Synthesis I. Strassnig et al. Paper

Stereoselective Total Synthesis of the Diastereomeric Tricyclic Alkaloids Tetraponerine-7 and Tetraponerine-8 Using O-Pivaloylated D-Arabinopyranosylamine as the Common Auxiliary

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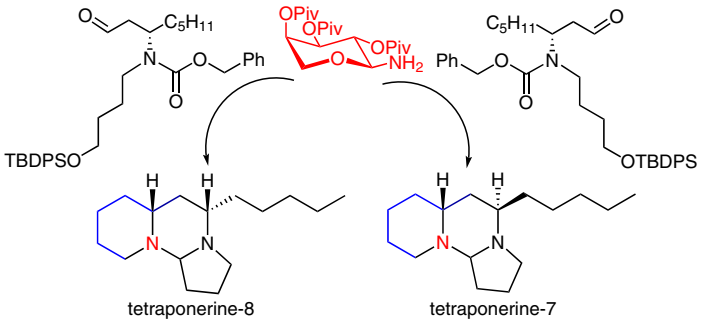
Dedicated to Professor Richard R. Schmidt on the occasion of his 80th birthday



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Abstract Based on a diastereoselective domino Mannich–Michael reaction cascade of 2-*N*-[(*S*)-3-{(benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octylidene]-2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine with the Danishefsky diene, the major component of the neurotoxic venom of the New Guinean ant *Tetraponera punctulata*, tetraponerine-8, and its diastereomer tetraponerine-7 were synthesized in pure form. While the Mannich reaction of the arabinosyl imine of the required (*S*)-configured β-aminoaldehyde gave the 2-substituted piperidinone precursor of tetraponerine-8 with excellent diastereoselectivity, the analogous Mannich reaction of the (*R*)-configured β-aminoaldehyde afforded the precursor of tetraponerine-7 with a selectivity of only 2:1 (mismatched case). The enantiomerically pure tetraponerine-8, described as highly toxic for ants, exhibited only moderate toxicity to sucking and stinging insects.

Key words piperidine alkaloids, tetraponerines, stereoselective Mannich–Michael reaction, carbohydrate auxiliaries, nicotinic acetylcholine receptor inhibitor

In 1987, J. C. Braekman et al.[1] discovered that the middle-sized tropical ant *Tetraponera punctulata* living in Papua New Guinea defends itself against larger sympatric ants not by injection of a toxin through a sting, but by smearing a segregated venom on the surface of the enemies. The paralyzing effect of this venom is caused by a group of structurally related tricyclic alkaloids, the tetraponerines 1–8 **T1**–**T8** (Figure 1).[1,2] While the structure and the relative configuration of the major component **T8** was confirmed by NMR and crystal structure analysis, the absolute configuration was clarified through diastereoselective total synthesis of enantiomerically pure natural tetraponerine-8.[3] The structures and configurations of other members of these tricyclic alkaloids have also been elucidated by chemical synthesis.[3–5]

In the original article, the strong paralyzing effect of tetraponerine-8 on the European red ant (*Myrmica rubra*) was described.[1] In addition to this interesting insecticidal effect, neurotoxic[6] and cytotoxic activities[7] of tetraponerines and some of their derivatives have been reported. It was shown that tetraponerines act as efficient inhibitors of nicotinic acetylcholine receptors (nAChRs). Pharmacological studies suggested that the different stereochemistry of **T7** and **T8** has an influence on the selective inhibition of the different nicotinic acetylcholine receptors.[6] The compounds with longer alkyl chains at C5, such as **T7** and **T8**, were generally more potent than those with shorter alkyl groups, such as **T4**. These results parallel the cytotoxic effects that tetraponerines and their analogues exhibit on HT29 (colorectal) tumor cells.[7]

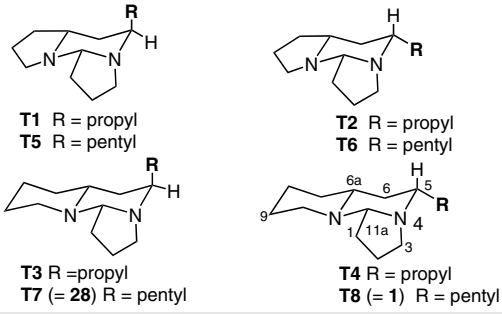


Figure 1 Structure and configuration of the natural tetraponerines

The interesting biological properties of these alkaloids have resulted in a number of stereoselective total syntheses of racemic[4,5,7–9] and enantiomerically enriched or pure tetraponerines.[3,10] Recently, Gonzalez-Gomez, Guijarro, and co-workers[11] used an elegant indium-promoted aminoallylation[12] of ω-bromoalkanals for syntheses of enantiomerically pure tetraponerines-3 and -4; the enantiomers of *tert*-

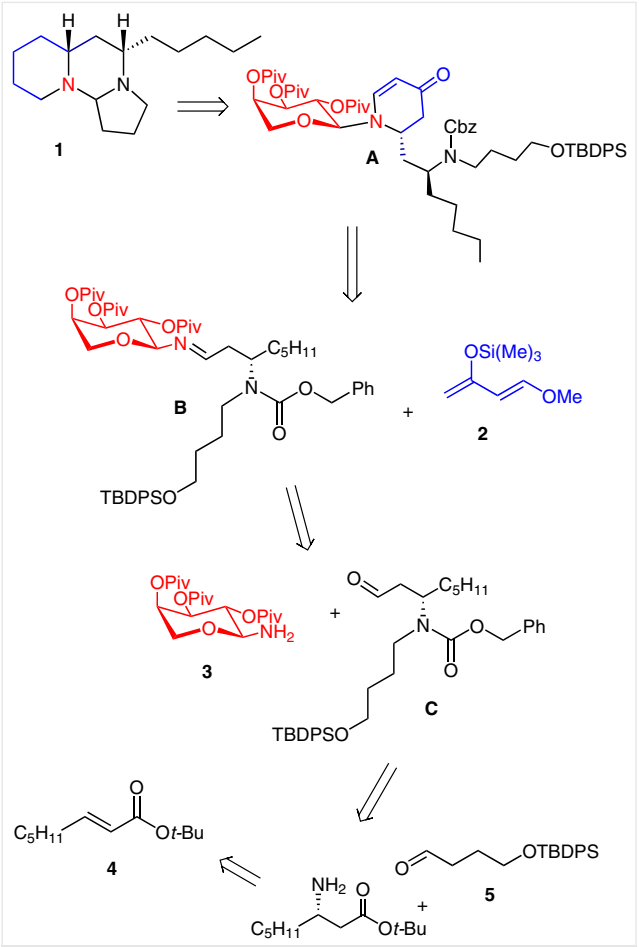
butylsulfinamide served as the diastereodifferentiating auxiliaries. These researchers successfully extended their strategy to a general stereoselective synthesis of the natural tetraponerines by combining this methodology with a cross-metathesis reaction for elongating the C_3 to a C_5 alkyl side chain at C5.[13] Comparative studies of the cytotoxicity of the different tetraponerines revealed that **T7** exhibits stronger growth inhibiting activity on MCF-7 (breast) tumor cells than **T8**,[13] both carrying the longer pentyl substituent at C5. These results again suggest that the 6-6-5 structure isomers **T7** and **T8** with the longer C5 side chain, but different configuration at C5 are of particular interest in terms of biological activity.

We here describe the stereoselective synthesis of both enantiomerically pure diastereomers **T7** and **T8** using O-pivaloylated D-arabinopyranosylamine[14] as the common stereodifferentiating tool in a Mannich–Michael domino reaction sequence.[15]

The retrosynthetic analysis (Scheme 1) illustrates that tetraponerine-8 (**T8**, **1**), the major component of the venom, is stereoselectively accessible from a (2*S*)-substituted piperidine precursor **A**, which can be obtained through a Mannich–Michael condensation reaction cascade of Danishefsky diene **2** with the imine **B** formed from 2,3,4-tri-*O*-pivaloyl-β-D-arabinopyranosylamine (**3**) and the (*S*)-β-aminooctanal **C**. The aldehyde **C** should be available by stereoselective hetero-Michael addition of a chiral amine to *tert*-butyl (*E*)-oct-2-enoate (**4**) and subsequent reaction of the adduct with silyl-protected 4-hydroxybutanal **5**.

While Danishefsky diene[16] **2** and arabinosylamine[14] **3** are obtained according to described procedures, the preparation of β-aminoaldehyde **C** requires the stereoselective addition of a chiral amine to an activated oct-2-enoic acid derivative. *tert*-Butyl oct-2-enoate **4** so far obtained through Wittig olefination reactions[17,18] was synthesized from commercially available oct-2-enoic acid by treatment with *tert*-butyl alcohol and di-*tert*-butyl dicarbonate in the presence of 4-(dimethylamino)pyridine.[19] The (*S*)-3-aminooctanoic ester **6*S***, which is previously undescribed, was prepared according to the strategy of Davies et al.[20] by diastereoselective addition of lithium benzyl[(*S*)-1-phenylethyl]amide to **4**. After single flash-chromatography, pure *tert*-butyl (*S*)-3-{benzyl[(*S*)-1-phenylethyl]amino}octanoate (**6*S***) was isolated in 80% yield (Scheme 2). Analogous addition of the (*R*)-enantiomer of the lithium amide afforded the known[18,21] (*R*)-3-aminooctanoic ester derivative **6*R*** useful for the total synthesis of tetraponerine-7 (vide infra).

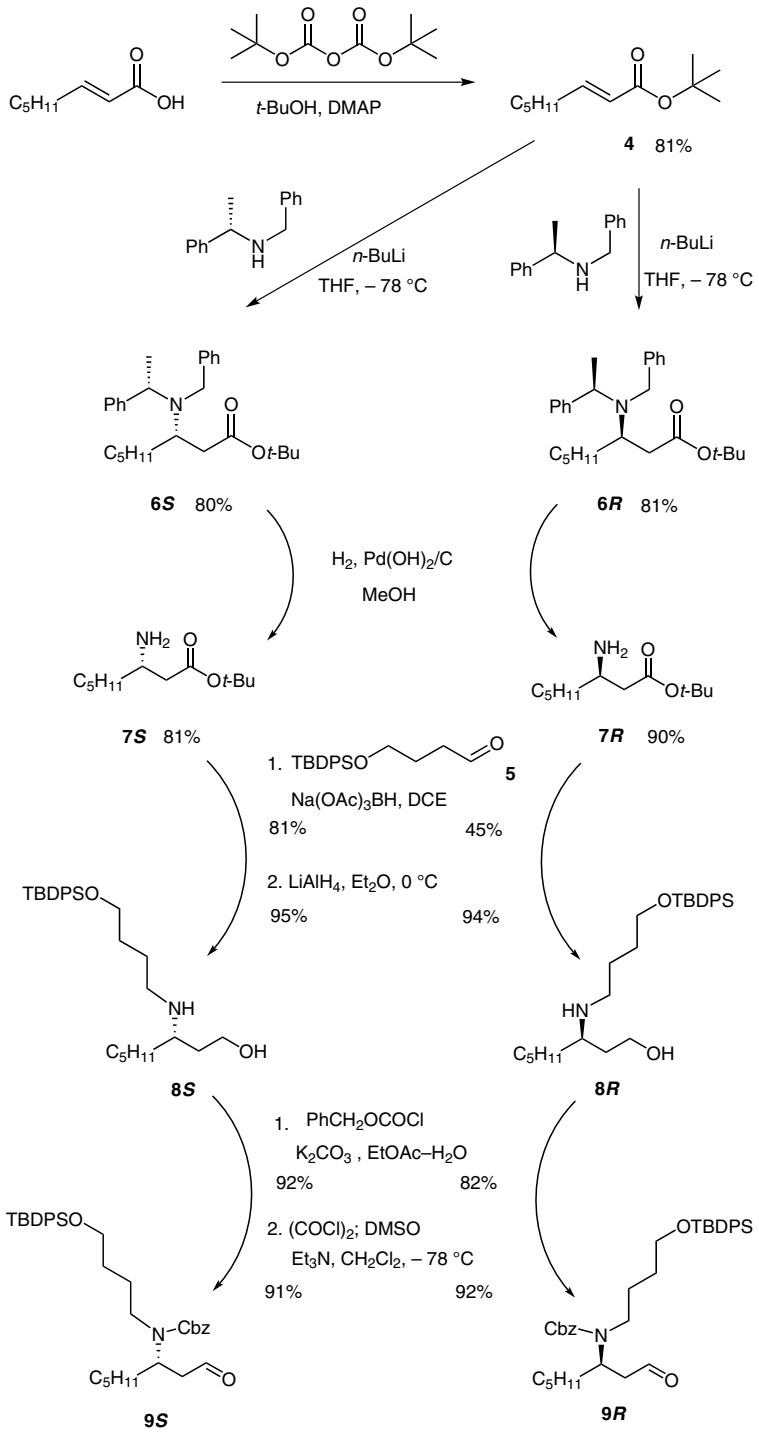
After hydrogenolytic removal of the N-benzylic groups both enantiomers of *tert*-butyl 3-aminooctanoate **7*S*** and **7*R*** were reacted with 4-(*tert*-butyldiphenylsiloxy)butanal[22] (**5**) under reductive alkylation conditions to give the 3-{[4-(*tert*-butyldiphenylsiloxy)butyl]amino} esters that were reduced to the enantiomers of the 3-aminooctanols **8*S*** and



Scheme 1 Retrosynthetic analysis for the stereoselective total synthesis of (+)-tetraponerine-8

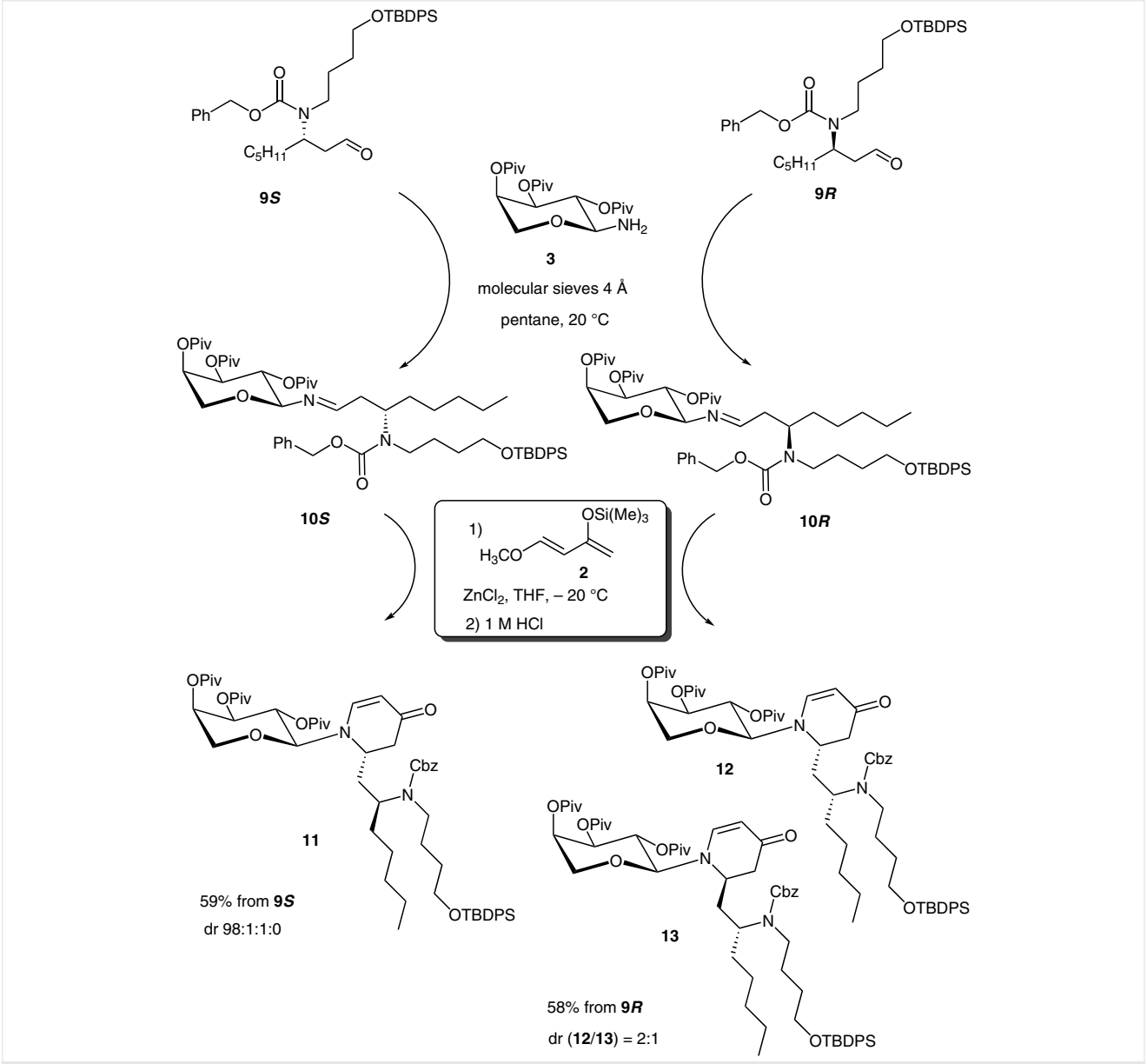
8*R* (Scheme 2). Hydrogenation of **6*S*** and **6*R*** as reported in the literature[21] in methanol under pressure of 6 atm using palladium on charcoal required reaction times of several days. Due to the long reaction time the methyl ester of the 3-aminooctanoate was formed as a byproduct. However hydrogenation of **6*S*** and **6*R*** using palladium hydroxide on charcoal as the catalyst under atmospheric pressure gave pure (*S*)-3-aminooctanoate **7*S*** (98.7% ee) within three days without formation of the methyl ester. Reductive N-alkylation of **7*S*** with TBDPS-protected 4-hydroxybutanal **5** using two equivalents of sodium triacetoxyborohydride smoothly afforded the *N*-(4-TBDPS-oxybutyl)substituted (*S*)-3-amino ester. In the corresponding reaction of the (3*R*)-enantiomer a distinctly lower yield was recorded. It was revealed during workup, that more N-dialkylated product was formed, probably because of the more reactive fresh charge of the sodium triacetoxyborohydride applied in this case. Both esters **7** were reduced with lithium aluminum hydride in diethyl ether to efficiently yield the 3-aminooctanol enantiomers **8*S*** and **8*R***.

In contrast to these reduction reactions the oxidation of alcohol **8*S*** was found to be very difficult. Neither Swern oxidation, described as selective in the presence of secondary amines,[23] nor reaction with Dess–Martin periodinane[24] afforded the desired aldehyde. To block the amino function of enantiomers **8** from interfering with the oxidation process, the benzyloxycarbonyl (Cbz) group was introduced under Schotten–Baumann conditions (Scheme 2). Subsequent Swern oxidation[25] at –78 °C gave the aldehydes **9*S*** and **9*R*** in high yields.



Scheme 2 Synthesis of both enantiomers of 3-aminooctanal derivatives **9**, see compound **C** in retrosynthetic Scheme 1

The condensation of 2,3,4-tri-*O*-pivaloyl-β-D-arabinopyranosylamine[14c,26] (**3**) with the enantiomers of aldehydes **9*S*** and **9*R*** was carried out in *n*-pentane at room temperature in the presence of molecular sieves. After stirring for 22 hours, filtration through Hyflo®, and evaporation of the solvent, the crude imines **10*S*** and **10*R*** were isolated as syrupy materials. Longer reaction times may result in the formation of anomers of the imines that do not react in the following reaction. At –20 °C in dry tetrahydrofuran in the presence of zinc chloride, imines **10*S*** and **10*R*** underwent initial Mannich reaction with diene **2**; it preferentially attacks from the *Re* side.[14,15] Subsequent Michael addition and elimination of methanol afforded the 2-substituted piperidinone derivatives **11** and **12** (Scheme 3). The diastereoselectivity of the two conversions was dramatically different. While the Mannich reaction of **10*S*** proceeded with excellent stereoselectivity to yield **11** [Figure 2 (a)], that of **10*R*** obviously constituted the mismatched case and gave the diastereomers **12** and **13** in a ratio of only 2:1 in favor of the desired precursor of tetraponerine-7 [Figure 2 (b)].



Scheme 3 Domino Mannich–Michael condensation cascade of *N*-arabinosyl imines **10*S*** and **10*R*** with diene **2** as matched and mismatched stereoselective processes

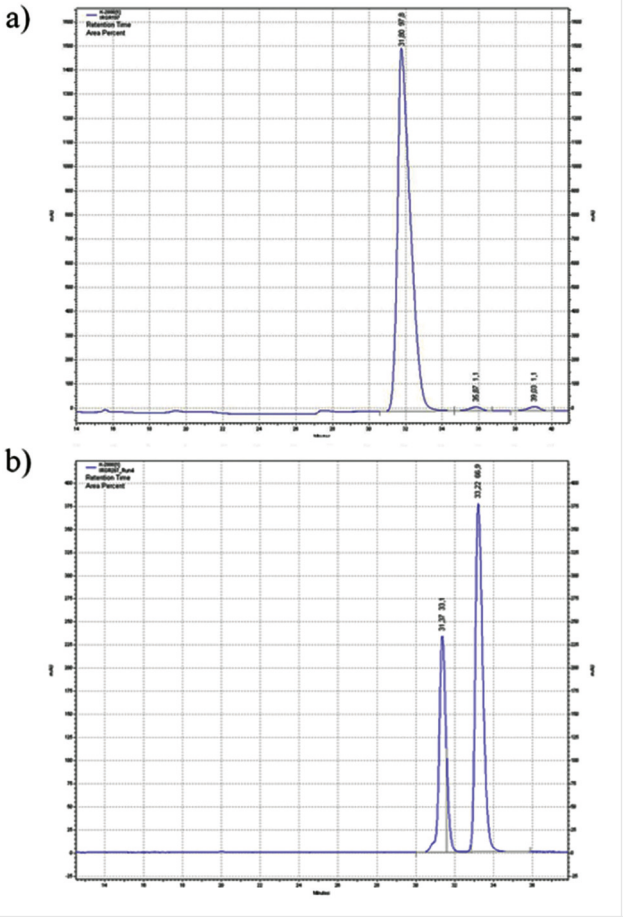


Figure 2 Analytical HPLC of (a) piperidinone **11** obtained from **10*S***, and (b) diastereomers **12**/**13** obtained from **10*R***

The single diastereomer **11** formed from **9*S*** in the matched Mannich–Michael cascade and isolated after flash chromatography surprisingly showed two sets of signals in its ^{1}H NMR spectrum due to the rotamers of the urethane protecting group. After hydrogenolysis of the Cbz group the compound gave a clean ^{1}H NMR spectrum, no signal doubling remained (Figure 3).

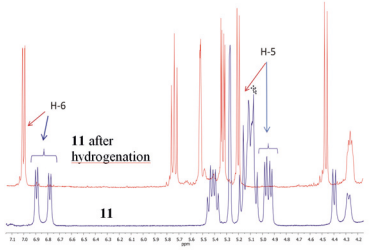


Figure 3 ^{1}H NMR of piperidinone **11** in $CDCl_3$ before (blue) and after (red) hydrogenation

The low diastereoselectivity of the Mannich reaction in case of the chiral aldimine **10*R*** certainly is caused through an interfering interaction of the urethane protecting group with the promoting Lewis acid (Figure 4). The steering effect of the carbohydrate auxiliary in these processes is mediated by the coordination of the zinc chloride to the imine nitrogen and to the carbonyl oxygen of the 2-*O*-pivaloyl group (Figure 4, **10*R***, **A**).[15] Because of the configuration of this aldimine the carbonyl oxygen of the Cbz protecting group is also in a favored position for cooperative coordination of the zinc ion. Thus, both diastereotopic sides of the imine are shielded and the reaction with the nucleophile, Danishefsky diene **2**, logically is of lower selectivity.

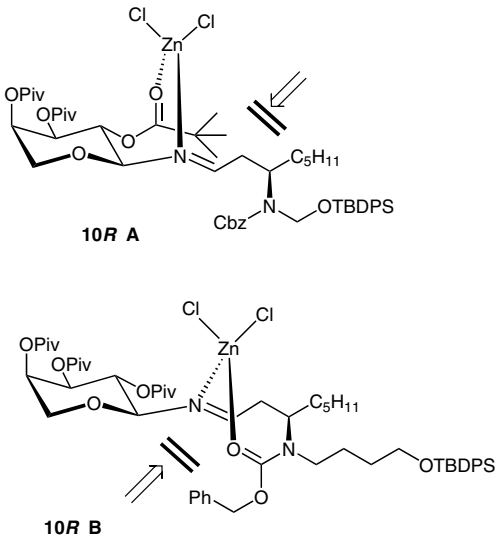
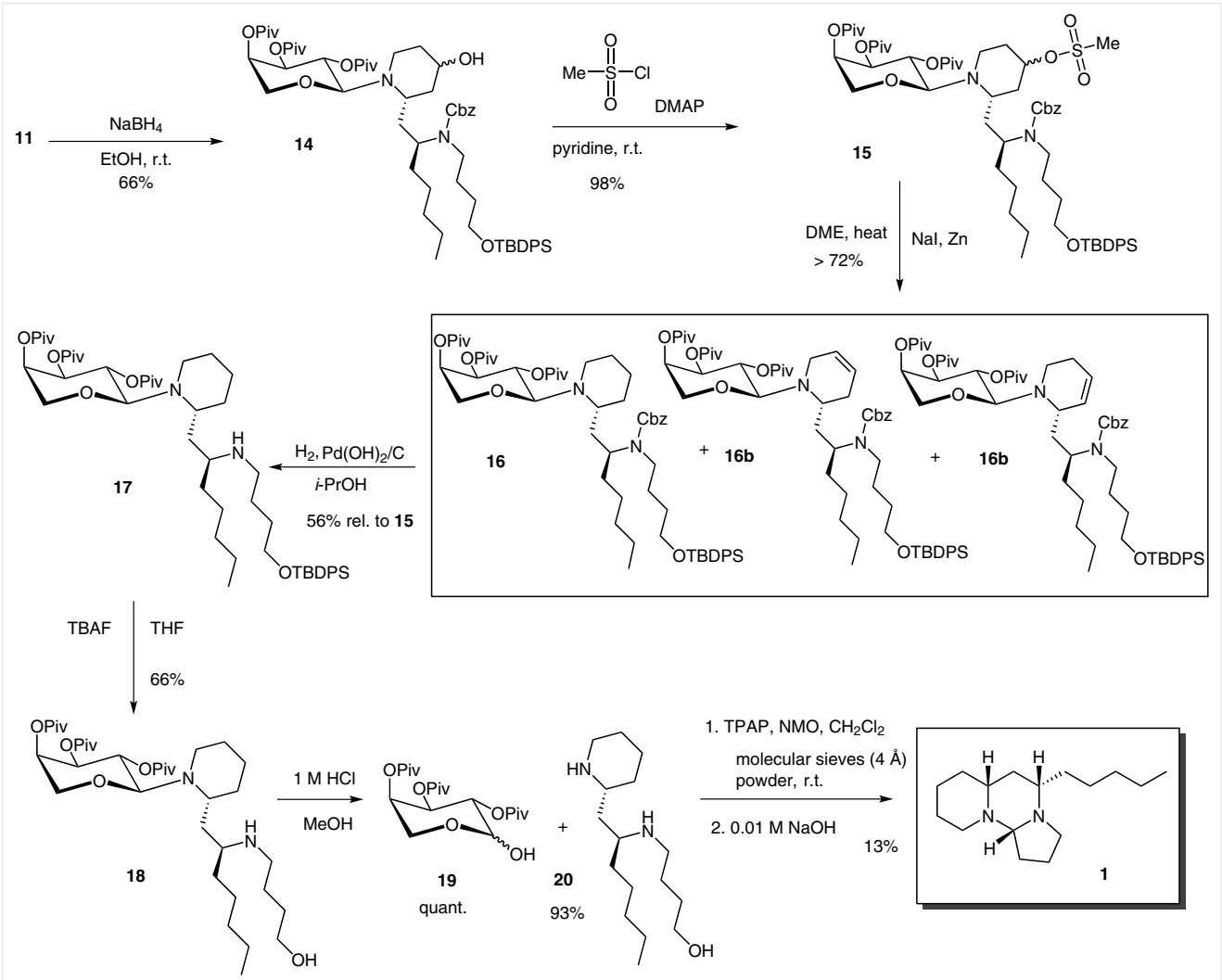


Figure 4 The role of the Cbz group in the mismatching coordination of zinc chloride in nucleophilic attacks at 3-amino-substituted *N*-arabinosyl aldimine **10*R***

For further conversion of the pure *N*-arabinosyl-piperidinone derivative **11**, reduction of the enone structure was attempted with L-Selectride in tetrahydrofuran at –78 °C. In contrast to closely related reactions the selective reduction[15,27] of the C=C bond was not achievable in this way, probably due to the urethane-functionalized side chain of the compound. The reduction of the enone structure was therefore carried out using sodium borohydride in ethanol at room temperature to yield the piperidin-4-ol derivative **14** (Scheme 4) with high diastereoselectivity according to TLC analysis. The reductive removal of the hydroxy group was not possible by conversion into the xanthate and treatment with tributyltin hydride[28] or mesylation and reduction with lithium triethylborohydride (Super Hydride®)[29] or elimination using potassium *tert*-butoxide[30] or DBU[31] in tetrahydrofuran. This problem was solved by treatment of mesylate **15** with sodium iodide and zinc in boiling 1,2-dimethoxyethane.[32] A mixture of the desired piperidine derivative **16** together with two elimination products **16a**,**b**

was obtained. Only a sample of the major product **16** was purified by chromatography, however the isolated mixture was subjected to hydrogenolysis of the Cbz group concomitantly resulting in saturation of the double bounds of **16a**,**b**.

Removal of the TBDPS group from the obtained *N*-arabinosyl piperidine **17** gave compound **18**, which was subjected to mild acidolytic removal of the auxiliary. Evaporation of the solvent in vacuo and extraction with diethyl ether quantitatively returned the arabinose auxiliary **19**, which after simple conversion can be re-introduced to the process. Treatment of the remaining hydrochloride dissolved in water with sodium carbonate and extraction with diethyl ether allowed for the isolation of the pure piperidine derivative **20** with the (4-hydroxybutyl)amino side chain. The now required oxidation of the alcohol to the aldehyde functionality proved to be the most difficult problem due to the presence of the secondary amine groups[33] in **20**. In a rare example,[34] Dess–Martin periodinane in dichloromethane was used for the successful oxidation of an alcohol in the presence of a secondary amine group within the molecule. Application of these conditions to **20** resulted in an inseparable mixture of products. Using Ley's tetrapropylammonium perruthenate (TPAP)[35] and *N*-methylmorpholine *N*-oxide, Kibayashi et al.[36] successfully oxidized an alcohol in the presence of a secondary amine and a phenol group. In this case, the formed aldehyde was trapped in a semi-aminal structure. This situation appeared similar to the oxidative conversion of amino alcohol **20** into the tetraponerine aminal structure. Treatment of **20** with catalytic tetrapropylammonium perruthenate and two equivalents of *N*-methylmorpholine *N*-oxide in dichloromethane in the presence of molecular sieves (4 Å) at room temperature actually afforded the target compound **1**. After the addition of 0.01 M sodium hydroxide in order to complete the aminal formation and purification by flash chromatography, tetraponerine-8 (**1**) was isolated as a colorless oil that, accord-



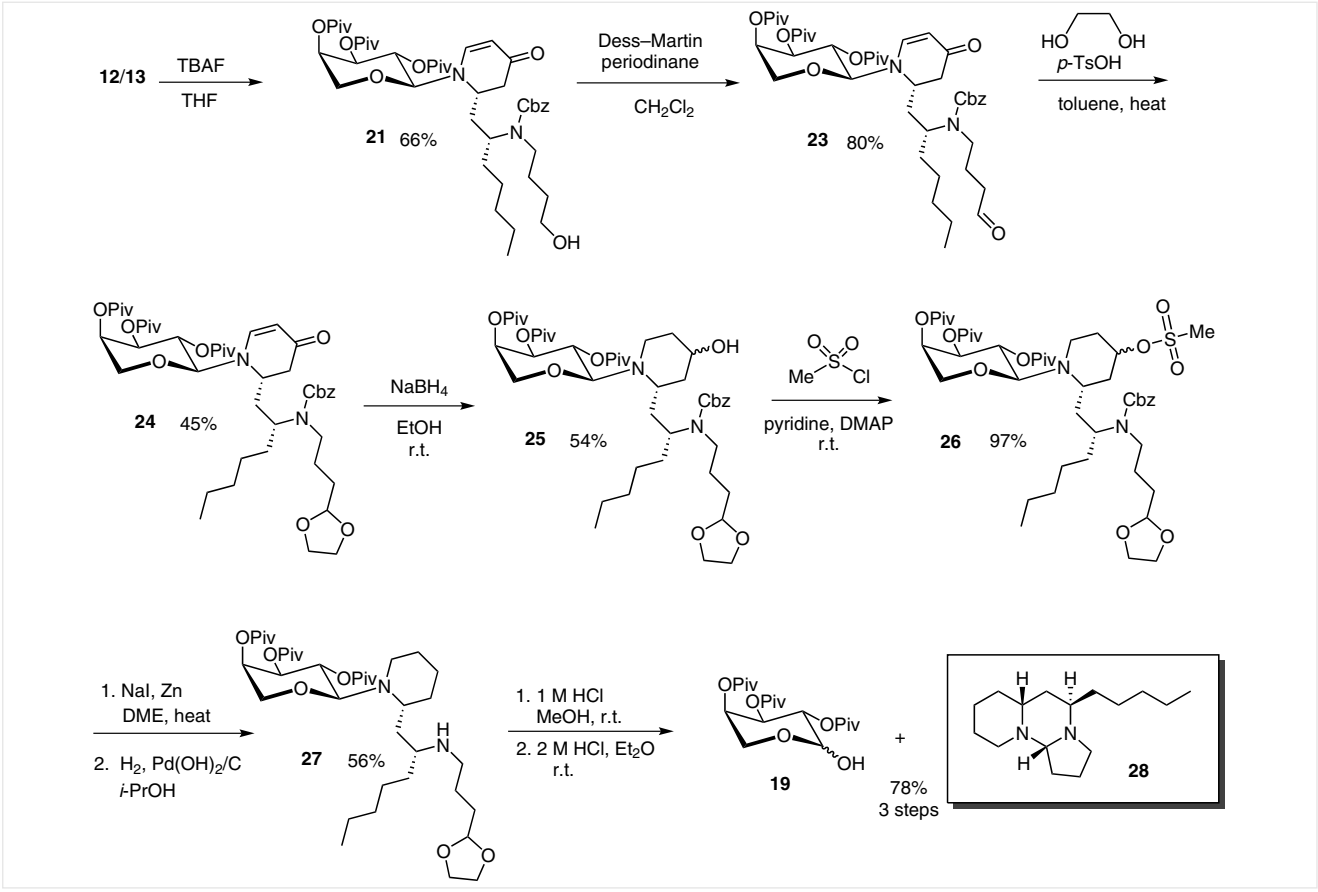
Scheme 4 Total synthesis of (+)-tetraponerine-8 from enantiomerically pure dehydropiperidinone **11**

ing to its NMR spectrum, was identical to the natural product.[1] The yield obtained after workup and purification was rather low. This is due to a number of byproducts arising from the interfering effect of the two amino functions in **20** during the oxidation reaction.

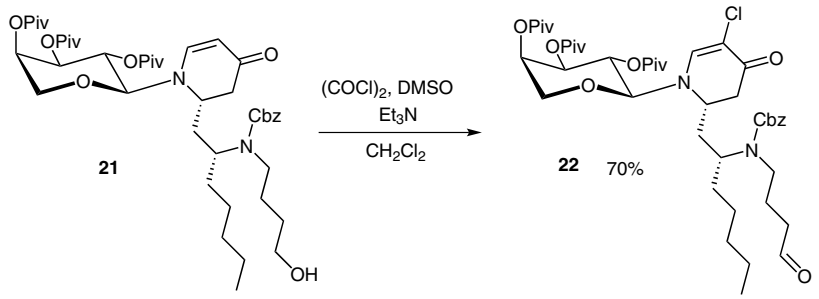
In order to prevent interferences caused by the amino groups during the oxidation of the side chain alcohol, the sequence of reactions was changed in the total synthesis of the diastereomer tetraponerine-7 (**T7**, **28**). The ^{1}H and ^{13}C NMR spectra of the mixture of diastereomers **12** and **13** (Scheme 2) showed a high degree of correspondence in the signals of the piperidine part of compounds **12** and **11** thus providing evidence that the major diastereomer **12** has 2*S* configuration. The mixture **12**/**13** was treated with tetrabutylammonium fluoride in tetrahydrofuran for removal of the TBDPS group. After purification by flash chromatography diastereomer **21** was isolated in highly enriched form in 66% yield (Scheme 5). Regarding the difficulties in the final oxidation reaction during the synthesis of tetraponerine-8 (**1**), the conversion of the alcohol into the corresponding aldehyde was performed at this stage.

Swern oxidation of **21** using dimethyl sulfoxide/oxalyl chloride resulted in the formation of the aldehyde with concomitant chlorination of the enaminone structure (Scheme 6). 5-Chloro-2,3-dihydropyridin-4(1*H*)-one **22**, interesting for further modification reactions of the piperidine portion, was isolated after flash chromatography in 70% yield.

Oxidation of the alcohol **21** with Dess–Martin periodinane yielded the desired aldehyde **23** without side reaction (Scheme 5). Its conversion into the protected 1,3-dioxolane **24** using ethylene glycol in toluene under reflux was not optimized; byproducts were formed due to the high temperature used. Chromatographic purification gave **24** in moderate yield. Reduction of the enaminone using sodium borohydride in ethanol afforded the piperidin-4-ol **25**, which was subjected to mesylation to give mesylate **26** almost quantitatively. Its treatment with sodium iodide/zinc in boiling 1,2-dimethoxymethane produced the reduced compound together with the two dehydropiperidines as was observed in the synthesis of tetraponerine-8 (Scheme 4). The mixture was subsequently subjected to hydrogenolytic removal of the Cbz group with concomitant saturation



Scheme 5 Total synthesis of (+)-tetraponerine-7 from dehydropiperidinones **12**/**13**



Scheme 6 Chlorination of the enaminone during Swern oxidation of alcohol **21**

of the carbon–carbon double bonds of the byproducts to furnish the piperidine **27** in satisfying yield after the two steps.

In the concluding part of the total synthesis of natural tetraponerine-7 (**28**), cleavage from the arabinose auxiliary and solvolysis of the acetal protection are achieved by acidolysis. Treatment of **27** with dilute hydrochloric acid in methanol at room temperature detached the precursor of the alkaloid from the carbohydrate auxiliary, and also effected solvolysis of the acetal to some extent. To complete the acetal hydrolysis the solvent was evaporated and the remaining substances were treated with aqueous 2 M hydrogen chloride and diethyl ether. The arabinose auxiliary **19** can be recovered from the ether solution, while the water solution was brought to pH 8 with 10% aqueous sodium hydroxide; extraction with dichloromethane gave the pure natural tetraponerine-7 (**28**) in 78% yield after three steps.

According to its ^{1}H NMR spectrum, the product **28** is identical with natural tetraponerine-7. In NOESY NMR experiments a cross-peak between H6a and H11a gives evidence of the correct annulation of the six-membered rings (Figure 5). The absence of any cross-peak between H6a and the proton at C5 confirms the correct configuration at C5.

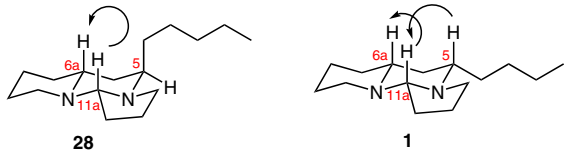


Figure 5 ^{1}H NMR NOE experiments confirming the configuration of (+)-tetraponerine-7 (**28**) and (+)-tetraponerine-8 (**1**)

In the ^{1}H NMR spectrum of tetraponerine-8 (**1**), the NOE contacts between H5, H6a, and H11a document the *cis* location of H5, H-6a, and H11a.

The strategy pursued in the synthesis of (+)-tetraponerine-7 (Scheme 5), involving the early oxidation of the primary side chain alcohol and protection of the formed aldehyde as an acetal prior to the removal of the N-protecting group, was more efficient compared to the route used for the synthesis of natural (+)-tetraponerine-8, in which the oxidation of this alcohol function was performed as the final step immediately resulting in the aminal structure (Scheme 4).

Both enantiomerically pure natural alkaloids are stereoselectively accessible using the same arabinopyranosylamine auxiliary, which induces the (*S*)-configuration at the α-position of the crucial piperidinone intermediates [which becomes the (*R*)-configuration at C6a in the target compounds **1** and **28**]. After disconnection from the stereoselectively synthesized tetraponerine precursors, the arabinosyl auxiliary **19** can quantitatively be recovered. A series of homologues in the piperidine, as well as in the pyrrolidine ring, of these alkaloids are accessible using this strategy by modification of the alk-2-enoic acid and/or the *N*-(siloxy)alkyl component. It also can be translated to the synthesis of bis-pyrrolidino tetraponerines **T1**, **T2**, **T5**, and **T6** if glycosyl imines of type **10** are reacted with allylsilanes[14c] or allylstannanes and the stereoselectively formed homoallylamines are subjected to ring-closing iodoamination.[37]

Preliminary investigations of the insecticidal effects showed that racemic tetraponerine-8 prepared according to the procedure described by Barluenga et al.[9b] had a 100% mortal effect on *Plutella xylostella* (diamond back moth) in a concentration of 500 ppm. The racemate of **1** also killed 75% of *Myzus persicae* (green peach aphid) at a concentration of 300 ppm. Surprisingly, the synthesized natural (+)-tetraponerine-8 (**1**) exhibited no toxic effects on both organisms in identical concentrations. Further studies are needed to clarify this astonishing result.

Solvents for moisture-sensitive reactions (THF, MeOH, CH_2Cl_2) were distilled and dried according to standard procedures.[18] Reactions were monitored by TLC with pre-coated silica gel 60 F_{254} aluminum plates (Merck). Flash column chromatography was performed with silica gel (35–70 µm) from Agros Chemicals. ^{1}H, ^{13}C, and 2D NMR spectra were recorded with Bruker AC-300, AM-400, or AV-400 spectrometers. Assignment of proton and carbon signals was achieved by additional COSY and HMQC experiments when noted. FD-MS were recorded on a Finnigan MAT-95 instrument; ESI-MS were measured on a Micromass-Q-TOF-Ultima-3 instrument, which when equipped with a LockSpray interface also served for measuring HRMS-ESI. Optical rotations $[\alpha]_D$ were measured with a Perkin Elmer polarimeter

241. RP-HPLC was performed using a Knauer Maxi-Star K-1000 gradient pump, a Knauer four-channel degasser and a Knauer diode array detector DAD K-2800 with application of Knauer Chromgate software. A Luna C18 RP column (Phenomenex) was used for analytical measurements (flow rate 1 mL/min). Semi-preparative RP-HPLC separations were performed on a Knauer HPLC system consisting of two Knauer K-500 pumps and a Phenomenex Luna C18 column at a flow rate of 10 mL/min.

tert-Butyl (*E*)-Oct-2-enoate (4)

To a solution of Boc_2O (21.7 g, 0.1 mol) in *t*-BuOH (150 mL) was added DMAP (1.8 g, 0.15 mol). After dissolution, (*E*)-oct-2-enoic acid (7.5 mL, 7.07 g, 0.05 mol) was added dropwise. Evolution of CO_2 started immediately, and within 15 min the color of the solution changed from yellow to orange and to reddish-brown. The mixture was stirred at r.t. for 4 h and then the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL), washed with 1 M HCl (150 mL), sat. $NaHCO_3$ solution (150 mL), and H_2O (150 mL). The solution was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The brown crude product was purified either by distillation in vacuo to give the product as a colorless oil; yield: 5.2 g (52%); bp 100 °C/22 mbar (Lit.[18] bp 100–120 °C/1.33 mbar); or purification was carried out by flash chromatography (cyclohexane–EtOAc, 30:1) to give the product as a yellowish oil; yield: 8.01 g (81%); R_f = 0.58 (cyclohexane–EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (dt, $J_{3,2}$ = 15.6 Hz, $J_{3,4}$ = 6.9 Hz, 1 H, C*H*=CHCO), 5.71 (dt, $J_{2,3}$ = 15.6 Hz, $J_{2,4}$ = 1.5 Hz, 1 H, CH=C*H*CO), 2.14 (qd, $J_{4,5}$ = $J_{4,3}$ = 7.3 Hz, $J_{4,2}$ = 1.5 Hz, 2 H, CH_2C*H*=CH), 1.46 [s, 9 H, C(CH_3)$_3$], 1.44–1.40 (m, 2 H, CH_2), 1.31–1.25 (m, 4 H, 2 CH_2), 0.87 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.32 (C=O), 148.32 (*C*H=CHCO), 122.99 (CH=*C*HCO), 80.04 [*C*(CH_3)$_3$], 32.13 (*C*H_2CH=CH), 31.46 (CH_2), 28.26 [C(*C*H_3)$_3$], 27.88 (CH_2), 22.56 (7-CH_2), 14.07 (*C*H_3CH_2).

tert-Butyl (*S*)-3-{Benzyl[(*S*)-1-phenylethyl]amino}octanoate (6*S*); Typical Procedure

(*S*)-*N*-Benzyl-1-phenylethylamine (8.5 mL, 8.59 g, 40.6 mmol) was dissolved in anhyd THF (130 mL) and cooled to –78 °C; 1.6 M BuLi in *n*-hexane (23.6 mL, 37.8 mmol) was slowly added dropwise and the color changed from pale rose to pink. The mixture was stirred at –78 °C for 30 min, and then a solution of *tert*-butyl (*E*)-oct-2-enoate (**4**; 5 g, 25.5 mmol) in anhyd THF (20 mL) was added. The solution was stirred at –78 °C under argon for 3 h. Subsequently sat. aq NH_4Cl (50 mL) was added, and the solution was allowed to warm up to r.t. THF was evaporated in vacuo. H_2O (150 mL) was added to the residue, and the solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL) and dried ($MgSO_4$), and the solvent was evaporated in vacuo to yield a yellow, slightly viscous liquid (13.3 g), which was purified by flash chromatography (cyclohexane–EtOAc, 19:1) to give a colorless oil; yield: 8.35 g (80%); R_f = 0.74 (cyclohexane–EtOAc, 19:1); $[\alpha]_D^{23}$ –7.60 (*c* 1.4, $CHCl_3$) [Lit.[21] (*R*,*R*)-enantiomer: $[\alpha]_D^{20}$ +7.60 (*c* 1.4, $CHCl_3$)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.17 (m, 10 H, H_{Ar}), 3.82 (q, $J_{\alpha CH,\alpha CHCH3}$ = 7.1 Hz, 1 H, NC*H*CH_3), 3.80 (d, $J_{NCHa,NCHb}$ = 15.1 Hz, 1 H, NC*H*$_a$$CH_b$Ph), 3.49 (d, $J_{NCHb,NCHa}$ = 15.0 Hz, 1 H, NCH_a*C*H_bPh), 3.38–3.23 (m, 1 H, CHCH_2CO_2), 1.96 (dd, $J_{H2a,H2b}$ = 14.5 Hz, $J_{H2a,H3}$ = 3.8 Hz, 1 H, *C*$H_a$$H_b$$CO_2$), 1.87 (dd, $J_{H2b,H2a}$ = 14.5 Hz, $J_{H2b,H3}$ = 9.2 Hz, 1 H, CH_a*H*$_b$$CO_2$), 1.65–1.09 (m, 8 H, 4-$CH_2$, 5-$CH_2$, 6-$CH_2$, 7-$CH_2$), 1.41 [s, 9 H, C($CH_3$)$_3$], 1.33 (d, $J_{\alpha CHCH3,\alpha CH}$ = 7.0 Hz, 3 H, NCHC*H*$_3$), 0.89 (t, $J_{8\text{-}CH3,7\text{-}CH2}$ = 7.1 Hz, 3 H, *C*H_3CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.41 (C=O), 143.29, 142.23 ($C1_{Ar}$), 128.34, 128.27, 128.20, 128.08 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 127.00, 126.63 ($C4_{Ar}$), 80.01 [*C*(CH_3)$_3$], 58.49 (N*C*HCH_3), 54.05 (*C*HCH_2CO_2), 50.22 (NCH_2Ph), 37.97 (*C*H_2CO_2), 33.58, 31.95, 26.73, 22.83 (C4, C5, C6, C7), 28.19 [C(*C*H_3)$_3$], 20.63 (NCH*C*H_3), 14.24 (*C*H_3CH_2).

MS (FD): *m*/*z* = 409.0 [M$^+$].

tert-Butyl (*R*)-3-{Benzyl[(*S*)-1-phenylethyl]amino}octanoate (6*R*)

Following the typical procedure for **6*S*** using *tert*-butyl (*E*)-oct-2-enoate (**4**; 5.9 g, 29.8 mmol), (*R*)-*N*-benzyl-1-phenylethylamine (10 mL), anhyd THF (150 mL), and 1.6 M BuLi in hexane (28 mL) gave **6*R*** as a yellowish oil; yield: 9.85 g (81%); R_f = 0.71 (cyclohexane–EtOAc, 19:1); $[\alpha]_D^{23}$ +6.27 (*c* 1, $CHCl_3$) [Lit.[21] $[\alpha]_D^{20}$ +7.60 (*c* 1.4, $CHCl_3$)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.08 (m, 10 H, H_{Ar}), 3.86–3.74 (m, 2 H, NC*H*CH_3, NC*H*$_a$$CH_b$Ph), 3.48 (d, $J_{NCHb,NCHa}$ = 15.0 Hz, 1 H, NCH_a*C*H_bPh), 3.36–3.22 (m, 1 H, C*H*CH_2CO_2), 1.96 (dd, $J_{H2a,H2b}$ = 14.6 Hz, $J_{H2a,H3}$ = 3.8 Hz, 1 H, *C*$H_a$$H_b$$CO_2$), 1.87 (dd, $J_{H2b,H2a}$ = 14.6 Hz, $J_{H2b,H3}$ = 9.1 Hz, 1 H, CH_a*H*$_b$$CO_2$), 1.63–1.13 (m, 8 H, 4-$CH_2$, 5-$CH_2$, 6-$CH_2$, 7-$CH_2$), 1.40 [s, 9 H, C($CH_3$)$_3$], 1.33 (d, $J_{\alpha CHCH3,\alpha CH}$ = 7.0 Hz, 3 H, NCHC*H*$_3$), 0.89 (t, *J* = 7.1 Hz, 3 H, *C*H_3CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.41 (C=O), 143.30, 142.24 ($C1_{Ar}$), 128.34, 128.27, 128.20, 128.08 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 127.00, 126.63 ($C4_{Ar}$), 80.01 [*C*(CH_3)$_3$], 58.49 (N*C*HCH_3), 54.07 (*C*HCH_2CO_2), 50.22 (NCH_2Ph), 37.98 (*C*H_2CO_2), 33.58, 31.95, 26.73, 22.83 (C4, C5, C6, C7), 28.19 [C(*C*H_3)$_3$], 20.63 (NCH*C*H_3), 14.24 (*C*H_3CH_2).

tert-Butyl (*S*)-3-Aminooctanoate (7*S*); Typical Procedure

To aminooctanoic ester **6*S*** (8.0 g, 19.5 mmol) dissolved in MeOH (100 mL) was added 10% $Pd(OH)_2$/C (2.0 g). The mixture was stirred under H_2 at r.t. for 3 d. After filtration through Hyflo® the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (EtOAc–MeOH, 9:1) to give a colorless oil; yield: 3.4 g (81%); 98.7% ee [chiral GC analysis (injector: 220 °C, column: 130 °C, detector: 150 °C, flow: 2.0 mL/min): t_R = 5.31, 5.67 min, space ratio: 0.66:99.34]; R_f = 0.15 (EtOAc–MeOH, 9:1); $[\alpha]_D^{23}$ +13.8 (*c* 0.7, $CHCl_3$) [Lit.[21] (*R*)-enantiomer: $[\alpha]_D^{20}$ –14.3 (*c* 0.7, $CHCl_3$)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20–3.05 (m, 1 H, *C*HNH_2), 2.37 (dd, $J_{H2a,H2b}$ = 15.5 Hz, $J_{H2a,H3}$ = 4.1 Hz, 1 H, *C*$H_a$$CH_b$$CO_2$), 2.16 (dd, $J_{H2b,H2a}$ = 15.6 Hz, $J_{H2b,H3}$ = 8.8 Hz, 1 H, CH_a*C*$H_b$$CO_2$), 1.76 (s, 2 H, NH_2), 1.44 [s, 9 H, C(CH_3)$_3$)], 1.40–1.21 (m, 8 H, 4-CH_2, 5-CH_2, 6-CH_2, 7-CH_2), 0.87 (t, $J_{8\text{-}CH3,7\text{-}CH2}$ = 6.6 Hz, 3 H, *C*H_3CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.95 (C=O), 80.39 [*C*(CH_3)$_3$], 48.40 (*C*HNH_2), 43.69 (*C*H_2CO_2), 37.33, 31.78, 25.68, 22.56 (C4, C5, C6, C7), 28.10 [C(*C*H_3)$_3$], 14.12 (*C*H_3CH_2).

MS (ESI): *m*/*z* = 216.2 [M + H]$^+$, 238.2 [M + Na]$^+$.

tert-Butyl (*R*)-3-Aminooctanoate (7*R*)

Following the typical procedure for **7*S*** using **6*R*** (9.82 g, 24.0 mmol), 10% $Pd(OH)_2$/C (2.4 g), and *i*-PrOH (90 mL) gave a colorless oil; yield: 4.67 g (90%); R_f = 0.13 (EtOAc–MeOH, 9:1); $[\alpha]_D^{23}$ –13.26 (*c* 0.7, $CHCl_3$) [Lit.[21] $[\alpha]_D^{20}$ –14.3 (*c* 0.7, $CHCl_3$)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.26–3.11 (m, 1 H, *C*HNH_2), 2.95 (s, 2 H, NH_2), 2.41 (dd, $J_{H2a,H2b}$ = 15.9 Hz, $J_{H2a,H3}$ = 4.0 Hz, 1 H, *C*$H_a$$CH_b$$CO_2$), 2.24 (dd, $J_{H2b,H2a}$ = 15.8 Hz, $J_{H2b,H3}$ = 8.6 Hz, 1 H, CH_a*C*$H_b$$CO_2$), 1.44 [s, 9 H, C($CH_3$)$_3$], 1.41–1.19 (m, 8 H, 4-$CH_2$, 5-$CH_2$, 6-$CH_2$, 7-$CH_2$), 0.87 (t, $J_{8\text{-}CH3,7\text{-}CH2}$ = 6.6 Hz, 3 H, *C*H_3CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.30 (C=O), 81.13 [*C*(CH_3)$_3$], 48.67 (*C*HNH_2), 42.55 (*C*H_2CO_2), 36.83, 31.83, 25.68, 22.66 (C4, C5, C6, C7), 28.22 [C(*C*H_3)$_3$], 14.12 (*C*H_3CH_2).

tert-Butyl (*S*)-3-{[4-(*tert*-Butyldiphenylsiloxy)butyl]amino}octanoate; Typical Procedure

To a solution of **7*S*** (3.3 g, 15.3 mmol) in DCE (70 mL) at 0 °C was added a solution of 4-(*tert*-butyldiphenylsiloxy)butanal[22] (**5**; 5.3 g, 16.2 mmol) in DCE (90 mL). The mixture was stirred for 15 min and, subsequently, $NaB(OAc)_3H$ (6.5 g, 30.6 mmol) was added. The solution was stirred at r.t. for 14 h. The solvent was evaporated in vacuo. EtOAc (150 mL) and sat. $NaHCO_3$ solution (200 mL) were added to the residue. The aqueous solution was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (2 × 150 mL) and dried ($MgSO_4$), and the solvent was evaporated in vacuo. The product was purified by flash chromatography (cyclohexane–EtOAc, 3:1) to give a pale yellow oil; yield: 6.5 g (81%); R_f = 0.27 (cyclohexane–EtOAc, 2:1); $[\alpha]_D^{23}$ +2.1 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.71–7.62 (m, 4 H, H_{Ar}), 7.46–7.33 (m, 6 H, H_{Ar}), 3.66 (t, $J_{4'\text{-}CH2,3'\text{-}CH2}$ = 6.1 Hz, 2 H, CH_2OSi), 2.93–2.85 (m, 1 H, $CHCH_2CO_2$), 2.57 (t, $J_{1'\text{-}CH2,2'\text{-}CH2}$ = 7.0 Hz, 2 H, $NHCH_2$), 2.31 (d, $J_{2\text{-}CH2,H3}$ = 6.3 Hz, 2 H, CH_2CO_2), 1.65–1.48 (m, 4 H, 2′-CH_2, 3′-CH_2), 1.45 [s, 9 H, $CO_2C(CH_3)_3$], 1.40–1.23 (m, 8 H, 4-CH_2, 5-CH_2, 6-CH_2, 7-CH_2), 1.04 [s, 9 H, $SiC(CH_3)_3$], 0.89 (t, $J_{8\text{-}CH3,7\text{-}CH2}$ = 6.9 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC): δ = 172.27 (C=O), 135.70, 127.72 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 134.17 ($C1_{Ar}$), 129.64 ($C4_{Ar}$), 80.42 [$C(CH_3)_3$], 63.96 (CH_2OSi), 55.11 (C3), 46.93 ($NHCH_2$), 40.61 (CH_2CO_2), 34.59, 32.15, 30.63, 27.02, 25.58, 22.75 (C4, C5, C6, C7, C2′, C3′), 28.26 [$CO_2C(CH_3)_3$], 26.99 [$SiC(CH_3)_3$], 19.34 [$SiC(CH_3)_3$], 14.20 (CH_3CH_2).

MS (ESI): *m*/*z* = 470.3 [M – O*t*-Bu + H_2O]$^+$, 526.3 [M + H]$^+$, 548.3 [M + Na]$^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{32}H_{52}NO_3Si$: 526.3716; found: 526.3709.

Anal. Calcd for $C_{32}H_{51}NO_3Si$: C, 73.09; H, 9.78; N, 2.66. Found: C, 73.07; H, 9.86; N, 4.02.

tert-Butyl (*R*)-3-{[4-(*tert*-Butyldiphenylsiloxy)butyl]amino}octanoate

Following the typical procedure for the *S*-enantiomer using **7*R*** (4.62 g, 21.5 mmol), 4-(*tert*-butyldiphenylsiloxy)butanal[22] (**5**; 7.35 g, 22.5 mmol), DCE (200 mL), and $NaB(OAc)_3H$ (8.9 g, 42.0 mmol) gave a pale yellow oil; yield: 4.93 g (9.38 mmol, 45%); R_f = 0.15 (cyclohexane–EtOAc, 7:2); $[\alpha]_D^{23}$ –2.6 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.59 (m, 4 H, H_{Ar}), 7.48–7.31 (m, 6 H, H_{Ar}), 3.67 (t, $J_{4'\text{-}CH2,3'\text{-}CH2}$ = 5.9 Hz, 2 H, CH_2OSi), 2.95–2.85 (m, 1 H, $CHCH_2CO_2$), 2.59 (t, $J_{1'\text{-}CH2,2'\text{-}CH2}$ = 6.8 Hz, 2 H, $NHCH_2$), 2.32 (d, $J_{2\text{-}CH2,H3}$ = 6.2 Hz, 2 H, CH_2CO_2), 1.67–1.48 (m, 4 H, 2′-CH_2, 3′-CH_2), 1.45 [s, 9 H, $CO_2C(CH_3)_3$], 1.36–1.20 (m, 8 H, 4-CH_2, 5-CH_2, 6-CH_2, 7-CH_2), 1.05 [s, 9 H, $SiC(CH_3)_3$], 0.89 (t, $J_{8\text{-}CH3,7\text{-}CH2}$ = 6.7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.26 (C=O), 135.69, 127.72 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 134.15 ($C1_{Ar}$), 129.64 ($C4_{Ar}$), 80.52 [$C(CH_3)_3$], 63.94 (CH_2OSi), 55.13 (C3), 46.86 ($NHCH_2$), 40.41 (CH_2CO_2), 34.42, 32.10, 30.59, 26.90, 25.57, 22.74 (C4, C5, C6, C7, C2′, C3′), 28.26 [$CO_2C(CH_3)_3$], 26.99 [$SiC(CH_3)_3$], 19.33 [$SiC(CH_3)_3$], 14.19 (CH_3CH_2).

HRMS: *m*/*z* [M + H] calcd for $C_{32}H_{52}NO_3Si$: 526.3716; found: 526.3717.

(*S*)-3-{[4-(*tert*-Butyldiphenylsiloxy)butyl]amino}octanol (8*S*); Typical Procedure

To *tert*-butyl (*S*)-3-{[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanoate (6.0 g, 11.4 mmol) in anhyd Et_2O (55 mL) at 0 °C was added dropwise 4 M $LiAlH_4$ in Et_2O (3 mL, 12.0 mmol). The mixture was stirred for 90 min at 0 °C and then cautiously and sequentially H_2O (0.5 mL), 15% aq NaOH solution (0.5 mL), and H_2O (1.5 mL) were added. After filtration the solution was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The product 8*S* was sufficiently pure for further conversion. Colorless oil; yield: 4.94 g (95%); R_f = 0.22 (EtOAc–MeOH, 3:1); $[\alpha]_D^{23}$ +18.1 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.72–7.60 (m, 4 H, H_{Ar}), 7.46–7.34 (m, 6 H, H_{Ar}), 3.87 (ddd, $J_{H1a,H1b}$ = 10.8 Hz, $J_{H1a,H2a}$ = 6.1 Hz, $J_{H1a,H2b}$ = 3.3 Hz, 1 H, CH_aH_bOH), 3.76 (ddd, $J_{H1b,H1a}$ = 10.9 Hz, $J_{H1b,H2b}$ = 8.4 Hz, $J_{H1b,H2a}$ = 3.0 Hz, 1 H, CH_aH_bOH), 3.66 (t, $J_{4'\text{-}CH2,3'\text{-}CH2}$ = 6.0 Hz, 2 H, CH_2OSi), 2.77–2.64 (m, 2 H, H3, $NHCH_aH_b$), 2.62–2.53 (m, 1 H, $NHCH_aH_b$), 1.73 (ddt, $J_{H2a,H2b}$ = 14.5 Hz, $J_{H2a,H1a}$ = 6.1 Hz, $J_{H2a,H1b}$ = $J_{H2a,H3}$ = 3.0 Hz, 1 H, H2a), 1.64–1.50 and 1.40–1.21 (2 × m, 5 H, 7 H, 2′-CH_2, 3′-CH_2, 4-CH_2, 5-CH_2, 6-CH_2, 7-CH_2), 1.48–1.41 (m, 1 H, H2b), 1.05 [s, 9 H, $C(CH_3)_3$], 0.90 (t, $J_{8\text{-}CH3,7\text{-}CH2}$ = 6.9 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 135.69, 127.74 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 134.09 ($C1_{Ar}$), 129.67 ($C4_{Ar}$), 63.81 (CH_2OSi), 62.90 (CH_2OH), 59.43 (C3), 46.59 ($NHCH_2$), 33.99 (C4), 33.58 (C2), 32.09, 30.42, 26.96, 25.77, 22.74 (C5, C6, C7, C2′, C3′), 26.99 [$C(CH_3)_3$], 19.34 [$C(CH_3)_3$], 14.17 (CH_3CH_2).

MS (ESI): *m*/*z* = 456.3 [M + H]$^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{28}H_{46}NO_2Si$ (455.75): 456.3298; found: 456.3311.

Anal. Calcd for $C_{28}H_{45}NO_2Si$: C, 73.79; H, 9.95; N, 3.07. Found: C, 73.58; H, 9.98; N, 5.02.

(*R*)-3-{[4-(*tert*-Butyldiphenylsiloxy)butyl]amino}octanol (8*R*)

Following the typical procedure for **8*S*** using *tert*-butyl (*R*)-3-{[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanoate (4.93 g, 9.38 mmol), 1 M $LiAlH_4$ (9.9 mL, 9.9 mmol), and anhyd Et_2O (45 mL) gave a colorless oil; yield: 4.01 g (94%); R_f = 0.04 (cyclohexane–EtOAc, 3:1); $[\alpha]_D^{23}$ –17.1 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.61 (m, 4 H, H_{Ar}), 7.46–7.33 (m, 6 H, H_{Ar}), 3.87 (ddd, $J_{H1a,H1b}$ = 10.7 Hz, $J_{H1a,H2a}$ = 6.1 Hz, $J_{H1a,H2b}$ = 3.4 Hz, 1 H, CH_aH_bOH), 3.80–3.72 (m, 1 H, CH_aH_bOH), 3.67 (t, $J_{4'\text{-}CH2,3'\text{-}CH2}$ = 5.8 Hz, 2 H, CH_2OSi), 2.79–2.64 (m, 2 H, H3, $NHCH_aH_b$), 2.63–2.52 (m, 1 H, $NHCH_aH_b$), 1.73 (ddt, $J_{H2a,H2b}$ = 14.4 Hz, $J_{H2a,H1a}$ = 6.1 Hz, $J_{H2a,H1b}$ = $J_{H2a,H3}$ = 3.0 Hz, 1 H, H2a), 1.64–1.14 (m, 13 H, 2′-CH_2, 3′-CH_2, H2b, 4-CH_2, 5-CH_2, 6-CH_2, 7-CH_2), 1.05 [s, 9 H, $C(CH_3)_3$], 0.90 (t, $J_{8\text{-}CH3,7\text{-}CH2}$ = 6.7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 135.67, 127.73 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 134.07 ($C1_{Ar}$), 129.67 ($C4_{Ar}$), 63.79 (CH_2OSi), 62.80 (CH_2OH), 59.39 (C3), 46.52 ($NHCH_2$), 33.89 (C4), 33.53 (C2), 32.07, 30.39, 26.87, 25.76, 22.72 (C5, C6, C7, C2′, C3′), 26.99 [$C(CH_3)_3$], 19.33 [$C(CH_3)_3$], 14.16 (CH_3CH_2).

MS (ESI): *m*/*z* = 456.3 [M + H]$^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{28}H_{46}NO_2Si$ (455.75): 456.3298; found: 456.3299.

(*S*)-3-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanol; Typical Procedure

To a solution of **8*S*** (4.9 g, 10.8 mmol) in EtOAc (70 mL) at 0 °C was added H_2O (70 mL), K_2CO_3 (3.0 g, 21.5 mmol), and finally benzyl chloroformate (3.1 mL, 3.7 g, 21.5 mmol). The ice bath was removed and the mixture stirred at r.t. for 90 min. After the addition of 1 M KH_2PO_4 solution (250 mL) the layers were separated and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 6:1) to give a pale yellow oil; yield: 5.86 g (92%); R_f = 0.24 (cyclohexane–EtOAc, 4:1); $[\alpha]_D^{23}$ –2.0 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.70–7.59 (m, 4 H, H_{Ar}, $SiPh_2$), 7.46–7.28 (m, 11 H, H_{Ar}, $SiPh_2$ and Bn), 5.22–5.08 (m, 2 H, PhCH_2), 4.34–4.19^R, 4.15–3.98 (m, 1 H, H3), 3.68, 3.63^R (t, $J_{4'\text{-CH2},3'\text{-CH2}}$ = 6.0 Hz, 2 H, CH_2OSi), 3.59–3.56, 3.56–3.50^R (m, 1 H, C$H_a$$H_b$OH), 3.41^R (dt, 1 H, $J_{H1b,H1a}$ = 11.4 Hz, $J_{H1b,2\text{-CH2}}$ = 3.0 Hz, $CH_a$$H_b$OH), 3.08, 3.02^R (t, $J_{1'\text{-CH2},2'\text{-CH2}}$ = 7.4 Hz, 2 H, NCH_2), 1.81–1.70^R (m, 1 H, H2a), 1.70–1.46 (m, 7 H, H2b, 4-CH_2, 2′-CH_2, 3′-CH_2), 1.34–1.19 (m, 6 H, 5-CH_2, 6-CH_2, 7-CH_2), 1.04 [s, 9 H, C(CH_3)$_3$], 0.92–0.82 (m, 3 H, C$H_3$$CH_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 158.28^R, 156.53 (C=O), 136.83 (C1′$_{Ar}$, Bn), 135.66, 127.76 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 133.95 (C1$_{Ar}$, $SiPh_2$), 129.74 (C4$_{Ar}$, $SiPh_2$), 129.69 (C4′$_{Ar}$, Bn), 128.69, 128.62^R, 128.24, 128.10^R (C2′$_{Ar}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 67.41^R, 67.23 (PhCH_2), 63.75, 63.60^R (CH_2OSi), 59.64, 58.84^R (CH_2OH), 52.78 (C3), 42.44 (NCH_2), 36.39, 35.97^R (C2), 33.75, 33.26^R, 31.76, 30.46, 27.08, 26.48^R, 26.33, 22.69, (C4, C5, C6, C7, C2′, C4′), 26.96 [C(CH_3)$_3$], 19.31 [C(CH_3)$_3$], 14.15 ($CH_3$$CH_2$).

MS (ESI): *m*/*z* = 590.4 [M + H]$^+$, 612.3 [M + Na]$^+$, 628.3 [M + K]$^+$, 1201.7 [2 M + Na]$^+$.

HRMS: *m*/*z* [M + Na] calcd for $C_{36}H_{51}NO_4SiNa$: 612.3485; found: 612.3497.

Anal. Calcd for $C_{36}H_{51}NO_4Si$: C, 73.30; H, 8.71; N: 2.37. Found: C, 73.01; H, 8.56; N, 2.43.

(*R*)-3-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanol

Following the typical procedure for the *S*-enantiomer using **8*R*** (3.92 g, 8.6 mmol), K_2CO_3 (2.37 g, 17.1 mmol), benzyl chloroformate (2.5 mL, 17.6 mmol), EtOAc (56 mL) and H_2O (56 mL) gave a pale yellow oil; yield: 4.18 g (82%); R_f = 0.23 (cyclohexane–EtOAc, 4:1); $[\alpha]_D^{23}$ +1.8 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.61 (m, 4 H, H_{Ar}, $SiPh_2$), 7.49–7.28 (m, 11 H, H_{Ar}, $SiPh_2$, Bn), 5.24–5.09 (m, 2 H, PhCH_2), 4.34–4.18^R, 4.12–4.00 (m, 1 H, H3), 3.68, 3.64^R (t, $J_{4'\text{-CH2},3'\text{-CH2}}$ = 6.0 Hz, 2 H, CH_2OSi), 3.60–3.50 (m, 1 H, C$H_a$$H_b$OH), 3.41^R (dt, 1 H, $J_{H1b,H1a}$ = 11.4 Hz, $J_{H1b,2\text{-CH2}}$ = 2.7 Hz, $CH_a$$H_b$OH), 3.10, 3.03^R (t, $J_{1'\text{-CH2},2'\text{-CH2}}$ = 7.9 Hz, 2 H, NCH_2), 1.83–1.40 (m, 8 H, H2a, H2b, 4-CH_2, 2′-CH_2, 3′-CH_2), 1.35–1.15 (m, 6 H, 5-CH_2, 6-CH_2, 7-CH_2), 1.04 [s, 9 H, C(CH_3)$_3$], 0.91–0.80 (m, 3 H, C$H_3$$CH_2$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 158.28 (C=O), 136.82 (C1′$_{Ar}$, Bn), 135.66, 127.76 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 133.96 (C1$_{Ar}$, $SiPh_2$), 129.74 (C4$_{Ar}$, $SiPh_2$), 128.67, 128.63^R, 128.11^R (C2′$_{Ar}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 127.09 (C4′$_{Ar}$, Bn), 67.42^R, 67.26 (PhCH_2), 63.73, 63.60^R (CH_2OSi), 59.61, 58.84^R (CH_2OH), 52.82, 52.79^R (C3), 42.43 (NCH_2), 36.33, 35.96^R (C2), 33.26, 31.75, 30.46, 27.08^R, 27.04, 26.48, 22.69, (C4, C5, C6, C7, C2′, C4′), 26.97 [C(CH_3)$_3$], 19.31 [C(CH_3)$_3$], 14.15 ($CH_3$$CH_2$).

MS (ESI): *m*/*z* = 590.4 [M + H]$^+$.

HRMS: *m*/*z* [M + Na] calcd for $C_{36}H_{51}NO_4SiNa$: 612.3485; found: 612.3456.

(*S*)-3-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanal (9*S*); Typical Procedure

To a stirred solution of oxalyl chloride (0.9 mL, 1.3 g, 10.5 mmol) in anhyd CH_2Cl_2 (32 mL) at –78 °C was added DMSO (1.46 mL, 1.6 g, 20.6 mmol). After 5 min a solution of (*S*)-3-{(benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanol (5.5 g, 9.3 mmol) in anhyd CH_2Cl_2 (11 mL) was added dropwise, and the mixture was stirred at –78 °C for 30 min. Then, Et_3N (6.4 mL) was added and stirring was continued for 5 min; the mixture was allowed to warm up to r.t., H_2O (50 mL) was added, and the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine (120 mL), 2 M HCl (100 mL), and sat. $NaHCO_3$ solution (120 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by flash chromatography (cyclohexane–EtOAc, 8:1) to give a colorless oil; yield: 4.98 g (91%); R_f = 0.26 (cyclohexane–EtOAc, 8:1); $[\alpha]_D^{23}$ –6.5 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 9.79–9.56 (m, 1 H, CHO), 7.73–7.58 (m, 4 H, H_{Ar}, $SiPh_2$), 7.47–7.27 (m, 11 H, H_{Ar}, $SiPh_2$, Bn), 5.22–5.06 (m, 2 H, PhCH_2), 4.43–4.27 (m, 1 H, H3), 3.68, 3.63^R (t, $J_{4'\text{-CH2},3'\text{-CH2}}$ = 6.1 Hz, 2 H, CH_2OSi), 3.22–3.06 (m, 2 H, NCH_2), 2.80–2.51 (m, 2 H, CH_2CHO), 1.74–1.45 (m, 6 H, 4-CH_2, 2′-CH_2, 3′-CH_2), 1.37–1.13 (m, 6 H, 5-CH_2, 6-CH_2, 7-CH_2), 1.05 [s, 9 H, C(CH_3)$_3$], 0.92–0.80 (m, 3 H, C$H_3$$CH_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 200.94^R, 200.41 (CHO), 156.26^R, 156.18 (C=O), 136.91^R, 136.75 (C1′$_{Ar}$, Bn), 135.67, 127.76 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 133.98 (C1$_{Ar}$, $SiPh_2$), 129.72 (C4$_{Ar}$, $SiPh_2$), 128.59, 128.22^R, 128.00, 127.71 (C2′$_{Ar}$, C3′$_{Ar}$, C4′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 67.31, 67.01^R (PhCH_2), 63.67, 63.60^R (CH_2OSi), 52.99^R, 52.17 (C3), 48.57, 48.01^R (CH_2CHO), 45.48, 45.33^R (NCH_2), 33.80, 33.24^R, 31.66, 30.27, 26.70^R, 26.21, 26.31^R, 25.85, 22.65 (C4, C5, C6, C7, C2′, C4′), 26.98 [C(CH_3)$_3$], 19.31 [C(CH_3)$_3$], 14.12 ($CH_3$$CH_2$).

MS (ESI): *m*/*z* = 588.4 [M + H]$^+$, 610.4 [M + Na]$^+$, 626.4 [M + K]$^+$, 1197.7 [2 M + Na]$^+$.

HRMS: *m*/*z* [M + Na] calcd for $C_{36}H_{49}NO_4SiNa$: 610.3329; found: 610.3318.

Anal. Calcd for $C_{36}H_{49}NO_4Si$: C, 73.55; H, 8.40; N, 2.38. Found C: 72.25; H, 8.11; N, 3.24.

(*R*)-3-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanal (9*R*)

Following the typical procedure for **9*S*** using (*R*)-3-{(benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octanol (4.13 g, 7.0 mmol), oxalyl chloride (0.68 mL, 7.9 mmol), DMSO (1.1 mL, 15.5 mmol), anhyd CH_2Cl_2 (35 mL), and Et_3N (4.8 mL, 34.6 mmol) gave a slightly yellow oil; yield: 3.77 g (92%); R_f = 0.26 (cyclohexane–EtOAc, 8:1); $[\alpha]_D^{23}$ +5.4 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.79–9.56 (m, 1 H, CHO), 7.73–7.55 (m, 4 H, H_{Ar}, $SiPh_2$), 7.48–7.22 (m, 11 H, H_{Ar}, $SiPh_2$ and Bn), 5.19–4.99 (m, 2 H, PhCH_2), 4.42–4.23 (m, 1 H, H3), 3.73–3.51 (m, 2 H, CH_2OSi), 3.21–3.02 (m, 2 H, NCH_2), 2.81–2.46 (m, 2 H, CH_2CHO), 1.71–1.44 (m, 6 H, 4-CH_2, 2′-CH_2, 3′-CH_2), 1.32–1.12 (m, 6 H, 5-CH_2, 6-CH_2, 7-CH_2), 1.02 [s, 9 H, C(CH_3)$_3$], 0.92–0.75 (m, 3 H, C$H_3$$CH_2$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 200.96^R, 200.43 (CHO), 156.26 (C=O), 136.96 (C1′$_{Ar}$, Bn), 135.69, 127.77 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 134.01 (C1$_{Ar}$, $SiPh_2$), 129.73 (C4$_{Ar}$, $SiPh_2$), 128.61, 128.21, 128.02 (C2′$_{Ar}$, C3′$_{Ar}$, C4′, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 67.33, 67.03^R (PhCH_2), 63.70, 63.63^R (CH_2OSi), 53.02^R, 52.20 (C3), 48.56, 48.04^R (CH_2CHO), 45.35 (NCH_2), 33.77, 33.25^R, 31.68, 30.29, 26.71, 26.32, 22.66 (C4, C5, C6, C7, C2′, C4′), 26.99 [C(CH_3)$_3$], 19.33 [C(CH_3)$_3$], 14.13 ($CH_3$$CH_2$).

MS (ESI): *m*/*z* = 588.4 [M + H]$^+$.

HRMS: *m*/*z* [M + Na] calcd for $C_{36}H_{49}NO_4SiNa$: 610.3329; found: 610.3323.

2-*N*-[(*S*)-3-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octylidene]-2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine (10*S*); Typical Procedure

To a solution of 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine[14c] (**3**, 2.09 g, 5.2 mmol) in *n*-pentane (40 mL) was added dropwise aldehyde **9*S*** (3.68 g, 6.26 mmol) dissolved in *n*-pentane (25 mL). The mixture turned turbid, and freshly dried molecular sieves (4 Å, 4.2 g) were

added. The mixture was stirred under argon at r.t. for 22 h, and then the suspension was filtered through Hyflo® and the solvent was evaporated in vacuo. The syrupy crude product **10*S*** was directly used for the subsequent reaction.

(2*S*)-2-[(*S*)-2-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2,3-dihydropyridine-4(1*H*)-one (11); Typical Procedure

To the crude imine **10*S*** (5.2 mmol) dissolved in anhyd THF (26 mL) was added, under stirring at –78 °C, 1 M $ZnCl_2$ in THF (11.4 mL, 11.4 mmol) and the mixture was stirred for 10 min. Danishefsky diene[16] **2** (1.1 g, 6.4 mmol) was added dropwise and the mixture was stirred for a further 30 min at –78 °C and then 48 h at –20 °C. The reaction was stopped by addition of 1 M aq HCl (5.2 mL). The mixture was concentrated in vacuo and the remainder taken up in Et_2O (100 mL). The organic layer was separated and then washed with sat. $NaHCO_3$ solution (3 × 30 mL) and 10% Titriplex® solution (2 × 30 mL) to eliminate zinc compounds. After additional washing with brine (50 mL), the solution was dried ($MgSO_4$) and the solvent was evaporated in vacuo to give an orange syrupy crude product (6.4 g) that was purified by flash chromatography (cyclohexane–EtOAc, 4:1) to give a yellow amorphous solid; yield: 3.18 g (3.06 mmol, 59%, 2 steps); dr 98:1:1:0 [HPLC (gradient: 95% MeCN, 5% H_2O to 100% MeCN (15 min), then 30 min 100% MeCN): t_R = 30.52 (major diastereomer), 34.48 and 37.67 min (minor diastereomers)]; R_f = 0.35 cyclohexane–EtOAc, (2:1); $[\alpha]_D^{23}$ +80.6 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.68–7.59 (m, 4 H, H_{Ar}, $SiPh_2$), 7.46–7.26 (m, 11 H, H_{Ar}, $SiPh_2$ and Bn), 6.89^R, 6.78 (d, $J_{H6,H5}$ = 7.9 Hz, 1 H, H6), 5.44^R, 5.39 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.6 Hz, 1 H, H2′), 5.31–5.24 (m, 1 H, H4′), 5.21–5.02 (m, 3 H, PhC*H*$_2$, H3′), 4.97^R, 4.93 (d, $J_{H5,H6}$ = 7.5 Hz, 1 H, H5), 4.40^R, 4.28 (d, $J_{H1',H2'}$ = 9.0 Hz, 1 H, H1′), 4.16–4.03, 4.03–3.92^R (m, 1 H, H2″), 3.85 (dd, $J_{H5'a,H5'b}$ = 13.3 Hz, 1 H, H5′a), 3.71–3.50 (m, 4 H, H5′b, H2, CH_2OSi), 3.26–3.08 (m, 1 H, N′C*H*$_a$CH$_b$), 3.06–2.89 (m, 1 H, N′CH$_a$C*H*$_b$), 2.69^R, 2.58 (dd, $J_{H3a,H3b}$ = 16.8 Hz, $J_{H3a,H2}$ = 5.9 Hz, 1 H, H3a), 2.46^R, 2.30 (d, $J_{H3b,H3a}$ = 16.4 Hz, 1 H, H3b), 2.17–2.02, 2.01–1.87^R (m, 2 H, H1″a, H1″b), 1.85–1.17 (m, 10 H, 2‴-CH_2, 3‴-CH_2, 3″-CH_2, 4″-CH_2, 5″-CH_2), 1.28–1.10 (m, 2 H, CH_3CH_2), 1.26^R, 1.19, 1.13, 1.11 [s, each 9 H, Piv-C$(CH_3)_3$], 1.03 [s, 9 H, SiC$(CH_3)_3$], 0.90–0.76 (m, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC): δ = 192.00 (C4), 177.39, 177.28, 177.00 (Piv-C=O), 156.35, 156.25^R (Cbz-C=O), 148.60, 148.38^R (C6), 137.06, 136.85^R (C1′$_{Ar}$, Bn), 135.65, 127.78 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 134.01, 133.95^R (C1$_{Ar}$, $SiPh_2$), 129.75 (C4$_{Ar}$, $SiPh_2$), 128.69, 128.60^R, 128.31^R, 128.22 (C2′$_{Ap}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 128.00 (C4′$_{Ar}$, Bn), 100.01^R, 99.73 (C5), 91.40, 90.86^R (C1′), 71.41^R, 71.22 (C3′), 67.88^R, 67.67 (C4′), 67.21, 67.01^R (PhCH$_2$), 66.98, 66.84^R (C5′), 66.73, 66.47^R (C2′), 63.74, 63.63^R (CH_2OSi), 54.53, 54.41^R (C2″), 51.30^R, 50.34 (C2), 42.31 (C1‴), 39.58 (C3), 39.04, 38.99, 38.93 [Piv-*C*$(CH_3)_3$], 33.96^R, 33.87 (C1″), 34.40, 31.92^R, 31.81, 30.69, 30.53^R, 26.38, 25.82 (C3″, C4″, C5″, C2‴, C3‴), 27.32, 27.22 [Piv-C$(CH_3)_3$], 26.97 [SiC$(CH_3)_3$], 22.68 (CH_3CH_2), 19.31 [Si*C*$(CH_3)_3$], 14.15 (CH_3CH_2).

MS (ESI): *m*/*z* = 1039.6 [M + H]$^+$, 1061.6 [M + Na]$^+$, 2079.3 [2 M + H]$^+$, 2101.2 [2 M + Na]$^+$.

HRMS: *m*/*z* [M + Na] calcd for $C_{60}H_{86}N_2O_{11}SiNa$: 1061.5899; found: 1061.5897.

2-*N*-[(*R*)-3-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}octylidene]-2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine (10*R*)

Following the typical procedure for **10*S*** using **3** (2.13 g, 5.3 mmol), **9*R*** (3.74 g, 6.36 mmol), *n*-pentane (65 mL), and molecular sieves (4.5 g).

(2*S*)-2-[(*R*)-2-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2,3-dihydropyridine-4(1*H*)-one (12) and (2*R*)-2-[(*R*)-2-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsiloxy)butyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2,3-dihydropyridine-4(1*H*)-one (13)

Following the typical procedure for **11** using imine **10*R*** (5.3 mmol), Danishefsky diene **2** (1.14 g, 6.4 mmol), 1 M $ZnCl_2$ in THF (11.6 mL, 11.6 mmol), and anhyd THF (27 mL) gave a pale yellow, viscous oil; yield: 3.23 g (58%, 2 steps); dr 67:33:0:0 [HPLC (gradient: 95% MeCN, 5% H_2O to 100% MeCN, 15 min, then 30 min 100% MeCN): t_R = 31.37 (minor diastereomer), 33.22 min (major diastereomer)]; R_f = 0.37 (cyclohexane–EtOAc, 2:1).

Major Diastereomer 12

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.69–7.59 (m, 4 H, H_{Ar}, $SiPh_2$), 7.46–7.27 (m, 11 H, H_{Ar}, $SiPh_2$ and Bn), 6.92^R, 6.85 (d, $J_{H6,H5}$ = 7.6 Hz, 1 H, H6), 5.53^R, 5.49 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.6 Hz, 1 H, H2′), 5.28–5.06 (m, 3 H, H4′, PhC*H*$_2$), 5.13 (dd, $J_{H3',H2'}$ = 9.9 Hz, $J_{H3',H4'}$ = 2.9 Hz, 1 H, H3′), 5.04^R, 4.99 (d, $J_{H5,H6}$ = 7.7 Hz, 1 H, H5), 4.69^R, 4.39 (d, $J_{H1',H2'}$ = 9.2 Hz, 1 H, H1′), 3.83, 3.72^R (d, $J_{H5'a,H5'b}$ = 13.1 Hz, 1 H, H5′a), 3.67–3.47 (m, 3 H, H2, CH_2OSi), 3.37–3.26 (m, 1 H, H2″), 3.52, 3.16^R (d, $J_{H5'b,H5'a}$ = 13.1 Hz, 1 H, H5′b), 3.10–2.91 (m, 2 H, N′CH_2), 2.76^R, 2.66 (dd, $J_{H3a,H3b}$ = 16.3 Hz, $J_{H3a,H2}$ = 6.4 Hz, 1 H, H3a), 2.34–1.84 (m, 3 H, H3b, 1″-CH_2), 1.76–1.39, 1.25–1.17 (m, 12 H, 2‴-CH_2, 3‴-CH_2, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.27, 1.14, 1.12 [s, each 9 H, Piv-C$(CH_3)_3$], 1.03 [s, 9 H, SiC$(CH_3)_3$], 0.85 (t, $J_{7''-CH3,6''-CH2}$ = 6.6 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 191.76^R, 191.40 (C4), 177.42, 177.29, 177.19 (Piv-C=O), 157.01^R, 156.35 (Cbz-C=O), 149.11, 147.27^R (C6), 137.26^R, 137.07 (C1′$_{Ar}$, Bn), 135.67, 127.78 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 134.04, 133.95^R (C1$_{Ar}$, $SiPh_2$), 129.76 (C4$_{Ar}$, $SiPh_2$), 128.76, 128.67^R, 128.41, 128.06^R (C2′$_{Ar}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 127.96 (C4′$_{Ar}$, Bn), 100.48^R, 100.29 (C5), 92.17, 90.84^R (C1′), 71.74^R, 71.19 (C3′), 68.30^R, 67.85 (C4′), 67.35, 67.18^R (PhCH$_2$), 66.34^R, 66.18 (C5′), 65.61 (C2′), 63.80, 63.72^R (CH_2OSi), 54.07 (C2″), 52.72^R, 51.63 (C2), 42.80 (C1‴), 40.66 (C3), 39.09, 39.02, 38.93 [Piv-*C*$(CH_3)_3$], 35.08, 34.88^R (C1″), 33.92, 33.84^R, 32.80, 31.93^R, 31.85, 30.52, 26.11 (C3″, C4″, C5″, C2‴, C3‴), 27.35, 27.23 [Piv-C$(CH_3)_3$], 26.99 [SiC$(CH_3)_3$], 22.72^R, 22.64 (CH_3CH_2), 19.32 [Si*C*$(CH_3)_3$], 14.16 (CH_3CH_2).

Minor Diastereomer 13

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.71–7.58 (m, 4 H, H_{Ar}, $SiPh_2$), 7.47–7.28 (m, 11 H, H_{Ar}, $SiPh_2$ and Bn), 7.16^R, 7.12 (d, $J_{H6,H5}$ = 7.9 Hz, 1 H, H6), 5.33 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.7 Hz, 1 H, H2′), 5.24–5.07 (m, 4 H, H5, H4′, PhC*H*$_2$), 5.06–4.97 (m, 1 H, H3′), 4.00 (d, $J_{H1',H2'}$ = 9.2 Hz, 1 H, H1′), 3.86 (d, $J_{H5'a,H5'b}$ = 13.4 Hz, 1 H, H5′a), 3.70–3.59 (m, 2 H, CH_2OSi), 3.59–3.50 (m, 1 H, H2″), 3.42 (d, $J_{H5'b,H5'a}$ = 13.3 Hz, 1 H, H5′b), 3.38–3.24 (m, 1 H, H2), 3.21–3.09 (m, 1 H, N′C*H*$_a$CH$_b$), 3.09–2.95 (m, 1 H, N′CH$_a$C*H*$_b$), 2.64^R, 2.56 (dd, $J_{H3a,H3b}$ = 16.3 Hz, $J_{H3a,H2}$ = 5.7 Hz, 1 H, H3a), 2.48–2.34 (m, 1 H, H3b), 2.10–1.98 (m, 2 H, 1″-CH_2), 1.76–1.36, 1.24–1.16 (m, 12 H, 2‴-CH_2, 3‴-CH_2, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.27, 1.13, 1.12 [s, each 9 H, Piv-C$(CH_3)_3$], 1.04 [s, 9 H, SiC$(CH_3)_3$], 0.89–0.77 (m, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 191.32 (C4), 177.31, 177.25, 176.60 (Piv-C=O), 156.20^R, 156.13 (Cbz-C=O), 147.54^R, 147.47 (C6), 137.22^R, 137.17 (C1′$_{Ar}$, Bn), 135.66, 127.82 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 133.97, 133.87^R (C1$_{Ar}$, $SiPh_2$), 129.81 (C4$_{Ar}$, $SiPh_2$), 128.77^R, 128.66, 128.58, 128.49^R (C2′$_{Ar}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 128.41, 128.35^R (C4′$_{Ar}$, Bn), 101.29, 101.20^R (C5), 91.13, 90.87^R (C1′), 71.28, 71.15^R (C3′), 67.97^R, 67.92 (C4′), 67.41^R, 67.33 (C2′), 67.04, 66.96^R (PhCH$_2$), 66.46^R, 66.39 (C5′), 63.71, 63.62^R (CH_2OSi), 58.99^R, 58.92 (C2), 55.77

(C2″), 46.48 (C1‴), 39.34 (C3), 39.12, 38.92 [Piv-*C*(CH$_3$)$_3$], 31.92^R, 31.86 (C1″), 34.53, 33.93, 31.82^R, 31.75, 30.51, 30.40^R, 26.45 (C3″, C4″, C5″, C2‴, C3‴), 27.35, 27.20, 27.18 [Piv-C(*C*H$_3$)$_3$], 26.99 [SiC(*C*H$_3$)$_3$], 22.65 (CH$_3$*C*H$_2$), 19.32 [Si*C*(CH$_3$)$_3$], 14.15 (*C*H$_3$CH$_2$).

MS (ESI): *m*/*z* = 1039.6 [M + H]$^+$, 1061.6 [M + Na]$^+$, 1077.6 [M + K]$^+$.

(2*S*)-2-[(*S*)-2-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsilyoxy)butyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidin-4-ol (14); Typical Procedure

To solution of **11** (2.94 g, 2.83 mmol) in EtOH (60 mL) was added NaBH$_4$ (0.42 g, 11.1 mmol) and the solution stirred at r.t. for 48 h. After the addition of H$_2$O (1.5 mL), the solution was concentrated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (150 mL) and this was washed with sat. NaHCO$_3$ solution (3 × 100 mL) and brine (2 × 100 mL). The solution was dried ((Na$_2$SO$_4$) and the solvent was evaporated in vacuo. MeOH (2 × 50 mL) was distilled from the residue to give crude product (2.8 g), which was purified by flash chromatography (cyclohexane–EtOAc, 3:1) to give a colorless oil; yield: 1.96 g (66%); R_f = 0.53 (cyclohexane–EtOAc, 2:1); major diastereomer: [α]$_D^{23}$ –12.7 (*c* 1, CHCl$_3$); mixture of diastereomers: [α]$_D^{23}$ –15. 6 (*c* 1, CHCl$_3$).

Major Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$, COSY): δ = 7.71–7.59 (m, 4 H, H$_{Ar}$, SiPh$_2$), 7.47–7.23 (m, 11 H, H$_{Ar}$, SiPh$_2$ and Bn), 5.45^R, 5.41 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.4 Hz, 1 H, H2′), 5.27–4.96 (m, 4 H, H4′, PhC*H*$_2$, H3′), 4.38^R, 4.20 (d, $J_{H1',H2'}$ = 9.1 Hz, 1 H, H1′), 4.15–4.03 (m, 1 H, H2″), 3.73 (dd, $J_{H5'a,H5'b}$ = 13.0 Hz, $J_{H5'a,H4'}$ = 1.6 Hz, 1 H, H5′a), 3.67–3.55 (m, 3 H, H5′b, CH$_2$OSi), 3.51–3.39 (m, 1 H, C*H*OH), 3.30–3.11 (m, 1 H, H6a), 3.10–2.94 (m, 2 H, N′CH$_2$), 2.59–2.44 (m, 1 H, H2), 2.43–2.26 (m, 1 H, H6b), 2.17–2.08^R, 2.00–1.92 (m, 1 H, H3a), 1.90–1.74 (m, 1 H, H5a), 1.72–1.40 (m, 6 H, 1″-CH$_2$, 2‴-CH$_2$, 3‴-CH$_2$), 1.36–1.06 (m, 8 H, 3″-CH$_2$, 4″-CH$_2$, 5″-CH$_2$, 6″-CH$_2$), 1.28–1.08 (m, 1 H, H5b), 1.25^R, 1.24, 1.14, 1.13 [s, each 9 H, Piv-C(CH$_3$)$_3$], 1.05, 1.04^R [s, 9 H, SiC(CH$_3$)$_3$], 1.03–0.91 (m, 1 H, H3b), 0.86 (t, $J_{7''\text{-}CH3,6''\text{-}CH2}$ = 6.8 Hz, 3 H, C*H*$_3$CH$_2$).

^{13}C NMR (100.6 MHz, CDCl$_3$, HMQC): δ = 177.42, 177.35, 176.99^R, 175.92 (Piv-C=O), 156.70^R, 156.25 (Cbz-C=O), 137.19^R, 136.92 (C1′$_{Ar}$, Bn), 135.65, 127.78 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, SiPh$_2$), 133.95, 133.89^R (C1$_{Ar}$, SiPh$_2$), 129.78 (C4$_{Ar}$, SiPh$_2$), 128.74^R, 128.52^R, 128.45, 127.92 (C2′$_{Ar}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 127.72 (C4′$_{Ar}$, Bn), 86.90, 86.85^R (C1′), 71.85^R, 71.78 (C3′), 69.12 (CHOH), 68.95^R, 68.68 (C4′), 67.23, 66.94^R (PhC*H*$_2$), 65.39^R, 65.29 (C2′), 65.03^R, 64.96 (C5′), 63.82, 63.66^R (CH$_2$OSi), 53.20 (C2), 52.93 (C2″), 42.84 (C6), 42.49 (C3), 41.73 (C1‴), 39.05, 38.84, 38.70 [Piv-*C*(CH$_3$)$_3$], 34.76^R, 34.65 (C5), 33.99 (C1″), 31.75^R, 31.68, 30.73, 30.59^R, 27.02, 26.25, 25.90 (C3″, C4″, C5″, C2‴, C3‴), 27.37, 27.29, 27.17 [Piv-C(*C*H$_3$)$_3$], 26.97 [SiC(*C*H$_3$)$_3$], 22.70 (CH$_3$*C*H$_2$), 19.29 [Si*C*(CH$_3$)$_3$], 14.17 (*C*H$_3$CH$_2$).

MS (ESI): *m*/*z* = 1043.6 [M + H]$^+$, 1065.6 [M + Na]$^+$.

HRMS: *m*/*z* [M + H] calcd for C$_{60}$H$_{91}$N$_2$O$_{11}$Si: 1043.6392; found: 1043.6417.

(2*S*)-2-[(*S*)-2-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsilyoxy)butyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidin-4-yl Methanesulfonate (15)

To piperidinol **14** (1.75 g, 1.68 mmol) dissolved in pyridine (20 mL) was added DMAP (14 mg, 0.11 mmol). The mixture was cooled an ice bath and MsCl (0.16 mL, 0.23 g, 2.02 mmol) was added dropwise, and the mixture was stirred at r.t. for 5 h. After the addition of brine (20 mL) to the mixture, the layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 15 mL). The combined organic layers were washed with sat. NaHCO$_3$ solution (40 mL) and sat. NaCl solution (40 mL). The solution was dried (Na$_2$SO$_4$) and the solvents were evaporated in vacuo to give product that was dried under high vacuum to give a yellow viscous oil; yield: 1.85 g (98%); R_f = 0.56 (cyclohexane–EtOAc, 3:1); [α]$_D^{23}$ –12.2 (*c* 1, CHCl$_3$).

Major Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$, COSY): δ = 7.70–7.57 (m, 4 H, H$_{Ar}$, SiPh$_2$), 7.47–7.27 (m, 11 H, H$_{Ar}$, SiPh$_2$ and Bn), 5.42 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.4 Hz, 1 H, H2′), 5.22–4.89 (m, 4 H, H4′, PhC*H*$_2$, H3′), 4.48–4.37 (m, 1 H, H4), 4.34^R, 4.17 (d, $J_{H1',H2'}$ = 9.1 Hz, 1 H, H1′), 4.23–4.00 (m, 1 H, H2″), 3.72 (dd, $J_{H5'a,H5'b}$ = 13.0 Hz, $J_{H5'a,H4'}$ = 1.6 Hz, 1 H, H5′a), 3.68–3.52 (m, 3 H, H5′b, CH$_2$OSi), 3.34–3.21 (m, 1 H, H6a), 3.08–2.95 (m, 2 H, N′CH$_2$), 2.96 (s, 3 H, SO$_2$CH$_3$), 2.61–2.51 (m, 1 H, H2), 2.49–2.33 (m, 1 H, H6b), 2.11–2.00 (m, 1 H, H5a), 1.99–1.78 (m, 1 H, H3a), 1.74–1.38 (m, 7 H, H5b, 1″-CH$_2$, 2‴-CH$_2$, 3‴-CH$_2$), 1.32–1.15 (m, 9 H, H3b, 3″-CH$_2$, 4″-CH$_2$, 5″-CH$_2$, 6″-CH$_2$), 1.25, 1.14, 1.13 [s, each 9 H, Piv-C(CH$_3$)$_3$], 1.04 [s, 9 H, SiC(CH$_3$)$_3$], 0.86 (t, $J_{7''\text{-}CH3,6''\text{-}CH2}$ = 6.7 Hz, 3 H, C*H*$_3$CH$_2$).

^{13}C NMR (100.6 MHz, CDCl$_3$, HMQC): δ = 177.38, 177.33, 177.06 (Piv-C=O), 156.86^R, 156.33 (Cbz-C=O), 137.14^R, 136.90 (C1′$_{Ar}$, Bn), 135.65, 127.79 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, SiPh$_2$), 133.97, 133.87^R (C1$_{Ar}$, SiPh$_2$), 129.79 (C4$_{Ar}$, SiPh$_2$), 128.63^R, 128.35, 127.70, 127.56^R (C2′$_{Ar}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 128.24, 128.03^R (C4′$_{Ar}$, Bn), 87.36, 86.76^R (C1′), 79.95 (C4), 71.76, 71.67^R (C3′), 68.85^R, 68.62 (C4′), 67.34, 66.05^R (PhC*H*$_2$), 65.37^R, 65.29 (C2′), 64.98 (C5′), 63.81, 63.66^R (CH$_2$OSi), 53.60 (C2), 53.44 (C2″), 42.60 (C6), 42.17 (C1‴), 39.07, 38.86, 38.74 [Piv-*C*(CH$_3$)$_3$], 38.71 (SO$_2$CH$_3$), 37.13 (C3), 33.80 (C1″), 32.76 (C5), 31.72, 30.70, 30.60^R, 27.06, 26.21, 25.97 (C3″, C4″, C5″, C2‴, C3‴), 27.38, 27.29, 27.18 [Piv-C(*C*H$_3$)$_3$], 26.98 [SiC(*C*H$_3$)$_3$], 22.69 (CH$_3$*C*H$_2$), 19.30 [Si*C*(CH$_3$)$_3$], 14.14 (*C*H$_3$CH$_2$).

MS (ESI): *m*/*z* = 1121.7 [M + H]$^+$, 1143.6 [M + Na]$^+$.

HRMS: *m*/*z* [M + H] calcd for C$_{61}$H$_{93}$N$_2$O$_{13}$SSi: 1121.6168; found: 1121.6184; *m*/*z* [M + Na] calcd for C$_{61}$H$_{92}$N$_2$O$_{13}$SSiNa: 1143.5987; found: 1143.6022.

(2*R*)-2-[(*S*)-2-{(Benzyloxycarbonyl)[4-(*tert*-butyldiphenylsilyoxy)butyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidine (16)

To a solution of mesylate **15** (1.85 g, 1.65 mmol) in DME (30 mL) were added dry NaI (1.24 g, 8.25 mmol) and zinc (1.08 g, 16.50 mmol). The mixture was stirred under reflux for 18 h and then filtered. The solution was washed with H$_2$O (20 mL) and the aqueous layer extracted with Et$_2$O (2 × 15 mL). The combined organic solutions were washed with brine (30 mL) and dried (Na$_2$SO$_4$). The solvent was evaporated in vacuo and the product purified by flash chromatography (cyclohexane–EtOAc, 12:1) to give a colorless viscous oil; yield: 1.21 g mixture of **16** and elimination products **16a**/**b**; R_f = 0.49 (**16**), R_f = 0.41 (**16a**/**b**) (cyclohexane–EtOAc, 12:1); major product **16**: [α]$_D^{23}$ –19.5 (*c* 1, CHCl$_3$).

Pure Major Product 16

^{1}H NMR (400 MHz, CDCl$_3$, COSY): δ = 7.71–7.60 (m, 4 H, H$_{Ar}$, SiPh$_2$), 7.48–7.23 (m, 11 H, H$_{Ar}$, SiPh$_2$ and Bn), 5.47^R, 5.43 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.5 Hz, 1 H, H2′), 5.22–4.94 (m, 4 H, PhC*H*$_2$, H4′, H3′), 4.38^R, 4.20 (d, $J_{H1',H2'}$ = 9.1 Hz, 1 H, H1′), 4.22–3.98 (m, 1 H, H2″), 3.76 (dd, $J_{H5'a,H5'b}$ = 13.0 Hz, $J_{H5'a,H4'}$ = 1.7 Hz, 1 H, H5′a), 3.71–3.54 (m, 3 H, H5′b, CH$_2$OSi), 3.24–2.94 (m, 3 H, H6a, N′CH$_2$), 2.57–2.45 (m, 1 H, H2), 2.45–2.32 (m, 1 H, H6b), 1.91–1.39 (m, 10 H, H3a, 4-CH$_2$, H5a, 1″-CH$_2$, 2‴-CH$_2$, 3‴-CH$_2$), 1.32–1.16 (m, 10 H, H3b, H5b, 3″-CH$_2$, 4″-CH$_2$, 5″-CH$_2$, 6″-CH$_2$), 1.26^R, 1.24, 1.14, 1.13 [s, each 9 H, Piv-C(CH$_3$)$_3$], 1.05, 1.04^R [s, 9 H, SiC(CH$_3$)$_3$], 0.86 (t, $J_{7''\text{-}CH3,6''\text{-}CH2}$ = 6.5 Hz, 3 H, C*H*$_3$CH$_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 177.48^R, 177.42, 177.39, 176.92^R, 176.87 (Piv-C=O), 156.69, 156.39^R (Cbz-C=O), 137.30^R, 136.83 (C1′$_{Ar}$, Bn), 135.67, 127.77 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$, $SiPh_2$), 134.00, 133.94^R (C1$_{Ar}$, $SiPh_2$), 129.75 (C4$_{Ar}$, $SiPh_2$), 128.64, 128.52^R, 127.85, 127.73^R (C2′$_{Ar}$, C3′$_{Ar}$, C5′$_{Ar}$, C6′$_{Ar}$, Bn), 128.44^R, 128.23 (C4′$_{Ar}$, Bn), 88.45, 88.08^R (C1′), 72.06^R, 72.01 (C3′), 69.09^R, 68.85 (C4′), 67.25, 66.85^R ($PhCH_2$), 65.36^R, 65.25 (C2′), 64.97^R, 64.86 (C5′), 63.84, 63.69^R (CH_2OSi), 55.48^R, 55.36 (C2), 53.79 (C2″), 45.14^R, 45.00 (C6), 42.61 (C1‴), 39.06, 38.85, 38.69 [Piv-$C(CH_3)_3$], 37.64 (C3), 34.57, 34.09^R (C1″), 37.16, 33.19^R, 32.52, 31.83^R, 31.75, 30.74, 30.62^R, 26.30^R, 26.07, 26.15^R, 25.91, 24.56^R, 24.27 (C4, C5, C3‴, C4‴, C5‴, C2‴, C3‴), 27.40, 27.31, 27.19 [Piv-$C(CH_3)_3$], 26.98 [$SiC(CH_3)_3$], 22.73 (CH_3CH_2), 19.29 [$SiC(CH_3)_3$], 14.18 (CH_3CH_2).

MS (ESI): *m*/*z* (**16**) = 1027.7 $[M + H]^+$, 1049.7 $[M + Na]^+$; *m*/*z* (**16a**/**b**) = 1025.7 $[M + H]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{60}H_{91}N_2O_{10}Si$: 1027.6443; found: 1027.6445.

(2*R*)-2-[(*S*)-2-{[4-(*tert*-Butyldiphenylsiloxy)butyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidine (17)

To a solution of the mixture **16** + **16a**/**b** (1.21 g) in *i*-PrOH (35 mL) was added 10% $Pd(OH)_2/C$ (400 mg) under an argon atmosphere. The mixture was stirred under H_2 at r.t. for 48 h. After filtration through Hyflo®, the solvent was evaporated in vacuo and the product was purified by flash chromatography (cyclohexane–EtOAc, (2:1) to give a pale yellow oil; yield: 825 mg (56%, 2 steps); R_f = 0.16 (cyclohexane–EtOAc, 2:1); $[\alpha]_D^{23}$ –10.4 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.69–7.60 (m, 4 H, H$_{Ar}$), 7.46–7.32 (m, 6 H, H$_{Ar}$), 5.48 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.5 Hz, 1 H, H2′), 5.21–5.13 (m, 1 H, H4′), 5.08 (dd, $J_{H3',H2'}$ = 9.9 Hz, $J_{H3',H4'}$ = 3.3 Hz, 1 H, H3′), 4.31 (d, $J_{H1',H2'}$ = 9.2 Hz, 1 H, H1′), 3.84 (dd, $J_{H5'a,H5'b}$ = 13.1 Hz, $J_{H5'a,H4'}$ = 2.1 Hz, 1 H, H5′a), 3.66 (t, $J_{4'''\text{-}CH2,3'''\text{-}CH2}$ = 5.9 Hz, 2 H, CH_2OSi), 3.53 (d, $J_{H5'b,H5'a}$ = 12.9 Hz, 1 H, H5′b), 3.23–3.12 (m, 1 H, H6a), 2.83–2.55 (m, 4 H, H2, H2″, N′CH_2), 2.54–2.38 (m, 1 H, H6b), 2.00–1.38 (m, 10 H, H3a, 4-CH_2, H5a, 1″-CH_2, 2‴-CH_2, 3‴-CH_2), 1.35–1.19 (m, 10 H, H3b, H5b, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.25, 1.16, 1.12 [s, each 9 H, Piv-$C(CH_3)_3$], 1.04 [s, 9 H, $SiC(CH_3)_3$], 0.88 (t, $J_{7''\text{-}CH3,6''\text{-}CH2}$ = 6.6 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 177.43, 176.97 (Piv-C=O), 135.67, 127.78 (C2$_{Ar}$, C3$_{Ar}$, C5$_{Ar}$, C6$_{Ar}$), 134.00 (C1$_{Ar}$), 129.73 (C4$_{Ar}$), 89.69 (C1′), 72.19 (C3′), 68.89 (C4′), 65.44 (C2′), 65.22 (C5′), 63.78 (CH_2OSi), 56.22 (C2″), 55.16 (C2), 46.41 (C1‴), 45.30 (C6), 39.07, 38.86, 38.77 [Piv-$C(CH_3)_3$], 34.11, 32.72, 32.07, 30.42, 29.83, 27.54, 26.06, 25.47, 23.63 (C3, C4, C5, C1″, C3″, C4″, C5″, C2‴, C3‴), 27.42, 27.33, 27.20 [Piv-$C(CH_3)_3$], 27.00 [$SiC(CH_3)_3$], 22.75 (CH_3CH_2), 19.34 [$SiC(CH_3)_3$], 14.18 (CH_3CH_2).

MS (ESI): *m*/*z* = 791.6 $[M - OPiv]^+$, 893.7 $[M + H]^+$, 915.7 $[M + Na]^+$, 931.7 $[M + K]^+$, 1823.4 $[2 M + K]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{52}H_{85}N_2O_8Si$: 893.6075; found: 893.6079.

(2*R*)-2-{(*S*)-2-[(4-Hydroxybutyl)amino]heptyl}-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidine (18)

To a solution of **17** (402 mg, 0.45 mmol) in anhyd THF (15 mL) was added 1 M TBAF in THF (0.9 mL, 0.9 mmol) dropwise; the color changed to yellow and orange. The mixture was stirred at r.t. for 20 h and then sat. NH_4Cl solution (15 mL) was added. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic solutions were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the remaining viscous brown oil purified by flash chromatography (EtOAc containing 2% Et_3N) to give yellow viscous oil; yield: 195 mg (66%); R_f = 0.21 (EtOAc containing 2% Et_3N); $[\alpha]_D^{23}$ –18.2 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.46 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.5 Hz, 1 H, H2′), 5.21–5.13 (m, 1 H, H4′), 5.08 (dd, $J_{H3',H2'}$ = 9.9 Hz, $J_{H3',H4'}$ = 3.3 Hz, 1 H, H3′), 4.28 (d, $J_{H1',H2'}$ = 9.2 Hz, 1 H, H1′), 3.88 (dd, $J_{H5'a,H5'b}$ = 13.1 Hz, $J_{H5'a,H4'}$ = 2.2 Hz, 1 H, H5′a), 3.66–3.44 (m, 3 H, CH_2OH, H5′b), 3.22–3.09 (m, 1 H, H6a), 2.76–2.63 (m, 1 H, H2), 2.63–2.54 (m, 2 H, N′CH_2), 2.51–2.36 (m, 2 H, H2″, H6b), 1.86–1.38 (m, 10 H, H3a, 4-CH_2, H5a, 1″-CH_2, 2‴-CH_2, 3‴-CH_2), 1.38–1.18 (m, 10 H, H3b, H5b, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.23, 1.14, 1.10 [s, each 9 H, Piv-$C(CH_3)_3$], 0.86 (t, $J_{7''\text{-}CH3,6''\text{-}CH2}$ = 6.7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 177.48, 177.46, 176.94 (Piv-C=O), 89.27 (C1′), 72.10 (C3′), 68.95 (C4′), 65.29 (C2′), 65.19 (C5′), 62.65 (CH_2OH), 55.86 (C2), 55.46 (C2″), 46.93 (C6), 45.22 (C1‴), 39.04, 38.83, 38.72 [Piv-$C(CH_3)_3$], 38.02 (C1″), 34.57, 33.32, 32.48, 32.09, 29.28, 26.12, 25.48, 24.08 (C3, C4, C5, C3″, C4″, C5″, C2‴, C3‴), 27.38, 27.27, 27.14 [Piv-$C(CH_3)_3$], 22.73 (CH_3CH_2), 14.15 (CH_3CH_2).

MS (ESI): *m*/*z* = 553.4 $[M - OPiv]^+$, 655.5 $[M + H]^+$, 1373.0 $[2 M + Na + CH_3CN]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{36}H_{67}N_2O_8$: 655.4897; found: 655.4916.

(2*R*)-2-{(*S*)-2-[(4-Hydroxybutyl)amino]heptyl}piperidine (20)

To a solution of *N*-arabinosyl piperidine **18** (184 mg, 0.28 mmol) in MeOH (6 mL), 1 M HCl (0.47 mL) was added and the mixture stirred at r.t. for 18 h. The solvent was evaporated in vacuo. Et_2O (35 mL) was added to the residue and the mixture extracted with H_2O (3 × 15 mL). The ether solution quantitatively contains 2,3,4-tri-*O*-pivaloyl-D-arabinopyranose (**19**). To the combined aqueous solutions, Na_2CO_3 was added until pH 11 was reached. The aqueous solution was extracted with Et_2O (3 × 20 mL). The combined ether solutions were dried ($MgSO_4$). Evaporation of the solvent afforded compound **20** sufficiently pure for further conversion as a colorless viscous oil; yield: 71 mg (93%); R_f = 0.12 (EtOAc containing 2% of Et_3N); $[\alpha]_D^{23}$ +10.9 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 3.62–3.46 (m, 2 H, CH_2OH), 3.07–2.94 (m, 1 H, H6a), 2.71–2.41 (m, 5 H, H2, H6b, H2′, 1″-CH_2), 1.83–1.70 (m, 1 H, H4a), 1.68–1.49 (m, 6 H, H3a, H5a, 2″-CH_2, 3″-CH_2), 1.46–1.18 (m, 12 H, H4b, H5b, 1′-CH_2, 3′-CH_2, 4′-CH_2, 5′-CH_2, 6′-CH_2), 1.12–0.98 (m, 1 H, H3b), 0.86 (t, $J_{7'\text{-}CH3,6'\text{-}CH2}$ = 6.9 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC): δ = 62.57 (CH_2OH), 56.16 (C2), 55.65 (C2′), 47.02 (C6), 46.69 (C1″), 41.82 (C1′), 34.09 (C3), 33.94, 32.43, 32.19, 29.23, 26.80, 25.19 (C5, 3′-CH_2, 4′-CH_2, 5′-CH_2, 2″-CH_2, 3″-CH_2), 24.96 (C4), 22.72 (CH_3CH_2), 14.17 (CH_3CH_2).

MS (ESI): *m*/*z* = 271.2 $[M + H]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{16}H_{35}N_2O$: 271.2749; found: 271.2760.

(+)-Tetraponerine-8 (1)

To a solution of piperidine derivative **20** (43.4 mg, 0.16 mmol) in anhyd CH_2Cl_2 (3 mL) were added freshly dried powdered molecular sieves (4 Å, 25 mg) and NMO (37.6 mg, 0.32 mmol). The mixture was stirred and to this was added TPAP (4 mg, 0.01 mmol). The color of the mixture changed to dark green then to black. The mixture was stirred at r.t. for 3 h and then the solvent was evaporated in vacuo. The residue was stirred with 0.01 M NaOH solution (6 mL) for 10 min. The aqueous suspension was extracted with Et_2O (2 × 10 mL). The combined ether solutions were washed with brine (15 mL) and dried ($MgSO_4$). After evaporation of the solvent, the product (35 mg) was

obtained as a brown oil that was purified by flash chromatography ($CHCl_3$–EtOH, 9:1) to give a colorless oil; yield: 5 mg (13%); R_f = 0.20 ($CHCl_3$–EtOH, 9:1); $[\alpha]_D^{23}$ +66.9 (*c* 0.2, $CHCl_3$) [Lit.[3] $[\alpha]_D^{20}$ +99.0 (*c* 0.6, $CHCl_3$)].

^{1}H NMR (400 MHz, C_6D_6, COSY): δ = 3.15 (ddd, $J_{H3b,H3a}$ = 8.1 Hz, $J_{H3b,H2a}$ = 8.1 Hz, $J_{H3b,H2b}$ = 2.2 Hz, 1 H, H3b), 2.83 (ddd, $J_{H10eq,H10ax}$ = 10.2 Hz, $J_{H10eq,H9ax}$ = 4.9 Hz, $J_{H10eq,H9eq}$ = 2.9 Hz, 1 H, $H10_{eq}$), 2.31 (dd, $J_{H11a,H1a}$ = 8.0 Hz, $J_{H11a,H1b}$ = 5.7 Hz, 1 H, H11a), 2.16–2.08 (m, 1 H, H5), 2.07–2.00 (m, 1 H, H3a), 1.82–1.12 (m, 22 H, 1-CH_2, 2-CH_2, $H10_{ax}$, H6a, 7-CH_2, 8-CH_2, 9-CH_2, 6-CH_2, pentyl 12-CH_2, 13-CH_2, 14-CH_2, 15-CH_2), 0.90 (t, $J_{16\text{-}CH3,15\text{-}CH2}$ = 7.0 Hz, 3 H, 16-CH_3).

^{13}C NMR (100.6 MHz, C_6D_6, HMQC): δ = 85.60 (C11a), 62.71 (C6a), 61.37 (C5), 51.56 (C10), 49.03 (C3), 37.98 (C6), 34.61 (C7), 32.99 (C12), 32.81 (C14), 29.73 (C1), 26.24 (C9), 25.23 (C13), 25.13 (C8), 23.16 (C15), 20.23 (C2), 14.39 (C16).

MS (ESI): *m*/*z* = 154.2 $[C_{10}H_{20}N]^+$, 249.2 [M – H]$^+$, 250.2 [M]$^+$, 251.3 [M + H]$^+$.

Anal. Calcd for $C_{16}H_{30}N_2$: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.25; H, 11.54; N, 11.56.

(2*S*)-2-{(*R*)-2-[(Benzyloxycarbonyl)(4-hydroxybutyl)amino]heptyl}-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2,3-dihydropyridin-4(1*H*)-one (21)

To the diastereomeric piperidinones **12**/**13** (2.36 g, 2.27 mmol) in anhyd THF (50 mL) was added 1 M TBAF in THF (4.5 mL, 4.5 mmol); the color changed to deep red. The mixture was stirred at r.t. for 24 h and then sat. NH_4Cl solution (40 mL) was added. The aqueous solution was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (80 mL) and dried ($MgSO_4$). After evaporation of the solvent the remaining brown oil was purified by flash chromatography (EtOAc–cyclohexane, 10:1) to give highly enriched **21**, which contained only small amounts of the (2*R*)-diastereomer, as a pale yellow oil; yield: 1.2 g (66%); R_f = 0.34 (EtOAc–cyclohexane, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.38–7.21 (m, 5 H, H_{Ar}), 6.94 (d, $J_{H6,H5}$ = 7.4 Hz, 1 H, H6), 5.48^R, 5.42 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.5 Hz, 1 H, H2′), 5.25–5.18 (m, 1 H, H4′), 5.17–5.04 (m, 3 H, PhCH_2, H3′), 5.01, 4.95^R (d, $J_{H5,H6}$ = 7.4 Hz, 1 H, H5), 4.71^R, 4.44 (d, $J_{H1',H2'}$ = 8.1 Hz, 1 H, H1′), 3.90–3.50 (m, 5 H, H5′a, H2, C$H_a$$H_b$OH, $CH_a$$H_b$OH, H2″), 3.43–3.20^R (m, 1 H, H5′b), 3.13–2.86 (m, 2 H, N′CH_2), 2.72^R, 2.62 (dd, $J_{H3a,H3b}$ = 16.2 Hz, $J_{H3a,H2}$ = 6.6 Hz, 1 H, H3a), 2.32^R, 2.24 (d, $J_{H3b,H3a}$ = 16.4 Hz, 1 H, H3b), 2.16–2.05^R, 2.03–1.92 (m, 1 H, H1″a), 1.87–1.70 (m, 1 H, H1″b), 1.69–1.53 (m, 2 H, 2‴-CH_2), 1.51–1.37 (m, 2 H, 3‴-CH_2), 1.28–1.12 (m, 8 H, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.24^R, 1.16, 1.10, 1.08^R, 1.06 [s, each 9 H, Piv-C(CH_3)$_3$], 0.87–0.75 (m, 3 H, C$H_3$$CH_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 193.48^R, 192.88 (C4), 177.23, 177.16, 177.00 (Piv-C=O), 156.75, 156.38^R (Cbz-C=O), 151.35^R, 149.20 (C6), 137.06^R, 136.28 ($C1_{Ar}$), 128.57^R, 128.17, 127.96, 127.85^R ($C2_{Ar}$, $C3_{Ar}$, $C4_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 99.74 (C5), 92.20^R, 90.96 (C1′), 71.56^R, 70.93 (C3′), 68.16^R, 67.85 (C4′), 67.13 (PhCH_2), 66.58, 66.40^R (C5′), 66.06^R, 65.68 (C2′), 62.31, 62.18^R (CH_2OH), 54.41 (C2″), 52.35 (C2), 43.17 (C1‴), 39.59, 38.50^R (C3), 38.98, 38.91, 38.81 [Piv-*C*(CH_3)$_3$], 34.52^R, 34.16 (C1″), 32.92, 31.82^R, 31.69, 29.92^R, 29.71, 26.45^R, 25.36, 25.96 (C3″, C4″, C5″, C2‴, C3‴), 27.27, 27.20, 27.13 [Piv-C(*C*H_3)$_3$], 22.61 (CH_3CH_2), 14.07 (*C*$H_3$$CH_2$).

MS (ESI): *m*/*z* [M = $C_{44}H_{68}N_2O_{11}$ (801.02)]= 801.5 [M + H]$^+$, 823.5 [M + Na]$^+$, 839.5 [M + K]$^+$, 1602.0 [2 M + H]$^+$, 1624.0 [2 M + Na]$^+$, 1640.0 [2 M + K]$^+$.

(2*S*)-2-{(*R*)-2-[(Benzyloxycarbonyl)(4-oxobutyl)amino]heptyl}-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2,3-dihydropyridin-4(1*H*)-one (23)

To a solution of **23** (923 mg, 1.15 mmol) in anhyd CH_2Cl_2 (12 mL) at 0 °C was slowly added dropwise 15% Dess–Martin periodinane solution in CH_2Cl_2 (4.96 g, 1.75 mmol) and the mixture was stirred at °C for 2 h. Subsequently, 1 M NaOH (20 mL) was added. After separation, the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic solutions were washed with brine (30 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the crude product purified by flash chromatography (EtOAc–cyclohexane, 5:1) to give a colorless oil; yield: 735 mg (80%); R_f = 0.56 (EtOAc–cyclohexane, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 9.73, 9.65^R (s, 1 H, CHO), 7.40–7.21 (m, 5 H, H_{Ar}), 6.88^R, 6.87 (d, $J_{H6,H5}$ = 7.6 Hz, 1 H, H6), 5.51^R, 5.48 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.6 Hz, 1 H, H2′), 5.28–5.20 (m, 1 H, H4′), 5.20–5.04 (m, 3 H, PhCH_2, H3′), 4.96 (d, $J_{H5,H6}$ = 7.3 Hz, 1 H, H5), 4.61^R, 4.42 (d, $J_{H1',H2'}$ = 9.1 Hz, 1 H, H1′), 4.13–3.97 (m, 1 H, H2″), 3.92, 3.83^R (d, $J_{H5'a,H5'b}$ = 12.9 Hz, 1 H, H5′a), 3.79–3.65 (m, 1 H, H2), 3.61, 3.36^R (d, $J_{H5'b,H5'a}$ = 13.1 Hz, 1 H, H5′b), 3.13–2.89 (m, 2 H, N′CH_2), 2.71^R, 2.64 (dd, $J_{H3a,H3b}$ = 16.4 Hz, $J_{H3a,H2}$ = 6.0 Hz, 1 H, H3a), 2.47–2.34 (m, 2 H, H1″a, H1″b), 2.27 (d, $J_{H3b,H3a}$ = 16.5 Hz, 1 H, H3b), 2.12–1.66 (m, 4 H, 2‴-CH_2, 3‴-CH_2), 1.61–1.14 (m, 8 H, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.26^R, 1.23, 1.11, 1.10 [s, each 9 H, Piv-C(CH_3)$_3$], 0.87–0.78 (m, 3 H, C$H_3$$CH_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC): δ = 201.76, 201.21^R (CHO), 192.15^R, 191.39 (C4), 177.28, 177.23, 177.10 (Piv-C=O), 156.63^R, 156.41 (Cbz-C=O), 149.36, 147.94^R (C6), 136.88^R, 136.79 ($C1_{Ar}$), 128.62, 128.11 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 128.30 ($C4_{Ar}$), 100.29^R, 100.10 (C5), 92.18, 91.23^R (C1′), 71.50^R, 71.03 (C3′), 68.12^R, 67.84 (C4′), 67.35 (PhCH_2), 66.64, 66.42^R (C5′), 66.21, 65.81^R (C2′), 54.47 (C2″), 52.40^R, 51.55 (C2), 42.48 (C1‴), 41.43, 41.34^R (C1″), 40.06 (C3), 39.02, 38.96, 38.86 [Piv-*C*(CH_3)$_3$], 34.78, 34.52^R, 33.29^R, 32.54, 31.81^R, 31.75, 29.75, 26.03 (C3″, C4″, C5″, C2‴, C3‴), 27.30, 27.19, 27.15 [Piv-C(*C*H_3)$_3$], 22.64^R, 21.73 (CH_3CH_2), 14.08 (*C*$H_3$$CH_2$).

MS (ESI): *m*/*z* [M = $C_{44}H_{66}N_2O_{11}$ (799.00)] = 799.4 [M + H]$^+$, 821.5 [M + Na]$^+$, 837.5 [M + K]$^+$, 1597.9 [2 M + H]$^+$, 1619.9 [2 M + Na]$^+$, 1635.9 [2 M + K]$^+$.

(2*S*)-2-[(*R*)-2-{(Benzyloxycarbonyl)[3-(1,3-dioxolan-2-yl)propyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2,3-dihydropyridin-4(1*H*)-one (24)

Aldehyde **23** (735 mg, 0.92 mmol) was dissolved in anhyd toluene (8 mL). Sequentially ethylene glycol (0.1 mL, 115 mg, 1.86 mmol) and TsOH·H_2O (5 mg, 0.03 mmol) were added. The mixture was stirred and heated under reflux until no more H_2O is separated (ca. 16 h, temp. of oil bath 120–130 °C). The mixture was cooled to r.t. and sat. $NaHCO_3$ solution (10 mL) was added. The aqueous layer was extracted with Et_2O (2 × 8 mL) and the combined organic solutions were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo to give a brown oil (736 mg) that was purified by flash chromatography (cyclohexane–EtOAc, (1:1) to give a colorless oil; yield: 353 mg (45%); R_f = 0.19 (cyclohexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.41–7.27 (m, 5 H, H_{Ar}), 6.89^R, 6.86 (d, $J_{H6,H5}$ = 7.7 Hz, 1 H, H6), 5.53^R, 5.48 (t, $J_{H2',H1'} = J_{H2',H3'}$ = 9.5 Hz, 1 H, H2′), 5.26–5.04 (m, 4 H, H4′, PhCH_2, H3′), 4.98^R, 4.96 (d, $J_{H5,H6}$ = 7.6 Hz, 1 H, H5), 4.84, 4.81^R (t, $J_{H4'''3'''\text{-}CH2}$ = 4.3 Hz, 1 H, H4‴), 4.72^R, 4.40 (d, $J_{H1',H2'}$ = 9.2 Hz, 1 H, H1′), 4.21–4.02 (m, 1 H, H2″), 3.97–3.77 (m, 4 H, OCH_2CH_2O), 3.71 (d, $J_{H5'a,H5'b}$ = 12.8 Hz, 1 H, H5′a), 3.66–3.58 (m, 1 H, H2), 3.24–3.05 (m, 2 H, H5′b, N′C$H_a$$CH_b$), 3.05–2.92 (m, 1 H, N′$CH_aCH_b$), 2.76^R, 2.66 (dd, $J_{H3a,H3b}$ = 16.3 Hz, $J_{H3a,H2}$ = 6.4 Hz, 1 H, H3a), 2.27, 2.16^R (d, $J_{H3b,H3a}$ = 16.1 Hz, 1 H, H3b), 2.08–1.87 (m, 1 H, H1″a),

1.79–1.43 (m, 6 H, H1″b, 2‴-CH_2, 3‴-CH_2, H3″a), 1.31–1.15 (m, 7 H, H3″b, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.25, 1.24, 1.12 [s, each 9 H, Piv-C$(CH_3)_3$], 0.84 (t, $J_{7''\text{-CH3},6''\text{-CH2}}$ = 6.5 Hz, 3 H, C$H_3$$CH_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 191.92^R, 191.46 (C4), 177.39, 177.25, 177.16 (Piv-C=O), 156.97^R, 156.39 (Cbz-C=O), 148.74, 146.62^R (C6), 137.20^R, 136.98 ($C1_{Ar}$), 128.64, 128.04 ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 128.39 ($C4_{Ar}$), 104.26, 103.99^R (C4‴), 100.65^R, 100.46 (C5), 92.03, 90.66^R (C1′), 71.80^R, 71.13 (C3′), 68.32^R, 67.89 (C4′), 67.19 (PhCH_2), 66.57, 66.26^R (C5′), 66.12, 65.54^R (C2′), 64.98 (OCH_2CH_2O), 54.06 (C2″), 52.73^R, 51.66 (C2), 42.70 (C1‴), 40.89^R, 39.35 (C3), 39.05, 38.98, 38.89 [Piv-$C(CH_3)_3$], 34.89 (C1″), 33.67^R, 32.72, 31.89^R, 31.85, 31.39, 31.29^R, 26.01, 24.71^R, 23.75 (C3″, C4″, C5″, C2‴, C3‴), 27.31, 27.18 [Piv-C(CH_3)$_3$], 22.66 (CH_3CH_2), 14.13 (CH_3CH_2).

MS (ESI): *m*/*z* [M = $C_{46}H_{70}N_2O_{12}$ (843.05)] = 843.5 [M + H]$^+$, 865.5 [M + Na]$^+$, 881.5 [M + K]$^+$, 1686.1 [2 M + H]$^+$, 1708.1 [2 M + Na]$^+$, 1724.0 [2 M + K]$^+$.

(2*S*)-2-[(*R*)-2-{(Benzyloxycarbonyl)[3-(1,3-dioxolan-2-yl)propyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidin-4-ol (25)

To piperidinone **24** (353 mg, 0.42 mmol) dissolved in EtOH (10 mL) was added $NaBH_4$ (63 mg, 1.66 mmol). The mixture was stirred at r.t. for 44 h. Then a few drops of H_2O were added, and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (25 mL), washed with $NaHCO_3$ solution (15 mL) and then brine (2 × 15 mL). The solution was dried ($MgSO_4$) and the solvent was evaporated in vacuo to give a yellow oil (347 mg) that was purified by flash chromatography (cyclohexane–EtOAc, 3:2) to give a colorless oil; yield: 191 mg (54%); R_f = 0.47 (major diastereomer) and 0.38 (minor diastereomer) (cyclohexane–EtOAc, 1:1).

Major Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.42–7.20 (m, 5 H, H_{Ar}), 5.47^R, 5.43 (t, $J_{H2',H1'}$ = $J_{H2',H3'}$ = 9.4 Hz, 1 H, H2′), 5.24–4.94 (m, 4 H, H4′, PhCH_2, H3′), 4.88, 4.81^R (t, $J_{H4''',3'''\text{-CH2}}$ = 4.3 Hz, 1 H, H4‴), 4.22^R, 4.06 (d, $J_{H1',H2'}$ = 9.4 Hz, 1 H, H1′), 4.15–3.97 (m, 1 H, H2″), 3.97–3.71 (m, 5 H, OCH_2CH_2O, H5′a), 3.66–3.48 (m, 2 H, C*H*OH, H5′b), 3.29–2.99 (m, 3 H, H6a, N′CH_2), 2.75–2.64^R, 2.64–2.55 (m, 1 H, H2), 2.52–2.35 (m, 1 H, H6b), 1.97–1.43 (m, 9 H, H3a, H5a, 1″-CH_2, 2‴-CH_2, 3‴-CH_2, H3″a), 1.33–0.99 (m, 9 H, H3b, H5b, H3″b, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.25, 1.16^R, 1.14, 1.12 [s, each 9 H, Piv-C$(CH_3)_3$], 0.87 (t, $J_{7''\text{-CH3},6''\text{-CH2}}$ = 6.7 Hz, 3 H, C$H_3$$CH_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC): δ = 177.46, 177.06, 177.00 (Piv-C=O), 156.64^R, 156.52 (Cbz-C=O), 137.18^R, 136.95 ($C1_{Ar}$), 128.66, 128.55^R, 127.93, 127.82^R ($C2_{Ar}$, $C3_{Ar}$, $C5_{Ar}$, $C6_{Ar}$), 128.45^R, 128.29 ($C4_{Ar}$), 104.25, 104.10^R (C4‴), 88.45^R, 88.01 (C1′), 72.02^R, 71.89 (C3′), 68.93 (CHOH), 68.86^R, 68.75 (C4′), 67.22, 66.95^R (PhCH_2), 65.49 (C5′), 65.35^R, 65.29 (C2′), 65.04 (OCH_2CH_2O), 53.68^R, 53.53 (C2), 52.54 (C2″), 42.37 (C6), 42.32 (C3), 41.98 (C1‴), 39.07, 38.87, 38.76 [Piv-$C(CH_3)_3$], 38.32^R, 37.75, 34.87^R, 34.78, 33.49, 33.09^R, 31.91, 31.46, 26.47, 24.59^R, 23.72 (C5, C1″, C3″, C4″, C5″, C2‴, C3‴), 27.40, 27.30, 27.18 [Piv-C(CH_3)$_3$], 22.73 (CH_3CH_2), 14.18 (CH_3CH_2).

MS (ESI): *m*/*z* [M = $C_{46}H_{74}N_2O_{12}$ (847.09)] = 847.6 [M + H]$^+$, 869.6 [M + Na]$^+$, 885.6 [M + K]$^+$, 1716.1 [2 M + Na]$^+$.

(2*S*)-2-[(*R*)-2-{(Benzyloxycarbonyl)[3-(1,3-dioxolan-2-yl)propyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidin-4-yl Methanesulfonate (26)

To a solution of piperidinol **25** (191 mg, 0.23 mmol) in anhyd pyridine (4 mL) at 0 °C were added DMAP (2 mg, 0.02 mmol) and MsCl (21 µL, 31.6 mg, 0.28 mmol). The mixture was stirred at r.t. for 4.5 h, then quenched by the addition of brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic solutions were washed with sat. $NaHCO_3$ solution (10 mL) and brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the product dried under high vacuum to give a yellow oil that was sufficiently pure for further conversion; yield: 205 mg (97%); R_f = 0.71 (cyclohexane–EtOAc, 1:1).

(2*S*)-2-[(*R*)-2-{(Benzyloxycarbonyl)[3-(1,3-dioxolan-2-yl)propyl]amino}heptyl]-*N*-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidine

To the crude mesylate **26** (205 mg, 0.22 mmol) dissolved in DME (5 mL) were sequentially added freshly dried NaI (165 mg, 1.1 mmol) and zinc (144 mg, 2.2 mmol). The mixture was stirred and heated under reflux for 16 h. After filtration, the filtrate was washed with H_2O (8 mL) and the aqueous layer extracted with Et_2O (2 × 5 mL). The combined organic solutions were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the remaining residue purified by flash chromatography (cyclohexane–EtOAc, 3:1) to give a colorless oil; yield (**27** which contains some amounts of elimination products): 105 mg of product; R_f = 0.51 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.18 (m, 5 H, H_{Ar}), 5.55–5.38 (m, 1 H, H2′), 5.28–4.92 (m, 4 H, H4′, PhCH_2, H3′), 4.86, 4.79^R (t, $J_{H4''',3'''\text{-CH2}}$ = 4.2 Hz, 1 H, H4‴), 4.19^R, 4.03 (d, $J_{H1',H2'}$ = 9.1 Hz, 1 H, H1′), 4.15–3.99 (m, 1 H, H2″), 3.99–3.62 (m, 5 H, OCH_2CH_2O, H5′a), 3.57–2.88 (m, 4 H, H5′b, H6a, N′CH_2), 2.74–2.57 (m, 1 H, H2), 2.56–2.41 (m, 1 H, H6b), 1.84–1.32 (m, 10 H, H3a, 4-CH_2, H5a, 1″-CH_2, 2‴-CH_2, 3‴-CH_2), 1.32–1.10 (m, 10 H, H3b, H5b, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.23, 1.14, 1.10 [s, each 9 H, Piv-C$(CH_3)_3$], 0.89–0.79 (m, 3 H, C$H_3$$CH_2$).

MS (ESI): *m*/*z* [M = $C_{46}H_{74}N_2O_{11}$ (831.09)] = 831.5 [M + H]$^+$, 853.5 [M + Na]$^+$, 869.5 [M + K]$^+$, 1684.0 [2 M + Na]$^+$.

(2*S*)-2-[(*R*)-2-{[3-(1,3-Dioxolan-2-yl)propyl]amino}heptyl]-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)piperidine (27)

To a solution of the product mixture described above (105 mg) in *i*-PrOH (4 mL) was added 10% $Pd(OH)_2$/C (25 mg). The mixture was stirred under H_2 atmosphere for 42 h. After filtration through Hyflo®, the solvent was evaporated from the filtrate and the remaining residue purified by flash chromatography ($CHCl_3$–EtOH, 9:1) to give a pale yellow oil; yield: 85 mg (56%, 2 steps); R_f = 0.50 ($CHCl_3$–EtOH, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.45 (t, $J_{H2',H1'}$ = $J_{H2',H3'}$ = 9.6 Hz, 1 H, H2′), 5.21–5.14 (m, 1 H, H4′), 5.06 (dd, $J_{H3',H2'}$ = 9.9 Hz, $J_{H3',H4'}$ = 2.9 Hz, 1 H, H3′), 4.84 (t, $J_{H4''',3'''\text{-CH2}}$ = 4.0 Hz, 1 H, H4‴), 4.21 (d, $J_{H1',H2'}$ = 9.2 Hz, 1 H, H1′), 4.01–3.75 (m, 5 H, OCH_2CH_2O, H5′a), 3.57 (d, $J_{H5'b,H5'a}$ = 13.2 Hz, 1 H, H5′b), 3.19–2.71 (m, 5 H, H6a, H2″, N′CH_2, H2), 2.61–2.48 (m, 1 H, H6b), 2.01–1.47 (m, 10 H, H3a, 4-CH_2, H5a, 1″-CH_2, 2‴-CH_2, 3‴-CH_2), 1.46–1.13 (m, 10 H, H3b, H5b, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.22, 1.13, 1.08 [s, each 9 H, Piv-C$(CH_3)_3$], 0.85 (t, $J_{7''\text{-CH3},6''\text{-CH2}}$ = 6.9 Hz, 3 H, C$H_3$$CH_2$).

MS (ESI): *m*/*z* [M = $C_{38}H_{68}N_2O_9$ (696.95)] = 595.4 [M – OPiv]$^+$, 697.5 [M + H]$^+$, 1456.9 [2 M + CH_3CN + Na]$^+$.

(+)-Tetraponerine-7 (28)

To arabinosyl piperidine **27** (85 mg, 0.12 mmol) dissolved in MeOH (3 mL) was added 1 M HCl (0.4 mL), the solution was stirred at r.t. for 18 h, and MeOH was evaporated in vacuo. The remaining residue was extracted with Et_2O (3 mL). The ether solution contains the 2,3,4-tri-*O*-pivaloyl-arabinose **19**. It was extracted with H_2O (2 × 3 mL). The H_2O

extracts and 2 M HCl (3 mL) were added to the remainder and it was stirred for 2 h. To the aqueous solution, 10% NaOH solution was added until pH 8 was reached. The basic solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic solutions were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The product was purified by flash chromatography ($CHCl_3$–EtOH, 9:1) to give a colorless oil; yield: 23 mg (78%, 3 steps); R_f = 0.13 ($CHCl_3$–EtOH, 9:1); $[\alpha]_D^{23}$ +22.5 (*c* 2.2, $CHCl_3$) [Lit.[4] $[\alpha]_D^{20}$ +30.0 (*c* 0.22, $CHCl_3$)].

^{1}H NMR (400 MHz, C_6D_6, COSY): δ = 3.32 (dd, $J_{H11a,H1a}$ = 4.7 Hz, $J_{H11a,H1b}$ = 2.9 Hz, 1 H, H11a), 3.18 (ddd, $J_{H3a,H3b}$ = 11.5 Hz, $J_{H3a,H2a}$ = 7.0 Hz, $J_{H3a,H2b}$ = 5.2 Hz, 1 H, H3a), 2.85–2.74 (m, 3 H, H5, H3b, $H10_{eq}$), 2.09–2.01 (m, 1 H, H6a), 1.94 (ddd, $J_{H6ax,H6eq}$ = 13.1 Hz, $J_{H6ax,H6a}$ = 11.6 Hz, $J_{H6ax,H5}$ = 5.5 Hz, 1 H, $H6_{ax}$), 1.85–1.17 (m, 19 H, 6-CH_2, 2-CH_2, $H10_{ax}$, 1-CH_2, 8-CH_2, 9-CH_2, pentyl 12-CH_2, 13-CH_2, 14-CH_2, 15-CH_2), 1.16–1.09 (m, 1 H, $H6_{eq}$), 0.93 (t, $J_{16\text{-}CH3,15\text{-}CH2}$ = 6.9 Hz, 3 H, 16-CH_3).

^{13}C NMR (100.6 MHz, C_6D_6, HMQC, HMBC): δ = 75.52 (C11a), 56.74 (C6a), 53.32 (C5), 50.99 (C10), 50.63 (C3), 34.22 (C7), 32.51 (C14), 32.23 (C6), 31.05 (C12), 30.52 (C1), 27.40 (C13), 26.52 (C9), 25.23 (C8), 23.24 (C15), 22.20 (C2), 14.43 (C16).

MS (ESI): *m*/*z* = 249.2 $[M - H]^+$, 250.2 $[M]^+$, 251.2 $[M + H]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{16}H_{31}N_2$: 251.2487; found: 251.2476.

(2*S*)-2-{(*R*)-2-[(Benzyloxycarbonyl)(4-oxobutyl)amino]heptyl}-5-chloro-1-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-2,3-dihydropyridin-4(1*H*)-one (22)

Following the typical procedure for **9*S*** using piperidinone **21** (404 mg, 0.5 mmol), oxalyl chloride (0.05 mL, 0.55 mmol), DMSO (0.08 mL, 1.1 mmol), Et_3N (0.35 mL, 2.5 mmol), and CH_2Cl_2 (6 mL) with a reaction time of 35 min and purification by flash chromatography (cyclohexane–EtOAc, 1:1) gave a colorless oil; yield: 292 mg (70%); R_f = 0.53 (cyclohexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.73, 9.66^R (br s, 1 H, CHO), 7.41–7.21 (m, 5 H, H_{Ar}), 7.12 (s, 1 H, H6), 5.54–5.35 (m, 1 H, H2′), 5.29–5.21 (m, 1 H, H4′), 5.19–5.01 (m, 3 H, PhCH_2, H3′), 4.65^R, 4.44 (d, $J_{H1',H2'}$ = 8.9 Hz, 1 H, H1′), 4.12–3.69 (m, 3 H, H2″, H2, H5′a), 3.63, 3.37^R (d, $J_{H5'b,H5'a}$ = 13.4 Hz, 1 H, H5′b), 3.12–2.90 (m, 2 H, N′CH_2), 2.88–2.68 (m, 1 H, H3a), 2.52–2.28 (m, 3 H, 1″-CH_2, H3b), 2.11–1.65 (m, 4 H, 2‴-CH_2, 3‴-CH_2), 1.60–1.15 (m, 8 H, 3″-CH_2, 4″-CH_2, 5″-CH_2, 6″-CH_2), 1.26, 1.23, 1.11 [s, each 9 H, Piv-C$(CH_3)_3$], 0.88–0.73 (m, 3 H, C$H_3$$CH_2$).

MS (ESI): *m*/*z* [M = $C_{44}H_{65}ClN_2O_{11}$ (833.45)] = 833.5 $[M(^{35}Cl) + H]^+$, 835.5 $[M(^{37}Cl) + H]^+$, 855.4 $[M(^{35}Cl) + Na]^+$, 857.4 $[M(^{37}Cl) + Na]^+$.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380215.

References

(1) Braekman, J. C.; Daloze, D.; Pasteels, J. M.; Vanhecke, P.; Declercq, J. P.; Sinnwell, V.; Francke, W. *Z. Naturforsch., C* **1987**, *42*, 627.
(2) Merlin, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *J. Chem. Ecol.* **1988**, *14*, 517.
(3) Yue, C.; Royer, J.; Husson, H. P. *J. Org. Chem.* **1990**, *55*, 1140.
(4) Macours, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1995**, *51*, 1415.
(5) Devijver, C.; Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **1995**, *51*, 10913.
(6) Kem, W. R.; Wildeboer, K.; LeFrancois, S.; Raja, M.; Marszalec, W.; Braekman, J. C. *Cell. Mol. Neurobiol.* **2004**, *24*, 535.
(7) Rouchaud, A.; Braekman, J. C. *Eur. J. Org. Chem.* **2009**, 2666.
(8) (a) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691. (b) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1991**, *47*, 3805. (c) Pleheiers, M.; Heilporn, S.; Ekelmans, D.; Leclercq, S.; Sangermano, M.; Breakman, J. C.; Daloze, D. *Can. J. Chem.* **2000**, *78*, 1030.
(9) (a) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 4543. (b) Barluenga, J.; Tomas, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 3699. (c) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697. (d) Charette, A. B.; Mathieu, S.; Martel, J. *Org. Lett.* **2005**, *7*, 5401.
(10) (a) Yue, C.; Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 4949. (b) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594. (c) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (d) Airian, E.; Girard, N.; Pizetti, M.; Salvadori, J.; Taddei, M.; Mann, A. *J. Org. Chem.* **2010**, *75*, 8670.
(11) Bosque, I.; Gonzalez-Gomez, J. C.; Guijarro, A.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 10340.
(12) Gonzalez-Gomez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308.
(13) Bosque, I.; Gonzalez-Gomez, J. C.; Loza, M. I.; Brea, M. *J. Org. Chem.* **2014**, *79*, 3982.
(14) (a) Kunz, H.; Pfrengle, W.; Sager, W. *Tetrahedron Lett.* **1989**, *30*, 4109. (b) Laschat, S.; Kunz, H. *Synlett* **1990**, 629. (c) Kunz, H.; Pfrengle, W.; Rück, K.; Sager, W. *Synthesis* **1991**, 1039.
(15) (a) Kunz, H.; Pfrengle, W. *Angew. Chem.* **1989**, *101*, 1041; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067. (b) Kranke, B.; Hebrault, D.; Schultz-Kukula, M.; Kunz, H. *Synlett* **2004**, 671. (c) Kranke, B.; Kunz, H. *Org. Biomol. Chem.* **2007**, *5*, 349.
(16) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(17) Bollbuck, B.; Kraft, P.; Tochtermann, W. *Tetrahedron* **1996**, *52*, 4581.
(18) Michael, J. P.; Gravestock, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1919.
(19) Steglich, W.; Höfle, G. *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(20) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.
(21) Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Mortimer, A. J. P.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793.
(22) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *J. Org. Chem.* **1992**, *57*, 1722.
(23) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10229.
(24) Kikuchi, H.; Yamamoto, K.; Horoiwa, S.; Hirai, S.; Kasahara, R.; Hariguchi, N.; Matsumoto, M.; Oshima, Y. *J. Med. Chem.* **2006**, *49*, 4698.
(25) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(26) Kranke, B.; Kunz, H. *Can. J. Chem.* **2006**, *84*, 625.
(27) (a) Klegraf, E.; Follmann, M.; Schollmeyer, D.; Kunz, H. *Eur. J. Org. Chem.* **2004**, 3346. (b) Knauer, S.; Kunz, H. *Tetrahedron: Asymmetry* **2005**, *16*, 529.
(28) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(29) Chiu, C. K. F. *Tetrahedron: Asymmetry* **1995**, *6*, 881.

(30) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177.
(31) Kitagawa, H.; Kumura, K.; Atsumi, K. *Chem. Lett.* **2006**, *35*, 712.
(32) Alonso, E.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **1997**, *62*, 417.
(33) Tojo, G.; Fernández, M. *Oxidation of Alcohols to Aldehydes and Ketones*; Springer: New York, **2006**.
(34) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.
(35) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(36) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469.
(37) Deloisy, S.; Tietgen, H.; Kunz, H. *Collect. Czech. Chem. Commun.* **2000**, *65*, 816.