# A Straightforward Route to Indolizidine and Quinolizidine Analogs as new Potential Antidiabetics

Christine Gravier-Pelletier, William Maton, Yves Le Merrer*

Université René Descartes, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, CNRS UMR 8601, 45 rue des Saints-Pères, 75270 Paris Cedex 06, France
Fax +33(1)42868387; E-mail: Yves.Le-Merrer@biomedicale.univ-paris5.fr
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**Abstract:** New polyhydroxylated indolizidine and quinolizidine analogs of castanospermine are efficiently obtained by a double reductive amination of enantiopure cyclic ketoaldehydes. As rigidified mimics of disaccharides, these compounds are expected to exhibit significant antidiabetic properties.

**Key words:** glycosidases, alkaloids, carbocycles, bicyclic compounds, reductive amination

Our field of investigations concerns α-glucosidase inhibitors. The activity of acarbose,[1] voglibose[2] or miglitol[3] has already been demonstrated as inhibitors of intestinal digestive enzymes (Figure 1) and these compounds were approved to treat non-insulinodependant *mellitus diabetes* in humans.[4] Both the naturally occurring voglibose and acarbose are believed, in the same way as other carbohydrate mimics such as polyhydroxylated piperidines (like miglitol), pyrrolidines, indolizidines and pyrrolizidines, to mimic the charge of the presumed transition state for enzymatic glycoside hydrolysis, due to the protonation of their nitrogen atom in the enzyme active site.

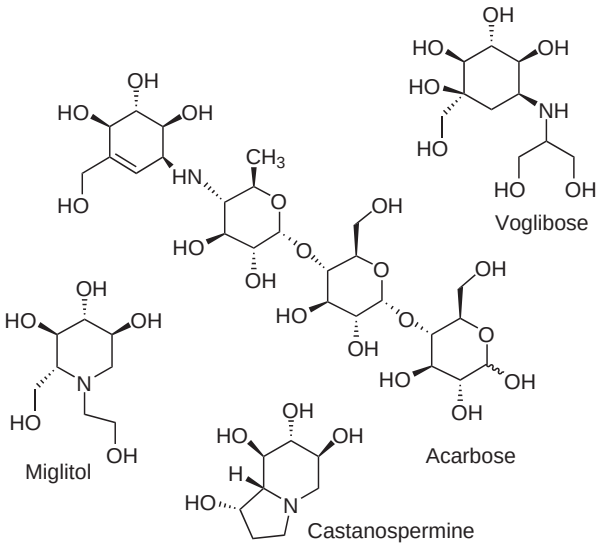


**Figure 1** Inhibitors of α-glucosidases.

If considerable synthetic efforts have been devoted to the synthesis of iminosugar analogs[5] and have sometimes shown interesting inhibitory activity,[6] to our knowledge, no indolizidine or quinolizidine analogs such as **1** and **2** (Figure 2) have ever been evaluated as potential glycosidase inhibitors. Furthermore, compounds **1** and **2** (polyhydroxy-octahydroindole and -decahydroquinoline, respectively) display a structure related to that encountered in castanospermine[5] which is a powerful inhibitor of α-glucosidase. So, taking advantage of the strategy that we recently described[7] towards the efficient carbocyclisation of D-*manno* or L-*ido* bis-epoxide readily obtained from D-mannitol, our retrosynthetic analysis is outlined in Figure 2.

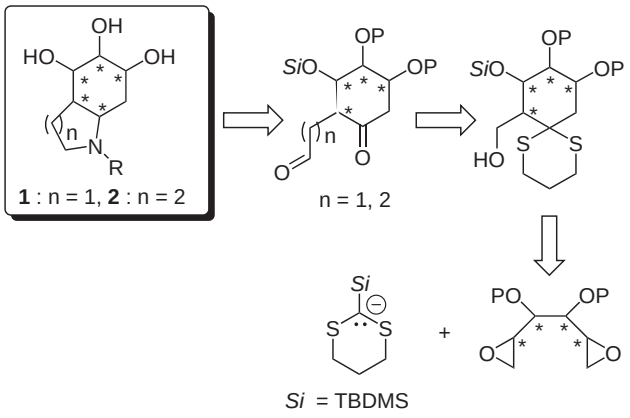


**Figure 2** Retrosynthetic analysis.

The key steps involve a one-pot tandem alkylation-cyclization of $C_2$-symmetrical L-*ido*-bis-epoxide leading to a polyhydroxy cyclohexanone masked as its dithioketal, followed by formal homologation with one or two carbon atom moieties to give the corresponding aldehyde. After dithioketal hydrolysis, a double reductive amination of the resulting 1,4- or 1,5-dicarbonyl compound achieves the construction of the structural skeleton. To reach an absolute configuration at chiral carbon atoms of the targeted compounds as close as possible to that of castanospermine, the 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-L-iditol **3** (Scheme 1) has been chosen as starting material.

We previously showed that carbocyclization could be directed to the major formation of either dithioketal of polyhydroxy-cycloheptanone or -cyclohexanone depending on the nature of the protective group for the central diol of

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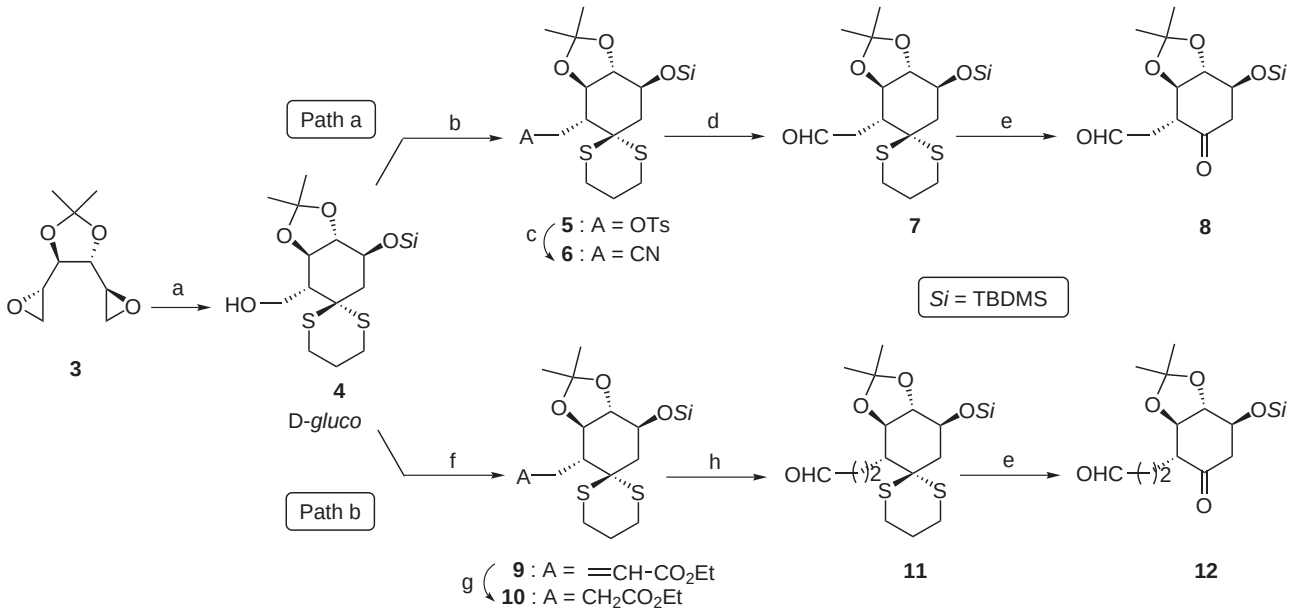
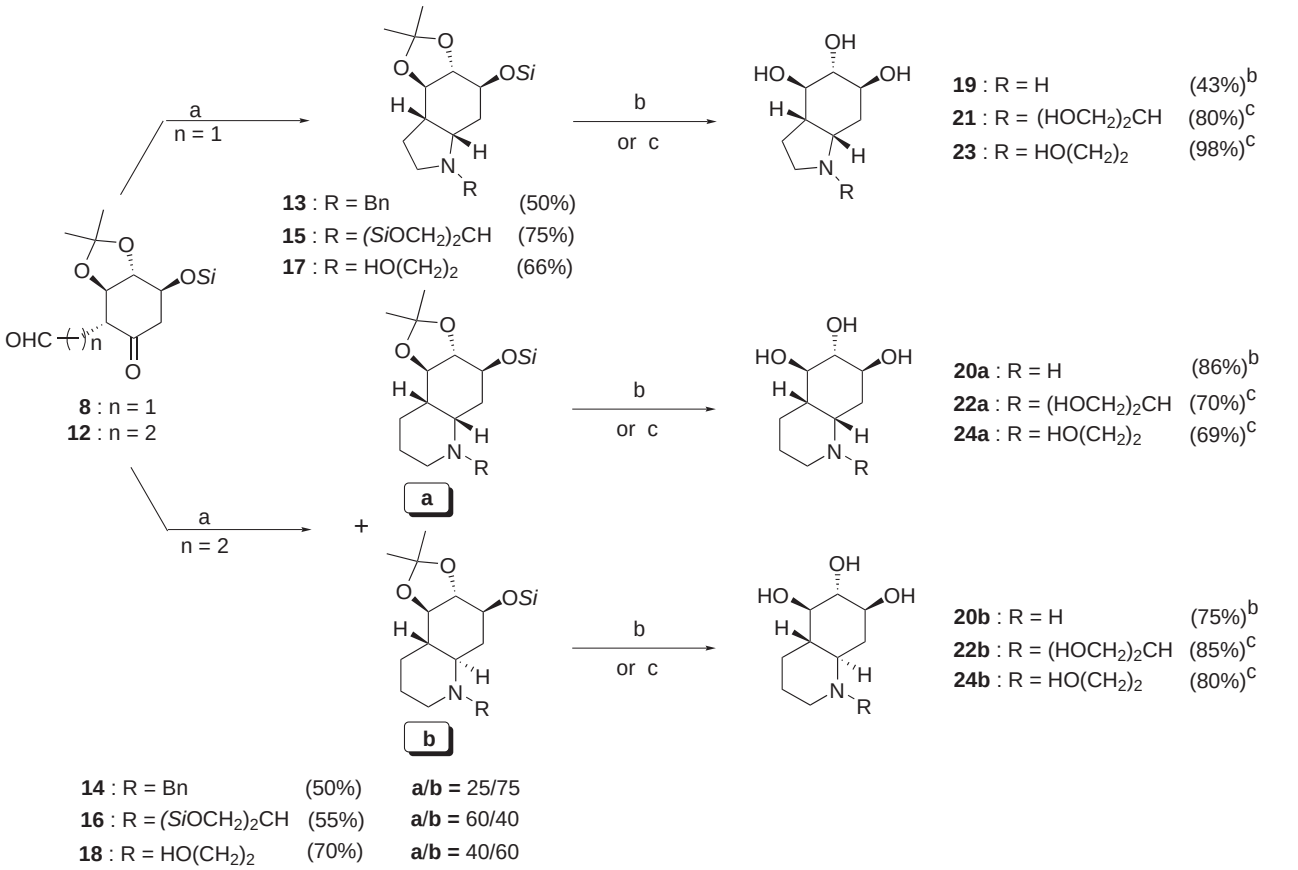



**Scheme 1** *Reagents and conditions*: (a) 2-*tert*-Butyldimethylsilyl-1,3-dithiane, THF–HMPA, 9:1, *tert*-BuLi, –78 °C to –30 °C, then **3**, 15 min, 72%; (b) TsCl, DMAP, $Et_3N$, $CH_2Cl_2$, 98%; (c) NaCN, DMSO, 90 °C, 92%; (d) DIBAL-H, toluene, –78 °C, 78%; e) NBS, $(CH_3)_2CO$, $H_2O$, –50 °C, 75%; (f) *i.* DMSO, $SO_3$, pyridine, $Et_3N$, $CH_2Cl_2$; *ii.* $(EtO)_2POCH_2CO_2Et$, *t*-BuOK, –78 °C, THF, 71% from **4**; (g) $TsNHNH_2$, NaOAc, THF:$H_2O$, 80 °C, 93%; (h) DIBAL-H, hexane, –78 °C, 60%.

the bis-epoxide.[7] Thus, condensation of the *tert*-butyllithium generated lithio derivative of 2-*tert*-butyldimethylsilyl-1,3-dithiane on the L-*ido*-bis-epoxide **3**, in THF:HMPA 9:1 at –30 °C (Scheme 1) led to the expected major formation of the D-*gluco*-cyclohexanone derivative **4** (72% yield).[8]

According to the preparation of either indolizidine **1** or quinolizidine **2** analogs (path a or b), the primary alcohol function of the common intermediate **4** was transformed by elongation with one or two carbon atoms into the ketoaldehyde **8** or **12**, respectively. The preparation of aldehyde **7** (path a) involved activation of the hydroxy group of **4** as tosylate **5** (98%), followed by substitution with sodium cyanide to afford nitrile **6**. Subsequent reduction by DIBAL-H at –78 °C led to the expected aldehyde **7** (78%). Finally, hydrolysis of the dithioketal moiety by *N*-bromosuccinimide in acetone–$H_2O$[9] at –50 °C gave the ketoaldehyde **8** (75%). On the other hand, ketoaldehyde **12** (path b) was obtained by oxidation of the alcohol function of **4** by $SO_3$–pyridine followed by a Wittig type reaction with the anion of triethylphosphonoacetate generated by potassium *tert*-butoxide to afford the corresponding α,β-ethylenic ester **9** (71% overall yield). Due to the presence of sulphur atoms in compound **9** the selective reduction of its double bond was troublesome and required careful choice of experimental conditions. Thus, neither the hydrogenation done in the presence of Wilkinson's catalyst (20 °C, toluene[10] or P = 6 bar, 60 °C[11] or benzene–EtOH, P = 6 bar, 60 °C[12]), nor heterogeneous hydrogenation (Pd black, EtOH, 20 °C) or rhodium on alumina (EtOAc, 20 °C)[13] gave any expected product. Both reduction involving copper(I) hydride cluster {[$(Ph_3P)CuH]_6$, $PhCH_3$, 0 °C}[14] or magnesium turnings (MeOH, reflux)[15] were ineffective and sodium borohydride in the presence of lithium iodide (MeOH, reflux)[16] only afforded the methyl ester resulting from transesterification. To overcome this difficulty, we finally demonstrated that tosylhydrazide in THF at 80 °C followed by slow addition of sodium acetate in $H_2O$[17] cleanly furnished the saturated ester **10** (93%). Then, reduction with DIBAL-H afforded the aldehyde **11** (60%) and the ketoaldehyde **12** was obtained under the same conditions as previously (75%).

We next turned to the further transformation of ketoaldehydes **8** and **12** (Scheme 2), which involved a double reductive amination at the origin of indolizidine or quinolizidine analogs, respectively. For example, treatment of **8** in methanol at 0 °C with sodium cyanoborohydride and benzylamine–acetic acid (1 equiv) in methanol[18] afforded the expected indolizidine analog **13** (50%).[19] $^1H$ and $^{13}C$ NMR analysis established without ambiguity firstly, the absence of epimerization during the reaction and secondly, the formation of a single stereoisomer displaying a *cis* relationship at the ring junction ($J_{7a,3a}$ = ca. 4.4 Hz). Finally, hydrogenolysis of the N-benzyl bond in the presence of palladium hydroxide followed by acidic hydrolysis of both acetonide and silyl ether in trifluoroacetic acid–$H_2O$ (9:1) and subsequent purification by ion exchange chromatography led to the desired indolizidine analog **19** (43%). Taking advantage of the late introduction of the primary amine, in order to target bicyclic analogs of voglibose and miglitol, we performed the same sequence of reactions with the O-persilylated serinol derivative and with ethanolamine, as aglycon part. Thus, the respective N-substituted bicyclic




**Scheme 2** *Reagents and conditions*: (a) $NaBH_3CN$ (2 equiv), MeOH, 0 °C then $RNH_2$·HOAc (1 equiv), MeOH, 0 °C to 20 °C; (b) *i*. $H_2$, $Pd(OH)_2$, EtOH, 20 °C; *ii*. TFA–$H_2O$, 9:1; (c) TFA–$H_2O$, 9:1.

compounds **21** and **23** have been obtained by double reductive amination (75% and 66%, respectively) and acidic hydrolysis (80% and 98%, respectively).

In a similar manner, access to the quinolizidine-like analogs **20**, **22** and **24** has been carried out from the ketoaldehyde **12**. It should be noted that, in the latter cases, the double reductive amination led to a mixture of two epimers at the bicyclic junction, which were easily separated by flash chromatography, and for which the *cis*/*trans* ratio varied from 25/75 to 60/40 in 50 to 70% yield ($J_{4a,8a}$ = ca. 3.2 and 12.8 Hz for the *cis* and *trans* isomer, respectively). Then complete deprotection of the corresponding polyhydroxy decahydroquinoline was carried out under similar conditions as above to afford **20ab**, **22ab**, **24ab** in good yields.

In summary, various enantiopure indolizidine and quinolizidine analogs (**19**–**24**) were obtained in a straightforward manner via a double reductive amination of a dicarbonyl compound. The latter was resulting from the formal one- or two-carbon atom elongation of the lateral primary alcohol function of a polyhydroxycyclohexanone easily available from D-mannitol via a tandem alkylation–cyclization reaction. According to the strategy, the analogues of indolizidine and quinolizidine have been either N-substituted with the aglycon part of voglibose or miglitol, two compounds used in diabetes treatment or unsubstituted to serve as a reference concerning the eventual biological effect of N-substitution of such derivatives. The biological activity of these new compounds was tested on various glycosidases such as α-D-glucosidase from *Bacillus stearothermophilus*, β-D-glucosidase from almonds, α-D-mannosidase from Jack beans, and α-L-fucosidase from bovine kidney. Among them, only compounds **22a** and **22b** exhibited significative activity (18 and 70 μM, respectively) on α-L-fucosidase. Further evaluations of potential activity of all these compounds towards digestive enzymes are now under progress and will be reported later on.

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(12) In this case, an unexpected lactone, resulting from double bond reduction followed by transketalization and subsequent lactonization, was isolated in a non-reproducible 63% yield (Figure 3).

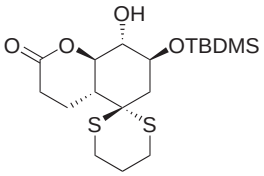


**Figure 3**

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(18) Manescalchi, F.; Nardi, A. R.; Savoia, D. *Tetrahedron Lett.* **1994**, *35*, 2775.
(19) **Typical Procedure for the Double Reductive Amination:** To a solution of ketoaldehyde **8** or **12** (387 μmol) in methanol (1 mL), at 0 °C, were successively added sodium cyanoborohydride (753 μmol, 1.9 equiv) and a mixture of primary amine (387 μmol, 1 equiv) and HOAc (387 μmol, 1 equiv) in MeOH (400 μL). After 24 h stirring at 20 °C and concentration in vacuo, a 10% aq solution of NaOH was added and the mixture was extracted with $CH_2Cl_2$. The combined organic layers were dried (anhyd $Na_2SO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue afforded the indolizidine or quinolizidine analog in yield ranging from 50% to 75% according to the ketoaldehyde and to the primary amine involved. Selected physical data for compounds **15**, **16a** and **16b** ($[\alpha]_D^{20}$ in $CH_2Cl_2$ $^1$H NMR [250 MHz unless indicated, δ (ppm), *J* (Hz) and $^{13}$C NMR (62.5 MHz, δ(ppm)] in $CDCl_3$. Hydrogen and carbon atoms of the heterocycle have been numbered according to the IUPAC nomenclature rules, and for the *N*-side chain by A, B and C:
**15**: $[\alpha]_D^{20}$ +24.5 (*c* 1.1). $^1$H NMR (500 MHz): δ = 3.89 (ddd, 1 H, $J_{6,7'}$ = 9.5 Hz, $J_{6,5}$ = 9.2 Hz, $J_{6,7}$ = 5.0 Hz, $H_6$), 3.75 (dd, 1 H, $J_{A,A'}$ = 10.4 Hz, $J_{A,B}$ = 6.2 Hz, $H_A$), 3.72 (dd, 1 H, $J_{A',A}$ = 10.4 Hz, $J_{A',B}$ = 5.0 Hz, $H_{A'}$), 3.60 (dd, 1 H, $J_{C,C'}$ = 10.0 Hz, $J_{C,B}$ = 5.9 Hz, $H_C$), 3.57 (dd, 1 H, $J_{C',C}$ = 10.0 Hz, $J_{C',B}$ = 6.4 Hz, $H_{C'}$), 3.44 (dd, 1 H, $J_{4,3a}$ = 10.0 Hz, $J_{4,5}$ = 9.2 Hz, $H_4$), 3.36 (ddd, $J_{7a,3a} = J_{7a,7'}$ = 4.4 Hz, $J_{7a,7}$ = 2.9 Hz, 1 H, $H_{7a}$), 3.26 (dd, 1 H, $J_{5,6} = J_{5,4}$ = 9.2 Hz, $H_5$), 2.97–2.87 (m, 2 H, $H_{B,2'}$), 2.83 (ddd, 1 H, $J_{2,2'}$ = 14.8 Hz, $J_{2,3'}$ = 9.4 Hz, $J_{2,3}$ = 5.6 Hz, $H_2$), 2.15 (ddd, 1 H, $J_{7,7'}$ = 14.2 Hz, $J_{7,6}$ = 5.0 Hz, $J_{7,7a}$ = 2.9 Hz, $H_7$), 2.13–2.06 (m, 1 H, $H_{3a}$), 1.86–1.73 (m, 2 H, $H_{3,3'}$), 1.42 (ddd, 1 H, $J_{7',7}$ = 14.2 Hz, $J_{7',6}$ = 9.5 Hz, $J_{7',7a}$ = 4.4 Hz, $H_{7'}$), 1.38, 1.36 (2 s, 6 H, $CMe_2$), 0.88 (s, 27 H, *t*-Bu), 0.05 (s, 18 H, $SiMe_2$). $^{13}$C NMR: δ = 109.1 ($CMe_2$), 83.9 ($C_5$), 79.1 ($C_4$), 69.4 ($C_6$), 63.3, 59.3 ($C_{A,C}$), 60.7, 59.4 ($C_{7a,B}$), 44.9 ($C_2$), 41.9 ($C_{3a}$), 35.3 ($C_7$), 29.7 ($C_3$), 27.0 ($CMe_2$), 25.9, 18.3, 18.2 (*t*-Bu), –4.5, –4.8, –5.4 ($SiMe_2$). HRMS (CI, $CH_4$) calcd for $C_{32}H_{68}NO_5Si_3$ [$M^+$ + 1]: 630.4405. Found: 630.4393.
**16a**: $[\alpha]_D^{20}$ +14 (*c* 1.0). $^1$H NMR: δ = 4.12 (dd, 1 H, $J_{5,4a}$ = 11.1 Hz, $J_{5,6}$ = 9.1 Hz, $H_5$), 3.95 (ddd, 1 H, $J_{7,8}$ = 11.0 Hz, $J_{7,6}$ = 9.0 Hz, $J_{7,8'}$ = 3.8 Hz, $H_7$), 3.72 (dd, 1 H, $J_{A',A}$ = 10.3 Hz, $J_{A',B}$ = 6.9 Hz, $H_{A'}$), 3.56 (dd, 1 H, $J_{A,A'}$ = 10.3 Hz, $J_{A,B}$ = 4.6 Hz, $H_A$), 3.60–3.49 (m, 2 H, $H_{C,C'}$), 3.24 (dd, 1 H, $J_{6,7} = J_{6,5}$ = 9.0 Hz, $H_6$), 3.20–3.10 (m, 1 H, $H_B$), 3.06 (ddd, 1 H, $J_{8a,4a} = J_{8a,8} = J_{8a,8'}$ = ca. 3.2 Hz, $H_{8a}$), 2.93–2.77 (m, 1 H, $H_2$), 2.39 (ddd, 1 H, $J_{8,8'}$ = 14.7 Hz, $J_{8,7} = J_{8,8a}$ = 3.2 Hz, $H_8$), 2.26 (ddd, 1 H, $J_{2',2} = J_{2',3'}$ = 11.5 Hz, $J_{2',3}$ = 1.9 Hz, $H_{2'}$), 2.04–1.85 (m, 1 H, $H_4$), 1.81–1.53 (m, 3 H, $H_{4a,3,3'}$), 1.52–1.40 (m, 1 H, $H_{4'}$), 1.38 (s, 6 H, $CMe_2$), 1.40–1.34 (m, 1 H, $H_{8'}$), 0.88, 0.87 (2 s, 27 H, *t*-Bu), 0.09, 0.08, 0.06, 0.04, 0.02 (s, 18 H, $SiMe_2$). $^{13}$C NMR: δ = 108.7 ($CMe_2$), 85.4 ($C_6$), 74.9 ($C_5$), 68.6 ($C_7$), 62.9 ($C_A$), 59.8 ($C_B$), 59.4 ($C_C$), 58.8 ($C_{8a}$), 47.8 ($C_2$), 40.0 ($C_{4a}$), 37.5 ($C_8$), 30.2 ($C_3$), 27.1, 26.9 ($CMe_2$), 25.9, 18.2 (*t*-Bu), 22.0 ($C_4$), –4.4, –4.7, –5.4, –5.6 ($SiMe_2$). HRMS (CI, $CH_4$) calcd for $C_{33}H_{70}NO_5Si_3$ [$M^+$ + 1]: 644.4562. Found: 644.4556.
**16b**: $[\alpha]_{Hg,\ 365}^{20}$ +5 (*c* 1.0). $^1$H NMR: δ = 3.75 (dd, 1 H, $J_{A',A}$ = 10.4 Hz, $J_{A',B}$ = 8.2 Hz, $H_{A'}$), 3.71 (dd, 1 H, $J_{A,A'}$ = 10.4 Hz, $J_{A,B}$ = 4.6 Hz, $H_A$), 3.81–3.66 (m, 1 H, $H_7$), 3.59 (dd, 1 H, $J_{C,C'}$ = 10.0 Hz, $J_{C,B}$ = 5.3 Hz, $H_C$), 3.53 (dd, 1 H, $J_{C',C}$ = 10.0 Hz, $J_{C',B}$ = 7.4 Hz, $H_{C'}$), 3.32 (dd, 1 H, $J_{6,7} = J_{6,5}$ = 9.1 Hz, $H_6$), 3.27–3.14 (m, 1 H, $H_B$), 2.97 (dd, 1 H, $J_{5,6}$ = 10.8 Hz, $J_{5,4a}$ = 9.1 Hz, $H_5$), 2.91–2.80 (m, 1 H, $H_2$), 2.48 (ddd, 1 H, $J_{8a,4a}$ = 12.8 Hz, $J_{8a,8'}$ = 9.0 Hz, $J_{8a,8}$ = 4.0 Hz, $H_{8a}$), 2.45–2.31 (m, 2 H, $H_{2',8}$), 2.04–1.90 (m, 1 H, $H_4$), 1.69–1.54 (m, 1 H, $H_3$), 1.50–1.39 (m, 2 H, $H_{4a,3'}$), 1.37, 1.36 (2 s, 6 H, $CMe_2$), 1.31–1.20 (m, 1 H, $H_{8'}$), 1.07–0.93 (m, 1 H, $H_{4'}$), 0.88, 0.87 (2 s, 27 H, *t*-Bu), 0.08, 0.07, 0.03, 0.02 (s, 18 H, $SiMe_2$). $^{13}$C NMR: δ = 111.3 ($CMe_2$), 84.2 ($C_6$), 79.9 ($C_5$), 70.3 ($C_7$), 64.2 ($C_A$), 61.4 ($C_B$), 60.6 ($C_C$), 59.2 ($C_{8a}$), 48.1 ($C_2$), 44.5 ($C_{4a}$), 38.6 ($C_8$), 28.5 ($C_3$), 27.0 ($CMe_2$), 25.9, 18.2 (*t*-Bu), 25.6 ($C_4$), –4.4, –4.9, –5.3, –5.4, –5.6 ($SiMe_2$). HRMS (CI, $CH_4$) calcd for $C_{33}H_{70}NO_5Si_3$ [$M^+$ + 1]: 644.4562. Found: 644.4570.