A Synthesis of (+)-Cyclophellitol from D-Xylose†

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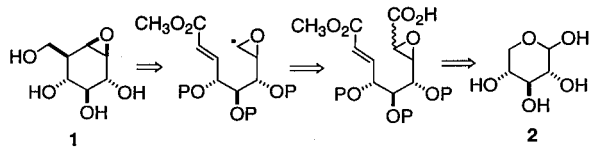
(+)-Cyclophellitol (**1**), a β-glucosidase inhibitor, originally isolated from the culture broth of the mushroom *Phellinus sp.*,[1] has been a popular target of synthetic chemists[2−7] owing to its potential inhibitor activity against human immunodeficiency virus (HIV).[8] Apart from its biological activity, this naturally occurring epoxide provided an opportunity to explore the formation of six-membered rings via the cyclization of oxiranyl radicals[9,10] using D-xylose (**2**) as the chiral pool (Scheme 1). During the course of our study, it became necessary to acquire the product of oxiranyl radical cyclization (**13**, Scheme 4) by an independent pathway. To this end, we utilized intermediates prepared from D-xylose to achieve an independent synthesis of (+)-cyclophellitol.

The primary hydroxyl of D-xylose diethyl thioacetal **3**[11] was silylated selectively, and the three secondary hydroxyl groups were benzylated without incident (Scheme 2). Thioacetal **4b** has served in our studies as a bidirectional synthetic intermediate, which in this instance called for the initial removal of the dithioacetal.

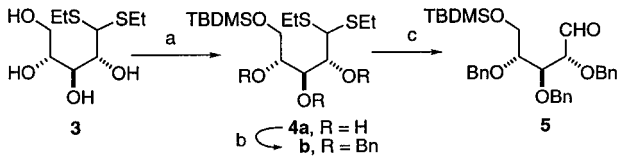
Methylenation of the aldehyde group of **5** under Wittig conditions provided the desired olefin (55−60% yield) in addition to the unsaturated aldehyde, and its diene, derived from β-elimination of benzyl alcohol from aldehyde **5**. To avoid the alkaline conditions of the Wittig reaction, Tebbe's reagent was employed. The yield of olefin **6** was increased to 80% without the appearance of elimination product (Scheme 3).

The synthetic approach now required stereoselective 1,4-addition, or the equivalent thereof, of a vinyl anion to α,β-unsaturated ester **8** (Scheme 4). Neither literature precedent[12,13] nor our own experience in a closely related system augured well for an Ireland−Claisen rearrangement route (**8** → **11** → **9**). Alternatively, the conjugate addition of cuprates to α,β-unsaturated esters bearing γ-alkoxy groups has been reported,[14,15] in particular, the addition of vinyl cuprates to these substrates.[16−18] These studies established the high diastereoselectivity of the conjugate addition, whose high diastereoselectivity is ascribed to a vinylogous, nonchelation Felkin−Anh transition state.[16,17] Although we experienced high stereoselective addition of several lithium-based vinyl cuprates, these experiments were capricious and, as had been observed by Roush,[16] variable in yield. On the other hand, magnesium-based vinyl cuprates, employed under the protocol reported by Hanessian,[18] gave both high yields and high selectivity (Scheme 4).

Scheme 1

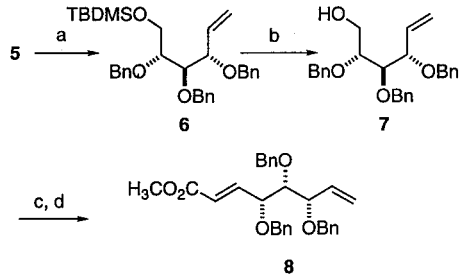


Scheme 2[a]



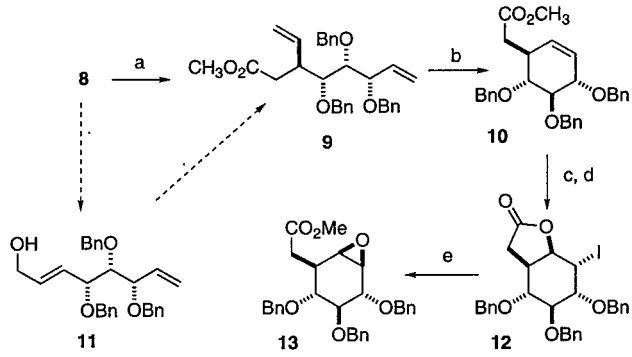
[a] Key: (a) TBDMSCl, imidazole, CH_2Cl_2, 25 °C; 90%; (b) NaH, BnBr, Bu_4NI (cat.), THF, 0 → 25 °C; 80%; (c) HgO/$HgCl_2$, aqueous acetone, reflux; 80%.

Scheme 3[a]



[a] Key: (a) $Cp_2TiClAlMe_3$, pyridine, toluene/THF, −78 °C; 80%; (b) TBAF, THF, 25 °C; 88%; (c) DMSO, $COCl_2$, Et_3N, CH_2Cl_2, −78 °C; (d) Ph_3PCHCO_2Me, CH_2Cl_2, −30 → 25 °C; 89% (two steps).

Scheme 4[a]



[a] Key: (a) $(CH_2{=}CH)_2CuMgBr$, TMSCl, THF, −78 °C; 90%; (b) 15 mol % $(Cy_3P)_2RuCl_2(CHPh)$, 0.02 M CH_2Cl_2, 25 °C, 60 h; 92%; (c) LiOH, aq THF, 25 °C; (d) KI, I_2, $KHCO_3$, aq THF, 25 °C; 92% (two steps); (e) Na_2CO_3, MeOH, 98%.

† This Communication is dedicated to the memory of Professor R. H. Schlessinger. Deceased Dec 11, 1997.

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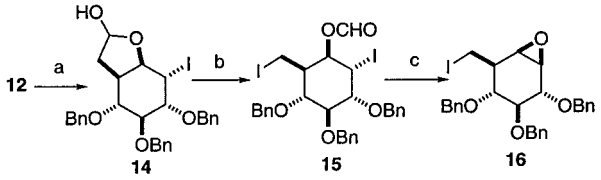
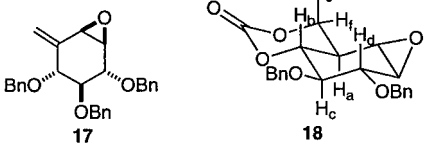
Scheme 5[a]



[a] Key: (a) DIBALH, $CH_2Cl_2-Et_2O$, −78 → −30 °C; 85%; (b) $PhI(OAc)_2$, I_2, cyclohexane, 500 W W-lamp, 10−30 °C; 78%; (c) KOH, aq THF; 76%.

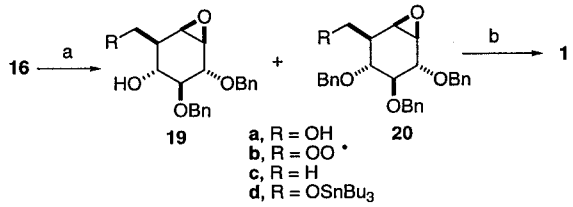
The application of ring-closing metathesis (RCM) using Grubbs's catalyst[19] delivered the cyclohexene **10** efficiently. Subsequent iodolactonization afforded iodide **12**, which was to serve as the genesis of the β-epoxide and β-hydroxymethyl group present in cyclophellitol.

Iodo lactone **12** required oxidative decarboxylation to realize our goal. To this end, several approaches, which proved to be unsuccessful, were attempted: (a) ozonolysis of the TMS silyl ketene acetal; (b) Tebbe methylenation, double-bond isomerization, ozonolysis; (c) alkoxy hydroperoxide rearrangement.[20,21] The degradation was accomplished through the Sáurez procedure (Scheme 5).[22,23] Lactol **14**, readily derived from lactone **12** by DIBALH reduction, efficiently afforded diiodoformate **15** upon irradiation in the presence of $PhI(OAc)_2/I_2$.[24] Subsequent base treatment gave iodo epoxide **16** without compromising the alkyl iodide portion of the molecule. On the other hand, treatment of diiodoformate **15** with Na_2CO_3/MeOH or KOH/DMF/H_2O led exclusively to epoxyolefin **17**, a compound that had been converted to benzylated cyclophellitol **20a**. The reaction of iodo epoxide **16** with KO_2/DMSO[25] as an oxygen nucleophile led to a 1:1 mixture of the desired alcohol **20a** and olefin **17**.



The iodine to hydroxyl transformation was accomplished by radical oxygenation,[26−28] affording a mixture of epoxy alcohol **20a** (70%) and epoxy diol **19a** (10%). Selective

Scheme 6[a]



[a] Key: (a) Bu_3SnH, AIBN, O_2, toluene, 3 h, 60 °C; (b) $Pd(OH)_2/C$, H_2, MeOH, 12 h; 85%.

debenzylation presumably occurred via the intermediate hydroperoxy radical **20b** and not the carbon radical because none of the deoxygenated product **19c** was detected.[29] That debenzylation occurred proximate to the radical site was confirmed by the formation of cyclic carbonate **18** (triphosgene, pyr, 25 °C), whose ^{1}H NMR coupling pattern (J_{ab} = J_{bc} =10.2 Hz; J_{ae} = 10.3 Hz) confirmed the stereochemistry of the vinyl cuprate addition and, ultimately, the stereochemistry of the epoxide through the known mechanism of iodolactone formation. Finally, hydrogenolysis of the benzyl groups in epoxy alcohols **19a** and **20a** afforded (+)-cyclophellitol in 85% yield [$[\alpha]^{20}_D$ +97° (c 0.35, H_2O) (lit.[1] $[\alpha]^{27}_D$ +103° (*c* 0.5, H_2O))], whose 500 MHz ^{1}H NMR spectrum was identical with that of an enantiomerically pure synthetic sample provided by Professor Tatsuta.

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Supporting Information Available: Experimental details and ^{1}H NMR spectra of **4b**, **5**, **8**, **15**, **16**, **18**, **19a**, **20a**, **1**, and **1** (authentic) for which combustion analyses were not obtained (23 pages).

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(29) A reviewer has offered the pausible suggestion that debenzylation may occur in **20a** by hydroperoxy radical abstraction of the methine site via a six-membered transition state followed by loss of a benzyl radical. The resultant ketone could then undergo reduction. Alternatively, a nucleophilic debenzylation may occur through chelation in **20d**.