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Further Hydroxyiodination of 1-Acetoxycyclohex-2-enes: Preparation of tetraAcetyl Conduritol D[1]

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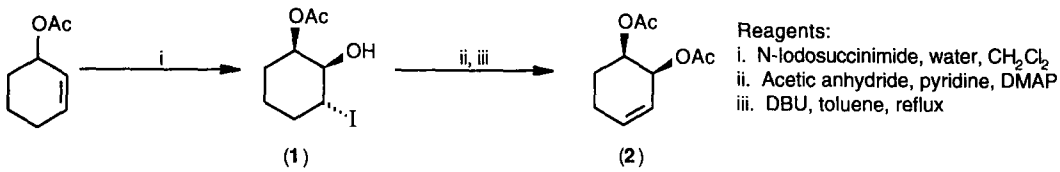
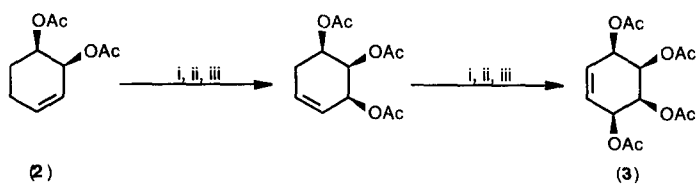
Abstract: *The 1,2-iodohydroxylation of 1-acetoxycyclohex-2-enes has been extrapolated:* tetraacetyl *Conduritol D may be prepared by iteration of the reaction.*

We recently reported that the reaction of acetoxycyclohex-2-ene with *N*-iodosuccinimide (NIS) is highly diastereoselective, favouring that *trans*-1,2-hydroxyiodide (**1**) in which the newly-attached oxygen atom was adjacent and *syn*- to the original oxygenation, while the iodine-carbon bond created was distal from it (scheme 1).[2] We rationalized this high selectivity as being due to an *intra*molecular delivery of oxygen *via* a neighbouring group participation of the adjacent sp^2-hybridized oxygen lone pair.



Scheme 1

We were, of course, curious to see whether a further hydroxyiodination of alkene (**2**) would proceed with a similar level of diastereoselectivity. Furthermore, it occurred to us that, *so long as the preference for internal delivery of oxygen was maintained in subsequent hydroxyiodinations*, repeated employment of this reaction sequence could be applied to provide a conceptually unique synthesis of all *cis*-1,2,3,4-*tetra*acetoxycyclohex-5-ene[3] (**3**), the peracylated version of the *meso*-cyclitol Conduritol D (scheme 2).[4] The remainder of this letter reports the preliminary results concerning the realization of this aim.



Reagents: i. N-Iodosuccinimide, water, CH_2Cl_2; ii. Acetic anhydride, pyridine, DMAP; iii. DBU, toluene, reflux

Scheme 2-Proposed Iterative Hydroxyiodination to Prepare tetraAcetyl Conduritol D

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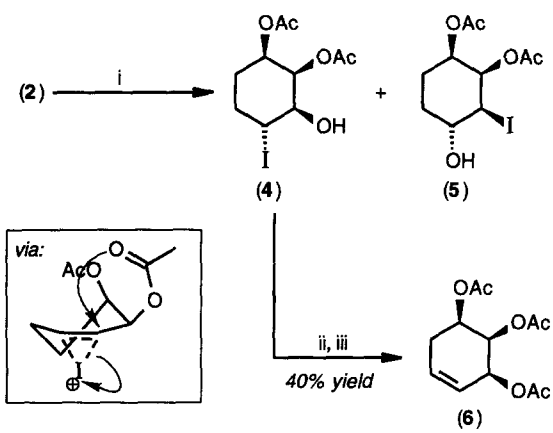
When diacetate (**2**) was reacted with NIS in the presence of water at ambient temperature in dichloromethane solution, the *minor* product of the reaction was 1,2-*trans*-2,3-*cis*-3,4-*cis*-3,4,-diacetoxy-2-hydroxy-1-iodocyclohexane (**4**), which product was isolated by flash chromatography in 39% yield (scheme 3).[5] The *major* product was the undesired regioisomer (**5**), obtained in 52% yield and arising from an addition mode not governed by a neighbouring group effect. Luckily, the reaction was solvent-dependent: when performed in dichloromethane/acetic acid (100:1) solution, (**4**) was the major product (46%) and (**5**) the minor (27%), with a small amount of starting material (8%) being returned. When acetonitrile was used as solvent for the reaction (**4**) was this time by far the major product of the reaction (60% yield *versus* 6%). Acetylation and dehydroiodination of (**4**) gave 1,2-*cis*-2,3-*cis*-1,2,3-triacetoxycyclohex-4-ene (**6**) in 40% yield (scheme 3).

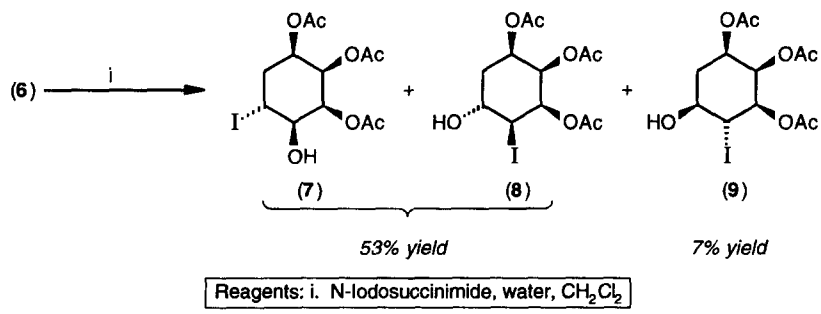


Yield (4)	*Yield* (5)	*Solvent*
39%	52%	CH_2Cl_2
46%	27%	CH_2Cl_2/AcOH
60%	6%	CH_3CN

Reagents:
i. N-Iodosuccinimide, water, solvent
ii. Acetic anhydride, pyridine, DMAP
iii. DBU, toluene, reflux

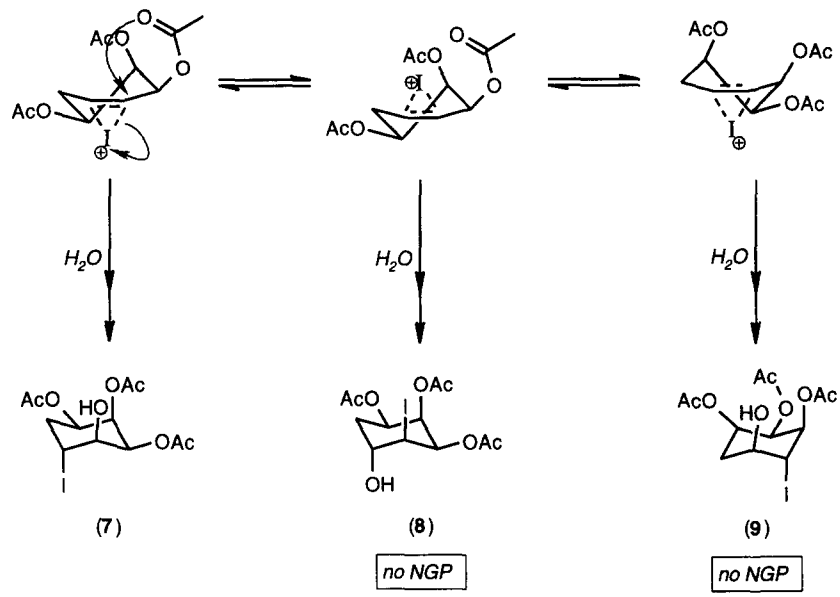
Scheme 3

Repetition of the hydroxyiodination reaction this time gave returned starting material (8%) and a mixture of three previously unknown compounds, 1,2-*trans*-2,3-*cis*-3,4-*cis*-4,5-*cis*-3,4,5-triacetoxy-2-hydroxy-1-iodocyclohexane (**7**) and the regioisomeric 1,2-*cis*-2,3-*cis*-3,4-*cis*-4,6-*trans*-2,3,4-triacetoxy-6-hydroxy-1-iodocyclohexane (**8**) and 1,2-*trans*-2,3-*cis*-3,4-*cis*-4,6-*cis*-2,3,4-triacetoxy-6-hydroxy-1-iodocyclohexane (**9**). Compounds (**7**) and (**8**) could not be separated by flash chromatography under a variety of conditions: these compounds were obtained in a yield of 53% and in a ratio of approximately 2:3 (as judged from ^1H NMR spectra), while (**9**) was obtained as a single compound in 7% yield (Scheme 4).



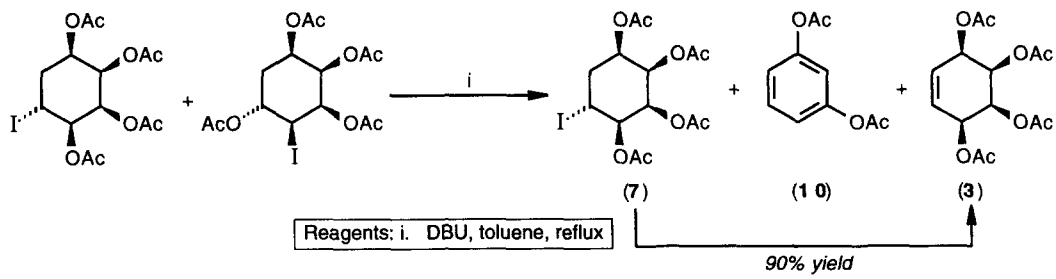
Scheme 4

The conformational effects responsible for this product distribution are summarized diagrammatically in scheme 5. Thus, we presume that the neighbouring group particpation which we proposed to explain our initial observations is of relatively little importance when there is greater steric constraint present in the substrate, so that the primary concern is to minimize axiality (both proper and *pseudo*-). Thus, (**7**) and (**8**) are favoured over (**9**) because they result from a reactive conformation in which there is a *pseudo*equatorial rather than a *pseudo*axial allylic acetoxy substituent. Furthermore, the presence of (**7**) and (**8**) in roughly equal amounts necessarily implicates two energetically similar iodonium ions, as shown in scheme 5



Scheme 5

Unfortunately, *this* reaction has not yet proved amenable to optimization in favour of our desired product, (**7**), *via* solvent effects: use of a wide range of solvents did not enhance the selectivity of the process of the reaction and led in many cases to even more complex mixtures of products. Although we did not expect (**8**) to give any Conduritol product upon attempted dehydroiodination, we acylated the mixture of (**7**) and (**8**) and then treated the resulting *tetra*acetates (which were also inseparable by flash chromatography) with DBU in refluxing toluene (scheme 6).



Scheme 6

Three compounds were isolated from the reaction: unreacted (**7**) (12% yield), 1,3-diacetoxybenzene (**10**) (59% yield) and our desired Conduritol derivative (**3**) (26% yield). All three compounds were separable by flash chromatography and when we re-exposed now-pure (**7**) to the reaction conditions, we were gratified to observe formation of *tetra*acetyl Conduritol D in excellent yield. If our final iodohydroxylation reaction could be controlled to give (**7**) as its primary product, then our synthetic route would be clearly be of some utility. Efforts to enable this improvement are proceding in our laboratory.

Thus, we have shown that the proposal of iterative hydroxyiodination of cyclohexenes as a synthetic entry to cyclitols has potential: our current efforts are directed to solving the poor regiocontrol of the ultimate iodohydrin-forming reaction. Clearly, the importance of *intra*molecular delivery of oxygen *via* a neighbouring group participation diminishes as increased substitution places excessive steric demands upon the transition state required for such an interaction.

Acknowledgment

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5. All new compounds exhibited appropriate spectroscopic and analytical data.

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