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Stereoselective Syntheses of the Octahydropyrano[2,3-*b*]pyridine DE Core of 'Upenamide via a Stannous Chloride-Induced Deacetalisation–Cyclisation Procedure

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Two stereoselective syntheses of the octahydropyrano[2,3-*b*]pyridine DE hemiaminal core of the macrocyclic alkaloid 'upenamide are described. The syntheses proceeded through an efficient stannous chloride-induced deacetalisation–cyclisation procedure. The aza-annulation was stereoselective affording a single stereoisomer having the same relative configuration as in the natural product. The *cis* ring junction and the *cis* relationship between 2-H and 8a-H were established by NMR spectroscopy and confirmed by X-ray crystallography. An asymmetric synthesis of the octahydropyrano[2,3-*b*]pyridine ring system is also disclosed.

Introduction

'Upenamide (**1**) is a macrocyclic alkaloid isolated in 2000 from the Indonesian branching sponge *Echinochalina* sp. (Figure 1).[1] Due to the scarcity of the natural product its biological activity has not yet been widely screened. 'Upenamide has an unprecedented structure comprising two core heterocyclic systems bearing eight chiral centres: a unique spiro-oxaquinolizidinone (ABC) tricyclic system linked to an unusual octahydropyrano[2,3-*b*]pyridine (DE) system which contains a *cis*-decalin-like hemiaminal. The C and D rings are linked by an all-*trans* triene system and a fully saturated aliphatic chain then completes the 20-membered macrocycle adjoining rings A and E. The absolute stereochemistry of the five chiral centres of the ABC core has been established, while the absolute configuration of the remaining three stereocentres contained within DE ring system is as yet unknown.

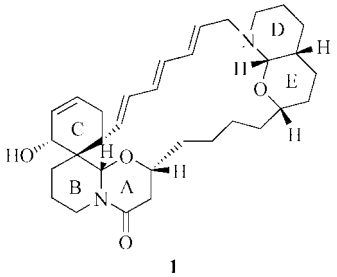

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Figure 1. Structure of 'upenamide (**1**).

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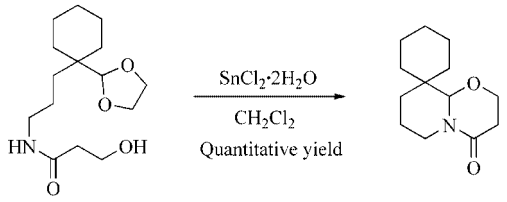
As part of our longstanding programme concerned with the synthesis of novel natural products, we became interested in the total synthesis of 'upenamide (**1**). To the best of our knowledge, no total synthesis has been reported so far. However, in a previous report,[2] we described a route for the preparation of the ABC model spirocyclic core of 'upenamide. Subsequently, Marazano et al. published the synthesis of a model of DE core in racemic form[3] and more recently, Sulikowski et al. reported the stereo- and enantio-controlled synthesis of an advanced intermediate containing the DE bicyclic system.[4] In this article, we wish to report our investigations concerning the synthesis of the DE hemiaminal ring system of 'upenamide.

Results and Discussion

Our approach to the synthesis of the ABC core of 'upenamide (**1**) relies on a novel Lewis acid-induced deacetalisation–cyclisation process (Scheme 1).[2] Thus, the spirohemiaminal **3** was obtained in quantitative yield by stirring dioxolane **2** with $SnCl_2{\cdot}2H_2O$ in dichloromethane. This approach was successfully adopted recently by a Taiwanese

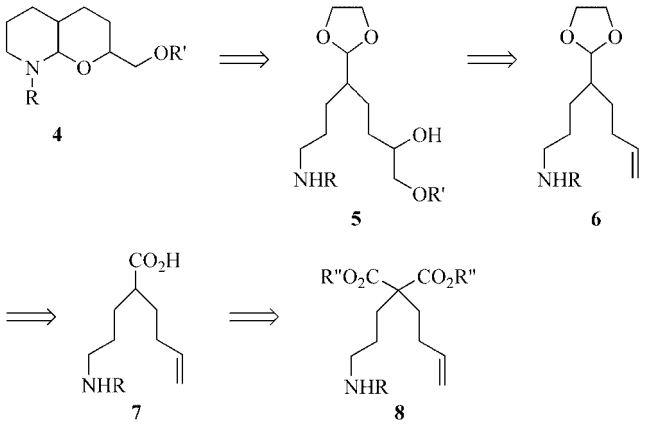


2 **3**

Scheme 1. Deacetalisation–cyclisation sequence induced by stannous chloride dihydrate.

group to prepare an organoiron complex of ABC model core.[5]

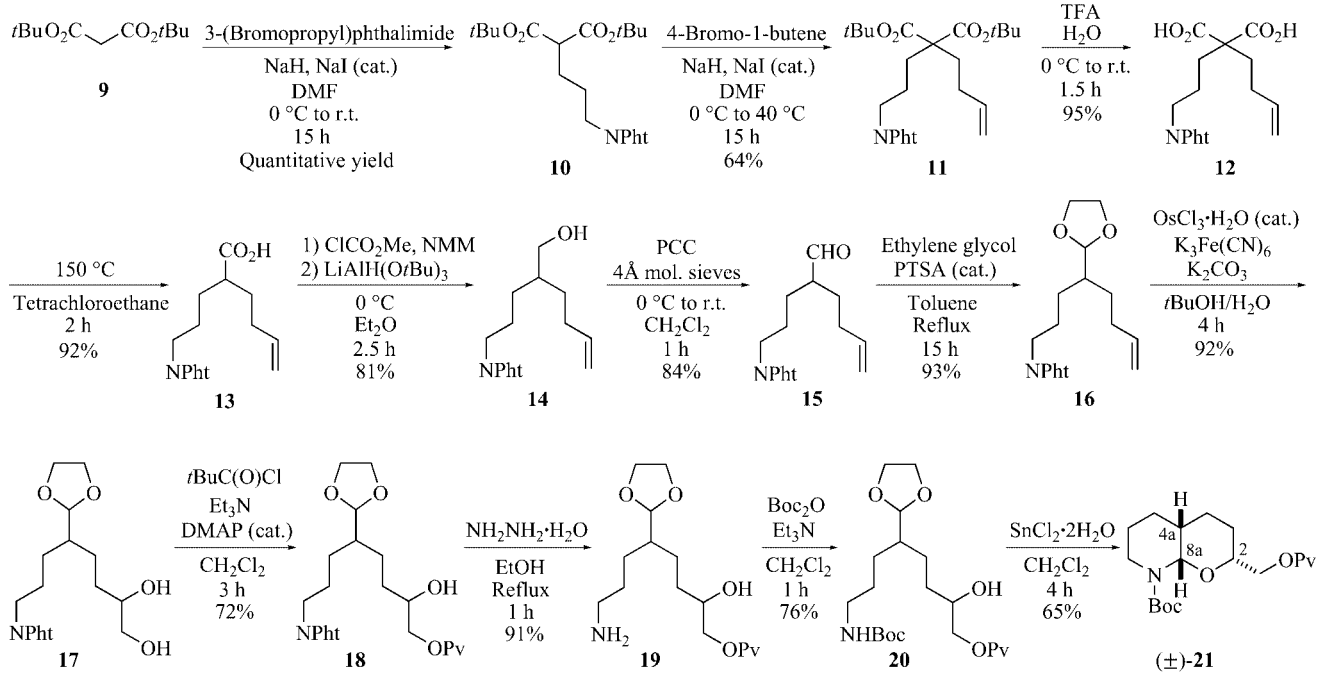
We hoped to apply the same tin chloride methodology to prepare the DE hemiaminal model core **4**. To this end, the initial retrosynthesis is outlined in Scheme 2. The ideal cyclisation precursor was identified as monoprotected diol **5**, which would arise from alkene **6**. The dioxolane moiety would be derived from carboxylic acid **7**. The most reliable route to compound **7** appeared to involve dialkylated malonate **8**.



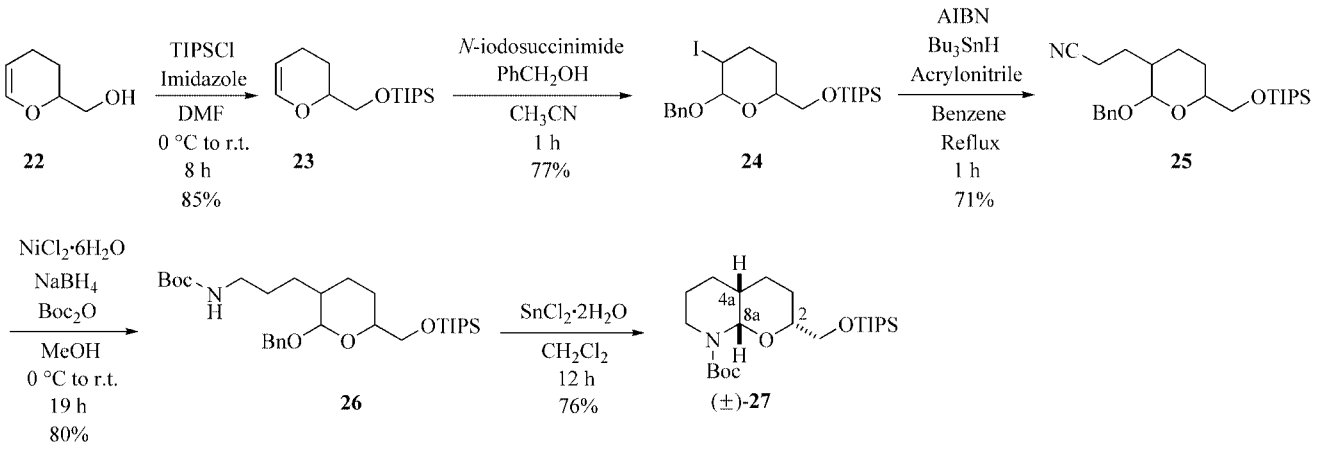
Scheme 2. Retrosynthetic analysis of DE hemiaminal model core **4**.

The first synthesis of the DE model ring system, based on malonate chemistry, is depicted in Scheme 3. Alkylation of di-*tert*-butyl malonate (**9**) with 3-(bromopropyl)phthalimide was effected in DMF with sodium hydride and a catalytic amount of sodium iodide in quantitative yield. Next, alkylation of **10** with 4-bromo-1-butene was achieved under the same conditions but at 40 °C leading to compound **11** in 64% yield. Treatment with TFA then afforded diacid **12**, and decarboxylation at 150 °C furnished acid **13** in excellent yield. We then performed a chemoselective reduction of the carboxylic acid group to the corresponding alcohol **14** with lithium tri-*tert*-butoxyaluminium hydride via the formation of a mixed anhydride. With alcohol **14** in hand, oxidation with PCC gave aldehyde **15** in 84% yield. Protection as a 1,3-dioxolane was carried out in high yield with ethylene glycol and a catalytic amount of PTSA in refluxing toluene using a Dean–Stark apparatus. Dihydroxylation of **16** using catalytic osmium trichloride and stoichiometric potassium ferricyanide gave the desired diol **17** in 92% yield as a 1:1 mixture of diastereoisomers.[6] The primary alcohol was then protected as pivalate ester **18**. Removal of phthalimide was conducted with hydrazine yielding amine **19** which was then Boc-protected in good yield.

Finally, the reactivity of dioxolane **20** with stannous chloride dihydrate was studied.[7] We were delighted to observe that compound **20** was converted into the required octahydropyrano[2,3-*b*]pyridine **21** in 65% yield, and the aza-annulation was stereoselective producing a single diastereoisomer of the DE hemiaminal ring system. The *cis* ring junction was determined on the basis of the small coupling constant between protons 4a-H and 8a-H and the chemical shift of the hemiaminal proton 8a-H ($\delta >$ 4.0 ppm).[8] Furthermore, the relative configuration at C-2 centre was established by an NOE between 2-H and 8a-H as previously observed by Sulikowski et al.[4] Most importantly, compound **21** has the same relative configuration as the corresponding DE ring system of **1**. Noteworthy is that the diastereoselective synthesis of DE model core **21** was completed in 10.5% overall yield although the route was rather lengthy (12 steps) and produced racemic products.



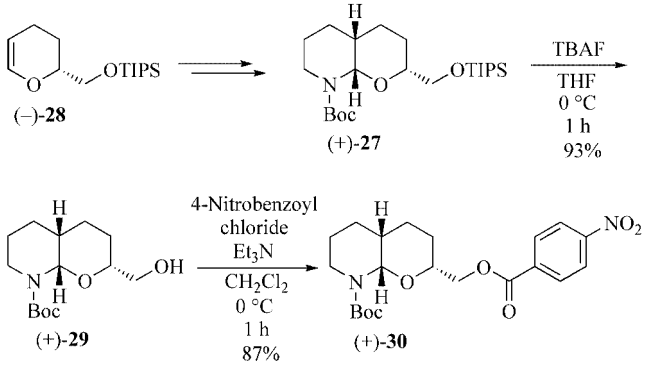
Scheme 3. Synthesis of DE ring system (±)-**21**.



Scheme 4. Synthesis of DE hemiaminal system (±)-**27**.

We therefore turned our attention to an alternative and shorter route to the DE bicyclic hemiaminal core of **1**. We designed a strategy based on the derivatisation of the commercially available 3,4-dihydro-2*H*-pyran derivative **22** (Scheme 4). First, protection of the alcohol moiety with triisopropylsilyl chloride furnished ether **23**. Treatment with *N*-iodosuccinimide and benzyl alcohol in acetonitrile led to the iodo compound **24** in good yield as a mixture of diastereoisomers. Next, in the key step, radical reaction with acrylonitrile in the presence of AIBN and tributyltin hydride in refluxing benzene afforded adduct **25** in a gratifying 71% yield. The nickel boride mediated reduction of nitrile **25** in the presence of di-*tert*-butyl dicarbonate gave Boc-protected amine **26** in 80% yield via a mild process employing a catalytic quantity of nickel(II) chloride with excess sodium borohydride.[9] Finally, with precursor **26** in hand, the deacetalisation–cyclisation sequence induced by stannous chloride dihydrate was examined. Again we were delighted to obtain the expected DE hemiaminal ring system **27** in good yield (76%). It should be noted that it was necessary to work at dilute concentration (ca. 0.02 M) with a catalytic amount of $SnCl_2·2H_2O$ to avoid removal of the TIPS group. As with the initial approach, the stereoselectivity of the cyclisation was excellent with the product being obtained as a single diastereoisomer. NOE experiments and analysis of the coupling constant between 4a-H and 8a-H allowed us to ascertain the relative stereochemistry of the three chiral centres of DE model core **27**. Using the second route shown in Scheme 4, the diastereoselective synthesis of octahydropyrano[2,3-*b*]pyridine **27** was efficiently achieved in 5 steps in 28% overall yield.

The next objective concerned the development of an enantioselective route to the bicyclic DE hemiaminal system of 'upenamide (Scheme 5). This required the preparation of 3,4-dihydro-2*H*-pyran derivative (–)-**28** in enantio-



Scheme 5. Asymmetric synthesis of DE ring system (+)-**30**.

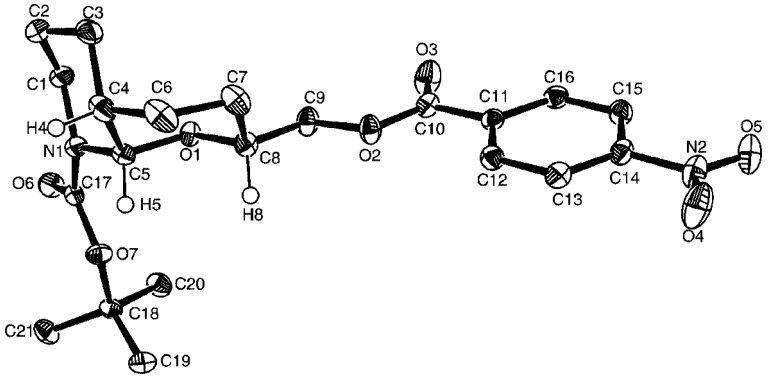


Figure 2. ORTEP drawing of derivative (+)-**30**.

merically pure form and this was achieved using the route developed by Ley et al.[10] Thus, using commercially available enantiopure (*S*)-glycidol as chiral starting material silyl ether compound (–)-**28** was prepared in 55% yield over four steps. Next, following the same approach illustrated in Scheme 4, the DE hemiaminal ring system (+)-**27** was synthesised as a single enantiomer {$[\alpha]_D^{23}$ = +34.7 (*c* = 0.32, $CHCl_3$)}.

In order to confirm the stereochemical assignments, silyl ether (+)-**27** was treated with TBAF and the resulting alcohol (+)-**29** was derivatised with 4-nitrobenzoyl chloride to afford enantiopure ester (+)-**30** in good yield (Scheme 5). Pleasingly, the ester crystallised from acetone and an X-ray analysis allowed us to confirm the relative (and absolute) configuration of DE ring system (+)-**30** (Figure 2). The DE bicyclic system adopts a chair–chair conformation where the oxygen atom is equatorial to the piperidine ring due to an *exo*-anomeric effect.[11] The substituent on the pyran ring adopts an equatorial position.

Conclusions

In summary, we have explored the scope of the stannous chloride-induced deacetalisation–cyclisation process for the construction of the octahydropyrano[2,3-*b*]pyridine core of 'upenamide. Two routes have been designed, one based on malonate chemistry and one on radical trapping in the key step. Both approaches were successful with aza-annulation occurring with excellent stereoselectivity leading to a single diastereoisomer possessing the same relative configuration as the corresponding core of 'upenamide. An asymmetric variant of the radical approach has also been developed. In addition, a crystalline derivative has been prepared and the stereochemical assignments have been confirmed by X-ray analysis. We are now applying this methodology to a total synthesis of 'upenamide.

Experimental Section

General Remarks: The reagents described in the following section as well as anhydrous acetonitrile, benzene, and DMF were purchased from commercial sources and were used directly without further purification. THF was dried with sodium and benzophenone and was distilled prior to use. Et_2O and CH_2Cl_2 were dried on a MBraun SPS Solvent Purification System. Petroleum ether refers to the fraction boiling in the range 40–60 °C. Lithium tri-*tert*-butoxyaluminium hydride and tetrabutylammonium fluoride were used as solutions in diglyme and in THF, respectively, as purchased. NH_4OH refers to ammonium hydroxide solution (28% in H_2O). All procedures requiring inert atmospheres were performed in dry glassware under an atmosphere of nitrogen or argon. Flash column chromatography was carried out either using silica gel 35–70 mesh, or alumina (purchased from Fluka, neutral Brockmann activity I deactivated to grade III with 6% water) and the eluent specified under bellows pressure. Thin layer chromatography (TLC) was carried out using Merck silica gel 60 F_{254} pre-coated aluminium foil plates with a thickness of 250 mm, and visualised with UV light (254 nm), followed by heating after treatment with $KMnO_4$ or vanillin solutions. Melting points (m.p.) were determined on a Gallen-Kamp melting point apparatus in open capillary tubes. Infra-red spectra were recorded on a ThermoNicolet IR100 spectrometer, as thin films between NaCl plates. Optical rotation values were recorded on a JASCO model DIP-370 digital polarimeter using sodium D line (589 nm radiation) and are expressed in units of 10^{-2} deg cm^{-2} g^{-1}. The ^1H and ^{13}C NMR spectra along with 2D experiments were recorded with a Jeol EX-400 spectrometer or with a Bruker AMX500 spectrometer (specified below), operating at ^1H frequencies of 400 and 500 MHz and ^{13}C frequencies of 100 and 125 MHz, respectively. The solutions were prepared in suitable deuterated solvents and referenced using residual protonated solvent or TMS. Diastereoisomeric ratios were obtained by ^1H NMR integration. Low- and high-field resolution chemical ionisation (CI) mass spectra were performed with a Waters Autospec spectrometer. Low resolution electrospray (ESI) mass spectrometry was recorded with either a Thermo-Finnigan LCQ instrument, or with a Bruker MicroTOF spectrometer. High-resolution electrospray mass spectra were obtained with a Bruker MicroTOF apparatus. High-resolution molecular ions described are within ±5 ppm of the required molecular mass. Microanalyses were carried out at the University of Newcastle (UK) using a Carlo–Erba 1108 Elemental Analyser.

Di-*tert*-Butyl 2-[3-(1,3-Dioxoisoindolin-2-yl)propyl]malonate (10): To a suspension of sodium hydride (60% w/w in mineral oil, 2.0 g, 50.0 mmol, 1.1 equiv.) in anhydrous DMF (100 mL) cooled to 0 °C was added dropwise a solution of di-*tert*-butyl malonate (**9**, 10.0 mL, 45.0 mmol, 1 equiv.) in anhydrous DMF (30 mL). After stirring at 0 °C for a further 10 min, the mixture was warmed to room temp. over 30 min, after which it was cooled to 0 °C and sodium iodide (2.0 g, 13.3 mmol, 0.3 equiv.) was added. A solution of *N*-(3-bromopropyl)phthalimide (12.6 g, 47.2 mmol, 1.05 equiv.) in anhydrous DMF (40 mL) was added dropwise. The reaction mixture was maintained at 0 °C for 10 min and then warmed to room temp. After stirring for 15 h, the mixture was quenched at 0 °C by the addition of water (1 mL) and was partitioned between Et_2O (300 mL) and water (200 mL). The aqueous layer was extracted with Et_2O (300 mL). The combined organic phases were successively washed with water (4 × 150 mL), brine (150 mL) and were dried with anhydrous $MgSO_4$. Filtration and concentration in vacuo gave the expected product **10** with a satisfactory purity (18.0 g, quantitative yield). NMR spectroscopic data are consistent to those reported in the literature.[12] White solid; m.p. 42–44 °C (m.p. not reported in ref.[12]). R_f = 0.35 (petroleum ether/EtOAc, 80:20). IR (neat): $\tilde{\nu}$ = 2978, 2936, 1773, 1715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 [s, 18 H, 2 × $C(CH_3)_3$], 1.64–1.72 (m, 2 H, C*H*$_2$–CH_2N), 1.78–1.84 (m, 2 H, C*H*$_2$–CH), 3.14 [t, ^3J = 7.5 Hz, 1 H, C*H*(CO_2tBu)$_2$], 3.67 (t, ^3J = 7.0 Hz, 2 H, CH_2N), 7.68 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 7.80 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (2 × CO), 168.7 (2 × CO), 134.1 (2 × arom. CH), 132.3 (2 × subst. arom. C), 123.4 (2 × arom. CH), 81.4 [2 × *C*$(CH_3)_3$], 53.2 [*C*H(CO_2tBu)$_2$], 37.2 (CH_2N), 27.5 (6 × CH_3), 25.8 (CH_2), 25.4 (CH_2) ppm. MS (ESI): *m*/*z* (%) = 426 (100) $[M + Na]^+$. HRMS (ESI): $C_{22}H_{29}NNaO_6$ calcd. 426.1887; found 426.1903 (–3.8 ppm error). $C_{22}H_{29}NO_6$ (403.47): calcd. C 65.49, H 7.24, N 3.47; found C 65.75, H 7.49, N 3.67.

Di-*tert*-Butyl 2-(But-3-enyl)-2-[3-(1,3-dioxoisoindolin-2-yl)propyl]-malonate (11): To a suspension of sodium hydride (60% w/w in mineral oil, 2.1 g, 52.5 mmol, 1.2 equiv.) in anhydrous DMF (40 mL) cooled to 0 °C was added dropwise a solution of **10** (17.9 g, 44.4 mmol, 1 equiv.) in anhydrous DMF (60 mL). After stirring at 0 °C for a further 10 min, the mixture was warmed to room temp. over 1 h, after which it was cooled to 0 °C and sodium iodide (2.0 g, 13.3 mmol, 0.3 equiv.) was added. A solution of 4-

bromo-1-butene (9.0 mL, 88.7 mmol, 2 equiv.) in anhydrous DMF (20 mL) was added dropwise. The reaction mixture was maintained at 0 °C for 10 min and then heated at 40 °C for 15 h. After quenching at 0 °C with water (1 mL), the mixture was partitioned between Et_2O (200 mL) and water (100 mL). The aqueous layer was extracted with Et_2O (200 mL). The combined organic phases were successively washed with water (4 × 100 mL), brine (100 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 87:13) to provide **11** (13.0 g, 64%). White solid; m.p. 70–72 °C. R_f = 0.40 (petroleum ether/EtOAc, 80:20). IR (neat): $\tilde{\nu}$ = 2977, 1773, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 [s, 18 H, 2 × $C(CH_3)_3$], 1.49–1.57 (m, 2 H, CH_2–CH_2N), 1.78–1.90 (m, 6 H, CH_2–CH_2–CH=CH_2, CH_2–CH_2–CH_2N), 3.64 (t, ^3J = 7.3 Hz, 2 H, CH_2N), 4.88–4.92 (m, 1 H, CH_2=CH), 4.94–5.00 (m, 1 H, CH_2=CH), 5.68–5.79 (m, 1 H, CH=CH_2), 7.68 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 7.80 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (2 × CO), 168.6 (2 × CO), 138.0 (*C*H=CH_2), 134.1 (2 × arom. CH), 132.3 (2 × subst. arom. C), 123.3 (2 × arom. CH), 115.0 (*C*H_2=CH), 81.2 [2 × *C*$(CH_3)_3$], 57.6 [*C*$(CO_2t$Bu$)_2$], 37.8 (CH_2N), 30.8 (CH_2), 28.7 (CH_2), 27.9 (CH_2), 27.5 (6 × CH_3), 22.9 (*C*H_2–CH_2N) ppm. MS (ESI): *m*/*z* (%) = 475 (100) $[M + NH_4]^+$. HRMS (ESI): $C_{26}H_{39}N_2O_6$ calcd. 475.2803; found 475.2801 (0.3 ppm error). $C_{26}H_{35}NO_6$ (457.56): calcd. C 68.25, H 7.71, N 3.06; found C 68.29, H 7.84, N 3.34.

2-(But-3-enyl)-2-[3-(1,3-dioxoisoindolin-2-yl)propyl]malonic Acid (12): To a suspension of **11** (12.8 g, 27.9 mmol) in water (6.6 mL) cooled to 0 °C was added trifluoroacetic acid (32.5 mL). The reaction mixture was maintained at 0 °C for 30 min and then stirred at room temp. for 1 h. After concentration in vacuo, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 90:10) to afford **12** (9.2 g, 95%). White solid; m.p. 142–144 °C. R_f = 0.35 (CH_2Cl_2/MeOH, 85:15). IR (neat): $\tilde{\nu}$ = 2944, 1706 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 1.53–1.68 (m, 2 H, CH_2–CH_2N), 1.80–1.97 (m, 6 H, 3 × CH_2), 3.65 (t, ^3J = 6.2 Hz, 2 H, CH_2N), 4.86–5.01 (m, 2 H, CH_2=CH), 5.19 (br. s, 2 H, 2 × CO_2H), 5.69–5.82 (m, 1 H, CH=CH_2), 7.73–7.84 (m, 4 H, 4 × arom. H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 175.7 (2 × COOH), 169.7 [2 × C(O)N], 138.9 (*C*H=CH_2), 135.3 (2 × arom. CH), 133.2 (2 × subst. arom. C), 124.1 (2 × arom. CH), 115.4 (*C*H_2=CH), 58.0 [*C*$(CO_2H)_2$], 38.8 (CH_2N), 33.8 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 24.7 (*C*H_2–CH_2N) ppm. MS (ESI): *m*/*z* (%) = 346 (100) $[M + H]^+$, 363 (65) $[M + NH_4]^+$. HRMS (ESI): $C_{18}H_{20}NO_6$ calcd. 346.1285; found 346.1293 (–2.3 ppm error).

2-[3-(1,3-Dioxoisoindolin-2-yl)propyl]hex-5-enoic Acid (13): A suspension of **12** (9.0 g, 26.1 mmol) in 1,1,2,2-tetrachloroethane (25 mL) was heated at 150 °C for 2 h. After concentration in vacuo, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:05) to furnish **13** (7.3 g, 92%). White solid; m.p. 75–77 °C. R_f = 0.40 (CH_2Cl_2/MeOH, 95:05). IR (neat): $\tilde{\nu}$ = 3100, 2942, 1772, 1711, 1399 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.58 (m, 2 H, CH_2), 1.60–1.77 (m, 4 H, CH_2–CH_2N, CH_2), 1.96–2.13 (m, 2 H, CH_2–CH=CH_2), 2.36–2.45 (m, 1 H, CH–CO_2H), 3.63–3.70 (m, 2 H, CH_2N), 4.90–4.95 (m, 1 H, CH_2=CH), 4.95–5.02 (m, 1 H, CH_2=CH), 5.67–5.80 (m, 1 H, CH=CH_2), 7.69 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 7.82 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.4 (CO_2H), 168.8 [2 × C(O)N], 137.8 (*C*H=CH_2), 134.2 (2 × arom. CH), 132.2 (2 × subst. arom. C), 123.4 (2 × arom. CH), 115.5 (*C*H_2=CH), 44.0 (*C*H–CO_2H), 37.4 (CH_2N), 31.0 (*C*H_2–CH=CH_2), 30.7 (CH_2), 28.8 (CH_2), 26.0 (CH_2) ppm. MS (ESI): *m*/*z* (%) = 302 (46) $[M + H]^+$, 319 (100) $[M + NH_4]^+$. HRMS (ESI): $C_{17}H_{23}N_2O_4$ calcd. 319.1652; found 319.1648 (1.5 ppm error). $C_{17}H_{19}NO_4$ (301.34): calcd. C 67.76, H 6.36, N 4.65; found C 67.32, H 6.26, N 4.72.

2-[4-(Hydroxymethyl)oct-7-enyl]isoindoline-1,3-dione (14): To a solution of **13** (6.2 g, 21.0 mmol, 1 equiv.) and *N*-methylmorpholine (2.3 mL, 21.0 mmol, 1 equiv.) in anhydrous Et_2O (100 mL) cooled to 0 °C was added dropwise methyl chloroformate (1.6 mL, 21.0 mmol, 1 equiv.). After stirring for 30 min at 0 °C, lithium tri-*tert*-butoxyaluminium hydride (0.5 M in diglyme, 145 mL, 72.5 mmol, 3.5 equiv.) was added at 0 °C with a syringe-pump over 2.5 h. The reaction mixture was maintained at 0 °C for 30 min and then quenched with saturated aqueous tartaric acid (35 mL). After stirring at 0 °C for a further 1 h, the mixture was partitioned between Et_2O (100 mL) and water (100 mL). The aqueous layer was extracted with Et_2O (200 mL). The combined organic phases were successively washed with water (3 × 150 mL), brine (150 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 60:40) to yield **14** (4.8 g, 81%). Colourless oil. R_f = 0.45 (cyclohexane/EtOAc, 50:50). IR (neat): $\tilde{\nu}$ = 3400 (br.), 2931, 2866, 1772, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.45 (m, 5 H, 2 × CH_2, CH–CH_2OH), 1.50–1.61 (m, 2 H, CH_2–CH_2N), 1.87–1.96 (m, 2 H, CH_2–CH=CH_2), 2.86 (br. s, 1 H, OH), 3.35–3.46 (m, 2 H, CH_2OH), 3.52 (t, ^3J = 7.3 Hz, 2 H, CH_2N), 4.73–4.79 (m, 1 H, CH_2=CH), 4.80–4.88 (m, 1 H, CH_2=CH), 5.57–5.70 (m, 1 H, CH=CH_2), 7.57 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 7.67 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 [2 × C(O)N], 138.8 (*C*H=CH_2), 133.9 (2 × arom. CH), 131.9 (2 × subst. arom. C), 123.0 (2 × arom. CH), 114.3 (*C*H_2=CH), 64.2 (CH_2OH), 38.9 (*C*H–CH_2OH), 37.7 (CH_2N), 30.5 (*C*H_2–CH=CH_2), 29.4 (CH_2), 27.4 (CH_2), 25.2 (*C*H_2–CH_2N) ppm. MS (CI): *m*/*z* (%) = 288 (43) $[M + H]^+$, 305 (100) $[M + NH_4]^+$. HRMS (CI): $C_{17}H_{25}N_2O_3$ calcd. 305.1865; found 305.1873 (–2.5 ppm error). $C_{17}H_{21}NO_3$ (287.35): calcd. C 71.06, H 7.37, N 4.87; found C 70.83, H 7.66, N 4.93.

2-[3-(1,3-Dioxoisoindolin-2-yl)propyl]hex-5-enal (15): To a solution of **14** (34 mg, 0.12 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (12 mL) over activated molecular sieves (4 Å, 150 mg) cooled to 0 °C was added pyridinium chlorochromate (128 mg, 0.59 mmol, 5 equiv.) in 3 portions. After stirring at 0 °C for a further 10 min, the reaction mixture was warmed to room temp. and was stirred for 1 h. The residue was purified by flash chromatography on silica gel with CH_2Cl_2 to give **15** (28 mg, 84%). Colourless oil. R_f = 0.25 (cyclohexane/EtOAc, 80:20). IR (neat): $\tilde{\nu}$ = 2936, 2860, 1773, 1712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41–1.56 (m, 2 H, CH_2), 1.61–1.79 (m, 4 H, CH_2–CH_2N, CH_2), 1.90–2.11 (m, 2 H, CH_2–CH=CH_2), 2.24–2.36 (m, 1 H, CH–CHO), 3.64–3.70 (m, 2 H, CH_2N), 4.93–5.02 (m, 2 H, CH_2=CH), 5.67–5.79 (m, 1 H, CH=CH_2), 7.71 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 7.83 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 9.58 (d, ^3J = 2.6 Hz, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1 (CHO), 168.8 [2 × C(O)N], 137.8 (*C*H=CH_2), 134.2 (2 × arom. CH), 132.3 (2 × subst. arom. C), 123.4 (2 × arom. CH), 115.7 (*C*H_2=CH), 50.4 (*C*H–CHO), 37.5 (CH_2N), 30.7 (*C*H_2–CH=CH_2), 27.5 (CH_2), 25.8 (CH_2), 25.5 (CH_2) ppm. MS (CI): *m*/*z* (%) = 286 (17) $[M + H]^+$, 303 (100) $[M + NH_4]^+$. HRMS (CI): $C_{17}H_{23}N_2O_3$ calcd. 303.1709; found 303.1709 (0 ppm error).

2-[4-(1,3-Dioxolan-2-yl)oct-7-enyl]isoindoline-1,3-dione (16): To a solution of **15** (555 mg, 1.95 mmol) in toluene (20 mL) were added ethylene glycol (2.5 mL) and a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was heated at reflux with a Dean–

Stark apparatus for 15 h. After cooling to room temp., the mixture was partitioned between Et_2O (50 mL) and aqueous saturated sodium hydrogen carbonate (50 mL). The aqueous layer was extracted with Et_2O (50 mL). The combined organic phases were successively washed with aqueous saturated sodium hydrogen carbonate (50 mL), water (50 mL), brine (50 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20) to afford **16** (595 mg, 93%). Colourless oil. R_f = 0.25 (cyclohexane/EtOAc, 80:20). IR (neat): $\tilde{\nu}$ = 2937, 2879, 1772, 1712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.40 (m, 2 H), 1.44–1.58 (m, 2 H), 1.60–1.77 (m, 3 H), 2.00–2.11 (m, 2 H), 3.64 (t, ^3J = 7.4 Hz, 2 H, CH_2N), 3.76–3.92 (m, 4 H, 2 × CH_2O dioxolane), 4.74 (d, ^3J = 4.0 Hz, 1 H, C*H* dioxolane), 4.87–4.92 (m, 1 H, CH_2=CH), 4.93–5.00 (m, 1 H, CH_2=CH), 5.69–5.81 (m, 1 H, C*H*=CH_2), 7.69 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 7.82 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 [2 × C(O)N], 139.1 (*C*H=CH_2), 134.1 (2 × arom. CH), 132.4 (2 × subst. arom. C), 123.4 (2 × arom. CH), 114.7 (*C*H_2=CH), 106.4 (*C*H dioxolane), 64.8 (2 × *C*H_2O dioxolane), 40.3 (*C*H–CH dioxolane), 38.1 (CH_2N), 31.1, 28.0, and 25.9 (4 × CH_2) ppm. MS (CI): *m*/*z* (%) = 347 (100) $[M + NH_4]^+$. HRMS (CI): $C_{19}H_{27}N_2O_4$ calcd. 347.1971; found 347.1973 (–0.7 ppm error).

2-[4-(1,3-Dioxolan-2-yl)-7,8-dihydroxyoctyl]isoindoline-1,3-dione (17): To a solution of **16** (257 mg, 0.78 mmol, 1 equiv.) in 1:1 *tert*-butyl alcohol–water (8 mL) were added potassium ferricyanide (772 mg, 2.34 mmol, 3 equiv.), potassium carbonate (323 mg, 2.34 mmol, 3 equiv.) and a catalytic amount of osmium(III) chloride hydrate. After stirring for 4 h, anhydrous sodium sulfite (1.1 g) was added and stirring continued for 1 h. The mixture was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic phases were successively washed with water (2 × 20 mL), brine (20 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 97:03) to provide **17** (261 mg, 92%) as an inseparable 1:1 mixture of diastereoisomers. Colourless oil. R_f = 0.25 (CH_2Cl_2/MeOH, 95:05). IR (neat): $\tilde{\nu}$ = 3350 (br.), 2941, 2875, 1771, 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.81 (m, 9 H, 4 × CH_2, C*H*–CH dioxolane), 2.36 (t, ^3J = 5.3 Hz, 1 H, CH_2OH), 2.62 (d, ^3J = 4.3 Hz, 0.5 H, CHO*H*), 2.69 (d, ^3J = 4.3 Hz, 0.5 H, CHO*H*), 3.38–3.47 (m, 1 H, CH_2OH), 3.57–3.71 (m, 4 H, CH_2N, CH_2OH, C*H*OH), 3.78–3.95 (m, 4 H, 2 × CH_2O dioxolane), 4.73 (d, ^3J = 3.9 Hz, 1 H, C*H* dioxolane), 7.70 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H), 7.82 (dd, ^3J = 5.5, ^4J = 3.0 Hz, 2 H, 2 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5 and 168.4 [2 × C(O)N], 133.9 (2 × arom. CH), 132.0 (2 × subst. arom. C), 123.2 (2 × arom. CH), 106.3 (*C*H dioxolane), 72.4 and 72.1 (CHOH), 66.7 and 66.6 (CH_2OH), 64.8 (2 × *C*H_2O dioxolane), 40.7 and 40.6 (*C*H–CH dioxolane), 38.2 and 38.1 (CH_2N), 30.6, 30.5, 26.6, 26.3, 26.0, 25.9, 24.8, and 24.7 (4 × CH_2) ppm. MS (ESI): *m*/*z* (%) = 381 (100) $[M + NH_4]^+$. HRMS (ESI): $C_{19}H_{29}N_2O_6$ calcd. 381.2020; found 381.2032 (–3.2 ppm error).

8-(1,3-Dioxoisoindolin-2-yl)-5-(1,3-dioxolan-2-yl)-2-hydroxyoctyl Pivalate (18): To a solution of **17** (325 mg, 0.90 mmol, 1 equiv.) in CH_2Cl_2 (9 mL) were added successively 4-dimethylaminopyridine (33 mg, 0.27 mmol, 0.3 equiv.), triethylamine (375 μL, 2.69 mmol, 3 equiv.) and pivaloyl chloride (120 μL, 0.98 mmol, 1.1 equiv.). After stirring for 3 h, the mixture was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic phases were successively washed with water (20 mL), brine (20 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 60:40) to furnish **18** (306 mg, 72%) as an inseparable 1:1 mixture of diastereoisomers. Colourless oil. R_f = 0.60 (CH_2Cl_2/MeOH, 95:05). IR (neat): $\tilde{\nu}$ = 3495 (br.), 2955, 2879, 1772, 1712, 1286, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 and 1.17 (s, 9 H, 3 × CH_3), 1.36–1.78 (m, 9 H, 4 × CH_2, C*H*–CH dioxolane), 2.35 (d, ^3J = 4.8 Hz, 0.5 H, CHO*H*), 2.40 (d, ^3J = 4.7 Hz, 0.5 H, CHO*H*), 3.63 (t, ^3J = 7.4 Hz, 2 H, CH_2N), 3.73–3.81 (m, 3 H, C*H*OH, CH_2O dioxolane), 3.85–3.91 (m, 2 H, CH_2O dioxolane), 3.91–3.97 (m, 1 H, CH_2OPv), 4.02–4.09 (m, 1 H, CH_2OPv), 4.71 (d, ^3J = 4.2 Hz, 1 H, C*H* dioxolane), 7.68 (dd, ^3J = 5.4, ^4J = 3.1 Hz, 2 H, 2 × arom. H), 7.80 (dd, ^3J = 5.4, ^4J = 3.1 Hz, 2 H, 2 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2 [*C*(O)*t*Bu], 168.8 [2 × C(O)N], 134.1 (2 × arom. CH), 132.4 (2 × subst. arom. C), 123.4 (2 × arom. CH), 106.5 (*C*H dioxolane), 70.1 (CHOH), 68.4 (*C*H_2OPv), 64.7 (2 × *C*H_2O dioxolane), 40.5 (*C*H–CH dioxolane), 38.6 [*C*(CH_3)$_3$], 38.0 and 37.9 (CH_2N), 30.7 and 30.5 (CH_2), 26.9 (3 × CH_3), 26.4, 26.2, 25.8, and 24.5 (3 × CH_2) ppm. MS (ESI): *m*/*z* (%) = 448 (6) $[M + H]^+$, 470 (65) $[M + Na]^+$. HRMS (ESI): $C_{24}H_{34}NO_7$ calcd. 448.2330; found 448.2330 (0 ppm error).

8-Amino-5-(1,3-dioxolan-2-yl)-2-hydroxyoctyl Pivalate (19): A solution of **18** (120 mg, 0.25 mmol, 1 equiv.) and hydrazine monohydrate (75 μL, 1.53 mmol, 6 equiv.) in absolute ethanol (2.5 mL) was heated at reflux for 1 h. After solvent removal in vacuo, CH_2Cl_2 (5 mL) was added to the residue and the resulting suspension was filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 75:20:05) to yield **19** (79 mg, 91%) as an inseparable 1:1 mixture of diastereoisomers. Colourless oil. R_f = 0.20 (CH_2Cl_2/MeOH/NH_4OH, 75:20:05). IR (neat): $\tilde{\nu}$ = 3325 (br.), 2937, 2874, 1726, 1286, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9 H, 3 × CH_3), 1.20–1.70 (m, 9 H, 4 × CH_2, C*H*–CH dioxolane), 2.05 (br. s, 3 H, NH_2, OH), 2.65 (t, ^3J = 5.6 Hz, 2 H, CH_2N), 3.73–4.10 (m, 7 H, CH_2OPv, 2 × CH_2O dioxolane, C*H*OH), 4.70–4.75 (m, 1 H, C*H* dioxolane) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 [*C*(O)*t*Bu], 106.4 and 106.3 (*C*H dioxolane), 70.0 and 69.9 (CHOH), 68.4 (*C*H_2OPv), 64.8 (2 × *C*H_2O dioxolane), 42.3 (CH_2N), 41.0 and 40.9 (*C*H–CH dioxolane), 38.8 [*C*(CH_3)$_3$], 31.0, 30.9, 30.8, 28.0, and 27.9 (CH_2, rotamers), 27.1 (3 × CH_3), 26.5, 26.3, 26.2, 26.1, 24.7, 24.4, and 24.3 (CH_2, rotamers) ppm. MS (ESI): *m*/*z* (%) = 318 (100) $[M + H]^+$. HRMS (ESI): $C_{16}H_{32}NO_5$ calcd. 318.2275; found 318.2285 (–3.3 ppm error).

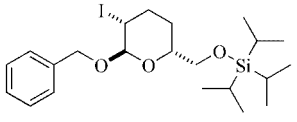
8-*tert*-Butoxycarbonylamino-5-(1,3-dioxolan-2-yl)-2-hydroxyoctyl Pivalate (20): To a solution of **19** (21 mg, 0.06 mmol, 1 equiv.) and triethylamine (17 μL, 0.12 mmol, 2 equiv.) in CH_2Cl_2 (1.2 mL) was added di-*tert*-butyl dicarbonate (26 mg, 0.12 mmol, 2 equiv.). After stirring for 1 h, 10% aqueous HCl (100 μL) was added at 0 °C. The mixture was partitioned between CH_2Cl_2 (15 mL) and water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic phases were successively washed with water (15 mL), brine (15 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:02) to give **20** (21 mg, 76%) as an inseparable 1:1 mixture of diastereoisomers. Colourless oil. R_f = 0.40 (CH_2Cl_2/MeOH, 95:05). IR (neat): $\tilde{\nu}$ = 3400 (br.), 2974, 2875, 1712, 1695, 1284, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 [s, 9 H, 3 × CH_3 (Pv)], 1.40 [s, 9 H, 3 × CH_3 (Boc)], 1.30–1.70 (m, 9 H, 4 × CH_2, C*H*–CH dioxolane), 2.45 (br. s, 1 H, OH), 2.97–3.15 (m, 2 H, CH_2N), 3.74–3.99 (m, 6 H, CH_2OPv, 2 × CH_2O dioxolane, C*H*OH), 4.05–4.11 (m, 1 H, CH_2OPv), 4.62 (br. s, 1 H, NH), 4.70–4.74 (m, 1 H, C*H* dioxolane)

ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9 and 178.6 [*C*(O)-*t*Bu], 155.9 (*C*O_2*t*Bu), 106.4 and 106.3 (*C*H dioxolane), 79.0 [*C*$(CH_3)_3$ (Boc)], 70.1 (CHOH), 68.4 (*C*H_2OPv), 64.8 (2 × *C*H_2O dioxolane), 40.8 and 40.7 (*C*H–CH dioxolane, CH_2N), 38.8 and 38.9 [*C*$(CH_3)_3$ (Pv)], 30.9 and 30.7 (CH_2), 28.4 [3 × CH_3 (Boc)], 28.0, 27.8, and 27.4 (CH_2, rotamers), 27.1 [3 × CH_3 (Pv)], 26.5, 26.3, 26.2, 24.8, 24.7, and 24.4 (CH_2, rotamers) ppm. MS (ESI): *m*/*z* (%) = 418 (28) $[M + H]^+$, 440 (26) $[M + Na]^+$. HRMS (ESI): $C_{21}H_{39}NNaO_7$ calcd. 440.2619; found 440.2630 (–2.8 ppm error).

(2*R,4a*R**,8a*S**)-*tert*-Butyl Octahydro-2-[(pivaloyloxy)methyl]pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate [(±)-21]:** To a solution of **20** (80 mg, 0.18 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added stannous chloride dihydrate (101 mg, 0.45 mmol, 2.5 equiv.). The reaction mixture was vigorously stirred for 4 h and then filtered. After concentration of the filtrate in vacuo, the residue was purified by flash chromatography on neutral Brockmann grade III alumina (petroleum ether/EtOAc, 97:03) to afford (±)-**21** (44 mg, 65%) as a single diastereoisomer. Light-yellow solid; m.p. 78–80 °C. R_f = 0.30 (petroleum ether/EtOAc, 90:10). IR (neat): $\tilde{\nu}$ = 2973, 2935, 2866, 1731, 1703, 1281, 1161 cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 20 °C): δ = 1.14 [s, 9 H, 3 × CH_3 (Pv)], 1.20–1.50 (m, 13 H), 1.52–1.88 (m, 5 H), 2.65–2.88 (m, 1 H, CH_2N), 3.56–3.74 (m, 2 H, CH_2N, 2-H), 3.92–4.10 (m, 2 H, C*H*$_2$OPv), 5.13 (br. s, 0.5 H, 8a-H rotamer), 5.22 (s, 0.5 H, 8a-H rotamer) ppm. ^{1}H NMR (500 MHz, [D_6]-DMSO, 80 °C): δ = 1.17 [s, 9 H, 3 × CH_3 (Pv)], 1.24–1.50 (m, 13 H), 1.56–1.87 (m, 5 H), 2.81 (br. t, *J* = 12.3 Hz, 1 H, CH_2N), 3.62–3.72 (m, 2 H, CH_2N, 2-H), 4.03 (d, ^3J = 5.0 Hz, 2 H, C*H*$_2$OPv), 5.20 (br. s, 1 H, 8a-H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO, 20 °C): δ = 177.1 [*C*(O)*t*Bu], 154.2 and 154.0 (*C*O_2*t*Bu, rotamers), 81.8 and 80.6 (C-8a, rotamers), 79.1 and 78.9 [*C*$(CH_3)_3$ (Boc), rotamers], 74.9 and 74.5 (C-2, rotamers), 66.1 and 65.7 (*C*H_2OPv, rotamers), 38.4 (CH_2N), 38.1 [*C*$(CH_3)_3$ (Pv)], 33.0 (C-4a), 27.8 [3 × CH_3 (Boc)], 27.5 (CH_2), 26.8 [3 × CH_3 (Pv)], 24.4, 24.1, 22.3, and 21.4 (3 × CH_2, rotamers) ppm. ^{13}C NMR (125 MHz, [D_6]-DMSO, 80 °C, relaxation time: 5 s): δ = 176.6 [*C*(O)*t*Bu], 153.7 (*C*O_2*t*Bu), 81.1 (C-8a), 78.6 [*C*$(CH_3)_3$ (Boc)], 74.4 (C-2), 65.6 (*C*H_2OPv), 38.5 (CH_2N), 37.7 [*C*$(CH_3)_3$ (Pv)], 32.8 (C-4a), 27.5 [3 × CH_3 (Boc)], 27.2 (CH_2), 26.4 [3 × CH_3 (Pv)], 23.8 (CH_2), 22.0 (CH_2), 21.2 (CH_2) ppm. MS (ESI): *m*/*z* (%) = 378 (100) $[M + Na]^+$. HRMS (ESI): $C_{19}H_{33}NNaO_5$ calcd. 378.2256; found 378.2259 (–0.8 ppm error). $C_{19}H_{33}NO_5$ (355.47): calcd. C 64.20, H 9.36, N 3.94; found C 64.66, H 9.89, N 4.00.

[(3,4-Dihydro-2*H*-pyran-2-yl)methoxy]triisopropylsilane (23): To a solution of (3,4-dihydro-2*H*-pyran-2-yl)methanol (**22**, 485 µL, 4.68 mmol, 1 equiv.) and imidazole (700 mg, 10.3 mmol, 2.2 equiv.) in anhydrous DMF (20 mL) cooled to 0 °C was added a solution of triisopropylsilyl chloride (1.1 mL, 5.14 mmol, 1.1 equiv.) in anhydrous DMF (3.5 mL). The reaction mixture was maintained at 0 °C for 5 min and then was stirred at room temp. for 8 h. The mixture was partitioned between Et_2O (50 mL) and water (50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic phases were successively washed with water (4 × 50 mL), brine (50 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O, 98:02) to furnish **23** (1.08 g, 85%). Colourless oil. Spectroscopic data are consistent to those reported in the literature.[10]

{[6-(Benzyloxy)-tetrahydro-5-iodo-2*H*-pyran-2-yl]methoxy}triisopropylsilane (24): To a solution of **23** (940 mg, 3.48 mmol, 1 equiv.) and benzyl alcohol (470 µL, 4.54 mmol, 1.3 equiv.) in anhydrous acetonitrile (10 mL) was added *N*-iodosuccinimide (940 mg, 4.18 mmol, 1.2 equiv.) in 4 portions. The reaction mixture was protected from light and stirred for 1 h. The mixture was partitioned between Et_2O (50 mL) and water (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic phases were successively washed with 10% aqueous sodium thiosulfate (2 × 100 mL), water (100 mL), brine (100 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 97:03) to yield **24** (1.35 g, 77%) as a mixture of 3 diastereoisomers (84:13:03). Colourless oil. R_f = 0.80 (petroleum ether/EtOAc, 90:10). IR (neat): $\tilde{\nu}$ = 2942, 2865, 1461, 1130, 1099, 1020 cm^{-1}. The major diastereoisomer **24a** was isolated in pure form from some fractions for characterisation: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.17 [m, 21 H, 3 × C*H*$(CH_3)_2$], 1.55–1.64 [m, 1 H, C*H*$_2$–CH(O)–CH_2OTIPS], 1.78–1.90 [m, 1 H, C*H*$_2$–CH(O)–CH_2OTIPS], 1.91–1.99 (m, 1 H, C*H*$_2$–CHI), 2.24–2.35 (m, 1 H, C*H*$_2$–CHI), 3.64–3.70 (m, 1 H, C*H*$_2$OTIPS), 3.79–3.84 (m, 1 H, C*H*$_2$OTIPS), 3.97 [dtd, ^3J = 8.1, 5.6, 2.5 Hz, 1 H, C*H*(O)–CH_2OTIPS], 4.35 (br. t, ^3J = 3.0 Hz, 1 H, CHI), 4.50 (AB, ^2J = 11.8 Hz, 1 H, C*H*$_2$Ph), 4.75 (AB, ^2J = 11.8 Hz, 1 H, C*H*$_2$Ph), 5.09 [br. s, 1 H, C*H*(O)–OBn], 7.28–7.39 (m, 5 H, 5 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5 (subst. arom. C), 128.4, 128.0, and 127.8 (5 × arom. CH), 99.5 [*C*H(O)–OBn], 70.3 [*C*H(O)–CH_2OTIPS], 68.6 (*C*H_2OBn), 66.7 (*C*H_2OTIPS), 29.0 (CHI), 27.7 (*C*H_2–CHI), 23.9 [*C*H_2–CH(O)–CH_2OTIPS], 18.0 (6 × CH_3), 11.9 (3 × CHSi) ppm. MS (ESI): *m*/*z* (%) = 527 (100) $[M + Na]^+$. HRMS (ESI): $C_{22}H_{37}INaO_3Si$ calcd. 527.1449; found 527.1460 (–2.2 ppm error).



(±)-**24a**

3-[2-Benzyloxy-tetrahydro-6-(triisopropylsilanyloxymethyl)pyran-3-yl]propionitrile (25): To a solution of AIBN (5 mg), **24** (198 mg, 0.39 mmol, 1 equiv.) and acrylonitrile (130 µL, 1.97 mmol, 5 equiv.) in anhydrous benzene (6 mL) heated at reflux was added a solution of AIBN (3 mg) and tributyltin hydride (120 µL, 0.45 mmol, 1.1 equiv.) in anhydrous benzene (2 mL) over 1 h. The reaction mixture was maintained at reflux for a further 10 min. After cooling to room temp., the mixture was concentrated in vacuo. Sodium fluoride (135 mg) in water (30 mL) was added and the mixture was vigorously stirred for 1 h. The mixture was then partitioned between CH_2Cl_2 (100 mL) and water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were successively washed with ammonium hydroxide (5% NH_3 in H_2O, 2 × 200 mL), water (200 mL), brine (200 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 96:04) to give **25** as a mixture of 4 diastereoisomers (120 mg, 71%). Colourless oil. R_f = 0.35 (petroleum ether/EtOAc, 90:10). IR (neat): $\tilde{\nu}$ = 2942, 2866, 2247, 1459, 1096, 1022 cm^{-1}. The major diastereoisomer was isolated in pure form from some fractions for characterisation: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.19 [m, 21 H, 3 × C*H*$(CH_3)_2$], 1.41–1.56 (m, 3 H, C*H*$_2$ tetrahydropyran), 1.75–1.94 [m, 3 H, C*H*–CH(O)OBn, C*H*$_2$–CH_2CN], 2.06–2.19 (m, 1 H, C*H*$_2$ tetrahydropyran), 2.31–2.37 (m, 2 H, CH_2CN), 3.59–3.66 (m, 1 H, C*H*$_2$OTIPS), 3.70–3.76 (m, 1 H, C*H*$_2$OTIPS), 3.87–3.97 [m, 1 H, C*H*(O)–CH_2O-TIPS], 4.51 (AB, ^2J = 11.9 Hz, 1 H, C*H*$_2$Ph), 4.67 [br. s, 1 H, C*H*(O)–OBn], 4.78 (AB, ^2J = 11.9 Hz, 1 H, C*H*$_2$Ph), 7.26–7.44 (m, 5 H, 5 × arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2

(subst. arom. C), 128.5, 128.0, and 127.7 (5×arom. CH), 119.5 (CN), 98.8 [*C*H(O)–OBn], 69.7 [*C*H(O)–CH_2OTIPS], 68.3 (*C*H_2OBn), 66.6 (*C*H_2OTIPS), 35.7 [*C*H–CH(O)–OBn], 25.4 (*C*H_2–CH_2CN), 21.8 and 20.8 (2×*C*H_2 tetrahydropyran), 17.6 (6×CH_3), 14.8 (*C*H_2CN), 11.5 (3×CHSi) ppm. MS (ESI): *m*/*z* (%) = 449 (100) $[M + NH_4]^+$. HRMS (ESI): $C_{25}H_{45}N_2O_3Si$ calcd. 449.3194; found 449.3187 (1.6 ppm error).

***tert*-Butyl [3-(2-Benzyloxy-tetrahydro-6-(triisopropylsilanyloxymethyl)pyran-3-yl)propyl]carbamate (26):** To a stirred solution of **25** (260 mg, 0.60 mmol, 1 equiv.) in MeOH (6 mL) cooled to 0 °C were added di-*tert*-butyl dicarbonate (263 mg, 1.21 mmol, 2 equiv.) and nickel(II) chloride hexahydrate (14 mg, 0.06 mmol, 0.1 equiv.). Sodium borohydride (160 mg, 4.23 mmol, 7 equiv.) was then added at 0 °C in 4 portions over 45 min. The reaction was exothermic and effervescent. The reaction mixture was warmed to room temp. and left to stir for a further 19 h. Diethylenetriamine (65 μL, 0.60 mmol, 1 equiv.) was added. The mixture was stirred for 3 h before solvent evaporation. The residue was partitioned between EtOAc (20 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic phases were successively washed with saturated aqueous sodium hydrogen carbonate (2×20 mL), water (20 mL), brine (20 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O, 92:08) to provide **26** as a mixture of diastereoisomers (257 mg, 80%). Colourless oil. R_f = 0.45 (petroleum ether/EtOAc, 90:10). IR (neat): $\tilde{\nu}$ = 3359, 2940, 2866, 1712, 1517, 1458, 1251, 1173 cm^{-1}. The major diastereoisomer was isolated in pure form from some fractions for characterisation: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00–1.16 [m, 21 H, 3×C*H*-(CH_3)$_2$], 1.37–1.75 (m, 17 H), 1.95–2.10 (m, 1 H), 2.97–3.15 (m, 2 H, CH_2N), 3.56–3.64 (m, 1 H, CH_2OTIPS), 3.68–3.75 (m, 1 H, CH_2OTIPS), 3.78–3.93 [m, 1 H, C*H*(O)–CH_2OTIPS], 4.48 (AB, ^2J = 12.0 Hz, 1 H, CH_2Ph), 4.65 [s, 1 H, C*H*(O)–OBn], 4.76 (AB, ^2J = 12.0 Hz, 1 H, CH_2Ph), 7.23–7.39 (m, 5 H, 5×arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (CO), 138.2 (subst. arom. C), 128.3, 127.8, and 127.4 (5×arom. CH), 99.7 [*C*H(O)–OBn], 79.0 [*C*(CH$_3$)$_3$], 69.9 [*C*H(O)–CH_2OTIPS], 68.3 (*C*H_2OBn), 66.9 (*C*H_2OTIPS), 40.6 (CH_2N), 36.6 [*C*H–CH(O)–OBn], 28.4 [3×CH_3 (Boc)], 28.0, 27.2, 22.4, and 21.7 (4×CH_2), 17.9 [6×CH_3 (TIPS)], 11.9 (3×CHSi) ppm. MS (ESI): *m*/*z* (%) = 553 (100) $[M + NH_4]^+$. HRMS (ESI): $C_{30}H_{57}N_2O_5Si$ calcd. 553.4031; found 553.4019 (2.2 ppm error).

(2*R,4a*R**,8a*S**)-*tert*-Butyl Octahydro-2-[(triisopropylsilanyloxy)methyl]pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate [(±)-27]:** To a solution of **26** (2.2 g, 4.11 mmol, 1 equiv.) in CH_2Cl_2 (200 mL) was added stannous chloride dihydrate (278 mg, 1.23 mmol, 0.3 equiv.). The reaction mixture was stirred for 12 h. After filtration and concentration of the filtrate in vacuo, the residue was purified by flash chromatography on neutral Brockmann grade III alumina (petroleum ether/Et_2O, 95:05) to afford (±)-**27** (1.3 g, 76%) as a single diastereoisomer. Colourless oil. R_f = 0.70 (petroleum ether/EtOAc, 90:10). IR (neat): $\tilde{\nu}$ = 2935, 2865, 1710, 1462, 1251, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97–1.10 [m, 21 H, 3×C*H*-(CH_3)$_2$], 1.21–1.50 (m, 13 H), 1.55–1.84 (m, 5 H), 2.78–2.98 (m, 1 H, CH_2N), 3.42–3.62 (m, 2 H, 2-H, CH_2OTIPS), 3.68–3.85 (m, 2 H, CH_2N, CH_2OTIPS), 5.15 (br. s, 0.5 H, 8a-H rotamer), 5.34 (br. s, 0.5 H, 8a-H rotamer) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1 and 155.0 (CO, rotamers), 82.5 and 81.1 (C-8a, rotamers), 79.6 [*C*(CH$_3$)$_3$], 78.4 and 77.9 (C-2, rotamers), 66.8 and 66.5 (*C*H_2OTIPS, rotamers), 39.7 and 38.8 (CH_2N, rotamers), 34.0 (C-4a), 28.4 (CH_2), 28.3 [3×CH_3 (Boc)], 25.0, 24.7, 23.0, 22.7, and 22.6 (CH_2, rotamers), 17.9 [6×CH_3 (TIPS)], 11.9 (3×CHSi) ppm. MS (ESI): *m*/*z* (%) = 450 (100) $[M + Na]^+$. HRMS (CI): $C_{23}H_{46}NO_4Si$ calcd. 428.3196 $[M + H]^+$; found 428.3192 (0.9 ppm error). $C_{23}H_{45}NO_4Si$ (427.69): calcd. C 64.59, H 10.61, N 3.27; found C 65.34, H 10.95, N 3.36.

(+)-(2*R*,4a*R*,8a*S*)-*tert*-Butyl Octahydro-2-[(triisopropylsilanyloxy)methyl]pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate [(+)-27]: The procedure used for the preparation of (±)-**27** was followed but using (–)-**28**.[10] The spectroscopic data are consistent to those of (±)-**27**. $[\alpha]_D^{23}$ = +34.7 (*c* = 0.32, $CHCl_3$).

(2*R*,4a*R*,8a*S*)-*tert*-Butyl Octahydro-2-(hydroxymethyl)pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate [(+)-29]: To a solution of (+)-**27** (95 mg, 0.22 mmol, 1 equiv.) in anhydrous THF (2 mL) cooled to 0 °C was added tetrabutylammonium fluoride (1.0 M in THF, 235 μL, 0.24 mmol, 1.05 equiv.). The reaction mixture was stirred at 0 °C for 1 h. The mixture was partitioned between Et_2O (20 mL) and water (20 mL). The aqueous layer was extracted with Et_2O (2×20 mL). The combined organic phases were successively washed with water (50 mL), brine (50 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on neutral Brockmann grade III alumina (petroleum ether/Et_2O, 50:50) to furnish (+)-**29** (56 mg, 93%). Yellow oil. $[\alpha]_D^{20}$ = +35.7 (*c* = 1.50, $CHCl_3$). R_f = 0.30 (petroleum ether/EtOAc, 50:50). IR (neat): $\tilde{\nu}$ = 3445 (br.), 2932, 2862, 1696, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.54 [m, 13 H, CH_2–CH_2N, CH_2–CH(O)–CH_2OH, 3×CH_3], 1.59–1.87 (m, 5 H, 4a-H, 2×CH_2–C-4a), 2.12–2.22 (m, 1 H, OH), 2.80–3.02 (m, 1 H, CH_2N), 3.45–3.67 (m, 3 H, 2-H, CH_2OTIPS), 3.72–3.87 (m, 1 H, CH_2N), 5.20 (br. s, 0.5 H, 8a-H rotamer), 5.38 (br. s, 0.5 H, 8a-H rotamer) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3 and 155.1 (CO, rotamers), 82.6 and 81.2 (C-8a, rotamers), 80.0 [*C*(CH$_3$)$_3$], 77.8 (C-2), 65.8 (CH_2OH), 39.8 and 39.0 (CH_2N, rotamers), 33.9 (C-4a), 28.3 (3×CH_3), 28.2 (CH_2), 24.9 and 24.6 (CH_2, rotamers), 22.9 (CH_2), 21.6 (CH_2) ppm. MS (ESI): *m*/*z* (%) = 294 (100) $[M + Na]^+$. HRMS (ESI): $C_{14}H_{25}NNaO_4$ calcd. 294.1676; found 294.1675 (0.3 ppm error).

(2*R*,4a*R*,8a*S*)-*tert*-Butyl 2-[(4-Nitrobenzoyloxy)methyl]octahydropyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate [(+)-30]: To a solution of (+)-**29** (43 mg, 0.16 mmol, 1 equiv.) and triethylamine (29 μL, 0.21 mmol, 1.3 equiv.) in CH_2Cl_2 (1.5 mL) cooled to 0 °C was added 4-nitrobenzoyl chloride (32 mg, 0.17 mmol, 1.1 equiv.). The reaction mixture was stirred at 0 °C for 1 h. The mixture was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic phases were successively washed with water (20 mL), brine (20 mL) and were dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by flash chromatography on neutral Brockmann grade III alumina (petroleum ether/Et_2O, 80:20) and recrystallised from acetone to yield (+)-**30** (58 mg, 87%). Yellow cubes; m.p. 118–120 °C. R_f = 0.20 (petroleum ether/Et_2O, 70:30). $[\alpha]_D^{20}$ = +10.4 (*c* = 1.85, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2934, 2862, 1727, 1700, 1273, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.59 [m, 13 H, CH_2–CH_2N, CH_2–CH(O)–CH_2OC(O)Ar, 3×CH_3], 1.61–1.91 (m, 5 H, 4a-H, 2×CH_2–C-4a), 2.80–3.01 (m, 1 H, CH_2N), 3.69–3.93 (m, 2 H, CH_2N, 2-H), 4.27–4.39 (m, 2 H, CH_2OTIPS), 5.19 (br. s, 0.5 H, 8a-H rotamer), 5.41 (br. s, 0.5 H, 8a-H rotamer), 8.17–8.28 (m, 4 H, 4×arom. H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0 and 164.9 [*C*(O)Ar, rotamers], 155.6 (*C*O$_2$*t*Bu), 150.8 (subst. arom. C), 135.9 and 135.8 (subst. arom. C, rotamers), 131.0 (2×arom. CH), 123.6 (2×arom. CH), 82.6 and 81.4 (C-8a, rotamers), 80.0 and 79.7 [*C*(CH$_3$)$_3$, rotamers], 75.0 (C-2), 67.9 [*C*H$_2$OC(O)Ar], 39.7 and 38.8 (CH_2N, rotamers), 33.3 (C-4a), 28.0 (3×CH_3), 27.9 (CH_2), 24.6 and 24.3 (CH_2, rotamers),

22.6 (CH_2), 21.9 (CH_2) ppm. MS (ESI): *m*/*z* (%) = 421 (17) [M + H]$^+$, 443 (28) [M + Na]$^+$. HRMS (ESI): $C_{21}H_{28}N_2NaO_7$ calcd. 443.1789; found 443.1798 (–2.2 ppm error).

X-ray Crystallographic Study of [(+)-30]: Formula = $C_{21}H_{28}N_2O_7$, *M*w = 420.45, temperature = 110(2) K, radiation Mo-K_α (λ = 0.71073 Å). The unit cell was determined as orthorhombic with *a* = 5.6690(3), *b* = 9.7350(5), *c* = 37.751(2) Å; $\alpha = \beta = \gamma = 90°$; *V* = 2083.37(19) Å^3, the space group was $P2_12_12_1$ with *Z* = 4, density (calculated) = 1.340 mg m^{-3}, *F*(000) = 896, crystal size $0.26 \times 0.23 \times 0.15$ mm^3. Data collection was carried out on a Bruker Smart Apex diffractometer using a SMART CCD camera, 28730 reflections were collected of which 5156 were unique over the range $1.08 < \theta < 28.29°$. The index ranges of data collection were $-7 \le h \le 7$, $-12 \le k \le 12$, $-50 \le l \le 50$. Diffractometer control, data collection and initial unit cell determination were performed using SMART.[13] Frame integration and unit-cell refinement software were carried out with the SAINT+.[13] Absorption corrections were applied by SADABS.[14] The structure was solved by direct methods using SHELXS-97.[15] It was refined by full-matrix least-squares based on F^2 using SHELXL-97[15] that gave $R1 = 0.0373$, $wR2 = 0.0963$ for all data and a goodness of fit, GooF = *S* = 1.108. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a riding model and included in the refinement at calculated positions. The final absolute structure (Flack) parameter was –0.2(6). The final Fourier difference synthesis showed the largest peak and hole to be 0.301 and –0.188 e Å^{-3}, respectively.

CCDC-638019 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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