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SYNTHESIS OF BRANCHED-CHAIN CYCLITOLS USING A PALLADIUM(0)-CATALYSED ALLYLIC COUPLING REACTION

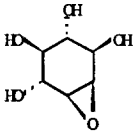
Derek H.R. Barton[a], Peter Dalko[a], Stephan D. Gero[b]*

[a]Department of Chemistry, Texas A&M University, College Station,Texas, 77843, USA
[b]Institut de Chimie des Substances Naturelles, CNRS, 91198, Gif-sur-Yvette, France

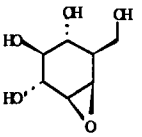
Abstract: *A carbanion derived from Meldrum's acid was used in a palladium(0)-catalysed allylic substitution reaction to prepare stereospecifically branched-chain cyclitols from the symmetrical 1,2,3,4,-tetraacetoxycyclohex-5-ene (**4**).*

As part of our ongoing program on branched-chain cyclitols and their congeners[1,2], we were interested in preparing **1**, a logical intermediate for the synthesis of hydroxylated cyclohexane epoxides and related pseudo-sugars.

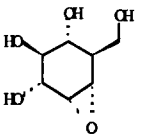
It has been known for over twenty years from the work of Legler[3a] and Gero[3b] that hydroxylated cyclohexene epoxides are active-site-directed inhibitors of glycosidases (Figure 1). These cyclitol-epoxides are not as specific as might be desired, since they lack the hydroxymethyl group of a true pseudo-hexose. Recently a Japanese group[3c] has uncovered a natural product ("cyclophellitol") which acts as an inactivator of β-glucosidases, (presumably by the Legler mechanism[3a]) and which contains a hydroxymethyl group.



conduritol B epoxide



cyclophellitol



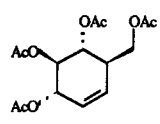
α-glucosidase inactivator

Figure 1

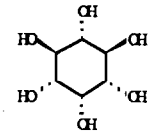
In addition these cyclitols exhibit antiviral properties and can be used as sweeteners. Also noteworthly is that there is a tendency to replace the sugar unit of different natural products by a pseudosugar, because of their conformational resemblance to the parent substance[4]. We have found that the replacement of the oxygen atom by a methylene group preserves the biological profile and confers *in vivo* and *in vitro* stability towards metabolising enzymes [5].

Despite many synthetic efforts[3c,4,7] the preparation of this kind of compound remains a challenge. In this communication we wish to report a short synthetic sequence to provide the target molecule, **1**, utilising a palladium(0)-catalysed allylic substitution of **4** as a key step.

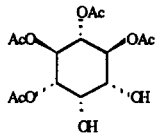
Compound **4** is known as *conduritol-B* peracetate[8a]. There are several syntheses in the literature providing **4**, and some of them are enantioselective[8b]. We were not interested however in the enantioselective preparation of **4** since the palladium-complex **5**, the key intermediate in our synthesis, is symmetrical: the two enantiomeric pairs of **4** yield the same complex. Hence we looked for a rapid methodology to obtain **4** by a simple and high yielding route.



1



myo-inositol



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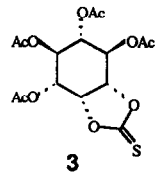

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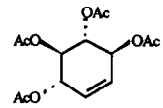

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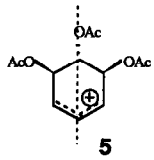

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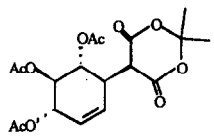

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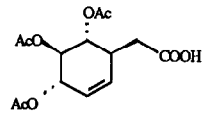


7

We chose as starting material compound **2**, prepared from the readily available myo-inositol: a selective protection of the cis-hydroxy function, by the method of Gigg[9] followed by acetylation and hydrolysis of the isopropylidene protecting group yielded the crystalline diol-tetraacetate **2** (mp: 142-143°C, EtOAc)[10].

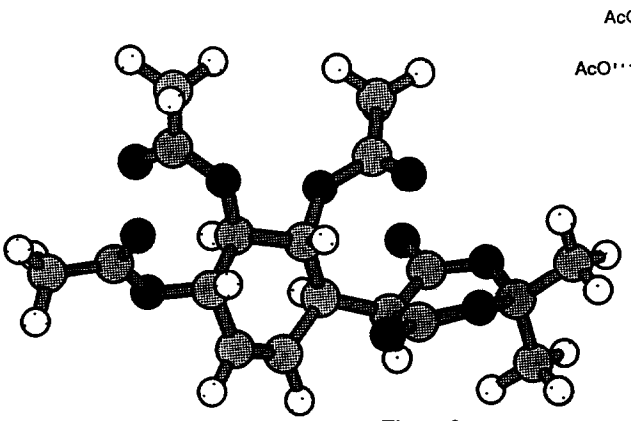
The transformation of the vicinal-diol to conduritol **4** was carried out in a two step sequence. In the first step the diol **2** was converted to thionocarbonate **3** using 1.2 eq. of thiophosgene in the presence of 2.4 eq. of DMAP as base[11]. After purification by flash chromatography compound **3** was isolated in 87% yield as pale yellow crystals (mp: 167-168°C, MeOH). The thionocarbonate **3** underwent a fragmentation reaction at 110°C in presence of trimethylphosphite[12] to give the crystalline olefin-tetraacetate **4** (89%, mp: 84-85°C, pentane)[13].

Compound **4** is a suitable substrate for homologation in the presence of a catalytic amount of palladium(0) and with a variety of different nucleophiles. It could be expected[14b] that this kind of substrate might permit a tandem palladisation: after the substitution of the first acetate group in the allylic position,

the second one could be displaced consecutively. Our goal was, however, to find a monoalkylation methodology.

It was found that the allyl-acetate **4** undergoes selective monoalkylation with the carbanion derived from Meldrum's acid in the presence of 5 molar % of palladium(0)-triphenylphosphine complex (prepared *in situ* from $Pd_2(dba)_3.CHCl_3$) in DMF at 70°C to give the adduct **6** as a cristalline solid (73%, mp: 147-148°C, $CHCl_3$/pentane). The reaction is stereospecific, compound **6** was obtained exclusively and with overall retention of configuration. No trace of dialkylated products was detected in the reaction. Apparently the second alkylation was inhibited by the introduction of the first substituent. Likewise the same selectivity was experienced in presence of the carbanion derived from diethyl malonate in THF at room temperature.

In order to explain the selectivity of the reaction an MM2 conformational analysis of compound **6** was carried out (Figure 2). It was found that the most stable conformation is when the two rings are nearly perpendicular. This conformation is preferred by 17.3 kJ over the conformation when the two rings are in the same plane. Consequently the approach of the bulky palladium(0)-triphenylphosphine complex for the substitution of the second allyl-acetoxy group is sterically inhibited.



6

Figure 2

Decarboxylative hydrolysis of **6** in a mixture of acetic acid / water 95:5 at 70°C provided the acid **7** (82%, mp: 121-122°C, EtOAc). Acid **7** was transformed to the corresponding *nor*-hydroxy derivative by a free-radical decarboxylation reaction[15] using an organoantimony intermediate. Accordingly in this procedure **7** was activated by oxalylchloride and the molecule was condensed with the sodium salt of N-hydroxypyridine-2-thione. The ester was irradiated in daylight, in presence of 2 eq. of $(PhS)_3Sb$ in a mixture of dichloromethane-diethylether (1:1). The corresponding *nor*-alcohol derivative was obtained in a slow reaction (10 hours). Hydrolysis of the organoantimony intermediate, followed by *in situ* acetylation afforded **1** in a good yield (71%)[6,16].

Our results concerning the preparation of the enantiomerically pure acid **7** and the conversion of **1** into the naturally occuring cyclophellitol[3c] will be published in a forthcoming paper.

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