2-Azetidinones: synthesis of new bis(indolyl)butyl-β-lactams

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New β-lactam compounds containing a bis(indolyl)-framework were synthesized. The key step in the synthetic strategy was a nucleophilic addition of unprotected indole to a suitable butyl aldehyde anchored on the C-4 side chain of azetidinone intermediates. The use of an ionic liquid as reaction medium allowed the use of a catalytic amount of $Dy(OTf)_3$ for the nucleophilic addition and facilitated the isolation of the product.

Introduction

β-Lactams have historically been viewed as a class of antimicrobials, but in the last few decades their role as enzyme inhibitors has been expanded.[1] β-Lactams are well-known as potent inhibitors of some enzymes that contain serine as the catalytic residue, including the bacterial penicillin binding proteins (PBPs) and Class A and Class C β-lactamases.[2]

β-Lactams have also been appropriately modified to develop active site-directed and mechanism-based inhibitors of Human Leukocyte Elastase (HLE),[3] and in this field some new monocyclic β-lactams have shown important activities as HLE inhibitors,[4] new antibiotics towards resistant bacteria,[5] and as inhibitors of platelet aggregation.[6]

Recently, relevant studies appeared on β-lactam compounds as anti-tumor drugs. Some aryl-β-lactam derivatives have been evaluated for cytotoxicity against a number of human tumour and normal cell lines.[7] In particular *N*-thiolated-β-lactams were found to induce DNA damage, cell growth arrest, and apoptosis in cultured human cancer cells, and anti proliferative effects on human breast cancer cells of some new azetidinones were evaluated.[8] Some bicyclic β-lactams were recently reported as inhibitors of Histone Deacetylases (HDACs), a family of proteins involved in the pattern of acetylation of chromatin proteins and thus in the regulation of gene expression.[9]

We recently reported the synthesis of some azetidinone derivatives which showed good affinity and specificity towards HDAC8 and HDAC6.[10] The design of those new azetidinones was based on the pharmacophore model of HDAC inhibitors which consists in a modular structure with a cap-group that interacts with receptor residues at the active site entrance, a linker group that binds in a hydrophobic channel and positions the metal-binding group for the interactions with the zinc atom in the active site. The azetidinone was identified as the zinc-binding group with an alkyl- or alkenyl chain as the linker, and a capping group typical of some known HDACs inhibitors.

In this paper, we report the synthesis of new azetidinones specifically designed on the modular structure for HDAC inhibition (Fig. 1), with the azetidinone as the zinc-binding group and a bis(indolyl)methane as capping group for specific receptor interaction, according to the finding of Giannini *et al.* on the HDAC activity of bis(indolyl)-hydroxamic acids,[11] and of Guo *et al.* on the role of bis(indolyl)methane on selective proteasomal degradation of Class I Histone Deacetylases.[12] The synthetic route for the new β-lactam compounds was accurately designed because of the sensitivity of the azetidinone ring towards ring-opening reaction by nucleophiles, and to preserve, at the same time, all the NH groups free (Fig. 1).

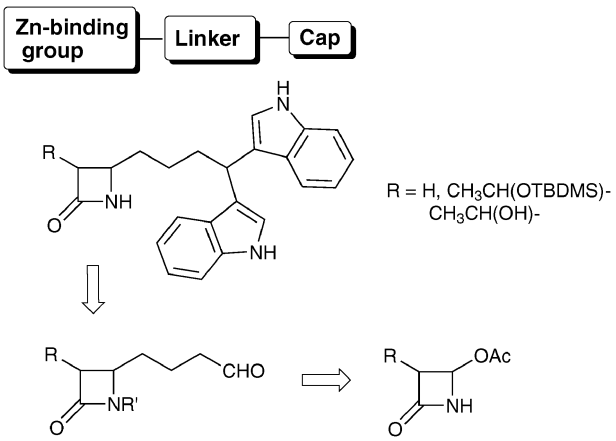

Fig. 1 New 3,3′-bis(indolyl)azetidinones designed on the pharmacophore model of HDAC inhibitors and synthetic strategy.

Results and discussion

Indole fragment is featured in a wide variety of pharmacologically and biologically active compounds, and bis(indolyl)-alkanes are found in bioactive metabolites of terrestrial and marine origin.[13] Therefore, there is a great deal of interest in the synthesis of this class of compounds.[14] Among several methods reported, the synthesis in the presence of Lewis acids, Brønsted acids or montmorillonite clay K-10 to promote the reaction of indoles with aromatic or aliphatic aldehydes and ketones has been widely studied.[13] More recently, bis(indolyl)-methanes (3,3′-BIMs) were found to be formed in acetonitrile in the presence of catalysts such as $InCl_3$, $In(OTf)_3$, and I_2.[15] However, many of these Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. So, the

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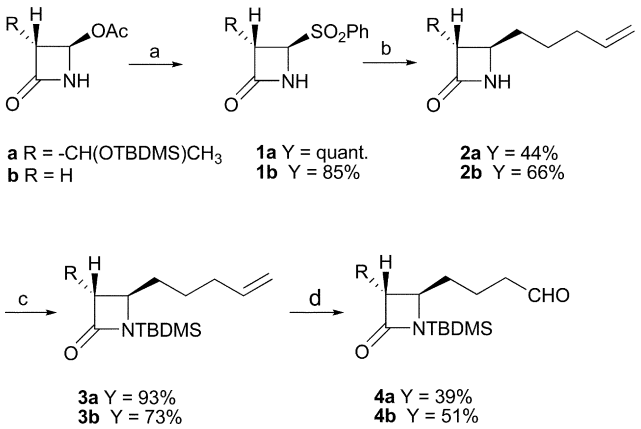
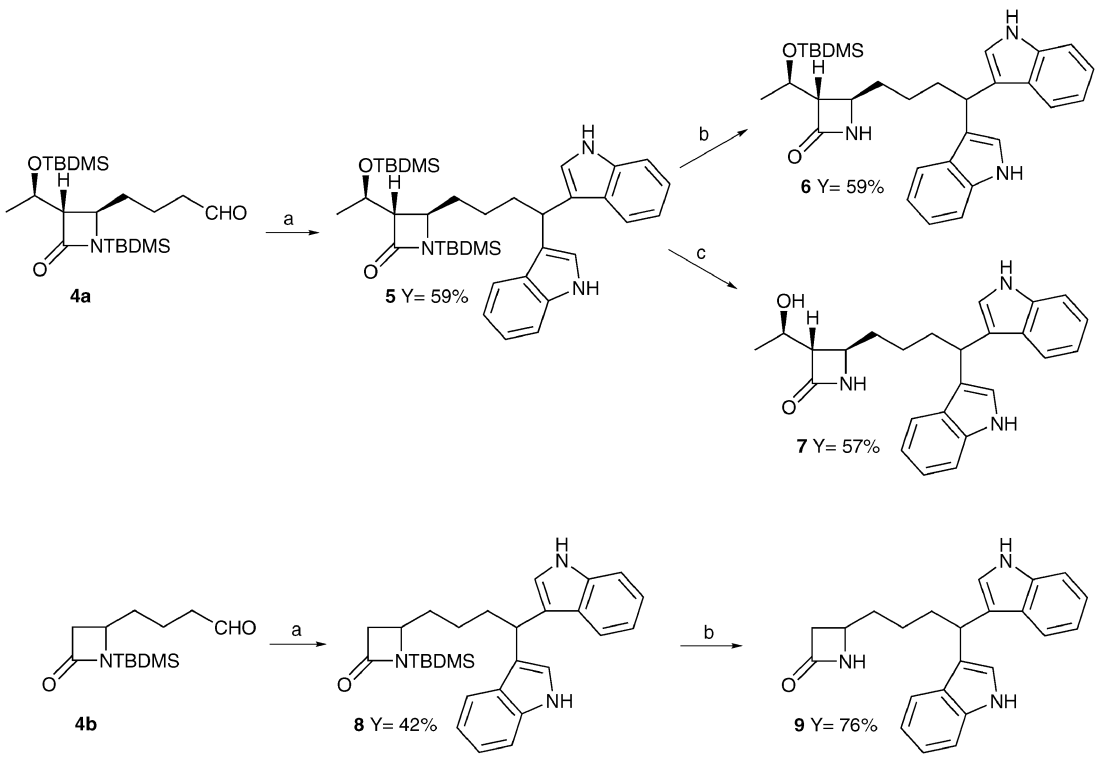


Scheme 1 *Reagents and conditions*: (a) $PhSO_2Na$, H_2O, reflux; (b) 4-pentenylMgBr, THF, −78 °C to rt; (c) *t*$BuMe_2SiCl$, DMF, TEA, 0 °C to rt; (d) O_3, DCM, −78 °C, then DMS −78 °C to rt.

synthesis of β-lactams containing a bis(indolyl) moiety presented some intrinsic difficulties. With the aim to limit to a minimum extent the use of protecting groups, we envisaged the possibility to insert the bis(indolyl) moiety at the end of the synthetic pathway on an azetidinone–aldehyde obtained with few steps from commercially available 4-acetoxy-azetidinone intermediates (Scheme 1).

The synthetic route to aldehyde intermediates was illustrated in Scheme 1. Starting from the commercially available enantiopure (3*S*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-azetidin-2-one or the racemic 4-acetoxy-azetidinone, they were converted to sulfones **1a** or **1b**. Treatment with 4-pentenylmagnesium bromide afforded the C4-alkylated derivatives **2a** or **2b**. The preliminary sulfonylation was dictated by the poor yields of the direct conversion of 4-acetoxy-azetidinones to 4-pentenyl derivatives **2a,b**. Retention of stereochemistry in substitution reactions on the C-4 position of 4-acetoxy- or 4-sulfonyloxy-azetidinones is typical, and the 3,4-*trans* configuration for compound **2a** was confirmed by ^{1}H NMR analysis which showed a low value of *J* coupling of H_3–H_4 on the azetidinone ring (2.2 Hz, see Experimental section). The ozonolysis of the C=C bond required a preliminary protection of the amide group and treatment with *tert*-butyldimethylsilyl chloride and TEA gave in good yields *N*-*tert*-butyldimethylsilyl-derivatives **3a** and **3b**. Then ozonolysis in dichloromethane at low temperature followed by dimethylsulfide addition (DMS) gave aldehydes **4a** and **4b**.

Syntheses of bis(indolyl)methanes were already reported starting from aromatic or aliphatic aldehydes under various conditions.[13] Green and eco-friendly conditions have also been explored and ionic liquids, as green solvents with low vapor pressure, have been already used in the synthesis of 3,3′-BIMs.[16] After a careful evaluation of the reaction conditions reported in the literature and with the requirement to have mild reaction conditions and reagents which preserve the quite susceptible azetidinone intermediates, we turned our attention to dysprosium triflate ($Dy(OTf)_3$) as Lewis acid immobilized in the ionic liquid 1-*n*-butyl-3-methyl-imidazolium tetrafluoroborate, [bmim]BF_4.[17] The condensation of two equivalents of indole with aldehydes **4a** or **4b** with 2% of $Dy(OTf)_3$ was successful (Scheme 2). The use of ionic liquid [bmim]BF_4 as reaction medium at room temperature served a double purpose, it was strategic to use $Dy(OTf)_3$ in a catalytic amount and to an easy recovery of the BIM-azetidinones **5** and **8**, since they were



Scheme 2 *Reagents and conditions*: (a) indole, $Dy(OTf)_3$ 2%, [bmim]BF_4; (b) TBAF, THF, 0 °C; (c) $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C.

weakly soluble in the ionic phase and were easily separated by simple extraction with diethyl ether. The bis(indolyl)azetidinone **5** was then selectively deprotected at the β-lactam nitrogen atom with tetrabutylammonium fluoride (TBAF) or fully deprotected with $BF_3{\cdot}OEt_2$ to give enantiopure compounds **6** and **7** in 59% and 57% yield, respectively, after flash chromatography. Deprotection of the C-3 unsubstituted derivative **8** with TBAF gave **9** in 76% yield.

As above mentioned, 3,3′-BIMs showed important biological activities, in particular they induce responses in multiple cancer cell lines and tumors including growth inhibition, apoptosis and antiangiogenic activities.[12,18] We thus submitted the new bis(indolyl)azetidinones **5**, **6**, **7**, and **9** to a preliminary evaluation. At present the derivatives did not show a cytotoxic activity at a significant level on two tumor cell lines (HCT-116 or NB4) and showed a low potency in HDAC inhibitory activity on *in vitro* tests. Further investigations on the biological activities, especially as antibiotics of these new molecules are in due course.

Conclusions

In conclusion, new β-lactam compounds containing a bis(indolyl)methane framework were synthesized. A butyl-aldehyde as the C-4 side chain was identified as suitable intermediate and obtained in a concise synthesis from the commercially available (3*S*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-azetidin-2-one or the racemic 4-acetoxy-azetidinone. The use of an ionic liquid as reaction medium allowed the use of a catalytic amount of $Dy(OTf)_3$ for the nucleophilic addition of indole to the azetidinone-aldehydes **4a,b** and greatly facilitated the recovery of the bis(indolyl)butyl-azetidinones. Simple management of protecting groups allows the access to new β-lactam-bis(indolyl)methane hybrids. The novelty of these molecules obtained through the combination of two pharmacophores in one frame, azetidinone and 3,3′-BIMs, deserves further investigations and tests on biological activities of these new molecules are in progress.

Experimental

General remarks

All reactions were performed under an inert atmosphere (N_2). Commercial reagents were used as received without additional purification. Anhydrous solvents (CH_3CN, CH_2Cl_2, THF, DMF) were obtained commercially. ^1H and ^{13}C NMR values were recorded on a Varian INOVA 400, INOVA 300, or a GEMINI 200 instrument with a 5 mm probe. All chemical shifts have been quoted relative to deuterated solvent signals, δ in ppm and J in Hz. FT-IR: Nicolet 205, measured as films between NaCl plates and wavenumbers reported in cm^{-1}. TLC: Merck 60 F_{254}. Column chromatography: Merck silica gel 200–300 mesh. GC-MS: Agilent Technologies, column HP5 5% Ph-Me Silicon. HPLC: Agilent Technologies HP1100, column ZOBRAX-Eclipse XDB-C8 Agilent Technologies, mobile phase: H_2O/CH_3CN, gradient from 30% to 80% of CH_3CN in 8 min, 80% of CH_3CN until 25 min, 0.4 mL min^{-1}. HPLC-MS: Agilent Technologies HP1100 column ZOBRAX-Eclipse XDB-C8 coupled with MSD1100 single-quadrupole mass spectrometer, full-scan mode from m/z 50 to m/z 2600, scan time 0.1 s in positive ion mode, ESI spray voltage 4500 V, nitrogen gas 35 psi, drying gas flow 11.5 mL min^{-1}, fragmentor voltage 20 V. Elemental analysis: Perkin-Elmer 2400 Series II CHN analyser. The $[\alpha]_D^{25}$ values are given in 10^{-1} deg cm^2 g^{-1}, determined with a Perkin-Elmer 343 polarimeter. β-Lactams **1a**, **2b**, **3b**, and **4b** are known, but obtained with different procedures.[19] 4-Benzenesulfonyl-azetidin-2-one (**1b**) was prepared from commercially available 4-acetoxy-azetidin-2-one in 85% yield, following the procedure reported in ref. 20.

(3*S*,4*R*)-4-Benzenesulfonyl-3-((1*R*)-1-(*tert*-butyldimethyl-silanyloxy)-ethyl)-azetidin-2-one 1a. Sodium phenyl sulfinate (189 mg, 1.15 mmol) was added to (3*S*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-azetidin-2-one (300 mg, 1.1 mmol) in water (3 mL). The reaction was refluxed for 20 min and then was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*, to afford product **1a** (400 mg, quantitative yield) as a white solid (found C, 55.2; H, 7.5; N, 3.8%. $C_{17}H_{27}NO_4SSi$ requires C, 55.25; H, 7.4; N, 3.8%); $[\alpha]_D^{25}$ −16 (*c* 1.1, $CHCl_3$), ν_{max} (CH_2Cl_2)/cm^{-1} 3166, 2954, 2921, 2848, 1781, 1446, 1262, 1148, and 727; δ_H (200 MHz, $CDCl_3$) 0.01 (3 H, s, Me), 0.04 (3 H, s, Me), 0.82 (9 H, s, *t*Bu), 1.10 (3 H, d, *J* 6.6, Me), 3.42 (1 H, d, *J* 2.2, 3-H), 4.25 (1 H, dq, *J* 2.2 and 6.2, C*H*(OTBS)), 4.80 (1 H, d, *J* 2.2, 4-H), 6.61 (1 H, br s, NH), 7.57–7.76 (3 H, m, Ph), 7.92–7.96 (2 H, m, Ph); δ_C (50 MHz, $CDCl_3$) −5.3, −4.5, 17.8, 22.2, 25.6, 63.0, 63.4, 66.7, 129.3, 129.6, 134.7, 135.3, and 166.2.

(3*S*,4*R*)-3-((1*R*)-1-(*tert*-Butyldimethylsilanyloxy)-ethyl)-4-pent-4-enyl-azetidin-2-one 2a. 4-Pentenylmagnesium bromide, freshly prepared from Mg (300 mg, 12.3 mmol) and 4-pentenyl-bromide (2.3 g, 15.4 mmol) in THF (12 mL), was added drop by drop to a solution of **1a** (1.9 g, 5.14 mmol) in THF (40 mL) at −78 °C. The mixture was stirred at 0 °C for 5 h, NH_4Cl sat. sol. was added, the aqueous layer was extracted with Et_2O, the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 80 : 20) to afford product **2a** (671 mg, 44%) as a colorless oil (found C, 64.7; H, 10.6; N, 4.7%. $C_{16}H_{31}NO_2Si$ requires C, 64.6; H, 10.5; N, 4.7%); ν_{max} (CH_2Cl_2)/cm^{-1} 3161, 2922, 1756, 1704, and 1586; δ_H (200 MHz, $CDCl_3$) 0.07 (6 H, s, 2 × Me), 0.88 (9 H, s, *t*Bu), 1.24 (3 H, d, *J* 6.2, Me), 1.36–1.71 (4 H, m, 2 × CH_2), 2.05–2.16 (2 H, m, CH_2), 2.72 (1 H, ddd, *J* 1.2, 2.2 and 5.2, 3-H), 3.63 (1 H, dt, *J* 2.2 and 6.6, 4-H), 4.16 (1 H, dq, *J* 5.2 and 6.2, C*H*(OTBS)), 4.96–5.07 (2 H, m, CH=CH_2), 5.68–5.90 (1 H, m, C*H*=CH_2), 6.00 (1 H, br s, 1-NH); δ_C (50 MHz, $CDCl_3$) −5.0, −4.3, 17.9, 22.7, 25.7, 25.8, 33.5, 34.5, 51.2, 64.3, 65.6, 115.0, 138.0, and 169.0; HPLC-MS (ESI) R_t = 12.70 min, m/z 298.1 $[M + H]^+$, 320.1 $[M + Na]^+$, 595.5 $[2M + H]^+$, 617.3 $[2M + Na]^+$.

4-Pent-4-enyl-azetidin-2-one 2b. 4-Pentenyl magnesium bromide, freshly prepared from Mg (0.042 g, 1.74 mmol) and 4-pentenylbromide (0.277 g, 1.86 mmol) in THF (5 mL), was added drop by drop to a solution of **1b** (0.131 g, 0.62 mmol) in THF (3 mL) at −78 °C. The mixture was stirred

at 0 °C for 5 h, NH_4Cl sat. sol. was added, the aqueous layer was extracted with Et_2O, the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 80 : 20) to afford product **2b** (57 mg, 66%) as a colorless oil. Characterization resulted in agreement with the reported data.[19]

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilanyl)-3-((1*R*)-1-(*tert*-butyldimethylsilanyloxy)-ethyl)-4-pent-4-enyl-azetidin-2-one 3a. Et_3N (0.657 mL, 4.72 mmol) and *t*$BuMe_2SiCl$ (283 mg, 1.9 mmol) were added to a solution of **2a** (470 mg, 1.57 mmol) in DMF (10 mL) at 0 °C and the mixture was stirred overnight at room temperature. To the reaction mixture was added sat. aq. $NaHCO_3$, the aqueous layer was extracted with Et_2O, the organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 90 : 10) to afford **3a** (600 mg, 93%) the product as a colorless oil (found C, 64.4; H, 11.0; N, 3.4%. $C_{22}H_{45}NO_2Si_2$ requires C, 64.2; H, 11.0; N, 3.4%); $[\alpha]_D^{25}$ −41 (*c* 1.3, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 2928, 2860, 1740, 1642, 1471, and 1258; δ_H (200 MHz, $CDCl_3$) 0.06 (3 H, s, Me), 0.08 (3 H, s, Me), 0.21 (3 H, s, Me), 0.23 (3 H, s, Me), 0.89 (9 H, s, *t*Bu), 0.96 (9 H, s, *t*Bu), 1.22 (3 H, d, *J* 6.2, Me), 1.36–1.51 (3 H, m, C*H*$_2$C*H*H), 1.76–1.90 (1 H, m, CH_2CH*H*), 2.04–2.14 (2 H, m, CH_2), 2.71 (1 H, dd, *J* 2.6 and 5.8, 3-H), 3.46–3.53 (1 H, m, 4-H), 4.10 (1 H, quintet, *J* 6.2, C*H*(OTBS)), 4.90–5.07 (2 H, m, CH=C*H*$_2$), 5.68–5.90 (1 H, m, C*H*=CH_2); δ_H (75 MHz, $CDCl_3$) −5.8, −5.1, −4.6, −4.4, 17.9, 18.2, 23.0, 25.3, 25.9, 26.3, 33.7, 35.4, 52.8, 64.6, 66.2, 114.9, 138.1, 173.5; HPLC-MS (ESI) R_t = 9.9 min, *m*/*z*: 412 $[M + H]^+$.

1-(*tert*-Butyldimethylsilanyl)-4-pent-4-enyl-azetidin-2-one 3b. Et_3N (0.31 mL, 2.25 mmol) and *t*$BuMe_2SiCl$ (148 mg, 1 mmol) were added to a solution of **2b** (104 mg, 0.75 mmol) in DMF (6 mL) at 0 °C and the mixture was stirred overnight at room temperature. To the reaction mixture was added sat. aq. $NaHCO_3$, the aqueous layer was extracted with Et_2O, the organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 90 : 10) to afford product **3b** (138 mg, 73%) as a colorless oil. Characterization resulted in agreement with the reported data.[19]

4-((2*R*,3*S*)-1-(*tert*-Butyldimethylsilanyl)-3-((1*R*)-1-(*tert*-butyldimethylsilanyloxy)-ethyl)-4-oxoazetidin-2-yl)-butanal 4a. A solution of **3a** (301 mg, 2 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C and treated with a stream of O_3 at −78 °C until the reagent completely disappeared. The reaction mixture was treated with a stream of O_2 at −78 °C to remove an excess amount of O_3. To the solution was added Me_2S (3 mL) at −78 °C, the mixture was allowed to stir at room temperature overnight and then concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 80 : 20) to afford product **4a** (117 mg, 39%) as a pale yellow oil (found C, 60.8; H, 10.5; N, 3.3%; $C_{21}H_{43}NO_3Si_2$ requires C, 61.0; H, 10.5; N, 3.4%); $[\alpha]_D^{25}$ −42 (*c* 1, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 2954, 2926, 2855, 1742, 1475, and 1258; δ_H (200 MHz, $CDCl_3$) 0.05 (3 H, s, Me), 0.08 (3 H, s, Me), 0.20 (3 H, s, Me), 0.22 (3 H, s, Me), 0.88 (9 H, s, *t*Bu), 0.94 (9 H, s, *t*Bu), 1.23 (3 H, d, *J* 6.2, Me), 1.38–1.90 (4 H, m, 2 × C*H*$_2$), 2.50 (2 H, dt, *J* 1.0 and 7.0, CHC*H*$_2$), 2.75 (1 H, dd, *J* 2.6 and 6.2, 3-H), 3.50 (1 H, dt, *J* 2.6 and 5.6 4-H), 4.10 (1 H, dq, *J* 5.6 and 6.2, C*H*(OTBS)), 9.78 (1 H, t, *J* 1.0, C*H*O). δ_C (50 MHz, $CDCl_3$) −5.9, −5.1, −4.6, −4.4, 17.9, 18.1, 18.6, 23.0, 25.8, 26.2, 35.3, 43.6, 52.7, 64.7, 66.4, 173.1, and 198.0; GC-MS R_t = 22.3 min, *m*/*z*: 284 (2), 242 (90), 224 (50), 75 (100).

4-(1-(*tert*-Butyldimethylsilanyl)-4-oxo-azetidin-2-yl)-butanal 4b. A solution of **3b** (138 mg, 0.54 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C and treated with a stream of O_3 at −78 °C until the reagent completely disappeared. The reaction mixture was treated with a stream of O_2 at −78 °C to remove the excess of O_3. To the solution was added Me_2S (2.5 mL) at −78 °C, the mixture was allowed to stir at room temperature overnight and then concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 80 : 20) to afford product **4b** (70 mg, 51%) as a pale yellow oil. Characterization resulted in agreement with the reported data.[19]

4-(3*S*,4*R*)-(4,4-Bis-(1*H*-indol-3-yl)-butyl)-1-(*tert*-butyldimethylsilanyl)-3-((1*R*)-1-(*tert*-butyldimethylsilanyloxy)-ethyl)-azetidin-2-one 5. Indole (63 mg, 0.54 mmol) and aldehyde **4a** (113 mg, 0.27 mmol) were added to a solution of $Dy(OTf)_3$ (3.3 mg, 2% mol) in $[bmim]BF_4$ (0.5 mL). The mixture was stirred overnight at room temperature, extracted with Et_2O and concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 70 : 30) to afford product **5** (100 mg, 59%) as a pale brown oil (found C, 70.6; H, 8.9; N, 6.75%; $C_{37}H_{55}N_3O_2Si_2$ requires C, 70.5; H, 8.8; N, 6.7%); $[\alpha]_D^{25}$ −29 (*c* 0.9, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 3414, 3330, 2919, 2854, 1734, 1462, and 1269; δ_H (200 MHz, $CDCl_3$) −0.01 (3 H, s, Me), 0.03 (3 H, s, Me), 0.14 (3 H, s, Me), 0.18 (3 H, s, Me), 0.84 (9 H, s, *t*Bu), 0.92 (9 H, s, *t*Bu), 1.03 (3 H, d, *J* 6.2, Me), 1.35–1.90 (4 H, m, 2 × CH_2), 2.20–2.36 (2 H, m, CHC*H*$_2$), 2.60 (1 H, dd, *J* 2.6 and 4.8, 3-H), 3.42–3.52 (1 H, m, 4-H), 4.04 (1 H, dt, *J* 5.4 and 6.2, C*H*(OTBS)), 4.48 (1 H, t, *J* 7.4, C*H*(ind)$_2$), 6.99–7.07 (2H, m, arom), 7.03 (2 H, s, C*H* arom ind), 7.03 (2 H, t, *J* 7.4, arom), 7.34 (2 H, d, *J* 7.2, arom), 7.58 (2 H, d, *J* 7.5, arom), 7.94 (2 H, br s, 2 × NH); δ_C (75 MHz, $CDCl_3$) −5.6, −4.8, −4.3, −4.2, 18.2, 18.4, 23.1, 25.0, 26.2, 26.6, 34.3, 36.1, 36.3, 52.7, 64.6, 66.0, 111.4, 119.3, 119.8, 119.9, 120.2, 121.6, 121.7, 122.0, 127.2, 127.3, 136.9, and 174.0; HPLC-MS (ESI) R_t = 27.7 min, *m*/*z* 630 $[M + H]^+$, 652 $[M + Na]^+$.

4-(3*S*,4*R*)-(4,4-Bis-(1*H*-indol-3-yl)-butyl)-3-((1*R*)-1-(*tert*-butyldimethylsilanyloxy)-ethyl)-azetidin-2-one 6. TBAF (1 M in THF, 0.185 mL, 0.185 mmol) was added to a solution of **5** (35 mg, 0.056 mmol) in THF (2 mL) at 0 °C. The mixture was stirred overnight at 0 °C. After adding phosphate buffer (0.1 M, pH 6.5) to the mixture at 0 °C, the aqueous mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 60 : 40) to afford product **6** (17 mg, 59%) as a pale yellow oil (found C, 72.2; H, 8.1; N, 8.1%; $C_{31}H_{41}N_3O_2Si$ requires C, 72.2; H, 8.0; N, 8.15%); $[\alpha]_D^{25}$ −2 (*c* 1.0, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 3421, 3300, 3055, 2929, 2852, 1740, 1617, 1455, 1255; δ_H (200 MHz, $CDCl_3$) 0.05 (3 H, s), 0.07 (3 H, s, Me), 0.87 (9 H, s, *t*Bu), 1.14

(3 H, d, *J* 6.6, Me), 1.40–1.76 (4 H, m, 2 × C*H*$_2$), 2.24–2.36 (2 H, m, CHC*H*$_2$), 2.67 (1 H, dd, *J* 1.6 and 4.8, 3-H), 3.60 (1 H, dt, *J* 4.8 and 6.6, 4-H), 4.13 (1 H, quintet, *J* 6.6, C*H*(OTBS)), 4.51 (1 H, t, *J* 7.4, C*H*(ind)$_2$), 5.68 (1 H, br s, 1-NH), 7.00–7.21 (6 H, m, arom), 7.37 (2 H, d, *J* 8.0, arom), 7.61 (2 H, d, *J* 8.2, arom), 7.98 (2 H, br s, 2 × NH); δ_C (50 MHz, $CDCl_3$) −4.9, −4.2, 18.0, 22.7, 25.4, 25.9, 34.1, 35.3, 35.6, 51.1, 64.4, 65.5, 111.3, 119.2, 119.6, 120.0, 120.1, 121.4, 121.5, 122.0, 127.1, 127.2, 136.7, and 169.0; HPLC-MS (ESI) R_t = 12.83 min, *m*/*z*: 538 $[M + Na]^+$.

4-(3*S*,4*R*)-(4,4-Bis-(1*H*-indol-3-yl)-butyl)-3-((1*R*)-1-hydroxy-ethyl)-azetidin-2-one 7. $BF_3{\cdot}OEt_2$ (8.9 μL, 0.07 mmol) was added to a solution of **5** (22 mg, 0.035 mmol) in CH_3CN (1 mL) at 0 °C. The mixture was allowed to stir at 0 °C for 3 days. The reaction was quenched by addition of ice-cold phosphate buffer (0.1 M, pH 6) and ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 20 : 80) to afford product **7** (8 mg, 57%) as a white solid (found C, 74.9; H, 6.85; N, 10.4%. $C_{25}H_{27}N_3O_2$ requires C, 74.8; H, 6.8; N, 10.5%); $[\alpha]_D^{25}$ +12 (*c* 0.5, $CHCl_3$). ν_{max} (CH_2Cl_2)/cm^{-1} 3346, 2921, 1736, 1703, and 1458. δ_H (200 MHz, $CDCl_3$) 1.25 (3 H, d, *J* 6.2, Me), 1.26–1.78 (4 H, m, 2 × C*H*$_2$), 2.20–2.34 (2 H, m, CHC*H*$_2$), 2.74–2.78 (1 H, m, 3-H), 3.56–3.64 (1 H, m, 4-H), 4.10–4.20 (1 H, m, C*H*(OH)), 4.41 (1 H, t, *J* = 7.6, C*H*(ind)$_2$), 5.81 (1 H, br s, 1-NH), 6.50 (1 H, s, OH), 7.01–7.61 (10 H, m, arom), 7.86 (1 H, br s, NH), 8.14 (1 H, br s, NH). δ_C (100 MHz, $CDCl_3$) 25.6, 29.4, 34.1, 34.9, 36.4, 51.5, 63.8, 65.2, 111.3, 119.4, 119.8, 121.1, 121.9, 122.5, 126.5, 128.6, 135.8, 136.6, and 168.4. HPLC-MS (ESI): R_t = 8.0 min, *m*/*z*: 402 $[M + H]^+$, 424 $[M + Na]^+$, 440 $[M + K]^+$, 825 $[2M + Na]^+$.

4-(4,4-Bis-(1*H*-indol-3-yl)-pentyl)-1-(*tert*-butyldimethylsilanyl)-azetidin-2-one 8. Indole (63 mg, 0.54 mmol) and aldehyde **4b** (70 mg, 0.27 mmol) were added to a solution of $Dy(OTf)_3$ (3.3 mg, 2% mol) in $[bmim]BF_4$ (0.5 mL). The mixture was stirred overnight at room temperature, extracted with Et_2O and concentrated. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 70 : 30) to afford product **8** (53 mg, 42%) as a pale brown oil (found C, 73.7; H, 7.9; N, 8.8%. $C_{29}H_{37}N_3OSi$ requires C, 73.8; H, 7.9; N, 8.9%); ν_{max} (CH_2Cl_2)/cm^{-1} 3406, 3323, 2926, 2848, 1720, and 1464; δ_H (300 MHz, $CDCl_3$) 0.20 (6 H, s, 2 × Me), 0.95 (9 H, s, *t*Bu), 1.30–1.50 (3 H, m, C*H*$_2$CH*H*), 1.80–1.95 (1 H, m, CH$_2$C*H*H), 2.19–2.32 (2 H, m, C*H*$_2$CH), 2.49 (1 H, dd, *J* 2.7 and 15.0, 3-*H*H), 3.00 (1 H, dd, *J* 5.4 and 15.0, 3-H*H*), 3.40–3.50 (1 H, m, 4-H), 4.48 (1 H, t, *J* 7.5, CH$_2$C*H*), 7.00–7.62 (10 H, m, arom), 8.02 (2 H, br s, 2 × NH); δ_C (75 MHz, $CDCl_3$) −5.8, −5.3, 18.3, 24.3, 26.2, 34.1, 35.5, 36.3, 43.7, 49.4, 111.1, 119.1, 119.5, 120.0, 121.3, 121.4, 121.9, 127.0, 136.6, and 170.1; HPLC-MS (ESI) R_t = 12.3 min, *m*/*z* 489 $[M + H_2O]^+$, 494 $[M + Na]^+$, 961 $[2MH + H_2O]^+$.

4-(4,4-Bis-(1*H*-indol-3-yl)-pentyl)-azetidin-2-one 9. TBAF (1 M in THF, 0.250 mL, 0.25 mmol) was added to a solution of **8** (53 mg, 0.11 mmol) in THF (1.5 mL) at 0 °C. The mixture was stirred overnight at 0 °C. After adding phosphate buffer (0.1 M, pH 6.5) to the mixture at 0 °C, the aqueous mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash-chromatography (cyclohexane/ethyl acetate, 60 : 40) to afford product **9** (30 mg, 76%) as a pale yellow oil (found C, 77.4; H, 6.5; N, 11.7%. $C_{23}H_{23}N_3O$ requires C, 77.3; H, 6.5; N, 11.8%); ν_{max} (CH_2Cl_2)/cm^{-1} 3406, 2927, 2855, 1736, 1592, and 1459; δ_H (200 MHz, $CDCl_3$) 1.34–1.73 (4 H, m, 2 × CH_2), 2.18–2.23 (2 H, m, C*H*$_2$CH), 2.49 (1 H, d, *J* 14.8, 3-*H*H), 2.98 (1 H, ddd, *J* 1.8 and 4.6 and 14.8, 3-H*H*), 3.48–3.57 (1 H, m, 4-H), 4.48 (1 H, t, *J* 7.8, C*H*(ind)$_2$), 5.75 (1 H, br s, 1-NH), 6.98–7.62 (10 H, m, arom), 7.99 (2 H, br s, 2 × NH); δ_C (75 MHz, $CDCl_3$) 24.9, 33.9, 35.2, 35.3, 43.4, 48.1, 111.2, 119.0, 119.4, 119.8, 121.4, 121.8, 126.9, 136.6, and 168.2; HPLC-MS (ESI) R_t = 8.0 min, *m*/*z* 380 $[M + Na]^+$, 737 $[2M + Na]^+$.

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