Synthesis of (–)-*N*-Acetylslaframine by C-1, C-5 Bis-hydroxyalkylation of (*S*)-2-(*N*,*N*-Dibenzylamino)-1,5-pentanediol via Highly Diastereoselective Lithiation of the Dicarbamate

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Abstract: (–)-*N*-Acetylslaframine, a stable form of the indolizidine alkaloid (–)-slaframine, has been synthesised by a new strategy. Applying highly stereoselective lithiation and substitution reactions, C-2, C-3 and C-8 of the bicyclic skeleton were introduced to an L-glutamic acid derived diol dicarbamate.

Key words: indolizidines, chiral 2-amino-1-ω-alkanediols, lithiated dicarbamates, diastereoselectivity, (–)-sparteine

(–)-Slaframine (**1**) is produced by the mould *Rhizoctonia leguminicola*, growing on rotting clover (Figure 1).[3] When eaten by ruminants, such as cattle, it causes the so-called 'slobber syndrome'. Several asymmetric total syntheses of **1**, the structure of which is usually characterised as its more stable *N*-acetyl derivative **2**, have been reported.[4]

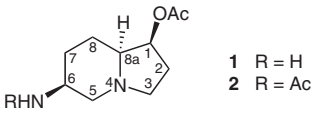
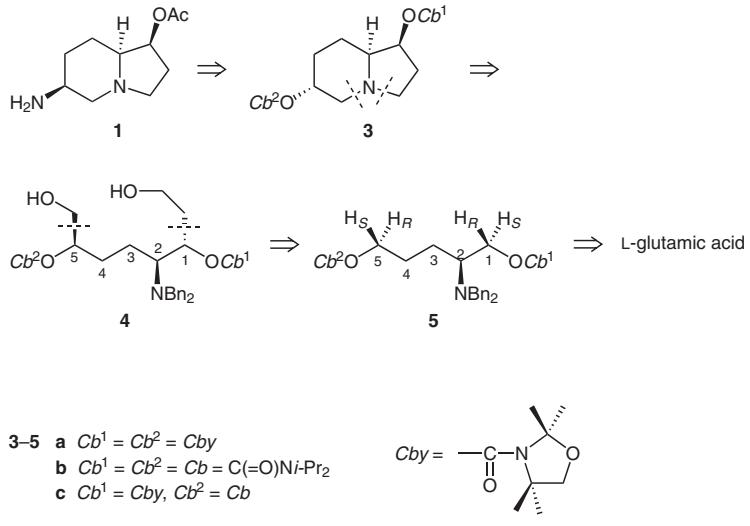


Figure 1

Our synthetic plan was based on the electrophilic introduction of a 2-hydroxyethyl residue at C-1 and a hydroxymethyl group at C-5 of an L-glutamic acid derived dicarbamate **5**,[5] to form the carbon skeleton of **1** and **2** (Scheme 1), followed by intramolecular double cycloalkylations at the nitrogen atom, to the chiral indolizidine **3**. Finally, functional group manipulations were envisaged to lead to the targets **1** or **2**.

The starting material, (*S*)-*N*,*N*-dibenzylglutaminediol (**6**), was prepared according to the method of Heymès et al.[6] via dibenzyl (*S*)-*N*,*N*-dibenzylglutamic acid ester (Scheme 2). Bis-acylation of **6** using the appropriate carbamoyl chlorides via standard methods, furnished the dicarbamates **5a** or **5b**.[5] For the synthesis of the mixed dicarbamate **5c**, a route via intermediate silyl protection of the more reactive 5-OH group was required.

Previously, we investigated the regio- and diastereoselectivity of the lithiation of dicarbamate **5a** (Scheme 3).[5,7] It was found that the position of lithiation could be directed by the conditions of deprotonation. Thus, the deprotonation in diethyl ether, in the absence of any diamine, and methylation led to the 1-substitution product **10** (presumably via lithium compound **9a**), whereas the same reaction



Scheme 1

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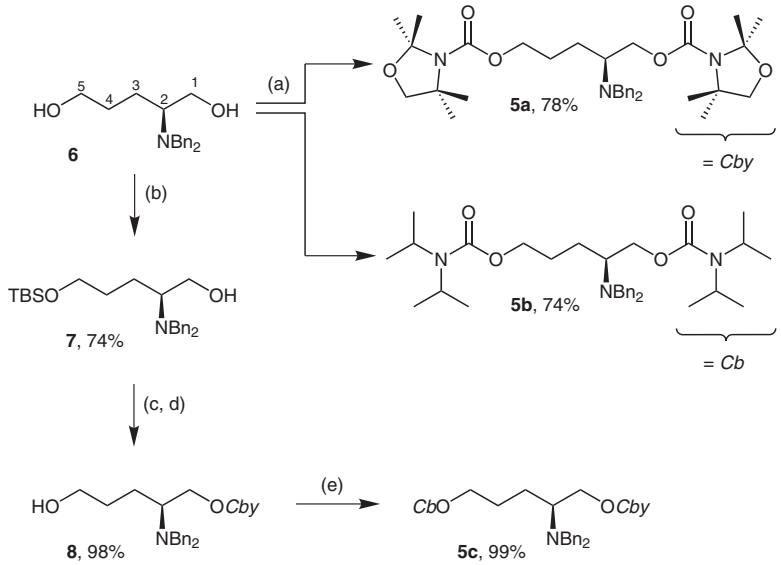
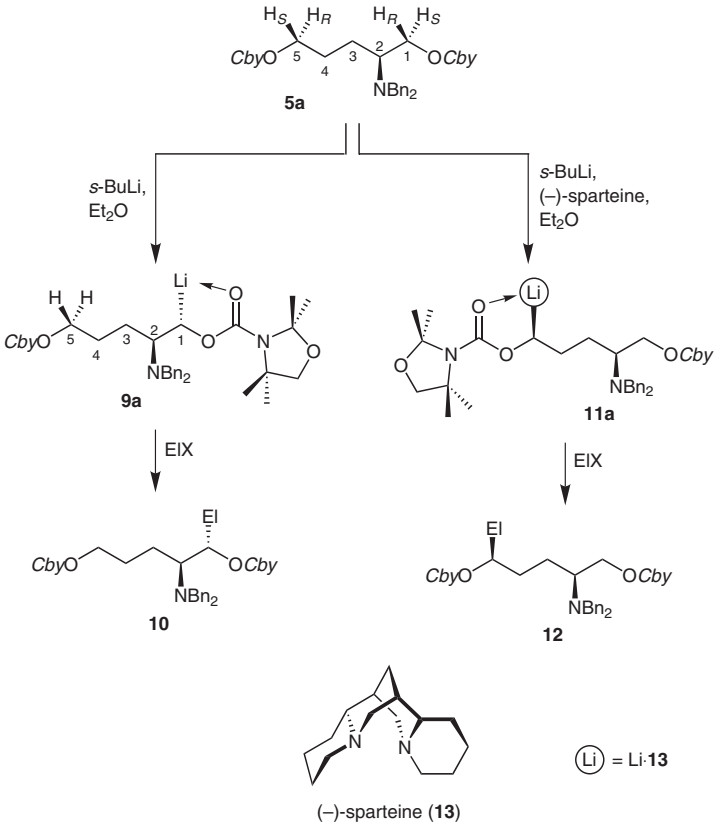


Scheme 2 *Reagents and conditions*: (a) NaH, THF, reflux, 1 h, CbCl or CbyCl, reflux, 16 h; (b) Et_3N, DMAP, TBSCl, CH_2Cl_2, 0 °C→r.t., 48 h; (c) NaH, THF, reflux, 1 h, CbyCl, reflux, 16 h; (d) TBAF, r.t., 72 h; (e) NaH, THF, reflux, 1 h, CbCl, reflux, 16 h.

sequence in the presence of (–)-sparteine (**13**) achieved the 5-substitution product **12** (via carbanionic intermediate **11a**). However, the selectivities appeared to be insufficient for the proposed synthesis. In addition, a differentiation between both *O*-carbamoyl groups was required during the course of the planned synthesis.

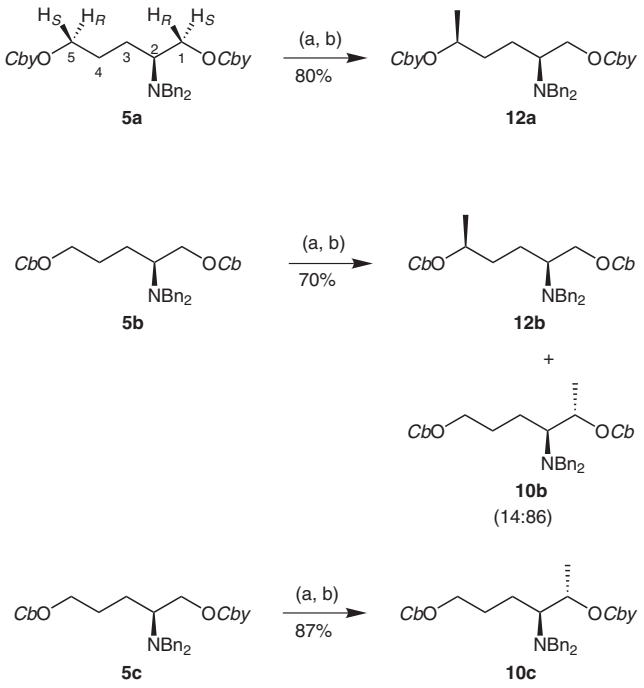
The 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl group (Cby) is easily removed under acidic conditions, whereas the *N*,*N*-diisopropylcarbamoyl group (Cb) requires the application of lithium aluminum hydride or excess diisobutylaluminum hydride (DIBAL-H).[8,9]

To find the best conditions for regio- and diastereoselective lithiation, a careful study was undertaken (Scheme 4).



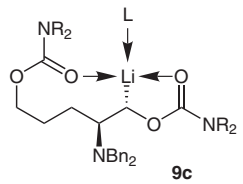
Scheme 3

As expected, after (–)-sparteine-mediated lithiation and methylation with iodomethane (MeI), dicarbamate **5a** afforded the 5*S*-substitution product **12a** with good yield and diastereoselectivity. From the bis(*N*,*N*-diisopropylcarbamate) **5b**, under identical conditions, the 1*S*-product **10b** was the major product, accompanied by 14% of **12b**. Fortunately, the mixed dicarbamate **5c** yielded the pure 1*S*-substitution product **10c** in high yield. Compound **10c**, albeit in lower yield (46%), was also produced when no additive was used.



Scheme 4 *Reagents and conditions*: (a) *s*-BuLi/**13**, Et_2O, –78 °C, 7 h; (b) MeI, –78 °C→20 °C, 14 h.

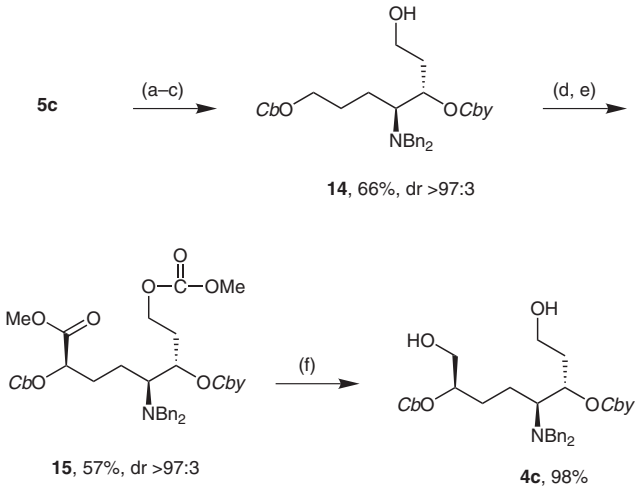
These surprising results reflect a delicate competition between (–)-sparteine (**13**) and both of the carbamoyl groups as complexing agents in the kinetically controlled deprotonation step. Obviously, the remote carbamoyl group at the 5-position plays an important role by internal complexation during deprotonation at the 1-position. The smaller 5-OCb group is more efficient than the bulky 5-OCby group in accomplishing internal complexation and formation of **9c** (Figure 2). As the control experiment demonstrates (see above), (–)-sparteine (**13**) is not required for achieving high regio- and diastereoselectivity, although it enhances the rate of lithiation.



L = OEt_2, or monodentate (–)-sparteine (**13**)

Figure 2

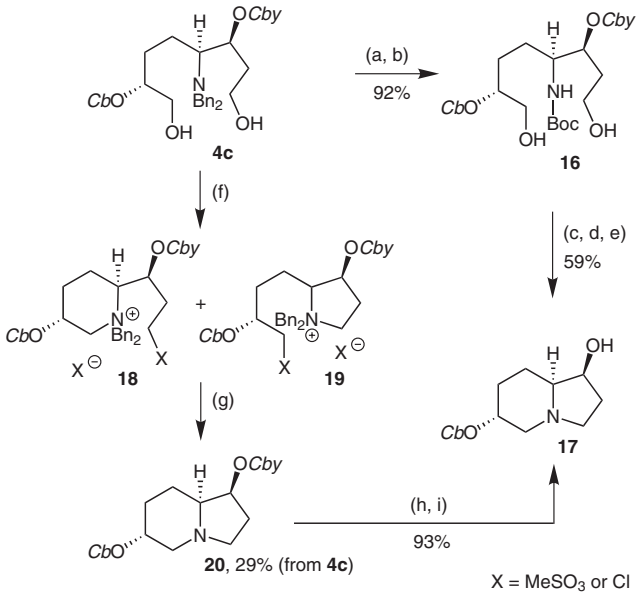
The synthesis of the key intermediate **4c** requires the diastereoselective introduction of a 2-hydroxyethyl group into the 1-position and a hydroxymethyl group into the 5-position of the dicarbamate. Consequently, mixed carbamate **5c** was deprotonated by *sec*-butyllithium/(–)-sparteine (**13**) and allowed to react with 3.0 equivalents of ethylene oxide and boron trifluoride–diethyl ether complex ($BF_3{\cdot}OEt_2$) (Scheme 5). Under optimum conditions, the diastereomerically pure alcohol **14** was isolated in 66% yield.[10] For the next step, double deprotonation of **14** with 3.5 equivalents of *sec*-butyllithium/(–)-sparteine (**13**) and subsequent quenching of the *O*,*C*-dianion with excess methyl chloroformate, gave the diastereomerically pure diester **15** in 57% yield. All attempts at using *O*-silyl ethers of **14** resulted in lower yields of **15** and more by-products.[11] Treatment of **15** with 6.0 equivalents of DIBAL-H in THF, led to the reduction of the methyl ester group and the reductive cleavage of the carbonic ester function, to afford diol **4c** in 98% yield.



Scheme 5 *Reagents and conditions*: (a) *s*-BuLi/**13**, Et_2O, –78 °C, 7 h; (b) ethylene oxide, –78 °C; (c) $BF_3{\cdot}OEt_2$, –78 °C→20 °C, 14 h; (d) *s*-BuLi/**13**, –78 °C, 7 h; (e) MeOC(=O)Cl, –78 °C→20 °C, 14 h; (f) DIBAL-H, THF, 0 °C, 2 h.

For the construction of the indolizidine core from diol **4c**, *N*,*N*-di-debenzylation and activation of both hydroxy groups for double cycloalkylation was required (Scheme 6). Initially, **4c** was converted into the dimesylate, however, a mixture of quaternary ammonium salts **18** and **19** was formed, which proved to be inseparable and apparently consisted of mesylates and chlorides. When this mixture was subjected to hydrogenolysis and base treatment, the mixed indolizidine dicarbamate **20** could be isolated in low yield (17%). Although many variations of both steps were attempted, no improvement in yield could be achieved. Compound **20**, as a colourless solid, was subjected to an X-ray crystal structure analysis (Figure 3), which confirmed the assumed structure.[12] A more efficient route began with a palladium-catalysed *N*,*N*-di-debenzylation of diol **4c**, followed by *tert*-butoxycarbonylation, leading to the *tert*-butoxycarbonyl (*N*-Boc) derivative **16**. This was converted into the *O*,*O*′-dimesylate and

the Boc group was removed by treatment with trifluoroacetic acid, which, in addition, cleaved the OCby group, yielding the indolizidine 6-monocarbamate **17**. Since the dicarbamate **20** could also easily be partially deprotected to form **17** in 93% yield, the configurations of **20** and **17** are identical.



Scheme 6 *Reagents and conditions*: (a) Pd/C, H_2, MeOH, 14 h at 20 °C, 5 h at 65 °C; (b) Boc_2O, Et_3N, MeOH, 3 h at 40 °C, 14 h at 20 °C; (c) MsCl, Et_3N, CH_2Cl_2, –20 °C, 14 h; (d) TFA, CH_2Cl_2, 20 °C, 14 h; (e) K_2CO_3, MeOH, 65 °C, 14 h; (f) MsCl, DMAP, pyridine, 0 °C, 2 h; (g) $Pd(OH)_2$/C, Et_3N, H_2, MeOH, 14 h at 20 °C, 5 h at 60 °C; (h) 5 N HCl, THF, MeOH, 65 °C, 14 h; (i) 5 N NaOH, 65 °C, 14 h.

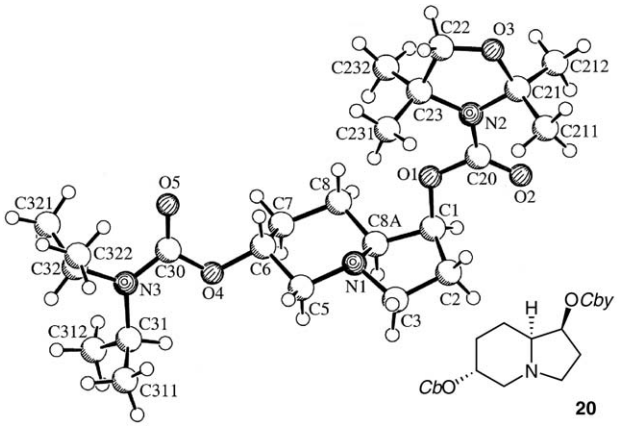
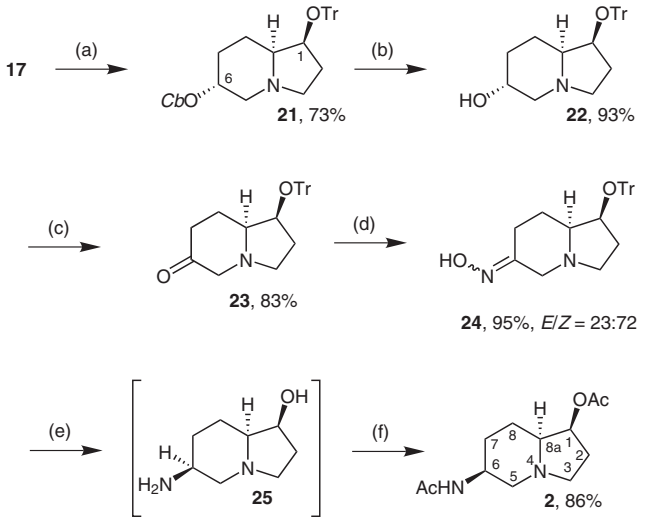


Figure 3

The synthesis of **2** was completed via the 1-*O*-protected diol **22**. The central issue of this synthetic sequence consisted of the substitution of the 6-OH group by an amino group with inversion of configuration (Scheme 7). The most obvious route – activation of the 6-OH group and S_N2-substitution by azide – is, according to results obtained by Wasserman[13] and Gmeiner,[4i] hampered by the formation of a tricyclic aziridinium ion. In a number of syntheses[4i–k,n–p] the problem was solved by preparing the ketone, its oxime, followed by hydrogenation from the *exo*-face combined with hydrogenolysis of the N–O bond. Following this standard route, alcohol **17** was converted into the 1*O*-trityl ether **21** and deprotected to the 6-alcohol **22**. This was oxidised to ketone **23**, transformed to oxime **24** (*E*/*Z* = 23:72) and then subjected to hydrogenation/hydrogenolysis under the influence of PtO_2 to afford the amino alcohol **25**. Bis-acetylation of **25** led to (–)-*N*-acetylslaframine (**2**).



Scheme 7 *Reagents and conditions*: (a) Ph_3CCl, DBU, CH_2Cl_2, 20 °C, 48 h; (b) DIBAL-H, THF, 2 h at –78 °C, 14 h at 20 °C; (c) $(COCl)_2$, CH_2Cl_2, –78 °C, DMSO, 5 h at –78 °C, Et_3N, 1 h at –78 °C, 1 h at 20 °C; (d) $HONH_2$·HCl, pyridine, EtOH, 4 h at 80 °C, 16 h at 20 °C; (e) PtO_2, H_2, EtOH, HCl, 20 °C, 14 h; (f) Ac_2O, pyridine, 20 °C, 2 h.

The melting point of **2** and the ^1H and ^{13}C NMR data of our sample match[14] well with those reported by Pearson.[4a] The optical rotation in chloroform (–18.0, *c* 0.40) is higher than reported by Pearson (–11.2, *c* 1.45).[4a,15]

In summary, a new strategy for the synthesis of (–)-slaframine (**1**) has been developed. Crucial steps are the highly diastereoselective introductions of C-2, C-3 and C-5 moieties for the construction of the indolizidine core by two electrophilic substitution reactions at C-1 and C-5 of a lithiated 2-amino-alkanediyl dicarbamate, which was derived from L-glutamic acid.

Reactions with air- and moisture-sensitive compounds were performed under an argon atmosphere. All solvents were refluxed over a suitable drying agent and distilled immediately before use. (–)-Sparteine (**13**) was purchased from Aldrich and used without further purification. Et_3N and DMSO were refluxed over CaH_2 and distilled under an argon atmosphere. *s*-BuLi was received as a 1.3 M solution in cyclohexane–hexane (92:8) and was filtered and titrated before use.[16] *N*,*N*-Diisopropylcarbamoyl chloride[17] and 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl chloride[18] were prepared following a procedure developed in the research group. Preparative liquid chromatography was performed with flash column chromatography (FCC) under 1.5 bar argon pressure using silica gel grade 40–60 μm from Merck, Darmstadt. TLC was performed using alu-

minum silica gel plates 60 F_{254} from Merck, Darmstadt. The detection of the products was performed under UV light at 254 nm as well as with staining agents followed by heating. Gas chromatography was performed on Agilent 6890 from Agilent, USA, using an achiral HP5-quarz column (program: 50 °C start temperature for 0 min, 10 °C/min heating rate, 300 °C final temperature for 15 min) from Hewlett–Packard, USA. The optical rotation was measured in a 10 cm cuvette on a polarimeter of the types Perkin–Elmer 241 or 341 from Perkin–Elmer & Co GmbH, Überlingen. Elemental analyses were performed on a Vario EL III from Elementar Analysensysteme GmbH, Hanau, or on a CHN-O-Rapid from Heraeus, Hanau. Melting points were measured on a MFB595 from Gallenkamp, UK, or on a Stuart Melting Point Apparatus SMP3 from Bibby Sterlin Ltd, UK, and are uncorrected. IR-measurements were performed on an IFS 28 from Bruker Optik GmbH, Karlsruhe, or 5 DXC from Nicolet, Offenbach. Mass spectrometry was carried out by electron spray ionization (ESI) or as exact mass determination on a MicroTof from Bruker Datronics, Bremen, or on Quattro LCZ, Micromass, UK, with a nanospray inlet. The ^{1}H and ^{13}C NMR spectra were measured on ARX300, AMX400 spectrometers from Bruker, Analytische Messtechnik, Karlsruhe, and Varian Inova 500, Varian Unity Plus 600 from Varian Associated, USA. TMS (δ = 0.0 ppm) or $CDCl_3$ (δ = 7.26 ppm for remaining $CHCl_3$) were used as internal standards in ^{1}H NMR and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectra. H-X_A and H-X_B indicate unassigned diastereotopic methylene protons. Chemical shifts in brackets give the values of the minor amide torsion isomers.

Synthesis of Dicarbamates 5a and 5b; General Procedure A

NaH (60% in mineral oil, 2.0–3.0 equiv) was suspended in THF (0.5 mL/mmol). A solution of the alcohol (1.0 equiv) in THF (0.5 mL/mmol) was added and the suspension was heated at reflux for 1 h. CbCl (2.0–3.0 equiv) or CbyCl (2.0–3.0 equiv) dissolved in THF (0.5 mL/mmol) was added dropwise and the mixture was heated at reflux overnight. After cooling to r.t., H_2O (1.0 mL/mmol) and Et_2O (1.0 mL/mmol) were added, the aqueous layer was washed with Et_2O (2 × 1.0 mL/mmol) and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the crude product was purified by FCC (Et_2O–PE).

(*S*)-2-(*N*,*N*-Dibenzylamino)-5-pentane-1,5-diyl Bis(2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate) (5a)

According to general procedure A, the product was formed by the reaction of NaH (60% in mineral oil, 1.20 g, 30.0 mmol, 2.0 equiv), diol **6** (4.0 g, 13.4 mmol) and CbyCl (5.73 g, 30.0 mmol, 2.0 equiv) in THF (50 mL). After aqueous workup, purification by FCC (Et_2O–PE, 1:3) gave **5a**.

Yield: 6.37 g, 10.5 mmol (78%); highly viscous oil; $[\alpha]_D^{20}$ –11.6 (*c* 1.02, $CHCl_3$); R_f = 0.45 (Et_2O–PE, 1:1).

IR (film): 1740, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.59 (m, 24 H, Cby-CH_3), 1.69 (m, 2 H, H-3), 1.83 (m, 2 H, H-4), 2.82 (m, 1 H, H-2), 3.53, 3.72 [2 × d, $^2J_{gem}$ = 13.6 Hz, 2 × 2 H, (PhCH_2)$_2$N], 3.65 (s, 4 H, Cby-CH_2), 3.93 (m, 2 H, H-5), 4.15 (m, $^2J_{gem}$ = 11.2 Hz, $^3J_{1-5}$ = 5.1 Hz, 1 H, H-1), 4.26 (dd, $^2J_{gem}$ = 11.2 Hz, $^3J_{1-5}$ = 5.1 Hz, 1 H, H-1), 7.11–7.38 (m, 10 H, H_{phenyl}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 25.8, 26.0, 26.5, 27.1 (Cby-CH_3), 26.9 (C-3), 27.0 (C-4), 54.2 [(PhCH_2)$_2$N], 56.8 (C-2), 60.0 (60.7), 60.9 (61.2) [NC(CH$_3$)$_2$CH$_2$], 64.0 (C-1), 65.0 (C-5), 76.5, 76.7 (Cby-CH_2), 95.1, 96.2 (96.4) [NC(CH$_3$)$_2$O], 127.4, 128.6, 129.3, 140.2 (C_{phenyl}),152.5, 153.2 (Cby-NC=O).

Anal. Calcd for $C_{35}H_{51}N_3O_6$: C, 68.94; H, 8.43; N, 6.89. Found: C, 68.78; H, 8.37; N, 6.97.

(*S*)-2-(*N*,*N*-Dibenzylamino)-5-pentane-1,5-diyl Bis(*N*,*N*-diisopropylcarbamate) (5b)

According to general procedure A, the product was formed by the reaction of NaH (60% in mineral oil, 0.84 g, 21.0 mmol, 3.0 equiv), diol **6** (2.1 g, 7.0 mmol) and CbCl (3.44 g, 21.0 mmol, 3.0 equiv) in THF (40 mL). After aqueous workup, purification by FCC (Et_2O–PE, 1:2) yielded **5b**.

Yield: 2.86 g, 5.2 mmol (74%); highly viscous oil; $[\alpha]_D^{20}$ –15.2 (*c* 1.02, $CHCl_3$); R_f = 0.37 (Et_2O–PE, 1:1).

IR (film): 3085, 3062, 3032, 2970, 2939, 2874, 1694, 1456, 1439, 749, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18, 1.19 (2 × d, $^3J_{CbCH-CbCH3}$ = 6.5 Hz, 2 × 6 H, Cb-CH_3), 1.22 (m, 12 H, Cb-CH_3), 1.47 (m, 1 H, H-4_A), 1.56 (m, 1 H, H-4_B), 1.73 (m, 1 H, H-3_A), 1.87 (m, 1 H, H-3_B), 2.89 (m, 1 H, H-2), 3.62, 3.78 [2 × d, $^2J_{gem}$ = 13.8 Hz, 2 × 2 H, (PhCH_2)$_2$N], 3.92 (m, $^3J_{CbCH-CbCH3}$ = 6.5 Hz, 4 H, Cb-CH), 4.00 (m, 1 H, H-5), 4.19 (dd, $^2J_{1A-1B}$ = 11.3 Hz, $^3J_{1A-2}$ = 5.9 Hz, 1 H, H-1_A), 4.26 (dd, $^2J_{1A-1B}$ = 11.3 Hz, $^3J_{1B-2}$ = 5.3 Hz, 1 H, H-1_B), 7.19–7.35 (m, 10 H, H_{phenyl}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (Cb-CH_3), 25.8 (C-4), 26.6 (C-3), 45.9 (Cb-CH), 53.9 [(PhCH_2)$_2$N], 56.3 (C-2), 63.9 (C-1), 64.7 (C-5), 126.8, 128.1, 128.8 (C_{phenyl}), 140.1 (C_q, C_{phenyl}), 155.1, 155.8 (Cb-NC=O).

MS (ESI): *m*/*z* = 554.5 [M + H]$^+$, 576.5 [M + Na]$^+$.

Anal. Calcd for $C_{33}H_{51}N_3O_4$: C, 71.57; H, 9.28; N, 7.59. Found: C, 71.29; H, 9.45; N, 7.41.

(*S*)-2-(*N*,*N*-Dibenzylamino)-5-(*tert*-butyldimethylsilyloxy)pentan-1-ol (7)

To (*S*)-2-(*N*,*N*-dibenzylamino)-1,5-pentanediol (**6**; 11.91 g, 39.8 mmol), dissolved in CH_2Cl_2 (50 mL), a mixture of Et_3N (4.02 g, 39.8 mmol, 1.0 equiv), DMAP (2.38 g, 19.5 mmol, 0.5 equiv) and *tert*-butylchlorodimethylsilane (7.05 g, 48.2 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) was added at 0 °C. After stirring for 48 h at r.t., the mixture was treated with H_2O (25 mL) and Et_2O (25 mL). The aqueous layer was washed with Et_2O (3 × 25 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under vacuum. Purification by FCC (Et_2O–PE, 1:3→1:2) yielded mainly **7** along with a few milligrams of the double *O*-silyl substituted product.

Yield: 12.18 g, 29.4 mmol (74%); colourless oil; $[\alpha]_D^{20}$ +63.4 (*c* 1.17, $CHCl_3$); R_f = 0.61 (Et_2O–PE, 1:1).

IR (film): 3420, 1680, 680 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 [s, 6 H, Si(CH_3)$_2$C(CH$_3$)$_3$], 0.85 [s, 9 H, Si(CH$_3$)$_2$C(CH_3)$_3$], 1.16 (m, 1 H, H-3_B), 1.40 (m, $^3J_{4-5}$ = 6.3 Hz, 2 H, H-3_A, H-4_B), 1.76 (m, 1 H, H-4_A), 2.72 (dddd, $^3J_{2-3}$ = 4.4 Hz, $^3J_{1-2}$ = 5.0, 9.8 Hz, 1 H, H-2), 3.04 (m, 1 H, OH), 3.36 [d, $^2J_{gem}$ = 13.4 Hz, 2 H, (PhCH_2)$_2$N], 3.39 (m, $^3J_{1-2}$ = 5.0, 9.8 Hz, 2 H, H-1), 3.53 (m, 2 H, H-5), 3.75 [d, $^2J_{gem}$ = 13.4 Hz, 2 H, (PhCH_2)$_2$N], 7.23–7.45 (m, 10 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –6.6 [Si(CH_3)$_2$C(CH$_3$)$_3$], 17.0 [Si(CH$_3$)$_2$C(CH$_3$)$_3$], 19.9 (C-3), 24.6 [Si(CH$_3$)$_2$C(CH_3)$_3$], 29.1 (C-4), 52.0 [(PhCH_2)$_2$N], 57.6 (C-2), 59.7 (C-5), 61.6 (C-1), 125.9, 127.1, 127.7, 138.1 (C_{phenyl}).

Anal. Calcd for $C_{25}H_{39}NO_2Si$: C, 72.59; H, 9.50; N, 3.39. Found: C, 72.81; H, 9.73; N, 3.12.

2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylic Acid (*S*)-2-(*N*,*N*-Dibenzylamino)-5-hydroxypent-1-yl Ester (8)

According to general procedure A, NaH (60% in mineral oil, 1.88 g, 47.0 mmol, 2.0 equiv), alcohol **7** (9.72 g, 23.5 mmol) and CbyCl (9.01 g, 47.0 mmol, 2.0 equiv) in THF (60 mL) were reacted. After aqueous workup, the crude product was treated with TBAF (1 M so-

lution in THF, 70.5 mL, 70.5 mmol, 3.0 equiv) for 72 h at r.t., without further solvent. H_2O (50 mL) and Et_2O (50 mL) were added, the aqueous layer was washed with Et_2O (2 × 30 mL) and the combined organic layers were dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude product was purified by FCC (Et_2O–PE, 1:1→Et_2O) to yield **8**.

Yield: 10.45 g, 23.0 mmol (98%); colourless oil; $[\alpha]_D^{20}$ –33.3 (*c* 0.93, $CHCl_3$); R_f = 0.16 (Et_2O–PE, 1:1).

IR (film): 3420, 1680, 740, 690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.60 (m, 14 H, Cby-CH_3, H-4), 1.70 (m, 2 H, H-3), 2.01 (m, 1 H, OH), 2.89 (m, 1 H, H-2), 3.47 (m, 2 H, H-5), 3.59, 3.80 [2 × d, $^2J_{gem}$ = 13.4 Hz, 2 × 2 H, (PhCH_2)$_2$N], 3.72 (s, 2 H, Cby-CH_2), 4.18 (m, $^2J_{gem}$ = 11.1 Hz, $^3J_{1-2}$ = 5.0 Hz, 1 H, H-1), 4.33 (dd, $^2J_{gem}$ = 11.1 Hz, $^3J_{1-2}$ = 5.0 Hz, 1 H, H-1), 7.15–7.35 (m, 10 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9, 27.3 (C-4, Cby-CH_3), 30.3 (C-3), 54.3 (C-2), 56.8 [(Ph*C*H_2)$_2$N], 60.1 (61.2) [N*C*(CH$_3$)$_2$CH$_2$], 63.0 (C-1), 64.1 (C-5), 76.2 (Cby-CH_2), 96.4 (95.3) [N*C*(CH$_3$)$_2$O], 127.4, 128.6, 129.4, 140.1 (C_{phenyl}), 153.2 (Cby-NC=O).

Anal. Calcd for $C_{27}H_{38}N_2O_4$: C, 71.34; H, 8.43; N, 6.16. Found: C, 71.25; H, 8.76; N, 6.40.

2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylic Acid (*S*)-2-(*N*,*N*-Dibenzylamino)-5-(*N*,*N*-diisopropylcarbamoyloxy)pent-1-yl Ester (5c)

According to general procedure A, the product was formed by the reaction of NaH (60% in mineral oil, 1.90 g, 47.4 mmol, 2.0 equiv), alcohol **8** (10.78 g, 23.7 mmol) and CbCl (7.76 g, 47.4 mmol, 2.0 equiv) in THF (80 mL). After aqueous workup, purification by FCC (Et_2O–PE, 1:3→1:2) yielded **5c**.

Yield: 13.76 g, 23.7 mmol (99%); light-yellow, highly viscous oil; $[\alpha]_D^{20}$ –11.5 (*c* 1.36, $CHCl_3$); R_f = 0.36 (Et_2O–PE, 1:1).

IR (film): 3086, 3062, 3030, 2970, 2938, 2878, 1697, 1455, 1437, 746, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.18, 1.23 (2 × d, $^3J_{CbCH-CbCH3}$ = 6.8 Hz, 2 × 6 H, Cb-CH_3), 1.32, 1.44, 1.49, 1.58 (4 × s, 12 H, Cby-CH_3), 1.40–1.60 (m, 2 H, H-3$_A$, H-4$_A$), 1.75 (m, 1 H, H-3$_B$), 1.90 (m, 1 H, H-4$_B$), 2.88 (m, 1 H, H-2), 3.60, 3.78 [2 × d, $^2J_{gem}$ = 13.7 Hz, 2 × 2 H, (PhCH_2)$_2$N], 3.72 (s, 2 H, Cby-CH_2), 3.90 (sept, $^3J_{CbCH-CbCH3}$ = 6.8 Hz, 2 H, Cb-CH), 4.00 (m, 2 H, H-5), 4.21 (dd, $^2J_{1A-1B}$ = 11.7 Hz, $^3J_{1A-2}$ = 4.4 Hz, 1 H, H-1$_A$), 4.32 (dd, $^2J_{1A-1B}$ = 11.7 Hz, $^3J_{1B-2}$ = 5.7 Hz, 1 H, H-1$_B$), 7.19–7.34 (m, 10 H, H_{phenyl}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 20.9, 21.2 (Cb-CH_3), 24.0, 25.1, 25.2, 25.3, 25.4 (Cby-CH_3), 25.8 (C-4), 26.5 (C-3), 45.8 (Cb-CH), 53.7 [(Ph*C*H_2)$_2$N], 56.3 (C-2), 59.5 (60.7) [N*C*(CH$_3$)$_2$CH$_2$], 63.6 (C-1), 64.5 (C-5), 75.9 (76.3) (Cby-CH_2), 94.5 (95.9) [N*C*(CH$_3$)$_2$O], 126.8, 128.0, 128.7 (C_{phenyl}), 139.7 (C_q, C_{phenyl}), 151.9 (152.6) (Cby-NC=O), 155.6 (Cb-NC=O).

MS (ESI): *m*/*z* = 582.4 $[M + H]^+$, 604.4 $[M + Na]^+$.

Anal. Calcd for $C_{34}H_{51}N_3O_5$: C, 70.19; H, 8.84; N, 7.22. Found: C, 69.78; H, 8.81; N, 7.13.

Methylation of Dicarbamates 5; General Procedure B

The carbamate (1.0 equiv) was dissolved in Et_2O (20 mL/mmol) and treated with (–)-sparteine (**13**; 1.4–3.5 equiv). After cooling to –78 °C, *s*-BuLi (1.0–1.3 M in hexane–cyclohexane, 92:8, 1.4–3.5 equiv) was added dropwise. After stirring at –78 °C for 5–7 h, the electrophile (1.6–7.0 equiv) was added. The mixture was warmed over night to r.t., then H_2O (20 mL/mmol) and Et_2O (20 mL/mmol) were added. The aqueous layer was washed with Et_2O (2 × 20 mL/mmol) and the combined organic layers were dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude product was purified by FCC (Et_2O–PE).

(2*S*,5*S*)-2-(*N*,*N*-Dibenzylamino)-5-methylpentane-1,5-diyl Bis(2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate) (12a)

According to general procedure B, the product was formed by the reaction of **5a** (710 mg, 1.16 mmol), (–)-sparteine (**13**; 436 mg, 1.86 mmol, 1.6 equiv), *s*-BuLi (1.60 mL, 1.86 mmol, 1.6 equiv) and MeI (0.12 mL, 1.86 mmol, 1.6 equiv) in Et_2O (10 mL). Aqueous workup and purification by FCC (Et_2O–PE, 1:4) yielded **12a**.

Yield: 577 mg, 0.92 mmol (80%); colourless oil; dr = 97:3; $[\alpha]_D^{20}$ –6.7 (*c* 1.00, $CHCl_3$); R_f = 0.42 (Et_2O–PE, 1:1).

IR (film): 1685, 695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, $^3J_{5-5-CH3}$ = 6.3 Hz, 3 H, 5-CH_3), 1.24–1.65 (m, 24 H, Cby-CH_3), 1.68 (m, 2 H, H-3), 1.83 (m, $^3J_{4-5}$ = 6.0 Hz, 2 H, H-4), 2.88 (m, 1 H, H-2), 3.59, 3.76 [2 × d, $^2J_{gem}$ = 13.5 Hz, 2 × 2 H, (PhCH_2)$_2$N], 4.18 (m, $^2J_{gem}$ = 11.2 Hz, $^3J_{1-2}$ = 5.3 Hz, 1 H, H-1), 4.30 (dd, $^2J_{gem}$ = 11.2 Hz, $^3J_{1-2}$ = 5.3 Hz, 1 H, H-1), 4.86 (tq, $^3J_{5-5-CH3}$ = 6.3 Hz, $^3J_{4-5}$ = 6.0 Hz, 1 H, H-5), 7.15–7.40 (m, 10 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (5-CH_3), 24.6, 25.8, 26.0, 27.1 (Cby-CH_3), 25.1 (C-4), 33.9 (C-3), 54.3 [(Ph*C*H_2)$_2$N], 57.3 (C-2), 59.9, 61.2 [N*C*(CH$_3$)$_2$CH$_2$], 64.1 (C-1), 71.5 (C-5), 76.5, 77.0 (Cby-CH_2), 96.2, 96.5 [N*C*(CH$_3$)$_2$O], 127.3, 128.6, 129.3, 140.2 (C_{phenyl}), 152.7, 153.1 (Cby-NC=O).

Anal. Calcd for $C_{36}H_{53}N_3O_6$: C, 69.31; H, 8.56; N, 6.74. Found: C, 69.27; H, 8.65; N, 6.46.

(2*S*,5*S*)-2-(*N*,*N*-Dibenzylamino)-5-methylpentane-1,5-diyl Bis(*N*,*N*-diisopropylcarbamate) (12b) and (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-methylpentane-1,5-diyl Bis(*N*,*N*-diisopropylcarbamate) (10b)

According to general procedure B, the product was formed by the reaction of **5b** (250 mg, 0.45 mmol), (–)-sparteine (**13**; 148 mg, 0.63 mmol, 1.4 equiv), *s*-BuLi (0.50 mL, 0.63 mmol, 1.4 equiv) and MeI (0.08 mL, 1.35 mmol, 3.0 equiv) in Et_2O (10 mL). Aqueous workup and purification by FCC (Et_2O–PE, 1:4) gave a colourless oil (164 mg, 0.29 mmol, 70%), which was an inseparable mixture of the isomers **12b** and **10b** (14:86).

$[\alpha]_D^{20}$ –0.6 (*c* 0.86, $CHCl_3$); R_f = 0.39 (Et_2O–PE, 1:1).

IR (film): 3086, 3065, 3033, 2969, 2934, 2871, 1697, 1681, 1456, 1436, 747, 699 cm^{-1}.

MS (ESI): *m*/*z* = 568.5 $[M + H]^+$, 590.4 $[M + Na]^+$, 606.5 $[M + K]^+$.

Anal. Calcd for $C_{34}H_{53}N_3O_4$: C, 71.92; H, 9.41; N, 7.40. Found: C, 71.94; H, 9.43; N, 7.38.

Main isomer (**10b**):

^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (2 × d, $^3J_{CbCH-CbCH3}$ = 6.8 Hz, 2 × 12 H, Cb-CH_3), 1.24 (d, 3 H, 1-CH_3), 1.51 (m, $^3J_{4-5B}$ = $^3J_{4-5A}$ = 6.4 Hz, 1 H, H-4$_A$), 1.60 (m, 1 H, H-3$_A$), 1.74 (m, 2 H, H-3$_B$, H-4$_B$), 2.65 (dt, $^3J_{2-3}$ = 6.0 Hz, $^3J_{1-2}$ = 4.8 Hz, 1 H, H-2), 3.61, 3.83 [2 × d, $^2J_{gem}$ = 13.7 Hz, 2 × 2 H, (PhCH_2)$_2$N], 3.90 (m, $^3J_{CbCH-CbCH3}$ = 6.8 Hz, 4 H, Cb-CH), 4.00 (t, $^3J_{4-5A}$ = 6.4 Hz, 1 H, H-5$_A$), 4.01 (t, $^3J_{4-5B}$ = 6.4 Hz, 1 H, H-5$_B$), 5.18 (dq, $^3J_{1-1-CH3}$ = 6.4 Hz, $^3J_{1-2}$ = 4.8 Hz, 1 H, H-1), 7.17–7.35 (m, 10 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (1-CH_3), 21.0 (Cb-CH_3), 22.9 (C-4), 26.9 (C-3), 45.8 (Cb-CH), 54.8 [(Ph*C*H_2)$_2$N], 60.7 (C-2), 64.7 (C-5), 71.0 (C-1), 126.8, 128.0, 128.9 (C_{phenyl}), 140.3 (C_q, C_{phenyl}), 154.4, 155.8 (Cb-NC=O).

Minor isomer (**12b**):

^1H NMR (300 MHz, $CDCl_3$): δ = 2.86 (m, 1 H, H-2), 4.17 (dd, $^2J_{1A-1B}$ = 11.3 Hz, $^3J_{1A-2}$ = 5.4 Hz, 1 H, H-1$_A$), 4.31 (dd, $^3J_{1B-2}$ = 6.3 Hz, $^2J_{1A-1B}$ = 11.3 Hz, 1 H, H-1$_B$), 4.86 (sext, $^3J_{4-5}$ = $^3J_{5-5-CH3}$ = 6.1 Hz, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4 (C-4), 28.3 (C-3), 53.9 [(Ph*C*H_2)$_2$N], 56.8 (C-2), 63.9 (C-1), 71.4 (C-5).

2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylic Acid (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-5-(*N*,*N*-diisopropylcarbamoyloxy)-1-methylpent-1-yl Ester (10c)

According to general procedure B, the product was formed by the reaction of **5c** (240 mg, 0.41 mmol), (–)-sparteine (**13**; 193 mg, 0.83 mmol, 2.0 equiv), *s*-BuLi (0.64 mL, 0.83 mmol, 2.0 equiv) and MeI (0.20 mL, 2.48 mmol, 6.0 equiv) in Et_2O (10 mL). Aqueous workup and purification by FCC (Et_2O–PE, 1:4) yielded **10c**. No other isomers were detected in the ^1H NMR spectrum.

Yield: 209 mg, 0.35 mmol (87%); colourless oil; $[\alpha]_D^{20}$ +0.2 (*c* 1.40, $CHCl_3$); R_f = 0.39 (Et_2O–PE, 1:1).

IR (film): 3086, 3063, 3029, 2972, 2939, 2871, 1695, 1682, 1456, 750, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19, 1.22 (2 × d, $^3J_{CbCH–CbCH3}$ = 6.8 Hz, 12 H, Cb-CH_3), 1.28, 1.30, 1.44, 1.54 (4 × s, 12 H, Cby-CH_3), 1.29 (d, $^3J_{1–1\text{-}CH3}$ = 6.4 Hz, 3 H, 1-CH_3), 1.40–1.59 (m, $^3J_{4–5}$ = 6.7 Hz, 2 H, H-3_A, H-4_B), 1.70–1.80 (m, 2 H, H-3_B, H-4_B), 2.69 (m, 1 H, H-2), 3.65, 3.78 [2 × d, $^2J_{gem}$ = 13.4 Hz, 2 × 2 H, (PhCH_2)$_2$N], 3.69 (s, 2 H, Cby-CH_2), 3.90 (m, $^3J_{CbCH–CbCH3}$ = 6.8 Hz, 2 H, Cb-CH), 4.01 (t, $^3J_{4–5}$ = 6.7 Hz, 2 H, H-5), 5.32 (dq, $^3J_{1–1\text{-}CH3}$ = 6.4 Hz, $^3J_{1–2}$ = 3.9 Hz, 1 H, H-1), 7.17–7.35 (m, 10 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7 (1-CH_3), 20.8 (Cb-CH_3), 23.1, 24.8, 24.9, 25.2, 25.3, 26.2 (Cby-CH_3), 23.4 (C-4), 26.5 (C-3), 45.5 (Cb-CH), 54.2 [(PhCH_2)$_2$N], 59.1 (60.6) [N*C*(CH$_3$)$_2$CH$_2$], 60.2 (C-2), 64.5 (C-5), 69.9 (C-1), 75.8 (76.2) (Cby-CH_2), 94.2 (95.8) [N*C*(CH$_3$)$_2$O], 126.6, 127.8, 128.7 (C_{phenyl}), 139.7 (C_q, C_{phenyl}), 151.2 (151.9) (Cby-NC=O), 155.5 (Cb-NC=O).

MS (ESI): *m*/*z* = 596.5 $[M + H]^+$, 618.5 $[M + Na]^+$.

Anal. Calcd for $C_{35}H_{53}N_3O_5$: C, 70.55; H, 8.97; N, 7.05. Found: C, 70.60; H, 8.98; N, 6.93.

2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylic Acid (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-5-(*N*,*N*-diisopropylcarbamoyloxy)-1-(2-hydroxyethyl)pent-1-yl Ester (14)

5c (1.004 g, 1.73 mmol) and (–)-sparteine (**13**; 0.56 mL, 2.42 mmol, 1.4 equiv) were dissolved in Et_2O (50 mL). The mixture was cooled to –78 °C, *s*-BuLi (1.93 mL, 2.42 mmol, 1.4 equiv) was added dropwise and, after stirring for 7 h, the mixture became dark red-brown. A precooled solution (–78 °C) of ethylene oxide [prepared by condensing ethylene oxide (228 mg, 5.18 mmol, 3.0 equiv) in a flask at –78 °C and dissolving the condensate in Et_2O (5 mL)] was added. After a few minutes BF_3·OEt_2 (0.33 mL, 2.59 mmol, 1.5 equiv) was added rapidly and the mixture became colourless. The mixture was warmed over night to r.t., then H_2O (10 mL) was added, the aqueous layer was washed with Et_2O (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and purified by FCC (*n*-pentane–Et_2O, 1:1→Et_2O) to give **14**.

Yield: 713 mg, 1.14 mmol (66%); colourless resin; $[\alpha]_D^{20}$ +7.7 (*c* 1.44, $CHCl_3$); R_f = 0.43 (Et_2O).

IR (film): 3339, 3086, 3063, 3028, 2974, 2937, 2875, 1690, 1667, 1493, 1453, 750, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.21, 1.22 (2 × d, $^3J_{CbCH–CbCH3}$ = 6.7 Hz, 12 H, Cb-CH_3), 1.24, 1.25, 1.39, 1.42, 1.44, 1.55, 1.59, 1.62 (8 × s, 12 H, Cby-CH_3), 1.45–1.65 (m, $^3J_{4–5}$ = 5.7 Hz, 2 H, H-3_A, H-4_A), 1.74 (m, $^3J_{1'–1''}$ = 5.8 Hz, 2 H, H-4_B, H-$1'_A$), 1.87 (m, 1 H, H-3_B), 1.97 (m, 1 H, H-$1'_B$), 2.76 (m, 1 H, H-2), 3.25 (m, 1 H, OH), 3.43 (t, $^3J_{1'–1''}$ = 5.8 Hz, 1 H, H-$1''_A$), 3.60, 3.85 [2 × d, $^2J_{gem}$ = 13.5 Hz, 2 × 2 H, Ph(CH_2)$_2$N], 3.65 (m, 1 H, H-$1''_B$), 3.70 (m, 2 H, Cby-CH_2), 3.90 (m, $^3J_{CbCH–CbCH3}$ = 6.7 Hz, 2 H, Cb-CH), 4.04 (t, $^3J_{4–5}$ = 5.7 Hz, 2 H, H-5), 5.00 (m, 1 H, minor diastereomer, dr >97:3), 5.39 (dt, $^3J_{1–2}$ = 11.3 Hz, $^3J_{1–1'}$ = 3.0 Hz, 1 H, H-1), 7.19–7.35 (m, 10 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (Cb-CH_3), 21.8 (C-4), 23.9, 24.1, 24.7, 24.9, 25.3, 25.4, 26.3, 26.6 (Cby-CH_3), 26.6 (C-3), 35.5 (C-1′), 45.8 (Cb-CH), 54.6 [(PhCH_2)$_2$N], 58.3 (C-1″), 59.5 (61.2) [N*C*(CH$_3$)$_2$CH$_2$], 59.8 (C-2), 64.6 (C-5), 70.6 (C-1), 75.9 (76.5) (Cby-CH_2), 94.6 (96.3) [N*C*(CH$_3$)$_2$O], 127.0, 128.2, 128.9 (C_{phenyl}), 139.6 (C_q, C_{phenyl}), 152.9 (153.6) (Cby-NC=O), 155.7 (Cb-NC=O).

MS (ESI): *m*/*z* = 626.4 $[M + H]^+$, 648.4 $[M + Na]^+$.

Anal. Calcd for $C_{36}H_{55}N_3O_6$: C, 69.09; H, 8.86; N, 6.71. Found: C, 68.86; H, 9.04; N, 6.59.

Methyl (2*R*,5*S*,6*S*)-5-(*N*,*N*-Dibenzylamino)-2-(*N*,*N*-diisopropylcarbamoyloxy)-8-(methoxycarbonyloxy)-6-(2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyloxy)octanoate (15)

According to general procedure B, the product was formed by the reaction of **14** (152 mg, 0.24 mmol), (–)-sparteine (**13**; 0.20 mL, 0.85 mmol, 3.5 equiv), *s*-BuLi (0.77 mL, 0.85 mmol, 3.5 equiv) and methyl chloroformate (0.13 mL, 1.70 mmol, 7.0 equiv) in Et_2O (10 mL). Aqueous workup and purification by FCC (Et_2O–PE, 1:3→1:1) gave **15** as a regio- and diastereomerically pure colourless resin.

Yield: 102 mg, 0.14 mmol (57%); $[\alpha]_D^{20}$ –18.5 (*c* 1.02, $CHCl_3$); R_f = 0.56 (Et_2O).

IR (film): 3088, 3064, 3029, 2969, 2934, 2872, 1760, 1747, 1691, 1681, 752, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (m, 12 H, Cb-CH_3), 1.27, 1.34, 1.39, 1.42, 1.52, 1.56, 1.57, 1.70 (8 × s, 12 H, Cby-CH_3), 1.48–1.60 (m, 1 H, H-4_A), 1.75 (m, $^3J_{3A–2}$ = 4.8 Hz, 1 H, H-3_A), 1.87 (m, 1 H, H-4_B), 1.91 (m, $^3J_{3B–2}$ = 6.3 Hz, 1 H, H-3_B), 1.95 (m, 1 H, H-7_A), 2.11 (m, 1 H, H-7_B), 2.64 (m, 1 H, H-5), 3.56, 3.87 [2 × d, $^2J_{gem}$ = 13.4, 14.2 Hz, 2 × 2 H, (PhCH_2)$_2$N], 3.64–3.76 (m, 2 H, Cby-CH_2), 3.71 [s, 3 H, O(CO)OCH_3], 3.75 [s, 3 H, CH_2(CO)OCH_3], 4.04 (m, 2 H, Cb-CH), 4.04 (m, 2 H, H-8), 5.03 (dd, $^3J_{3A–2}$ = 4.8 Hz, $^3J_{3B–2}$ = 6.3 Hz, 1 H, H-2), 5.33 (m, 1 H, H-6), 7.19–7.31 (m, 10 H, H_{phenyl}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (Cb-CH_3), 20.5 (C-3), 23.3, 23.9, 24.1, 24.4, 25.3, 25.5, 26.4, 27.6 (Cby-CH_3), 29.0 (C-4), 31.6 (C-7), 45.7, 46.7 (Cb-CH), 51.9 (OCH_3), 54.4 [(PhCH_2)$_2$N], 54.6 (OCH_3), 59.4 (61.0) [N*C*(CH$_3$)$_2$CH$_2$], 60.1 (C-5), 64.2 (C-8), 70.3 (C-6), 72.4 (C-2), 75.9 (76.4) (Cby-CH_2), 94.4 (96.2) [N*C*(CH$_3$)$_2$O], 127.0, 128.2, 129.0 (C_{phenyl}), 139.5 (C_q, C_{phenyl}), 151.1 (152.0) (Cby-NC=O), 154.7 (Cb-NC=O), 155.5 [O(*C*O)OCH$_3$], 171.2 [CH$_2$(*C*O)OCH$_3$].

MS (ESI): *m*/*z* = 742.5 $[M + H]^+$, 764.6 $[M + Na]^+$, 780.5 $[M + K]^+$.

Anal. Calcd for $C_{40}H_{59}N_3O_{10}$: C, 64.76; H, 8.02; N, 5.66. Found: C, 64.71; H, 8.27; N, 5.51.

2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylic Acid (1*S*,2*S*,5*R*)-2-(*N*,*N*-Dibenzylamino)-5-(*N*,*N*-diisopropylcarbamoyloxy)-6-hydroxy-1-(2-hydroxyethyl)hex-1-yl Ester (4c)

To a solution of **15** (399 mg, 0.54 mmol), dissolved in THF (10 mL) and cooled to –78 °C, was added a solution of DIBAL-H (1.0 M in hexane, 3.23 mL, 3.23 mmol, 6.0 equiv). After stirring for 1 h at –78 °C, the mixture was warmed to 0 °C and stirred for 2 h. MeOH (5 mL) and H_2O (3 mL) were added and the mixture was stirred for 1 h at 0 °C, then warmed to r.t. $MgSO_4$ was added and, after filtration, the solvent was removed under vacuum. Purification by FCC (Et_2O–PE, 1:1→Et_2O) gave **4c**.

Yield: 347 mg, 0.53 mmol (98%); colourless resin; dr = 97:3; $[\alpha]_D^{20}$ +16.9 (*c* 0.97, $CHCl_3$); R_f = 0.12 (Et_2O).

IR (film): 3422, 3090, 3066, 3032, 2974, 2940, 2878, 1685, 1670, 1654, 1456, 1438, 750, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.23, 1.24 (2 × d, $^3J_{CbCH–CbCH3}$ = 6.8 Hz, 12 H, Cb-CH_3), 1.38, 1.41, 1.43, 1.54, 1.59 (5 × s, 12 H,

Cby-CH_3), 1.36–1.66 (m, $^3J_{4-5} = {}^3J_{5-6} = 5.3$ Hz, 2 H, H-4), 1.67 (m, 1 H, H-1′$_A$), 1.70 (m, 1 H, H-3$_A$), 1.83 (m, 1 H, H-3$_B$), 1.99 (m, 1 H, H-1′$_B$), 2.70 (m, 1 H, H-2), 3.29 (br s, 2 H, OH), 3.40 (m, 1 H, H-1″$_A$), 3.56, 3.85 [2 × m, 4 H, (PhCH_2)$_2$N], 3.61 (m, 1 H, H-1″$_B$), 3.67 (m, 2 H, H-6), 3.69 (3.71) (s, 2 H, Cby-CH_2), 4.04 (m, $^3J_{CbCH-CbCH3} = 6.8$ Hz, 2 H, Cb-CH), 4.83 (quin, $^3J_{4-5} = {}^3J_{5-6} = 5.3$ Hz, 1 H, H-5), 5.36 (dt, $^3J_{1-2} = 11.1$ Hz, $^3J_{1-1'} = 3.2$ Hz, 1 H, H-1), 7.21–7.34 (m, 10 H, H$_{phenyl}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (C-4), 20.3 (Cb-CH_3), 23.8, 24.0, 24.6, 24.9, 25.3, 25.5, 26.2, 26.5 (Cby-CH_3), 28.6 (C-3), 35.5 (C-1′), 46.4 (Cb-CH), 54.7 [(PhCH_2)$_2$N], 58.3 (C-1″), 59.5 (61.2) [NC(CH$_3$)$_2$CH$_2$], 60.1 (C-2), 65.6 (C-6), 70.7 (C-1), 75.8 (76.4) (Cby-CH_2), 76.8 (C-5), 94.5 (96.3) [NC(CH$_3$)$_2$O], 127.0, 128.3, 128.8 (C$_{phenyl}$), 139.5 (C$_q$, C$_{phenyl}$), 152.9 (153.6) (Cby-NC=O), 156.3 (Cb-NC=O).

MS (ESI): *m*/*z* = 656.6 [M + H]$^+$, 678.6 [M + Na]$^+$, 694.6 [M + K]$^+$.

Anal. Calcd for $C_{37}H_{57}N_3O_7$: C, 67.76; H, 8.76; N, 6.41. Found: C, 67.73; H, 8.77; N, 6.26.

2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylic Acid (1*S*,2*S*,5*R*)-2-(*tert*-Butoxycarbonylamino)-5-(*N*,*N*-diisopropylcarbamoyloxy)-6-hydroxy-1-(2-hydroxyethyl)hex-1-yl Ester (16)

Palladium on activated carbon (10% Pd, 883 mg, 0.83 mmol, 0.4 equiv) was suspended in MeOH (20 mL). A solution of **4c** (1.363 g, 2.08 mmol) in MeOH (10 mL) was added and the flask was cycled between vacuum and H_2 6 times. After stirring for 14 h at r.t. under H_2, the flask was evacuated and filled with H_2 again and the mixture was stirred for a further 5 h at 60 °C. After cooling to r.t., the mixture was filtered through a silica gel packed column and washed with MeOH (40 mL). The solvent was removed under vacuum and the residue was dissolved in MeOH (20 mL). Et_3N (2.04 mL, 14.55 mmol, 7.0 equiv) and a solution of di-*tert*-butyl dicarbonate (1.120 g, 5.20 mmol, 2.5 equiv) in MeOH (10 mL) were added and the mixture was stirred for 3 h at 40 °C, then for 14 h at r.t. Without further workup, the solvent was removed under vacuum and the crude product was purified by FCC (EtOAc) to give **16**.

Yield: 1.101 g, 1.91 mmol (92%); colourless solidified resin; $[\alpha]_D^{20}$ –3.0 (*c* 0.20, $CHCl_3$); R_f = 0.22 (EtOAc).

IR (film): 3429, 2974, 2935, 2874, 1695, 1681, 1478, 1444 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, $^3J_{CbCH-CbCH3} = 6.8$ Hz, 12 H, Cb-CH_3), 1.34, 1.46, 1.49, 1.52 (4 × s, 12 H, Cby-CH_3), 1.39 [s, 9 H, C(CH$_3$)$_3$], 1.38–1.43 (m, 1 H, H-3$_A$), 1.68 (m, 3 H, H-4, H-1′$_A$), 1.83 (m, 1 H, H-3$_B$), 1.87 (m, 1 H, H-1′$_B$), 3.06 (br s, 2 H, OH), 3.48 (m, 1 H, H-1″$_A$), 3.62 (m, 3 H, H-1″$_B$, H-6), 3.71 (s, 2 H, Cby-CH_2), 3.76 (m, 1 H, H-2), 4.00 (m, $^3J_{CbCH-CbCH3} = 6.8$ Hz, 2 H, Cb-CH), 4.53 (m, 1 H, NH), 4.78 (m, 1 H, H-5), 4.99 (m, 1 H, H-1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 21.3 (Cb-CH_3), 23.9, 24.1, 25.3, 25.4, 25.7, 26.7, 26.8, 27.6 (Cby-CH_3), 27.6 (C-4), 28.3 [C(CH_3)$_3$], 29.0 (C-3), 35.1 (C-1′), 45.8 (46.4) (Cb-CH), 53.9 (C-2), 58.3 (C-1″), 59.8 (61.1) [NC(CH$_3$)$_2$CH$_2$], 65.7 (C-5′), 72.7 (C-1), 76.0 (76.2) (Cby-CH_2), 76.4 (C-5), 79.6 [C(CH$_3$)$_3$], 94.7 (96.2) [NC(CH$_3$)$_2$O], 152.4 (153.1) (Cby-NC=O), 155.8 (Cb-NC=O), 156.2 (Boc-NHC=O).

MS (ESI): *m*/*z* = 576.4 [M + H]$^+$, 598.4 [M + Na]$^+$, 1173.7 [2 × M + Na]$^+$.

Anal. Calcd for $C_{28}H_{53}N_3O_9$: C, 58.41; H, 9.28; N, 7.30. Found: C, 58.17; H, 9.37; N, 7.02.

(1*S*,6*R*,8a*S*)-6-(*N*,*N*-Diisopropylcarbamoyloxy)-1,2,3,5,6,7,8,8a-octahydroindolizin-1-yl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (20)

4c (170 mg, 0.26 mmol) and DMAP (48 mg, 0.39 mmol, 1.5 equiv) were dissolved in pyridine (5 mL) and cooled to 0 °C. MsCl (104 mg, 0.77 mmol, 3.0 equiv) was added slowly and the mixture was stirred for 2 h at 0 °C. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the organic layer was washed with aq sat. $CuSO_4$ (2 × 10 mL) and H_2O (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was dissolved in MeOH (10 mL) and added to a suspension of Pd(OH)$_2$/C (20% Pd, 100 mg) in MeOH (15 mL). Et_3N (0.20 mL, 1.30 mmol, 5.0 equiv) was added and the flask was cycled between vacuum and H_2 6 times. After stirring for 14 h at r.t., the flask was evacuated and filled with H_2 again and the mixture was kept for 5 h at 60 °C. After cooling to r.t., the mixture was filtered through a silica gel packed column, which was washed with MeOH (40 mL). The solvent was removed under vacuum and the product was purified by FCC (Et_2O–PE, 1:1→Et_2O) to give **20**.

Yield: 33 mg, 0.08 mmol (29%); colourless solid; mp 93.4 °C; t_R = 20.82 min (HP-5); $[\alpha]_D^{20}$ +10.4 (*c* 0.24, $CHCl_3$); R_f = 0.14 (Et_2O–PE, 1:1).

IR (film): 2978, 2935, 2864, 1699, 1680, 1474, 1439 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, $^3J_{CbCH-CbCH3} = 6.7$ Hz, 12 H, Cb-CH_3), 1.37, 1.39, 1.41, 1.54, 1.56 (5 × s, 12 H, Cby-CH_3), 1.35 (m, 1 H, H-7$_A$), 1.52 (m, 1 H, H-8$_A$), 1.77 (m, 1 H, H-8$_B$), 1.81 (m, $^3J_{2A-3A} = {}^3J_{2A-3B} = {}^3J_{2B-3A} = 8.7$ Hz, 1 H, H-2$_A$), 1.92 (m, $^2J_{5A-5B} = 9.7$ Hz, 1 H, H-5$_A$), 1.93 (m, 1 H, H-8a), 2.06 (q, $^2J_{3A-3B} = 8.7$ Hz, 1 H, H-3$_A$), 2.20 (m, 1 H, H-7$_B$), 2.25 (m, $^3J_{2B-3B} = 2.4$ Hz, 1 H, H-2$_B$), 3.08 (dt, $^2J_{3A-3B} = {}^3J_{2A-3B} = 8.7$ Hz, $^3J_{2B-3B} = 2.4$ Hz, 1 H, H-3$_B$), 3.38 (dd, $^2J_{5A-5B} = 9.7$ Hz, $^3J_{5B-6} = 4.7$ Hz, 1 H, H-5$_B$), 3.72 (s, 2 H, Cby-CH_2), 4.06 (m, $^3J_{CbCH-CbCH3} = 6.7$ Hz, Cb-CH), 4.78 (m, 1 H, H-6), 5.18 (m, 1 H, H-1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (Cb-CH_3), 23.2 (C-8), 24.0, 24.3, 25.1, 25.4, 25.5, 25.5, 26.4, 27.0 (Cby-CH_3), 30.4 (C-7), 31.4 (C-2), 45.7 (Cb-CH), 52.4 (C-3), 57.2 (C-5), 59.9 (60.5) [NC(CH$_3$)$_2$CH$_2$], 67.1 (C-8a), 70.2 (C-6), 74.6 (C-1), 76.0 (76.5) (Cby-CH_2), 95.1 (95.8) [NC(CH$_3$)$_2$O], 151.9 (152.6) (Cby-NC=O), 155.1 (Cb-NC=O).

MS (ESI): *m*/*z* = 440.5 [M + H]$^+$, 462.4 [M + Na]$^+$, 478.4 [M + K]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{41}N_3O_5$: 440.3124 [M + H]$^+$, 462.2944 [M + Na]$^+$; found: 440.3161 [M + H]$^+$, 462.2945 [M + Na]$^+$.

6-(1*S*,6*R*,8a*S*)-1-Hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl *N*,*N*-Diisopropylcarbamate (17)

Variant 1

16 (415 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (20 mL), cooled to –20 °C and Et_3N (0.48 mL, 3.17 mmol, 4.4 equiv) followed by MsCl (0.22 mL, 2.88 mmol, 4.0 equiv) were added slowly. After 14 h at –20 °C, the solution was treated with CH_2Cl_2 (10 mL) and aq HCl (1 N, 10 mL). The organic layer was washed with H_2O (10 mL), sat. aq brine (10 mL) and dried with $MgSO_4$. After filtration, the solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (20 mL). TFA (3.33 mL, 43.0 mmol, 60.0 equiv) was added and the solution was stirred for 14 h at r.t. The solvent was removed under vacuum and the residue was dissolved in MeOH (20 mL) and treated with K_2CO_3 (2.97 g, 21.5 mmol, 30.0 equiv, pH >10). The mixture was heated for 14 h at reflux, then the mixture was allowed to come to r.t., filtered and the solvent was removed under vacuum. Purification by FCC (CH_2Cl_2–MeOH, 20:1→10:1) gave **17**.

Yield: 121 mg, 0.43 mmol (59%); colourless solid.

Variant 2

20 (142 mg, 0.32 mmol) was dissolved in a mixture of THF (5 mL), MeOH (3 mL) and aq HCl (5 N, 5 mL). After 14 h reflux, the mixture was cooled to r.t. and aq NaOH (5 N) was added until pH >10. Additional aq NaOH (5 N, 1 mL) was added and the mixture was

heated again for 14 h at reflux. The solvent was removed under vacuum and the residue was treated with Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was washed with Et_2O (2 × 5 mL) and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and purified by FCC (CH_2Cl_2–MeOH, 20:1→10:1) to give **17**.

Yield: 85 mg, 0.30 mmol (93%); colourless solid; mp 104.4 °C; $[\alpha]_D^{20}$ +39.8 (*c* 1.04, $CHCl_3$); R_f = 0.35 (CH_2Cl_2–MeOH, 10:1).

IR (film): 3419, 3187, 2972, 2956, 2938, 2804, 1690, 1478, 1443 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.19 (d, $^3J_{CbCH–CbCH3}$ = 6.8 Hz, 12 H, Cb-CH_3), 1.38 (m, 1 H, H-7_{ax}), 1.70 (m, 1 H, H-8_A), 1.76 (m, $^3J_{2A–3A} = {}^3J_{2A–3B} = {}^3J_{2B–3A}$ = 9.1 Hz, 1 H, H-2_A), 1.79 (m, 1 H, H-8_B), 1.84 (m, 1 H, H-8a), 1.97 (t, $^2J_{5ax–5eq}$ = 9.7 Hz, $^3J_{5ax–6ax} = {}^3J_{6ax–7ax}$ = 10.4 Hz, 1 H, H-5_{ax}), 2.11 (q, $^2J_{3A–3B}$ = 9.1 Hz, 1 H, H-3_A), 2.21 (m, $^3J_{2B–3B}$ = 2.5 Hz, 1 H, H-2_B), 2.23 (m, 1 H, H-7_{eq}), 2.41 (br s, 1 H, OH), 3.13 (dt, $^3J_{2A–3B}$ = 9.1 Hz, $^3J_{2B–3B}$ = 2.5 Hz, 1 H, H-3_B), 3.41 (ddd, $^3J_{5eq–6ax} = {}^3J_{6ax–7eq}$ = 4.6 Hz, $^4J_{5eq–7eq}$ = 1.4 Hz, 1 H, H-5_{eq}), 3.67, 4.06 (2 × m, $^3J_{CbCH–CbCH3}$ = 6.8 Hz, 2 H, Cb-CH), 4.07 (m, 1 H, H-1), 4.80 (tt, $^3J_{6ax–7A}$ = 10.3 Hz, $^3J_{5ax–6ax} = {}^3J_{6ax–7ax}$ = 10.4 Hz, $^3J_{5eq–6ax} = {}^3J_{6ax–7eq}$ = 4.6 Hz, 1 H, H-6_{ax}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (Cb-CH_3), 22.5 (C-8), 30.0 (C-7), 33.9 (C-2), 45.7 (Cb-CH), 51.9 (C-3), 56.9 (C-5), 67.8 (C-8a), 70.0 (C-6), 72.2 (C-1), 155.1 (Cb-NC=O).

MS (ESI): *m*/*z* = 285.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{28}N_2O_3$: 285.2178; found: 285.2200.

(1*S*,6*R*,8a*S*)-1-Trityloxy-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl *N*,*N*-Diisopropylcarbamate (21)

17 (130 mg, 0.46 mmol) and triphenylmethyl chloride (3.80 g, 13.7 mmol, 30.0 equiv) were dissolved in CH_2Cl_2 (10 mL), treated with DBU (2.73 mL, 18.3 mmol, 40.0 equiv) and stirred at r.t. for 48 h. CH_2Cl_2 (20 mL) and H_2O (10 mL) were added, the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was purified by FCC (Et_2O–PE, 1:2→1:1) to give **21**.

Yield: 173 mg, 0.33 mmol (73%); colourless resin; t_R = 30.59 min (HP-5); $[\alpha]_D^{20}$ –3.8 (*c* 0.49, $CHCl_3$); R_f = 0.18 (*n*-pentane–Et_2O, 1:1).

IR (film): 3087, 3059, 3032, 2967, 2936, 2867, 1684, 1490, 1477, 1444, 755, 704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17, 1.18 (2 × d, $^3J_{CbCH–CbCH3}$ = 6.6 Hz, 12 H, Cb-CH_3), 1.25–1.33 (m, $^3J_{2A–3B}$ = 9.0 Hz, 2 H, H-2_A, H-7_A), 1.39 (m, 1 H, H-8_A), 1.59 (m, 1 H, H-8a), 1.85–2.00 (m, $^2J_{3A–3B}$ = 9.0 Hz, $^2J_{5A–5B}$ = 10.4 Hz, $^3J_{5A–6} = {}^3J_{6–7A}$ = 10.7 Hz, 4 H, H-2_B, H-3_A, H-5_A, H-8_B), 2.23 (m, 1 H, H-7_B), 2.86 (dt, $^2J_{3A–3B} = {}^3J_{2A–3B}$ = 9.0 Hz, $^4J_{3B–5B}$ = 0.9 Hz, 1 H, H-3_B), 3.30 (ddd, $^2J_{5A–5B}$ = 10.4 Hz, $^3J_{5B–6} = {}^3J_{6–7B}$ = 4.6 Hz, $^4J_{3B–5B}$ = 0.9 Hz, 1 H, H-5_B), 3.62, 4.12 (2 × m, $^3J_{CbCH–CbCH3}$ = 6.6 Hz, 2 H, Cb-CH), 4.21 (m, 1 H, H-1), 4.89 (tt, $^3J_{5A–6} = {}^3J_{6–7A}$ = 10.7 Hz, $^3J_{5B–6} = {}^3J_{6–7B}$ = 4.6 Hz, 1 H, H-6), 7.20–7.48 (m, 15 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (Cb-CH_3), 23.4 (C-8), 30.6 (C-7), 32.4 (C-2), 45.0 (46.4) (Cb-CH), 51.5 (C-3), 56.2 (C-5), 66.4 (C-8a), 68.9 (C-6), 74.2 (C-1), 86.9 (*C*Ph_3), 126.9, 127.7, 129.1 (C_{phenyl}), 145.0 (C_q, C_{phenyl}), 155.2 (Cb-NC=O).

MS (ESI): *m*/*z* = 243.1 $[CPh_3]^+$, 527.3 $[M + H]^+$, 549.3 $[M + Na]^+$, 1053.6 $[2 × M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{42}N_2O_3$: 527.3268; found: 527.3231.

(1*S*,6*R*,8a*S*)-1-Trityloxy-1,2,3,5,6,7,8,8a-octahydroindolizin-6-ol (22)

21 (142 mg, 0.27 mmol) was dissolved in THF (10 mL) and cooled to –78 °C. DIBAL-H (1.0 M in hexane, 5.39 mL, 5.39 mmol, 20.0 equiv) was slowly added and the solution was stirred for 2 h at –78 °C, then allowed to come to r.t. and stirred for 14 h. THF (10 mL) and MeOH (2 mL) were added, stirring was continued for 1 h, then H_2O (1 mL) was added and the mixture was stirred for a further 1 h. The mixture was dried over Na_2SO_4 and, after filtration, the solvent was removed under vacuum. Purification by FCC (CH_2Cl_2–MeOH, 20:1→10:1) gave **22**.

Yield: 100 mg, 0.25 mmol (93%); colourless resin; $[\alpha]_D^{20}$ +3.3 (*c* 0.69, $CHCl_3$); R_f = 0.18 (CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3430, 3150, 3057, 3019, 2943, 2849, 2784, 1490, 1449, 746, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.25 (m, $^3J_{2A–3B}$ = 8.8 Hz, 2 H, H-2_A, H-7_A), 1.38 (m, 1 H, H-8_A), 1.64 (m, 1 H, H-8a), 1.80–1.90 (m, $^2J_{3A–3B}$ = 8.8 Hz, $^2J_{5A–5B}$ = 10.4 Hz, $^3J_{5A–6} = {}^3J_{6–7A}$ = 10.4 Hz, 4 H, H-2_B, H-3_A, H-5_A, OH), 1.97 (m, 1 H, H-8_B), 2.15 (m, 1 H, H-7_B), 2.82 (t, $^2J_{3A–3B} = {}^3J_{2A–3B}$ = 8.8 Hz, 1 H, H-3_B), 3.26 (dd, $^3J_{5B–6} = {}^3J_{6–7B}$ = 4.6 Hz, 1 H, H-5_B), 3.90 (tt, $^3J_{5A–6} = {}^3J_{6–7A}$ = 10.4 Hz, $^3J_{5B–6} = {}^3J_{6–7B}$ = 4.6 Hz, 1 H, H-6), 4.23 (m, 1 H, H-1), 7.21–7.48 (m, 15 H, H_{phenyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7 (C-8), 32.8 (C-7), 33.7 (C-2), 52.2 (C-3), 59.8 (C-5), 66.7 (C-6), 67.2 (C-8a), 73.9 (C-1), 87.0 (*C*Ph_3), 127.0, 127.7, 129.2 (C_{phenyl}), 144.9 (C_q, C_{phenyl}).

MS (ESI): *m*/*z* = 243.1 $[CPh_3]^+$, 400.2 $[M + H]^+$, 422.2 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{29}NO_2$: 400.2271 $[M + H]^+$, 422.2079 $[M + Na]^+$; found: 400.2254 $[M + H]^+$, 422.2091 $[M + Na]^+$.

(1*S*,8a*S*)-1-Trityloxy-1,2,3,5,6,7,8,8a-octahydroindolizin-6-one (23)

Oxalyl chloride (0.13 mL, 1.57 mmol, 7.2 equiv) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C. DMSO (0.23 mL, 3.14 mmol, 14.4 equiv) was added slowly and the mixture was stirred for 30 min. A solution of **22** (87 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added slowly (generation of gas was observed). After 5 h at –78 °C, Et_3N (0.89 mL, 6.53 mmol, 30.0 equiv) was added and stirring was continued for 1 h at –78 °C, then at r.t. for 1 h. H_2O (10 mL) and CH_2Cl_2 (10 mL) were added, the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the product was purified by FCC (*n*-pentane–Et_2O, 1:1→Et_2O) to give **23**.

Yield: 72 mg, 0.18 mmol (83%); colourless resin; $[\alpha]_D^{20}$ –40.6 (*c* 0.69, $CHCl_3$); R_f = 0.38 (Et_2O).

IR (KBr): 3150, 3057, 3033, 2979, 2935, 2777, 1715, 1490, 1447, 750, 707 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.46 (m, $^3J_{2A–3A} = {}^3J_{2B–3A}$ = 8.6 Hz, $^3J_{2A–3B} = {}^3J_{2B–3B}$ = 2.9 Hz, 1 H, H-2_A), 1.56 (m, 1 H, H-2_B), 1.77 (m, 1 H, H-8_A), 2.06 (q, $^2J_{3A–3B}$ = 8.6 Hz, 1 H, H-3_A), 2.24 (m, 1 H, H-8_B), 2.25 (m, 1 H, H-7_A), 2.33 (m, 1 H, H-8a), 2.53 (m, 1 H, H-7_B), 2.83 (dt, $^2J_{3A–3B}$ = 8.6 Hz, $^3J_{2A–3B} = {}^3J_{2B–3B}$ = 2.9 Hz, 1 H, H-3_B), 2.85 (d, $^2J_{5A–5B}$ = 15.1 Hz, 1 H, H-5_A), 3.35 (dd, $^2J_{5A–5B}$ = 15.1 Hz, $^4J_{5B–7B}$ = 1.7 Hz, 1 H, H-5_B), 4.33 (dt, $^3J_{1–2A} = {}^3J_{1–8a}$ = 5.6 Hz, $^3J_{1–2B}$ = 8.0 Hz, 1 H, H-1), 7.22–7.48 (m, 15 H, H_{phenyl}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.9 (C-8), 32.4 (C-2), 38.4 (C-7), 51.7 (C-3), 62.6 (C-5), 64.1 (C-8a), 74.0 (C-1), 87.2 (*C*Ph_3), 127.1, 127.8, 129.0 (C_{phenyl}), 144.7 (C_q, C_{phenyl}), 208.1 (C-6).

MS (ESI): *m*/*z* = 243.1 $[CPh_3]^+$, 398.2 $[M + H]^+$, 420.2 $[M + Na]^+$, 430.2 [M + MeOH + H]$^+$, 452.2 [M + MeOH + Na]$^+$.

HRMS (ESI): *m/z* calcd for $C_{27}H_{27}NO_2$: 398.2099 [M + H]$^+$, 420.1916 [M + Na]$^+$, 430.2353 [M + MeOH + H]$^+$, 452.2172 [M + MeOH + Na]$^+$; found: 398.2115 [M + H]$^+$, 420.1916 [M + Na]$^+$, 430.2377 [M + MeOH + H]$^+$, 452.2196 [M + MeOH + Na]$^+$.

(1*S*,8a*S*)-6-Hydroxyimino-1-trityloxy-1,2,3,5,6,7,8,8a-octahydroindolizin (24)

23 (58 mg, 0.15 mmol) and hydroxylamine hydrochloride (42 mg, 0.60 mmol, 4 equiv) were dissolved in EtOH (6 mL) and pyridine (2 mL). The mixture was kept for 4 h at 80 °C and then at r.t. for 16 h. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (20 mL) and treated with sat. aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL), the combined organic layers were dried over $MgSO_4$ and, after filtration, the solvent was removed under vacuum. Purification by FCC (*n*-pentane–Et_2O, 1:1→Et_2O) gave (*E*)-**24** and (*Z*)-**24**.

(*E*)-24

Yield: 14 mg, 0.03 mmol (23%); colourless resin; $[\alpha]_D^{20}$ –30.1 (*c* 0.41, $CHCl_3$); R_f = 0.30 (Et_2O).

IR (film): 3169, 3088, 3055, 3030, 2955, 2920, 2840, 1490, 1448, 758, 706 cm^{-1}.

MS (ESI): *m/z* = 243 [CPh_3]$^+$, 413 [M + H]$^+$.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{27}H_{28}N_2O_2$: 413.2224; found: 413.2197.

(*Z*)-24

Yield: 43 mg, 0.10 mmol (72%); colourless resin; $[\alpha]_D^{20}$ –7.2 (*c* 1.13, $CHCl_3$); R_f = 0.11 (Et_2O).

IR (film): 3170, 3087, 3056, 3031, 2952, 2921, 2841, 1490, 1448, 752, 706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (m, $^3J_{2A–3B}$ = 9.1 Hz, 1 H, H-2_A), 1.59 (m, $^3J_{2B–3B}$ = 3.7 Hz, 1 H, H-2_B), 1.68 (m, 2 H, H-7_A, H-8_A), 1.92 (m, 1 H, H-8_B), 2.17 (m, $^2J_{3A–3B}$ = 9.1 Hz, 1 H, H-3_A), 2.24 (m, 1 H, H-8a), 2.86 (dt, $^2J_{3A–3B}$ = $^3J_{2A–3B}$ = 9.1 Hz, $^3J_{2B–3B}$ = 3.7 Hz, 1 H, H-3_B), 2.93 (m, $^2J_{5A–5B}$ = 11.3 Hz, 1 H, H-5_A), 3.40 (d, $^2J_{5A–5B}$ = 11.3 Hz, 1 H, H-5_B), 3.41 (m, 1 H, H-7_B), 4.32 (m, 1 H, H-1), 7.24–7.48 (m, 15 H, H_{phenyl}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 (C-8), 22.7 (C-7), 31.5 (C-2), 49.9 (C-3), 54.3 (C-5), 64.5 (C-8a), 74.3 (C-1), 87.1 (*C*Ph_3), 127.0, 127.8, 129.0, 144.8 (C_{phenyl}), 155.4 (C-6).

MS (ESI): *m/z* = 413.4 [M + H]$^+$, 435.3 [M + Na]$^+$.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{27}H_{28}N_2O_2$: 413.2224; found: 413.2240.

(1*S*,6*S*,8a*S*)-1-Acetoxy-6-(*N*-acetylamino)-1,2,3,5,6,7,8,8a-octahydroindolizin (2)

24 (*E*/*Z*-mixture, 16 mg, 0.039 mmol) and platinum(IV) oxide (10 mg, 0.04 mmol, 1.0 equiv) were added to a mixture of EtOH (4 mL) and concd HCl (0.3 mL). The flask was cycled between vacuum and H_2 6 times and, after stirring for 14 h under H_2, the mixture was filtered, the solvent was removed under vacuum and the residue was dissolved in pyridine (5 mL). Ac_2O (2 mL) was added and the mixture was stirred at r.t. for 2 h. The solvent was removed under vacuum and the residue was purified by FCC (CH_2Cl_2–MeOH, 20:1→10:1) to give **2**.

Yield: 8 mg, 0.033 mmol (86%); colourless solid; mp 140 °C; $[\alpha]_D^{20}$ –18.0 (*c* 0.40, CH_2Cl_2); R_f = 0.38 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$):[14] δ = 1.39–1.46 (m, 1 H, H-7_{ax}), 1.47–1.56 (m, $^3J_{8ax–8a}$ = 11.1 Hz, 1 H, H-8_{ax}), 1.56–1.61 (m, $^3J_{8eq–8a}$ = 2.8 Hz, 1 H, H-8_{eq}), 1.75 (dtd, $^2J_{2A–2B}$ = 14.4 Hz, $^3J_{2A–3A}$ = $^3J_{2A–3B}$ = $^3J_{2B–3A}$ = 9.1 Hz, 1 H, H-2_A), 1.86 (ddd, $^3J_{1–8a}$ = 4.9 Hz, $^3J_{8ax–8a}$ = 11.1 Hz, $^3J_{8eq–8a}$ = 2.8 Hz, 1 H, H-8a), 1.89–1.94 (m, 1 H, H-7_{eq}), 1.98 [s, 3 H, NH(CO)CH_3], 2.00 (q, $^2J_{3A–3B}$ = 9.1 Hz, 1 H, H-3_A), 2.07 [s, 3 H, O(CO)CH_3], 2.15 (dd, $^2J_{5ax–5eq}$ = 11.4 Hz, $^3J_{5eq–6}$ = 2.6 Hz, 1 H, H-5_{eq}), 2.28 (dddd, $^2J_{2A–2B}$ = 14.4 Hz, $^3J_{2B–3A}$ = 9.1 Hz, $^3J_{1–2B}$ = 8.5 Hz, $^3J_{2B–3B}$ = 1.8 Hz, 1 H, H-2_B), 3.00 (ddd, $^2J_{5ax–5eq}$ = 11.4 Hz, $^3J_{5ax–6}$ = $^3J_{5eq–6}$ = $^3J_{6–7ax}$ = $^3J_{6–7eq}$ = 2.6 Hz, $^4J_{5ax–7}$ = 1.7 Hz, 1 H, H-5_{ax}), 3.06 (td, $^2J_{3A–3B}$ = $^3J_{2A–3B}$ = 9.1 Hz, $^3J_{2B–3B}$ = 1.8 Hz, 1 H, H-3_B), 4.16 (dq, $^3J_{5ax–6}$ = $^3J_{5eq–6}$ = $^3J_{6–7ax}$ = $^3J_{6–7eq}$ = 2.6 Hz, 1 H, H-6), 5.22 (ddd, $^3J_{1–2A}$ = 2.5 Hz, $^3J_{1–2B}$ = 8.5 Hz, $^3J_{1–8a}$ = 4.9 Hz, 1 H, H-1), 6.27 (br d, $^3J_{6–NH}$ = 8.2 Hz, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$):[14] δ = 20.6 (C-8), 21.1 [O(CO)*C*H_3], 23.5 [NH(CO)*C*H_3], 28.2 (C-7), 30.6 (C-2), 43.9 (C-6), 53.0 (C-3), 57.5 (C-5), 67.3 (C-8a), 74.8 (C-1), 169.1 [NH(*C*O)CH_3], 170.7 [O(*C*O)CH_3].

MS (ESI): *m/z* = 241.15 [M + H]$^+$, 263.15 [M + Na]$^+$.

HRMS (ESI): *m/z* calcd for $C_{12}H_{30}N_2O_3$: 241.1574 [M + H]$^+$, 263.1366 [M + Na]$^+$; found: 241.1515 [M + H]$^+$, 263.1333 [M + Na]$^+$.

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