Facile Synthesis of Fluorinated Benzofuro- and Benzothieno[2,3-*b*]pyridines, α-Carbolines and Nucleosides Containing the α-Carboline Framework

Viktor O. Iaroshenko,*[a,b] Yan Wang,[c] Biao Zhang,[c] Dmitriy Volochnyuk,[d] Vyacheslav Ya. Sosnovskikh[e]

[a] Enamine Ltd., 23 A. Matrosova st., 01103 Kyiv, Ukraine
Fax +380(44)5373253; E-mail: yaroshenko@enamine.net

[b] National Taras Shevchenko University, 62 Volodymyrska st., 01033 Kiev 33, Ukraine

[c] Fachbereich Chemie, Universität Konstanz, Fach M-720, Universitätsstr. 10, 78457 Konstanz, Germany

[d] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska 5, 02094 Kiev 94, Ukraine

[e] Department of Chemistry, Ural State University, 51 Lenina Ave., 620083 Ekaterinburg, Russian Federation

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Dedicated to Professor Volodymir Kovtunenko on the occasion of his 60th birthday

Abstract: Fluorinated benzofuro[2,3-*b*]pyridines, benzothieno[2,3-*b*]pyridines and 9*H*-pyrido[2,3-*b*]indoles (α-carbolines) were synthesized via regiospecific pyridine core annulation of a number of fluoro-containing 1,3-CCC-dielectrophiles to benzofuran-2-amine, benzothiophen-2-amine and 1*H*-indol-2-amine. Based on the 2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole thus synthesized, the preparative approach towards a set of nucleosides and nucleoside mimetics bearing the α-carboline framework was elaborated.

Key words: pyridines, fluorine, annulation, functionalization, α-carbolines, nucleosides

Continuing our research on the functionalization of electron-rich aminoheterocycles,[1] with the purpose of synthesizing a set of diverse α-carbolines and benzofuro- and benzothieno[2,3-*b*]pyridines, the reaction of 1*H*-indol-2-amine, benzofuran-2-amine and benzothiophen-2-amine with a number of 1,3-CCC-dielectrophiles **1**–**7** (Figure 1) was investigated in detail. Benzofuran-2-amine and benzothiophen-2-amine are not stable; thus, they were not isolated, neither in the pure form nor as a salt. In contrast, 1*H*-indol-2-amine is a stable and commercially available reagent, which was used in the present study.

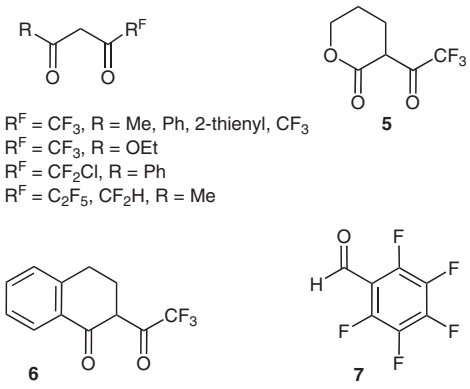

Figure 1 Variety of 1,3-CCC-dielectrophiles used for pyridine ring annulation

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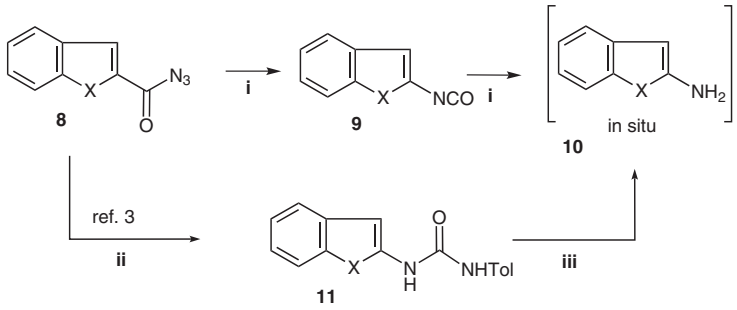
Our previous experience[2] indicated that the optimal preparative method leading to amines **10** (X = O, S) via generation in situ is based upon the Curtius rearrangement of the commercially available acyl azides **8** to isocyanates **9** (Scheme 1). The latter, after hydrolysis, form amines **10**. Very recently,[2] we have conducted this reaction as a two-step, two-pot process. Herein, we report a simplified one-pot, two-step method starting directly from azides **8**. It was found that the formation of **10** can proceed directly from **8** in acetic acid under intense reflux. Another approach to generate **10** in situ starts from ureas **11**, prepared from the corresponding acyl azides **8** and anilines in boiling toluene,[3] by prolonged reflux in a mixture of acetic acid, acetic anhydride and *N*,*N*-dimethylformamide in the presence of the electrophile.

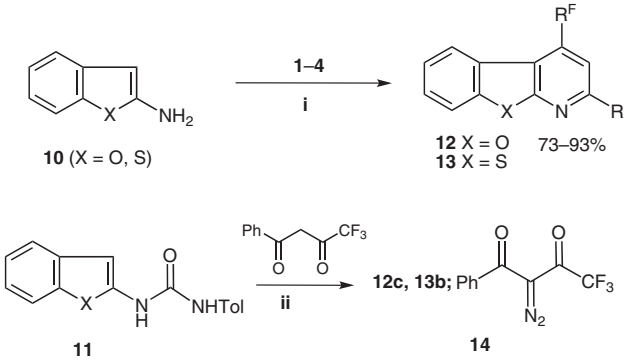
Benzofuran-2-amine and benzothiophen-2-amine (**10**, X = O, S), generated in situ according to the previously mentioned procedure, react with a number of 1,3-CCC-dielectrophiles **1**–**4** (Scheme 2). The reaction proceeds regiospecifically to form a set of fluorinated benzofuro[2,3-*b*]pyridines **12** and [1]benzothieno[2,3-*b*]pyridines **13** bearing an electron-withdrawing substituent at the γ-position of the annulated pyridine core (Table 1). During a study of the reaction mixture by HPLC and ^{19}F NMR spectroscopy, insertion of the diazo group into the starting dielectrophile compound was revealed in the case of fast addition of azide **8**. Thus, side products of type **14** were detected in the ^{19}F NMR spectra of the reaction mixture, as well as traces of initial acids as products of acyl azide **8** hydrolysis, which were observed by HPLC.

Reaction of 1*H*-indol-2-amine (**15**) with dielectrophiles **1**–**4** in boiling acetic acid delivers 9*H*-pyrido[2,3-*b*]indoles **16** with an unsubstituted 9-position. Methylation of the 9*H*-pyrido[2,3-*b*]indoles **16** with iodomethane readily occurs at the 9-position of the carboline core. This reaction proceeds smoothly in anhydrous dimethyl sulfoxide at room temperature with 7 equivalents of potassium hydroxide and leads to the formation of the methylated products **17** in excellent yields (Scheme 3, Table 1).

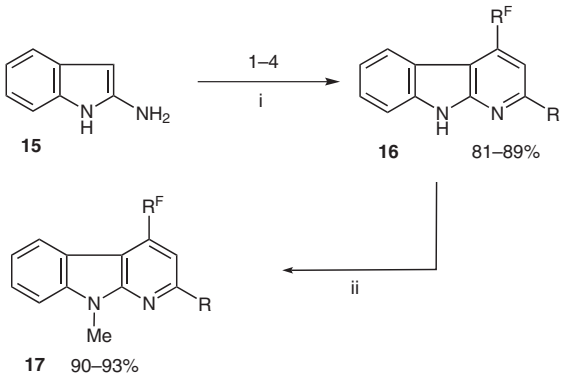
The cyclic dicarbonyl compounds **6** and **5** were no exception to the general rule. Thus, they are suitable for pyri-



Scheme 1 *Reagents and conditions*: i: AcOH, DMF, reflux; ii: $ArNH_2$, toluene, reflux; iii: AcOH–Ac_2O–DMF (1:1:1), intense reflux.



Scheme 2 *Reagents and conditions*: i: AcOH, DMF, reflux, 2–3 h; ii: AcOH–Ac_2O–DMF (1:1:1), intense reflux.



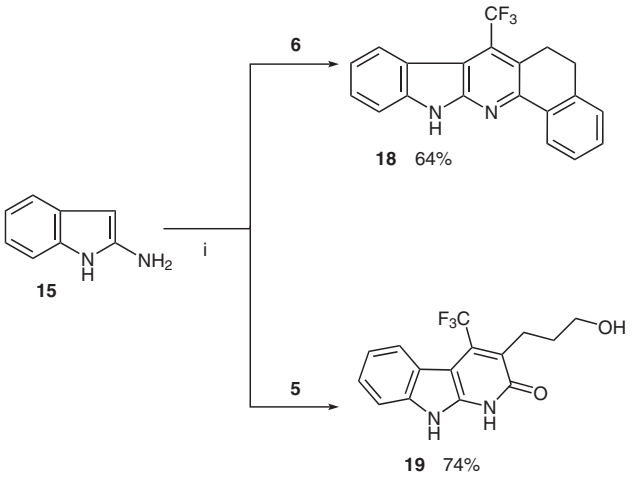
Scheme 3 *Reagents and conditions*: i: AcOH, reflux, 2 h; ii: MeI (3 equiv), KOH (7 equiv), DMSO, r.t., 30 min, then 80 °C, 1.5 h.

dine ring annulation, which led to the formation of polycyclic carboline **18** and 3-(3-hydroxypropyl)-4-(trifluoromethyl)-1,9-dihydro-2*H*-pyrido[2,3-*b*]indol-2-one (**19**) (Scheme 4). However, it should be noted that in this case a number of side products were detected during examination of the reaction mixture by ^{19}F NMR spectroscopy. Attempts to isolate these side products failed. α-Carbolines **16**–**19** can easily be purified by flash chromatography or by recrystallization from an appropriate solvent.

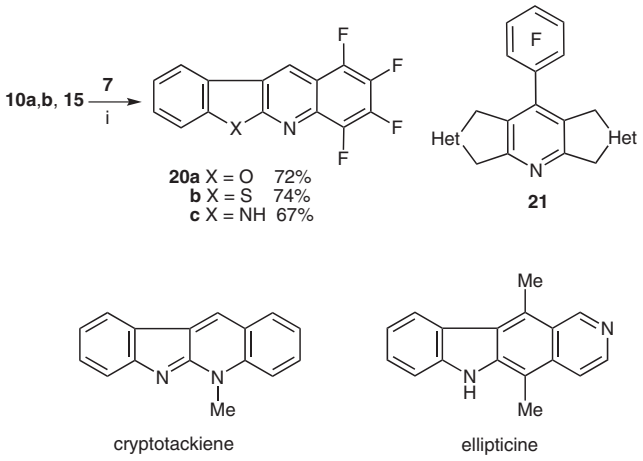
The discovery of the alkaloids ellipticine and cryptotackiene, two naturally occurring pyridine analogues (Scheme 5), has led to an intensification of the synthesis and biological evaluation of similar polyheteroaromatic systems. Now, their derivatives are well known for their antitumour activity.[4]

Previously, pentafluorobenzaldehyde (**7**) was known as a 1,3-CCC-dielectrophile used for constructing heteroannulated tetrafluoroquinolines.[5] Aldehyde **7** reacts under harsh conditions (AcOH, DMF, 135–145 °C) with aminoheterocycles **10** and **15** affording the annulated tetrafluoroquinolines **20**. The latter can be considered as fluoro-containing isosteres of ellipticine and cryptotackiene. Measurement of the ^{13}C NMR spectra of quinolines **20** was unsuccessful due to low solubility in organic solvents such as dimethyl sulfoxide and *N*,*N*-dimethylformamide. When the reaction mixture was analyzed by means of HPLC with mass detection, it was found that the reaction proceeds in two different directions: one is via cycloaddition by a CCN + CCC path to form the major products **20**, the other is by a CCN + C + CC path to deliver **21** as side products in small amounts (Scheme 5). We have not isolated any of these side products, but they were detected and clearly observed by HPLC. We have started attempts to develop synthetic methods towards compounds of type **21**.

The structure of the fluorine-containing condensed pyridines was proven by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. For the determination of the position of the polyfluoroalkyl group, 2D NMR methods including ROESY measurements[2] were applied to model compounds **12g**, **13d** and **16d**.



Scheme 4 *Reagents and conditions*: i: AcOH, reflux, 2 h.



Scheme 5 *Reagents and conditions*: i: AcOH, DMF, reflux, 2–3 h.

The structure of compound **13d** was unambiguously confirmed by a single crystal X-ray analysis (Figure 2) at 153 K. This compound crystallized in a monoclinic *C2/c* space group. An asymmetric unit consists of one molecule of **13d**, which multiplies in eight molecules per unit cell. The heterocyclic system is completely planar. The crystal packing of this compound is based on compact impalement of 2D layers of **13d**.

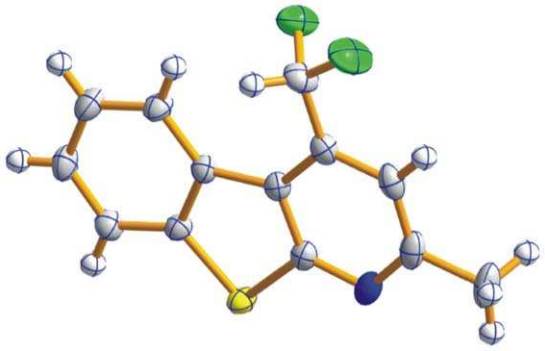
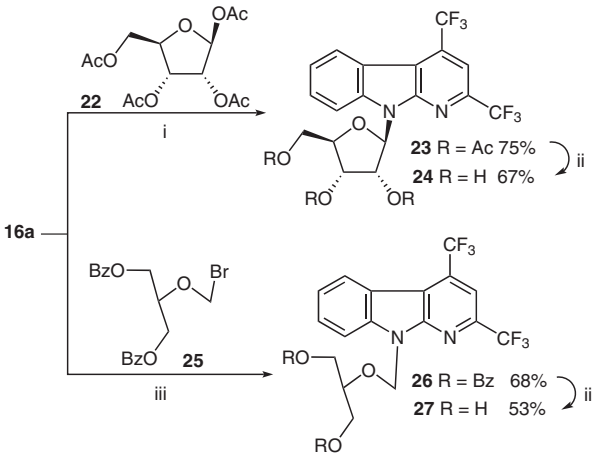


Figure 2 Molecular structure of compound **13d**

Nucleoside mimetics[6] have attracted attention due to the discovery of some antiviral and antineoplastic agents among them. Well-known acyclovir,[7] an anti-inflammatory agent, also contains a sugar-mimicking group. In nature, the 'salvage' nucleoside synthesis pathway[8] is an important route for purine and pyrimidine nucleotide synthesis. It shares the common approach of catalyzing the addition of nucleobases to anomerically activated ribose. A modification of this biosynthesis can be a potent tool for assembling diverse fluorinated nucleosides.

Nucleosides containing an α-carboline group are rare in the literature; however, the known representatives, such as rebeccamycin analogues containing one azaindole unit, have been described as potent antiproliferative[9] and antitumour[10] agents and kinase inhibitors.[11]

In the course of the synthesis of acyclic and carbocyclic nucleoside analogues containing a fluorinated α-carboline framework, starting from building blocks **22**, **25**, **28**–**32**, and carboline **16a**, a method incorporating the corresponding sugar (sugar analogues) was developed. For the synthesis of carbocyclic nucleoside analogues, we used the known N-glycosylation procedure. For the synthesis of riboside **23**, the silyl-Hilbert–Johnson reaction[12] was used. This reaction takes place in dichloromethane with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and trimethylsilyl triflate as a catalyst. The subsequent acetyl moiety cleavage with ammonia gave compound **24** in 67% yield (Scheme 6).



Scheme 6 *Reagents and conditions*: i: BSA, TMSOTf; ii: NH_3, MeOH, r.t., 12 h; iii: NaH, MeCN.

Carboline **26** bearing an acyclic sugar mimetic was synthesized by the direct base-catalyzed alkylation of **16a** with halide **25** in the same way as described previously.[13] Deprotection of the product **26** to diol **27** was conducted with ammonia in methanol (Scheme 6).[13]

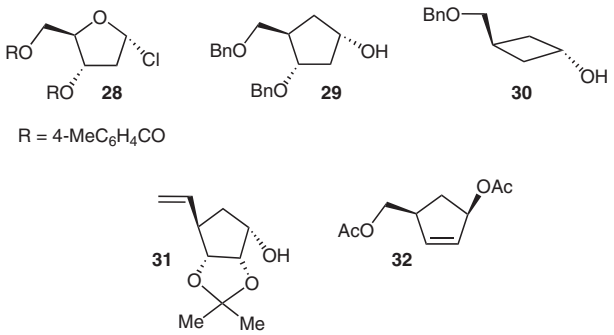


Figure 3 Variety of compounds used for deoxyriboside and carbocyclic sugar synthesis

1-Chloro-3,5-di-*O*-*p*-toluoyl-2-deoxy-α-D-*erythro*-pentofuranose (**28**) (Figure 3) reacts smoothly with carboline **16a** under basic conditions (NaH in MeCN)[13] to deliver deoxyriboside **35**. Cleavage of the protecting groups was carried out with ammonia in methanol, giving the 2-deoxy-α-D-*erythro*-pentofuranose **36** in 83% yield.

Concerning the synthesis of the carbocyclic nucleosides **34** and **37**–**41** (Scheme 7), direct coupling of the hetero-

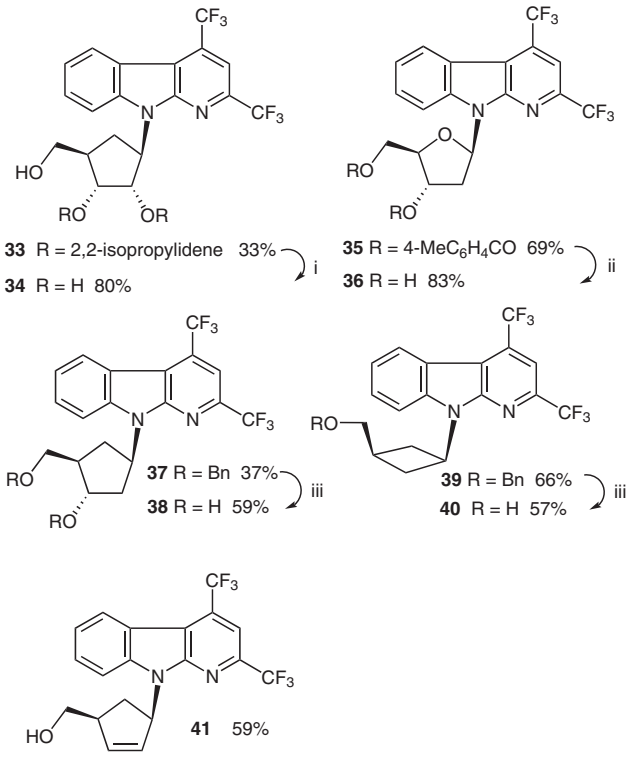
base **16a** with the corresponding carbocyclic pseudo sugar (Figure 3) was applied.

The Mitsunobu coupling reaction was recently used for the synthesis of many carbocyclic nucleosides.[14] We have used this method for the synthesis of compounds **34**, **38** and **40**. Attachment of **31** to carboline **16a** was carried out according to the previously described procedure used for the synthesis of carbocyclic AdoazaMet.[14a] After attachment of the pseudo sugar group, oxidation of the double bond was performed with sodium periodate and osmium tetroxide in methanol–water, and reduction of the formed aldehyde was carried out with sodium borohydride in methanol. Deprotection of compound **33** was performed in trifluoroacetic acid–water according to the procedure described by us previously.[1d] Thus, the synthesis of **34** was performed from **16a** and **31** as a one-pot, three-step procedure, without isolation of the intermediate products.

For the synthesis of **37**, enantiomerically pure (1*S*,3*S*,4*R*)-3-benzyloxy-4-(benzyloxymethyl)cyclopentanol (**29**), a precursor for carbocyclic 2-deoxynucleoside analogues, was condensed to carboline **16a** in acetonitrile according to a slightly modified Mitsunobu protocol.[15] The resultant β-isomer **37** was easily deprotected in one step by hydrogenolysis in ethanol, leading to **38**.

Palladium-catalyzed allylation of a heterobase possessing a free NH position is one of the highly useful strategies for assembling carbocyclic nucleosides.[16] We have successfully used this method for the synthesis of carbocyclic nucleoside **41** from carboline **16a** and *cis*-diacetate **32**.

In conclusion, a convenient synthetic approach to fluorinated benzofuro[2,3-*b*]pyridines, benzothieno[2,3-*b*]pyridines and α-carbolines based on cycloaddition of fluorine-containing 1,3-CCC-dielectrophiles to the corresponding aminoheterocyclic moiety was developed. Also, 2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (**16a**) was coupled with a number of sugars, and carbocyclic and acyclic sugar analogues, to give a set of diverse nucleosides and nucleoside mimetics. Simple synthetic and purification procedures and high yields of the target compounds enable the synthesis of functionally diverse α-carbolines, which are interesting objects for medicinal chemistry and drug discovery.



Scheme 7 *Reagents and conditions*: i: TFA–H_2O (9:1), 45 min; ii: NH_3, MeOH, r.t., 12 h; iii: H_2, 10% Pd/C, EtOH, r.t., 2–3 h.

Table 1 Yields,[a] Melting Points,[b] and ^1H and ^{19}F NMR Data of Compounds **12**, **13**, **16** and **17**[c]

Compound	R	R_F	Yield (%)	Mp (°C)	^1H NMR data δ (ppm)	^{19}F NMR data δ (ppm)
12a	CF_3	CF_3	89	71–73	($CDCl_3$): 7.45 (td, *J* = 8.0, 1.4 Hz, 1 H), 7.62–7.68 (m, 2 H), 7.90 (s, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H)	($CDCl_3$): –65.0, –68.3
12b	Me	CF_3	90	115–117	(DMSO-d_6): 2.68 (s, 3 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.66 (t, *J* = 8.0 Hz, 1 H), 7.73 (s, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H)	(DMSO-d_6): –63.5
12c	Ph	CF_3	88	131–132	(CF_3CO_2D): 7.09 (s, 1 H), 7.42–7.63 (m, 5 H), 7.86–7.99 (m, 3 H), 8.20 (d, *J* = 7.8 Hz, 1 H)	(DMSO-d_6): –63.2
12d	2-thienyl	CF_3	93	177–179	(DMSO-d_6): 7.23 (br s, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.65 (t, *J* = 7.8 Hz, 1 H), 7.76–7.82 (m, 2 H), 7.79 (d, *J* = 3.2 Hz, 1 H), 8.10 (s, 1 H), 8.22 (s, 1 H)	(DMSO-d_6): –63.7
12e	OH	CF_3	79	174–175	(DMSO-d_6): 7.05 (s, 1 H), 7.45 (t, *J* = 7.8 Hz, 1 H), 7.54 (t, *J* = 7.8 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 12.70 (br s, 1 H)	(DMSO-d_6): –64.0

Table 1 Yields,[a] Melting Points,[b] and ^{1}H and ^{19}F NMR Data of Compounds **12**, **13**, **16** and **17**[c] (continued)

Compound	R	R_F	Yield (%)	Mp (°C)	^{1}H NMR data δ (ppm)	^{19}F NMR data δ (ppm)
12f	Ph	CF_2Cl	79	119–120	(DMSO-d_6): 7.52–7.55 (m, 4 H), 7.68 (d, J = 7.8 Hz, 1 H), 7.83 (d, J = 7.8 Hz, 1 H), 8.17 (d, J = 7.8 Hz, 1 H), 8.19 (s, 1 H), 8.30 (d, J = 7.8 Hz, 2 H)	
12g	Me	CF_2H	85	112–113	($CDCl_3$): 2.72 (s, 3 H), 7.04 (t, $^2J_{HF}$ = 56 Hz, 1 H), 7.31 (s, 1 H), 7.39 (t, J = 8.0 Hz, 1 H), 7.53 (t, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 8.01 (d, J = 8.0 Hz, 1 H)	
13a	CF_3	CF_3	80	111–112	($CDCl_3$): 7.33 (t, J = 7.8 Hz, 1 H), 7.49 (t, J = 7.8 Hz, 1 H), 7.55 (d, J = 7.8 Hz, 1 H), 7.81 (s, 1 H), 8.21 (d, J = 7.8 Hz, 1 H)	
13b	Ph	CF_3	83	178–179	(DMSO-d_6): 7.30 (s, 1 H), 7.51–7.58 (m, 3 H), 7.61–7.67 (m, 3 H), 8.18 (dd, J = 7.8, 1.4 Hz, 1 H), 8.26 (dd, J = 7.8, 1.4 Hz, 1 H), 8.30 (d, J = 7.8 Hz, 1 H)	(DMSO-d_6): –63.1
13c	OH	CF_3	73	257–258	(DMSO-d_6): 7.08 (s, 1 H), 7.42–7.59 (m, 3 H), 8.08 (m, 1 H), 12.60 (br s, 1 H)	(DMSO-d_6): –62.4
13d	Me	CF_2H	90	112–114	($CDCl_3$): 2.70 (s, 3 H), 7.02 (t, $^2J_{HF}$ = 56 Hz, 1 H), 7.37 (s, 1 H), 7.39 (t, J = 7.8 Hz, 1 H), 7.54 (t, J = 7.8 Hz, 1 H), 7.60 (d, J = 7.8 Hz, 1 H), 8.07 (d, J = 7.8 Hz, 1 H)	(DMSO-d_6): –115.3 (d, $^2J_{FH}$ = 56 Hz)
16a	CF_3	CF_3	86	211–213	(DMSO-d_6): 7.37 (m, 2 H), 7.71 (d, J = 7.2 Hz, 1 H), 7.94 (s, 1 H), 8.21 (d, J = 7.2 Hz, 1 H), 13.00 (s, 1 H)	(DMSO-d_6): –63.3, –65.3
16b	Me	CF_3	84	283	(DMSO-d_6): 2.70 (s, 3 H), 7.30 (d, J = 7.2 Hz, 1 H), 7.43 (s, 1 H), 7.59 (m, 2 H), 8.07 (d, J = 7.2 Hz, 1 H), 12.3 (s, 1 H)	(DMSO-d_6): –63.2
16c	Ph	CF_3	89	287–290	(DMSO-d_6): 7.33 (t, J = 7.8 Hz, 1 H), 7.44–7.57 (m, 4 H), 7.78 (t, J = 7.8 Hz, 1 H), 8.00 (s, 1 H), 8.11 (d, J = 7.8 Hz, 2 H), 8.28 (d, J = 7.8 Hz, 1 H), 12.19 (s, 1 H)	
16d	Me	CF_2H	81	259	(DMSO-d_6): 2.68 (s, 3 H), 7.25 (m, 2 H), 7.46 (t, J = 7.8 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.64 (t, $^2J_{HF}$ = 56 Hz, 1 H), 8.09 (d, J = 7.8 Hz, 1 H), 12.01 (s, 1 H)	(DMSO-d_6): –115.7 (d, $^2J_{FH}$ = 56 Hz)
16e	Ph	CF_2Cl	85	271	(DMSO-d_6): 7.41 (t, J = 7.8 Hz, 1 H), 7.52–7.62 (m, 4 H), 7.70 (d, J = 7.8 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 8.02 (s, 1 H), 8.23 (d, J = 7.8 Hz, 1 H), 8.33 (d, J = 7.8 Hz, 1 H), 12.01 (s, 1 H)	(DMSO-d_6): –51.7
16f	Me	C_2F_5	87	222–224	(DMSO-d_6): 2.73 (s, 3 H), 7.35 (t, J = 7.2 Hz, 1 H), 7.58 (s, 1 H), 7.65 (m, 2 H), 8.15 (d, J = 7.2 Hz, 1 H), 12.07 (s, 1 H)	
17a	CF_3	CF_3	90	188–190	(DMSO-d_6): 3.95 (s, 3 H), 7.36 (t, J = 7.8 Hz, 1 H), 7.49 (t, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.97 (s, 1 H), 8.09 (d, J = 7.8 Hz, 1 H)	
17b	Ph	CF_3	90	108	(CF_3CO_2D): 4.05 (s, 3 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.55–7.76 (m, 5 H), 7.79 (d, J = 7.2 Hz, 1 H), 8.02 (s, 1 H), 8.15 (d, J = 7.2 Hz, 1 H), 8.34 (d, J = 7.2 Hz, 1 H)	
17c	Me	CF_2H	93	217	(DMSO-d_6): 2.69 (s, 3 H), 3.26 (s, 3 H), 7.25 (m, 2 H), 7.60–7.70 (m, 3 H), 8.14 (d, J = 7.8 Hz, 1 H)	(DMSO-d_6): –115.6 (d, $^2J_{FH}$ = 56 Hz)

[a] Yields refer to pure isolated product.
[b] Melting points are uncorrected.
[c] Satisfactory microanalyses obtained: C ± 0.33; H ± 0.45; N ± 0.25.

All solvents were purified and dried by standard methods. NMR spectra were recorded on Jeol JNM-LA 400, Varian VXR-300 or Varian Mercury-400 spectrometers. ^{1}H and ^{13}C NMR spectra (300 and 100 MHz, respectively) were recorded using TMS as an internal standard, and ^{19}F NMR spectra (282 MHz) with $CFCl_3$ as an internal standard. Mass spectra were obtained on a Hewlett-Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on an MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60F254 plates were used for TLC. Tetra-O-acetylated ribofuranose **22** is a commercially available reagent. Precursors **25**,[17] **28**,[18] **29**[19] and **30**[20] were synthesized according to previously described procedures. Compound **31** was obtained from D-ribose following a multistep sequence.[21] *cis*-3-Acetoxy-5-(acetoxymethyl)cyclopentene (**32**) is available in two steps[22] from *rel*-(1*R*,4*S*,6*R*)-6-bromo-2-oxabicyclo[2.2.1]heptan-3-one.

X-ray Crystallography of 13d

$C_{13}H_9F_2NS$, $M = 249.27$, monoclinic, $a = 18.056(8)$ Å, $b = 13.388(9)$ Å, $c = 11.900(6)$ Å, $\beta = 129.53(6)°$, $V = 2219(2)$ Å^3, pale yellow cuboid with size $0.8 \times 0.6 \times 0.4$ mm. Crystallographic measurements were performed on a CAD4 Enraf-Nonius diffractometer operating in the ω-2θ-scan mode (scanning rate ratio ω/2θ = 1.2), $11.197 \le \theta \le 13.976$, $T = 153$ K. The structure was solved with direct methods using the SHELXS-97 program and refined with the full-matrix least-squares method on F^2 using the SHELXL-97 program. Space group $C2/c$, $Z = 8$, $D_c = 1.493$ g·cm^{-3}, μ(Mo Kα) = 0.292 mm^{-1}, $F(000) = 1024$, 4474 reflections measured, 2179 unique ($R_{int} = 0.0428$), which were used in all calculations. The final $wR(F^2)$ was 0.0925 (all data).

Crystallographic data for the structure **13d** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 713529 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

Benzofuro[2,3-*b*]pyridines 12, 20a and [1]Benzothieno[2,3-*b*]pyridines 13, 20b; General Procedure

To a boiling soln of AcOH (300 mL) and H_2O (10 mL; temperature in the oil bath was ca. 145 °C), a mixture of the dielectrophile (5 mmol) and the acyl azide (12.5 mmol) in anhyd DMF (50 mL) was added dropwise through the condenser. After the addition was completed, the mixture was refluxed for a further 3 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel or was recrystallized from an appropriate solvent.

2,4-Bis(trifluoromethyl)benzofuro[2,3-*b*]pyridine (12a)

Yield: 1.36 g (89%); colourless solid; $R_f = 0.75$ (EtOAc–hexane, 1:2).

^{13}C NMR ($CDCl_3$): δ = 111.8, 112.5, 117.0 (q, $J_{CF} = 1.6$ Hz), 118.8, 120.7 (q, $^1J_{CF} = 275$ Hz), 122.2 (q, $^1J_{CF} = 275$ Hz), 124.4 (q, $J_{CF} = 4.0$ Hz), 124.8, 131.3, 133.0 (q, $^2J_{CF} = 35$ Hz), 144.6 (q, $^2J_{CF} = 35$ Hz), 156.1, 162.8.

MS: *m*/*z* (%) = 306 (15) [M$^+$ + 1], 305 (100) [M$^+$].

2-Methyl-4-(trifluoromethyl)benzofuro[2,3-*b*]pyridine (12b)

Yield: 1.08 g (90%); colourless solid; $R_f = 0.65$ (EtOAc–hexane, 1:2).

^{13}C NMR (DMSO-d_6): δ = 24.4, 109.8, 112.7, 115.5, 119.7, 123.4, 123.7 ($^1J_{CF} = 275$ Hz), 124.7, 126.7, 129.9 ($^2J_{CF} = 35$ Hz), 154.5, 158.1, 163.1.

MS: *m*/*z* (%) = 252 (14) [M$^+$ + 1], 251 (100) [M$^+$], 210 (37), 182 (41) [M$^+$ – CF_3].

2-Phenyl-4-(trifluoromethyl)benzofuro[2,3-*b*]pyridine (12c)

Yield: 1.38 g (88%); colourless solid; $R_f = 0.55$ (EtOAc–hexane, 1:2).

^{13}C NMR (DMSO-d_6): δ = 109.5, 112.1, 115.6, 119.5, 123.3, 123.7 ($^1J_{CF} = 275$ Hz), 124.8, 126.3, 126.5, 126.9, 129.8 ($^2J_{CF} = 35$ Hz), 133.3, 134.7, 154.4, 158.2, 163.4.

MS: *m*/*z* (%) = 314 (20) [M$^+$ + 1], 313 (100) [M$^+$], 263 (18), 261 (53), 236 (11), 77 (35).

2-(2-Thienyl)-4-(trifluoromethyl)benzofuro[2,3-*b*]pyridine (12d)

Yield: 1.48 g (93%); colourless solid; $R_f = 0.4$ (EtOAc–hexane, 1:2).

^{13}C NMR (DMSO-d_6): δ = 110.1, 112.8, 115.0, 119.0, 122.2, 123.3, 123.9 ($^1J_{CF} = 275$ Hz), 124.3, 127.0, 128.7, 130.0 ($^2J_{CF} = 35$ Hz), 130.7, 145.2, 154.2, 158.2, 163.0.

MS: *m*/*z* (%) = 320 (17) [M$^+$ + 1], 319 (100) [M$^+$].

4-(Trifluoromethyl)benzofuro[2,3-*b*]pyridin-2(1*H*)-one (12e)

Yield: 0.99 g (79%); colourless solid; $R_f = 0.75$ (EtOAc–hexane, 1:1).

^{13}C NMR (DMSO-d_6): δ = 102.6, 112.1, 118.7 ($^1J_{CF} = 275$ Hz), 121.2, 121.3, 124.2, 124.3, 127.6, 133.2 ($^2J_{CF} = 35$ Hz), 153.2, 162.5, 163.4.

MS: *m*/*z* (%) = 254 (11) [M$^+$ + 1], 253 (100) [M$^+$], 201 (29), 183 (81) [M$^+$ – 1 – CF_3], 133 (10).

4-(Chlorodifluoromethyl)-2-phenylbenzofuro[2,3-*b*]pyridine (12f)

Yield: 1.30 g (79%); colourless solid; $R_f = 0.6$ (EtOAc–hexane, 1:2).

^{13}C NMR (DMSO-d_6): δ = 110.7, 110.9 (t, $J_{CF} = 5.0$ Hz), 112.2, 119.9, 124.5 (t, $J_{CF} = 3.8$ Hz), 124.8, 124.9 ($^1J_{CF} = 289$ Hz), 127.6, 129.4, 130.2, 130.5, 137.3, 138.5 ($^2J_{CF} = 27$ Hz), 155.1, 155.2, 163.8.

MS: *m*/*z* (%) = 331 (33) [M$^+$ + 2], 330 (22) [M$^+$ + 1], 329 (100) [M$^+$], 295 (20), 294 (87), 245 (10) [M$^+$ + 1 – CF_2Cl], 146 (17).

4-(Difluoromethyl)-2-methylbenzofuro[2,3-*b*]pyridine (12g)

Yield: 0.99 g (85%); colourless solid; $R_f = 0.5$ (EtOAc–hexane, 1:2).

^{13}C NMR ($CDCl_3$): δ = 24.5, 110.8, 112.4 ($^1J_{CF} = 240$ Hz), 113.1, 115.5, 120.9, 123.4, 124.3, 128.6, 136.8 ($^2J_{CF} = 26$ Hz), 154.6, 157.0, 163.4.

MS: *m*/*z* (%) = 234 (15) [M$^+$ + 1], 233 (100) [M$^+$], 182 (16) [M$^+$ – CF_2H].

7,8,9,10-Tetrafluorobenzofuro[2,3-*b*]quinoline (20a)

Yield: 1.05 g (72%); colourless solid; mp 235–237 °C (*i*-PrOH).

^{1}H NMR (DMSO-d_6): δ = 7.55 (t, $J = 8.0$ Hz, 1 H), 7.74 (t, $J = 8.0$ Hz, 1 H), 7.81 (d, $J = 8.0$ Hz, 1 H), 8.40 (d, $J = 8.0$ Hz, 1 H), 9.35 (s, 1 H).

MS: *m*/*z* (%) = 292 (17) [M$^+$ + 1], 291 (100) [M$^+$], 262 (10), 145 (10).

2,4-Bis(trifluoromethyl)[1]benzothieno[2,3-*b*]pyridine (13a)

Yield: 1.28 g (80%); colourless solid; $R_f = 0.55$ (EtOAc–hexane, 1:3).

^{13}C NMR ($CDCl_3$): δ = 112.8, 121.1 (q, $^1J_{CF} = 275$ Hz), 122.7 (q, $^1J_{CF} = 275$ Hz), 123.2, 126.0, 127.0 (q, $J_{CF} = 6.4$ Hz), 127.7, 129.2, 129.6, 133.0 (q, $^2J_{CF} = 35$ Hz), 140.1, 145.9 (q, $^2J_{CF} = 35$ Hz), 164.1.

MS: *m*/*z* (%) = 322 (15) [M$^+$ + 1], 321 (100) [M$^+$], 271 (12), 232 (13).

2-Phenyl-4-(trifluoromethyl)[1]benzothieno[2,3-*b*]pyridine (13b)

Yield: 1.37 g (83%); colourless solid; $R_f = 0.70$ (EtOAc–hexane, 1:2).

^{13}C NMR (DMSO-d_6): δ = 112.1, 121.1 (q, $^1J_{CF} = 275$ Hz), 123.2, 126.2, 126.5, 126.7, 127.0, 127.6, 129.0, 129.5, 130.7, 133.2 (q, $^2J_{CF} = 35$ Hz), 135.1, 139.7, 144.1, 164.9.

MS: *m*/*z* (%) = 330 (27) [M$^+$ + 1], 329 (100) [M$^+$], 260 (16) [M$^+$ – CF_3], 259 (13).

4-(Trifluoromethyl)[1]benzothieno[2,3-*b*]pyridin-2(1*H*)-one (13c)

Yield: 0.98 g (73%); colourless solid; $R_f = 0.45$ (EtOAc–hexane, 1:1).

^{13}C NMR (DMSO-d_6): δ = 113.1, 116.6, 119.4, 121.1, 122.0 (q, $^1J_{CF}$ = 275 Hz), 125.6, 125.9, 133.7 (q, $^2J_{CF}$ = 35 Hz), 135.5, 138.9, 150.3, 163.7.

MS: *m*/*z* (%) = 270 (15) [M$^+$ + 1], 269 (100) [M$^+$], 241 (51), 172 (15), 145 (13).

4-(Difluoromethyl)-2-methyl[1]benzothieno[2,3-*b*]pyridine (13d)
Yield: 1.12 g (90%); colourless solid; R_f = 0.55 (EtOAc–hexane, 1:2).

^{13}C NMR ($CDCl_3$): δ = 24.6, 112.4 (t, $^1J_{CF}$ = 240 Hz), 116.1 (t, $^3J_{CF}$ = 8.0 Hz), 123.3, 123.5 (t, J_{CF} = 4.1 Hz), 125.2 (t, J_{CF} = 4.1 Hz), 125.5, 127.5, 131.4, 136.8 (t, $^2J_{CF}$ = 26 Hz), 138.2, 157.0, 162.8.

MS: *m*/*z* (%) = 250 (13) [M$^+$ + 1], 249 (100) [M$^+$].

7,8,9,10-Tetrafluoro[1]benzothieno[2,3-*b*]quinoline (20b)
Yield: 1.14 g (74%); colourless solid; mp 243–245 °C (*i*-PrOH).

^{1}H NMR (100 °C, DMSO-d_6): δ = 7.60 (t, *J* = 7.8 Hz, 1 H), 7.67 (t, *J* = 7.8 Hz, 1 H), 8.09 (d, *J* = 7.8 Hz, 1 H), 8.65 (d, *J* = 7.8 Hz, 1 H), 9.44 (s, 1 H).

MS: *m*/*z* (%) = 308 (21) [M$^+$ + 1], 307 (100) [M$^+$].

9*H*-Pyrido[2,3-*b*]indoles 16, 18 and 19; General Procedure
A mixture of a dielectrophile (5 mmol) and 1*H*-indol-2-amine (**15**; 0.66 g, 5 mmol) in AcOH (30 mL) was refluxed under an inert atmosphere for 2 h. After evaporation of the volatiles, the residue was purified by column chromatography on silica gel or was recrystallized from an appropriate solvent.

2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (16a)
Yield: 1.31 g (86%); colourless solid (recrystallized from *i*-PrOH).

^{13}C NMR (DMSO-d_6): δ = 107.5, 109.9, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.4, 122.2 (q, $^1J_{CF}$ = 275 Hz), 124.7 (q, J_{CF} = 4.2 Hz), 129.5, 131.1 (q, $^2J_{CF}$ = 35 Hz), 135.1, 142.2, 144.1 (q, $^2J_{CF}$ = 35 Hz), 151.9, 157.0.

MS: *m*/*z* (%) = 305 (14) [M$^+$ + 1], 304 (100) [M$^+$], 285 (18), 284 (39).

2-Methyl-4-(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (16b)
Yield: 1.05 g (84%); colourless solid (recrystallized from *i*-PrOH).

^{13}C NMR (DMSO-d_6): δ = 24.9, 107.7 (q, J_{CF} = 2.6 Hz), 110.6, 110.9 (q, J_{CF} = 5.0 Hz), 120.9, 121.2 (q, $^1J_{CF}$ = 275 Hz), 125.2, 125.5, 127.5, 130.1 (q, $^2J_{CF}$ = 35 Hz), 140.5, 152.2, 156.6.

MS: *m*/*z* (%) = 251 (12) [M$^+$ + 1], 250 (100) [M$^+$], 249 (31).

2-Phenyl-4-(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (16c)
Yield: 1.38 g (89%); colourless solid (recrystallized from MeOH).

^{13}C NMR (DMSO-d_6): δ = 106.5 (q, J_{CF} = 2.8 Hz), 110.4 (q, J_{CF} = 4.6 Hz), 110.6, 120.7, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.9, 125.0, 126.1, 127.5, 130.4, 130.8, 131.4 (q, $^2J_{CF}$ = 35 Hz), 134.1, 140.5, 152.8, 156.9.

MS: *m*/*z* (%) = 313 (32) [M$^+$ + 1], 312 (100) [M$^+$], 311 (15) [M$^+$ – 1], 242 (16) [M$^+$ – 1 – CF_3], 156 (10).

4-(Difluoromethyl)-2-methyl-9*H*-pyrido[2,3-*b*]indole (16d)
Yield: 0.94 g (81%); colourless solid (recrystallized from *i*-PrOH).

^{13}C NMR (DMSO-d_6): δ = 24.3, 111.2, 111.5 ($^1J_{CF}$ = 240 Hz), 114.3, 118.5, 119.9, 123.1, 126.7, 134.8 ($^2J_{CF}$ = 26 Hz), 138.9, 152.6, 155.6, 163.4.

^{19}F NMR (DMSO-d_6): δ = –115.7 (d, $^2J_{FH}$ = 56 Hz).

MS: *m*/*z* (%) = 233 (14) [M$^+$ + 1], 232 (100) [M$^+$], 231 (22) [M$^+$ – 1].

4-(Chlorodifluoromethyl)-2-phenyl-9*H*-pyrido[2,3-*b*]indole (16e)
Yield: 1.4 g (85%); colourless solid (recrystallized from EtOH).

^{13}C NMR (DMSO-d_6): δ = 106.0 (t, J_{CF} = 3.2 Hz), 110.2, 110.9 (t, J_{CF} = 4.6 Hz), 120.0, 121.2, 121.9 (t, $^1J_{CF}$ = 286 Hz), 125.9, 126.6, 127.9, 130.0, 131.0 (t, $^2J_{CF}$ = 29 Hz), 132.7, 134.4, 140.9, 152.3, 157.0.

MS: *m*/*z* (%) = 330 (32) [M$^+$ + 2], 329 (20) [M$^+$ + 1], 328 (100) [M$^+$], 327 (23) [M$^+$ – 1].

2-Methyl-4-(perfluoroethyl)-9*H*-pyrido[2,3-*b*]indole (16f)
Yield: 1.31 g (87%); colourless solid (recrystallized from *i*-PrOH).

^{13}C NMR (DMSO-d_6): δ = 25.1, 109.0 (t, J_{CF} = 4.5 Hz), 111.9 (t, J_{CF} = 5.8 Hz), 112.7, 120.0, 125.0, 127.1, 127.3, 130.7, 131.0 (t, $^2J_{CF}$ = 25 Hz), 134.7, 142.0, 154.0, 158.0.

MS: *m*/*z* (%) = 301 (17) [M$^+$ + 1], 300 (100) [M$^+$].

7-(Trifluoromethyl)-6,12-dihydro-5*H*-12,13-diazaindeno[1,2-*b*]phenanthrene (18)
Yield: 1.08 g (64%); colourless solid; mp 207 °C (*i*-PrOH).

^{1}H NMR (DMSO-d_6): δ = 2.96 (br s, 2 H), 3.25 (br s, 2 H), 7.28 (t, *J* = 7.8 Hz, 1 H), 7.38–7.45 (m, 3 H), 7.49–7.57 (m, 2 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 8.30 (d, *J* = 7.8 Hz, 1 H), 12.4 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 26.9, 27.1, 107.3, 110.9, 111.5, 120.9, 121.2, 123.0 (q, $^1J_{CF}$ = 275 Hz), 125.0, 125.5, 127.0, 127.5, 129.7, 131.1, 132.2 (q, $^2J_{CF}$ = 35 Hz), 132.4, 137.1, 140.5, 152.2, 156.6.

^{19}F NMR (DMSO-d_6): δ = –55.4.

MS: *m*/*z* (%) = 339 (24) [M$^+$ + 1], 338 (100) [M$^+$], 337 (43) [M$^+$ – 1], 269 (15) [M$^+$ – CF_3], 268 (24).

3-(3-Hydroxypropyl)-4-(trifluoromethyl)-1,9-dihydro-2*H*-pyrido[2,3-*b*]indol-2-one (19)
Yield: 1.15 g (74%); colourless solid; mp 199–200 °C; R_f = 0.50 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 1.95 (br s, 2 H), 3.15 (br s, 2 H), 4.18 (br s, 2 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.91 (d, *J* = 7.2 Hz, 1 H), 11.92 (s, 1 H), 12.13 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 20.6, 25.8, 62.6, 102.1, 110.3, 111.5, 119.1, 121.4, 123.1 (q, $^1J_{CF}$ = 275 Hz), 123.3, 130.9 (q, $^2J_{CF}$ = 35 Hz), 137.7, 148.0, 161.6, 170.2.

^{19}F NMR (DMSO-d_6): δ = –56.1.

MS: *m*/*z* (%) = 310 (12) [M$^+$], 303 (23), 298 (56), 233 (15), 178 (100).

9-Methyl-9*H*-pyrido[2,3-*b*]indoles 17; General Procedure for the Methylation of Compounds 16
To a mixture of a 9*H*-pyrido[2,3-*b*]indole **16** (2 mmol) and KOH (0.39 g, 14 mmol) in anhyd DMSO (10 mL), MeI (0.42 g, 6 mmol) in DMSO (5 mL) was added dropwise. After the addition of MeI, the mixture was kept at r.t. for 30 min, and then at 80 °C for 1.5 h. Then, the mixture was poured into H_2O (75–100 mL) and left overnight. The formed precipitate was collected by filtration, washed with H_2O (3 ×) and dried in air. The obtained sample was recrystallized (*i*-PrOH).

9-Methyl-2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (17a)
Yield: 0.48 g (75%); colourless solid.

^{13}C NMR (DMSO-d_6): δ = 28.2, 107.9 (q, J_{CF} = 2.6 Hz), 110.6, 110.8 (q, J_{CF} = 5.0 Hz), 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.4, 122.2 (q, $^1J_{CF}$ = 275 Hz), 124.0, 130.1, 131.4 (q, $^2J_{CF}$ = 35 Hz), 137.3, 142.9, 144.4 (q, $^2J_{CF}$ = 35 Hz), 150.8.

MS: *m*/*z* (%) = 319 (17) [M$^+$ + 1], 318 (100) [M$^+$], 299 (92), 132 (11).

9-Methyl-2-phenyl-4-(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (17b)

Yield: 0.59 g (90%); colourless solid.

^{13}C NMR (DMSO-d_6): δ = 27.7, 106.0 (q, J_{CF} = 2.8 Hz), 110.7, 110.9 (q, J_{CF} = 4.6 Hz), 120.7, 121.4 (q, $^1J_{CF}$ = 275 Hz), 121.7, 125.1, 126.2, 127.9, 130.5, 130.4, 131.0 (q, $^2J_{CF}$ = 35 Hz), 134.5, 140.9, 153.1, 157.2.

MS: *m*/*z* (%) = 327 (21) [M$^+$ + 1], 326 (100) [M$^+$], 325 (58) [M$^+$ – 1], 163 (11).

4-(Difluoromethyl)-2,9-dimethyl-9*H*-pyrido[2,3-*b*]indole (17c)

Yield: 0.46 g (93%); colourless solid.

^{13}C NMR (DMSO-d_6): δ = 24.3, 28.5, 111.2, 111.5 ($^1J_{CF}$ = 240 Hz), 114.3, 118.5, 119.9, 123.1, 126.7, 134.8 ($^2J_{CF}$ = 26 Hz), 138.9, 152.6, 155.6, 163.4.

MS: *m*/*z* (%) = 247 (17) [M$^+$ + 1], 246 (100) [M$^+$], 245 (80) [M$^+$ – 1], 195 (10).

1,2,3,4-Tetrafluoro-6*H*-indolo[2,3-*b*]quinoline (20c)

To a boiling soln of pentafluorobenzaldehyde (**7**; 0.98 g, 5 mmol) in AcOH (40 mL; temperature of the oil bath was 135 °C) under an inert atmosphere, a soln of 1*H*-indol-2-amine (**15**; 0.79 g, 6 mmol) in anhyd DMF (15 mL) was added dropwise through the condenser. After the addition was completed, the mixture was refluxed for a further 2 h. Then, the solvent was evaporated and the residue was recrystallized (MeOH).

Yield: 0.97 g (67%); colourless solid; mp >320 °C (MeOH).

^{1}H NMR (CF_3CO_2D): δ = 7.50 (t, *J* = 7.8 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 8.75 (d, *J* = 7.8 Hz, 1 H), 9.84 (s, 1 H).

MS: *m*/*z* (%) = 291 (25) [M$^+$ + 1], 290 (100) [M$^+$], 145 (12).

9-(Tri-*O*-acetyl-β-D-ribofuranosyl)-2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (23)

Compound **23** was prepared according to the classical silyl-Hilbert–Johnson reaction.[12] Purification was by column chromatography.

Yield: 1.69 g (75%); colourless solid; mp 125–129 °C; R_f = 0.65 (EtOAc–hexane, 1:4).

^{1}H NMR (DMSO-d_6): δ = 1.91–2.10 (br s, 9 H), 3.48 (m, 1 H), 3.69 (m, 1 H), 4.00 (q, *J* = 4.4 Hz, 1 H), 4.39 (br s, 1 H), 4.64 (d, *J* = 4.4 Hz, 1 H), 6.49 (d, *J* = 4.8 Hz, 1 H), 7.39–7.51 (m, 2 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.74 (s, 1 H), 8.07 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 20.1, 20.3, 20.9, 63.7, 67.9, 73.0, 79.0, 88.9, 99.0, 105.9, 107.8, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.9, 122.2 (q, $^1J_{CF}$ = 275 Hz), 124.9 (q, J_{CF} = 4.0 Hz), 129.9, 131.3 (q, $^2J_{CF}$ = 35 Hz), 142.7, 144.2 (q, $^2J_{CF}$ = 35 Hz), 149.2, 153.1, 170.4, 170.6, 171.0.

MS: *m*/*z* (%) = 562 (47) [M$^+$], 560 (33) [M$^+$ – 2], 502 (54), 490 (11), 459 (10), 458 (14), 401 (70), 400 (11), 388 (17), 387 (50), 386 (13), 305 (100), 284 (88), 211 (22), 57 (39), 43 (71).

Compounds 26 and 35

For the synthesis of compounds **26** and **35**, and their deprotection, a literature method[14] was used without change. Alkylation was conducted with NaH in MeCN. Purification was by column chromatography.

2-{[2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indol-9-yl]methoxy}propane-1,3-diyl Dibenzoate (26)

Yield: 1.68 g (68%); yellow oil; R_f = 0.45 (EtOAc–hexane, 1:3).

^{1}H NMR (DMSO-d_6): δ = 4.33 (m, 4 H), 4.80 (m, 1 H), 6.11 (br s, 2 H), 7.37 (m, 6 H), 7.67 (m, 2 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.87 (d, *J* = 7.2 Hz, 4 H), 7.89 (s, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 62.0, 72.5, 79.0, 107.0, 109.4, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.7, 122.4 (q, $^1J_{CF}$ = 275 Hz), 124.3 (q, J_{CF} = 4.1 Hz), 128.2, 129.5, 129.6, 129.8, 130.7, 131.1 (q, $^2J_{CF}$ = 35 Hz), 133.5, 135.1, 135.2, 142.4, 144.0 (q, $^2J_{CF}$ = 35 Hz), 152.1, 154.9, 173.6, 173.7.

MS: *m*/*z* (%) = 616 (57) [M$^+$], 495 (21), 494 (11), 385 (51), 333 (17), 331 (33), 284 (40), 283 (40), 105 (60), 77 (100).

9-(3,5-Di-*O*-*p*-toluoyl-2-deoxy-α-D-ribofuranosyl)-2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (35)

Yield: 1.81 g (69%); colourless solid; mp 97–100 °C; R_f = 0.85 (EtOAc–hexane, 1:3).

^{1}H NMR (DMSO-d_6): δ = 2.31 (s, 3 H), 2.40–2.47 (br m, 2 H), 2.45 (s, 3 H), 3.80 (br s, 2 H), 4.43 (m, 1 H), 4.49 (m, 1 H), 6.84 (t, *J* = 6.1 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 7.37 (t, *J* = 7.8 Hz, 1 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.77 (t, *J* = 7.8 Hz, 1 H), 7.90–7.95 (br m, 4 H), 8.03 (s, 1 H), 8.22 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 21.8, 22.0, 38.9, 62.0, 69.4, 81.7, 88.5, 108.1, 111.3, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.7, 122.1 (q, $^1J_{CF}$ = 275 Hz), 124.0 (q, J_{CF} = 4.0 Hz), 125.3, 128.9, 129.1, 129.7, 131.4 (q, $^2J_{CF}$ = 35 Hz), 135.3, 137.7, 138.8, 143.0, 144.1 (q, $^2J_{CF}$ = 35 Hz), 153.0, 156.2, 169.3, 169.4.

MS: *m*/*z* (%) = 656 (41) [M$^+$], 601 (10), 554 (13), 553 (11), 520 (100), 497 (22), 490 (17), 452 (14), 305 (50), 285 (67), 221 (33), 187 (11), 185 (13), 119 (53), 91 (77).

Compounds 24, 27 and 36; General Procedure for the Deprotection of Acylated Nucleosides

To a soln of the acylated nucleoside (1 mmol) in abs MeOH (5 mL), a sat. soln of NH_3 in MeOH (20 mL) was added dropwise at 0 °C. The mixture was stirred for another 30 min and left overnight at r.t. The solvent was removed under reduced pressure, and the formed material was kept for the next 24 h on a vacuum line. The resultant yellow material was purified by column chromatography on silica gel.

9-(β-D-Ribofuranosyl)-2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (24)

Yield: 0.29 g (67%); colourless solid; mp 201–205 °C; R_f = 0.65 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.39 (m, 1 H), 3.60 (m, 1 H), 4.21 (q, *J* = 4.1 Hz, 1 H), 4.37 (br s, 1 H), 4.44 (d, *J* = 4.1 Hz, 1 H), 5.15 (m, 1 H), 5.65 (br s, 2 H), 6.44 (d, *J* = 5.2 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.91 (s, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 62.4, 67.0, 71.9, 77.3, 86.9, 99.9, 105.9, 107.8, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.9, 122.2 (q, $^1J_{CF}$ = 275 Hz), 124.9 (q, J_{CF} = 4.0 Hz), 129.9, 131.3 (q, $^2J_{CF}$ = 35 Hz), 142.7, 144.2 (q, $^2J_{CF}$ = 35 Hz), 154.1, 157.1.

MS: *m*/*z* (%) = 436 (13) [M$^+$], 419 (21), 418 (17), 401 (30), 400 (13), 355 (11), 333 (17), 305 (100), 301 (11), 300 (27), 284 (47), 273 (15), 211 (10), 187 (14), 167 (10), 166 (15).

2-{[2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indol-9-yl]methoxy}propane-1,3-diol (27)

Yield: 0.22 g (53%); yellow oil; R_f = 0.25 (EtOAc–hexane, 1:2).

^{1}H NMR (DMSO-d_6): δ = 4.25 (m, 4 H), 4.43 (br s, 2 H), 4.50 (m, 1 H), 5.91 (br s, 2 H), 7.39 (m, 2 H), 7.70 (t, *J* = 7.8 Hz, 1 H), 7.81 (s, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 60.8, 71.5, 81.3, 108.8, 109.5, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.3, 122.3 (q, $^1J_{CF}$ = 275 Hz), 124.5 (q, J_{CF} = 4.2 Hz), 129.4, 131.1 (q, $^2J_{CF}$ = 35 Hz), 142.9, 143.9 (q, $^2J_{CF}$ = 35 Hz), 152.3, 155.0.

MS: *m*/*z* (%) = 408 (14) [M$^+$], 406 (71), 401 (14), 389 (100), 304 (79), 285 (18), 284 (39), 47 (11).

9-(2-Deoxy-α-D-ribofuranosyl)-2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (36)

Yield: 0.35 g (83%); colourless solid; mp 189–193 °C; R_f = 0.25 (EtOAc–hexane, 1:1).

^{1}H NMR (DMSO-d_6): δ = 2.35–2.49 (br m, 2 H), 3.67 (br s, 2 H), 4.33 (m, 1 H), 4.45 (m, 1 H), 5.27 (br s, 2 H), 6.59 (t, *J* = 5.8 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.79 (t, *J* = 7.8 Hz, 1 H), 7.99 (s, 1 H), 8.15 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 38.9, 62.0, 69.4, 81.7, 88.5, 108.1, 111.3, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.7, 122.1 (q, $^1J_{CF}$ = 275 Hz), 124.0 (q, J_{CF} = 4.4 Hz), 129.7, 131.4 (q, $^2J_{CF}$ = 35 Hz), 135.3, 143.0, 144.1 (q, $^2J_{CF}$ = 35 Hz), 153.0, 156.2.

MS: *m*/*z* (%) = 420 (24) [M$^+$], 403 (18), 402 (100), 385 (10), 309 (19), 304 (82), 287 (12), 285 (10), 284 (22), 280 (17), 221 (20), 220 (37), 199 (11), 119 (12), 118 (11), 56 (14).

{(3a*R*,4*R*,6*R*,6a*S*)-6-[2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indol-9-yl]-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}methanol (33)

Compound **33** was synthesized from carboline **16a** and **31** using the Mitsunobu protocol, with subsequent oxidation of the double bond.[14a] Purification was by column chromatography.

Yield: 0.63 g (33%); colourless solid; mp 138–140 °C; R_f = 0.45 (EtOAc–hexane, 1:3).

^{1}H NMR (DMSO-d_6): δ = 1.28 (s, 3 H), 1.50 (s, 3 H), 2.30 (m, 3 H), 3.47 (br s, 2 H), 4.55 (d, *J* = 4.1 Hz, 1 H), 4.80–4.86 (m, 2 H), 5.17 (d, *J* = 6.4 Hz, 1 H), 7.35 (m, 2 H), 7.71 (t, *J* = 7.8 Hz, 1 H), 7.77 (s, 1 H), 8.10 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 24.7, 27.1, 34.7, 47.8, 61.7, 61.9, 80.9, 82.3, 109.3, 110.1, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.9, 122.3 (q, $^1J_{CF}$ = 275 Hz), 124.9, 131.0 (q, $^2J_{CF}$ = 35 Hz), 142.4, 144.9 (q, $^2J_{CF}$ = 35 Hz), 152.4, 156.0.

MS: *m*/*z* (%) = 474 (38) [M$^+$], 457 (53), 441 (100), 402 (16), 304 (43), 285 (39), 171 (12), 166 (15), 162 (18), 161 (19), 155 (23), 153 (18), 147 (13), 43 (21).

(1*R*,2*S*,3*R*,5*R*)-3-[2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indol-9-yl]-5-(hydroxymethyl)cyclopentane-1,2-diol (34)

Deprotection of compound **33** was performed in TFA–H_2O, according to the procedure described previously.[1d] Purification was by column chromatography.

Yield: 0.35 g (80%); colourless solid; mp 299–300 °C; R_f = 0.65 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 1.60–1.70 (br s, 2 H), 1.99–2.04 (m, 1 H), 2.31 (m, 1 H), 3.43–3.51 (m, 2 H), 3.84 (m, 1 H), 4.38 (m, 1 H), 4.65–4.74 (m, 1 H), 4.85 (br t, *J* = 5.8 Hz, 1 H), 4.95 (d, *J* = 6.2 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.71 (t, *J* = 7.8 Hz, 1 H), 7.84 (s, 1 H), 8.05 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 29.3, 45.1, 58.3, 63.0, 74.7, 77.3, 108.5, 111.9, 121.3 (q, $^1J_{CF}$ = 275 Hz), 121.9, 122.4 (q, $^1J_{CF}$ = 275 Hz), 124.0, 131.2 (q, $^2J_{CF}$ = 35 Hz), 141.7, 144.0 (q, $^2J_{CF}$ = 35 Hz), 153.1, 155.3.

MS: *m*/*z* (%) = 434 (13) [M$^+$], 416 (43), 339 (100), 377 (17), 331 (14), 330 (11), 305 (50), 285 (41), 284 (22), 143 (15), 141 (10), 130 (19).

Compounds 37 and 39

Carbocyclic nucleosides **37** and **39** were obtained according to the Mitsunobu protocol.[16]

A soln of DEAD (8.9 mmol) in anhyd MeCN was added dropwise to a stirred, cooled soln (0 °C) of a carbocyclic sugar (3.7 mmol). Then, a soln of carboline **16a** (1.26 g, 4 mmol) and Ph_3P (2.31 g, 8.8 mmol) in anhyd MeCN was added. The reaction mixture was stirred at 0 °C for 1 h, then heated to r.t. and stirred for another 12 h. The solvent was then removed under reduced pressure. The residue was dried under reduced pressure for 12 h and purified by column chromatography on silica gel.

9-[(1*R*,3*S*,4*R*)-3-Benzyloxy-4-(benzyloxymethyl)cyclopentyl]-2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (37)

Yield: 0.88 g (37%); yellow oil; R_f = 0.40 (EtOAc–hexane, 1:5).

^{1}H NMR (DMSO-d_6): δ = 1.30–1.37 (m, 1 H), 1.75–1.84 (m, 1 H), 2.10–2.17 (m, 3 H), 3.30 (ddd, ^2J = 10.8 Hz, ^3J = 5.8, 5.3 Hz, 1 H), 3.43 (ddd, ^2J = 10.8 Hz, ^3J = 5.6, 5.3 Hz, 1 H), 4.00–4.05 (m, 1 H), 4.59–4.75 (m, 4 H), 5.00–5.05 (m, 1 H), 7.25–7.48 (m, 12 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 7.93 (s, 1 H), 8.21 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 31.7, 34.3, 51.0, 54.9, 65.0, 72.2, 73.1, 73.9, 106.9, 109.0, 121.1 (q, $^1J_{CF}$ = 275 Hz), 121.7, 122.3 (q, $^1J_{CF}$ = 275 Hz), 124.5, 127.3, 127.9, 128.7, 129.0, 131.2 (q, $^2J_{CF}$ = 35 Hz), 137.9, 138.1, 143.1, 144.3 (q, $^2J_{CF}$ = 35 Hz), 152.2, 154.4.

MS: *m*/*z* (%) = 598 (73) [M$^+$], 504 (31), 491 (26), 490 (68), 467 (12), 377 (44), 321 (32), 304 (40), 285 (17), 278 (11), 261 (30), 204 (14), 191 (17), 161 (11), 91 (100).

9-[*cis*-3-(Benzyloxymethyl)cyclobutyl]-2,4-bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (39)

Yield: 1.17 g (66%); colourless solid; mp 116–118 °C; R_f = 0.85 (EtOAc–hexane, 1:3).

^{1}H NMR ($CDCl_3$): δ = 1.90 (m, 2 H), 2.19 (m, 1 H), 2.59 (m, 2 H), 3.39 (d, *J* = 6.0 Hz, 2 H), 4.30 (s, 2 H), 6.03 (d, *J* = 6.6 Hz, 1 H), 7.29 (m, 5 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.79 (t, *J* = 7.8 Hz, 1 H), 7.88 (s, 1 H), 8.13 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 25.5, 32.0, 66.7, 73.3, 74.7, 108.8, 109.5, 121.0, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.3, 122.3 (q, $^1J_{CF}$ = 275 Hz), 124.5 (q, J_{CF} = 4.2 Hz), 126.4, 127.7, 129.4, 131.1 (q, $^2J_{CF}$ = 35 Hz), 133.3, 136.7, 142.9, 143.9 (q, $^2J_{CF}$ = 35 Hz), 152.9, 156.3.

MS: *m*/*z* (%) = 478 (59) [M$^+$], 371 (79), 370 (90), 304 (100), 301 (15), 285 (59), 91 (90), 65 (11), 57 (41).

Compounds 38 and 40; General Procedure for Benzyl Group Cleavage by Hydrogenation

The benzylated carbocyclic nucleoside (1 mmol) was dissolved in EtOH and 10% Pd/C (70 mg) was added. The reaction mixture was stirred under H_2 at r.t. until complete conversion was observed by TLC (ca. 2–3 h). The reaction mixture was filtered through a Celite® pad which was washed with EtOH. The mother liquid was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel.

(1*S*,2*R*,4*R*)-4-[2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indol-9-yl]-2-(hydroxymethyl)cyclopentanol (38)

Yield: 0.25 g (59%); colourless solid; mp 175–177 °C; R_f = 0.45 (EtOAc–hexane, 1:1).

^{1}H NMR (DMSO-d_6): δ = 1.34–1.42 (m, 1 H), 1.70–1.81 (m, 1 H), 2.05–2.14 (m, 2 H), 2.17–2.25 (m, 1 H), 3.37 (ddd, ^2J = 11.2 Hz,

^3J = 5.8, 5.0 Hz, 1 H), 3.57 (ddd, ^2J = 11.2 Hz, ^3J = 5.4, 5.0 Hz, 1 H), 4.07–4.12 (m, 1 H), 4.61 (t, J = 5.2 Hz, 1 H), 4.73 (d, J = 4.5 Hz, 1 H), 5.02–5.08 (m, 1 H), 7.39–7.50 (m, 2 H), 7.77 (d, J = 7.8 Hz, 1 H), 7.90 (s, 1 H), 8.08 (d, J = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 31.7, 34.3, 51.0, 54.9, 65.0, 73.7, 106.9, 109.0, 121.1 (q, $^1J_{CF}$ = 275 Hz), 121.7, 122.3 (q, $^1J_{CF}$ = 275 Hz), 123.9, 124.5 (q, J_{CF} = 4.2 Hz), 129.0, 131.2 (q, $^2J_{CF}$ = 35 Hz), 143.1, 144.3 (q, $^2J_{CF}$ = 35 Hz), 152.4, 153.9.

MS: m/z (%) = 418 (31) [M$^+$], 417 (10), 401 (10), 399 (100), 389 (20), 388 (10), 340 (12), 339 (15), 299 (11), 285 (13), 251 (17), 209 (13), 189 (13), 111 (10).

{*cis*-3-[2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indol-9-yl]cyclobutyl}methanol (40)

Yield: 0.22 g (57%); colourless solid; mp 152–155 °C; R_f = 0.60 (EtOAc–hexane, 1:2).

^{1}H NMR (DMSO-d_6): δ = 1.85 (m, 2 H), 2.01 (m, 1 H), 2.35 (m, 2 H), 3.37 (d, J = 5.2 Hz, 2 H), 4.60 (br s, 1 H), 5.01 (m, 1 H), 7.41 (t, J = 7.8 Hz, 1 H), 7.67 (d, J = 7.8 Hz, 1 H), 7.70 (t, J = 7.8 Hz, 1 H), 7.91 (s, 1 H), 8.05 (d, J = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 27.1, 33.7, 63.0, 66.7, 108.9, 109.3, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.3, 122.2 (q, $^1J_{CF}$ = 275 Hz), 124.3, 129.5, 131.2 (q, $^2J_{CF}$ = 35 Hz), 133.3, 142.9, 143.7 (q, $^2J_{CF}$ = 35 Hz), 151.9, 154.0.

MS: m/z (%) = 388 (31) [M$^+$], 387 (11), 353 (100), 305 (12), 299 (17), 245 (13), 207 (19), 189 (17), 167 (11), 158 (11), 131 (10), 57 (33).

{*cis*-4-[2,4-Bis(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indol-9-yl]cyclopent-2-en-1-yl}methanol (41)

Under an inert atmosphere, carboline **16a** (0.91 g, 3 mmol) was added to a stirred suspension of NaH (0.1 g, 4.4 mmol) in DMF (30 mL) at r.t. The mixture was stirred at r.t. for 1 h, then *cis*-diacetate **32** (0.65 g, 3.3 mmol) and Pd(PPh$_3$)$_4$ (1.27 g, 1.1 mmol) were added. The reaction vessel was protected from light by tin foil and the mixture was heated to 60 °C for 2 h, then cooled to r.t. Abs MeOH (2 mL) was added to the reaction mixture which was kept for 1 h at r.t. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to furnish product **41** as only the *cis*-isomer.

Yield: 0.71 g (59%); colourless solid; mp 134–136 °C; R_f = 0.80 (EtOAc–hexane, 1:1).

^{1}H NMR (DMSO-d_6): δ = 1.61 (dt, ^2J = 11.8 Hz, ^3J = 5.1 Hz, 1 H), 2.68 (dt, ^2J = 13.0 Hz, ^3J = 8.0 Hz, 1 H), 3.08 (m, 1 H), 3.41 (d, J = 10.6 Hz, 2 H), 3.58 (br s, 1 H), 5.23–5.32 (m, 1 H), 5.81 (dt, ^2J = 5.7 Hz, ^3J = 2.2 Hz, 1 H), 6.11 (dt, ^2J = 13.1 Hz, ^3J = 2.5 Hz, 1 H), 7.37 (t, J = 7.8 Hz, 1 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.79 (t, J = 7.8 Hz, 1 H), 7.84 (s, 1 H), 8.10 (d, J = 7.8 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 33.9, 48.1, 56.3, 66.1, 107.0, 109.6, 120.3, 121.2 (q, $^1J_{CF}$ = 275 Hz), 121.9, 122.3 (q, $^1J_{CF}$ = 275 Hz), 124.9 (q, J_{CF} = 4.0 Hz), 129.0, 131.5 (q, $^2J_{CF}$ = 35 Hz), 132.7, 138.7, 142.9, 144.7 (q, $^2J_{CF}$ = 35 Hz), 154.1, 155.5.

MS: m/z (%) = 400 (41) [M$^+$], 382 (70), 358 (13), 357 (100), 304 (20), 285 (35), 222 (23), 221 (10), 210 (12), 138 (35), 96 (14).

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