DOI: 10.1002/ejoc.200700459

First Total Synthesis of (+)-Adenophorine, a Naturally Occurring Inhibitor of Glycosidases

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Dedicated to Dr. André Guingant on the occasion of his 60th birthday

Keywords: Iminosugars / Adenophorine / RCM / Allylation / Imine / Epoxidation

The first total synthesis of a naturally occurring iminosugar, (+)-adenophorine, in 14 steps from the (+)-enantiomer of Garner's aldehyde, is reported. The strategy is based on the preparation and functionalization of enantiomerically pure *trans*-6-ethyl-2-hydroxymethyl-1,2,5,6-tetrahydropyridine.

Introduction

Since the discovery of nojirimycin (**1**, Figure 1) in 1966,[1] many iminosugars have been isolated from plants and microorganisms[2] and many syntheses of these compounds have been reported.[3] These natural or unnatural analogues of carbohydrates, in which the endocyclic oxygen atom is replaced by a nitrogen atom, are believed to modulate and to block the catalytic processes of glycosidases by mimicking the sugar moieties of natural substrates of the enzymes.[4] Because of the involvement of glycosidases in various important biological processes, such as intestinal digestion, post-translational processing of glycoproteins, or lysosomal catabolism of glycoconjugates, potential glycosidase inhibitors such as *N*- or *C*-alkylated iminosugars have been designed as therapeutic solutions for several diseases (type II diabetes, viral and bacterial infections, lysosomal storage disorders, tumor metastasis).[5] Currently, two iminosugars have been approved as therapeutic agents: miglitol (**2**, Glyset®)[6] as a second-generation α-glucosidase inhibitor for treatment of type II diabetes and *N*-butyl-deoxynojirimycin (NB-DNJ, **3**, Zavesca®)[7] as a glucosylceramide inhibitor in Gaucher disease. In 2000, Asano and co-workers isolated a series of α-1-*C*-alkylated analogues of 1,2-dideoxynojirimycin (fagomine) and 1-deoxy-homonojirimycin from *Lobelia sessilifolia* and *Adenophora* spp.[8,9] Their structural determination was accomplished by classical NMR (^{1}H and ^{13}C NMR) and mass spectroscopy studies (HRFABMS). Their inhibitory activities toward various glycosidases showed IC_{50} values of around 30 μM with β-galactosidase (bovine liver) for the α-1-*C*-alkylated 1,2-dideoxy-iminosugar **4** (Figure 1) and poor or no activity on α-glucosidase (rice),[9] whereas 1-deoxy-iminosugars such as α-1-deoxy-1-*C*-methylhomonojirimycin (named adenophorine, **5**, Figure 1) was active on α-glucosidase (IC_{50}: 34 μM) but not on β-galactosidase.[8] These results demonstrated that α-1-*C*-alkylation of natural deoxy-iminosugars is not a negative factor for glycosidase inhibition and that the presence and relative positions of the hydroxy substituents on the iminosugar seem to be determinant for selectivity. However, the rules of selectivity are not yet clearly understood.

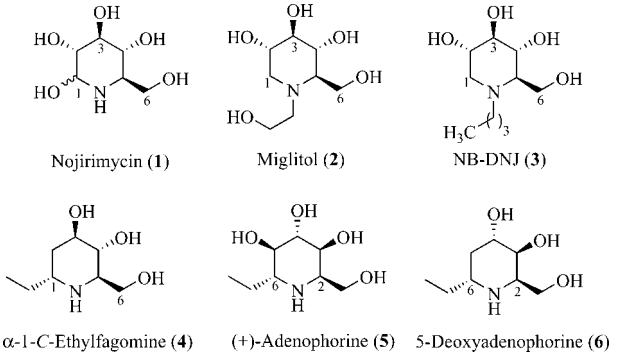

Figure 1. Nojirimycin and homonojirimycin analogues.

As part of our ongoing program involving the synthesis of alkaloids, we have developed an efficient route to chiral *trans*-6-alkyl-2-hydroxymethyl-1,2,5,6-tetrahydropyridines.[10]

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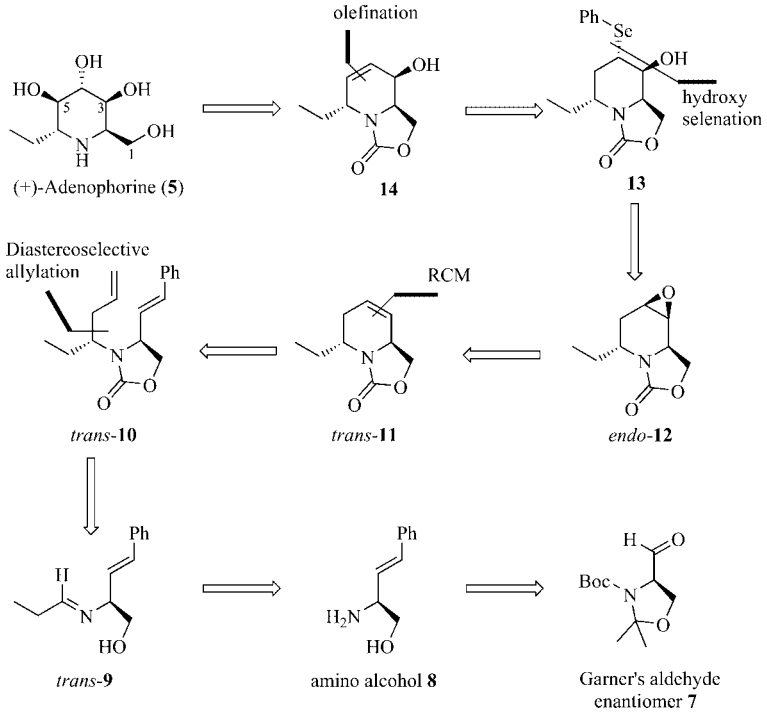


Scheme 1. Retrosynthetic analysis.

Recently, we reported the use of these intermediates for the synthesis of enantiomerically pure 5-deoxyadenophorine (**6**, Figure 1),[11] a naturally occurring α-1-*C*-ethyl-1-deoxyiminosugar, and of some α-1-*C*-alkyl analogues as racemic mixtures, in the idose and galactose series.[12] We wish to describe here the asymmetric total synthesis of (+)-adenophorine (**5**), another rare example of a naturally occurring iminosugar bearing a lipophilic substituent at the anomeric position. The absolute configuration of this (+)-iminosugar, isolated from *Adenophora* spp. by Ikeda and co-workers in 2000,[8] was determined three years later by optical rotation measurements performed on the (–) enantiomer synthesized by Davis et al.[13]

Iminosugars are frequently synthesized from carbohydrates as chiral pool starting materials with use of an amination–intermolecular cyclization sequence or an intramolecular reductive amination cyclization as the key step.[3c] We intended, however, to access these types of polyhydroxylated piperidines from amino acids by our previously described methodology.[10,11] In our strategy, the configuration of each stereogenic center has to be controlled during the building steps. We planned to construct the piperidine moiety and to introduce the three hydroxy groups diastereoselectively by applying key reactions as depicted in the retrosynthetic Scheme 1: diastereoselective allylation of imine **9**, ring-closing metathesis reaction to build the *trans*-2,6-disubstituted 1,2,5,6-tetrahydropyridine skeleton **11**, and an olefination step following the oxidation of the selenide **13**. The 1,2,5,6-tetrahydropyridine moiety **11** could thus be prepared in an enantiomerically pure form from (*R*)-(+)-Garner's aldehyde enantiomer **7** as already described.[11]

Results and Discussion

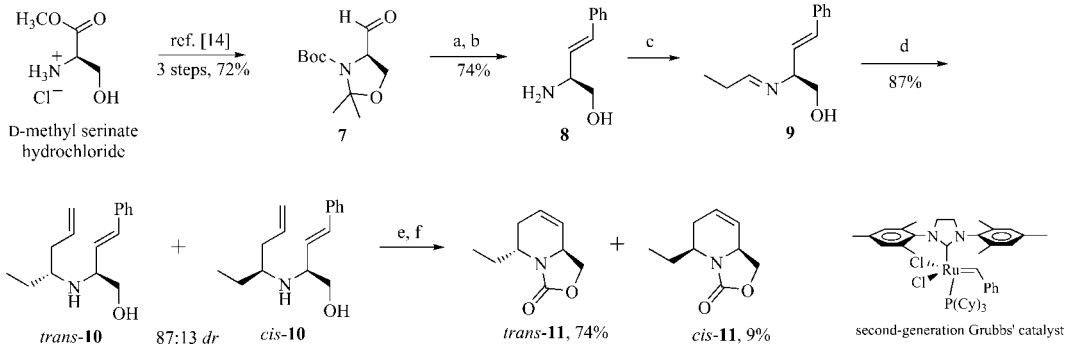
Preparation of *trans*-6-Ethyl-2-hydroxymethyl-1,2,5,6-tetrahydropyridine Derivative 11

(+)-Garner's aldehyde enantiomer **7** was prepared from commercially available D-methyl serinate hydrochloride in 72% overall yield by the three-step sequence reported by McKillop and co-workers (Scheme 2).[14] This aldehyde was then converted into amino alcohol **8** by means of a Horner–Wadworth–Emmons olefination reaction [100% (*E*) isomer], followed by acidic hydrolysis of the protecting groups.[10,15] Condensation of propionaldehyde with **8** furnished imine **9**, to which excess allylmagnesium bromide was added to give diethylenic amino alcohol **10** as an inseparable 87:13 mixture of *trans* and *cis* diastereoisomers. We have previously confirmed the relative configuration of the major adduct *trans*-**10** with the aid of a chelation model and the X-ray structure of an elaborated piperidine intermediate.[11]

From **10**, the formation of a tetrahydropyridine ring through a ring-closing metathesis reaction[16] was optimized after the protection of the diethylenic amino alcohols *trans*-**10** and *cis*-**10**[17] as the corresponding *trans* and *cis* oxazolidinones, which were not separable on silica gel (Scheme 2). Treatment of the diastereoisomeric mixture with second-generation Grubbs' catalyst and separation of the diastereoisomers by flash chromatography provided the pure tetrahydropyridine *trans*-**11** in 74% yield over two steps.

Stereoselective Addition of the Secondary Hydroxy Groups

Of the reported methods concerning the transformation of olefins into allylic alcohols,[18] we decided to apply a

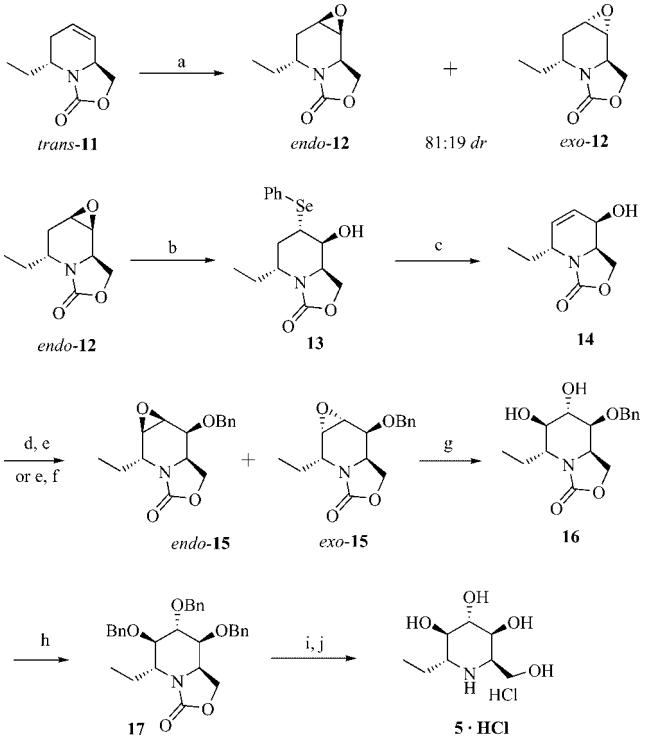


Scheme 2. Reagents and conditions: a) diethyl benzylphosphonate, *n*-BuLi, THF, –78 °C to room temp., 14 h, 75%; b) concentrated HCl, MeOH, reflux, 4 h, 98%; c) EtCHO, $MgSO_4$, THF, room temp., 12 h; d) excess allylmagnesium bromide, THF, Et_2O, –78 °C to –10 °C, 6 h, 87%; e) carbonyldiimidazole, Et_3N, CH_2Cl_2, 18 h, 88%; f) second-generation Grubbs' cat. (5 mol-%), CH_2Cl_2, reflux, 1 h, 84% *trans*-**11**, 10% *cis*-**11**.

three-step process designed to introduce the alcohol function in a regioselective and stereoselective manner. Epoxidation of tetrahydropyridine *trans*-**11** with a freshly distilled solution of dimethyldioxirane (DMDO) in acetone[19,20] afforded a crude 81:19 mixture of *endo*/*exo* epoxides. The known epoxide *endo*-**12**[11] was isolated in a consistent 60% yield after separation by flash chromatography (Scheme 3). When *m*CPBA was used as described previously,[11] the yield of pure *endo*-**12** could vary from 40 to 86%. Regioselective opening of the epoxide ring with a "selenium-boron complex" generated in situ from diphenyldiselenide and sodium borohydride provided compound **13** as a single product, obtained in 72% yield after purification. When this compound was oxidized with an aqueous solution of hydrogen peroxide, phenylselenic acid elimination occurred spontaneously to give allylic alcohol **14** (63% yield after purification).

Our next goal was to obtain epoxide *exo*-**15** stereoselectively from allylic alcohol **14**. We decided to avoid the use of *m*CPBA as epoxidation agent because of its known ability to assist allylic alcohol epoxidation;[21] in a single assay, we obtained a 1:1 mixture of epoxides *endo*- and *exo*-**15** after subsequent benzylation. We therefore set out to carry out the epoxidation reaction with DMDO, which could not form any intermolecular hydrogen bond with the hydroxy group. Under these conditions we obtained a crude 5:95 mixture of diastereoisomers **15**, which were separable by flash chromatography only after benzylation of the hydroxy group (Scheme 3, steps d and e). The major product *exo*-**15** was isolated in 41% yield over two steps from allylic alcohol **14** and its absolute configuration was unambiguously determined by an X-ray crystal structure (Figure 2).

However, the yield could be optimized to 60% over two steps when allylic alcohol **14** was protected beforehand by treatment with benzyl bromide and the resulting benzylated derivative (82% yield) was subjected to epoxidation with *m*CPBA (Scheme 3, steps e and f). This process led to a 2:98 mixture of diastereoisomers, and purification by flash chromatography provided epoxide *exo*-**15** in 73% yield. Opening of this epoxide by use of acetic acid as solvent or with sodium acetate in acetic acid[22] or alkoxide in DMF[23]



Scheme 3. Reagents and conditions: a) DMDO, acetone, room temp., 4 h, 60% *endo*-**12** (*exo*-**12** not isolated); b) Ph_2Se_2, $NaBH_4$, EtOH, room temp., 12 h, 72%; c) 50% aq. H_2O_2, THF, room temp., 2 h, 63%; d) DMDO, acetone, room temp., 4 h; e) BnBr, NaH, THF, room temp., 12 h, 41% for *exo*-**15** (2 steps); f) *m*CPBA, CH_2Cl_2, room temp., 72 h, 60% for *exo*-**15** (2 steps); g) 1 M H_2SO_4 (3 equiv.), 1:1 mixture of H_2O/dioxane, 80 °C, 12 h; h) BnBr, NaH, DMF, room temp., 2 h, 60% (2 steps); i) 8 M NaOH, MeOH, 95 °C, 48 h, 76%; j) H_2, HCl, $Pd(OH)_2$, EtOH, room temp., 24 h, quant.

was unsuccessful. More strongly acidic conditions were necessary to provide the desired product. In a first assay, conducted in acetic acid in the presence of trifluoroacetic acid,[24] a mixture of acylated derivatives of **16** was observed. After methanolysis and benzylation of the two free hydroxy groups under classical conditions, the expected compound **17** could be purified in 32% yield over the three steps. In a secondary assay, treatment of epoxide **15** with

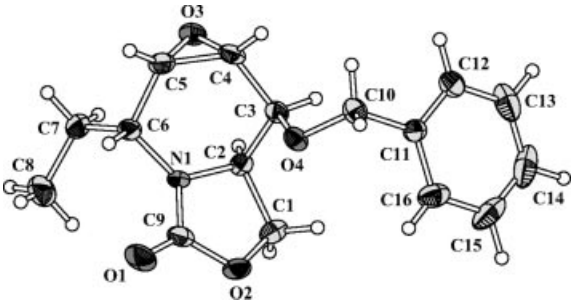


Figure 2. Molecular diagram of *exo*-**15**. Atoms of the asymmetric unit are depicted as ellipsoids at the 50% probability level.

sulfuric acid (3 equiv.) in a 1:1 water/dioxane mixture[25] afforded the single diol **16**, which was benzylated for the purification step. In this way, compound **17** was prepared from *exo*-**15** in 60% yield for the two steps.

To achieve our total synthesis of adenophorine, cleavage of the protecting groups was performed. In the first step, hydrolysis of the oxazolidinone group was carried out under basic conditions with aqueous NaOH in methanol at reflux. Then, in the second step, hydrogenolysis of the resulting dibenzylated derivative in an acidic medium[26] with $Pd(OH)_2$ as the catalyst afforded the expected adenophorine as its hydrochloride. ^1H and ^{13}C NMR spectra measured in D_2O/NaOD were compared to those in D_2O published by Asano and co-workers for natural (+)-adenophorine.[8] No difference was observed for the chemical displacements and coupling constants of the protons, while carbon displacements were systematically shifted from 1.5 to 2 ppm. We concluded that we had successfully synthesized the natural (+)-adenophorine, which was supported by the optical rotation measurement of +44 (c = 0.16, H_2O, NaOD) in comparison with the literature value of +59.7 (c = 1, H_2O).[8]

Conclusions

Four years after the publication of the (–)-adenophorine synthesis by Maughan and co-workers,[13] we have performed the first total synthesis of naturally occurring (+)-adenophorine in 14 steps from the Garner's aldehyde enantiomer and in 3.5% overall yield. We have once again exploited the synthetic potential of the *trans*-2,6-disubstituted 1,2,5,6-tetrahydropyridine key intermediate for the preparation of enantiomerically pure α-1-*C*-alkyl-iminosugars. Starting from (2*S*,6*R*)-6-ethyl-2-hydroxymethyl-1,2,5,6-tetrahydropyridine, we have controlled the stereoselectivity of the introduction of the three secondary hydroxy groups of adenophorine. Successive epoxidations of enantiopure substituted tetrahydropyridines *trans*-**11** and **14** and regioselective opening of these epoxides with selenium-boron complex and water, respectively, could be achieved with good stereoselectivity, undoubtedly controlled by the conformation of the starting materials and the steric effects induced by the substituents on the piperidine moiety. These substituted tetrahydropyridine intermediates *trans*-**11** and **14** offer the possibility of performing modulations on the adenophorine structure and we are currently investigating the synthesis of adenophorine isomers.

Experimental Section

General Methods: All reactions were performed under N_2 in flame-dried flasks using anhydrous solvents and monitored by TLC (Kieselgel $60F_{254}$ MERCK aluminium sheet) with detection by UV light and/or with ethanolic phosphomolybdic acid solution. Flash column chromatography was performed on silica gel (60 ACC 40–63 μm, CARLO–ERBA REACTIFS - SDS). Optical rotation values were measured in a 100 mm cell on a Perkin–Elmer 341 polarimeter with Na lamp radiation. Melting points were determined on an RCH (C. REICHERT) microscope equipped with a Koffer heating system. IR spectra were recorded with a BRUKER Vector 22 spectrometer. NMR spectra were recorded on a BRUKER Avance 300 at 300 MHz (^1H) and 75 MHz (^{13}C) or on a BRUKER ARX 400 at 400 MHz (^1H) and 100 MHz (^{13}C), in an appropriate solvent (Me_4Si as an internal standard for $CDCl_3$), and chemical shifts were assigned with the aid of DEPT experiments and by 2D correlation techniques (COSY and HMQC). Mass spectra were accomplished with an HP 5889A quadripolar spectrometer by electronic impact EI (70 eV) or chemical ionization CI (500 eV) with NH_3 gas. HRMS spectra were recorded at the "Centre Régional de Mesures Physiques de l'Ouest" (CRMPO, Université de Rennes 1). Dimethyldioxirane solution in acetone was prepared by the procedure of Adam et al. and the concentration was determined by the iodometric titration method.[19]

Compounds **7** to **11** are described in a preceding paper published by our group.[11]

(1a*R*,3*R*,7a*R*,7b*S*)-3-Ethylperhydro[1,3]oxazolo[3,4-*a*]oxireno[2,3-*c*]-pyridin-5-one (*endo*-12): A freshly distilled solution of dimethyldioxirane (47 mL, c = 0.05 M, 2.36 mmol) was added to a solution of tetrahydropyridine **11** (198 mg, 1.18 mmol) in acetone (5 mL), cooled to 0 °C. After stirring at 0 °C for 15 min and at room temperature for an additional 4 h, the solution was concentrated in vacuo to give a crude 81:19 mixture of epoxides *endo*-**12** and *exo*-**12**. Purification by flash chromatography (100% petroleum ether, then EtOAc/petroleum ether 60%) afforded *endo*-**12** (130 mg, 60%) as a colorless oil (*exo*-**12** was not isolated in a pure form). R_f = 0.35 (EtOAc/petroleum ether 80%). $[\alpha]_D^{20}$ = –10.8 (c = 0.926, $CHCl_3$) [ref.[11] $[\alpha]_D^{20}$ = –13.9 (c = 0.720, $CHCl_3$)]. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.50 (t, J = 8.6 Hz, 1 H, 7-H), 4.32 (dd, J = 5.5, J = 8.6 Hz, 1 H, 7-H), 4.15 (dd, J = 5.5, J = 8.6 Hz, 1 H, 7a-H), 3.71 (m, 1 H, 3-H), 3.33 (t, J = 4.6 Hz, 1 H, 1a-H), 3.12 (d, J = 3.9 Hz, 1 H, 7b-H), 2.27 (dd, J = 7.8, J = 15.7 Hz, 1 H, 2-H), 1.76 (dd, J = 5.3, J = 15.7 Hz, 1 H, 2-H), 1.63–1.46 (m, 2 H, CH_3–CH_2), 0.94 (t, J = 7.4 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0 (C-5), 65.1 (7-C), 50.1, 49.9 (C-1a, C-7b), 48.8 (C-7a), 47.0 (C-3), 26.0, 25.3 (C-2, CH_3–CH_2), 10.5 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = 2923, 2853, 1742 cm^{-1}. MS (EI): m/z (%) = 183 (6) $[M]^+$, 154 (100), 92 (24), 55 (35).

(5*R*,7*S*,8*S*,8a*R*)-5-Ethyl-8-hydroxy-7-(phenylselenyl)perhydro[1,3]-oxazolo[3,4-*a*]pyridin-3-one (13): Diphenyl diselenide (157 mg, 0.50 mmol) was suspended in dry ethanol (2 mL). At 0 °C, $NaBH_4$ (38 mg, 1.01 mmol) was slowly added and the suspension was stirred until complete dissolution. At room temperature, a solution of the epoxide *endo*-**12** (154 mg, 0.84 mmol) in ethanol (3 mL) was added, and the reaction mixture was stirred overnight at room temperature. At 0 °C, the yellow solution was quenched with a satu-

rated aqueous solution of NH_4Cl and concentrated under reduced pressure. The residue was partitioned between EtOAc (20 mL) and water (20 mL) and the aqueous phase was extracted with EtOAc (twice). The combined organic fractions were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/petroleum ether, 40%) yielded **13** (205 mg, 72%) as a white solid. R_f = 0.30 (EtOAc/petroleum ether 50%). M.p. 110 °C (CH_2Cl_2). $[\alpha]_D^{20}$ = –26.4 (c = 1.040, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 2 H, Ph), 7.32–7.62 (m, 3 H, Ph), 4.45 (m, 1 H, 8a-H), 4.40–4.34 (m, 2 H, 1-H), 3.84 (m, 1 H, 5-H), 3.70 (br. s, 1 H, 8-H), 3.61 (m, 1 H, 7-H), 3.21 (d, J = 6.6 Hz, 1 H, OH), 2.70 (dt, J = 6.3, J = 15.2 Hz, 1 H, 6-H), 1.95–1.75 (m, 2 H, 6-H, CH_3–CH_2), 1.64 (m, 1 H, CH_3–CH_2), 0.96 (t, J = 7.4 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9 (Ph), 158.0 (C-3), 133.7, 129.5, 128.0 (Ph), 68.3 (C-8), 63.9 (C-1), 50.6, 50.2 (C-5, C-8a), 41.9 (7-C), 26.8, 26.5 (C-6, CH_3–CH_2), 11.2 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = $\tilde{\nu}$ = 3500–3100, 2925, 1722, 1434 cm^{-1}. MS (EI): m/z (%) = 341 (12) $[M]^+$ (^{80}Se), 339 (7) $[M]^+$ (^{78}Se), 312 (12) (^{80}Se), 310 (6) (^{78}Se), 184 (55), 99(42), 57 (100). HRMS (EI) calcd. for $C_{15}H_{19}NO_3{}^{80}Se$ $[M]^+$: 341.0530; found 341.0542.

(5*R*,8*R*,8a*R*)-5-Ethyl-8-hydroxy-1,5,8,8a-tetrahydro[1,3]oxazolo-[3,4-*a*]pyridin-3-one (14): A solution of hydrogen peroxide (560 µL, 50% in water, 8.2 mmol) was added to a solution of the alcohol **13** (280 mg, 0.82 mmol) in THF (6 mL), cooled to 0 °C. The solution was stirred at room temperature for 2 h. EtOAc (15 mL) and water (15 mL) were added and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and then with brine. After drying over anhydrous $MgSO_4$, filtration, and removal of the solvent under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether 10%, then EtOAc/petroleum ether 60%) to give **14** (95 mg, 63%) as white crystals. R_f = 0.29 (90% EtOAc/petroleum ether). M.p. 134 °C (Et_2O). $[\alpha]_D^{20}$ = –327.5 (c = 0.224, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.10 (ddd, J = 2.2, J = 5.6, J = 10.2 Hz, 1 H, 7-H), 5.98 (dd, J = 3.3, J = 10.2 Hz, 1 H, 6-H), 4.65 (dd, J = 4.2, J = 8.6 Hz, 1 H, 1-H), 4.40 (t, J = 8.6 Hz, 1 H, 1-H), 4.17 (m, 1 H, 5-H), 3.93–3.83 (m, 2 H, 8-H, 8a-H), 2.33 (d, J = 9.6 Hz, 1 H, OH), 1.78–1.48 (m, 2 H, CH_3–CH_2), 0.98 (t, J = 7.5 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9 (C-3), 132.4 (C-6), 125.5 (C-7), 63.9 (C-1), 62.1, 53.6 (C-8, C-8a), 52.0 (C-5), 26.7 (CH_3–CH_2), 10.2 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = 3584, 3500–3100, 1724, 1429 cm^{-1}. MS (EI): m/z (%) = 183 (3) $[M]^+$, 154 (51), 98 (100), 83 (42). HRMS (EI) calcd. for $C_9H_{13}NO_3$ $[M]^+$: 183.0895; found 183.0898.

(1a*S*,2*R*,6a*R*,7*S*,7a*S*)-7-Benzyloxy-2-ethylperhydro[1,3]oxazolo[3,4-*a*]oxireno[2,3-*d*]pyridin-4-one (15): NaH (16 mg, 60% mineral oil dispersion, 0.40 mmol) was slowly added to a solution of the allylic alcohol **14** (61 mg, 0.33 mmol) in dry THF (3 mL), cooled to 0 °C. The suspension was stirred at 0 °C until the evolution of H_2 had ceased (15 min) and at room temperature for an additional 15 min. Benzyl bromide (59 µL, 0.50 mmol) was added and the mixture was stirred at room temperature for 12 h. At 0 °C, a saturated aqueous NH_4Cl solution (5 mL) was added and the resulting aqueous phase was extracted with EtOAc (3×). The combined organic fractions were washed with brine, dried with anhydrous $MgSO_4$, and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether 30%) to give the expected benzylated derivative (74 mg, 82%) as white crystalline plates. R_f = 0.34 (EtOAc/petroleum ether 30%). M.p. 44 °C (from CH_2Cl_2). $[\alpha]_D^{20}$ = –271.1 (c = 0.820, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H, Ph), 6.16–6.02 (m, 2 H, 6-H, 7-H), 4.68 (d, J = 12.0 Hz, 1 H, Ph-CH_2-O), 4.59 (m, 1 H, 1-H), 4.49 (d, J = 12.0 Hz, 1 H, Ph-CH_2-O), 4.37 (t, J = 8.0 Hz, 1 H, 1-H), 4.24 (m, 1 H, 5-H), 3.88 (m, 1 H, 8a-H), 3.76 (m, 1 H, 8-H), 1.84–1.54 (m, 2 H, CH_3–CH_2), 1.0 (t, J = 7.4 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (C-3), 137.9 (Ph), 133.8, 123.2 (C-6, C-7), 128.3, 127.6, 127.3 (Ph), 69.8 (Ph-CH_2-O), 67.1 (C-8), 63.9 (C-1), 53.0 (C-8a), 52.0 (C-5), 26.9 (CH_3–CH_2), 10.0 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = $\tilde{\nu}$ = 2926, 1734, 1423 cm^{-1}. MS (CI): m/z = 291 $[M + NH_4]^+$, 274 $[M + H]^+$. HRMS (EI) calcd. for $C_{16}H_{19}NO_3$ $[M]^+$: 273.1365; found 273.1363.

This protected allylic alcohol (47 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. After addition of *m*CPBA (170 mg, 70% in water, 0.69 mmol), the solution was stirred at 0 °C for 1 h and at room temperature for an additional 72 h. An aqueous solution of $Na_2S_2O_3$ (10%, 3 mL) was added and the mixture was stirred at room temperature for 15 min before addition of a saturated aqueous $NaHCO_3$ solution (5 mL).The resulting solution was stirred for a further 5 min and the aqueous phase was extracted with CH_2Cl_2 (4×). After drying over anhydrous $MgSO_4$ and filtration, the organic fraction was concentrated in vacuo to give a crude 2:98 mixture of epoxides. Purification by flash chromatography (EtOAc/petroleum ether 30%) afforded *exo*-**15** (36 mg, 73%) as white crystalline plates. The epoxide *endo*-**15** was not isolated. R_f = 0.35 (EtOAc/petroleum ether 40%). M.p. 121 °C (from CH_2Cl_2). $[\alpha]_D^{20}$ = –130.8 (c = 0.424, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.40 (m, 5 H, Ph), 4.77 (d, J = 12.1 Hz, 1 H, Ph-CH_2-O), 4.68 (d, J = 12.1 Hz, 1 H, Ph-CH_2-O), 4.24–4.18 (m, 2 H, 6-H), 4.06 (td, J = 3.1, J = 7.2 Hz, 1 H, 2-H), 3.93–3.86 (m, 1 H, 6a-H), 3.81 (m, 1 H, 7-H), 3.39 (dd, J = 3.9, J = 6.8 Hz, 1 H, 7a-H), 3.35 (m, 1 H, 1a-H), 1.78–1.67 (m, 2 H, CH_3–CH_2), 1.03 (t, J = 7.4 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0 (C-4), 137.2, 128.7, 128.3, 127.9 (Ph), 73.2 (Ph-CH_2-O), 71.8 (C-7), 63.1 (C-6), 52.7, 52.0 (C-1a, C-7a), 51.0 (C-6a), 49.7 (C-2), 24.8 (CH_3–CH_2), 10.0 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = 3050, 2969, 2927, 1742, 1464, 1421, 1226, 1040 cm^{-1}. MS (CI): m/z = 307 $[M + NH_4]^+$, 290 $[M + H]^+$.

(5*R*,6*R*,7*S*,8*S*,8a*R*)-8-Benzyloxy-5-ethyl-6,7-dihydroxyperhydro-[1,3]oxazolo[3,4-*a*]pyridin-3-one (16): The epoxide *exo*-**15** (175 mg, 0.605 mmol) was dissolved in a mixture of dioxane and water (1:1, 30 mL). An aqueous H_2SO_4 solution (1 M, 1.8 mL, 1.81 mmol) was added, and the mixture was stirred at 80 °C for 12 h. A saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the mixture was stirred at room temperature for 10 min. The aqueous phase was extracted with EtOAc (3×), and the combined organic extracts were washed with brine. After drying over anhydrous $MgSO_4$ and filtration, the organic fraction was concentrated in vacuo to give **16** as a white oil. The residue was used without further purification. R_f = 0.30 (EtOAc/petroleum ether 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 5 H, Ph), 4.80 (d, J = 11.6 Hz, 1 H, Ph-CH_2-O), 4.56 (d, J = 11.6 Hz, 1 H, Ph-CH_2-O), 4.35–4.25 (m, 2 H, 6-H, 1-H), 4.24–4.16 (m, 2 H, 8a-H, 1-H), 3.93 (dd, J = 5.8, J = 10.1 Hz, 1 H, 5-H), 3.72 (br. s, 1 H, 7-H), 3.52 (br. s, 1 H, 8-H), 1.86 (m, 1 H, CH_3–CH_2), 1.66 (m, 1 H, CH_3–CH_2), 0.96 (t, J = 7.4 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0 (C-3), 138.0, 128.8, 128.7, 128.3 (Ph), 75.4 (C-8), 73.1 (Ph-CH_2-O), 71.0 (C-7), 66.6 (C-6), 63.1 (C-1), 58.7 (C-5), 48.9 (C-8a), 23.4 (CH_3–CH_2), 11.1 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = 3418, 3032, 2964, 2927, 2876, 1726, 1433, 1261 cm^{-1}. MS (CI) or MS (EI): m/z = no results, unstable compound.

(5*R*,6*R*,7*S*,8*S*,8a*R*)-6,7,8-Tribenzyloxy-5-ethylperhydro[1,3]oxazolo-[3,4-*a*]pyridin-3-one (17): NaH (154 mg, 60% mineral oil dispersion, 3.63 mmol) was slowly added to a solution of the crude diol **16** (0.605 mmol) in dry DMF (30 mL), cooled to 0 °C. The suspension was stirred at 0 °C until the evolution of H_2 had ceased (10 min)

and at room temperature for an additional 10 min. Benzyl bromide (289 μL, 2.42 mmol) was added, and the mixture was stirred at room temperature for 2 h. At 0 °C, saturated aqueous NH_4Cl solution (30 mL) was slowly added and the resulting aqueous phase was extracted with Et_2O (4×). The combined organic fractions were washed with brine (3×), dried with anhydrous $MgSO_4$, and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether 30%) to give **17** (177 mg, 60% for the 2 steps from **15**) as a colorless oil. R_f = 0.38 (EtOAc/petroleum ether 30%). $[\alpha]_D^{20}$ = –47.2 (c = 0.392, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.18 (m, 15 H, Ph), 4.71 (d, J = 11.0 Hz, 2 H, Ph-CH_2-O), 4.52–4.32 (m, 5 H, 1-H, Ph-CH_2-O), 4.26 (t, J = 8.7 Hz, 1 H, 1-H), 4.11 (ddd, J = 2.6, J = 4.6, J = 8.7 Hz, 1 H, 8a-H), 4.04 (br. t, J = 7.9 Hz, 1 H, 5-H), 3.90 (t, J = 2.6 Hz, 1 H, 7-H), 3.57 (br. s, 1 H, 6-H), 3.37 (t, J = 2.6 Hz, 1 H, 8-H), 1.82 (m, 1 H, CH_3–CH_2), 1.65 (m, 1 H, CH_3–CH_2), 0.93 (t, J = 7.4 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1 (C-3), 138.0, 137.5, 137.3, 128.6, 128.4, 128.1, 127.9, 127.7 (Ph), 73.7, 73.1, 72.5, 72.4, 71.4, 71.1 (C-6, C-7, C-8, Ph-CH_2-O), 63.2 (C-1), 53.7 (C-5), 49.8 (C-8a), 23.4 (CH_3–CH_2), 10.7 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = 3031, 2930, 1748, 1496, 1456, 1426 cm^{-1}. MS (CI): m/z = 505 $[M + NH_4]^+$, 488 $[M + H]^+$. HRMS (ESI) calcd. for $C_{30}H_{34}NO_5$ $[M + H]^+$: 488.2437; found 488.2443.

(+)-Adenophorine Hydrochloride (5·HCl): The oxazolidinone **17** (131 mg, 0.27 mmol) was dissolved in MeOH (13 mL) and an aqueous solution of NaOH (8 M, 3.4 mL, 2.70 mmol) was added. The mixture was stirred at 95 °C for 72 h and the solvent was removed under reduced pressure. The resulting white solid was dissolved in CH_2Cl_2 (20 mL) and water was added (20 mL). The basic aqueous phase was extracted with CH_2Cl_2 (6×) and the combined organic fractions were dried with anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the white solid was purified by flash chromatography (MeOH/CH_2Cl_2 10%) to give the expected amino alcohol (94 mg, 76%) as a white solid. R_f = 0.50 (MeOH/CH_2Cl_2 10%). $[\alpha]_D^{20}$ = +17.6 (c = 0.424, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 15 H, Ph), 4.92 (d, J = 9.3 Hz, 2 H, Ph-CH_2-O), 4.80 (d, J = 10.8 Hz, 1 H, Ph-CH_2-O), 4.69 (s, 2 H, Ph-CH_2-O), 4.62 (d, J = 10.8 Hz, 1 H, Ph-CH_2-O), 3.84 (dd, J = 5.5, J = 10.9 Hz, 1 H, HO–CH_2), 3.78–3.68 (m, 3 H, 3-H, 4-H, HO–CH_2), 3.36 (m, 1 H, 2-H), 3.07 (t, J = 8.8 Hz, 1 H, 5-H), 2.64 (td, J = 2.9, J = 8.8 Hz, 1 H, 6-H), 1.96 (m, 1 H, CH_3–CH_2), 1.25 (m, 1 H, CH_3–CH_2), 0.97 (t, J = 7.4 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 138.3, 138.1, 128.4, 127.9, 127.8, 127.7, 127.6 (Ph), 83.8, 83.2, 81.5 (C-3, C-4, C-5), 75.5, 75.2, 72.9 (Ph-CH_2-O), 58.1 (HO–CH_2), 54.6, 54.1 (C-2, C-6), 24.8 (CH_3–CH_2), 10.3 (CH_3–CH_2) ppm. IR (CCl_4): $\tilde{\nu}$ = 3335, 3031, 2925, 2361, 1496, 1456, 1361, 1067 cm^{-1}. MS (CI): m/z = 462 $[M + H]^+$. HRMS (EI) calcd. for $C_{28}H_{32}NO_3$ $[M – CH_2OH]^+$: 430.2382; found 430.2414. HRMS (EI) calcd. for $C_{22}H_{28}NO_4$ $[M – CH_2Ph]^+$: 370.2018; found 370.1995.

This amino alcohol (54 mg, 0.12 mmol) was dissolved in ethanol (10 mL) and a solution of HCl in propan-2-ol (5 M, 50 μL, 0.24 mmol) was added. The solution was stirred at room temperature under N_2 for 5 min. $Pd(OH)_2$/C (20%, 17 mg) was added, and the mixture was stirred at room temperature for 48 h under H_2. The reaction mixture was filtered through celite and washed with MeOH. Concentration in vacuo afforded (+)-adenophorine hydrochloride (**5**·HCl, 27 mg, quant.) as a colorless oil. $[\alpha]_D^{20}$ = +44 (c = 0.16, H_2O, NaOD) [ref.[8] $[\alpha]_D^{20}$ = +59.7 (c = 1, H_2O)]. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.83 (dd, J = 4.8, J = 12.0 Hz, 1 H, 1-H), 3.78 (m, 1 H, 3-H or 4-H or 5-H), 3.62–3.47 (m, 3 H, 1-H, 3-H and/or 4-H and/or 5-H), 3.43 (m, 1 H, 2-H or 6-H), 3.19 (m, 1 H, 2-H or 6-H), 2.02 (m, 1 H, CH_3–CH_2), 1.65 (m, 1 H, CH_3–CH_2), 0.97 (t, J = 7.5 Hz, 3 H, CH_3–CH_2) ppm. ^{1}H NMR (400 MHz, D_2O, NaOD): δ = 3.90–3.75 (m, 2 H, 1-H), 3.71 (dd, J = 6.0, J = 9.6 Hz, 1 H, 3-H), 3.45 (t, J = 9.6 Hz, 1 H, 4-H), 3.21 (m, 1 H, 2-H), 3.09 (t, J = 9.6 Hz, 1 H, 5-H), 2.62 (m, 1 H, 6-H), 1.83 (m, 1 H, CH_3–CH_2), 1.32 (m, 1 H, CH_3–CH_2), 0.93 (t, J = 7.6 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 73.2, 71.2, 69.7 (C-3, C-4, C-5), 57.7 (1-H), 59.0, 56.6 (C-2, C-6), 22.8 (CH_3–CH_2), 10.1 (CH_3–CH_2) ppm. ^{13}C NMR (100 MHz, D_2O, NaOD): δ = 75.7 (C-4, C-5), 72.9 (C-3), 57.9 (C-2), 57.5 (C-1), 54.4 (C-6), 24.8 (CH_3–CH_2), 9.7 (CH_3–CH_2) ppm. HRMS (ESI) calcd. for $C_8H_{18}NO_4$ $[M – Cl]^+$: 192.1236; found 192.1231.

X-ray Crystallographic Study: Data were collected on a Bruker–Nonius KappaCCD diffractometer at 150 K using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.7 Å^{-1} at a temperature of 150 K. The structure was solved by direct methods[27]and refined with the JANA2006 program.[28] Non-hydrogen atoms were defined anisotropically. The hydrogen atoms, all visible from the difference Fourier map, were placed in geometrically optimized positions and refined with a "riding" model.

Crystal Data for *exo*-15: $C_{16}H_{19}NO_4$, M_w = 289.3, 0.42 × 0.35 × 0.12 mm^3, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 4.8413(3), b = 12.5775(14), c = 23.537(3) Å, V = 1433.2(3) Å^3, Z = 4, $D_{calcd.}$ = 1.341 g cm^{-3}, μ(Mo-K_α) = 0.096 mm^{-1}. Of 18552 reflections measured, 4109 were unique (R_{int} = 0.116). R_1/wR_2 [$I \geq 2\sigma(I)$] = 0.0584/0.1039. R_1/wR_2 [all reflections] = 0.0988/0.1122, S = 1.28. Residual electron density is between –0.22 and 0.28 e$^-$ Å^{-3}

CCDC-643149 contains the supplementary crystallographic data for *exo*-**15**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

This program is supported by the Conseil Général de la Loire-Atlantique, the Centre National de la Recherche Scientifique, the Université de Nantes and the Ministère de l'Education Nationale, de la Recherche et de la Technologie with a doctoral fellowship for M. S. M. Pearson. We warmly thank Dr N. Asano (Hokuriku University, Japan) and Dr. B. G. Davis (University of Oxford, UK) for providing NMR spectra of adenophorine.

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Received: May 22, 2007
Published Online: July 30, 2007

