An Efficient Synthesis of Cyclophellitol Utilizing Unusual Regioselectivity of Oxirane Ring Opening with Mes$_2$BCH$_2$Li

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Abstract

Cyclophellitol has been synthesized from 5,6-enoglucoside efficiently. The carbacyclic skeleton was constructed through a Ferrier reaction mediated by PdCl$_2$. The regioselectivity on the oxirane ring opening with Mes$_2$BCH$_2$Li at the key step is found to be controlled by the hydroxy protecting group. © 1998 Elsevier Science Ltd. All rights reserved.

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Glycosidases are a family of essential enzymes in the human body and play important roles in maintaining many biological functions.[1] The discovery of potent glycosidase inhibitors, therefore, is generally recognized as leading to promising candidates for new drug development. [2-6] Some of them are practically used as an antidiabetic agent; also, it is reported that glucosidase inhibitors have the interesting activity to inhibit HIV infection and metastasis. [7-8] Cyclophellitol is a potent β-glucosidase inhibitor (IC$_{50}$ value against almond β-glucosidase : 0.8 μg/ml), which was isolated from culture filtrates of a mushroom, *Phellinus sp.* by Umezawa and coworkers.[9-10] In addition, cyclophellitol has a unique structural feature: the fully oxygenated carbacyclic analogue of D-glucopyranose containing a β-epoxide moiety. More interestingly, Tatsuta also reported that the stereoisomer of this compound, *epi*-cyclophellitol, which has an α-epoxide configuration, displayed potent α-glucosidase inhibitory activity.[11-12] This finding means that there is high possibility that specific inhibitors can be expected by alteration of the stereochemistry of cyclophellitol. For these reasons, several syntheses of cyclophellitol and its analogues have been reported recently.[12-21] Herein we disclose an efficient synthesis of cyclophellitol which is applicable to the syntheses of diastereomers of cyclophellitol.

† Deceased March 16, 1997.

Our synthetic strategy is illustrated in Scheme 1. Final epoxide formation is the known procedure.[12] An introduction of the preceding hydroxymethyl moiety could be accomplished by oxirane opening with a hydroxymethyl anion equivalent under unusual regioselectivity (equatorial attack).

Scheme 1

cyclophellitol
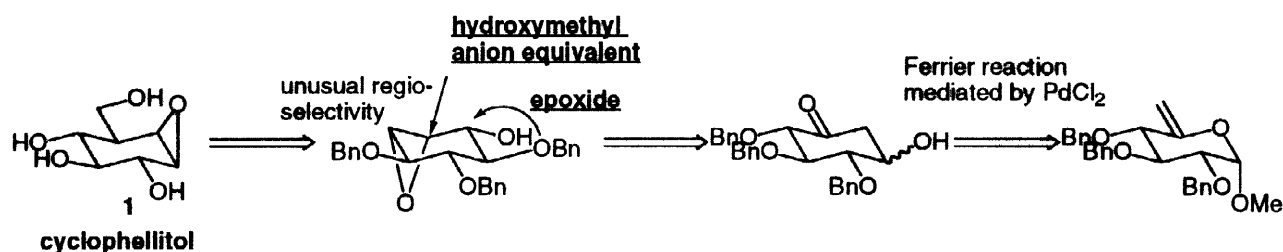
The highly oxygenated carbacyclic skeleton would be constructed in the early stage of the synthesis by a $PdCl_2$-mediated Ferrier reaction developed in our laboratory.[22] Scheme 2 shows the first half of our synthetic route.

Scheme 2
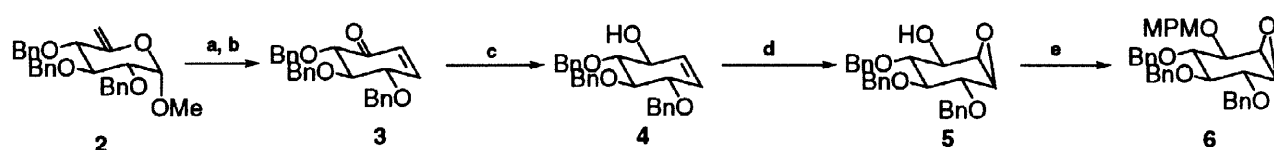
Reagents and conditions: a)$PdCl_2$, dioxane - H_2O, 60 °C, 3 h, 81%; b) MsCl, Et_3N, CH_2Cl_2, r.t., 9 h, 74%; c) $CeCl_3$•$7H_2O$, $NaBH_4$, MeOH, 0 °C, 15 min, 87%; d) mCPBA, Na_2HPO_4, CH_2Cl_2, r.t., 4 days, quant.; e) NaH, MPMCl, DMF - THF, r.t., 2 h, 93%.

The synthesis commenced with the Ferrier reaction of 2 promoted by a catalytic amount (5 mol%) of $PdCl_2$ followed by dehydration with MsCl-pyridine to give enone 3 (60% yield for 2 steps). Stereoselective reduction of the ketone moiety with $CeCl_3$/$NaBH_4$[23] afforded β-alcohol 4 in 87% yield. Subsequent oxidation with mCPBA yielded epoxide 5 efficiently in a highly diastereoselective manner. The remaining hydroxy group was protected as an MPM ether to give 6 (93% yield). The reason why the MPM group was selected is described later.

The following introduction of a hydroxymethyl group by nucleophilic opening of the epoxide with a hydroxymethyl anion equivalent was the most challenging task in the synthesis. In general, the nucleophilic opening of an epoxide on a six-membered ring results in high regioselectivity; only an axial attack occurs.[24] According to the generally recognized rule, most nucleophiles are presumed to attack to the C-5 carbon of 6. For our purpose, a hydroxymethyl anion equivalent should attack at the C-6. Some nucleophiles examined resulted in a change in regioselectivity.

Scheme 3
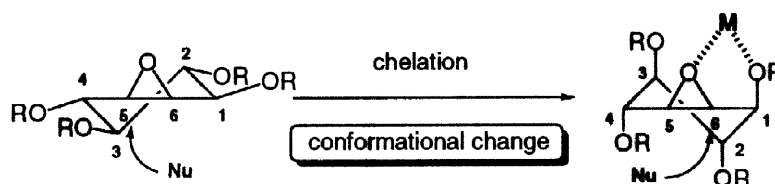
After several attempts, (lithiomethyl)dimesitylborane[25-26] was found to display the requisite unusual selectivity in some cases. Although a similar observation has been reported by Frost,[27] the factors governing the regioselectivity have not been fully understood. In our case, an appropriate choice of the protecting group of the C-1 hydroxy group was important to obtain high C-6 selectivity. Table 1 indicates the regioselectivity by a variety of the C-1 alkoxy group.

Table 1: Regioselectivity of hydroxymethylation

R	Yield (%)	A : B
Bn	60	> 99 : 1
MPM	78	> 99 : 1
BOM	65	94 : 6
TBDMS*	83	< 1 : 99
Ac	0	− : −

*Oxidation condition: mCPBA (9.0 eq)
Na$_2$HPO$_4$ (10.0 eq)
r.t., 30 h

A significant difference in the selectivity was observed depending on the nature of the protecting group. Presumably, this change in selectivity originated from the difference in coordinative power by the oxygen of the protected OH group. As shown in Scheme 3, chelation of the metal to both oxygens of the oxirane and the C-1 alkoxy group might change the conformation of the substrates to cause unusual regioselectivity. On the other hand, the oxygen of the siloxy group might not coordinate to the metal because of bulkiness of the silyl group. In this case, the usual selectivity was observed. Among the protecting groups leading to the C-6 selectivity, MPM provided the best yield and selectivity. Thus, the compound 6 protected with an MPM group was used in the course of our synthesis.

With an efficient method for the hydroxymethyl introduction in hand, the remaining synthetic operations were only an epoxide formation and deprotection. Scheme 4 shows the final stage of our synthesis. Benzylation of 7 afforded 8 in 93% yield. Deprotection of 8 with DDQ and mesylation provided the mesylate 9, which was subjected to hydrogenolysis using 1 atm of H$_2$ and Pd(OH)$_2$ in MeOH to generate the deprotected mesylate in 77% yield. Finally, treatment of 10 with aqueous NaOH afforded the crystalline cyclophellitol 1 in 82% yield.

Scheme 4
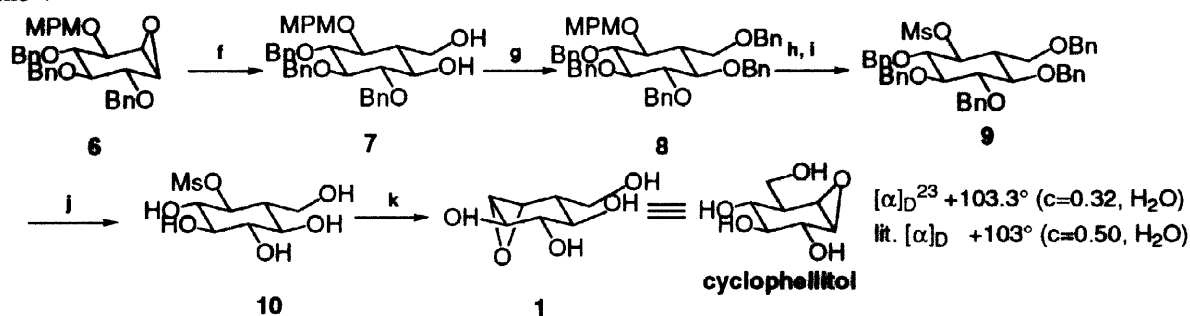
Reagents and conditions: f) Mes_2BCH_2Li, THF, r.t., 6 h; NaOH, H_2O_2, THF - MeOH, r.t., 1 day, 78%; g) NaH, BnBr, DMF - THF, r.t., 4 days, 93%; h) DDQ, $CH_2Cl_2 - H_2O$, 0 °C, 1.5 h, 96%; i) MsCl, Et_3N, CH_2Cl_2, r.t., 12 h, 91%; j) $Pd(OH)_2/C$, MeOH, r.t., 1 day, 77%; k) $1.0M$ NaOH, 1 h,82%.

In summary, during the synthesis, we found that the regioselectivity of an oxirane ring opening with (lithiomethyl)dimesitylborane could be controlled by a protecting group of a hydroxy group. This method enables not only the synthesis of various diastereomers of cyclophellitol but also application of the new strategy for the regioselective hydroxymethylation reaction of highly oxygenated cyclohexanes. Further work on syntheses of cyclophellitol diastereomers is now under way in our laboratory.

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