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ORIGINAL PAPER

Stereoselective synthesis of *trans*-dihydronarciclasine derivatives containing a 1,4-benzodioxane moiety

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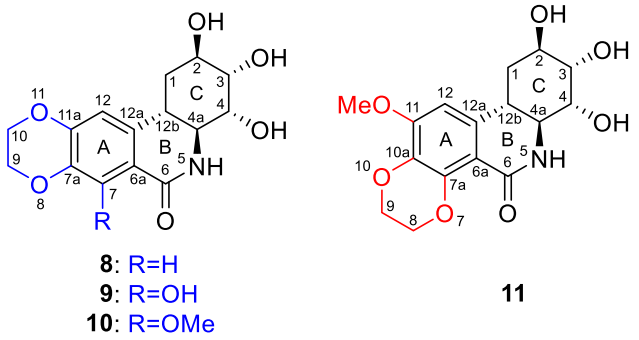
Abstract

Some new *trans*-dihydronarciclasine derivatives containing a 1,4-benzodioxane moiety were stereoselectively synthesised using our feasible and efficient method developed recently. These new phenanthridone alkaloid analogues were obtained in both racemic and optically active forms. High enantioselectivities (up to 99% *ee*) were achieved by applying (8*S*,9*S*)-9-amino(9-deoxy)epiquinine as an organocatalyst. Due to a side reaction, various methoxyphenanthridine regioisomers were also prepared which afforded further synthetic *trans*-dihydronarciclasine analogues modified in the ring A of the phenanthridone scaffold.

Graphical abstract



Keywords Alkaloids · Antitumor agents · Heterocycles · Organocatalysis · Total synthesis

Introduction

Nowadays, hundreds of members of alkaloids are known, which have been isolated from the plants of *Amaryllidaceae* family. After recognising their anticancerous properties, more and more attention has been paid to their isolation and structural elucidation [1]. The alkaloids prepared from this plant family are divided into 12 groups according to their ring systems [2]. Among these diverse structures, the most potent antitumorous alkaloids can be found in the phenanthridone subgroup. Surprisingly, the detailed investigations of *Amaryllidaceae* alkaloids started only at the end of the nineteenth century, when Gerrard isolated lycorine (**1**, Fig. 1) from *Narcissus*

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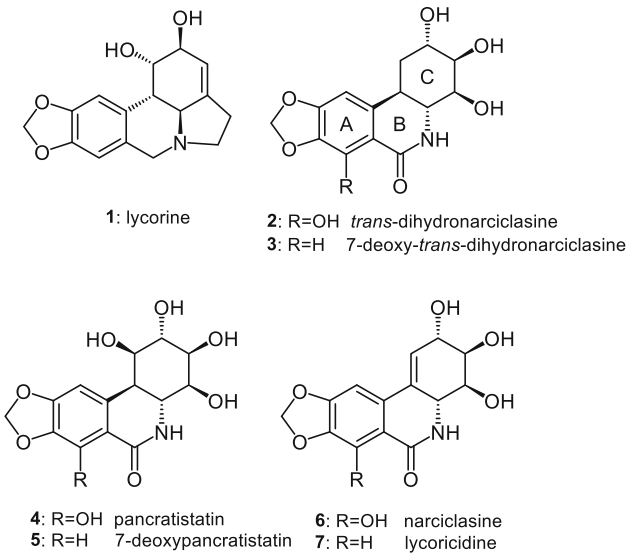


Fig. 1 Structures of the most important *Amaryllidaceae* alkaloids (**1**–**7**)

pseudonarcissus in 1877 [3, 4]. Since then, several alkaloids have been obtained from various *Amaryllidaceae* plants including *trans*-dihydronarciclasine (**2**, Fig. 1) isolated by Pettit and co-workers from *Zephyranthes candida* in 1990 [5].

Compound **2** is the most potent natural anticancerous alkaloid among the *Amaryllidaceae* ones according to the data from National Cancer Institute (NCI, USA) [6]. Its 7-deoxy analogue (**3**, Fig. 1) was also isolated by Pettit and co-workers from *Hymenocallis caribaea* and *Hymenocallis latifolia*, in pure form, but its biological activity was found to be weaker than that of **2** [6]. This can be explained by the lack of hydroxyl group at the position A-7, similarly to the comparison of other representatives, such as pancratistatin (**4**) and 7-deoxypancratistatin (**5**) or narciclasine (**6**) and lycoricidine (**7**) (Fig. 1) [6]. Further structure–activity relationship studies have intensively been made to find more effective synthetic analogues, but the modifications rather touched the ring C of the phenanthridone skeleton [7–20] than its ring A [21–28].

Furthermore, the *Amaryllidaceae* alkaloids also showed significant antiviral effects. Thus, compound **1** has strong activity against herpes simplex 1 and varicella zoster DNA viruses [29] and against several RNA viruses, such as avian influenza virus (H5N1) [30] or SARS coronavirus [31]. It has also inhibitory effects against reverse transcriptase enzyme in the HIV-1 virus [32]. Besides, strong antiviral activities of some phenanthridone alkaloids including compounds **4**, **6**, and **7** were reported by Gabrielsen and co-workers [33, 34]. Very recently, *trans*-dihydronarciclasine, pancratistatin, and narciclasine have also been found to be active against Zika virus [35].

Previously, the racemic [36] and the *ent*-forms of **3** [37], as well as those of **2** [38, 39], were stereoselectively

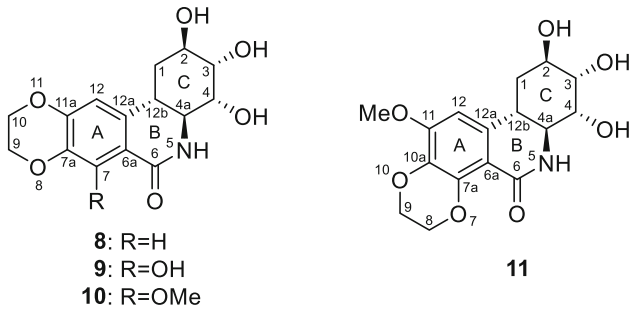


Fig. 2 Structures of *trans*-dihydronarciclasine derivatives containing a 1,4-benzodioxane moiety (**8**–**11**)

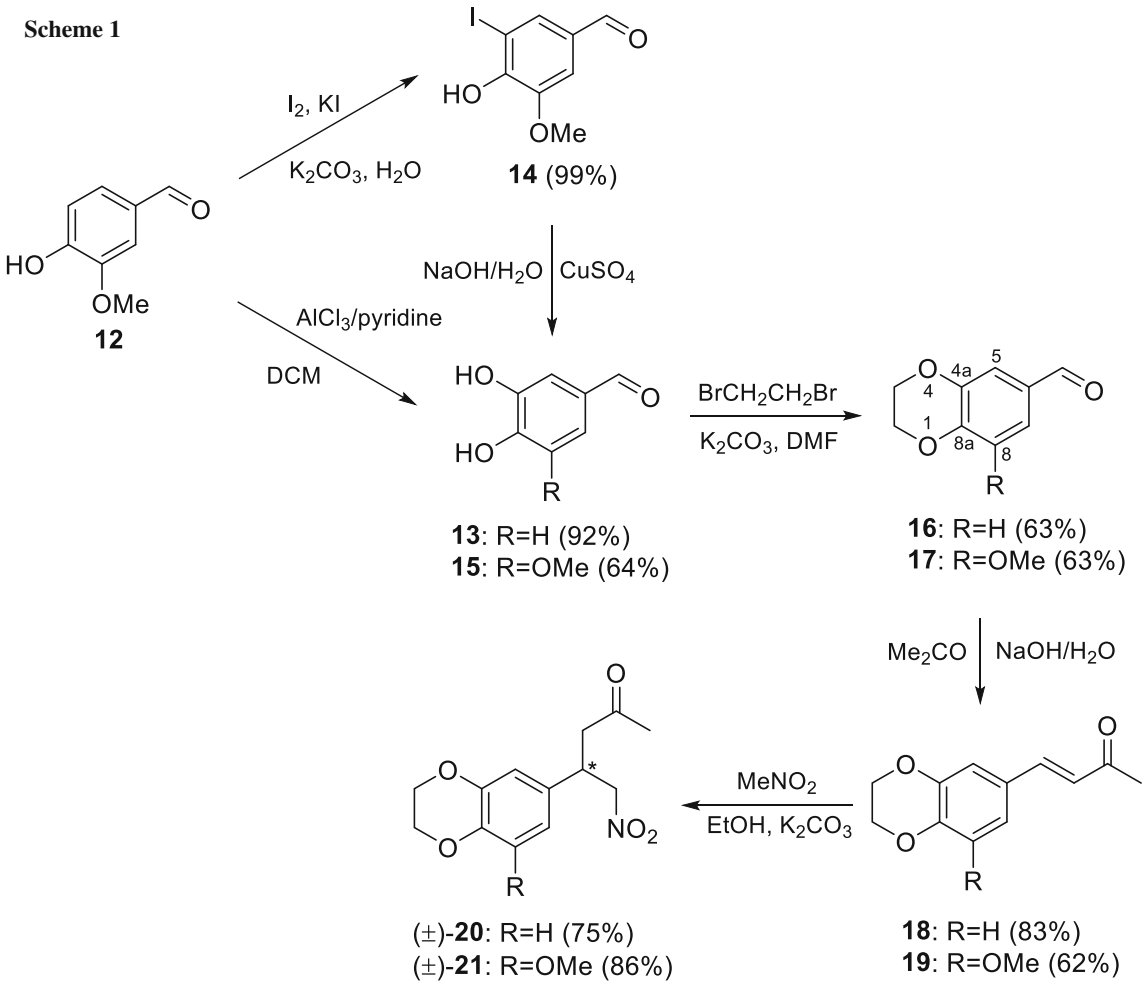
synthesised using our facile and efficient process developed recently. Later, we also reported the highly stereoselective synthesis of a series of analogues of **2** substituted by alkyloxy groups (ethoxy and/or methoxy) in the aromatic ring [40]. In this work, focusing further on the modification of ring A of the phenanthridone scaffold by introducing a relatively rigid substituent, the stereoselective syntheses of some new *trans*-dihydronarciclasine analogues containing a 1,4-benzodioxane moiety (Fig. 2), such as 2,3,4-trihydroxy-1,3,4,4a,5,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]-phenanthridin-6(2*H*)-one (**8**), 2,3,4,7-tetrahydroxy-1,3,4,4a,5,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]-phenanthridin-6(2*H*)-one (**9**), 2,3,4-trihydroxy-7-methoxy-1,3,4,4a,5,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridin-6(2*H*)-one (**10**) and 2,3,4-trihydroxy-11-methoxy-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridin-6(2*H*)-one (**11**), were described in both racemic and enantiopure forms.

Our modifying strategy related to ring A of the phenanthridone skeleton aimed at the methylenedioxy (–OCH_2O–) structural part, a rigid functional group, in *trans*-dihydronarciclasine, because this molecule part may also be responsible for the anticancerous activity of this alkaloid. Thus, the homologous ethylenedioxy (–OCH_2CH_2O–) one was introduced into the aromatic ring to obtain new analogues for further structure–activity relationship studies.

Results and discussion

Similarly to our previous synthetic works [38–40], the starting material was vanillin (**12**), an inexpensive and readily available substance. As seen in Scheme 1, in the initial step, compound **12** was demethylated to 3,4-dihydroxybenzaldehyde (**13**) in dichloromethane by $AlCl_3$ and pyridine, using a known method [41], in good yield (92%). Hydroxyvanillin (**15**) was also obtained from **12**, but in this case, at first, it was selectively iodinated to 5-iodovanillin (**14**) [42] almost quantitatively, and then compound **14** was

Scheme 1



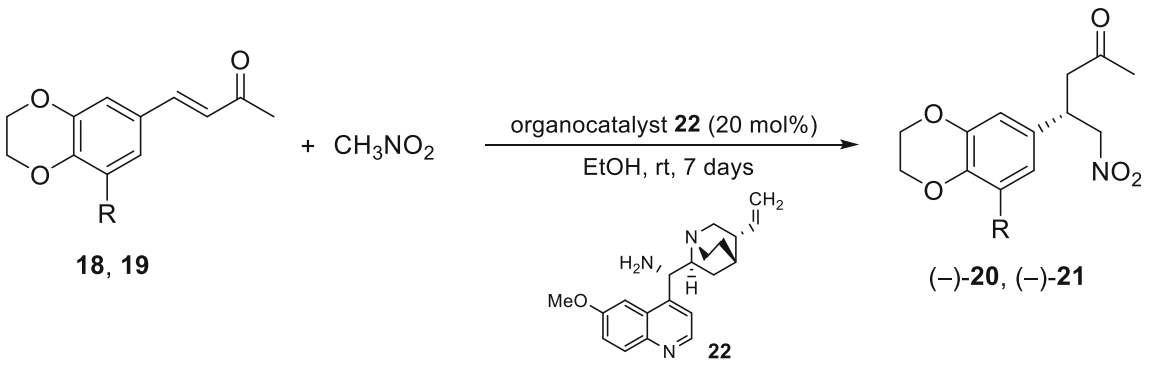
hydrolysed with 20% aqueous NaOH solution in presence of $CuSO_4$ [43] to give **15** in 64% yield. The dihydrobenzodioxine ring was formed with 1,2-dibromoethane in DMF, in the presence of K_2CO_3 [44] to afford 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (**16**) and 8-methoxy-2,3- dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (**17**) in good yield (63%). In the next step, acetone was condensed with these benzaldehyde derivatives **16** and **17** in the Claisen–Schmidt reaction applying a high excess of acetone in water and basic conditions (NaOH) to give 4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)but-3-en-2-one (**18**) and 4-(8-methoxy-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)but-3-en-2-one (**19**) in good yields (83 and 62%, respectively). Since dibenzylidene acetone derivatives may also be formed during this reaction, the pure products were obtained after distillation.

The first asymmetric centre of the title molecules was formed by Michael addition of nitromethane to compounds **18** and **19** to afford (±)-4-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-5-nitropentan-2-one [(±)-**20**] and (±)-4-(8-methoxy-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-nitropentan-2-one [(±)-**21**]. These racemic representatives were prepared by using Peseke and co-workers' mild method ($MeNO_2$, EtOH, K_2CO_3) [45] in very good yields (75–86%). Moreover, this reaction allows an opportunity to obtain these intermediates in enantiomerically pure form.

The results of the enantioselective Michael addition are summarised in Table 1. Using 20 mol % (8*S*,9*S*)-9-amino(9-deoxy)epiquinine (**22**) organocatalyst [46–53] under conditions applied previously [39, 40], the optically active nitropentanones (−)-**20** and (−)-**21** were prepared in good yield (67%) and excellent enantioselectivity (92–98% *ee*) after 7 days. The negative optical rotation values suggest, in accordance with our previous studies [39, 40], that these new intermediates enable synthesising further *ent*-forms of natural alkaloid analogues.

Henceforth, only the syntheses of the optically active compounds are shown, but the racemic derivatives can be afforded in the same way. As seen in Scheme 2, the ring C was built by the Claisen–Henry reaction using ethyl

Table 1 Enantioselective Michael addition of nitromethane to **18** and **19** catalysed by (8*S*,9*S*)-9-amino(9-deoxy)epiquinine (**22**)



Entry	R	Product	Yield/%[a]	*ee*/%[b]
1	H	(−)-**20**	67	92
2	OMe	(−)-**21**	67	98

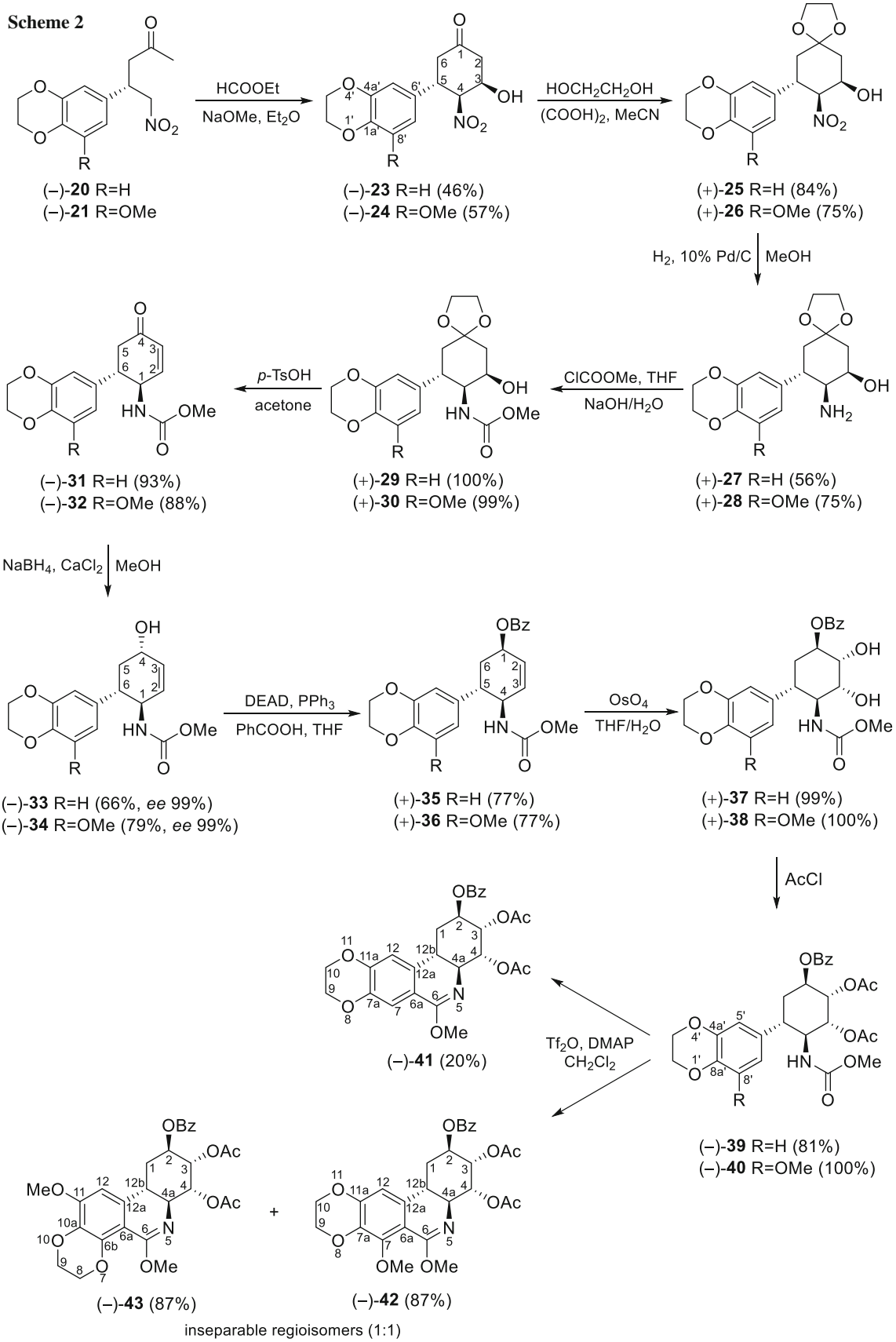
[a]Isolated yield

[b]Determined by chiral HPLC

formate and dry sodium methoxide in anhydrous diethyl ether to give (−)-3-hydroxy-5-(2′,3′-dihydrobenzo-[*b*][1,4]dioxin-6′-yl)-4-nitrocyclohexanone [(−)-**23**] and (−)-3-hydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]-dioxin-6′-yl)-4-nitrocyclohexanone [(−)-**24**] in moderate yields (46–57%) after column chromatography or recrystallisation from ethyl acetate. Full diastereoselectivity was achieved in this cyclisation step which can be explained by the H-bond formation between the C-3 hydroxy and C-4 nitro groups (Fig. 3), as described by Walker [54] and observed by us previously [36–40]. Prior to the reduction of the nitro group into the amino one, the carbonyl group of (−)-**23** and (−)-**24** was protected with ethylene glycol, in the presence of oxalic acid, in anhydrous acetonitrile to afford (+)-3-hydroxy-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-nitrocyclohexanone ethylene acetal [(+)-**25**] and (+)-3-hydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]-dioxin-6′-yl)-4-nitrocyclohexanone ethylene acetal [(+)-**26**] in good yields (75–84%). Compound (+)-**25** or (+)-**26** was converted to the corresponding amino derivatives, such as (+)-4-amino-3-hydroxy-5-(2′,3′-dihydrobenzo[*b*]-[1,4]dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-**27**] and (+)-4-amino-3-hydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-**28**], in good yields (56–75%) using our catalytic hydrogenation method [39, 55]: 10% Pd/C (Selcat Q [56]), methanol, 60–80 °C and 12 bar. Subsequently, amino ketal (+)-**27** or (+)-**28** was reacted with methyl chloroformate in a biphasic solvent mixture (water and THF) to obtain (+)-3-hydroxy-4-methoxycarbonylamino-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-**29**] or (+)-3-hydroxy-4-methoxycarbonylamino-5-(8′-methoxy-2′,3′-dihydrobenzo-[*b*][1,4]dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-**30**] quantitatively. The ketal protective group of (+)-**29** or (+)-**30** was removed in acetone containing a catalytic amount of *p*-toluenesulphonic acid under reflux, but water elimination also took place to afford (−)-6-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-oxocyclohex-2-enyl)carbamic acid methyl ester [(−)-**31**] or (−)-6-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-oxocyclohex-2-enyl)carbamic acid methyl ester [(−)-**32**] in excellent yields (88–93%).

Then the oxo group of (−)-**31** or (−)-**32** was stereoselectively reduced with $NaBH_4$, in the presence of $CaCl_2$, in methanol (Utimoto's method [57]) to obtain (−)-6-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-hydroxycyclohex-2-enyl)carbamic acid methyl ester [(−)-**33**] or (−)-6-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-hydroxycyclohex-2-enyl)carbamic acid methyl ester [(−)-**34**] in good yields (67–79%) and excellent enantiopurity (> 99% *ee*) after recrystallisation from hexane/ethyl acetate (2:1). This very high stereoselectivity was achieved with an axial attack of the small hydride ion derived from $NaBH_4$ enhanced by the coordination with Ca^{2+}, resulting in an equatorial position of the hydroxy group formed newly (Scheme 3). However, the structure of the title compounds requires the inversion of this asymmetry centre. For this purpose, the Mitsunobu reaction [58] (triphenylphosphine, diethyl azodicarboxylate, anhydrous THF) seemed to be an obvious choice. Thus, compound (−)-**33** or (−)-**34** was converted to (+)-5-(2′,3′-dihydrobenzo-[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohex-2-enyl benzoate [(+)-**35**] and (+)-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)-

Scheme 2



(–)-**20** R=H
(–)-**21** R=OMe

(–)-**23** R=H (46%)
(–)-**24** R=OMe (57%)

(+)-**25** R=H (84%)
(+)-**26** R=OMe (75%)

(+)-**27** R=H (56%)
(+)-**28** R=OMe (75%)

(+)-**29** R=H (100%)
(+)-**30** R=OMe (99%)

(–)-**31** R=H (93%)
(–)-**32** R=OMe (88%)

(–)-**33** R=H (66%, *ee* 99%)
(–)-**34** R=OMe (79%, *ee* 99%)

(+)-**35** R=H (77%)
(+)-**36** R=OMe (77%)

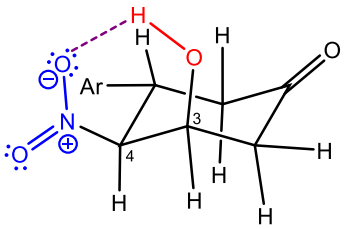
(+)-**37** R=H (99%)
(+)-**38** R=OMe (100%)

(–)-**39** R=H (81%)
(–)-**40** R=OMe (100%)

(–)-**41** (20%)

(–)-**43** (87%) + (–)-**42** (87%)

inseparable regioisomers (1:1)



(–)-**23** Ar = 2',3'-dihydrobenzo[*b*][1,4]dioxin-6'-yl
(–)-**24** Ar = 8'-methoxy-2',3'-dihydrobenzo[*b*][1,4]dioxin-6'-yl

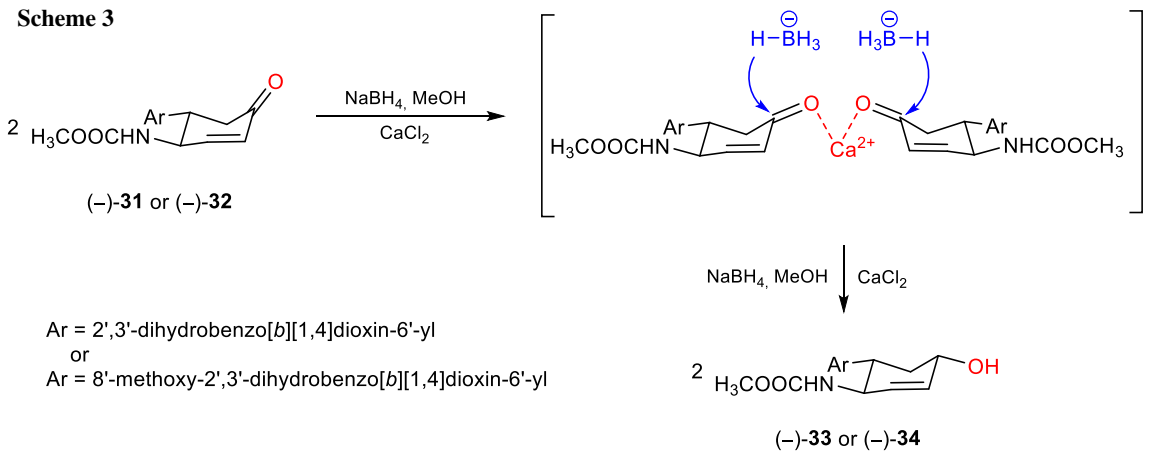
Fig. 3 Presumed structure of the 3-hydroxy-4-nitrocyclohexanone derivatives [(−)-**23** or (−)-**24**] and its stabilisation by hydrogen bonding

cyclohex-2-enyl benzoate [(+)-**36**] using benzoic acid, under Mitsunobu conditions, in good yields (77%) after column chromatography. In the next step, the stereoselective attack of osmium tetroxide to the C=C bond of (+)-**35** or (+)-**36**, adapting the Sharpless–Upjohn method [59] (OsO_4, *N*-methyl-morpholine *N*-oxide, THF-H_2O), was favoured by the steric hindrance of the bulky benzoyl group in axial position resulting in *cis*-diols, such as (+)-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-2,3-dihydroxy-4-(methoxycarbonylamino)cyclohexyl benzoate [(+)-**37**] and (+)-2,3-dihydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*]-[1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohexyl benzoate [(+)-**38**], in excellent yields (99–100%). Prior to the Bischler–Napieralski cyclisation modified by Banwell and co-workers [60], the hydroxy groups of (+)-**37** or (+)-**38** were protected by acetyl chloride to afford (−)-2,3-diacetoxy-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohexyl benzoate [(−)-**39**] and (−)-2,3-diacetoxy-5-(8′-methoxy-2′,3′-dihydrobenzo[1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohexyl benzoate [(−)-**40**] in excellent yields (81–100%). The ring closure reaction was performed with trifluoromethanesulphonic anhydride (Tf_2O) and 4-(dimethylamino)pyridine (DMAP) in dichloromethane to give (−)-2-benzoyloxy-6-methoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]-dioxino-[2,3-*j*]phenanthridin-3,4-diyl diacetate [(−)-**41**] in 20% yield, as well as an inseparable mixture of (−)-2-benzoyloxy-6,7-dimethoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]-dioxino[2,3-*j*]phenanthridin-3,4-diyl diacetate [(−)-**42**] and (−)-2-benzoyloxy-6,11-dimethoxy-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridin-3,4-diyl diacetate [(−)-**43**] in a ratio of 1:1, in very good yield (87%). Although the 8′-deoxy derivative (−)-**39** gave selectively compound (−)-**41**, it was converted spontaneously into the corresponding lactam one resulting in its poor yield.

As seen in Scheme 4, the acidic treatment of (−)-**41** with 2 M HCl in THF afforded (−)-2-benzoyloxy-6-oxo-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridine-3,4-diyl diacetate [(−)-**44**] in moderate yield (54%), which was subsequently deacylated by the Zemplén's method [61] (NaOMe/MeOH) in THF to give the title compound (−)-**8** in good yield (71%).

In the next reactions the racemic form of (±)-**42** and (±)-**43** was used, but the same results could be obtained by applying their optically active ones. When the 1:1 mixture of regioisomers (±)-**42** and (±)-**43** was quantitatively converted into lactams, such as (±)-2-benzoyloxy-7-methoxy-6-oxo-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridine-3,4-diyl diacetate [(±)-**45**] and (±)-2-benzoyloxy-11-methoxy-6-oxo-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridine-3,4-diyl diacetate [(±)-**46**], in the same way (Scheme 5), the methyl group of 7-methoxy derivative (±)-**45** was selectively cleaved with iodotrimethylsilane (TMS-I) prepared in situ from chlorotrimethylsilane (TMS-Cl) and potassium iodide, in anhydrous acetonitrile to obtain (±)-2-benzoyloxy-7-hydroxy-6-oxo-1,2,3,4,4a,9,10,12b-octahydro[1,4]-dioxino[2,3-*j*]phenanthridine-3,4-diyl diacetate [(±)-**47**],

Scheme 3

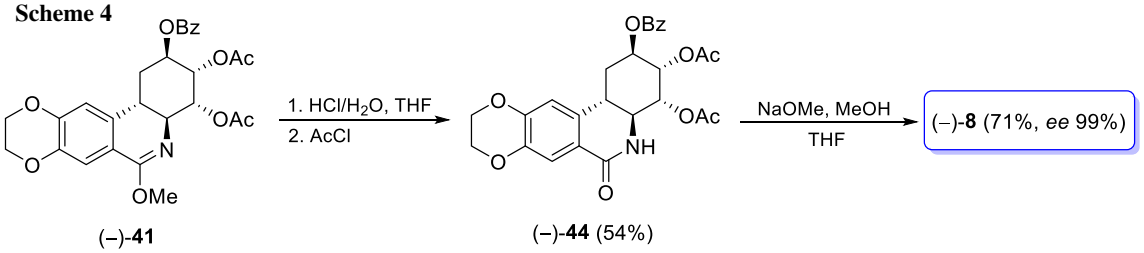


(–)-**31** or (–)-**32**

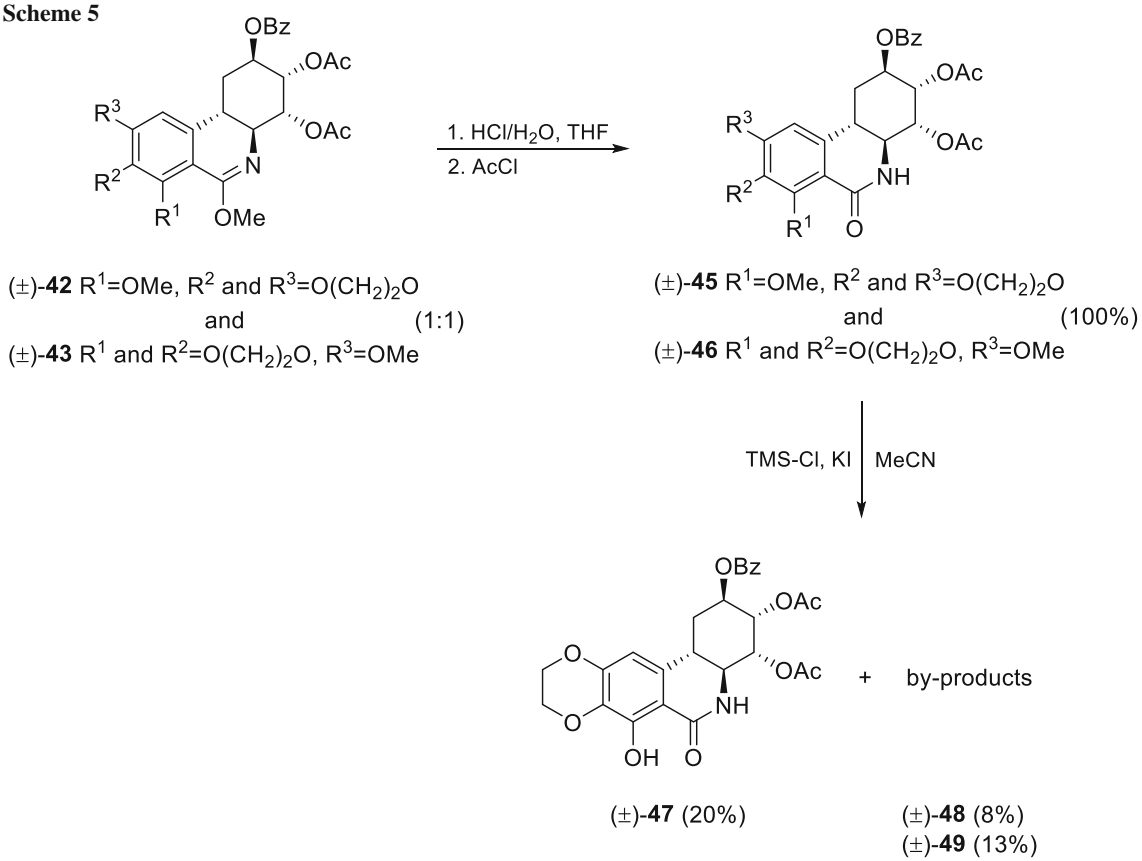
Ar = 2',3'-dihydrobenzo[*b*][1,4]dioxin-6'-yl
or
Ar = 8'-methoxy-2',3'-dihydrobenzo[*b*][1,4]dioxin-6'-yl

(–)-**33** or (–)-**34**

Scheme 4



Scheme 5



while the methyl group in A-11 position of another regioisomer (±)-**46** remained untouched allowing their separation. However, due to the poor yield (20%) of (±)-**47** and the formation of further two by-products, such as (±)-3-acetamido-6-benzoyloxy-4-(8′-methoxy-7′-methoxycarbonyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexane-1,2-diyl diacetate [(±)-**48**] and (±)-3-acetamido-6-benzoyloxy-4-(8′-methoxy-5′- methoxycarbonyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexane-1,2-diyl diacetate [(±)-**49**], which proved also to be regioisomers (Fig. 4), our synthesis strategy was modified. The structures of these regioisomers were distinguished by the chemical shifts of 5′-H_{Ar} and 5′-C_{Ar} of (±)-**48**, as well as 7′-H_{Ar} and 7′-C_{Ar} of (±)-**49**, because there were significant differences between the positions of these peaks both in the ^{1}H NMR (6.72 ppm for 5′-H_{Ar} and 6.54 ppm for 7′-H_{Ar}) and ^{13}C NMR spectra (110.8 ppm for 5′-C_{Ar} and 102.0 ppm for 7′-C_{Ar}). These diversions were due to the anisotropic shielding effect of the adjacent methoxy group in compound (±)-**49,** which resulted in lower chemical shifts for those aromatic hydrogen and carbon atoms at position A-7.

At first, as shown in Scheme 6, the 1:1 mixture of regioisomers (−)-**42** and (−)-**43** was also deacylated using the Zemplén's method resulting in (−)-6,7-dimethoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridine-2,3,4-triol [(−)-**50**] and (−)-6,11-dimethoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridine-2,3,4-triol [(−)-**51**] in pure forms, in moderate yields (22–23%) after column chromatography (ethyl acetate–ethanol, 20:1). After peracetylation of (−)-**50** and (−)-**51**, the afforded (−)-7-methoxy-6-oxo-1,2,3,4,4a,9,-10,12b-octahydro[1,4]dioxino-[2,3-*j*]phenanthridine-2,3,-

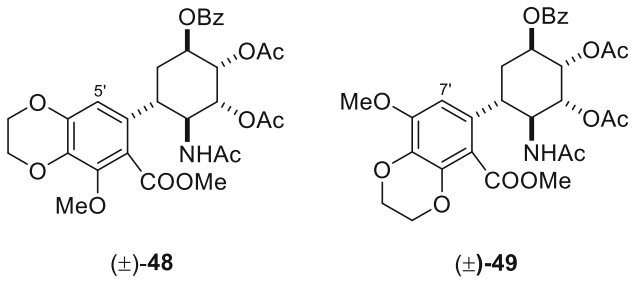
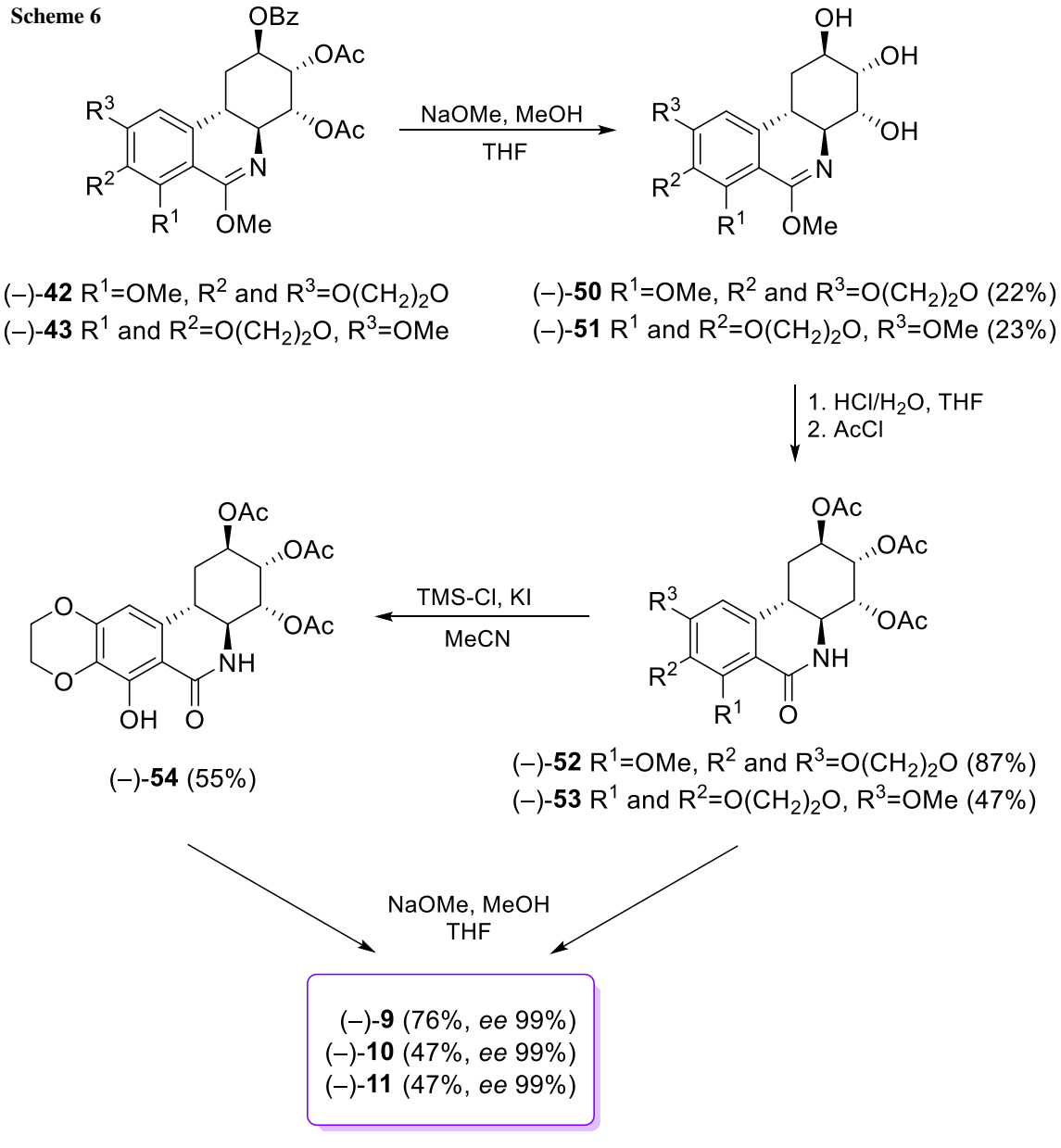


Fig. 4 Structures of the isolated side products (±)-**48** and (±)-**49**

4-triyl triacetate [(−)-**52**] and (−)-11-methoxy-6-oxo-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridine-2,3,4-triyl triacetate [(−)-**53**] were also demethylated selectively at the position A-7 using the above-mentioned method (TMS-I, acetonitrile). As a result of this cleavage, (−)-7-hydroxy-6-oxo-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridine-2,3,4-triyl triacetate [(−)-**54**] was obtained in moderate yield (55%). Then, compound (−)-**52**, (−)-**53**, or (−)-**54** was also deacetylated by Zemplén's method to afford (−)-**9** in good yield (76%),

Scheme 6



and due to the regioisomer formation, two further synthetic analogues of *trans*-dihydronarciclasine (−)-**10** and (−)-**11** in moderate yields (47%).

Conclusion

In conclusion, four new synthetic *trans*-dihydronarciclasine analogues [(−)-**8**–(−)-**11**)] containing a relatively rigid 1,4-benzodioxane moiety in ring A were synthesised from vanillin using stereo- and enantioselective synthetic routes. These new, optically active derivatives were obtained with excellent enantiomeric purity (99% *ee*). According to their negative optical rotation values, these compounds appear to be new analogues of (−)-*trans*-dihydronarciclasine. The preparation of compounds (−)-**10** and (−)-**11** was due to a side reaction and regioisomer formation, and based on our modified synthesis strategy. Biological evaluations of these potentially anticancerous and antiviral molecules are in progress.

Experimental

All reagents are commercially available from Merck. Melting points were measured on a Büchi 510 apparatus using a certified mercury thermometer (ASTM 2C). Optical rotations were measured on a Perkin Elmer 241 polarimeter. IR spectra were obtained on a PerkinElmer 1600 FT-IR instrument. NMR spectra were recorded on a Bruker AV-300 instrument. HPLC analyses were carried out with a Jasco PU-1580 apparatus equipped with a Jasco UV-1575 detector (λ = 256 nm) using a Daicel Chiralpack® OD (250 × 4.6 mm × 5 µm) column (eluent: hexane/*i*-PrOH, 8:2; flow rate: 2.0 cm^3 min^{-1}; 20 °C). Elemental analyses were performed on a vario EL III instrument (Elementar Analysensysteme). Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column cromatography. Compounds **14**, **15**, and **22** were prepared as described previously [39], and their spectral data were found to be identical with the ones described in Ref [39].

3,4-Dihydroxybenzaldehyde (13) A solution of 35.00 g **12** (0.23 mol) in 300 cm^3 dichloromethane was cooled to 0 °C and subsequently 36.81 g $AlCl_3$ (0.28 mol) was added. Then it was allowed to warm to rt, 81.67 cm^3 pyridine (80.20 g, 1.01 mol) was added dropwise and the reaction mixture was refluxed for 24 h. After cooling, it was acidified with 20% aqueous hydrochloric acid to pH = 2. The precipitated pyridinium salt was dissolved by adding 300 cm^3 water and then the aqueous phase was extracted with ethyl acetate (4 × 250 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give 29.22 g **13** (92%) as a pale yellow solid, which was used without further purification. M.p.: 152–153 °C (Ref. [41] 153–154 °C); its spectral data were found to be identical with the ones described in Ref. [62].

General procedure for the synthesis of 1,4-benzodioxanes 16 and 17

43.80 g potassium carbonate (0.32 mol) and 15.1 cm^3 1,2-dibromoethane (32.90 g, 0.18 mol) were added to a solution of 22.00 g **13** (0.16 mol) or 26.70 g **15** (0.16 mol) in 250 cm^3 DMF. The reaction mixture was stirred at 100–110 °C for 4–8 h. After cooling to rt, the precipitated inorganic salts were filtered and the reaction mixture was evaporated to 80 cm^3 in vacuo. The residue was poured into 670 cm^3 water. The product was isolated as specified.

2,3-Dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (16) The aqueous phase was extracted with ethyl acetate (4 × 200 cm^3), and the combined organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by distillation in vacuo to afford **16**. Yield: 63%; white solid; m.p.: 48–49 °C (Ref. [63] 49.5–50.5 °C); b.p.: 105–108 °C (0.3 mbar); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.82 (s, 1H, CHO), 7.42–7.38 (m, 2H, 5-H_{Ar} and 7-H_{Ar}), 6.98 (d, J = 8.7 Hz, 1H, 8-H_{Ar}), 4.35–4.28 (m, 4H, OCH_2CH_2O) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.0 (OCH_2CH_2O), 64.7 (OCH_2CH_2O), 117.8 (5-C_{Ar} or 8-C_{Ar}), 118.4 (5-C_{Ar} or 8-C_{Ar}), 124.2 (7-C_{Ar}), 130.7 (6-C_{Ar}), 143.9 (4a-C_{Ar}), 149.1 (8a-C_{Ar}), 190.7 (CHO) ppm; IR (KBr): $\bar{\nu}$ = 3001, 2883, 1687, 1581, 1506, 1458, 1394, 1291, 1156, 1062, 887, 777 cm^{-1}.

8-Methoxy-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (17) The precipitated crystals were filtered, washed with water, and dried to give **17**, which was used without further purification. Yield: 63%; white crystals; m.p.: 78–79 °C. (Ref. [64] 69–72 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (s, 1H, CHO), 7.06 (s, 2H, 5-H_{Ar} and 7-H_{Ar}), 4.40–4.28 (m, 4H, OCH_2CH_2O), 3.93 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.3 (OCH_3), 63.9 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 103.0 (7-C_{Ar}), 114.5 (5-C_{Ar}), 129.2 (6-C_{Ar}), 138.8 (8a-C_{Ar}), 144.0 (8-C_{Ar}), 149.6 (4a-C_{Ar}), 190.7 (CHO) ppm; IR (KBr): $\bar{\nu}$ = 2982, 2948, 2892, 1698, 1590, 1503, 1470, 1454, 1392, 1324, 1125, 1046, 891, 840 cm^{-1}.

General procedure for the synthesis of 2,3-dihydrobenzodioxine butenones 18 and 19

A solution of 16.46 g **16** (0.10 mol) or 19.41 g **17** (0.10 mol) in 95 cm^3 acetone (75.15 g, 1.29 mol) was added into 42 cm^3 water; then the starting material was precipitated in a fine crystal form. Aqueous sodium

hydroxide solution (from 1.51 g (37.76 mmol) NaOH and 6.8 cm^3 H_2O) and 378 cm^3 water were also added and the yellow mixture was stirred for 20 h intensively at room temperature. The yellow crude product was filtered, washed with water, and dried. Finally, it was purified by distillation in vacuo to afford **18** or **19**.

4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)but-3-en-2-one (18, $C_{12}H_{12}O_3$) Yield: 83%; white crystals; m.p.: 90–91 °C; b.p.: 153 °C (0.2 mbar); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, J = 16.2 Hz, 1H, Ar–*CH* = CH), 7.08–7.04 (m, 2H, 5-H_{Ar} and 7-H_{Ar}), 6.88 (d, J = 8.4 Hz, 1H, 8-H_{Ar}), 6.58 (d, J = 16.2 Hz, 1H, Ar–CH = *CH*), 4.31–4.27 (m, 4H, OCH_2CH_2O), 2.36 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 ($CO\mathit{CH_3}$), 64.2 ($O\mathit{CH_2}CH_2O$), 64.5 ($OCH_2\mathit{CH_2}O$), 116.8 (5-C_{Ar} or 8-C_{Ar}), 117.8 (5-C_{Ar} or 8-C_{Ar}), 122.3 (7-C_{Ar}), 125.5 (Ar–CH = *CH*), 128.0 (6-C_{Ar}), 143.1 (Ar–*CH* = CH), 143.7 (4a-C_{Ar}), 149.2 (8a-C_{Ar}), 192.2 (CO) ppm; IR (KBr): $\bar{\nu}$ = 2989, 2894, 1668, 1641, 1579, 1513, 1455, 1427, 1360, 1300, 1251, 1122, 1061, 977, 884, 806, 779 cm^{-1}.

4-(8-Methoxy-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)but-3-en-2-one (19, $C_{13}H_{14}O_4$) Yield: 62%; light yellow solid; m.p.: 96–98 °C; b.p.: 183 °C (0.2 mbar); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, J = 16.2 Hz, Ar–*CH* = CH), 6.75 (d, J = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 6.69 (d, J = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 6.57 (d, J = 15.9 Hz, 1H, Ar–CH = *CH*), 4.36–4.26 (m, 4H, OCH_2CH_2O), 3.90 (s, 3H, OCH_3), 2.35 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 ($CO\mathit{CH_3}$), 56.2 (OCH_3), 64.1 ($O\mathit{CH_2}CH_2O$), 64.7 ($OCH_2\mathit{CH_2}O$), 103.6 (7-C_{Ar}), 111.0 (5-C_{Ar}), 125.8 (Ar–CH = *CH*), 126.8 (6-C_{Ar}), 135.5 (8a-C_{Ar}), 143.4 (Ar–*CH* = CH), 144.1 (8-C_{Ar}), 149.2 (4a-C_{Ar}), 192.2 (CO) ppm; IR (KBr): $\bar{\nu}$ = 2996, 2940, 1666, 1638, 1589, 1508, 1453, 1321, 1274, 1126, 977, 822 cm^{-1}.

General procedure for the synthesis of racemic nitropentanones (±)-20 and (±)-21

To a solution of 7.70 g **18** (37.74 mmol) or 8.84 g **19** (37.74 mmol) in a mixture of anhydrous 15.1 cm^3 ethanol and 10.22 cm^3 nitromethane (11.52 g, 0.19 mol) was added 0.11 g anhydrous potassium carbonate (0.81 mmol) and the reaction mixture was refluxed for 5–8 h. Then, it was cooled to rt and 14.3 cm^3 water was added. The product was isolated as specified.

(±)-4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-nitropentan-2-one [(±)-20, $C_{13}H_{15}NO_5$] The aqueous phase was extracted with ethyl acetate (3 × 40 cm^3), and the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. Recrystallisation from ethyl acetate gave (±)-**20**. Yield: 75%; white crystals; m.p.: 101–102 °C; R_f = 0.52 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (d, J = 8.1 Hz, 1H, 8-H_{Ar}), 6.70 (d, J = 1.8 Hz, 1H, 5-H_{Ar}), 6.67 (dd, J = 8.4, 2.1 Hz, 1H, 7-H_{Ar}), 4.63 (dd, J = 12.3, 6.9 Hz, 1H, CH_2-NO_2), 4.53 (dd, J = 12.3, 7.8 Hz, 1H, CH_2NO_2), 4.23 (s, 4H, OCH_2CH_2O), 3.89 (quint, J = 7.2 Hz, 1H, Ar–CH), 2.86 (d, J = 7.2 Hz, 2H, CH_2CO), 2.12 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.4 ($CO\mathit{CH_3}$), 38.4 (Ar–CH), 46.2 ($\mathit{CH_2}CO$), 64.3 ($O\mathit{CH_2}CH_2O$), 64.3 ($OCH_2\mathit{CH_2}O$), 79.6 ($\mathit{CH_2}NO_2$), 116.1 (5-C_{Ar} or 8-C_{Ar}), 117.7 (5-C_{Ar} or 8-C_{Ar}), 120.3 (7-C_{Ar}), 131.9 (6-C_{Ar}), 143.1 (8a-C_{Ar} or 4a-C_{Ar}), 143.7 (4a-C_{Ar} or 8a-C_{Ar}), 205.4 (CO) ppm; IR (KBr): $\bar{\nu}$ = 2878, 1717, 1592, 1508, 1433, 1384, 1313, 1220, 1161, 1130, 1071, 903, 819, 639 cm^{-1}.

(±)-4-(8-Methoxy-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-nitropentan-2-one [(±)-21, $C_{14}H_{17}NO_6$] After crystallisation at 0 °C, the precipitated crystals were filtered, washed with water and dried to afford (±)-**21**. Yield: 86%; white solid; m.p.: 99–101 °C; R_f = 0.33 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.35 (d, J = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 6.34 (d, J = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 4.63 (dd, J = 12.3, 6.9 Hz, 1H, CH_2NO_2), 4.53 (dd, J = 12.3, 7.8 Hz, 1H, CH_2NO_2), 4.29–4.22 (m, 4H, OCH_2CH_2O), 3.88 (quint, J = 7.2 Hz, 1H, Ar–CH), 3.86 (s, 3H, OCH_3), 2.86 (dd, J = 6.9, 1.5 Hz, 2H, $\mathit{C}H_2CO$), 2.12 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.4 ($CO\mathit{CH_3}$), 38.9 (Ar–CH), 46.2 ($\mathit{CH_2}CO$), 56.2 (OCH_3), 64.2 ($O\mathit{CH_2}CH_2O$), 64.4 ($OCH_2\mathit{CH_2}O$), 79.5 (CH_2NO_2), 103.8 (7-C_{Ar}), 108.3 (5-C_{Ar}), 131.0 (8a-C_{Ar}), 132.6 (6-C_{Ar}), 144.2 (8-C_{Ar}), 149.4 (4a-C_{Ar}), 205.4 (CO) ppm; IR (KBr): $\bar{\nu}$ = 2962, 1716, 1599, 1513, 1438, 1386, 1326, 1221, 1130, 1046, 951, 844, 669 cm^{-1}.

General procedure for the enantioselective Michael addition using organocatalyst 22

A solution of 8.17 g **18** (40.00 mmol) or 9.37 g **19** (40.00 mmol) and 20 mol % (8*S*,9*S*)-9-amino(9-deoxy)epiquinine (**22**) in 54 cm^3 anhydrous nitromethane was stirred at rt for 7 d, and then the solvent was evaporated in vacuo. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to obtain optically active (−)-**20** or recrystallised from MeOH to give (−)-**21**. Spectroscopic data and elemental analysis for these compounds matched those for the racemates as given above.

(−)-4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-nitropentan-2-one [(−)-20, $C_{13}H_{15}NO_5$] Yield: 67%; white solid; m.p.: 75–77 °C; R_f = 0.52 (hexane/EtOAc, 1:1); HPLC: Chiralpack® OD (hexane/*i*-PrOH = 8:2, flow rate 2.0 cm^3 min^{-1}, 256 nm, 20 °C), $t_{(-)}$: 25 min, $t_{(+)}$: 18 min; $[\alpha]_D^{22}$ = − 16.1° (c = 0.94, acetone); *ee* 92%.

(−)-4-(8-Methoxy-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-nitropentan-2-one [(−)-21, $C_{14}H_{17}NO_6$] Yield: 67%; white crystals; m.p.: 111–115 °C; R_f = 0.33 (hexane/EtOAc, 1:1); HPLC: Chiralpack® OD (hexane/*i*-PrOH = 8:2, flow rate 2.0 cm^3 min^{-1}, 256 nm, 20 °C), $t_{(-)}$: 32 min, $t_{(+)}$: 28 min; $[\alpha]_D^{22} = -15.0°$ (c = 1.5, acetone); *ee* 98%.

General procedure for the Claisen–Henry reaction

Dry and freshly prepared sodium methoxide powder (from 2.90 g sodium (0.13 mol) and 70 cm^3 anhydrous methanol) was suspended in 100 cm^3 anhydrous diethyl ether. Subsequently, 14.50 cm^3 ethyl formate (13.36 g, 0.18 mol) and 8.07 g (−)-**20** (30.48 mmol) or 9.00 g (−)-**21** (30.48 mmol) were added, and the reaction mixture was stirred at rt for 20 h. It was cooled to 0 °C and 51 cm^3 water was added dropwise. After separating, the aqueous phase was acidified with acetic acid to pH = 4 at 0 °C. The precipitated crystals were filtered, washed with water and dried. The crude product (−)-**23** or (−)-**24** was purified as specified.

(−)-3-Hydroxy-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-nitrocyclohexanone [(−)-23, $C_{14}H_{15}NO_6$] Recrystallisation from ethyl acetate gave light yellow crystals. Yield: 46%; m.p.: 206 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.96 (d, J = 1.8 Hz, 1H, 5-H_{Ar}), 6.86 (dd, J = 8.4, 1.8 Hz, 1H, 7-H_{Ar}), 6.78 (d, J = 8.1 Hz, 1H, 8-H_{Ar}), 5.98 (d, J = 4.5 Hz, 1H, OH), 5.67 (dd, J = 11.7, 2.1 Hz, 1H, 4-H), 4.69–4.63 (m, 1H, 3-H_{Cy}), 4.21 (s, 4H, OCH_2CH_2O), 3.83 (td, J = 12.9, 4.5 Hz, 1H, 5-H), 3.04 (dd, J = 14.4, 2.7 Hz, 1H, 2-$H_{\beta,Cy}$), 2.65 (t, J = 14.1 Hz, 1H, 6-H_β), 2.39 (dt, J = 14.4, 3.0 Hz, 1H, 2-$H_{\alpha,Cy}$), 2.31 (ddd, J = 14.7, 5.1, 2.1 Hz, 1H, 6-H_α) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 40.4 (5-C), 46.4 (2-C_{Cy}), 47.3 (6-C), 63.9 (OCH_2CH_2O), 64.0 (OCH_2CH_2O), 69.6 (3-C_{Cy}), 89.4 (4-C), 115.7 (8-C_{Ar}), 117.0 (5-C_{Ar}), 120.1 (7-C_{Ar}), 133.6 (6-C_{Ar}), 142.3 (8a-C_{Ar}), 143.2 (4a-C_{Ar}), 206.0 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3318, 2984, 2919, 1714, 1591, 1554, 1511, 1461, 1373, 1309, 1248, 1127, 1067, 889, 814 cm^{-1}; $[\alpha]_D^{22} = -18.4°$ (c = 1, $CHCl_3$).

(−)-3-Hydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]-dioxin-6′-yl)-4-nitrocyclohexanone [(−)-24, $C_{15}H_{17}NO_7$] It was purified by column chromatography (hexane/EtOAc, 1:2) to afford a light yellow solid. Yield: 57%; m.p.: 200–201 °C; R_f = 0.19 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.66 (d, J = 1.2 Hz, 1H, 5-H_{Ar}), 6.56 (d, J = 1.5 Hz, 1H, 7-H_{Ar}), 5.99 (d, J = 4.5 Hz, 1H, OH), 5.70 (dd, J = 11.7, 1.8 Hz, 1H, 4-H), 4.70–4.64 (m, 1H, 3-H_{Cy}), 4.18 (s, 4H, OCH_2CH_2O), 3.81 (td, J = 12.9, 4.2 Hz, 1H, 5-H), 3.74 (s, 3H, OCH_3), 3.02 (dd, J = 14.1, 2.1 Hz, 1H, 2-$H_{\beta,Cy}$), 2.67 (t, J = 14.1 Hz, 1H, 6-H_β), 2.40 (dt, J = 14.7, 2.7 Hz, 1H, 2-$H_{\alpha,Cy}$), 2.33 (ddd, J = 14.7, 4.5, 2.1 Hz, 1H, 6-H_α) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 39.3 (5-C), 46.4 (2-C_{Cy}), 47.3 (6-C), 55.8 (OCH_3), 63.6 (OCH_2CH_2O), 63.9 (OCH_2CH_2O), 69.6 (3-C_{Cy}), 89.2 (4-C), 104.0 (7-C_{Ar}), 108.1 (5-C_{Ar}), 132.0 (8a-C_{Ar}), 132.6 (6-C_{Ar}), 143.5 (4a-C_{Ar}), 148.6 (8-C_{Ar}), 206.1 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3337, 2962, 2867, 1709, 1599, 1554, 1514, 1465, 1376, 1253, 1130, 1050, 888, 825 cm^{-1}; $[\alpha]_D^{22} = -11.4°$ (c = 0.5, THF).

General procedure for the synthesis of ethylene acetals (+)-25 and (+)-26

36 cm^3 ethylene glycol (39.89 g, 0.64 mol) and 4.40 g (−)-**23** (15.00 mmol) or 4.85 g (−)-**24** (15.00 mmol) were added to a solution of 12.62 g anhydrous oxalic acid (0.14 mol) in 213 cm^3 anhydrous acetonitrile. The mixture was stirred at rt for 3–4 d. Then, it was poured into a cooled and saturated 594 cm^3 $NaHCO_3$ solution. The precipitated solid was collected by filtration, washed with water, and dried to give (+)-**25** or (+)-**26**.

(+)-3-Hydroxy-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-nitrocyclohexanone ethylene acetal [(+)-25, $C_{16}H_{19}NO_7$] Yield: 84%; white solid; m.p.: 224–228 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79 (d, J = 8.1 Hz, 1H, 8-H_{Ar}), 6.75–6.70 (m, 2H, 5-H_{Ar} and 7-H_{Ar}), 4.70 (dd, J = 12.0, 3.0 Hz, 1H, 4-H), 4.63 (dq, J = 10.2, 3.0 Hz, 1H, 3-H_{Cy}), 4.22 (s, 4H, $OCH_2CH_2O_{benzodioxane}$), 4.09–3.91 (m, 5H, OH and $OCH_2CH_2O_{acetal}$), 3.75 (td, J = 12.6, 3.9 Hz, 1H, 5-H), 2.19 (dt, J = 14.4, 3.0 Hz, 1H, 2-$H_{\alpha,Cy}$), 2.04 (dd, J = 14.4, 2.7 Hz, 1H, 2-$H_{\beta,Cy}$), 2.00 (dt, J = 12.9, 3.6 Hz, 2H, 6-H_α), 1.79 (t, J = 13.5 Hz, 1H, 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7 (5-C), 38.5 (2-C_{Cy}), 41.5 (6-C), 64.3 ($OCH_2CH_2O_{acetal}$, 2′-C or 3′-C), 64.4 (2′-C or 3′-C), 65.1 ($OCH_2CH_2O_{acetal}$), 69.7 (3-C_{Cy}), 91.1 (4-C_{Cy}), 107.6 (1-C), 116.1 (5-C_{Ar}), 117.6 (8-C_{Ar}), 120.2 (7-C_{Ar}), 132.6 (6-C_{Ar}), 140.3 (8a-C_{Ar}), 141.9 (4a-C_{Ar}) ppm; IR (KBr): $\bar{\nu}$ = 3502, 2980, 2943, 2887, 1592, 1551, 1507, 1458, 1386, 1362, 1243, 1125, 1050, 953, 890, 820, 640 cm^{-1}; $[\alpha]_D^{22} = +47.0°$ (c = 0.5, DMF).

(+)-3-Hydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]-dioxin-6′-yl)-4-nitrocyclohexanone ethylene acetal [(+)-26, $C_{17}H_{21}NO_8$] Yield: 75%; white solid; m.p.: 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.40 (s, 2H, 5-H_{Ar} and7-H_{Ar}), 4.71 (dd, J = 12.0, 2.7 Hz, 1H, 4-H), 4.63 (dq, J = 9.9, 3.0 Hz, 1H, 3-H_{Cy}), 4.28–4.22 (m, 4H, $OCH_2CH_2O_{benzodioxane}$), 4.09–3.92 (m, 5H, OH and $OCH_2CH_2O_{acetal}$), 3.86 (s, 3H, OCH_3), 3.74 (td, J = 12.6, 4.2 Hz, 1H, 5-H), 2.19 (dt, J = 14.7, 3.0 Hz, 1H, 2-$H_{\alpha,Cy}$), 2.07–1.98 (m, 2H, 2-$H_{\beta,Cy}$ and 6-H_α), 1.80 (t, J = 13.5 Hz, 1H, 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.2 (5-C), 38.4 (2-C_{Cy}), 41.5 (6-C), 56.2 (OCH_3), 64.2 ($OCH_2CH_2O_{acetal}$),

64.3 (2′-C and 3′-C), 65.1 ($OCH_2CH_2O_{acetal}$), 69.6 (3-C_{Cy}), 91.0 (4-C), 104.0 (7-C_{Ar}), 107.6 (1-C), 108.3 (5-C_{Ar}), 131.8 (8a-C_{Ar}), 132.4 (6-C_{Ar}), 144.1 (4a-C_{Ar}), 148.9 (8-C_{Ar}) ppm; IR (KBr): $\bar{\nu}$ = 3514, 2974, 2939, 2895, 1599, 1544, 1513, 1460, 1385, 1352, 1249, 1127, 1051, 950, 840 cm^{-1}; $[\alpha]_D^{22}$ = + 13.8° (*c* = 1, $CHCl_3$).

General procedure for the synthesis of amines (+)-27 and (+)-28

Over a 10% Pd/C catalyst (Selcat Q, 0.75 g), 2.53 g (+)-**25** (7.50 mmol) or 2.75 g (+)-**26** (7.50 mmol) was hydrogenated in 50 cm^3 MeOH, in a 250 cm^3 stainless steel autoclave equipped with a magnetic stirrer (stirring speed: 1100 rpm). The reduction was carried out at 12 bar and 60–80 °C for 6 h. After the hydrogen uptake was finished, the catalyst was removed by filtration and the filtrate was concentrated in vacuo to afford (+)-**27** or (+)-**28**.

(+)-4-Amino-3-hydroxy-5-(2′,3′-dihydrobenzo[*b*][1,4]-dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-27, $C_{16}H_{21}NO_5$] Yield: 56%; light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (d, *J* = 8.4 Hz, 1H, 8-H_{Ar}), 6.71 (d, *J* = 1.2 Hz, 1H, 5-H_{Ar}), 6.67 (dd, *J* = 8.4, 1.8 Hz, 1H, 7-H_{Ar}), 4.23 (s, 4H, $OCH_2CH_2O_{benzodioxane}$), 4.06–3.85 (m, 5H, 3-$H_{Cy}$ and $OCH_2CH_2O_{acetal}$), 2.77–2.71 (m, 2H, 4-H, 5-H), 2.20 (bs, 2H, NH_2), 2.11 (dt, *J* = 14.1, 2.7 Hz, 1H, 2-$H_{\alpha,Cy}$), 1.80 (dd, *J* = 14.1, 3.0 Hz, 1H, 2-$H_{\beta,Cy}$), 1.88–1.77 (m, 2H, 6-H_α and 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.2 (2-C_{Cy}), 41.6 (6-C), 43.7 (5-C), 57.3 (4-C), 64.0 ($OCH_2CH_2O_{acetal}$), 64.3 (2′-C and 3′-C), 64.8 ($OCH_2CH_2O_{acetal}$), 70.4 (3-C_{Cy}), 108.8 (1-C), 116.4 (8-C_{Ar}), 117.4 (5-C_{Ar}), 120.7 (7-C_{Ar}), 135.4 (6-C_{Ar}), 142.4 (8a-C_{Ar}), 143.6 (4a-C_{Ar}) ppm; IR (KBr): $\bar{\nu}$ = 3503, 2929, 2880, 1589, 1508, 1433, 1371, 1289, 1245, 1110, 1067, 1002, 948, 888, 815, 747 cm^{-1}; $[\alpha]_D^{22}$ = + 15.5° (*c* = 1, $CHCl_3$).

(+)-4-Amino-3-hydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-28, $C_{17}H_{23}NO_6$] Yield: 75%; grey semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.40 (d, *J* = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 6.35 (d, *J* = 1.2 Hz, 5-H_{Ar} or 7-H_{Ar}), 4.30–4.24 (m, 4H, $OCH_2CH_2O_{benzodioxane}$), 4.07–3.87 (m, 5H, 3-$H_{Cy}$ and $OCH_2CH_2O_{acetal}$), 3.86 (s, 3H, OCH_3), 2.76–2.73 (m, 2H, 4-H and 5-H), 2.12 (dt, *J* = 14.1, 2.7 Hz, 1H, 2-$H_{\alpha,Cy}$), 2.07 (bs, 2H, NH_2), 1.94 (dd, *J* = 14.1, 3.0 Hz, 1H, 2-$H_{\beta,Cy}$), 1.90–1.78 (m, 2H, 6-H_α and 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.2 (2-C_{Cy}), 41.6 (6-C), 44.3 (5-C), 56.1 (OCH_3), 57.3 (4-C), 64.1 ($OCH_2CH_2O_{acetal}$), 64.3 (2′-C or 3′-C), 64.5 (2′-C or 3′-C), 64.8 ($OCH_2CH_2O_{acetal}$), 70.5 (3-C_{Cy}), 103.7 (7-C_{Ar}), 108.9 (1-C), 109.1 (5-C_{Ar}), 131.9 (6-C_{Ar}), 134.5 (8a-C_{Ar}), 144.1 (8-C_{Ar}), 149.0 (4a-C_{Ar}) ppm; IR (KBr):$\bar{\nu}$ = 3503, 2929, 1598, 1558, 1508, 1458, 1371, 1341, 1216, 1126, 1069, 952, 887 cm^{-1}; $[\alpha]_D^{22}$ = + 6.3° (*c* = 1, methanol).

General procedure for the synthesis of carbamates (+)-29 and (+)-30

Half of the required methyl chloroformate (0.64 cm^3, 0.80 g, 8.47 mmol), 3% aqueous NaOH solution (20 cm^3), and subsequently the other half of methyl chloroformate (0.64 cm^3, 0.80 g, 8.47 mmol) were added to a solution of 2.54 g (+)-**27** (8.27 mmol) or 2.79 g (+)-**28** (8.27 mmol) in 51 cm^3 tetrahydrofuran. The reaction mixture was stirred rigorously at rt for 2 h, then it was poured into 113 cm^3 water and extracted with ethyl acetate (4 × 105 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo to give (+)-**29** or (+)-**30**.

(+)-3-Hydroxy-4-methoxycarbonylamino-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-29, $C_{18}H_{23}NO_7$] Yield: 100%; brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8.1 Hz, 1H, 8-H_{Ar}), 6.72–6.68 (m, 2H, 5-H_{Ar} and 7-H_{Ar}), 4.98 (d, *J* = 9.0 Hz, 1H, NH), 4.22 (s, 4H, $OCH_2CH_2O_{benzodioxane}$), 4.15–4.08 (m, 1H, 3-$H_{Cy}$), 4.04–3.88 (m, 4H, $OCH_2CH_2O_{acetal}$), 3.81 (m, 1H, 4-H), 3.56 (d, *J* = 9.6 Hz, 1H, OH), 3.50 (s, 3H, $NHCOOCH_3$), 2.91 (td, *J* = 11.7, 3.6 Hz, 1H, 5-H), 2.08 (dt, *J* = 14.4, 2.7 Hz, 1H, 2-$H_{\alpha,Cy}$), 2.00 (dd, *J* = 14.4, 2.7 Hz, 1H, 2-$H_{\beta,Cy}$), 1.91 (dt, *J* = 13.2, 3.3 Hz, 1H, 6-H_α), 1.84 (t, *J* = 12.6 Hz, 1H, 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.6 (2-C_{Cy}), 40.8 (5-C), 42.5 (6-C), 51.9 ($NHCOOCH_3$), 56.3 (4-C), 64.2 ($OCH_2CH_2O_{acetal}$), 64.3 (2′-C and 3′-C), 64.9 ($OCH_2CH_2O_{acetal}$), 69.6 (3-C_{Cy}), 108.5 (1-C), 116.6 (5-C_{Ar}), 117.2 (8-C_{Ar}), 120.4 (7-C_{Ar}), 134.5 (6-C_{Ar}), 142.3 (8a-C_{Ar}), 143.3 (4a-C_{Ar}), 156.4 ($NHCOOCH_3$) ppm; IR (KBr): $\bar{\nu}$ = 3471, 3318, 2950, 2890, 1712, 1589, 1543, 1506, 1447, 1341, 1289, 1226, 1132, 1065, 993, 950, 919, 882, 817, 777, 723 cm^{-1}; $[\alpha]_D^{22}$ = + 17.8° (*c* = 1, methanol).

(+)-3-Hydroxy-4-methoxycarbonylamino-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexanone ethylene acetal [(+)-30, $C_{19}H_{25}NO_8$] Yield: 99%; white solid (fluffy); m.p.: 84–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.39 (s, 2H, 5-H_{Ar} and 7-H_{Ar}), 4.96 (d, *J* = 9.3 Hz, 1H, NH), 4.30–4.22 (m, 4H, $OCH_2CH_2O_{benzodioxane}$), 4.15–4.08 (m, 1H, 3-$H_{Cy}$), 4.05–3.91 (m, 5H, 4-H, $OCH_2CH_2O_{acetal}$), 3.86 (s, 3H, OCH_3), 3.57 (d, *J* = 9.6 Hz, 1H, OH), 3.51 (s, 3H, $NHCOOCH_3$), 2.90 (td, *J* = 11.4, 3.0 Hz, 1H, 5-H), 2.09 (dt, *J* = 14.4, 3.0 Hz, 1H, 2-$H_{\alpha,Cy}$), 2.01 (dd, *J* = 14.1, 3.3 Hz, 1H, 2-$H_{\beta,Cy}$), 1.92 (dt, *J* = 13.2, 3.3 Hz, 1H, 6-H_α), 1.83 (t, *J* = 13.2 Hz, 1H, 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.7 (2-C_{Cy}), 41.2 (5-C), 42.8 (6-C), 51.9 ($NHCOOCH_3$), 56.0 (4-C), 56.1 (OCH_3), 64.2

($OCH_2CH_2O_{acetal}$, 2′-C or 3′-C), 64.5 (2′-C or 3′-C), 64.9 ($OCH_2CH_2O_{acetal}$), 69.7 (3-C_{Cy}), 103.2 (7-C_{Ar}), 108.5 (1-C), 109.4 (5-C_{Ar}), 131.8 (8a-C_{Ar}), 133.6 (6-C_{Ar}), 143.8 (8-C_{Ar}), 148.7 (4a-C_{Ar}), 156.4 (NH*CO*OCH$_3$) ppm; IR (KBr): $\bar{\nu}$ = 3447, 3340, 2944, 1714, 1596, 1536, 1511, 1457, 1435, 1340, 1259, 1225, 1123, 1080, 1052, 887 cm^{-1}; $[\alpha]_D^{22}$ = + 10.0° (*c* = 1, $CHCl_3$).

General procedure for the synthesis of enones (−)-31 and (−)-32

A solution of 3.62 g (+)-**29** (9.91 mmol) or 3.92 g (+)-**30** (9.91 mmol) and 3.37 g *p*-TsOH (17.72 mmol) in 235 cm^3 acetone was heated to reflux and stirred for 1 h. After cooling to rt, it was poured into 461 cm^3 saturated $NaHCO_3$ solution and extracted with ethyl acetate (4 × 138 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford (−)-**31** or (−)-**32**.

(−)-6-(2′,3′-Dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-oxocyclohex-2-enyl)carbamic acid methyl ester [(−)-31, $C_{16}H_{17}NO_5$] Yield: 93%; white solid; m.p.: 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 10.2 Hz, 1H, 2-H_{Cy}), 6.83 (d, *J* = 8.1 Hz, 1H, 8-H_{Ar}), 6.74 (d, *J* = 1.8 Hz, 1H, 5-H_{Ar}), 6.70 (dd, *J* = 8.1, 1.8 Hz, 1H, 7-H_{Ar}), 6.07 (dd, *J* = 10.2, 2.4 Hz, 1H, 3-H_{Cy}), 4.82–4.71 (m, 1H, NH), 4.61–4.56 (m, 1H, 1-H), 4.25 (s, 4H, OCH_2CH_2O), 3.60 (s, 3H, NHCOO*CH$_3$*), 3.20–3.11 (m, 1H, 6-H), 2.68–2.65 (m, 2H, 5-H_α and 5-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.9 (5-C), 47.1 (6-C) 52.3 (C-1), 53.3 (NHCOO*CH$_3$*), 64.3 (O*CH$_2$CH$_2$*O), 116.0 (5-C_{Ar}), 117.6 (8-C_{Ar}), 120.2 (7-C_{Ar}), 129.2 (3-C_{Cy}), 132.9 (6-C_{Ar}), 143.0 (8a-C_{Ar}), 143.7 (4a-C_{Ar}), 151.6 (2-C_{Cy}), 156.6 (NH*CO*OCH$_3$), 197.5 (4-C) ppm; IR (KBr): $\bar{\nu}$ = 3330, 2984, 2884, 1698, 1683, 1591, 1541, 1509, 1458, 1385, 1244, 1130, 1053, 927, 890, 817, 773 cm^{-1}; $[\alpha]_D^{22}$ = − 162.0° (*c* = 1, acetone).

(−)-6-(8′-Methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-oxocyclohex-2-enyl)carbamic acid methyl ester [(−)-32, $C_{17}H_{19}NO_6$] Yield: 88%; light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 9.9, 1H, 2-H_{Cy}), 6.40 (d, *J* = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 6.36 (d, *J* = 1.8 Hz, 1H, 5- H_{Ar} or 7-H_{Ar}), 6.07 (dd, *J* = 10.2, 2.4 Hz, 1H, 3-H_{Cy}), 4.82 (d, *J* = 7.5 Hz, 1H, NH), 4.65–4.59 (m, 1H, 1-H), 4.30–4.24 (m, 4H, OCH_2CH_2O), 3.86 (s, 3H, OCH_3) 3.61 (s, 3H, NHCOO*CH$_3$*), 3.20–3.11 (m, 1H, 6-H), 2.68–2.64 (m, 2H, 5-H_α and 5-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.0 (5-C), 47.6 (6-C), 52.3 (NHCOO*CH$_3$*), 53.1 (1-C), 56.1 (OCH_3), 64.2 (O*CH$_2$*CH$_2$O), 64.4 (OCH_2*CH$_2$*O), 103.0 (7-C_{Ar}), 108.8 (5-C_{Ar}), 129.2 (3-C_{Cy}), 132.0 (8a-C_{Ar}), 132.4 (6-C_{Ar}), 144.1 (8a-C_{Ar}), 149.1 (4a-C_{Ar}), 151.7 (2-C_{Cy}), 156.3 (NH*CO*OCH$_3$), 197.5 (4-C) ppm; IR (KBr): $\bar{\nu}$ = 3341, 2946, 1699, 1680, 1598, 1512, 1462, 1385, 1342, 1242, 1127, 1050, 887, 652 cm^{-1}; $[\alpha]_D^{22}$ = − 116.2° (*c* = 1, $CHCl_3$).

General procedure for the synthesis of enols (−)-33 and (−)-34

A solution of 2.63 g (−)-**31** (8.67 mmol) or 2.89 g (−)-**32** (8.67 mmol) and 1.97 g $CaCl_2$ (17.75 mmol) in 264 cm^3 methanol was stirred for 30 min at rt. Then, it was cooled to 0 °C and 0.49 g $NaBH_4$ (12.95 mmol) was added in one portion. It was further stirred at 0 °C for 30 min, then poured into 372 cm^3 water and extracted with ethyl acetate (4 × 188 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was recrystallised from hexane/EtOAc (2:1) to give (−)-**33** or (−)-**34**.

(−)-6-(2′,3′-Dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-hydroxycyclohex-2-enyl)carbamic acid methyl ester [(−)-33, $C_{16}H_{19}NO_5$] Yield: 67%; white solid; m.p.: 166–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (d, *J* = 8.1 Hz, 1H, 8-H_{Ar}), 6.72 (d, *J* = 1.8 Hz, 1H, 5-H_{Ar}), 6.68 (dd, *J* = 8.1, 1.8 Hz, 1H, 7-H_{Ar}), 5.81 (dd, *J* = 10.2, 1.2 Hz, 1H, 3-H_{Cy}), 5.75 (d, *J* = 10.2 Hz, 1H, 2-H_{Cy}), 4.60–4.50 (m, 1H, NH), 4.50–4.38 (m, 1H, 4-H), 4.34–4.27 (m, 1H, 1-H), 4.24 (s, 4H, OCH_2CH_2O), 3.55 (s, 3H, NHCOO*CH$_3$*), 2.65–2.57 (m, 1H, 6-H), 2.24 (dd, *J* = 12.0, 5.4 Hz, 1H, 5-H_β), 1.80 (td, *J* = 12.9, 9.9 Hz, 1H, 5-H_α) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.6 (5-C), 45.7 (6-C), 52.0 (NHCOO*CH$_3$*), 53.5 (1-C), 64.3 (OCH_2CH_2O), 67.8 (4-C), 116.0 (5-C_{Ar}), 117.3 (8-C_{Ar}), 120.2 (7-C_{Ar}), 131.1 (2-C_{Cy}), 132.4 (3-C_{Cy}), 135.1 (6-C_{Ar}), 142.5 (8a-C_{Ar}), 143.5 (4a-C_{Ar}), 156.5 (NH*CO*OCH$_3$) ppm; IR (KBr): $\bar{\nu}$ = 3329, 2926, 2876, 1687, 1592, 1533, 1509, 1457, 1435, 1315, 1290, 1126, 1102, 1049, 928, 885, 759, 634 cm^{-1}; HPLC: Chiralpack® OD (hexane/*i*-PrOH = 8:2, flow rate 2.0 cm^3 min^{-1}, 256 nm, 20 °C), $t_{(-)}$: 23 min, $t_{(+)}$: 30 min; $[\alpha]_D^{22}$ = − 129.0° (*c* = 1, $CHCl_3$); *ee* > 99%.

(−)-6-(8′-Methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-hydroxycyclohex-2-enyl)carbamic acid methyl ester [(−)-34, $C_{17}H_{21}NO_6$] Yield: 79%; white solid; m.p.: 166 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.39 (d, *J* = 1.8 Hz, 1H, 5-H_A or 7-H_{Ar}), 6.36 (d, *J* = 1.8 Hz, 1H, 5-H_A or 7-H_{Ar}), 5.82 (dd, *J* = 10.2, 1.2 Hz, 1H, 3-H_{Cy}), 5.76 (d, *J* = 10.8 Hz, 1H, 2-H_{Cy}), 4.60–4.50 (m, 1H, NH), 4.50–4.40 (m, 1H, 4-H), 4.24–4.30 (m, 5H, 1-H and OCH_2CH_2O), 3.86 (s, 3H, OCH_3) 3.56 (s, 3H, NHCOO*CH$_3$*), 2.66–2.56 (m, 1H, 6-H), 2.26 (dd, *J* = 12.3, 5.4 Hz, 1H, 5-H_β), 1.80 (td, *J* = 12.9, 9.9 Hz, 1H, 5-H_α) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.0 (5-C), 46.1 (6-C), 52.1 (NHCOO*CH$_3$*), 53.7 (1-C), 56.1 (OCH_3), 64.3 (O*CH$_2$*CH$_2$O), 64.5 (OCH_2*CH$_2$*O), 67.7 (4-C), 103.1 (7-C_{Ar}), 108.9 (5-C_{Ar}), 131.1 (2-C_{Cy}), 132.4 (3-C_{Cy}), 133.7

(6-C_{Ar}), 134.1 (8a-C_{Ar}), 143.9 (8-C_{Ar}), 148.9 (4a-C_{Ar}), 156.4 (NH*CO*OCH$_3$) ppm; IR (KBr): $\bar{\nu}$ = 3333, 2930, 1693, 1599, 1539, 1512, 1457, 1341, 1239, 1129, 1049, 887, 655 cm^{-1}; HPLC: Chiralpack® OD (hexane/*i*-PrOH = 8:2, flow rate 2.0 cm^3 min^{-1}, 256 nm, 20 °C), $t_{(-)}$: 30 min, $t_{(+)}$: 25 min; $[\alpha]_D^{22} = -107.8°$ (c = 1, $CHCl_3$); $ee > 99\%$.

General procedure for the Mitsunobu reaction

0.74 cm^3 diethyl azodicarboxylate (0.82 g, 4.71 mmol) in 2.6 cm^3 anhydrous THF at 0 °C was added dropwise to a solution of 1.09 g (−)-**33** (3.58 mmol) or 1.20 g (−)-**34** (3.58 mmol) and 1.15 g triphenylphosphine (4.38 mmol) in 56 cm^3 anhydrous THF, and the mixture was stirred for 10 min. Then 0.47 g benzoic acid (3.85 mmol) was also added, and the reaction mixture was stirred at 0 °C for 2 h, then heated to 45–50 °C and further stirred for 5 h. The solvent was evaporated in vacuo and the residue was purified as specified.

(+)-5-(2′,3′-Dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohex-2-enyl benzoate [(+)-35, $C_{23}H_{23}NO_6$] It was purified by column chromatography (CH_2Cl_2/acetone, 20:1) to afford a pale yellow solid. Yield: 77%; m.p.: 58–63 °C; R_f = 0.51 ($CHCl_3$/methanol, 100:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.57 (t, J = 7.2 Hz, 1H, 4-H_{Bz}), 7.45 (t, J = 7.2 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.81 (d, J = 8.4 Hz, 1H, 8-H_{Ar}), 6.76 (d, J = 1.8 Hz, 1H, 5-H_{Ar}), 6.72 (dd, J = 8.4 Hz, 7-H_{Ar}), 6.08–5.99 (m, 2H, 2-H_{Cy} and 3-H_{Cy}), 5.53–5.48 (m, 1H, 1-H), 4.67–4.54 (m, 1H, NH), 4.41–4.29 (m, 1H, 4-H), 4.24 (s, 4H, OCH_2CH_2O), 3.58 (s, 3H, NHCOO*CH$_3$*), 2.93–2.83 (m, 1H, 5-H), 2.19–2.15 (m, 2H, 6-H_α and 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.0 (6-C), 42.9 (5-C), 52.1 (NHCOO*CH$_3$*), 53.2 (4-C), 64.3 (O*CH$_2$*CH$_2$O), 64.4 (OCH$_2$*CH$_2$*O), 66.8 (1-C), 116.3 (5-C_{Ar}), 117.4 (8-C_{Ar}), 120.3 (7-C_{Ar}), 125.5 (2-C_{Cy}), 128.4 (3-C_{Bz} and 5-C_{Bz}), 129.6 (2-C_{Bz} and 6-C_{Bz}), 130.3 (1-C_{Bz}), 133.0 (4-C_{Bz}), 135.1 (6-C_{Ar}), 135.8 (3-C_{Cy}), 141.2 (8a-C_{Ar}), 143.5 (4a-C_{Ar}), 156.4 (NH*CO*OCH$_3$), 165.9 (PhCO) ppm; IR (KBr): $\bar{\nu}$ = 3356, 3036, 2947, 1716, 1591, 1510, 1452, 1315, 1271, 1109, 1053, 1025, 953, 896, 810, 713 cm^{-1}; $[\alpha]_D^{22} = +82.5°$ (c = 1, $CHCl_3$).

(+)-5-(8′-Methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohex-2-enyl benzoate [(+)-36, $C_{24}H_{25}NO_7$] It was isolated by column chromatography ($CHCl_3$/acetone, 20:1) to give a white solid. Yield: 77%; m.p.: 66–71 °C; R_f = 0.35 ($CHCl_3$/methanol, 100:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 6.9 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.58 (tt, J = 7.2, 1.2 Hz, 1H, 4-H_{Bz}), 7.45 (t, J = 7.5 Hz, 2H, 3-H_B and 5-H_{Bz}), 6.43 (d, J = 1.8 Hz, 1H, 5- H_{Ar} or 7-H_{Ar}), 6.40 (d, J = 1.8 Hz, 1H, 5- H_{Ar} or 7-H_{Ar}), 6.08–5.99 (m, 2H, 2-H_{Cy} and 3-H_{Cy}), 5.54–5.49 (m, 1H, 1-H), 4.68–4.65 (m, 1H, NH), 4.43–4.33 (m, 1H, 4-H), 4.30–4.24 (m, 4H, OCH_2CH_2O), 3.87 (s, 3H, OCH_3), 3.58 (s, 3H, NHCOO*CH$_3$*), 2.92–2.84 (m, 1H, 5-H), 2.20–2.16 (m, 2H, 6-H_α and 6-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.0 (6-C), 42.0 (5-C), 52.1 (NHCOO*CH$_3$*), 53.4 (4-C), 56.2 (OCH_3), 64.3 (O*CH$_2$*CH$_2$O), 64.5 (OCH$_2$*CH$_2$*O), 66.7 (1-C), 103.2 (7-C_{Ar}), 109.2 (5-C_{Ar}), 125.6 (2-C_{Cy}), 128.4 (3-C_{Bz} and 5-C_{Bz}), 129.6 (2-C_{Bz} and 6-C_{Bz}), 130.3 (1-C_{Bz}), 132.0 (6-C_{Ar}), 133.0 (4-C_{Bz}), 134.1 (8a-C_{Ar}), 135.8 (3-C_{Cy}), 143.9 (8-C_{Ar}), 148.9 (4a-C_{Ar}), 156.4 (NH*CO*OCH$_3$), 165.9 (PhCO) ppm; IR (KBr): $\bar{\nu}$ = 3362, 2931, 1716, 1599, 1511, 1453, 1362, 1340, 1271, 1129, 1053, 1025, 887, 649 cm^{-1}; $[\alpha]_D^{22} = +90.3°$ (c = 1, $CHCl_3$).

General procedure for synthesis of *cis*-diols (+)-37 and (+)-38

To a solution of 1.15 g (+)-**35** (2.80 mmol) or 1.23 g (+)-**36** (2.80 mmol) in a mixture of 17 cm^3 tetrahydrofuran and 2.8 cm^3 water, 0.71 g *N*-methylmorpholine-*N*-oxide (6.06 mmol) and subsequently 1.22 cm^3 4% aqueous OsO_4 solution (48.6 mg, 0.19 mmol) under argon were added. The mixture was stirred at rt for 24 h, then it was poured into 112 cm^3 saturated $Na_2S_2O_3$ solution and extracted with ethyl acetate (4 × 60 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford (+)-**37** or (+)-**38**.

(+)-5-(2′,3′-Dihydrobenzo[*b*][1,4]dioxin-6′-yl)-2,3-dihydroxy-4-(methoxycarbonylamino)cyclohexyl benzoate [(+)-37, $C_{23}H_{25}NO_8$] Yield: 99%; white solid (fluffy); m.p.: 92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.5 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.60 (t, J = 7.5 Hz, 1H, 4-H_{Bz}), 7.47 (t, J = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.80 (d, J = 8.1 Hz, 1H, 8-H_{Ar}), 6.73 (d, J = 1.8 Hz, 1H, 5-H_{Ar}), 6.68 (dd, J = 8.1, 1.8 Hz, 1H, 5-H_{Ar}), 5.41 (q, J = 2.7 Hz, 1H, 1-H), 4.71–4.62 (m, 1H, NH), 4.25–4.18 (m, 5H, OCH_2CH_2O and 2-H_{Cy}), 4.06–3.95 (m, 2H, 3-H_{Cy} and 4-H), 3.58 (s, 3H, NHCOO*CH$_3$*), 2.82 (ddd, J = 13.5, 11.1, 3.0 Hz, 1H, 5-H), 2.30 (ddd, J = 15.9, 11.4, 2.4 Hz, 1H, 6-H_β), 2.02 (dt, J = 14.7, 3.3 Hz, 1H, 6-H_α) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.9 (6-C), 41.9 (5-C), 52.6 (NHCOO*CH$_3$*), 55.7 (4-C), 64.3 (OCH_2CH_2O), 70.1 (2-C_{Cy}), 71.3 (1-C), 74.4 (3-C_{Cy}), 116.3 (5-C_{Ar}), 117.6 (8-C_{Ar}), 120.4 (7-C_{Ar}), 128.5 (3-C_{Bz} and 5-C_{Bz}), 129.6 (2-C_{Bz} and 6-C_{Bz}), 130.0 (1-C_{Bz}), 133.3 (4-C_{Bz}), 133.8 (6-C_{Ar}), 142.7 (8a-C_{Ar}), 143.7 (4a-C_{Ar}), 158.9 (NH*CO*OCH$_3$), 165.1 (PhCO) ppm; IR (KBr): $\bar{\nu}$ = 3421, 2928, 2877, 1716,

1591, 1541, 1509, 1456, 1374, 1338, 1273, 1113, 1070, 1045, 887, 714 cm^{-1}; $[\alpha]_D^{22} = +65.2°$ (c = 1, $CHCl_3$).

(+)-2,3-Dihydroxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohexyl benzoate [(+)-38, $C_{24}H_{27}NO_9$] Yield: 100%; white solid (fluffy); m.p.: 112–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (dd, J = 7.2, 1.5 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.61 (t, J = 7.2 Hz, 1H, 4-H_{Bz}), 7.48 (t, J = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.39 (d, J = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 6.35 (d, J = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 5.43 (q, J = 3.0 Hz, 1H, 1-H), 4.65–4.64 (m, 1H, NH), 4.56 (bs, 1H, OH), 4.30–4.23 (m, 4H, OCH_2CH_2O), 4.21–4.18 (m, 1H, 2-H_{Cy}), 4.06–3.95 (m, 2H, 3-H_{Cy} and 4-H), 3.86 (s, 3H, OCH_3), 3.59 (s, 3H, NHCOO*CH*$_3$), 3.18 (bs, 1H, OH), 2.80 (ddd, J = 12.9, 10.8, 3.0 Hz, 1H, 5-H), 2.31 (ddd, J = 14.1, 12.0, 2.4 Hz, 1H, 6-H_β), 2.04 (dt, J = 14.4, 3.0 Hz, 1H, 6-H_α) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.9 (6-C), 42.6 (5-C), 52.6 (NHCOO*CH*$_3$), 55.5 (4-C), 64.2 (O*CH*$_2$CH$_2$O), 64.4 (O*CH*$_2$CH$_2$O), 70.2 (2-C_{Cy}), 71.4 (1-C), 74.1 (3-C_{Cy}), 103.0 (7-C_{Ar}), 109.3 (5-C_{Ar}), 128.5 (3-C_{Bz} and 5-C_{Bz}), 129.6 (2-C_{Bz} and 6-C_{Bz}), 129.9 (1-C_{Bz}), 132.1 (6-C_{Ar}), 132.9 (8a-C_{Ar}), 133.3 (4-C_{Bz}), 144.0 (8-C_{Ar}), 149.2 (4a-C_{Ar}), 158.9 (NH*CO*OCH$_3$), 165.1 (PhCO) ppm; IR (KBr): $\bar{\nu}$ = 3364, 2930, 1716, 1599, 1541, 1511, 1455, 1370, 1339, 1274, 1127, 1071, 1048, 887, 715 cm^{-1}; $[\alpha]_D^{22} = +63.2°$ (c = 1, $CHCl_3$).

General procedure for acetylation

A solution of 0.99 g (+)-**37** (2.22 mmol) or 1.05 g (+)-**38** (2.22 mmol) in 8.28 cm^3 acetyl chloride (9.14 g, 0.12 mol) was stirred at rt for 20–24 h. Then, it was poured into 618 cm^3 saturated $NaHCO_3$ solution at 0 °C and extracted with ethyl acetate (4 × 110 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give (−)-**39** or (−)-**40**.

(−)-2,3-Diacetoxy-5-(2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohexyl benzoate [(−)-39, $C_{27}H_{29}NO_{10}$] Yield: 81%; colourless semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (dd, J = 7.2, 1.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.62 (t, J = 7.2 Hz, 1H, 4-H_{Bz}), 7.49 (t, J = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.79 (d, J = 8.1 Hz, 1H, 8-H_{Ar}), 6.73 (d, J = 1.8 Hz, 1H, 5-H_{Ar}), 6.70 (dd, J = 8.4, 1.8 Hz, 1H, 7-H_{Ar}), 5.49 (t, J = 3.0 Hz, 1H, 1-H_{Cy} or 2-H_{Cy}), 5.37 (dd, J = 10.8, 3.0 Hz, 1H, 3-H_{Cy}), 5.28 (q, J = 3.3 Hz, 1H, 1-H_{Cy} or 2-H_{Cy}), 4.44 (d, J = 9.0 Hz, 1H, NH), 4.27–4.16 (m, 5H, OCH_2CH_2O and 4-H), 3.50 (s, 3H, NHCOO*CH*$_3$), 2.95 (td, J = 10.8, 7.2 Hz, 1H, 5-H), 2.23 (s, 3H, $COCH_3$), 2.19–2.09 (m, 2H, 6-H_α and 6-H_β), 2.02 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CO*CH*$_3$), 21.0 (CO*CH*$_3$), 33.6 (6-C), 42.9 (5-C), 52.1 (NHCOO*CH*$_3$), 53.4 (4-C), 64.3 (OCH_2CH_2O), 69.3 (2-C_{Cy}), 69.4 (1-C), 71.4 (3-C_{Cy}), 116.5 (5-C_{Ar}), 117.3 (8-C_{Ar}), 120.6 (7-C_{Ar}), 128.6 (3-C_{Bz} and 5-C_{Bz}), 129.4 (1-C_{Bz}), 129.8 (2-C_{Bz} and 6-C_{Bz}), 133.5 (4-C_{Bz}), 133.6 (6-C_{Ar}), 142.6 (8a-C_{Ar}), 143.4 (4a-C_{Ar}), 156.4 (NH*CO*OCH$_3$), 164.9 (PhCO), 169.4 (*CO*CH$_3$), 170.7 (*CO*CH$_3$) ppm; IR (KBr): $\bar{\nu}$ = 3397, 2926, 1749, 1721, 1591, 1522, 1509, 1456, 1373, 1271, 1249, 1157, 1070, 1052, 933, 887, 808, 776, 717 cm^{-1}; $[\alpha]_D^{22} = -22.4°$ (c = 1, $CHCl_3$).

(−)-2,3-Diacetoxy-5-(8′-methoxy-2′,3′-dihydrobenzo[*b*][1,4]dioxin-6′-yl)-4-(methoxycarbonylamino)cyclohexyl benzoate [(−)-40, $C_{28}H_{31}NO_{11}$] Yield: 100%; white solid (fluffy); m.p.: 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (dd, J = 7.2, 1.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.62 (t, J = 7.5 Hz, 1H, 4-H_{Bz}), 7.49 (t, J = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.40 (d, J = 1.8 Hz, 1H, 5-H_{Ar} or 7-H_{Ar}), 6.28 (s, 1H, 5-H_{Ar} or 7-H_{Ar}), 5.49 (t, J = 3.3 Hz, 1H, 1-H_{Cy} or 2-H_{Cy}), 5.38 (dd, J = 10.5, 3.0 Hz, 1H, 3-H_{Cy}), 5.28 (q, J = 3.3 Hz, 1H, 1-H_{Cy} or 2-H_{Cy}), 4.49 (d, J = 9.9 Hz, 1H, NH), 4.29–4.21 (m, 5H, OCH_2CH_2O, 4-H), 3.86 (s, 3H, OCH_3), 3.51 (s, 3H, NHCOO*CH*$_3$), 2.96 (td, J = 11.1, 7.2 Hz, 1H, 5-H), 2.23 (s, 3H, CO*CH*$_3$), 2.19 (dd, J = 8.4, 2.4 Hz, 1H, 6-H_β), 2.12 (dt, J = 15.3, 2.7 Hz, 1H, 6-H_α), 2.02 (s, 3H, CO*CH*$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CO*CH*$_3$), 21.0 (CO*CH*$_3$), 33.9 (6-C), 43.2 (5-C), 52.1 (NHCOO*CH*$_3$), 53.5 (4-C), 64.2 (O*CH*$_2$CH$_2$O), 64.5 (OCH_2*CH*$_2$O), 69.3 (2-C_{Cy}), 69.4 (1-C), 71.4 (3-C_{Cy}), 103.7 (7-C_{Ar}), 109.1 (5-C_{Ar}), 128.6 (3-C_{Bz} and 5-C_{Bz}), 129.4 (1-C_{Bz}), 129.8 (2-C_{Bz} and 6-C_{Bz}), 133.6 (6-C_{Ar}), 120.6 (8a-C_{Ar}), 133.5 (4-C_{Bz}), 143.9 (8-C_{Ar}), 148.8 (4a-C_{Ar}), 156.5 (NH*CO*OCH$_3$), 164.9 (PhCO), 169.4 (*CO*CH$_3$), 170.6 (*CO*CH$_3$) ppm; IR (KBr): $\bar{\nu}$ = 3365, 2930, 1750, 1726, 1599, 1540, 1512, 1455, 1370, 1273, 1240, 1128, 1051, 887, 715 cm^{-1}; $[\alpha]_D^{22} = -6.0°$ (c = 1, $CHCl_3$).

General procedure for the modified Bischler–Napieralski cyclisation

A solution of 1.39 g (−)-**39** (2.64 mmol) or 1.47 g (−)-**40** (2.64 mmol) and 0.97 g 4-(dimethylamino)pyridine (7.94 mmol) in 73 cm^3 anhydrous dichloromethane was cooled to 0 °C. A solution of 2.34 cm^3 trifluoromethanesulphonic anhydride (3.92 g, 13.91 mmol) in 12 cm^3 anhydrous dichloromethane was added dropwise. The reaction mixture was stirred for 20–24 h while being allowed to warm to rt. Then, it was diluted with 46 cm^3 dichloromethane, subsequently washed with 656 cm^3 saturated $NaHCO_3$ solution, 656 cm^3 20% aqueous AcOH, and 656 cm^3 saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified as specified.

(−)-2-Benzoyloxy-6-methoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridin-3,4-diyl diacetate [(−)-41, $C_{27}H_{27}NO_9$] This product was converted spontaneously into the corresponding lactam due to traces of acid. It was separated from the lactam derivative by column chromatography ($CHCl_3$/acetone, 20:1) to afford a pale yellow oil. Yield: 20%; $R_f = 0.69$ (CH_2Cl_2/methanol, 100:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05$ (dd, $J = 8.1$, 1.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.58 (t, $J = 7.5$ Hz, 1H, 4-H_{Bz}), 7.44 (t, $J = 7.5$ Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 7.21 (s, 1H, 7-H_{Ar}), 6.74 (s, 1H, 12-H_{Ar}), 5.57–5.53 (m, 1H, 3-H), 5.52 (dd, $J = 10.8$, 3.0 Hz, 1H, 4-H), 5.43 (q, $J = 2.4$ Hz, 1H, 2-H), 4.30–4.20 (m, 4H, OCH_2CH_2O), 3.80 (s, 3H, OCH_3), 3.51 (dd, $J = 13.8$, 10.8 Hz, 1H, 4a-H), 2.90 (td, $J = 12.9$, 3.6 Hz, 1H, 12b-H), 2.60 (dt, $J = 14.4$, 3.0 Hz, 1H, 1-H_α), 2.13 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3), 2.07–1.97 (m, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.8$ (COCH_3), 21.0 (COCH_3), 27.4 (1-C), 32.8 (12b-C), 52.5 (NCOCH_3), 57.5 (4a-C), 64.2 (O$CH_2$$CH_2$O), 64.6 ($OCH_2CH_2$O), 69.4 (3-C), 69.6 (2-C), 72.4 (4-C), 112.5 (12-C_{Ar}), 114.5 (7-C_{Ar}), 119.1 (6a-C_{Ar}), 128.5 (3-C_{Bz} and 5-C_{Bz}), 129.4 (1-C_{Bz}), 129.8 (3-C_{Bz} and 5-C_{Bz}), 133.5 (4-C_{Bz}), 134.4 (12a-C_{Ar}), 142.1 (8a-C_{Ar}), 146.1 (4a-C_{Ar}), 160.5 (6-C), 165.1 (PhCO), 169.4 ($CO$$CH_3$), 170.5 ($CO$$CH_3$) ppm; $[\alpha]_D^{22} = -63.9°$ ($c = 1$, $CHCl_3$).

(−)-2-Benzoyloxy-6,7-dimethoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridin-3,4-diyl diacetate [(−)-42, $C_{28}H_{29}NO_{10}$]/(−)-2-Benzoyloxy-6,11-dimethoxy-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridin-3,4-diyl diacetate [(−)-43, $C_{28}H_{29}NO_{10}$] It was purified by column chromatography ($CHCl_3$/acetone, 20:1) to give a light brown solid (fluffy). Yield: 87%; mixture of regioisomers (1:1); $R_f = 0.53$ (CH_2Cl_2/methanol, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$ (dd, $J = 6.9$, 1.5 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 8.05 (dd, $J = 6.9$, 1.5 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.58 (tt, $J = 7.5$, 1.5 Hz, 1H, 4-H_{Bz}), 7.46 (t, $J = 7.5$ Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 7.45 (t, $J = 7.5$ Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.55 (s, 1H, H_{Ar}), 6.40 (s, 1H, H_{Ar}), 5.57–5.53 (m, 2H, 2 × 3-H), 5.49 (dd, $J = 10.8$, 3.0 Hz, 2H, 2 × 4-H), 5.46–5.40 (m, 2H, 2 × 2-H), 4.42–4.16 (m, 8H, 2 × OCH_2CH_2O), 3.91 (s, 3H, Ar-OCH_3), 3.84–3.83 (3 × s, 9H, Ar-OCH_3, 2 × CNOCH_3), 3.40 (2 × dd, $J = 13.5$, 10.5 Hz, 2H, 2 × 4a-H), 2.82–2.55 (m, 4H, 2 × 12b-H, 2 × 1-H_α), 2.12 (s, 6H, 2 × $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 1.90 (2 × dt, $J = 12.3$, 2.7 Hz, 2H, 1-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.8$ (COCH_3), 21.0 (COCH_3), 27.5 (1-C), 27.6 (1-C), 33.4 (10b-C), 33.6 (10b-C), 52.6 (2 × CNOCH_3), 56.9 (OCH_3), 57.0 (2 × 4a-C), 61.7 (OCH_3), 63.9 (O$CH_2$$CH_2$O), 64.2 (O$CH_2$$CH_2$O), 64.3 ($OCH_2CH_2$O), 64.5 (O$CH_2$$CH_2$O), 69.3 (2 × 3-$C_{Cy}$), 69.6 (2-$C_{Cy}$), 69.7 (2-$C_{Cy}$), 72.4 (4-C), 72.6 (4-C), 99.4 (12-C), 108.1 (12-C), 128.5 (3-C_{Bz} and 5-C_{Bz}), 128.6 (3-C_{Bz} and 5-C_{Bz}), 129.3 (1-C_{Bz}), 129.4 (1-C_{Bz}), 129.8 (2-C_{Bz} and 6-C_{Bz}), 132.1 (2 × 6a-C), 133.4 (4-C_{Bz}), 133.5 (4-C_{Bz}), 134.9 (2 × 12a-C), 135.3 (7a-C and 10a-C), 142.5 (6b-C), 146.5 (7-C), 150.6 (11-C and 11a-C), 160.4 (6-C), 165.1 (PhCO), 165.2 (PhCO), 169.4 (2 × $CO$$CH_3$), 170.4 (2 × $CO$$CH_3$) ppm; IR (KBr): $\bar{\nu} = 2944$, 1752, 1637, 1600, 1500, 1437, 1371, 1334, 1269, 1239, 1096, 1070, 714 cm^{-1}; $[\alpha]_D^{22} = -114.1°$ ($c = 1$, $CHCl_3$).

General procedure for the synthesis of lactams (−)-44 and (±)-45/(±)-46

To a solution of 0.61 g (−)-**41** (1.13 mmol) or 0.70 g (±)-**42**/(±)-**43** (1.13 mmol) in 55 cm^3 tetrahydrofuran, 2.80 cm^3 2 M aqueous HCl was added, and it was stirred at rt for 22 h. Then, it was poured into 120 cm^3 saturated $NaHCO_3$ solution and extracted with ethyl acetate (4 × 30 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude product was dissolved in 5.30 cm^3 acetyl chloride (4.78 g, 0.061 mol) and stirred at rt for 20 h. Then, it was poured into 380 cm^3 saturated $NaHCO_3$ solution and extracted with ethyl acetate (4 × 80 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford (−)-**44** or (±)-**45**/(±)-**46**.

(−)-2-Benzoyloxy-6-oxo-1,2,3,4,4a,9,10,12b-octahydro[1,4]-dioxino[2,3-*j*]phenanthridine-3,4-diyl diacetate [(−)-44, $C_{26}H_{25}NO_9$] Yield: 54%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05$ (dd, $J = 7.2$, 1.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.59 (tt, $J = 7.5$, 1.2 Hz, 1H, 4-H_{Bz}), 7.46 (t, $J = 7.5$ Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.74 (s, 1H, 7-H_{Ar}), 6.57 (s, 1H, 12-H_{Ar}), 6.08 (s, 1H, NH), 5.60 (t, $J = 3.0$ Hz, 1H, 3-H), 5.44 (q, $J = 3.0$ Hz, 1H, 2-H), 5.36 (dd, $J = 10.8$, 3.0 Hz, 1H, 4-H), 4.31–4.22 (m, 4H, OCH_2CH_2O), 3.87 (dd, $J = 12.0$, 11.1 Hz, 1H, 4a-H), 3.26 (td, $J = 12.6$, 3.6 Hz, 1H, 12b-H), 2.62 (dt, $J = 14.4$, 3.0 Hz, 1H, 1-H_α), 2.11 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.08–1.08 (m, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.8$ (COCH_3), 20.9 (COCH_3), 26.8 (1-C), 34.7 (12b-C), 53.0 (4a-C), 64.1 (O$CH_2$$CH_2$O), 64.8 ($OCH_2CH_2$O), 67.7 (2-C), 69.3 (4-C), 71.9 (3-C), 112.6 (7-C), 117.8 (12-C), 122.3 (6a-C), 128.7 (3-C_{Bz}, 5-C_{Bz}), 129.1 (1-C_{Bz}), 129.8 (2-C_{Bz}, 6-C_{Bz}), 133.7 (4-C_{Bz}), 137.0 (12a-C), 142.8 (7a-C), 147.4 (11a-C), 165.0 (6-C), 165.7 (PhCO), 169.2 ($CO$$CH_3$), 170.3 ($CO$$CH_3$) ppm; IR (KBr): $\bar{\nu} = 2928$, 1754, 1726, 1669, 1498, 1455, 1368, 1368, 1317, 1266, 1234, 1097, 1065, 925, 803, 712 cm^{-1}; $[\alpha]_D^{22} = -78.7°$ ($c = 1$, $CHCl_3$).

(±)-2-Benzoyloxy-7-methoxy-6-oxo-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridine-3,4-diyl diacetate [(±)-45, $C_{27}H_{27}NO_{10}$]/(±)-2-Benzoyloxy-11-methoxy-6-oxo-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridine-3,4-diyl diacetate [(±)-46, $C_{27}H_{27}NO_{10}$] The mixture of these regioisomers (1:1) proved to be inseparable in this step. Their isolation was achieved after selective demethylation, as described below.

General procedure for the Zemplén deacylation

77 cm^3 0.56 M methanolic solution of sodium methoxide was added dropwise at rt to a solution of 1.15 g (−)-**42**/(−)-**43** (2.13 mmol) in 153 cm^3 anhydrous tetrahydrofuran, and the reaction mixture was stirred for 2 h. Then it was poured into 500 cm^3 water and extracted with ethyl acetate (4 × 120 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The regioisomers were separated by column chromatography (EtOAc/ethanol, 20:1) to give (−)-**50** and (−)-**51**.

(−)-6,7-Dimethoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridine-2,3,4-triol [(−)-50, $C_{17}H_{21}NO_7$] Yield: 22%; white solid; m.p.: 133–136 °C; R_f = 0.42 (EtOAc/methanol, 20:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.55 (s, 1H, 12-H), 4.83 (d, J = 3.3 Hz, 1H, OH), 4.53 (d, J = 3.6 Hz, 1H, OH), 4.31–4.18 (m, 5H, OCH_2CH_2O and OH), 3.87 (q, J = 2.7 Hz, 1H, 2-H), 3.79–3.74 (m, 4H, 3-H and OCH_3), 3.71 (s, 3H, $CNOCH_3$), 3.68 (dd, J = 10.2, 3.0 Hz, 1H, 4-H), 2.87 (dd, J = 13.2, 9.9 Hz, 1-H, 4a-H), 2.39 (td, J = 12.9, 3.3 Hz, 1H, 12b-H), 2.04 (dt, J = 13.8, 3.3 Hz, 1H, 1-H_α), 1.62 (ddd, J = 14.4, 11.1, 1.8 Hz, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.9 (1-C), 32.2 (12b-C), 52.1 ($CNOCH_3$), 58.9 (4a-C), 60.8 (OCH_3), 63.7 (OCH_2CH_2O), 64.2 (OCH_2CH_2O), 68.6 (2-C), 71.2 (4-C), 71.8 (3-C), 107.5 (12-C), 111.9 (6a-C), 135.8 (7a-C), 136.7 (12a-C), 146.1 (7-C), 146.6 (11a-C), 159.1 (6-C) ppm; IR (KBr): $\bar{\nu}$ = 3408, 2926, 1717, 1637, 1608, 1574, 1483, 1437, 1333, 1226, 1122, 1040, 812 cm^{-1}; $[\alpha]_D^{22}$ = − 49.0° (c = 0.3, methanol).

(−)-6,11-Dimethoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridine-2,3,4-triol [(−)-51, $C_{17}H_{21}NO_7$] Yield: 23%; white solid; m.p.: 132–134 °C; R_f = 0.26 (EtOAc/methanol, 20:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.49 (s, 1H, 12-H), 4.84 (d, J = 3.3 Hz, 1H, OH), 4.54 (d, J = 3.3 Hz, 1H, OH), 4.34–4.14 (m, 5H, OCH_2CH_2O and OH), 3.89 (q, J = 2.4 Hz, 1H, 2-H), 3.80 (s, 3H, OCH_3), 3.77 (t, J = 3.0 Hz, 1H, 3-H), 3.71 (s, 3H, $CNOCH_3$), 3.69 (overlapped dd, 1H, 4-H), 2.87 (dd, J = 13.8, 10.2 Hz, 1-H, 4a-H), 2.42 (td, J = 12.9, 3.3 Hz, 1H, 12b-H), 2.14 (dt, J = 12.9, 3.0 Hz, 1H, 1-H_α), 1.62 (ddd, J = 14.4, 12.0, 2.4 Hz, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.9 (1-C), 32.5 (12b-C), 51.9 ($CNOCH_3$), 55.6 (OCH_3), 58.9 (4a-C), 63.0 (OCH_2CH_2O), 63.8 (OCH_2CH_2O), 68.6 (2-C), 71.3 (4-C), 71.8 (3-C), 99.6 (12-C), 107.2 (6a-C), 131.4 (10a-C), 136.9 (12a-C), 141.9 (6b-C), 150.5 (11-C), 159.4 (6-C) ppm; IR (KBr): $\bar{\nu}$ = 3420, 2924, 1716, 1699, 1635, 1602, 1558, 1457, 1384, 1334, 1132, 1065 cm^{-1}; $[\alpha]_D^{22}$ = − 63.8° (c = 0.3, methanol).

General procedure for the synthesis of triacetoxy lactams (−)-52 and (−)-53

To a solution of 0.23 g (−)-**50** (0.65 mmol) or 0.23 g (−)-**51** (0.65 mmol) in 32 cm^3 tetrahydrofuran, 1.60 cm^3 2 M aqueous HCl was added and the reaction mixture was stirred at rt for 22 h. After evaporation of the solvent in vacuo, the residue was dissolved in 2.44 cm^3 acetyl chloride (2.20 g, 28.03 mmol) and stirred at rt for 20 h. Then, it was poured into 186 cm^3 saturated $NaHCO_3$ solution at 0 °C and extracted with ethyl acetate (4 × 40 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by preparative TLC ($CHCl_3$/acetone, 3:1) to afford (−)-**52** or (−)-**53**.

(−)-7-Methoxy-6-oxo-1,2,3,4,4a,9,10,12b-octahydro[1,4]-dioxino[2,3-*j*]phenanthridine-2,3,4-triyl triacetate [(−)-52, $C_{22}H_{25}NO_{10}$] Yield: 87%; white solid; m.p.: 122–125 °C; R_f = 0.39 ($CHCl_3$/acetone, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.52 (s, 1H, 12-H), 6.03 (s, 1H, NH), 5.42 (t, J = 3.0 Hz, 1H, 3-H), 5.18 (q, J = 3.0 Hz 1H, 2-H), 5.16 (dd, J = 11.1, 2.7 Hz, 1H, 4-H), 4.36–4.26 (m, 4H, OCH_2CH_2O), 3.94 (s, 3H, OCH_3), 3.71–3.63 (m, 1H, 4a-H), 3.06 (td, J = 12.6, 3.6 Hz, 1H, 12b-H), 2.40 (dt, J = 14.7, 3.0 Hz, 1H, 1-H_α), 2.13 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 1.87 (ddd, J = 14.7, 12.9, 2.4 Hz, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 ($CO\mathit{CH_3}$), 20.8 ($CO\mathit{CH_3}$), 21.0 ($CO\mathit{CH_3}$), 26.7 (1-C), 35.3 (12b-C), 52.2 (4a-C), 61.9 ($O\mathit{CH_3}$), 64.1 ($O\mathit{CH_2}$-CH_2O), 64.6 ($OCH_2\mathit{CH_2}O$), 67.4 (3-C), 68.6 (2-C), 71.6 (4-C), 107.9 (12-C), 115.5 (6a-C), 133.8 (7a-C), 137.1 (12a-C), 147.4 (7-C), 151.0 (11a-C), 163.6 (6-C), 169.1 ($\mathit{CO}CH_3$), 169.4 ($\mathit{CO}CH_3$), 170.4 ($\mathit{CO}CH_3$) ppm; IR (KBr): $\bar{\nu}$ = 3197, 3089, 2931, 2874, 1751, 1670, 1606, 1476, 1372, 1332, 1244, 1224, 1118, 1062, 1041, 859 cm^{-1}; $[\alpha]_D^{22}$ = − 77.2° (c = 0.5, $CHCl_3$).

(−)-11-Methoxy-6-oxo-1,2,3,4,4a,8,9,12b-octahydro[1,4]-dioxino[2,3-*i*]phenanthridine-2,3,4-triyl triacetate [(−)-53, $C_{22}H_{25}NO_{10}$] Yield: 47%; white solid; m.p.: 208–211 °C; R_f = 0.17 ($CHCl_3$/acetone, 3:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.98 (s, 1H, NH), 6.48 (s, 1H, 12-H), 5.23 (t, J = 3.0 Hz, 1H, 3-H), 5.06 (q, J = 2.7 Hz, 1H, 2-H), 4.91 (dd, J = 10.8, 2.7 Hz, 2H, 4-H), 4.37–4.12 (m, 4H,

OCH_2CH_2O), 3.83 (s, 3H, OCH_3), 3.53–3.45 (m, 1H, 4a-H), 2.95 (td, J = 12.3, 3.3 Hz, 1H, 12b-H), 2.11 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.95 (s, 3H, $COCH_3$), 1.78 (ddd, J = 14.4, 12.9, 2.4 Hz, 1H, 1-H_β) ppm (the sign of 1-H_α is covered by that of DMSO-d_6); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.4 (COCH_3), 20.7 (COCH_3), 20.9 (COCH_3), 26.0 (1-C), 35.3 (12b-C), 51.6 (4a-C), 55.7 (OCH_3), 63.0 (O$CH_2$$CH_2$O), 63.1 ($OCH_2CH_2$O), 66.6 (3-C), 68.1 (2-C), 70.5 (4-C), 99.5 (12-C), 111.0 (6a-C), 131.9 (7a-C), 134.1 (12a-C), 144.6 (7-C), 150.6 (11a-C), 162.5 (6-C), 169.1 (*CO*CH_3), 169.3 (*CO*CH_3), 169.9 (*CO*CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3195, 3091, 2939, 1752, 1667, 1597, 1494, 1451, 1370, 1330, 1251, 1157, 1128, 1060, 1028, 799 cm^{-1}; $[\alpha]_D^{22}$ = − 135.5° (c = 0.5, $CHCl_3$).

General procedure for the selective demethylation

To a solution of 0.18 g (±)-**45**/(±)-**46** (0.35 mmol) or 0.16 g (−)-**52** (0.35 mmol) and 57.3 mg potassium iodide (0.35 mmol) in 16 cm^3 anhydrous acetonitrile, 48.7 mg chlorotrimethylsilane (0.45 mmol) in 3.1 cm^3 anhydrous acetonitrile was added. The reaction mixture was heated to 60 °C and stirred for 4 h. Then, it was cooled to 0 °C and 26 cm^3 water was added dropwise to quench the reaction. After extraction with ethyl acetate (4 × 26 cm^3), the combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by preparative TLC (EtOAc/heptane, 1:1) to give (±)-**47** or (−)-**54**. Compound (±)-**46**, as well as the by-products (±)-**48** and (±)-**49,** was isolated from the crude product obtained by the conversion of (±)-**45**/(±)-**46**.

(±)-2-Benzoyloxy-7-hydroxy-6-oxo-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridine-3,4-diyl diacetate [(±)-47, $C_{26}H_{25}NO_{10}$] Yield: 20%; white solid; m.p.: 201–204 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.52 (s, 1H, OH), 8.03 (dd, J = 7.8, 1.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.59 (tt, J = 7.5, 1.2 Hz, 1H, 4-H_{Bz}), 7.46 (t, J = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.27 (s, 1H, 12-H), 6.10 (s, 1H, NH), 5.60 (t, J = 3.0 Hz, 1H, 3-H), 5.43 (q, J = 3.0 Hz, 1H, 2-H), 5.33 (dd, J = 10.8, 2.7 Hz, 1H, 4-H), 4.31 (s, 4H, OCH_2-CH_2O), 3.85 (dd, J = 12.3, 11.1 Hz, 1H, 4a-H), 3.20 (td, J = 12.9, 3.3 Hz, 1H, 12b-H), 2.60 (dt, J = 14.7, 2.7 Hz, 1H, 1-H_α), 2.12 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.01 (ddd, J = 14.7, 12.6, 2.4 Hz, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (COCH_3), 20.8 (COCH_3), 26.5 (1-C), 34.3 (12b-C), 52.8 (4a-C), 64.1 (O$CH_2$$CH_2$O), 64.8 ($OCH_2CH_2$O), 67.5 (3-C), 69.1 (2-C), 71.9 (4-C), 103.7 (12-C), 104.5 (6a-C), 128.6 (3-C_{Bz} and 5-C_{Bz}), 129.1 (1-C_{Bz}), 129.8 (2-C_{Bz} and 6-C_{Bz}), 131.1 (7a-C), 132.2 (12a-C), 133.7 (4-C_{Bz}), 148.2 (7-C), 152.6 (11a-C), 164.9 (6-C), 169.2 (COPh), 170.1 (*CO*CH_3), 170.3 (*CO*CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3446, 2930, 1753, 1731, 1683, 1652, 1448, 1362, 1270, 1239, 1157, 1069, 1028, 803, 711 cm^{-1}.

(−)-7-Hydroxy-6-oxo-1,2,3,4,4a,9,10,12b-octahydro[1,4]-dioxino[2,3-*j*]phenanthridine-2,3,4-triyl triacetate [(−)-54, $C_{21}H_{23}NO_{10}$] Yield: 55%; white solid; m.p.: 154–156 °C; R_f = 0.85 (hexane/EtOAc, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.54 (s, 1H, OH), 6.25 (s, 1H, 12-H), 5.95 (s, 1H, NH), 5.44 (t, J = 3.0 Hz, 1H, 3-H), 5.20–5.16 (m, 2H, 2-H and 4-H), 4.32 (s, 4H, OCH_2CH_2O), 3.76 (dd, J = 12.6, 11.1 Hz, 1H, 4a-H), 3.10 (td, J = 13.2, 3.3 Hz, 1H, 12b-H), 2.43 (dt, J = 14.4, 2.7 Hz, 1H, 1-H_α), 2.13 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 1.90 (ddd, J = 14.4, 12.6, 2.7 Hz, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (COCH_3), 20.8 (COCH_3), 21.0 (COCH_3), 26.4 (1-C), 34.1 (12b-C), 52.8 (4a-C), 64.1 (O$CH_2$$CH_2$O), 64.8 ($OCH_2CH_2$O), 67.3 (3-C), 68.5 (2-C), 71.8 (4-C), 103.7 (12-C), 104.5 (6a-C), 131.1 (7a-C), 132.2 (12a-C), 148.2 (7-C), 152.6 (11a-C), 169.1 (6-C), 169.3 (*CO*CH_3), 170.1 (COCH_3), 170.3 (COCH_3) ppm; IR (KBr): $\bar{\nu}$ = 3337, 2937, 1752, 1652, 1586, 1447, 1370, 1246, 1225, 1125, 1056, 1035, 858 cm^{-1}; $[\alpha]_D^{22}$ = − 58.0° (c = 0.5, $CHCl_3$).

(±)-2-Benzoyloxy-11-methoxy-6-oxo-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridine-3,4-diyl diacetate [(±)-46, $C_{27}H_{27}NO_{10}$] Yield: 18%; white solid (fluffy); m.p.: 237–238 °C; R_f = 0.51 (hexane/EtOAc, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (dd, J = 8.1, 0.9 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.60 (tt, J = 7.5, 1.2 Hz, 1H, 4-H_{Bz}), 7.47 (t, J = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 7.08 (s, 1H, 12-H_{Ar}), 6.37 (s, 1H, NH), 5.59 (t, J = 3.0 Hz, 1H, 3-H), 5.45 (q, J = 3.0 Hz, 1H, 2-H), 5.36 (dd, J = 10.8, 3.0 Hz, 1H, 4-H), 4.54–4.50 (m, 1H, OH*CH*CH_2O), 4.39–4.23 (m, 3H, O*H*CH*CH*$_2$O), 3.92 (s, 3H, OCH_3), 3.77 (dd, J = 12.0, 11.4 Hz, 1H, 4a-H), 3.19 (td, J = 12.0, 3.0 Hz, 1H, 12b-H), 2.64 (dt, J = 12.6, 3.0 Hz, 1H, 1-H_α), 2.11 (s, 6H, 2 × $COCH_3$), 2.07–1.97 (m, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (COCH_3), 20.8 (COCH_3), 27.0 (1-C), 35.5 (12b-C), 52.1 (4a-C), 56.2 (OCH_3), 63.9 (O$CH_2$$CH_2$O), 64.6 ($OCH_2CH_2$O), 67.7 (2-C), 69.2 (4-C), 71.5 (3-C), 99.2 (6a-C), 110.6 (12-C), 128.7 (3-C_{Bz} and 5-C_{Bz}), 129.0 (1-C_{Bz}), 129.8 (2-C_{Bz} and 6-C_{Bz}), 132.5 (10a-C), 133.7 (4-C_{Bz}), 134.2 (12a-C), 145.5 (6b-C), 151.7 (11-C), 165.0 (6-C), 165.1 (COPh), 169.2 (*CO*CH_3), 170.4 (*CO*CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3179, 3078, 2935, 1753, 1723, 1668, 1598, 1495, 1451, 1369, 1330, 1269, 1238, 1137, 1097, 1060, 715 cm^{-1}.

(±)-3-Acetamido-6-benzoyloxy-4-(8′-methoxy-7′-methoxycarbonyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexane-1,2-diyl diacetate [(±)-48, $C_{30}H_{33}NO_{12}$] Yield: 8%; white solid; m.p.: 244–245 °C; R_f = 0.48 ($CHCl_3$/acetone, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (dd, J = 7.8, 1.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.61 (tt, J = 7.5, 1.2 Hz, 1H, 4-H_{Bz}), 7.49 (t, J = 7.2 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.72 (s, 1H, 5-H_{Ar}), 6.17 (d, J = 9.6 Hz, 1H, NH), 5.46 (t, J = 2.7 Hz, 1H, 2-H_{Cy}), 5.29 (q, J = 3.0 Hz, 1H, 1-H), 5.22 (dd, J = 10.8, 3.0 Hz, 1H, 3-H_{Cy}), 4.49 (q, J = 10.5 Hz, 1H, 4-H), 4.34–4.23 (m, 4H, OCH_2CH_2O), 3.81 (s, 3H, Ar-OCH_3), 3.60 (s, 3H, $COOCH_3$), 2.97 (td, J = 12.0, 4.2 Hz, 1H, 5-H), 2.25 (s, 3H, 2-CHOCO*CH*$_3$), 2.25–2.21 (m, 1H, 6-H_α), 2.17–2.13 (m, 1H, 6-H_β), 2.01 (s, 3H, 3-CHOCO*CH*$_3$), 1.75 (s, 3H, NHCO*CH*$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (3-CHOCO*CH*$_3$), 21.1 (2-CHOCO*CH*$_3$), 23.1 (NHCO*CH*$_3$), 32.4 (6-C), 38.8 (5-C), 51.5 (4-C), 52.2 (COO*CH*$_3$), 61.5 (Ar-OCH_3), 64.1 (O*CH*$_2$$CH_2O$), 64.3 ($OCH_2$*CH*$_2$O), 69.0 (2-$C_{Cy}$), 69.4 (1-C), 72.0 (3-$C_{Cy}$), 110.8 (5-$C_{Ar}$), 121.3 (7-$C_{Ar}$), 128.6 (3-$C_{Bz}$ and 5-C_{Bz}), 129.4 (1-C_{Bz}), 129.7 (2-C_{Bz} and 6-C_{Bz}), 130.3 (6-C_{Ar}), 133.6 (4-C_{Bz}), 135.9 (8a-C_{Ar}), 146.0 (8-C_{Ar}) 146.2 (4a-C_{Ar}), 164.6 (OCOPh), 169.1 (*CO*OCH_3), 169.6 (2-CHO*CO*CH_3), 170.0 (NH*CO*CH_3), 170.8 (3-CHO*CO*CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3368, 2951, 1755, 1731, 1675, 1608, 1541, 1509, 1442, 1374, 1337, 1274, 1221, 1168, 1128, 1110, 1069, 716 cm^{-1}.

(±)-3-Acetamido-6-benzoyloxy-4-(8′-methoxy-5′-methoxycarbonyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6′-yl)cyclohexane-1,2-diyl diacetate [(±)-49, $C_{30}H_{33}NO_{12}$] Yield: 13%; white solid (fluffy); m.p.: 109–112 °C; R_f = 0.40 ($CHCl_3$/acetone, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (dd, J = 7.8, 1.2 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.62 (tt, J = 7.5, 1.2 Hz, 1H, 4-H_{Bz}), 7.50 (t, J = 7.2 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.54 (s, 1H, 7-H_{Ar}), 5.83 (d, J = 9.9 Hz, 1H, NH), 5.48 (t, J = 3.0 Hz, 1H, 2-H_{Cy}), 5.27 (q, J = 3.0 Hz, 1H, 1-H), 5.25 (dd, J = overlapped and 3.3 Hz, 1H, 3-H_{Cy}), 4.66 (q, J = 10.8 Hz, 1H, 4-H), 4.32–4.22 (m, 4H, OCH_2CH_2-O), 3.92 (s, 3H, Ar-OCH_3), 3.53 (s, 3H, $COOCH_3$), 3.09 (td, J = 12.0, 4.2 Hz, 1H, 5-H), 2.26 (s, 3H, 2-CHOCO*CH*$_3$), 2.26–2.22 (m, 1H, 6-H_α), 2.17–2.13 (m, 1H, 6-H_β), 2.02 (s, 3H, 3-CHOCO*CH*$_3$), 1.74 (s, 3H, NHCO*CH*$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (3-CHOCO*CH*$_3$), 21.2 (2-CHOCO*CH*$_3$), 23.2 (NHCO*CH*$_3$), 33.2 (6-C), 39.2 (5-C), 50.6 (4-C), 52.2 (COO*CH*$_3$), 56.4 (Ar-OCH_3), 64.2 (O*CH*$_2$$CH_2O$), 64.4 ($OCH_2$*CH*$_2$O), 69.1 (2-$C_{Cy}$), 69.5 (1-C), 71.8 (3-$C_{Cy}$), 102.0 (7-$C_{Ar}$), 116.2 (5-$C_{Ar}$), 128.6 (3-$C_{Bz}$ and 5-C_{Bz}), 129.4 (1-C_{Bz}), 129.7 (2-C_{Bz} and 6-C_{Bz}), 130.3 (6-C_{Ar}), 131.8 (8a-C_{Ar}), 133.6 (4-C_{Bz}), 141.2 (4a-C_{Ar}), 150.2 (8-C_{Ar}) 164.6 (O*CO*Ph), 168.5 (*CO*OCH_3), 169.6 (2-CHO*CO*CH_3), 169.9 (NH*CO*CH_3), 170.7 (3-CHO*CO*CH_3) ppm; IR (KBr): $\bar{\nu}$ = 2948, 1750, 1729, 1670, 1541, 1493, 1456, 1371, 1332, 1276, 1239, 1160, 1112, 1069, 716 cm^{-1}.

General procedure for the modified Zemplén's deacetylation

To a solution of 84.2 mg (−)-**44** (0.17 mmol), 78.7 mg (−)-**52** (0.17 mmol), 78.7 mg (−)-**53** (0.17 mmol), or 76.3 mg (−)-**54** (0.17 mmol) in 12.5 cm^3 anhydrous tetrahydrofuran, 6.50 cm^3 0.53 M methanolic solution of sodium methoxide was added dropwise at rt and the reaction mixture was stirred also at rt for 2 h. Then Amberlyte IR-120 (strongly acidic resin) was added until the pH became 6. The solid resin was filtered and washed with 10 cm^3 methanol, and then the filtrate was concentrated in vacuo. The crude product was purified by preparative TLC (EtOAc/ethanol, 6:1) to afford (−)-**8**, (−)-**9**, (−)-**10**, or (−)-**11**.

(−)-2,3,4-Trihydroxy-1,3,4,4a,5,9,10,12b-octahydro[1,4]-dioxino[2,3-*j*]phenanthridin-6(2*H*)-one [(−)-8, $C_{15}H_{17}NO_6$] Yield: 71%; white solid (fluffy); m.p.: 162 °C; R_f = 0.52 (EtOAc/methanol, 20:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.30 (s, 1H, NH), 6.90 (s, 1H, 7-H), 6.77 (s, 1H, 12-H), 5.17–4.93 (m, 2H, 2 × OH), 4.93–4.79 (m, 1H, OH), 4.29–4.24 (m, 4H, OCH_2CH_2O), 3.91–3.84 (m, 1H, 2-H), 3.72–3.68 (m, 2H, 3-H and 4-H), 2.86 (td, J = 11.7, 3.0 Hz, 1H, 12b-H), 2.09 (dt, J = 13.5, 3.0 Hz, 1H, 1-H_α), 1.63 (ddd, J = 14.7, 11.7, 2.1 Hz, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.7 (1-C), 34.2 (12b-C), 55.7 (4a-C), 64.4 (O*CH*$_2$$CH_2O$), 64.9 ($OCH_2$*CH*$_2$O), 69.1 (2-C), 70.2 (4-C), 72.2 (3-C), 112.8 (7-C), 116.5 (12-C), 123.1 (6a-C), 136.4 (12a-C), 142.3 (7a-C), 147.1 (11a-C), 164.7 (6-C) ppm; IR (KBr): $\bar{\nu}$ = 3446, 2910, 1716, 1683, 1580, 1509, 1473, 1374, 1315, 1225, 1148, 1076, 1034, 912, 889, 790 cm^{-1}; $[\alpha]_D^{22}$ = − 26.7° (c = 1, methanol); *ee* > 99%.

(−)-2,3,4,7-Tetrahydroxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridin-6(2*H*)-one [(−)-9, $C_{15}H_{17}NO_7$] Yield: 76%; white solid; m.p.: 174–176 °C; R_f = 0.76 (EtOAc/methanol, 4:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.0 (s, 1H, OH), 7.45 (s, 1H, NH), 6.25 (s, 1H, 12-H), 5.01–4.92 (m, 2H, 2 × OH), 4.89–4.82 (m, 1H, OH), 4.28–4.22 (m, 4H, OCH_2CH_2O), 3.91–3.83 (m, 1H, 2-H or 3-H or 4-H), 3.77–3.65 (m, 2H, 2 × 2-H or 3-H or 4-H), 2.81 (td, J = 12.3, 3.3 Hz, 1H, 12b-H), 2.10–1.98 (m, 1H, 1-H_α), 1.66–1.56 (m, 1H, 1-H_β) ppm (the sign of 4a-H is covered by that of water in DMSO-d_6); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.8 (1-C), 33.1 (12b-C), 55.1 (4a-C), 63.4 (O*CH*$_2$$CH_2O$), 64.4 ($OCH_2$*CH*$_2$O), 68.4 (2-C), 69.5 (4-C), 71.6 (3-C), 102.8 (12-C), 104.4 (6a-C), 130.1 (8a-C), 134.4 (12a-C), 147.5 (7-C), 151.5 (11a-C), 169.7 (6-C) ppm; IR (KBr): $\bar{\nu}$ = 3421, 2926, 1647, 1626, 1587,

1448, 1400, 1362, 1281, 1230, 1126, 1064, 1030, 910, 811 cm^{-1}; $[\alpha]_D^{22} = -18.5°$ ($c = 0.13$, ethanol); $ee > 99\%$.

(−)-2,3,4-Trihydroxy-7-methoxy-1,2,3,4,4a,9,10,12b-octahydro[1,4]dioxino[2,3-*j*]phenanthridin-6(2*H*)-one [(−)-10, $C_{16}H_{19}NO_7$] Yield: 47%; white solid; m.p.: 163–168 °C; $R_f = 0.39$ (EtOAc/methanol, 4:1); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.91$ (s, 1H, NH), 6.53 (s, 1H, 12-H), 5.10–4.91 (m, 1H, OH), 4.91–4.67 (m, 2H, 2 × OH), 4.31–4.21 (m, 4H, OCH_2CH_2O), 3.89–3.84 (m, 1H, 2-H or 3-OH or 4-H), 3.74 (s, 3H, OCH_3), 3.72–3.65 (m, 2H, 2 × 2-H or 3-OH or 4-H), 3.17 (dd, $J = 11.1$, 10.5 Hz, 1H, 4a-H), 2.74 (td, $J = 12.6$, 3.6 Hz, 1H, 12b-H), 2.03 (dt, $J = 12.9$, 2.7 Hz, 1H, 1-H_α), 1.63–1.53 (m, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 28.3$ (1-C), 34.8 (12b-C), 54.5 (4a-C), 60.9 (OCH_3), 63.6 (OCH_2CH_2O), 64.2 (OCH_2CH_2O), 68.5 (2-C), 69.4 (4-C), 71.5 (3-C), 107.3 (12-C), 116.1 (6a-C), 135.9 (10a-C), 136.1 (12a-C), 146.5 (6b-C), 149.4 (11-C), 162.6 (6-C) ppm; IR (KBr): $\bar{\nu} = 3392$, 2927, 1717, 1652, 1475, 1331, 1226, 1122, 1068, 1039, 910 cm^{-1}; $[\alpha]_D^{22} = -34.5°$ ($c = 0.63$, ethanol); $ee > 99\%$.

(−)-2,3,4-Trihydroxy-11-methoxy-1,2,3,4,4a,8,9,12b-octahydro[1,4]dioxino[2,3-*i*]phenanthridin-6(2*H*)-one [(−)-11, $C_{16}H_{19}NO_7$] Yield: 47%; white solid; m.p.: 204–207 °C; $R_f = 0.20$ (EtOAc/methanol, 4:1); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.76$ (s, 1H, NH), 6.45 (s, 1H, 12-H), 4.96 (d, $J = 3.3$ Hz, 1H, OH), 4.89 (d, $J = 6.3$ Hz, 1H, OH), 4.78 (d, $J = 2.4$ Hz, 1H, OH), 4.31–4.11 (m, 4H, OCH_2CH_2O), 3.91–3.86 (m, 1H, 2-H or 3-H or 4-H), 3.81 (s, 3H, OCH_3), 3.73–3.65 (m, 2H, 2 × 2H or 3-H or 4-H), 3.19 (dd, $J = 11.4$, 10.2 Hz, 1H, 4a-H), 2.77 (td, $J = 12.6$, 3.3 Hz, 1H, 12b-H), 2.13 (dt, $J = 13.2$, 3.3 Hz, 1H, 1-H_α), 1.69–1.60 (m, 1H, 1-H_β) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 28.3$ (1-C), 35.0 (12b-C), 54.5 (4a-C), 55.6 (OCH_3), 63.0 (OCH_2CH_2O), 63.7 (OCH_2CH_2O), 68.6 (2-C), 69.6 (4-C), 71.6 (3-C), 99.3 (12-C), 111.0 (6a-C), 131.5 (10a-C), 136.1 (12a-C), 144.5 (6b-C), 150.5 (11-C), 162.7 (6-C) ppm; IR (KBr): $\bar{\nu} = 3399$, 2923, 1648, 1600, 1495, 1455, 1363 1329, 1131, 1068, 900 cm^{-1}; $[\alpha]_D^{22} = -66.5°$ ($c = 0.25$, ethanol); $ee > 99\%$.

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