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Enantioselective Synthesis of (*R*)-(-)-Laudanosine and (*R*)-(-)-Glaucine from *L*-Ascorbic Acid

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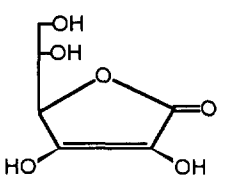
Abstract: *L*-Ascorbic acid **1** was converted into *L*-gulonolactone **2** by catalytic hydrogenation. Treatment of **2** with 3,4-dimethoxyphenylethyl amine **3** afforded amide **4**, which in several steps was transformed into the title alkaloids in good enantiomeric excesses. Also, chromium(III) oxide is proposed as an effective catalyst for the conversion of (*R*)-(-)-laudanosine into (*R*)-(-)-glaucine.

INTRODUCTION

L-(+)-Ascorbic acid (vitamin C) **1** is an enantiomerically pure and readily accessible starting material for the synthesis of chiral building blocks[1,2]. The number of stereogenic centers in this molecule may be easily increased by catalytic hydrogenation, which proceeds with the complete diastereoselectivity, affording *L*-(+)-gulono-1,4-lactone **2**, which has proved useful in the enantioselective synthesis of natural products[3].



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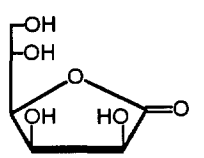


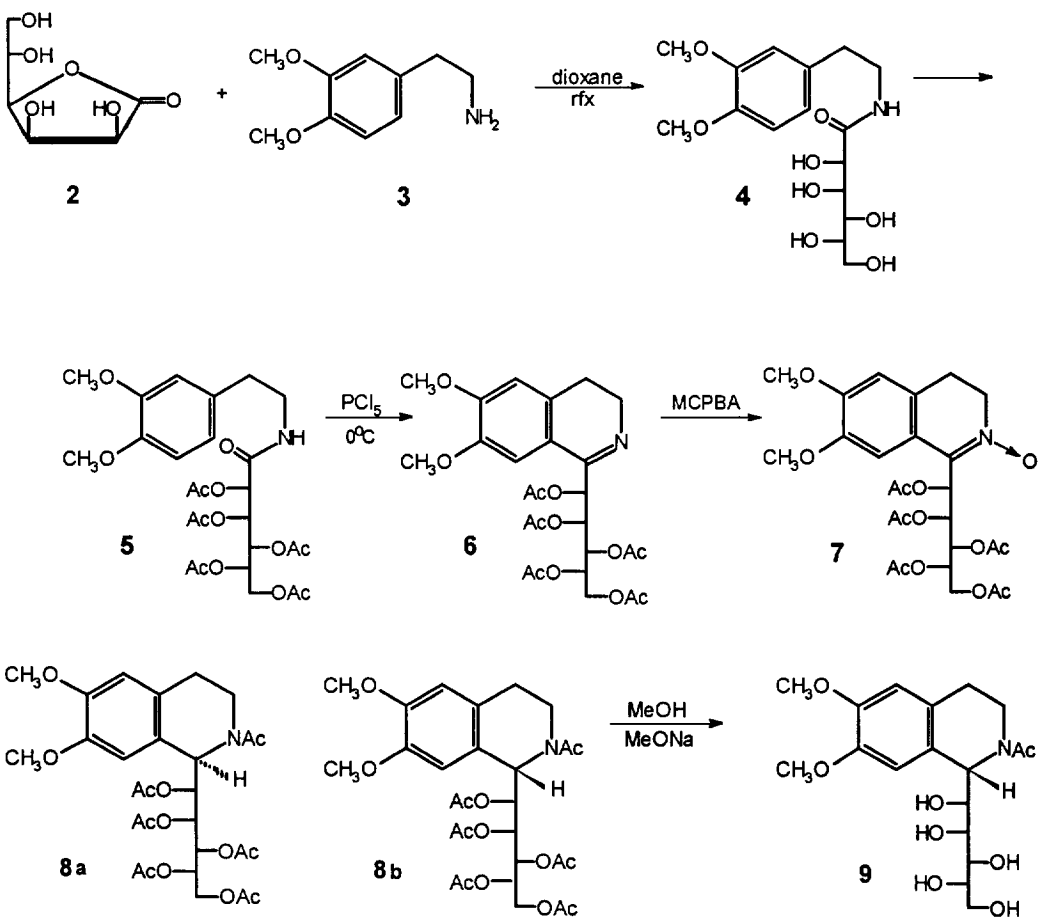
2

This homochiral compound has not yet been employed in the chemistry of isoquinoline alkaloids, which are ubiquitous in nature and the types of their biological activity are nearly as varied as the structures themselves. Having been interested in using carbohydrate substrates in this area, we have already demonstrated[4] the utility of this approach by the synthesis of (*R*)-(-)-calycotomine and (*S*)-(-)-xylopinine from commercially available *D*-ribono-1,4-lactone. During the past decade, however, the costs of *D*-ribono-1,4-lactone have increased dramatically, which prompted us to seek alternative chiral auxiliaries. On the other hand, it seemed advisable to elaborate the synthetic method allowing the preparation of other classes of isoquinoline alkaloids, preferably of opposite configuration than already obtained from a *D*-substrate. In this respect *L*-ascorbic acid **1** appeared to be a favourable chiral starting material.

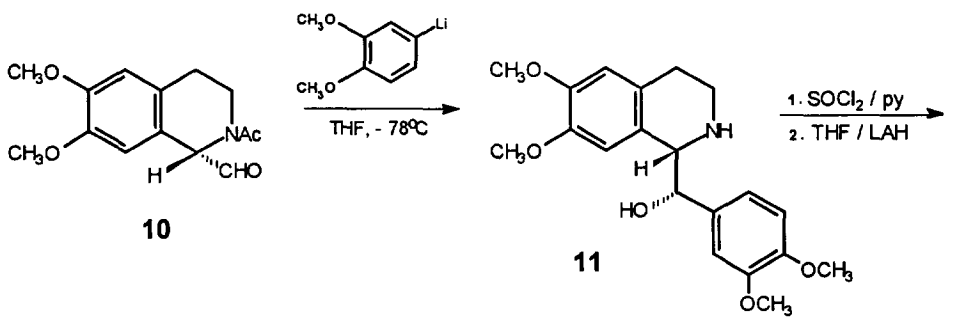
RESULTS AND DISCUSSION

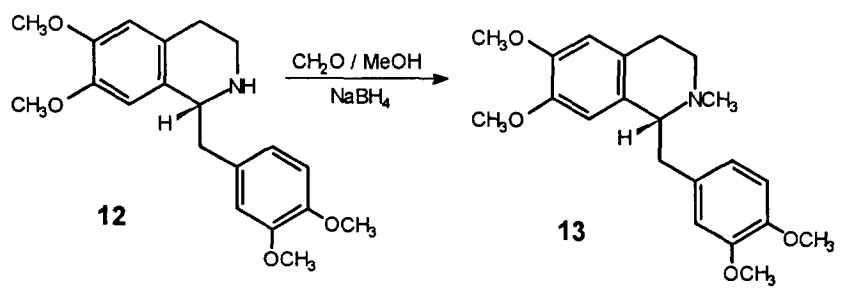
The catalytic hydrogenation appears to be the method of choice for the conversion of *L*-ascorbic acid **1** into *L*-(+)-gulono-1,4-lactone **2**. Surprisingly, not until 1981[5] was there a straitforward route for this

transformation. Having experienced some difficulties with reproducing the method described in the literature[5], we slightly modified the procedure changing the temperature, hydrogen pressure and the catalyst. The product **2** thus obtained appeared free from traces of the starting material and was used in further transformations. Reaction of **2** with 3,4-dimethoxyphenylethylamine **3** afforded amide **4** in nearly quantitative yield. Acetylation of hydroxy groups in **4** gave a peracetyl compound **5** which was subjected to a Bischler-Napieralski cyclisation to form a very unstable imine **6**. Disappointingly, imine **6** resisted all our attempts to hydrogenate the C=N bond. We found, however, that oxidation with m-chloroperbenzoic acid (MCPBA) proceeded smoothly giving nitrone **7** as a sole, stable product. Subsequent hydrogenation of **7** over Adams' catalyst followed by *in situ N*-acetylation proceeded less diastereoselectively as in the case of our earlier experiments with a series of *D*-ribonolactone derivatives[4]. Two diastereomers **8a** and **8b** were formed in the ratio 13:87 as indicated by ^{1}H NMR and HPLC analyses. The predominant epimer **8b** was isolated by column chromatography in 54% yield from **5**.



Sodium methoxide-catalyzed de-*O*-acetylation of **8b** afforded pentahydroxy compound **9**, which was then subjected to a metaperiodate treatment to give an aldehyde **10**, which was isolated in a crystalline form in 78% yield. The enantiomer of **10** has been already prepared in our laboratory from *D*-ribonolactone[4, 6]. Treatment of **10** with 5 molar amounts of 3,4-dimethoxyphenyllithium at -78°C brought about the formation of hydroxyamine **11**. The diastereoselectivity of this reaction is noteworthy; no trace of the *erythro* isomer was detected by HPLC analysis nor by ^{1}H NMR spectroscopy. The *N*-acetyl group was simultaneously removed during this process which simplified the further transformations. Thus, hydroxyamine **11** was subjected to our modified procedure for deoxygenation of benzylic alcohols[8]. We found that attempted isolation of nor-laudanosine **12** formed as a product, resulted in signifficant loss of the yield and purity of the sample, probably due to facile aerial oxidation and water solubility. For this reason we abandoned the isolation of **12** and directly converted the crude reaction mixture into (*R*)-(-)-laudanosine **13** by treatment with formaldehyde and subsequent borohydride reduction.

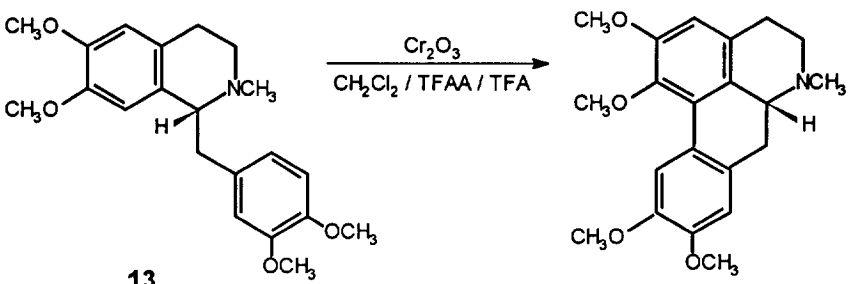




The chiral HPLC analysis (ChiraDex column) of the final (*R*)-(-)-laudanosine **13** showed that the enantiomeric purity of the sample was >94% ee. The specific rotation value of **13** was compared with the reported[9] value for natural laudanosine of known absolute configuration, thus proving the stereochemistry at C-1.

In order to extend the synthetic utility of our methodology to other classes of isoquinoline alkaloids we decided to convert **13** into an aporphine alkaloid, glaucine. This transformation can be achieved using different

protocols, among them the cyclizations in the presence of metals trifluoroacetates appears to be the most effective[10,11]. The method became even more convenient when the *in situ* preparation of trifluoroacetates from the corresponding metal oxides became available. We undertook a search for another metal oxides that can serve for the coupling reaction and we found that chromium(III) oxide and cobalt(II,III) oxide gave good results. In particular Cr_2O_3 seems to be of interest being easy to access and giving a high yield for the conversion of **13** into **14** with no observable racemisation.



13 **14**

In conclusion, the reported strategy provides an alternative approach to the enantioselective synthesis of benzylisoquinoline as well as aporphine alkaloids having (*R*) configuration, starting from easily accessible chiral synthon as **2**. Also, two new catalysts for the non-phenolic oxidative coupling of laudanosine **13** to give glaucine**14** were described.

EXPERIMENTAL

Infrared (IR) spectra were obtained using a Nicolet Magna IR 500 spectrophotometer. NMR spectra were recorded on a Varian Gemini spectrometer operating at 200 MHz for ^{1}H NMR and at 50.3 MHz for ^{13}C NMR, and on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. Tetramethylsilane (TMS) or solvents were used as an internal standards. Chemical shifts are reported in ppm. Mass spectra were collected on AMD 604 apparatus; high resolution mass spectra were accuired using LSIMS (positive ion mode). Optical rotation was measured on a Perkin-Elmer 247 MC polarimeter. TLC analyses were performed on Merck 60 silica gel glass plates and visualized using iodine vapor. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230-400 mesh, Merck). Elemental analyses were performed in a Microanalytical Laboratory of the Institute for Organic Chemistry, Polish Academy of Sciences, Warsaw. HPLC analyses were performed on a Knauer (model 64) apparatus with Eurochrom 2000 software using 4 mm x 250 mm silica (5μm) column . Chiral HPLC separations were done using a ChiraSep (DNBPG) column from Merck with hexane / 2-propanol 95:5 (v/v) or ChiraDex column (Merck) with methanol / water 4:1 (v/v) as eluents. For better separation the columns were cooled to 10°C. Melting points were determined on a Boetius hot-plate microscope and are uncorrected. All reactions were carried out under argon atmosphere using anhydrous solvents except the hydrogenation of ascorbic acid and hydrolysis.

Preparation of *L*-gulonolactone 2: Palladium chloride (5 g, 28.2 mmol) was dissolved in 22 mL of boiling 1N hydrochloric acid and the solution was added to a suspension of 30 g of activated carbon (Merck, analytical grade) at 100°C. After cooling, the catalyst was filtered, washed with several portions of distilled water and used to the hydrogenation step without further treatment. A 1000 mL autoclave was charged with the palladium catalyst prepared as above, 250 g (1.42 mole) of *L*-ascorbic acid (pharmaceutical grade) and 600 mL of doubly distilled water. The hydrogenation was carried out at 50°C during 72 h under constant hydrogen pressure (50 atmospheres). After cooling, the catalyst was filtered off and washed thoroughly with water. The combined filtrates were evaporated under reduced pressure until first crystals of the product appeared. The mixture was then quenched immediately with 300 mL of boiling 1-propanol and allowed to stand overnight in refrigerator. The crystalline product was filtered, washed with 50 mL of 1-propanol and dried under reduced pressure over P_2O_5 for 5 h at 40°C. The product (220 g, 85% yield) appears to be sufficiently pure for most of the synthetic applications. Mp 188°-190°C, $[\alpha]^{23}_D$ +54.8 (*c* 4.0, H_2O). Lit[5]. mp 182°-183.5°C, $[\alpha]^{23}_D$ +55.3 (H_2O). ^{13}C NMR (50.7MHz, D_2O, dioxane): 62.4, 70.4, 70.9, 71.6, 82.1, 178.7.

Preparation of amide 4: A mixture of 15 g (84.3 mmol) of *L*-gulonolactone **2** and 15.3 g (84.44 mmol) of 3,4-dimethoxyphenylethylamine **3** was refluxed in 50 mL of dioxane for 3 h under argon. The product precipitated upon cooling and addition of 30 mL of diethyl ether. Filtration afforded amide **4** as white solid in 91% yield. Mp 107°-108°C, $[\alpha]^{23}_D$ -10.9 (*c* 1.25, H_2O). IR (KBr, cm^{-1}): 3160-3535, 2950, 1640, 1525, 1445, 1265, 1245, 1150, 1045, 980. ^1H NMR (500MHz, DMSO-d_6): 7.86 (t, 1H, J=6.0Hz, disappeared with D_2O, NH); 6.85 (d, 1H, J=8.2Hz, H-8); 6.80 (d, 1H, J=2.0Hz, H-5); 6.72 (dd, 1H, J_1=2.0Hz, J_2=8.2Hz, H-9); 5.49 (d, 1H, J=6.4Hz, disappeared with D_2O, OH); 4.66 (d, 1H, J=4.7Hz, disappeared with D_2O, OH); 4.47 (d, 1H, J=4.8Hz, disappeared with D_2O, OH); 4.43 (t, 1H, J=5.6Hz, H-1'); 4.35 (d, 1H, J=5.97Hz, disappeared with D_2O, OH); 3.92 (t, 1H, J=6.3Hz, disappeared with D_2O, OH-5'); 3.71 and 3.74 (two s, 3H each, 2xOCH_3); 2.62-2.67 (m, 2H, 2H-5'); 3.54-3.58 (m, 1H, H-4'); 3.43-3.47 (m, 1H, H-3'); 3.35 (dd, 1H, J_1=5.6Hz, J_2=11.1Hz, H-2'); 3.27-3.31 (m, 2H, 2H-3); 2.66 (t, 2H, J=7.4Hz, 2H-4). ^{13}C NMR (125MHz, D_2O): 174.68; 148.73; 147.42; 132.85; 121.96; 113.13; 112.48; 73.36; 73.04; 72.82; 70.81; 63.28;2x56.35; 41.07; 34.89. **$C_{16}H_{25}NO_8$ (359.38)** Calcd. C, 53.47; H, 7.01; N, 3.90. Found: C, 53.24; H, 6.82; N, 3.77.

Acetylation of amide 4 to form a per-acetylamide 5: To a stirred solution of 27.3 g of amide **4** in 500 mL of pyridine at 0°C a freshly distilled acetic anhydride (144 mL, 1.53 mole) was added in one portion. The mixture was stirred for 2 h at 0°C and for 3 days at room temperature. The volatile solvents were evaporated *in vacuo* and the residue was dissolved in 200 mL of chloroform. The organic phase was washed with 4x50 mL portions of brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crystals that deposited upon addition of 150 mL of diethyl ether were collected by filtration and washed with cold ether-hexanes (2:1) mixture to afford compound **5** as white crystals (35.9 g, 83%); $[\alpha]^{23}_D$-20.8 (*c* 1.50, $CHCl_3$).

IR (KBr, cm^{-1}): 3395; 2950; 1740; 1680; 1520; 1375; 1230; 1040; 950. ^1H NMR (500MHz, $CDCl_3$): 6.81 (dd, 1H, J_1=1.8Hz, J_2=8.6Hz, H-8); 6.72-6.74 (m, 2H, H-5, H-9); 6.20 (t, 1H, J=5.8Hz, NH); 5.71 (dd, 1H, J_1=3.9Hz, J_2=6.7Hz, H-3'); 5.60 (ddd, 1H, J_1=3.9Hz, J_2=4.8Hz, J_3=6.5Hz, H-4'); 5.48 (dd, 1H, J_1=3.9Hz, J_2=6.7Hz, H-2'); 5.25 (d, 1H, J=3.9Hz, H-1'); 4.3 (dd, 1H, J_1=4.8Hz, J_2=11.7Hz, H-5'); 4.03 (dd,1H, J_1=6.5Hz, J_2=11.7Hz, H-5'); 3.88 and 3.86 (two s, 3H each, 2xOCH_3); 3.46-3.59 (m, 2H, 2H-3); 2.78 (td, 2H, J_1=2.2Hz, J_2=6.8Hz, 2H-4); 2.00; 2.02; 2.05; 2.06; 2.15 (five s, 3H each, 5xOAc). ^{13}C NMR (125MHz, $CDCl_3$): 2x170.34; 169.82; 169.58; 168.57; 165.67; 149.12; 147.79; 131.13; 120.70; 112.09; 111.49; 70.93; 70.75; 69.78; 69.17; 61.87; 55.88; 55.86; 40.44; 34.93; 20.74; 20.57; 3x20.48. **$C_{26}H_{35}NO_{13}$ (569.56)** Calcd. C, 54.81; H, 6.20; N, 2.46. Found: C, 54.67; H, 6.32; N, 2.20.

Bischler-Napieralski cyclisation of per-acetyl amide 5: A suspension of 3.7 g (17.8 mmol) of phosphorus pentachloride was boiled to reflux in 50 mL of methylene chloride for 15 min. After cooling to 0°C a sample of 5 g (8.8 mmol) of compound **5** was added in one portion. The mixture was then stirred for 3h at the same temperature. The resulted pink solution was poured slowly into a suspension of 7.5 g (89 mmol) of sodium bicarbonate. The organic layer was then separated, washed twice with cold water and after brief drying ($MgSO_4$) it was used immediately to the next step. The solution consists of virtually pure imine **6** which is stable witin a few minutes below 10°C.

Preparation of nitrone 7: The methylene chloride solution of imine **6** was added in one portion to a gently refluxed mixture of 2.35 g (13.6 mmol) of freshly purified m-chloroperbenzoic acid (MCPBA) in 80 mL of methylene chloride. The mixture was then stirred for 15 min without external heating, cooled to room temperature and washed successively with 30 mL portions of 10% sodium sulfite, 5% sodium bicarbonate solutions and brine. The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* affording a brown residue which was subjected to column chromatography on silica gel. Elution with 2% (v/v) methanol in chloroform gave nitrone 7 in 54.1% yield in the form of amorphous yellowish solid. $[\alpha]^{23}_D$+73.3 (*c* 1.01, $CHCl_3$). IR (KBr, cm^{-1}): 3035; 1750; 1520; 1375; 1220; 1050; 760. ^1H NMR (500MHz, $CDCl_3$): 7.23 (s, 1H, H-8); 6.68 (s, 1H, H-5); 6.27 (d, 1H, J=8.1Hz, H-1'); 6.20 (dd, 1H, J_1=3.4Hz, J_2=8.1Hz, H-2'); 5.65 (dd, 1H, J_1=3.4Hz, J_2=7.1Hz, H-3'); 5.36 (ddd, 1H, J_1=3.5Hz, J_2=7.1Hz, J_3=13.2Hz, H-4'); 4.41 (dd,1H, J_1=3.5Hz, J_2=12.3Hz, H-5'); 4.02-4.08 (m, 3H, 2H-3 and H-5'); 3.90 and 3.91 (two s, 3H each, 2xOCH_3); 3.06-3.13 (m, 1H, H-4_{eq}); 2.86 (dt, 1H, J_1=5.9Hz, J_2=16.3Hz, H-4_{ax}); 2.07; 2.07; 2.08; 2.11 (four s, 3H each, 4xOAc); 1,88 (s, 3H, Oac). ^{13}C NMR (125MHz, $CDCl_3$): 170.37; 169.91; 169.71; 169.61; 169.44; 149.37; 147.89; 137.69; 125.23; 121.38; 120.25; 110.57; 108.15; 69.92; 68.83; 68.70; 66.45; 62.07; 59.86; 56.17; 55.95; 27.44; 20.67; 20.58; 20.49; 20.41. LSIMS (+) 8 kV (%): 1157 $(2M+Na)^+$ (1); 1135 $(2M+H)^+$ (1); 703 (1); 590 $(M+Na)^+$ (19); 568 $(M+H)^+$(100); 508 (38); 448 (10); 406 (6); 290 (11); 220 (21).

Catalytic hydrogenation of nitrone 7; formation of diastereomers 8a and 8b: A solution of 1 g (1.76 mmol) of nitrone 7 in glacial acetic acid (30 mL) containing 2 mL of 12N HCl was hydrogenated over 50 mg of platinum(II) oxide under atmospheric pressure of hydrogen at 10°C. After 1 h of stirring a cooling bath

was removed, a fresh portion (50 mg) of the catalyst was added along with 1 mL of 12N HCl and the hydrogenation was continued for additional 6 h at room temperature. Hydrogen was then replaced by argon and 5 g of sodium acetate and 3 mL of acetic anhydride were introduced to the mixture. After 12 h of stirring the catalyst was filtered off and the solution was carefully poured in a suspension of 60 g of sodium bicarbonate in 250 mL of water. The water layer was then extracted with 4x40 mL portions of chloroform. The organic phase after drying ($MgSO_4$) and evaporation afforded the mixture of **8a** and **8b** in quantitative yield. The HPLC analysis of this mixture (5μm silica gel, 0.75% v/v MeOH in CH_2Cl_2) revealed the presence of two components in the ratio 13:87 with the major one being more polar. Careful column chromatography on silica gel using 1%(v/v) methanol in chloroform allowed partial separation of the diastereomers:

Diastereomer 8a: isolated in 7% yield as a foam, $[\alpha]^{23}_D$ -3.9 (*c* 1.97, $CHCl_3$). IR (KBr, cm^{-1}): 2945; 1750; 1670; 1510; 1430; 1370; 1215; 1050. ^1H NMR (500MHz, $CDCl_3$): 6.80 (s, 1H, H-8); 6.57 (s, 1H, H-5); 6.02 (dd, 1H, J_1=2.2Hz, J_2=8.9Hz, H-1'); 5.75 (d, 1H, J=8.9Hz, H-1); 5.58-5.65 (m, 1H, H-4'); 5.34-5.41 (m, 1H, H-5'); 5.26-5.31 (m, 1H, H-5'); 5.23 (dd, 1H, J_1=2.2Hz, J_2=3.4Hz, H-2'); 5.15 (dd, 1H, J_1=3.4Hz, J_2=15.2Hz, H-3'); 4.35 (dt, 1H, J_1=2.5Hz, J_2=12.0Hz, H-3_{eq}); 4.03 (dt, 1H, J_1=6.8Hz, J_2=12.0Hz, H-3_{ax}); 3.84 and 3.88 (two s, 3H each, 2xOCH_3); 2.82-2.90 (m, 2H, 2H-4); 2.04; 2.09; 2.09; 2.14; 2.18 (five s, 3H each, 5xOAc); 1.78 (s, 3H, Nac). ^{13}C NMR (125MHz, $CDCl_3$): 170.52; 170.38; 170.33; 169.98; 169.11; 168.48; 148.31; 147.59; 126.52; 124.18; 120.25; 110.90; 72.51; 69.58; 69.27; 68.34; 62.31; 55.84; 55.78; 51.08; 41.96; 27.64; 21.85; 20.75; 20.70; 20.62; 20.53; 20.40. LSIMS (+) 8kV (%): 618 $(M+Na)^+$ (22); 596 $(M+H)^+$ (46); 536 (14); 522 (11); 246 (20); 234 (85); 220 (100); 192 (25); 176 (30).

Diastereomer 8b: isolated in 58% yield as a foam, $[\alpha]^{23}_D$ -21.1 (*c* 2.01, $CHCl_3$). IR (KBr, cm^{-1}): 2945; 1750; 1655; 1520; 1430; 1375; 1215; 1040. ^1H NMR (500MHz, $CDCl_3$): 6.58 (s, 1H, H-5); 6.74 (s, 1H, H-8); 5.95 (d, 1H, J=5.3Hz, H-1); 5.54 (dd, 1H, J_1=1.8Hz, J_2=5.3Hz, H-1'); 5.29-5.32 (m, 2H, 2H-5'); 5.14 (dd, 1H, J_1=2.5Hz, J_2=4.9Hz, H-4'); 5.03 (dd, 1H, J_1=1.8Hz, J_2=11.4Hz, H-2'); 4.21 (ddd, 2H, J_1=2.8Hz, J_2=4.5Hz, J_3=5.5Hz, 2H-3); 3.99 (dd, 1H, J_1=2.5Hz, J_2=11.4Hz, H-3'); 3.84 and 3.88 (two s, 3H each, 2xOCH_3); 2.82-2.88 (m, 2H, 2H-4); 2.05; 2.05; 2.08; 2.12; 2.16 (five s, 3H each, 5xOAc); 1.74 (s, 3H, Nac). ^{13}C NMR (125MHz, $CDCl_3$): 170.45; 170.42; 170.31; 170.08; 169.77; 168.79; 148.28; 147.36; 126.45; 123.97; 120.25; 111.00; 72.37; 69.57; 69.19; 68.37; 61.61; 55.85; 55.81; 50.69; 41.99; 27.76; 21.81; 20.69; 20.59; 20.55; 20.50; 20.40; LSIMS (+) 8 kV (%): 618 $(M+Na)^+$ (16); 596 $(M+H)^+$ (41); 536 (15); 314 (8); 272 (6); 246 (25); 234 (100); 220 (35); 192 (34); 176 (10).

Preparation of compound 9: To a stirred solution of 18 mg of sodium in 40 mL of methanol a solution of 300 mg (0.50 mmol) of compound **8b** in 5 mL of methanol was added in one portion. After 30 min of stirring at room temperature the reaction was terminated by the addition of 0.05 mL of acetic acid and solvents were evaporated. The residue was quenched with 20 mL of brine and the water layer was extracted ten times with 15 mL portions of chloroform. The combined extracts were dried ($MgSO_4$), evaporated and subjected to column chromatography on silica gel using 4% (v/v) methanol in chloroform as eluent. Compound **9** was

isolated as white crystals in 83% yield. Mp 153°-154°C, $[\alpha]^{23}_D$ -91.5 (*c* 0.99, H_2O). IR (KBr, cm^{-1}): 3145-3600; 2945; 1615; 1520; 1455; 1255; 1225; 1130; 1030. ^1H NMR (500MHz, D_2O): 6.89 (s, 1H, H-8); 6.78 (s, 1H, H-5); 5.50 (br s, 1H, $w_{1/2}$=4.1Hz, H-1); 4.33 (dd, 1H, J_1=1.9Hz, J_2=9.5Hz, H-2'); 3.97-3.99 (m, 1H, H-1'); 3.91-3.93 (m, 1H, H-4'); 3.85-3.87 (m, 2H, H-3_{eq}, H-3_{ax}); 3.83 and 3.84 (two s, 3H each, 2xOCH_3); 3.77 (dd, 1H, J_1=3.5Hz, J_2=11.9Hz, H-5'); 3.65 (dd, 1H, J_1=6.0Hz, J_2=11.9Hz, H-5'); 3.55 (dd, 1H, J_1=1.3Hz, J_2=9.5Hz, H-3'); 2.77 (dd, 2H, J_1=4.0Hz, J_2=7.7Hz, 2H-4); 2.30 (s, 3H, Nac). ^{13}C NMR (125MHz, $CDCl_3$): 172.30; 147.92; 147.80; 126.93; 125.62; 111.15; 109.42; 75.64; 73.77; 72.96; 69.47; 63.68; 56.11; 55.78; 53.18; 43.49; 28.34; 21.45. **$C_{18}H_{27}NO_8$ (385.41)** Calcd. C, 56.09; H, 7.06; N, 3.63. Found: C, 56.17, H, 6.78; N, 3.41.

Preparation of aldehyde 10: To a stirred and cooled to 5°C solution of 341 mg (0.88 mmol) of compound **9** in 50 mL of water a solution of 940 mg (4.4 mmol) in 5 mL of water was added in one portion. After 15 min stirring at the same temperature 0.5 mL of ethylene glycol was added and the mixture was extracted 3x15 mL of chloroform. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated below 30°C leaving an oil which, upon quenching with diethyl ether afforded compound **10** as white crystals in 89% yield. The aldehyde **10** racemises extensively when stored at room temperature and should be used immediately for the next step. Mp 118°-120°C (dec.), $[\alpha]^{23}_D$ +65.9 (*c* 0.94, $CHCl_3$). IR (KBr, cm^{-1}): 2940; 2840; 1730; 1610; 1520. ^1H NMR (500MHz, $CDCl_3$): 9.45 (br s, 1H, $w_{1/2}$=4.0Hz, H-1'); 6.67 and 6.87 (two s, 1H each, H-5, H-8); 5.73 (br s, 1H, $w_{1/2}$=4.0Hz, H-1); 3.87 and 3.89 (two s, 3H each, 2xOCH_3); 3.71 (apparent t, 2H, J=7.0Hz, 2H-3); 2.84 (apparent t, 2H, J=7Hz, 2H-4); 2.25 (s, 3H, $COCH_3$). ^{13}C NMR (125MHz, $CDCl_3$): 195.80; 170.64; 148.82; 148.23; 127.29; 119.68; 111.39; 110.80; 62.90; 56.12; 55.94; 38.45; 28.73; 21.62. **$C_{14}H_{17}NO_4$ (263.29)** Calcd. C, 63.86; H, 6.51; N, 5.32. Found C, 64.02; H, 6.42; N, 5.11.

Preparation of *threo*-α-hydroxynorlaudanosine 11: A stirred solution of 0.57 mL (3.9 mmol) of 4-bromoveratrole in 25 mL of THF was treated with 2.4 mL of 1.6M *n*-butyllithium in hexanes at -78°C for 20 min. A solution of aldehyde **10** (206 mg, 0.78 mmol) in 3 mL of THF was slowly added, and the mixture was kept at -78°C for 20 min. and at -20°C for 30 min. After quenching with 1 mL of methanol and evaporation the mixture was treated with saturated solution of NH_4Cl (10 mL) and chloroform (15 mL). The water layer was extracted with two additional portions of chloroform and the combined extracts were dried ($MgSO_4$), evaporated and the residue was chromatographed on silica gel using 4% (v/v) MeOH in $CHCl_3$ as eluent, affording compound **11** as a crystalline mass in 77% yield. Crystallization from ethanol gave an analytical sample: mp 198°-200°C, $[\alpha]_D^{23}$ -96.6 (*c* 1.38, $CHCl_3$). IR (KBr, cm^{-1}): 3320; 2920; 2790; 1600; 1520; 1470; 1270; 1220; 1025; 850; 750. ^1H NMR (200 MHz, $CDCl_3$): 6.95 (s, 1H, H-5'); 6.82 (br s, 2H, H-3' and H-4'); 6.56 (s, 1H, H-7'); 5.71 (s, 1H, H-8); 4.59 (d, 1H, H-1'); 3.92-3.78 (m, 2H, H-1 and NH); 3.88; 3.87; 3.83; 3.42 (four s, 3H each, 4xOCH_3); 3.27-3.03 (m, 3H, 2H-3 and OH); 2.82-2.68 (apparent t, 2H, 2H-4).

^{13}C NMR (125MHz, $CDCl_3$): 149.03; 148.65; 147.63; 146.13; 134.45; 127.22; 126.32; 120.47; 111.39; 110.95; 110.82; 110.50; 74.61; 61.14; 58.91; 55.98; 55.75; 55.30; 38.62; 28.97. LSIMS (+) 8 kV (%): 360 $(M+H)^+$ (25); 342 (18); 194 (10); 192 (100).

Deoxygenation of compound 11. Preparation of (*R*)-(-)-Laudanosine 13: To a stirred mixture of 200 mg (0.56 mmol) of compound **11** and 0.11 mL (1.4 mmol) of pyridine in 20 mL of THF cooled to -78°C a solution of thionyl chloride (51 μL, 0.7 mmol) in 1 mL of toluene was slowly added. After 15 min stirring the cooling bath was removed and the mixture was allowed to reach -10°C. The flask was then immersed in ice-salt mixture and lithium aluminum hydride (5x20 mg) was carefully added. The mixture was subsequently refluxed for 0.5 h, cooled and the excess of the hydride was destroyed by slow addition of 25% NaOH solution (0.5 mL). The inorganic precipitate was removed by filtration and washed with several portions of boiling THF. The combined washing were dried ($MgSO_4$) evaporated and filtered through a pad of silica gel. Norlaudanosine **12** thus obtained appeared to be sensitive to aerial oxidation and therefore it was subjected directly to the *N*-methylation step without purification. Thus, the crude mixture was dissolved in methanol (5 mL) and was left stand overnight with 0.5 mL 30% formaldehyde solution. Sodium borohydride (500 mg) was then added in five portions with stirring at 0°-5°C. Subsequent evaporation of the solvent, addition of water (5 mL) and extraction with chloroform afforded a colourless oil which was purified by column chromatography to give *R*-(-)-laudanosine **13** as a white solid in 51% yield (from **11**). The crude *R*-(-)-laudanosine **13** was submitted to HPLC analysis on a ChiraDex column (Merck) using methanol / water 4:1 (v/v) as eluent. The (*S*) congener of **13** was detected in the amount <3%, thus proving the enantiomeric purity of *R*-(-)-laudanosine **13** to be >94% ee. $[\alpha]_D^{23}$ -97.1 (*c* 1.54, EtOH). IR (KBr, cm^{-1}): 3400; 2930; 1520; 1450; 1370; 1270; 1225; 1140; 1030; 860. ^{1}H NMR (500MHz, $CDCl_3$): 6.77 (d, 1H, J=8.3Hz, H-5); 6.64 (dd, 1H, J_1=2.0Hz, J_2=8.3Hz, H-3'); 6.60 (d, 1H, J=2.0Hz, H-4'); 6.56 (s, 1H, H-7'); 6.08 (s, 1H, H-8); 3.84; 3.83; 3.79 (three s, 3H each, 3xOCH_3); 3.69 (dd, 1H, J_1=2.4Hz, J_2=7.3Hz, H-1); 3.58 (s, 3H, OCH_3); 3.19-3.12 (m, 2H, 2H-3); 2.85-2.73 (m, 3H, H-1'$_{eq}$ and 2H-4); 2.58 (dt, 1H, J_1=4.9Hz, J_2=16.1Hz, H-1'$_{ax}$); 2.54 (s, 3H, NCH_3). ^{13}C NMR (125MHz, $CDCl_3$): 176.36; 162.39; 147.20; 146.25; 132.47; 129.20; 125.99; 121.83; 112.93; 111.11; 111.01; 110.93; 64.58; 55.90; 55.80; 55.75; 55.54; 46.97; 42.71; 40.89; 25.54. LSIMS (+) 8kV (%): 380 $(M+Na)^+$ (2); 358 $(M+H)^+$ (25); 206 (100); 192 (6); 151 (9). HR LSIMS: $(M+H)^+$ Calcd. for $\mathbf{C_{21}H_{28}NO_4}$ 358.20183 Found: 358.20183

Transformation of (*R*)-(-)-Laudanosine 13 into (*R*)-(-)-Glaucine 14: Chromium(III) oxide was freshly prepared by pyrolytic decomposition of ammonium dichromate and was used without further treatment. Thus, chromium(III) oxide (170 mg, 1.1 mmol) was suspended in 10 mL of dichloromethane containing 2.5 mL of trifluoroacetic acid along with 0.32 mL of trifluoroacetic anhydride. The mixture was refluxed for 20 min and cooled to 0°C. (*R*)-(-)-Laudanosine **13** (79 mg, 22.1 mmol) in 1 mL of dichloromethane was then added dropwise with stirring followed by the addition of 0.11 mL (0.44 mmol) of $BF_3{\cdot}Et_2O$. The mixture was stirred at room temperature under argon while monitoring the progress of the reaction by TLC analysis. After 48 h the

mixture was evaporated and treated with sat. sodium bicarbonate. Dichloromethane (10 mL) was added and the solids were removed by filtration. The water layer was extracted twice with 5 mL portions of dichloromethane and the combined extracts were dried and evaporated. Column chromatography of the residue (silica gel, 1.5% MeOH in $CHCl_3$ afforded (*R*)-(-)-glaucine **14** in 83% yield as an oil, which crystallizes on standing. The final product was subjected to HPLC analysis on a ChiraSep (DNBPG) column (Merck) using 2% (v/v) 2-propanol in hexane as eluent. The enantiomer of (*R*)-(-)-glaucine **14** was not detected. $[\alpha]_D^{23}$ -118.4 (*c* 0.89, $CHCl_3$). IR (KBr, cm^{-1}): 3400; 2980; 2890; 1750; 1520; 1460; 1390; 1320; 1250; 1110; 1090; 1010; 850; 600. ^1H NMR (200MHz, $CDCl_3$): 8.09 (s, 1H, H-11); 6.78 (s, 1H, H-3); 6.59 (s, 1H, H-8); 3.93; 3.90; 3.89; 3.65 (four s, 3H each, 4xOCH_3); 3.19-3.12 (m, 1H, H-5_{eq}); 3.08-2.90 (m, 3H, H-5_{ax} and H-7_{eq} and H-6a); 2.72-2.48 (m, 3H, H-7_{ax} and 2H-4); 2.55 (s, 3H, NCH_3). ^{13}C NMR (125MHz, $CDCl_3$): 151.92; 147.96; 147.44; 144.25; 129.33; 128.93; 127.22; 126.89; 124.49; 111.56; 110.78; 110.35; 62.58; 60.19; 55.92; 55.78; 53.36; 44.10; 34.58; 29.31; 28.93. LSIMS (+) 8kV (%): 354 (100); 340 (54); 338 (14); 324 (29); 312 (17); 308 (20); 297 (16); 281 (25); 266 (5); 162 (7). HR LSIMS: $(M)^+$ Calcd. for $\mathbf{C_{21}H_{25}NO_4}$ 355.17835 Found: 355.17835

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