A Divergent Route for a Total Synthesis of Cyclophellitol and Epicyclophellitol from a [2.2.2]Oxabicyclic Glycoside Prepared from D-Glucal[1]

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Summary: D-Glucal has been used for syntheses of Tatsuta's penultimate intermediate for cyclophellitol and epicyclophellitol *via* a 6-*exo*-*trig* radical cyclization of 2-deoxy-2-iodo-6-alkynyl glycoside, the diastereomeric mixture produced thereby being separated into two sets, each of which leads to one or other target materials.

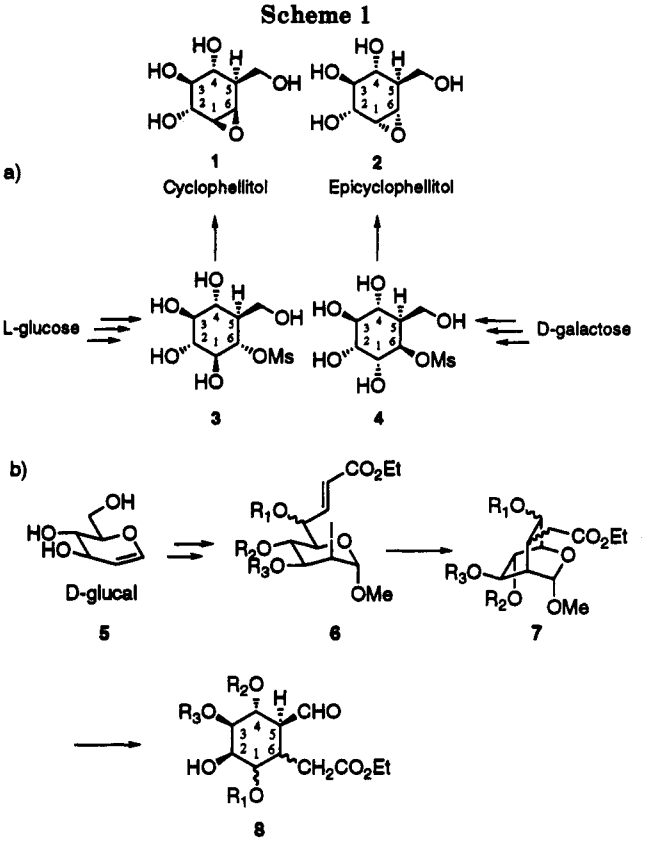
Cyclophellitol, **1**, isolated from the culture filtration of a *Phellinus* species of mushroom, is a β-glucosidase inhibitor that currently attracts additional interest as a potential therapeutic agent against human immunodeficiency virus (HIV) and metastasis.[3] The first synthesis of cyclophellitol was achieved by Tatsuta and co-workers (Scheme 1a) in which L-glucose was used as starting material, the correct absolute configuration being established thereby.[4] For purposes of biological evaluation these workers also prepared the diastereomeric oxirane, epicyclophellitol **2**, with D-galactose as starting material.[4] More recently, a synthesis of **1** in racemic form has been reported by Moritz and Vogel.[5]

Compounds **1** and **2** attracted our attention because of our program in developing free-radical methodology for the preparation of densely-functionalized carbocycles from carbohydrates.[6,7] In this paper we describe syntheses of Tatsuta's penultimate intermediates, **3** and **4**, which feature a divergent strategy *via* a key [2.2.2]oxabicyclic precursor, the latter being obtained from D-glucose, (*via* D-glucal **5**), as the starting material.

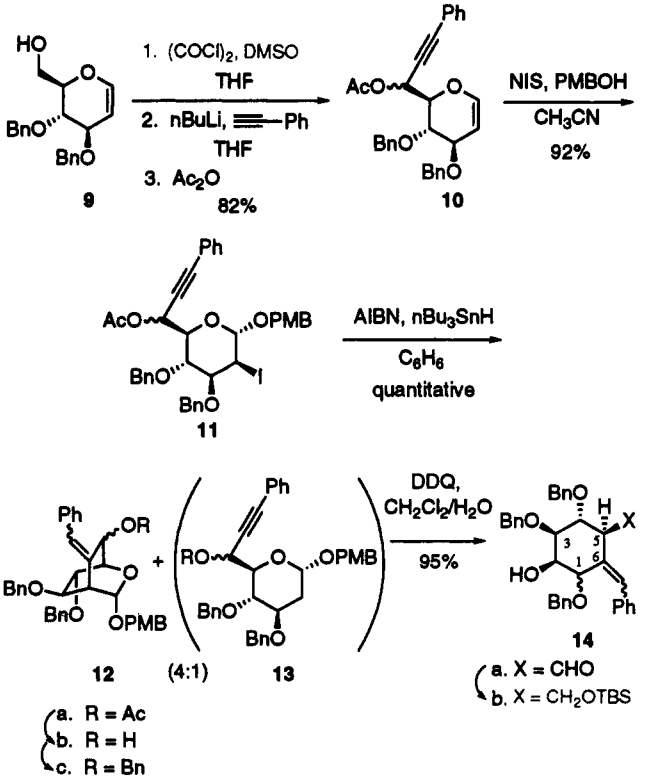
Previous studies in this laboratory have reported that the iodohexenylpyranoside **6** which is readily prepared from D-glucal **5** underwent radical cyclization to give the [2.2.2]oxabicyclopyranoside **7**. Hydrolysis of the latter provided ready access to the carbocycle **8** (Scheme 1b).[7] Comparison with the Tatsuta intermediates **3** and **4** indicates that three centers of coincidence, carbons 3, 4, and 5, exist in **8** and a fourth can be added by epimerization of its C2-OH. The remaining sites at C1 and C6, which exist as epimeric mixtures, are seen to embody the differentiation between intermediates **3** and **4**. However the C6-CHCOOMe group of **8** is not a felicitous synthon for the C6-CH_2Ms groups of the target molecules. A carbonyl group at this site would be more serviceable, and our approach was initiated with this concept in mind.

A promising synthon for the desired C6-carbonyl group,

Scheme 1



Scheme 2



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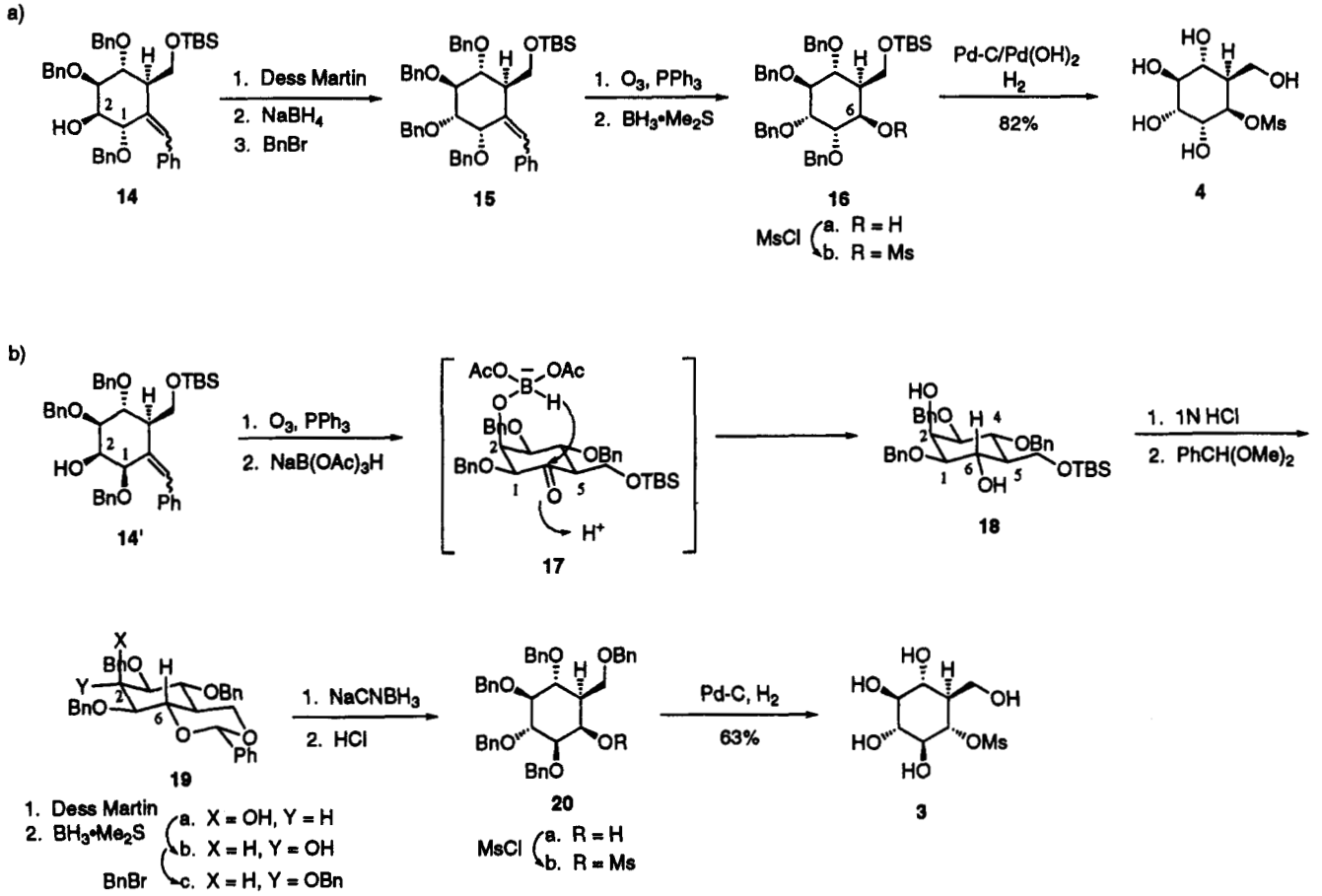
Scheme 3



would be furnished if the unsaturated center in the precursor had been alkynyl rather than the alkenyl residue present in **6**. Accordingly, the previously reported glycal **9**[7] (Scheme 2) was oxidized, directly alkynylated, and then acetylated to give the epimeric mixture **10** in 82% overall yield. Iodoalkylation by Thiem's procedure[8] gave **11** which, upon treatment with Bu_3SnH and AIBN in benzene at reflux, gave quantitative yield of material which, after deacetylation, could be fractionated into two sets of isomers comprised of the diastereomeric [2.2.2]oxabicycloglycosides **12a** and the 2-deoxy epimers **13** in 4:1 ratio.

For the former set, the hydroxyl groups were protected as benzyl ethers, and the resulting material **12c** was subjected to oxidative hydrolysis with DDQ[9] leading to the hydroxy aldehyde mixture **14a**, this being reduced immediately so as to avoid epimerization. Selective silylation of the resulting diol then afforded the monoalcohol **14b**.

On the basis of their C1 configurations, the components of this diastereomeric mixture can be divided into two sets, **14** and **14'** (Scheme 3), these being correlated with Tatsuta intermediates **4** and **3**, respectively. For each set the retrosynthetic plan described above requires (a) that the C2-OH be inverted and (b) that the olefinic center be processed to give the C6-OMs functionality.

For **14** (Scheme 3a), the C2-OH inversion defied S_N2-type procedures including Mitsunobu protocols[10] and modifications thereof.[11] However, an oxidation/reduction sequence for which the Dess–Martin reagent[12]/$NaBH_4$ proved best, paving the way to **15**. Ozonolysis followed by BH_3·Me_2S reduction then gave **16a** and 6-*epi*-**16a** in 1:1 ratio. The latter could be readily separated and recycled. The former was sulfonated, and hydrogenolysis of the product **16** occurred smoothly to give the desired Tatsuta intermediate **4** for epicyclophellitol, **2**.

Application of a similar sequence to **14'** (Scheme 3b), the other set of diastereomers, was conceivable. However, an attractive alternative pathway was pursued by which advantage could be taken of the free C2-OH for stereocontrolled creation of the C6-OMs center in the cyclophellitol intermediate. Thus, ozonolytic cleavage of the olefinic moiety led to a ketone, whose stereocontrolled reduction with sodium triacetoxyborohydride[14] could be achieved *via* the complex **17** leading to diol **18** as the exclusive product. The *trans*-fused benzylidene ring was then installed in compound **19a** for two synthetic purposes, the first being to provide a conformational lock to facilitate C2-OH inversion leading to **19b**. Dess–Martin oxidation[12] followed by BH_3·MeS reduction and benzylation then afforded **19c**.

The second objective for installing the benzylidene ring was now exploited, this being chemoselective cleavage by use of Garegg's procedure.[13] Thus, the product, **20a**, contained only one site for sulfonation, and the resulting

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material, **20b**, could then be hydrogenolyzed leading to the other Tatsuta intermediate, **3**, for cyclophellitol **1**.

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Supplementary Material Available: General experimental procedures and characterization data are given (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.