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Stereoselective Michael Addition of Thiophenols, Amino Acids and Hydrazoic Acid to (2*S*)-Hydroxymethyl-dihydropyridone as a Convenient Route to Novel Azasugar Derivatives

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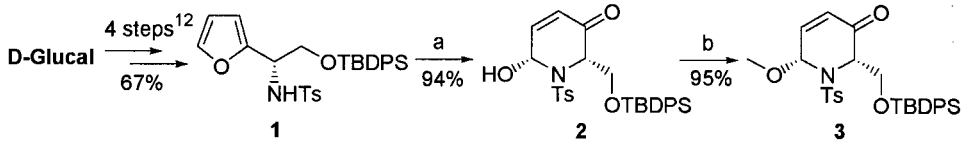
Abstract—The outcome and stereochemical aspects of 1,4-conjugate addition of thiophenols, α-aminoacid derivatives and hydrazoic acid to chiral (2*S*)-hydroxymethyl-dihydropyridone **3** is presented. Subsequent reduction with $NaBH_4$ provided predominantly the kinetically favored axial 3-piperidinol adducts. The stereochemistry of the products, which depends on electrostatic interaction and steric hindrance, was revealed by ^1H NMR and 2D NOESY spectroscopic analysis.

Naturally occurring and synthetic derivatives of piperidinose type aminosugars are a well-known class of selective inhibitors of the oligosaccharide processing enzymes known as glycosidases.[1] These compounds have attracted a great deal of attention as synthetic targets, since they have been used as probes for the study of the biological functions of oligosaccharides[2] and for the treatment of various carbohydrate-mediated diseases.[3] Thus, a variety of natural and synthetic azasugars are now finding clinical application as anti-HIV,[4] anticancer[5] or antidiabetic agents[6] and their effectiveness has prompted considerable effort toward their structural modification targeting the development of additional glycosidase inhibitors.[7,8] The literature abounds with methods concerning the efficient stereoselective synthesis of various piperidinol derivatives based on carbohydrate[9] and non-carbohydrate[10] building blocks.

Recently, a general approach to this class of compounds was introduced by the application of the aza-Achmatowicz rearrangement for the synthesis of optically active 1,6-dihydropyridin-3(2*H*)-ones, which serve as flexible chiral building blocks for the synthesis of various novel piperidinol type azasugars and alkaloids.[11] In this context, we have developed a new synthetic methodology for the stereoselective transformation of D-glucal to (2*S*)-hydroxymethyl-dihydropyridone **2**.[12] The latter allowed us to carry out an efficient stereoselective total synthesis of (−)-prosophylline.[13]

As a part of our long-standing interest in the study of Michael additions to heterocyclic α,β-unsaturated carbonyl compounds[14] and quinones,[15] we envisaged the use of (2*S*)-hydroxymethyl-dihydropyridone **3** as a suitable substrate for the stereoselective synthesis of novel 5-amino- and 5-thio-3,6-piperidinol derivatives. Available methods for the preparation of similar compounds are few in number,[16] despite the biological activity and ubiquity in nature of their corresponding sugars.[17] Thus, we report herein the outcome and stereochemical aspects of 1,4-conjugate addition of various α-aminoacid derivatives, thiophenols and hydrazoic acid to this chiral α,β-unsaturated system as a



Scheme 1. (a) *m*-CPBA, CH_2Cl_2. (b) $HC(OMe)_3$, $BF_3{\cdot}OEt_2$, 4 Å molecular sieves, THF, 0°C.

Keywords: azasugar; Michael addition; amino acid; thiophenol; hydrazoic acid.
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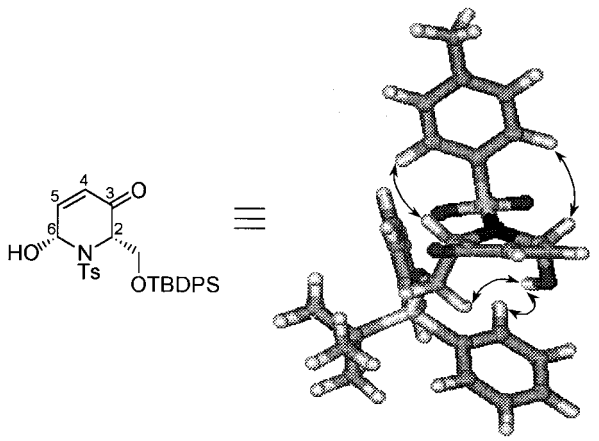
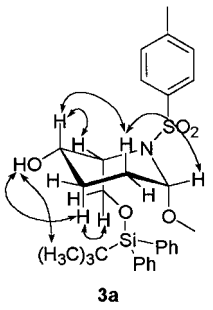


Figure 1. The structure of (2*S*, 6*R*)-dihydropyridine-3-one **2** based on 2D NOESY studies and Molecular Modeling (the observed NOE are indicated by arrows).

convenient means for the preparation of asymmetric aza-sugar conjugates of these compounds.

Results and Discussion

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)-1-(2-furyl)-*N*-tosylethylamine **1** was prepared in excellent enantiomeric excess (>98%), by stereoselective transformation of D-glucal according to our previously reported method.[12] Efficient oxidative cyclization of this compound to (2*S*)-dihydropyridone **2** was achieved using a modified version of the standard aza-Achmatowich rearrangement conditions[18] (Scheme 1). The diastereomeric purity of the product was revealed by ^{1}H NMR and HPLC, while the stereochemistry of the newly formed stereocenter (C-6) was determined by 2D NOESY spectroscopic analysis (the absolute configuration at C-2 derives from the starting material). Thus, the clear strong cross peak observed between the hydroxy proton and the protons of *tert*-butyldiphenylsilanyloxymethyl group is indicative of the *cis* diaxial conformation. Furthermore, the observed NOE between the aromatic protons of the tosyl group and protons on C-2 and C-6 confirmed this configuration, which is in good accordance with the theoretically calculated model using molecular mechanics calculations (Fig. 1). This formation of the *cis* isomer may be rationalized considering that the $A^{(1,3)}$ strain between the tosyl and *tert*-butyldiphenylsilyloxymethyl groups force the latter to adopt a *pseudo*-axial orientation and the tosyl group shields the opposite side of the molecule, favoring the formation of the *cis*-product. It is noticeable however, that this assignment does not comply with previous literature results, which have either reported that *trans*-dihydropyridone[11,19] is the outcome of this oxidative cyclization, or the configuration of the product was not unequivocally elucidated.[20] Another addition to this discussion is a recent paper of Zhou,[21] who revised his previous results and reported that a (2*R*)-dihydropyridone prepared by similar oxidative cyclization has the *cis*-configuration (structure deduced by X-ray analysis). Treatment of **2** with trimethyl orthoformate in the presence of $BF_3{\cdot}Et_2O$ produced acetal **3** in very good yield.[†] The ^{1}H and 2D NMR data of this compound are comparable with those of a similar 2,6-*cis*-disubstituted compound of the literature,[20] but not conclusive for an unequivocal stereochemical assignment. On the other hand, reduction of compound **3** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ and subsequent hydrogenation (H_2, Pd/C) produced stereoselectively compound **3a** (Scheme 2), whose configuration was elucidated by 2D COSY and NOESY NMR studies. Thus, the NOE correlation between the H-5_{ax} and H-3_{ax} and the small coupling constant between the β H-2 and H-3 are indicative of the $^4C_1$ chair conformation and the α equatorial disposition of the hydroxy group (Fig. 2). Furthermore, the small coupling constants exhibited between H-6 and the two H-5 are consistent with the β equatorial orientation of H-6 and consequently the α axial orientation of the methoxy group.

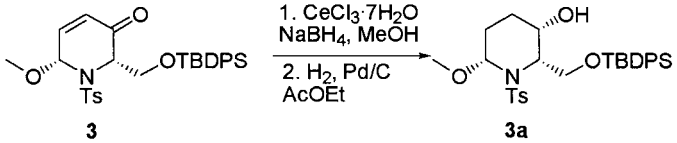


3a

Figure 2.

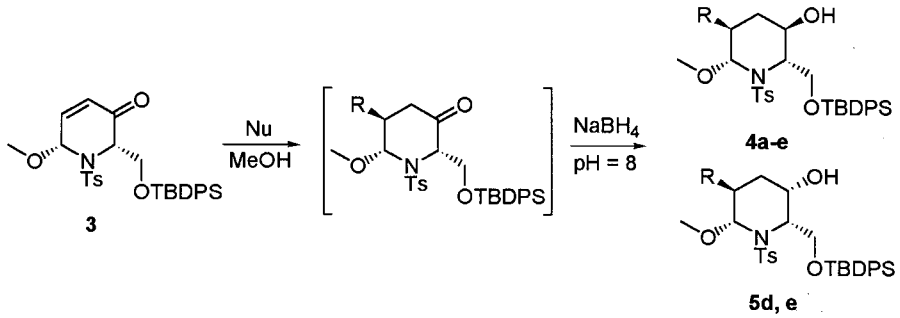
The optimal reaction conditions for the Michael addition of various nucleophiles to this dihydropyridone system were determined considering previous experimental procedures on the relative dihydropyranuloside system.[22] Thus, we were able to avoid undesirable side reactions[23] such as *retro*-Michael addition, *self*-condensation and polymerisation which often limit the utility of the method. The reaction was performed in a polar solvent (CH_3OH) in order to stabilize the enolate anion, using a large excess of nucleophile. Moreover, a slightly alkaline pH environment prevented the possibility of a *retro*-Michael reaction to occur. The results

[†] In our hands this compound proved to be fairly stable and did not undergo epimerization upon chromatography on silica gel, as was reported previously for a similar compound by Altenbach,[19b] in an attempt to explain the formation of the *cis* acetal product from the erroneously considered as the *trans* dihydropyridone.



3 **3a**

Scheme 2.



Compound	R-	Yield (%) 4	Yield (%) 5
a	C_6H_5S-	80	-
b	p-$NH_2C_6H_4S$-	83	-
c	-$SCH_2CH(NH_2)CO_2C_2H_5$	81	-
d	-$NHCH_2CO_2CH_3$	53	22
e	-N_3	70	8

Scheme 3.

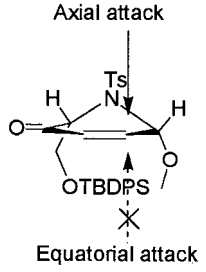
obtained for the 1,4-conjugate addition of various nucleophiles to the examined (2*S*)-dihydropyridone substrate are summarized in Scheme 3. The reaction proved to be remarkably stereospecific, providing the desired Michael adducts in pure diastereomeric form. This may be attributed to the steric hindrance between the *pseudo*-axially oriented 2,6-bulky substituents and the equatorially approaching nucleophile (Scheme 4), which explains the exclusive formation of the kinetically favored axial 1,4-adduct. Similar experiments in the literature using dihydropyranulosides as substrates led to the formation of a mixture of diasteroisomers,[22] presumably because the absence of the tosyl group makes the molecules more flexible, permitting the attack from the opposite side. Finally, the stereochemistry of the in situ reduction of the carbonyl group was affected by the existence of a bulky nucleophile on C-5, because the *syn*-axial attack of the hydride anion was hindered, leading to the formation of the kinetically favored axial product. It is noticeable, however, that this selectivity also depends on the nature of C-5 substituent. Thus, when thiol was used as the nucleophile, $NaBH_4$ reduction furnished exclusively the kinetically favored axial product, while in the case of compounds with a carbon–nitrogen bond at C-5, the formation of a small amount of the thermodynamically favored equatorial product was also detected.

Finally, the tosyl protective group may efficiently be cleaved by reaction with sodium in liquid ammonia,[21] furnishing the corresponding azasugar derivatives.

Structural analyses

The stereochemistry of the Michael addition products were unambiguously assigned based on NMR spectroscopic analysis. Thus, the ^{1}H NMR data (confirmed by 2D COSY spectra) presented in the Experimental and the absence of NOE interaction between H-6 and H-2, provided evidence that all target compounds (**4a**–**e** and **5d**,**e**) adopted the $^4C_1$ chair conformation (Fig. 3), which disposes the α *cis* located methoxy and *tert*-butyl-diphenyl-silanyloxy residues in diaxial positions. Moreover, in the case of thiophenol addition product **4a**, the small coupling constants between both H-4 and H-3,5 in conjunction with the absence of a 1,3-diaxial NOE interaction between the H-3 and H-5 are indicative of a β diaxial orientation of the nucleophile and hydroxy groups.

Since thiols are very effective nucleophiles, in the case of *p*-amino-thiophenol and L-cysteine ethylester, the 1,4-conjugate addition resulted in the formation of a carbon–sulfur bond furnishing compounds **4b** and **4c**. The stereochemistry of the addition and reduction is similar, while the observed positive enhancement between H-2 and the protons of the



Scheme 4. Spatial view of the nucleophile attack on 2-(*tert*-butyl-diphenyl-silanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2H-pyridin-3-one **3**.

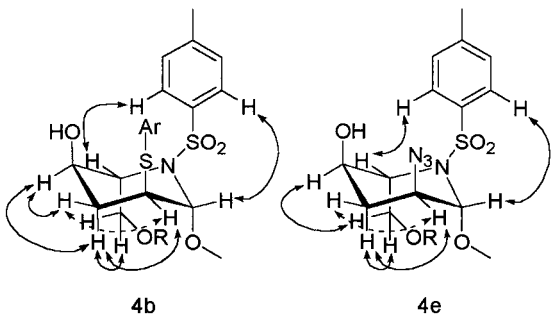


Figure 3.

amino acid supports the conclusion of the axial orientation of the conjugate addition.

When nitrogen containing groups were used as nucleophiles (glycine methylester and hydrazoic acid), the spectral data of the products are similar with those reported for thiol additions (Fig. 3) and are conclusive of an axial 1,4-conjugate addition. In this case, however, the ketone reduction furnished a small amount of the thermodynamically favored products **5d**,**e** in addition to the predominantly formed diaxial derivatives (**4d**,**e**). The equatorial orientation of the hydroxy group on C-3 was revealed by the observed diaxial coupling between H-4_{ax} and H-3_{ax} at ^{1}H NMR (see Experimental).

In summary, we have shown that the use of chiral (2*S*)-hydroxymethyl-dihydropyridone **3** as substrate for the 1,4-conjugate addition of various nucleophiles and in situ reduction provides a useful strategy for the preparation of novel enantiomerically pure 5-amino- and 5-thio-3,6-piperidinol derivatives. Further studies on synthetic applications and biological activity of these compounds are currently in progress.

Experimental

General comments

^{1}H and 2D NMR spectra were recorded at 400 MHZ on a Bruker DRX-400 spectrometer in $CDCl_3$, using TMS as internal standard. IR spectra were obtained on a Nicolet Magna 750, series II spectrometer. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at ambient temperature. HPLC separations were performed using a Hewlett Packard 1100 series instrument with a variable wavelength UV detector and coupled to HP Chem-Station utilizing the manufactorer's 5.01 software package. TLC was conducted on Merck glass plates coated with silica gel 60 F_{254}. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM).

All reactions (except hydrogenation) were carried out under argon atmosphere. Solvents were dried by distillation prior to use. Starting materials were purchased from Aldrich (analytical reagent grades) and used without further purification. *N*-[2-(*tert*-Butyl-diphenyl-silanyloxy)-1-furan-2-yl-ethyl]-4-methyl-benzenesulfonamide **1** was prepared according to a published procedure.[12]

Molecular mechanics calculations were performed using the MM^+ force field of the HyperChem program (HyperChem is developed and licensed from Hypercube; the MM^+ force field used in this software for molecular mechanics calculations is an extension of MM2 using the MM2 (1991) parameters and atom types with the 1997 functional form). The Polac–Ribiere (conjugate gradient) minimization method with an energy convergence criterion of 0.01 kcal mol^{-1} was used for geometry optimization.

(2*S*,6*R*)-2-(*tert*-Butyl-diphenylsilyloxymethyl)-6-hydroxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridine-3-one 2. To a stirred solution of *N*-tosylfurfurylamine **1** (0.38 g, 0.73 mmol) in anhydrous CH_2Cl_2 (5 mL), was added *m*-chloroperbenzoic acid 70% (0.26 g, 1.10 mmol). The reaction was run at room temperature for 4 h, then washed successively with 20% KI, 30% $Na_2S_2O_3$, saturated $NaHCO_3$, water, brine and concentrated under reduced pressure to a yellowish solid. Purification by flash chromatography (ethyl acetate/hexane 1:4, R_f 0.23) gave the title compound as a pale white solid (0.35 g, 94%). A small sample was recrystallized from a diethylether/hexane mixture as off white prisms; mp 97–98°C; $[\alpha]_D^{22}=+27.9$, (*c* 1.0, MeOH); IR (neat): ν_{max} 3356 (OH), 1739 (C=O) cm^{-1}; ^{1}H NMR: δ_H 0.91 (s, 9H, C–CH_3), 2.43 (s, 3H, ArCH_3), 3.60 (dd, *J*=10.6, 2.4 Hz, 1H, CH_{2a}), 3.89 (dd, *J*=10.6, 2.4 Hz, 1H, CH_{2b}), 4.54 (m, 1H, H-2), 4.90 (d, *J*=7 Hz, 1H, OH), 6.09 (m, 1H, H-6), 6.19 (d, *J*=10.4 Hz, 1H, H-4), 7.07 (dd, *J*=10.4, 4.8 Hz, 1H, H-5), 7.32 (m, 12H, ArH), 7.78 (d, *J*=8 Hz, 2H, ArH). Anal. Calcd for $C_{29}H_{33}NO_5SSi$ (535.7): C, 65.02; H, 6.21; N, 2.61. Found: C, 64.97; H, 6.32; N, 2.57.

(2*S*,6*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one 3. To an ice-cold solution of azapyranone **2** (2.00 g, 3.72 mmol), trimethyl orthoformate (0.8 mL, 7.44 mmol) and 4 Å molecular sieves (0.35 g) in dry THF (25 mL) was added $BF_3{\cdot}Et_2O$ (0.7 mL). The reaction mixture was stirred for 3 h at 0°C, quenched with water and extracted with diethylether (2×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a yellowish solid which was chromatographed (ethyl acetate/hexane 1:4, R_f 0.27) to furnish the desired product **2** (1.96 g, 95%) as colorless fine needles; mp 83–84°C (diethylether/hexane); $[\alpha]_D^{22}=+122.9$ (*c* 0.3, MeOH); IR(neat): ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR: δ_H 1.06 (s, 9H, C–CH_3), 2.38 (s, 3H, ArCH_3), 3.53 (s, 3H, OCH_3), 3.95 (dd, *J*=10, 6.7 Hz, 1H, CH_{2a}), 4.05 (dd, *J*=10, 6.7 Hz, 1H, CH_{2b}), 4.45 (t, *J*=6.7 Hz, 1H, H-2), 5.50 (d, *J*=4.2 Hz, 1H, H-6), 5.74 (d, *J*=10.4 Hz, 1H, H-4), 6.66 (dd, *J*=10.4, 4.2 Hz, 1H, H-5), 7.23 (d, *J*=8 Hz, 2H, ArH), 7.35–7.47 (m, 6H, ArH), 7.54 (d, *J*=8 Hz, 2H, ArH), 7.65 (d, *J*=8 Hz, 4H, ArH). Anal. Calcd for $C_{30}H_{35}NO_5SSi$ (549.8): C, 65.54; H, 6.42; N, 2.55. Found: C, 65.39; H, 6.44; N, 2.71.

(2*S*,6*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ol 3a. To a stirred solution of compound **3** (1.0 g, 1.78 mmol) and $CeCl_3{\cdot}7H_2O$ (0.33 g, 0.89 mmol) in methanol (20 mL) at −30°C was added portionwise $NaBH_4$ (0.24 g, 6.23 mmol). After 40 min of stirring at that temperature, the reaction was quenched with sat. aqueous NH_4Cl (15 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and chromatographed (ethyl acetate/hexane 1:4) to afford (0.8 g, 78%) of the allylic alcohol, which was dissolved in ethyl acetate (20 mL) and hydrogenated over 10% Pd/C (0.07 g) under 1 bar pressure for 40 min. The mixture was filtered over Celite and evaporated to a yellowish solid which was chromatographed (ethyl acetate/hexane 1:4, R_f 0.23) to give compound **3a** as a white solid which was crystallized from diethylether/hexane (0.76, 94%); mp 105–107°C; $[\alpha]_D^{22}=+81.2$ (*c* 0.90, MeOH); IR (neat): ν_{max}

3476 (OH) cm^{-1}; ^1H NMR: δ_H 1.05 (s, 9H, C–CH_3), 1.35 (tt, J=14.4, 4 Hz, 1H, H-5_{ax}), 1.66 (m, 1H, H-4_{eq}), 1.85 (m, 1H, H-5_{eq}), 1.92 (m, 1H, H-4_{ax}), 2.40 (s, 3H, $ArCH_3$), 3.20 (s, 3H, OCH_3), 3.36 (m, 1H, H-3), 3.86 (dd, J=10.4, 3.4 Hz, 1H, CH_{2a}), 4.16 (dt, J=10.4, 3.4 Hz, 1H, H-2), 4.36 (d, J=7.4 Hz, 1H, OH), 4.47 (t, J=10.4 Hz, 1H, CH_{2b}), 5.05 (d, J=2.5 Hz, 1H, H-6), 7.25 (d, J=8.3 Hz, 2H, ArH), 7.36–7.47 (m, 6H, ArH), 7.59–7.70 (m, 6H, ArH). Anal. Calcd for $C_{30}H_{39}NO_5SSi$ (553.79): C, 65.07; H, 7.10; N, 2.53. Found: C, 64.95; H, 7.02; N, 2.39.

General procedure for the syntheses of 5-sulfanyl piperidin-3-oles (4a–c)

The pH of a methanolic (2 mL) solution of thiol derivative (2.27 mmol) was adjusted to 8 by addition of triethylamine (ca 3 drops) and a methanolic solution (2 mL) of azapyranone **3** (0.25 g, 0.45 mmol) was added. The resulting mixture was stirred at room temperature until the Michael addition was complete (monitored by TLC). Extractive workup with ethyl acetate (3×15 mL) gave a yellowish oil which was purified by flash chromatography (ethyl acetate/hexane 1:4) furnishing the desired Michael adducts. Subsequently, these compounds were dissolved in ice-cold methanol (3 mL) and sodium borohydride (0.09 g, 2.27 mmol) was added portionwise under stirring. The pH of the reaction was adjusted and maintained to 4–5 (by addition of acetic acid) and stirring was continued at 0°C for 40 min. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3×15 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a yellowish solid. Flash chromatographic purification (ethyl acetate/hexane) afforded the title compounds as white solids, which were crystallized from diethylether/hexane.

(2*S*, 3*R*, 5*S*, 6*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-methoxy-5-phenyl sulfanyl-1-(toluene-4-sulfonyl)-piperidin-3-ol 4a. This compound was obtained as colorless prisms (80%); mp 104–106°C (diethylether/hexane); R_f 0.43 (ethyl acetate/hexane 1:4); $[\alpha]_D^{22}$=−77.5 (*c* 0.78, MeOH); IR (neat): ν_{max} 3553 (OH) cm^{-1}; ^1H NMR: δ_H 1.03 (s, 9H, C–CH_3), 1.67 (dt, J=15.2, 3.6 Hz, 1H, H-4_{eq}), 1.94 (ddd, J=15.2, 3.0, 4.9 Hz, 1H, H-4_{ax}), 2.41 (s, 3H, $ArCH_3$), 2.89 (d, J=9.7 Hz, 1H, OH), 3.12 (s, 3H, OCH_3), 3.12 (m, 1H, H-5), 3.79 (d, J=5.3 Hz, 1H, CH_{2b}), 3.80 (s br, 1H, H-2) 3.91 (d, J=5.3 Hz, 1H, CH_{2a}), 4.10 (s br, 1H, H-3) 5.19 (d, J=1 Hz, 1H, H-6), 6.62 (d, J=8.5 Hz, 2H, ArH), 7.23–7.31 (m, 5H, ArH), 7.33–7.45 (m, 6H, ArH), 7.58–7.65 (m, 4H, ArH), 7.82 (d, J=8 Hz, 2H, ArH). Anal. Calcd for $C_{36}H_{43}NO_5S_2Si$ (661.95): C, 65.32; H, 6.55; N, 2.12. Found: C, 65.15; H, 6.45; N, 2.22.

(2*S*, 3*R*, 5*S*, 6*R*)-5-(4-Amino-phenylsulfanyl)-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ol 4b. This compound was obtained as pale yellow needles (83%); mp 82–84°C (diethylether/hexane); R_f 0.34 (ethyl acetate/hexane 1:4); $[\alpha]_D^{22}$=−76.9 (*c*0.55, MeOH); IR(neat): ν_{max} 3492 (OH), 3375 (NH_2) cm^{-1}; ^1H NMR: δ_H 1.08 (s, 9H, C–CH_3), 1.68 (dt, J=15.2, 3.9 Hz, 1H, H-4_{eq}), 2.08 (ddd, J=15.2, 3.2, 5.1 Hz, 1H, H-4_{ax}), 2.46 (s, 3H, $ArCH_3$), 2.64 (d, J=8.8 Hz, 1H, OH), 3.18 (s, 3H, OCH_3), 3.42 (ddd, J=5.1, 3.9, 1.5 Hz, 1H, H-5), 3.85 (d, J=5.1 Hz, 1H, CH_{2b}), 3.86 (s br, 1H, H-2) 3.97 (d, J=5.1 Hz, 1H, CH_{2a}), 4.17 (s br, 1H, H-3) 5.21 (d, J=1 Hz, 1H, H-6), 6.62 (d, J=8.5 Hz, 2H, ArH), 7.31–7.50 (m, 12H, ArH), 7.62–7.7 (m, 4H, ArH), 7.83 (d, J=8 Hz, 2H, ArH). Anal. Calcd for $C_{36}H_{44}N_2O_5S_2Si$ (676.96): C, 63.87; H, 6.55; N, 4.14. Found: C, 63.91; H, 6.33; N, 4.10.

(2′*R*, 3′*S*, 5′*R*, 6′*S*)-2*R*-Amino-3-[6′-(*tert*-butyl-diphenyl-silanyloxymethyl)-5′-hydroxy-2′-methoxy-1′-(toluene-4-sulfonyl)-piperidin-3′-ylsulfanyl]-propionic acid ethyl ester 4c. This compound was obtained as an off white hygroscopic solid (81%); R_f 0.48 (ethyl acetate/hexane 1:1); $[\alpha]_D^{22}$=−25 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$ solution in ZnSe cells): ν_{max} 3071 (NH_2), 1735 (COO) cm^{-1}; ^1H NMR: δ_H 1.04 (s, 9H, C–CH_3), 1.28 (t, J=7.0 Hz, 3H, CH_2CH_3), 1.61 (dt, J=14.6, 3.0 Hz, 1H, H-$4'_{eq}$), 1.92(s br, 2H, NH_2), 2.02 (dt, J=14.6, 3.0 Hz, 1H, H-$4'_{ax}$), 2.41 (s, 3H, $ArCH_3$), 2.83 (dd, J=13.0, 7.0 Hz, 1H, CH_2S), 2.92 (dd, J=13.0, 4.5 Hz, 1H, CH_2S), 3.05 (t, J=3 Hz, 1H, H-5′), 3.20 (s, 3H, OCH_3), 3.64 (dd, J=7, 4.5 Hz, 1H, $CHNH_2$), 3.77 (s br, 1H, H-2′) 3.79 (d, J=6.1 Hz, 1H, CH_{2b}), 3.91 (d, J=6.1 Hz, 1H, CH_{2a}), 4.07 (s br, 1H, H-3′) 4.2 (q, J=7.0 Hz, 2H, CH_2CH_3) 5.16 (s, 1H, H-6), 7.26 (d, J=6.7 Hz, 2H, ArH), 7.34–7.48 (m, 6H, ArH), 7.58–7.66 (m, 4H, ArH), 7.77 (d, J=8 Hz, 2H, ArH). Anal. Calcd for $C_{35}H_{48}N_2O_7S_2Si$ (700.98): C, 59.97; H, 6.90; N, 4.00. Found: C, 59.69; H, 6.71; N, 3.89.

[6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5-hydroxy-2-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ylamino]-acetic acid methyl ester (4d and 5d). The pH of a stirred solution of glycine methylester hydrochloride (0.46 g, 3.64 mmol) in absolute methanol (5 mL) was adjusted to 8.5 by addition of triethylamine (0.57 mL) and a methanolic solution (5 mL) of azapyranone **3** (0.5 g, 0.91 mmol) was added. The resulting mixture was stirred at room temperature until TLC analysis indicated that the Michael addition was complete. Then, the reaction mixture was cooled to 0°C and sodium borohydride (0.17 g, 4.55 mmol) was added portionwise, while the pH of the reaction was adjusted and maintained to 7.5–8.5 (by addition of acetic acid). After 40 min of stirring at that temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and purified by flash chromatography (ethyl acetate/hexane 2:3, R_f 0.31) to yield the title compound as mixture of diastereoisomers in 75% total yield (3*R*/3*S*=7:3, determined by ^1H NMR); Separation by semi-preparative HPLC[24] furnished as the less mobile crop (retention time=29.07) the major diastereoisomer *(2S, 3R, 5S, 6R)-[6-(tert-butyl-diphenyl-silanyloxymethyl)-5-hydroxy-2-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ylamino]-acetic acid methyl ester* **4d**; white gum; $[\alpha]_D^{22}$=−56.5 (*c* 1.0, MeOH); IR (film): ν_{max} 3492 (OH), 3308 (NH), 1751 (COO) cm^{-1}; ^1H NMR: δ_H 1.07 (s, 9H, C–CH_3), 1.65 (dt, J=15.2, 3.0 Hz, 1H, H-4_{eq}), 1.74 (dt, J=15.2, 3.0 Hz, 1H, H-4_{ax}), 2.42 (s, 3H, $ArCH_3$), 2.90 (br s, 1H, H-5), 3.21 (s, 3H, OCH_3), 3.37 (s, 2H, CH_2NH), 3.75 (s, 3H, $COOCH_3$), 3.85 (t, J=10.4 Hz, 1H, CH_{2b}), 3.89 (dd, J=10.4, 4.1 Hz, 1H, H-2) 4.06 (dd, J=10.4, 4.3 Hz, 1H, CH_{2a}), 4.09 (s br, 1H, H-3), 5.03 (d, J=1.8 Hz, 1H, H-6), 7.26 (d, J=6.7 Hz, 2H, ArH), 7.35–7.52 (m, 6H, ArH), 7.62–7.71

(m, 4H, ArH), 7.74 (d, J=8 Hz, 2H, ArH). Anal. Calcd for $C_{33}H_{44}N_2O_7SSi$ (640.86): C, 61.85; H, 6.92; N, 4.37. Found: C, 61.57; H, 6.81; N, 4.27.

The more mobile crop (retention time=27.38) corresponded to the minor diastereoisomer *(2S, 3S, 5S, 6R)-[6-(tert-butyl-diphenyl-silanyloxymethyl)-5-hydroxy-2-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ylamino]-acetic acid methyl ester* **5d**; clear oil; $[\alpha]_D^{22}=-16.3$ (c 1.0, MeOH); IR (film): ν_{max} 3490 (OH), 3310 (NH), 1748 (COO) cm^{-1}; ^1H NMR: δ_H 1.07 (s, 9H, C–CH_3), 1.79 (dt, J=14.5, 3.4 Hz, 1H, H-4_{eq}), 2.09 (td, J=14.5, 3.4 Hz, 1H, H-4_{ax}), 2.44 (s, 3H, ArCH_3), 2.98 (br s, 1H, H-5), 3.17 (s, 3H, OCH_3), 3.37 (d, J=17 Hz, 1H, CH_2NH), 3.45 (d, J=17 Hz, 1H, CH_2NH), 3.75(s, 3H, $COOCH_3$), 3.93 (m, 1H, H-3), 4.00 (dd, J=10.2, 6.5 Hz, 1H, CH_{2b}), 4.14 (d, J=6.5 Hz, 1H, H-2) 4.46 (t, J=10.2 Hz, 1H, CH_{2a}), 4.89 (d, J=1.8 Hz, 1H, H-6), 7.26 (d, J=6.7 Hz, 2H, ArH), 7.35–7.52 (m, 6H, ArH), 7.62–7.71 (m, 4H, ArH), 7.82 (d, J=8 Hz, 2H, ArH). Anal. Calcd for $C_{33}H_{44}N_2O_7SSi$ (640.86): C, 61.85; H, 6.92; N, 4.37. Found: C, 61.61; H, 6.76; N, 4.31.

5-Azido-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ol (4e and 5e). To an ice-cold stirred solution of azapyranone **3** (0.5 g, 0.91 mmol) in tetrahydrofuran (5 mL) was added an aqueous solution (1 mL) of sodium azide (0.24 g, 3.64 mmol) and acetic acid (0.40 mL). The resulting solution was stirred at room temperature for 2 h. Subsequently, the reaction mixture was cooled to 0°C and sodium borohydride (0.14 g, 3.64 mmol) was added portionwise. The reaction was run for 40 min at that temperature, quenched with water and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and chromatographed (ethyl acetate/hexane 1.5:8, R_f 0.43) to yield the desired azide as mixture of diastereoisomers in 78% total yield (3*R*/3*S*=9:1, determined by ^1H NMR); Separation by semi-preparative HPLC[24] furnished as the less mobile crop (retention time=27.70 min) the major diastereoisomer *(2S, 3R, 5S, 6R)-5-azido-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ol* **4e**, which was crystallized from diethylether/hexane mixture as colorless prisms; mp 105–106°C; $[\alpha]_D^{22}=-41.6$ (*c* 0.4, MeOH); IR (solution in $CHCl_3$): ν_{max} 3536 (OH), 2115 (N_3) cm^{-1}; ^1H NMR: δ_H 1.03 (s, 9H, C–CH_3), 1.67 (dt, J=15.2, 3 Hz, 1H, H-4_{eq}), 1.78 (dt, J=15.2, 3 Hz, 1H, H-4_{ax}), 2.40 (s, 3H, ArCH_3), 3.2 (s, 3H, OCH_3), 3.73 (t, J=10.4 Hz, 1H, CH_{2b}), 3.73 (s br, 1H, H-5) 3.86 (dd, J=10.4, 4.3 Hz, 1H, CH_{2a}), 3.91 (dd, J=10.4, 4.1 Hz, 1H, H-2), 4.01(s br, 1H, H-3) 5.05 (d, J=1.8 Hz, 1H, H-6), 7.28 (d, J=8 Hz, 2H, ArH), 7.33–7.44 (m, 6H, ArH), 7.58–7.65 (m, 4H, ArH), 7.73 (d, J=8 Hz, 2H, ArH). Anal. Calcd for $C_{30}H_{38}N_4O_5SSi$ (594.8): C, 60.58; H, 6.44; N, 9.42. Found: C, 60.41; H, 6.49; N, 9.30.

The more mobile crop (retention time=25.54) corresponded to the minor diastereoisomer *(2S, 3S, 5S, 6R)-5-azido-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ol* **5e**; mp 99–101°C; $[\alpha]_D^{22}=-26.4$ (*c*0.4, MeOH); IR (solution in $CHCl_3$): ν_{max} 3533 (OH), 2111 (N_3) cm^{-1}; ^1H NMR: δ_H 1.03 (s, 9H, C–CH_3), 1.92 (dt, J=14.3, 3.3 Hz, 1H, H-4_{eq}), 2.04 (td, J=14.3, 3.3 Hz, 1H, H-4_{ax}), 2.38 (s, 3H, ArCH_3), 3.15 (s, 3H, OCH_3), 3.73 (s br, 1H, H-5) 3.86 (dd, J=10.4, 4.3 Hz, 1H, CH_{2a}), 4.01(s br, 1H, H-3), 4.22 (d, J=6.5 Hz, 1H, H-2), 4.38 (t, J=10.4 Hz, 1H, CH_{2b}), 4.89 (d, J=1.8 Hz, 1H, H-6), 7.28 (d, J=8 Hz, 2H, ArH), 7.33–7.44 (m, 6H, ArH), 7.58–7.65 (m, 4H, ArH), 7.73 (d, J=8 Hz, 2H, ArH); Anal. Calcd for $C_{30}H_{38}N_4O_5SSi$ (594.8): C, 60.58; H, 6.44; N, 9.42. Found: C, 60.51; H, 6.49; N, 9.45.

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24. Column: Kromasil 10-5C18 (25 cm×10 mm); Mobile phase: H_2O/CH_3CN (9:1); Detector: UV λ 254 nm; Flow: 4 ml/min; Load: 3 mg/200 μL solution in mobile phase.