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Creation of quaternary stereocentres: synthesis of new polyhydroxylated indolizidines

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Abstract—(6*R*,7*S*,8a*R*)- and (6*S*,7*R*,8a*R*)-8a-*tert*-butyldimethylsilyloxymethyl-6,7-dihydroxy-indolizidin-3-ones **14** and **15** were synthesized from bicyclic silyloxypyrrole **2** by the selective formation of a quaternary stereogenic centre and a ring-closing metathesis as the main steps. They were converted into new polyhydroxyindolizidines **20** and **21** with high diastereoselectivity.

1. Introduction

The synthesis of several polyhydroxyindolizidine alkaloids has been the subject of intense investigation due to their important biological properties and, particularly, their ability to inhibit glycosidases.[1] Furthermore, a wide range of structural analogues have also been synthesized to be evaluated as selective inhibitors and potential therapeutic agents.[2] However, among these synthetic hydroxylated indolizidines, only a few structures contain a quaternary carbon at the α-position to the nitrogen at the ring junction.[3–8] The methodologies developed for their construction include the creation of the quaternary centre by C–C bond formation through alkylation[3] and aldol[4] reactions of *tert*-butyl α-aminoester derivatives, or through nucleophilic addition to *N*-acyliminium ions.[6–8] In the case involving a bicyclic tertiary iminium ion, its trapping has been accomplished by an intramolecular nucleophilic species.[6]

In connection with our previous work using bicyclic silyloxypyrrole **2** to stereoselectively introduce nucleophilic species at C-5,[9–12] we here report the synthesis of new indolizidines of type **1** bearing a hydroxymethyl group at the ring junction, through ring-closure metathesis as the key step to form the six-membered ring.

2. Results and discussion

2.1. Synthesis

(*R*)-Silyloxypyrrole **2** prepared from inexpensive (*S*)-pyroglutaminol, as previously described,[12] was used as starting material to investigate the validity of the retrosynthetic route depicted in Scheme 1.

It was envisaged that (8a*R*)-6,7-dihydroxy-8a-hydroxymethyl-indolizidines **1** was formed by the reduction of the γ-lactam carbonyl of **3**, which could result from the *cis*-dihydroxylation of **4**. Compound **4** could be generated by the ring-closing metathesis of 1,5-diallyl-derivative **5**. This intermediate could in turn be prepared from bicyclic 5-allyl-lactam **6** derived from silyloxypyrrole **2**.

It is noteworthy that, in the literature, only a few examples of external *C*-nucleophile addition to tertiary *N*-acyliminium ions at a ring junction have been described.[13–15] Starting from **2**, we developed a new and simple access, in one step, to bicyclic 5-hydroxylactam **7**, which acts as a precursor to a trisubstituted acyliminium ion (Scheme 2).[9,12] The formation of **7** was the result of a double protonation at C-7 and C-6, followed by trapping the *N*-acyliminium ion thus obtained by the

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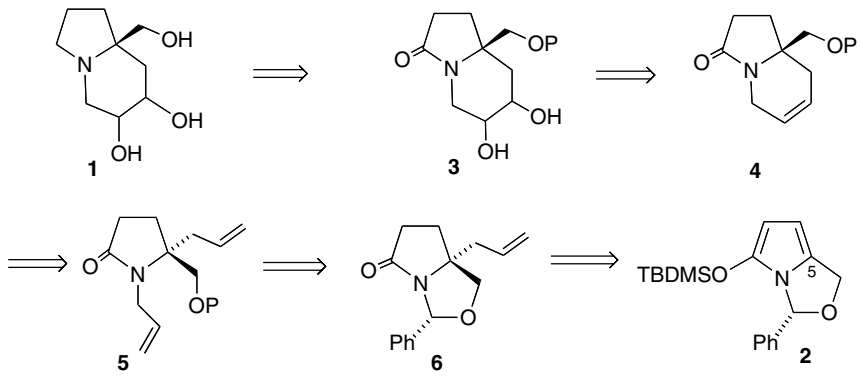
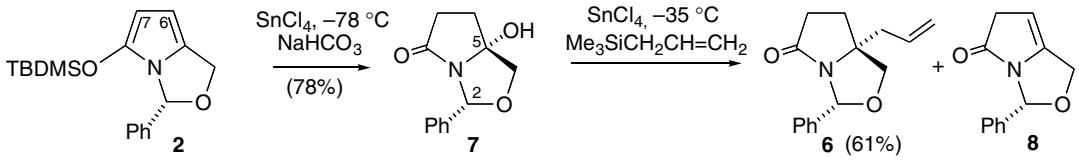


Scheme 1.



Scheme 2.

nucleophile. This probably occurred during the hydrolysis of the complex between silyloxypyrrole **2** and $SnCl_4$ with aqueous $NaHCO_3$. The configurations of **7** have been ascertained by X-ray analysis,[16a] and semiempirical RHF/AM1 calculations have been performed to explain the complete facial stereoselectivity of the hydroxide anion addition to this flattened iminium ion: at the approach of the nucleophile, the molecule becomes convex and this conformation decreases the steric hindrance of the phenyl group.[16b]

In turn, starting from **7**, the subsequent stereoselective addition of *C*-nucleophiles at C-5, and particularly of an allyl group, to form the quaternary centre of enantiomerically pure bicyclic 5-allyllactam **6**, was accomplished as shown in Scheme 2, compared to the addition of trimethylsilyl cyanide in several syntheses.[10–12]

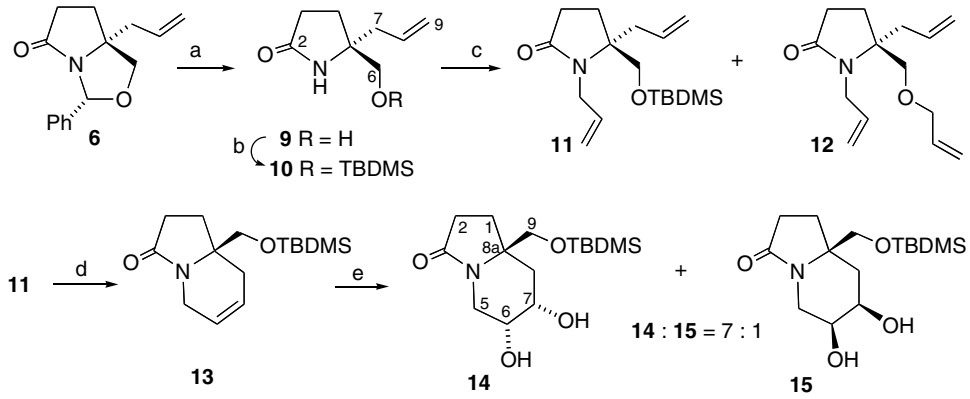
Accordingly, the addition of allyltrimethylsilane to a dichloromethane solution of (2*R*,5*R*)-5-hydroxy-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane-8-one **7** was performed at −35 °C in the presence of $SnCl_4$ (2 equiv) to give only one diastereomer **6** (61%), together with starting **7** (12%) and β,γ-unsaturated lactam **8** (ca. 10%). The configuration of the newly created quaternary centre in **6** was postulated to be (5*R*) on the basis of the facial stereoselectivity observed for **7**, and of the high H-2 chemical shift in the ^1H NMR spectrum of **6** ($CDCl_3$, 6.34 ppm). As observed by Nagasaka and Imai,[17] examination of molecular models indicated that the anisotropy of the lactam carbonyl deshields the *endo* C-2 proton and explained this high chemical shift. Furthermore, the stability of **6** supports this assignment. In structurally related compounds, diastereomers with an opposite configuration at C-5 are unstable, probably due to steric congestion induced by the *endo* aromatic group;[17,18] the configuration assigned to **6** was corroborated by the following synthesis.

The oxazolidine ring of **6** was hydrolyzed in high yield with trifluoroacetic acid in a mixture of THF–H_2O (1:1) at 45 °C to furnish **9** (91%). Pyrrolidinone **9** was then *O*-protected before the *N*-allylation. The first attempts at preparing the corresponding benzoate led to poor results, owing to the low reactivity of this primary alcohol towards selective *O*-benzoylation, whereas the *tert*-butyldimethylsilyl derivative **10** could be obtained in 90% yield. A classical *N*-allylation (NaH–KI in THF) gave rise to **11** (70%) and some recovered starting material **10** (18%). A tri-allylated by-product **12** was also isolated in small amounts (4%), probably as a result of the desilylation of **10** by the sodium amide, followed by subsequent *O*-allylation.[19]

Ring-closing metathesis reactions have been widely used to prepare *N*-heterocycles,[20,21] including RCM of 5-alkyl-1,5-diallylpyrrolidin-2-ones in the presence of first generation Grubbs' catalyst to form the six-membered ring of 8a-alkylindolizidinones.[7,8] In our case, the more active second generation Grubbs' catalyst (4.5%) was used in CH_2Cl_2 at 40 °C to perform a very efficient RCM of 1,5-diallyl-derivative **11**.[22] The ring closure was complete after 2 h and indolizinone **13** isolated in 96% yield.

The *cis*-dihydroxylation of **13** using catalytic osmium tetroxide (OsO_4) and *N*-methylmorpholine *N*-oxide (NMO) in acetone afforded the diastereomeric diols **14** and **15** (87%) in a 7:1 dr (Scheme 3).

As we anticipated, the facial selectivity in the osmylation can be rationalized in terms of steric hindrance exerted by the bulky *tert*-butyldimethylsilyloxymethyl group. A NOESY study of the major diastereomer **14** indicated correlations between one of the protons H-9 and Hb-5, and between Hb-5 and the two protons H-6 and H-7. These data are consistent with a *trans* relationship



Scheme 3. Reagents: (a) CF_3CO_2H, THF–H_2O; (b) TBDMSCl, Im., DMF; (c) NaH–KI, allyl bromide, THF; (d) second Grubbs' catalyst (4.5%), CH_2Cl_2; (e) OsO_4, NMO, CH_3COCH_3–H_2O.

between the *tert*-butyldimethylsilyloxymethyl and the two hydroxyl groups (Fig. 1).

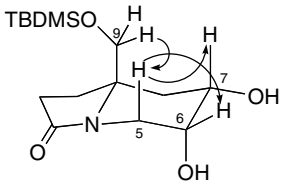


Figure 1.

The X-ray analysis of **14** confirmed this attribution and supported the (*R*)-configuration of the quaternary centre in precursor **6** (Fig. 2).[23]

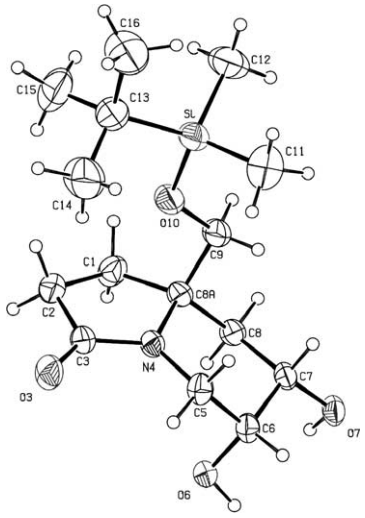


Figure 2.

The two hydroxyl groups of **14** and **15** were protected as acetonides before the reduction of the lactam carbonyls. The classical protocol for this (2,2-dimethoxypropane, TsOH) led to partial deprotection of the primary alcohol. Thus, in order to overcome this drawback, acetonides **16** and **17** were prepared, respectively, in 100% and 88% yield in the presence of powdered $CuSO_4$.[24]

The reduction was achieved with BH_3·DMS complex in THF affording **18** and **19** in 82% and 84% yield, respectively (Scheme 4).

The corresponding indolizidines **20** and **21** were then obtained as hydrochlorides in high yields after full deprotection with HCl (1 M) (98% and 93%, respectively).

2.2. Evaluation of glycosidase inhibition

Though the synthesized indolizidines **20** and **21** possess a CH_2OH group in the L-configuration, which is unfavourable for enzyme recognition compared to the hexose sugars, they were evaluated as inhibitors against commercial glycosidases. The results are shown in Table 1. They are essentially inactive, and only weakly active against α-glucosidase and, for **20**, against β-galactosidase.

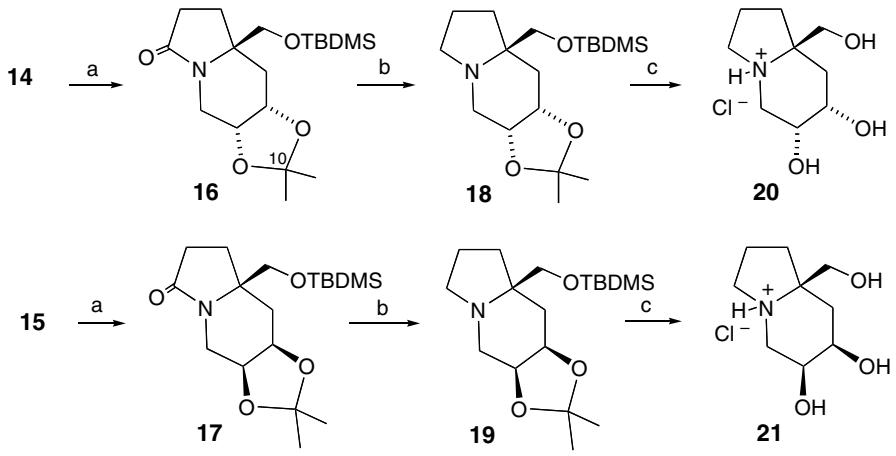
3. Conclusion

In conclusion, we herein report the unusual stereoselective addition of a *C*-nucleophile to tertiary *N*-acyl iminium ions at a bicyclic ring junction. The synthetic scheme presented constitutes as an efficient route to new polyhydroxyindolizidines bearing a quaternary hydroxymethyl group, compound **20** being diastereoselectively prepared in 20% overall yield from silyloxypyrrole **2**. This scheme, which could be applied to the synthesis of the enantiomers as potential glycosidase inhibitors, also involves lactam intermediates and, therefore, could lead to other analogues bearing hydroxyl groups on the five membered ring.

4. Experimental

4.1. General

Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1010 polarimeter and the concentrations given in g/100 mL. IR spectra (cm^{-1}, film, $CHCl_3$) were recorded on Perkin Elmer Spectrum BX



Scheme 4. Reagents: (a) $CH_3C(OCH_3)_2CH_3$, $CuSO_4$, CH_3COCH_3; (b) BH_3·DMS, THF; (c) 1 M HCl.

Table 1. Inhibition data for indolizines **20** and **21** against commercial glycosidases (IC_{50} in mM)[a]

Glycosidases	Glucosidases		Mannosidases		Galactosidases	
	α	β	α	β	α	β
20	0.57		No inh.	No inh.	No inh.	0.56
21	0.59	No inh.	No inh.	No inh.	No inh.	No inh.

[a] No inh.: no inhibition, $IC_{50} > 1$ mM.

(FT). ^{1}H NMR spectra were obtained ($CDCl_3$, $CHCl_3$ $\delta = 7.27$ ppm, unless otherwise indicated) from Bruker AM 300 (s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets and multiplet, respectively). ^{13}C NMR spectra were recorded on AM 300 (75.0 MHz, $CDCl_3$ centred at 77.14 ppm). Mass spectra and high-resolution mass spectra were measured on a Navigator (ESI), or a Micromass LC-TOF spectrometer. Chromatography was performed on silica gel (SDS 230–400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254+366). Usual workup means that the organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure.

4.2. (2*R*,5*R*)-5-Allyl-2-phenyl-3-oxa-1-azabicyclo-[3.3.0]octan-8-one 6

Allyltrimethylsilane (2.7 mL, 17.0 mmol) and $SnCl_4$ (2.0 mL, 17.1 mmol) were successively added under argon to a stirred solution of (2*R*,5*R*)-5-hydroxy-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octan-8-one **7** (1.80 g, 8.25 mmol) at −35 °C. The mixture was stirred at the same temperature for 5 h before the addition of a saturated solution of $NaHCO_3$ and extraction with CH_2Cl_2. The crude product obtained after usual workup was purified by chromatography (eluent: Et_2O) to afford allyl-derivative **6** as a colourless oil (1.22 g, 61%) [together with starting **7** (0.21 g, 12%) and β,γ-unsaturated lactam **8** (ca. 10%)]. Compound **6**: $[\alpha]_D^{23} = +193$ (*c* 1.15, $CHCl_3$). IR: 3065, 2978, 2875, 1704, 1641, 1493, 1451. MS (ESI, MeOH): 244 (MH^+). ^{1}H NMR ($CDCl_3$): 7.52 (m, 2H, H–Ar), 7.36 (m, 3H, H–Ar), 6.34 (s, 1H, H-2), 5.69 (m, 1H, H-10), 5.11 (m, 1H, Ha-11), 5.03 (m, 1H, Hb-11,), 4.09 (d, 1H, $J_{4a,4b} = 8.3$, Ha-4), 3.65 (d, 1H, $J_{4b,4a} = 8.3$, Hb-4), 2.87 (m, 1H, Ha-9), 2.54 (m, 1H, Hb-9), 2.31 (m, 1H), 2.22 (m, 2H) and 2.06 (m, 1H): H_2-7 and H_2-6. ^{13}C NMR ($CDCl_3$): 178.78 (CO), 139.23 (qC, Ar), 128.38 (CH, Ar, C-10), 125.88 (CH, Ar), 119.87 (C-11), 87.63 (C-2), 76.42 (C-4), 69.35 (C-5), 42.11 (C-9), 33.90, 28.47 (C-6, C-7). Anal. Calcd for $C_{15}H_{19}NO_2$ (%): C, 74.05; H, 7.04; N, 5.76. Found (%): C, 73.46; H, 7.01; N, 5.64.

4.3. (5*R*)-5-Allyl-5-hydroxymethyl-pyrrolidin-2-one 9

Trifluoroacetic acid (0.3 mL, 4.04 mmol) was added dropwise to a solution of bicyclic derivative **6** (0.49 g, 2.02 mmol) in a mixture of THF (2.0 mL) and H_2O (2.0 mL) at rt. After being stirred at 45 °C for 6 h, the solvent and benzaldehyde were evaporated under reduced pressure. EtOAc and Na_2CO_3 were added to the residue and the mixture was stirred at rt for 30 min, and filtered. The crude product obtained after evaporation to dryness was purified by chromatography (eluent: CH_2Cl_2–MeOH 95:5) to afford pyrrolidinone **9** as a colourless oil (284.5 mg, 91%). $[\alpha]_D^{23} = +18$ (*c* 1.8, CH_3OH). IR: 3276 (broad), 2938, 2876, 1676, 1289. MS (ESI, CH_3CN+H_2O): 178 (MNa^+, 100%). HRMS (ESI, CH_3CN+H_2O): calcd for $C_8H_{13}NO_2Na$ (MNa^+): 178.0844, found: 178.0885. ^{1}H NMR (CD_3OD, $\delta = 3.34$ ppm): 5.86 (m, 1H, H-8), 5.18 (m, 2H, H_2-9), 3.50 (d, 1H, $J_{6a,6b} = 11.4$, Ha-6), 3.45 (d, 1H, $J_{6b,6a} = 11.4$, Hb-6), 2.34 (m, 4H) and 2.01 (m, 2H): H_2-7, H_2-3 and H_2-4. ^{13}C NMR (CD_3OD, $\delta = 49.00$ ppm): 180.62 (CO), 133.98 (C-8), 119.69 (C-9), 68.68 (C-6), 64.68 (C-5), 42.07 (C-7), 31.78, 27.98 (C-3, C-4).

4.4. (5*R*)-5-Allyl-5-(*tert*-butyldimethylsilyloxymethyl)-pyrrolidin-2-one 10

Imidazole (0.78 g, 11.5 mmol) and TBDMSCl (0.8 g, 5.25 mmol) were successively added under argon to a stirred solution of pyrrolidinone **9** (0.38 g, 2.44 mmol) in DMF (2.0 mL) at rt. After stirring for 26 h, the reaction was quenched by the addition of cold water and Et_2O. The product was extracted with Et_2O and the

organic layers washed with cold water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (0.68 g) was purified by chromatography on silica gel (eluent: Et_2O) to afford silylether **10** as a white solid (589.2 mg, 90%). Mp = 53 °C. $[\alpha]_D^{23} = +38$ (*c* 1.98, $CHCl_3$). IR: 3198, 2929, 2857, 1698, 1463, 1362, 1255. MS (ESI, CH_3OH): 292 (MNa^+, 100%). ^1H NMR ($CDCl_3$): 5.94 (s, 1H, NH), 5.75 (m, 1H, H-8), 5.18, 5.13 (2H, H_2-9), 3.50 (d, 1H, $J_{6a,6b} = 11.4$, Ha-6), 3.45 (d, 1H, $J_{6b,6a} = 11.4$, Hb-6), 2.37 (2 m, 3H, Ha-7 and H_2-3 or H_2-4), 2.27 (dd, 1H, $J = 13.8$, $J' = 8.2$, Hb-7), 1.86 (m, 2H, H_2-4 or H_2-3), 0.90 (s, 9H, CH_3, *t*-Bu), 0.04 (2 s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 177.46 (CO), 132.72 (C-8), 119.56 (C-9), 68.79 (C-6), 62.58 (C-5), 41.41 (C-7), 30.36, 27.76 (C-3, C-4), 25.89 (CH_3, *t*-Bu), 18.26 (qC, *t*-Bu), −5.45 ($SiCH_3$), −5.48 ($SiCH_3$). Anal. Calcd for $C_{14}H_{27}NO_2Si$ (%): C, 62.41; H, 10.10; N, 5.20; Found (%): C, 61.99; H, 10.22; N, 5.26.

4.5. (5*R*)-1,5-Diallyl-5-(*tert*-butyldimethylsilyloxymethyl)-pyrrolidin-2-one 11

Potassium iodide (382.0 mg, 2.3 mmol) was added under argon to a suspension of NaH (60% in oil, 92.0 mg, 2.3 mmol) in THF (4.0 mL) and stirred at rt. After cooling at 0 °C, a solution of silylether **10** (580 mg, 2.2 mmol) in THF (4.0 mL) was added dropwise. The mixture was stirred for 1.5 h at rt and cooled to 0 °C. Then, allylbromide (0.2 mL, 2.3 mmol) was added dropwise and the mixture was stirred at rt for additional 24 h. After the addition of H_2O and Et_2O, the organic layer was separated and the aqueous layer was extracted twice more with Et_2O to give the crude product after usual workup. Purification by chromatography (eluent: heptane–Et_2O 4:1) gave rise to diallyl-derivative **11** (475.7 mg, 70%) as a colourless oil, together with triallyl-compound **12** (20.3 mg, 4%) and starting compound **10** (104 mg, 18%). Compound **11**: $[\alpha]_D^{23} = +35$ (*c* 0.60, $CHCl_3$). IR: 2954, 2928, 2857, 1695, 1462, 1403, 1255. MS (ESI, CH_3OH): 310 (MH^+, 100%). HRMS (ESI, CH_3OH): calcd for $C_{17}H_{32}NO_2Si$ (MH^+): 310.2202, found: 310.2205. ^1H NMR ($CDCl_3$): 5.86 (m, 1H, H-11), 5.66 (m, 1H, H-8), 5.20–5.08 (4H, H_2-12 and H_2-9), 3.94 (dd, 1H, $J = 15.5$, $J' = 5.8$, Ha-10), 3.82 (dd, 1H, $J = 15.5$, $J' = 5.8$, Hb-10), 3.56 (d, 1H, $J_{6a,6b} = 10.3$, Ha-6), 3.46 (d, 1H, $J_{6b,6a} = 10.3$, Hb-6), 2.34 (2 m, 4H, H_2-7, H_2-3 or H_2-4), 1.87 (m, 2H, H_2-4 or H_2-3), 0.88 (s, 9H, CH_3, *t*-Bu), 0.04 (2 s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 175.81 (CO), 134.99, 132.33 (C-11, C-8), 119.49, 116.33 (C-9, C-12), 67.85 (C-6), 66.87 (C-5), 42.81 (C-10), 39.31 (C-7), 30.03, 26.49 (C-3, C-4), 25.87 (CH_3, *t*-Bu), 18.20 (qC, *t*-Bu), −5.54 ($2SiCH_3$).

4.6. (5*R*)-1,5-Diallyl-5-allyloxymethyl-pyrolidin-2-one 12

$[\alpha]_D^{23} = +42$ (*c* 1.47, $CHCl_3$). IR: 2928, 1681, 1402, 1257. MS (ESI, CH_3OH): 258 (MNa^+, 100%). HRMS (ESI, CH_3OH): calcd for $C_{14}H_{21}NO_2Na$ (MNa^+): 258.1470, found: 258.1486. ^1H NMR ($CDCl_3$): 5.84 (m, 2H, H-11, H-14), 5.67 (m, 1H, H-8), 5.26–5.05 (6H, H_2-9, H_2-12, H_2-15), 3.98 (dd, 1H, $J = 15.6$, $J' = 5.8$, Ha-10), 3.91 (2H, H_2-13), 3.78 (dd, 1H, $J = 15.6$, $J' = 6.0$, Hb-10), 3.37 (d, 1H, 1H, $J_{6a,6b} = 10$, Ha-6), 3.30 (d, 1H, $J_{6b,6a} = 10$, Hb-6), 2.34 (m, 4H) and 1.91 (m, 2H): H_2-3, H_2-4 and H_2-7. ^{13}C NMR ($CDCl_3$): 175.72 (CO), 134.83, 134.40, 132.20 (C-8, C-11, C-14), 119.62, 117.07, 116.28 (C-9, C-12, C-15), 74.80 (C-6), 72.15 (C-13), 65.93 (C-5), 42.85 (C-10), 39.61 (C-7), 29.87, 26.76 (C-3, C-4).

4.7. 8a*R*-*tert*-Butyldimethylsilyloxymethyl-1,5,8,8a-tetrahydro-2*H*-indolizin-3-one 13

A solution of diallyl-derivative **11** (99.4 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (48.0 mL) and second Grubbs' catalyst (12.5 mg, 4.5%) were stirred at 40 °C for 2 h. The solvent was evaporated at the same temperature and the residue was purified by preparative TLC (eluent: Et_2O) to remove the catalyst. Bicyclic compound **13** (86.8 mg, 96%) was obtained as a white solid. Mp = 40 °C. $[\alpha]_D^{23} = -27$ (*c* 1.37, $CHCl_3$). IR: 2948, 2928, 2889, 2855, 1694, 1412. MS (ESI, CH_3OH): 585 ($2MNa^+$), 304 (MNa^+), 282 (MH^+, 100%). HRMS (ESI, CH_3OH): calcd for $C_{15}H_{27}NO_2SiNa$ (MNa^+): 304.1709, found: 304.1711. ^1H NMR ($CDCl_3$): 5.70 (m, 2H, H-6, H-7), 4.29 (broad d, 1H, $J = 18.5$, Ha-5), 3.58 (d, 1H, 1H, $J_{9a,9b} = 10$, Ha-9), 3.43 (d, 1H, $J_{9b,9a} = 10$, Hb-9), 3.43 (masked d, 1H, Hb-5), 2.48 (m, 1H), 2.30 (2 m, 3H), 2.11 (m, 1H) and 1.75 (m, 1H): H_2-8, H_2-2 and H_2-1, 0.87 (s, 9H, CH_3, *t*-Bu), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): 174.63 (CO), 123.63, 122.53 (C-6, C-7), 65.30 (C-9), 61.16 (C-8a), 38.66 (C-5), 33.81 (C-8), 30.43, 30.14 (C-1, C-2), 25.86 (CH_3, *t*-Bu), 18.20 (qC, *t*-Bu), −5.48 ($SiCH_3$), −5.86 ($SiCH_3$).

4.8. 8a-*tert*-Butyldimethylsilyloxymethyl-6,7-dihydroxy-indolizidin-3-ones 14 and 15

A solution of OsO_4 in *tert*-butanol (0.1 M, 0.23 mL, 0.023 mmol) was added to a solution of *N*-methylmorpholine *N*-oxide (137.0 mg, 1.16 mmol) in a mixture of acetone (0.50 mL) and H_2O (0.11 mL) at 0 °C. A solution of compound **13** (220.0 mg, 0.78 mmol) in acetone (0.70 mL) was then added and the reaction mixture stirred at 0 °C for 6 h. An aqueous saturated solution of $NaHSO_4$ was added and the products extracted with EtOAc. The usual workup gave rise to diastereomers **14** and **15**, which were separated by chromatography (eluent: CH_2Cl_2–MeOH 95:5) to afford **14** (186.6 mg, 76%) and **15** (27.0 mg, 11%) as colourless crystals.

4.9. (6*R*,7*S*,8a*R*)-8a-*tert*-Butyldimethylsilyloxymethyl-6,7-dihydroxy-indolizidin-3-one 14

Mp = 176–177 °C. $[\alpha]_D^{23} = -6.7$ (*c* 0.65, $CHCl_3$). IR: 3316 (broad), 2928, 2858, 1655, 1445, 1414. MS (ESI, CH_3OH): 338 (MNa^+, 100%). HRMS (ESI, CH_3OH): calcd for $C_{15}H_{29}NO_4SiNa$ (MNa^+): 338.1764, found: 338.1772. ^1H NMR ($CDCl_3$): 4.20 (dd, 1H, $J = 14.5$, $J' = 2.5$, Ha-5), 3.98 (m, 1H, H-6), 3.86 (m, 1H, H-7), 3.65 (d, 1H, $J_{9a,9b} = 10.3$, Ha-9), 3.48 (d, 1H,

$J_{9b,9a} = 10.3$, Hb-9), 2.85 (broad d, 1H, $J = 14.5$, Hb-5), 2.46 (m, 1H), 2.36 (m, 1H) and 2.11 (m, 1H): H_2-2 and Ha-1, 1.94 (dd, 1H, $J = 12.9$, $J' = 4.9$, Ha-8), 1.74 (m, 2H, Hb-8, Hb-1), 0.87 (s, 9H, CH_3, *t*-Bu), 0.04 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): 176.03 (CO), 67.49, 66.96 (C-6, C-7), 65.42 (C-8a), 64.18 (C-9), 42.11 (C-5), 36.57 (C-8), 30.65, 30.32 (C-1, C-2), 25.98 (CH_3, *t*-Bu), 18.19 (qC, *t*-Bu), −5.47 ($2SiCH_3$); NOESY: correlations were observed between: Hb-5 and Ha-9, Hb-5, H-6 and H-7.

4.10. Crystal structure determination of compound 14

Suitable crystals for X-ray structure determination of compound **14** were obtained from a dilute solution in ethyl acetate at rt. X-ray diffraction data were recorded from a single colourless plate, $0.6 \times 0.4 \times 0.2$ mm, at ambient temperature on an Enraf–Nonius Kappa-CCD diffractometer, using graphite-monochromated Mo-Kα radiation ($l = 0.71073$ Å). On a CAD4 diffractometer, 244 Bijvoet pairs showing the strongest differences were later measured, using the Cu-Kα radiation ($l = 1.5418$ Å) to support the correct absolute structure from weak Si anomalous signal. The structure was solved by direct methods with the program SHELX-S97 (Sheldrick, 1997)[23a] and all non-hydrogen atoms were refined anisotropically on F^2 values by full-matrix least-square methods using SHELX-L97. All hydrogen atoms were located on difference-Fourier syntheses and were refined with a riding model and with U_{iso} set to 1.15 time that of the carrier atom (or 1.2 in methyl or hydroxyl groups, and waters). The asymmetric unit of the crystal consists of one compound **14** molecule and two waters involved in the hydrogen bonding with the two hydroxyl groups and the carbonyl one. Bijvoet-pair analysis as implemented within PLATON (Spek, 2003),[23b] performed on the dataset using the copper radiation, supports the selected relative stereochemistry of the asymmetric carbons, namely 6*R*,7*S*, and 8a*R*. $C_{15}H_{29}NO_4Si$, $2(H_2O)$, M_r=351.51, monoclinic, space group $P2_1$, $a = 6.819(4)$, $b = 7.304(3)$, $c = 20.655(4)$ Å, $b = 99.43(2)°$, $V = 1014.8(8)$ Å^3, $r_{calcd} = 1.150$ g/cm^3, $F(000) = 384$, $\mu = 0.141$ mm^{-1}, no absorption correction, $Z = 2$, $l = 0.71073$ Å, $T = 293$ K, *j*/*w*-scans, 10328 measured reflections ($-8 \leqslant h \leqslant 8$, $-9 \leqslant k \leqslant 9$, $-26 \leqslant l \leqslant 26$), 4293 independent (1832 Friedel pairs separated) and 3472 observed reflections with $I > 2s(I)$ ($R = 0.0440$), 215 parameters, 1 restraint, $R = 0.0601$, $wR_2 = 0.1184$ for all reflections, $w = 1/[s^2(F^2) + (0.0536P)^2 + 0.1441P]$, where $P = (\max(F_o^2, 0) + 2F_c^2)/3$. The largest difference peak and hole are meaningless, 0.256 and −0.174 e Å^3, Flack parameter −0.19(14) (its meaningfulness was confirmed by the good agreement (20 over 22) between the strongest $DF^{+/-}_{obsd}$ and $DF^{+/-}_{calcd}$ (above one sigma) among 244 Bijvoet pairs measured using Cu-Kα radiation).

CCDC 280270 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336033; or deposit@ccdc.cam.uk).

4.11. (6*S*,7*R*,8a*R*)-8a-*tert*-Butyldimethylsilyloxymethyl-6,7-dihydroxy-indolizidin-3-one 15

Mp = 183 °C. $[\alpha]_D^{23} = -9.5$ (*c* 0.78, $CHCl_3$). IR: 3338 (broad), 2950, 2858, 1640, 1462, 1414. MS (ESI, CH_3OH): 338 (MNa^+, 100%). ^1H NMR (C_6D_6, $\delta =$ 7.15 ppm+D_2O): 4.39 (dd, 1H, $J = 12$, $J' = 5$, Ha-5), 4.17 (d, 1H, $J = 10$, Ha-9), 3.88 (m, 1H, H-7), 3.50 (m, 1H, H-6), 3.36 (d, 1H, $J = 10$, Hb-9), 3.02 (dd, 1H, $J \sim J' \sim 12$, Hb-5), 2.43 (m, 1H), 2.11 (m, 1H) and 1.91 (m, 1H): H_2-2 and Ha-1, 1.84 (dd, 1H, $J = 15$, $J' = 3.0$, Ha-8), 1.06 (m, 1H, Hb-1), 1.00 (dd, 1H, Hb-8), 0.91 (s, 9H, CH_3, *t-Bu*), 0.02 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): 174.33 (CO), 67.61, 67.48 (C-6, C-7), 67.49 (C-9), 61.74 (C-8a), 40.03 (C-5), 38.25 (C-8), 31.41, 31.22 (C-1 and C-2), 25.94 (CH_3, *t*-Bu), 18.29 (qC, *t*-Bu), −5.43 ($2SiCH_3$). Anal. Calcd for $C_{15}H_{29}NO_4Si$ (%): C, 57.11; H, 9.27; N, 4.44. Found (%): C, 57.01; H, 9.24; N, 4.33.

4.12. (6*R*,7*S*,8a*R*)-8a-*tert*-Butyldimethylsilyloxymethyl-6,7-isopropylidendioxy-indolizidin-3-one 16

Dimethoxypropane (0.5 mL) and dried powdered $CuSO_4$ (76.0 mg, 0.475 mmol) were successively added to a suspension of diol **14** (30.0 mg, 0.095 mmol) in anhydrous acetone (0.5 mL) and the mixture was stirred at rt for 5 days. After filtration, $CuSO_4$ was washed with acetone. The solvent was evaporated to afford compound **16** (34.0 mg, 100%) as colourless crystals. Mp = 56 °C. $[\alpha]_D^{23} = +47$ (*c* 0.96, $CHCl_3$). IR: 2928, 2855, 1682, 1412, 1380, 1368. MS (ESI, CH_3OH): 378 (MNa^+, 100%), 356 (MH^+). HRMS (ESI, CH_3OH): calcd for $C_{18}H_{33}NO_4SiNa$ (MNa^+): 378.2077, found: 378.2086. ^1H NMR ($CDCl_3$): 4.51 (m, 1H, H-7), 4.26 (masked d, 1H, $J = 14.9$, Ha-5), 4.23 (m, 1H, H-6), 3.51 (d, 1H, $J_{9a,9b} = 10.3$, Ha-9), 3.49 (d, 1H, $J_{9b,9a} =$ 10.3, Hb-9), 3.02 (ddd, 1H, $J = 14.6$, $J' = 3.0$, $J'' = 1.0$, Hb-5), 2.52 (m, 1H, Ha-2), 2.33 (m, 1H, Hb-2), 2.11 (m, 1H, Ha-1), 1.95 (m, 1H, Hb-1), 1.93 (masked dd, 1H, $J' = 4.6$, Ha-8), 1.88 (dd, 1H, $J = 14.7$, $J' = 5.5$, Hb-8), 1.44 (s, 3H, CH_3-10), 1.32 (s, 3H, CH_3-10), 0.91 (s, 9H, CH_3, *t*-Bu), 0.05 (s, 6H, $2SiCH_3$). ^{13}C NMR ($CDCl_3$): 175.52 (CO), 108.32 (qC, C-10), 72.34, 71.10 (C-6, C-7), 68.27 (C-9), 61.61 (C-8a), 39.99 (C-5), 32.63 (C-8), 30.54, 29.96 (C-1 and C-2), 27.14 (CH_3-10), 25.97 (CH_3, *t*-Bu), 24.75 (CH_3-10), 18.32 (qC, *t*-Bu), −5.41 ($2SiCH_3$).

4.13. (6*S*,7*R*,8a*R*)-8a-*tert*-Butyldimethylsilyloxymethyl-6,7-isopropylidendioxy-indolizidin-3-one 17

Minor diol **15** (33.2 mg, 0.105 mmol) was treated as its diastereomer **14** in anhydrous acetone (0.2 mL) with dimethoxypropane (0.2 mL) and $CuSO_4$ (84.0 mg, 0.525 mmol) to afford the protected diol **17** (32.8 mg, 88%) as a white solid. Mp = 55 °C. $[\alpha]_D^{23} = -27.5$ (*c* 2.55, $CHCl_3$). IR: 2983, 2946, 2928, 2881, 2856, 1692, 1454, 1424, 1410. MS (ESI, CH_3OH): 733 [($2M+Na^+$), 100%], 378 (MNa^+), 356 (MH^+). HRMS (ESI, CH_3OH): calcd for $C_{18}H_{33}NO_4SiNa$ (MNa^+): 378.2077, found: 378.2072. ^1H NMR ($CDCl_3$): 4.25 (m, 2H, H-7, Ha-5), 4.10 (m, 2H, Ha-9, H-6), 3.42 (d,

1H, $J_{9b,9a} = 10.5$, Hb-9), 2.62 (dd, 1H, $J = 13.3$, $J' = 7.9$, Hb-5), 2.51 and 2.30 (2 m, 2H, H_2-2 or H_2-1), 2.25 and 1.63 (2 m, 1H, H_2-1 or H_2-2), 2.18 (dd, 1H, $J = 15.3$, $J' = 2.7$, Ha-8), 1.75 (dd, 1H, $J = 15.3$, $J' = 4.6$, Hb-8), 1.51 (s, 3H, CH_3-10), 1.34 (s, 3H, CH_3-10), 0.87 (s, 9H, CH_3, *t*-Bu), 0.05 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): 174.34 (CO), 109.26 (C-10), 72.46, 70.15 (C-7, C-6), 65.23 (C-9), 61.21 (C-8a), 38.13 (C-5), 34.64 (C-8), 31.27, 30.49 (C-1, C-2), 28.54, 26.04 ($2CH_3$-10), 25.87 (CH_3, *t*-Bu), 18.18 (qC, *t*-Bu), −5.40 ($SiCH_3$), −5.43 ($SiCH_3$).

4.14. (6*R*,7*S*,8a*R*)-8a-*tert*-Butyldimethylsilyloxymethyl-6,7-isopropylidendioxy-indolizidine 18

A solution of BH_3·DMS (2 M in THF, 0.38 mL, 0.76 mmol) was added under argon at rt to a solution of compound **16** (90.0 mg, 0.25 mmol) in THF (1.25 mL). The mixture was heated at 60 °C for 90 min and then cooled at 0 °C before the addition of MeOH (0.1 mL). After evaporation to dryness, methanol (2.0 mL) was added to the residue and the solution was heated at 60 °C for 14 h. The solvent was eliminated under reduced pressure and indolizidine **18** (69.8 mg, 82%) was obtained after purification by preparative TLC (eluent: EtOAc), as a colourless oil. $[\alpha]_D^{23} = -5$ (*c* 1.19, $CHCl_3$). IR: 2953, 2925, 2855, 1462, 1378, 1258. MS (ESI, CH_3OH): 342 (MH^+, 100%). HRMS (ESI, CH_3OH): calcd for $C_{18}H_{36}NO_3Si$ (MH^+): 342.2464, found: 342.2448. ^1H NMR (C_6D_6, $\delta = 7.15$ ppm): 4.49 (m, 1H, H-7), 4.30 (m, 1H, H-6), 3.16 (s, 2H, H_2-9), 3.07 (dd, 1H, $J = 10.8$, $J' = 5.0$, Ha-5), 2.96 (m, 1H, Ha-3), 2.67 (dd, 1H, $J = 10.8$, $J' = 9.5$, Hb-5), 2.53 (dd, 1H, $J = 13.3$, $J' = 6.5$, Ha-8), 2.42 (m, 1H, Hb-3), 1.90 (m, 1H, Ha-1), 1.58–1.41 (2 m, 2H, H_2-2), 1.52 (s, 3H, CH_3-10), 1.27 (s, 3H, CH_3-10), 1.19 (m, 1H, Hb-1), 0.92 (s, 9H, CH_3, *t*-Bu), 0.08 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$). ^{13}C NMR (C_6D_6, $\delta = 128.00$ ppm): 108.51 (C-10), 73.91, 71.91 (C-6, C-7), 68.62 (C-9), 55.79 (C-3), 52.25 (C-5), 35.91 (C-8), 32.90, 30.17 (C-1, C-2), 27.69 (CH_3-10), 26.05 (CH_3, *t*-Bu), 24.75 (CH_3-10), 18.38 (qC, *t*-Bu), −5.38 ($SiCH_3$), −5.44 ($SiCH_3$).

4.15. (6*S*,7*R*,8a*R*)-8a-*tert*-Butyldimethylsilyloxymethyl-6,7-isopropylidendioxy-indolizidine 19

Compound **17** (24.8 mg, 0.07 mmol) was reduced with BH_3·SMe_2 as described for **16** to afford indolizidine **19** (19.9 mg, 84%). $[\alpha]_D^{23} = +3.6$ (*c* 0.84, $CHCl_3$). IR: 2929, 2855, 1462, 1378, 1253. MS (ESI, CH_3OH): 342 (MH^+, 100%). HRMS (ESI, CH_3OH): calcd for $C_{18}H_{36}NO_3Si$ $(MH)^+$: 342.2464, found: 342.2454. ^1H NMR ($CDCl_3$): 4.47 (m, 1H, H-6), 4.35 (m, 1H, H-7), 3.44 (d, 1H, $J_{9a,9b} = 9.4$, Ha-9), 3.35 (d, 1H, $J_{9b,9a} = 9.4$, Hb-9), 3.14 (dd, 1H, $J = 13.7$, $J' = 5.8$, Ha-5), 3.08 (m, 1H, Ha-3), 2.85 (dd, 1H, $J = 13.7$, $J' = 8.2$, Hb-5), 2.74 (m, 1H, Hb-3), 1.80 (m, 2H, H_2-8), 1.96 (m, 1H), 1.69 (m, 2H) and 1.48 (m, 1H): H_2-1, H_2-2, 1.49 (s, 3H, CH_3-10), 1.33 (s, 3H, CH_3-10), 0.89 (s, 9H, CH_3, *t*-Bu), 0.04 (2 s, 6H, $2SiCH_3$). ^{13}C NMR ($CDCl_3$): 107.95 (C-10), 71.54, 69.88 (C-6, C-7), 68.61 (C-9), 53.94 (C-3), 48.79 (C-5), 34.09, 33.19 (C-8, C-1), 30.02 (C-2), 27.35 (CH_3-10), 26.04 (CH_3, *t*-Bu), 24.78 (CH_3-10), 18.35 (qC, *t*-Bu), −5.26 ($SiCH_3$), −5.39 ($SiCH_3$).

4.16. (6*R*,7*S*,8a*R*)-6,7-Dihydroxy-8a-hydroxymethyl-indolizidine hydrochloride 20

A solution of HCl in H_2O (1 M, 1.88 mL) was added at rt to a solution of the derivative **18** (69.1 mg, 0.16 mmol) in THF (0.8 mL) and the mixture was stirred for 72 h at the same temperature. The solvents were evaporated under reduced pressure to give indolizidine hydrochloride **20** crystallized in MeOH–Et_2O (35.0 mg, 98%). Mp = 198 °C. $[\alpha]_D^{23} = -10$ (*c* 2.95, H_2O). IR: 3291 (broad), 2962, 2895, 1467, 1444, 1360. MS (ESI, CH_3OH): 188 (MH^+, 100%). HRMS (ESI, CH_3OH): calcd for $C_9H_{18}NO_3$ (MH^+): 188.1287, found: 188.1295. ^1H NMR (D_2O, $\delta = 4.65$ ppm): 3.90 (m, 1H, H-6), 3.86 (m, 1H, H-7), 3.76 (m, 1H, Ha-3), 3.59 (d, 1H, $J_{9a,9b} = 12.3$, Ha-9), 3.50 (d, 1H, $J_{9b,9a} = 12.3$, Hb-9), 3.43 (m, 1H, Hb-3), 3.30 (dd, 1H, $J = 14.3$, $J' = 4.0$, Ha-5), 3.13 (dd, 1H, $J = 14.3$, $J' = 2.7$, Hb-5), 2.06–1.75 (m, 5H, H_2-2, H_2-1, Ha-8), 1.70 (dd, 1H, $J = 14.4$, $J' = 4.4$, Hb-8). ^{13}C NMR (D_2O, δ $CD_3OD = 49.00$ ppm): 71.67 (C-8a), 66.03, 65.12 (C-6, C-7), 61.46 (C-9), 54.91 (C-3), 48.83 (C-5), 30.57 (C-8), 32.86, 20.30 (C-1, C-2).

4.17. (6*S*,7*R*,8a*R*)-6,7-Dihydroxy-8a-hydroxymethyl-indolizidine hydrochloride 21

Compound **19** (18.7 mg, 0.055 mmol) in THF (0.3 mL) was treated as its diastereomer **18** by an aqueous solution HCl (1 M, 0.6 mL) to afford indolizidine **21** hydrochloride (11.4 mg, 93%). Mp = 196 °C. $[\alpha]_D^{23} = +9.5$ (*c* 0.85, H_2O). IR: 3337, 3270, 3236, 3142, 1472, 1443, 1415, 1379, 1346, 1297, 1278. MS (ESI, H_2O): 210 $(MNa)^+$, 188 $[(MH)^+$, 100%]. HRMS (ESI, H_2O): calcd for $C_9H_{18}NO_3$ (MH^+): 188.1287, found: 188.1287. ^1H NMR (D_2O, $\delta = 4.65$ ppm): 3.95 (m, 2H, H-6, H-7), 3.49 (m, 3H, H_2-9, Ha-3), 3.28 (dd, 1H, $J = 13.6$, $J' = 4.4$, Ha-5), 3.15 (m, 2H, Hb-5, Hb-3), 2.03 (m, 4H, H_2-1, Ha-8, Ha-2), 1.79 (m, 2H, Hb-8, Hb-2). ^{13}C NMR (D_2O, δ $CD_3OD = 49.00$ ppm): 72.75 (C-8a), 65.84, 65.06 (C-6, C-7), 63.75 (C-9), 52.99, 52.87 (C-3, C-5), 28.29 (C-8), 30.18, 19.53 (C-1, C-2).

4.18. Enzyme inhibitions

General conditions for the determination of glycosidase inhibitions:[25]

Tested glycosidases: α-D-glucosidase (EC 3.2.1.20) from baker's yeast ($K_m = 0.21$ mM, pH = 7.0), β-D-glucosidase (EC 3.2.1.21) from almonds ($K_m = 1.3$ mM, pH = 5.0), α-D-mannosidase (EC 3.2.1.24) from Jack beans ($K_m = 1.0$ mM, pH = 4.5), β-D-mannosidase (EC 3.2.1.25) from snail, acetone powder ($K_m = 1.3$ mM, pH = 4.0), α-D-galactosidase (EC 3.2.1.22) from *Aspergillus niger* ($K_m = 0.25$ mM, pH = 6.5), and β-D-galactosidase (EC 3.2.1.23) from *Escherichia coli* ($K_m = 0.2$ mM, pH = 7.0). Used buffer: K_2HPO_4/KH_2PO_4 for pH 6.5 and 7.0, AcOH/AcOK for pH 4.0–5.5.

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