EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202401307

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

5-Substituted 1,2-Dihydroxyindolizidines and -Pyrrolizidines Related to Swainsonine: Synthesis and Inhibition Study

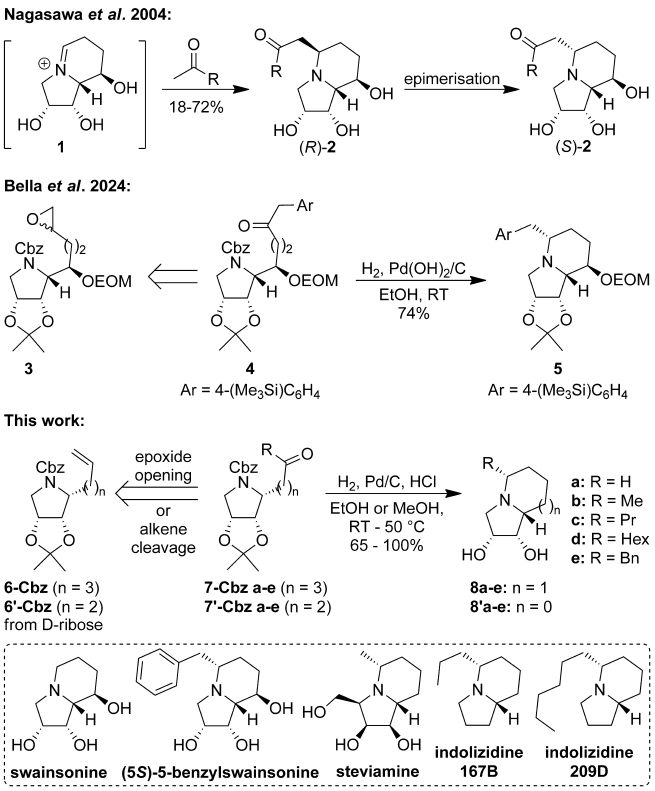
Peter Gabko,[a] Sergej Šesták,[a] Ján Moncoľ,[b] and Maroš Bella*[a]

Development of selective Golgi α-mannosidase II inhibitors possessing a modified swainsonine skeleton has recently become a popular field of study due to their great potential in suppressing metastasis. However, most of the studied modifications involve addition of a substituent on the bicycle which makes the synthesis rather complex as five stereogenic centres have to be generated. Inspired by our previously developed synthesis of (5*S*)-5-benzylswainsonines utilizing a fully stereoselective intramolecular reductive amination, we decided to further investigate the versatility of this strategy by preparing a small collection of simplified analogues bearing only two hydroxy groups, thus eliminating one of the stereogenic centres. This contribution reports a concise synthesis of 5-substituted 1,2-dihydroxyindolizidines and -pyrrolizidines whose key features include small number of steps, high yields and excellent stereoselectivity. The title compounds were also tested for inhibitory activity against a Golgi and a lysosomal α-mannosidase to assess the effects of the substituents, ring size and missing C8-hydroxyl on potency and selectivity.

Introduction

Swainsonine is a natural alkaloid that was originally isolated from the fungus *Rhizoctonia leguminicola*, but has also been found in plants such as the locoweed *Astragalus lentiginosus*.[1,2] Owing to its notorious toxic effect, known as locoism, observed in livestock upon consumption of the locoweed, swainsonine became a subject of intensive biochemical research to identify its mechanism of action. Eventually, it was found that this relatively simple trihydroxylated indolizidine in its protonated form mimics mannose and strongly inhibits α-mannosidases, particularly Golgi α-mannosidase II [K_i(hGMII) = 5 nM] and lysosomal α-mannosidase [(K_i(hLMan) = 23 nM].[3–6] Further research revealed that only inhibition of the latter enzyme is detrimental, as it leads to toxic accumulation of mannose-based oligosaccharides in cells. On the other hand, inhibition of the Golgi enzyme diverts biosynthesis of complex *N*-glycans to the hybrid-type, which has beneficial effects on cancer patients, including suppression of metastasis and stimulation of the immune system.[3,7–12] Therefore, attention has been focused on developing analogues of swainsonine that would be more selective towards Golgi α-mannosidase II, as this would alleviate the toxicity and allow the compound to be used in cancer treatment.[6,13,14]

One of the highly promising modifications of the bicycle to increase the selectivity seems to be addition of a substituent in the 5-position,[15] and to date only two syntheses of 5-substituted swainsonines have been reported (Scheme 1). The



Scheme 1. Previous methodologies and our current work.

[a] *P. Gabko, Dr. S. Šesták, Dr. M. Bella*
Institute of Chemistry
Slovak Academy of Sciences
Dúbravská cesta 9, SK-845 38 Bratislava, Slovakia
E-mail: maros.bella@savba.sk

[b] *Prof. Dr. J. Moncoľ*
Department of Inorganic Chemistry
Faculty of Chemical and Food Technology, Slovak University of Technology
Radlinského 9, SK-812 37 Bratislava, Slovakia

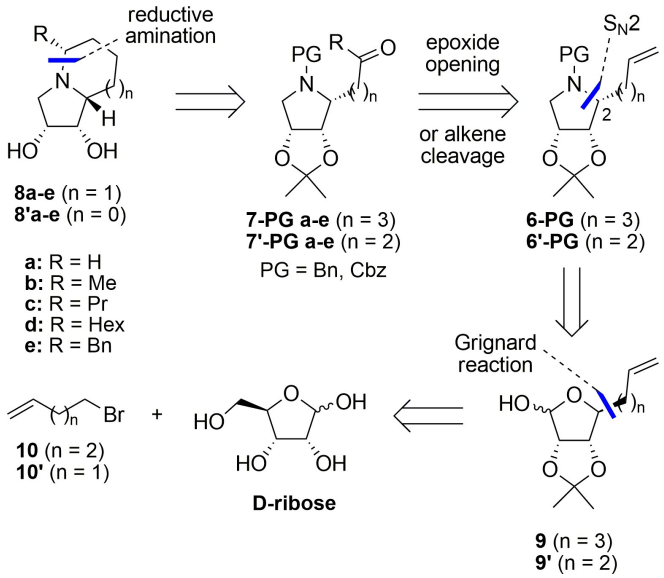
Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202401307

Research Article
doi.org/10.1002/ejoc.202401307

Chemistry Europe
European Chemical Societies Publishing

first protocol emerged from the Nagasawa group in 2004 who developed a stereoselective Mannich reaction using iminium intermediate **1**.[16] Although the reaction was mostly low-yielding due to a competing dimerisation, it exhibited complete diastereoselectivity and the products could be further epimerised under mild conditions. The second strategy, featuring a fully stereoselective intramolecular reductive amination of protected amino-ketone **4**, was established in our group with the aim to synthesise novel (5*S*)-5-(*p*-halobenzyl)-swainsonines.[13] Because the benzyl group was installed through a ring-opening of the late epoxide intermediate **3**, this methodology provides access to a wider range of substituents since epoxides can be opened by essentially any nucleophile.

Realising the synthetic potential of this epoxide-opening/reductive amination sequence, we decided to further investigate its versatility by preparing a small collection of 5-substituted 8-deoxyswainsonines **8**, as well as their ring-contracted analogues **8′** to test the feasibility of constructing 5-membered rings. In this contribution, we report a practical synthesis of 5-substituted 1,2-dihydroxyindolizidines and -pyrrolizidines, together with the results of their inhibition study against AMAN-2 and Jack bean α-mannosidases, which serve as suitable models for human Golgi α-mannosidase II and lysosomal α-mannosidase, respectively.[13] The substituents were selected based on other alkaloids, namely steviamine (methyl),[17] indolizidine 167B (*n*-propyl) and 209D (*n*-hexyl),[18] as well as the most potent and selective (5*S*)-5-benzylswainsonine analogue from our previous report (benzyl).[13]



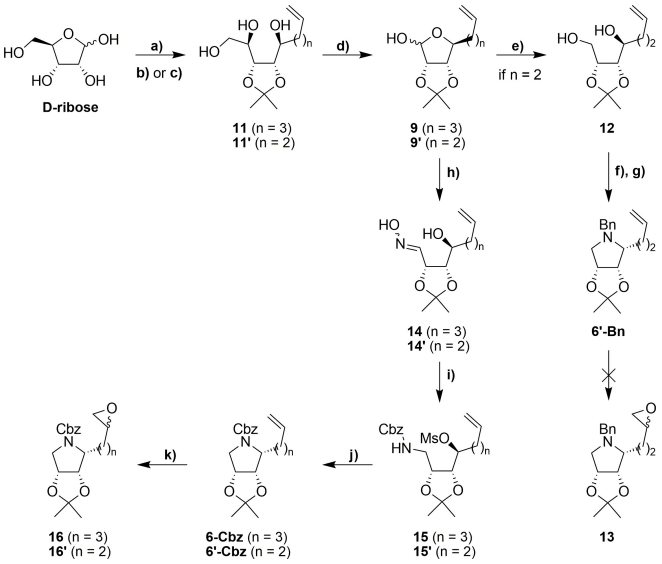
Scheme 2. Retrosynthetic analysis of the target bicycles **8a–e** and **8′a–e**.

Results and Discussion

Synthesis

As depicted in Scheme 2, the first two disconnections in our retrosynthetic analysis build on the reaction sequence previously established in our group: intramolecular reductive amination to forge the bicycle and regioselective epoxide opening to allow for a late-stage derivatisation; in case of the unsubstituted analogues, the alkene in intermediates **6-PG/6′-PG** might be transformed into aldehyde by a standard oxidative cleavage. The pyrrolidine ring was envisioned to be constructed by an S_N2 substitution to fully control the stereochemistry at C2, which could be achieved after a few simple functional group manipulations on lactols **9/9′**. Finally, a stereoselective Grignard reaction with protected D-ribose would install the alkene side-chain.

Our synthetic investigations began with the pyrrolizidine analogues and selecting the benzyl protecting group for the pyrrolidine nitrogen (Scheme 3). Standard protection of D-ribose with acetone followed by a highly diastereoselective Grignard addition[19,20] furnished triol **11′** in 72% yield over 2 steps. Oxidative cleavage of the vicinal diol with $NaIO_4$ afforded lactol **9′** which was subsequently reduced to diol **12**. Activation of the alcohols with mesyl chloride followed by heating of the corresponding dimesylate in benzylamine[21,22] resulted in a smooth cyclisation, providing pyrrolidine **6′-Bn** in 76% yield over 2 steps. Subsequent epoxidation of the alkene by standard



Scheme 3. Reagents and conditions: **a)** Me_2CO, H_2SO_4 (cat.), RT, 2.5 h, 86%; **b)** but-3-en-1-ylmagnesium bromide, THF, 0 °C–RT, 24 h, 84%; **c)** pent-4-en-1-ylmagnesium bromide, THF, 0 °C–RT, 24 h, 87%; **d)** aq. $NaIO_4$, DCM, 0 °C–RT, 2.5 h, 84% for **9** (n = 3), 82% for **9′** (n = 2); **e)** $NaBH_4$, MeOH, 0 °C–RT, 4 h, 88%; **f)** MsCl, Et_3N, DCM, 0 °C–RT, 23 h, 99%; **g)** $BnNH_2$, 120 °C, 24 h, 77%; **h)** $HONH_2 \cdot HCl$, $NaHCO_3$, MeOH, RT, 18 h, 96% for **14** (n = 3), 96% for **14′** (n = 2); **i)** 1.) $LiAlH_4$, THF, 0 °C–RT, 15–17 h, then H_2O, CbzCl in PhMe, 0 °C, 4 h, 2.) MsCl, Et_3N, DCM, 0 °C–RT, 5 h, 92% for **15** (n = 3), 86% for **15′** (n = 2); **j)** NaH, DMF, 0 °C–RT, 2–5 h, 87% for **6-Cbz** (n = 3), 92% for **6′-Cbz** (n = 2); **k)** *m*-CPBA, DCM, 0 °C–RT, 16–23 h, 92% for **16** (n = 3), 91% for **16′** (n = 2). Ms = methanesulfonyl, Cbz = benzyloxycarbonyl, *m*-CPBA = 3-chloroperoxybenzoic acid.

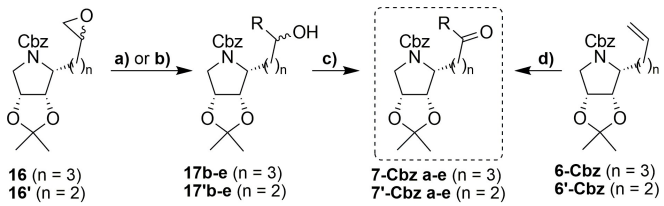
Research Article
doi.org/10.1002/ejoc.202401307

methods, such as treatment with *m*-CPBA or hydroxybromination/cyclisation, proved difficult as the tertiary amine readily underwent oxidation and decomposition, even if initially turned into the tosylate salt.

Thus, we turned our attention to the Cbz-protected pyrrolidine **6′-Cbz** and modified the synthetic plan so that the Cbz group could be incorporated "directly" without reprotection of the benzyl moiety, thus minimising the use of protecting groups. Inspired by the work of Hashimoto *et al.*,[23] lactol **9′** was first turned into oxime **14′** in an almost quantitative yield, and then subjected to a reduction with $LiAlH_4$ and *in situ* protection of the resulting amine with CbzCl. The protected amino-alcohol was obtained in sufficient purity after work-up and was immediately mesylated to afford mesylate **15′** in 86% yield over 3 transformations. Subsequent treatment with NaH promoted the cyclisation and the resulting Cbz-protected pyrrolidine **6′-Cbz** smoothly underwent epoxidation with *m*-CPBA. With the key intermediates (**6′-Cbz** and **16′**) in hand, we replicated the established procedures to generate the analogues leading to indolizidines by employing pent-4-en-1-ylmagnesium bromide in the Grignard reaction (as seen in step **c**), and proceeded to the derivatisation phase.

First, the epoxides were opened with commercial Grignard reagents in presence of catalytic CuI (Scheme 4), and then the resulting alcohols were oxidised with DMP, thus destroying the stereogenic centre introduced in the epoxidation, affording ketones **7-Cbz c–e/7′-Cbz c–e** in high to excellent yields. As for the methyl-substituted analogues, the epoxides had to be selectively reduced in presence of the carbamate, which required a short optimisation study to carefully tune the temperature, reaction time and amount of the reducing agent. Eventually, treatment with 1.5 eq. of $LiBHEt_3$ at −20 °C for 10 min smoothly opened the epoxides in excellent yields and without touching the carbamate, and then again, the resulting alcohols were oxidised with DMP. To generate the unsubstituted target bicycles, the alkene in **6-Cbz/6′-Cbz** was cleaved into aldehyde in a single step employing catalytic $K_2OsO_4 \cdot 2H_2O$ and $NaIO_4$ as the oxidant.[24]

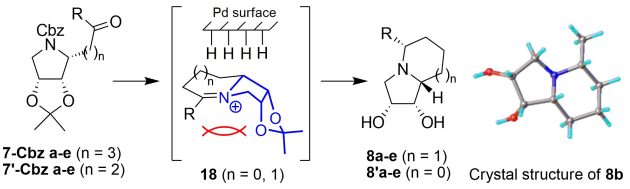
Once we possessed all the carbonyl substrates, we began investigating the final intramolecular reductive amination. Initial hydrogenation in MeOH using 10% Pd/C promoted the desired cyclisation but with very little conversion. Swapping the catalyst for 20% $Pd(OH)_2/C$, increasing the temperature or changing the solvent (EtOH, EtOAc, AcOH) and source of hydrogen (Et_3SiH or HCO_2H) did not bring about any significant improvement. We found those results rather surprising because this reaction proceeded smoothly on the highly similar substrate **4** (Scheme 1) with $Pd(OH)_2/C$ in ethanol. Therefore, we hypothesised that since these bicyclic products **8/8′** lack the relatively bulky and electronegative -OEOM group, they might be more prone to coordination to the palladium through the nitrogen atom, thus poisoning the catalyst and lowering the rate of hydrogenolysis – an effect which is often observed for example in case of triethylamine or pyridine.[25,26] Based on this hypothesis, we tried adding HCl to the reaction mixture to protonate the product and render it unreactive towards Pd-complex formation, which turned out to be a crucial improvement. After some additional optimisations, we managed to devise a robust, high-yielding protocol that smoothly transformed all the carbonyl precursors to the corresponding deprotected bicycles in full conversion, in a single step and with complete diastereocontrol (Table 1). In case of the benzyl analogues, however, higher catalyst loadings and methanol instead of ethanol had to be employed to further push the reaction to completion. As for stereoselectivity of the hydrogenation, we believe it proceeds from the sterically more accessible *exo*-face of the *cis*-fused 5/5 ring system (highlighted in blue) of tricyclic iminium[27] intermediate **18** (Table 1), which was confirmed by an X-ray analysis of indolizidine analogue **8b**.[28] To further support the assignment of configuration at C5, we also carried out a 2D NMR analysis of pyrrolizidine **8′b** (crystallographic analysis not possible for the pyrrolizidine analogues due to their poor crystallisability) including NOE experiments, which showed



a: R = H, **b:** R = Me, **c:** R = Pr, **d:** R = Hex, **e:** R = Bn

Scheme 4. Reagents and conditions: **a)** R′MgBr (R′ = Et, Pe, Ph), CuI (cat.), THF, −20–5 °C, 2–3 h, 93% for **17c**, 91% for **17d**, 93% for **17e**, 82% for **17′c**, 88% for **17′d**, 99% for **17′e**; **b)** $LiBHEt_3$, THF, −20 °C, 10 min, 91% for **17b**, 95% for **17′b**; **c)** DMP, DCM, 0 °C–RT, 2.5–5 h, 91% for **7-Cbz b**, 77% for **7-Cbz c**, 78% for **7-Cbz d**, 96% for **7-Cbz e**, 89% for **7′-Cbz b**, 93% for **7′-Cbz c**, 87% for **7′-Cbz d**, 94% for **7′-Cbz e**; **d)** $K_2OsO_4 \cdot 2H_2O$ (cat.), $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O 3:1, RT, 5–6 h, 84% for **7-Cbz a**, 81% for **7′-Cbz a**. DMP = Dess-Martin periodinane.

Table 1. Intramolecular reductive amination.



Carbonyl substrate n	R	Pd/C loading, solvent	Product (% yield)
3	H	50 wt%, EtOH	**8a** (73)
3	Me	50 wt%, EtOH	**8b** (65)
3	Pr	50 wt%, EtOH	**8c** (88)
3	Hex	50 wt%, EtOH	**8d** (77)
3	Bn	100 wt%, MeOH	**8e** (93)
2	H	50 wt%, EtOH	**8′a** (83)
2	Me	50 wt%, EtOH	**8′b** (100)
2	Pr	50 wt%, EtOH	**8′c** (100)
2	Hex	50 wt%, EtOH	**8′d** (100)
2	Bn	100 wt%, MeOH	**8′e** (91)

Reagents and conditions: H_2, 10% Pd/C, 2 M aq. HCl (2 eq.), solvent, RT, then aq. HCl (excess), RT–50 °C, 1–2 d.

correlations only possible for the (5*S*)-configuration (see NOESY spectra in Supporting Information).

Enzyme Assay

After completion of the synthesis, we wanted to investigate the effect of the missing C8-hydroxyl (relative to swainsonine), ring contraction and substituents on potency and selectivity, so all compounds were submitted for an inhibition study against a Golgi and a lysosomal α-mannosidase. Because the human homologues of Golgi α-mannosidase II are generally difficult to obtain in sufficient amounts and purity,[29] more readily obtainable Golgi α-mannosidase AMAN-2 from *Caenorhabditis elegans* was selected instead based on a previously devised homology model,[13] which was calculated by the Modeller9v2 program[30] employing the sequences UniProtKB–QZPJ74 (AMAN-2) and UniProtKB–Q16706 (hGMII). As for the lysosomal α-mannosidase, commercially available Jack bean mannosidase from *Canavalia ensiformis* was used since it possesses broad specific catalytic activities towards cleavage of α-mannosidic bonds and operates at a lower pH optimum similar to lysosomal-type α-mannosidases.[13] The results showed that all synthesised indolizidines **8** are incomparably weaker inhibitors than swainsonine as their activity was at the micromolar level (see **Table S1** in Supporting Information), which underlines the important role of the C8 hydroxyl in mimicking mannose and driving the potency. The significant decrease in inhibitory activity towards AMAN-2 could be explained by the missing interactions of the C8 hydroxyl with Tyr727 and Asp472 observed for swainsonine in the X-ray structure with *Drosophila* GMII (dGMII, PDB ID: 3BLB),[11,31,32] and for (5*S*)-5-benzylswainsonine docked into the active site of dGMII.[13] Also, the pyrrolizidines **8'** exhibited virtually no inhibitory activity (IC_{50} > 1 mM for both AMAN-2 and JB-Man) so the ring contraction is not a viable modification. To get a better picture of the selectivity of the indolizidines, their IC_{50} values were determined and compared to swainsonine and our previous (5*S*)-5-benzylswainsonine (Table 2). It was found that the larger substituents (R = Hex, Bn) do induce a small degree of selectivity that is 3 times greater than for swainsonine, but still about 40 times lower than for 5-benzylswainsonine, which indicates that the C8-hydroxyl is also important for selectivity. The most potent inhibitor among evaluated compounds **8** was the unsubstituted indolizidine **8a**, which is most likely due to its closest resemblance to the parent natural product.

Table 2. Inhibitory activity and selectivity [IC_{50}(JB-Man)/IC_{50}(AMAN-2)] of the synthesised indolizidines.

Indolizidine	IC_{50} [μM]		Selectivity
	AMAN-2	JB-Man	
8a (R = H)	27 ± 4	90 ± 7	3
8b (R = Me)	530 ± 60	6 700 ± 550	13
8c (R = Pr)	540 ± 55	11 000 ± 1800	20
8d (R = Hex)	240 ± 30	10 000 ± 1200	42
8e (R = Bn)	90 ± 6	3 500 ± 1200	39
Swainsonine[13]	0.0034	0.045	13
(5*S*)-5-Benzyl swainsonine[13]	0.032	53	1656

Conclusions

In summary, we devised a highly practical and divergent 11-step synthesis of 5-substituted 1,2-dihydroxyindolizidines and -pyrrolizidines related to swainsonine and other alkaloids. Configuration at C5 was introduced via intramolecular reductive amination with full stereocontrol, and all intermediates as well as final targets were obtained in high to excellent yields. Therefore, this methodology constitutes a powerful expansion of the set of strategies used to synthesise bicyclic alkaloids. Our synthesised compounds, particularly the indolizidines, were found to be micromolar and weakly selective inhibitors of AMAN-2 (a Golgi α-mannosidase II), so the C8-hydroxyl present in swainsonine plays a critical role in driving both potency and selectivity and probably cannot be excluded from future inhibitors. Additionally, it appears that larger hydrophobic groups at C5 could potentially serve as selectivity-inducing substituents in novel, swainsonine-based α-mannosidase inhibitors.

Acknowledgements

The financial support received from the Scientific Grant Agency of the Ministry of Education of the Slovak Republic and Slovak Academy of Sciences (VEGA 2/0010/23), Slovak Research and Development Agency (APVV-20-0591) and SAS-Taiwan project (SAS-MOST/JRP/2019/882/GM-INHIB) is gratefully acknowledged. This contribution is the result of the project implementation: Centre of Excellence for Glycomics, ITMS26240120031, supported by the Research & Development Operational Program funded by the ERDF. Authors gratefully acknowledge the financial support of "Large Project for Excellent Researchers" No. 09I03-03-V03-00029. Dr. Michal Šoral is gratefully acknowledged for performing NOESY experiments and for helpful discussions of the results. Mrs. Beata Kalivodová and Mrs. Kvetoslava Sabová are gratefully acknowledged for their technical assistance.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: amination · inhibitors · mannosidases · swainsonine · synthesis

[1] M. J. Schneider, F. S. Ungemach, H. P. Broquist, T. M. Harris, *Tetrahedron* **1983**, *39*, 29.
[2] D. R. Gardner, S. T. Lee, R. J. Molyneux, J. A. Edgar, *Phytochem. Anal.* **2003**, *14*, 259.
[3] P. E. Goss, M. A. Baker, J. P. Carver, J. W. Dennis, *Clin. Cancer Res.* **1995**, *1*, 935.
[4] P. Heikinheimo, R. Helland, H.-K. S. Leiros, I. Leiros, S. Karlsen, G. Evjen, R. Ravelli, G. Schoehn, R. Ruigrok, O.-K. Tollersrud, S. McSweeney, E. Hough, *J. Mol. Biol.* **2003**, *327*, 631.
[5] W. Chenchen, W. Wenlong, L. Xiaoxue, M. Feng, C. Dandan, Y. Xiaowen, W. Shanshan, G. Pengshuai, L. Hao, Z. Baoyu, *Environ. Toxicol. Pharmacol.* **2014**, *37*, 336.
[6] W.-A. Chen, Y.-H. Chen, C.-Y. Hsieh, P.-F. Hung, C.-W. Chen, C.-H. Chen, J.-L. Lin, T.-J. R. Cheng, T.-L. Hsu, Y.-T. Wu, C.-N. Shen, W.-C. Cheng, *Chem. Sci.* **2022**, *13*, 6233.
[7] P. E. Goss, C. L. Reid, D. Bailey, J. W. Dennis, *Clin. Cancer Res.* **1997**, *3*, 1077.
[8] K. W. Moremen, *Biochim. Biophys. Acta Gen. Subj.* **2002**, *1573*, 225.
[9] J. W. Dennis, K. Koch, S. Yousefi, I. VanderElst, *Cancer Res.* **1990**, *50*, 1867.
[10] K. Olden, P. Breton, K. Grzegorzewski, Y. Yasuda, B. L. Gause, O. A. Oredipe, S. A. Newton, S. L. White, *Pharmacol. Ther.* **1991**, *50*, 285.
[11] J. M. H. van den Elsen, D. A. Kuntz, D. R. Rose, *EMBO J.* **2001**, *20*, 3008.
[12] D. A. Kuntz, C. A. Tarling, S. G. Withers, D. R. Rose, *Biochemistry* **2008**, *47*, 10058.
[13] M. Kalník, P. Gabko, J. Kóňa, S. Šesták, J. Moncoľ, M. Bella, *Bioorg. Chem.* **2024**, *150*, 107578.
[14] T. Koemans, M. Bennett, M. J. Ferraz, Z. Armstrong, M. Artola, J. M. F. G. Aerts, J. D. C. Codée, H. S. Overkleeft, G. J. Davies, *Chem. Commun.* **2024**, *60*, 11734.
[15] D. A. Kuntz, S. Nakayama, K. Shea, H. Hori, Y. Uto, H. Nagasawa, D. R. Rose, *ChemBioChem* **2010**, *11*, 673.
[16] T. Fujita, H. Nagasawa, Y. Uto, T. Hashimoto, Y. Asakawa, H. Hori, *Org. Lett.* **2004**, *6*, 827.
[17] A. Michalik, J. Hollinshead, L. Jones, G. W. J. Fleet, C.-Y. Yu, X.-G. Hu, R. van Well, G. Horne, F. X. Wilson, A. Kato, S. F. Jenkinson, R. J. Nash, *Phytochem. Lett.* **2010**, *3*, 136.
[18] J. W. Daly, T. F. Spande, H. M. Garraffo, *J. Nat. Prod.* **2005**, *68*, 1556.
[19] T. K. M. Shing, D. A. Elsley, J. G. Gillhouley, *J. Chem. Soc. Chem. Commun.* **1989**, 1280.
[20] T. K. M. Shing, A. W. F. Wong, T. Ikeno, T. Yamada, *J. Org. Chem.* **2006**, *71*, 3253.
[21] S. Šesták, M. Bella, T. Klunda, S. Gurská, P. Džubák, F. Wöls, I. B. H. Wilson, V. Sladek, M. Hajdúch, M. Poláková, J. Kóňa, *ChemMedChem* **2018**, *13*, 373.
[22] M. Kalník, S. Šesták, J. Kóňa, M. Bella, M. Poláková, *Beilstein J. Org. Chem.* **2023**, *19*, 282.
[23] H. Setoi, H. Takeno, M. Hashimoto, *J. Org. Chem.* **1985**, *50*, 3948.
[24] S. Roesner, J. M. Casatejada, T. G. Elford, R. P. Sonawane, V. K. Aggarwal, *Org. Lett.* **2011**, *13*, 5740.
[25] H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981.
[26] Y. Yamamoto, E. Shimizu, K. Ban, Y. Wada, T. Mizusaki, M. Yoshimura, Y. Takagi, Y. Sawama, H. Sajiki, *ACS Omega* **2020**, *5*, 2699.
[27] Z. Hong, X. Ge, S. Zhou, *Int. J. Mol. Sci.* **2022**, *23*, 7621.
[28] CCDC no. 2390526 (**8b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[29] Z. Y. Lee, J. S. E. Loo, A. Wibowo, M. F. Mohammat, J. B. Foo, *Carbohydr. Res.* **2021**, *508*, 108395.
[30] A. Sali, T. L. Blundell, *J. Mol. Biol.* **1993**, *234*, 779.
[31] S. Numao, D. A. Kuntz, S. G. Withers, D. R. Rose, *J. Biol. Chem.* **2003**, *278*, 48074.
[32] D. A. Kuntz, D. R. Rose, "Crystal Structure of Golgi Mannosidase II in Complex with Swainsonine at 1.3 Angstrom Resolution", can be found under https://www.wwpdb.org/pdb?id=pdb_00003blb, **2008**.
[33] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176.
[34] W. H. Kim, J. Kang, H. Lee, A. Park, P. Chun, B. Lee, J. Kim, J. Kim, L. S. Jeong, H. R. Moon, *Carbohydr. Res.* **2009**, *344*, 2317.
[35] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.
[36] L. J. Bourhis, O. V. Dolomanov, R. J. Gildea, J. A. K. Howard, H. Puschmann, *Acta Crystallogr.* **2015**, *A71*, 59.
[37] P. D. Boyle, *J. Appl. Crystallogr.* **2014**, *47*, 467.
[38] L. J. Farrugia, *J. Appl. Crystallogr.* **2012**, *45*, 849.
[39] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339.
[40] H. D. Flack, *Acta Crystallogr.* **1983**, *A39*, 876.
[41] K. Paschinger, M. Hackl, M. Gutternigg, D. Kretschmer-Lubich, U. Stemmer, V. Jantsch, G. Lochnit, I. B. H. Wilson, *J. Biol. Chem.* **2006**, *281*, 28265.

Manuscript received: November 25, 2024
Revised manuscript received: January 31, 2025
Accepted manuscript online: February 12, 2025
Version of record online: February 21, 2025