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An expedient total synthesis of *ent*-(−)-7-deoxy-*trans*-dihydronarciclasine

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ABSTRACT

A short and efficient stereoselective total synthesis of (−)-7-deoxy-*trans*-dihydronarciclasine, an *ent*-form of a highly potent antineoplastic agent constituent of the Amaryllidaceae alkaloids, is described. Starting from the enantiopure form of a known arylcyclohexylamine type precursor **6**, which was synthesized enantioselectively utilizing a highly enantioselective nitromethane addition, the three hydroxy groups on the C-ring with the required stereochemistry were introduced by a chemo- and stereoselective enone reduction ($NaBH_4/CaCl_2$ system) followed by a Mitsunobu reaction and subsequent osmylation. The ring closure of the B-ring was accomplished by the Banwell modification of the Bischler–Napieralski reaction.

1. Introduction

Amongst the family of Amaryllidaceae alkaloids the non-basic hydroxylated phenanthridones, possessing high cytostatic activity, constitute a small sub-group[1] that has been reviewed extensively.[2–5] After isolation of the first derivatives narciclasine (**1**)[6] and lycoricidine (**2**),[7] the most active[8,9] pancratistatin (**3**) was isolated from the bulbs of *Hymenocallis littoralis* by Pettit and co-workers[10] in 1984. Due to its very strong anticancer activity,[8–13] a large number of total syntheses of pancratistatin have been reported,[14–25] however, little was known about the mechanism of action. In a recent study McLachlan et al.[26] demonstrated that pancratistatin **3** induced rapid apoptosis in SHSY-5Y neuroblastoma cells, accompanied by disruption of mitochondrial membrane potential. Additionally, a decrease in ATP synthesis and an increase in the production of reactive oxygen species, which are indicative of a dysfunction of the mitochondrial respiratory chain, were observed. Narciclasine **1** was originally described as antimitotic and as displaying colchicine-like effects.[27] It was also found to be an inhibitor of peptide bond formation in eukaryotic ribosomes, given its ability to bind to the peptidyl-transferase centre.[28,29] Furthermore, unlike many other anticancer drugs, narciclasine has been found not to interact or form a complex with DNA.[30] More recently, narciclasine **1** has also been shown to induce marked apoptosis-mediated cytotoxic effects in human MCF-7 breast and PC-3 prostate carcinoma cells, but not in normal fibroblasts, by triggering the activation of the death receptor pathway.[31] These new observations may draw attention to the narciclasine analogues **4** and **5**, which also exhibit notable cytotoxic activity despite their simpler structure (Scheme 1). The elucidation of their mechanism of action could help in identifying the essential pharmacophore groups of the family.[32]

trans-Dihydronarciclasine **4**[10] and 7-deoxy-*trans*-dihydronarciclasine **5**[33] were also isolated by Pettit and co-workers. So far only a few total syntheses have been reported for these alkaloids, **4**[34] and **5**.[35–37] Surprisingly, the first total synthesis of compound **5** was realized before[35] its first isolation.[33] This and the two subsequent syntheses[36,37] are lengthy, complicated (for illustration a brief representation is outlined in Scheme 1) and resulted in low overall yields. Thus, an efficient synthesis of alkaloid **5** is required to enable a thorough biological evaluation. Recently, in a short communication[38] we have described a new approach to the synthesis of (±)-**5**, which is significantly shorter and simpler than those previously reported, even if the preparation of **6** is taken into account. In this paper the extension of our research work to the first total synthesis of the non-natural *ent*-(−)-**5** is presented.

2. Results and discussion

2.1. Synthesis of *ent*-(−)-5

As seen in Scheme 2, the first step is the selective acylation of (−)-enantiomer of the known aminoketal **6**[39] to urethane (−)-**7** using a two-phase (THF/H_2O) reaction with methyl chloroformate,

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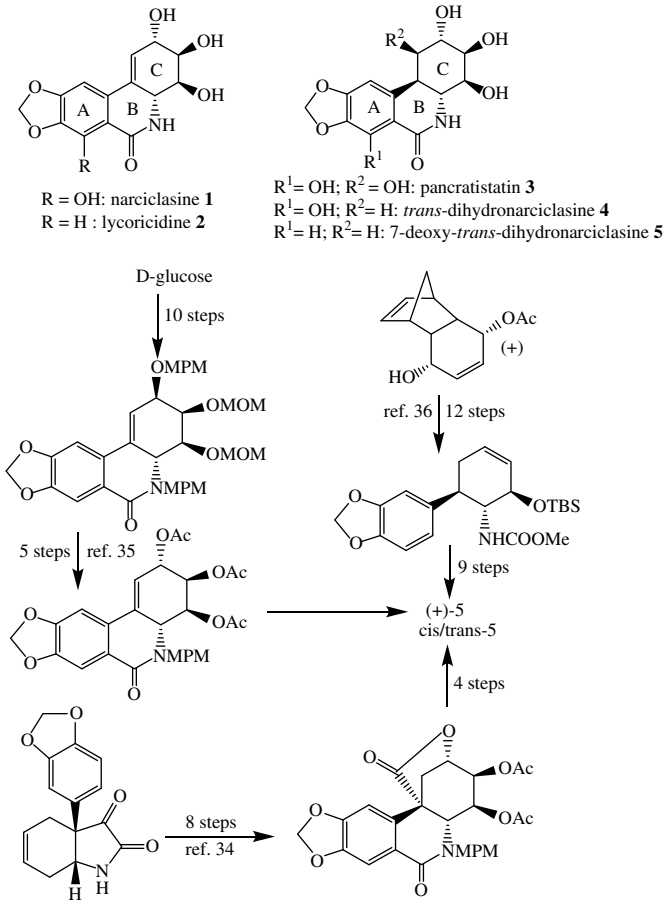


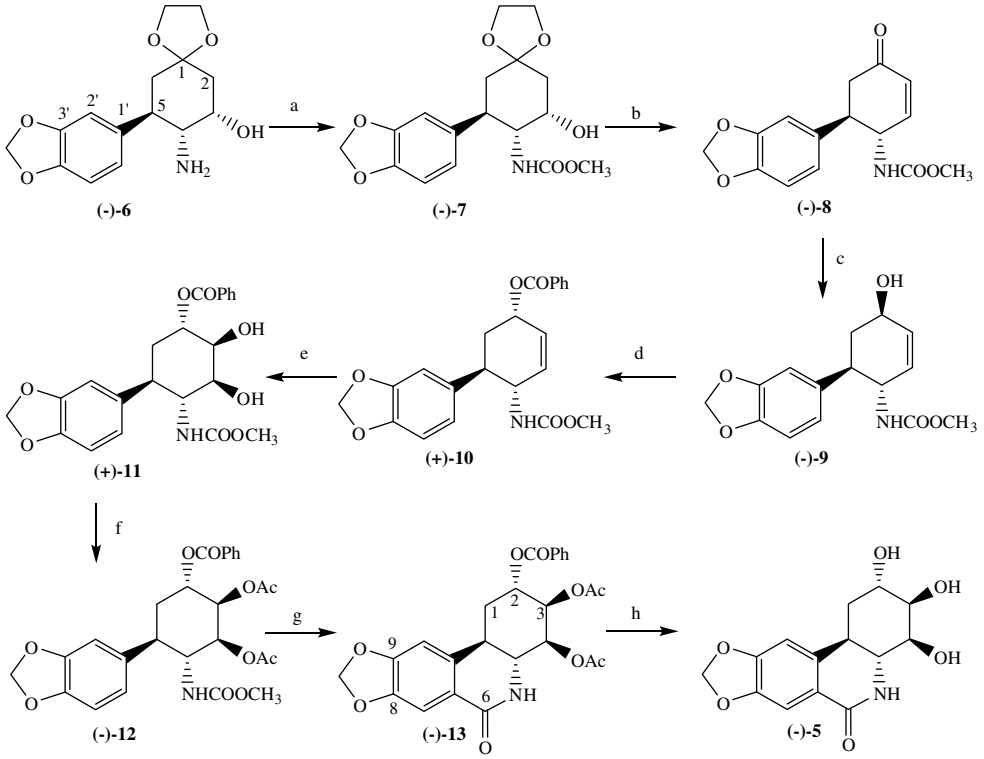
Scheme 1. Structure of phenanthridone alkaloids **1**–**5** and illustration of the literature syntheses of compound **5**.

while keeping the hydroxy group intact. During the deketalization of (−)-**7** using stoichiometric *p*-TsOH, the elimination of water also takes place giving enone (−)-**8**, which was then reduced by Utimoto's reduction method[40] ($NaBH_4$, in the presence of $CaCl_2$) affording stereoselectively allylic alcohol (−)-**9** in a good yield (84%). Calcium chloride forms a chelate during the reduction ensuring the quasi *cis*-equatorial position of the new hydroxy group.[41,42] Since the orientation of the hydroxy group in the target molecule is quasi *trans*-axial, inversion of the hydroxy group in (−)-**9** is necessary. For this purpose the Mitsunobu reaction seemed to be the best method.[43] Thus, reaction of (−)-**9** under Mitsunobu conditions resulted in benzoate (+)-**10**, after column chromatography in moderate yield (56%). The *cis*-dihydroxylation of (+)-**10** with OsO_4/NMO took place smoothly in THF/water, and the major product proved to be the required diol (+)-**11**. Protection of the hydroxy groups was carried out with acetyl chloride to afford compound (−)-**12** in a very good yield (90%).

The B-ring was closed by the Banwell modification[44] of the Bischler–Napieralski reaction of urethane (−)-**12**. The cyclization proceeds via a lactim ether intermediate and hence the reaction mixture contains a proportion of lactim ether after the cyclization. This was converted to the corresponding lactam under acidic conditions, however, a reacetylation step with acetyl chloride was necessary due to partial hydrolysis of the acetoxy groups under the conditions used. Thus, phenanthridone (−)-**13** was obtained in a satisfactory yield (53%). Finally, the protecting groups were removed by Zemplén deacetylation with 1% methanolic sodium hydroxide solution resulting in the title compound *ent*-(−)-**5** in an overall yield of 13% based on (−)-**6**.

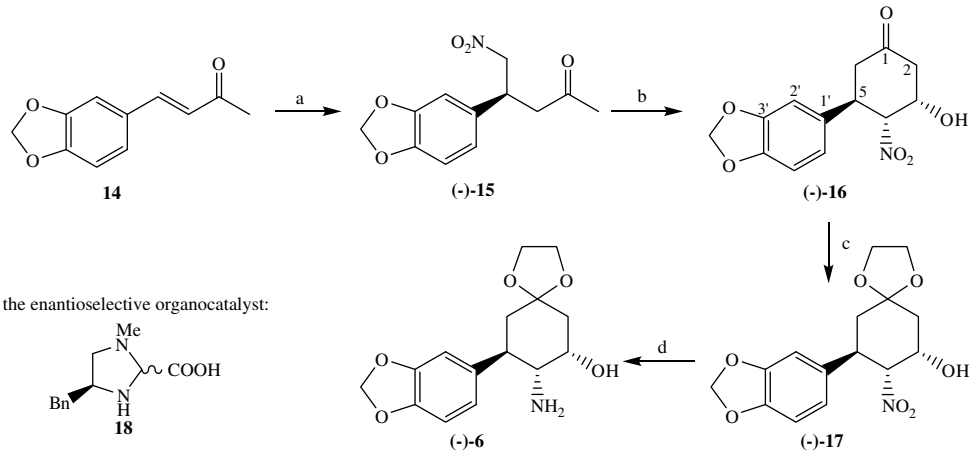
2.2. Modified synthesis of (−)-6

Racemic compound **6** was first described by Weller and Seebach.[39] They synthesized it from the appropriate nitrostyrene under harsh conditions followed by two further steps. The yields were



Scheme 2. Synthesis of *ent*-(−)-**5**. Reagents and conditions: (a) $ClCOOCH_3$, THF/H_2O (70:30), NaOH, rt (80%); (b) TsOH, rt (75%); (c) $NaBH_4/CaCl_2$ (1:1), MeOH, 0 °C (84%); (d) DEAD, PPh_3, PhCOOH, THF, 0 °C→rt (56%); (e) OsO_4/NMO, THF/H_2O (85:15), rt (99%); (f) AcCl, rt (90%); (g) (i) Tf_2O, 4-DMAP, CH_2Cl_2, 0 °C→rt, (ii) H+/H_2O, rt, (iii) AcCl, rt (53%); (h) 1% NaOH/MeOH, rt (95%).

only partly given.[39,45] According to our new and more practical method, (−)-**6** was obtained as seen in Scheme 3. At first, an enantioselective conjugate addition with nitromethane to **14**[46] was carried out in the presence of a novel and easily accessible chiral catalyst, 4-(*S*)-benzyl-1-methylimidazolidine-2-carboxylic acid (**18**) discovered by Jørgensen et al. and used for the addition of substituted nitromethanes to benzylideneacetones.[47] Recently, we have extended their investigation using nitromethane as Michael donor and a series of substituted nitropentanones were obtained with 67–100% ee's. Gratifyingly, complete enantioselectivity (100%) was achieved in the case of nitropentanone (−)-**15**[46] that was then cyclized with ethyl formate via a Claisen aldol reaction[48] followed by the protection of the oxo group in (−)-**16** with ethylene glycol. Finally, the nitro group of (−)-**17** was catalytically reduced to amine (−)-**6** over 10% Pd/C catalyst, at 12 bar and 60 °C. The overall yield of (−)-**6**, based on **14**, was 39%.



Scheme 3. Preparation of the starting material (−)-**6**. Reagents and conditions: (a) $MeNO_2$, catalyst **18**, rt (52%); (b) HCOOEt, NaOMe/Et_2O, rt (85%); (c) oxalic acid, MeCN, ethylene glycol, rt (83%); (d) H_2, 10% Pd/C, MeOH, 12 bar, 60 °C, 7 h (80%).

Thus, according to the reaction sequences in Scheme 3, (−)-**6** was successfully prepared without altering the configuration of the chiral centres. Starting from enantiomerically pure (−)-**6** and following the series of reactions in Scheme 2, *ent*-(−)-**5** was obtained with similar but opposite specific optical rotation ($[\alpha]_D^{22}$=−131.2, *c* 1, DMSO) as described for (+)-**5** ($[\alpha]_D^{23}$=+125, *c* 0.8, DMSO;[36] $[\alpha]_D^{23}$=+138, *c* 0.96, DMSO[33]). The optical purity was checked by chiral HPLC and found to be exclusively a single enantiomer.

Attempts to prepare catalyst (*R*)-**18** to apply for the synthesis of (+)-**6** and thereby accessing to (+)-**5** are in progress in our laboratory.

3. Conclusions

Starting from the (−)-enantiomer of the known amine **6**, a simple and efficient total synthesis was developed for *ent*-(−)-7-deoxy-*trans*-dihydronarciclasine (*ent*-(−)-**5**) in 8 steps in 13% overall yield. Furthermore, an efficient four-step synthesis of (−)-**6** was also developed, thereby the overall yield of the 12 steps reaches 3.7% that significantly exceeds the literature results. In addition, our approaches have further advantages: cheap and available reagents, simple reactions suitable for scaling-up. The synthetic potential of this new route was demonstrated by the first total synthesis of the non-natural *ent*-(−)-**5** based on the highly enantioselective organocatalytic nitromethane addition to benzylideneacetone **14** allowing the preparation of (−)-**6** and thereby the access to *ent*-(−)-**5** with retention of the configuration of all chiral centres.

4. Experimental

4.1. General

Melting points were determined using a Büchi 510 apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance DRX-500 or on a Bruker AV-300 instrument. The optical rotations were measured on a Perkin–Elmer 241 polarimeter. High resolution mass spectra were obtained on a Varian MAT312 instrument. The IR spectra were measured on a Perkin Elmer 1600 FT-IR instrument. HPLC analysis was performed with a JASCO UV-1575 instrument supplied with Kromasil 5 Cellucoat OD chiral stationary phase. Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column chromatography. All chemicals were reagent grade (FLUKA) and used without further purification.

4.2. Synthesis of *ent*-(−)-7-deoxy-*trans*-dihydronarciclasine [*ent*-(−)-(5)]

The synthesis exactly follows the racemic route described for (±)-**5**[38] but starting from enantiomerically pure (−)-**15**.[46] All analytical data are given for the respective enantiomers only.

*4.2.1. (−)-3-Hydroxy-4-methoxycarbonylamino-5-(3,4-methylenedioxyphenyl)cyclohexanone ethylene ketal [(−)-(**7**)].* Amine (−)-**6** (0.58 g, 1.98 mmol) was dissolved in THF (15 ml), methyl chloroformate (0.31 ml, 4 mmol) and 3% NaOH solution (5 ml) were added to the mixture in one portion, then it was stirred for 90 min at room temperature, poured into water, extracted with chloroform, dried and evaporated to give a pale yellow solid. Yield: 80%; mp 136–138 °C; $[\alpha]_D^{22}$=−4.2 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz, *δ*): 1.86 (t, *J* 13.1, 1H, H_{ax}-6); 1.92 (ddd, *J* 13.6, 6.4 and 3.2, 1H, H_{eq}-6); 2.02 (dd, *J* 14.1 and 2.2, 1H, H_{ax}-2); 2.09 (dt, *J* 14.3 and 3.1, 1H, H_{eq}-2); 2.95 (td, *J* 12.2 and 3.9, 1H, H-5); 3.50 (s, 3H, $COOCH_3$); 3.60 (d, *J* 9.2, 1H, OH); 3.81 (ddd, *J* 11.1, 9.8 and 2.2, 1H, H-4); 3.93–4.03 (m, 4H, OCH_2CH_2O); 4.11 (dd, *J* 9.2 and 2.6, 1H, H-3); 5.01 (d, *J* 9.2, 1H, NH); 5.93 (s, 2H, OCH_2O); 6.67–6.73 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz, *δ*): 38.7 (C-2), 41.3 (C-5), 42.5 (C-6), 51.9 (COO**C**H_3), 56.4 (C-4), 64.2 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 69.7 (C-3), 100.9 (OCH_2O), 108.0 (C-2′/C-5′), 108.2 (C-2′/C-5′), 108.5 (C-1), 120.9 (C-6′), 135.2 (C-1′), 146.4 (C-4′), 147.7 (C-3′), 156.5 (**C**$OOCH_3$); HRMS calcd for $C_{17}H_{21}NO_7$ $(M)^+$ 351.1318, found 351.1314.

*4.2.2. (−)-3-Hydroxy-4-methoxycarbonylamino-5-(3,4-methylenedioxyphenyl)cyclohex-2-enone [(−)-(**8**)].* Urethane **7** (0.55 g, 1.57 mmol) was dissolved in acetone (10 ml) containing 1% water, followed by the

addition of *p*-TsOH (0.52 g, 2.76 mmol), and the mixture was stirred at 60 °C for 1 h. Then it was poured into saturated $NaHCO_3$ solution, extracted with chloroform. The organic phase was dried and evaporated to yield enone (−)-**8** as a pale yellow solid. Yield: 75%; mp 140–141 °C; $[\alpha]_D^{22}=-145.9$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz, *δ*): 2.67 (d, *J* 9.5, 2H, H_{ax}-6 and H_{eq}-6); 3.19 (q, *J* ~9, 1H, H-5); 3.61 (s, 3H, $COOCH_3$); 4.64 (t, *J* ~9, 1H, H-4); 4.81 (br d, *J* 8.6, 1H, NH); 5.96 (s, 2H, OCH_2O); 6.08 (dd, *J* 10.1 and 2.5, 1H, H-2); 6.68 (dd, *J* 8.0 and 1.8, 1H, H-6′); 6.74 (d, *J* 1.8, 1H, H-2′); 6.77 (d, *J* 7.9, 1H, H-5′); 6.93 (dd, *J* 10.1 and 1.9, 1H, H-3); (DMSO-d_6, 500 MHz, *δ*): 2.34 (ddd, *J* 16.0, 3.7 and 1.1, 1H, H_{eq}-6); 2.93 (dd, *J* 16.0 and 13.9, 1H, H_{ax}-6); 3.23 (ddd, *J* 14.0, 10.5 and 3.5, 1H, H-5); 3.44 (s, 3H, $COOCH_3$); 4.57 (ddt, *J* 10.8, 8.6 and 2.2, 1H, H-4); 5.94 (dd, *J* 2.5 and 1.1, 1H, H-2); 5.96–5.99 (m, 2H, OCH_2O); 6.76 (dd, *J* 7.9 and 1.7, 1H, H-6′); 6.82 (d, *J* 7.9, 1H, H-5′); 6.86 (dd, *J* 10.1 and 2.0, 1H, H-3); 6.98 (d, *J* 1.6, 1H, H-2′); 7.46 (d, *J* 8.9, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz, *δ*): 45.0 (C-6), 47.6 (C-5), 53.1 ($COO\mathbf{C}H_3$), 53.4 (C-4), 101.2 (OCH_2O), 107.4 (C-2′), 108.6 (C-5′), 120.8 (C-6′), 129.4 (C-2′), 133.5 (C-1′), 147.1 (C-4′), 148.1 (C-3′), 151.6 (C-3), 156.4 (**C**$OOCH_3$), 197.7 (C-1); (DMSO-d_6, 125 MHz, *δ*): 44.2 (C-6), 46.2 (C-5), 51.4 ($COO\mathbf{C}H_3$), 52.7 (C-4), 100.8 (OCH_2O), 107.9 (C-2′, C-5′), 121.1 (C-6′), 128.2 (C-2), 135.2 (C-1′), 145.9 (C-4′), 147.1 (C-3′), 153.7 (C-3), 156.2 (**C**$OOCH_3$), 197.8 (C-1); IR (KBr) 3327, 2954, 2911, 1861, 1694, 1543, 1497, 1310, 1246 cm^{-1}; HRMS calcd for $C_{15}H_{15}NO_5$ $(M)^+$ 289.0950, found 289.0941.

*4.2.3. (−)-4-Methoxycarbonylamino-5-(3,4-methylenedioxyphenyl) cyclohex-2-en-1-ol [(−)-(**9**)].* Enone (−)-**8** (0.34 g, 1.18 mmol) and $CaCl_2$ (0.26 g, 2.36 mmol) were suspended in methanol (7 ml) and stirred for 30 min at room temperature. After that, the mixture was cooled to 0 °C, and $NaBH_4$ (66 mg, 1.74 mmol) was added in one portion. After 1.5 h stirring at 0 °C, the mixture was poured into water, and extracted with ethyl acetate. The organic layer was dried, evaporated to give a pale yellow solid. Yield: 84%; mp 143–144 °C; $[\alpha]_D^{22}=-170.8$ (*c* 1, acetone); ^{1}H NMR ($CDCl_3$, 500 MHz, *δ*): 1.82 (dt, *J* 12.5 and 10.0, 1H, H-6_{ax}); 2.24 (dd, *J* 12.5 and 5.5, 1H, H-6_{eq}); 2.63 (t, *J* 8.0, 1H, H-5); 3.54 (s, 3H, $COOCH_3$); 4.30–4.32 (br m, 1H, H-1/H-4/NH); 4.43–4.46 (m, 1H, H-1/H-4/NH); 4.58–4.61 (m, 1H, H-1/H-4/NH); 5.74 (d, *J* 10.0, 1H, H-2/H-3); 5.81 (dd, *J* 10.0 and 1.0, 1H, H-2/H-3); 5.94 (s, 2H; OCH_2O); 6.66 (dd, *J* 7.8 and 2.0, 1H, H-6′); 6.72 (d, *J* 2.0, 1H, H-2′); 6.74 (d, *J* 7.8, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 75 MHz, *δ*): 40.9 (C-6), 46.6 (C-5), 52.3 ($COOCH_3$), 53.8 (C-4), 68.0 (C-1), 101.2 (OCH_2O), 107.7 (C-2′), 108.5 (C-5′), 120.8 (C-6′), 131.3 (C-2/C-3), 132.8 (C-2/C-3), 135.9 (C-1′), 146.7 (C-4′), 148.1 (C-3′), 156.7 ($COOCH_3$); IR (KBr) 3327, 2938, 2936, 1694, 1537, 1504, 1255, 1042 cm^{-1}; HRMS calcd for $C_{15}H_{17}NO_5$ $(M)^+$ 291.1107, found 291.1111.

*4.2.4. (+)-1-Benzoyloxy-4-(methoxycarbonylamino)-5-(3,4-methylenedioxyphenyl)cyclohex-2-ene [(+)-(**10**)].* Triphenyl phosphine (0.30 g, 1.16 mmol) and 40% solution of diethyl azodicarboxylate in toluene (0.52 ml, containing 1.18 mmol DEAD) were dissolved in THF (7 ml), and the solution was cooled to 0 °C. To this mixture were added cyclohexenol (−)-**9** (0.28 g, 0.97 mmol) in THF (3.5 ml) and benzoic acid (0.14 g, 1.27 mmol) in THF (3.5 ml). This mixture was stirred for 30 min at 0 °C and 3 h at room temperature, then the mixture was evaporated and the product was isolated by column chromatography on silica (eluent: $CHCl_3$/acetone=20:1). Yield: 56%; semisolid; $[\alpha]_D^{22}=+87.3$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz, *δ*): 2.13–2.22 (m, 2H, H_{ax}-6 and H_{eq}-6); 2.93 (br t, *J* 2.1, 1H, H-5); 3.56 (s, 3H, CO_2CH_3); 4.36 (br m, 1H, H-4); 4.73 (br m, 1H, NH); 5.52 (q, *J* 2.6, 1H, H-1); 5.93 (m, 2H, OCH_2O); 6.03 (m, 2H, H-2 and H-3); 6.68–6.80 (m, 3H, H-2′, H-5′ and H-6′); 7.40–7.60 (m, 3H, Bz-H); 8.05 (d, *J* 8.2, 2H, Bz-H); (DMSO-d_6, 300 MHz, *δ*): 1.95 (d, *J* 14.4, 1H, H_{eq}-6); 2.30 (td, *J* 13.5 and 3.3, 1H, H_{ax}-6); 3.05 (t, *J* 11.6, 1H, H-5); 3.42 (s, 3H, $COOCH_3$); 4.18 (t, *J* 9.3, 1H, H-4); 5.40 (br, 1H, H-1); 5.93–5.98 (m, 4H, OCH_2O, H-2 and H-3); 6.78–6.93 (m, 3H, ArH); 7.30 (d, *J* 8.7, 1H, NH); 7.52–7.69 and 7.98–8.00 (m, 3H, ArH); 7.55 (t, *J* 7.4, 2H, Bz-3,5); 7.60 (t, *J* 7.1, 1H, Bz-4); 7.99 (d, *J* 7.8, 2H, Bz-2,6); ^{13}C NMR (DMSO-d_6, 75 MHz, *δ*): 34.9 (C-6), 40.0 (C-5), 51.2 (C-4/$COO\mathbf{C}H_3$), 52.9 (C-4/$COO\mathbf{C}H_3$), 67.0 (C-1), 100.7 (OCH_2O), 107.9 (C-2′/C-5′), 108.0 (C-2′/C-5′), 121.0 (C-6′), 124.3 (Bz-4), 128.7 (Bz-2,6/Bz-3,5), 129.1 (Bz-2,6/Bz-3,5), 130.0 (Bz-1), 133.4 (C-2/C-3), 136.9 (C-1′), 137.1 (C-2/C-3), 145.7 (C-4′), 147.2 (C-3′), 156.3 (**C**$OOCH_3$), 165.2 (Bz-**C**OO); HRMS calcd for $C_{22}H_{21}NO_6$ $(M)^+$ 395.1369, found 395.1379.

*4.2.5. (+)-1-Benzoyloxy-2,3-dihydroxy-4-(methoxycarbonylamino)-5-(3,4-methylenedioxyphenyl)cyclohexane [(+)-(**11**)].* Benzoate (+)-**10** (0.21 g, 0.525 mmol) was dissolved in a mixture of THF (3.2 ml) and water (0.53 ml) followed by the addition of 4-methylmorpholine-4-oxide-monohydrate (0.15 g, 1.12 mmol) and 4% solution of osmium tetroxide in water (0.225 ml, containing 0.036 mmol OsO_4). This mixture was then stirred overnight under argon atmosphere. After that, the mixture was poured into saturated $Na_2S_2O_3$ solution, and the product was extracted with ethyl acetate. The organic layer was dried, evaporated to give a pale yellow solid. Yield: 99%; mp 187–189 °C; $[\alpha]_D^{22}=+37.6$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, *δ*): 2.01 (dt, *J* 14.0 and 3.5, 1H, H_{eq}-6); 2.33 (t, *J* 14.0, 1H, H_{ax}-6); 2.91 (ddd, *J* 13.4, 10.2 and 3.5, 1H, H-5); 3.55 (s, 3H, $COOCH_3$); 3.96–3.99 (m, 1H, H-3); 4.02–4.06 (m, 1H, H-4); 4.25 (t, br, *J* 3.3, 1H, H-2); 4.94 (br, 1H, NH); 5.41 (q, br, *J* 2.6, 1H, H-1); 5.88 (m, 2H, OCH_2O); 6.66–6.77 (m, 3H, ArH); 7.42–7.66 and 8.01–8.03 (m, 5H, Bz-H); ^{13}C NMR ($CDCl_3$, 75 MHz, *δ*): 32.9 (C-6), 42.7 (C-5), 52.5 ($COO\mathbf{C}H_3$), 55.7 (C-4), 70.3 (C-2), 71.7 (C-1), 73.8 (C-3), 101.0 (OCH_2O), 107.7 (C-2′), 108.3 (C-5′), 121.1 (C-6′), 128.5 (Bz-3,5) 128.7 (Bz-4), 129.6 (Bz-2,6), 130.0 (Bz-1), 135.0 (C-1′), 146.8 (C-4′), 148.2 (C-3′), 158.8 (**C**$OOCH_3$), 165.4 (Bz-**C**OO); IR (KBr) 3361, 2926, 2924, 1717, 1506, 1489, 1272, 1250 cm^{-1}; HRMS calcd for $C_{22}H_{23}NO_8$ $(M)^+$ 429.1424, found 429.1426.

*4.2.6. (−)-1-Benzoyloxy-2,3-diacetoxy-4-(methoxycarbonylamino)-5-(3,4-methylenedioxyphenyl)cyclohexane [(−)-(**12**)].* Diol (+)-**11** (0.22 g, 0.52 mmol) and acetyl chloride (2 ml, 28 mmol) were mixed, stirred overnight, poured into a cooled, saturated aq $NaHCO_3$ solution, and the product was extracted with chloroform. The organic layer was dried and evaporated to give a pale yellow solid. Yield: 90%; mp 135–136 °C; $[\alpha]_D^{22}=-30.9$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, *δ*): 2.03 (s, 3H, $COCH_3$); 2.16–2.19 (m, 2H, H_{ax}-6 and H_{eq}-6); 2.24 (s, 3H, $COCH_3$); 3.00 (td, *J* 10.2 and 6.5, 1H, H-5); 3.50 (s, 3H, $COOCH_3$); 4.20–4.22 (m, 1H, H-4); 4.53 (d, *J* 9.0, 1H, NH); 5.30 (br, 1H, H-1/H-2); 5.37 (d, *J* 10.5, 1H, H-3); 5.50 (br, 1H, H-1/H-2); 5.93 (s, 2H, OCH_2O); 6.67–6.79 (m, 3H, ArH); 7.46–7.71 and 8.06–8.09 (m, 5H, Bz-H); ^{13}C NMR ($CDCl_3$, 75 MHz, *δ*): 20.8 ($OOC\mathbf{C}H_3$), 21.0 ($OOC\mathbf{C}H_3$), 33.7 (br, C-6), 43.4 (C-5), 52.1 ($COO\mathbf{C}H_3$), 53.6 (br, C-4), 69.3 (C-1/C-2/C-3), 69.5 (C-1/C-2/C-3), 71.4 (C-1/C-2/C-3), 101.0 (OCH_2O), 108.0 (C-2′/C-5′), 108.3 (C-2′/C-5′), 121.3 (C-6′), 128.6 (Bz-4), 128.7 (Bz-3,5), 129.4 (Bz-1), 129.8 (Bz-2,6), 133.6 (C-1′), 146.6 (C-4′), 147.8 (C-3′), 156.7 (**C**$OOCH_3$), 164.1 (Bz-**C**OO), 169.6 ($OO\mathbf{C}CH_3$), 170.9 ($OO\mathbf{C}CH_3$); IR (KBr) 3369, 2953, 2926, 1728, 1725, 1506, 1491, 1369, 1247 cm^{-1}; HRMS calcd for $C_{26}H_{27}NO_{10}$ $(M)^+$ 513.1635, found 513.1630.

*4.2.7. (−)-2-Benzoyloxy-3,4-diacetoxy-8,9-methylenedioxy-1,2,3,4,4a,5-hexahydrophenanthridin-6(10bH)-one [(−)-(**13**)].* Urethane (−)-**12** (0.236 g, 0.46 mmol) and 4-DMAP (170 mg, 1.39 mmol) were dissolved in dry CH_2Cl_2 (12 ml), and cooled to 0 °C. To this mixture was added a solution of triflic anhydride (0.4 ml, 2.42 mmol) in dry CH_2Cl_2 (2 ml) over a period of 15 min. The mixture was stirred overnight at ambient temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution, 20% acetic acid and saturated $NaHCO_3$ solution, subsequently. The organic layer was evaporated, and the residue was dissolved in THF (10 ml), 2 M HCl solution (10 ml) was added, and the mixture was stirred overnight at room temperature. After that, it was poured into saturated aq

$NaHCO_3$, extracted with chloroform, dried, evaporated, and acetyl chloride (2 ml, 28 mmol) was added to the residue. The mixture was stirred overnight at room temperature, poured into saturated aq $NaHCO_3$, and extracted with chloroform. After evaporating the solvent, the product was isolated by column chromatography on silica (eluent: $CHCl_3$/acetone=20:1). Yield: 53%; pale yellow solid; mp>270 °C; $[\alpha]_D^{22}=-80.3$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz, δ): 2.04 (td, *J* 13.6 and 2.2, 1H, H_{ax}-1); 2.11 (s, 6H, $COCH_3$); 2.62 (dt, *J* 14.4 and 3.1, 1H, H_{eq}-1); 3.28 (td, *J* 12.6 and 3.8, 1H, H-10b); 3.87 (dd, *J* 12.7 and 11.0, 1H, H-4a); 5.37 (dd, *J* 10.8 and 2.8, 1H, H-4); 5.45 (q, *J* 3.0, 1H, H-2); 5.61 (t, *J* 3.1, 1H, H-3); 6.02 (m, 2H, OCH_2O); 6.67 (s, 1H, NH); 6.74 (s, 1H, H-10); 7.45–7.69 and 8.04–8.06 (m, 6H, H-7, Bz-H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 21.0 (OCO**C**H_3), 21.1 (CO**C**H_3), 27.1 (C-1), 35.3 (C-10b), 53.1 (C-4a), 67.8 (C-2/C-3/C-4), 69.4 (C-2/C-3/C-4), 72.0 (C-2/C-3/C-4), 102.0 (OCH_2O), 104.2 (C-10), 108.6 (C-7), 123.3 (C-6a), 128.9, 129.3 (Bz-1), 130.1, 132.3, 132.4, 135.8 (C-10a), 147.3 (C-8), 151.8 (C-9), 165.2 (C-6/Bz-COO), 165.9 (C-6/Bz-COO), 169.4 (O**C**OCH$_3$), 170.5 O**C**OCH$_3$; HRMS calcd for $C_{25}H_{23}NO_9$ $(M)^+$ 481.1373, found 481.1379.

*4.2.8. (−)-2,3,4-Trihydroxy-8,9-methylenedioxy-1,2,3,4,4a,5-hexahydrophenanthridin-6(10bH)-one [(−)-(**5**)].* The cyclized product (−)-**13** (110 mg, 0.23 mmol) was dissolved in methanol (10 ml) containing 1% NaOH, and the mixture was stirred for 30 min at room temperature, then it was poured into water and the product was extracted with ethyl acetate. The organic phase was dried, evaporated to give a pale yellow solid. Yield: 95%; mp 295–297 °C, lit. mp 299–303 °C;[36] $[\alpha]_D^{22}=-131.2$ (*c* 1, DMSO); ^1H NMR (DMSO-d_6, 300 MHz, δ): 1.65 (td, *J* 13.5 and 1.1, 1H, H_{ax}-1); 2.14 (td, *J* 13.5 and 1.1, 1H, H_{eq}-1); 2.89 (td, *J* 13.2 and 2.7, 1H, H-10b); 3.29–3.34 (m, 1H, H-4a); 3.72 (br s, 2H, H-2/H-3/H-4); 3.89 (br s, 1H, H-2/H-3/H-4); 4.80 (d, *J* 2.4, 1H, OH); 4.93 (d, *J* 5.7, 1H, OH); 4.99 (d, *J* 2.8, 1H, OH); 6.07 (s, 2H, OCH_2O); 6.92 (br, 2H, H-10 and NH); 7.30 (s, 1H, H-7); ^{13}C NMR (DMSO-d_6, 75 MHz, δ): 28.3 (C-1), 34.3 (C-10b), 55.1 (C-4a), 68.6 (C-2/C-3/C-4), 69.7 (C-2/C-3/C-4), 71.7 (C-2/C-3/C-4), 101.6 (OCH_2O), 104.3 (C-10), 106.9 (C-7), 123.2 (C-6a), 138.0 (C-10a), 145.9 (C-8), 150.6 (C-9), 164.3 (C-6); HRMS calcd for $C_{14}H_{15}NO_6$ $(M)^+$ 293.0899, found 293.0896.

4.3. Preparation of (−)-4-amino-3-hydroxy-5-(3,4-methylenedioxyphenyl)cyclohexanone ethylene ketal [(−)-(6)]

*4.3.1. (−)-3-Hydroxy-5-(3,4-methylenedioxyphenyl)-4-nitrocyclohexanone [(−)-(**16**)].* Freshly prepared sodium methoxide (0.80 g, 14.8 mmol) was suspended in dry diethyl ether (10 ml), followed by the addition of ethyl formate (1.70 ml, 23.0 mmol) and nitropentanone (−)-**15**[47] (0.90 g, 3.58 mmol). Then the mixture was stirred overnight at room temperature, water (5 ml) was added and the phases were separated. The inorganic layer was cooled and acidified with 96% acetic acid to pH 4. The precipitation was filtered and dried in vacuum desiccator. Yield: 85%; yellow solid; mp 145–146 °C; $[\alpha]_D^{22}=-57,7$ (*c* 1, MeOH); ^1H NMR (DMSO-d_6, 500 MHz, δ): 2.32 (ddd, *J* 14.7, 5.1 and 2.5, 1H, H_{eq}-6); 2.41 (dt, *J* 14.7 and 2.9, 1H, H_{eq}-2); 2.67 (t, *J* 14.0, 1H, H_{ax}-6); 3.03 (dd, *J* 14.5 and 3.1, 1H, H_{ax}-2); 3.89 (td, *J* 12.5 and 5.1, 1H, H-5); 4.65–4.70 (m, 1H, H-3); 5.68 (dd, *J* 11.7 and 2.3, 1H, H-4); 5.98–6.00 (m, 3H, OCH_2O and OH); 6.84 (d, *J* 8.0, 1H, H-5′); 6.87 (dd, *J* 8.1 and 1.4, 1H, H-6′); 7.08 (d, *J* 1.6, 1H, H-2′); ^{13}C NMR (DMSO-d_6, 75 MHz, δ): 39.4 (C-5), 46.5 (C-6), 47.3 (C-2), 69.4 (C-3), 89.5 (C-4), 100.9 (OCH_2O), 107.6 (C-2′), 108.3 (C-5′), 120.7 (C-6′), 134.5 (C-1′), 146.2 (C-4′), 147.4 (C-3′), 206.0 (C-1); HRMS calcd for $C_{13}H_{13}NO_6$ $(M)^+$ 279.0743, found 279.0751.

*4.3.2. (−)-3-Hydroxy-5-(3,4-methylenedioxyphenyl)-4-nitrocyclohexanone ethylene ketal [(−)-(**17**)].* Anhydrous oxalic acid (2.34 g, 26.01 mmol) was dissolved in dry acetonitrile (40 ml), followed by the addition of ethylene glycol (6.68 ml, 119.4 mmol) and nitrocyclohexanolone (−)-**16** (0.85 g, 2.77 mmol). The mixture was stirred for 2 days at room temperature, then it was poured into saturated aq $NaHCO_3$ solution, the product was extracted with chloroform and after drying, the solvent was removed in vacuo to give a pale yellow solid. Yield: 83%; mp 199–200 °C; $[\alpha]_D^{22}=-6.2$ (*c* 1, acetone); ^1H NMR ($CDCl_3$, 500 MHz, δ): 1.80 (t, *J* 13.5, 1H, H_{ax}-6); 2.00 (dt, *J* 13.8 and 3.7, 1H, H_{eq}-6); 2.04 (dd, *J* 14.5 and 3.0, 1H, H_{ax}-2); 2.19 (dt, *J* 14.4 and 3.3, 1H, H_{eq}-2); 3.78 (td, *J* 12.6 and 4.2, 1H, H-5); 3.90–4.10 (m, 4H, OCH_2CH_2O); 3.99 (d, *J* 10.2, 1H, OH); 4.64 (dq, *J* 10.2 and 3.1, 1H, H-3); 4.70 (dd, *J* 12.1 and 3.0, 1H, H-4); 5.93 (s, 2H, OCH_2O); 6.70–6.75 (m, 3H, ArH); (DMSO-d_6, 500 MHz, δ): 1.77 (m, 1H, H_{eq}-6); 1.81 (t, *J* 13.5, 1H, H_{ax}-6); 1.98 (dt, *J* 13.5 and 2.1, 1H, H_{eq}-2); 2.06 (dd, *J* 14.0 and 3.5, 1H, H_{ax}-2); 3.62 (td, *J* 12.0 and 5.5, 1H, H-5); 3.75–3.86 and 3.91–3.98 (m, 4H, OCH_2CH_2O); 4.46 (dq, *J* 5.9 and 3.0, 1H, H-3); 5.29 (dd, *J* 12.0 and 3.0, 1H, H-4); 5.93–6.00 (m, 2H, OCH_2O); 6.79 (dd, *J* 8.0 and 1.5, 1H, H-6′); 6.82 (d, *J* 8.0, 1H, H-5′); 6.98; (d, *J* 1.5, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 38.4 (C-2/C-5), 38.7 (C-2/C-5), 41.8 (C-6), 64.6 (OCH_2CH_2O), 65.3 (OCH_2CH_2O), 69.9 (C-3), 91.4 (C-4), 101.3 (OCH_2O), 107.8 (C-1/C-2′/C-5′), 108.0 (C-1/C-2′/C-5′), 108.8 (C-1/C-2′/C-5′), 120.8 (C-6′), 133.6 (C-1′), 147.1 (C-4′), 148.1 (C-3′); (DMSO-d_6, 125 MHz, δ): 37.9 (C-5); 38.7 (C-2); 41.1 (C-6); 63.2 (OCH_2CH_2O); 64.3 (OCH_2CH_2O); 68.4 (C-3); 90.2 (C-4); 100.8 (OCH_2O), 106.7 (C-1); 107.6 (C-2′); 108.2 (C-5′); 120.6 (C-6′); 135.3 (C-1′); 145.9 (C-4′); 147.3 (C-3′); HRMS calcd for $C_{15}H_{17}NO_7$ $(M)^+$ 323.1005, found 323.1007.

*4.3.3. (−)-4-Amino-3-hydroxy-5-(3,4-methylenedioxyphenyl)cyclohexanone ethylene ketal [(−)-(**6**)].* Ketal (−)-**17** (0.81 g, 2.51 mmol) was dissolved in methanol, 10% Pd/C (0.24 g) was added and hydrogenated at 12 bar and 60 °C for 7 h. The product was obtained by evaporating the solvent in vacuo. Yield: 80%; semisolid; $[\alpha]_D^{22}=-10.6$ (*c* 1, MeOH); ^1H NMR ($CDCl_3$, 500 MHz, δ): 1.79 (t, *J* 13.2, 1H, H_{ax}-6); 1.86 (dt, *J* 13.4 and 3.4, 1H, H_{eq}-6); 1.95 (dd, *J* 14.2 and 3.2, 1H, H_{ax}-2); 2.11 (dt, *J* 14.3 and 3.1, 1H, H_{eq}-2); 2.75 (dd, *J* 11.0 and 2.5, 1H, H-4), 2.82 (td, *J* 12.3 and 3.6, 1H, H-5); 3.89–4.05 (m, 4H, OCH_2CH_2O); 4.08 (d, *J* 2.8, 1H, H-3); 5.94 (s, 2H, OCH_2O); 6.68 (dd, *J* 7.9 and 1.5, 1H, H-6′); 6.71 (d, *J* 1.3, 1H, H-2′); 6.77; (d, *J* 7.9, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 39.3 (C-2), 41.9 (C-6), 43.8 (C-5), 57.5 (C-4), 64.3 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 70.1 (C-3), 101.2 (OCH_2O), 108.1 (C-1/C-2′/C-5′), 108.7 (C-1/C-2′/C-5′), 108.9 (C-1/C-2′/C-5′), 121.5 (C-6′), 135.9 (C-1′), 146.7 (C-4′), 148.3 (C-3′); HRMS calcd for $C_{15}H_{19}NO_5$ $(M)^+$ 293.1263, found 293.1257.

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