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Stereoselective synthesis of swainsonines from pyridines

Gerres Heimgärtner, Dirk Raatz and Oliver Reiser*

Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, D-93040, Germany

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Abstract—An efficient synthesis of (−)-swainsonine and (−)-2,8a-di-*epi*-swainsonine was developed starting from readily available 2-pyridinecarbaldehyde and 3-hydroxypyridine. In particular, it was demonstrated that the mixture of simple indolizidines, i.e. lentiginosine and *epi*-lentiginosine, being readily available by a number of different synthetic routes, can be directly converted to swainsonine.

1. Introduction

Indolizidines belong to an important class of alkaloids that have received broad attention due to their biological properties such as antimetastatic, antitumor-proliferative, anticancer or immunoregulating activity.[1] Most prominent, (−)-swainsonine (**1b**) is a very potent α-mannosidase inhibitor, being currently under clinical evaluation.[2] Despite their relative simple structure, the synthesis of indolizidines has remained challenging, although a number of elegant routes towards them have been reported[3] (Fig. 1).

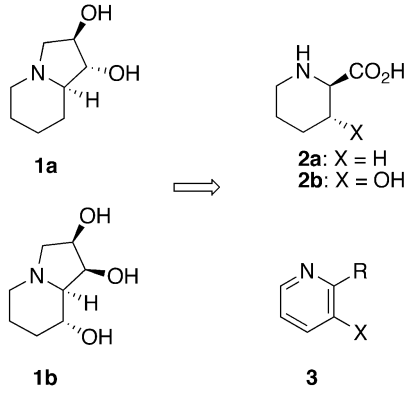

Figure 1. Retrosynthetic analysis of indolizidines.

One obvious approach towards indolizidines would be construction of the five-membered ring by appropriate functionalization of (hydroxylated) pipecolic acids, and indeed, this approach was successfully developed for the synthesis of (−)-lentiginosine (**1a**) and also of (−)-swainsonine (**1b**).[4]

However, even the parent pipecolic acid (**2a**) is not readily available in enantiomerically pure form since it is not available from the chiral pool, and—despite contrary announcements[5]—an efficient chemical large scale process is yet to be developed.

An alternate approach towards indolizidines can be envisioned from pyridines, requiring the efficient transformation of the pyridine into a piperidine ring at some point in the synthesis.[6] Following our interest to use heteroaromatic starting materials such as pyrrols,[7] furans[8] or pyridines[9] for the synthesis of natural products and analogs, we report here such a strategy that leads stereoselectively to (−)-swainsonine (**1b**) and to the epimer (−)-2,8a-di-*epi*-swainsonine.

We have reported that acrylates of pyridines cannot be used as substrates in the Sharpless asymmetric aminohydroxylation (AA) due to poisoning of the osmium catalyst by the pyridine nitrogen.[10] However, we demonstrated that the corresponding pyridine *N*-oxides **7** readily underwent this transformation, which was applied to the enantioselective synthesis of pyridine analogous side chains of paclitaxel. Recently, this strategy was taken up for the synthesis of (−)-lentiginosine (**1a**), using an asymmetric dihydroxylation of **7a** as the key step,[11] which prompts us to report our own results for the synthesis of swainsonine epimers.

2. Results and discussion

Asymmetric dihydroxylations of pyridine *N*-oxides **7a–e**, which were readily prepared from pyridines **3** and **8**

Keywords: Indolizidines; Swainsonine; 2,8a-Di-*epi*-swainsonine; Pyridine-*N*-oxides; Asymmetric dihydroxylation.
* Corresponding author. Tel.: +49 941 9434631; fax: +49 941 9434121; e-mail: oliver.reiser@chemie.uni-regensburg.de

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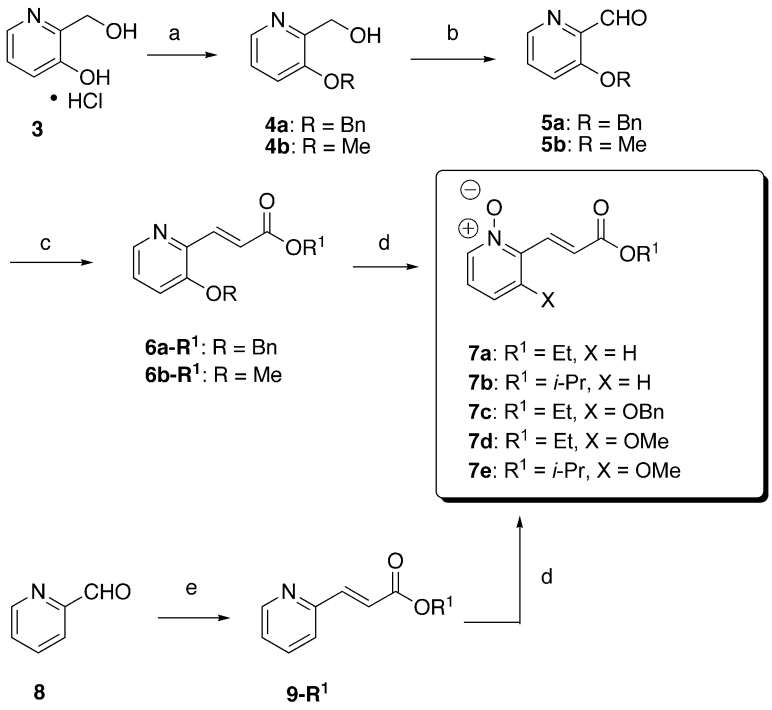
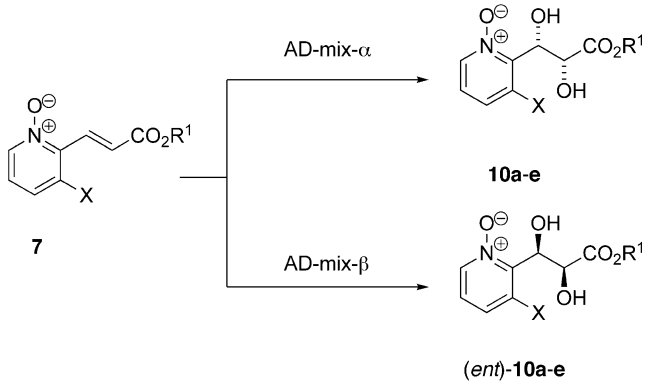


Scheme 1. Reagents and conditions: (a) (i) NaOEt, ethanol; (ii) DMSO, (**4a**: benzyl chloride; **4b**: methyl iodide), 28–39%. (b) SeO_2, dioxane, reflux, 83–84%. (c) LiBr, acetonitrile, NEt_3, $(R^1O)_2POCH_2COOR^1$, 62–84%. (d) Glacial acetic acid, hydrogen peroxide (30%), 60 °C, 77–97%. (e) LiBr, acetonitrile, NEt_3, $(R^1O)_2POCH_2COOR^1$, 62–86%.

(Scheme 1), were investigated using commercially available AD-mix.

7a gave the desired dihydroxylated products **10a**, as recently reported,[11] or (*ent*)-**10a**, respectively, with high enantioselectivity, either by employing AD-mix-α or AD-mix-β (Table 1). Likewise, the alkoxy substituted *N*-oxides **7c** and **7d** could be converted to the corresponding diols with respectable yields, however, the enantioselectivity of the reaction was distinctively dependent on the protecting group at the hydroxyl group in the 3-position on the pyridine ring: while the benzyloxy derivative **7c** gave the diols **10c** or (*ent*)-**10c** with only 53–66% ee, **7d**, substituted with the smaller methoxy group gave rise to the diols **10d** or (*ent*)-**10d** with excellent enantioselectivity. Switching from the ethyl to the isopropyl esters **7b** and **7e** considerably improved the yields by retaining the high selectivities (93–98% ee) of the dihydroxylation reaction due to the increased hydrolytic stability of the starting materials and products.

Table 1. Asymmetric dihydroxylation of **7** to **10a–e** (AD-mix-α) or (*ent*)-**10a–e** (AD-mix-β)[a]



	AD-mix-α		AD-mix-β	
	% ee	Yield (%)	% ee	Yield (%)
7a	97	39	96	36
7b	97	66	98	65
7c	53	55	66	59
7d	97	52	98	54
7e	97	93	93	72

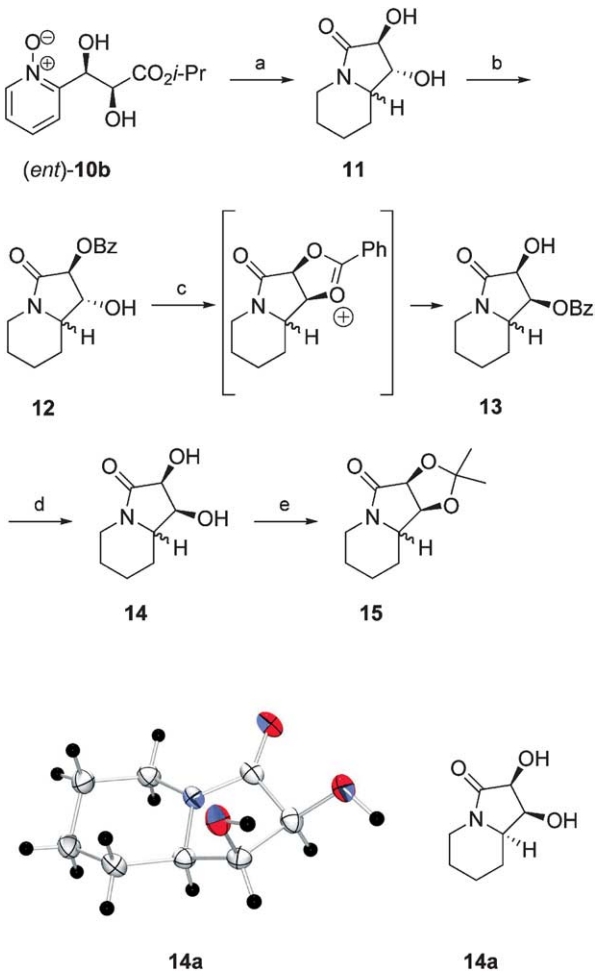
[a] Reagents and conditions: AD-Mix, $MeSO_2NH_2$, *t*-BuOH/H_2O, room temperature, 24–72 h.

2.1. Synthesis of (−)-Swainsonine

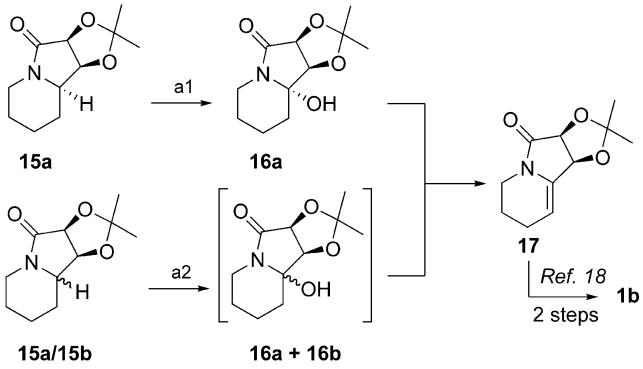
Hydrogenation of (*ent*)-**10b** was achieved at ambient pressure in methanol using platinum dioxide as catalyst. Under these conditions, reduction of the pyridine *N*-oxide to the piperidine with concurrent ring closure takes place, giving rise directly to the bicyclic derivative **11**. If palladium on charcoal was used as the catalyst instead, selective reduction of the pyridine-*N*-oxides to the corresponding pyridines takes place in quantitative yield. Compound **11** was obtained from (*ent*)-**10b** as an inseparable mixture of epimers (60:40) with respect to the stereocenter at C-2 (Scheme 2).[12] In order to invert the stereocenter[13] at C-1, this mixture was selectively benzoylated at C-2 to yield **12**, followed by treatment with triflic anhydride. The resulting **13** was debenzoylated to **14**[14] and subsequently converted to the acetonide **15**. If desired, the major epimer **14a** can be obtained in pure form by recrystallization, and its X-ray structure[15] analysis confirmed the successful establishment of the *syn*-stereochemistry of the two hydroxy groups.

The α-oxidation of *N*-acylated piperidines by ruthenium-(VIII)-catalyzed hydroxylation[16] or electrochemical alkoxylation[17] has ample precedent. As a general rule it was shown that bicyclic derivatives could be selectively oxidized at the ring junction, while acyclic substituted piperidines will be oxidized at the less substituted α-carbon.

Treatment of the mixture of epimers **15** with ruthenium-tetroxide, being generated in situ from rutheniumdioxide and sodium hypochlorite, indeed resulted in a regioselective oxidation to form **16** (Scheme 3). However, the two epimers **15** differ largely in their reactivity as well as in their stereospecifity as could be shown by carrying out the oxidation with the individual isomers: While **15a**, having the hydrogen to be oxidized oriented on the convex face of the tricyclic ring system readily formed exclusively **16a** with retention of configuration, **15b** reacted much more sluggishly and unspecifically to a mixture of **16a** and **16b**, which upon elimination gave rise to the known compound **17**.[18] Thus, when the epimeric mixture **15a/15b** (60:40) is used in this oxidation/elimination sequence, **17** is obtained (50% yield) along with unreacted **15b** (29%) which can readily be separated and recovered by chromatography. Compound **17** was subsequently converted to (−)-swainsonine (**1b**) as previously described in the literature.[18]



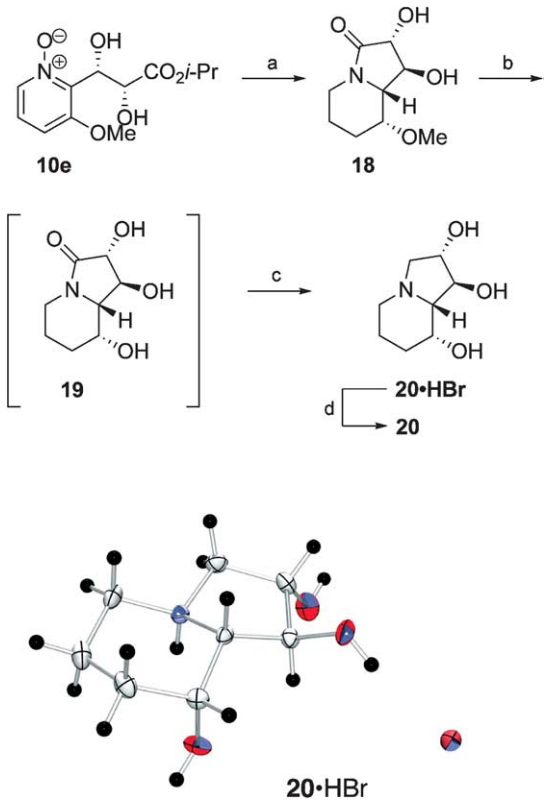
Scheme 2. Reagents and conditions: (a) $PtO_2 \cdot H_2O$, MeOH, H_2, 89%. (b) Benzoyl chloride, DMAP, pyridine, −30 °C, 84%. (c) Triflic anhydride, pyridine, CH_2Cl_2, 53%. (d) NaOMe, MeOH, 78%. (e) 2,2-Dimethoxypropane, *p*-TsOH, CH_2Cl_2, 98%.



Scheme 3. Reagents and conditions: (a1) (i) $RuO_2 \cdot H_2O$, 12% aqueous NaOCl, ethyl acetate, 0 °C→10 °C; (ii) HOAc, $CHCl_3$, 79% (2 steps). (a2) (i) $RuO_2 \cdot H_2O$, 12% aqueous NaOCl solution, ethyl acetate, 0 °C; (ii) HOAc, $CHCl_3$, 50% (2 steps) **17** + 29% recovered **15b**.

2.2. Synthesis of (−)-2,8a-di-*epi*-Swainsonine

Hydrogenation of **10e** could be analogously carried out under conditions as described for (*ent*)-**10b**. From the possible four diastereomers, **18** was formed as the major one (7:1:1:0.5) which could be obtained pure after recrystallization (Scheme 4). The configuration of **18** was confirmed by X-ray crystal analysis (not shown) as well as by subsequent chemical transformation to the known (−)-2,8a-di-*epi*-swainsonine (**20**).[19] Thus, **18** was demethylated using concentrated HBr, and the resulting crude **19** which contained ammonium bromide as a byproduct was directly reduced without purification to give rise to **20**·**HBr**. Recrystallization of **20**·**HBr** gave suitable crystals for X-ray structure analysis[15] which confirmed the relative and absolute (Flack parameter = 0.00(1)) stereochemical assignment of the product. These crystals were converted to the salt-free (−)-2,8a-di-*epi*-swainsonine (**20**) by ion exchange chromatography, showing identical melting point and NMR



Scheme 4. Reagents and conditions: (a) Pt/C (5%), HOAc, H_2, 47%. (b) HBr (48%), 140 °C, 88%. (c) $BH_3 \cdot DMS$, THF, 0 °C, 59%. (d) (i) Recrystallization ethyl acetate/MeOH 1:1, 55%; (ii) Dowex 1×8, 100–200 mesh, 100%.

data, but a different value of optical rotation (−8.8) as previously reported (−24.0) in literature.[19]

The greatly improved diastereoselectivity in the hydrogenation of **10e** compared to (*ent*)-**10b** clearly must be attributable to the alkoxy substituent in the pyridine moiety. The preferred formation of **18** from **10e** can therefore be rationalized by chelation of platinum by that group and a side chain hydroxy group as depicted in Figure 2. Restriction of the conformation in **10e** by a hydrogen bond of the second hydroxy group in the side chain with the *N*-oxide might very well be an additional control factor in this hydrogenation.

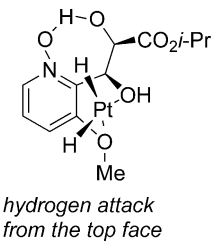


Figure 2. Model for the stereoselective hydrogenation of **10e**.

In conclusion, we have demonstrated that readily available pyridines provide a convenient access to swainsonines in diastereo- and enantiopure form.

3. Experimental

3.1. General

Reactions with moisture-sensitive chemicals were performed under nitrogen in a flame-dried reaction flask. Solvents were dried by standard methods.

Chromatography: Macherey–Nagel silica gel (0.03–0.06 mm). Enantiomeric excesses were determined by analytical HPLC using a Chiracel OD-H column (flow: 1 ml/min) and a UV detector at 254 nm. Diastereomeric ratios were determined by integration of the respective diastereomeric peaks in ^{1}H NMR. TLC: commercially precoated aluminum sheets 60 F 254 (Merck). Uncorrected melting point: Büchi SMP 20. IR: Mattson Genesis series FT-IR, Perkin–Elmer 298, Bruker IFS 66, ν in cm^{-1}. ^{1}H NMR and ^{13}C NMR: Bruker Avance 600, ARX 400, Avance 300, AC 250 F, δ in ppm, J in Hz. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer) measurements, + signifies a positive signal (CH, CH_3), − signifies a negative signal (CH_2) in DEPT 135. MS: Finnigan MAT 95, Varian MAT 311A. Elemental analysis: Heraeus CHN-Rapid. XRD: Stoe Imaging Plate System, Siemens Stoe AED2. Optical rotation: Perkin–Elmer polarimeter PE 241.

3.1.1. 3-Benzyloxy-2-hydroxymethylpyridine (4a). Sodium (4.60 g, 0.20 mol, 2.0 equiv) was added to ethanol (80 ml). After 2 h of stirring 3-hydroxy-2-(hydroxymethyl)-pyridine hydrochloride (16.2 g, 0.10 mol, 1.0 equiv) was added and the solution was stirred further for 1 h at room temperature. After addition of DMSO (125 ml), ethanol was removed under reduced pressure. Benzyl chloride (12.55 g, 11.5 ml, 0.10 mol, 1.0 equiv) was added and stirred for 12 h at room temperature. After addition of H_2O (1.5 l), the aqueous layer was extracted with $CHCl_3$ (4×100 ml). The combined organic layers were dried over $MgSO_4$, and the solution was concentrated under reduced pressure. The crude product was extracted with hot hexane (3×250 ml), and after removal of the solvent recrystallized from hexane (500 ml) to give **4a** (8.39 g, 0.04 mmol, 39%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.39 (br s, 1H), 4.82 (s, 2H), 5.11 (s, 2H), 7.16–7.17 (m, 2H), 7.34–7.40 (m, 5H), 8.15–8.17 (m, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 60.1 (−, CH_2), 69.9 (−, CH_2), 118.0 (+, Aryl-C), 122.2 (+, Aryl-C), 127.2 (+, 2C, Aryl-C), 128.3 (+, Aryl-C), 128.7 (+, 2C, Aryl-C), 136.0 (quat C), 139.8 (+, Aryl-C), 148.8 (quat C), 151.4 (quat C).

3.1.2. 3-Methoxy-2-hydroxymethylpyridine (4b). Sodium (11.5 g, 0.50 mol, 2.0 equiv) was added to ethanol (200 ml). After 3 h of stirring, DMSO (300 ml) and 3-hydroxy-2-(hydroxymethyl)-pyridine hydrochloride (40.4 g, 0.25 mol, 1.0 equiv) were added. Ethanol was removed under reduced pressure. The mixture was cooled to 0 °C, methyl iodide (35.5 g, 15.6 ml, 0.25 mol, 1.0 equiv) was added and stirred for 12 h at room temperature. After addition of H_2O (1.0 l) the aqueous layer was extracted with CH_2Cl_2 (5×100 ml). The combined organic layers were washed with brine (300 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica to yield **4b** (9.75 g, 0.07 mol,

28%) as colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 3H, OCH_3), 4.72 (s, 2H, CH_2), 7.10 (dd, J=8, 1 Hz, 1H, Aryl-H), 7.18 (dd, J=8, 4 Hz, 1H, Aryl-H), 8.12 (dd, J=4, 1 Hz, 1H, Aryl-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.1 (+, CH_3), 60.0 (−, CH_2), 116.4 (+, Aryl-C), 122.6 (+, Aryl-C), 139.3 (+, Aryl-C), 148.3 (quat C), 152.3 (quat C).

3.1.3. 3-Benzyloxypyridine-2-carbaldehyde (5a).[20] Compound **4a** (3.86 g, 17.9 mmol, 1.0 equiv) and SeO_2 (1.99 g, 17.9 mmol, 1.0 equiv) were dissolved in 50 ml of dioxane. The solution was refluxed, filtrated and concentrated. The crude product was purified by chromatography on silica to yield **5a** (3.21 g, 15.1 mmol, 84%); R_f 0.26 (hexanes/ethyl acetate 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.25 (s, 2H, CH_2Ph), 7.30–7.50 (m, 7H, Aryl-H), 8.40 (dd, J=3.6 Hz, 2.0 Hz, 1H, Aryl-H), 10.44 (s, 1H, CHO).

3.1.4. 3-Methoxypyridine-2-carbaldehyde (5b). Compound **4b** (9.00 g, 64.7 mmol, 1.0 equiv) and SeO_2 (7.17 g, 64.7 mmol, 1.0 equiv) were dissolved in dioxane (180 ml). The solution was refluxed (4 h), filtrated and concentrated. The crude product was purified by chromatography on silica to yield **5b** (7.33 g, 53.5 mmol, 83%). R_f 0.32 (ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.98 (s, 3H, OCH_3), 7.43 (dd, J=8.6 Hz, 1.4 Hz, 1H, Aryl-H), 7.50 (dd, J=8.6 Hz, 4.3 Hz, 1H, Aryl-H), 8.41 (dd, J=4.3 Hz, 1.4 Hz, 1H, Aryl-H), 10.35 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8 (+, OCH_3), 120.2 (+, Aryl-C), 128.8 (+, Aryl-C), 141.0 (C quat), 142.0 (+, Aryl-C), 157.9 (C quat), 190.3 (C quat).

3.1.5. (*E*)-Ethyl 3-(3-(benzyloxy)pyridin-2-yl)acrylate (6a-Et). To a stirred suspension of LiBr (1.04 g, 12.0 mmol, 1.2 equiv) in dry acetonitrile (50 ml) was added triethylamine (1.11 g, 1.5 ml, 11 mmol, 1.1 equiv), triethyl phosphonoacetate (1.24 g, 10 mmol, 1.0 equiv) and finally 3-benzyloxy-pyridine-2-carboxaldehyde (2.13 g, 10 mmol, 1.0 equiv). The solution was stirred 72 h at room temperature. H_2O (40 ml) was added and the aqueous layer was extracted with ethyl acetate (3×30 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica (ethyl acetate/hexanes 1:3) to yield **6a-Et** (2.39 g, 8.4 mmol, 84%, *E*/*Z*=99:1) as yellow solid. R_f 0.48 (hexanes/ethyl acetate 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.32 (t, J=7.1 Hz, 3H, CH_2CH_3), 4.26 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 5.15 (s, 2H, CH_2Ph), 7.04 (d, J=15.8 Hz, 1H, CH=CHCO$_2$Et), 7.15–7.45 (m, 7H, Aryl-H), 8.16 (dd, J=15.8 Hz, J=0.45 Hz, 1H, CH=CHCO$_2$Et), 8.22 (ddd, J=4.1 Hz, J=1.6 Hz, J=0.45 Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 60.5 (−, CH_2CH_3), 70.4 (−, CH_2Ph), 120.0 (+, Aryl-C), 122.4 (+, Aryl-C), 125.1 (+, Aryl-C), 127.2 (+, 2C, Aryl-C), 128.3 (+, CH=CHCO$_2$Et), 128.8 (+, 2C, Aryl-C), 135.8 (quat, Aryl-C), 137.8 (+, CH=CHCO$_2$Et), 141.9 (+, Aryl-C), 142.9 (quat, Aryl-C), 153.7 (quat, Aryl-C), 167.2 (quat, CO_2Et). IR (KBr) ν: 3056, 2982, 2937, 2877, 1684, 1573, 1444, 1391, 1365, 1297, 1274, 1245, 1169, 1108, 1048, 981, 927, 880, 859, 793, 773, 750, 705, 626, 598, 556 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 283.3 (3.7, M^+), 210.1 (28.9), 146.9 (1.1), 118.9 (2.7), 90.9 (100), 65.0 (7.6). Anal. Calcd for $C_{17}H_{17}NO_3$ (283.32) C 72.07, H 6.05, N 4.94. Found C 72.05, H 6.09, N 4.85.

3.1.6. (*E*)- and (*Z*)-Ethyl 3-(3-methoxypyridin-2-yl)acrylate (6b-Et). To a stirred suspension of LiBr (3.72 g, 42.7 mmol, 1.5 equiv) in dry acetonitrile (100 ml) was added triethylamine (3.18 g, 4.4 ml, 31.4 mmol, 1.1 equiv), triethyl phosphonoacetate (6.40 g, 28.5 mmol, 1.0 equiv) and finally 3-methoxypyridine-2-carbaldehyde (3.92 g, 28.5 mmol, 1.0 equiv). The solution was stirred 18 h at room temperature. H_2O (40 ml) was added and the aqueous layer was extracted with ethyl acetate (3×100 ml). The combined organic layers were washed with brine (100 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (*E*/*Z*=93:7) was purified by chromatography on silica (ethyl acetate/hexanes 1:2) to yield (*E*)-**6b-Et** (4.81 g, 23.2 mmol, 81%) as colorless solid and (*Z*)-**6b-Et** (382 mg, 1.8 mmol, 6.5%) as yellow oil. (*E*)-**6b-Et**: R_f 44 (hexanes/ethyl acetate 1:1). Mp 63 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.33 (t, J=7.1 Hz, 3H, CH_2CH_3), 3.87 (s, 3H, OCH_3), 4.27 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 7.01 (d, J=15.8 Hz, 1H, CH=CHCO$_2$Et), 7.18–7.29 (m, 2H, Aryl-H), 8.07 (dd, J=15.8, 0.46 Hz, 1H, CH=CHCO$_2$Et), 8.21 (ddd, J=3.9, 1.9, 0.42 Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.2 (+, CH_2CH_3), 55.4 (+, OCH_3), 60.3 (−, CH_2CH_3), 118.3 (+, Aryl-C), 122.1 (+, Aryl-C), 125.2 (+, CH=CHCO$_2$Et), 137.8 (+, Aryl-C), 141.4 (+, CH=CHCO$_2$Et), 142.3 (quat, Aryl-C), 154.6 (quat, Aryl-C), 167.1 (quat, CO_2Et). IR (KBr) ν: 3016, 2990, 2940, 2904, 1707, 1635, 1573, 1464, 1440, 1423, 1365, 1303, 1276, 1259, 1235, 1166, 1108, 1069, 1035, 1012, 980, 895, 876, 799, 774, 595, 574 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 207.0 (39.2 M^+), 177.9 (30.4), 161.9 (100.0), 133.9 (50.2), 119.9 (28.1), 105.9 (19.0), 90.9 (11.5). Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23) C 63.76, H 6.32, N 6.76. Found C 63.64, H 6.29, N 6.81. (*Z*)-**6b-Et**: R_f 0.30 (hexanes/ethyl acetate 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.20 (t, J=7.2 Hz, 3H, CH_2CH_3), 3.82 (s, 3H, OCH_3), 4.18 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 6.13 (d, J=12.1 Hz, 1H, CH=CHCO$_2$Et), 7.09 (d, J=12.1 Hz, 1H, CH=CHCO$_2$Et), 7.12–7.22 (m, 2H, Aryl-H), 8.15 (ddd, J=3.9, 2.1, 0.27 Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.0 (+, CH_2CH_3), 55.4 (+, OCH_3), 60.3 (−, CH_2CH_3), 117.5 (+, Aryl-C), 123.90 (+, Aryl-C), 123.96 (+, CH=CHCO$_2$Et), 132.8 (+, CH=CHCO$_2$Et), 140.7 (+, Aryl-C), 143.9 (quat, Aryl-C), 153.4 (quat, Aryl-C), 167.6 (quat, CO_2Et). IR (Film) ν: 3059, 2982, 2941, 2840, 1724, 1637, 1580, 1462, 1432, 1398, 1277, 1189, 1118, 1069, 1029, 948, 858, 830, 798, 749 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 207.1 (34.2, M^+), 178.0 (32.1), 162.0 (100.0), 148.0 (14.4), 134.0 (44.4), 119.9 (26.4), 106.0 (17.8), 91.0 (11.5). Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23) C 63.76, H 6.32, N 6.76. Found C 63.36, H 6.36, N 6.76.

3.1.7. (*E*)- and (*Z*)-Isopropyl 3-(3-methoxypyridin-2-yl)acrylate (6b-*i*Pr). To a stirred suspension of LiBr (4.51 g, 51.9 mmol, 1.5 equiv) in dry acetonitrile (100 ml) under nitrogen atmosphere was added at room temperature triethylamine (3.85 g, 5.3 ml, 38.1 mmol, 1.1 equiv), triisopropyl phosphonoacetate (9.23 g, 34.6 mmol, 1.0 equiv) and finally 3-methoxypyridine-2-carbaldehyde (4.75 g, 34.6 mmol, 1.0 equiv). The solution was stirred for 120 h at room temperature. H_2O (100 ml) was added and the aqueous layer was extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with H_2O (100 ml) and brine (100 ml), dried over $MgSO_4$ and

concentrated under reduced pressure. The crude product (*E*/*Z*=86:14) was purified by chromatography on silica (ethyl acetate/hexanes 1:2) to yield (*E*)-**6b**-***i*Pr** (4.76 g, 21.5 mmol, 62%) and (*Z*)-**6b**-***i*Pr** (567 mg, 2.6 mmol, 7%) as colorless oils. (*E*)-**6b**-***i*Pr**: R_f 0.30 (ethyl acetate/hexanes 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (d, J=6.2 Hz, 6H, CH(CH_3)$_2$), 3.90 (s, 3H, OCH_3), 5.14 (hept, J=6.2 Hz, 1H, CH(CH_3)$_2$), 6.99 (d, J=15.8 Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.23 (d, J=1.7 Hz, 1H, Aryl-H), 7.24 (d, J=4.2 Hz, 1H, Aryl-H), 8.05 (d, J=15.8 Hz, 1H, CH=CHCO$_2$*i*-Pr), 8.22 (dd, J=4.2, 1.7 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.9 (+, 2C, CH(CH_3)$_2$), 55.4 (+, OCH_3), 67.7 (+, CH(CH_3)$_2$), 118.3 (+, CH=CHCO$_2$*i*-Pr), 122.9 (+, Aryl-C), 125.1 (+, Aryl-C), 137.7 (+, CH=CHCO$_2$*i*-Pr), 141.5 (+, Aryl-C), 142.6 (quat, Aryl-C), 154.6 (quat, Aryl-C), 166.7 (quat, CO$_2$*i*-Pr). MS (DCI, NH_3) *m*/*z* (%): 222.3 (100, MH^+). IR (film) ν: 3061, 2979, 2940, 2839, 1712, 1638, 1576, 1466, 1429, 1301, 1271, 1235, 1179, 1109, 1069, 1017, 986, 917, 879, 834, 799, 772 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25) C 65.14, H 6.83, N 6.33. Found C 64.75, H 6.76, N 6.30. (*E*)-**6b**-***i*Pr**: R_f 0.22 (ethyl acetate/hexanes 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, J=6.2 Hz, 6H, CH(CH_3)$_2$), 3.84 (s, 3H, OCH_3), 5.09 (hept, J=6.2 Hz, 1H, CH(CH_3)$_2$), 6.12 (d, J=12.1 Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.07 (d, J=12.1 Hz, 1H, CH=CHCO$_2$-*i*-Pr), 7.17 (d, J=1.9 Hz, 1H, Aryl-H), 7.18 (d, J=4.4 Hz, 1H, Aryl-H), 8.15 (dd, J=4.2 Hz, 1.7 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.7 (+, 2C, CH(CH_3)$_2$), 55.3 (+, OCH_3), 67.9 (+, CH(CH_3)$_2$), 117.4 (+, CH=CHCO$_2$-*i*-Pr), 123.8 (+, Aryl-C), 124.5 (+, Aryl-C), 132.1 (+, CH=CHCO$_2$*i*-Pr), 140.6 (+, Aryl-C), 144.0 (quat, Aryl-C), 153.3 (quat, Aryl-C), 167.2 (quat, CO$_2$*i*-Pr). MS (DCI, NH_3) *m*/*z* (%): 266.3 (13.2), 222.3 (100, MH^+). IR (film) ν: 3057, 2980, 2938, 2838, 1718, 1637, 1579, 1454, 1431, 1395, 1275, 1179, 1115, 1069, 961, 859, 828, 799, 782, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25) C 65.14, H 6.83, N 6.33. Found C 64.65, H 6.81, N 6.33.

3.1.8. (*E*)-Ethyl 3-(*N*-oxypyridin-2-yl)acrylate (7a). To a cooled solution (0 °C) of 70% *m*-chlorperbenzoic acid (1.45 g, 7.9 mmol, 1.1 equiv) in CH_2Cl_2 (50 ml) was added a solution of (*E*)-**9**-**Et** (1.43 g, 8.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 ml). After 30 min the solution was refluxed for 20 h, cooled to room temperature and concentrated. The crude product was purified by chromatography on neutral aluminium oxide ($CHCl_3$/MeOH 19:1) to give **7a** (1.54 g, 8.0 mmol, 97%) as a yellow solid. Mp 71 °C. R_f 0.41 ($CHCl_3$/MeOH 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, J=7.2 Hz, 3H, CH_2CH_3), 4.29 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 6.98 (d, J=16.3 Hz, 1H, CH=CHCO$_2$Et), 7.23–7.29 (m, 2H, Aryl-H), 7.53–7.57 (m, 1H, Aryl-H), 8.07 (d, J=16.3 Hz, 1H, CH=CHCO$_2$Et), 8.25–8.28 (m, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 61.0 (−, CH$_2$CH$_3$), 124.9 (+, CH=CHHCO$_2$-Et), 125.1 (+, Aryl-C), 125.7 (+, Aryl-C), 125.8 (+, Aryl-C), 133.9 (+, Aryl-C), 140.4 (+, CH=CHCO$_2$Et), 145.2 (quat, Aryl-C), 166.3 (quat, CO$_2$Et). IR (KBr) ν: 3090, 3042, 2980, 2440, 1700, 1625, 1480, 1425, 1365, 1305, 1230, 1180, 1020, 985, 875, 860, 832, 808, 740, 727, 580, 540 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 193.1 (6.1), 177.1 (5.7), 148.0 (21.3), 132.1 (19.9), 120.1 (100), 104.1 (7.7), 92.0 (74.8). Anal. Calcd for $C_{10}H_{11}NO_3$ (193.20) C 62.17, H 5.74, N 7.25. Found C 61.97, H 5.65, N 7.18.

3.1.9. (*E*)-Isopropyl 3-(*N*-oxypyridin-2-yl)acrylate (7b). To a solution of (*E*)-**9**-***i*Pr** (4.39 g, 28.2 mmol, 1.0 equiv) in glacial acid (10.9 g, 10.3 ml, 181 mmol, 6.4 equiv) was added hydrogen peroxide (30%, 10.3 ml, 102 mmol, 3.6 equiv), and the mixture was heated for 12 h at 60 °C. The resulting solution was concentrated under reduced pressure to give a yellow oil, which was purified by chromatography on silica (ethyl acetate) to give **7b** (4.59 g, 22.1 mmol, 79%) as a yellow solid. Mp 98 °C. R_f 0.42 ($CHCl_3$/MeOH 19:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.32 (d, J=6.3 Hz, 6H, CH(CH_3)$_2$), 5.15 (hept, J=6.3 Hz, 1H, CH(CH_3)$_2$), 6.95 (d, J=16.3 Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.26–7.34 (m, 2H, Aryl-H), 7.56–7.61 (m, 1H, Aryl-H), 8.07 (d, J=16.3 Hz, 1H, CH=CHCO$_2$*i*-Pr), 8.26–8.31 (m, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.8 (+, 2C, CH(CH_3)$_2$), 68.4 (+, CH(CH_3)$_2$), 125.2 (+, Aryl-C), 125.4 (+, Aryl-C), 125.7 (+, Aryl-C), 125.8 (+, CH=CHCO$_2$*i*-Pr), 133.6 (+, CH=CHCO$_2$*i*-Pr), 140.4 (+, Aryl-C), 145.3 (quat, Aryl-C), 165.6 (quat, CO$_2$*i*-Pr). MS (EI, 70 eV) *m*/*z* (%): 207.0 (3.4, MH^+), 191.0 (5.36), 147.9 (23.3), 131.9 (23.2), 119.9 (100), 104.9 (11.9), 103.9 (10.4), 91.9 (84.4), 77.9 (16.7), 65.0 (23.9). IR (film) ν: 3076, 2989, 1701, 1491, 1473, 1435, 1377, 1350, 1317, 1279, 1240, 1228, 1209, 1178, 1163, 1146, 1109, 989, 897, 876, 841, 812, 758, 569, 526 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23) C 63.76, H 6.32, N 6.76. Found C 63.64, H 6.25, N 6.70.

3.1.10. (*E*)-Ethyl 3-(3-(benzyloxy)-*N*-oxypyridin-2-yl)-acrylate (7c). To a solution of (*E*)-**6a**-**Et** (3.41 g, 12.0 mmol, 1.0 equiv) in glacial acetic acid (4.62 g, 4.4 ml, 76.8 mmol, 6.4 equiv), hydrogen peroxide (30%, 4.90 g, 4.4 ml, 43.2 mmol, 3.6 equiv) was added, and the mixture was heated for 12 h at 60 °C. The mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica (ethyl acetate) to give **7c** (2.77 g, 9.26 mmol, 77%) as a yellow solid. Mp 87 °C. R_f 0.35 ($CHCl_3$/MeOH 19:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.32 (t, J=7.1 Hz, 3H, CH_2CH_3), 4.26 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 5.23 (s, 2H, CH_2C$_6$H$_5$), 6.85 (ddd, J=8.7, 0.92, 0.30 Hz, 1H, Aryl-H), 7.07 (dd, J=8.7, 6.5 Hz, 1H, Aryl-H), 7.29–7.46 (m, 5H, Aryl-H), 7.64 (d, J=16.2 Hz, 1H. CH=CHCO$_2$Et), 7.94 (ddd, J=6.54, 0.95, 0.46 Hz, 1H, Aryl-H), 8.20 (d, J=16.2 Hz, 1H, CH=CHCO$_2$Et). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 60.7 (−, CH$_2$CH$_3$), 71.5 (−, CH$_2$C$_6$H$_5$), 109.0 (+, Aryl-C), 124.1 (+, Aryl-C), 126.4 (+, Aryl-C), 127.2 (+, 2C, Aryl-C), 128.6 (+, CH=CHCO$_2$Et), 128.9 (+, 2C, Aryl-C), 129.2 (+, Aryl-C), 133.8 (+, CH=CHCO$_2$Et), 134.9 (quat, Aryl-C), 136.6 (quat, Aryl-C), 156.4 (quat, Aryl-C), 167.7 (quat, CO$_2$Et). IR (KBr) ν: 3121, 3074, 2983, 1714, 1696, 1627, 1558, 1499, 1463, 1434, 1394, 1367, 1312, 1282, 1257, 1233, 1212, 1177, 1146, 1088, 1045, 988, 869, 782, 743, 721, 689, 632, 583, 545 cm^{-1}. MS (EI, 70 eV) 299.3 (1.02, M^+), 283.3 (0.69), 226.1 (16.7), 210.1 (8.54), 107.9 (1.41), 90.9 (100.0). Anal. Calcd for $C_{17}H_{17}NO_4$ (299.32) C 68.21, H 5.72, N 4.68. Found C 67.94, H 5.71, N 4.51.

3.1.11. (*E*)-Ethyl 3-(3-(methoxy)-*N*-oxypyridin-2-yl)-acrylate (7d). To the solution of (*E*)-**6b**-**Et** (2.07 g, 10.0 mmol, 1.0 equiv) in glacial acetic acid (4.08 g, 3.7 ml, 120.0 mmol, 12.0 equiv), hydrogen peroxide (30%, 3.85 g, 3.7 ml, 19.2 mmol, 1.9 equiv) was added, and the mixture was heated for 12 h at 60 °C. The resulting solution

was concentrated under reduced pressure and the residue was purified by chromatography on silica (ethyl acetate/MeOH 49:1) to give **7d** (1.80 g, 8.05 mmol, 81%) as a yellow solid. Mp 100 °C. R_f 0.24 ($CHCl_3$/MeOH 9:1). ^1H NMR (250 MHz, $CDCl_3$) δ: 1.34 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 3.97 (s, 3H, OCH_3), 4.28 (q, $J=7.1$ Hz, 2H, CH_2CH_3), 6.87 (ddd, $J=8.6$, 0.89, 0.38 Hz, 1H, Aryl-H), 7.16 (dd, $J=8.7$, 6.6 Hz, 1H, Aryl-H), 7.57 (d, $J=16.2$ Hz, 1H, CH=CHCO$_2$Et), 7.95 (ddd, $J=6.6$, 0.99, 0.43 Hz, 1H, Aryl-H), 8.14 (d, $J=16.2$ Hz, 1H, CH=CHCO$_2$Et). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 56.6 (+, OCH_3), 60.7 (−, CH_2CH_3), 107.5 (+, Aryl-C), 124.3 (+, Aryl-C), 126.0 (+, Aryl-C), 129.3 (+, CH=CHCO$_2$Et), 133.4 (+, CH=CHCO$_2$Et), 136.1 (quat, Aryl-C), 157.4 (quat, Aryl-C), 167.6 (quat, CO$_2$Et). IR (KBr) ν: 3123, 2991, 2901, 1719, 1623, 1555, 1458, 1447, 1424, 1362, 1291, 1235, 1186, 1170, 1084, 984, 951, 872, 843, 785, 746, 684, 653, 622, 576, 545, 535, 511 cm^{-1}. MS (EI, 70 eV) 223.1 (3.16, M^+), 207.1 (13.9), 178.0 (22.2), 162.1 (38.4), 150.0 (54.6), 134.0 (20.4), 122.0 (39.7), 106.0 (10.3), 92.0 (100.0). Anal. Calcd for $C_{11}H_{13}NO_4$ (223.23) C 59.19, H 5.87, N 6.27. Found C 59.08, H 5.90, N 6.17.

3.1.12. (*E*)-Isopropyl 3-(3-(methoxy)-*N*-oxypyridin-2-yl)acrylate (7e). To a solution of (*E*)-**6b**-***i*Pr** (3.06 g, 13.8 mmol, 1.0 equiv) in glacial acetic acid (5.63 g, 5.0 ml, 166 mmol, 12.0 equiv), hydrogen peroxide (30%, 5.31 g, 5.0 ml, 46.8 mmol, 3.4 equiv) was added, and the mixture was heated for 12 h at 60 °C. The resulting solution was concentrated under reduced pressure, and the residue was purified by chromatography on silica (ethyl acetate/methanol 30:1) to give **7e** (2.93 g, 12.3 mmol, 90%) as a yellow solid. R_f 0.33 ($CHCl_3$/MeOH 9:1). ^1H NMR (250 MHz, $CDCl_3$) δ: 1.31 (d, $J=6.3$ Hz, 6H, CH(CH_3)$_2$), 3.96 (s, 3H, OCH_3), 5.15 (hept, $J=6.3$ Hz, 1H, CH(CH$_3$)$_2$), 6.84 (ddd, $J=8.6$, 0.48, 0.48 Hz, 1H, Aryl-H), 7.14 (dd, $J=8.7$, 6.6 Hz, 1H, Aryl-H), 7.55 (d, $J=16.2$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.96 (ddd, $J=6.6$, 0.99, 0.46 Hz, 1H, Aryl-H), 8.13 (ddd, $J=16.2$, 0.45, 0.45 Hz, 1H, CH=CHCO$_2$*i*-Pr). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.9 (+, 2C, CH(CH_3)$_2$), 56.5 (+, OCH_3), 68.1 (+, CH(CH$_3$)$_2$), 107.4 (+, Aryl-C), 124.1 (+, Aryl-C), 126.7 (+, Aryl-C), 129.0 (+, CH=CHCO$_2$*i*-Pr), 133.5 (+, CH=CHCO$_2$*i*-Pr), 136.3 (quat, Aryl-C), 157.4 (quat, Aryl-C), 167.2 (quat, CO$_2$*i*-Pr). IR (KBr) ν: 3117, 3094, 3061, 2979, 2954, 2932, 1712, 1629, 1595, 1562, 1477, 1422, 1375, 1361, 1313, 1293, 1265, 1221, 1203, 1100, 1074, 985, 959, 911, 871, 789, 740, 545 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 255.3 (4.1, $M+NH_4^+$), 238.3 (10.7, MH^+), 222.2 (100). Anal. Calcd for $C_{12}H_{15}NO_4$ (237.25): C 60.75, H 6.37, N 5.90. Found C 60.14, H 6.36, N 5.88.

3.1.13. (*E*)-Ethyl 3-(pyridin-2-yl)acrylate (9-Et).[21] To a stirred suspension of LiBr (10.4 g, 120 mmol, 1.2 equiv) in dry acetonitrile (250 ml) was added triethylamine (11.1 g, 15.3 ml, 110 mmol, 1.1 equiv), triethyl phosphonoacetate (22.4 g, 20.0 ml 100 mmol, 1.0 equiv) and finally pyridine-2-carbaldehyde (**8**) (10.7 g, 9.7 ml, 100 mmol, 1.0 equiv). The solution was stirred for 18 h at room temperature. H_2O (200 ml) was added and the aqueous layer was extracted with ethyl acetate (5×50 ml). The combined organic layers were dried over $MgSO_4$ and the solution was concentrated under reduced pressure. The crude product was dissolved in ethyl acetate (100 ml), and the solution was filtrated, concentrated and distilled under reduced pressure to get **9-Et** (15.2 g; 85.8 mmol, 86%, *E*/*Z*=95:5) as colorless oil ($bp_{0.1}$ 80 °C), R_f 0.33 (hexanes/ethyl acetate 1:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 4.28 (q, $J=7.2$ Hz, 2H, CH_2CH_3), 6.92 (d, $J=15.7$ Hz, 1H, CH=CHCO$_2$Et), 7.25–7.74 (m, 3H, Aryl-H), 7.69 (d, $J=15.7$ Hz, 1H, CH=CHCO$_2$Et), 8.58–8.66 (m, 1H, Aryl-H).

3.1.14. (*E*)- and (*Z*)-Isopropyl 3-(pyridin-2-yl)acrylate ((*E*)-9-*i*Pr and (*Z*)-9-*i*Pr). To a stirred suspension of LiBr (5.21 g, 60 mmol, 1.2 equiv) in dry acetonitrile (150 ml) under nitrogen atmosphere was added at room temperature triethylamine (5.57 g, 7.6 ml, 55 mmol, 1.1 equiv), triisopropyl phosphonoacetate (13.3 g, 50 mmol, 1.0 equiv) and finally pyridine-2-carbaldehyde (**8**) (5.36 g, 4.8 ml, 50 mmol). The solution was stirred 48 h at room temperature. H_2O (200 ml) was added and the aqueous layer was extracted with ethyl acetate (3×100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica (ethyl acetate/hexanes 1:2) to yield (*E*)-**9-*i*Pr** (5.91 g, 30.9 mmol, 62%) and (*Z*)-**9-*i*Pr** (0.27 g, 1.4 mmol, 2.9%). (*E*)-**9-*i*Pr**: R_f 0.52 (ethyl acetate/hexane 1:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (d, $J=6.3$ Hz, 6H, CH(CH_3)$_2$), 5.15 (hept, $J=6.3$ Hz, 1H, CH(CH$_3$)$_2$), 6.89 (d, $J=15.6$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.23-7.73 (m, 3H, Aryl-H), 7.67 (d, $J=15.7$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 8.63–8.65 (m, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.9 (+, 2C, CH(CH_3)$_2$), 67.9 (+, CH(CH$_3$)$_2$), 123.0 (+, Aryl-C), 123.9 (+, Aryl-C), 124.1 (+, Aryl-C), 136.7 (+, CH=CHCO$_2$*i*-Pr), 143.0 (+, CH=CHCO$_2$*i*-Pr), 150.1 (+, Aryl-C), 153.1 (quat, Aryl-C), 166.2 (quat, CO$_2$*i*-Pr). MS (EI, 70 eV) *m/z* (%): 191.0 (19.6, MH^+), 148.9 (21.4), 145.9 (14.6), 131.9 (100.0). IR (film) ν: 3051, 2981, 2937, 2875, 1721, 1647, 1581, 1468, 1433, 1373, 1350, 1315, 1296, 1275, 1109, 1049, 985, 916, 876, 823, 787, 744 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32. Found C 69.00, H 6.82, N 7.38. (*Z*)-**9-*i*Pr**: R_f 0.40 (ethyl acetate/hexanes 1:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (d, $J=6.2$ Hz, 6H, CH(CH_3)$_2$), 5.10 (hept, $J=6.3$ Hz, 1H, CH(CH$_3$)$_2$), 6.11 (d, $J=12.5$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 6.91 (d, $J=12.5$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.16–7.21 (m, 1H, Aryl-H), 7.59–7.69 (m, 2H, Aryl-H), 8.58 (d, $J=4.8$ Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.7 (+, 2C, CH(CH_3)$_2$), 68.1 (+, CH(CH$_3$)$_2$), 122.9 (+, Aryl-C), 123.7 (+, Aryl-C), 124.3 (+, CH=CHCO$_2$*i*-Pr), 135.9 (+, Aryl-C), 138.9 (+, CH=CHCO$_2$*i*-Pr), 149.1 (+, Aryl-C), 153.7 (quat, Aryl-C), 166.3 (quat, CO$_2$*i*-Pr). MS (EI, 70 eV) *m/z* (%): 191.0 (10.3, MH^+), 247.9 (31.4), 131.9 (100.0), 104.9 (39.0), 77.9 (27.6). IR (film) ν: 3053, 2981, 2935, 2877, 1720, 1637, 1585, 1566, 1468, 1435, 1387, 1373, 1244, 1211, 1178, 1147, 1109, 1049, 995, 960, 904, 835, 798, 746 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32. Found C 68.80, H 6.80, N 7.34.

3.2. General procedure GP1 for the dihydroxylation of 7

A mixture of AD-mix (1.40 g), methansulfonamide (95 mg, 1.0 mmol, 1.0 equiv) and **7** (1.0 mmol, 1.0 equiv) in *tert*-butanol–water (15 ml, 1:1 v/v) was stirred vigorously at room temperature. After 24 h water (5 ml) was added and

the aqueous layer was extracted ten times with $CHCl_3$/MeOH (9:1 v/v, 20 ml each). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography on silica to give **10**.

3.2.1. (2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate (10a). According to GP1 **10a** (86 mg, 0.39 mmol, 39%) was obtained as colorless solid. R_f 0.24 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20} = +14.1$ ($c=0.69$, $CHCl_3$). ^{1}H NMR (250 MHz, [D$_6$]-DMSO) δ: 1.20 (t, $J=7.1$ Hz, 3H, CH_2CH_3), 4.14 (q, $J=7.1$ Hz, 2H, CH_2CH_3), 4.69 (dd, $J=7.9$, 2.4 Hz, 1H, C*H*OHCO$_2$Et), 5.30 (d, $J=7.9$ Hz, 1H, CHO*H*CO$_2$Et), 5.39 (dd, $J=6.9$ Hz, 1H, C*H*OHCHOHCO$_2$Et), 5.94 (d, $J=6.9$ Hz, 1H, CHO*H*CHOHCO$_2$Et), 7.33 (ddd, $J=7.6$, 6.0, 2.3 Hz, 1H, Aryl-H), 7.39 (ddd, $J=7.7$, 7.6, 1.4 Hz, 1H, Aryl-H), 7.57 (dd, $J=7.5$, 2.3 Hz, 1H, Aryl-H), 8.22 (ddd, $J=5.9$, 1.5, 0.44 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, D_2O) δ: 13.5 (+, CH_2CH_3), 62.9 (−, CH_2CH_3), 69.4 (+, CHOHCHOHCO$_2$Et), 70.8 (+, CHOHCHOHCO$_2$Et), 125.9 (+, Aryl-C), 126.1 (+, Aryl-C), 131.6 (+, Aryl-C), 139.6 (+, Aryl-C), 150.4 (quat, Aryl-C), 173.3 (quat, CO$_2$Et). IR (KBr) ν: 3411, 3235, 2993, 1920, 2852, 1723, 1489, 1437, 1283, 1248, 1224, 1128, 1068, 831, 772, 682, 552 cm^{-1}. MS (DCI) *m/z* (%): 228.2 (42.5, MH$^+$), 212.2 (100.0), 210.2 (26.6), 194.1 (19.8), 178.1 (7.2), 125.1 (12.6), 108.1 (58.1). Anal. Calcd for $C_{10}H_{13}NO_5$ (227.21): C 52.86, H 5.77, N 6.16. Found C 52.53, H 5.70, N 6.11. Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 18.6 min (**10a**), 20.9 min ((*ent*)-**10a**).

3.2.2. (2*S*,3*R*)-Ethyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate ((*ent*)-10a). According to GP1 (*ent*)-**10a** (82 mg, 0.36 mmol, 36%) was obtained as colorless solid. Analytical data according to **10a**; $[\alpha]_D^{20} = -25.3$ ($c=1.03$, $CHCl_3$). Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 18.0 min (**10a**), 19.7 min ((*ent*)-**10a**).

3.2.3. (2*R*,3*S*)-Isopropyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate (10b). According to GP1 **10b** (158 mg, 0.66 mmol, 66%) was obtained as colorless solid. R_f 0.24 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20} = +26.7$ ($c=0.88$, $CHCl_3$). ^{1}H NMR (250 MHz, [D$_6$]-DMSO) δ: 1.21 (dd, $J=6.2$, 3.8 Hz, 6H, CH(C*H*$_3$)$_2$), 4.56 (dd, $J=7.9$, 2.5 Hz, 1H, C*H*OHCO$_2$*i*-Pr), 4.96 (hept, $J=6.3$ Hz, 1H, C*H*(CH$_3$)$_2$), 5.23 (d, $J=7.9$ Hz, 1H, CHO*H*CO$_2$*i*-Pr), 5.36 (dd, $J=6.9$, 2.4 Hz, 1H, C*H*OHCHOHCO$_2$*i*-Pr), 5.89 (d, $J=6.9$ Hz, 1H, CHO*H*CHOHCO$_2$*i*-Pr), 7.28–7.44 (m, 2H, Aryl-H), 7.55 (dd, $J=7.6$, 2.5 Hz, 1H, Aryl-H), 8.22 (ddd, $J=5.8$, 1.6, 0.66 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.57, 21.67 (+, 2C, CH(*C*H$_3$)$_2$), 67.8, 69.2, 69.8 (+, 3C, *C*HOHCHOHCO$_2$*i*-Pr, *C*HOHCO$_2$*i*-Pr and *C*H(CH$_3$)$_2$), 124.6 (+, Aryl-C), 125.1 (+, Aryl-C), 125.4 (+, Aryl-C), 138.7 (+, Aryl-C), 151.2 (quat, Aryl-C) 171.7 (quat, *C*O$_2$*i*-Pr). IR (film) ν: 3386, 3203, 3120, 2983, 2937, 1747, 1726, 1637, 1489, 1437, 1375, 1321, 1277, 1261, 1199, 1132, 1105, 1068, 970, 914, 827, 769, 682 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 483.3 (2.0), 467.3 (0.4), 242.1 (100, MH$^+$), 226.1 (65), 224.1 (24), 208 (6.9), 125.0 (4.1), 108.0 (30). HRMS ($C_{11}H_{16}NO_5$) calcd 242.1028, found 242.1028. Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 95:5, 0.8 ml/min, 20 °C, ret.-times: 51.4 min (**10b**), 62.9 min ((*ent*)-**10b**).

3.2.4. (2*S*,3*R*)-Isopropyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate ((*ent*)-10b). According to GP1 (*ent*)-**10b** (157 mg, 0.65 mmol, 65%) was obtained as colorless solid. Analytical data according to **10b**; $[\alpha]_D^{20} = -21.2$ ($c=0.99$, $CHCl_3$). Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 95:5, 0.8 ml/min, 20 °C, ret.-times: 49.4 min (**10b**), 53.9 min ((*ent*)-**10b**).

3.2.5. (2*R*,3*S*)-Ethyl 3-(3-(benzyloxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate (10c). According to GP1 **10c** (185 mg, 0.55 mmol, 55%) was obtained as colorless solid. R_f 0.12 (ethyl acetate/MeOH 50:1). $[\alpha]_D^{20} = -39.0$ ($c=1.23$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.23 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 4.14–4.29 (m, 2H, CH_2CH_3), 4.60 (d, $J=3.7$ Hz, 1H, C*H*OHCO$_2$Et), 5.03 (bs, 1H, O*H*), 5.12–5.24 (m, 2H, CH_2Ph), 5.71 (d, $J=3.7$ Hz, 1H, C*H*OHCHOHCO$_2$Et), 7.10 (dd, $J=8.7$, 0.7 Hz, 1H, Aryl-H, 7.24 (ddd, $J=8.7$, 6.4, 0.2 Hz, 1H, Aryl-H), 7.33–7.42 (m, 5H, Aryl-H), 7.66 (bs, 1H, O*H*), 7.92 (ddd, $J=6.4$, 0.74, 0.24 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.1 (+, CH_2CH_3), 61.4 (−, CH_2CH_3), 70.0 (+, CHOHCHOHCO$_2$Et), 71.4 (−, CH_2Ph), 74.9 (+, CHOHCO$_2$Et), 112.8 (+, Aryl-C), 124.7 (+, Aryl-C), 127.0 (+, 2C, Aryl-C), 128.6 (+, Aryl-C), 128.9 (+, 2C, Aryl-C), 133.3 (+, Aryl-C), 134.7 (quat, Aryl-C), 139.2 (quat, Aryl-C), 154.1 (quat, Aryl-C), 171.4 (quat, CO$_2$Et). IR (KBr) ν: 3335, 3094, 2981, 1746, 1569, 1438, 1388, 1289, 1199, 1128, 1062, 862, 791, 741, 697 cm^{-1}. MS (FAB, pos) *m/z* (%): 667.2 (3.9), 334.1 (100, MH$^+$), 318.1 (8.4), 230.0 (9.1). HRMS ($C_{17}H_{20}NO_6$) calcd 334.1291, found 334.1287. Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (260 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 52.7 min (**10c**), 58.1 min ((*ent*)-**10c**).

3.2.6. (2*S*,3*R*)-Ethyl 3-(3-(benzyloxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate ((*ent*)-10c). According to GP1 (*ent*)-**10c** (197 mg, 0.59 mmol, 59%) was obtained as colorless solid. Analytical data according to **10c**; $[\alpha]_D^{20} = +44.7$ ($c=0.97$, $CHCl_3$). Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (260 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 53.9 min (**10c**), 57.2 min ((*ent*)-**10c**).

3.2.7. (2*R*,3*S*)-Ethyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate (10d). According to GP1 **10d** (134 mg, 0.52 mmol, 52%) was obtained as colorless solid. Mp 103 °C. R_f 0.30 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20} = -122.0$ ($c=0.86$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.29 (t, $J=7.1$ Hz, 3H, CH_2CH_3), 3.94 (s, 3H, OCH_3), 4.27 (q, $J=7.1$ Hz, 2H, CH_2CH_3), 4.56 (dd, $J=6.1$, 4.1 Hz, 1H, C*H*OHCO$_2$Et), 5.04 (d, $J=6.8$ Hz, 1H, O*H*), 5.59 (dd, $J=11.0$, 4.0 Hz, 1H, C*H*OHCHOHCO$_2$Et), 7.07 (dd, $J=8.8$, 0.81 Hz, 1H, Aryl-H), 7.31 (dd, $J=8.8$, 6.6 Hz, 1H,

Aryl-H), 7.59 (d, $J=11.1$ Hz, 1H, O*H*), 7.94 (dd, $J=6.5$, 0.84 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.2 (+, CH_2CH_3), 56.8 (+, OCH_3), 61.5 (−, CH_2CH_3), 69.8 (+, *C*HOHCHOHCO$_2$Et), 75.0 (+, *C*HOHCO$_2$Et), 111.4 (+, Aryl-C), 124.8 (+, Aryl-C), 133.1 (+, Aryl-C), 138.9 (quat, Aryl-C), 155.1 (quat, Aryl-C), 171.4 (quat, *C*O$_2$Et). IR (film) ν: 3392, 3097, 2990, 2938, 1756, 1739, 1604, 1570, 1467, 1430, 1364, 1339, 1280, 1196, 1131, 1079, 1057, 1029, 967, 877, 784, 767, 693, 680, 647, 597, 562, 519 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 258.2 (100.0, MH$^+$), 242.2 (75.4), 224.2 (12.8), 138.1 (59.6). Anal. Calcd for $C_{11}H_{15}NO_6$ (257.24): C 51.36, H 5.88, N 5.45. Found C 51.39, H 5.83, N 5.41. Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated an enantiomeric excess >97%.

3.2.8. (2*S*,3*R*)-Ethyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate ((*ent*)-10d). According to GP1 (*ent*)-**10d** (138 mg, 0.54 mmol, 54%) was obtained as colorless solid. Analytical data according to **10d**; $[\alpha]_D^{20}=+122.7$ ($c=1.21$, $CHCl_3$). Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated an enantiomeric excess >98%.

3.2.9. (2*R*,3*S*)-Isopropyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate (10e). A mixture of AD-mix α (11.0 g) and methansulfonamide (0.75 g, 7.88 mmol, 1.0 equiv) in *tert*-butanol–water (120 ml, 1:1 v/v) was stirred vigorously at room temperature. After 30 min the (*E*)-**7e** (1.87 g, 7.88 mmol, 1.0 equiv) was added and stirring was continued for 18 h. H_2O (30 ml) was added and the aqueous layer was extracted five times with $CHCl_3$/MeOH (9:1 v/v, 25 ml each). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent at reduced pressure afforded a yellow oil, which was fractionated by chromatography on silica gel ($CHCl_3$/MeOH 19:1) to give **10e** (1.99 g, 7.32 mmol, 93%) as a colorless solid. R_f 0.42 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=-101.7$ (*c* 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (dd, $J=8.6$, 6.3 Hz, 6H, CH(CH_3)$_2$), 3.94 (s, 3H, OCH_3), 4.54 (dd, $J=6.9$, 4.1 Hz, 1H, C*H*OHCO$_2$*i*-Pr), 4.97 (d, $J=$ 6.9 Hz, 1H, CHO*H*CO$_2$*i*-Pr), 5.14 (hept, $J=6.3$ Hz, 1H, C*H*(CH_3)$_2$), 5.57 (dd, $J=11.2$, 4.1 Hz, 1H, C*H*OHCHOHCO$_2$*i*-Pr), 7.00 (dd, $J=8.7$, 0.82 Hz, 1H, Aryl-H), 7.27 (dd, $J=8.7$, 6.5 Hz, 1H, Aryl-H), 7.51 (d, $J=11.2$ Hz, 1H, CHOHCHO*H*CO$_2$*i*-Pr), 7.92 (dd, $J=6.5$, 0.74 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.7, 21.8 (+, 2C, CH(*C*H$_3$)$_2$), 56.7 (+, O*C*H$_3$), 69.4 (+, *C*H), 69.8 (+, *C*H), 74.9 (+, *C*H), 111.1 (+, Aryl-C), 124.6 (+, Aryl-C), 133.1 (+, Aryl-C), 139.1 (quat, Aryl-C), 155.1 (quat, Aryl-C), 171.0 (quat, *C*O$_2$*i*-Pr). MS (DCI, NH_3) *m/z* (%): 272.2 (7.6, MH$^+$), 152.1 (10.2), 138.0 (100), 124.0 (16.7), 110.0 (28.0), 96.0 (6.2). IR (film) ν: 3369, 3281, 3103, 3011, 2985, 2919, 2852, 1744, 1603, 1571, 1473, 1435, 1375, 1355, 1291, 1218, 1193, 1134, 1110, 1093, 1080, 1055, 968, 915, 874, 826, 787, 760, 695, 648 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_6$ (271.27): C 53.15, H 6.32, N 5.16. Found C 53.10, H 6.44, N 5.30. Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol indicated an enantiomeric excess >97%.

3.2.10. (2*S*,3*R*)-Isopropyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate ((*ent*)-10e). According to GP1 (*ent*)-**10e** (138 mg, 0.54 mmol, 54%) was obtained as colorless solid. Analytical data according to **10e**; $[\alpha]_D^{20}=+105.9$ ($c=1.16$, $CHCl_3$). Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated an enantiomeric excess >93%.

3.2.11. Measurement of the enantiomeric excess of 10d–e and (*ent*)-10d-e. The measurement of the enantiomeric excess of **10d** and **10e** was performed by NMR utilizing the solvating agent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle alcohol) in $CDCl_3$. For this purpose, **10d–e** (4 mg) was dissolved in 1.0 ml of $CDCl_3$. To this solution was added (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (10 mg for **10e**, 21 mg for **10d**). The ^{1}H NMR spectrum of this mixture was run in order to determine the ee. A similar analysis was performed on racemic mixture of **10d** and **10e**.

3.3. Synthesis of swainsonine (1b)

3.3.1. (1*R*,2*S*,8a*S*)- and (1*R*,2*S*,8a*R*)-1,2-Dihydroxy-hexahydroindolizin-3(5*H*)-one (11a and 11b). A solution of (*ent*)-**10b** (8.06 g, 33.4 mmol, 1.0 equiv) in MeOH (50 ml) was stirred at room temperature in the presence of $PtO_2\cdot H_2O$ (82 mg, 0.33 mmol, 0.01 equiv) under an atmospheric pressure of hydrogen for 14 d. After removal of the catalyst by filtration through a celite pad, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica ($CHCl_3$/MeOH 9:1) to give **11** as a mixture of epimers (5.08 g, 29.7 mmol, 89%, **11a**:**11b**=60:40). For analytical purposes, a small sample of **11** was separated by converting the diol to the corresponding bis-OTBDMS ether followed by chromatography on silica. Subsequent cleavage with TBAF resulted in pure samples of **11a** or **11b**, respectively. **11a**: R_f 0.15 (CHCl3/MeOH 9:1). $[\alpha]_D^{20}=-61.4$ ($c=1.04$, $CHCl_3$) ^{1}H NMR (250 MHz, CD_3OD) δ: 1.03–1.52 (m, 3H, Piperidin-H), 1.64–1.76 (m, 1H, Piperidin-H), 1.80–1.92 (m, 1H, Piperidin-H), 2.04–2.16 (m, 1H, Piperidin-H), 2.64 (dddd, $J=13.0$, 12.7, 3.7, 1.7 Hz, 1H, CH_2N), 3.07 (ddd, $J=11.5$, 6.5, 3.8 Hz, 1H, NC*H*), 3.65 (dd, $J=7.4$, 6.5 Hz, 1H, NCHC*H*OH), 3.92–4.02 (m, 1H, CH_2N), 4.02 (dd, $J=7.4$, 1.7 Hz, 1H, N(CO)C*H*OH). ^{13}C NMR (250 MHz, CD_3OD) δ: 24.1 (−, NCHCH$_2$*C*H$_2$), 25.3 (−, *C*H$_2$), 31.7 (−,*C*H$_2$), 40.7 (−, N*C*H$_2$), 60.5 (+, N*C*H), 77.6 (+, NCH*C*HOH), 80.9 (+, N(CO)*C*HOH), 173.0 (quat, N(*C*O)). IR (KBr) ν: 3444, 3347, 3256, 2963, 2932, 1871, 1686, 1460, 1425, 1278, 1253, 1151, 1080, 1026, 838, 654, 611, 555 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_3$ (171.19): C 56.13, H 7.56, N 8.18. Found C 55.79, H 7.62, N 8.08. **11b**: R_f 0.15 (CHCl3/MeOH 9:1). $[\alpha]_D^{20}=-58.4$ ($c=0.93$, $CHCl_3$) ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.13–153 (m, 3H, Piperidin-H), 1.53–1.72 (m, 1H, Piperidin-H), 1.73–2.05 (m, 2H, Piperidin-H), 2.51–2.76 (m, 1H, NCH_2), 3.40–3.64 (m, 1H, NC*H*), 3.94–4.13 (m, 1H, N(CO)C*H*OH), 4.20–4.39 (m, 2H, NCHC*H*OH, NCH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 23.7 (−, NCHCH$_2$*C*H$_2$), 24.9 (−, NCH$_2$*C*H$_2$), 25.9 (−, NCH*C*H$_2$), 41.0 (−, N*C*H$_2$), 58.7 (+, N*C*H), 73.1 (+, NCH*C*HOH), 76.3 (+, N(CO)*C*HOH), 171.2 (quat, N(*C*O)). IR (film) ν: 3362, 2926, 2856, 1676, 1446, 1357, 1281, 1227, 1152, 1103, 1004, 855, 804 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 343.2 (5.2), 189.1 (100, MH$^+$), 172.1 (42), 155.1 (6.7), 138.0 (5.9). HRMS ($C_8H_{13}NO_3$) calcd 171.0895, found 171.0897.

3.3.2. (1*R*,2*S*,8a*S*)- and (1*R*,2*S*,8a*R*)-1-Hydroxy-3-oxo-octahydroindolizin-2-yl benzoate (12a and 12b). To a stirred solution of the epimeric mixture of **11** (**11a**:**11b**=60:40, 1.10 g, 6.43 mmol, 1.0 equiv) in pyridine (30.0 ml) and DMAP (0.01 g, 0.06 mmol, 0.01 equiv) was added dropwise with a syringe pump a solution of benzoyl chloride (0.81 g, 5.78 mmol, 0.9 equiv) in pyridine (5.0 ml) at −30 °C during 1 h. The mixture was stirred for an additional 80 min at −30 °C and was then allowed to warm up during 2 h to 0 °C and subsequently kept in the refrigerator (+4 °C) for 12 h. Ethyl acetate was added (50 ml) and the mixture was washed with 2 N HCl (20 ml). The aqueous layer was washed twice with ethyl acetate (50 ml) and the combined organic layers were washed with brine (50 ml) and then again with 2 N HCl (10 ml). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica (ethyl acetate/hexanes 5:1) to give **12** as a mixture of epimers (**12a**:**12b**=60:40, 1.49 g, 5.41 mmol, 84%). IR (KBr) *ν*: 3334, 3244, 2950, 2870, 1678, 1455, 1335, 1304, 1240, 1167, 1123, 1106, 1001, 915, 829, 731, 663, 507, 3464, 2940, 2859, 1693, 1445, 1372, 1317, 1287, 1267, 1219, 1147, 1107, 1080, 978, 930, 912, 867, 837, 799, 731, 573, 503, 436, 3505, 3065, 2943, 2858, 1698, 1601, 1447, 1341, 1318, 1273, 1157, 1113, 1105, 984, 860, 802, 708, 586, 449 cm^{-1}. (EI, 70 eV) *m/z* (%): 275.1 (4.9, $M^{+\cdot}$), 257.1 (5.1), 154.1 (30.7), 153.0 (92.0), 122.0 (13.1), 105.0 (100.0), 84.0 (63.6), 83.0 (21.7), 77.0 (47.5), 51.0 (13.0). HRMS ($C_{15}H_{17}NO_4$) calcd 275.1158, found 275.1158. For analytical purposes, a small sample of **12** was separated by column chromatography. **12a**: R_f 0.41 (ethyl acetate/hexanes 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.13–1.77 (m, 4H, CH_2), 1.90–2.08 (m, 2H, CH_2), 2.69–2.81 (m, 1H), 3.63–3.75 (m, 1H), 4.22–4.31 (m, 1H), 4.47 (dd, *J*=8.1, 5.7 Hz, 1H), 5.21 (d, *J*=5.7 Hz, 1H), 7.41–7.50 (m, 2H, Aryl-H), 7.60–7.64 (m, 1H, Aryl-H), 8.08–8.13 (m, 2H, Aryl-H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 23.8 (−, *C*H_2), 24.9 (−, *C*H_2), 26.7 (−, *C*H_2), 41.1 (−, *C*H_2), 58.5 (+, *C*H), 72.4 (+, *C*H), 80.6 (+, *C*H), 128.5 (+, 2C, Aryl-C), 128.6 (quat, Aryl-C), 130.23 (+, 2C, Aryl-C), 133.91 (+, Aryl-C), 165.5 (quat, *C*OPh), 168.2 (quat, N*C*O). **12b**: R_f 0.36 (ethyl acetate/hexanes 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.17–1.50 (m, 3H), 1.73–1.81 (m, 1H), 1.90–1.99 (m, 1H), 2.18–2.27 (m, 1H), 2.67–2.97 (m, 1H), 3.29–3.38 (m, 1H), 4.03 (t, *J*=6.2 Hz, 1H), 4.16–4.25 (m, 1H), 5.29 (dd, *J*=6.2, 1.5 Hz, 1H), 7.41–7.49 (m, 2H), 7.57–7.64 (m, 1H), 8.09–8.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 23.1 (−, *C*H_2), 23.9 (−, *C*H_2), 31.1 (−, *C*H_2), 40.1 (−, *C*H_2), 59.5 (+, *C*H), 78.8 (+, *C*H), 80.9 (+, *C*H), 128.5 (+, 2C, Aryl-C), 128.6 (quat, Aryl-C), 130.3 (+, 2C, Aryl-C), 133.9 (+, Aryl-C), 165.8 (quat, *C*O), 168.3 (quat, *C*O).

3.3.3. (1*S*,2*S*,8a*S*)- and (*1S*,*2S*,8a*R*)-*2*-Hydroxy-3-oxo-octahydroindolizin-1-yl benzoate (13a and 13b). A vigorously stirred solution of **12** (**12a**:**12b**=60:40, 1.10 g, 3.99 mmol, 1.0 equiv) and pyridine (0.63 g, 7.98 mmol, 2.0 equiv) in dry CH_2Cl_2 under nitrogen atmosphere was cooled to −30 °C. To this solution triflic anhydride (1.80 g, 6.38 mmol, 1.6 equiv) was added dropwise and the mixture was slowly allowed to reach room temperature. Stirring was continued for 1H, subsequently water (2.0 ml) was added and the reaction mixture was further stirred overnight. Water (15 ml) was added, and the mixture was extracted with CH_2Cl_2 (4×15 ml). The combined organic layers were extracted with aqueous $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica (ethyl acetate/hexane 5:1) to yield **13** as a mixture of epimers (0.58 g, 2.11 mmol, 53% yield). (EI, 70 eV) *m/z* (%): 275.1 (3.6, $M^{+\cdot}$), 153.0 (100.0), 105.0 (69.3), 84.0 (36.4), 77.0 (37.1). HRMS ($C_{15}H_{17}NO_4$) calcd 275.1158, found 275.1158. For analytical purposes, a small sample of **13** was separated by column chromatography: **13a**: R_f 0.12 (hexanes/ethyl acetate 1:5). $[\alpha]_D^{20}=-15.4$ (*c*=1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.18–1.53 (m, 3H), 1.63–1.73 (m, 1H), 1.88–1.99 (m, 1H), 2.04–2.13 (m, 1H), 2.74 (dt, *J*=35, 12.9 Hz, 1H), 3.55–2.63 (m, 1H), 4.12–4.20 (m, 1H), 4.53 (d, *J*=6.4 Hz, 1H), 5.23 (dd, *J*=6.4, 2.4 Hz, 1H), 7.28–7.45 (m, 2H), 7.52–7.59 (m, 1H), 8.05–8.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 23.6 (−, *C*H_2), 24.4 (−, *C*H_2), 29.5 (−, *C*H_2), 40.8 (−, *C*H_2), 61.0 (+, *C*H), 69.3 (+, *C*H), 72.5 (+, *C*H), 128.4 (+, 2C, Aryl-C), 129.4 (quat, Aryl-C), 130.0 (+, 2C, Aryl-C), 133.4 (+, Aryl-C), 166.2 (quat, *C*O), 170.5 (quat, *C*O). **13b**: R_f 0.21 (hexanes/ethyl acetate 1:5). $[\alpha]_D^{20}=-24.7$ (*c*=1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.38–1.57 (m, 3H), 1.70–1.82 (m, 2H), 1.90–1.97 (m, 1H), 2.67–2.79 (m, 1H), 2.8–2.99 (bs, 1H, OH), 3.63–3.70 (m, 1H), 4.13–4.22 (m, 1H), 4.47 (dd, *J*=5.6, 1.7 Hz, 1H), 5.78 (dd, *J*=5.6, 4.2 Hz, 1H), 7.41–7.48 (m, 1H), 7.54–7.61 (m, 1H), 8.02–8.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 22.9 (−, *C*H_2), 24.0 (−, *C*H_2), 24.9 (−, *C*H_2), 40.4 (−, *C*H_2), 56.6 (+, *C*H), 69.8 (+, *C*H), 70.7 (+, *C*H), 128.5 (+, 2C, Aryl-C), 129.2 (quat, Aryl-C), 129.9 (+, 2C, Aryl-C), 133.5 (+, Aryl-C), 165.9 (quat, *C*O), 171.4 (quat, *C*O).

3.3.4. (1*S*,2*S*,8a*S*)- and (1*S*,2*S*,8a*R*)-1,2-Dihydroxyhexahydroindolizin-3-one (14a and 14b). To a solution of **13** (0.52 g, 1.89 mmol) in anhydrous methanol (10 ml) was added under stirring 0.1 N MeONa (2 ml) at room temperature. Stirring was continued for 3 h (TLC control), subsequently a small piece of dry ice was added, and the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica ($CHCl_3$/MeOH 9:1) to give **14** (0.25 g, 1.48 mmol, 78% yield). IR (KBr) *ν*: 3334, 3244, 2950, 2870, 1678, 1455, 1335, 1304, 1240, 1167, 1123, 1106, 1001, 915, 829, 731, 663, 507 cm^{-1}. MS (EI, 70 eV) *m/z* (%). 171.0 (47, $M^{+\cdot}$), 142.0 (34.0), 128.0 (16), 127.0 (10), 126.0 (40), 110.0 (14), 84 (100), 83.0 (26), 82.0 (12), 70.0 (11), 60.0 (24), 56.0 (16), 55.0 (29), 41.0 (19.3). HRMS ($C_8H_{13}NO_3$) calcd 171.0895, found 171.0896. For analytical purposes, a small sample of **14** was separated by column chromatography. **14a**[14]: R_f 0.43 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=-15.0$ (*c*=1.07, MeOH). ^{1}H NMR (600 MHz, [D_6]-DMSO) *δ*: 1.00–1.15 (m, 2H), 1.33–1.41 (m, 1H), 1.55–1.61 (m, 1H), 1.74–1.79 (m, 1H), 1.83–1.88 (m, 1H), 2.60 (dt, *J*=12.9, 3.52 Hz, 1H), 5.15 (dt, *J*=12.0, 3.3 Hz, 1H), 3.69–3.73 (m, 1H), 3.87 (dd, *J*=12.9, 4.8 Hz, 1H), 3.91 (t, *J*=5.4 Hz, 1H), 4.84 (d, *J*=5.4 Hz, 1H), 5.37 (d, *J*=6.4 Hz, 1H). ^{13}C NMR (75 MHz, [D_6]-DMSO) *δ*: 22.9 (−, *C*H_2), 24.1 (−, *C*H_2), 29.0 (−, *C*H_2), 39.3 (−, *C*H_2), 61.5 (+, *C*H), 69.6 (+, *C*H), 70.7 (+, *C*H), 170.4 (quat, *C*O). **14b**: R_f 0.38 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=-60.0$ (*c*=1.30, MeOH). ^{1}H NMR (600 MHz, [D_6]-DMSO) *δ*: 1.16–1.24 (m, 1H), 1.32–1.41 (m, 1H), 1.46–1.51 (m, 1H), 1.53–1.60 (m, 1H), 1.61–1.66 (m, 1H),

1.79–1.85 (m, 1H), 2.50–2.56 (m, 1H), 3.27 (dt, $J=11.4$, 3.7 Hz, 1H), 3.80 (dd, $J=12.9$, 4.8 Hz, 1H), 3.96–4.00 (m, 2H), 4.68 (d, $J=4.2$ Hz, 1H), 5.20 (d, $J=6.6$ Hz, 1H). ^{13}C NMR (75 MHz, [D$_6$]-DMSO) δ: 22.6 (−, *C*H$_2$), 23.8 (−, *C*H$_2$), 23.8 (−, *C*H$_2$), 38.9 (−, *C*H$_2$), 56.3 (+, *C*H), 67.2 (+, *C*H), 71.1 (+, *C*H), 171.4 (quat, *C*O).

3.3.5. (1*S*,2*S*,8a*S*)- and (1*S*,2*S*,8a*R*)-1,2-(Isopropylidenedioxy)-1,5,6,7,8,8a-hexahydro-3(2*H*)-indolizinone (15a and 15b). To a stirred solution of the diol **14** (0.20 g, 1.17 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 ml) was added 2,2-dimethoxypropane (0.72 ml, 5.84 mmol, 5.0 equiv) followed by *p*-TsOH (0.01 g, 0.05 mmol, 0.04 equiv). The solution was stirred at room temperature for 2 h, concentrated under reduced pressure, and the residue was purified by chromatography on silica ($CHCl_3$/MeOH 9:1) to afford **15** (0.24 g, 0.14 mmol, 98%). IR (KBr) ν: 3334, 3244, 2950, 2870, 1678, 1455, 1335, 1304, 1240, 1167, 1123, 1106, 1001, 915, 829, 731, 663, 507, 3464, 2940, 2859, 1693, 1445, 1372, 1317, 1287, 1267, 1219, 1147, 1107, 1080, 978, 930, 912, 867, 837, 799, 731, 573, 503, 436 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 211.0 (17.1, M$^{+\cdot}$), 197.0 (10.5), 196.0 (100.0), 154.0 (13.2), 153.0 (16.9), 136.0 (69.9), 100.0 (29.5), 84.9 (22.5), 84.0 (16.9), 83.0 (51.3), 55.0 (11.6), 42.9 (14.2). HRMS ($C_{11}H_{17}NO_3$) calcd 211.1208, found 211.1212. For analytical purposes, a small sample of **15** was separated by column chromatography. **15a** (colorless solid)[14]. Mp 106–107 °C. R_f 0.32 (ethyl acetate/hexanes 5:1). $[\alpha]_D^{20}=+24$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (dddd, $J=3.5$, 12.7, 12.7, 12.7 Hz, 1H), 1.20–1.33 (m, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.45–1.59 (m, 1H), 1.62–1.72 (m, 1H), 1.87–2.01 (m, 2H), 2.70 (ddd, $J=3.5$, 12.9, 12.9 Hz, 1H), 3.46 (dd, $J=2.7$, 12.5 Hz, 1H), 4.13–4.21 (m, 1H), 4.34 (d, $J=6.6$ Hz, 1H), 4.62 (d, $J=6.6$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=23.8$ (−, *C*H$_2$), 24.6 (−, *C*H$_2$), 25.3 (+, *C*H$_3$), 26.8 (+, *C*H$_3$), 30.8 (−, *C*H$_2$), 40.5 (−, *C*H$_2$), 62.2 (+, *C*H), 77.4 (+, 2C, *C*H), 112.6 (quat C), 168.5 (quat, *C*O). **15b** (viscous oil) R_f 0.20 (ethyl acetate/hexanes 5:1). $[\alpha]_D^{20}=-15$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21–1.48 (m, 2H), 1.39 (s, 3H), 1.44 (s, 3H), 1.62–1.81 (m, 3H), 1.91–2.00 (m, 1H), 2.63 (dt, $J=3.4$, 12.8 Hz, 1H), 3.42–3.51 (m, 1H), 4.10–4.18 (m, 1H), 4.64 (d, $J=2.6$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3 (−, *C*H$_2$), 24.1 (−, *C*H$_2$), 25.1 (−, *C*H$_2$), 26.0 (+, *C*H$_3$), 27.1 (+, *C*H$_3$), 40.1 (−, *C*H$_2$), 57.8 (+, *C*H), 74.4 (+, *C*H), 78.0 (+, *C*H), 112.6 (quat, *C*(CH$_3$)$_2$), 169.6 (quat, *C*O).

3.3.6. (1*S*,2*S*)-1,2-Isopropylidenedioxy-1,2,6,7-tetrahydroindolizin-3(5*H*)-one (17).[17] Aqueous NaOCl solution (3 ml, 12%) was added dropwise during 9 h to a stirred suspension of **15** (40.0 mg, 0.189 mmol) in ethyl acetate (3 ml) and $RuO_2\cdot H_2O$ (5 mg) under cooling at 0 °C. Isopropanol (1 ml) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2×2 ml), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product was dissolved in $CHCl_3$ (2 ml) and a small amount of HOAc was added. The solution was stirred for 1 h at room temperature, concentrated under reduced pressure and the residue was purified by chromatography on silica (hexanes/ethyl acetate 1:5) to afford **17** (19.8 mg, 0.094 mmol, 50%) and **15b** (11.6 mg, 0.055 mmol, 29%). Analogously **15a** was converted to **17** via **16a** in 79% yield. **16a**: R_f 0.51 ($CHCl_3$/MeOH 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21–1.28 (m, 1H), 1.38 (s, 3H), 1.41 (s, 3H), 1.70–1.95 (m, 5H), 2.84–2.96 (m, 1H), 3.80–3.89 (m, 1H), 3.91–4.04 (br s, 1H, OH), 4.47 (d, $J=5.8$ Hz, 1H), 4.86 (dd, $J=1.0$, 5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.9 (−, *C*H$_2$), 24.0 (−, *C*H$_2$), 26.0 (+, *C*H$_3$), 27.2 (+, *C*H$_3$), 30.2 (−, *C*H$_2$), 37.0 (−, *C*H$_2$) 77.1 (+, *C*H), 81.3 (+, *C*H), 87.7 (quat C), 113.4 (quat C), 170.6 (quat, *C*O). **17**. Mp 67–69 °C. R_f 0.57 (ethyl acetate/hexanes 5:1). $[\alpha]_D^{20}=+25.5$ ($c=1.1$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 3H), 1.44 (s, 3H), 1.66–1.78 (m, 1H), 1.83–1.95 (m, 1H), 2.16–2.24 (m, 2H), 3.36–3.46 (m, 1H), 3.69–3.78 (m, 1H), 4.67 (d, $J=6.4$ Hz, 1H), 4.96 (d, $J=6.4$ Hz, 1H), 5.25 (t, $J=4.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.0 (−, *C*H$_2$), 21.5 (−, *C*H$_2$), 25.6 (+, *C*H$_3$), 26.9 (+, *C*H$_3$), 39.0 (−, *C*H$_2$), 73.7 (+, *C*H), 76.5 (+, *C*H), 104.6 (+, *C*H), 113.2 (+, *C*H), 136.0 (quat, *C*(CH$_3$)$_2$), 169.7 (quat, *C*O). IR (KBr) ν: 2984, 2940, 2893, 1722, 1686, 1458, 1414, 1378, 1314, 1252, 1213, 1153, 1093, 1067, 1041, 1010, 972, 930, 899, 868, 779, 710, 644, 617, 563, 519 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 209.1 (59.1, M$^{+\cdot}$), 194.1 (26.1), 166.1 (14.1), 152.1 (100.0), 43.0 (10.3). HRMS ($C_{11}H_{15}NO_3$) calcd 209.1052, found 209.1053.

3.3.7. Swainsonine (1b). 17 was converted in two steps into swainsonine (**1b**) in 77% overall yield as described[17] in the literature. The spectroscopic data obtained for **1b** was identical to those described in the literature[3d]: ^{1}H NMR (300 MHz, D_2O): $\delta=1.02$–1.13 (m, 1H), 1.29–1.47 (m, 1H), 1.53–1.64 (m, 1H), 1.75–1.84 (m, 2H), 1.88–1.98 (m, 1H), 2.42 (dd, $J=11$, 4 Hz, 1H), 2.72–2.78 (m, 2H), 3.67 (ddd, $J=11$, 10, 5 Hz, 1H), 4.12 (dd, $J=6$, 4 Hz, 1H), 4.22 (ddd, $J=8$, 6, 3 Hz, 1H). ^{13}C NMR (75.5 MHz, D_2O): $\delta=22.8$ (−, *C*H$_2$), 32.1 (−, *C*H$_2$), 51.2 (−, *C*H$_2$), 60.2 (−, *C*H$_2$), 65.9 (+, *C*H), 68.6 (+, *C*H), 69.2 (+, *C*H), 72.4 (+, *C*H).

3.4. Synthesis of 2,8a-di-*epi*-swainsonine

3.4.1. (1*S*,2*R*,8*R*,8a*R*)-1,2-Dihydroxy-8-methoxy-hexahydroindolizin-3(5*H*)-one (18). A solution of **10e** (1.58 g, 5.82 mmol, 1.0 equiv) in glacial acetic acid (60 ml) was stirred in the presence of platinum on carbon (470 mg, 5% Pt/C, 0.24 mmol, 0.02 equiv) under an atmospheric pressure of hydrogen for 7 d. After removal of the catalyst by filtration through a celite pad, the solvent was removed under reduced pressure. To the crude product $CHCl_3$ (50 ml) and NEt_3 (2 ml) was added and the solution was stirred for 24 h at room temperature. Evaporation of the solvent at reduced pressure afforded a yellow oil, which was purified by chromatography on silica (chloroform/methanol 9:1). The crude product was recrystallized from ethyl acetate/methanol (4:1) to give **18** (551 mg, 2.74 mmol, 47%) as white crystals. Mp 181 °C. R_f 0.16 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=+33.7$ (*c* 0.99, MeOH). ^{1}H NMR (300 MHz, [D$_6$]-DMSO) δ: 1.30–1.51 (m, 3H, Piperidine-H), 2.08–2.17 (m, 1H, Piperidine-H), 2.53–2.64 (m, 1H, C*H*$_2$N), 3.08 (dd, $J=6.8$, 2.5 Hz, 1H, C*H*N), 3.26 (s, 3H, OC*H*$_3$), 3.43–3.48 (m, 1H, C*H*OMe), 3.73–3.78 (m, 1H, C*H*$_2$N), 3.78–3.86 (m, 1H, NCHC*H*OH), 3.97–4.06 (m, 1H, NCOC*H*OH), 5.47 (d, $J=5.8$ Hz, 1H, NCHCHO*H*), 5.56 (d, $J=6.0$ Hz, 1H,

NCOCHO*H*). ^{13}C NMR (75.5 MHz, [D$_6$]-DMSO) δ: 16.8 (−, *C*H$_2$), 24.5 (−, *C*H$_2$), 38.1 (−, *C*H$_2$), 55.8 (+, O*C*H$_3$), 61.5 (+, N*C*H), 70.2 (+, *C*HOCH$_3$), 71.5 (+, NCH*C*HOH), 75.7 (+, NCO*C*HOH), 170.7 (quat, *C*O). MS (DCI, NH$_3$) *m*/*z* (%): 403.1 (5.17, 2MH$^+$), 219.0 (100.0, M+NH$_4^+$), 202.0 (100, MH$^+$), 185.9 (3.3). IR (film) ν: 3409, 3243, 2977, 2953, 1894, 2866, 2835, 1686, 1462, 1439, 1366, 1282, 1263, 1253, 1219, 1197, 1152, 1107, 1083, 1030, 976 cm^{-1}. Anal. Calcd for C$_9$H$_{15}$NO$_4$ (201.22): C 53.72, H 7.51, N 6.96. Found C 53.74, H 7.38, N 6.83.

3.4.2. (1*S*,2*S*,8*R*,8a*S*)-Octahydroindolizine-1,2,8-triol ((−)-2,8a-di-*epi*-swainsonine) (20). A mixture of **18** (0.25 g, 1.24 mmol) and HBr (48%, 0.6 ml) was heated at 140 °C for 30 min. The solution was evaporated to dryness under reduced pressure and evaporation was repeated after addition of ethanol (3.5 ml). The crude product was purified by chromatography on silica (CH$_2$Cl$_2$/MeOH/NH$_3$ 40:8:1) to give crude **19**, which was contaminated with ammonium bromide (0.31 g, 1.08 mmol, 88%) as a brownish solid, which was used in the next step without further purification. Analytical pure **19** can be obtained by recrystallization form ethyl acetate/methanol (2:1). **19**. Mp 181–184 °C, R_f 0.28 (CH$_2$Cl$_2$/MeOH/NH$_3$ 40:8:1), $[\alpha]_D^{20}=+56$ (*c* 1.10, MeOH). ^{1}H NMR (300 MHz, [D$_6$]-DMSO) δ: 1.29–1.88 (m, 4H), 2.52–2.64 (m, 1H), 2.99 (dd, *J*=6.5, 2.2 Hz, 1H), 3.74–3.87 (m, 3H), 3.98–4.06 (m, 1H), 4.80 (d, *J*=4.3 Hz, 1H), 5.32 (d, *J*=5.8 Hz, 1H), 5.52 (d, *J*=5.9 Hz, 1H). ^{13}C NMR (75.5 MHz, [D$_6$]-DMSO) δ: 16.7 (−, *C*H$_2$), 29.9 (−, *C*H$_2$), 38.2 (−, *C*H$_2$), 60.5 (+, *C*H), 62.1 (+, *C*H), 71.8 (+, *C*H), 76.0 (+, *C*H), 170.9 (quat, *C*O). IR (KBr) ν: 3406, 3246, 1684, 1463, 1366, 1281, 1255, 1215, 1197, 1153, 1105, 1081, 1030, 976, 873, 851, 814, 753, 658, 600, 555, 448 cm^{-1}. To a stirred solution of crude **19** (98 mg) in THF (5 ml) was added BH$_3$·Me$_2$S complex (150 µl) at 0 °C under nitrogen atmosphere. After warming to room temperature, the mixture was stirred for 12 h, and additional BH$_3$·Me$_2$S complex (100 µl) was added. After further stirring for 20 h, ethanol and water were added to the mixture. The aqueous layer was extracted with ethyl acetate (3×5 ml) and the combined organic layers were dried over MgSO$_4$. The mixture was concentrated, and the residue was purified by chromatography on silica (CH$_2$Cl$_2$/MeOH/NH$_3$ 40:8:1) to give **20·HBr** (51 mg, 0.20 mmol, 59%) as a colorless solid, which was recrystallized from ethyl acetate/methanol 1:1 to give **20·HBr** (28 mg, 0.11 mmol, 32%) to obtain crystals suitable for X-ray analysis. Treatment of **20·HBr** (28 mg, 0.11 mmol) on an ion exchange column (Dowex 1×8; 100–200 mesh, eluent water) yielded **20** (19 mg, 0.11 mmol, 32% yield starting from **18**). **20·HBr**: R_f 0.35 (CH$_2$Cl$_2$/Me OH/NH$_3$ 40:8:1). $[\alpha]_D^{20}=-12.7$ (*c*=1.28, MeOH). ^{1}H NMR (400 MHz, D$_2$O) δ: 1.60–1.79 (m, 2H), 1.87–2.01 (m, 2H), 2.93–3.02 (m, 1H), 3.17 (d, *J*=9.4 Hz, 1H), 3.37 (dd, *J*=12.6, 4.5 Hz, 1H), 3.40–3.52 (m, 2H), 4.08 (dd, *J*=9.4, 3.7 Hz, 1H), 4.27–4.31 (m, 2H). ^{13}C NMR (75.5 MHz, D$_2$O) δ: 17.1 (−, *C*H$_2$), 28.1 (−, *C*H$_2$), 52.5 (−, *C*H$_2$), 58.7 (−, *C*H$_2$), 61.1 (+, *C*H), 71.3 (+, *C*H), 73.0 (+, *C*H), 75.3 (+, *C*H). MS (DCI, NH$_3$) *m*/*z* (%): 174.1 (100.0, MH$^+$). **20**[18]. Mp 138–142 °C (lit.[19] mp 138–142 °C). $[\alpha]_D^{20}=-8.8$ (*c*=0.91, MeOH) (lit.[19] $[\alpha]_D^{26}=-24.0$ (*c*=1.14, MeOH)). ^{1}H NMR (400 MHz, D$_2$O) δ: 1.32–1.45 (m, 2H), 1.53–1.81 (m, 2H), 1.87–1.99 (m, 2H), 2.48 (dd, *J*=11.0, 7.3 Hz, 1H), 2.70–2.75 (m, 1H), 2.77–2.84 (m, 1H), 3.86 (dd, *J*=8.7, 3.6 Hz, 1H), 3.92–3.98 (m, 2H). ^{13}C NMR (75.5 MHz, D$_2$O) δ: 18.5 (−, *C*H$_2$), 29.6 (−, *C*H$_2$), 52.3 (−, *C*H$_2$), 60.3 (−, *C*H$_2$), 62.8 (+, *C*H), 71.5 (+, *C*H), 75.6 (+, *C*H), 77.7 (+, *C*H). IR (KBr) ν: 3415, 2922, 2822, 2297, 1334, 1240, 1209, 1154, 1105, 1006, 891, 812, 693 cm^{-1}. HRMS (EI, 70 eV) calcd 173.1052, found 173.1052.

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