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An Orthogonally Protected Cyclitol for the Construction of Nigerose- and Dextran-Mimetic Cyclophellitols

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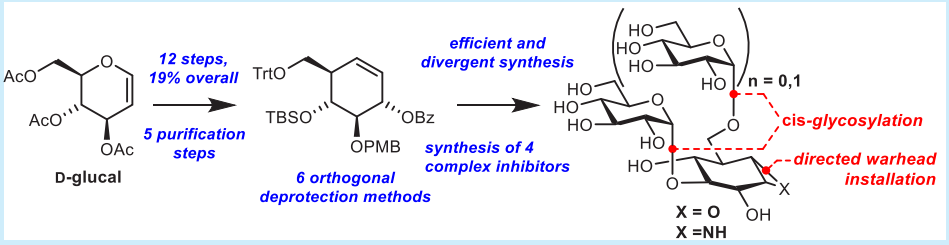

ABSTRACT: Cyclophellitols are potent inhibitors of exo- and endoglycosidases. Efficient synthetic methodologies are needed to fully capitalize on this intriguing class of mechanism-based enzyme deactivators. We report the synthesis of an orthogonally protected cyclitol from D-glucal (19% yield over 12 steps) and its use in the synthesis of α-(1,3)-linked di- and trisaccharide dextran mimetics. These new glycomimetics may find use as Dextranase inhibitors, and the developed chemistries in widening the palette of glycoprocessing enzyme-targeting glycomimetics.

Cyclophellitol is a natural product isolated from species of the *Phellinus* sp. mushroom and is a potent irreversible inhibitor of retaining β-exoglucosidases.[1,2] Since its discovery, a number of syntheses of cyclophellitol have appeared in the literature.[3−6] Cyclophellitol is a densely functionalized cyclohexane featuring the β-D-glucopyranose configuration with an epoxide bridging C1 and C7.[1,2] The epoxide forces the cyclohexane ring into a $^4H_3$ conformation, which is also the expected conformation of the transition state oxocarbenium ion that emerges during the enzyme-catalyzed hydrolysis of β-glucosidic linkages by retaining β-glucosidase enzymes.[7] Binding in the active site results in a stable ester-linked enzyme−inhibitor adduct, effectively incapacitating the enzyme. This mode of action makes it attractive for use in activity-based protein profiling (ABPP).[7−10] We showed that tagging cyclophellitol, and its nitrogen congener, cyclophellitol aziridine, with a reporter entity (biotin or a fluorophore) allows for very sensitive profiling of retaining β-glucosidases.[11] In a follow-up study, we revealed that the same holds true for 1,7-epi-cyclophellitol (or α-cyclophellitol) and the corresponding aziridine in inhibiting and tagging retaining α-glucosidases.[12] ABPP now finds wide use in glycobiology research, and a host of configurational and functional cyclophellitol analogues have been reported, each targeting unique retaining exo- and endoglycosidases in the context of drug discovery and bulk polysaccharide processing enzyme discovery.[13−18] However, retaining glycosidase ABPP has not yet been exploited to its fullest potential, and this is, at least in part, due to the challenges associated with the synthesis of cyclophellitol-based inhibitors and probes, challenges that reside in the manipulations of the functionalized cyclohexene/cyclitol epoxide/aziridine cores that are required to create diverse substitution patterns including glycosidic linkages. With the aim of extending the scope of synthetic cyclophellitol-based glycosidase inhibitors and probes, we revisited our synthesis strategies for α-cyclophellitols with a special focus on the orthogonality of protection group arrays in advanced intermediates. The results of these studies are presented here and entail the synthesis of a fully orthogonal cyclophellitol building block in 12 steps, starting from commercially available 3,4,6-tri-*O*-acetyl-D-glucal, and the demonstration of its versatility in the construction of glycosylated α-cyclophellitols mimicking linear and branched dextran substructures.

The synthesis of orthogonally protected cyclitol **7** started from compound **1** (Scheme 1), synthesized as described by Ma and co-workers.[19] The ensuing key thermal [3,3]-sigmatropic Claisen rearrangement (heating of **1** in diphenyl ether to 210 °C) yielded intermediate aldehyde **2**, which was directly reduced with $NaBH_4$ to give alcohol **3** (80% over two steps) according to literature precedent.[20−22] Tritylation of the

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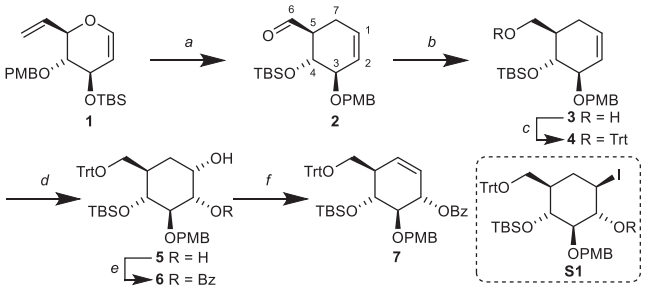
Scheme 1. Synthesis of 7[a]



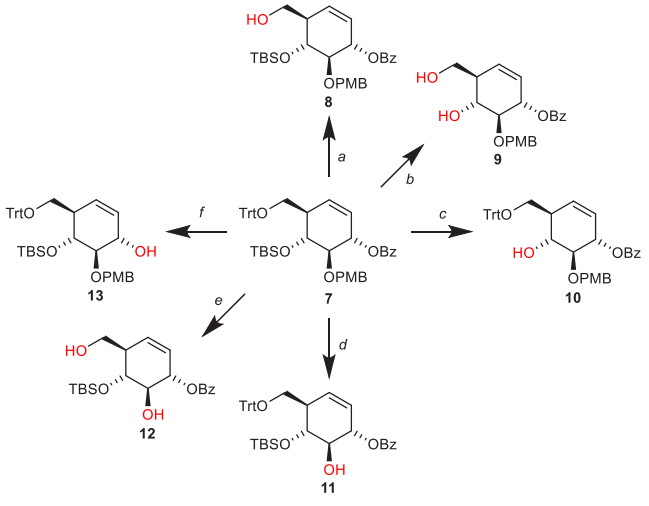
[a]Reagents and conditions: (a) Ph_2O, 210 °C; (b) $NaBH_4$, THF, EtOH (80% over two steps); (c) TrtCl, Et_3N, DMAP, DCM; (d) OsO_4, NMO, acetone, H_2O; (e) BzCl, pyridine, −15 °C (79% over three steps); (f) (i) MTPI, 2,6-lutidine, DMF, 100 °C; (ii) *m*-CPBA, $NaHCO_3$, 0 °C (75%).

primary alcohol in **3** followed by dihydroxylation of the alkene (OsO_4 and NMO) yielded α-glucopyranose-configured *syn*-diol **5** as the single isolated product. Subsequently, the 2-OH was regioselectively protected with BzCl in pyridine at −15 °C to yield compound **6** (79% over three steps).[23]

With intermediate **6** in hand, attempts were made to regioselectively eliminate the 1-OH to afford alkene **7**. To this end, we screened a number of elimination conditions (Table S1). The best results were obtained upon treating compound **6** with methyltriphenoxyphosphonium iodide (MTPI) and the sterically hindered base 2,6-lutidine in DMF at an elevated temperature.[24] This procedure gave the desired elimination product **7**, together with an iodide **S1**. We found that careful exposure of this mixture of compounds to *m*-CPBA and $NaHCO_3$ resulted in oxidation and subsequent *syn* elimination of hypoiodous acid, while leaving the alkene intact (see Scheme S1).[25] Alkene **7** was thus obtained in a total yield of 75%.[26]

We then turned to the orthogonal deprotection of **7**, using various conditions (Scheme 2). Treatment of **7** with a Lewis acid ($ZnCl_2$) in the presence of a nucleophile (methanol)

Scheme 2. Orthogonal Deprotection of Cyclohexene 7[a]

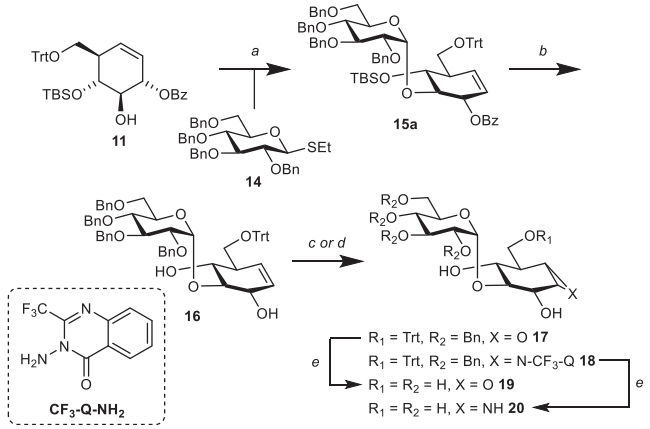


[a]Reagents and conditions: (a) $ZnCl_2$, MeOH, DCM (87%); (b) *p*-TsOH, MeOH, DCM (84%); (c) TBAF, THF (95%); (d) DDQ, DCM, aqueous phosphate buffer (pH 7.4)[27] (91%); (e) TFA, TES, DCM (84%); (f) NaOMe, MeOH, DCM (86%).

resulted in the clean removal of the trityl protecting group in high yield (compound **8**, 87%), whereas treatment with a Brønsted acid (TsOH) under the same conditions resulted in the simultaneous removal of the trityl and TBS protecting groups (compound **9**, 84%). Selective, orthogonal removal of the TBS protecting group could be achieved by treatment with TBAF in THF, to yield compound **10** (95%). The PMB protecting group was oxidatively removed using DDQ in a biphasic medium consisting of DCM and aqueous phosphate buffer,[27] leading to compound **11** (91%). The PMB and trityl protecting groups were removed by subjecting **7** to TFA and TES in anhydrous DCM to yield diol **12** (84%). The TBS protecting group was left untouched due to the absence of a nucleophile. The benzoyl protecting group was removed by saponification with NaOMe in DCM/MeOH, affording compound **13** (86%). Larger scale deprotections were performed successfully using crude cyclohexene **7** (see Scheme S2).

Having established the full orthogonality of the protective group pattern in cyclohexene **7**, we thought to demonstrate their value by the synthesis of a set of α(1,3)-linked di- and trisaccharide structures. These structures [**19**/**20** and **27**/**28** (Schemes 3 and 4, respectively)] can be regarded as

Scheme 3. Assembly of Disaccharide Target Structures 19 and 20[a]



[a]Reagents and conditions: (a) TTBP, Ph_2SO, donor **14**,[30] 3 Å molecular rods, DCM, −78 °C, then **11** (88%; 4:1 α:β); (b) (i) TBAF, THF; (ii) NaOMe, DCM, MeOH (66%); (c) *m*-CPBA, $NaHCO_3$, DCM (70% for **17**); (d) BAIB, CF_3-Q-NH_2, DCM (76% for **18**); (e) Na, *t*-BuOH, NH_3, −60 °C (71% for **19**, 86% for **20**).

cyclophellitol derivatives of nigerose [α(1,3)-linked glucose] and dextran [α(1,6)-branched α(1,3)-linked glucose] and are thus envisioned as potential inhibitors for the corresponding nigerase and Dextranase enzymes.[28,29]

Preactivation-based glycosylation of **11** with glucose donor **14**[30] yielded a separable mixture of stereoisomers (**15a**/**15b**, 4:1, 88%). Removal of the TBS and benzoyl protecting groups from disaccharide **15a** by standard deprotection procedures gave **16** in 66% yield over two steps. The stereoselective installation of the epoxide and aziridine warheads was achieved making use of the directing effect of the allylic alcohol on the C2 position. Treatment of **16** with *m*-CPBA and $NaHCO_3$ in anhydrous DCM yielded exclusively α-epoxide **17** in 70% yield. Conversion of precursor **16** to the aziridine was accomplished using 3-amino-2-(trifluoromethyl)quinazolin-

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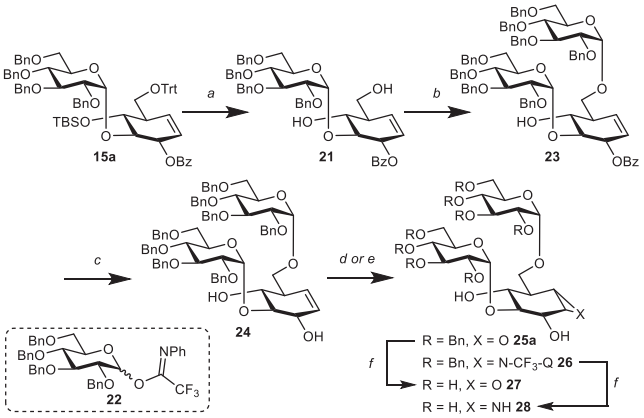
Scheme 4. Assembly of Trisaccharide Target Structures 27 and 28[a]



[a]Reagents and conditions: (a) (i) TES, TFA, DCM, 0 °C; (ii) TBAF, THF (72%); (b) donor **22**, PPh_3O, TMSI, 3 Å molecular rods, DCM (79%); (c) NaOMe, MeOH, DCM (72%); (d) *m*-CPBA, $NaHCO_3$, DCM (69%; 1:1 α:β); (e) BAIB, CF_3-Q-NH_2, DCM (62%); (f) Na, *t*-BuOH, NH_3, −60 °C (91% for **27**, 87% for **28**).

4(3*H*)-one (CF_3-Q-NH_2) and BAIB in anhydrous DCM, exclusively yielding α-aziridine **18** in 76% yield.[31] Birch reduction of compounds **17** and **18** resulted in the clean removal of the benzyl, trityl, and CF_3-Q protecting groups, yielding compounds **19** and **20** in 71% and 86% yields, respectively.

The synthesis of dextran analogue trisaccharidic compounds **27** and **28** (Scheme 4) started by subjecting alkene **15a** to TFA and TES in anhydrous DCM, to selectively remove the trityl protecting group, followed by removal of the TBS protecting group by treatment with TBAF in THF, yielding compound **21** (72% over two steps). Acceptor **21** was treated with an excess of *N*-phenyltrifluoroacetimidate donor **22**[32] in the presence of PPh_3O and TMSI in anhydrous DCM, following the literature procedures,[33,34] to yield α(1,6)-linked trimer **23** (79%). Saponification of the benzoyl protecting group then liberated the 2-OH to direct the epoxidation/aziridination reactions. Surprisingly, conversion of alkene **24** to the epoxide with *m*-CPBA and $NaHCO_3$ in anhydrous DCM proceeded with no stereoselectivity to yield a mixture of separable stereoisomers (**25a** and **25b**), with a combined yield of 69%. The stereochemistry of the two isomers was unequivocally established by NOESY NMR experiments (see the Supporting Information). Conversion of **24** to the aziridine was accomplished by treatment with CF_3-Q-NH_2 and BAIB in anhydrous DCM, and this transformation did proceed with complete diastereotopic selection to yield α-aziridine **26** in 76%. Final deprotection of both **25a** and **26** under Birch conditions resulted in the cleavage of all benzyl and CF_3-Q protecting groups to afford trisaccharides **27** and **28** in 91% and 87% yields, respectively.

In conclusion, we have developed a synthetic route toward a versatile, fully orthogonal cyclophellitol building block, which can be obtained on a multigram scale with an overall yield of 19% over 12 steps. The synthesis route has been optimized to require only five column purification steps. The key transformation involved the two-step, regioselective elimination of the C1-OH in carbaglucose **6** using MTPI and subsequent treatment with *m*-CPBA, leading to the overall transposition of the initially formed 1,2-alkene to the corresponding 1,7-alkene. Subjecting this building block to several deprotection methods demonstrated the orthogonal nature of the protecting groups. To illustrate its versatility, a number of complex glycomimetics resembling the structures of the natural polysaccharides nigerose and dextran were synthesized. Combined, we believe the methodology presented here will assist in the generation of complex inhibitors and activity-based probes for use in understanding and modulating carbohydrate-processing enzymes in glycobiology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03723.

Experimental procedures, characterization data, and ^1H, ^{13}C, and two-dimensional NMR spectra for representative compounds (PDF)

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Notes

The authors declare no competing financial interest.

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