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Pd Catalyzed Kinetic Resolution of Conduritol B. Asymmetric Synthesis of (+)-Cyclophellitol

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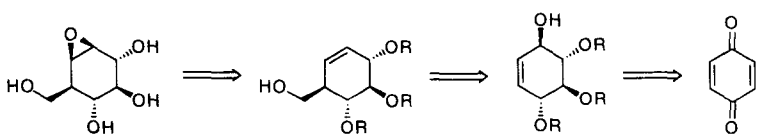
Summary: Enantiomerically pure (+)-cyclophellitol is readily available from benzoquinone employing an asymmetric palladium catalyzed kinetic resolution of racemic conduritol B and a novel easily cleavable pivalate analogue.

Glycosidase inhibitors not only aid in the understanding of glycoprotein processing but also may find applications in immunology, diabetes, virology, and cancer. The properties of (+)cyclophellitol (**1**), isolated from the mushroom *Phellinus sp.*, as an inactivator of β-glucosidase and an inhibitor of HIV,[1] have stimulated much synthetic activity. Most syntheses start with enantiomerically pure natural products, notably carbohydrates.[2] Such strategies normally entail rather long routes because of the need to manipulate the functionality. De novo asymmetric syntheses provide flexibility to produce either enantiomer. In pursuing derivatives, access to both enantiomeric series would be important. Only one asymmetric synthesis employing a chiral auxiliary has been reported.[3] We wish to report a concise asymmetric synthesis of **1** based on the palladium catalyzed kinetic resolution of racemic conduritol B tetraacetate (**5**).

In considering a synthesis of cyclophellitol, we focused on a de novo asymmetric synthesis so that equal access to either enantiomer becomes possible. Scheme 1 illustrates our retrosynthetic analysis which relies upon a hydroxyl directed epoxidation of the differentially protected homoallylic alcohol **2**. This intermediate is available via a 2,3-sigmatropic rearrangement of an alkoxymethyl anion derived from the differentially protected conduritol B derivative **3**. Since racemic conduritol B is easily accessed from benzoquinone (**4**),[4] two questions needed to be addressed—1) how could racemic conduritol B easily be "resolved"[5,6,7] and 2) how could the hydroxyl groups be readily differentiated. Asymmetric palladium catalysts offer a simple solution to both of these questions.[8,9]

Scheme 1. Retrosynthetic Analysis of (+)-Cyclophellitol



1 **2** **3** **4**

A palladium catalyzed kinetic resolution of the racemic C_2-symmetric tetraacetate **5** should be possible using the chiral ligand (*R,R*)-**8**, since, with respect to the ligand, one enantiomer of **5** would provide a "matched" substrate for ionization while the other would be "mismatched".[8] A pivalate was chosen as the

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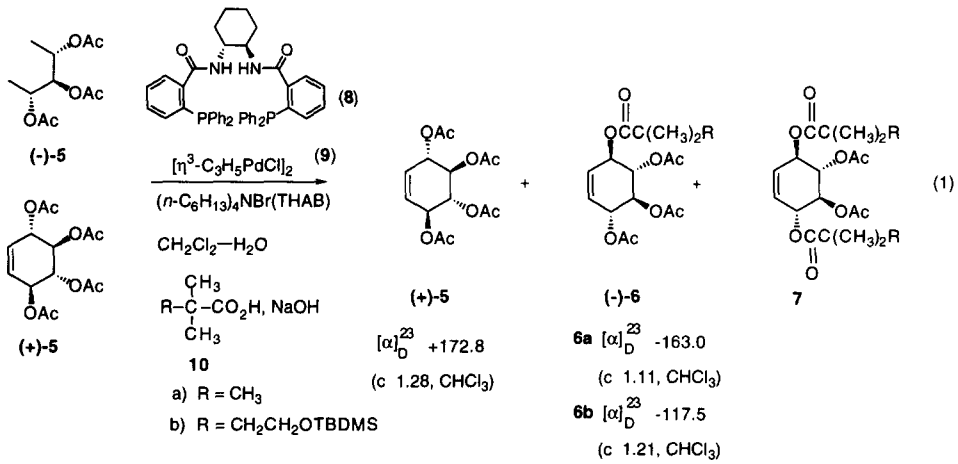
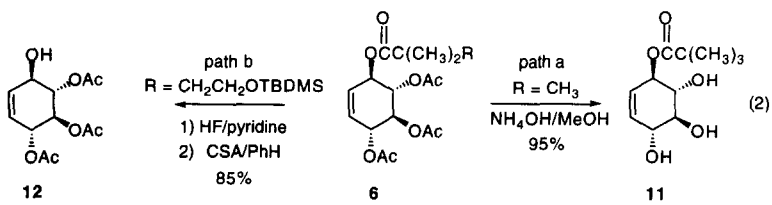
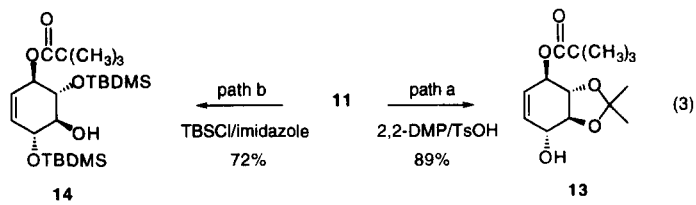
carboxylate nucleophile for the resolution because the resultant allyl pivalate was anticipated to ionize much more slowly than the starting material, and the pivalate should provide a means for easy differentiation of the alcohol protecting groups later on. A potential problem at this stage is the further reaction of monopivalate **6** to provide the dipivalate **7**. Due to the C_2-symmetry of the system, the remaining allylic acetate in **6** is also "matched" for ionization with respect to the ligand **8**. This second ionization requires the catalyst to complex the face of the double bond *cis* to the pivalate substituent in **6**. The steric bulk of the pivalate was anticipated to hamper this undesired ionization.



The tetraacetate (±)-**5** was synthesized in 3 steps from benzoquinone (**4**) by a simple modification of the method of Guo et.al.[4] The kinetic resolution (eq. 1) was carried out using 0.65 equiv. of sodium pivalate (formed *in situ* from 0.80 equiv. of pivalic acid and 0.65 equiv. of sodium hydroxide) with 1 mol% of **9** and 3 mol% of **8** at 0.5M in a two phase methylene chloride/water system with tetrahexylammonium bromide (THAB) as a phase transfer catalyst. The reaction stopped cleanly at 50% conversion providing a quantitative yield (based upon 50% theoretical yield) of recovered tetraacetate ((**+**)-**5**) and an 88% yield (based upon a 50% theoretical yield) of monopivalate (**-**)-**6a**[11] with only 1% of dipivalate **7** isolated. Chiral hplc analysis (Chiracel® AD column) of recovered tetraacetate showed it to have 83% ee which increased to >99% ee after one recrystallization from ether/pet ether. The monopivalate using the same analytical method had an ee of 97%. A nearly identical result was obtained using the pivalic acid analogue **10b**. Again, the recovered tetraacetate (quantitative yield) had an ee of 87% that could be increased to >98% ee. The pivalate analogue (**-**)-**6b**[11] had an ee of 95% (88% yield) and 5% of the dialkylated derivative **7b** also formed.



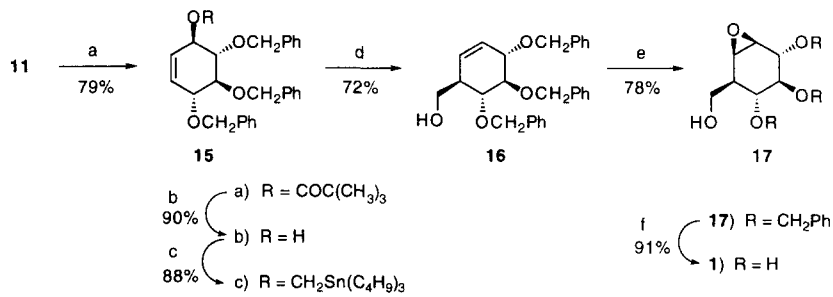


14 13

With easy access to the hydroxyl differentiated enantiomerically pure triacetates **6a** and **6b**, selective unmasking was pursued. Cleavage of the acetates in the presence of the pivalate was straightforward with ammonium hydroxide in methanol (eq. 2, path a) whereby triol **11**[11] was obtained. A further advantage of the pivalate is its ability to provide differentiation of the remaining hydroxyl groups as shown in eq. 3. Acetonide formation with 2,2-dimethoxypropane in the presence of TsOH in toluene at 100 °C selectively protect the 2,3-diol as shown in **13**[11] (eq. 3, path a). On the other hand, treatment with 2 equiv. of TBDMS-Cl and imidazole in 1:1 THF/DMF at 0° gave a 80% yield of the bis-silyl ether **14**[11] (eq. 3, path b), exposing the 3-hydroxyl group for further reactions. In addition 8% of the 3,4-bis-silyl ether was found. The pivalate analogue **10b** was designed to permit the cleavage of the resulting esters in the presence of the acetates. Exposure of **6b** to HF/pyridine complex in THF at room temperature to effect desilylation followed by CSA in benzene at room temperature to effect lactonization liberated the 1-hydroxyl group selectively to provide triacetate **12**[11] (eq. 2, path b).

With access to enantiomerically pure triol **11**, the stage was set for a simple synthesis of (+)-cyclophellitol as summarized in Scheme 2. Use of the 2,3-sigmatropic rearrangement[12] required protection of

Scheme 2. An Asymmetric Synthesis of (+)-Cyclophellitol



a) $PhCH_2Br$, $(C_4H_9)_4NI$, KH, DME, room temperature; b) DIBAL-H, CH_2Cl_2, -78°; c) $(C_4H_9)_3SnCH_2I$, KH, DME, 0°; d) *n*-C_4H_9Li, THF, -78°; e) MCPBA, CH_2Cl_2, 0°; f) H_2 (1 atm), $Pd(OH)_2/C$, CH_3OH, room temperature.

the free hydroxyl groups as the benzyl ethers as in **15**. After pivalate cleavage to the mono-ol **15b**, the tin derivative **15c** was readily formed. Tin-lithium exchange promoted the 2,3-sigmatropic rearrangement to put the hydroxymethyl group in place with correct regio- and diastereochemistry with production of **16**.[11] Epoxidation with MCPBA, directed by the homoallylic alcohol, gave a 78% yield of the desired epoxide **17** with a 7% yield of the diastereomeric epoxide. Comparison of the spectral data for **17** with that reported in the literature[2f] confirmed the stereochemistry as depicted. Completion of the synthesis by the published hydrogenation procedure[2f] gave (+)-cyclophellitol (**1**), whose physical and spectral properties fully agree with the natural product.

Thus, a facile method for the synthesis of enantiomerically pure chemodifferentiated conduritol B from benzoquinone derives from the utility of asymmetric palladium catalyzed reactions. A further advantage of this strategy is the ease of access to either enantiomer, which does not readily occur using starting materials from the chiral pool. The use of 4-*t*-butyldimethylsiloxy-2,2-dimethylbutyric acid as a useful carboxylate nucleophile that can be selectively cleaved may find more general use.[13] An effective synthesis of the glycosidase inhibitor (+)-cyclophellitol illustrates the utility of these methods.

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