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Synthesis of vinca alkaloids and related compounds. Part 110: A new synthetic method for the preparation of pandoline-type alkaloid-like molecules

Flórián Tóth [a], Julianna Oláh [b], György Kalaus [a,*], István Greiner [c], Áron Szőllősy [d], Ágnes Gömöry [e], László Hazai [a], Csaba Szántay [a,e]

[a] Department of Organic Chemistry and Technology, Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, Gellért tér 4, H-1521 Budapest, Hungary
[b] Centre for Computational Chemistry, School of Chemistry, University of Bristol, Bristol BS8 1TS, UK
[c] Chemical Works of Gedeon Richter Ltd, Gyömrői út 19-21, H-1103 Budapest, Hungary
[d] Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, Gellért tér 4, H-1521 Budapest, Hungary
[e] Institute of Chemistry, Chemical Research Center, Hungarian Academy of Sciences, Pusztaszeri út 59-67, H-1025 Budapest, Hungary

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ABSTRACT

A practicable synthesis of a pandoline-type alkaloid-like molecule is reported through an efficient preparation of carbinolamine ether intermediates (**9a** and **9b**). The key step of the synthesis consists of an intramolecular cycloaddition of the secodine-type intermediate (**2**), which was formed from the tryptamine derivative (**3**) and lactol (**4**). The mechanism of the cycloaddition reaction was investigated by quantum chemical calculations and it was found to follow a step-wise mechanism involving a zwitterionic intermediate (**15**). By employing this strategy, other members of the family of pandoline alkaloids or alkaloid-like molecules could be synthesized by reacting the tryptamine derivative with appropriately functionalized aldehydes.

1. Introduction

In 1981 Kan and co-workers reported the structures of several new monoterpenoid indole alkaloids, which had been isolated from a Tabernaemontana species known as *Tabernaemontana albiflora*. One component of the alkaloidal extracts was identified as 19-hydroxy-20-epipandoline (**1**).[1] The interesting biological activities of aspidospermane and Ψ-aspidospermane alkaloids and their synthetically challenging structures make the molecule (**1**) an attractive target for synthesis.[2] Previously we reported some biomimetic route for the construction of aspidospermane, Ψ-aspidospermane alkaloids and alkaloid-like molecules (Fig. 1).[3]

As part of this ongoing project we sought to develop a strategy for the efficient preparation of the pandoline-type alkaloids.[4] Our planned synthesis of **1** is shown in Scheme 1. For preparation of the Ψ-aspidospermane skeleton, we used as a key step, the [4+2] internal cycloaddition reaction of **2**, which was obtained by coupling of the tryptamine derivative (**3**)[3a] with the appropriately functionalized and masked aldehyde (**4**).

2. Results and discussion

Our synthesis of **4** began with the protection of methyl 4-methylene-5-oxohexanoate (**5**)[3d] with ethanediol leading to **6** in excellent yield. Next the epoxide ring was formed by oxidation of **6** with 3-chloroperoxybenzoic acid and the resulting epoxide-ester (**7**) reacted with $MgBr_2$ in the presence of $NaHCO_3$ affording the five-membered lactone (**8**) in a ring-opening and cyclization

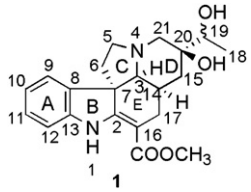

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Figure 1. 19-Hydroxy-20-epipandoline (**1**).

* Corresponding author. Tel.: +36 1 463 1285; fax: +36 1 463 3297.
E-mail address: kalaus@mail.bme.hu (G. Kalaus).

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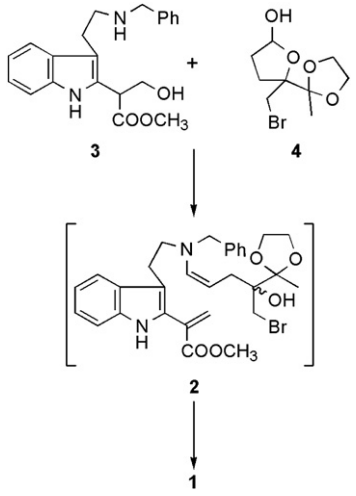
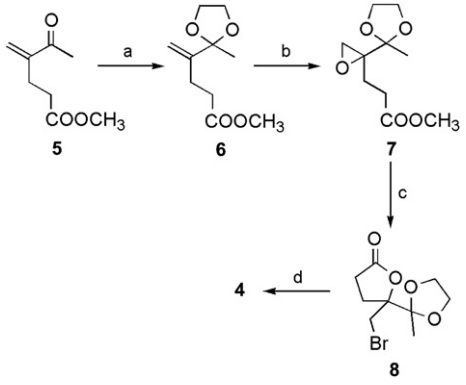


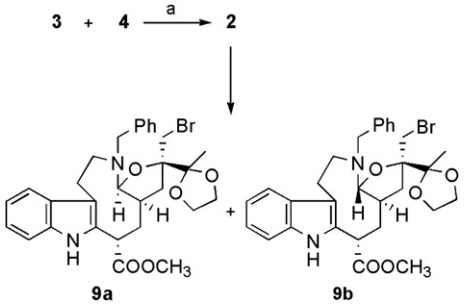
Scheme 1. Planned synthesis of **1**.

reaction. Finally, reduction of lactone (**8**) with diisobutylaluminium hydride at −78 °C furnished the expected masked aldehyde (**4**) (Scheme 2).



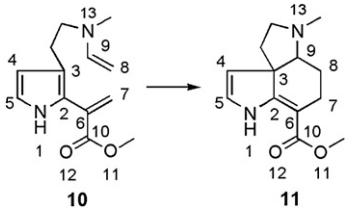
Scheme 2. *Reagents and conditions*: (a) HO–$(CH_2)_2$–OH, *p*-TsOH, benzene, Δ (91%); (b) *m*-CPBA, satd $NaHCO_3$, CH_2Cl_2, 25 °C (82%); (c) $MgBr_2$, satd Na_2CO_3, THF, 25 °C (78%); (d) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −78 °C (85%).

The coupling of tryptamine derivative (**3**) with lactol (**4**) was carried out in boiling toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate to provide intermediate (**2**), the key molecule for the [4+2] cycloaddition reaction. Unexpectedly, under the reaction conditions, the secodine-type intermediate (**2**)—without isolation—was smoothly converted into the unique cyclic carbinolamine ethers (**9a** and **9b**) in a good yield (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) *p*-TsOH·H_2O, toluene, Δ (**9a** (44%) and **9b** (26%)).

The formation of **9a** and **9b** could not be explained by our previous hypothesis, i.e., a concerted [4+2] intramolecular cycloaddition of **2**, as it should lead to the expected product in one step. However, in a few cases experimental evidence was given for step-wise DA reactions involving zwitterionic[5] or biradical intermediates,[6] and there are an abundant number of theoretical studies on the mechanism of DA reactions.[7,8] Therefore we performed quantum mechanical calculations at the B3LYP/6-31G(d) level in order to establish a possible reaction mechanism. As our target compound **2** was too large to be modelled by accurate methods, we changed the indole to a pyrrole ring, the benzyl group on the nitrogen was substituted by a methyl group and the appropriately functionalized enamine with a vinyl group as shown in Scheme 4. These substitutions are not expected to influence the reactivity of the molecule in an intramolecular DA reaction. The calculations predict that the reaction follows a step-wise mechanism, involving two transition states and a zwitterionic intermediate (Fig. 2). In Table 1 we collected the relative energies and partial charges of selected atoms for these species.



Scheme 4. Intramolecular DA reaction studied by computational methods (10→11).

In the first part of the reaction (from the reactant via TS1 to the intermediate) electrons flow from the dienophile part of the molecule towards the ester group and C3, leaving a partial positive charge on C9 and N13, and the structure of the aromatic ring remains almost unperturbed (see Table S1 in Supplementary data). In the intermediate the C7–C8 distance indicates an almost completely formed single bond, but the C3–C9 distance (the other future single bond) still exceeds 3 Å. The partial charge separation between positive C9 and N13 fragment and the negative ester group stabilizes the intermediate via favourable Coulombic interactions. In the second step of the reaction, C3 performs a nucleophilic attack on C9 leading to the final cyclic product via TS2. This step is accompanied by the transfer of electrons from the ester group back to the C9–N13 fragment. The transformation of bond distances during the whole reaction pathway follows four different patterns. (1) Bond distances C6–C7 and C7–C8 show the largest changes in the first part of the reaction between the reactant and the intermediate. (2) Bond distances in the pyrrole ring and C3–C9 undergo substantial changes only at the end of the reaction, after the second TS. (3) The C2–C6 and C8–C9 distances change gradually during the reaction and finally (4) the C–O distances show a maximum value and the C6–C10 and C9–N13 distances a minimum value in the intermediate. The change of bond distances is accompanied by a systematic change in the partial charges of the atoms: in the intermediate, negative partial charge accumulates on the ester group and on C3, and positive partial charge on C9 and N13, facilitating the nucleophilic attack in the second step of the reaction. The intermediate has a zwitterionic character, which is stabilized by favourable Coulombic interactions. The calculations were performed in the gas phase but the interaction of the zwitterionic intermediate with the solvent is expected to increase its stability, thereby its life-time. Based on these calculations, our theory for

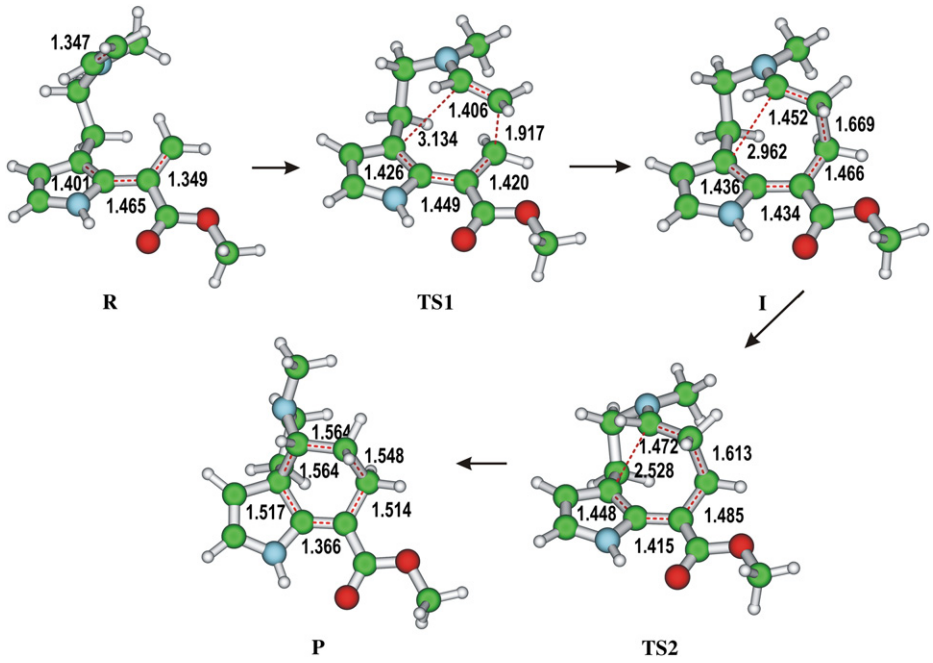


Figure 2. Structure of the reactant (**10** (R)), transition states, intermediate and product (**11** (P)) in reaction 1 in the gas phase. Distances are shown in Å.

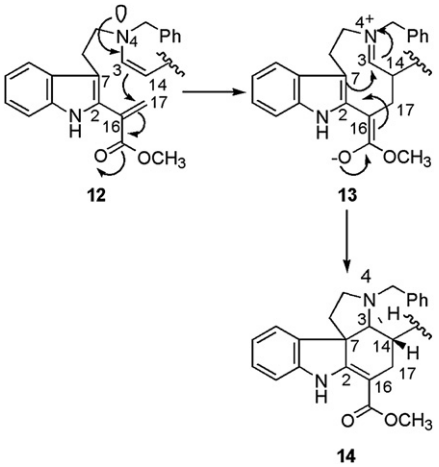
Table 1
NBO charges (q), relative energies (ΔE^{gas}) and Gibbs free energies (ΔG^{gas}) for the reactant (R, **10**), transition states (TS1 and TS2), intermediate (I) and product (P, **11**) of reaction 1 in the gas phase[a]

	ΔE^{gas}	ΔG^{gas}	q (C3)	q (C7)	q (C8)	q (C9)	q (N13)	q (COOCH$_3$)
R	0	0	−0.096	−0.347	−0.575	−0.02	−0.466	0.002
TS1	17.0	20.6	−0.137	−0.390	−0.541	0.045	−0.417	−0.136
I	15.8	20.2	*−0.143*	−0.431	−0.530	*0.064*	*−0.402*	*−0.182*
TS2	16.7	21.7	−0.143	−0.441	−0.520	0.051	−0.431	−0.168
P	−13.4	−7.2	−0.119	−0.467	−0.478	−0.038	−0.511	−0.096

[a] Energies are given in kcal/mol and NBO charges in electrons.

the cycloaddition reactions of secodine-type intermediates is shown in Scheme 5.

This reaction mechanism can explain the formation of the unique cyclic carbinolamine ethers (**9a** and **9b**) shown in Scheme 3. From intermediate **2**, two reaction routes are possible leading to two different final products (Scheme 6). Based on our theory, one of these reactions provides the D-*seco*-Ψ-aspidospermane molecule (**16**), where a single bond is formed between C3 and C7. The other one, the intramolecular trapping of the iminium function (**15**) with hydroxyl group results in the cyclic carbinolamine ethers (**9a** and **9b**).



Scheme 5. Hypothesis for the cycloaddition reaction mechanism.

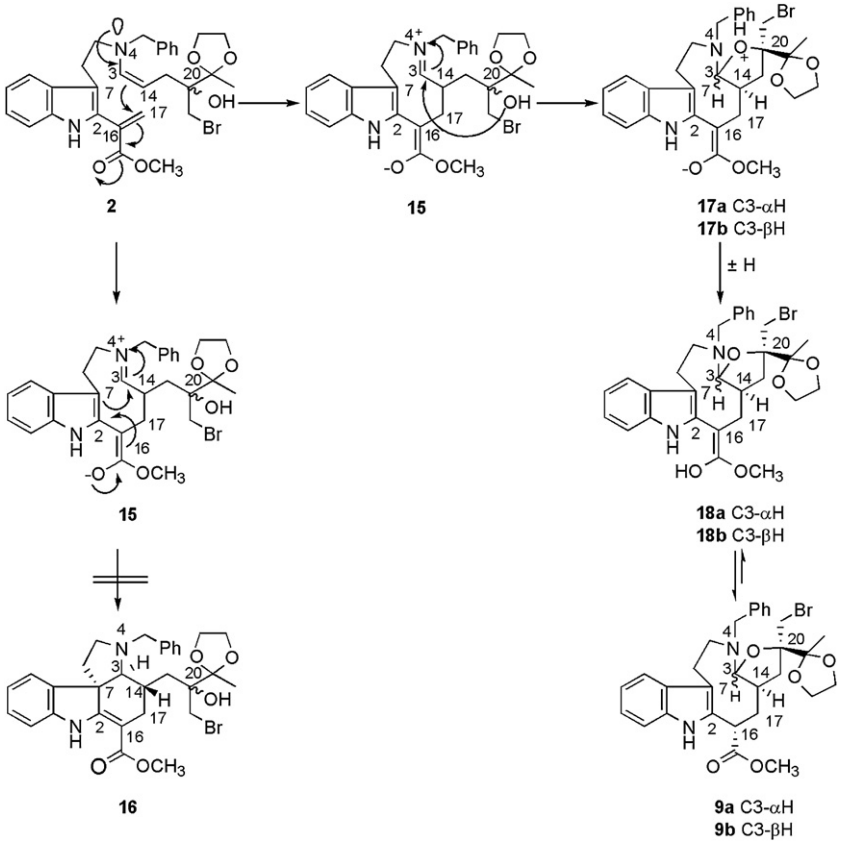
Comparison of the relative energy of potential products (models are shown in Fig. 3) showed that the carbinol ethers **9a** (ΔE=0.0 kcal/mol (**20a**)) and **9b** (ΔE=3.5 kcal/mol (**20b**)) had lower energies than the tetracyclic product **16** (ΔE=7.0 kcal/mol (**19**)). For this reason we could isolate only **9a** and **9b** from the reaction mixture (Fig. 3.).

In the next step of the synthesis, the required cyclization of the cycloadducts (**9a** and **9b**) provided two molecules with D-*seco*-Ψ-aspidospermane skeleton (**21a$_1$** and **21a$_2$**). From several alternatives, mercury(II) acetate was chosen as the oxidant for this purpose.[9] The furano ring was opened and the transannular cyclization process of **9a** led to the desired product (**21a$_1$**), while the reaction of **9b** with mercury(II) acetate furnished **21a$_2$** (Scheme 7).

Afterwards the D-ring of the Ψ-aspidospermane skeleton was formed. Hydrogenolysis of **21a$_1$** and **21a$_2$** in methanol resulted in the secondary amines (**22a$_1$** and **22a$_2$**), which without isolation and purification were heated in dimethylformamide at 90 °C in the presence of K_2CO_3. Unfortunately only one stereoisomer (**22a$_1$**) was converted to the pentacyclic alkaloid-like molecule (**23a**) with trans D/E ring connection and low yield (Scheme 8).

3. Conclusion

We have described a new, biomimetic synthesis pathway for the construction of the pandoline-type skeleton. The reaction of the tryptamine derivative (**3**)—containing a latent acrylic ester function—with lactol (**4**) resulted in the unexpected tetracyclic intermediates (**9a** and **9b**), which led us to the quantum chemical investigation of the mechanism of the cycloaddition reaction. We showed that in this case the first step of the reaction is the nucleophilic attack of the diene by the dienophile and the reaction follows a step-wise mechanism through a zwitterionic



Scheme 6. Theory for the cycloaddition reaction mechanism.

intermediate. Negative charge accumulates on the ester group and C3 in the aromatic ring, while positive charge is on C9. In the second step of the reaction C3 performs a nucleophilic attack on C9 and a new single bond is formed, and at the same time the bonds in the pyrrole ring are also transformed. These results explain our previous unsuccessful attempts to perform intramolecular DA cycloadditions, without the ester group.[10] Finally, D-ring of the Ψ-aspidospermane skeleton was formed in two steps, which led to the pentacyclic alkaloid-like molecule with trans D/E ring connection (**23a**).

4. Experimental

4.1. Computational data

The calculations were performed by the Gaussian 03 program package[11] at the B3LYP/6-31G(d) level of theory, which was shown to give activation energies in good agreement with the experimental results.[8e] We performed second-derivative calculations to characterize the nature of the located stationary points on the potential energy surface. NBO charges were calculated by the NBO program[12] as implemented in Gaussian 03.[13]

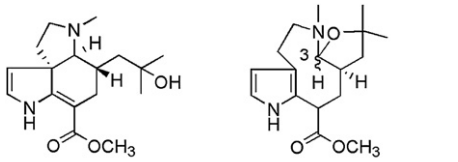
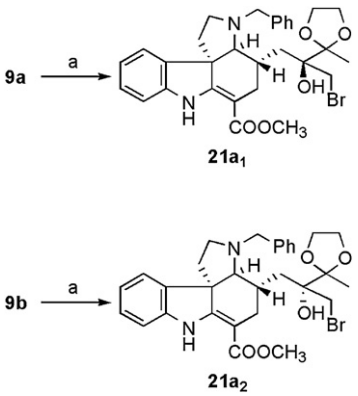


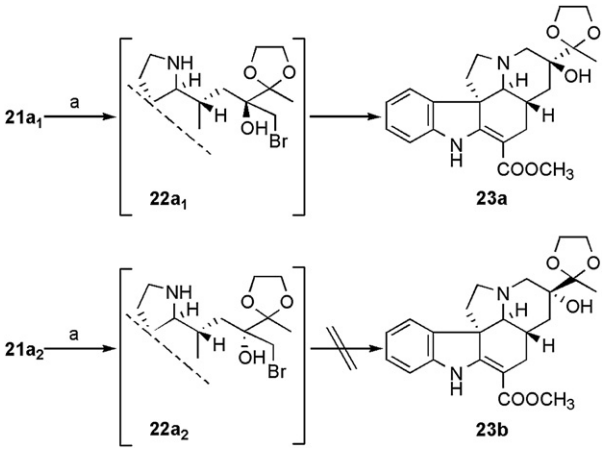
Figure 3. Relative energies of model compounds.

4.2. General

IR spectra were recorded on a Specord JR-75 spectrophotometer. NMR spectra were recorded on a Bruker DRX-500 instrument at 500 MHz for ^{1}H and 125 MHz for ^{13}C, and on a Varian Unity INOVA-400 instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All NMR spectra were recorded at rt. Chemical shifts are reported relative to Me_4Si (δ=0 ppm). MS spectra were recorded on a PE Sciex API 2000 triple-quadrupole mass spectrometer equipped with a Turbo Ion Spray source and VG ZAB2-SEQ tandem mass spectrometer (high resolution mass spectra).



Scheme 7. *Reagents and conditions*: (a) $Hg(OOCH_3)_2$, CH_3COOH, 25 °C (**21a$_1$** (67%) and **21a$_2$** (61%)).



Scheme 8. *Reagents and conditions*: (a) Pd/C, H_2, CH_3OH, 25 °C then K_2CO_3, DMF, 90 °C (**23a** (39%)).

4.2.1. 4-(2-Methyl-[1,3]dioxolan-2-yl)-pent-4-enoic acid methyl ester (**6**)

A mixture of **5** (5.00 g, 32.0 mmol), ethylene glycol (2.19 g, 35.0 mmol) and 50 mg of *p*-toluenesulfonic acid monohydrate in dry benzene (150 mL) was purged with argon for 30 min and the colourless reaction mixture was then heated with vigorous stirring for 12 h. During this time the water was collected in a Dean–Stark trap. Then the yellow reaction mixture was allowed to cool to rt and the benzene was removed under reduced pressure. The residue was taken up into dichloromethane (250 mL) and washed with 5% aqueous solution of Na_2CO_3 (25 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo yielding 5.83 g (91%) of **6** as a colourless oil (TLC: ether/hexane=1:1, R_f=0.45). IR (neat) ν_{max} 2992, 1740, 1440, 1200, 1040. ^{1}H NMR δ_H ($CDCl_3$): 1.49 (3H, s, C(6)–H_3), 2.42 (2H, m, C(3)–H_2), 2.52 (2H, m, C(2)–H_2), 3.68 (3H, s, OCH_3), 3.78–4.00 (4H, m, OCH_2CH_2O), 4.86+5.59 (2×1H, 2×m, C(4)=CH_2). ^{13}C NMR δ_C ($CDCl_3$): 24.3 (C6), 26.0 (C3), 32.9 (C2), 51.6 (OCH_3), 64.4 (OCH_2CH_2O), 109.3 (C5), 110.7 (C(4)=CH_2), 147.9 (C4), 173.6 (C1). MS (EI) *m*/*z* (%) (relative intensity) 200 (35.0, [M^+]), 185 (26.0), 169 (19.0), 113 (63.0), 87 (100.0), 43 (32.0). HRMS (EI) calcd for $C_{10}H_{16}O_4$: 200.1049, found: 200.1053.

4.2.2. 3-[2-(2-Methyl-[1,3]dioxolan-2-yl)-oxiranyl]-propionic acid methyl ester (**7**)

To a stirred solution of **6** (5.00 g, 25.0 mmol) in dichloromethane (70 mL) was added saturated $NaHCO_3$ solution (2 mL) and 55% *m*-CPBA (8.63 g, 50 mmol). The reaction mixture was stirred at 4 h and then the mixture was diluted with ether (30 mL). The phases were separated and the organic layer was washed with a 10% aqueous solution of NaOH (20 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (eluting with ether/hexane=1:1, R_f=0.41) to afford **7** (4.43 g, 82%) as a colourless oil. IR (neat) ν_{max} 2952, 1736, 1440, 1200, 1132. ^{1}H NMR δ_H ($CDCl_3$): 1.43 (3H, s, C(6)–H_3), 2.00–2.48 (4H, m, C(2)–H_2+C(3)–H_2), 2.52+2.84 (2×1H, 2×d, J_{gem}=5.0 Hz, C(4)–CH_2), 3.68 (3H, s, OCH_3), 3.88–4.00 (4H, m, OCH_2CH_2O). ^{13}C NMR δ_C ($CDCl_3$): 22.1 (C6), 24.6 (C3), 28.7 (C2), 48.4 (C(4)–CH_2), 51.7 (OCH_3), 60.9 (C4), 65.4+66.0 (OCH_2CH_2O), 108.2 (C5), 173.8 (C1). MS (EI) *m*/*z* (%) (relative intensity) 217 (18.0, [M^+]), 206 (14.0), 181 (9.0), 157 (31.0), 141 (19.0), 125 (33.0), 115 (60.0), 87 (46.0), 43 (100.0). HRMS (EI) calcd for $C_{10}H_{16}O_5$: 216.2310, found: 216.2311.

4.2.3. 5-Bromomethyl-5-(2-methyl-[1,3]dioxolan-2-yl)-dihydrofuran-2-one (**8**)

To a solution of **7** (5.00 g, 23.1 mmol) in THF (100 mL) 5 mL of saturated Na_2CO_3 solution and $MgBr_2$ (12.77 g, 69.4 mmol) were added at rt. The reaction mixture was stirred for 8 h at this temperature then the solvent was removed in vacuo. The residue was dissolved in ether (120 mL), washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=1:1, R_f=0.23) and the isolated compound was treated with ether to yield **8** (4.78 g, 78%) as white crystals: mp 103–104 °C. IR (KBr) ν_{max} 2934, 1768, 1448, 1168, 1064. ^{1}H NMR δ_H ($CDCl_3$): 1.38 (3H, s, C(6)–H_3), 2.20–2.75 (4H, m, 2C(2)–H_2+C(3)–H_2), 3.55+3.92 (2×1H, 2×d, J_{gem}=11.2 Hz, CH_2Br), 3.94–4.14 (4H, m, OCH_2CH_2O). ^{13}C NMR δ_C ($CDCl_3$): 20.8 (C6), 26.4 (C3), 29.4 (C2), 37.5 (CH_2Br), 66.1+66.2 (OCH_2CH_2O), 89.3 (C4), 110.3 (C5), 176.3 (C1). MS (EI) *m*/*z* (%) (relative intensity) 265 (26.0, [$M+H^+$]), 221 (22.0), 179 (39.0), 139 (52.0), 121 (33.0), 87 (100.0). HRMS (EI) calcd for $C_9H_{14}BrO_4$: 265.0075, found: 265.0073.

4.2.4. 5-Bromomethyl-5-(2-methyl-[1,3]dioxolan-2-yl)-tetrahydrofuran-2-ol (**4**)

To a solution of **4** (5.00 g, 18.86 mmol) in dry dichloromethane (100 mL) was added a 1 M solution of diisobutylaluminium hydride in hexane (20.75 mL, 20.75 mmol) over 15 min at −78 °C. The mixture was stirred for 1 h then 10 mL of saturated aqueous ammonium chloride solution was added to the solution and was allowed to warm up to rt. The organic phase was washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to give 4.28 g of **4** (85%, R_f=0.38) as a colourless oil (5:1 mixture of the diastereoisomers). IR (neat) ν_{max} 3472, 2976, 1184, 1060, 988. ^{1}H NMR δ_H ($CDCl_3$): 1.40 and 1.34 (3H, s, C(6)–H_3), 1.86+2.33 and 1.91+2.28 (2×1H, 2×dddd, J_{gem}=12.5 Hz, J_{vic}=1.0+2.2+8.6 and 5.0+10.2+10.7 Hz, C(2)–H_2), 1.98+2.17 and 2.06+2.18 (2×1H, 2×ddd, J_{gem}=13.0 Hz, J_{vic}=2.2+10.2 and 8.6+10.7 Hz, C(3)–H_2), 3.56+3.70 and 3.65+3.78 (2×1H, 2×d, J_{gem}=10.8 Hz, CH_2Br), 3.90 and 2.76 (1H, d, *J*=10.7 Hz, OH), 3.95–4.15 (4H, m, OCH_2CH_2O), 5.50 and 5.52 (1H, ddd, J_{vic}=10.7+1.0+5.0 Hz, C(1)–H). ^{13}C NMR δ_C ($CDCl_3$): 21.2 and 21.0 (C6), 28.4 and 28.8 (C3), 35.8 and 35.3 (C2), 38.9 and 39.0 (CH_2Br), 65.7+65.8 and 65.7+65.8 (OCH_2CH_2O), 89.9 (C4), 100.8 and 100.7 (C1), 110.5 (C5). MS (EI) *m*/*z* (%) (relative intensity) 266 (37.0, [M^+]), 249 (28.0), 220 (31.0), 207 (22.0), 185 (21.0), 159 (44.0), 115 (17.0), 87 (100.0). HRMS (EI) calcd for $C_9H_{15}BrO_4$: 267.1170, found: 267.1168.

4.2.5. Methyl 9-benzyl-6-(bromomethyl)-6-(2-methyl-1,3-dioxolan-2-yl)-7-oxa-9,19-diazatetracyclo-[10.7.0.0^{4,8}.0.^{13,18}]-nonadeca-1(12),13,15,17-tetraen-2-carboxylate (**9a** and **9b**)

A solution of **3**[3a] (1.00 g, 2.85 mmol), **4** (0.84 g, 3.14 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol) in dry toluene (50 mL) was heated at reflux under argon over 24 h, then the reaction mixture was cooled and extracted with brine (2×40 mL), the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=2:1, the less polar compound R_f=0.53 (**9a**) and the more polar product R_f=0.39 (**9b**)) to yield 730 mg (44%) of **9a** and 432 mg (26%) of **9b** as yellow oils. Compound **9a**: IR (neat) ν_{max} 3416, 1724, 1464, 1168, 1052, 744. ^{1}H NMR δ_H ($CDCl_3$): 1.15 (3H, s, 18-H_3), 1.71+2.03 (2×1H, 2×ddd, J_{gem}=12.5 Hz, J_{vic}=10.5+3.6 and 12.8+2.0 Hz, 17-H_2), 1.78 (2H, d, *J*=3.0 Hz, 15-H_2), 1.80 (1H, m, 14-H), 2.44+2.84 (2×1H, 2×m, 6-H_2), 2.78+3.20 (2×1H, 2×m, 5-H_2), 3.41+3.74 (2×1H, 2×d, J_{gem}=10.6 Hz, 21-H_2), 3.55–3.85 (4H, m, O–CH_2–CH_2–O), 3.76 (3H, s, OCH_3), 4.03+4.22 (2×1H, 2×d, J_{gem}=13.0 Hz, N–CH_2Ph), 4.80 (1H, br d, *J*=8.8 Hz, 3-H), 4.99 (1H, dd, *J*=12.8+3.6 Hz, 16-H), 7.04 (1H, m, 10-H), 7.12 (1H, m, 11-H), 7.25–7.38 (4H, m, 12-H+3′-H+4′-H+5′-H), 7.43 (1H, m, 9-H), 7.51 (2H, m, 2′-H+6′-H), 8.68 (1H, br s, N1–H). ^{13}C NMR δ_C ($CDCl_3$): 20.2 (C18), 25.2 (C6), 35.3 (C15), 35.8 (C17), 36.8 (C14), 40.4 (C16), 41.1 (C21), 47.5 (C5), 52.2

(OCH_3), 60.7 (NCH_2Ph), 65.1+65.2 (O–CH_2–CH_2–O), 82.9 (C20), 99.8 (C3), 110.6 (C12), 111.2 (C19), 114.5 (C7), 117.9 (C9), 118.9 (C10), 121.5 (C11), 127.2 (C4′), 128.3 (C8), 128.3 (C3′+C5′), 130.0 (C2′+C6′), 130.6 (C2), 135.7 (C13), 139.3 (C1′), 175.6 ($COOCH_3$). MS (EI) *m*/*z* (%) (relative intensity) 582 (8.0, [M^+]), 495 (46.0), 440 (21.0), 354 (15.0), 261 (10.0), 214 (9.0), 87 (100.0). HRMS (EI) calcd for $C_{30}H_{35}BrN_2O_5$: 582.1729, found: 582.1717. Compound **9b**: IR (neat) ν_{max} 3340, 2920, 1724, 1464, 1188, 1060, 744. ^{1}H NMR δ_H ($CDCl_3$): 1.23 (3H, s, 18-H_3), 1.73+2.10 (2×1H, 2×ddd, J_{gem}=12.5 Hz, J_{vic}=11.5+3.6 and 12.8+2.5 Hz, 17-H_2), 1.75 (2H, d, *J*=10.0 Hz, 15-H_2), 1.90 (1H, m, 14-H), 2.38 (1H, m, 6-H_A), 2.80–2.90 (2H, m, 6-H_B+5-H_A), 3.38–3.55 (2×1H, 2×d, J_{gem}=10.8 Hz, 21-H_2), 3.50 (1H, m, 5-H_B), 3.78 (3H, s, OCH_3), 3.85–3.99+4.09 (3H+1H, m, O–CH_2–CH_2–O), 4.10+4.21 (2×1H, 2×d, J_{gem}=13.2 Hz, NCH_2Ph), 4.58 (1H, d, *J*=9.4 Hz, 3-H), 5.07 (1H, dd, *J*=12.8+3.6 Hz, 16-H), 7.04 (1H, m, 10-H), 7.12 (1H, m, 11-H), 7.25–7.38 (4H, m, 12-H+3′-H+4′-H+5′-H), 7.43 (1H, br d, *J*=7.9 Hz, 9-H), 7.48 (2H, m, 2′-H+6′-H), 8.68 (1H, br s, N1–H). ^{13}C NMR δ_C ($CDCl_3$): 21.4 (C18), 25.1 (C6), 36.0 (C17), 36.2 (C15), 37.1 (C14), 39.2 (C21), 40.4 (C16), 47.7 (C5), 52.3 (OCH_3), 60.9 (NCH_2Ph), 65.5+66.1 (O–CH_2–CH_2–O), 83.0 (C20), 99.9 (C3), 110.7 (C12), 112.0 (C19), 114.4 (C7), 118.0 (C9), 118.9 (C10), 121.5 (C11), 127.3 (C4′), 128.2 (C8), 128.4 (C3′+C5′), 129.5 (C2′+C6′), 130.2 (C2), 135.7 (C13), 139.5 (C1′), 175.5 ($COOCH_3$). NOE: 1.90 (14-H)→2.10 (17-H_B), 3.50 (5-H_B), 4.58 (3-H)→1.73 (17-H_A), 3.87 (O–CH_2–CH_2–O), 4.10+4.21 (NCH_2Ph), 5.07 (16-H_β), 5.07 (16-H_β)→1.73 (17-H_A), 2.38 (6-H_A), 4.58 (3-H), 7.48 (2′-H+6′-H). MS (EI) *m*/*z* (%) (relative intensity) 582 (12.0, [M^+]), 495 (34.0), 440 (20.0), 354 (18.0), 261 (9.0), 214 (11.0), 87 (100.0). HRMS (EI) calcd for $C_{30}H_{35}BrN_2O_5$: 582.1729, found: 582.1721.

*4.2.6. 3-Benzyl-4-[3-bromo-2-hydroxy-2-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-2,3,3a,4,5,7-hexahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylic acid methyl ester (**21a$_1$**)*

To a stirred solution of **9a** (1.00 g, 1.71 mmol) in glacial acetic acid (10 mL) was added mercury(II) acetate (1.64 g, 5.14 mmol). The reaction mixture was stirred at rt for 2 h. The precipitated mercury(II) acetate was filtered off and the filtrate was treated with hydrogen sulfide gas. The resulting mixture was filtered through Celite, and the filtrate was poured into ice-water and neutralized with saturated Na_2CO_3 solution. The aqueous phase was extracted with dichloromethane (2×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC (eluting with ether/hexane=2:1, R_f=0.35) to afford **21a$_1$** (668 mg, 67%) as a yellow oil. IR (neat) ν_{max} 3384, 1672, 1608, 1440, 1248, 1208, 744. ^{1}H NMR δ_H ($CDCl_3$): 1.23+1.44 (2×1H, 2×dd, J_{gem}=15.0 Hz, J_{vic}=6.0 and 5.0 Hz, 15-H_2), 1.29 (3H, s, 18-H_3), 1.67+2.03 (2×1H, 2×ddd, J_{gem}=11.6 Hz, J_{vic}=4.6+1.0 and 12.4+6.5 Hz, 6-H_2), 2.35 (1H, br s, OH), 2.41 (1H, m, 14-H), 2.55–2.68 (2H, m, 5-H_A+17-H_A), 2.80 (1H, m, 17-H_B), 2.91 (1H, m, 5-H_B), 3.24 (1H, m, 3-H), 3.42+3.52 (2×1H, 2×d, J_{gem}=10.8 Hz, 21-H_2), 3.78 (3H, s, OCH_3), 3.65–4.00 (5H, m, NCH_AH_BPh+O–CH_2–CH_2–O), 4.34 (1H, br d, J_{gem}=13.2 Hz, NCH_AH_BPh), 8.78–6.84 (2H, m, 10-H+12-H), 6.96 (1H, m, 9-H), 7.12 (1H. m, 11-H), 7.25–7.50 (5H, m, Ph), 8.92 (1H, br s, N1–H). ^{13}C NMR δ_C ($CDCl_3$): 20.4 (C18), 24.3 (C17), 34.2 (C14), 34.7 (C15), 39.1 (C21), 42.6 (C6), 50.4 (C5), 51.0 (OCH_3), 55.0 (C7), 57.7 (NCH_2Ph), 65.2+65.5 (O–CH_2–CH_2–O), 73.2 (C3), 77.3 (C20), 91.3 (C16), 109.2 (C12), 111.8 (C19), 120.5 (C10), 122.2 (C9), 127.1 (C4′), 127.8 (C11), 128.3 (C3′+C5′), 129.0 (C2′+C6′), 137.7 (C8), 143.0 (C13), 165.5 (C2), 169.2 ($COOCH_3$). MS (EI) *m*/*z* (%) (relative intensity) 582 (6.0, [M^+]), 495 (19.0), 442 (8.0), 373 (12.0), 356 (15.0), 326 (10.0), 228 (17.0), 180 (9.0), 91 (46.0), 87 (100.0). HRMS (EI) calcd for $C_{30}H_{35}^{79}BrN_2O_5$: 582.1729, found: 582.1729.

*4.2.7. 3-Benzyl-4-[3-bromo-2-hydroxy-2-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-2,3,3a,4,5,7-hexahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylic acid methyl ester (**21a$_2$**)*

To a stirred solution of **9b** (1.00 g, 1.71 mmol) in glacial acetic acid (10 mL) was added mercury(II) acetate (1.64 g, 5.14 mmol). The reaction mixture was stirred at rt for 2 h. The precipitated mercury(II) acetate was filtered off and the filtrate was treated with hydrogen sulfide gas. The resulting mixture was filtered through Celite, and the filtrate was poured into ice-water and neutralized with saturated Na_2CO_3 solution. The aqueous phase was extracted with dichloromethane (2×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC (eluting with ether/hexane=2:1, R_f=0.30) to afford **21a$_2$** (610 mg, 61%) as a yellow oil. IR (neat) ν_{max} 3384, 2944, 1672, 1608, 1440, 1280, 1204, 748. ^{1}H NMR δ_H ($CDCl_3$): 1.21+1.40 (2×1H, 2×dd, J_{gem}=13.6 Hz, J_{vic}=5.0 and 4.7 Hz, 15-H_2), 1.24 (3H, s, 18-H_3), 1.65+2.00 (2×1H, 2×ddd, J_{gem}=11.5 Hz, J_{vic}=12.1+6.3 and 4.5+1.1 Hz, 6-H_2), 2.32 (1H, br s, OH), 2.37 (1H, br m, 14-H), 2.58–2.64 (2H, m, 5-H_A+17-H_A), 2.74 (1H, dm, J_{gem}=3.0 Hz, 17-H_B), 2.86 (1H, br m, 5-H_B), 3.24 (1H, s, 3-H), 3.45+3.55 (2×1H, 2×d, J_{gem}=10.7 Hz, 21-H_2), 3.67 (1H, J_{gem}=13.6 Hz, NCH_ACH_BPh), 3.77 (3H, s, OCH_3), 3.84–3.94 (4H, m, OCH_2CH_2O), 4.31 (1H, d, J_{gem}=13.6 Hz, NCH_ACH_BPh), 6.81–6.84 (2H, m, 10-H+12-H), 7.04 (1H, br s, 9-H), 7.13 (1H, m, 11-H), 7.27–7.43 (5H, m, Ph), 8.93 (1H, br s, N1–H). ^{13}C NMR δ_C ($CDCl_3$): 20.5 (C18), 24.9 (C17), 34.2 (C14), 35.2 (C15), 39.7 (C21), 43.1 (C6), 50.86 (C5), 51.2 ($COOCH_3$), 55.3 (C7), 58.2 (NCH_2Ph), 65.1+65.7 (OCH_2CH_2O), 73.8 (C3), 77.5 (C20), 91.5 (C16), 109.4 (C12), 111.9 (C19), 120.7 (C10), 122.4 (C9), 127.1 (C4′), 127.9 (C11), 128.5 (C3′+C5′), 129.0 (C2′+C6′), 138.1 (C8), 139.9 (C1′), 143.2 (C13), 166.1 (C2), 169.4 ($COOCH_3$). MS (EI) *m*/*z* (%) (relative intensity) 582 (8.0, [M^+]), 495 (17.0), 442 (12.0), 373 (14.0), 356 (11.0), 326 (7.0), 228 (17.0), 180 (19.0), 91 (41.0), 87 (100.0). HRMS (EI) calcd for $C_{30}H_{35}BrN_2O_5$: 582.1729, found: 582.1725.

*4.2.8. 2-Hydroxy-2-(2-methyl-[1,3]dioxolan-2-yl)-2,3,3a,4,6,11,12,12b-octahydro-1H-6,12a-diaza-indeno-[7,1-cd]flourene-5-carboxylic acid methyl ester (**23a**)*

A mixture of **21a$_1$** (500 mg, 0.86 mmol) and 10% palladium/charcoal (50 mg) in dry methanol (10 mL) was hydrogenated for 1 h at rt, then filtered and the solvent was evaporated in vacuo. The residue was dissolved in dry DMF (10 mL), K_2CO_3 (130 mg, 0.94 mmol) was added to the solution and heated at 100 °C for 16 h. After heating, the reaction mixture was allowed to cool to rt and poured into water (10 mL). The aqueous phase was extracted with ether (2×30 mL), the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The main component was separated by preparative TLC (eluting with acetone/hexane=1:2, R_f=0.37) to yield **23a** (138 mg, 39%) as a yellow oil. IR (neat) ν_{max} 3360, 2944, 1672, 1608, 1464, 1440, 1240, 1200, 748. ^{1}H NMR δ_H ($CDCl_3$): 1.35 (3H, s, 18-H_3), 1.55 (1H, dd, J_{gem}=13.0 Hz, J_{vic}=12.6 Hz, 15-H_A), 1.77 (1H, ddd, J_{gem}=13.0 Hz, J_{vic}=2.8 and 2.7 Hz, 15-H_B), 1.82+2.58 (2×1H, dd, J_{gem}=11.5 Hz, J_{vic}=4.6 Hz, 6-H_2), 2.00 (1H, dd, J_{gem}=16.0 Hz, J_{vic}=13.0 Hz, 17-H_A), 2.39 (1H, m, 14-H), 2.42 (1H, br s, OH), 2.52 (1H, dd, J_{gem}=16.0 Hz, J_{vic}=6.0 Hz, 17-H_B), 2.78 (1H, d, J_{gem}=10.2 Hz, 3-H), 3.13+3.24 (2×1H, 2×d, J_{gem}=14.5 Hz, 21-H_2), 3.28+3.78 (2×1H, br m, 5-H_2), 3.74 (3H, s, OCH_3), 3.90–4.08 (4H, m, OCH_2CH_2O), 6.76 (1H, d, J_{gem}=7.6 Hz, 12-H), 6.83 (1H, m, 10-H), 7.09 (1H, m, 11-H), 7.45 (1H, m, 9-H), 9.04 (1H, br s, N1–H). ^{13}C NMR δ_C ($CDCl_3$): 19.1 (C18), 27.0 (C14), 30.1 (C17), 36.6 (C15), 41.5 (C6), 47.8 (C5), 51.2 ($COOCH_3$), 51.4 (C21), 55.03 (C7), 65.6+65.7 (OCH_2CH_2O), 66.0 (C3), 77.4 (C20), 94.3 (C16), 109.3 (C12), 111.9 (C19), 121.0 (C10), 123.1 (C9), 127.6 (C11), 137.8 (C8), 144.2 (C13), 164.7 (C2), 169.3 ($COOCH_3$). MS (EI) *m*/*z* (%) (relative intensity) 412 (16.0, [M^+]), 356 (6.0), 229 (17.0), 181 (12.0), 87 (100.0). HRMS (EI) calcd for $C_{23}H_{28}N_2O_5$: 412.4788, found: 412.4786.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for all new compounds and computational data are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.015.

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