_3$), 62.8 (1-*C*), 52.9 (O*C*H_3), 48.6 (10b-*C*), 47.9 (5-*C*), 41.9 (N*C*H_3), 14.8 (CH_2*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 2938, 2842, 2781, 1737, 1628, 1606, 1243, 1037, 932, 845. MS [APCI (*m*/*z*)] calcd for $(C_{24}H_{26}N_2O_6 + H)^+$ = 439, found 439.

(±)-Methyl (3a*R*,10b*R*)-4-(3-Cyanobenzoyl)-2-methyl-2,3,3a,4,5,10b-hexahydro-1*H*,8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*c*]isoquinoline-3a-carboxylate 15h. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.79−7.75 (m, 2 ^{1}H, 2′-C*H* + 4′-C*H*), 7.68 (dt; J = 7.8, 1.3 Hz; 1 ^{1}H, 6′-C*H*), 7.58 (t, J = 8.1 Hz, 1 ^{1}H, 5′-C*H*), 6.71 (s, 1 ^{1}H, 10-C*H*), 6.53 (s, 1 ^{1}H, 6-C*H*), 5.97 (d, J = 1.2 Hz, 1 ^{1}H, 8-CH*H*), 5.95 (d, J = 1.2 Hz, 1 ^{1}H, 8-C*H*H), 4.43−4.33 (m, 2 ^{1}H, 5-CH_2), 4.17 (d, J = 10.8 Hz, 1 ^{1}H, 3-CH*H*), 3.70 (s, 3 ^{1}H, OCH_3), 3.56 (dd; J = 9.0, 7.8 Hz; 1 ^{1}H, 10b-C*H*), 3.17 (dd; J = 9.3, 7.8 Hz; 1 ^{1}H, 1-CH*H*), 2.77 (d, J = 10.8 Hz, 1 ^{1}H, 3-C*H*H), 2.46 (t, J = 9.3 Hz, 1 ^{1}H, 1-C*H*H), 2.44 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 172.3 (*C*O_2), 168.8 (*C*ON), 147.7 (9a-*C*), 147.0 (6a-*C*), 137.0 (1′-*C*), 133.9 (4′-*C*), 131.6 (6′-*C*), 131.1 (2′-*C*), 129.7 (5′-*C*), 127.5 (10a-*C*), 126.0 (5a-*C*), 118.0 (*C*N), 113.3 (3′-*C*), 109.1 (10-*C*), 106.4 (6-*C*), 101.4 (8-*C*), 68.4 (3a-*C*), 65.4 (3-*C*), 62.5 (1-*C*), 53.0 (O*C*H_3), 48.5 (10b-*C*), 48.1 (5-*C*), 41.8 (N*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 2948, 2842, 2782, 2230, 1737, 1634, 1246, 1037, 933, 735. MS [APCI (*m*/*z*)] calcd for $(C_{23}H_{21}N_3O_5 + H)^+$ = 420, found 420.

(±)-Methyl (3a*R*,10c*R*)-4-Acetyl-2,6-dimethyl-1,2,3,3a,4,5,6,10c-octahydropyrrolo [3′,4′:5,6]pyrido[3,4-*b*]indole-3a-carboxylate 16a. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.47 (d, J = 7.8 Hz, 1 ^{1}H, 10-C*H*), 7.31 (d, J = 8.1 Hz, 1 ^{1}H, 7-C*H*), 7.24 (t, J = 8.1 Hz, 1 ^{1}H, 8-C*H*), 7.12 (t, J = 7.4 Hz, 1 ^{1}H, 9-C*H*), 4.78 (s, 2 ^{1}H, 5-CH_2), 4.26 (d, J = 11.1 Hz, 1 ^{1}H, 3-CH*H*), 3.84 (dd; J = 9.7, 6.9 Hz; 1 ^{1}H, 10c-C*H*), 3.70 (s, 3 ^{1}H, OCH_3), 3.69 (s, 3 ^{1}H, 6-NCH_3), 3.51 (dd; J = 8.1, 6.9 Hz; 1 ^{1}H, 1-CH*H*), 2.49 (d, J = 11.1 Hz, 1 ^{1}H, 3-C*H*H), 2.38 (s, 3 ^{1}H, 2-NCH_3), 2.32 (s, 3 ^{1}H, COCH_3), 2.24 (t, J = 9.0 Hz, 1 ^{1}H, 1-C*H*H). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.4 (*C*O_2), 173.9 (*C*ON), 137.9 (6a-*C*), 128.8 (5a-*C*), 125.8 (10a-*C*), 122.1 (8-*C*), 119.7 (9-*C*), 118.5 (10-*C*), 109.1 (7-*C*), 105.3 (10b-*C*), 69.3 (3-*C*), 68.4 (3a-*C*), 63.2 (1-*C*), 53.0 (O*C*H_3), 42.8 (5-*C*), 42.6 (10c-*C*), 41.9 (2-N*C*H_3), 29.6 (6-N*C*H_3), 23.7 (CO*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 2947, 2838, 2780, 1735, 1657, 1246, 742. MS [APCI (*m*/*z*)] calcd for $(C_{19}H_{23}N_3O_3 + H)^+$ = 342, found 342.

(±)-Methyl (3a*R*,10c*R*)-2,6-Dimethyl-4-[4-(trifluoromethyl)benzoyl]-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole-3a-carboxylate 16g. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.79−7.73 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 7.70−7.63 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 7.49 (d, J = 7.8 Hz, 1 ^{1}H, 10-C*H*), 7.32−7.19 (m, 2 ^{1}H, 7-C*H* + 8-C*H*), 7.17−7.09 (m, 1 ^{1}H, 9-C*H*), 4.70 (d, J = 15.3 Hz, 1 ^{1}H, 5-CH*H*), 4.62 (dd; J = 15.3, 1.2 Hz; 1 ^{1}H, 5-C*H*H), 4.33 (d, J = 11.1 Hz, 1 ^{1}H, 3-CH*H*), 3.96 (dd; J = 9.6, 6.6 Hz; 1 ^{1}H, 10c-C*H*), 3.78 (s, 3 ^{1}H, OCH_3), 3.61 (dd; J = 8.7, 6.6 Hz; 1 ^{1}H, 1-CH*H*), 3.48 (s, 3 ^{1}H, 6-NCH_3), 2.61 (d, J = 11.1 Hz, 1 ^{1}H, 3-C*H*H), 2.45 (s, 3 ^{1}H, 2-NCH_3), 2.35 (t, J = 9.2 Hz, 1 ^{1}H, 1-C*H*H). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.9 (*C*ON), 173.7 (*C*O_2), 140.1 (1′-*C*), 137.7 (6a-*C*), 131.9 (q, J = 31.9 Hz, 4′-*C*), 129.3 (5a-*C*), 127.7 (2′-*C* + 6′-*C*), 126.1 (q, J = 3.7 Hz, 3′-*C* + 5′-*C*), 125.9 (10a-*C*), 123.7 (q, J = 280.6 Hz, *C*F_3), 122.2 (8-*C*), 119.9 (9-*C*), 118.5 (10-*C*), 109.2 (7-*C*), 105.6 (10b-*C*), 68.9 (3a-*C*), 68.7 (3-*C*), 63.1 (1-*C*), 53.1 (O*C*H_3), 44.2 (5-*C*), 43.0 (10c-*C*), 42.0 (2-N*C*H_3), 29.6 (6-N*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 2948, 2840, 2782, 1735, 1651, 1321, 1241, 854, 741. MS [APCI (*m*/*z*)] calcd for $(C_{25}H_{24}F_3N_3O_3 + H)^+$ = 472, found 472.

(±)-Methyl (5a*R*,8a*R*)-7-Methyl-5-(2-phenylacetyl)-5,5a,6,7,8,8a-hexahydro-4*H*-furo[2,3-*d*]pyrrolo[3,4-*b*]pyridine-5a-carboxylate 17b. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.38−7.20 (m, 6 ^{1}H, 2-C*H* + Ph), 6.22 (d, J = 1.8 Hz, 1 ^{1}H, 3-C*H*), 4.64−4.52 (m, 2 ^{1}H, 4-CH_2), 4.04 (d, J = 11.1 Hz, 1 ^{1}H, 6-CH*H*), 3.86 (d, J = 15.6 Hz, 1 ^{1}H, 2′-CH*H*), 3.82 (d, J = 15.6 Hz, 1 ^{1}H, 2′-C*H*H), 3.70 (s, 3 ^{1}H, OCH_3), 3.46 (bt, J = 6.8 Hz, 1 ^{1}H, 8a-C*H*), 3.12 (dd; J = 8.7, 6.6 Hz; 1 ^{1}H, 8-CH*H*), 2.59 (d, J = 11.1 Hz, 1 ^{1}H, 6-C*H*H), 2.51 (dd; J = 8.7, 7.5 Hz; 1 ^{1}H, 8-C*H*H), 2.35 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.7 (*C*ON), 173.6 (*C*O_2), 146.1 (8b-*C*), 142.6 (2-*C*), 134.2 (1″-*C*), 129.1 (2″-*C* + 6″-*C*), 128.8 (3″-*C* + 5″-*C*), 127.1 (4″-*C*), 112.4 (3a-*C*), 108.0 (3-*C*), 69.9 (5a-*C*), 68.2 (6-*C*), 60.8

(8-*C*), 52.9 (O*C*H$_3$), 43.8 (4-*C*), 42.4 (8a-*C*), 42.3 (2′-*C*), 41.7 (N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 2946, 2839, 2783, 1736, 1648, 1247, 757, 728, 699. MS [APCI (*m*/*z*)] calcd for $(C_{20}H_{22}N_2O_4 + H)^+ = 355$, found 355.

(±)-Methyl (5a*R*,8a*R*)-5-[3-(Ethoxycarbonyl)propanoyl]-7-methyl-5,5a,6,7,8,8a-hexahydro-4*H*-furo[2,3-*d*]pyrrolo[3,4-*b*]pyridine-5a-carboxylate 17c. ^{1}H NMR [300 MHz, δ (ppm), CDCl$_3$]: 7.35 (d, $J = 1.8$ Hz, 1 ^{1}H, 2-C*H*), 6.28 (d, $J = 1.8$ Hz, 1 ^{1}H, 3-C*H*), 4.64 (dd; $J = 14.1$, 0.9 Hz; 1 ^{1}H, 4-CH*H*), 4.58 (dd; $J = 14.1$, 1.8 Hz; 1 ^{1}H, 4-C*H*H), 4.14 (q, $J = 7.2$ Hz, 2 ^{1}H, C*H*$_2$CH$_3$), 4.02 (d, $J = 11.1$ Hz, 1 ^{1}H, 6-CH*H*), 3.70 (s, 3 ^{1}H, OC*H*$_3$), 3.48 (bt, $J = 7.2$ Hz, 1 ^{1}H, 8a-C*H*), 3.15 (dd; $J = 8.7$, 6.6 Hz; 1 ^{1}H, 8-CH*H*), 2.82−2.73 (m, 2 ^{1}H, 2′-C*H*$_2$), 2.68 (t, $J = 6.1$ Hz, 2 ^{1}H, 3′-C*H*$_2$), 2.56 (d, $J = 11.1$ Hz, 1 ^{1}H, 6-C*H*H), 2.51 (dd; $J = 8.7$, 7.8 Hz; 1 ^{1}H, 8-C*H*H), 2.35 (s, 3 ^{1}H, NC*H*$_3$), 1.26 (t, $J = 7.2$ Hz, 3 ^{1}H, CH$_2$C*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), CDCl$_3$]: 174.2 (*C*ON), 173.7 (*C*O$_2$), 172.9 (4′-*C*O$_2$), 146.0 (8b-*C*), 142.7 (2-*C*), 112.3 (3a-*C*), 108.0 (3-*C*), 69.8 (5a-*C*), 68.2 (6-*C*), 60.7 (8-*C* + *C*H$_2$CH$_3$), 53.0 (O*C*H$_3$), 43.4 (4-*C*), 42.3 (8a-*C*), 41.6 (N*C*H$_3$), 29.9 (2′-*C*), 29.2 (3′-*C*), 14.3 (CH$_2$*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 2949, 2840, 2783, 1731, 1655, 1248, 746. MS [APCI (*m*/*z*)] calcd. for $(C_{18}H_{24}N_2O_6 + H)^+ = 365$, found 365.

Acknowledgment. We would like to thank Dr. Richard H. Blaauw and Chiralix B.V. (Nijmegen, The Netherlands) for the use of their parallel-synthesis facilities.

Supporting Information Available. Experimental copies of ^{1}H and ^{13}C NMR spectra for compounds **1**−**5**, **14a**, **14d**, **14f**, **15e**, **15h**, **16a**, **16g**, **17b**, and **17c** and ^{1}H spectra for compounds **14b**, **14g**, **15a**, **15b**, **15g**, **16b**, **16c**, **16h**, **17e**, and **17h**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036. (e) For reviews, see: (b) Tinsley, J. M. Pictet−Spengler Isoquinoline Synthesis. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Corey, E. J., Eds.; Wiley & Sons: Hoboken, NJ, 2005; pp 469−479. (c) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. (d) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151–190.

(2) (a) Cao, R.; Chen, Q.; Hou, X.; Chen, H.; Guan, H.; Ma, Y.; Peng, W.; Xu, A. *Bioorg. Med. Chem.* **2004**, *12*, 4613–4623. (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1309–1316. (c) Leonard, J.; Hague, A. B.; Jones, M. F. *Tetrahedron Lett.* **1997**, *38*, 3071–3074.

(3) (a) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866–867. (b) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425–6426.

(4) Yu, J.; Wearing, X. Z.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543–547.

(5) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.

(6) von Bohlen und Halbach, O.; Dermietzel, R. *Neurotransmitters and Neuromodulators: Handbook of Receptors and Biological Effects*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2006.

(7) (a) Campbell, L. M. *Int. J. Clin. Pract.* **2002**, *56*, 783–790. (b) Skidmore, I. F.; Lunts, L. H. C.; Finch, H.; Naylor, A. Phenethanolamin-Verbindungen, Verfahren zu Ihrer Herstellung und Diese Verbindungen Enthaltende Arzneimittel. German Patent DE 3414752, October 18, 1984;*Chem. Abstr.* **1985**, *102*, 95383.

(8) (a) Johnson, D. S.; Li, J. J. *The Art of Drug Synthesis*; Wiley-Interscience: New York, 2007. (b) Yardley, J. P.; Husbands, G. E. M.; Stack, G.; Butch, J.; Bisckler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H., III.; James, M. N. G.; Sieleck, A. R. *J. Med. Chem.* **1990**, *33*, 2899–2905. (c) Husbands, G. E. M.; Yardley, J. P.; Muth, E. A. 2-Phenyl-2-(1-hydroxycycloalkyl or 1-hydroxycycloalk-2-enyl)ethylamine Derivatives. U.S. Patent 4,535,186, August 13, 1985;*Chem. Abstr.* **1985**, *102*, 5895.

(9) Carlucci, D. R.; Aitken, M. IMS Intelligence.360, 2007. IMS Health Home Page. http://www.imshealth.com/ims/portal/front/articleC/0,2777,6266_41382706_81567488,00.html (accessed June 20, 2008).

(10) (a) Shulgin, A.; Shulgin, A. *Pihkal: A Chemical Love Story*; Transform Press: Berkeley, CA, 1991. (b) Shulgin, A.; Shulgin, A. *Tihkal: The Continuation*; Transform Press: Berkeley, CA, 1997.

(11) (a) O'Dell, D. K.; Rimmerman, N.; Pickens, S. R.; Walker, J. M. *Bioorg. Med. Chem.* **2007**, *15*, 6164–6169. (b) Gudmundsson, K. Carboline Derivatives and Their Use as Inhibitors of Flaviviridae Infections. Int. Patent WO 2007002051, January 4, 2007;*Chem. Abstr.* **2007**, *146*, 100663. (c) Collins, M. A. *Neurotoxicology* **2004**, *25*, 117–120. (d) Rolf, S.; Bruns, H.-J.; Wichter, T.; Kirchhof, P.; Ribbing, M.; Wasmer, K.; Paul, M.; Breithardt, G.; Haverkamp, W.; Eckardt, L. *Eur. Heart J.* **2003**, *24*, 1104–1112. (e) Peng, J.; Hu, J.-F.; Kazi, A. B.; Li, Z.; Avery, M.; Peraud, O.; Hill, R. T.; Franzblau, S. G.; Zhang, F.; Schinazi, R. F.; Wirtz, S. S.; Tharnish, P.; Kelly, M.; Wahyuono, S.; Hammann, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 13382–13386. (f) Kim, H.-J.; Soh, Y.; Jang, J.-H.; Lee, J.-S.; Oh, Y. J.; Surh, Y.-J. *Mol. Pharmacol.* **2001**, *60*, 440–449. (g) Nagatsu, T. *Neurosci. Res.* **1997**, *29*, 99–111. (h) Rohloff, J. C.; Dyson, N. H.; Gardner, J. O.; Alfredson, T. V.; Sparacino, M. L.; Robinson, J., III. *J. Org. Chem.* **1993**, *58*, 1935–1938. (i) Charifson, P. S. *Drugs Fut.* **1989**, *14*, 1179–1185. (j) Rinehart, K. L., Jr.; Kobayasi, J.; Harbour, G. C.; Hughes, R. G., Jr.; Mizak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524–1526. (k) Collins, M. A.; Nijm, W. P.; Borge, G. F.; Teas, G.; Goldfarb, C. *Science* **1979**, *206*, 1184–1186.

(12) (a) Unver, N. *Phytochem. Rev.* **2007**, *6*, 125–135. (b) Baxendale, I. R.; Ley, S. V. *Ind. Eng. Chem. Res.* **2005**, *44*, 8588–8592.

(13) Teller, S.; Eluwa, S.; Koller, M.; Uecker, A.; Beckers, T.; Baasner, S.; Böhmer, F.-D.; Mahboobi, S. *Eur. J. Med. Chem.* **2000**, *35*, 413–427.

(14) An, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311–3340.

(15) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(16) Blanco-Ania, D.; Hermkens, P. H. H.; Sliedregt, L. A. J. M.; Scheeren, H. W.; Rutjes, F. P. J. T. *Tetrahedron*, [Online early access]. DOI: 10.1016/j.tet.2009.04.059. Published online: April 24, 2009.

(17) (a) Jiang, W.; Guan, J.; Macielag, M. J.; Zhang, S.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; John, T. M.; Haynes-Johnson, D.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2005**, *48*, 2126–2133. (b) Daugan, A.; Grondin, P.; Ruault, C.; Le Monnier de Gouville, A.-C.; Coste, H.; Linget, J. M.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. *J. Med. Chem.* **2003**, *46*, 4533–4542. (c) Rousseau, J.-F.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 2731–2737. (d) Plate, R.; van Hout, R. H. M.; Behm, H.; Ottemheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 555–560.

(18) For reactions in the 3-position of furans with *N*-acyliminium ions, see: (a) Rose, M. D.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *J. Org. Chem.* **2007**, *72*, 538–549. (b) Nielsen, T. E.; Meldal, M. *J. Org. Chem.* **2004**, *69*, 3765–3773.

(19) For an example in the 3-position of a benzo[*b*]furan, see: (a) Van der Mey, M.; Windhorst, A. D.; Klok, R. P.; Herscheid, J. D. M.; Kennis, L. E.; Bischoff, F.; Bakker, M.; Langlois,

X.; Heylen, L.; Jurzak, M.; Leysen, J. E. *Bioorg. Med. Chem.* **2006**, *14*, 4526–4534.
(20) For examples of cyclization in the 4-position of an indole, see: (a) Somei, M.; Teranishi, S.; Yamada, K.; Yamada, F. *Chem. Pharm. Bull.* **2001**, *49*, 1159–1165. (b) Nakatsuka, S.; Miyazaki, H.; Goto, T. *Chem. Lett.* **1981**, 407–410.
(21) For an example of cyclization in the 2-position, see: (a) Kametani, T.; Fukumoto, K.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Wakisaka, K. *J. Chem. Soc. C* **1971**, 1805.
(22) (a) Dardennes, E.; Kovács-Kulyassa, Á.; Boisbrun, M.; Petermann, C.; Laronze, J.-Y.; Sapi, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1329–1339. (b) Boisbrun, M.; Jeannin, L.; Toupet, L.; Laronze, J.-Y. *Eur. J. Org. Chem.* **2000**, 3051–3057.
(23) (a) Kim, S.; Ko, H.; Kim, S.; Lee, T. *J. Comb. Chem.* **2002**, *4*, 549–551. (b) Nikam, S. S.; Kornberg, B. E.; Ault-Justus, S. E.; Rafferty, M. F. *Tetrahedron Lett.* **1998**, *39*, 1121–1124.
(24) Biotage Home Page. http://www.biotage.com/DynPage.aspx?id=23908#SCX2 (accessed Nov 13, 2008).

CC800191W