Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal



Cite this: DOI: 10.1039/c5ob02624e

# Concise asymmetric syntheses of novel phenanthroquinolizidines†

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Received 21st December 2015,
Accepted 13th January 2016

DOI: 10.1039/c5ob02624e

www.rsc.org/obc

The first preparation of enantioenriched phenanthroquinolizidines with a quaternary center at $C_{14a}$ was accomplished in seven steps from readily available starting materials. Key steps were an efficient dynamic kinetic allylation of a diastereomeric mixture of chiral *tert*-butylsulfinyl ketimines and the construction of a piperidine E ring by rhodium catalyzed hydroformylation. The Stevens rearrangement of the corresponding *N*-benzyl derivatives took place smoothly, allowing the installation of a benzyl moiety at $C_9$ in a *trans* relationship with the methyl group. The cytoxicity of the prepared phenanthroquinolizidines was evaluated against different human cancer cell lines.

## Introduction

Compared with synthetic drugs, natural product derivatives show lower toxicity and easier decomposition, which is also more environmentally friendly.[1] These advantages, in addition to their unique mode of action, are responsible for the growing interest in the synthesis and biological evaluation of natural based compounds. Among natural alkaloids are a small group of phenanthroquinolizidines (*e.g.* cryptopleurine and boehmeriasin A in Fig. 1) which are produced by the Lauraceae, Vitaceae, and Urticaceae family of plants.[2] Remarkably, these compounds exhibit very high cytotoxic activities with $IC_{50}$ in the nanomolar range, being in some cases more potent than taxol.[3] Moreover, they have shown higher antiproliferative activity than their structurally related phenanthroindolizidine alkaloids.[4] It is reported that these alkaloids and their analogs display a wide range of biological activities and they are currently being used as lead compounds in order to optimize these activities.[5]

Some natural phenanthroindolizidine alkaloids bearing a methyl group at the 13a-position (*e.g.* hypoestestatin 1 and 2, Fig. 1) have been identified as extremely potent antitumor agents.[6] Recent studies have shown that the inclusion of a substituent next to the nitrogen atom disrupts the molecular planarity, decreasing the crystal packing energy and therefore increasing its water solubility.[7] It is worth mentioning that enhancing the hydrophilicity of these compounds is an established strategy to improve their bioavailability, so as to lower their blood–brain barrier permeability, which potentially might minimize their CNS toxicity.[8] In this context, the asymmetric syntheses of some 13a-substituted phenanthroindolizidine alkaloids have been successfully accomplished, using proline derivatives as chiral building blocks.[9] However, to the best of our knowledge, the enantioselective synthesis of structurally related phenanthroquinolizidines with a quaternary center at $C_{14a}$ remains unexplored. Given the unique biological activities of 7-methoxycryptopleurine,[10] we considered that this compound would offer a good platform to explore this strategy.

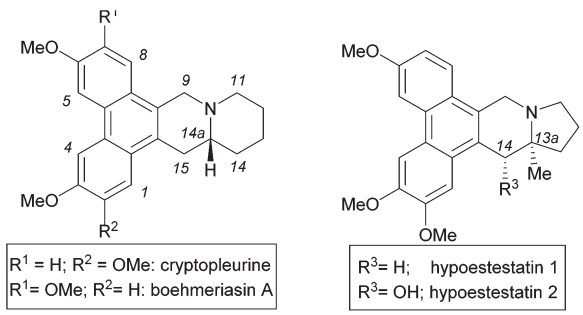


**Fig. 1** Some phenanthroizidine alkaloids.

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†Electronic supplementary information (ESI) available: Copies of $^1H$ and $^{13}C$ NMR spectra for compounds **2–10**, and HPLC traces used for the determination of enantiomeric ratios of compounds **8** and **10**. The dose–response curves for cytotoxic compounds against four cancer cell lines, as well as the general information related to the cytotoxicity assays. See DOI: 10.1039/c5ob02624e

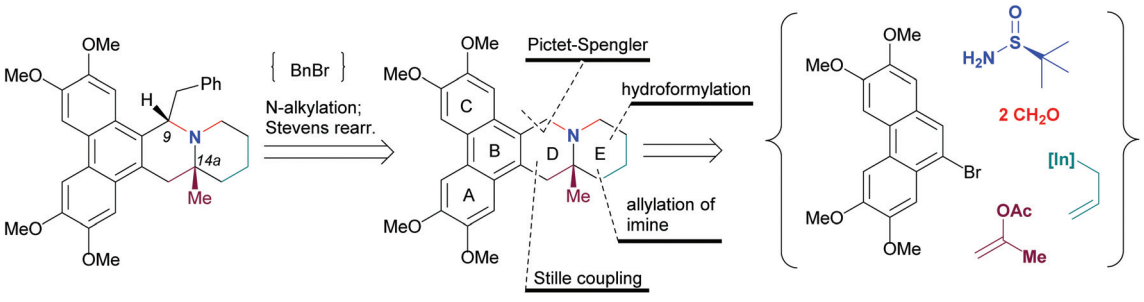
## Results and discussion

We describe herein a protocol for the asymmetric preparation of 7-(*R*)- and (*S*)-methoxy-14a-methylcryptopleurine,[11,12] as well as the first regio- and diastereoselective Stevens rearrangement of the corresponding *N*-benzyl ammonium salt.

In our retrosynthetic analysis (Scheme 1), we envisaged that a benzyl group could be diastereoselectively installed at C-9 by *N*-benzylation of the corresponding phenanthroquinolizidine, followed by the Stevens rearrangement. The synthesis of this scaffold was planned by building ring D in the last step using Pictet–Spengler annulation, while ring E could be formed by hydroformylation of the corresponding homoallylic amine.[13] Importantly, the chiral quaternary center was anticipated to be formed by allylation of the chiral *tert*-butylsulfinyl ketimine derived from the corresponding methylketone. As outlined in Scheme 1, the target molecule was traced back to 9-bromo-2,3,6,7-tetramethoxyphenanthrene, chiral *tert*-butylsulfinamide, allylindium reagent, formaldehyde and isoprenyl acetate; all of them commercially or easily available starting materials.

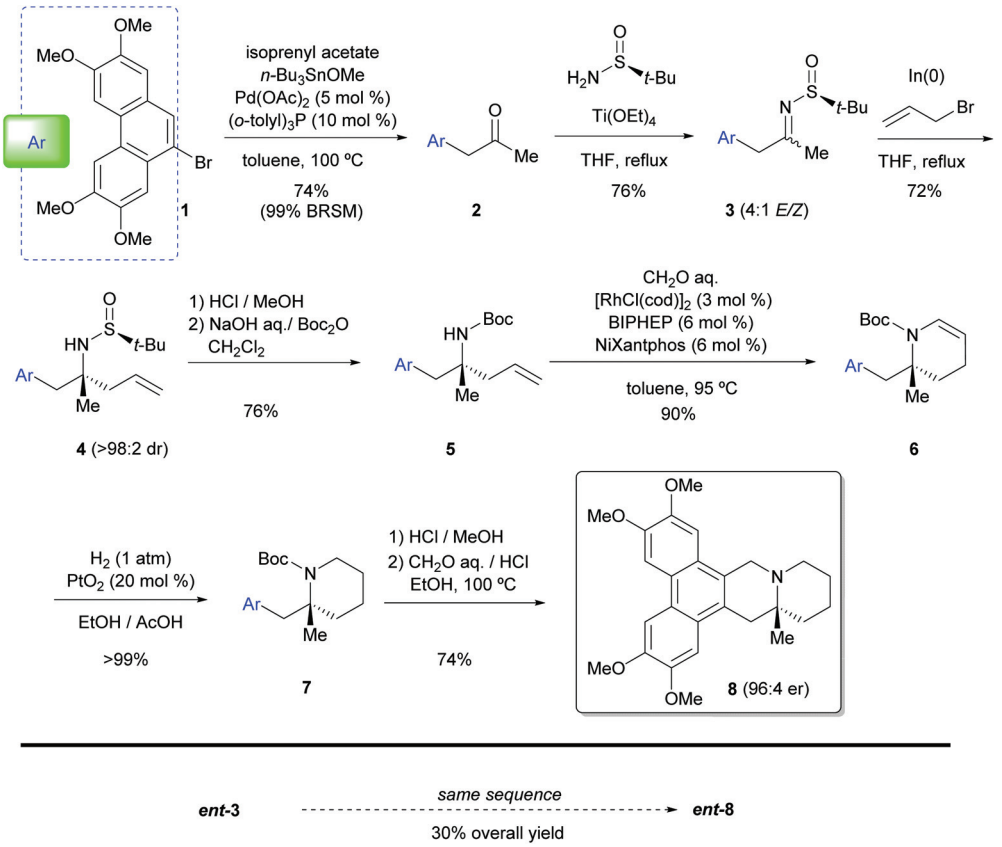
The realization of our synthetic plan is outlined in Scheme 2. The palladium catalyzed cross coupling of isoprenyl acetate with the readily available 9-bromo-2,3,6,7-tetramethoxyphenanthrene[14] was efficiently promoted by tributyltin methoxide to afford the desired methylketone **2** in high yield.[15] Condensation of ketone **2** with (*Ss*)-*tert*-butylsulfinamide afforded the corresponding ketimine as a 4 : 1 mixture of *E*/*Z* isomers-**3**, which upon addition of *in situ* formed allylindium reagent furnished the expected chiral amine **4** with an α-quaternary center as a single isomer (>98 : 2 dr according to NMR).[16] This efficient dynamic kinetic transformation of *tert*-butylsulfinyl ketimines to homoallylic amines has been previously reported[17,18] and it is worth mentioning that the one-pot indium mediated direct aminoallylation of the methyl ketone – a procedure that we have previously developed and successfully used in our group[19] – gave significantly lower conversion in this case (up to 30%). Our next key step was the rhodium catalyzed linear hydroformylation to build ring E as an enamine. Given our previous experience with this strategy,[13] the sulfinyl group was replaced by an *N*-Boc protecting group. We thus subjected compound **5** to rhodium(I) catalyzed hydroformylation with formalin, using two different phosphane ligands (BIPHEP and NiXantphos). The characteristics of this hydroformylation protocol are unique because the syngas ($CO/H_2$) is conveniently substituted by formaldehyde, with excellent linear selectivity.[20] Under these conditions, the formation of the corresponding terminal aldehyde was followed by *in situ* cyclization to furnish the protected enamine **6**. We were pleased to observe that by only increasing the loading of rhodium catalyst from 1 mol% to 3 mol%, the isolated yield of compound **6** increased from 61% to 90%. Catalytic hydrogenation of enamine **6** using Adams's catalyst, followed by acidic removal of the Boc group and Pictet–Spengler cyclomethylenation under standard conditions (formalin, HCl, EtOH, 100 °C),[21] allowed the preparation of the target compound **8** with very good overall yield. The same synthetic sequence was applied to obtain *ent*-**8** from (*Rs*)-*tert*-butylsulfinamide with a similar efficiency in terms of isolated yields. Chiral HPLC analysis of both enantiomers (**8** and *ent*-**8**) shows that racemization did not take place over the synthetic sequence (96 : 4 er, see the ESI†).

During the optimization of the biological activities of phenanthroquinolizidines, diverse substituted compounds have been reported in the literature.[4b,10d,22] However, substitutions at C-9 of this skeleton remain scarce.[23] With this in mind, we decided to explore the Stevens rearrangement[24] of the *N*-benzyl isoquinolinium salts **9** and *ent*-**9**, which were efficiently prepared using conventional methods (Scheme 3). It is worth noting that the NMR data ($^1H$ and $^{13}C$) obtained for these compounds are consistent with a single diastereoisomer. In contrast with other related alkaloids that contain the quinolizidine moiety (*e.g.* berbines),[25] inversion at the N bridgehead of the starting material is unlikely in phenanthroquinolizidines and the adjacent methyl group should stabilize the *trans* isomer. It is generally assumed that, either by formation of an iminium ion or *via* recombination of radical pairs in the solvent-cage,[26] the Stevens rearrangement is suprafacial. Given that only *trans*-isoquinolinium isomer **9** seems to be present, deprotonation at the benzylic C-9 position, followed by the rearrangement should only afford *trans*-**10** compound. Given the good results obtained in the synthesis of 8-benzylberbines, by using *in situ* prepared dimsyl sodium solution at room temperature for the Stevens rearrangement,

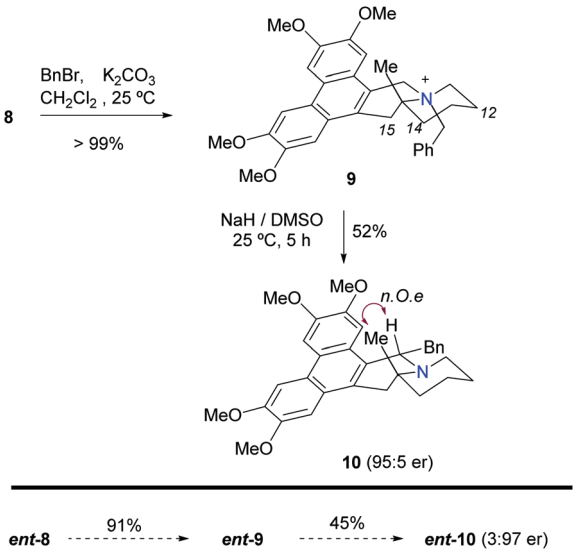



**Scheme 1** Retrosynthetic analysis of the target molecule.




**Scheme 2** Syntheses of phenanthroquinolizidines **8** and *ent*-**8**.




**Scheme 3** Regio-and stereoselective Stevens rearrangement of compound **9**.

we adopted these conditions and compound **10** was obtained in a moderate yield.[27] Although we were not able to identify the by-products formed in this reaction, we reasoned that hydrogens at β-positions ($H_{12eq}$, $H_{14eq}$ and $H_{15eq}$) make Hofmann eliminations competitive pathways. Importantly, a significant H,H-n.O.e was observed between the Me at $C_{14a}$ and $H_9$ of compound **10** (see the ESI†), confirming the presumed *trans*-configuration for this compound. Using the same method, *ent*-**9** was transformed into *ent*-**10**. Having prepared both enantiomers, the enantiomeric purity of the samples was determined by chiral HPLC analysis, being above 90% ee in both cases.

Compounds **8**, **9**, **10** and their enantiomers were tested against four human cancer cell lines, using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltretrazolium bromide) method and CDDP [*cis*-diaminedichloroplatinum(II)] as the positive control. The $IC_{50}$ values were determined from the corresponding inhibition/concentration curves (see the ESI†) when more than 50% cellular growth inhibition was achieved at 100 μM and the results are shown in Table 1. The best results were obtained for compound **8**, with the (*R*)-configuration (as in natural cryptopleurine), against human breast cancer cell lines (MCF-7) and with leukemia cells (HL-60). The potency of this compound was 20-fold (for MCF-7) or 10-fold (for HL-60) superior to that of its enantiomer, but it was significantly lower than the one of the (*R*)-7-methoxycryptopleurine, without a methyl group at $C_{14a}$.[13] Unfortunately, when the benzyl group was attached to the nitrogen atom and then

Table 1 Cytotoxicity of the compounds evaluated

| | IC50 [a] (μM) | | | |
|---|---|---|---|---|
| Compounds | MCF-7[b] | NCI-H460[c] | HL-60[d] | NCI/ADR-RES[e] |
| CDDP | 16 ± 1 | 5.7 ± 0.2 | 8.3 ± 0.2 | 6.3 ± 0.2 |
| **8**·HCl | 1.1 ± 0.1 | 34[f] ± 7 | 0.51 ± 0.02 | 69[f] ± 26 |
| *ent*-**8**·HCl | 21 ± 2 | 42 ± 1 | 4.9 ± 0.1 | 26 ± 1 |
| **9** | 80[f] ± 14 | n.d.[g] | 65[f] ± 5 | n.d.[g] |
| *ent*-**9** | 76[f] ± 7 | 393[f] ± 168 | n.d.[g] | n.d.[g] |
| **10** | 35[f] ± 1 | n.d.[g] | 80[f]±3 | n.d.[g] |
| *ent*-**10** | 36 ± 1 | n.d.[g] | n.d.[g] | n.d.[g] |

[a] Average of three assays each. [b] MCF-7 = human breast carcinoma. [c] NCI-H460 = human lung carcinoma. [d] HL-60 = human promyelocytic leukemia. [e] NCI-ADR-RES = drug-resistant human ovarian adenocarcinoma. [f] Extrapolated values from an incomplete concentration–response curve (see the ESI). [g] Not determined.

rearranged to $C_9$, the obtained compounds showed poorer cellular growth inhibition.

## Conclusions

We have developed a seven step procedure to prepare enantioenriched 14a-methyl-7-methoxycryptopleurine in 18–21% overall yield from readily available starting materials. The salient features of the synthetic procedure are: (a) the straightforward formation of methyl ketone **2**; (b) the efficient dynamic kinetic allylation of *tert*-butylsulfinyl ketimines **3** (4 : 1 *E*/*Z* mixture) to obtain compound **4** as a single isomer; and (c) a rhodium catalyzed linear hydroformylation with formalin that allows the construction of ring E in excellent yield. *N*-Benzylation of phenanthroquinolizidine **8**, followed by the Stevens rearrangement at room temperature allows for regio- and stereoselective placement of a benzyl group and $C_9$. The cytotoxic evaluation of compound **8** (*ent*-**8**) indicates that the introduction of a methyl group at $C_{14a}$ decreases the potency of 7-methoxycryptopleurine. In addition, the introduction of a benzyl group at $C_9$ of the same scaffold had a more significant negative impact on its cytotoxicity. The synthetic route developed herein opens the access to enantioenriched phenathroquinolizidines with a quaternary center at $C_{14a}$ and *trans*-$C_9$ benzyllic derivatives, which hopefully can display different biological activities.

## Experimental

### General information

TLC was performed on silica gel 60 $F_{254}$, using aluminium plates and visualized by exposure to ultraviolet light. Flash chromatography was carried out on handpacked columns of silica gel 60 (230–400 mesh). Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 °C and concentrations (*c*) are given in g per 100 mL. Infrared analysis was performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in $cm^{-1}$. HRMS analyses were carried out using the Electron Impact (EI) mode at 70 eV or by Q-TOF using Electro Spray Ionization (ESI) mode. HPLC analyses were performed using a Chiralpak IB column for enantiomeric ratios. $^1$H NMR spectra were recorded at 300 or 400 MHz for $^1$H NMR and 75 or 100 MHz for $^{13}$C NMR, using $CDCl_3$ as the solvent and TMS as an internal standard (0.00 ppm). $^{13}$C NMR spectra were recorded with $^1$H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, $CH_2$ and $CH_3$.

**1-(2,3,6,7-Tetramethoxyphenanthren-9-yl)propan-2-one (2).** A dry flask was charged with 9-bromo-2,3,6,7-tetramethoxyphenanthrene[14] (391 mg, 1.04 mmol), $Pd(OAc)_2$ (11.67 mg, 0.05 mmol, 5 mol%) and tri-*ortho*-tolylphosphine (33 mg, 0.10 mmol). The reaction mixture was evacuated and backfilled with argon (3 cycles) before adding toluene (1.21 mL), tributyltin methoxide (463 μL, 1.60 mmol) and isoprenyl acetate (174 μL, 1.57 mmol). The reaction mixture was stirred while heating at 100 °C for 6 h. The reaction mixture was cooled down to room temperature and diluted with EtOAc (2.0 mL) and 4 M aqueous potassium fluoride solution (1.5 mL) and stirred for 15 min, before being filtered through a short pad of Celite, washed with EtOAc and concentrated *in vacuo*. The residue was purified by flash chromatography (6 : 4 to 1 : 1 hexane/EtOAc), recovering the starting material (98 mg, 25%) and obtaining the desired product as a ochre yellow solid (274 mg, 74%): $R_f$ 0.24 (1 : 1 hexane/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.83 (s, 1H), 7.78 (s, 1H), 7.53 (s, 1H), 7.28 (s, 1H), 7.21 (s, 1H), 4.12 (s, 3H), 4.12 (s, 3H), 4.06 (s, 2H), 4.04 (s, 3H), 4.02 (s, 3H), 2.09 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 208.0 (*C*), 149.5 (*C*), 149.2 (*C*), 149.1 (*C*), 127.3 (*C*), 126.6 (*C*H), 126.34 (*C*), 125.6 (*C*), 125.1 (*C*), 124.4 (*C*), 108.2 (*C*H), 105.1 (*C*H), 103.5 (*C*H), 102.9 (*C*H), 56.2 ($CH_3$), 56.19 ($CH_3$), 56.0 ($CH_3$), 50.8 ($CH_2$), 28.7 ($CH_3$); HRMS (ESI) calcd for $C_{21}H_{23}O_5$ 355.1545, found 355.1549.

**(*E*/*Z*,*S*$_S$)-*N*-(*tert*-Butylsulfinyl)-1-(2,3,6,7-tetramethoxy-phenanthren-9-yl)propan-2-imine (3).** To a dry flask were sequentially added ($S_S$)-*tert*-butylsulfinamide (1.83 mg, 1.50 mmol), compound **2** (531 mg, 1.5 mmol) and THF (3.0 mL), followed by $Ti(OEt)_4$ (675 μL, 3.0 mmol). The reaction mixture was stirred overnight at 65 °C. After cooling to room temperature, it was carefully added over a stirring mixture of 4 : 1 EtOAc/brine. The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and concentrated to dryness. The residue was purified by flash chromatography (4 : 6 to 3 : 7 hexane/EtOAc,), affording the imine as a yellow foam solid (401 mg, 76%, 80 : 20 *E*/*Z*): $R_f$ 0.23 (3 : 7 hexane/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.83 (s, 1H), 7.78 (s, 1H), 7.55–7.48 (m, 1H), 7.47–7.42 (m, 1H), 7.23–7.19 (m, 1H), 4.13 (s, 6H), 4.04 (s, 3H), 4.02 (s, 3H), 2.29 (s, 1.84H, *E*-isomer), 2.09 (s, 0.36H, *Z*-isomer), 1.23 (s, 1.31H, *Z*-isomer), 1.20 (s, 5.69H, *E*-isomer); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.5 (*C*), 149.2 (*C*), 149.1 (*C*), 149.0 (*C*), 128.1 (*C*), 126.6, 126.2 (*C*), 125.8 (*C*), 125.1 (*C*), 124.4 (*C*), 108.2 (*C*H), 105.6 (*C*H), 103.5 (*C*H), 102.9 (*C*H), 56.6 (*C*), 56.3 ($2CH_3$), 56.2 ($CH_3$), 56.1 ($CH_3$), 49.3 ($CH_2$), 22.3

($CH_3$), 21.8 ($CH_3$); HRMS (ESI) calcd for $C_{25}H_{31}NO_5NaS$ 480.1821, found 480.1827.

**(*ent*-3).** It was prepared from ($R_S$)-*tert*-butylsulfinamide (228.7 mg, 1.89 mmol), following the same procedure described for the preparation of **3**, with a similar yield (571 mg, 66%). It was obtained as a 4 : 1 *E*/*Z* mixture with identical characterization data as that of compound **3**.

**(1*R*,$S_S$)-*N*-(*tert*-Butylsulfinyl)-1-allyl-1-methyl-2-[2,3,6,7-tetramethoxyphenanthren-9-yl]-ethylamine (4).** To a mixture of imine **3** (505 mg, 1.10 mmol) in dry THF (2.2 mL) were sequentially added indium powder (159 mg, 1.38 mmol) and allyl bromide (144 μL, 1.66 mmol). The reaction mixture was stirred overnight under an argon atmosphere at 65 °C. Afterwards, the mixture was filtered through a short pad of Celite, washed with EtOAc and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3 : 7) to obtain the desired product as a white amorphous solid (398 mg, 72%, >98 : 2 dr according to $^1$H-NMR[16]): $[\alpha]_{20}^{D}$ −3.0 (*c* 6.56, $CHCl_3$); $R_f$ 0.18 (3 : 7 hexane/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.80 (s, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 7.43 (s, 1H), 7.18 (s, 1H), 6.09–5.92 (m, 1H), 5.29 (d, *J* = 3.2 Hz, 1H), 5.23 (s, 1H), 4.11 (s, 3H), 4.11 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H), 3.77 (s, 1H), 3.43 (d, *J* = 14.2 Hz, 1H), 3.28 (d, *J* = 14.2 Hz, 1H), 2.66 (d, *J* = 7.3 Hz, 2H), 1.23 (s, 3H), 1.07 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.3 (*C*), 149.1 (*C*), 148.9 (*C*), 148.6 (*C*), 133.7 (*C*H), 128.9 (*C*), 127.9, 126.6 (*C*), 126.1 (*C*), 125.1 (*C*), 123.9 (*C*), 120.1 (*C*), 108.1 (*C*H), 105.9 (*C*H), 103.5 (*C*H), 102.8 (*C*H), 59.4 (*C*), 56.8 (*C*), 56.3 (2$CH_3$), 56.2 ($CH_3$), 56.1 ($CH_3$), 46.0($CH_2$), 42.2 ($CH_2$), 26.5 ($CH_3$), 22.8 ($CH_3$); HRMS (ESI) calcd for $C_{28}H_{38}NO_5S$ 500.2471, found 500.2478.

**(*ent*-4).** It was prepared from *ent*-**3** (925 mg, 2.02 mmol), following the same procedure described for the preparation of **4**, with a better yield (819 mg, 81%) and identical characterization data, except for optical rotation: $[\alpha]_{20}^{D}$ +6 (*c* 4.13, $CHCl_3$).

**(2*R*)-*tert*-Butyl-(2-methyl-1-(2,3,6,7-tetramethoxy-phenanthren-9-yl)pent-4-en-2-yl)carbamate (5).** To a solution of compound **4** (313 mg, 0.76 mmol) in MeOH (7.6 mL) was added a solution of 4 M HCl in dioxane (0.76 mL, 3.04 mmol) at 0 °C. The reaction mixture was stirred 1.5 h at 25 °C and then was concentrated to dryness. The residue was dissolved in $CH_2Cl_2$ (7.6 mL) and after cooling down the solution to 0 °C, a 2 M aqueous solution of NaOH (7.6 mL) and $Boc_2O$ (188.1 mg, 0.84 mmol) was sequentially added. The mixture was stirred under an argon atmosphere at 25 °C for 2.5 h. The mixture was extracted with $CH_2Cl_2$ (3 × 20 mL), the collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash chromatography (7 : 3 hexane/EtOAc) to obtain the desired product as a white amorphous solid (286 mg, 76%): $[\alpha]_{20}^{D}$ −18 (*c* 6.83, $CHCl_3$); $R_f$ 0.20 (7 : 3 hexane/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.82 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 7.15 (s, 1H), 5.97–5.78 (m, 1H), 5.21–5.05 (m, 2H), 4.44 (s, 1H), 4.13 (s, 3H), 4.12 (s, 3H), 4.09 (s, 3H), 4.02 (s, 3H), 3.69–3.59 (m, 1H), 3.41 (d, *J* = 14.1 Hz, 1H), 2.87 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.34 (dd, *J* = 13.7, 7.4 Hz, 1H), 1.49 (s, *J* = 10.3 Hz, 9H), 1.18 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 154.7 (*C*), 149.2 (*C*), 148.9 (*C*), 148.8 (*C*), 148.5 (*C*), 134.1 (*C*H), 130.2 (*C*), 127.1 (*C*H), 127.0 (*C*), 126.2 (*C*), 124.9 (*C*), 123.8 (*C*), 118.9 ($CH_2$), 108.0 (*C*H), 106.6 (*C*H), 103.2 (*C*H), 102.9 (*C*H), 78.9 (*C*), 56.4 ($CH_3$), 56.3 ($CH_3$), 56.1 ($CH_3$), 55.9 ($CH_3$), 43.4 ($CH_2$), 40.1 ($CH_2$), 28.7 ($CH_3$), 25.3 ($CH_3$); HRMS (ESI) calcd for $C_{29}H_{37}NO_6Na$ 518.2519, found 518.2523.

**(*ent*-5).** It was prepared from *ent*-**4** (819 mg, 1.64 mmol), following the same procedure described for the preparation of **5**, with a similar yield (568 mg, 70%) and identical characterization data, except for optical rotation: $[\alpha]_{20}^{D}$ +15 (*c* 7.50, $CHCl_3$).

**(2*R*)-*tert*-Butyl-2-methyl-2-((2,3,6,7-tetramethoxy-phenanthren-9-yl)methyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (6).** To a pressure tube were sequentially added $[RhCl(cod)]_2$ (6.92 mg, 0.014 mmol), BIPHEP (14.97 mg, 0.028 mmol), NiXantphos (15.80 mg, 0.028 mmol) and toluene (2.8 mL). The system was then evacuated and filled back with argon before compound **5** (232 mg, 0.468 mmol) and aqueous formalin (37%, 0.3 mL, 12.65 mmol) were added. The reaction mixture was deoxygenated *via* three cycles of freeze–pump and thaw under an argon atmosphere and heated to 90 °C. The mixture was stirred for 40 h at the same temperature and then left to reach room temperature, before being concentrated and purified by flash chromatography (hexane/EtOAc 7 : 3) to obtain the desired product as a white amorphous solid (213 mg, 90%): $[\alpha]_{20}^{D}$ −21 (*c* 6.86, $CHCl_3$); $R_f$ 0.21 (7 : 3 hexane/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.95 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.37 (s, 1H), 7.16 (s, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 5.00–4.91 (m, 1H), 4.14 (s, 3H), 4.12 (s, 3H), 4.12 (s, 3H), 4.04 (s, 3H), 3.97 (s, 1H), 3.08 (d, *J* = 14.0 Hz, 1H), 2.45–2.27 (m, 1H), 2.17–1.95 (m, 2H), 1.80–1.65 (m, 1H), 1.45 (s, 3H), 1.26 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.7 (*C*), 149.0 (*C*), 148.9 (*C*), 148.8 (*C*), 148.6 (*C*), 131.0 (*C*), 127.5 (*C*), 127.4 (*C*H), 126.6 (*C*H), 126.2 (*C*), 124.8 (*C*), 123.9 (*C*), 108.0 (*C*H), 107.1 (*C*H), 104.3 (*C*H), 103.0 (*C*H), 102.9 (*C*H), 80.5 (*C*), 58.3 (*C*), 56.3 ($CH_3$), 56.2 ($CH_3$), 56.1 ($CH_3$), 56.0 ($CH_3$), 37.6 ($CH_2$), 35.9 ($CH_2$), 28.2 ($CH_3$), 25.9 ($CH_3$), 19.2 ($CH_2$); HRMS (ESI) calcd for $C_{30}H_{37}NO_6Na$ 530.2519, found 530.2510.

**(*ent*-6).** It was prepared from *ent*-**5** (473 mg, 0.95 mmol), following the same procedure described for the preparation of **6**, with a similar yield (353 mg, 82%) and identical characterization data, except for optical rotation: $[\alpha]_{20}^{D}$ +27 (*c* 4.6, $CHCl_3$).

**(*R*)-*tert*-Butyl-2-methyl-2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)piperidine-1-carboxylate (7).** A dry flask was charged with compound **6** (93 mg, 0.18 mmol), $PtO_2$ (83% content Pt, 10.0 mg, 0.04 mmol) and a mixture of EtOH/AcOH (3.4 mL : 1.4 mL). The flask was connected to a balloon of hydrogen through a three-way valve and the reaction mixture was put under a hydrogen atmosphere (1 atm) after 3 cycles of freeze–pump and thaw. The resulting suspension was stirred at 25 °C for 24 h, and then was filtered through Celite and washed with EtOAc (3 × 15 mL). The organic solution was concentrated to dryness and the desired product was obtained as a white amorphous solid (90 mg, >99%): $[\alpha]_{20}^{D}$ +16 (*c* 7.90, $CHCl_3$); $R_f$ 0.21 (7 : 3 hexane/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.95 (s, 1H), 7.83 (s, 1H), 7.79 (s, 1H), 7.38 (s, 1H), 7.15 (s, 1H), 4.13 (s, 6H), 4.12 (s, 3H), 4.04 (s, 3H), 3.86–3.71

(m, 2H), 3.43 (d, $J$ = 14.0 Hz, 1H), 3.11–2.96 (m, 1H), 1.98–1.84 (m, 1H), 1.77–1.57 (m, 4H) 1.48 (s, 13H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 155.9 (*C*), 149.0 (*C*), 148.9 (*C*), 148.79 (*C*), 148.5 (*C*), 131.3 (*C*), 127.5 (*C*), 126.5 (*C*H), 126.3 (*C*), 124.9 (*C*), 123.8 (*C*), 108.1 (*C*H), 107.3 (*C*H), 103.1 (*C*H), 103.0 (*C*H), 79.3 (*C*), 59.2 (*C*), 56.3 (2*C*H$_3$), 56.1 (*C*H$_3$), 56.0 (*C*H$_3$), 41.4 (*C*H$_2$), 38.2 (*C*H$_2$), 35.6 (*C*H$_2$), 28.7 (*C*H$_3$), 26.3 (*C*H$_3$), 23.3 (*C*H$_2$), 17.6 (*C*H$_2$); HRMS (ESI) calcd for $C_{30}H_{39}NO_6Na$ 532.2675, found 532.2663.

**(*ent*-7).** It was prepared from *ent*-**6** (370 mg, 0.73 mmol), following the same procedure described for the preparation of **7**, with a similar yield (568 mg, >99%) and identical characterization data, except for optical rotation: $[\alpha]_{20}^{D}$ −20 (*c* 2.42, $CHCl_3$).

**(*R*)-2,3,6,7-Tetramethoxy-14a-methyl-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f*,*h*]pyrido[1,2-*b*]isoquinoline (8).** To a solution of compound **7** (67 mg, 0.16 mmol) in MeOH (2.4 mL) at 0 °C was added concentrated HCl (12 M, 0.5 mL) and the mixture was stirred for 24 h at room temperature. At this point the solvent was replaced by EtOH (4.5 mL), followed by the sequential addition of aqueous formaldehyde (37%, 0.83 mL) and concentrated HCl (12 M, 0.12 mL). The reaction mixture was put under an argon atmosphere, protected from light irradiation and stirred at 90 °C for 72 h. After cooling to room temperature, the mixture was concentrated under vacuum and the residue was dissolved in $CH_2Cl_2$ (10 mL) and 2 M aqueous solution of NaOH (5 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL) and washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated to dryness. Purification by flash column chromatography (7 : 3 hexane/(3 : 1 EtOAc/EtOH with 2% $NH_4OH$)) afforded the desired product as a pale yellow solid (50 mg, 74%): $[\alpha]_{20}^{D}$ −52 (*c* 5.84, MeOH); $R_f$ 0.19 (7 : 3, hexane/(3 : 1 EtOAc/EtOH with 2% $NH_4OH$)); 96 : 4 er according to chiral HPLC analysis [$t_R$ (minor) 16.69 min, $t_R$ (major) 18.95 min, see the ESI† for details]; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.85 (s, 2H), 7.30 (s, 1H), 7.16 (s, 1H), 4.18 (br. d, $J$ = 16.2 Hz, 1H), 4.12 (s, 3H), 4.12 (s, 3H), 4.08 (s, 3H), 4.06 (s, 3H), 3.94 (br. d, $J$ = 15.4 Hz, 1H), 3.09 (br. d, $J$ = 15.8 Hz, 1H), 2.98–2.84 (m, 2H), 2.74–2.58 (m, 1H), 1.91–1.64 (m, 6H), 1.06 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 148.8 (2*C*), 148.6 (*C*), 148.5 (*C*), 125.9 (*C*), 124.8 (*C*), 124.2 (*C*), 124.1 (*C*), 123.8 (*C*), 123.4 (*C*), 104.0 (*C*H), 103.7 (*C*H), 103.6 (*C*H), 103.2 (*C*H), 56.2 (*C*H$_3$), 56.1 (*C*H$_3$), 52.1 (*C*), 51.9 (*C*H$_2$), 50.3 (*C*H$_2$), 40.2 (*C*H$_2$), 39.7 (*C*H$_2$), 26.4 (*C*H$_2$), 20.8 (*C*H$_2$), 14.3 (*C*H$_3$); HRMS (ESI) calcd for $C_{26}H_{32}NO_4$ 422.2331, found 422.2326.

**(*ent*-8).** It was prepared from *ent*-**7** (135 mg, 0.33 mmol), following the same procedure described for the preparation of **8**, with a similar yield (196 mg, 72%) and identical characterization data, except for optical rotation: $[\alpha]_{20}^{D}$ +52 (*c* 5.81, $CHCl_3$).

**(14a*R*)-10-Benzyl-2,3,6,7-tetramethoxy-14a-methyl-9,10,11,12,13,14,14a,15-octahydrodibenzo[*f*,*h*]pyrido[1,2-*b*]isoquinolin-10-ium bromide (9).** To a solution of **8** (362 mg, 0.86 mmol) in dry $CH_2Cl_2$ (9.8 mL) were sequentially added $K_2CO_3$ (264 mg, 1.89 mmol) and benzyl bromide (114 μL, 0.95 mmol) and the reaction mixture was stirred at 25 °C overnight. Afterwards, the reaction mixture was filtered and the organic layer was concentrated to dryness. The residue was purified by flash column chromatography (95 : 5 to 9 : 1 $CHCl_3$/MeOH), to obtain the desired product as an orange solid (508 mg, >99%): $[\alpha]_{20}^{D}$ −82.0 (*c* 7.34, $CHCl_3$); $R_f$ 0.36 (9 : 1 $CHCl_3$/MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.88 (br s, 2H), 7.41–7.30 (m, 2H), 7.27–7.12 (m, 2H), 7.01 (br s, 1H), 6.96–6.81 (m, 2H), 5.15 (br d, $J$ = 13.5 Hz, 2H), 4.56 (d, $J$ = 17.3 Hz, 1H), 4.31 (d, $J$ = 13.0 Hz, 1H), 4.16 (s, 6H), 4.14–4.07 (m, 3H), 3.99–3.91 (m, 3H), 3.68 (d, $J$ = 18.4 Hz, 1H), 3.51–3.33 (m, 2H), 2.81–2.63 (m, 1H), 2.60–2.37 (m, 1H), 2.35–1.93 (m, 5H), 1.84 (s, 3H);$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.0 (*C*), 149.9 (*C*), 149.8 (*C*), 149.6 (*C*), 132.7 (2*C*H + *C*), 131.0(*C*H), 129.4(2*C*H), 126.9 (*C*), 124.8 (*C*), 124.4 (*C*), 124.2 (*C*), 122.3 (*C*), 122.2 (*C*), 118.2 (*C*), 104.0 (*C*H), 103.7 (*C*H), 103.6 (*C*H), 103.1 (*C*H), 68.0 (*C*), 56.9 (*C*H$_3$), 56.5 (*C*H$_3$), 56.3 (*C*H$_3$), 56.2 (*C*H$_3$), 54.9 (*C*H$_2$), 54.1 (*C*H$_2$), 53.5 (*C*H$_2$), 37.4 (*C*H$_2$), 32.7 (*C*H$_2$), 21.9 (*C*H$_3$), 20.3 (*C*H$_2$), 17.7(*C*H$_2$); HRMS (ESI) cald for $C_{33}H_{38}NO_4$ 512.2801, found 512.2799.

**(*ent*-9).** It was prepared from *ent*-**8** with a similar yield (112 mg, 91%) and identical characterization data, except for optical rotation: $[\alpha]_{20}^{D}$ +86.6 (*c* 6.33, $CHCl_3$).

**(9*S*,14a*R*)-9-Benzyl-2,3,6,7-tetramethoxy-14a-methyl-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f*,*h*]pyrido[1,2-*b*]isoquinoline (10).** Into a dry two-necked round-bottom flask, equipped with a condenser, was added NaH (60% mineral oil dispersion, 188.0 mg, 7.85 mmol). The solid was washed twice with hexane, removing the solvent and drying the solid with cycles of vacuum/argon, before dry DMSO (8 mL) was added. The mixture was heated to 60 °C for 2 h until the evolution of gas ($H_2$) ceased and complete dissolution of solids was observed. At this point, compound **9** (224.5 mg, 0.38 mmol) was added and the mixture was stirred 5 h at 25 °C, before being quenched with $H_2O$ (15 mL). The resulting white precipitate was filtered, washed with water and dried under vacuum. The obtained solid was purified by flash column chromatography (100% $CHCl_3$ to 99 : 1 $CHCl_3$/i-PrOH) to obtain the desired product as a pale yellow foam solid (102 mg, 52%): $[\alpha]_{20}^{D}$ −154.5 (*c* 5.95, $CHCl_3$); $R_f$ 0.28 (99 : 1 $CHCl_3$/$^i$PrOH); 95 : 5 er according to chiral HPLC analysis [$t_R$ (minor) 7.67 min, $t_R$ (major) 8.43 min, see the ESI† for details]; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.89 (s, 1H), 7.85 (s, 1H), 7.40 (s, 1H), 7.09 (s, 1H), 6.99 (ddd, $J$ = 6.3, 3.7, 1.3 Hz, 1H), 6.96–6.86 (m, 2H), 6.63–6.56 (m, 2H), 4.37 (t, $J$ = 3.7 Hz, 1H), 4.14 (s, 3H), 4.12 (s, 3H), 4.04 (s, 3H), 4.00 (s, 3H), 3.15 (dd, $J$ = 13.1, 4.1 Hz, 1H), 3.07–2.94 (m, 2H), 2.74–2.58 (m, 2H), 1.93 (d, $J$ = 15.1 Hz, 1H), 1.78–1.59 (m, 6H), 0.76 (s, 3H).$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 148.8 (*C*), 148.6 (2*C*), 148.2 (*C*), 139.0 (*C*), 130.6(2*C*H), 128.7(*C*), 128.3 (*C*), 126.7(2*C*H), 125.62(*C*), 125.6(*C*H), 124.1(*C*), 123.9(*C*), 123.5(*C*), 104.9(*C*H), 104.3(*C*H), 104.0(*C*H), 103.5(*C*H), 60.0 (*C*H), 56.2(2*C*H$_3$), 56.1(*C*H$_3$), 56.0(*C*H$_3$), 51.2(*C*), 46.9(*C*H$_2$), 41.9(*C*H$_2$), 41.1(*C*H$_2$), 40.1(*C*H$_2$), 26.8(*C*H$_2$), 20.9(*C*H$_2$), 13.9 (*C*H$_3$). HRMS (ESI) cald for $C_{33}H_{38}NO_4$ 512.2801, found 512.2794.

**(*ent*-10).** It was prepared from *ent*-**9** with a similar yield (12 mg, 45%) and identical data as **10**, except for optical rotation: $[\alpha]_{20}^{D}$ +155.2 (*c* 4.50, $CHCl_3$).

## Acknowledgements

We thank the Spanish Ministerio de Ciencia e Innovación (CTQ2011-24165) and the University of Alicante (VIGROB-173) for financial support. C. A.-T. thanks the ISO for a grant.

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