Stereoselective Synthesis of Quinolizidine Alkaloids: (–)-Lasubin II

Markus Weymann and Horst Kunz

Institut für Organische Chemie, Universität Mainz, Duesbergweg 10 – 14, D-55128 Mainz, Germany

Reprint requests to Prof. Dr. Horst Kunz. E-mail: hokunz@uni-mainz.de

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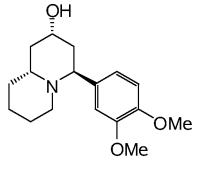
Based on a higly diastereoselective Mannich reaction of *N*-(3,4-dimethoxybenzylidene) 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **3** with the Danishefsky diene the quinolizidine alkaloid lasubin II was synthesized in enantiomerically pure form in six steps.

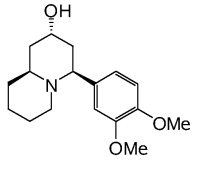
Key words: Quinolizidine Alkaloids, Carbohydrate Auxiliaries, Domino Mannich-Michael Reactions, Cuprate Addition, Lasubin II

Introduction

A number of biologically and structurally interesting alkaloids have the quinolizidine framework [1]. (–)-Lasubin I and (–)-lasubin II isolated from *Lagerstroemia subcostata Koehne* [2] recently received increasing attention as target compounds for the validation of stereoselective syntheses of quinolizidine alkaloids.



(–)-Lasubin I



(–)-Lasubin II

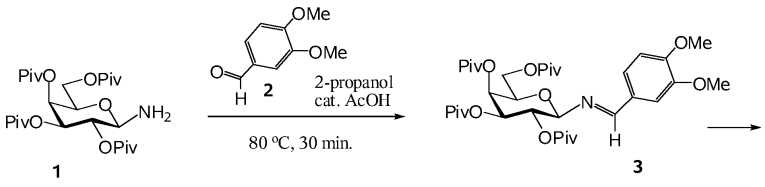
Initially, lasubin II was synthesized diastereoselectively in racemic form [3]. Asymmetric syntheses of lasubin II were achieved based on stereoselective transformations of enantiomerically pure substrates [4] or, for example, *via* a diastereoselective aza-Diels-Alder reaction using a resolved chiral arylaldehyde tricarbonylchromium complex [5]. Recently, an enantioselectively catalyzed aza-Diels-Alder reaction [6] and a [2+2+2] cycloaddition reaction [7] were successfully used for the synthesis of enantiomerically pure lasubin II.

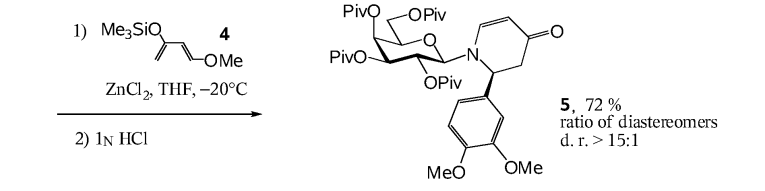
Stereoselective Synthesis of the Quinolizidine Alkaloid Lasubin II

We here describe a short stereoselective synthesis of (–)-lasubin II based on a domino Mannich-Michael condensation reaction sequence [8] starting from 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**) and veratrum aldehyde (**2**). The imine **3** formed from these components reacts with the Danishefsky diene [9] **4** promoted by $ZnCl_2$ to give the dehydro-piperidinone **5** with high yield and excellent diastereoselectivity ($> 15:1$ according to ^{1}H NMR spectroscopy, Scheme 1).

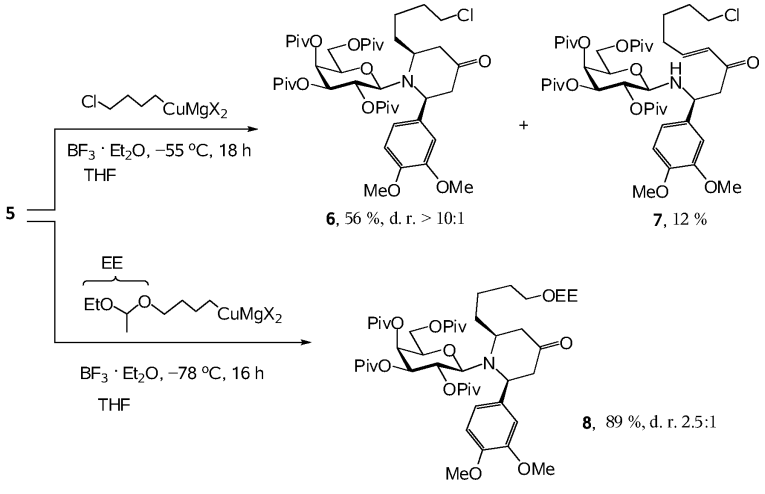
Dehydropiperidinones like **5** are vinylogous carboxamides and, therefore, of low electrophilic reactivity. They do not react with Grignard compounds or organolithium reagents at low temperature. However, once subjected to a stress between a soft nucleophile, *e. g.* a cuprate, and a hard electrophile the conjugate addition of the cuprate smoothly proceeds. Reaction with the 4-chlorobutyl-magnesiocuprate obtained from 4-chloro-butylbromide *via* the Grignard reagent and subsequent addition of CuI furnished the 2,6-*cis*-disubstituted piperidinones **6** with high diastereoselectivity. However, a byproduct **7** obviously resulting from a β-elimination was also formed (Scheme 2). The chromatographic separation of the mixture turned out to be difficult. By changing the Lewis acid from BF_3 etherate to trimethylchlorosilane (TMS-Cl), the formation of **7** could be prevented, but the 1,4-addition now proceeded more slowly and with almost no diastereoselectivity.

The conjugate addition of the (1-ethoxy)ethyl-(EE)-protected 4-hydroxybutyl magnesiocuprate to dehydropiperidinone **5** promoted by $BF_3 \cdot Et_2O$ proceeded with high yield to give the 2,6-disubstituted piperidinones **8** (Scheme 2). No byproduct analogous to **7** was observed. The 2,6-*cis*-disubstituted compound





Scheme 1.

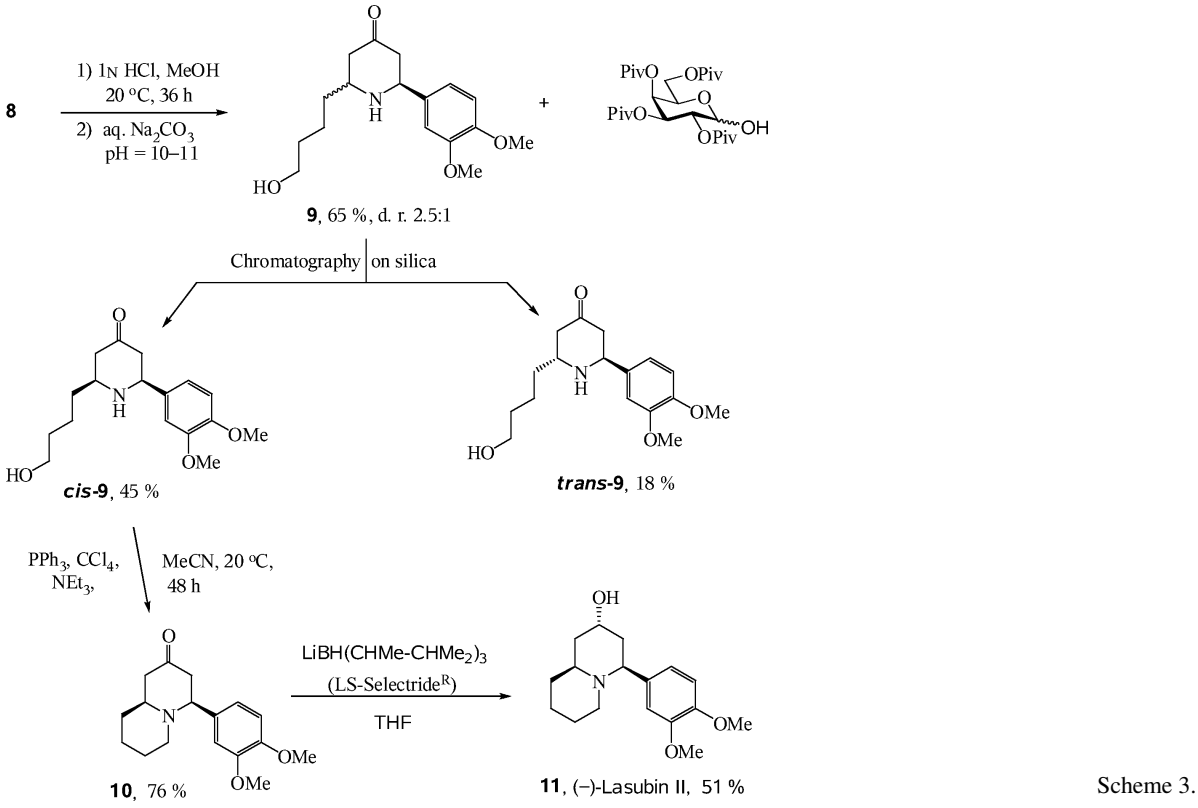


Scheme 2.

was preferentially formed, but with only moderate diastereoselectivity of 5 : 2. Probably, the 1-ethoxy-ethoxy functionality participates in the coordination of the Lewis acid and of the metal ions. This could prevent an elimination to give byproducts like **7**, but also could interfere with the coordination phenomena responsible for the stereodifferentiation.

Simultaneous mildly acidic cleavage of the ethoxyethyl group and of the *N*-glycosidic bond with 1N HCl in methanol gave the hydrochloride of the piperidinones. The pivaloylated galactose auxiliary was quantitatively recollected by extraction with diethyl ether. Treatment of the piperidinone hydrochloride with Na_2CO_3 solution (pH = 10 – 11) and extraction with CH_2Cl_2 gave the free piperidinone **9** as a mixture of the diastereomers ***cis*-9** and ***trans*-9** (65 %, d. r. 2.5 : 1, Scheme 3). After separation by column chromatography on silica in CH_2Cl_2 (15 : 1), the pure 2,6-*cis*-disubstituted piperidinone ***cis*-9** was isolated (69 %) besides the minor diastereomer ***trans*-9** (27 %).

Reaction of ***cis*-9** with triphenylphosphine/carbon tetrachloride [10] in the presence of triethylamine in acetonitrile resulted in a sequence of nucleophilic substitution of the hydroxyl group and subsequent ring-closing *N*-alkylation to furnish the *cis*-disubstituted piperidinone **10**. The stereoselective reduction of the carbonyl group of **10** to give the thermodynamically less favored *trans*-configured compound lasubin II **11** is best accomplished using lithium tris-siamylborohydride (LS-Selectride®) [3c] as the sterically demanding hydride transfer reagent. After hydrolytic work up and chromatography (–)-lasubin II was isolated in a not optimized yield of 51 %. Its IR-spectroscopic [3c] and NMR-spectroscopic data [3a, b, d] as well as its optical rotation value [2] are in agreement with those reported in the literature.



Scheme 3.

Conclusion

Owing to the stereodifferentiating potential of the carbohydrate framework [10] in the O-pivaloylated galactosylamine **1**, the enantiomerically pure Lythraceae alkaloid lasubin II is accessible from veratrum aldehyde (**2**) in six steps. A separation of diastereomers was only necessary on the stage of the *cis*/*trans*-diastereomeric 2,6-disubstituted piperidinones **9**. Although inexpensive, the carbohydrate auxiliary can be recollected almost quantitatively and after conversion to the glycosylamine re-used for the same process.

Experimental Section

General procedures

Reagents and solvents were distilled before use: Tetrahydrofuran, dioxane, and Et_2O were distilled from potassium/benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. Light petroleum refers to b. p. 60 – 80 °C. All reactions and distillations were carried out in flame-dried glassware under argon atmosphere.

TLC was performed on silica gel 60 F_{254} (E. Merck, Darmstadt, Germany). Flash chromatography was carried out on silica gel MN 60 (0.04 – 0.063 mm), Macherey und Nagel, for chromatography under atmospheric pressure, silica gel 60 (0.06 – 0.2 mm) (Baker) was used. Analytical HPLC was carried out in MeOH/H_2O mixtures using a LKB (Pharmacia) 2150 unit equipped with diode array detection (LKB 2140). ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AC-400 NMR instruments. Optical rotation values were measured with a Perkin-Elmer 241 polarimeter. FAB-MS spectra were recorded on a Finnigan-MAT-95 spectrometer.

2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**) was prepared as reported in the literature [11], however, applying a varied procedure *via* penta-*O*-acetyl-galactopyranose as described for the corresponding D-arabinopyranosylamine [12].

*N-(3,4-Dimethoxybenzylidene)-2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosylamine (**3**)*

To a solution of tetra-*O*-pivaloyl-galactosylamine (**1**) (5.2 g, 10 mmol) and 3,4-dimethoxybenzaldehyde (2.0 g, 12 mmol) in isopropanol (20 mL) 10 drops of glacial acidic acid were added, and the solution was heated to 80 °C for 30 min. After removal of the solvent *in vacuo* the crude *N*-galactosyl imine remained as an amorphous solid. Further

purification was not necessary. Characterization of the compound was carried out *via* its subsequent products.

*N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3,4-dimethoxyphenyl)-5,6-dehydropiperidin-4-one (**5**)*

In analogy to a reported procedure [8], imine **3** (7.3 g, 10 mmol) was dissolved in dry tetrahydrofuran (50 mL) and cooled to −78 °C. A 1 M solution (11 mL) of $ZnCl_2$ in THF/CH_2Cl_2 (1 : 1, v/v) was added. After 10 min Danishefky diene **4** [9] (2.5 mL, 12.5 mmol) was added. After stirring for 30 min at −78 °C, the solution was stirred at −20 °C for 36 h (monitoring by TLC). Aqueous 1 N HCl (10 mL) was added, and the solvent evaporated *in vacuo*. Diethyl ether (200 mL) was added, the acidic aqueous solution separated, and the organic solution extracted three times with aq. $NaHCO_3$ solution. Remaining zinc salts were removed by extraction with 10 % Titriplex®III solution (2 × 50 mL). After washing with brine and drying with $MgSO_4$, the solvent was evaporated *in vacuo*, and the product was purified by chromatography on silica (20 × 5 cm) in light petroleum/ethyl acetate 2 : 1.

Yield: 5.26 g (72 %, based on glycosylamine **1**); pale yellow crystalline solid; m. p. 148 °C; $[\alpha]_D^{22}$ = 33.7 (*c* = 1.0, $CHCl_3$); R_f = 0.08 (light petroleum/ethyl acetate 3 : 1). Diastereomeric ratio: > 15 : 1 (^{1}H NMR). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08, 1.15, 1.16 and 1.25 (4s, each 9H, piv-CH_3), 2.66 – 2.75 (m, 2H, CH_2C=O), 3.68 (m, 1H, H-5′), 3.85 (s, 3H, OCH_3), 3.86 (m, 1H, H-6a′), 3.90 (s, 3H, OCH_3), 4.02 (m, 1H, H-6b′), 4.28 (d, 1H, $J_{1',2'}$ = 9.5 Hz, H-1′), 4.72 (dd, 1H, J_{vic} = 5.7 Hz, $J_{vic'}$ = 11.1 Hz, aryl-CHN), 4.95 (dd, 1H, $J_{3',4'}$ = 3.1 Hz, $J_{3',2'}$ = 9.9 Hz, H-3′), 5.26 (d, 1H, *J* = 8.1 Hz, =CHCO), 5.31 (d, 1H, $J_{4',3'}$ = 2.7 Hz, H-4′), 5.66 (t, 1H, *J* = 9.8 Hz, H-2′), 6.79 – 6.91 (m, 3H, arom.), 7.29 (d, 1H, *J* = 8.0 Hz, NCH=C). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.07, 27.09 and 27.15 (piv-CH_3), 38.65, 38.72, 28.81 und 39.04 (piv-C_{quart}), 43.94 (CH_2C=O), 55.89 and 56.05 (OCH_3), 60.90 (aryl*C*HN), 60.94 (C-6′), 65.00, 66.75, 71.64 and 72.53 (C-2′, C-3′, C-4′, C-5′), 87.15 (C-1′), 103.79 (=*C*HCO), 110.64, 111.44, 120.45 and 130.15 (arom.), 149.29 (NCH=), 149.47 and 149.56 (arom.), 176.44, 176.79, 177.03 and 177.64 (pivC=O), 192.04 (C=O). – $C_{39}H_{57}NO_{12}$ (731.87): calcd. C 64.00, H 7.85, N 1.91; found C 63.97, H 7.82, N 2.10.

*(2S,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3,4-dimethoxyphenyl)-6-(4-chlor-butyl)-piperidin-4-one (**6**) and N-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-1-amino-1-(3,4-dimethoxyphenyl)-9-chloro-4-nonen-3-one (**7**)*

Dibromomethane (5 – 10 drops) was added to a stirred suspension of magnesium cuttings (0.12 g, 10 mmol) in diethyl ether (10 mL). After opacity occurred the mixture was cooled to 0 °C, and 1-bromo-4-chlorobutane (0.58 mL, 5 mmol) was added. After 3 h, the magnesium has been dissolved, and the Grignard solution was given *via* a steel syringe to a cooled (−78 °C) suspension of CuI (0.9 g, 5 mmol) in tetrahydrofuran (15 mL). The clear brown solution was warmed up to −50 °C within 2 h and was cooled again to −78 °C. $BF_3 \cdot Et_2O$ (0.6 mL, 5 mmol) was added. After 15 min (temperature < −55 °C) a solution of dehydropiperidinone **5** (0.73 g, 1 mmol) in tetrahydrofuran (10 mL) was added and the mixture stirred for 18 h. The mixture was diluted with diethyl ether (50 mL) and treated with conc. aq. NH_4OH/NH_4Cl 1 : 1 (v/v). The aqueous layers were extracted twice with diethyl ether, the combined ether solutions were washed with brine and dried with $MgSO_4$. After evaporation of the solvent the remainder was purified by chromatography on silica (15 × 3 cm) in light petroleum/ethyl acetate (4 : 1). Yield: 0.46 g (56 %) of a mixture of **6** and **7**. The composition was determined by ^{1}H NMR spectroscopy, ratio of **6**/**7** 4 : 1. Diastereomeric ratio for **6**: > 10 : 1. – NMR data for **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06, 1.15, 1.20 and 1.23 (4s, each 9H, piv-CH_3), 1.48 (m, 2-3H, CH_2), 1.74 (m, 2H, CH_2), 2.08 (m, 1H, CH_2), 2.44 (m, 3H, CH_2C=O, CH_2C=O′), 2.57 (dd, 1H, J_{vic} = 11.0 Hz, J_{gem} = 14.6 Hz, CH_2C=O), 3.29 (dd, 1H, J_1 = 7.0 Hz, J_2 = 7.5 Hz, alkyl-C*H*N), 3.50 (m, 2H, CH_2Cl), 3.77 – 3.94 (m, 8H, H-5′, H-6a′, OCH_3, OCH_3'), 3.97 (d, 1H, $J_{1',2'}$ = 9.6 Hz, H-1), 4.08 (dd, 1H, $J_{6b',5'}$ = 6.4 Hz, $J_{6b',6a'}$ = 11.0 Hz, H-6b′), 4.38 (dd, 1H, J_{vic} = 3.6 Hz, $J_{vic'}$ = 11.0 Hz, aryl-C*H*N), 4.84 (dd, 1H, $J_{3',4'}$ = 3.2 Hz, $J_{3',2'}$ = 9.8 Hz, H-3′), 5.23 (d, 1H, $J_{4',3'}$ = 3.0 Hz, H-4′), 5.48 (t, 1H, *J* = 9.7 Hz, H-2′), 6.76 – 6.84 (m, 3H, arom.). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.95 (CH_2), 27.09, 27.22 and 27.42 (piv-CH_3), 31.05 and 32.87 (CH_2), 38.71, 38.83 and 39.03 (piv-C_{quart}), 44.68 (CH_2C=O), 45.76 (CH_2C=O′), 49.27 (CH_2Cl), 54.15 (alkyl-*C*HN), 55.91 and 56.10 (OCH_3, OCH_3'), 58.09 (aryl-*C*HN), 61.06 (C-6′), 65.27, 67.07, 71.56 and 72.53 (C-2′, C-3′, C-4′, C-5′), 88.53 (C-1′), 111.22, 111.46, 120.98, 131.72, 149.32 and 149.53 (arom.), 176.52, 176.98 and 177.11 (pivC=O), 208.37 (C=O). – NMR data for **7**: ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.24, 31.53 and 31.88 (CH_2), 44.45 (CH_2C=O), 48.74 (CH_2Cl), 54.15 and 55.91 (OCH_3, OCH_3'), 56.02 (aryl-*C*HN), 61.53 (C-6′), 65.82, 67.37 and 68.83 (C-2′, C-3′, C-4′, C-5′), 110.89 (C-1′), 110.89 and 120.12 (arom.), 130.90 (alkene), 133.88 (arom.), 146.86 (alkene), 197.95 (C=O).

*(2S,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3,4-dimethoxyphenyl)-6-(4-(1-ethoxyethyloxy)-butyl)-piperidin-4-one (**8**)*

To stirred magnesium cuttings (0.39 g, 16 mmol) in tetrahydrofuran (12 mL) 4-chlorobutyl-(1-ethoxy)ethyl ether (2.17 g, 12 mmol) was given. After addition of a few drops of dibromomethane the mixture was heated under reflux

for 5 h. The resulting Grignard solution was added dropwise *via* a steel syringe to a cooled (−60 °C) and vigorously stirred suspension of CuBr (1.72 g, 12 mmol) in tetrahydrofuran (60 mL). Within 1 h the mixture was warmed up to −40 °C thereby changing the color from greyish brown to grey black. After cooling again to −78 °C, $BF_3 \cdot OEt_2$ (2.8 mL, 22.5 mmol) was added dropwise. *Via* a steel syringe and under exclusion of moisture, a solution of the dehydropiperidone **5** (2.2 g, 3.0 mmol) in tetrahydrofuran was added within 25 min. The color changed to ochre-yellow. After completion of the reaction (1.5 h, TLC monitoring), conc. NH_4OH/sat. NH_4Cl (50 mL, 1 : 1 v/v) was added. After warming up to r. t., the mixture was diluted with diethyl ether (300 mL), the organic layer was extracted with conc. NH_4OH/sat. NH_4Cl (50 mL, 1 : 1 v/v). The combined aqueous solutions were washed with diethyl ether (2 × 100 mL) and the combined organic solutions dried with $MgSO_4$. The solvent was evaporated *in vacuo* and the remaining crude product **8** purified by chromatography on silica (17 × 4.5 cm) in light petroleum/ethyl acetate (2 : 1). Yield 2.35 g (89 %), colorless amorphous solid; $[\alpha]_D^{22}$ = −13.3 (*c* = 1.7, $CHCl_3$), R_f = 0.48 (light petroleum/ethyl acetate 2 : 1), diastereomeric ratio: 2.5 : 1 (according to ^{1}H NMR spectroscopy). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 9H, piv-CH_3), 1.04 – 1.51 (m, 38H, piv-CH_3, EEO-CH_3, CH_2), 2.02 (m, 1H, CH_2), 2.39 (m, 3H, CH_2C=O, CH_2C=O′), 2.51 (dd, 1H, J_{vic} = 11.1 Hz, J_{gem} = 14.6 Hz, CH_2C=O), 3.22 – 3.59 (m, 4H, EEO-CH_2, alkyl-C*H*N), 3.70 – 3.81 (m, 5H, OCH_3, H-5′, H-6a′), 3.85 (s, 3H, OCH_3), 3.92 (d, 1H, $J_{1',2'}$ = 9.6 Hz, H-1′), 4.01 (dd, 1H, $J_{6b',5'}$ = 6.3 Hz, $J_{6b',6a'}$ = 11.0 Hz, H-6b′), 4.35 (dd, 1H, J_{vic} = 3.4 Hz, $J_{vic'}$ = 10.9 Hz, aryl-C*H*N), 4.60 (q, 1H, *J* = 5.3 Hz, OC*H*OCH_3), 4.79 (dd, 1H, $J_{3',4'}$ = 3.0 Hz, $J_{3',2'}$ = 9.7 Hz, H-3′), 5.18 (d, 1H, $J_{4',3'}$ = 3.0 Hz, H-4′), 5.44 (t, 1H, *J* = 9.6 Hz, H-2′), 6.72 (s, 1H, arom.), 6.80 (s, 2H, arom.). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.26 and 19.78 (EEO-CH_3), 24.36 (CH_2), 27.01, 27.12 and 27.34 (piv-CH_3), 30.29 and 31.64 (CH_2), 38.63, 38.74 and 38.92 (piv-C_{quart}), 45.69 (CH_2C=O), 49.15 (CH_2C=O′), 54.23 (alkyl-*C*HN), 55.82 and 56.01 (OCH_3), 57.93 (aryl-*C*HN), 60.44 and 60.50 (EEO-CH_2), 60.98, 64.98 (C-6′), 65.22, 67.01, 71.40 and 72.30 (C-2′, C-3′, C-4′, C-5′), 88.48 (C-1), 99.41, 99.46 (O*C*HOCH_3), 111.17, 111.37, 120.93, 131.79, 149.20 and 149.43 (arom.), 176.41, 176.87, 177.02 and 177.60 (pivC=O), 208.35 (C=O). – $C_{47}H_{75}NO_{14}$ (878.10): calcd. C 64.29, H 8.61, N 1.60; found C 64.40, H 8.64, N 1.59.

*(2S,6S)-2-(3,4-Dimethoxyphenyl)-6-(4-hydroxy-butyl)-piperidin-4-one (**9**)*

To a stirred solution of the *N*-galactosyl piperidinone **8** (2.3 g, 2.6 mmol) in methanol (50 mL) at r. t. was added 1N HCl (9 mL). After 36 h the hydrolysis was completed (TLC monitoring). The solvent was evaporated *in vacuo* and the residue dissolved in diethyl ether (100 mL). The ether solution was washed with water (5 × 20 mL). The combined aqueous solutions were concentrated *in vacuo* to a volume of 30 mL. Na_2CO_3 was added until a pH of 10 – 11 was reached and the mixture stirred for 20 min. Extraction with CH_2Cl_2 (3 × 50 mL), drying with Na_2SO_4 and evaporation of the solvent *in vacuo* gave the crude piperidinone **9** as a brown oil. Purification was carried out by chromatography on silica (13 × 3 cm) in CH_2Cl_2/MeOH 15 : 1. Yield: 0.76 g (65 %), yellow amorphous solid. – $C_{17}H_{25}NO_4$ (307.39): calcd. C 66.43, H 8.20, N 4.56; found C 66.06, H 8.10, N 4.65.

Separation of the diastereomers was achieved by repeated chromatography:

Major diastereomer (***cis*-9**): Yield: 0.53 g (45 %), $[\alpha]_D^{22}$ = −26.0 (*c* = 1.0, $CHCl_3$), R_f = 0.48 (CH_2Cl_2/MeOH 9 : 1). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 – 1.54 (m, 6H, CH_2), 2.15 (dd, 1H, J_{vic} = 11.6 Hz, J_{gem} = 13.5 Hz, CH_2C=O), 2.34 – 2.45 (m, 4H, CH_2C=O, CH_2C=O′, OH), 2.89 (m, 1H, alkyl-CHN), 3.55 (dd, 1H, J_1 = 5.8 Hz, J_2 = 6.2 Hz, CH_2OH), 3.80 (m, 7H, OCH_3, OCH_3', aryl-C*H*N), 6.75 – 6.89 (m, 3H, arom.). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.93, 32.52 and 36.61 (CH_2), 48.03 and 50.48 (*C*H_2C=O, *C*H_2C=O′), 55.87 and 55.91 (OCH_3, OCH_3'), 56.69 and 60.81 (alkyl-*C*HN, aryl-*C*HN), 62.38 (CH_2OH), 109.76, 111.29, 118.58 and 135.34 (arom.), 208.75 (C=O).

Minor diastereomer (***trans*-9**): Yield: 0.21 g, 18 %), $[\alpha]_D^{22}$ = 23.3 (*c* = 2.0, $CHCl_3$), R_f = 0.41 (CH_2Cl_2/MeOH 9 : 1). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10 – 1.56 (m, 6H, CH_2), 2.06 (s_{broad}, 2H, NH, OH), 2.22 (dd, 1H, J_{vic} = 5.4 Hz, J_{gem} = 14.3 Hz, CH_2C=O), 2.56 (m, 3H, CH_2C=O, CH_2C=O′), 3.21 (m, 1H, alkyl-C*H*N), 3.59 (dd, 1H, J_1 = 4.8 Hz, J_2 = 6.2 Hz, C*H*2OH), 3.84 and 3.86 (2s, each 3H, OCH_3, OCH_3'), 4.29 (dd, 1H, J_1 = 5.9 Hz, J_2 = 6.3 Hz, aryl-C*H*N), 6.80 – 6.91 (m, 3H, arom.). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.18, 32.27 and 33.79 (CH_2), 47.35 and 48.46 (CH_2C=O, CH_2C=O′), 52.37 and 55.07 (alkyl-*C*HN, aryl-*C*HN), 55.87 and 55.91 (OCH_3, OCH_3'), 62.34 (CH_2OH), 110.05, 111.12, 118.87, 135.13, 148.44 and 149.16 (arom.), 209.33 (C=O).

*(4S,9aS)-4-(3,4-Dimethoxyphenyl)-decahydroquinolizidin-2-one (**10**)*

To a solution of piperidone ***cis*-9** (0.51 g, 1.66 mmol) in 5 mL of acetonitrile, triethylamine (0.22 mL, 1.6 mmol) and CCl_4 (0.24 mL, 2.5 mmol) were given. After cooling to 0 °C triphenylphosphine (0.52 g, 2.0 mmol) was added. The mixture was stirred at 0 °C for 30 min and allowed to warm up to r. t. After 48 h (montoring by TLC) sat. $NaHCO_3$ solution (10 mL) and diethyl ether (60 mL) were added. The organic solution was washed with brine. The aqueous layer was extracted twice with diethyl ether (50 mL).

The combined organic solutions were dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. Purification of the crude quinolizidinone **10** was carried out by chromatography on silica (19 × 3 cm) in light petroleum/ethyl acetate (1 : 2.5). The NMR spectroscopic data of **10** are in agreement with those given in the literature [3c]. Yield: 0.38 g (76 %), pale yellow, amorphous solid; $[\alpha]_D^{22} = -41.9$ (c = 1.5, $CHCl_3$), R_f = 0.22 (light petroleum/ethyl acetate 1 : 2). – FT-IR ($CDCl_3$): 1719 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.18 – 1.66 (m, 7H, CH_2), 2.25 – 2.78 (m, 6H, NCH_2, $NCHR_2$, $CH_2C{=}O$, $CH_2C{=}O'$), 3.17 (dd, 1H, J_{vic} = 2.3 Hz, $J_{vic'}$ = 11.7 Hz, aryl-C*H*N), 3.83 und 3.86 (2s, each 3H, OCH_3, OCH_3'), 6.79 (s, 1H, arom.), 6.87 (m, 2H, arom.). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 24.10, 25.75 and 34.26 (CH_2), 48.65 and 50.78 ($CH_2C{=}O$, $CH_2C{=}O'$), 52.71 (NCH_2), 55.80 and 55.91 (OCH_3, OCH_3'), 62.39 ($NCHR_2$), 69.90 (aryl-*C*HN), 109.71, 110.99, 119.45, 135.10, 148.28 and 149.28 (arom.), 207.75 (C=O).

*(–)-(2S,4S,9aS)-2-Hydroxy-4-(3,4-dimethoxyphenyl)-decahydroquinolizidine (**11**) (Lasubin II)*

To a solution of quinolizidinone **10** (0.33 g, 1.14 mmol) in dry tetrahydrofuran (10 mL) at −78 °C 1.5 mL of a 1 M solution (1.5 mmol) of lithium tris-siamylborohydride (LS-Selectride®) in tetrahydrofuran were given, and the solution was stirred for 2.5 h [3c]. Sat. $NaHCO_3$ solution (3 mL) was added and the tetrahydrofuran removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), washed with sat. NaCl solution (10 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude lasubin II was purified by chromatography on silica (8 × 2.5 cm) in CH_2Cl_2/MeOH 9 : 1, subsequently in 100 % MeOH. The spectroscopic data (IR [3c], NMR [3b]) of **11** are in agreement with those given in the literature. Yield: 0.17 g (51 %), yellow, amorphous solid; diastereomeric ratio: ≫ 10 : 1 (^1H NMR), $[\alpha]_D^{22} = -34.2$ (c = 0.57, $CHCl_3$), $[\alpha]_D^{22} = -30.8$ (c = 0.34, MeOH); lit.: [2] $[\alpha]_D^{22} = -34.7$ (c = 0.32, MeOH). – FT-IR ($CDCl_3$): ν = 3614, 3456, 3155, 3007, 2973, 2839, 2798, 2254, 1818, 1794, 1709, 1641, 1606, 1694, 1563, 1516, 1465, 1443, 1421, 1386, 1341, 1314, 1300, 1261, 1232, 1197, 1179, 1152, 1133, 1094, 1076, 1047, 1029, 1014, 986, 908, 810, 732 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 – 1.27 (m, 4H, CH_2), 1.28 – 1.35 (m, 2H, CH_2), 1.40 – 1.62 (m, 4H, CH_2), 1.72 (d, 1H, J_{gem} = 14.0 Hz, NCH_2), 1.82 (dt, 1H, J_{vic} = 2.6 Hz, J_{gem} = 14.2 Hz, NCH_2), 2.34 (m, 1H, $NCHR_2$), 2.61 (d, 1H, J = 11.5 Hz, C*H*OH), 3.27 (dd, 1H, J_{vic} = 3.0 Hz, $J_{vic'}$ = 11.8 Hz, aryl-CHN), 3.77 and 3.88 (2s, each 3H, OCH_3, OCH_3'), 4.07 (t, 1H, J = 2.6 Hz, OH), 6.70 – 6.86 (m, 3H, arom.). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.84, 26.10, 33.59, 40.32 and 42.72 (CH_2), 53.18 (NCH_2), 55.83, 55.92 and 56.50 (OCH_3, OCH_3', R_2CHOH), 63.45 ($NCHR_2$), 64.77 (aryl-*C*HN), 110.63, 111.06, 119.77, 137.22, 147.83 and 149.04 (arom.).

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