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A new approach for the asymmetric syntheses of 2-*epi*-deoxoprosopinine and azasugar derivatives

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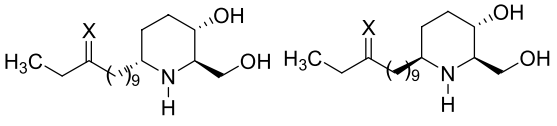
Dedicated to, Professor Ben-Li Huang on the occasion of his 80th birthday

Abstract—A new approach to 2-*epi*-deoxoprosopinine **11**, 1-deoxygulonojirimycin **7**, and L-gulono-1,5-lactam **9** was described. The C-2 hydroxymethyl group was introduced regioselectively using SmI_2 mediated coupling of (*S*)-3-silyloxyglutarimide **13b** with either chloromethyl benzyl ether **16a** or the Beau–Skrydstrup reagent **16b**, followed by debenzylation and highly *cis*-diastereoselective reductive deoxygenation. Adoption of the Savoi's chemoselective ring-opening alkylation method allowed a highly diastereoselective introduction of the lipid side chain of 2-*epi*-deoxoprosopinine **11** in a straightforward manner. Dehydration followed by highly *trans*-diastereoselective dihydroxylation led to polyoxygenated lactam derivative **27** as a key intermediate for the syntheses of **7** and **9**.

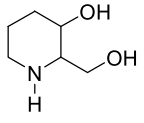
1. Introduction

2-Hydroxymethyl-3-piperidinol **1** is a salient structural feature found in two classes of natural products, namely, piperidine alkaloids[1] and azasugars (or iminosugars).[2] Several 2,3,6-trisubstituted piperidine alkaloids (e.g., prosopinine **2** and prosophylline **3**) have been isolated from the leaves of the West African savanna tree *Prosopis africana* Taub[3] and from the leaves of *Microcos philippinensis* (Perk) Burrett (*Tiliaceae*).[4] These alkaloids and their deoxygenated analogs (e.g., deoxoprosopinine **4** and deoxoprosophylline **5**) exhibit antibiotic, anesthetic, analgesic, and CNS stimulating properties, and are of considerable pharmaceutical interest.[5] Many synthetic approaches have thus been developed.[6,7] Moreover, many azasugars are inhibitors of glycosidases and related enzymes, showing therapeutic potential for the treatment of diseases related to metabolic disorders such as diabetes, cancer, AIDS, and viral infections. For example, 1-deoxymannojirimycin (DMJ, **6**) is a mannosidase inhibitor;[8] 1-deoxygulonojirimycin[9–12] (DGJ, **7**) is a potent and selective inhibitor of fucosidases,[12e–g] which was isolated from the back of *Angylocalyx pynaertii* (*Leguminosae*);[9] D-mannonolactam (**8**) is a powerful inhibitor of rat epididymal α-mannosidases, and of apricot β-glucosidase;[13] other δ-lactams have been shown to be glycosidase inhibitors.[14] As a result, the synthesis of azasugars and their synthetic analogs has attracted a great deal of attention.[12,15,16]



prosopinine **2.** X=O
deoxoprosopinine **4.** X=2H

prosophylline **3.** X=O
deoxoprosophylline **5.** X=2H



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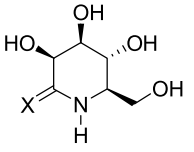
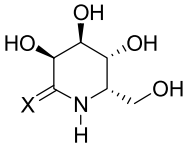


1-deoxymannojirimycin **6.** X=2H
D-mannonolactam **8.** X=O



L-1-deoxygulonojirimycin **7.** X=2H
L-gulono-1,5-lactam **9.** X=O

As the part of our ongoing project aimed at the development of 3-hydroxyglutarimides-based synthetic methodology,[17] we wish to report herein a versatile approach to (2*S*,3*S*,6*R*)-2-*epi*-deoxoprosopinine **11**,[18] L-1-deoxygulonojirimycin **7**,[12] and L-gulono-1,5-lactam **9**.[16]

Keywords: Piperidine; Alkaloid; Hydroxymethylation; Diastereoselective reaction; Regioselective reaction; Building block.
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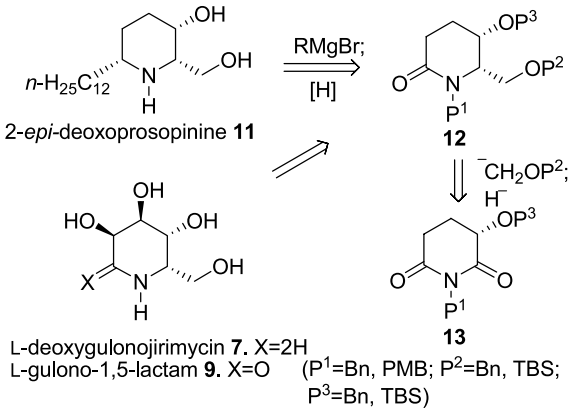
2. Results and discussion

As depicted retrosynthetically in Scheme 1, our approach featured, firstly, the use of protected (5*S*,6*S*)-5-hydroxy-6-hydroxymethyl-2-piperidinone **12** as a common intermediate to **11**, **9**, and **7**. The presence of the amide functionality would not only allow the introduction of the C-6 side chain of the *Prosopis* alkaloids as well as the two hydroxyl groups of L-gulono-1,5-lactam **9** and 1-deoxygulonojirimycin **7**, but also allow its transformation into cyclic amidine sugars, which demonstrated good to excellent inhibition toward glycosidases.[19] The second feature of the approach was the installation of the hydroxymethyl group by a stepwise regio- and diastereo-selective reductive hydroxymethylation procedure (**13**→**12**). The introduction of the C-6 side chain in the piperidine ring (**12**→**11**) by a straightforward method constituted the third feature of the approach.

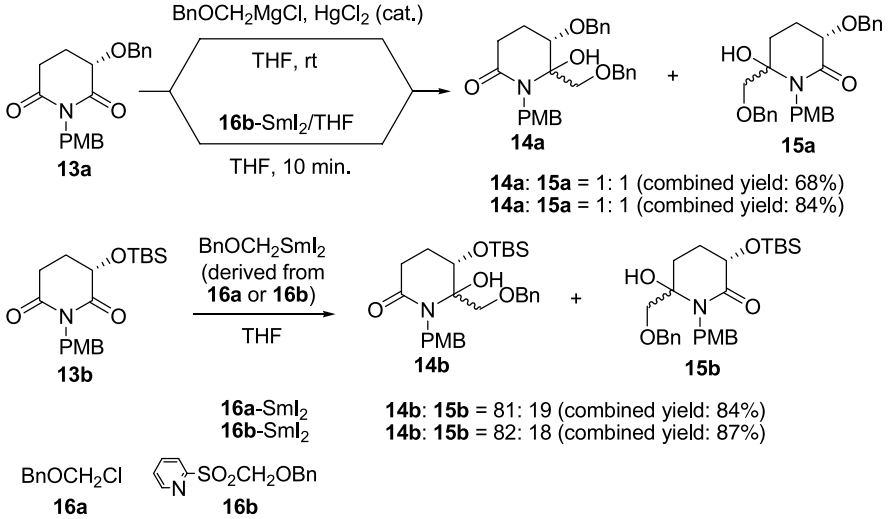


Scheme 1.

Our first task was the introduction of a hydroxymethyl group[20,21] to the C-2 position of protected 3-hydroxyglutarimides **13**. Although the stepwise reductive alkylation of **13a** with un-functionalized Grignard reagents has been demonstrated to proceed with high C-2 regioselectivity and high *trans*-diastereoselectivity,[17a,c] considerable difficulties were encountered in attempts to introduce a protected hydroxymethyl group in a regio- and diastereo-selective manner. For example, in the presence of a catalytic amount of mercury chloride(II),[22] addition of benzyloxymethyl magnesium chloride, derived from commercially available benzyl chloromethyl ether (**16a**) with **13a**, yielded two regioisomers **14a** and **15a** in disappointing 1:1 ratio (Scheme 2). Reaction of the Beau–Skrydstrup benzyloxymethylation reagent[23] **16b** with **13a** gave once again a 1:1 regioisomeric mixture, albeit in higher combined yield (84%).

After several unsuccessful attempts, including performing the reaction at lower temperature and using less reactive chloromethyl benzyl ether (**16a**)—SmI_2[20c–f] as a benzyloxymethylation system, we were delighted to find that the benzyloxymethylation of *O*-*tert*-butyldimethylsilyl protected 3-hydroxyglutarimide **13b** provided better results. Thus, when a 1:1.2 mixture of glutarimide **13b** and benzyl chloromethyl ether **16a** was treated with 3 molar equiv of a freshly prepared solution of SmI_2 (0.1 M in THF) at rt for 10 min, the C-2 addition product **14b** and the C-6 addition regioisomer **15b** were obtained in a ratio of 81:19 with a combined yield of 84%. Similar treatment of **13b** with the Beau–Skrydstrup reagent **16b** gave similar C-2/C-6 regioselectivity (82:18) and slightly higher combined yield (87%).

The observed protecting group effect (TBS vs Bn) on the regioselectivity of the SmI_2 mediated Barbier type benzyloxymethylation of **13a/13b** was contrary to the Grignard reagents addition to malimides, where the *O*-benzyl protected malimide gave excellent C-2 regioselectivity, whereas the *O*-TBS protected malimide gave nearly 1:1 C-2/C-5 regioselectivity.[24] The regioselectivity observed during the benzyloxymethylation of **13b** might be attributed to the oxyphilicity of the samarium(III) species, which formed a five-membered chelating structure, and polarized the Si–O bond, thus rending the Si/I interaction via a four-membered chelating structure plausible (Fig. 1). In such a manner, the steric hindrance of the TBS group was recompensed and consequently the C-2 carbonyl was activated.



Scheme 2.

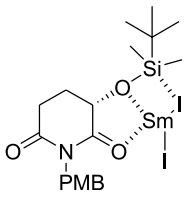
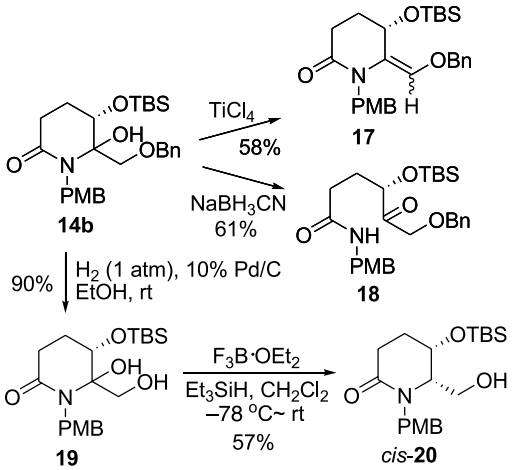


Figure 1.

With the *N*,*O*-acetal **14b** in hand, we then investigated its reductive deoxygenation. Much to our surprise, when **14b** was subjected to ionic hydrogenation conditions ($BF_3 \cdot OEt_2$, Et_3SiH, CH_2Cl_2, −78 °C to rt), only the starting material was recovered (Scheme 3). Even after heated to 40 °C for 3 days, only 5% of the desired product was isolated. Other ionic hydrogenation conditions led to either dehydrated product **17** ($TiCl_4$, Et_3SiH, −78 °C to rt)[25] or ring-opening product **18** ($NaBH_3CN$, at pH 3, rt).[26] It was envisioned that the failure to perform the reductive deoxygenation might be due to the steric hindrance of the *N*,*O*-acetal **14b**. To test this hypothesis, the benzyl group was cleaved (1 atm H_2, 10% Pd/C, rt, 8 h), and the resulted *N*,*O*-semiacetal **19** was subjected to $BF_3 \cdot OEt_2$ mediated Et_3SiH reduction. In such a manner, the desired product **20** was obtained in 57% yield, with a diastereoselectivity of 93:7. The stereochemistry of the major diastereomer **20** was assigned as *cis*[12,15,16,18,27] by comparing with the known (5*S*,6*R*)-*trans*-**20**.[28]



Scheme 3.

The stereochemical course of the reductive deoxygenation of **19** deserved comments. The fact that the reductive deoxygenation of a diastereomeric mixture of **19** led to preponderant formation of a diastereomer, implicating that the transformation involved an *N*-acyliminium intermediate[17] (**A**/**B**) (Fig. 2). Among the two possible conformers **A** and **B**, $A^{1,2}$ interaction and $A^{1,3}$ interaction[29] existed in the conformers **A** and **B**, respectively. Possible interactions between and *F*∼*Si* would compensate for the unfavorable $A^{1,2}$ interaction existed in **A**, rending thus conformer **A** the more favored one. Subsequent nucleophilic attack of a hydride was expected to take place from the axial direction owing to the stereoelectronic effects.[30] Thus, starting from the more stable conformer **A**, a hydride approached from the β-face of the ring, leading to the more stable chair conformer (*cis*-**20**).

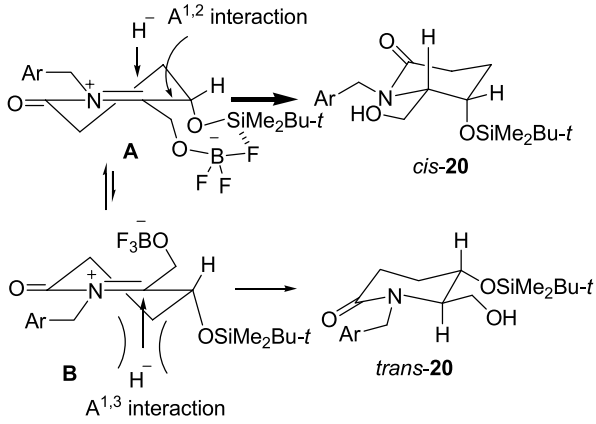
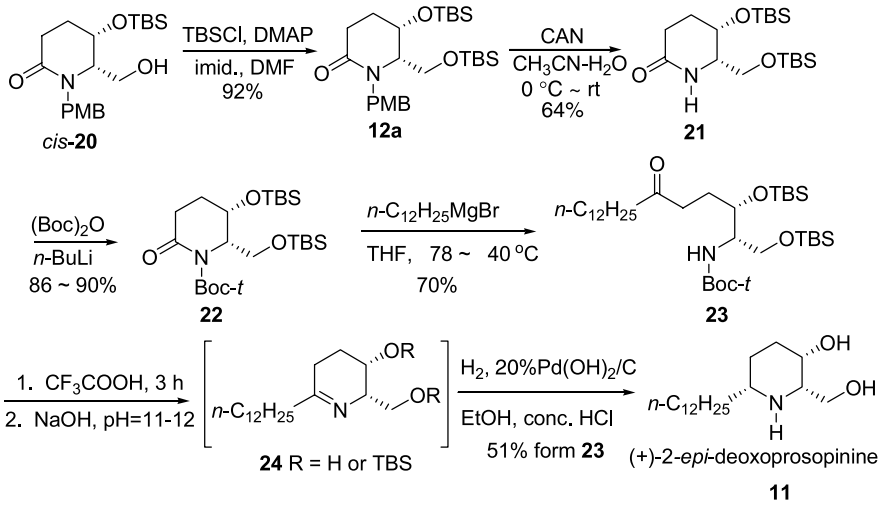


Figure 2.

The next stage for the synthesis of 2-*epi*-deoxoprosopinine **11** was the introduction of the C-6 side chain in a *cis*-diastereoselective manner. Most known methods for the *cis*-diastereoselective installation of a C-6 side chain in a 2-substituted piperidine ring involve α-amidoallylation of an appropriate piperidine *N*,*O*-acetal with allyltrimethylsilane, followed by multistep chain elongation manipulation.[7f–h] A direct method, however, was required to prepare the nucleophilic allylic silane C_{12} side chain in several steps.[7a] Keeping in mind that the 2,6-*cis*-stereochemistry was also a key structural feature found in prosophylline, micropine, cassine, spectaline, azmic acid, canavaline, and other 3-piperidinol alkaloids,[1] it was desirable to develop a flexible method enabling the diastereoselective introduction of different C-6 side chains in a straightforward manner.

In this context, Savoia's flexible organometallic ring-opening method[31] appeared to be promising. This turned out to be true, when *N*-Boc activated δ-lactam **22**, prepared from *cis*-**20** via successive *O*-silylation (TBSCl, DMAP, imid., DMF, rt, 12 h, 92%), CAN mediated cleavage of PMB group (CAN, MeCN/H_2O 9:1, 0 °C to rt, 4 h), and lactam activation ($(Boc)_2O$, *n*-BuLi, −78 °C, 0.5 h), was treated with a solution of *n*-$C_{12}H_{25}MgBr$ in THF at −78 °C for 3 h, then at −40 °C for 40 min, the desired ketone **23** was obtained in 70% yield based on the recovered starting material (81% conversion) (Scheme 4). *N*-Deprotection with TFA, followed by treating with a 30% NaOH solution led to cyclic imines **24** (containing partially desilylated products), which, without purification, was hydrogenated (H_2, 1 atm, 20% $Pd(OH)_2$, EtOH/concd HCl 10:1, rt, 30 h)[7j,s] under acidic conditions to provide (+)-2-*epi*-deoxoprosopinine **11** (51% overall yield from **23**) as a single diastereomer {$[\alpha]_D^{20}+3.0$ (*c* 0.6, CH_3OH); lit.[18] $[\alpha]_D^{26}+2.7$ (*c* 1.0, CH_3OH)}. The spectroscopic and physical data of the synthetic product were identical with those reported.[18] Noteworthy was that starting from the keto-amide **23**, the deprotection of *t*-Boc and two TBS protective groups, cyclisation, and hydrogenation were accomplished without chromatographic separation of the intermediates. The stereochemistry of the newly formed chiral center in **11** was ascertained by comparing with the known compound.[18]

As regarding the stereochemical course[71] of the reaction, in the light of the preponderant formation of the *cis*-isomer, it was reasonable to assume that among two possible



Scheme 4.

conformers **C** and **D** (Fig. 3), conformer **C** predominated over **D** due to an intramolecular hydrogen bond. The stereoelectronic controlled axial attack of hydrogen occured from the β-face of **C** leading to the desired product **11** with chair conformation, where the formation of intramolecular hydrogen bonds was possible.

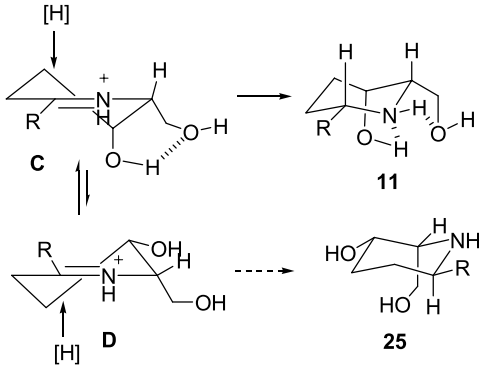
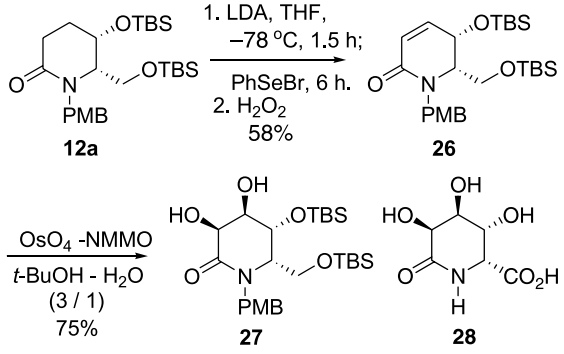


Figure 3.

Having accomplished the synthesis of (+)-2-*epi*-deoxoprosopinine, we then turned our attention to explore an entrance to **7** and **9**. Thus, successive treatment of lactam **12a** with LDA (THF, −78 °C) and phenylselenium bromide yielded the α-phenylselenide derivative of **12a**,[32] which without purification, was subjected to H_2O_2 oxidation in wet CH_2Cl_2 at rt to give directly **26** in 58% overall yield from **12a** (Scheme 5).



Scheme 5.

Diastereoselective dihydroxylation[11b,15d,33] of **26** was achieved by treating with OsO_4 (cat)-NMMO system in a mixed solvent system (*t*-BuOH-H_2O 3:1, rt, 3 h) to give **27** (yield: 75%) as the only isolable product. Lactam **27** can be easily converted, via deprotection and/or reduction, to azasugars **7**, **9** and other analogous, such as (2*R*,3*R*,4*S*,5*S*)-trihydroxypipecolic acid δ-lactam derivative **28**[2→b], according to the known procedures.[11b,12g,15a,15e,27b]

3. Conclusion

In summary, taking advantages of the multifunctionality of the TBS protected 3-hydroxyglutarimide **13b** and the protecting group effect, we were able to introduce both the C-2 hydroxymethyl group and the C-6 side chain in good regioselectivity (C-2/C-6 81:19) and in excellent diastereoselectivities (C-2/C-3 93:7; C-2/C-6 100:0). Using a Grignard reagent as a carbon nucleophile to introducing the C-6 side chain made this method flexible, this would find applications in the synthesis of other piperidine alkaloids.

4. Experimental

4.1. General methods

Melting points are uncorrected. Optical rotations were recorded on an automatic polarimeter. IR spectra were recorded on a FT-IR spectrophotometer. NMR spectra were recorded in $CDCl_3$ (^1H at 500 MHz and ^{13}C at 125 MHz), and chemical shifts were expressed in parts per million (δ) relative to internal Me_4Si. HRESIMS spectra were recorded on a FTMS apparatus. Silica gel (300–400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Dichloromethane, DMF, and diisopropylamine were distilled over calcium hydride under N_2. Ether and THF were distilled over sodium benzophenone ketyl under N_2.

4.1.1. (5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-(hydroxymethyl)-1-(4-methoxybenzyl)piperidin-2-one (20). *Method 1*. To a mixture of **13b** (1.452 g, 4.0 mmol)

and benzyloxymethyl chloride **16a** (60% purity, 1.2 mL, ca. 12 mmol) in anhydrous THF (10 mL) was quickly added a freshly prepared THF solution of SmI_2[34] (12 mmol, 120 mL) under an argon atmosphere at rt. After stirring for 45 min at rt, saturated NH_4Cl (10 mL) was added. The clear solution was poured into ether (200 mL), and the solid was washed successively with ether (30 mL×3). The combined organic layers were washed with saturated aqueous NH_4Cl (30 mL×3) and brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **14b** (*C*-2 addition regioisomer, 1.319 g, yield: 67%) and **15b** (*C*-5 addition regioisomer, 304 mg) both as inseparable diastereomeric mixtures.

Method 2. Following the same procedure as described above, treatment of **13b** with the Beau–Skrydstrup reagent **16b**[23] for 10 min at rt gave **14b** and **15b** in 82:18 ratio with a combined yield of 87%.

Major diastereomer of **14b**. Colorless oil. $[\alpha]_D^{20}-5.6$ (*c* 1.0, $CHCl_3$). IR (film) *ν*: 3528, 3364, 2952, 2929, 1651, 1513, 1402, 1246, 1101 cm^{-1}. ^1H NMR (500 MHz, CD_3CN) *δ*: 7.42–7.20 (m, 7H, Ar-H), 6.82–6.78 (m, 2H, Ar-H), 4.64 (d, *J*=15.5 Hz, 1H, NCH_2), 4.49 (d, *J*=15.5 Hz, 1H, NCH_2), 4.44 (d, *J*=11.7 Hz, 1H, OCH_2), 4.26–4.24 (m, 1H, H-5), 4.25 (d, *J*=11.7 Hz, 1H, OCH_2), 3.76 (s, 3H, OCH_3), 3.82 (s, 1H, OH, exchangeable), 3.58 (s, 2H, $BnCH_2O$), 2.56 (ddd, *J*=6.6, 9.5, 17.7 Hz, 1H, H-3), 2.29 (ddd, *J*=5.2, 6.2, 17.7 Hz, 1H, H-3), 2.16–2.10 (m, 1H, H-4), 1.98–1.92 (m, 1H, H-4), 0.96 (s, 9H, *t*-Bu–H), −0.32 (s, 3H, $SiCH_3$), −0.41 (s, 3H, $SiCH_3$). ^{13}C NMR (125 MHz, CD_3CN) *δ*: 171.2 (C═O), 159.2 (Ar), 139.2 (Ar), 133.4 (Ar), 129.4 (Ar), 129.0 (Ar), 128.7 (Ar), 128.6 (Ar), 118.4 (4C, Ar), 114.3 (Ar), 88.0 (C-6), 73.7 (C-5), 71.9 (CH_2O), 70.6 (CH_2O), 55.8 (OCH_3), 44.2 (NCH_2), 28.4 (C-3), 26.2 (C-4), 24.8 (3C, *t*-BuC), 18.7 (SiC), −4.09 ($SiCH_3$), −4.86 ($SiCH_3$). MS (ESI): 486 ($M+H^+$, 100). HRESIMS calcd for ($C_{27}H_{39}NO_5Si+Na$): 508.2495, found: 508.2491.

To a suspension of 10% Pd/C (1.1 g, 30%) in EtOH (5 mL) was added a solution of diastereomeric **14b** (3.811 g, 7.86 mmol) in EtOH (30 mL) under a H_2 atmosphere at rt. After stirring for 8 h, the mixture was filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **19** as an inseparable mixture (2.794 g, yield: 90%).

Major diastereomer of **19**. Colorless solid. Mp 111–112 °C (CH_3OH). $[\alpha]_D^{20}-71.4$ (*c* 1.0, CH_3OH). IR (film) *ν*: 3410, 2956, 2929, 2855, 1625, 1512, 1463, 1246, 1105, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.30–7.20 (m, 2H, Ar-H), 6.84–6.78 (m, 2H, Ar-H), 4.71 (d, *J*=15.5 Hz, 1H, NCH_2), 4.62 (d, *J*=15.5 Hz, 1H, NCH_2), 4.23–4.22 (m, 1H, H-5), 3.80 (s, 3H, OCH_3), 3.61–3.52 (m, 3H, CH_2O and OH), 2.73–2.66 (m, 1H, H-3), 2.47–2.40 (m, 1H, H-3), 2.12–2.07 (m, 1H, H-4), 1.99–1.94 (m, 1H, H-4), 1.92 (br s, 1H, OH), 0.86 (s, 9H, *t*-Bu–H), −0.35 (s, 3H, $SiCH_3$), −0.47 (s, 3H, $SiCH_3$). ^{13}C NMR (125 MHz, CD_3CN) *δ*: 170.9 (C═O), 158.5 (Ar), 131.8 (Ar), 128.1 (2C, Ar), 114.0 (2C, Ar), 87.5 (C-6), 68.2 (CH_2O), 63.7 (C-5), 55.2 (OCH_3), 43.2 (NCH_2), 27.1 (C-3), 25.6 (C-4), 23.9 (3C, *t*-BuC), 17.9 (SiC), −4.4 ($SiCH_3$), −5.3 ($SiCH_3$). MS (ESI): 396 ($M+H^+$, 100). HRESIMS calcd for ($C_{20}H_{33}NO_5Si+Na$): 418.2026, found: 418.2025.

To a mixture of diastereomeric **19** (3.618 g, 9.16 mmol) in anhydrous CH_2Cl_2 (90 mL, 0.1 M) were added dropwise Et_3SiH (14.5 mL, 91.6 mmol) and $BF_3\cdot OEt_2$ (2.8 mL, 23 mmol) at −78 °C under a N_2 atmosphere. The reaction mixture was allowed to warm to rt and stirred for 5–7 h. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/PE) to yield **20** (1.978 g, yield: 57%) as a colorless solid. Mp 108–109 °C ($CHCl_3$). $[\alpha]_D^{20}-66.8$ (*c* 0.7, CH_3OH). IR (film) *ν*: 3409, 2955, 2926, 2855, 1611, 1512, 1463, 1248, 1105, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.22–7.18 (m, 2H, Ar-H), 6.86–6.82 (m, 2H, Ar-H), 5.27 (d, *J*=14.5 Hz, 1H, NCH_2), 4.04 (ddd, *J*=4.2, 4.9, 10.3 Hz, 1H, H-5), 3.96–3.92 (m, 1H, CH_2O), 3.95 (d, *J*=14.5 Hz, 1H, NCH_2), 3.80 (s, 3H, OCH_3), 3.78–3.73 (m, 1H, CH_2O), 3.37 (ddd, *J*=3.4, 4.2, 7.8 Hz, 1H, H-6), 2.91 (br s, 1H, OH), 2.64 (ddd, *J*=3.9, 7.7, 18.2 Hz, 1H, H-3), 2.48 (ddd, *J*=8.0, 8.8, 18.2 Hz, 1H, H-3), 2.14–2.06 (m, 1H, H-4), 1.91–1.85 (m, 1H, H-4), 0.88 (s, 9H, *t*-Bu–H), −0.23 (s, 3H, $SiCH_3$), −0.36 (s, 3H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 169.5 (C═O), 159.1 (Ar), 129.3 (3C, Ar), 114.1 (2C, Ar), 69.7 (OCH_2), 60.7 (C-5), 59.0 (C-6), 55.3 (OCH_3), 47.8 (NCH_2), 28.8 (C-3), 26.2 (C-4), 25.7 (3C, *t*-BuC), 17.9 (SiC), −4.8 ($SiCH_3$), −5.3 ($SiCH_3$). MS (ESI): 380 ($M+H^+$, 100). HRESIMS calcd for ($C_{20}H_{34}NO_4Si+H$): 380.2257, found: 380.2249.

4.1.2. (5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-[(*tert*-butyldimethylsilyloxy)methyl]-1-(4-methoxybenzyl) piperidin-2-one (12a).

To a mixture of *cis*-**20** (1.960 g, 5.17 mmol), imidazole (703 mg, 10.34 mmol) and a catalytic amount of DMAP in anhydrous DMF (15 mL) was added a solution of *tert*-butyldimethylchlorosilane (930 mg, 6.20 mmol) in anhydrous DMF (5 mL). After being stirred at rt for 12 h, water (20 mL) was added, and the mixture was extracted with Et_2O (30 mL×3). The combined organic layers were washed with brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **12a** (2.341 g, yield:92%) as a colorless oil. $[\alpha]_D^{20}-51.9$ (*c* 1.0, $CHCl_3$). IR (film) *ν*: 2954, 2929, 2857, 1650, 1512, 1462, 1250, 1116 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.18 (d, *J*=8.6 Hz, 2H, Ar-H), 6.85 (d, *J*=8.7 Hz, 2H, Ar-H), 5.35 (d, *J*=14.7 Hz, 1H, NCH_2), 3.98 (d, *J*=14.7 Hz, 1H, NCH_2), 3.90 (dd, *J*=4.6, 10.5 Hz, 1H, CH_2O), 3.87–3.84 (m, 2H, H-6 and CH_2O), 3.80 (s, 3H, OCH_3), 3.19 (m, 1H, H-5), 2.62 (ddd, *J*=2.6, 8.2, 18.3 Hz, 1H, H-3), 2.47 (ddd, *J*=8.5, 9.1, 18.3 Hz, 1H, H-3), 2.09–2.01 (m, 1H, H-4), 1.82–1.74 (m, 1H, H-4), 0.92 (s, 9H, *t*-Bu), 0.84 (s, 9H, *t*-Bu), 0.38 (s, 6H, $SiCH_3$), 0.16 (s, 6H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 169.8 (C═O), 158.9 (Ar), 129.8 (Ar), 129.3 (2C, Ar), 113.9 (2C, Ar), 67.7 (C-5), 60.4 (CH_2O), 55.3 (OCH_3), 47.9 (NCH_2), 29.4 (C-5), 27.0 (C-4), 25.8 (3C, *t*-Bu), 25.6 (3C, *t*-Bu), 18.1 ($SiCMe_3$), 17.9 ($SiCMe_3$), −4.9 ($SiCH_3$), −5.2 ($SiCH_3$), −5.6 (2C,

$SiCH_3$). MS (ESI): 494 ($M+H^+$, 100). HRESIMS calcd for ($C_{26}H_{47}NO_4Si_2+Na$): 516.2941, found: 516.2939.

4.1.3. (5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-[(*tert*-butyldimethylsilyloxy)methyl]piperidin-2-one (21). To a solution of **12a** (1.228 g, 2.49 mmol) in CH_3CN (90 mL, 0.025 M) and H_2O (10 mL) was added CAN (6.822 g, 12.45 mmol) in one portion. The mixture was stirred at 0 °C to rt for 4 h. To the resulting mixture was added H_2O (30 mL) and the mixture was extracted with EtOAc (40 mL×3). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ (20 mL×3) and brine (20 mL×2). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **21** (594 mg, yield: 64%) as a colorless oil. $[\alpha]_D^{20}-23.8$ (*c* 0.9, $CHCl_3$). IR (film) *ν*: 3231, 2947, 1652, 1504, 1458, 1246, 1107 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 5.96 (br s, 1H, N-H), 4.06–4.00 (m, 1H, H-5), 3.66–3.59 (m, 2H, OCH_2), 3.43 (ddd, *J*=3.2, 4.0, 8.4 Hz, 1H, H-6), 2.56 (ddd, *J*=6.4, 12.5, 18.1 Hz, 1H, H-3), 2.29 (ddd, *J*=2.1, 5.8, 18.1 Hz, 1H, H-3), 1.94–1.88 (m, 1H, H-4), 1.83–1.77 (m, 1H, H-4), 0.86 (s, 18H, *t*-Bu), 0.32 (s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 171.3 (C=O), 64.3 (C-5), 64.1 (CH_2O), 58.8 (C-6), 28.1 (C-3), 26.4 (C-4), 25.8 (3C, *t*-Bu), 25.6 (3C, *t*-Bu), 18.2 ($SiCMe_3$), 18.0 ($SiCMe_3$), −4.5 ($SiCH_3$), −5.2 ($SiCH_3$), −5.5 (2C, $SiCH_3$). MS (ESI): 374 ($M+H^+$). HRESIMS calcd for ($C_{18}H_{40}NO_3Si_2+H$): 374.2547, found: 374.2538.

4.1.4. *tert*-Butyl [(2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-oxo-piperidin-1-yl] carboxylate (22). To a solution of **21** (242 mg, 0.65 mmol) in anhydrous THF (8 mL) was added *n*-BuLi (1.6 M in hexane, 0.40 mL, 0.63 mmol) at −78 °C. After being stirred at −78 °C for 10 min, a solution of Boc_2O (0.23 mL, 0.97 mmol) in anhydrous THF (2 mL) was added dropwise. After being stirred for 30 min at the same temperature, the mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with EtOAc (10 mL) and brine (5 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **22** (275 mg, yield:90%) as a colorless oil. $[\alpha]_D^{20}+25.8$ (*c* 0.9, $CHCl_3$). IR (film) *ν*: 2954, 2930, 2858, 1775, 1720, 1471, 1367, 1294, 1253, 1160, 1115 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 4.08 (dd, *J*=5.2, 10.4 Hz, 1H, CH_2O), 4.06–4.04 (m, 1H, H-5), 3.90–3.89 (m, 1H, H-6), 3.83 (dd, *J*=4.2, 10.4 Hz, 1H, CH_2O), 2.54–2.42 (m, 2H, H-3), 2.28–2.22 (m, 1H, H-4), 1.77–1.73 (m, 1H, H-4), 1.52 (s, 9H, *t*-Bu–H), 0.96 (s, 9H, *t*-Bu–H), 0.87 (s, 9H, *t*-Bu–H), 0.40 (s, 6H, $SiCH_3$), −0.20 (s, 6H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 171.2 (C=O), 153.1 (C=O), 82.6 (Boc *t*-C), 67.6 (C-5), 59.7 (CH_2O), 59.0 (C-6), 33.0 (C-4), 28.0 (C-3), 25.9 (3C, *t*-Bu–C), 25.7 (3C, *t*-BuC), 25.7 (3C, *t*-BuC), 18.2 ($SiCMe_3$), 18.0 ($SiCMe_3$), −4.6 ($SiCH_3$), −4.9 ($SiCH_3$), −5.8 ($SiCH_3$), −5.9 ($SiCH_3$). MS (ESI): 496 ($M+Na^+$, 100). HRESIMS calcd for ($C_{23}H_{47}NO_5Si_2+Na$): 496.2890, found: 496.2891.

4.1.5. *tert*-Butyl [(2*S*,3*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)-6-oxo-octadecan]-2-yl carbamate (23). To a solution of **22** (105 mg, 0.22 mmol) in anhydrous THF (10 mL) was added *n*-$C_{12}H_{25}MgBr$ (0.289 mmol) at −78 °C. After being stirred for 3 h at −78 °C, the reaction was allowed to warm to −40 °C and stirred for 40 min. The mixture was quenched with a saturated aqueous NH_4Cl (2 mL), diluted with EtOAc (10 mL) and brine (5 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **23** (81 mg) in 70% yield based on the recovered starting **22** (20 mg). Compound **23**: colorless oil. $[\alpha]_D^{20}+8.2$ (*c* 0.9, $CHCl_3$). IR (film) *ν*: 3450, 2927, 2855, 1718, 1491, 1471, 1365, 1254, 1171, 1101 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 4.70 (d, *J*=8.5 Hz, 1H, NH), 3.93 (dd, *J*=5.7, 7.8 Hz, 1H, CH_2O), 3.55–3.53 (m, 2H, CHOTBS and CH_2O), 3.45–3.41 (m, 1H, $NCHCH_2O$), 2.46–2.33 (m, 4H, CH_2COCH_2), 1.77–1.69 (m, 2H), 1.56 (m, 4H), 1.42 (s, 9H, *t*-Bu–H), 1.24 (m, 20H), 0.96 (s, 18H, *t*-Bu–H), 0.40 (s, 6H, $SiCH_3$), −0.2 (s, 6H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 204.6 (C=O) 155.9 (C=O), 79.2 (Boc *t*-C), 69.0 (C–TBS), 61.8 (CH_2O), 53.7 (C–HCH), 43.0 ($COCH_2$), 38.4 ($COCH_2$), 31.9 ($COCH_2CH_2$ CHOTBS), 29.6 (2C), 29.5 (2C), 29.4, 29.3, 29.2, 28.4 (3C, *t*-BuC), 28.0, 25.9 (3C, *t*-BuC), 25.8 (3C, *t*-BuC), 23.9, 22.7, 18.1 (2C, $SiCMe_3$), 14.1 (CH_3), −4.3 ($SiCH_3$), −4.9 ($SiCH_3$), −5.3 ($SiCH_3$), −5.4 ($SiCH_3$). MS (ESI): 644 ($M+H^+$). HRESIMS calcd for ($C_{35}H_{74}NO_5Si_2+H$): 644.5106, found: 644.5094, calcd for (M+Na): 666.4925, found: 666.4903.

4.1.6. (+)-2-*epi*-Deoxoprosopinine (11). Trifluoroacetic acid (1 mL) was added dropwise to **23** (120 mg, 0.187 mmol) at 0 °C, and the resulting solution was stirred at rt for 3 h. To the reaction mixture was added, at 0 °C, a 30% aqueous sodium hydroxide until pH was 11–12. The resulting mixture was extracted with ether (20 mL×3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product, without further purification, was dissolved in EtOH (4 mL), to which was added 20% $Pd(OH)_2/C$ (60 mg) under H_2 atmosphere (1 atm). After being stirred for 2 h, concd HCl (0.4 mL) was added and the mixture was stirred for 28 h. The reaction mixture was filtered, washed with MeOH, and concentrated in vacuum. The residue was dissolved in water (5 mL) and extracted with ether (6 mL). The aqueous layer was basified by addition of 1 N NaOH solution and extracted thoroughly with $CHCl_3$ (10 mL×5). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/$NH_3\cdot H_2O$ 100:15:2) to give **11** (28 mg, yield:51%) as a colorless solid. Mp 56–57 °C (Et_2O/MeOH) [lit.[18]mp 59 °C (acetone/pentane)]. $[\alpha]_D^{20}+3.0$ (*c* 0.6, CH_3OH) {lit.[18] $[\alpha]_D^{26}+2.7$ (*c* 1.0, CH_3OH)}. IR (film) *ν*: 3341, 3239 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) *δ*: 3.84–3.82 (m, 1H, H-3), 3.67–3.60 (m, 2H, CH_2OH), 2.76–2.74 (m, 1H, H-2), 2.62–2.58 (m, 1H, H-6), 1.91–1.86 (m, 1H, H-4), 1.64–1.38 (m, 3H, H-4 and H-5), 1.39–1.22 (m, 22H), 0.89 (t, *J*=6.7 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, CD_3OD) *δ*: 66.2 (C-3), 64.7 (CH_2OH), 61.1 (C-2), 56.9 (C-6), 36.8, 31.9, 31.8, 29.7–29.4 (7C), 26.2, 25.8, 22.7,

14.1. MS (ESI): ($M+H^+$, 100). HRESIMS calcd for ($C_{18}H_{37}NO_2+H$): 300.2903, found: 300.2922.

4.1.7. (5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-[(*tert*-butyldimethylsilyloxy)methyl]-1-(4-methoxybenzyl)-5,6-dihydropyridin-2(1*H*)-one (26). To a freshly prepared solution of LDA (0.34 mmol, 1.4 mL THF) was added dropwise a solution of **12a** (80 mg, 0.23 mmol) in THF (0.8 mL) at −78 °C, and the mixture was stirred at the same temperature for 1.5 h. To the resulting mixture was added a THF solution (0.8 mL) of PhSeBr (76 mg, 0.32 mmol), and the mixture was stirred at −78 °C for 5 h. The mixture was poured into a saturated aqueous $NaHCO_3$ (2 mL) and extracted with EtOAc (4 mL×3). The combined organic layers were washed successively with water (3 mL×2) and brine (3 mL×2), dried over Na_2SO_4, filtered and concentrated in vacuum. To a solution of the residue in wet CH_2Cl_2 (4 mL containing 0.01 mL of H_2O) was added a solution of 30% H_2O_2 (0.06 mL, 0.49 mmol). After stirred for 1 h, a second portion of H_2O_2 (0.45 mL, 3.69 mmol) was added and the stirring was continued for another 1 h. The resulting mixture was quenched with water (2 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 mL×3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **26** (45 mg, yield: 58%) as a colorless oil. $[\alpha]_D^{20}+4.5$ (*c* 1.1, $CHCl_3$). IR (film) *ν*: 2957, 2926, 2854, 1677, 1607, 1506, 1252 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.20–6.80 (m, 5H, Ar-H), 6.15 (d, *J*=10.0 Hz, 1H, H-3), 5.76 (dd, *J*=2.2, 10.0 Hz, 1H, H-4), 5.41 (d, *J*=14.8 Hz, 1H, NCH_2), 4.60–4.56 (m, 1H, H-5), 3.98 (d, *J*=14.8 Hz, 1H, NCH_2), 3.97–3.89 (m, 2H, CH_2O), 3.76 (s, 3H, OCH_3), 3.38–3.33 (m, 1H, H-6), 0.87 (s, 9H, *t*-Bu), 0.78 (s, 9H, *t*-Bu), 0.01 (s, 6H, $SiCH_3$), −0.09 (s, 6H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 163.0 (C=O), 158.9 (Ar), 143.2 (C-4), 130.6 (Ar), 129.4 (2C), 123.7 (C-3), 113.9 (Ar) 67.7 (C-5), 61.5 (CH_2O), 60.8 (C-6), 55.3 (OCH_3), 48.7 (NCH_2), 25.9 (3C, *t*-Bu), 25.6 (3C, *t*-Bu), 18.2 ($SiCMe_3$), 18.0 ($SiCMe_3$), −5.2 ($SiCH_3$), −5.4 ($SiCH_3$), −5.6 (2C, $SiCH_3$). HRESIMS calcd for ($C_{26}H_{46}NO_4Si_2+H$): 492.2965, found: 492.2962.

4.1.8. (3*S*,4*R*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-[(*tert*-butyldimethylsilyloxy)methyl]-3,4-dihydroxy-1-(4-methoxybenzyl)piperidin-2-one (27). To a solution of **26** (28 mg, 0.08 mmol) and *N*-methylmorpholine *N*-oxide (NMMO, 10 mg, 0.32 mmol) in *t*-BuOH (1.6 mL) was added a solution of OsO_4 (3 mg, 0.01 mmol) in water (0.4 mL) at rt. After stirring for 3 h, the mixture was quenched with an excess of solid Na_2SO_3. The solvent was removed under reduced pressure until the color of the reaction mixture began to turn gray. The mixture was diluted with MeOH, filtered and washed successively with CH_2Cl_2 and MeOH (10 mL×3). The crude product was purified by chromatography on silica gel (EtOAc/PE) to give **27** (23 mg, yield: 75%) as a colorless oil. $[\alpha]_D^{20}-47.7$ (*c* 1.9, $CHCl_3$). IR (film) *ν*: 3409, 2952, 2926, 2851, 1645, 1513, 1470, 1252, 1108 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.18–6.83 (m, 5H, Ar-H), 5.13 (d, *J*=15.0 Hz, 1H, NCH_2), 4.50 (d, *J*=4.8 Hz, 1H, H-3), 4.21 (d, *J*=15.0 Hz, 1H, NCH_2), 4.15 (dd, *J*=4.8, 5.7 Hz, 1H, H-5), 3.99 (dd, *J*=4.8, 4.8 Hz, 1H, H-4), 3.83 (dd, *J*=6.0, 10.7 Hz, 1H, CH_2O), 3.80–3.75 (m, 1H, H-6), 3.57 (dd, J=5.5, 10.7 Hz, 1H, CH_2O), 0.90 (s, 9H, *t*-Bu–H), 0.86 (s, 9H, *t*-Bu–H), 0.22 (s, 6H, $SiCH_3$), −0.20 (s, 6H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 172.0 (C=O), 158.9 (Ar), 128.8 (2C, Ar), 128.4 (Ar), 114.0 (2C, Ar), 70.9, 70.3, 67.1, 60.9, 59.3, 55.3, 47.9, 25.8 (3C, *t*-Bu), 25.7 (3C, *t*-Bu), 18.2 ($SiCMe_3$), 17.9 ($SiCMe_3$), −4.7 ($SiCH_3$), −5.4 ($SiCH_3$), −5.5 ($SiCH_3$), −5.5 ($SiCH_3$). HRESIMS calcd for ($C_{26}H_{48}NO_6Si_2+H$): 526.3020, found: 526.3010.

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