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Carbohydrate Auxiliaries in Stereoselective Syntheses of Decahydroquinoline Alkaloids[a]

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Summary. Using tetra-O-pivaloyl-β-*D*-galactopyranosylamine as the chiral auxiliary, both *trans*- and *cis*-annelated decahydroquinoline alkaloids can be synthesized stereoselectively. This methodology of asymmetric synthesis is based on the effect that both enantiomers of 2,6-disubstituted piperidin-4-ones are selectively and alternatively accessible using the auxiliary as the identical stereodifferentiating tool. In addition, the carbohydrate auxiliary controls the stereoselective protonation of enolates formed by conjugate addition of cuprates to N-galactosyl octahydroquinolin-4-ones. The syntheses of *trans*-4a-*epi*-pumiliotoxin C and *cis*-4a-*epi*-perhydro-219A illustrate this concept of asymmetric synthesis of decahydroquinoline alkaloids.

Keywords. Asymmetric synthesis; Decahydroquinoline alkaloids; Glycosylamine auxiliary; Domino *Mannich-Michael* reactions; Conjugate curprate addition.

Introduction

In contrast to their extensive application as enantiopure starting materials in ex-chiral-pool syntheses [1], the utility of carbohydrates as chiral auxiliaries in asymmetric synthesis was recognized only during the past 10 years [2]. Owing to their high content of stereogenic centers and functional groups, carbohydrates facilitate arrangements of a reacting group relative to shielding or coordinating groups which give rise to a distinct stereodifferentiation during the attack of a reagent.

In this sense, glycosylamines proved to be efficient chiral auxiliaries in reactions of imines with nucleophiles, *e.g.* in *Strecker* syntheses of α-amino nitriles [3], *Ugi* reactions [4, 5], syntheses of α-amino phosphonic acids [6], *Mannich* reactions [7], and domino *Mannich-Michael* reaction sequences [8] by which glycosylimines **1** are converted into chiral piperidinone derivatives **2** (Scheme 1).

Taking advantage of the excellent stereocontrol in these reactions and subsequent conjugate additions of cuprates to compounds **2**, we have stereoselectively synthesized alkaloids of the decahydroquinoline series. Such alkaloids have been isolated from glandular secretions of South American frogs of the family *Dendrobates*. Some of these compounds show marked biological effects, *e.g.* on

[a] Dedicated to Professor Dr. *Joachim Thiem* on the occasion of his 60th birthday

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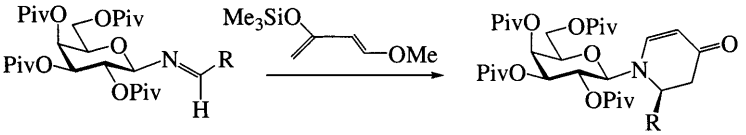
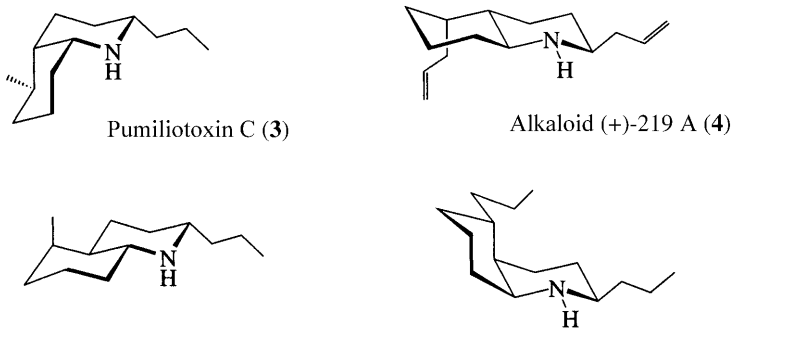


1 **2**

Scheme 1



Pumiliotoxin C (**3**) Alkaloid (+)-219 A (**4**)

trans-epi-Pumiliotoxin C (**5**) *cis-epi*-(+)-perhydro-219 A (**6**)

Scheme 2

the transport of ions through membranes and on the transduction of stimuli in the nervous system [9]. Interestingly, decahydroquinoline alkaloids from *Dendrobates pumilio* such as pumiliotoxin C (**3**) [10] have a *cis*-annelated decahydroquinoline structure, whereas those from *Dendrobates histrionicus* exclusively have *trans*-configuration, such as the alkaloid (+)-219A (**4**) [11].

Stereoselective syntheses of natural (−)-(**3**) and (+)-pumiliotoxin C have already been reported [12]. An auxiliary-controlled asymmetric synthesis of **3** was achieved by *Comins et al.* [13] who applied nucleophilic addition reactions to N-alkoxycarbonyl-3-trimethylsilyl-4-trimethylsilyloxy pyridinium salts derived from 8-phenylmenthol in the key step [13].

A stereoselective synthesis of alkaloid 219A (**4**) has also been described [14]. It is based on a reductive conversion of an enol triflate and subsequent hydrogenation of the formed chiral alkene (diastereomeric ratio 87:13). Perhydro 219A and its *cis*-annelated epimer **6** have been obtained from chiral trisubstituted cyclohexanes [15].

We here describe an alternative and uniform concept for the stereoselective syntheses of both *cis*- and *trans*-annelated decahydroquinoline alkaloids. In this strategy, 2,3,4,6-tetra-O-pivaloyl-galactosylamine **7** [3, 7] as the auxiliary not only controls the stereoselective formation of the stereogenic centers in 2-, 5-, and 8a-position, but also the diastereoselective protonation of an enolate at position C-4a which can be steered to either form the *trans*- or the *cis*-annelated bicyclic compounds. The principle is demonstrated for the syntheses of *epi-trans*-pumiliotoxin C [16] (**5**) and *epi-cis*-perhydro-219A (**6**), having opposite configuration to each other at C-2 and representing the *cis-trans*-annelated epimers of the natural alkaloids **3** and **4**, respectively.

Results and Discussion

Stereoselective syntheses of both enantiomers of 2-propyl-octahydroquinolin-4-one using the identical galactosylamine auxiliary **7**

Using galactosylamine **7**, both enantiomers of 2,6-*cis*-disubstituted piperidones can selectively be obtained depending upon the choice of the aldehyde in the formation of the imine **1** and the cuprate in the conjugate addition to product **2** [8].

Condensation of **7** with hex-5-enal gave the imine **8a**, whereas the analogous reaction with butyraldehyde formed the imine **8b** [8]. Domino *Mannich-Michael* reactions of imines **8** furnished the dehydropiperidiones **9a** and **9b** (Scheme 3).

Conjugate addition of the propylcuprate BF_3 complex [17] to **9a** resulted in the formation of N-galactosyl-(2*S*,6*R*)-2-propyl-6-pentenyl-piperidone **10a** with excellent stereoselectivity. On the other hand, 1,4 addition of *bis*-(4-(1-ethoxy-ethyloxy)-butyl)-cuprate to **9b** in presence of trimethylchlorosilane and subsequent treatment of the intermediate silyl enolether with fluoride gave (2*R*,6*S*)-2-propyl-6-(ethoxyethyloxy)-butyl-piperidinone **10b** in good diastereoselectivity. It should be noticed that reactions of the enaminone **9b** with pentenyl or functionalized butylcuprate/BF_3 complexes produced the 1,4 adducts in distinctly lower diastereoselectivity.

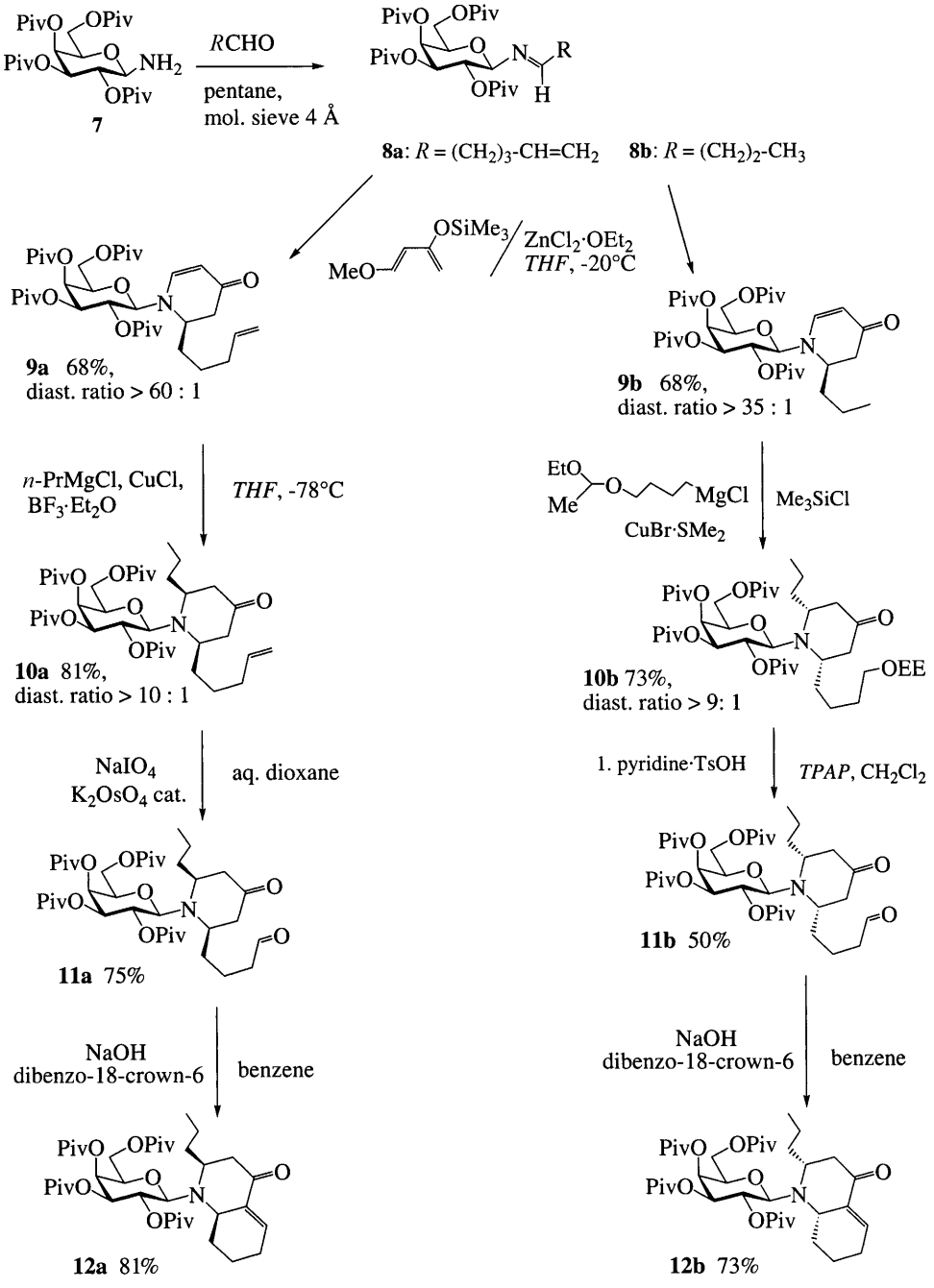
Oxidative cleavage of the olefinic double bound of **10a** using potassium osmate/sodium periodate and subsequent cyclizing aldol condensation of the formed aldehyde **11a** furnished the octahydroquinoline **12a** with (2*S*,8a*R*)-configuration. In contrast, removal of the (1-ethoxy)-ethyl (*EE*) group from **10b** using pyridinium *p*-toluenesulfonate (*PPTS*) followed by oxidation of the alcohol with tetrapropylammonium perruthenate (*TPAP*) [18] gave aldehyde **11b**, which under aldol condensation yielded the N-galactosyl octahydroquinolinone **12b** with opposite enantiomeric configuration of the N-heterocyclic system compared to that in **12a**. These syntheses illustrate that both enantiomers of such hydroquinoline derivatives can stereoselectively be obtained by this strategy using the identical glycosylamine auxiliary.

It should be noted that, apart from usual chromatographic purification, no separation of a minor diastereomer was required during the synthesis to obtain the pure diastereomers **11** and **12**.

Stereoselective synthesis of trans-annelated decahydroquinolines: trans-epi-4a-pumiliotoxin C (**5**)

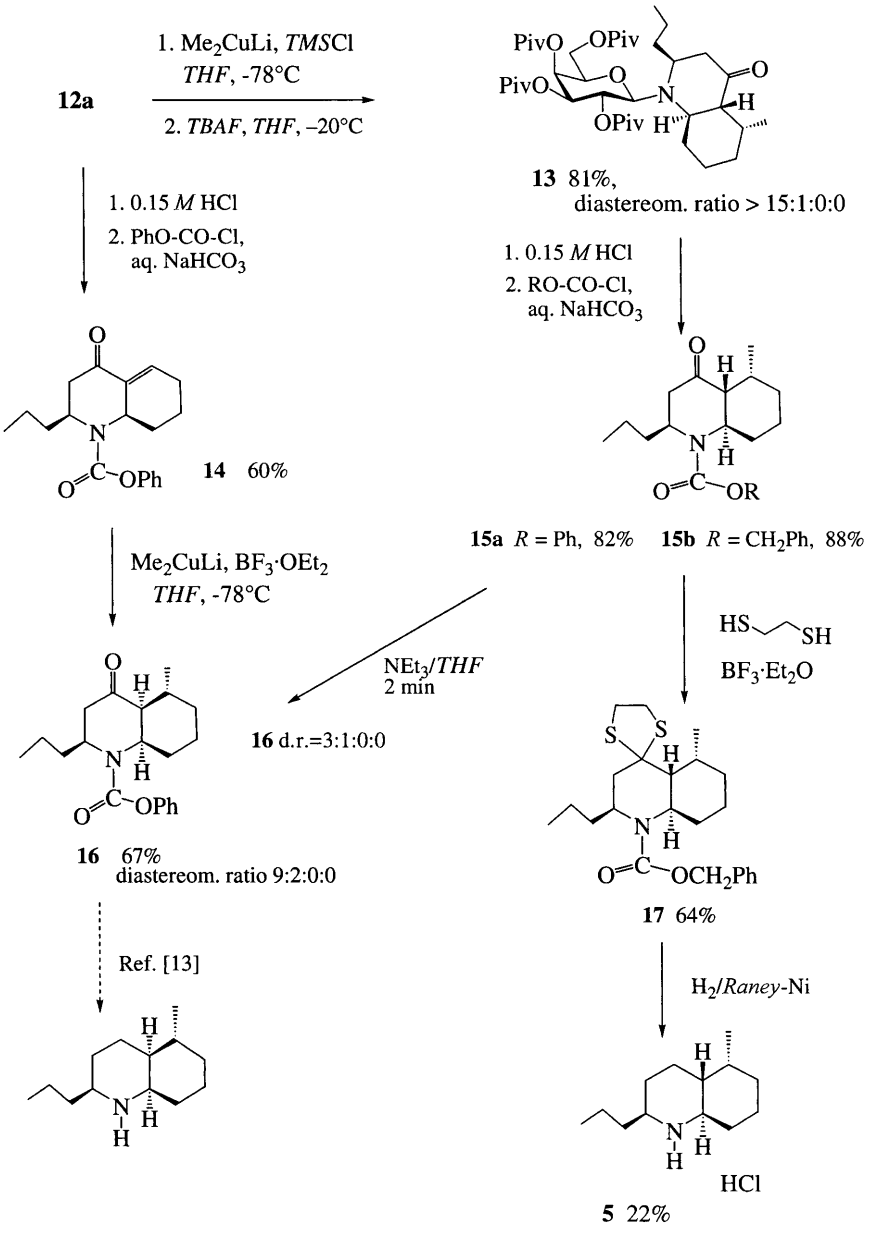
For the conversion of the (2*S*)-propyl-octahydroquinolinone diastereomer **12a** into pumiliotoxin C (**3**), 1,4 addition of lithium dimethylcuprate to the enone in presence of trimethylsilyl chloride was carried out (Scheme 4). Cleavage of the intermediate silyl enolether resulted in the formation of the adduct **13** with excellent diastereoselectivity and the expected configuration [13] at C-5 (5*R*).

However, **13** proved to be a *trans*-decahydroquinolinone derivative as was confirmed by the ^{1}H NMR signal of H-8a ($\delta = 3.26$ ppm (dt, $J_{8a,4a} = J_{8a,8'} = 11.2$ Hz, $J_{8a,8} = 3.5$ Hz)) and by X-ray analysis [16]. This result was unexpected, since *Comins et al.* [13] had carried out 1,4-methylcuprate addition to a octahydroquinolinone analogous to **12a** which carries a N-phenoxycarbonyl group instead of the



Scheme 3

N-galactosyl moiety and noted the formation of the *cis*-annelated decahydroquinolinone with high preference (97:3). In order to clarify the contradictory situation, the galactosyl auxiliary of **12a** was cleaved off by treatment with dilute HCl in methanol and substituted by the phenoxycarbonyl group (**14**). Compound **14** was identical with the precursor of the optically active pumiliotoxin C described by *Comins et al.* [13]. Conjugate addition of lithium dimethylcuprate to **14** in presence of



Scheme 4

trimethylchlorosilane and subsequent fluoridolysis of the intermediate silyl enolether preferentially yielded, in contrast to **13**, the *cis*-annelated decahydroquinolinone **16**.

To prove the hypothesis that the carbohydrate auxiliary actually steers the protonation of the enolate during the cleavage of the intermediate silyl enolether obtained by 1,4-addition of the cuprate to **12a**, the galactosyl moiety was also removed from product **13** and substituted by the phenoxycarbonyl (**15a**) or benzyloxycarbonyl group (**15b**).

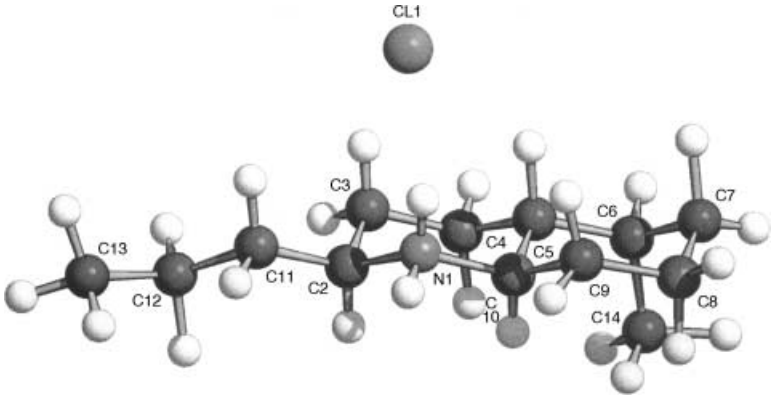


Fig. 1. X-Ray analysis of *trans*-4a-*epi*-pumiliotoxin C (**5**)

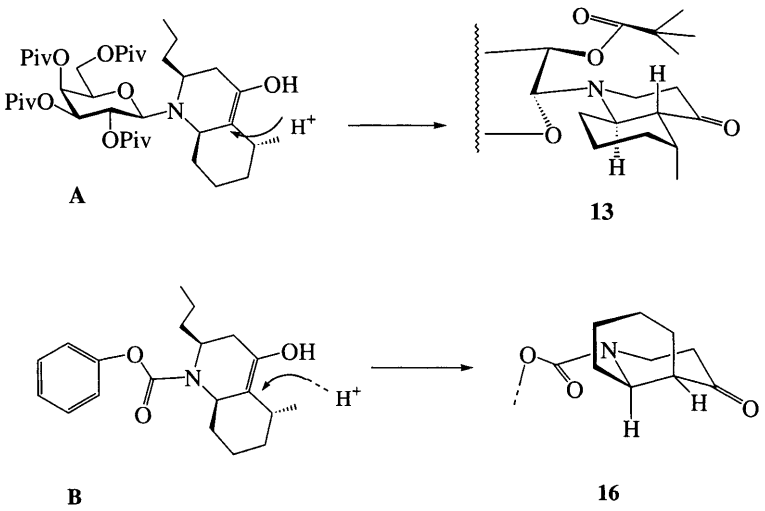
Treatment of the thus obtained *trans*-annelated decahydroquinolinone **15a** with triethylamine/*THF* (1:200 v/v) caused epimerization to form the preferred *cis*-annelated epimer **16** (*cis*:*trans* = 3:1, analytical HPLC) within 2 minutes. These results suggest that the *cis*-annelated decahydroquinolinone **16** constitutes the thermodynamically favoured epimer. It can be concluded that the carbohydrate auxiliary obviously directs the enolate protonation even against the thermodynamical preference in this simple cyclic system. Taking profit of this effect, the carbohydrate auxiliary opens up the possibility to readily synthesize *trans*-annelated decahydroquinolinone alkaloids usually requiring multistep procedures. In this sense, we have converted the *Z*-protected *trans*-decahydroquinolinone **15b** into its dithiolane derivative **17**. Treatment of **17** with hydrogen/*Raney* nickel resulted in simultaneous removal of the *Z* group and desulfurization. The hydrochloride of *trans*-4a-*epi*-pumiliotoxin C (**5**) was obtained in enantiomerically pure form. The configuration of **5** was confirmed by X-ray analysis (Fig. 1).

Interpretation of the stereoselective enolate protonation steered by the N-galactosyl auxiliary

The astonishing stereoselective protonation of the enolate **A** formed from the silyl enolether to give the *trans*-annelated decahydroquinolinone can be rationalized by stereoelectronic and steric effects.

The X-ray analysis of decahydroquinolinone **13** [16] gives evidence that the *exo*-anomeric effect, *i.e.* the delocalization of the nitrogen lone pair into the σ^*-orbital of the ring C–O bond, stabilizes the N-galactosyl heterocycle in conformation **A** with carbohydrate and heterocyclic ring systems arranged almost perpendicular to each other. Approach of the proton from the front side reduces the steric strain during ketone formation, since the carboxylic ring moves backwards, *i.e.* away from the bulky 2-pivaloyloxy group. If this steric hindrance is not present as in the case of the N-phenoxycarbonyl substituted enolate **B**, protonation preferentially leads to the *cis*-annelated decahydroquinoline **16**.

The *cis*-annelated compound **16** is the weaker CH-acid since its H-4a is located almost in the σ-plane of the carboxyl group. In contrast, the C_{4a}–H_{4a} bond of the *trans*-compound is located coaxial with the π^*-orbital of the carbonyl group and,



Scheme 5

therefore, the compound is considerably more acidic. If the outlined interpretation is correct, 1,4-cuprate additions to the enone in the N-galactosyl octahydroquinolinone **12b** should logically give *cis*-annelated decahydroquinolinones.

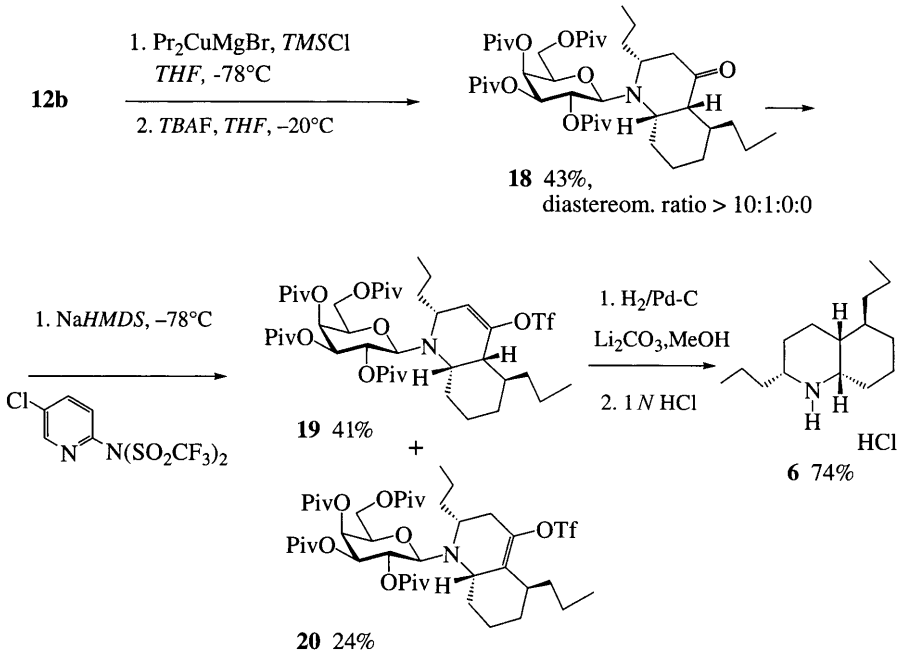
Stereoselective synthesis of cis-perhydro 219A

Reaction of N-galactosyl octahydroquinolinone **12b** with propylcuprate in the presence of trimethylsilyl chloride and subsequent cleavage of the intermediate silyl enolether gave the *cis*-annelated decahydroquinolinone **18** as predicted (Scheme 6).

The diastereoselectivity of the reaction was high, but the yield of **18** was only moderate. Obviously, the addition reaction is sterically more hindered compared to that with **12a** (Scheme 4). In the ^{1}H NMR spectrum of **18**, the double triplet with diaxial couplings $J_{h8a,H4a} = J_{H8a,8} \sim 11$ Hz characteristic for H-8a in *trans*-decahydroquinolinones is not observed. Instead, H-8a causes a multiplet at $\delta =$ 3.54 ppm which is not well structurized.

The galactosyl decahydroquinolinone **18** (as well as **13**) resists conversion into a dithiolane. Since reduction with $NaBH_4$ also failed, transformation to the corresponding enol triflate was applied. The only reagent to achieve this reaction was N-trifluoromethanesulfonyl-5-chloro-pyrid-2-yl-trifluoromethanesulfonamide (Cl*Pyr*N*Tf*$_2$) [19]. Unfortunately, the desired enol triflate **19** was formed in a mixture with its undesired regioisomer **20**. Separation of **19** was achieved by chromatography. Hydrogenation of **19** followed by acidolytic cleavage of the N-glycosidic bond gave the hydrochloride of *cis*-4a-*epi*-perhydro-219A (**6**). Comparison of the NMR data of this hydrochloride and those of the free amine **6** with those reported in the literature for the racemic [20] and optically active *cis*-perhydro-219A [15] confirm the structure of **6** and the correct stereochemistry at C-5.

The stereoselective syntheses of *trans-epi*-pumiliotoxin C (**5**) and *cis-epi*-perhydro-219A (**6**) illustrate the versatility of the galactosylamine **7** as the chiral auxiliary in stereoselective syntheses of *trans*- and of *cis*-annelated



Scheme 6

decahydroquinoline alkaloids. Moreover, *cis*-annulated decahydroquinolines of enantiomeric configuration opposite to **6** are also selectively accessible *via* the detachment and epimerization pathway (Scheme 4). The value of this methodology can be expanded even more if tri-O-pivaloyl-β-*D*-arabinopyranosylamine [21] is applied as the virtual enantiomer of the *D*-galactopyranosyl amine **7**. By this way, enantiomers of *trans*-annelated decahydroquinolines, like **5**, can selectively be constructed.

Experimental

NMR spectra were recorded on Bruker AM 400 (400 MHz ^{1}H, 100.6 MHz ^{13}C) and Bruker WT 200 (200 MHz ^{1}H, 50.3 MHz ^{13}C) NMR spectrometers. Chemical shifts are given in ppm relative to *TMS*. For N-galactosylated heterocyclic compounds, protons and carbons of the carbohydrate moiety are marked with a superscribed dash, *e.g.* H-2′. Analytical HPLC was carried out using a Pharmacia LBK 2150 unit with diode array detection. Columns: A: Eurospher 100, RP 18, 5 μ, 250 × 4 mm, Knauer Eurochrom, B: Sperisorb ODS II, RP 18, 5 μ, 250 × 4 mm, Bischoff; flow rate: 1 cm^3/min. Thin layer chromatography (TLC) was performed on Merck silica gel 60$_{F254}$, column chromatography on silica gel 60 (0.06–0.2 mm, Baker). FAB and FD mass spectra were measured on a Finnigan MAT 95 spectrometer, optical rotations on a Perkin Elmer 241 polarimeter. Melting points were taken on a Büchi Dr. Tottoli apparatus and are uncorrected. Elemental analysis data of new compounds were in agreement with the calculated values.

Schiff bases **8** of commercially available galactosylamine **7** (Merck-Schuchardt) were prepared according to a described procedure [22]. The synthesis of compound **9b** is described in Ref. [8].

(2R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(4-pentenyl)-5,6-didehydropiperidin-4-one (**9a**; $C_{36}H_{57}NO_{10}$)

9a was synthesized according to the general procedure described in Ref. [8] and purified by chromatography (petroleum ether:ethyl acetate = 4:1).

Yield: 68%; m.p.: 155–158°C; $[\alpha]_D^{22} = -61.5$ ($c = 1$, $CHCl_3$); $R_f = 0.30$ (petroleum ether: EtOAc = 3:1); *d.r.* = 65:1 (HPLC, column A; MeOH/H_2O 4:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 1.09, 1.15 and 1.26 (4s, 4 × 9H, piv-CH_3), 1.41 (m, 1H, CH_2), 1.60 (m, 2H, CH_2), 1.88 (m, 1H, CH_2), 2.00 (m, 2H, CH_2), 2.34 (d, 1H, $J_{gem} = 16.6$ Hz, H-3*ax*), 2.60 (dd, 1H, $J_{vic} = 6.3$ Hz, $J_{gem} = 16.6$ Hz, H-3*eq*), 3.70 (m, 1H, H-2), 3.95 (dd, 1H, $J_{6a',5'} = 6.9$ Hz, $J_{6a',6b'} = 10.5$ Hz, H-6a′), 4.02 (dd, 1H, $J_{5',6a'} = 6.8$ Hz, $J_{5',6b'} = 6.4$ Hz, H-5′), 4.14 (dd, 1H, $J_{6b',5'} = 6.3$ Hz, $J_{6b',6a'} = 10.5$ Hz, H-6b′), 4.54 (d, 1H, $J_{1',2'} = 9.1$ Hz, H-1′), 4.96 (m, 3H, H-5 and CH=CH_2), 5.16 (dd, 1H, $J_{3',4'} = 3.1$ Hz, $J_{3',2'} = 10.1$ Hz, H-3′), 5.41 (d, 1H, $J_{4',3'} = 3.0$ Hz, H-4′), 5.52 (dd, 1H, $J_{2',3'} = 9.8$ Hz, $J_{2',1'} = 9.5$ Hz, H-2′), 5.71 (dddd, 1H, $J_1 = 6.7$ Hz, $J_2 = 10.2$ Hz, −CH=CH_2), 6.88 (dd, 1H, $J_1 = 0.9$ Hz, $J_2 = 7.7$ Hz, H-6) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 25.08 (CH_2), 26.98, 27.08, 27.14 (piv-CH_3), 30.22, 33.34 (CH_2), 38.65, 38.71, 38.85, 39.03 (piv-C_{quart}), 53.60 (Alkyl-CHN), 60.81 (C-6′), 65.77, 66.52, 71.28, 72.88 (C-2′, C-3′, C-4′, C-5′), 91.56 (C-1′), 99.96 (C-5), 115.01, 137.85 (−CH=CH_2), 149.75 (C-6), 176.42, 176.99, 177.03, 177.63 (pivC=O), 191.91 (C=O) ppm.

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(5-pentenyl)-6-propyl-piperidin-4-one (**10a**; $C_{39}H_{65}NO_{10}$)

10a was synthesized from **9a** (0.66 g, 1 mmol) according to the general procedure for conjugate addition of $RCu \cdot BF_3$ described in Ref. [8] and purified by column chromatography (petroleum ether: EtOAc = 4:1).

Yield: 0.57 g (81%); m.p.: 122°C; $[\alpha]_D^{22} = -15.9$ ($c = 1$, $CHCl_3$); $R_f = 0.56$ (petroleum ether:EtOAc = 3:1); *d.r.* ≫ 10:1; (^{1}H NMR); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 0.86 (t, 3H, $J = 6.8$ Hz, CH_3), 1.10, 1.14, 1.15 and 1.24 (4s, 4 × 9H, piv-CH_3), 1.38 (m, 7H, CH_2), 1.61 (m, 1H, CH_2), 1.99 (m, 2H, CH_2), 2.26 (dd, 1H, $J_{vic} = 7.0$ Hz, $J_{gem} = 15.5$ Hz, CH_2C=O), 2.35 (d, 1H, $J_{gem} = 15.6$ Hz, CH_2C=O′), 2.61 (dd, 1H, $J_{vic} = 5.6$ Hz, $J_{gem} = 15.0$ Hz, CH_2C=O), 2.69 (dd, 1H, $J_{vic} = 6.6$ Hz, $J_{gem} = 15.4$ Hz, CH_2C=O), 3.32 (m, 1H, H-2), 3.46 (m, 1H, H-6), 3.85–3.96 (m, 2H, H-5′, H-6a′), 4.09 (dd, 1H, $J_{6b',5'} = 9.2$ Hz, $J_{6b',6a'} = 13.1$ Hz, H-6b′), 3.88 (d, 1H, $J_{1',2'} = 9.2$ Hz, H-1′), 4.91–5.01 (m, 2H, olefin-CH_2), 5.08 (dd, 1H, $J_{3',4'} = 2.9$ Hz, $J_{3',2'} = 9.9$ Hz, H-3′), 5.35 (d, 1H, $J_{4',3'} = 2.9$ Hz, H-4′), 5.45 (t, 1H, $J = 9.6$ Hz, H-2′), 5.71 (ddd, 1H, $J_1 = 6.5$ Hz, $J_2 = 10.2$ Hz, $J_3 = 16.9$ Hz, C*H*=CH_2) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.91 (CH_3), 20.65, 25.75 (CH_2), 27.05, 27.16, 27.25 (piv-CH_3), 33.59, 37.17 (CH_2), 38.71, 39.02 (piv-C_{quart}), 40.77 (CH_2), 44.12, 44.43 (C-3, C-5), 61.66 (C-6′), 65.91, 67.22, 71.90, 72.55 (C-2′, C-3′, C-4′, C-5′), 94.07 (C-1′), 114.99, 138.11 (−CH=CH_2), 176.66, 176.77, 177.37, 177.84 (piv-C=O) ppm.

(2S,6R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(4-(1-ethoxyethyloxy)-butyl)-6-propyl-piperidin-4-one (**10b**; $C_{42}H_{73}NO_{12}$)

10b was prepared from 3.56 cm^3 **9b** [8] (5.6 mmol) according to the general procedure for conjugate addition of R_2CuMgX in presence of Me_3SiCl as described in Ref. [8] and purified by column chromatography (petroleum ether:EtOAc = 5:1).

Yield: 3.19 g (73%); colorless oil; $[\alpha]_D^{22} = -11.8$ ($c = 1$, $CHCl_3$); $R_f = 0.61$ (petroleum ether: EtOAc = 3:1); *d.r.* > 9:1 (^{1}H NMR); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.82 (t, 3H, $J = 7.0$ Hz, propyl-CH_3), 1.01–1.43 (m, 48H, piv-CH_3, CH_2, *EE*O-CH_3), 1.45–1.57 (m, 4H, CH_2), 2.19 (dd, 1H, $J_{vic} = 7.0$ Hz, $J_{gem} = 15.5$ Hz, CH_2C=O), 2.31 (d, 1H, $J_{gem} = 15.4$ Hz, CH_2C=O), 2.55 (dd, 1H, $J_{vic} = 5.9$ Hz, $J_{gem} = 15.3$ Hz, CH_2C=O′), 2.63 (dd, 1H, $J_{vic} = 6.4$ Hz, $J_{gem} = 15.2$ Hz, CH_2C=O′), 3.27–3.60 (m, 6H, H-2, H-6, *R*CH_2O, CH_3CH_2O), 3.81–3.89 (m, 2H, H-5′, H-6a′), 4.03 (dd, 1H, $J_{6b',5'} = 9.3$ Hz, $J_{6b',6a'} = 13.2$ Hz, H-6b′), 4.33 (d, 1H, $J_{1',2'} = 9.3$ Hz, H-1′), 4.59 (m, 1H, OCHO), 5.04 (dd, 1H, $J_{3',2'} = 9.9$ Hz, $J_{3',4'} = 3.0$ Hz, H-3′), 5.30 (d, 1H, $J_{4',3'} = 2.8$ Hz, H-4′), 5.38 (t, 1H, $J = 9.6$ Hz, H-2′) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.87 (propyl-CH_3), 15.27 (OCH_2*C*H_3), 19.66 (CH_2), 19.83 (OCHO*C*H_3), 24.13, 24.17 (CH_2), 27.03, 27.16, 27.21 (piv-CH_3), 29.73, 29.84 (CH_2), 38.35, 38.65, 38.69, 39.00 (piv-C_{quart}), 44.00, 44.46 (C-3, C-5), 52.02 (NCH*R*), 60.60 (C-6′),

61.65 (*R*CH_2O), 65.01 (CH_3CH_2O), 66.03, 67.26, 71.96, 72.56 (C-2′, C-3′, C-4′, C-5′), 94.20 (C-1′), 99.51 (OCHO), 176.57, 176.62, 177.25, 177.72 (piv-C=O), 210.00 (C=O) ppm.

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(4-oxy-butyl)-6-propyl-piperidin-4-one (**11a**; $C_{38}H_{63}NO_{11}$)

To a solution of 0.58 g (0.81 mmol) **10a** in 20 cm^3 oxygen-free 1,4-dioxane under Ar, a solution of 10 cm^3 $K_2OsO_4 \cdot 2H_2O$ (3.5 mol%) in 5 cm^3 oxygen-free H_2O was added. The yellowish-brown solution was stirred for 15 min, and 0.87 g (4.1 mmol) $NaIO_4$ were added. After stirring for 15 h, 20 cm^3 diethyl ether and 40 cm^3 H_2O were added, and the aqueous layer was separated and extracted with 3×30 cm^3 diethyl ether. The combined organic solutions were washed with 2×20 cm^3 10% Na_2SO_3 solution and dried with Na_2SO_4. After evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography (petroleum ether:EtOAc = 3:1).

Yield: 0.43 g (73%); amorphous solid; $[\alpha]_D^{22} = -11.9$ ($c = 1$, $CHCl_3$); $R_f = 0.57$ (petroleum ether:EtOAc = 2:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.84 (t, 3H, $J = 7.2$ Hz, CH_3), 1.07, 1.12 and 1.22 (4s, 4×9H, piv-CH_3), 1.27 and 1.38 (m, 5H, CH_2), 1.51–1.74 (m, 3H, CH_2), 2.25 (dd, 1H, $J_{vic} = 6.7$ Hz, $J_{gem} = 15.4$ Hz, CH_2C=O), 2.33 (d, 1H, $J_{gem} = 15.0$ Hz, CH_2C=O′), 2.40 (m, 2H, CH_2CHO), 2.60–2.70 (m, 2H, H-3, H-5), 3.34 (m, 1H, H-2), 3.46 (m, 1H, H-6), 3.84–3.92 (m, 2H, H-5′, H-6a′), 4.08 (dd, 1H, $J_{6b',5'} = 9.2$ Hz, $J_{6b',6a'} = 13.0$ Hz, H-6b′), 4.36 (d, 1H, $J_{1',2'} = 9.2$ Hz, H-1′), 5.07 (dd, 1H, $J_{3',4'} = 2.9$ Hz, $J_{3',2'} = 9.9$ Hz, H-3), 5.34 (d, 1H, $J_{4',3'} = 2.9$ Hz, H-4′), 5.44 (t, 1H, $J = 9.6$ Hz, H-2′), 9.71 (s, 1H, CHO) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.85 (CH_3), 19.16, 20.62 (CH_2), 27.06, 27.17, 27.24 (piv-CH_3), 37.09 (CH_2), 38.69, 38.72, 39.03 (piv-C_{quart}), 40.67 (CH_2), 43.59, 44.14, 44.43 (C-3, C-5, *C*H_2CHO), 61.70 (C-6′), 66.01, 67.30, 72.09, 72.57 (C-2′, C-3′, C-4′, C-5′), 94.34 (C-1′), 176.60, 176.69, 177.30, 177.78 (piv-C=O), 201.22 (CHO), 209.70 (C=O) ppm.

(2S,6R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(4-hydroxy-butyl)-6-propyl-piperidin-4-one ($C_{38}H_{65}NO_{11}$)

To a solution of 2.93 g (3.73 mmol) **10b** in dry 70 cm^3 CH_2Cl_2, 15.6 g (62 mmol) pyridinium *p*-toluenesulfonate were added in 5 portions after every 8 h. Monitoring by TLC is necessary in order to terminate the reaction before cleavage of the N-glycosidic bond occurs (3 d, conversion about 85%). 200 cm^3 CH_2Cl_2 were added, and the solution was extracted with 50 cm^3 H_2O, 50 cm^3 sat. $NaHCO_3$, and 80 cm^3 brine. After drying with Na_2SO_4 and evaporation of the solvent *in vacuo*, the remaining residue was purified by chromatography (petroleum ether:EtOAc = 2:1).

Yield: 1.59 g (60%); amorphous solid; $[\alpha]_D^{22} = -18.3$ ($c = 1$, $CHCl_3$); $R_f = 0.15$ (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.85 (t, 3H, $J = 7.2$ Hz, CH_3), 1.07–1.46 (m, 42H, piv-CH_3, CH_2), 1.52–1.62 (m, 2H, CH_2), 2.23 (dd, 1H, $J_{vic} = 7.1$ Hz, $J_{gem} = 15.4$ Hz, CH_2C=O), 2.36 (d, 1H, $J_{gem} = 15.6$ Hz, CH_2C=O′), 2.62 (dd, 1H, $J_{vic} = 5.4$ Hz, $J_{gem} = 15.3$ Hz, CH_2C=O), 2.70 (dd, 1H, $J_{vic} = 6.7$ Hz, $J_{gem} = 15.4$ Hz, CH_2C=O′), 3.11 (s, 1H, OH), 3.30 (m, 1H, NCHR), 3.44 (m, 1H, NCH*R*′), 3.57 (dd, 2H, $J_1 = 6.5$ Hz, $J_2 = 5.3$ Hz, CH_2OH), 3.87–3.92 (m, 2H, H-5′, H-6a′), 4.08 (dd, 1H, $J_{6b',5'} = 9.3$ Hz, $J_{6b',6a'} = 13.1$ Hz, H-6b′), 4.37 (d, 1H, $J_{1',2'} = 9.2$ Hz, H-1′), 5.08 (dd, 1H, $J_{3',4'} = 3.0$ Hz, $J_{3',2'} = 9.9$ Hz, H-3′), 5.34 (d, 1H, $J_{4',3'} = 2.9$ Hz, H-4′), 5.42 (t, 1H, $J = 9.6$ Hz, H-2′) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.86 (CH_3), 19.60, 23.38 (CH_2), 27.04, 27.06, 27.18 (piv-CH_3), 32.02, 37.93 (CH_2), 38.68, 38.73, 39.04 (piv-C_{quart}), 39.89 (CH_2), 44.19, 44.47 (C-3, C-5), 47.50, 54.65 (C-2, C-6), 61.62 (CH_2OH), 61.67 (C-6′), 66.38, 67.22, 71.97, 72.49 (C-2′, C-3′, C-4′, C-5′), 94.15 (C-1′), 176.61, 177.30, 177.36, 177.80 (piv-C=O) ppm.

(2S,6R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(4-oxo-butyl)-6-propyl-piperidin-4-one (**11b**; $C_{38}H_{63}NO_{11}$)

To a solution of 15 g (2.1 mmol) of the afore-described hydroxybutyl piperidone in 40 cm^3 CH_2Cl_2, molecular sieve (4 Å, 5 g) was added. After stirring for 10 min, 0.5 g dry N-methylmorpholine

(4.1 mmol) and 74 cm^3 tetrapropylammonium perruthenate (*TPAP*) [18] (10 mol%) were added, and the solution was stirred in the dark at room temperature. After 3 h, the catalyst was filtered off through celite/silica gel and washed with 200 cm^3 CH_2Cl_2. The solvent was evaporated from the combined organic solutions, and the remainder was purified by chromatography (petroleum ether: EtOAc = 5:2) to give pure **11b**.

Yield: 1.23 g (83%); colorless amorphous solid; $[\alpha]_D^{22} = -10.2$ ($c = 1.1$, $CHCl_3$); $R_f = 0.14$ (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.85 (t, 3H, $J = 7.1$ Hz, CH_3), 1.07–1.40 (m, 42H, piv-CH_3, CH_2), 1.46–1.66 (m, 2H, CH_2), 2.22 (dd, 1H, $J_{vic} = 6.9$ Hz, $J_{gem} = 15.4$ Hz, $CH_2C{=}O$), 2.33–2.39 (m, 3H, C*H*$_2$CHO, $CH_2C{=}O'$), 2.61 (dd, 1H, $J_{vic} = 5.7$ Hz, $J_{gem} = 15.5$ Hz, $CH_2C{=}O$), 2.61 (dd, 1H, $J_{vic} = 6.7$ Hz, $J_{gem} = 15.5$ Hz, $CH_2C{=}O'$), 3.31 (m, 1H, NCH*R*), 3.47 (m, 1H, NCH*R*′), 3.90 (m, 2H, H-5′, H-6a′), 4.08 (dd, 1H, $J_{6b',5'} = 9.3$ Hz, $J_{6b',6a'} = 13.1$ Hz, H-6b′), 4.36 (d, 1H, $J_{1',2'} = 9.3$ Hz, H-1′), 5.08 (dd, 1H, $J_{3',4'} = 3.0$ Hz, $J_{3',2'} = 9.9$ Hz, H-3′), 5.34 (d, 1H, $J_{4',3'} = 2.9$ Hz, H-4′), 5.41 (t, 1H, $J = 9.6$ Hz, H-2′), 9.71 (t, 1H, $J = 1.5$ Hz, CHO) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.82 (CH_3), 19.61, 20.00 (CH_2), 27.01, 27.04, 27.16 (piv-CH_3), 37.95 (CH_2), 38.66, 39.01 (piv-C_{quart}), 39.89 (CH_2), 43.46, 44.01, 44.38 (C-3, C-5, *C*H_2CHO), 61.62 (C-6′), 66.02, 67.21, 72.02, 72.46 (C-2′, C-3′, C-4′, C-5′), 94.26 (C-1′), 176.54, 176.85, 177.25, 177.72 (piv-C=O), 201.86 (CHO), 209.65 (C=O) ppm.

(2S,8aR)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propyl-4a,5-didehydro-decahydroquinolin-4-one (**12a**; $C_{38}H_{61}NO_{10}$)

In 40 cm^3 benzene, 0.17 g (4.25 mmol) powdered NaOH and dibenzo [18] crown [6] were heated under reflux. A solution of 1.4 g (1.97 mmol) **11a** in 20 cm^3 dry benzene was added, and the reflux was continued until completion of the conversion (1.5 h). After cooling, the reaction mixture was poured into 50 cm^3 sat. NH_4Cl solution and extracted with 200 cm^3 diethyl ether. The organic layer was washed with 40 cm^3 sat. $NaHCO_3$ solution and 60 cm^3 brine, dried over $MgSO_4$, and concentrated *in vacuo* to 50% of its volume. After filtration and complete evaporation of the solvent, the remaining residue was purified by chromatography (petroleum ether:EtOAc = 4:1).

Yield: 1.10 g (81%); colorless amorphous solid; $[\alpha]_D^{22} = -28.0$ ($c = 0.5$, $CHCl_3$); $R_f = 0.57$ (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.81 (t, 3H, $J = 6.8$ Hz, CH_3), 1.09, 1.12, 1.14, 1.24 (4s, 4 × 9H, piv-CH_3), 1.26–1.32 (m, 4H, H-7, H-8), 1.40, 1.52, 1.71, 1.97 (4m, 4 × 1H, CH_2), 2.24 (m, 2H, H-6), 2.48 (dd, 1H, $J_{vic} = 2.3$ Hz, $J_{gem} = 16.4$ Hz, H-3*ax*), 2.87 (dd, 1H, $J_{vic} = 4.8$ Hz, $J_{gem} = 16.4$ Hz, H-3*eq*), 3.36 (m, 1H, H-2), 3.82–3.90 (m, 3H, H-8a, H-5′, H-6a′), 4.12 (dd, 1H, $J_{6b',5'} = 9.5$ Hz, $J_{6b',6a'} = 13.6$ Hz, H-6b′), 4.37 (d, 1H, $J_{1',2'} = 9.4$ Hz, H-1′), 5.06 (dd, 1H, $J_{3',4'} = 3.0$ Hz, $J_{3',2'} = 9.9$ Hz, H-3′), 5.34 (d, 1H, $J_{4',3'} = 2.9$ Hz, H-4′), 5.43 (t, 1H, $J = 9.6$ Hz, H-2′), 6.91 (d, 1H, $J = 2.7$ Hz, H-5) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.72 (CH_3), 19.62, 20.14, 25.87 (CH_2), 27.03, 27.07, 27.17, 27.25 (piv-CH_3), 37.02 (CH_2), 38.67, 38.69, 38.72, 39.04 (piv-C_{quart}), 39.34 (CH_2), 43.27 (C-3), 54.18 (C-2), 61.35 (C-6′), 65.65, 67.25, 71.91, 72.80 (C-2′, C-3′, C-4′, C-5′), 92.39 (C-1′), 135.65, 137.76 (C-4a, C-5), 176.60, 176.67, 177.37, 177.77 (piv-C=O), 198.13 (C=O) ppm.

(2R,8aS)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propyl-4a,5-didehydro-decahydroquinolin-4-one (**12b**; $C_{38}H_{61}NO_{10}$)

12b was obtained from 1.10 g (1.54 mmol) **11b** according to the afore-described procedure for the synthesis of its diastereomer **12a**.

Yield: 0.78 g (73%); colorless amorphous solid; $[\alpha]_D^{22} = +37.6$ ($c = 1$, $CHCl_3$); $R_f = 0.50$ (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.82 (t, 3H, $J = 7.0$ Hz, CH_3), 1.07, 1.11, 1.13, 1.21 (4s, 9H, piv-CH_3), 1.25–1.38 (m, 4H, CH_2), 1.51–1.59 (m, 2H, CH_2), 1.80, 1.93 (2m, 1H, CH_2), 2.22 (m, 2H, CH_2), 2.29 (d, 1H, $J_{gem} = 18.0$ Hz, H-3*ax*), 2.85 (d, 1H, $J_{gem} = 13.0$ Hz, H-3*eq*), 3.13 (m, 1H, H-2), 3.87–3.98 (m, 4H, H-8a, H-5′, H-6a′, H-6b′), 4.39 (d, 1H, $J_{1',2'} = 9.2$ Hz,

H-1′), 5.01 (dd, 1H, $J_{3',4'} = 3.0$ Hz, $J_{3',2'} = 9.8$ Hz, H-3′), 5.28 (t, 1H, $J = 9.5$ Hz, H-2′), 5.31 (d, 1H, $J_{4',3'} = 2.7$ Hz, H-4)′, 6.66 (d, 1H, $J = 2.9$ Hz, H-5) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.70 (CH_3), 20.12, 21.39, 25.65 (CH_2), 26.92, 26.98, 27.03 (piv-CH_3), 32.52, 38.32 (CH_2), 38.50, 38.56, 38.61, 38.87 (piv-C_{quart}), 43.81 (C-3), 61.92 (C-6′), 66.70, 67.21, 71.50, 72.64 (C-2′, C-3′, C-4′, C-5′), 94.45 (C-1′), 137.18 (C-5.), 137.67 (C-4a), 176.49, 176.73, 177.16, 177.70 (piv-C=O), 198.73 (C=O) ppm.

(2S,4aR,5R,8aR)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propyl-5-methyl-decahydroquinolin-4-one (**13**; $C_{39}H_{65}NO_{10}$)

To a suspension of 0.28 g (1.47 mmol) CuI in 10 cm^3 dry *THF* under argon cooled to −28°C, 1.8 cm^3 of a 1.6 *M* solution of methyllithium in diethyl ether (2.88 mmol) were added. After 30 min of stirring, the now clear colorless solution was cooled to −78°C. A solution of 0.5 g (0.72 mmol) of the enone **12a** and 0.73 cm^3 (5.76 mmol) trimethyl chlorosilane in 25 cm^3 dry *THF* was added. The color changed to yellow. After 2–3 h (TLC monitoring) the reaction was complete. A mixture of 15 cm^3 conc. NH_4OH/NH_4Cl (1:1 v/v) was added. The solution was warmed to room temperature, 100 cm^3 diethyl ether were added, and the separated organic layer was washed with conc. NH_4OH/NH_4Cl (1:1 v/v) until the blue color in the aqueous layer vanished. The collected aqueous solutions were extracted with 2×100 cm^3 diethyl ether, and the combined organic solutions were washed with 50 cm^3 brine and dried over $MgSO_4$. After removal of the solvent *in vacuo*, the crude silyl enolether ($R_f = 0.67$, petroleum ether:EtOAc = 3:1, *d.r.* > 10:1, ^{1}H NMR) was obtained; yield: 0.56 g (quantitative), yellowish amorphous solid.

In 3 cm^3 *THF*, 0.10 g (0.128 mmol) of this silyl enolether were dissolved and cooled to −20°C. 0.3 cm^3 of a 1 *M* solution of tetrabutylammonium fluoride (0.3 mmol) in *THF* was added, and the mixture was stirred for 36 h (TLC monitoring). After addition of 2×20 cm^3 diethyl ether, the organic solutions were washed with 40 cm^3 brine and dried over $MgSO_4$. After evaporation of the solvent, the remaining compound **13** was purified by chromatography (petroleum ether:EtOAc = 5:1).

Yield: 73 mg (81%); m.p. 168°C (MeOH); $[\alpha]_D^{22} = -60.0$ ($c = 1$, $CHCl_3$); $R_f = 0.67$ (petroleum ether:EtOAc = 3:1); *d.r.* > 15:1:0:0 (^{1}H NMR); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.77 (d, 3H, $J = 7.1$ Hz, CH_3), 0.82 (t, 3H, $J = 6.8$ Hz, propyl-CH_3), 1.07–1.53 (m, 45 H, piv-CH_3, CH_2), 2.04 (m, 1H, CH_2), 2.19 (dd, 1H, $J_{vic} = 3.7$ Hz, $J_{vic'} = 12.0$ Hz, H-4a), 2.47 (d, 1H, $J_{gem} = 16.2$ Hz, H-3*ax*), 2.63 (m, 2H, H-3*eq*, H-5), 3.26 (dt, 1H, $J_{8a,8} = 3.5$ Hz, $J_{8a,4a} = J_{8a,8'} = 11.2$ Hz, H-8a), 3.36 (m, 1H, H-2), 3.64 (m, 2H, H-5′, H-6a′), 4.10 (dd, 1H, $J_{6b',5'} = 9.5$ Hz, $J_{6b',6a'} = 13.2$ Hz, H-6b′), 4.43 (d, 1H, $J_{1',2'} = 9.3$ Hz, H-1′), 5.04 (dd, 1H, $J_{3',4'} = 2.9$ Hz, $J_{3',2'} = 9.9$ Hz, H-3′), 5.34 (d, 1H, $J_{4',3'} = 3.0$ Hz, H-4′), 5.35 (t, 1H, $J = 9.5$ Hz, H-2′) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.62, 13.83 (propyl-CH_3, CH_3), 19.59, 20.16 (CH_2), 27.08, 27.19, 27.25 (piv-CH_3), 28.34 (C-5), 32.12, 36.17 (CH_2), 38.69, 39.04 (piv-C_{quart}), 41.59 (CH_2), 44.22 (C-3), 49.67 (C-4a), 52.11, 54.23 (H-8a, C-2), 61.81(C-6′), 65.84, 67.47, 71.94, 72.86 (C-2′, C-3′, C-4′, C-5′), 90.42 (C-1′), 176.64, 176.69, 177.41, 177.84 (piv-C=O), 211.04 (C=O) ppm; X-ray: see Ref. [16].

(2S,8aR)-N-Phenoxycarbonyl-2-propyl-4a,5-didehydro-quinolin-4-one (**14**; $C_{19}H_{23}NO_3$)

To a solution of 0.4 g (0.58 mmol) **12a** in 5 cm^3 MeOH, 1 cm^3 of 1 *M* HCl was added, the mixture was stirred at room temperature for 48 h, the MeOH was evaporated *in vacuo*, and 20 cm^3 diethyl ether were added to the remaining residue. This mixture was extracted five times with 10 cm^3 H_2O. After evaporation of the H_2O, the hydrochloride of the quinolinone remained (133 mg, >95%), which was dissolved in 5 cm^3 H_2O. 5 cm^3 of sat. $NaHCO_3$ solution were added, the mixture was stirred for 1 h, and then 0.1 cm^3 (0.68 mmol) phenyl chloroformate were added. After stirring for 2 h, the mixture was extracted with 3×30 cm^3 diethyl ether. The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The remaining crude **14** was purified by chromatography (petroleum ether: EtOAc = 10:1).

Yield: 110 mg (60%); colorless oil; $[\alpha]_D^{22} = -145.6$ ($c = 1$, $CHCl_3$) (Ref. [13]: $[\alpha]_D^{22} = -164$ ($c = 3$, $CHCl_3$)); $R_f = 0.49$ (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.92 (t, 3H, CH_3), 1.16–1.52 (m, 5H, CH_2), 1.53–1.95 (3m, 3H, CH_2), 2.32 (dd, 2H, $J_1 = 3.8$ Hz, H-6), 2.49 (dd, 1H, $J_{gem} = 17.6$ Hz, $J_{vic} = 1.6$ Hz, H-3a), 2.60 (m, 1H, CH_2), 2.74 (dd, 1H, $J_{gem} = 16.7$ Hz, H-3*eq*), 4.68 (m, 2H, H-2, H-8a), 6.91 (d, 1H, H-5), 7.09 (d, 2H, $J = 7.9$ Hz, phenyl-H), 7.17 (t, 1H, $J = 7.3$ Hz, phenyl-H), 7.34 (t, 2H, $J = 7.0$ Hz, phenyl-H) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.7 (CH_3), 19.64, 20.72, 20.92, 25.79, 36.49 (CH_2), 44.28 (C-3), 50.41, 52.61 (C-2, C-8a), 121.61, 125.22, 129.27, 129.54 (phenyl), 134.33, 139.54 (C-5, C-4a), 151.37 (N–COO–Ph), 195.88 (C=O) ppm.

(2S,4aR,5R,8aR)-N-Phenoxycarbonyl-2-propyl-5-methyl-decahydroquinolin-4-one
(**15a**; $C_{20}H_{27}NO_3$)

Removal of the N-galactosyl group from 400 mg (0.56 mmol) quinolinone **13** was carried out as described for **12a**, as well as the subsequent acylation with phenyl chloroformate. Purification of the crude product by chromatography (petroleum ether:EtOAc = 12:1) gave **15a** (*d.r.* 7(*trans*):1(*cis*):0:0).

Yield: 150 mg (82%); colorless oil; $[\alpha]_D^{22} = -160.3$ ($c = 1$, $CHCl_3$); $R_f = 0.48$ (petroleum ether:EtOAc = 5:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.96 (d, 3H, $J = 7.0$ Hz, CH_3), 0.97 (t, 3H, $J = 7.1$ Hz, propyl-CH_3), 1.28 (m, 1H, H-6), 1.49 (m, 3H, H-8*ax*, CH_2), 154–1.66 (m, 4H, H-7, H-7′, H-6, CH_2), 1.84 (m, 1H, CH_2), 2.48 (dd, 1H, $J_{vic} = 1.5$ Hz, $J_{gem} = 18.8$ Hz, H-3*ax*), 2.64 (dd, 1H, $J_{vic} = 7.0$ Hz, $J_{gem} = 19.0$ Hz, H-3*eq*), 2.65–2.72 (m, 2H, H-5, H-8*eq*), 2.73 (dd, 1H, $J_{4a,8a} = 12.0$ Hz, $J_{4a,5} = 3.2$ Hz, H-4a), 4.02 (dt, 1H, $J_{8a,4a} = J_{8a,8} = 11.5$ Hz, $J_{8a,8} = 3.1$ Hz, H-8a), 4.68 (ddt, 1H, $J_{2,3} = 1.5$ Hz, $J_{vic} = 7.6$ Hz, H-2), 7.10 (m, 2H, phenyl-H), 7.19 (m, 1H, phenyl-H), 7.36 (m, 2H, phenyl-H) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.25, 13.85 (propyl-CH_3, CH_3), 20.22 (CH_2), 27.73 (C-5), 32.19, 35.98, 39.39, 44.33 (CH_2), 51.34, 52.03, 53.93 (C-2, C-4a, C-8a), 121.65, 125.36, 129.29 (phenyl) 151.37 (NCOOPh), 154.82 (phenyl-O), 207.25 (C=O) ppm.

(2S,4aR,5R,8aR)-N-Benzylycarbonyl-2-propyl-5-methyl-decahydroquinolin-4-one
(**15b**; $C_{21}H_{29}NO_3$)

15b was synthesized in a completely analogous manner to **15a** from 0.4 g (0.58 mmol) **13** and 0.1 cm^3 benzyl chloroformate (0.68 mmol) and purified by chromatography (petroleum ether: EtOAc = 10:1).

Yield: 0.17 g (88%); colorless oil; $[\alpha]_D^{22} = -132.1$ ($c = 1$, $CHCl_3$); $R_f = 0.46$ (petroleum ether:EtOAc = 5:1); FD-MS: $m/z = 342.9$ [M^+]; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.9 (t, 3H, $J = 7.3$ Hz, propyl-CH_3), 0.91 (d, 3H, $J = 7.0$ Hz, CH_3), 1.19 (m, 1H, CH_2), 1.3–1.65 (m, 7H, CH_2, CH), 1.75 (m, 1H, CH_2), 2.39 (dd, 1H, $J_{cis} = 1.5$ Hz, $J_{gem} = 19.5$ Hz, H-3*ax*), 2.51 (dd, 1H, $J_{trans} = 6.8$ Hz, $J_{gem} = 19.5$ Hz, H-3*eq*), 2.59 (m, 2H, H-5, H-8), 2.66 (dd, 1H, $J_{4a,5} = 3.6$ Hz, $J_{4a,8a} = 11.3$ Hz, H-4a), 3.91 (dt, 1H, $J_{8a,4a} = J_{8a,8} = 11.3$ Hz, $J_{8a,8'} = 2.9$ Hz, H-8a), 4.55 (m, 1H, H-2), 5.12 (m, 2H, benzyl-CH_2), 7.33 (m, 5H, phenyl-H) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.16, 13.75 (propyl-CH_3, CH_3), 27.59 (*C*H-CH_3), 32.12, 35.94, 39.13, 43.53, 44.21 (CH_2), 50.71, 51.51, 53.81, (C-4a, C-2, C-8a), 67.18 (benzyl-CH_2), 127.65, 127.9, 128.42 (phenyl), 136.58 (phenyl-*ipso*), 156.08 (N–CO–O), 207.51 (C=O) ppm.

(2S,4aS,5R,8aR)-N-Phenyloxycarbonyl-2-propyl-5-methyl-decahydroquinolin-4-one
(**16**; $C_{20}H_{27}NO_3$)

For the preparation of **16**, of also Ref. [13].

To a stirred suspension of 0.28 g (1.47 mmol) CuI in 10 cm^3 dry *THF* under argon at −30°C, 1.8 cm^3 of a 1.6 *M* solution of methyllithium in diethyl ether (2.88 mmol) were added. The clear

solution was cooled to −78°C, and 1.6 cm^3 $BF_3 \cdot OEt_2$ (12 mmol) were added dropwise. After 20 min, a solution of 11 mg (0.035 mmol) **15a** in 2 cm^3 *THF* was added, and the mixture was stirred for 30 min at −78°C and for 2 h at −18°C. At this temperature, 8 cm^3 MeOH and, at room temp., 50 cm^3 diethyl ether were added. The organic solution was washed with conc. NH_4OH/NH_4Cl (1:1, v/v) solution until blue color vanished. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude product **16** was purified by chromatography (petroleum ether:EtOAc = 15:1).

Yield: 7 mg (67%); colorless oil; $[\alpha]_D^{22} = +30.9$ ($c = 1$, $CHCl_3$); $R_f = 0.64$ (petroleum ether: EtOAc = 3:1); *d.r.* (**16**:**15a**) = 9:2:0:0; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.91 (t, 3H, $J = 7.3$ Hz, propyl-CH_3), 1.03 (d, 3H, $J = 7.3$ Hz, CH_3), 1.24–1.70 (m, 9H, CH_2), 1.93 (d, 1H, $J = 9.4$ Hz, H-8*endo*), 2.34 (dd, 1H, $J_{vic} = 2.1$ Hz, $J_{gem} = 14.1$ Hz, H-3*eq*), 2.60 (m, 1H, H-5), 2.65 (d, 1H, $J = 6.5$ Hz, H-4a), 2.78 (dd, 1H, $J_{vic} = 8.2$ Hz, $J_{gem} = 14.1$ Hz, H-3*eq*), 4.71 (m, 1H, H-2), 4.86 (m, 1H, H-8a), 7.11 (m, 2H, phenyl-H), 7.20 (m, 1H, phenyl-H), 7.36 (m, 2H, phenyl-H) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.75, 18.36 (propyl-CH_3, CH_3), 18.08, 26.62 (C-4a, C-5), 20.08, 20.28, 27.27, 36.60, 39.76, 43.66 (CH_2), 53.57, 54.22 (C-2, C-8a), 121.68, 125.40, 129.30 (phenyl), 151.44 (NCOOPh), 154.17 (phenyl-*ipso*), 208.84 (C=O) ppm.

Epimerization of **15a**

To a solution of N-phenoxycarbonyl decahydroquinolin-4-one, 5 mg **15a** (*trans*:*cis* = 7:1) in 3 cm^3 *THF* and two drops of triethylamine (∼6 mg) were added. The mixture was stirred at room temperature. After 2 min, an analytical sample was poured into a mixture of diethyl ether/1 *M* HCl. The solvent was evaporated, and the remaining residue was investigated by analytical HPLC, column B; ratio of diastereomers: **15a**(*trans*):**16**(*cis*) = 1:3; eluent: acetonitrile:water, gradient: 60/40→75/25 (0–20 min); R_t(**15a**) = 13.5 min, R_t(**16**) = 14 min.

(2S,4aR,5R,8aR)-N-Benzyloxycarbonyl-2-propyl-5-methyl-decahydroquinolin-4-one-ethane-1,2-diyl dithioacetal (**17**; $C_{23}H_{33}NO_2S_2$)

To a solution of 160 mg (0.38 mmol) **15b** and 0.1 cm^3 (0.9 mmol) ethane dithiol in 5 cm^3 dry CH_2Cl_2 at 0°C, 0.3 cm^3 borontrifluoride etherate (2.5 mmol) were added dropwise. After 2 h at 0°C the mixture was stirred at room temperature for 15 h, diluted with 30 cm^3 CH_2Cl_2, and washed with 2 × 20 cm^3 sat. $NaHCO_3$ solution and H_2O. After drying over $MgSO_4$, the solvent was evaporated *in vacuo*.

Yield: 120 mg (64%); colorless oil; $[\alpha]_D^{22} = -24.8$ ($c = 1$, $CHCl_3$); $R_f = 0.35$ (petroleum ether: EtOAc = 7:1); FD-MS: $m/z = 419.9$ [M^+]; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.85 (t, 3H, $J = 7.3$ Hz, propyl-CH_3), 1.08 (d, 3H, $J = 7.0$ Hz, CH_3), 1.26 (m, 3H, CH_2), 1.39–1.66 (m, 6H, CH_2), 1.91 (dd, 1H, $J_{gem} = 13.5$ Hz, $J_{cis} = 3.8$ Hz, H-3*eq*), 2.09 (dd, 1H, $J_{4a,8a} = 12$ Hz, $J_{4a,5} = 3.5$ Hz, H-4a), 2.18 (m, 1H, CH_2), 2.62 (m, 1H, H-5), 2.76 (dd, 1H, $J_{gem} = 13.3$ Hz, $J_{trans} = 11.4$ Hz, H-3*ax*), 3.22 (m, 4H, S-CH_2), 4.10 (dt, $J_{8a,4a} = J_{8a,8} = 11.7$ Hz, $J_{8a,8'} = 3.5$ Hz, H-8a), 4.39 (m, 1H, H-2), 5.16 (m, 2H, benzyl-CH_2), 7.32 (m, 5H, phenyl-H) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.42, 13.81 (propyl-CH_3, CH_3), 19.3, 20.57 (CH_2), 31.35 (CH), 34.64, 34.97 (CH_2), 38.33, 38.67 (S-CH_2), 42.79 (CH_2), 49.33, 50.07, 54.29 (CH, NCH*R*), 52.42 (CH_2), 66.89 (benzyl-CH_2), 127.38, 127.59, 128.32 (phenyl-C), 137.29 (quart. phenyl-C), 156.33 (N–CO–O) ppm.

(2S,4aR,5R,8aR)-2-Propyl-5-methyl-decahydroquinoline hydrochloride (trans-4a-epi-pumiliotoxin C) (**5**; $C_{13}H_{26}NCl$)

To a solution of 90 mg (0.22 mmol) of the dithioacetal **17** in 20 cm^3 dry isopropanol, 1.5 g freshly prepared and neutral washed *Raney* nickel were added. A gentle stream of hydrogen was passed through the solution at room temperature for 2 h. After stirring for additional 14 h, the catalyst was

filtered off. The catalyst was dissolved in aqueous HCl, neutralized with conc. aq. ammonia, and the solution was extracted with $2 \times 30\,cm^3$ $CHCl_3$. The organic layer was extracted with aq. HCl, and the acidic aq. solution was evaporated to dryness *in vacuo*. Impurities were removed from the crude hydrochloride **5** by silica layer chromatography with EtOAc as the eluent.

Yield: 11 mg (22%); m.p. 256–258°C; $[\alpha]_D^{22} = -11.3$ ($c = 0.5$, $CHCl_3$); FD-MS: $m/z = 195.8$ $[M\text{-}Cl]^+$; ^1H NMR (400 MHz, δ, $CDCl_3$): 0.82 (d, 3H, $J = 7.3$ Hz, CH_3), 0.88 (t, 3H, $J = 7.3$ Hz, propyl-CH_3), 1.2–2.0 (m, 14H, m CH_2), 2.05, 2.36 (2m, 2H, CH), 2.87 (m, 2H, N-CH*R*) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 12.68, 13.73 (propyl-CH_3, CH_3), 18.79, 19.0, 30.31 (CH_2), 31.96 (CH), 32.16, 35.1 (CH_2), 41.45 (C-4a), 56.85, 58.25 (C-2, C-8a) ppm; X-ray analysis: $P2_12_12_1$ (orthorhombic), $a = 7.2852(2)$, $b = 8.7387(3)$, $c = 22.0953(5)$ Å, $V = 1406.67(7)$ Å^3, $z = 4$, $F(000) = 512$, Cu-K_α, SIR-92, SHELXL-97 [23].

(2R,4aR,5S,8aS)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2,5-di-propyl-decahydroquinolin-4-one (**18**; $C_{41}H_{69}NO_{10}$)

To 0.34 g (1.6 mmol) $CuBr \cdot SMe_2$ in 20 cm^3 dry *THF* at −78°C under argon, 1.2 cm^3 of a 2 *M* solution of *n*-propyl magnesium chloride in diethyl ether (3.2 mmol) were added. The pale yellow suspension was warmed to −55°C within 60 min and became clear. This solution was cooled again to −78°C, and a solution of 0.39 g (0.56 mmol) enone **12b** and 0.85 cm^3 trimethylchlorosilane (0.67 mmol) in 20 cm^3 dry *THF* was added through a syringe. The color of the reaction mixture changed first to deep red and then to orange. After 45 min stirring, only traces of the starting material could be detected (monitoring by *TLC*). After 1.5 h, 20 cm^3 of conc. NH_4OH/NH_4Cl (1:1, v/v) were added. The mixture was warmed up to room temperature, 140 cm^3 diethyl ether were added, and the organic layer was extracted with conc. NH_4OH/NH_4Cl (1:1, v/v) as long as a blue color occurred in the aqueous layer. The collected aq. solutions were extracted with $2 \times 130\,cm^3$ diethyl ether, the combined organic solutions were washed with 70 cm^3 brine, dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The remaining crude silyl enolether was dissolved in 7 cm^3 *THF*, cooled to −20°C, and 0.8 cm^3 (0.8 mmol) of a 1 *M* solution of tetrabutylammonium fluoride in *THF* were added. After 24 h the solvent was evaporated, and the remaining residue was dissolved in 55 cm^3 diethyl ether and washed with 60 cm^3 H_2O. The aq. layer was extracted with $2 \times 25\,cm^3$ diethyl ether. The combined organic solutions were washed with 50 cm^3 brine and dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the crude **18** was purified by chromatography (petroleum ether:EtOAc = 7:1).

Yield: 0.18 g (43%); colorless amorphous solid; $[\alpha]_D^{22} = -46.7$ ($c = 1.1$, $CHCl_3$); $R_f = 0.51$ (petroleum ether:EtOAc = 5:1); *d.r.* > 10:1:0:0 (^1H NMR); ^1H NMR (400 MHz, δ, $CDCl_3$): 0.87 (t, 6H, $J = 6.9$ Hz, CH_3, CH_3'), 1.08–1.42 (m, 48 H, piv-CH_3, CH_2), 1.54 (m, 1H, CH_2), 1.65 (m, 1H, CH_2), 2.25 (dd, 1H, $J_{vic} = 9.7$ Hz, $J_{vic'} = 16.6$ Hz, H-3*ax*), 2.44 (m, 1H, H-5), 2.43 (m, 2H, $CH_2C{=}O$, CHC=O), 3.28, 3.54 (2m, 1H, H-2, H-8a), 3.93 (m, 2H, H-5′, H-6a′), 4.10 (dd, 1H, $J_{6b',5'} = 9.5$ Hz, $J_{6b',6a'} = 13.6$ Hz, H-6b′), 4.38 (d, 1H, $J_{1',2'} = 9.4$ Hz, H-1′), 5.09 (dd, 1H, $J_{3',4'} = 3.2$ Hz, $J_{3',2'} = 10.0$ Hz, H-3′), 5.38 (d, 1H, $J_{4',3'} = 3.4$ Hz, H-4′), 5.38 (dd, 1H, $J_{2',1'} = 9.3$ Hz, $J_{2',3'} = 9.9$ Hz, H-2′) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 14.00, 14.07 (CH_3, CH_3'), 20.83, 20.92, 25.07 (CH_2), 27.04, 27.10, 27.23, 27.29 (piv-CH_3), 32.13 (C-5), 33.40, 35.00 (CH_2), 38.70, 38.74, 39.03 (piv-C_{quart}), 40.27 (CH_2), 44.29 (C-3), 54.44, 56.23 (C-2, H-8a), 61.46 (C-6′), 66.04, 67.28, 72.12, 72.69 (C-2′, C-3′, C-4′, C-5′), 176.73, 176.82, 177.32, 177.79 (piv-C=O), 211.34 (C=O) ppm.

(2R,4aR,5S,8aS)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2,5-di-propyl-4-trifluoromethane-sulfonyloxy-3,4-didehydro-decahydroquinoline (**19**; $C_{42}H_{68}NO_{12}SF_3$)

To a solution of 0.15 g (0.20 mmol) **18** in 6 cm^3 dry *THF* at 78°C, 0.3 cm^3 (3.0 mmol) of a 1 *M* solution of sodium hexamethyldisilazane (Na*HMDS*) in *THF* were added. After stirring for 1 h, 0.86 cm^3 (0.43 mmol) of a 0.5 *M* solution of 5-chloro-pyridine-2-N,N-*bis*-trifluoromethanesulfonimide (dried with molecular sieve 4 Å) were added, and stirring was continued for 2 h at −78°C. After

additional stirring at −20°C for 12 h, 5 cm^3 sat. NH_4Cl solution was added, followed by addition of 50 cm^3 diethyl ether at room temperature. The organic layer was washed with 30 cm^3 brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo*. Column chromatography with petroleum ether:EtOAc = 8:1 gave 25 mg of the starting material, 41 mg of the regioisomer **20**, and the product **19**.

Yield: 71 mg (41%); oil containing traces of impurities; $[\alpha]_D^{22} = +4.82$ ($c = 0.5$, $CHCl_3$); $R_f = 0.59$ (petroleum ether:EtOAc = 5:1); ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.81–0.91 (m, 6H, CH_3, CH_3'), 1.07–1.61 (m, 50 H, piv-CH_3, CH_2), 2.14 (m, 1H, CH_2), 2.82 (br s, 1H, H-4a), 3.43 (m, 1H, H-8a), 3.80 (dd, 1H, $J_{5',6a'} = 6.9$ Hz, $J_{5',6b'} = 6.4$ Hz, H-5′), 3.89 (m, 2H, H-6a′, H-1′), 4.03 (dd, 1H, $J_{6b',5'} = 6.6$ Hz, $J_{6b',6a'} = 17.6$ Hz, H-6b′), 4.23 (m, 1H, H-2), 5.08 (dd, 1H, $J_{3',4'} = 3.3$ Hz, $J_{3',2'} = 10.0$ Hz, H-3′), 5.34 (d, 1H, $J_{4',3'} = 3.4$ Hz, H-4′), 5.48 (t, 1H, $J = 9.6$ Hz, H-2′), 5.69 (t, 1H, $J = 3.0$ Hz, H-3) ppm; ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.88, 14.14 (CH_3, CH_3'), 20.17, 20.87 (CH_2), 27.07, 27.11, 27.24, 27.28 (piv-CH_3), 30.14 (CH_2), 33.20 (C-5), 34.09 (CH_2), 38.33, 38.65, 38.73, 39.01 (piv-C_{quart}), 43.94 (C-4a), 61.20 (C-6′), 65.48, 67.22, 72.06, 72.51 (C-2′, C-3′, C-4′, C-5′), 96.10 (C-1′), 119.21 (C-3), 148.66 (C-4), 176.64, 176.84, 176.94, 177.20 (piv-C=O) ppm.

(2R,4aR,5S,8aS)-2,5-Di-propyl-decahydroquinoline (cis-4a-epi-(+)-perhydro 219A) (**6**; $C_{15}H_{29}N$)

To a solution of 50 mg (0.57 mmol) of enol triflate **19** in 10 cm^3 dry MeOH, 100 mg lithium carbonate and 10 mg palladium on charcoal (5%) were added. The mixture was vigorously stirred under hydrogen at room temperature for 24 h. After filtration through celite and washing of the solid with 50 cm^3 MeOH, the solvent was evaporated from the combined MeOH solutions. The remaining residue was dissolved in 30 cm^3 diethyl ether, washed with 25 cm^3 H_2O and 25 cm^3 brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in 3 cm^3 MeOH; subsequently, 0.1 cm^3 1 *N* HCl were added, and the mixture was stirred for 24 h at room temperature. After evaporation of the solvents, 15 cm^3 diethyl ether were added to the residue, and the solution was extracted with 5 × 10 cm^3 H_2O. Evaporation of H_2O *in vacuo* gave 14 mg of the crude hydrochloride **6**. The residue was stirred with 0.5 cm^3 sat. Na_2CO_3 solution and extracted with 3 × 10 cm^3 CH_2Cl_2 to give the free amine **6** (yield: 9 mg, 74%). NMR spectroscopic data of both the free amine **6** and its hydrochloride are in agreement with those reported in Refs. [15] and [20].

Hydrochloride of **6**: $[\alpha]_D^{22} = +12.2$ ($c = 0.7$, MeOH); ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 13.81, 14.42 (CH_3, CH_3'), 18.75, 19.21, 20.66, 23.39, 25.02, 29.13, 31.11, 31.43, 34.71, 35.10, 38.89 (CH_2), 58.64, 60.27 (C-2, C-8a) ppm.

Free amine **22**: ^{13}C NMR (100.6 MHz, δ, $CDCl_3$): 14.09, 14.46 (CH_3, CH_3'), 18.99, 19.11, 21.03, 26.64, 27.09, 31.55, 32.01, 32.99, 35.46, 39.29 (9CH_2, CH), 40.27 (C-4a), 56.24, 57.78 (C-2, C-8a) ppm.

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