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Synthesis of novel hymenialdisine analogues using solvent-free and silica gel-promoted ring opening of epoxides

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ABSTRACT

A silica gel-promoted regioselective ring-opening reaction of epoxides with indoles and pyrrole under mild and solvent-free conditions is described. This reaction provides a synthetic pathway for a diverse class of novel hymenialdisine analogues.

1. Introduction

Epoxides are versatile building blocks for novel biologically active compounds since they can be readily opened with different nucleophiles giving a variety of functionalized diverse products.[1] Nucleophilic epoxide opening reactions play a key role especially in the construction of carbon–carbon and carbon–oxygen bonds, essential components of organic compounds.[1,2] These reactions are generally performed with acid or base catalysts. In the absence of such catalysts, the reaction is moderately slow.[3]

More specifically, it has been reported that epoxide ring-opening reactions with indoles and pyrroles can be carried out under acid catalysts[4] or high pressure conditions.[5] In addition, Lewis acid catalysts such as lanthanide triflates,[6] nano-crystalline titanium(IV) oxide,[7] $RuCl_3 \cdot nH_2O$,[8] HBF_4/SiO_2[9] and $InCl_3$/silica[10] have been also reported for such transformations. Some of these known methods require comparably long reaction time, high temperature or pressure conditions, expensive reagents and gave unsatisfactory yields. Thus, the development of clean, efficient and mild conditions for the ring opening of epoxides with indoles and pyrroles is desirable.

Small molecule kinase inhibitors are of significant actual interest, both as potential therapeutics and as experimental tools for understanding the physiological role of these enzymes.[11] Protein kinases act pivotally in signal transduction as well as in cellular proliferation, differentiation and various regulatory mechanisms.[12] Kinase inhibitors have emerged as promising therapeutic molecules for treatment of a number of diseases including cancer and asthma.[12,13] In recent years, intense effort has been devoted towards the development and identification of such small molecule inhibitors associated with diseases; currently 20–30% of pharmaceutical discovery programmes are focused on kinase functions.[11,12] Staurosporine (**1**), a bisindole alkaloid has been found as one of the first kinase inhibitors in nanomolar concentrations (Fig. 1).[14] Several kinase inhibitors have progressed to human clinical trials.[12,15,16] Among them, hymenialdisine (HMD) (**2**), a natural product, exhibited promising results in inhibiting various kinases.[16] We were intrigued by the fascinating structure and highly significant kinase inhibiting activity exhibited by staurosporine (**1**) and hymenialdisine (**2**). As a part of our ongoing efforts to apply catalytic oxidation methodology[18] to synthesize potential bio-active compounds,[19,20] we became interested in preparing a small library of novel bisindoles as hybrid analogues (**3**) of staurosporine and hymenialdisine.[16] It has been reported that the kinase inhibiting activity of HMDs vary much if other heterocycles instead of imidazoles are introduced in its core structure.[17] Therefore, we decided to introduce indoles on annulated HMD scaffold to evaluate their biological activity. Our initial efforts in this field culminated recently in the establishment of a novel strategy for annulated

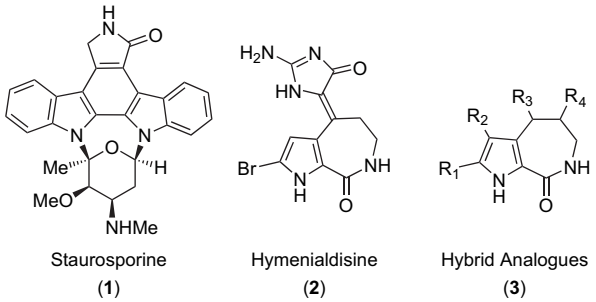

Figure 1. Structures of staurosporine (**1**), hymenialdisine (**2**) and hybrid analogues (**3**).

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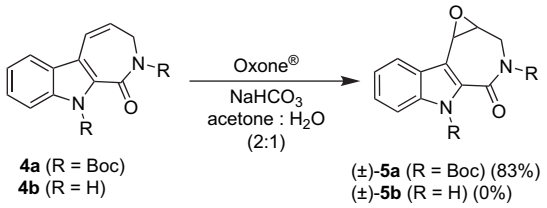
HMD-type bisindoles using aziridines and hydroxyl precursors as starting materials.[20] Here, we disclose another amenable, diversified strategy using silica gel as solid support for ring opening of epoxide (±)-**5a** under mild and solvent-free reaction conditions to give novel bisindole-type hymenialdisine analogues (±)-**8** with a free hydroxyl group.

2. Results and discussion

We initiated a synthetic effort that began with the large scale preparation of the Boc-protected olefin **4a** from commercially available indole-2-carboxylic acid following a previous protocol reported by us.[20] Initial efforts for the epoxidation of **4a** to produce (±)-**5a** utilizing methods such as *m*-CPBA[21] or MTO[22] were unsuccessful. To our delight, we found that the reaction proceeded smoothly to give epoxide (±)-**5a** in 83% yield with in situ generated dimethyloxirane using Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as the terminal oxidant (Scheme 1).[23] The structure of the epoxide (±)-**5a** was confirmed by X-ray crystal structural analysis (Fig. 2). However, when the same reaction conditions were applied to the unprotected olefin **4b**, the formation of the desired epoxide (±)-**5b** was not observed. Transformations of (±)-**5a** into (±)-**5b** have not been performed to avoid unwanted epoxide ring-opening reactions employing the typical Boc-deprotection conditions (HCl/MeOH, TFA/CH_2Cl_2, heat, Na_2CO_3/MeOH, etc.). With the key building block (±)-**5a** in hand, we envisioned to explore silica gel-promoted[21] epoxide ring opening under easily manageable solvent-free conditions to produce hymenialdisine analogues.



Scheme 1. Selective epoxidation of **5a**.

Initial attempts to open epoxide (±)-**5a** with indoles and deprotection of both Boc groups in situ following our previous protocol[20] at 70 °C resulted in the desired ring opened product in moderate to good yields (39–60%). However, the reaction mixture was complicated with concomitant formation of several side products, which in our hands could not be separated and characterized. We hypothesized that the epoxide ring-opening reaction proceeds much faster than the deprotection of the Boc groups. This

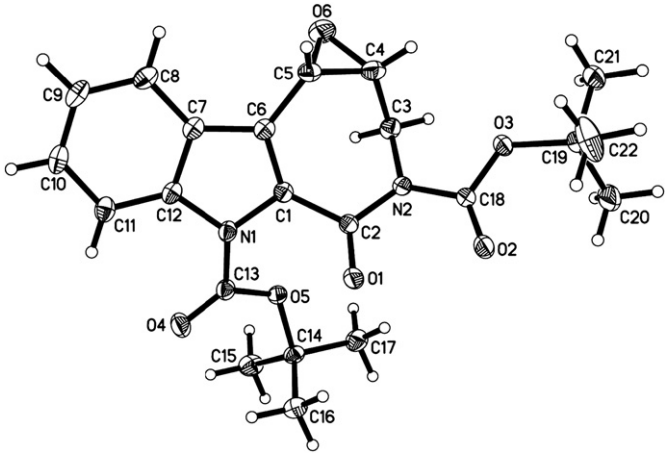
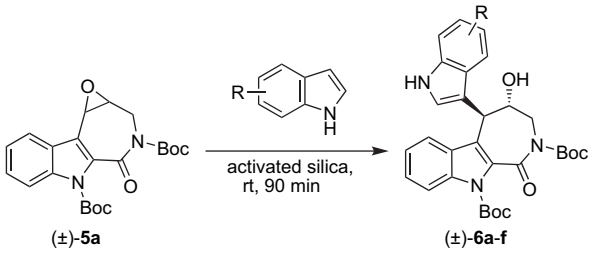
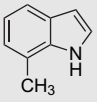
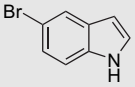
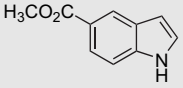
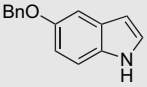
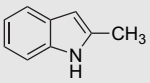


Figure 2. Molecular structure of epoxide (±)-**5a**. The thermal ellipsoids correspond to 30% probability.

Table 1
Ring-opening reactions of (±)-**5a**[a]



Entry	Substrate	Product	Yield[b] (%)
1		(±)-**6a**	74
2		(±)-**6b**	64
3		(±)-**6c**	72
4		(±)-**6d**	55[c]
5		(±)-**6e**	56
6		(±)-**6f**	0

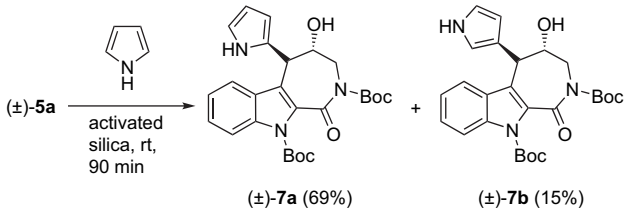
[a] Reaction conditions: epoxide (±)-**5a** (300 mg, 0.72 mmol), indole derivative (7.2 mmol), activated silica (0.040–0.063 mm, 1.56 g), argon, rt, 90 min.
[b] Isolated yield.
[c] Reaction time: 10 h.

enforced us to turn our focus in searching milder conditions to achieve higher selectivity. Fortunately, the reaction proceeded smoothly at room temperature and went to completion with preservation of both Boc groups to give (±)-**6a** in 74% yield.

Next, we applied this protocol to prepare unsymmetrical bisindoles starting from epoxide (±)-**5a** (Table 1). Most of the reactions proceeded at room temperature to give (±)-**6a**–**e** in moderate to good yields (55–74%). Functional groups on the indole ring such as alkyl, halide, alkoxy and ester groups were tolerated under these mild reaction conditions (Table 1, entries 2–5). However, we were unable to isolate the desired product with 2-methyl indole (Table 1, entry 6). The ring-opening reaction of the very reactive epoxide on silica possibly proceeds much faster than the nucleophilic attack of the sterically hindered 2-methyl indole. It is noteworthy to mention that the regioselectivity in all other reactions was excellent. As expected, only one diastereomer is obtained during ring-opening reaction. It takes place at the benzylic position of the (±)-**5a** and at the 3-position of the attached indole, which is in full agreement with an electrophilic substitution mechanism.[10]

Pyrrole opens (±)-**5a** under the same conditions (Scheme 2). The reaction was also regioselective at benzylic position of the substrate affording the corresponding product (±)-**7a** as the major product along with a minor amount of (±)-**7b**.[9]

Standard procedure using TFA to deprotect the Boc groups of (±)-**6a** at room temperature[24] resulted in decomposition of the substrate. As we noticed formation of the desired deprotected compound in the initial screening using our previous protocol,[20] we assumed that the Boc groups can be removed at higher temperature using activated silica as solid support.



Scheme 2. Epoxide opening reaction with pyrrole.

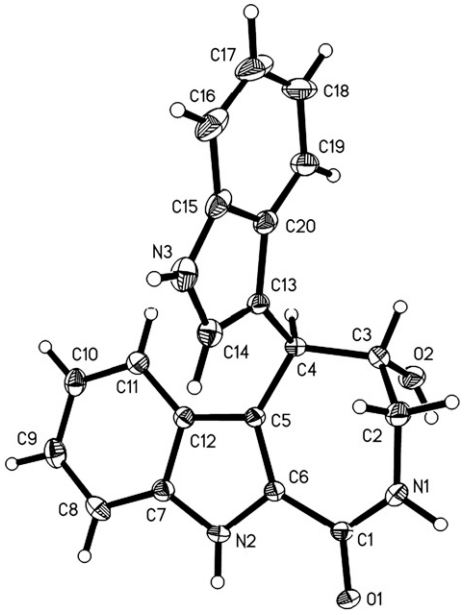
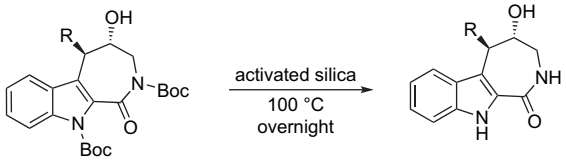


Figure 3. Molecular structure of (±)-**8a**. Only one molecule of the asymmetric unit is depicted. The thermal ellipsoids correspond to 30% probability.

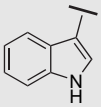
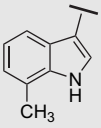
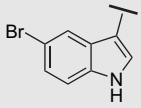
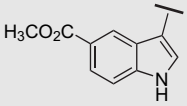
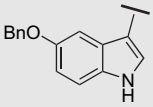
Thus, compound (±)-**6a** was adsorbed on activated silica gel and heated at 100 °C for overnight to give the desired product (±)-**8a**. This is in agreement with our hypothesis that the epoxide ring-opening reaction proceeds much faster than the deprotection of the Boc-protecting groups. Structure of (±)-**8a** was confirmed again by X-ray crystal structural analysis (Fig. 3). This method was successfully employed to all the other epoxide ring opened products to give the desired products in 56–75% yield (Table 2, entries 2–6).

The selective epoxidation and subsequent ring opening prompted us to explore a synthetic route to prepare the enantiomerically pure epoxide of the Boc-protected olefin **4a**. For this purpose, we tested Shi's catalyst[25] using Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as the oxidant. But with our substrate, the conversion was negligible. Next, we checked the feasibility of Jacobson's protocol[26] for the epoxidation of olefin **4a**, for its simple work up procedure.[26b] When **4a** was treated with 4 mol % Jacobson's catalyst using NaOCl as the oxidant, the desired epoxide was yielded in 66% with 74% ee. The product was recrystallized using a mixture of hexane/ethyl acetate (9:1). After two consecutive recrystallizations, (+)-**5a** was obtained in >99% ee from the mother liquor in 34% yield. Subsequently, this enantiopure epoxide was subjected to the ring-opening reaction with indole. Indeed, the desired bisindole (+)-**6a** was obtained with 99% ee and 67% yield (Scheme 3).

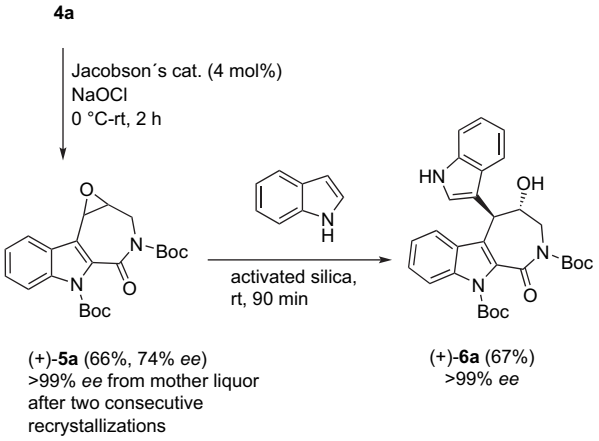
Table 2
Deprotection of Boc groups of (±)-**6**[a]



(±)-**6a-e** & **7a** (±)-**8a-e** & **9a**

Entry	R	Product	Yield[b] (%)
1		(±)-**8a**	75
2		(±)-**8b**	66
3		(±)-**8c**	65
4		(±)-**8d**	71
5		(±)-**8e**	56
6		(±)-**9a**	65

[a] Reaction conditions: (±)-**6a–e** and **7a** (0.415 mmol), activated silica (0.040–0.063 mm, 0.92 g), argon, 100 °C, overnight.
[b] Isolated yield.



Scheme 3. Synthesis of enantiomerically pure bisindoles.

3. Conclusions

In conclusion, we developed a convenient method for the opening of epoxide with indoles and pyrrole on solid support to synthesize novel unsymmetrical bisindoles. The advantages of the present protocol are the ease of work up, solvent-free conditions and the high selectivity. This method can also be extended to synthesize enantiomerically pure bisindole-type hymenialdisine analogues.

4. Experimental section

4.1. General

All solvents and chemicals were obtained commercially and were used as-received. NMR spectra were measured using a Bruker

ARX 300 or ARX 400 spectrometer at 300 or 400 MHz (^{1}H) and 75 or 100 MHz (^{13}C). All spectra were recorded in DMSO-d_6 or $CDCl_3$ and chemical shifts (δ) are reported in parts per million relative to tetramethylsilane referenced to the residual solvent peaks. Spectra were recorded at room temperature unless otherwise stated. Mass spectra were in general recorded on an AMD 402/3 or an HP 5989A mass selective detector. In each case characteristic fragments with their relative intensities in percentages are shown. Infrared spectra were recorded on a Nicolet 6700 spectrometer using KBr plates or on the same machine equipped with a smart endurance (Thermo Electron Corporation) for ATR-IR. Wave numbers (ν) are reported in cm^{-1}. HPLC analysis was performed on an HP 1090 machine with DAD detector. Melting points were measured with a Stuart melting point apparatus (SMP3) and are not corrected. Activated silica gel was obtained by heating silica gel (0.040–0.063 mm) at 140 °C in vacuum overnight.

4.2. X-ray diffraction

Diffraction data were collected with an STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structures were solved by direct methods[27] and refined by full-matrix least-squares techniques on F^2.[28] XP (BRUKER AXS) was used for graphical representations. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 681249 [(±)-**5a**] and CCDC 682863 [(±)-**8a**]. Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk.

4.2.1. Crystal data for (±)-*5a*

Space group $P\bar{1}$, triclinic, a=7.791(2), b=9.354(2), c=14.997(3) Å, α=96.86(3), β=102.25(3), γ=98.00(3)°, V=1045.1(4) Å^3, Z=2, ρ_{calcd}=1.317 g cm^{-3}, 15,688 reflections measured, 4551 were independent of symmetry, of which 3120 were observed ($I>2\sigma(I)$), R_1=0.042, wR_2 (all data)=0.113, 271 parameters.

4.2.2. Crystal data for (±)-*8a*

Space group $P\bar{1}$, triclinic, a=12.1668(7), b=13.1234(7), c=14.0402(9) Å, α=70.049(5), β=84.851(5), γ=64.600(4)°, V=1899.3(2) Å^3, Z=4, ρ_{calcd}=1.327 g cm^{-3}, 29,081 reflections measured, 8062 were independent of symmetry, of which 4604 were observed ($I>2\sigma(I)$), R_1=0.051, wR_2 (all data)=0.131, 539 parameters.

4.3. Synthesis

4.3.1. Epoxidation of (Z)-di-tert-butyl 1-oxoazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-*5a*

To a vigorously stirred mixture of olefin **4a** (0.80 g, 2.0 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in acetone (200 mL) at 0 °C was added dropwise a solution of Oxone® (3.71 g, 6.0 mmol) in H_2O (120 mL) over a period of 30 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, the solid residue was washed with acetone and the filtrate was concentrated in vacuum. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuum. The crude compound was purified by column chromatography (silica gel 70–230 mesh, *n*-hexane/ethyl acetate 9:1) to yield a white fluffy solid (692 mg, 83%). Crystals suitable for X-ray analysis were obtained by recrystallizing with ethyl acetate.Mp R_f=0.27 (*n*-hexane/ethyl acetate 8:2). Mp: 164 °C (ethyl acetate). HPLC analysis: column, Chiralcel OD-H; solvent, heptane/ethanol 97:3; flow=1.0 mL/min, t_R=10.11, 13.97 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=8.09 (1H, d, J=8.5 Hz), 7.75 (1H, d, J=7.8 Hz), 7.48 (1H, unresolved dd), 7.34 (1H, unresolved dd), 4.46–4.23 (1H, m), 4.18 (1H, unresolved d), 4.06–3.90 (1H, m), 3.90–3.79 (1H, m), 1.59 (18H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=160.0, 152.0, 148.9, 137.8, 129.6, 127.6, 127.3, 123.6, 120.0, 119.0, 114.6, 85.1, 84.0, 47.1, 28.0, 27.6. ^{1}H NMR (400 MHz, 323 K, $CDCl_3$): δ (ppm)=8.14–8.07 (1H, m), 7.78–7.72 (1H, m), 7.46 (1H, unresolved ddd), 7.33 (1H, unresolved ddd), 4.30 (1H, unresolved d), 4.16 (1H, d, J=3.9 Hz), 4.02–3.91 (1H, m), 3.87–3.81 (1H, m), 1.6 (18H, m). ^{13}C NMR (100 MHz, 323 K, $CDCl_3$): δ (ppm)=159.9, 152.2, 149.0, 138.0, 129.9, 127.5, 127.5, 123.6, 119.9, 119.0, 114.9, 85.1, 83.9, 54.6, 47.2, 45.5, 28.1, 27.7. ATR-IR (cm^{-1})=3057w, 2980w, 2935w, 1768m, 1720s, 1559m, 1477w, 1448m, 1368s, 1322s, 1290m, 1258w, 1226w, 1206m, 1145s, 1119m, 1079s, 1024w, 985m, 944m, 894w, 851s, 780s, 746s. MS (EI): *m*/*z* (rel int.) 69 (20), 70 (18), 71 (22), 83 (19), 84 (24), 85 (11), 86 (10), 97 (14), 102 (12), 112 (10), 128(16), 129 (91), 130 (11), 157 (51), 158 (10), 169 (31), 170 (11), 185 (28), 186 (22), 197 (23), 198 (52), 214 (100), 215 (12), 414 (6). HRMS (EI): calcd for $C_{22}H_{26}N_2O_6$ (M^+) 414.1785, found 414.1782.

4.3.2. Asymmetric epoxidation of (Z)-di-tert-butyl 1-oxoazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (+)-*5a*

A solution of 0.05 M Na_2HPO_4 (5 mL) was added to a 6 mL aqueous solution of bleach (~14% NaOCl). The pH value of the resulting buffered solution (~1 M in NaOCl) was ~12.0 and was adjusted to pH 11.5 by addition of a few drops of 5% HCl solution. The solution was cooled to 0 °C from which 8.7 mL were added at once to a 0 °C solution of **4a** (1.0 g, 2.5 mmol) and Jacobson's catalyst (64.0 mg, 0.10 mmol) in 4 mL of dichloromethane. The reaction mixture was stirred at room temperature for 2 h. Ethyl acetate (20 mL) was added to the mixture, the organic phase was separated, dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by column chromatography (silica gel 70–230 mesh, *n*-hexane/ethyl acetate 9:1) to afford a white fluffy solid (671 mg, 66%, 74% ee). The product was recrystallized with hexane. White solid precipitated out with 33% ee and the enantiomerically enriched compound with 82% ee was obtained after drying the mother liquor. It was again recrystallized using hexane/ethyl acetate mixture (9:1) to produce (+)-**5a** in >99% ee from mother liquor with 34% yield as a fluffy solid. Mp: 78 °C (ethyl acetate/hexane). HPLC analysis: >99% ee (Chiralcel OD-H, solvent: heptane/ethanol 97:3, flow=1.0 mL/min); t_R=13.97 min (major). $[\alpha]_D^{22}$ +4.65 (*c* 1.0, $CHCl_3$).

4.4. General procedure for the ring-opening reaction of the epoxide (±)-5a with indoles (general procedure A)

Epoxide (±)-**5a** (300 mg, 0.72 mmol) and an indole derivative (7.2 mmol) were dissolved in dichloromethane and activated silica (1.56 g, 0.040–0.063 mm) was added. The solvent was removed under reduced pressure at room temperature and the solid mixture was kept under argon for 90 min. Purification by column chromatography (silica gel 70–230 mesh, *n*-hexane/ethyl acetate 9:1 to *n*-hexane/ethyl acetate 8:2 as the gradient eluent) yielded the pure product. It was then washed or recrystallized as described below.

4.4.1. Di-tert-butyl 4-hydroxy-5-(1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-*6a*

The desired product was obtained following general procedure A (287 mg, 74%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. Mp R_f=0.35 (ethyl acetate/hexane 4:6). Mp: 190 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.21 (1H, br s), 8.13 (1H, d, J=9.1 Hz), 7.71–7.68 (1H, m), 7.43 (1H, unresolved ddd), 7.38–7.32 (2H, m), 7.23–7.20 (2H, m), 7.14–7.09 (1H, m), 6.71 (1H, unresolved d), 5.19–5.13 (1H, m), 4.98–4.95 (1H, m), 4.76 (1H, d, J=3.6 Hz), 3.68–3.60 (1H, m), 2.96–2.87 (1H, m), 1.69 (9H, s), 1.43 (9H, s). ^{13}C

NMR (75 MHz, $CDCl_3$): δ (ppm)=157.6, 156.1, 149.2, 139.9, 136.1, 135.6, 129.0, 126.7, 124.3, 123.9, 123.5, 123.4, 122.6, 121.2, 120.5, 118.3, 115.3, 111.6, 109.1, 85.1, 80.6, 79.8, 42.7, 32.5, 28.4, 27.9. ATR-IR (cm^{-1})=3369br, 2978w, 2931w, 1711s, 1611w, 1506m, 1444m, 1415m, 1392w, 1354s, 1315m, 1280m, 1250m, 1152s, 1083s, 1015m, 964w, 942w, 907w, 854w, 836m, 740s. MS (EI): *m*/*z* (rel int.) 41 (100), 43 (30), 44 (99), 55 (43), 56 (74), 57 (25), 60 (10), 69 (18), 71 (10), 83 (15), 97 (12), 272 (26), 531 (1). HRMS (EI): calcd for $C_{30}H_{33}N_3O_6$ (M^+) 531.2364, found 531.2368. HPLC analysis: column, Chiralcel OD-H; solvent, heptane/isopropanol 90:10; flow=1.0 mL/min; t_R=7.81, 9.95 min.

4.4.2. Di-tert-butyl 4-hydroxy-5-(1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (+)-**6a**

Enantiomerically pure (+)-**6a** was obtained as a white solid from (+)-**5a** following the same procedure as described for (±)-**6a** (258 mg, 67%). Mp: 136 °C (ethyl acetate/hexane). HPLC analysis: >99% ee; column, chiracel OD-H; solvent, heptane/ethanol 90:10; flow=1.0 mL/min; t_R=9.54 min major. $[\alpha]_D^{22}$ +409.5 (*c* 0.097, $CHCl_3$).

4.4.3. Di-tert-butyl 4-hydroxy-5-(7-methyl-1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6b**

The desired product was obtained as a white solid following general procedure A (252 mg, 64%).Mp R_f=0.51 (ethyl acetate/hexane 2:3) Mp: 154 °C (ethyl acetate/hexane).. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.07–8.04 (2H, m), 7.49 (1H, d, *J*=8.1 Hz), 7.36 (1H, unresolved ddd), 7.26 (1H, d, *J*=7.9 Hz), 7.11–6.93 (3H, m), 6.62 (1H, unresolved d), 5.11–5.06 (1H, m), 4.89–4.85 (1H, m), 4.68 (1H, d, *J*=3.5 Hz), 3.59–3.49 (1H, m), 2.88–2.78 (1H, m), 2.38 (3H, s), 1.62 (9H, s), 1.36 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.6, 156.0, 149.1, 139.8, 135.7, 135.7, 129.0, 126.3, 124.3, 123.5, 123.5, 123.3, 123.0, 121.2, 120.8, 120.6, 116.0, 115.2, 109.5, 85.0, 80.5, 79.7, 42.7, 32.5, 28.3, 27.8, 16.5. ATR-IR (cm^{-1})=3342br, 3054w, 2976w, 2930w, 1711s, 1612w, 1505m, 1444m, 1416w, 1392w, 1365s, 1354s, 1315m, 1280m, 1245m, 1153s, 1088s, 1016w, 967w, 943w, 928w, 906w, 853w, 835m, 785m, 768m, 744s, 633w. MS (EI): *m*/*z* (rel int.) 41 (94), 43 (14), 44 (100), 55 (31), 56 (77), 57 (13), 286 (36), 545 (3). HRMS (ESI^+): calcd for $C_{31}H_{35}N_3O_6$+Na^+ (M+Na^+) 568.2418, found 568.2416.

4.4.4. Di-tert-butyl 5-(5-bromo-1H-indol-3-yl)-4-hydroxy-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6c**

The desired product was obtained following general procedure A (318 mg, 72%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as a white solid. R_f=0.44 (ethyl acetate/hexane 2:3). Mp: 207 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.35 (1H, br s), 8.13 (1H, d, *J*=8.5 Hz), 7.87 (1H, unresolved d), 7.45 (1H, ddd, *J*=8.5, 7.2, 1.3 Hz), 7.34–7.22 (3H, m), 7.17–7.12 (1H, m), 6.69 (1H, unresolved d), 5.20–5.14 (1H, m), 4.96–4.92 (1H, m), 4.68 (1H, d, *J*=3.4 Hz), 3.60–3.51 (1H, m), 2.96–2.86 (1H, m), 1.68 (9H, s), 1.44 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.5, 155.9, 149.0, 139.9, 135.4, 134.6, 129.1, 128.5, 125.5, 125.1, 124.1, 123.6, 123.2, 121.1, 120.6, 115.3, 113.8, 113.1, 85.1, 80.2, 79.9, 42.5, 32.0, 28.1, 27.8. ATR-IR (cm^{-1})=3424s, 2978w, 2925w, 1742w, 1727s, 1689m, 1561w, 1508w, 1458m, 1446m, 1417w, 1393w, 1368s, 1354m, 1316m, 1280m, 1256w, 1195m, 1157s, 1100s, 1056w, 1016w, 945w, 905w, 886w, 835w, 797w, 770w, 750m, 626w, 472w, 424w. HRMS (EI): calcd for $C_{30}H_{32}Br_1N_3O_6$ (M^+) 609.1469, found 609.1477.

4.4.5. Di-tert-butyl 4-hydroxy-5-(5-(methoxycarbonyl)-1H-indol-3-yl)-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6d**

The desired product was obtained following general procedure A (235 mg, 55%). This was recrystallized from methanol to yield pure analytical sample as a white solid.Mp R_f=0.23 (ethyl acetate/hexane 4:6). Mp: 205 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.50 (1H, unresolved d), 8.40 (1H, br s), 8.00 (1H, d, *J*=8.5 Hz), 7.73 (1H, dd, *J*=8.5, 1.5 Hz), 7.56–7.51 (1H, m), 7.46–7.30 (2H, m), 7.23–7.18 (1H, m), 7.11 (1H, unresolved dd), 6.99 (1H, m), 5.23 (1H, d, *J*=3.4 Hz), 5.11–5.06 (1H, m), 3.85 (3H, s), 3.30–3.21 (1H, m), 2.83–2.71 (1H, m), 1.62 (9H, s), 1.34 (9H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=167.2, 156.8, 155.5, 148.6, 139.1, 138.8, 135.9, 129.1, 126.5, 126.3, 124.1, 123.6, 123.2, 122.2, 121.6, 121.3, 120.8, 114.5, 111.8, 109.5, 84.6, 79.5, 78.0, 51.7, 42.4, 31.3, 28.1, 27.3 ATR-IR (cm^{-1})=3340br, 2978w, 2931w, 1708s, 1619m, 1508m, 1442m, 1416w, 1392w, 1355s, 1314m, 1279m, 1241s, 1189w, 1153s, 1090s, 1016w, 964w, 905m, 835m, 767w, 746s. HRMS (ESI^+): calcd for $C_{32}H_{35}N_3O_8$+Na^+ (M+Na^+) 612.2317, found 612.2316.

4.4.6. Di-tert-butyl 5-(5-(benzyloxy)-1H-indol-3-yl)-4-hydroxy-1-oxo-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**6e**

The desired product was obtained following general procedure A (258 mg, 56%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.32 (ethyl acetate/hexane 4:6). Mp: 142 °C (hexane/ethyl acetate) ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.13 (1H, d, *J*=8.5 Hz), 8.10 (1H, br s), 7.55–7.48 (2H, m), 7.47–7.36 (3H, m), 7.35–7.21 (2H, m), 7.20–7.08 (3H, m), 6.97 (1H, dd, *J*=8.7, 2.3 Hz), 6.77–6.67 (1H, m), 5.20 (3H, br s), 5.02–4.91 (1H, m), 4.70 (1H, d, *J*=3.4 Hz), 3.62–3.50 (1H, m), 3.04–2.92 (1H, m), 1.70 (9H, s), 1.44 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=156.0, 153.8, 149.2, 140.0, 137.5, 135.7, 131.4, 129.0, 128.6, 127.9, 127.7, 127.1, 124.6, 124.4, 123.6, 123.4, 121.2, 115.3, 113.6, 112.4, 108.9, 101.5, 85.1, 80.4, 79.8, 70.8, 32.5, 28.4, 27.9. ATR-IR (cm^{-1})=3367br, 2975w, 2928w, 2857w, 1713s, 1624w, 1581w, 1499w, 1483w, 1446m, 1415w, 1392w, 1365s, 1315m, 1280m, 1249w, 1153s, 1092s, 1016w, 966w, 938w, 907w, 836m, 744s, 696s. HRMS (ESI^+): calcd for $C_{37}H_{39}N_3O_7$+Na^+ (M+Na^+) 660.2680, found 660.2676.

4.4.7. Di-tert-butyl 4-hydroxy-1-oxo-5-(1H-pyrrol-2-yl)-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**7a**

The desired product was obtained following general procedure A (240 mg, 69%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.60 (ethyl acetate/hexane 2:3). Mp: 175 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=8.58 (1H, br s), 8.15–8.13 (1H, m), 7.50–7.45 (2H, m), 7.25–7.21 (1H, m), 6.67–6.66 (1H, m), 6.08 (1H, dd, *J*=5.6, 2.9 Hz), 6.01–5.95 (1H, m), 4.98–4.91 (2H, m), 4.55 (1H, d, *J*=3.6 Hz), 3.67–3.59 (1H, m), 3.14–3.07 (1H, m), 1.67 (9H, s), 1.45 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.0, 156.3, 149.0, 139.8, 133.4, 129.2, 124.3, 123.8, 123.7, 123.5, 121.2, 118.9, 115.3, 109.1, 108.6, 85.2, 80.3, 42.2, 34.8, 28.4, 27.8. ATR-IR (cm^{-1})=3342br, 2978w, 2931w, 1733s, 1611w, 1512m, 1445m, 1414w, 1392w, 1356s, 1314s, 1279m, 1248m, 1153s, 1089s, 1016w, 979w, 945w, 906w, 853w, 835m, 768w, 746m, 722m. MS (EI): *m*/*z* (rel int.) 41 (99), 43 (15), 44 (97), 55 (36), 56 (83), 57 (38), 192 (10), 193 (64), 194 (17), 207 (11), 220 (10), 221 (30), 222 (100), 223 (41), 263 (16), 264 (30), 280 (10), 281 (14), 325 (10), 481 (4). HRMS (EI): calcd for $C_{26}H_{31}N_3O_6$ (M^+) 481.2207, found 481.2222.

4.4.8. Di-tert-butyl 4-hydroxy-1-oxo-5-(1H-pyrrol-3-yl)-4,5-dihydroazepino[3,4-b]indole-2,10(1H,3H)-dicarboxylate (±)-**7b**

The desired product was obtained following general procedure A (53 mg, 15%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.40 (ethyl acetate/hexane 2:3). Mp: 100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.20 (1H, br s), 8.15–8.10 (1H, m), 7.52–7.42 (2H, m), 7.23 (1H, unresolved ddd), 6.66 (1H, dd, *J*=4.7, 2.4 Hz), 6.46 (1H, unresolved dd), 6.03–5.98 (1H, m), 5.07–4.93 (2H, m), 4.37 (1H, d, *J*=3.6 Hz), 3.66–3.54 (1H, m), 3.16–3.03 (1H, m), 1.67 (9H, s), 1.45 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=157.5, 156.1, 149.2, 139.9, 136.0, 128.7, 124.6, 123.5, 123.1, 121.2, 118.6, 116.7, 116.5, 115.3, 108.7, 85.0, 80.4, 79.8, 43.0, 34.5, 28.4, 27.9. MS (EI): *m*/*z* (rel int.) 41

(93), 55 (26), 56 (73), 57 (25), 193 (32), 194 (14), 221 (26), 222 (100), 223 (37), 234 (13), 239 (24), 251 (5), 264 (19), 280 (20), 281 (14), 324 (13), 325 (13). 481 (1). ATR-IR (cm^{-1})=3322m, 2983w, 2935w, 1728s, 1685s, 1530s, 1478w, 1446m, 1409m, 1366m, 1350s, 1313m, 1275s, 1251s, 1227w, 1192w, 1154s, 1124w, 1087s, 1042m, 1008m, 976w, 944m, 902w, 871w, 854w, 838w, 829w, 805w, 784m, 767w, 752s, 739w, 694w. HRMS (ESI^+): calcd for $C_{26}H_{31}N_3O_6+Na^+$ ($M+Na^+$) 504.2110, found 504.2104.

4.5. General procedure for the deprotection of Boc groups (general procedure B)

Compounds (±)-**6a–e** and **7a** (0.415 mmol) were dissolved in dichloromethane, and activated silica (0.92 g, 0.040–0.063 mm) was added. The solvent was removed under reduced pressure and the solid mixture was heated at 100 °C overnight. Purification by column chromatography (silica gel 70–230 mesh, methanol/dichloromethane 0.5:9.5 as the gradient eluent) yielded the pure product. It was then washed or recrystallized as described below.

*4.5.1. 4-Hydroxy-5-(1H-indol-3-yl)-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8a***

The desired product was obtained following general procedure B (93 mg, 75%). This was recrystallized from methanol to yield pure analytical sample as colourless crystals. R_f=0.31 (methanol/dichloromethane 0.5:9.5). Mp: 306 °C (methanol, dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.24 (1H, br s), 10.80 (1H, unresolved d), 7.96 (1H, unresolved dd), 7.43(1H, d, J=7.9 Hz), 7.36 (1H, d, J=8.1 Hz), 7.31 (1H, d, J=8.1 Hz), 7.12–6.97 (3H, m), 6.93–6.88 (2H, m), 6.74 (1H, unresolved dd), 5.22 (1H, d, J=4.9 Hz), 4.73 (1H, d, J=5.1 Hz), 4.24–4.10 (1H, m), 3.29–3.20 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.3, 136.4, 136.2, 127.8, 127.2, 126.0, 124.0, 123.4, 120.8, 118.5, 118.3, 118.3, 117.6, 116.6, 112.0, 111.6, 71.4, 44.1, 42.6. ATR-IR (cm^{-1})=3281br, 2924w, 2851w, 1626s, 1548m, 1483m, 1454m, 1338m, 1069s, 1013m, 740s, 681m. MS (EI): m/z (rel int.) 44 (13), 117 (15), 128 (11), 129 (24), 130 (10), 144 (27), 188 (100), 189 (16), 214 (10), 216 (14), 242 (15), 243 (37), 244 (11), 245 (12), 257 (18), 258 (15), 271(35), 272 (76), 273 (24), 286 (15), 313 (30), 331 (68), 332 (14). HRMS (EI): calcd for $C_{20}H_{17}N_3O_2$ (M^+) 331.1315, found 331.1315.

*4.5.2. 4-Hydroxy-5-(7-methyl-1H-indol-3-yl)-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8b***

The desired product was obtained as a white solid following general procedure B (83 mg, 66%). R_f=0.26 (methanol/dichloromethane 0.5:9.5). Mp: 168 °C (methanol/dichloromethane). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.23 (1H, br s), 10.76 (1H, unresolved d), 7.95 (1H, unresolved dd), 7.36 (1H, d, J=8.2 Hz), 7.30–7.25 (1H, m), 7.12–7.04 (2H, m), 6.86–6.80 (3H, m), 6.76 (1H, unresolved dd), 5.20 (1H, d, J=4.6 Hz), 4.72 (1H, d, J=5.2 Hz), 4.18–4.07 (1H, m), 3.27–3.18 (1H, m), 2.40 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.3, 136.2, 135.8, 127.8, 127.2, 125.7, 123.7, 123.4, 121.3, 120.8, 120.7, 118.5, 118.1, 116.6, 116.0, 112.0, 71.3, 44.0, 42.8, 16.7. ATR-IR (cm^{-1})=3375m, 3288s, 2973w, 2917w, 1633s, 1579w, 1537m, 1480s, 1452m, 1398w, 1375w, 1338s, 1286w, 1228m, 1181w, 1155w, 1129w, 1105m, 1076s, 1003m, 970m, 936w, 914w, 870m, 834w, 816w, 778w, 773w, 741s, 680m, 653w. MS (EI): m/z (rel int.) 41 (14), 43 (30), 44 (81), 55 (12), 57 (11), 60 (10), 69 (17), 71 (15), 73 (18), 128 (16), 129 (10), 130 (12), 131 (22), 256 (11), 257 (26), 259 (12), 271 (25), 272 (16), 284 (10), 285 (33), 286 (94), 287 (23), 300 (15), 327 (33), 345 (100), 346 (18). HRMS (EI): calcd for $C_{21}H_{19}N_3O_2$ (M^+) 345.1472, found 345.1472.

*4.5.3. 5-(5-Bromo-1H-indol-3-yl)-4-hydroxy-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8c***

The desired product was obtained following general procedure B (87 mg, 65%). This was washed with diethyl ether and hexane to yield pure analytical sample as an off-white solid. R_f=0.26 (methanol/dichloromethane 0.5:9.5). Mp: 234–238 °C (ether/hexane, dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.28 (1H, br s), 11.02 (1H, unresolved d), 8.00 (1H, unresolved dd), 7.62 (1H, d, J=1.9 Hz), 7.37 (1H, d, J=8.4 Hz), 7.29 (1H, d, J=8.5 Hz), 7.19–7.03 (3H, m), 6.91 (1H, d, J=2.3 Hz), 6.77 (1H, unresolved dd), 5.28 (1H, d, J=4.5 Hz), 4.69 (1H, d, J=5.3 Hz), 4.14–4.01 (1H, m), 3.32–3.20 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.2, 136.2, 135.0, 128.0, 127.7, 127.2, 125.7, 123.5, 123.2, 120.7, 120.6, 118.7, 117.6, 116.1, 113.7, 112.0, 111.0, 71.7, 44.1, 42.5. ATR-IR (cm^{-1})=3401m, 3286w, 3054w, 2920w, 1630s, 1546s, 1478s, 1451s, 1408w, 1335s, 1286w, 1242w, 1154w, 1079s, 1003w, 971w, 931w, 909w, 883m, 791m, 768w, 740s, 660w. MS (EI): m/z (rel int.) 44 (18), 59 (10), 69 (12), 102 (12), 103 (19), 115 (10), 123 (19), 128 (15), 129 (44), 144 (77), 188 (100), 189 (46), 409 (5). HRMS (EI): calcd for $C_{20}H_{16}Br_1N_3O_2$ (M^+) 409.0420, found 409.0412.

*4.5.4. Methyl 3-(4-hydroxy-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]indol-5-yl)-1H-indole-5-carboxylate (±)-**8d***

The desired product was obtained following general procedure B (92 mg, 71%). This was recrystallized from methanol to yield pure analytical sample as colourless crystals. R_f=0.21 (methanol/dichloromethane 0.5:9.5). Mp: 201 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.30 (1H, br s), 11.23 (1H, unresolved d), 8.32 (1H, unresolved d), 7.98 (1H, unresolved dd), 7.73 (1H, dd, J=8.7, 1.7 Hz), 7.44–7.35 (2H, m), 7.11–6.98 (2H, m), 6.90 (1H, d, J=2.3 Hz), 6.75 (1H, unresolved ddd), 5.34 (1H, d, J=4.7 Hz), 4.80 (1H, d, J=5.3 Hz), 4.17–4.08 (1H, m), 3.83 (3H, s), 3.31–3.20 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=167.3, 164.1, 138.9, 136.2, 127.6, 127.3, 125.9, 125.8, 123.5, 122.0, 121.2, 120.6, 120.0, 119.5, 118.6, 116.0, 112.0, 111.5, 71.4, 51.6, 43.8, 42.3. ATR-IR (cm^{-1})=3296br, 3059w, 2924w, 2854w, 1691m, 1616s, 1546m, 1480m, 1435m, 1336m, 1282w, 1242s, 1214w, 1147w, 1102w, 1078w, 1003w, 972w, 932w, 870m, 768m, 742s, 668w, 661w. MS (EI): m/z (rel int.) 43 (11), 44 (35), 121 (22), 129 (13), 144 (17), 149 (13), 175 (16), 214 (21), 215 (15), 216 (12), 241 (18), 242 (31), 243 (31), 256 (15), 257 (10), 269 (12), 270 (14), 271 (65), 272 (86), 273 (17), 299 (11), 300 (15), 301 (23), 302 (10), 303 (16), 304 (13), 315 (20), 316 (13), 328 (16), 329 (38), 330 (100), 331 (39), 332 (10), 344 (20), 357 (13), 358 (24), 371 (70), 372 (14), 389 (97), 390 (31). HRMS (EI): calcd for $C_{22}H_{19}N_3O_4$ (M^+) 389.1370, found 389.1380.

*4.5.5. 5-(5-(Benzyloxy)-1H-indol-3-yl)-4-hydroxy-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**8e***

The desired product was obtained following general procedure B (77 mg, 56%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as an off-white solid. R_f=0.20 (methanol/dichloromethane 0.5:9.5). Mp: 203 °C (ethyl acetate/hexane, dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.27 (1H, br s), 10.63 (1H, unresolved d), 8.00 (1H, unresolved dd), 7.48–7.27 (6H, m), 7.19 (1H, d, J=8.9 Hz), 7.14–7.04 (3H, m), 6.83 (1H, unresolved d), 6.81–6.71 (2H, m), 5.22 (1H, d, J=4.7 Hz), 5.00 (2H, s), 4.69 (1H, d, J=4.9 Hz), 4.17–4.06 (1H, m), 3.30–3.17 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): 164.4, 151.7, 137.6, 136.2, 131.6, 128.4, 127.8, 127.7, 127.6, 127.5, 127.2, 126.3, 124.7, 123.4, 120.8, 118.5, 117.4, 116.6, 112.2, 112.0, 111.3, 102.0, 71.2, 69.7, 44.0, 42.6, 38.7. ATR-IR (cm^{-1})=3292br, 3060w, 2956w, 2924w, 2855w, 1722m, 1622s, 1579w, 1545m, 1478s, 1451m, 1378w, 1335m, 1285s, 1219w, 1182m, 1154w, 1074m, 1044w, 1003w, 846w, 786m, 739s, 696m, 666w. MS (EI): m/z (rel int.) 71 (13), 73 (25), 91 (40),149 (11), 223 (10), 243 (11), 259 (30), 260 (11), 261 (31), 271 (10), 272 (18), 273 (9), 285 (13), 287 (33), 288 (12), 289 (11), 328 (17), 346 (32), 419 (25), 437 (100), 438 (28). HRMS (EI): calcd for $C_{27}H_{23}N_3O_3$ (M^+) 437.1734, found 437.1733.

4.5.6. 4-Hydroxy-5-(1H-pyrrol-2-yl)-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (±)-**9a**

The desired product was obtained following general procedure B (76 mg, 65%). This was recrystallized from ethyl acetate/hexane to yield pure analytical sample as a brown solid. R_f=0.33 (methanol/dichloromethane 0.5:9.5). Mp: 209 °C (hexane/ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.24 (1H, br s), 10.55 (1H, unresolved d), 7.91 (1H, unresolved dd), 7.38–7.33 (1H, m), 7.13–7.06 (2H, m), 6.86–6.79 (1H, m), 6.53–6.51 (1H, m), 5.84 (dd, 1H, J=3.0, 2.6 Hz), 5.61–5.59 (1H, m), 5.16 (1H, d, J=4.7 Hz), 4.48 (1H, d, J=5.8 Hz), 4.06–3.99 (1H, m), 3.29–3.16 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)=164.1, 136.0, 134.0, 127.8, 127.3, 123.4, 120.7, 118.6, 116.3, 115.2, 111.9, 107.0, 105.8, 71.9, 44.4, 44.3. IR (KBr) (cm^{-1})=3533w, 3321s, 2876w, 1619s, 1552s, 1483s, 1455m, 1412w, 1367w, 1334s, 1299m, 1250w, 1217m, 1196w, 1156w, 1131w, 1093w, 1069s, 1027w, 1012w, 1003w, 977w, 930w, 913w, 875w, 846w, 802s, 785w, 768m, 745w, 733s, 633m, 612m, 550m, 481w, 449w, 432w. MS (EI): m/z (rel int.) 44 (32), 166 (11), 192 (17), 193 (63), 194 (17), 195 (17), 207 (19), 208 (10), 220 (22), 221 (36), 222 (98), 223 (24), 262 (11), 263 (100), 264 (15), 281 (39). HRMS (EI): calcd for $C_{16}H_{15}N_3O_2$ (M^+) 281.1159, found 281.1161.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.092.

References and notes

1. Neilsen, P. C. L.; Jacobsen, E. N. *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 229–269.
2. (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323; (b) Smith, J. G. *Synthesis* **1984**, 629; (c) Hirose, T.; Sunazuka, T.; Zhi-Ming, T.; Handa, M.; Uchida, R.; Shiomi, K.; Harigaya, Y.; Omura, S. *Heterocycles* **2000**, *53*, 777; (d) Crotti, P.; Pineschi, M. *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 271–313.
3. Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979.
4. Tanis, S. P.; Raggon, J. W. *J. Org. Chem.* **1987**, *52*, 819.
5. (a) Kotsuki, H.; Hayashida, K.; Shimanouchi, T.; Nishizawa, H. *J. Org. Chem.* **1996**, *61*, 984; (b) Kotsuki, H.; Nishiuchi, M.; Kobayashi, S.; Nishizawa, H. *J. Org. Chem.* **1990**, *55*, 2969.
6. Kotsuki, H.; Teraguchi, M.; Shimomoto, N.; Ochi, M. *Tetrahedron Lett.* **1996**, *37*, 3727.
7. Kantam, M. L.; Laha, S.; Yadav, J.; Sreedhar, B. *Tetrahedron Lett.* **2006**, *47*, 6213.
8. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Tetrahedron Lett.* **2008**, *49*, 1450.
9. Bandgar, B. P.; Patil, A. V. *Tetrahedron Lett.* **2007**, *48*, 173.
10. (a) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490; (b) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471.
11. (a) Bishop, A. C.; Ubersax, J. A.; Petsch, D. T.; Matheos, D. P.; Gray, N. S.; Blethrow, J.; Shimizu, E.; Tsien, J. Z.; Schultz, P. G.; Rose, M. D.; Wood, J. L.; Morgan, D. O.; Shokat, K. M. *Nature* **2000**, *407*, 395; (b) Gray, N. S. *Science* **1998**, *281*, 533.
12. Cohen, P. *Nat. Rev. Drug Discovery* **2002**, *1*, 309.
13. Bridges, A. J. *Chem. Rev.* **2001**, *101*, 2541.
14. (a) Cimino, G.; De Rosa, S.; De Stefano, S.; Mazzarella, L.; Puliti, R.; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 767; (b) Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321.
15. Huwe, A.; Mazitschek, R.; Giannis, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2122.
16. (a) Wan, Y.; Hur, W.; Cho, C. Y.; Liu, Y.; Adrin, F. J.; Lozach, O.; Bach, S.; Mayer, T.; Fabbro, D.; Meijer, L.; Gray, N. S. *Chem. Biol.* **2004**, *11*, 247; (b) Sharma, V.; Lansdell, T. A.; Jin, G.; Tepe, J. J. *J. Med. Chem.* **2004**, *47*, 3700.
17. (a) Sharma, V.; Tepe, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4319; (b) He, Q.; Chen, W.; Qin, Y. *Tetrahedron Lett.* **2007**, *48*, 1899.
18. For recent publications in this area, see: (a) Tse, M. K.; Döbler, C.; Bhor, S.; Klawonn, M.; Mägerlein, W.; Hugl, H.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5255; (b) Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Spannenberg, A.; Döbler, C.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem.—Eur. J.* **2006**, *12*, 1875; (c) Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem.—Eur. J.* **2006**, *12*, 1855; (d) Anilkumar, G.; Bitterlich, B.; Gelalcha, F. G.; Tse, M. K.; Beller, M. *Chem. Commun.* **2007**, 289; (e) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293.
19. (a) Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Böttcher, H.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 746; (b) Michalik, D.; Kumar, K.; Zapf, A.; Tillack, A.; Arlt, M.; Heinrich, T.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 2057; (c) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 7703; (d) Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M. *Tetrahedron* **2005**, *61*, 7622; (e) Neumann, H.; Strübing, D.; Lalk, M.; Klaus, S.; Hübner, S.; Spannenberg, A.; Lindequist, U.; Beller, M. *Org. Biomol. Chem.* **2006**, *4*, 1365.
20. (a) Kaiser, H. M.; Lo, W. F.; Riahi, A. M.; Spannenberg, A.; Beller, M.; Tse, M. K. *Org. Lett.* **2006**, *8*, 5761; (b) Kaiser, H. M.; Zenz, I.; Lo, W. F.; Spannenberg, A.; Schröder, K.; Jiao, H.; Gördes, D.; Beller, M.; Tse, M. K. *J. Org. Chem.* **2007**, *72*, 8847.
21. (a) Haywood-Farmar, J.; Friedlander, B. T.; Hammond, L. M. *J. Org. Chem.* **1973**, *38*, 3145; (b) Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, *21*, 3587.
22. (a) Herrmann, V. W. A.; Fischer, R. W.; Marz, D. W. *Angew. Chem.* **1991**, *103*, 1706; (b) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189.
23. (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187; (b) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847; (c) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979; (d) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488; (e) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497.
24. Shendage, D. M.; Fröhlich, R.; Haufe, G. *Org. Lett.* **2004**, *6*, 3675.
25. (a) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435; (b) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293.
26. (a) Jacobsen, E. N. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, NY, 1993; pp 159–202; (b) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.
27. Sheldrick, G. M. *SHELXS-97*; University of Göttingen: Göttingen, Germany, 1997.
28. Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Göttingen, Germany, 1997.