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Synthesis and Glycosidase Inhibitory Study of New Polyhydroxylated Indolizidines

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The synthesis of two polyhydroxylated indolizidines as potenticial glycosidase inhibitors is reported. The piperidine ring was formed by an intramolecular Mannich-type reaction between ethyl *trans*-4-oxo-2-butenoate and the two β-amino ketones (–)-1-(2-methyl-1,3-dioxan-2-yl)propan-2-amine and (+)-1-(benzyloxymethyl)-2-(2-methyl-1,3-dioxan-2-yl)ethylamine. The synthesis of this amine was performed in eight steps from L-aspartic acid. The key steps of the formation of the framework involved dihydroxylation, nucleophilic substitution, and reduction. The last hydroxy group was introduced by hydrolysis of the acetal moiety followed by reduction of the resulting ketone. The inhibitory properties of the two synthesized indolizidines were evaluated against a variety of commercial glycosidases.

Introduction

During the last decade, glycosidase inhibitors have been extensively studied for their biological and therapeutic applications. Glycosidases represent a class of enzymes involved in a wide range of biological events such as intestinal digestion, post-translational processing of glycoproteins, and lysosomal catabolism of glycoconjugates. For this reason, glycosidase inhibitors have been widely investigated as drug candidates to treat a variety of diseases such as diabetes, viral infections including HIV, cancer metastasis, hepatitis, and Gaucher's disease.[1] Most glycosidase inhibitors are sugar mimics characterized by a polyhydroxylated structure containing an endocyclic nitrogen, namely polyhydroxylated piperidine, pyrrolidine, pyrrolizidine, or nortropane alkaloids. The glycosidase inhibition activity of these compounds is related to their structural analogy to the natural sugar. Under physiological pH, these heterocyles are presumed to be partially protonated in the active site of the enzyme, mimicking the positively charged oxygen of the transition state of the glucoside during its enzymatic hydrolysis.[2]

In the past forty years, more than 100 polyhydroxylated alkaloids have been isolated from plants and microorganisms.[3] Among these alkaloids, representative examples are deoxynojirimycin, swainsonine, castanospermine, and lentiginosine (Figure 1). These alkaloids have been described as potent inhibitors of various glycosidases.[4]

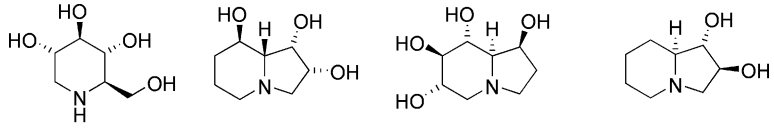

Figure 1. Examples of glycosidase inhibitors.

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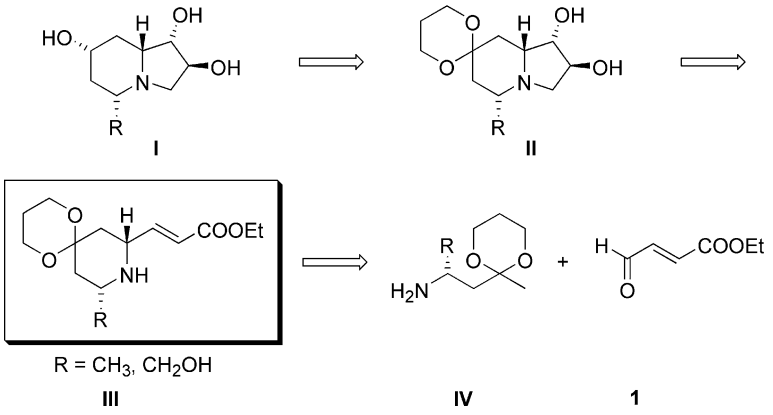
Due to the wide range of biological activities of polyhydroxylated alkaloids and their scarcity in natural sources, many stereoselective syntheses of natural and unnatural analogues have already been described.[5] The synthesis of stereoisomeric analogues of these natural compounds is of considerable interest since it could open the way to structure-activity relationship (SAR) studies. Among them, the syntheses of swainsonine, castanospermine, and bicyclic an-



Scheme 1. Retrosynthetic strategy.

alogues have been rigorously studied. The majority of these known syntheses are based on one-directional strategies with carbohydrates as starting materials,[6] although asymmetric synthesis through non carbohydrate substrates is becoming popular.[7] In this context, a new versatile synthetic strategy that could lead to polyhydroxylated indolizidines would be highly useful for further SAR studies and drug discovery.

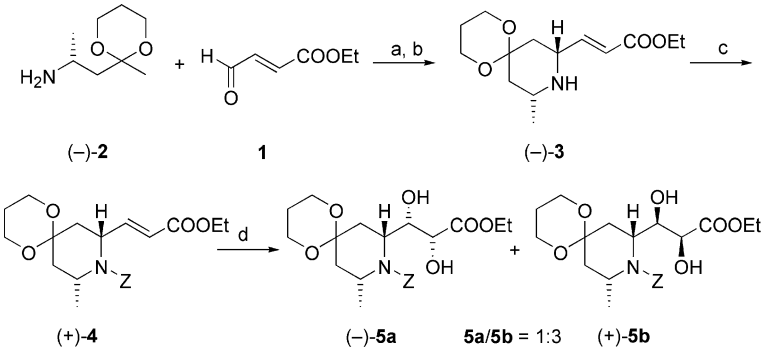
We report herein the synthesis of new trihydroxylated indolizidines with the methodology developed within our group to synthesize polysubstituted piperidines. This method, based on an intramolecular Mannich-type reaction between an aldehyde and an enantiopure β-amino ketone, allows for the formation of optically pure *cis*-2,6-disubstituted piperidines[8] and has been applied to the synthesis of several natural products.[9]

We focused our attention on the synthesis of polyhydroxylated indolizidines of type **I** substituted on the piperidine ring (Scheme 1). These indolizidines could be obtained from indolizidines of type **II** by cleavage of the acetal moiety and stereoselective reduction of the resulting carbonyl group. Compounds of type **II** could be isolated from the diastereoselective dihydroxylation of a key intermediate of type **III**, followed by cyclization on the ester moiety and subsequent reduction of the amide group. Finally, compounds of type **III** could be prepared through an intramolecular Mannich-type reaction between the β-amino ketones of type **IV** and the commercially available aldehyde **1**.

As several methods have been developed within our group to prepare substituted optically pure β-amino ketones of type **IV**, we envisage the preparation of a wide range of indolizidines of type **I** by simply changing the nature of the R substituent.

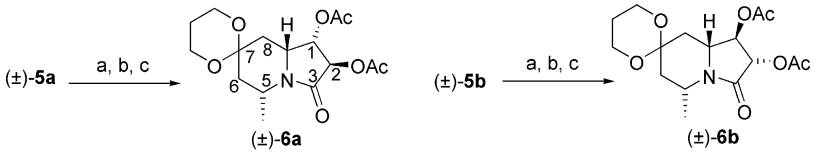
Results and Discussion

We initially checked the validity of the proposed synthetic scheme with chiral amine (–)-**2** (R = Me, Scheme 2), since its preparation in enantiomerically pure form, by resolution of the racemic mixture with tartaric acid, is well known.[10] In a second step, in order to increase the affinity with the receptor, a new hydroxy functionality (R = CH_2OH) was introduced. The key intermediate, (–)-**3**, was obtained by the condensation of amine (–)-**2** with aldehyde **1** under conditions developed by our group to prepare piperidines in good yield (90%) and high diastereoselectivity (*de* > 95%). Herein, only the *cis*-2,6-piperidine was detected in the ^{1}H NMR spectrum. Further protection of the piperidine with a carbamate group under standard conditions furnished the expected compound (+)-**4** in high yield.



Reagents and conditions : (a) CH_2Cl_2, $MgSO_4$, Δ. (b) *p*-TsOH, toluene, Δ (80%).
(c) ZCl, Na_2CO_3 (0.4 M), CH_2Cl_2 (90%). (d) K_2OsO_4, 2 H_2O, NMO, acetone/H_2O (80%).

Scheme 2. Synthesis of diols (–)-**5a** and (+)-**5b**.



Reagents and conditions : (a) H_2, Pd/C, MeOH. (b) DIPEA, toluene. (c) Ac_2O, pyridine, DMAP (66% over 3 steps).

Scheme 3. Synthesis of indolizidinones (±)-**6a** and (±)-**6b**.

We then tried the asymmetric dihydroxylation[11] with AD-mix-α or AD-mix-β, since this sequence had been successfully applied on a very similar model.[12] However, in this case, no reaction was observed, probably due either to the electron-poor double bond or to the high steric hindrance between the catalyst and the bulky protective group of piperidine (+)-**4**. Dihydroxylation was eventually achieved with a catalytic amount of K_2OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as an oxidant[13] and gave a diastereomeric mixture of diols (–)-**5a** and (+)-**5b** in a 1:3 ratio, resulting from the OsO_4 approach to each of the two diastereotopic double-bond faces. At this stage of the synthesis, one crucial point was the determination of the configuration of the stereogenic centres created during the dihydroxylation step.

We checked this relative configuration with a more rigid bicyclic skeleton by NOE experiments. The determination of the relative configuration of the two hydroxy groups was performed on the more accessible racemic compounds. As shown in Scheme 3, hydrogenolysis of carbamates (±)-**5a** and (±)-**5b**, followed by treatment of the resulting piperidines with DIPEA, cleanly afforded the corresponding indolizidinones, and at this stage, the hydroxy groups were converted into the corresponding acetates to furnish the indolizidinones (±)-**6a** and (±)-**6b**, suitable for convenient NMR measurements.

The NOESY ^{1}H spectrum of (±)-**6a** showed a 6% NOE enhancement between H-1′ and H-8a′ (Figure 2), which corresponds to a calculated distance of 2.24 Å, whereas the same analysis conducted with (±)-**6b** showed an effect between H-1′ and H-8′$_{ax}$ (enhancement: 6%; distance 2.24 Å). This is in agreement with the calculated distances (2.36 Å and 2.43 Å, respectively) of the most stable conformations obtained after geometry optimization (MACROMODEL).[14] These experiments allowed us to assign the configuration (1′*SR*,2′*RS*) to isomer (±)-**6a** and (1′*RS*,2′*SR*) configuration to isomer (±)-**6b**.

The synthesis of polyhydroxylated indolizidine (–)-**12** (Scheme 4) was pursued with the major diol (+)-**5b**. Hydrogenolysis of carbamate (+)-**5b** cleanly afforded piperidine (+)-**7**, which was treated with DIPEA to give the corresponding indolizidinone.[15] The lactam carbonyl was directly reduced with $LiAlH_4$, and the alcohols were protected as benzyl ethers to afford the corresponding indolizidine (–)-**9** in 35% yield over three steps. Regeneration of the keto group of (–)-**9** was realized in acidic medium and cleanly afforded indolizidinone (–)-**10** in 69% yield. Stereoselective reduction of the carbonyl group with $NaBH_4$[16]

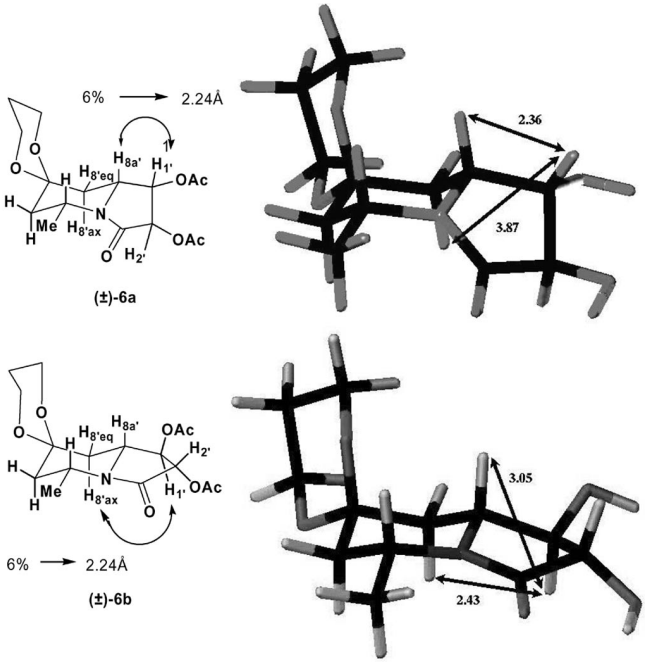
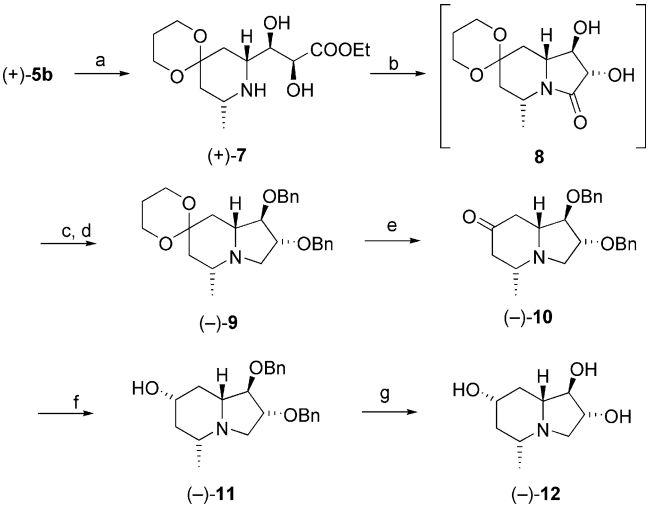


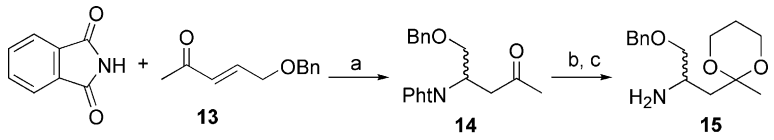
Figure 2. Selected NOE studies and molecular models of compounds (±)-**6a** and (±)-**6b**.



Reagents and conditions : (a) H_2, Pd/C, MeOH, (95%). (b) DIPEA, toluene. (c) $LiAlH_4$, THF, Δ. (d) NaH, THF, BnBr, DMF (35% over 3 steps). (e) TFA aq. 50%, CH_2Cl_2 (69%). (f) $NaBH_4$, MeOH, –10°C (90%). (g) H_2, $PdCl_2$, MeOH (100%).

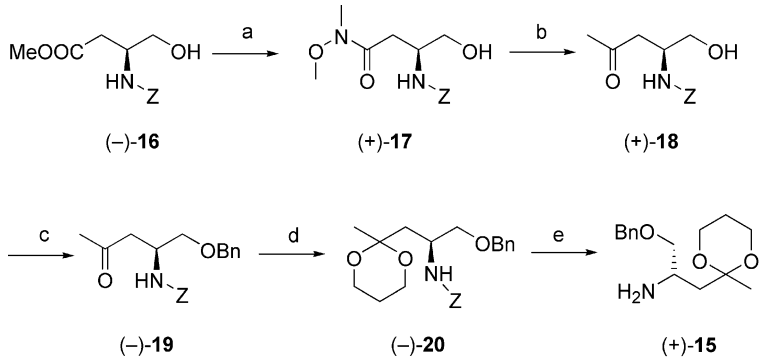
Scheme 4. Synthesis of the indolizidine (–)-**12**.

furnished exclusively equatorial piperidinol (–)-**11** (*de* > 95% from NMR spectra). The stereochemistry of compound (–)-**11** was confirmed by careful examination of the coupling constants between H-7 and H-5$_{ax}$ ($^3J_{H,H}$ = 11.5 Hz) and H-7 and H-6$_{ax}$ ($^3J_{H,H}$ = 11.5 Hz), which were characteristic of *trans* diaxial coupling constants. Finally, hydrogenolysis of the benzyl groups over $PdCl_2$[17] gave target compound (–)-**12** in quantitative yield.



Reagents and conditions : (a) Triton B®, AcOEt, Δ (89%).
(b) 1,3-propanediol, *p*-TsOH, toluene, Δ (90%). (c) NH_2-NH_2·H_2O, MeOH (99%).

Scheme 5. Synthesis of amine **15**.



Reagents and conditions : (a) $AlMe_3$, NH(OMe)Me·HCl, CH_2Cl_2 (70%).
(b) CH_3MgBr, THF, 0°C (50%). (c) Ag_2O, BnBr, CH_2Cl_2 (70%).
(d) 1,3-propanediol, $CH(OCH_3)_3$, *p*-TsOH (70%). (e) H_2, Pd/C, MeOH (100%).

Scheme 6. Synthesis of optically pure amine (+)-**15**.

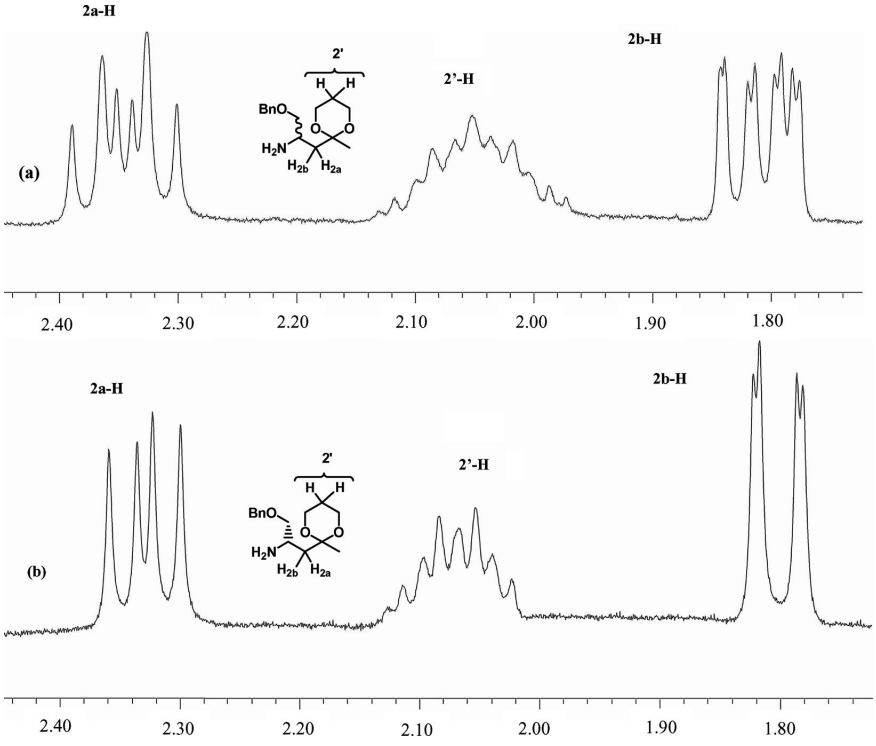


Figure 3. Determination of the optically purity of amine (+)-**15** by NMR spectroscopy with (+)-mandelic acid as a chiral solvating agent. a) racemic mixture, b) enantiomer (+)-**15**.

Since the synthetic route proved to be efficient, we then concentrated our efforts on the synthesis of the hydroxymethyl analogue of (–)-**12**, which required the synthesis of the corresponding amine of type **IV**, in which R is a protected hydroxymethyl group. Therefore, we envisaged the preparation of amine **15** (R = CH_2OBn, Scheme 5), as this benzyl ether should be stable under the conditions used in the synthesis. We hoped to obtain the corresponding optically pure amine **15** by resolution of the racemic mixture, as described for amine (–)-**2**.

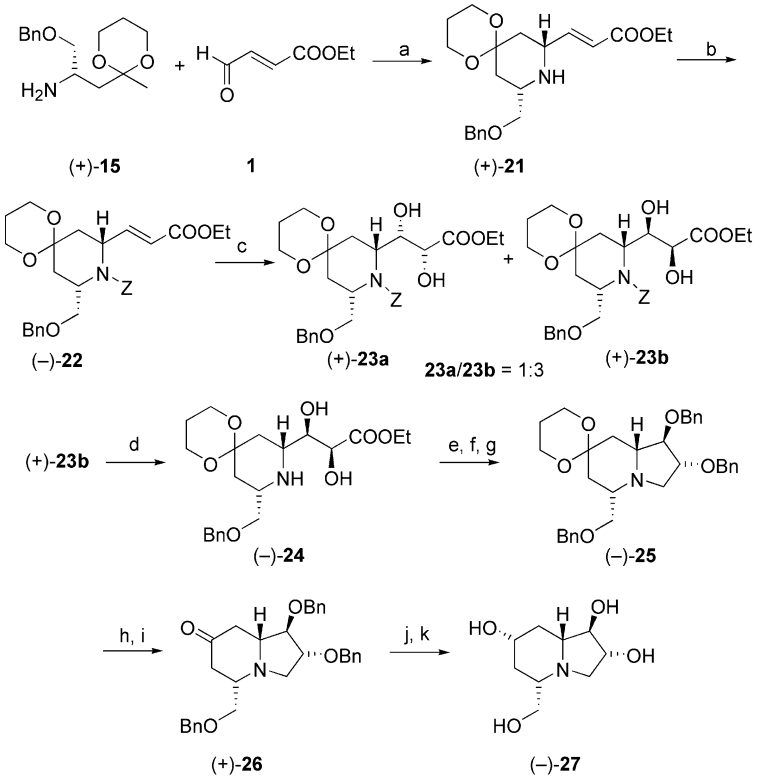
Michael addition of phthalimide to α,β-unsaturated ketone **13**[18] gave the phthalimido ketone **14** in good yield. Protection of the ketone as a dioxane followed by hydrazinolysis of the phthalimide moiety furnished desired amine **15** in excellent yield.

Unfortunately, all attempts at the resolution of the racemic mixture of amine **15** by fractional crystallization with tartaric or dibenzoyl tartaric acid were unsuccessful. Thus, we decided to develop an asymmetric synthesis of amine **15**, starting from the known chiral amino ester (–)-**16**[19] (Scheme 6), readily obtained in three steps from L-aspartic acid.

The transformation of ester (–)-**16** to the corresponding methyl ketone (+)-**18** was performed by the corresponding Weinreb amide[20] (+)-**17** in moderate yield. At this stage of the synthesis, compulsory protection of the alcohol was required to obtain a subsequent efficient protection of the carbonyl group. While standard conditions (NaH, benzyl bromide) did not furnish benzyl ether (–)-**19** in an acceptable yield, treatment of (+)-**18** with Ag_2O and benzyl bromide furnished desired compound (–)-**19** in 70% yield.[21] Acetalation of the carbonyl group of (–)-**19** was then achieved[22] in the presence of trimethyl orthoformate and 1,3-propanediol to give the corresponding acetal (–)-**20**. Finally, selective hydrogenolysis of the benzyl carbamate furnished amine (+)-**15**, which was prepared in 8 steps in 6.3% overall yield starting from L-aspartic acid.

The enantiomeric purity of amine (+)-**15** was checked by ^1H NMR spectroscopy with (+)-mandelic acid as a chiral solvating agent.[23] Comparison of spectra obtained from racemic **15** (Figure 3a) and its (+) isomer (Figure 3b) demonstrated an excellent stereoisomeric ratio (better than 95%, Figure 3), proving that no racemisation had occurred during the synthesis.

With optically pure amine (+)-**15** in hand, the asymmetric synthesis of the indolizidine (–)-**27** (Scheme 7) was achieved with the strategy developed for the synthesis of the indolizidine (–)-**12**. Condensation of amine (+)-**15** with



Reagents and conditions : (a) (1) CH_2Cl_2, $MgSO_4$, Δ ; (2) *p*-TsOH, toluene, Δ (60%).
(b) ZCl, Na_2CO_3 (0.4 M), CH_2Cl_2 (90%). (c) K_2OsO_4, $2H_2O$, NMO, acetone/H_2O (57%).
(d) H_2, Pd/C, MeOH (100%). (e) DBU, toluene. (f) $LiAlH_4$, THF, Δ.
g) NaH, THF, BnBr, DMF (35% over 3 steps).
(h) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (80%). (i) $PhI(TFA)_2$, TFA, CH_3CN/H_2O (50%).
(j) $NaBH_4$, MeOH, –10°C (80%). (k) H_2, $PdCl_2$, MeOH (80%).

Scheme 7. Synthesis of indolizidine (–)-**27**.

aldehyde **1** under the conditions previously described gave the corresponding piperidine (+)-**21**. Protection of the piperidine moiety and dihydroxylation furnished diols (+)-**23a** and (+)-**23b** in a 1:3 ratio.

As for the previous synthesis, the final steps were conducted on the major isomer (+)-**23b**. Cleavage of the carbamate by hydrogenolysis in the presence of palladium on charcoal furnished compound (–)-**24** quantitatively.[24] Treatment of the latter under more basic conditions (DBU instead of DIPEA) led to the cyclization of the resulting amine on the ester. Reduction of the amide with $LiAlH_4$ and conversion of the hydroxy groups into benzyl ethers afforded (–)-**25**. Regeneration of the keto functionality under the conditions previously described did not furnish the desired product but a mixture, in which no identifiable compound was obtained. Thus, the cleavage of the acetal moiety was achieved by a two-step sequence:[25] formation of the corresponding thioacetal, cleanly obtained by transacetalation of (–)-**25** with propanedithiol, followed by hydrolysis of the thioacetal in the presence of [bis(trifluoroacetoxy)-iodo]benzene [$PhI(TFA)_2$] and trifluoroacetic acid. The corresponding indolizidinone (+)-**26** was obtained in 40% overall yield. Stereoselective reduction[16] of the ketone with $NaBH_4$, followed by hydrogenolysis of the benzyl groups over $PdCl_2$[17] gave indolizidine (–)-**27** in excellent yield (Scheme 7).

Following a standard procedure,[26] indolizidines (–)-**12** and (–)-**27**, together with their racemic analogues (±)-**12** and (±)-**27**, were evaluated as inhibitors of six commercially available glycosidases: Baker's yeast α-glucosidase, almond β-glucosidase, green coffee bean α-galactosidase, β-galactosidase from *Aspergillus oryzae*, jack bean α-mannosidase and α-fucosidase from bovine kidney, with the corresponding *p*-nitrophenyl glycopyranoside as a substrate. While compounds **12** and (–)-**12** showed no inhibitory activity against the selected glycosidases, indolizidine **27** selectively inhibited *Aspergillus oryzae* β-galactosidase (K_i = 157 μM), yet (–)-**27** had no activity on the same glycosidase.

Conclusions

In conclusion, we have developed a new versatile and efficient synthetic route to prepare optically pure polyhydroxylated indolizidines, in which we could introduce various substituents on the piperidine moiety. The synthesis is based on an intramolecular Mannich-type reaction, followed by an asymmetric dihydroxylation and cyclization. The evaluation of the inhibitory properties revealed that only racemic indolizidine **27** showed a modest inhibitory activity on *Aspergillus oryzae* β-galactosidase.

Experimental Section

Ethyl (*E*)-3-[(8*R*,10*R*)-10-Methyl-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]acrylate [(–)-3]: To a solution of amine (–)-**2** (2.00 g, 12.6 mmol) in anhydrous dichloromethane (100 mL) were added ethyl *trans*-4-oxo-2-butenoate **1** (1.22 mL, 13.8 mmol) and anhydrous magnesium sulfate. The mixture was refluxed for 2 h under an inert atmosphere and then cooled to room temperature and transferred to a solution of dry *p*-toluenesulfonic acid (4.80 g, 25.2 mmol) in toluene (150 mL). The resulting mixture was stirred at 60 °C for 2 h and then washed with saturated aqueous $NaHCO_3$ (50 mL). The resulting aqueous layer was extracted with dichloromethane (3 × 50 mL), and the combined organic layers were washed with brine (2 × 50 mL), dried, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate and then ethyl acetate/MeOH, 9:1) to give piperidine (–)-**3** (2.71 g, 80%) as a yellow oil. R_f (ethyl acetate/MeOH, 9:1) = 0.54. $[\alpha]_D^{25}$ = –16.7 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3311, 1720, 1656, 1144, 1011 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.91 (dd, $^3J_{H,H}$ = 15.6 Hz, 1 H, H-3), 5.98 (d, $^3J_{H,H}$ = 15 Hz, 1 H, H-2), 4.20 (q, $^3J_{H,H}$ = 7 Hz, 2 H, CH_2 ester), 3.91 (m, 4 H, 2 × OCH_2 dioxane), 3.53 (m, 1 H, H-8′), 2.92 (m, 1 H, H-10′), 2.31 (m, 1 H, H-7′$_{eq}$), 2.21 (m, 1 H, H-11′$_{eq}$), 1.78 (m, 2 H, CH_2 dioxane), 1.27 (t, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3 ester), 1.21 (t, $^3J_{H,H}$ = 12, $^2J_{H,H}$ = 12 Hz, 1 H, H-7′$_{ax}$), 1.13–1.06 (m, 4 H, CH_3, H-11′$_{ax}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5 (C=O), 149.5 (C-3), 120.5 (C-2), 97.1 (C-6′), 60.4 (OCH_2 ester), 59.4, 59.2 (2 × OCH_2 dioxane), 53.8 (C-10′), 47.8 (C-8′), 41.1 (C-11′), 38.2 (C-7′), 25.5 (CH_2 dioxane), 22.3 (CH_3), 14.2 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{14}H_{24}NO_4$ $[M + H]^+$ 270.1705; found 270.1709.

Ethyl (*E*)-3-[(8*R*,10*R*)-9-Benzyloxycarbonyl-10-methyl-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]acrylate [(+)-4]: To a solution of piperidine (–)-**3** (3.38 g, 12.6 mmol) in dichloromethane (400 mL) was added K_2CO_3 (0.4 M solution, 66 mL, 25.2 mmol). The mixture was cooled to 0 °C, and a solution of benzyl chloroformate (2.34 mL, 18.9 mmol) in dichloromethane (50 mL) was added dropwise. The mixture was stirred at room temperature for 24 h, and the resulting aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 1:1) to afford piperidine (+)-**4** (4.57 g, 90%) as a yellow oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.56. $[\alpha]_D^{25}$ = +3.1 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1714, 1698, 1655, 1149 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 5 H, Ph), 7.05 (dd, $^3J_{H,H}$ = 16, 7 Hz, 1 H, H-3), 5.87 (d, $^3J_{H,H}$ = 16 Hz, 1 H, H-2), 5.14 (s, 2 H, CH_2Ph), 4.94 (m, 1 H, H-8′), 4.40 (m, 1 H, H-10′), 4.09 (q, $^3J_{H,H}$ = 7 Hz, 2 H, CH_2 ester), 3.88 (m, 4 H, 2 × OCH_2 dioxane), 2.26 (dt, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-11′$_{eq}$), 2.15 (dt, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-7′$_{eq}$), 1.84 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 7 Hz, 1 H, H-11′$_{ax}$), 1.82 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 7 Hz, 1 H, H-7′$_{ax}$), 1.65 (m, 2 H, CH_2 dioxane), 1.27 (d, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3 ester), 1.20 (t, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (C=O ester), 155.4 (C=O carbamate), 149.2 (C-3), 136.5 (C *ipso*), 128.5, 128.0, 127.9 (C_{ar}), 121.7 (C-2), 96.1 (C-6′), 67.4 (CH_2Ph), 60.3 (CH_2 ester), 59.5 (2 × OCH_2 dioxane), 51.4 (C-10′), 48.8 (C-8′), 35.9 (C-11′), 35.7 (C-7′), 25.2 (CH_2 dioxane), 21.8 (CH_3), 14.2 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{22}H_{29}NO_6Na$ $[M + Na]^+$ 426.1893; found 426.1901.

Benzyl (8*R*,10*R*)-8-[(1*S*,2*R*)-2-Ethoxycarbonyl-1,2-dihydroxyethyl]-10-methyl-1,5-dioxa-9-azaspiro[5.5] undecane-9-carboxylate [(–)-5a] and Benzyl (8*R*,10*R*)-8-[(1*R*,2*S*)-2-Ethoxycarbonyl-1,2-dihydroxyethyl]-10-methyl-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate [(+)-5b]: To a solution of piperidine (+)-**4** (1.0 g, 2.5 mmol) in acetone/water (15:10, 25 mL) were added *N*-methylmorpholine oxide (577 mg, 5 mmol) and $K_2OsO_4 \cdot 2H_2O$ (45 mg, 0.13 mmol). The mixture was stirred at room temperature for 12 h. Solvents were evaporated off, and osmium salts were removed by filtration through a pad of silica gel. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 1:1), to give the two

diastereoisomers, (–)-**5a** (212 mg, 20%) and (+)-**5b** (638 mg, 60%), as pale yellow oils.

(–)-5a: R_f (ethyl acetate) = 0.57. $[a]_D^{25}$ = –9.5 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3478, 1714, 1680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, Ph), 5.15 (s, 2 H, CH_2Ph), 4.69 (m, 1 H, H-8), 4.57 (m, 1 H, H-10), 4.39 (m, 1 H, H-1′), 4.30–4.23 (m, 3 H, CH_2 ester, H-2′), 4.00–3.84 (m, 4 H, 2 × OCH_2 dioxane), 2.32 (m, 1 H, H-11_{eq}), 2.19 (m, 1 H, H-7_{eq}), 1.87 (m, 1 H, CH_2 dioxane), 1.85 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 7.5 Hz, 1 H, H-7_{ax}), 1.77 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 7.5 Hz, 1 H, H-11_{ax}), 1.62 (m, 1 H, CH_2 dioxane), 1.37 (d, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3), 1.29 (t, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3 ester) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.1 (C=O ester), 173.4 (C=O carbamate), 136.5 (C *ipso*), 128.5, 128.1, 127.9 (C_{ar}), 96.2 (C-6), 71.3, 71.1 (C-1′, C-2′), 67.6 (CH_2Ph), 62.1 (CH_2 ester), 59.7 (2 × OCH_2 dioxane), 51.9 (C-10), 46.5 (C-8), 37.1 (C-11), 33.3 (C-7), 25.2 (CH_2 dioxane), 20.7 (CH_3), 14.1 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{22}H_{31}NO_8Na$ [M + Na]$^+$ 460.1947; found 460.1955.

(+)-5b: R_f (ethyl acetate) = 0.52. $[a]_D^{25}$ = +9.5 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3442, 1732, 1690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, Ph), 5.19, 5.14 (2 d, *J* = 12.5 Hz, 2 H, CH_2Ph, AB system), 4.58 (m, 1 H, H-11), 4.33 (m, 1 H, H-1′), 4.24 (m, 3 H, H-2′, CH_2 ester), 3.95 (m, 4 H, 2 × OCH_2 dioxane), 3.03 (m, 1 H, H-11_{eq}), 2.02 (d, $^2J_{H,H}$ = 14 Hz, 1 H, H-7_{eq}), 1.81 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 7.5 Hz, 1 H, H-7_{ax}), 1.61 (m, 3 H, H-11_{ax}, CH_2 dioxane), 1.29 (d, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3), 1.27 (t, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3 ester) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4 (C=O ester), 169.5 (C=O carbamate), 135.9 (C *ipso*), 128.6, 128.4, 128.0 (C_{ar}), 96.2 (C-6), 72.4, 69.9 (C-1′, C-2′), 68.2 (CH_2Ph), 61.3 (CH_2 ester), 59.7, 59.6 (2 × OCH_2 dioxane), 52.6 (C-10), 46.7 (C-8), 41.3 (C-11), 37.1 (C-7), 25.2 (CH_2 dioxane), 21.3 (CH_3), 14.1 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{22}H_{31}NO_8Na$ [M + Na]$^+$ 460.1947; found 460.1951.

(1′*SR*,2′*RS*,5′*RS*,8a′*RS*)-5′-Methyl-3′-oxohexahydro-1′*H*-spiro-[1,3-dioxane-2,7′-indolizine]-1′,2′-diyl Diacetate [(±)-6a] and (1′*RS*,2′*SR*,5′*SR*,8a′*SR*)-5′-Methyl-3′-oxohexahydro-1′*H*-spiro-[1,3-dioxane-2,7′-indolizine]-1′,2′-diyl Diacetate [(±)-6b]: A solution of piperidine (±)-**5a** (290 mg, 0.66 mmol) in methanol (10 mL) containing 10% Pd/C (66 mg) was stirred under hydrogen for 2 h. The catalyst was filtered off, and the filtrate was concentrated to afford the diol (190 mg, 95%) as a pale yellow oil. R_f (ethyl acetate/MeOH, 5:1) = 0.2. To a solution of the diol (80 mg, 0.27 mmol) in anhydrous toluene (10 mL) was added DIPEA (128 μL, 0.66 mmol). The mixture was refluxed for 12 h. Evaporation of the solvents gave the indolizidinone as a pale yellow oil. The crude product was directly engaged in the next step. R_f (ethyl acetate/MeOH, 9:1) = 0.36. To a solution of the previously prepared piperidine (15.0 mg, 0.06 mmol) in anhydrous pyridine (85 μL, 1.05 mmol) were added acetic anhydride (100 μL, 1.05 mmol, 18 equiv.) and a crystal of DMAP. The mixture was stirred at room temperature under an inert atmosphere for 12 h. Solvents were removed under reduced pressure, and the majority of the pyridine was eliminated by the addition and evaporation of toluene. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 1:1) to give (±)-**6a** (14.3 mg, 70%) as a colourless oil. R_f (ethyl acetate/MeOH, 9:1) = 0.75. ^1H NMR (400 MHz, C_6D_6): δ = 5.57 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, H-2′), 5.36 (dd, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 5.5 Hz, 1 H, H-1′), 3.78 (m, 1 H, H-8′a), 3.36 (m, 4 H, 2 × OCH_2 dioxane), 3.12 (m, 1 H, H-5′), 2.13 (dt, $^2J_{H,H}$ = 13, $^3J_{H,H}$ = 3 Hz, 1 H, H-$8'_{eq}$), 1.96 (dt, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 3 Hz, 1 H, H-$6'_{eq}$), 1.71 (s, 3 H, $COCH_3$), 1.66 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH_3), 1.49 (s, 3 H, $COCH_3$), 1.34–1.11 (m, 4 H, CH_2 dioxane, H-$6'_{eq}$, H-$8'_{ax}$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 170.4, 166.2 (3 × C *ipso*), 96.4 (C-7′), 75.0 (C-1′), 71.9 (C-2′), 59.1, 59.0 (2 × OCH_2 dioxane), 55.1 (C-5′), 50.0 (C-8′a), 40.8 (C-6′), 34.1 (C-8′), 25.5 (CH_2 dioxane), 20.1 (OCH_3), 19,0 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{24}NO_7$ [M + H]$^+$ 342.1553; found 342.1557.

Following the procedure described for piperidine (±)-**6a**, starting from piperidine (±)-**5b** (27.5 mg, 0.06 mmol), piperidine (±)-**6b** (14.3 mg, 66% over 3 steps) was obtained as a colourless oil. R_f (ethyl acetate/MeOH, 9:1) = 0.72. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.37 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, H-2′), 5.00 (t, $^3J_{H,H}$ = 6.5 Hz, 1 H, H-1′), 3.96–3.85 (m, 4 H, 2 × OCH_2 dioxane), 3.53 (m, 1 H, H-5′), 3.44 (ddd, $^2J_{H,H}$ = 13, $^3J_{H,H}$ = 6, $^3J_{H,H}$ = 3 Hz, 1 H, H-8′a), 2.68 (dt, $^2J_{H,H}$ = 13, $^3J_{H,H}$ = 3 Hz, 1 H, H-$8'_{eq}$), 2.18–2.12 (m, 4 H, H-$6'_{eq}$, $COCH_3$), 2.10 (s, 3 H, $COCH_3$), 1.81–1.69 (m, 2 H, CH_2 dioxane), 1.66 (d, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3), 1.50 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 11.5 Hz, 1 H, H-$6'_{ax}$), 1.42 (t, $^2J_{H,H}$ = 13, $^3J_{H,H}$ = 13 Hz, 1 H, H-$8'_{ax}$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 170.4, 166.2 (3 × C *ipso*), 96.1 (C-7′), 76.3 (C-1′), 75.4 (C-2′), 59.2, 59.1 (2 × OCH_2 dioxane), 56.2 (C-5′), 49.1 (C-8′a), 41.1 (C-6′), 37.4 (C-8′), 25.5 (CH_2 dioxane), 20.2 (OCH_3), 19.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{24}NO_7$ [M + H]$^+$ 342.1553; found 342.1558.

Ethyl (2*S*,3*R*)-2,3-dihydroxy-3-[(8*R*,10*R*)-10-methyl-1,5-dioxa-9-aza-spiro[5.5]undec-8-yl]propanoate [(+)-7]: A solution of piperidine (+)-**5b** (290 mg, 0.66 mmol) in methanol (10 mL) containing 10% Pd/C (66 mg) was stirred under hydrogen for 2 h. The catalyst was filtered off, and the filtrate was concentrated to afford piperidine (+)-**7** (190 mg, 95%) as a white solid; m.p. 118 °C. R_f (ethyl acetate/MeOH, 9:1) = 0.3 $[a]_D^{25}$ = +2.9 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1652, 1436, 1385, 1288, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.95 (br. s, 3 H, 2 × OH, NH), 4.40 (d, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-3), 4.25 (qd, $^3J_{H,H}$ = 7, $^4J_{H,H}$ = 2 Hz, 2 H, CH_2 ester), 4.00–3.85 (m, 5 H, H-2, 2 × OCH_2 dioxane), 3.27 (ddd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-8′), 3.01 (m, 1 H, H-10′), 2.54 (td, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 2.5, $^4J_{H,H}$ = 2.5 Hz, 1 H, H-$7'_{eq}$), 2.22 (td, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 3, $^4J_{H,H}$ = 3 Hz, 1 H, H-$11'_{eq}$), 1.82–1.64 (m, 2 H, CH_2 dioxane), 1.43 (dd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 12.5 Hz, 1 H, H-$7'_{ax}$), 1.37–1.27 (m, 4 H, H-$11'_{ax}$, CH_3 ester), 1.18 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (C=O ester), 96.2 (C-6′), 72.1, 71.9 (C-3, C-2), 62.1 (CH_2 ester), 59.5, 59.4 (2 × OCH_2 dioxane), 56.9 (C-10′), 49.4 (C-8′), 40.4 (C-11′), 32.7 (C-7′), 25.4 (CH_2 dioxane), 20.6 (CH_3), 14.2 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{14}H_{26}NO_6$ [M + H]$^+$ 304.1760; found 304.1774.

(1′*R*,2′*R*,5′*R*,8a′*R*)-1′,2′-bis(benzyloxy)-5′-methylhexahydro-1′*H*-spiro[1,3-dioxane-2,7′-indolizine] [(–)-9]: To a solution of piperidine (+)-**7** (80 mg, 0.27 mmol) in anhydrous THF (10 mL) was added DIPEA (128 μL, 0.66 mmol). The mixture was refluxed for 12 h. Evaporation of the solvents gave the indolizidinone **8** as a pale yellow oil. The crude product **8** was directly engaged in the next step. R_f (ethyl acetate/MeOH, 9:1) = 0.35. To a stirred solution of crude indolizidinone **8** (46.3 mg, 0.18 mmol) in anhydrous THF (10 mL) was added $LiAlH_4$ (28 mg, 0.72 mmol). The mixture was refluxed for 2 h. After cooling to 0 °C, water was added (2 mL) followed by NaOH (1 N, 1 mL). The residue was filtered trough Celite® and Na_2SO_4, washed with ethyl acetate, and then the solvents were removed to afford a pale yellow oil. The product was directly engaged in the next step. R_f (ethyl acetate/MeOH, 9:1) = 0.17. To a solution of the last product (35 mg, 0.144 mmol) in anhydrous THF (4 mL), cooled to 0 °C, was added NaH (14 mg, 0.58 mmol). The mixture was stirred at 0 °C under Ar for 45 min. To this mixture was added dropwise a solution of benzyl bromide (35 μL, 0.3 mmol) in DMF (4 mL), and the mixture was stirred for

48 h under an inert atmosphere and then quenched by the addition of water. The resulting solution was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 2:8) to give indolizidine (–)-**9** (40 mg, 35% over 3 steps) as a pale oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.63. $[\alpha]_D^{25}$ = –21.9 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2964, 2930, 2868, 1454, 1378, 1325, 1300, 1142, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 10 H, 2 × Ph), 4.54, 4.39 (2 d, *J* = 12 Hz, 2 H, CH_2Ph, AB system), 4.52, 4.48 (2 d, *J* = 12 Hz, 2 H, CH_2Ph, AB system), 3.93–3.74 (m, 5 H, 2 × OCH_2 dioxane, H-2′), 3.61 (m, 1 H, H-1′), 3.45 (m, 1 H, H-3′a), 3.14 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, H-3′b), 2.55 (m, 1 H, H-5′), 2.29 (m, 1 H, H-8′a), 2.19 (m, 1 H, H-8′$_{eq}$), 1.98 (m, 1 H, H-6′$_{eq}$), 1.65 (m, 2 H, CH_2 dioxane), 1.31 (m, 2 H, H-6′$_{ax}$, H-8′$_{ax}$), 0.98 (d, $^3J_{H,H}$ = 6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 138.1 (2 × C *ipso*), 128.7, 128.3, 127.9, 127.7, 127.6 (C_{ar}), 97.4 (C-7′), 88.9 (C-1′), 82.5 (C-2′), 72.1, 71.4 (2 × CH_2Ph), 64.1 (C-5′), 59.5, 59.1 (2 × OCH_2 dioxane), 55.5 (C-3′), 53.7 (C-8′a), 41.7 (C-6′), 34.9 (C-8′), 25.6 (CH_2 dioxane), 19.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{26}H_{34}NO_4$ $[M + H]^+$ 424.2488; found 424.2481.

(1*R*,2*R*,5*R*,8a*R*)-1,2-Bis(benzyloxy)-5-methylhexahydroindolizin-7-one [(–)-10]: To a solution of indolizidine (–)-**9** (39 mg, 0.09 mmol) in dichloromethane (5 mL) was added dropwise TFA (50% aqueous, 160 μL, 1.1 mmol). The mixture was stirred at room temperature for 3 h and quenched with a saturated solution of $NaHCO_3$. The resulting aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 1:2) to give indolizidine (–)-**10** (23.3 mg, 69%) as a pale yellow oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.66. $[\alpha]_D^{25}$ = –4.8 (*c* = 0.88, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.27 (m, 10 H, 2 × Ph), 4.53, 4.49 (2 d, *J* = 11.5 Hz, 2 H, CH_2Ph, AB system), 4.55, 4.42 (2 d, *J* = 12 Hz, 2 H, CH_2Ph, AB system), 3.99 (dd, $^3J_{H,H}$ = 6, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-2), 3.79 (dd, $^3J_{H,H}$ = 7, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-1), 3.32 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, H-3a), 2.65 (m, 1 H, H-8$_{eq}$), 2.50–2.35 (m, 4 H, H-8a, H-8$_{ax}$, H-5, H-3b), 2.28 (m, 2 H, H-6$_{ax}$, H-6$_{eq}$), 1.17 (d, $^3J_{H,H}$ = 6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0 (C-7), 137.8, 137.7 (2 × C *ipso*), 128.4, 128.1, 127.9, 127.7 (C_{ar}), 89.5 (C-1), 82.1 (C-2), 72.1, 71.5 (2 × CH_2Ph), 67.5 (C-5), 56.7 (C-8a), 55.3 (C-3), 48.3 (C-6), 45.5 (C-8), 20.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2069; found 366.2057.

(1*R*,2*R*,5*R*,7*S*,8a*R*)-1,2-Bis(benzyloxy)-5-methyloctahydroindolizin-7-ol [(–)-11]: $NaBH_4$ (6.3 mg, 0.17 mmol) was added to a solution of indolizidine (–)-**10** (60 mg, 0.17 mmol, 1 equiv.) in methanol (5 mL), under an inert atmosphere, and the mixture was cooled to –10 °C. The mixture was stirred at –10 °C for 15 min, and the solvent was removed. The residue was dissolved in water (0.1 mL) and extracted with ethyl acetate (4 × 3 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 1:1) to give indolizidinol (–)-**11** (56 mg, 90%) as a pale yellow oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.23. $[\alpha]_D^{25}$ = –12.5 (*c* = 0.82, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3390, 2854, 1496, 1453, 1198, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 10 H, 2 × Ph), 4.60, 4.45 (2 d, *J* = 12 Hz, 2 H, CH_2Ph, AB system), 4.57, 4.54 (2 d, *J* = 12 Hz, 2 H, CH_2Ph, AB system), 3.94 (m, 1 H, H-2), 3.75 (dd, $^3J_{H,H}$ = 8.5, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-1), 3.65 (tt, $^3J_{H,H}$ = 11.5, $^3J_{H,H}$ = 4.5 Hz, 1 H, H-7), 3.23 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, H-3a), 2.36–2.24 (m, 2 H, H-3b, H-6$_{eq}$), 2.12–2.02 (m, 2 H, H-8a, H-5), 1.87 (m, 1 H, H-8$_{eq}$), 2.21–1.42 (m, 3 H, H-8$_{ax}$, H-6$_{ax}$, OH), 1.09 (d, $^3J_{H,H}$ = 6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1 (2 × C *ipso*), 128.4, 128.3, 127.9, 127.8, 127.7 (C_{ar}), 88.7 (C-1), 82.4 (C-2), 73.1, 72.2 (2 × CH_2Ph), 69.6 (C-7), 66.4 (C-5), 55.8 (C-8a), 55.5 (C-3), 42.8 (C-6), 38.4 (C-8), 20.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{30}NO_3$ $[M + H]^+$ 368.2226; found 368.2209.

(1*R*,2*R*,5*R*,7*S*,8a*R*)-5-Methyloctahydroindolizin-1,2,7-triol [(–)-12]: To a solution of indolizidinol (–)-**11** (80 mg, 0.22 mmol) in methanol (10 mL) was added $PdCl_2$ (76 mg, 0.43 mmol). The mixture was stirred under hydrogen for 3 d, filtered through Celite®, and washed with dichloromethane. The solvents were removed, and the crude product was eluted on DOWEX® 50WX8 (200–400 mesh, H^+) with water and then aqueous NH_4OH (1 N) to give polyhydroxylated indolizidine (–)-**12** (41 mg, quantitative) as a pale yellow oil. R_f (ethyl acetate/MeOH, 5:1) = 0.10. $[\alpha]_D^{25}$ = –28.8 (*c* = 0.77, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 3.93 (ddd, $^3J_{H,H}$ = 6, $^3J_{H,H}$ = 4, $^3J_{H,H}$ = 2 Hz, 1 H, H-2), 3.59 (dd, $^3J_{H,H}$ = 9, $^3J_{H,H}$ = 4 Hz, 1 H, H-1), 3.54 (m, 1 H, H-7), 2.97 (dd, $^2J_{H,H}$ = 11, $^3J_{H,H}$ = 1.5 Hz, 1 H, H-3a), 2.58 (dd, $^2J_{H,H}$ = 11, $^3J_{H,H}$ = 7.5 Hz, 1 H, H-3b), 2.26 (m, 1 H, H-5), 2.16–2.06 (m, 2 H, H-8a, H-6$_{eq}$), 1.83 (m, 1 H, H-8$_{eq}$), 1.21 (m, 5 H, H-8$_{ax}$, H-6$_{ax}$, 3 × OH), 1.03 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 83.9 (C-1), 77.7 (C-2), 69.2 (C-8a, C-7), 59.4 (C-3), 57.8 (C-5), 43.2 (C-8), 37.9 (C-6), 19.8 (CH_3) ppm. HRMS (ESI): calcd. for $C_9H_{18}NO_3$ $[M + H]^+$ 188.1287; found 188.1290.

2-(1-Benzyloxymethyl-3-oxobutyl)isoindol-1,3-dione [(±)-14]: To a solution of (*E*)-5-(benzyloxy)pent-3-en-2-one [(±)-**13**, 10.1 g, 53.3 mmol)] in ethyl acetate (250 mL) was added phthalimide (7.9 g, 53.7 mmol). The reaction mixture was stirred for 5 min, and a solution of benzyltrimethylammonium hydroxide (Triton B®, 200 μL) was added. The mixture was refluxed for 3 h, and the solution was neutralized by the addition of NaOH (1 N). The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried on Na_2SO_4, filtered, and concentrated. Recrystallization of the residue from ethanol gave 5-benzyloxy-4-phthalimido-2-pentanone [(±)-**14**, 16.2 g, 89%)] as a white solid; m.p. 138 °C; R_f (ethyl acetate/cyclohexane, 1:1) = 0.60. IR (film): $\tilde{\nu}$ = 1774, 1706, 1608, 1496, 1172, 1090, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (m, 2 H, Ph), 7.68 (m, 2 H, Ph), 7.27 (m, 5 H, Ph), 5.05 (m, 1 H, H-4), 4.54 (d, $^2J_{H,H}$ = 12 Hz, 1 H, CH_2Ph), 4.53 (d, $^2J_{H,H}$ = 12 Hz, 1 H, CH_2Ph), 3.75 (m, 2 H, H-5), 3.15 (m, 2 H, H-3), 2.15 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1 (C-2), 168.3 (2 × C=O imide), 137.7 (C *ipso*), 134.3, 133.9 (C_{ar}), 131.8 (2 × C *ipso*), 128.3, 127.7, 123.5, 123.2 (C_{ar}), 72.8 (CH_2Ph), 69.1 (C-5), 46.1 (C-3), 42.3 (C-4), 30.1 (C-1) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}NO_4$ $[M + H]^+$ 360.1210; found 360.0921.

1-Benzyloxymethyl-2-(2-methyl-1,3-dioxan-2-yl)ethylamine [(±)-15]: To a solution of phthalimide (±)-**14** (8 g, 23.8 mmol) in toluene (70 mL) were added 1,3-propanediol (3.5 mL, 47.5 mmol) and *p*-toluenesulfonic acid (5 mg). The mixture was refluxed with a Dean–Stark apparatus for 6 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with dichloromethane (3 × 30 mL), and the combined organic layers were washed with brine (2 × 20 mL), dried on Na_2SO_4, filtered, and concentrated. To a solution of this crude phthalimide (8.40 g, 21.3 mmol) in methanol (100 mL) was added hydrazine monohydrate (1.27 g, 25.3 mmol). The mixture was refluxed for 5 h, and the methanol was evaporated. The white precipitate thus formed was treated with aqueous KOH (2.6 N, 14 mL) and extracted with dichloromethane (5 × 30 mL). The combined

organic layers were dried with Na_2SO_4, filtered, and concentrated to furnish amine (±)-**15** (5.6 g, 90% over two steps) as a white solid; m.p. 146 °C; R_f (ethyl acetate/MeOH, 9:1) = 0.10. IR (KBr): $\tilde{\nu}$ = 3422, 1605, 1579, 1246, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br. s, 2 H, NH_2), 7.40–7.25 (m, 5 H, Ph), 4.60, 4.57 (2 d, J = 12 Hz, 2 H, CH_2Ph, AB system), 3.92–3.05 (m, 4 H, 3 × OCH dioxane, CH), 3.88–3.79 (m, 2 H, OCH dioxane, CH_2OBn), 3.78–3.72 (m, 1 H, CH_2OBn), 2.17 (m, 1 H, CH_2), 2.10–1.96 (m, 1 H, CH_2 dioxane), 1.79 (dd, 1 H, CH_2), 1.46 (s, 3 H, CH_3), 1,36 (d, 1 H, CH_2 dioxane) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4 (C *ipso*), 128.5, 127.9, 127.8 (C_{ar}), 98.9 (C), 73.3 (CH_2Ph), 69.5 (CH_2OBn), 60.1, 60.0 (2 × OCH_2 dioxane), 48.1 (CH), 40.6 (CH_2), 25.2 (CH_2 dioxane), 18.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{24}NO_3$ $[M + H]^+$ 266.1756; found 266.1750.

Benzyl {(2*S*)-1-Hydroxy-4-[methoxy(methyl)amino]-4-oxobutan-2-yl}carbamate [(+)-17]: To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.82 g, 18.7 mmol) in anhydrous dichloromethane (90 mL), cooled to 0 °C, was added a solution of trimethylaluminium (2 M in hexane, 9.35 mL, 18.7 mmol). The mixture was stirred at room temperature for 2 h, and then a solution of β-amino ester (–)-**16** (9.36 mmol, 2.5 g) in anhydrous dichloromethane (20 mL) was added dropwise. The mixture was stirred for 12 h, cooled to 0 °C, and neutralised with saturated aqueous NH_4Cl. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried on Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate) to give amide (+)-**17** (1.9 g, 70%) as a colourless oil. R_f (ethyl acetate) = 0.59. $[\alpha]_D^{25}$ = +4.2 (c = 1.03, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1715, 1650, 1531, 1455, 1255, 1056 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H, Ph), 5.79 (m, 1 H, NH), 5.08 (s, 2 H, CH_2Ph), 4.05 (m, 1 H, H-2), 3.75 (m, 2 H, H-1), 3.70 (s, 3 H, OCH_3), 3.30 (br. s, 1 H, OH), 3.16 (s, 3 H, NCH_3), 2.82 (m, 2 H, H-3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C=O amide), 156.3 (C=O carbamate), 136.4 (C *ipso*), 128.5, 128.2, 128.1 (C_{ar}), 66.7 (CH_2Ph), 64.4 (C-1), 61.3 (CH_3), 49.7 (C-2), 33.4 (C-3), 32.0 (NCH_3) ppm. HRMS (ESI): calcd. for $C_{14}H_{20}N_2O_5Na$ $[M + Na]^+$ 319.1270; found 319.1283.

Benzyl [(2*S*)-1-Hydroxy-4-oxopentan-2-yl]carbamate [(+)-18]: A solution of amide (+)-**17** (1.4 g, 4.7 mmol) in anhydrous THF (100 mL) under Ar was cooled to 0 °C, and methylmagnesium bromide (3 M in THF, 16 mL, 47.3 mmol) was added slowly. The mixture was stirred at room temperature for 15 min, cooled to 0 °C, and neutralised with saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL), and the combined organic layers were dried on Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 9:1) to furnish ketone (+)-**18** (0.6 g, 50%) as a white solid; m.p. 81–81.5 °C; R_f (ethyl acetate) = 0.58. $[\alpha]_D^{25}$ = +4.8 (c = 1.01, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1712, 1690, 1539, 1316, 1166, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 7.34 (m, 5 H, Ph), 5.38 (br. s, 1 H, NH), 5.09 (s, 2 H, CH_2Ph), 4.03 (m, 1 H, H-2), 3.71 (m, 2 H, H-1), 2.78 (m, 2 H, H-3), 3.35 (br. s, 1 H, OH), 2.15 (s, 3 H, H-5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.1 (C-4), 156.4 (C=O carbamate), 136.3 (C *ipso*), 128.5, 128.2, 128.1 (C_{ar}), 66.8 (CH_2Ph), 63.9 (C-1), 49.4 (C-2), 44.3 (C-3), 30.5 (C-5) ppm. HRMS (ESI): calcd. for $C_{13}H_{17}NO_4Na$ $[M + Na]^+$ 274.1055; found 274.1055.

Benzyl [(2*S*)-1-(Benzyloxy)-4-oxopentan-2-yl]carbamate [(–)-19]: To a solution of ketone (+)-**18** (390 mg, 1.55 mmol) in anhydrous dichloromethane (5 mL) were added benzyl bromide (280 μL, 2.33 mmol) and silver oxide (216 mg, 0.93 mmol, 0.6 equiv.). The mixture was stirred for 4 h, and then benzyl bromide (280 μL, 2.33 mmol) and silver oxide (216 mg, 0.93 mmol) were added. The mixture was stirred for 4 h, and benzyl bromide (280 μL, 2.33 mmol) and silver oxide (216 mg, 0.93 mmol) were added again. The precipitate was filtered trough Celite® and washed with dichloromethane (3 × 10 mL). The filtrate was concentrated, and the residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 1:9) to give (–)-**19** (370 mg, 70%) as a white solid; m.p. 52 °C; R_f (ethyl acetate/cyclohexane, 1:4) = 0.19. $[\alpha]_D^{25}$ = –8.5 (c = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1711, 1686, 1543, 1410, 1268, 1062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 10 H, 2 × Ph), 5.39 (m, 1 H, NH), 5.08 (s, 2 H, CH_2Ph), 4.48 (s, 2 H, CH_2Ph), 4.20 (m, 1 H, H-2), 3.56 (m, 2 H, H-1), 2.78 (m, 2 H, H-3), 2.12 (s, 3 H, H-5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3 (C-3), 155.7 (C=O carbamate), 137.8, 136.5 (2 × C *ipso*), 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 126.9 (C_{ar}), 73.2 (C-1), 70.8 (OCH_2Ph), 66.7 ($COOCH_2Ph$), 47.4 (C-2), 44.4 (C-3), 30.5 (C-5) ppm. HRMS (ESI): calcd. for $C_{20}H_{23}NO_4Na$ $[M + Na]^+$ 364.1525; found 364.1526.

Benzyl [(2*S*)-1-(Benzyloxy)-3-(2-methyl-1,3-dioxan-2-yl)propan-2-yl]carbamate [(–)-20]: To a solution of (–)-**19** (172 mg, 0.504 mmol) in trimethylorthoformate (552 μL, 5.04 mmol) were added 1,3-propanediol (373 μL, 5.04 mmol) and *p*-toluenesulfonic acid (3.8 mg, 0.02 mmol). The mixture was stirred at room temperature for 12 h, diluted with dichloromethane (10 mL), and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 1:9) to give (–)-**20** (140 mg, 70%) as a colourless oil. R_f (ethyl acetate/cyclohexane, 1:4) = 0.20. $[\alpha]_D^{25}$ = –18.8 (c = 1.02, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1715, 1513, 1430, 1249, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 10 H, 2 × Ph), 5.39 (m, 1 H, NH), 5.10 (s, 2 H, CH_2Ph), 4.52 (s, 2 H, CH_2Ph), 4.12 (m, 1 H, H-2), 3.97–3.89 (m, 2 H, OCH_2 dioxane), 3.85–3.75 (m, 2 H, OCH_2 dioxane), 3.66–3.51 (m, 2 H, H-1), 2.05 (m, 2 H, H-3), 1.92–1.76 (m, 2 H, CH_2 dioxane), 1.43 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0 (C=O carbamate), 138.4, 136.9 (2 × C *ipso*), 128.8, 128.5, 128.3, 127.9, 127.7, 127.5 (C_{ar}), 98.7 (C-4), 73.1 (C-1), 72.5 (OCH_2Ph), 66.4 ($COOCH_2Ph$), 59.7 (2 × OCH_2 dioxane), 47.6 (C-2), 41.3 (C-3), 25.4 (CH_2 dioxane), 19.9 (C-5) ppm. HRMS (ESI): calcd. for $C_{23}H_{29}NO_5Na$ $[M + Na]^+$ 422.1943; found 422.1927.

(*S*)-1-Benzyloxymethyl-2-(2-methyl-1,3-dioxan-2-yl)ethylamine [(+)-15]: To a solution of carbamate (–)-**20** (80 mg, 0.2 mmol) in methanol (15 mL), 10% Pd/C (20 mg) was added. The mixture was stirred for 1 h at room temperature, and the catalyst was filtered through Celite® and washed with methanol. The solvents were removed to give amine (+)-**15** (45 mg, quantitative) as a white solid; m.p. 146 °C. R_f (ethyl acetate) = 0.4. $[\alpha]_D^{25}$ = +6.5 (c = 1.03, $CHCl_3$). HRMS (ESI): calcd. for $C_{15}H_{24}NO_3$ $[M + H]^+$ 266.1756; found 266.1750.

Ethyl (*E*)-3-[(8*R*,10*S*)-10-Benzyloxymethyl-1,5-dioxa-9-azaspiro-[5.5]undec-8-yl]acrylate [(+)-21]: Following the procedure described for piperidine (–)-**3**, starting from amine (+)-**15** (2.00 g, 7.5 mmol), piperidine (+)-**21** (1.69 g, 60%) was obtained as a pale yellow oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.25. $[\alpha]_D^{25}$ = +3.3 (c = 1.01, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3311, 1719, 1655, 1145, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H, Ph), 6.83 (dd, $^3J_{H,H}$ = 16, $^3J_{H,H}$ = 6 Hz, 1 H, H-3), 5.89 (d, $^3J_{H,H}$ = 16 Hz, 1 H, H-2), 4.46, 4.43 (2 d, J = 12 Hz, 2 H, CH_2Ph, AB system), 4.11 (q, $^3J_{H,H}$ = 7 Hz, 2 H, CH_2 ester), 3.83 (m, 4 H, 2 × OCH_2 dioxane), 3.43 (m, 2 H, H-8′, H-1′′a), 3.29 (m, 1 H, H-1′′b), 3.03 (m, 1 H, H-

10′), 2.25 (m, 1 H, H-7′$_{eq}$), 2.07 (m, 1 H, H-11′$_{eq}$), 2.02 (br. s, 1 H, NH), 1.65 (m, 2 H, CH_2 dioxane), 1.25–1.17 (m, 4 H, H-7′$_{ax}$, CH_3 ester), 1.12 (t, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 12.5 Hz, 1 H, H-11′$_{ax}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5 (C=O ester), 149.4 (C-3), 138.1 (C *ipso*), 128.9, 128.5, 127.7 (C$_{ar}$), 120.7 (C-2), 96.8 (C-6′), 74.6 (C-1′′), 73.4 (CH_2Ph), 60.6 (OCH_2 ester), 59.3, 59.2 (2 × OCH_2 dioxane), 53.3 (C-8′), 52.0 (C-10′), 38.5 (C-7′), 35.5 (C-11′), 25.5 (CH_2 dioxane), 14.2 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{21}H_{30}NO_5$ [M + H]$^+$ 376.2124; found 376.2106.

Ethyl (*E*)-3-[(8*R*,10*S*)-9-Benzyloxycarbonyl-10-benzyloxymethyl-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]acrylate [(–)-22]: Following the procedure described for piperidine (+)-**4**, starting from piperidine (+)-**21** (2.10 g, 5.6 mmol), protected piperidine (–)-**22** (2.5 g, 90%) was isolated as a yellow oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.62. $[\alpha]_D^{25}$ = –4.1 (*c* = 1.03, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1713, 1768, 1656, 1290, 1113 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.17 (m, 10 H, 2 × Ph), 6.95 (dd, $^3J_{H,H}$ = 16, $^3J_{H,H}$ = 6.5 Hz, 1 H, H-3), 5.84 (d, $^3J_{H,H}$ = 16 Hz, 1 H, H-2), 5.14, 5.11 (2 d, *J* = 12.5 Hz, 2 H, CH_2Ph, AB system), 4.97 (m, 1 H, H-8′), 4.56 (m, 1 H, H-10′), 4.52, 4.47 (2 d, *J* = 12 Hz, 2 H, CH_2Ph, AB system), 4.11 (q, $^3J_{H,H}$ = 7 Hz, 2 H, CH_2 ester), 3.92–3.71 (m, 4 H, 2 × OCH_2 dioxane), 3.61 (m, 1 H, H-1′′a), 3.48 (m, 1 H, H-1′′b), 2.54 (m, 1 H, H-11′$_{eq}$), 2.20 (m, 1 H, H-7′$_{eq}$), 1.85 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 7 Hz, 1 H, H-7′$_{ax}$), 1.72 (m, 1 H, CH2a dioxane), 1.64 (dd, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 7 Hz, 1 H, H-11′$_{ax}$), 1.59 (m, 1 H, CH_{2b} dioxane), 1.19 (m, 3 H, CH_3 ester) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5 (C=O ester), 155.7 (C=O carbamate), 148.9 (C-3), 138.3, 136.4 (2 × C *ipso*), 128.5, 128.3, 128.1, 128.0, 127.7, 127.6, 126.9 (C$_{ar}$), 121.6 (C-2), 95.8 (C-6′), 72.9 (C-1′′), 71.1, 67.7 (2 × CH_2Ph), 60.3 (CH_2 ester), 59.5 (2 × OCH_2 dioxane), 51.2 (C-8′), 50.3 (C-10′), 36.6 (C-7′), 29.7 (C-11′), 25.1 (CH_2 dioxane), 14.2 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{29}H_{35}NO_7Na$ [M + Na]$^+$ 532.2329; found 532.2285.

Benzyl (8*S*,10*R*)-8-Benzyloxymethyl-10-[(1*S*,2*R*)-2-ethoxycarbonyl-1,2-dihydroxyethyl]-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate [(+)-23a] and Benzyl (8*S*,10*R*)-8-Benzyloxymethyl-10-[(1*R*,2*S*)-2-ethoxycarbonyl-1,2-dihydroxyethyl]-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate [(+)-23b]: Following the procedure described for piperidines (–)-**5a** and (+)-**5b**, starting from piperidine (–)-**22** (710 mg, 1.4 mmol), diastereomeres (+)-**23a** (106 mg, 14%) and (+)-**23b** (327 mg, 43%) were obtained as pale yellow oils.

(+)-23a: R_f (ethyl acetate/cyclohexane, 1:1) = 0.28. $[\alpha]_D^{25}$ = +1.3 (*c* = 0.95, $CHCl_3$). The ^{1}H NMR (400 MHz, $CDCl_3$) was a complex spectrum due to the coexistence of carbamate rotamers. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (C=O ester), 158.2 (C=O carbamate), 138.2, 135.8 (2 × C *ipso*), 128.5, 128.3, 128.2, 128.0, 127.6, 127.3 (C$_{ar}$), 95.9 (C-6), 72.7 (CH_2Ph), 72.6 (C-1′), 72.1 (C-1′′), 70.1 (C-2′), 68.4 (CH_2Ph), 61.3 (CH_2 ester), 59.7, 59.6 (2 × OCH_2 dioxane), 52.9 (C-10), 50.3 (C-8), 34.5 (C-11), 27.9 (C-7), 25.1 (CH_2 dioxane), 14.3 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{29}H_{37}NO_9Na$ [M + Na]$^+$ 566.2366; found 566.2387.

(+)-23b: R_f (ethyl acetate/cyclohexane, 1:1) = 0.27. $[\alpha]_D^{25}$ = +16.9 (*c* = 0.95, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3442, 1732, 1692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.20 (m. 10 H, 2 × Ph), 5.10 (s, 2 H, CH_2Ph), 4.75 (m, 1 H, H-10), 4.55 (m, 1 H, CH_2Ph), 4.42 (m, 1 H, CH_2Ph), 4.35–4.19 (m, 4 H, CH_2 ester, H-1′, H-2′), 4.12–3.99 (m, 2 H, OCH_2 dioxane), 3.90–3.80 (m, 2 H, OCH_2 dioxane), 3.68 (m, 1 H, H-1′′a), 3.50 (m, 1 H, H-1′′b), 3.14 (m, 1 H, H-8), 2.08 (m, 1 H, H-11$_{eq}$), 1.86 (m, 1 H, H-7$_{eq}$), 1.77 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 7.5 Hz, 1 H, H-11$_{ax}$), 1.58 (m, 1 H, H-7$_{ax}$), 1.29 (t, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3 ester) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4 (C=O ester), 169.5 (C=O carbamate), 138.3, 135.9 (2 × C *ipso*), 128.6, 128.4, 128.0 (C$_{ar}$), 96.2 (C-6), 72.6 (CH_2Ph), 72.0 (C-1′′), 70.0 (C-1′, C-2′), 68.3 (CH_2Ph), 61.3 (CH_2 ester), 59.7, 59.6 (2 × OCH_2 dioxane), 50.2 (C-8, C-10), 34.5 (C-11), 27.9 (C-7), 25.0 (CH_2 dioxane), 14.1 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{29}H_{37}NO_9Na$ [M + Na]$^+$ 566.2366; found 566.2387.

Ethyl (2*S*,3*R*)-3-[(8*R*,10*S*)-10-benzyloxymethyl-1,5-dioxa-9-azaspiro-[5,5]undec-8-yl]-2,3-dihydroxy-propionate [(–)-24]: Following the procedure described for (+)-**5b**, starting from (+)-**23b** (270 mg, 0.5 mmol), piperidine (–)-**24** (204 mg. quantitative) was obtained as a colourless oil. R_f (ethyl acetate/MeOH, 9:1) = 0.35. $[\alpha]_D^{25}$ = –6.8 (*c* = 0.55, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3436, 1737, 1250, 1218 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H, Ph), 4.56–4.44 (m, 2 H, CH_2Ph), 4.28 (qd, $^3J_{H,H}$ = 7, $^4J_{H,H}$ = 2.5 Hz, 2 H, CH_2 ester), 4.00–3.78 (m, 6 H, 2 × OCH_2 dioxane, H-3, H-2), 3.46 (m, 1 H, H-1′′a), 3.35 (m, 1 H, H-1′′b), 3.10 (m, 1 H, H-8′), 3.00 (m, 1 H, H-10′), 2.50 (m, 1 H, H-7′$_{eq}$), 2.17 (m, 1 H, H-11′$_{eq}$), 1.78–1.63 (m, 2 H, CH_2 dioxane), 1.35–1.20 (m, 5 H, H-7′$_{ax}$, H-11′$_{ax}$, CH_3 ester) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (C=O ester), 138.1 (C *ipso*), 128.4, 128.3, 127.8, 127.7, 127.5 (C$_{ar}$), 97.2 (C-6′), 74.0 (CH_2Ph), 73.4 (C-3 or C-2), 73.3 (C-1′′), 72.2 (C-3 or C-2), 61.8 (CH_2 ester), 59.3 (2 × OCH_2 dioxane), 55.4 (C-10′), 52.2 (C-8′), 36.3 (C-11′), 35.1 (C-7′), 25.5 (CH_2 dioxane), 14.2 (CH_3 ester) ppm. HRMS (ESI): calcd. for $C_{21}H_{32}NO_7$ [M + H]$^+$ 410.2179; found 410.2169.

(1′*R*,2′*R*,5′*S*,8a′*R*)-1′,2′-Bis(benzyloxy)-5′-[(benzyloxy)methyl]hexahydro-1′*H*-spiro[1,3-dioxane-2,7′-indolizine] [(–)-25]: Following the procedure described for piperidine (–)-**9**, starting from piperidine (–)-**24** (80 mg, 0.2 mmol), indolizidine (–)-**25** (38 mg. 35%) was isolated as a pale yellow oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.63. $[\alpha]_D^{25}$ = –15.3 (*c* = 0.99, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1496, 1454, 1246, 1092 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 15 H, Ph), 4.61–4.50 (m, 4 H, 2 × CH_2Ph), 4.50, 4.36 (2 d, *J* = 12 Hz, 2 H, CH_2Ph, AB system), 3.87 (m, 5 H, 2 × OCH_2 dioxane, H-2′), 3.71 (dd, $^3J_{H,H}$ = 8.5, $^3J_{H,H}$ = 3 Hz, 1 H, H-1′), 3.45, 3.30 (m, $J_{H1'a,H5'}$ = 5, $J_{H1'b,H5'}$ = 4.5, $J_{H1'a,H1'b}$ = 10 Hz, 2 H, H-1′a, H-1′b, AB part of ABX system), 3.23 (d, $^2J_{H,H}$ = 10.5 Hz, 1 H, H-3′a), 2.57 (dt, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 3, $^4J_{H,H}$ = 3 Hz, 1 H, H-8′$_{eq}$), 2.53–2.43 (m, 2 H, H-3′b, H-5′), 2.33 (m, 1 H, H-8′a), 2.23 (dt, $^2J_{H,H}$ = 13, $^3J_{H,H}$ = 3, $^4J_{H,H}$ = 3 Hz, 1 H, H-6′$_{eq}$), 1.80–1.63 (m, 2 H, CH_2 dioxane), 1.45 (m, 1 H, H-6′$_{ax}$), 1.37 (m, 1 H, H-8′$_{ax}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3 (C *ipso*), 128.4, 128.3, 127.9, 127.7, 127.6 (C$_{ar}$), 97.3 (C-7′), 88.4 (C-1′), 82.8 (C-2′), 73.1, 73.0, 72.1, 71.4 (3 × CH_2Ph, CH_2OBn), 64.3 (C-8′a), 59.5, 59.1 (2 × OCH_2 dioxane), 57.9 (C-5′), 56.0 (C-3′), 36.5 (C-6′), 35.4 (C-8′), 25.5 (CH_2 dioxane) ppm. HRMS (ESI): calcd. for $C_{33}H_{40}NO_5$ [M + H]$^+$ 530.3866; found 530.3892.

(1*R*,2*R*,5*S*,8a*R*)-1,2-Bis(benzyloxy)-5-[(benzyloxy)methyl]hexahydroindolizin-7(1*H*)-one [(+)-26]: To a solution of piperidine (–)-**25** (250 mg, 0.47 mmol, 1 equiv.) in anhydrous dichloromethane (50 mL) were added dropwise 1,3-propanedithiol (237 μL, 2.36 mmol) and $BF_3{\cdot}OEt_2$ (302 μL, 2.36 mmol). The mixture was stirred at room temperature under an inert atmosphere over 24 h, diluted with dichloromethane, and washed with saturated aqueous NaOH (1 N). The two phases were separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried on Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 2:8) to give the dithiane-indolizine (175 mg, 80%) as a colourless oil. R_f (ethyl acetate/cyclohexane, 3:7) = 0.62. $[\alpha]_D^{25}$ = –18.6 (*c* = 0.88, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1496, 1453, 1112, 1075 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 15 H, 3 × Ph), 4.50, 4.45 (2 d, *J* = 11.5 Hz, 2 H,

CH_2Ph, AB system), 4.44 (s, 2 H, CH_2Ph), 4.49, 4.36 (2 d, J = 12 Hz, 2 H, CH_2Ph, AB system), 3.86 (dd, $^3J_{H,H}$ = 6, $^3J_{H,H}$ = 3 Hz, 1 H, H-2′), 3.63 (dd, $^3J_{H,H}$ = 8, $^3J_{H,H}$ = 3 Hz, 1 H, H-1′), 3.45, 3.29 (m, $J_{H1'a,H5'}$ = 5, $J_{H1',H5'}$ = 4.5, $J_{H1'a,H1'b}$ = 9.5 Hz, 2 H, H-1′a, H-1′b, AB part of ABX system), 3.15 (d, $^2J_{H,H}$ = 10.5 Hz, 1 H, H-3′a), 2.82–2.52 (m, 7 H, H-8′$_{eq}$, 2 × OCH_2 thioacetal, H-8′a, H-5′), 2.48 (m, 1 H, H-3′b), 2.27 (td, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 2.5 Hz, 1 H, H-6′$_{eq}$), 1.93 (m, 2 H, CH_2 thioacetal), 1.68 (dd, $^2J_{H,H}$ = 14, $^3J_{H,H}$ = 11.5 Hz, 1 H, H-6′$_{ax}$), 1.64 (dd, $^2J_{H,H}$ = 13, $^3J_{H,H}$ = 11.5 Hz, 1 H, H-8′$_{ax}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 138.2, 138.1 (3 × C *ipso*), 130.5, 128.9, 128.5, 128.4, 127.9, 127.8, 127.7, 126.9, 125.9 (C_{ar}), 88.5 (C-1′), 82.4 (C-2′), 73.3, 72.8, 72.2, 71.4 (3 × CH_2-Ph, C-1′′), 63.1 (C-5′), 57.5 (C-8′a), 56.1 (C-3′), 48.6 (C-7′), 40.5 (C-6′), 37.3 (C-8′), 26.3, 25.9, 25.6 (2 × SCH_2, CH_2) ppm. HRMS (ESI): calcd. for $C_{33}H_{39}NO_3S_2$ [M + H]$^+$ 562.2408; found 562.2429. To a solution of the dithiane-indolizine (175 mg, 0.31 mmol) in acetonitrile/water (9:1, 11 mL) was added [bis(trifluoroacetoxy)iodo]benzene (342 mg, 0.78 mmol) and trifluoroacetic acid (235 μL, 3.1 mmol). The mixture was stirred under Ar at room temperature for 12 h, and that diluted with cyclohexane (15 mL). The aqueous layer was extracted with cyclohexane (3 × 8 mL) and neutralized with saturated aqueous K_2CO_3. 1,2-Ethanedithiol (1.4 mL) was added, and the mixture was stirred for 5 min. The aqueous layer was extracted with dichloromethane (3 × 8 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/cyclohexane, 3:7) to give indolizidinone (+)-**26** (87 mg, 50%) as a pale yellow oil. R_f (ethyl acetate/cyclohexane, 1:1) = 0.75. $[\alpha]_D^{25}$ = +1.25 (c = 0.64, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1719, 1496, 1454, 1241, 1103 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.17 (m, 15 H, Ph), 4.52, 4.40 (2 d, J = 12 Hz, 2 H, CH_2Ph, AB system), 4.44 (m, 4 H, 2 × CH_2Ph), 3.92 (m, 1 H, H-2′), 3.73 (m, 1 H, H-1′), 3.46, 3.36 (m, $J_{H1'a,H5'}$ = 5, $J_{H1'b,H5'}$ = 4.5, $J_{H1'a,H1'b}$ = 10 Hz, 2 H, H-1′a, H-1′b, AB part of ABX system), 3.25 (d, $^2J_{H,H}$ = 11 Hz, 1 H, H-3′a), 2.58 (d, $^2J_{H,H}$ = 11 Hz, 1 H, H-8′$_{eq}$), 2.49 (m, 2 H, H-5′, H-3′b), 2.36 (m, 4 H, H-2, H-6′$_{ax}$, H-6′$_{eq}$, H-8′$_{ax}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8 (C-7′), 137.9, 137.8, 137.7 (3 × C *ipso*), 128.9, 128.5, 128.0, 127.9, 127.8 (C_{ar}), 89.1 (C-1′), 82.4 (C-2′), 73.3, 72.5, 72.1, 71.5 (3 × CH_2Ph, C-1′′), 67.5 (C-8′a), 60.6 (C-5′), 55.8 (C-3′), 45.4 (C-8′), 43.5 (C-6′) ppm. HRMS (ESI): calcd. for $C_{30}H_{34}NO_4$ [M + H]$^+$ 472.2504; found 472.2488.

(1*R*,2*R*,5*S*,7*S*,8a*R*)-5-(Hydroxymethyl)octahydroindolizine-1,2,7-triol [(–)-27]: Following the procedure for indolizidinone (–)-**12**, starting from (+)-**26** (80 mg, 0.17 mmol), piperidinol (–)-**27** (22 mg, 64% over two steps) was isolated as a pale yellow oil. R_f (ethyl acetate/MeOH, 5:1) = 0.10. $[\alpha]_D^{25}$ = –12.0 (c = 0.30, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.02 (m, 1 H, H-2′), 3.82–3.47 (m, 3 H, H-1′, H-7′, H-1′′a), 3.32–3.25 (m, 1 H, H-1′′b), 3.27 (m, 1 H, H-3′a), 3.09 (m, 1 H, H-3′b), 2.84–2.56 (m, 2 H, H-8′a, H-5′), 2.19 (m, 1 H, H-8′$_{eq}$), 1.92 (m, 1 H, H-6′$_{eq}$), 1.62–1.35 (m, 2 H, H-6′$_{ax}$, H-8′$_{ax}$) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 84.1 (C-1′), 78.3 (C-2′), 69.5 (C-8′a, C-7′), 64.9 (C-1′′), 64.3 (C-5′), 59.9 (C-3′), 38.2 (C-6′, C-8′) ppm. HRMS (ESI): calcd. for $C_9H_{18}NO_4$ [M + H]$^+$ 205.2479; found 205.2458.

Supporting Information (see also the footnote on the first page of this article): General experimental methods, conformational analysis of (±)-**6a** and (±)-**6b**, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds.

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