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Enantiospecific Synthesis of (+)-Ribasine

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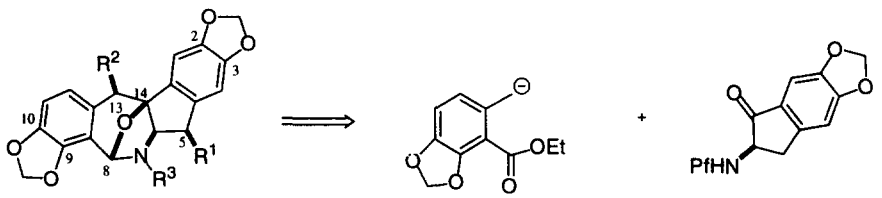
Abstract. The alkaloid (+)-ribasine was synthesized by stereocontrolled addition of substituted α–lithium-*o*-toluate **6d** to enantiomerically pure (*R*)-*N*-(9-phenylfluoren-9-yl)-2-amino-5,6-(methylenedioxy)indan-1-one [(+)-**5**]. Aminoindanone (+)-**5** was prepared from amino acid (-)-**15** obtained by diastereoselective alkylation of a chiral glycine enolate synthon.

Ribasine (**1**),[1] isolated in our laboratory in 1983, was the first-discovered member of a class of alkaloids, whose other three known members are its hydroxy derivatives himalayamine (**2**)[2] and ribasidine (**3**)[3] and the *N*-demethyl analogue norribasine (**4**).[4] These natural products of *Fumariaceae* and *Papaveraceae* plants have a unique 8,14-epoxy-indano-[2,1-c][2]benzazepine framework (Scheme 1).



1, R^1=R^2=H, R^3=Me
2, R^1=OH, R^2=H, R^3=Me
3, R^1=H, R^2=OH, R^3=Me
4, R^1=R^2=R^3=H

6d (+)-**5**

Scheme 1

We recently reported[5] the first total synthesis of racemic ribasine by a route in which addition of *o*-toluate **6d** to aminoindanone **5** establishes the key stereorelationship between C6 and C14, prior to formation of the benzazepine ring and the ether bridge. We have now achieved enantiospecific synthesis of (+)-ribasine by means of the same strategy, using enantiomerically pure (*R*)-**5** prepared by anionic cyclization of the corresponding oxazolidinone.[6]

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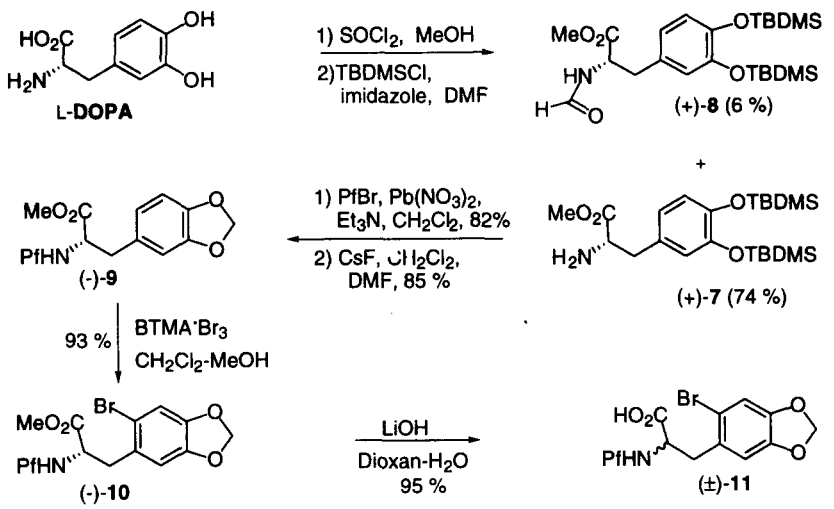


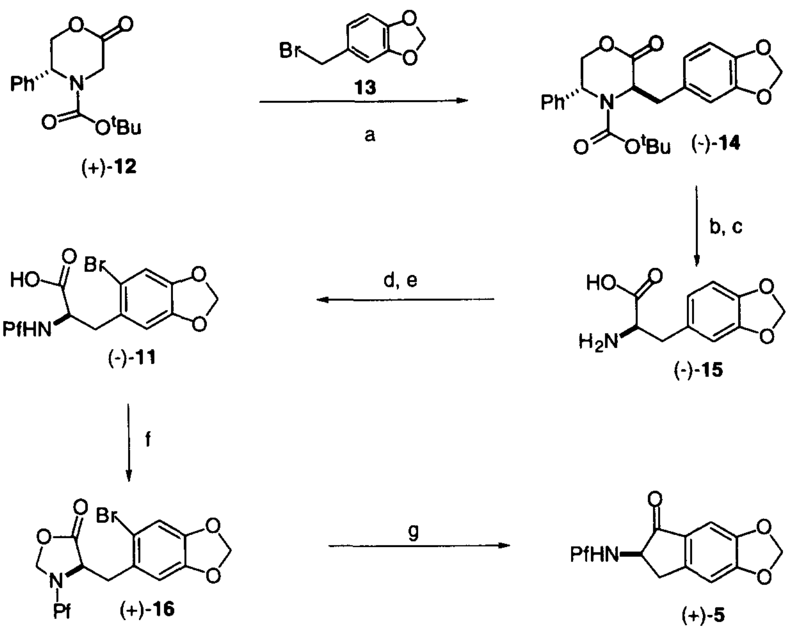
Scheme 2

We first considered preparing *(R)*-**5** starting from D-DOPA. Because of the cost of D-DOPA we investigated the feasibility of this route by trying to prepare *(S)*-**5** from the cheaper L-DOPA (Scheme 2). First, it was necessary to esterify L-DOPA as per Brenner and Huber[7] to improve its solubility and stability, since subsequent attempts to protect the amine or form the methylenedioxy group directly failed because of instability of the phenolic hydroxyls, and we also protected the latter: silylation in DMF gave the silyl ether **7** and a small amount of the formamide **8**. It was then possible to protect the amino group of **7** with 9-phenylfluoren-9-yl bromide (PfBr) under standard Rapoport conditions,[8] after which the silyl groups were removed and the methylenedioxy group formed in one step using CH_2Cl_2 and CsF in DMF.[9] Bromination of the resulting compound **9** with benzyltrimethylammonium tribromide ($BTMA{\cdot}Br_3$)[10] afforded the required aminoester **10**, but hydrolysis of the latter using LiOH in dioxane-H_2O at 60°C surprisingly afforded an optically inactive product. Other hydrolysis conditions (NaOH, MeOH, rt; LiCl, DMF, reflux) left the starting material unchanged, and BBr_3 cleaved the methylenedioxy group.

In view of the above results, we decided to prepare the required optically active aminoacid **11** by a direct route avoiding the ester. Of the various possible methods[11] we chose diastereoselective alkylation of a chiral glycine enolate because of its ease, high yields and high d.e.[12]

The glycine enolate chosen for preparation of **11** is the oxazinone **12** (Scheme 3), in which, in order to avoid an A(1,3) interaction with the urethane protecting group, the C5-phenyl is forced to adopt an axial orientation that makes the opposite face of the ring the more susceptible to electrophilic attack.

Deprotonation of **12** with NaHMDS in THF-DME and alkylation of the resulting enolate with the substituted benzylic bromide **13**[13] afforded the alkylation adduct **14** in 82% yield and more than 99.5% d.e.



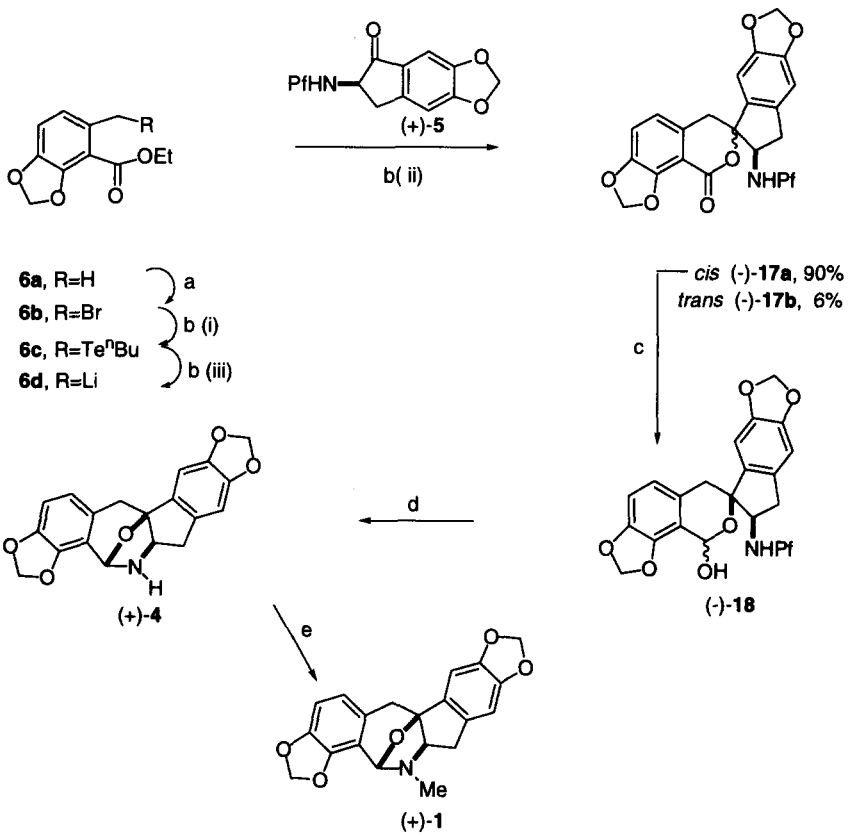
a) i: NaHMDS, THF-DME, -78°C, 30 min; ii: addition of 13, DME, -78°C , 2h, 82%; b) MeOH-HCl, reflux, 20h; c) H_2, $Pd(OH)_2$, MeOH-H_2O-TFA, rt, 20h; 98% two steps; d) i:TMSCl , CH_2Cl_2, reflux, 2h; ii) Et_3N, $Pb(NO_3)_2$, PfBr, CH_2Cl_2, rt, 2 days, 82% e) BTMA·Br_3, CH_2Cl_2-MeOH, rt, 1h, 92%; f)H_2CO/*p*-TsOH, THF, rt, 16h, 95%; g) *n*-BuLi, THF, -78°C, 30 min, 80%

Scheme 3

The amino and carboxyl groups of **14** were deprotected in a one-pot, two-step procedure: exposure of **14** to a refluxing 6:1 mixture of MeOH and 3M HCl for 20 h and removal of the volatiles afforded the 1,2-aminoalcohol, and treatment with hydrogen (1 atm) in MeOH-H_2O-TFA in the presence of palladium catalyst ($Pd(OH)_2$/C) at room temperature gave the aminoacid **15**, which was isolated, in 98% yield from oxazinone **14**, by washing the crude reaction residue with acetone. Protection with BrPf and aromatic bromination with BTMA·Br_3 afforded optically active **11**, and after N,O-protection, cyclization of the resulting oxazolidinone **16** with *n*BuLi gave aminoindanone **5**. ^1H NMR experiments with chiral (+)-Eu(hfc)$_3$ shift reagent indicated an enantiomeric ratio >99:1 (the limit of detection), whereas racemic **5**[6] showed signals for both enantiomers.

The stereocontrolled synthesis of racemic ribasine[5] is based on the *in situ* generation of benzylic anion **6d** from the tellurium compound **6c**, in the presence of aminoindanone **5** (Scheme 4). In this work, benzylic bromide **6b** was treated with *n*-butyltellurolate in THF at 0°C, the reaction was cooled to -105°C, and (+)-**5** and *n*-BuLi were added in that order. Fast lithium-tellurium exchange gave **6d**, which reacted with (+)-**5** *in situ* affording a 90% yield of the desired *cis*-dihydroisocoumarin **17a**, together with a 6% yield of the *trans* isomer **17b**. Lactone **17a** was reduced with DIBAL-H to an anomeric mixture of lactol **18**, and removal of the

phenyl-fluorenyl group by treatment with TFA in CH_2Cl_2 at 0°C achieved cyclization affording (+)-norribasine (**4**) in 80% yield. ^1H NMR experiments with chiral (+)-Eu(hfc)$_3$ shift reagent showed no signals of (-)-norribasine, whereas a racemic sample obtained previously,[5] showed signals for both enantiomers. Finally, methylation of the (+)-norribasine by treatment with formaldehyde in refluxing methanol and subsequent reduction with $NaBH_4$ at room temperature afforded a product whose NMR spectra, melting point and optical rotation were identical to those of an authentic sample of natural ribasine.



a) NBS, CCl_4, hv, reflux, 2h, 77%; b) i:*n*-BuTeLi, THF, 0°C, 30 min; ii: Addition of (+)-**5**, -105°C; iii: *n*-BuLi, -105°C, 15 min; c) DIBAL-H, THF, -78°C, 2h, 95%; d) TFA, CH_2Cl_2, 0°C, 5h, 80% ; e) i: CH_2O, MeOH, reflux, ii: $NaBH_4$, MeOH, rt, 77%

Scheme 4

In summary, we have carried out the first enantioselective synthesis of (+)-ribasine by a short route in which the key step is the stereocontrolled addition of appropriately substituted α–lithiated *o*-toluate **6d** to homochiral *N*-Pf-2-aminoindan-1-one *(R)*-**5**, prepared by Dellaria's method from oxazinone (+)-**12**.

EXPERIMENTAL SECTION

General. All nonaqueous reactions were conducted under an inert atmosphere of argon, using flame-dried glassware. Unless specified otherwise, solvents and reagents were commercially available products and were used as received. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium metal/benzophenone ketyl. Dichloromethane, diisopropylethylamine, triethylamine and tetramethylsilyl chloride were distilled from calcium hydride. L-(+)-α–Phenylglycinol, lithium bis(trimethylsilyl)amide (1.0 M solution in hexanes) and phenyl bromoacetate were purchased from Aldrich Chemical Co.

Methyl (*S*)-2-amino-3-[3,4-bis(*tert*-butyldimethylsilyloxy)phenyl]propanoate [(+)-7]. Imidazole (4.12 g, 60.6 mmol) was added to a cold solution of the hydrochloride of the methyl ester of L-Dopa[7] (1g, 4.04 mmol) and TBDMSCl (2.13 g, 14.14 mmol) in anhydrous DMF (10 mL). After stirring for 3.5 h and addition of sat. $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2, and the organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue obtained was purified by flash chromatography (1:4 EtOAc/hexane) to afford 1.31 g (74%) of aminoester **7** and 113 mg (6%) of formamide **8** as white foam compounds.

[(+)-7]. IR (film on NaCl) ν 1740 (COO) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) 0.18 (s, 12H), 0.96 (s, 9H), 0.97 (s, 9H), 2.74 (dd, J=7.6, 13.6 Hz, 1H), 2.94 (dd, J=5.4, 13.6 Hz, 1H), 3.67 (dd, J=5.4, 7.6 Hz, 1H), 3.68 (s, 3H, Me), 6.60 (dd, J=2.0, 8.1 Hz, 1H), 6.65 (d, J=2.0 Hz, 1H), 6.74 (d, J=8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.83 MHz) δ -4.12 (CH_3), 18.39 (C), 25.89 (CH_3), 40.36 (CH_2), 51.84 (CH_3), 55.82 (CH), 120.96 (CH), 122.11 (CH), 122.16 (CH), 130.06 (C), 145.75 (C), 146.69 (C), 175.38 (COO). MS m/z (relative intensity) 439 (M^+, 2), 352 (22), 351 (70), 208 (7), 179 (19), 73 (100). $[\alpha]^{25}_D$ =+5 (c =1.0, CH_2Cl_2). HRMS Calcd for $C_{22}H_{41}NO_4Si_2$: 439.25741, found: 439.25636.

Methyl (*S*)-3-[3,4-bis(*tert*-butyldimethylsilyloxy)phenyl]-2-formylaminopropanoate [(+)-8]. IR (film on NaCl) ν 3296 (NH), 1745 (COO), 1675 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.11 (s, 12H), 0.90 (s, 9H), 0.91 (s, 9H), 2.93 (d, J = 5.8 Hz, 2H), 3.63 (s, 3H, Me), 4.80 (dd, J = 5.8, 7.9 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H, NH), 6.48 (dd, J = 2.1, 8.1 Hz, 1H), 6.53 (d, J = 2.1 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 8.07 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.83 MHz) δ -4.22 (CH_3), 18.25 (C), 18.27 (C), 25.78 (CH_3), 25.86 (CH_3), 36.91 (CH_2), 51.78 (CH_3), 51.86 (CH), 120.88 (CH), 122.01 (CH), 122.08 (CH), 128.41 (C), 145.97 (C), 146.65 (C), 160.41 (COH), 171.53 (COO). MS m/z (relative intensity) 467 (M^+, 1), 410 (33), 351 (13), 218 (10), 179 (28), 73 (100). $[\alpha]^{25}_D$ =+26 (c =1.50, CH_2Cl_2). HRMS Calcd for $C_{23}H_{41}NO_5Si_2$: 467.25233, found: 467.25186.

Methyl (*S*)-2-[*N*-(9-phenylfluoren-9-yl)amino]-3-[3,4-bis(*tert*-butyldimethylsilyloxy)phenyl] propanoate. To a stirred solution of aminoester **7** (2g, 4.55 mmol) in CH_2Cl_2 (9 mL) in a Morton flask was added triethylamine (0.95 mL, 6.82 mmol), followed by lead nitrate (1.31g, 4.09 mmol) and 9-bromo-9-phenylfluorene (1.6 g, 5.00 mmol) in CH_2Cl_2 (9 mL). The resulting mixture was vigorously stirred at room temperature for 72 h, after which the solution was filtered and the filtrate was concentrated. The oily residue was purified by flash chromatography (1:5 EtOAc/hexane) to afford 2.54 g (82%) of a colorless oil. IR (film on NaCl) ν 1736 (COO). ^1H NMR ($CDCl_3$, 250 MHz) 0.20 (s, 3H), 0.21 (s, 3H), 0.25 (s, 3H), 0.26 (s, 3H),

1.03 (s, 9H), 1.04 (s, 9H), 2.65-2.68 (m, 1H), 2.68 (s, 1H, NH), 2.81-2.87 (m, 2H), 3.19 (s, 3H, Me), 6.51 (dd, J = 2.0, 8.0 Hz, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.18-7.43 (m, 9 H), 7.69 (t, J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 62.83 MHz) δ -4.13 (CH_3), -4.04 (CH_3), 18.39 (C), 18.46 (C), 25.95 (CH_3), 40.65 (CH_2), 51.20 (CH_3), 57.54 (CH), 72.91 (C), 119.69 (CH), 119.75 (CH), 120.61 (CH), 122.41 (CH), 122.58 (CH), 125.07 (CH), 126.12 (CH), 126.20 (CH), 127.08 (CH), 127.19 (CH), 127.72 (CH), 128.10 (CH), 128.14 (CH), 128.19 (CH), 130.49 (C), 140.04 (C), 140.93 (C), 144.58 (C), 145.47 (C), 146.32 (C), 148.51 (C), 148.68 (C), 176.10 (COO). MS m/z (relative intensity) 679 (M^+, 1), 242 (20), 241 (100), 73 (29). $[\alpha]^{25}_D$ =-38.9 (c =1.44, CH_2Cl_2). HRMS Calcd for $C_{41}H_{53}NO_4Si_2$: 679.35132, found: 679.34837.

Methyl (*S*)-3-[3,4-(methylenedioxy)phenyl]-2-[*N*-(9-phenylfluoren-9-yl)amino]propanoate [(-)-9]. CH_2Cl_2 (235 μL, 3.67 mmol) was added to a stirred solution of the above aminoester (1g, 1.47 mmol) and cesium fluoride (2.23 g, 14.7 mmol) in anhydrous DMF (5 mL), and the mixture was heated at 110°C for one hour. The cooled reaction mixture was then diluted with ethyl ether, washed with H_2O, dried (Na_2SO_4), filtered and concentrated in vacuo to an oil. Flash chromatography (1:5 EtOAc/hexane) afforded 580 mg (85%) of a white amorphous solid. IR(film on NaCl) ν 1734 (COO). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.52-2.55 (m, 2H), 2.65-2.69 (m, 1H), 2.79 (s, 1H, NH), 3.11 (s, 3H, Me), 5.76 (d, J = 1.5Hz, 1H, OCH_2O), 5.77 (d, J = 1.5Hz, 1H, OCH_2O), 6.40 (s, 1H), 6.42 (d, J = 7.7 Hz, 1H), 6.72 (d, J =7.7 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 7.06-7.30 (m, 9 H), 7.54 (t, J = 8.1 Hz, 2H).^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 40.91 (CH_2), 51.25 (CH_3), 57.50 (CH), 72.79 (C), 100.63 (OCH_2O), 107.75 (CH), 109.88 (CH), 119.60 (CH), 119.73 (CH), 122.56 (CH), 124.95 (CH), 126.01 (CH), 126.08 (CH), 127.05 (CH), 127.13 (CH), 127.51 (CH), 127.98 (CH), 128.05 (CH), 128.12 (CH), 131.13 (CH), 139.87 (C), 140.86 (C), 144.39 (C), 146.06 (C), 147.24 (C), 148.38 (C), 148.62 (C), 175.91 (COO). MS m/z (relative intensity) 463 (M^+, 1), 329 (1), 328 (5), 242 (20), 241 (100), 239 (15), 226 (3), 135 (7), 77 (4). $[\alpha]^{25}_D$ = -55.4 (c =1.86, CH_2Cl_2).
HRMS Calcd for $C_{30}H_{25}NO_4$: 463.17836, found: 463.17727.

Methyl (*S*)-2-[*N*-(9-phenylfluoren-9-yl)amino]-3-[2-bromo-4,5-(methylenedioxy)phenyl] propanoate [(-)-10]. BTMA·Br_3 (1.68g, 4.32 mmol) was added to a solution of **9** (1g, 2.16 mmol) in dichloromethane (15 mL) and methanol (5 mL). After stirring at room temperature for 2 h addition of water and removal of the organic solvent, the mixture was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4 and condensed under reduced pressure to give 1.09 g (93%) of a white solid after recrystallization from EtOAc/hexane; Mp: 104-105 °C. IR(film on NaCl) ν 1740 (COO). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.70-2.84 (m, 3H), 3.21 (s, 3H, Me), 5.95 (d, J = 1.3 Hz, 1H, OCH_2O), 5.97 (d, J = 1.3 Hz, 1H, OCH_2O), 6.60 (s, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 6.98 (m, 1H), 7.39-7.14 (m, 9H), 7.69-7.60 (m, 2H).^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 41.22 (CH_2), 51.48 (CH_3), 55.88 (CH), 72.93 (C), 101.58 (OCH_2O), 111.57 (CH), 112.54 (CH), 115.52 (C), 119.75 (CH), 119.99 (CH), 125.06 (CH), 126.20 (CH), 127.26 (CH), 127.81 (CH), 128.16 (CH), 128.30 (CH), 130.32 (C), 139.98 (C), 141.28 (C), 144.43 (C), 147.04 (C), 147.16 (C), 148.56 (C), 148.78 (C), 176.23 (COO). $[\alpha]^{25}_D$ = -77.0 (c =0.68, CH_2Cl_2). HRMS Calcd for $C_{30}H_{24}NO_4Br$: 462.17053, found: 462.17061.

2-[*N*(9-Phenylfluoren-9-yl)amino]-3-[2-bromo-4,5-(methylenedioxy)phenyl]propanoic acid (11). A solution of the α–amino ester **10** (1g, 1.85 mmol) in 20 mL of 1:1 dioxan-water was treated with LiOH-H_2O (1.11g, 26.5 mmol) and the mixture was stirred for 20h at 60°C, cooled to rt and brought to pH 2 by addition of 5% HCl. This solution was extracted repeatedly with EtOAc, the combined organic layers were washed with water and brine and dried over Na_2SO_4, and the solvent was evaporated to leave a solid which was recrystallized from EtOAc/hexane to give 0.92g (95%) of racemic amino acid **11**. Mp: 216-219 °C. IR (film on NaCl) ν 1710 (COO). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.78 (dd, J = 9.6, 4.6 Hz, 1H), 2.89 (m, 2H), 5.97 (d, J = 1.3 Hz, 1H, OCH_2O), 6.00 (d, J = 1.3 Hz, 1H, OCH_2O), 6.36 (s, 1H), 6.51 (d, J = 7.6 Hz, 1H), 6.93 (s, 1H), 6.94 (m, 1H), 7.19-7.38 (m, 9H), 7.65 (m, 2H).^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 40.67 (CH_2), 55.63 (CH), 72.49 (C), 101.68 (OCH_2O), 111.84 (CH), 111.91 (CH), 114.59 (C), 119.82 (CH), 119.94 (CH), 124.56 (CH), 125.66 (CH), 125.75 (CH), 126.90 (CH), 127.40 (CH), 127.88 (CH), 128.11 (CH), 128.17 (CH), 130.42 (C), 139.40 (C), 140.33 (C), 144.95 (C), 146.61 (C), 146.81 (C), 148.48 (C), 148.79 (C), 175.87 (CO). HRMS ([M-Br]$^+$) Calcd for $C_{29}H_{22}NO_4$: 448.15488, found: 448.15487.

(*3R,5R*)-2,3,5,6-Tetrahydro-5-phenyl-3-[[3,4-(methylenedioxy)phenyl]methyl]-*N*-(*tert*-butyloxycarbonyl)-4*H*-1,4-oxazin-2-one [(-)-14]. The oxazinone (+)-**12**[12] (1g, 3.61 mmol) was placed in a flame-dried, argon-filled 50 mL flask, dissolved in anhydrous THF/DME (3.5/3.5 mL) and cooled to -78°C. Sodium bis(trimethylsilyl)amide (3.54 mL of a 1M solution in THF, 3.54 mmol) was added and the reaction mixture was stirred for 30 min at -78°C. Then, a solution of benzyl bromide **13**[13] (0.85 g, 3.97 mmol) in DME (3.5 mL) was added, and after stirring for 2 h at -78°C the reaction was quenched with saturated aqueous solution of ammonium chloride. The resulting two-phase solution was diluted with ethyl ether, washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to an oil which was purified by flash chromatography (1:2, EtOAc/hexane) to afford 1.21 g (82%) of white crystalline **14**. Mp: 143-145 °C. IR(film on NaCl) ν 1751 (COO), 1696 (CO).^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (bs, 6H, 2Me), 1.26 (bs, 3H, Me), 3.20 (dd, J = 3.5, 13.8 Hz, 1H), 3.50-3.63 (m, 2H), 3.99-4.16 (m, 1H), 4.8-5.12 (m, 2H), 5.96 (d, J = 1.2 Hz, 1H, OCH_2O), 5.98 (d, J = 1.2 Hz, 1H, OCH_2O), 6.65-6.94 (m, 2H), 6.79 (d, J = 7.9 Hz, 1H), 7.01-7.04 (m, 2H), 7.23-7.34 (m, 3H).^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 28.16 (CH_3), 39.06 (CH_2), 54.41 (CH), 58.94 (CH), 69.45 (CH_2), 81.47 (C), 101.08 (OCH_2O), 108.65 (CH), 110.28 (CH), 123.04 (CH), 125.52 (CH), 127.72 (CH), 128.86 (CH), 129.85 (C), 140.06 (C), 147.19 (C), 148.06 (C), 153.68 (CO), 169.00 (COO). MS m/z (relative intensity) 411 (M^+, 5), 355 (3), 176 (13), 149 (8), 136 (16), 135 (100), 77 (9).
$[\alpha]^{25}_D$ = -82.3 (c =0.26, CH_2Cl_2). HRMS Calcd for $C_{23}H_{25}NO_6$: 411.16819, found: 411.16797.

(*R*)-2-Amino-3-[3,4-(methylenedioxy)phenyl]propanoic acid [(-)-15]. A solution of the oxazinone **14** (1g, 2.43 mmol) in MeOH (30 mL) and 3M HCl (5 mL) was refluxed for 20 h and then concentrated in vacuo. The unpurified material was dissolved in MeOH/H_2O/TFA (25/2/0.5 mL), $Pd(OH)_2$ (0.68g, 4.86 mmol) was added and the mixture was stirred at room temperature under hydrogen (1 atm.) for 20 h. After filtration through a Celite pad the filtrate was concentrated in vacuo. The neutral organic materials were easily removed from the hydrogenolysis product by washing the crude reaction mixture with acetone, leaving 500 mg (98%) of the amino acid **15** as a white solid. Mp: 243-245 °C. ^{1}H NMR (DMSO, 250 MHz) δ 3.00-3,14

(m, 2H), 4.07 (t, J =6.1 Hz, 1H), 5.97 (s, 2H, OCH_2O), 6.72 (dd, J =1.5, 7.9 Hz, 1H), 6.82-7.75 (m, 2H), 8.44 (bs).^{13}C NMR (DMSO, 62.83 MHz) δ 35.22 (CH_2), 53.30 (CH), 100.93 (OCH_2O), 108.33 (CH), 109.84 (CH), 122.85 (CH), 128.44 (C), 146.43 (C), 147.29 (C), 170.23 (CO). MS m/z (relative intensity) 209 (M^+, 6), 164 (3), 163 (1), 136 (14), 135 (100), 81 (6), 79 (6), 77 (16). $[\alpha]^{25}_D$ =-92.0 (c =0.12, MeOH). HRMS Calcd for $C_{10}H_{11}NO_4$: 209.06881, found: 209.06931.

(*R*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]-3-[3,4-(methylenedioxy)phenyl]propanoic acid. A stirred suspension of amino acid **15** (500 mg, 2.4 mmol) and $(CH_3)_3SiCl$ (320 μL, 2.51 mmol) in anhydrous CH_2Cl_2 (4.75 mL) under an argon atmosphere was heated under reflux for 2 h, cooled to rt and treated with Et_3N (835 μL, 6 mmol). After stirring for 15 min at rt, $Pb(NO_3)_2$ (664 mg, 2.16 mmol) was added, followed by a solution of BrPf (1g, 3.12 mmol) in anhydrous CH_2Cl_2 (4.75 mL). The resulting mixture was vigorously stirred for 2 days at rt, and then excess MeOH (5 mL) was added. After stirring for 1 h, filtration and subsequent concentration gave a residue which was chromatographed on silica gel (1:2, EtOAc/hexane) to give 875 mg (82%) of a white solid. Mp: 129-131°C. IR(film on NaCl) ν 1708 (CO). ^1H NMR ($CDCl_3$, 250 MHz) δ 2.65 (dd, J =7.8, 16.2 Hz, 1H), 2.75-2.82 (m, 2H), 5.99 (d, J =1.4 Hz, 1H, OCH_2O), 6.02 (d, J =1.4 Hz, 1H, OCH_2O), 6.48 (d, J =1.6 Hz, 1H), 6.56 (dd, J =1.6, 7.9 Hz, 1H), 6.76-6.83 (m, 2H), 7.14-7.43 (m, 10H), 7.75 (m, 2H).^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 38.90 (CH_2), 57.04 (CH), 72.63 (C), 101.01 (OCH_2O), 108.27 (CH), 109.65 (CH), 119.96 (CH), 120.21 (CH), 122.56 (CH), 124.43 (CH), 125.81 (CH), 125.86 (CH), 127.55 (CH), 127.89 (CH), 128.01 (CH), 128.53 (CH), 128.61 (CH), 129.04 (CH), 129.56 (CH), 140.43 (C), 140.66 (C), 143.12 (C), 146.65 (C), 146.86 (C), 148.04 (C), 148.05 (C), 176.07 (CO). MS m/z (relative intensity) 449 (M^+, 1), 314 (3), 293 (1), 242 (21), 241 (100), 240 (8), 239 (19), 149 (4), 135 (14), 77 (5). $[\alpha]^{25}_D$ = -93.0 (c =0.31, CH_2Cl_2). HRMS Calcd for $C_{29}H_{23}NO_4$: 449.16271, found: 449.16185.

(*R*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]-3-[2-bromo-4,5-(methylenedioxy)phenyl] propanoic acid [(-)-11]. To a solution of the above *N*-Pf amino acid (500 mg, 1.11 mmol) in CH_2Cl_2 -MeOH (10-4 mL)was added BTMA·Br_3 (866 mg, 2.22 mmol). The mixture was stirred at room temperature for 1 h. Water was added and the organic solvent destilled off. The mixture was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give 540 mg (92 %) of a white solid after recrystallization from EtOAc/hexane with spectroscopic data identical to those of racemic **11**.
Mp: 89-90 °C. $[\alpha]^{25}_D$ = -70.1 (c =0.1, CH_2Cl_2).

(*R*)-3-(9-Phenylfluoren-9-yl)-4-[(2-bromo-4,5-methylenedioxy)phenyl]methyl]oxazolidin -5-one [(+)-16]. Amino acid **11** (500 mg, 0.95 mmol), formaldehyde (37 % solution in water, 1.3 mL, 14.2 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) were dissolved in 10 mL of THF and stirred for 16 h at rt. The organic solvent was evaporated in vacuo, the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried, and the solvent was evaporated to leave 490 mg (95%) of a white solid. Mp: 120-122 °C. ^1H NMR ($CDCl_3$, 250 MHz) δ 2.78 (dd, J = 10.2, 19.2 Hz, 1H), 2.96-3.07 (m, 2H), 5.45 (d, J = 8.0 Hz, 1H), 5.49 (d, J = 8.0 Hz, 1H), 5.98 (d, J = 1.3 Hz, 1H, OCH_2O), 6.00 (d, J = 1.3 Hz, 1H, OCH_2O), 6.37 (s, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.83 (m, 1H),6.99 (s, 1H), 7.16-

7.49 (m, 9H), 7.56 (d, J = 7.5 Hz, 1H), 7.69 (m, 1H).^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 35.28 (CH_2), 59.45 (CH), 77.23 (C), 77.34, 83.94 (CH_2), 101.68 (OCH_2O), 110.80 (CH), 112.55 (CH), 115.60(C), 119.58 (CH), 120.28 (CH), 125.19 (CH), 126.15 (CH), 126.89 (CH), 127.65 (CH), 127.77 (CH), 128.22 (CH), 128.79 (CH), 129.29 (CH), 129.54 (CH), 139.07 (C), 141.57 (C), 142.33 (C), 144.21 (C), 146.80 (C), 147.44 (C), 147.54 (C), 175.98 (CO). $[\alpha]^{25}_D$ =+87.7 (c =0.35, CH_2Cl_2).

HRMS (FAB) Calcd for $C_{30}H_{22}NO_4Br$ ($[M+H]^+$): 540.08104, found: 540.07883.

(*R*)-*N*-(9-Phenylfluoren-9-yl)-2-amino-5,6-(methylenedioxy)indan-1-one [(+)-5]. In a flamed, dried 50 mL round-bottomed flask equipped with a stirring bar, septum cap and Ar inlet, the oxazolidinone (+)-**16** (500 mg, 0.925 mmol) was dissolved in 10 mL of anhydrous THF, cooled to -105°C and treated dropwise with *n*-BuLi (1.6 M in hexane, 1.017 mL). The yellowish solution so obtained was stirred for 30 min and the reaction was then quenched by addition of a few drops of AcOH. The mixture was allowed to warm to rt, the organic solvent was evaporated, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ and brine, and concentration followed by recrystallization from DME gave 320 mg (80%) of a white solid. Mp: 210-212°C . ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.16 (dd, J = 7.2, 16.6 Hz, 1H), 2.46 (dd, J = 4.4, 16.6 Hz, 1H), 3.02 (dd, J =4.4, 7.2 Hz, 1H), 3.4 (bs, 1H), 5.97 (d, J =1.1 Hz, 1H, OCH_2O), 5.98 (d, J =1.1 Hz, 1H, OCH_2O), 6.53 (s, 1H), 6.99 (s, 1H), 7.19-7.46 (m, 11H), 7.37-7.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 37.48 (CH_2), 60.45 (CH), 73.23 (C), 102.02 (OCH_2O), 102.39 (CH), 105.60 (CH), 119.65 (CH), 119.94 (CH), 124.93 (CH), 126.11 (CH), 126.22 (CH), 127.22 (CH), 127.69 (CH), 128.30 (CH), 128.37 (CH), 128.39 (CH), 128.49 (CH), 128.96 (C), 139.60 (C), 141.58 (C), 144.49 (C), 148.06 (C), 149.19 (C), 149.92 (C), 150.05 (C), 154.39 (C), 203.75 (CO). MS m/z (relative intensity) 431 (M^+, 5), 354 (5), 285 (6), 256 (11), 242 (23), 241 (100), 240 (10), 239 (27), 172 (12). $[\alpha]^{25}_D$ = +140.5 (c =0.20, $CHCl_3$). HRMS Calcd for $C_{29}H_{21}NO_3$: 431.15214, found: 431.15282.

Ethyl 6-bromomethyl-2,3-(methylenedioxy)benzoate (6b). A solution of ethyl 6-methyl-2,3-(methylenedioxy)benzoate (**6a**)[14] (287 mg, 1 mmol) and N-bromosuccinimide (187 mg, 1.05 mmol) in CCl_4 (10 mL) was heated under reflux and irradiated with a 100 W lamp for 2 h. The resulting suspension was filtered and the filtrate was concentrated under vacuum. Flash chromatography of the residue (1:5, EtOAc/hexane) afforded 220 mg (77%) of white crystals. Mp: 51-53°C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.42 (t, J = 7.1 Hz, 3H, CH_3), 4.43 (c, J = 7.1 Hz, 2H), 4.81 (s, 2H), 6.06 (s, 2H, OCH_2O), 6.81 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H).^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 14.07 (CH_3), 32.11 (CH_2), 61.44 (CH_2), 102.15 (OCH_2O), 110.35 (CH), 113.46 (C), 124.66 (CH), 131.08 (C), 148.69 (C), 164.45 (COOEt). MS m/z (relative intensity) 288 (M+1, 5), 287 (M^+, 3), 286 (M-1, 5), 243 (7), 241 (8), 207 (61), 179 (100), 149 (74). Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.01; H, 3.86, found: C, 46.33; H, 3.98.

Dihydroisocoumarins (-)-17a and (-)-17b. *n*-BuLi (1.05 M in hexane, 620 μL, 0.65 mmol) was added dropwise to a suspension of metallic tellurium (83 mg, 0.65 mmol) in THF (5 mL) at 20°C. After stirring for 20 min, the dark purple solution was cooled to 0°C and a solution of α–bromo-*o*-toluate **6b** (187 mg, 0.65 mmol) in THF (5 mL) was added. The mixture was stirred for 30 min, the orange solution formed was cooled to -105°C, and a solution of aminoindanone (+)-**5** (200 mg, 0.464 mmol) in THF (20 mL) was added,

followed dropwise by *n*-BuLi (1.05 M in hexane, 620 μL, 0.65 mmol) at the same temperature. After stirring for 15 min, the reaction was quenched by addition of a few drops of MeOH, the solvent was evaporated in vacuo and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography afforded 245 mg (90%) of dihydroisocoumarin **17a** and 16 mg of dihydroisocoumarin **17b** (6%) as white solids.

17a. Mp 123-125°C. IR (film on NaCl) ν 1711 (COO).^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.89 (d, J = 9.3 Hz, 1H, NH), 2.03 (dd, J = 7.6, 15.4 Hz, 1H), 2.18 (dd, J = 6.9, 15.4 Hz, 1H), 3.18 (d, J = 16.5 Hz, 1H), 3.24 (m, 1H), 3.49 (d, J = 16.5 Hz, 1H), 5.82 (s, 2H, OCH_2O), 6.20 (d, J = 1 Hz, 1H, OCH_2O), 6.23 (d, J = 1 Hz, 1H, OCH_2O), 6.35 (s, 1H), 6.49 (s, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.97-7.33 (m, 11 H), 7.42 (t, J = 7.3 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.83 Mhz) δ 32.72 (CH_2), 37.79 (CH_2), 64.35 (CH), 72.79 (C), 92.37 (C), 101.07 (OCH_2O), 102.88 (OCH_2O), 103.96 (CH), 105.24 (CH), 109.34 (C), 112.75 (CH), 119.67 (CH), 120.02 (CH), 120.26 (CH), 124.76 (CH), 125.50, 125.94 (CH), 127.22 (CH), 127.67 (CH), 128.13 (CH), 128.46 (CH), 128.61 (CH), 131.18 (C), 133.10 (C), 135.16 (C), 139.69 (C), 141.03 (C), 145.11 (C), 146.80 (C), 148.22 (C), 148.50 (C), 149.39 (C), 151.02 (C), 162.00 (COO). MS m/z (relative intensity) 593 (M^+, 3), 352 (92), 334 (41), 241 (100). $[\alpha]^{25}_D$ = -90.0 (c =0.18, CH_2Cl_2). Anal. Calcd for $C_{38}H_{27}NO_6$: C, 76.88; H, 4.58; N, 2.35, found C, 77.16; H, 4.81; N, 2.42.

17b. Mp 143-145°C . IR (film on NaCl) ν 1718 (COO).^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.74 (m, 1H), 2.43 (m, 1H), 2.79 (m, 2H), 2.87 (d, J = 16.2 Hz, 1H), 3.76 (d, J = 16.2 Hz, 1H), 5.78 (s, 2H, OCH_2O), 6.12 (s, 1H), 6.19 (d, J = 1 Hz, 1H, OCH_2O), 6.21 (d, J = 1 Hz, 1H, OCH_2O), 6.36 (s, 1H), 6.76 (d, J = 7.8 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 7.12-7.48 (m, 11 H), 7.65 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.83 MHz) δ 33.59 (CH_2), 38.55 (CH_2), 62.08 (CH), 72.30 (C), 81.62 (C), 100.99 (OCH_2O), 102.87 (OCH_2O), 103.95 (CH), 105.53 (CH), 109.10 (C), 112.80 (CH), 119.67 (CH), 120.03 (CH), 125.27 (CH), 126.11 (CH), 127.16 (CH), 127.87 (CH), 128.08 (CH), 128.19 (CH), 128.29 (CH), 128.49 (CH), 131.32, (C) 133.35 (C), 136.84 (C), 140.08 (C), 140.48 (C), 144.61 (C), 146.16 (C), 148.14 (C), 148.77 (C), 149.00 (C), 149.35 (C), 151.95 (C), 162.44 (COO). MS m/z (relative intensity) 593 (M^+, 2), 352 (97), 334 (36), 241 (100). $[\alpha]^{25}_D$ = -109.5 (c =0.20, CH_2Cl_2). Anal. Calcd for $C_{38}H_{27}NO_6$: C, 76.88; H, 4.58; N, 2.35, found C, 76.65; H, 4.97; N, 2.30.

Lactol (-)-18. A solution of dihydroisocoumarin **17a** (200 mg, 0.34 mmol) in THF (15 mL) was cooled to -78°C and DIBAL-H (1 M in hexane, 2.04 mL, 2.04 mmol) was added. The reaction mixture was stirred for 2 h at the same temperature and then allowed to warm to rt. The organic solvent was evaporated and the residue dissolved in CH_2Cl_2-H_2O. The organic layer was separated, dried and concentrated in vacuo to afford 190 mg (95%) of **18**, as an 8:1 mixture of anomers. Mp: 157-159°C . ^{1}H NMR δ 1.75-1.79 (m, 2H), 2.86 (d, J = 16.8 Hz, 1H), 3.00 (d, J = 16.8 Hz, 1H), 3.51-3.58 (m, 1H), 5.79 (s, 2H, OCH_2O), 6.08(d, J = 1 Hz, 1H, OCH_2O), 6.15 (d, J = 1 Hz, 1H, OCH_2O), 6.22-6.30 (m, 2H), 6.50 (d, J = 7.0 Hz, 1H), 6.67-7.73 (m, 16 H). ^{13}C NMR δ 32.67 (CH_2), 35.86 (CH_2), 65.74 (CH), 71.71 (C), 83.25 (C), 88.74 (CH), 100.77 (OCH_2O), 101.83 (OCH_2O), 103.20 (CH), 104.77 (CH), 108.62 (CH), 119.33 (C), 119.50 (CH), 120.08 (CH), 120.24 (CH), 123.70 (CH), 125.07 (CH), 125.27 (C), 126.14 (CH), 126.77 (CH), 127.85 (CH), 128.18 (CH), 128.49

(CH), 128.56 (CH), 128.78 (CH), 130.75 (C), 138.75 (C), 140.23 (C), 140.51 (C), 144.15 (C), 144.77 (C), 146.24 (C), 146.74 (C), 146.82 (C), 147.53(C), 152.29 (C). MS m/z (relative intensity) 595 (M^+, 1), 577 (3), 336 (19), 319 (15), 241 (100). $[\alpha]^{25}_D$ = -77.0 (*c* =0.32, CH_2Cl_2). HRMS Calcd for $C_{38}H_{29}NO_6$: 595.19949, found: 595.19672.

Norribasine [(+)-4]. TFA (337 μL, 3.46 mmol) was added to a cooled solution of **18** (100 mg, 0.173 mmol) in anhydrous CH_2Cl_2 (3.3 mL), the mixture was stirred at 0°C for 5 h, treated with saturated $NaHCO_3$ solution (3 mL) and extracted with CH_2Cl_2 (3x5 mL). The pooled organic fraction was extracted with 5% HCl (3x5 mL), and the resulting combined aqueous fraction was basified with 10% NaOH (10 mL) and extracted with CH_2Cl_2. After drying and concentration, 46 mg (83%) of norribasine was obtained as white crystals. Mp: 190-191°C. ^{1}H NMR δ 2.61-2.72 (m, 1H), 2.73 (d, *J* = 16.1 Hz, 1H), 3.38 (dd, *J* = 8.9, 17.2 Hz, 1H), 3.60 (d, *J* = 16.1 Hz, 1H), 3.88-3.93 (m, 1H), 5.95-6.01 (m, 5H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.65 (s, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H). ^{13}C NMR δ 36.73 (CH_2), 38.45 (CH_2), 65.85 (CH), 86.56 (CH), 91.18(C), 101.38 (OCH_2O), 101.43 (OCH_2O), 104.48 (CH), 105.41 (CH), 107.95 (CH), 119.23 (C), 121.41 (CH), 126.05 (C), 132.88 (C), 136.20 (C), 142.79 (C), 145.78 (C), 147.50 (C), 149.65 (C). $[\alpha]^{25}_D$ = +58 (*c* =0.60, CH_2Cl_2).

Ribasine [(+)-1]. A solution of norribasine (25 mg, 0.074 mmol) and formaldehyde (37 % solution in water, 0.3 mL) in MeOH (10 mL) was heated under reflux for 1 h and then allowed to cool to rt. This crude reaction mixture was treated with $NaBH_4$ (300 mg) and stirred at rt for 5 h. Then 5% HCl (5 mL) was added, followed by $NaHCO_3$ (5 mL). After extraction with CH_2Cl_2, the organic layer was dried, filtered and concentrated in vacuo to afford 20 mg (77 %) of ribasine. Mp : 195-196 °C [Lit.[1] Mp: 194-195 °C] . ^{1}H NMR δ 2.34 (s, 3H), 2.69 (d, *J* = 16.2, 1H), 2.88-3.18 (m, 3H), 3.57 (d, *J* = 16.2 Hz, 1H), 5.67 (s, 1H), 5.90-5.97 (m, 4H), 6.64 (d, *J* = 7.9 Hz, 1H), 6.66 (s, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.87 (s, 1H). ^{13}C NMR δ 35.16 (CH_3), 37.10 (CH_2), 37.26 (CH_2), 69.74 (CH), 89.55 (CH), 93.67 (C), 101.12 (OCH_2O), 101.32 (OCH_2O), 103.80 (CH), 105.67 (CH), 107.88 (CH), 115.61 (C), 121.64 (CH), 126.68 (C), 133.20 (C), 137.42 (C), 144.30 (C), 145.19 (C), 147.22 (C), 149.56 (C). MS m/z (relative intensity) 352 (M+1, 15), 351 (M+, 73), 350 (100), 336 (3), 322 (13), 320 (3), 292 (11), 188 (89), 149 (68). $[\alpha]^{25}_D$ =+121 (*c* =0.13, $CHCl_3$) [Lit.[1] $[\alpha]^{25}_D$ =+126 (*c* =0.13, $CHCl_3$)].

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