RSC Advances



View Article Online

View Journal | View Issue

PAPER

Check for updates

Cite this: RSC Adv., 2018, 8, 30076

Highly reactive 2-deoxy-2-iodo-D-allo and D-gulo pyranosyl sulfoxide donors ensure β-stereoselective glycosylations with steroidal aglycones[†]

Jordi Mestre, David Collado, David Benito-Alifonso, Miguel A. Rodríguez, M. Isabel Matheu, (10) Yolanda Díaz, (10) Sergio Castillón (10) and Omar Boutureira (10)*

The preparation of well-defined D-*xylo* and D-*ribo* glycosides represents a synthetic challenge due to the limited configurational availability of starting materials and the laborious synthesis of homogeneous 2-deoxy- β -glycosidic linkages, in particular that of the sugar-steroid motif, which represents the "stereoselective determining step" of the overall synthesis. Herein we describe the use of 2-deoxy-2-iodo-glycopyranosyl sulfoxides accessible from widely available D-xylose and D-ribose monosaccharides as privileged glycosyl donors that permit activation at very low temperature. This ensures a precise kinetic control for a complete 1,2-*trans* stereoselective glycosylation of particularly challenging steroidal aglycones.

Received 6th August 2018 Accepted 11th August 2018

DOI: 10.1039/c8ra06619a

rsc.li/rsc-advances

Introduction

2-Deoxy- and 2,6-dideoxy-β-glycosides are common architectures present in many biologically active ingredients such as antibiotics, appetite suppressants, and nucleosides.1 These deoxyglycosides, and especially cardiac glycosides (e.g., cardenolides N-1 from Nerium oleander or those from chrysomelid beetles,³ and helveticoside4), are usually composed of uncommon glycosyl moieties including D-ribo and D-xylo-configured pyranoses (Fig. 1). While these glycoconjugates, with the general structure $[sugar]_n$ -aglycone, are nicely produced in nature, most of the chemical glycosylation approaches⁵ for their preparation are mainly focused on the sugar-sugar motif but are still inefficient for the β -stereoselective synthesis of the sugar-steroid portion. In addition, the β -stereoselectivity is typically better for the construction of the sugar–sugar motif (up to only β) compared to that of the sugar-steroid fragment (up to 9 : 1 β/α) and thus, the latter glycosylation step represents the overall "stereoselective determining step" in 2-deoxy and 2,6-dideoxyglycoconjugates featuring such particular configurations.^{5,6} Our group has developed an indirect⁷ synthetic approach for the stereoselective synthesis of 2-deoxy- and 2,6-dideoxy-2-iodoglycosides that utilizes 2-deoxy-2-iodo-1-thioglycoside donors, being particularly effective for the production of β-D-allo and β-D-gulo pyranosides.^{2,8-10} The resulting configuration is predefined by the starting furanose and thus, D-ribo and D-xylo structures serve as configurational templates for *D-allo* and *D-gulo* pyranosides, respectively. Our findings determined the key β -selective

glycosylation step is kinetically-controlled and the presence of iodine favours the stereoselective formation of a 1,2-trans glycoside via the least energetic transition state upon preferential nucleophilic attack to the oxonium intermediate ³H₄. This is consistent with the Felkin-Anh-Eisenstein 1,2-induction model with stabilizing hyperconjugative interactions between σ_{C-I}^* and σ_{C-OR} (Scheme 1). According to most current models,¹¹ the stereoselectivity is determined by the interplay between (a) the ground-state conformational preferences of oxocarbenium intermediates $({}^{4}H_{3} vs. {}^{3}H_{4})$ in which electronegative substituents such as I and OBn prefer a pseudo-axial disposition due to stabilizing electrostatic and/or hyperconjugative interactions (e.g., between σ_{C-I} and π^*_{C-O}) and (b) the relative reactivity of each conformer under the S_N1 paradigm, according to a Curtin-Hammett kinetics scenario. In this context, while glycosylations of 2-deoxy-2-iodo-1-thioglycosides with sugar acceptors proceed at ca. -40 °C and provided reasonably good selectivities (up to 16 : 1 β/α), we observed a reduction to 8 : 1 β/α with steroidal aglycones (Scheme 1).8 We reasoned that prior oxidation of the 1thiophenyl donor to a glycosyl sulfoxide (SPh \rightarrow S(O)Ph) would enhance reactivity enabling its activation at lower



Fig. 1 Naturally occurring 2-deoxy and 2,6-dideoxy- β -glycosides with "rare" D-xylo and D-ribo configurations.

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo 1, 43007 Tarragona, Spain. E-mail: omar.boutureira@urv.cat † Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra06619a



Scheme 1 Scope and limitations of the stereoselective synthesis of β -steroidal glycosides of D-*ribo* and D-*xylo* configurations – using sulfoxides to improve key "sugar–aglycone" glycosylation step.

temperatures.^{12,13} Hence, iodine control will perform better at lower temperatures restoring the kinetic control in challenging glycosylations as those using steroidal aglycones, favouring the selective formation of β -glycosides.

Results and discussion

Preliminary oxidation studies of 1 with mCPBA (in $CHCl_3$)¹³ and Selectfluor[™] (in CH₃CN)¹⁴ revealed the high reactivity of the resulting sulfoxide 2, which evaded isolation due to decomposition. The best protocol used mCPBA as the sole oxidant in CH₂Cl₂ from -80 °C to -50 °C, followed by neutralization of the residual benzoic acid with NaHCO₃, removal of the precipitate, and conducting the following glycosylation in sequence (Table 1). Thus, dichloromethane perfectly combines chemical inertness towards oxidants, good oxidation rate of sulfides using peroxy acids at the low temperatures necessitated to avoid decomposition,15 and good β -selective properties in the subsequent glycosylation reaction with sulfoxides (up to $3:1 \beta/\alpha$ ratio with Bn as protecting groups).¹³ To verify the formation of 2, oxidation was monitored by ¹H NMR in CD₂Cl₂ (Scheme 2). The signal peak at 5.10 ppm corresponding to the H-1 proton of the predominant 1β-anomer was gradually converted to two new doublets at 5.14 and 5.02 ppm, tentatively assigned to $2\beta(S)$ and $2\beta(R)$, respectively with a 88 : 12 dr. Although the signal of $2\beta(S)$ was gradually shifted upfield upon warming from -70 to -15 °C, the $\Delta\delta$ of *ca*. 0.2 ppm between the two stereoisomers was in accordance with previously reported diastereomeric sulfoxides.16

The identity of 2 was further confirmed by high-resolution mass spectrometry analysis (HRMS). Next, glycosylation was explored comparing the selectivities obtained for the activation of 1 and 2 (Table 1). Standard glycosylation using 1-thiophenyl donor 1 resulted in excellent β -stereoselectivities with primary 4-nitro-benzyl alcohol 3a (up to 30 : 1 β/α) and secondary methyl glucoside alcohol 3b (16 : 1 β/α) (entries 1 and 3).⁸ In contrast, employing cholesterol 3c as representative steroidal acceptor substantially decreased the selectivity to 8 : 1 β/α ratio and the

thermodynamically more stable α -anomer could not be separated from its β -counterpart. Alternatively, oxidation of **1** followed by activation using the Tf₂O/DTBMP system at -80 °C afforded the corresponding glycosides in very short reaction times and good yields (up to 80%). Glycosylation with primary benzylic **3a** and

Table 1 Glycosylation scope (SPh vs. S(O)Ph)^a



Entry	ROH	Conditions	$\operatorname{Yield}^{b}(\%)$	β/α ratio ^c
1	3a	А	4a (72)	30:1
2	3a	В	4a (80)	40:1
3^d	3b	Α	4b (61)	16:1
4	3b	В	4b (69)	24:1
5^d	3c	Α	4c (66)	8:1
6	3c	В	4c (63)	21:1

^{*a*} Conditions A: **1** (1 mmol), ROH **3a-c** (2 mmol) and 4 Å molecular sieves (MS) in CH₂Cl₂ (4 mL) at -80 °C. Then, addition of NIS (3 mmol) and TfOH (0.2 mmol) at -80 °C to -40 °C. Conditions B: **1** (1 mmol), *m*CPBA (1.1 mmol) and 4 Å MS in CH₂Cl₂ (30 mL) at -80 °C. Then, NaHCO₃ (5 mmol), filtration and addition of ROH **3a-c** (2 mmol), DTBMP (3 mmol), 4 Å MS and Tf₂O (2 mmol) at -80 °C. ^{*b*} Isolated yield. ^{*c*} Calculated by integration of anomeric protons in the ¹H NMR spectrum of the crude reaction mixture. ^{*d*} See ref. 8.





Finally, the unique combination of oxidation/glycosylation sequence of this strategy was utilized for the synthesis of 2-deoxy-2-iodo- β -pyranosides 7 and 8 with high stereoselectivities (>22 : 1 β/α) and good yields (up to 64%) using the steroidal acceptor digitoxigenin 6 and *D-gulo-* and *D-allo-*1-thiopyranosides 1 and 5a as glycosyl donors (Scheme 3). The stereochemistry of the C-4 substituent had little effect on the selectivity although the slight improvement in the *D-allo* configuration may be explained by the less entropically disfavored β -transition state resulting from the stabilizing pseudoaxial positioning of OBn in the ³H₄ conformer (Scheme 1).^{11,17} Elaboration of 7 and 8 under conventional deiodination and debenzylation conditions² afforded final 2-deoxy cardiac glycosides 9 and 10 in excellent yields (up to 95%).

Likewise, cholesterol **3c** was subjected to the same oxidation/ glycosylation sequence with the more challenging 2,6-dideoxy glycosyl donor **5b** to afford 2,6-dideoxy-2-iodo-*D*-*allo* derivative **11** with good stereoselectivity (20 : 1 β/α)^{2,9d} and moderate overall yield (52%). Final products **9** and **10** as well as their precursors **7**, **8** and **11** adopted a ${}^{4}C_{1}$ conformation as determined by NOE experiments and the analysis of diagnostic coupling constants (${}^{3}J_{1,2} \sim 9$ Hz and ${}^{1}J_{C1-H1} \sim 163$ Hz).



Scheme 3 Synthesis of 2-deoxy- and 2,6-dideoxy-2-iodo- β -pyranosides 7, 8 and 11 and deprotection steps to digitoxigenyl 2-deoxy- β -*D*-xylo and D-*ribo* cardiac glycosides 9 and 10. Reagents and conditions: (a) *m*CPBA, 4 Å MS, CH₂Cl₂ from -80 °C to -40 °C, 30 min; (b) 3,6, DTBMP, 4 Å MS, Tf₂O, -80 °C, 30 min; (c) Bu₃SnH, Et₃B, toluene, rt, 1 h; (d) H₂ (1 atm), 10% Pd/C, 1 : 1 EtOAc/MeOH, 0 °C, 1–3 h.

Conclusions

In conclusion, the present work upgrades the previous reported methodology (using 1-thioglycosides) for the stereoselective synthesis of 2-deoxy- β -glycosides with D-*ribo* and D-*xylo* configurations, improving the overall β -control using challenging steroidal aglycones. The enhanced reactivity of glycosyl sulfoxides and the presence of an equatorial steering iodine permitted the precise formation of complex 2-deoxy- β -glycosides after removal of the temporary directing element. We expect that the present protocol will find broad application in the chemical synthesis of steroidal glycosides for the medicinal research field.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Spanish Government-MINECO and the national agency of investigation-AEI (CTQ2017-89750-R and CTQ2017-

90088-R), the European Regional Development Fund, and the Universitat Rovira i Virgili (Martí Franquès Research Fellowship Programme to J. M. and D. C.) for financial support. We also thank Arnau R. Rubio for preliminary experiments. O. B. is a Ramón y Cajal Fellow (RYC-2015-17705).

Notes and references

- (a) B. Heasley, Chem.-Eur. J., 2012, 18, 3092; (b) J. Zhang, H. Shi, Y. Ma and B. Yu, Chem. Commun., 2012, 48, 8679; (c) R. M. De Lederkremer and C. Marino, Adv. Carbohydr. Chem. Biochem., 2008, 61, 143; (d) H. P. Albrecht, in Naturally Occurring Glycosides, ed. R. Ikan, Wiley, Chichester, 1999; (e) A. C. Weymouth-Wilson, Nat. Prod. Rep., 1997, 14, 99; (f) L. D. Nord, N. K. Dalley, P. A. McKernan and R. K. Robins, J. Med. Chem., 1987, 30, 1044; (g) A. Kirschning, A. F.-W. Bechthold and J. Rohr, Top. Curr. Chem., 1997, 188, 1.
- 2 J. Mestre, M. I. Matheu, Y. Díaz, S. Castillón and O. Boutureira, *J. Org. Chem.*, 2017, **82**, 3327.
- 3 D. Daloze, F. Broeders, J.-C. Braekman, J. Araujo and J. M. Pasteels, *Biochem. Syst. Ecol.*, 1995, 23, 113.
- 4 T. Nakamura, Y. Goda, S. Sakai, K. Kondo, H. Akiyama and M. Toyoda, *Phytochemistry*, 1998, **49**, 2097.
- 5 (a) C. S. Bennett and M. C. Galan, *Chem. Rev.*, 2018, DOI: 10.1021/acs.chemrev.7b00731; (b) J. Zeng, Y. Xu, H. Wang, L. Meng and Q. Wan, *Sci. China: Chem.*, 2017, **60**, 1162; (c) S. Medina and M. C. Galan, in *Carbohydrate Chemistry*, Royal Society of Chemistry, Cambridge, 2016, 41, p. 59; (d) A. Borovika and P. Nagorny, *J. Carbohydr. Chem.*, 2012, **31**, 255; (e) D. Hou and T. L. Lowary, *Carbohydr. Res.*, 2009, **344**, 1911; (f) C. H. Marzabadi and R. W. Franck, *Tetrahedron*, 2000, **56**, 8385.
- 6 (a) J. Zeng, G. Sun, R. Wang, S. Zhang, S. Teng, Z. Liao, L. Menga and Q. Wan, Org. Chem. Front., 2017, 4, 2450; (b)
 K. N. Baryal, S. Adhikari and J. Zhu, J. Org. Chem., 2013, 78, 12469; (c) Y. Ma, Z. Li, H. Shi, J. Zhang and B. Yu, J. Org. Chem., 2011, 76, 9748; (d) H. Tanaka, A. Yoshizawa and T. Takahashi, Angew. Chem., Int. Ed., 2007, 46, 2505; (e)
 M. Zhou and G. A. O'Doherty, J. Org. Chem., 2007, 72, 2485; (f) K. Toshima, Carbohydr. Res., 2006, 341, 1282; (g)
 M. Zhou and G. A. O'Doherty, Org. Lett., 2006, 8, 4339; (h)
 F. E. McDonald and K. S. Reddy, Angew. Chem., Int. Ed., 2001, 40, 3653; (i) F. E. McDonald, K. S. Reddy and Y. Díaz, J. Am. Chem. Soc., 2000, 122, 4304; (j) K. Wiesner, T. Y. R. Tsai and H. Jin, Helv. Chim. Acta, 1985, 68, 300.
- 7 (a) S. K. Battina and S. Kashyap, *Tetrahedron Lett.*, 2016, 57, 811; (b) H. Wang, J. Tao, X. Cai, W. Chen, Y. Zhao, Y. Xu, W. Yao, J. Zeng and Q. Wan, *Chem.-Eur. J.*, 2014, 20, 17319; (c) M. De Castro and C. H. Marzabadi, *Tetrahedron*, 2010, 66, 3395; (d) T. B. Durham and W. R. Roush, *Org. Lett.*, 2003, 5, 1871; (e) P. Y. Chong and W. R. Roush, *Org. Lett.*, 2002, 4, 4523.
- 8 M. A. Rodríguez, O. Boutureira, X. Arnés, Y. Díaz,
 M. I. Matheu and S. Castillón, *J. Org. Chem.*, 2005, **70**, 10297.
- 9 (a) A. Kövér, O. Boutureira, M. I. Matheu, Y. Díaz and S. Castillón, *J. Org. Chem.*, 2014, **79**, 3060; (b)

O. Boutureira, M. I. Matheu, Y. Díaz and S. Castillón, *RSC Adv.*, 2014, 4, 19794; (c) I. Cobo, M. I. Matheu, S. Castillón,
O. Boutureira and B. G. Davis, *Org. Lett.*, 2012, 14, 1728; (d)
M. A. Rodríguez, O. Boutureira, M. I. Matheu, Y. Díaz and
S. Castillón, *Eur. J. Org. Chem.*, 2007, 2470; (e)
M. A. Rodríguez, O. Boutureira, M. I. Matheu, Y. Díaz,
S. Castillón and P. H. Seeberger, *J. Org. Chem.*, 2007, 72, 8998; (f)
O. Boutureira, M. A. Rodríguez, M. I. Matheu,
Y. Díaz and S. Castillón, *Org. Lett.*, 2006, 8, 673.

- 10 (a) O. Boutureira, M. A. Rodríguez, Y. Díaz, M. I. Matheu and S. Castillón, *Carbohydr. Res.*, 2010, 345, 1041; (b)
 O. Boutureira, M. A. Rodríguez, D. Benito, M. I. Matheu, Y. Díaz and S. Castillón, *Eur. J. Org. Chem.*, 2007, 3564; (c)
 O. Boutureira, M. I. Matheu, Y. Díaz and S. Castillón, *Carbohydr. Res.*, 2007, 342, 736.
- 11 (a) A. Martin, A. Arda, J. Désiré, A. Martin-Mingot, N. Probst, P. Sinaÿ, J. Jiménez-Barbero, S. Thibaudeau and Y. Blériot, Nat. Chem., 2016, 8, 186; (b) M. T. C. Walvoort, J. Dinkelaar, L. J. van den Bos, G. Lodder, H. S. Overkleeft, J. D. C. Codée and G. A. van der Marel, Carbohydr. Res., 2010, 345, 1252; (c) M. Heuckendorff, C. M. Pedersen and M. Bols, Chem.-Eur. J., 2010, 16, 13982; (d) D. Hou, H. A. Taha and T. L. Lowary, J. Am. Chem. Soc., 2009, 131, 12937; (e) M. G. Beaver, S. B. Billings and K. A. Woerpel, J. Am. Chem. Soc., 2008, 130, 2082; (f) D. M. Smith and K. A. Woerpel, Org. Biomol. Chem., 2006, 4, 1195; (g) F. Bravo, A. Viso, E. Alcázar, P. Molas, C. Bo and S. Castillón, J. Org. Chem., 2003, 68, 686.
- 12 (a) B. Yang, W. Yang, S. Ramadan and X. Huang, *Eur. J. Org. Chem.*, 2018, 1075; (b) W. Yang, B. Yang, S. Ramadan and X. Huang, *Beilstein J. Org. Chem.*, 2017, 13, 2094; (c) M. A. Fascione, R. Brabham and W. B. Turnbull, *Chem.-Eur. J.*, 2016, 22, 3916; (d) M. C. Aversa, A. Barattucci and P. Bonaccorsi, *Tetrahedron*, 2008, 64, 7659.
- 13 D. Kahne, S. Walker, Y. Cheng and D. Van Engen, *J. Am. Chem. Soc.*, 1989, **111**, 6881.
- 14 S. P. Vincent, M. D. Burkart, C.-Y. Tsai, Z. Zhang and C.-H. Wong, *J. Org. Chem.*, 1999, **64**, 5264.
- 15 R. Curci, R. A. DiPrete, J. O. Edwards and G. Modena, *J. Org. Chem.*, 1970, **35**, 740.
- 16 (a) T. Taniguchi, M. Asahata, A. Nasu, Y. Shichibu, K. Konishi and K. Monde, *Chirality*, 2016, 28, 534; (b) J. F. Moya-López, E. Elhalem, R. Recio, E. Álvarez, I. Fernández and N. Khiar, *Org. Biomol. Chem.*, 2015, 13, 1904.
- 17 (a) N. Aiguabella, M. C. Holland and R. Gilmour, Org. Biomol. Chem., 2016, 14, 5534; (b) N. Santschi and R. Gilmour, Eur. J. Org. Chem., 2015, 6983; (c) E. Durantie, C. Bucher and R. Gilmour, Chem.-Eur. J., 2012, 18, 8208; (d) C. Bucher and R. Gilmour, Angew. Chem., Int. Ed., 2010, 49, 8724; (e) J. A. C. Romero, S. A. Tabacco and K. A. Woerpel, J. Am. Chem. Soc., 2000, 122, 168; (f) R. J. Woods, C. W. Andrews and J. P. Bowen, J. Am. Chem. Soc., 1992, 114, 850; (g) R. J. Woods, C. W. Andrews and J. P. Bowen, J. Am. Chem. Soc., 1992, 114, 859.