FROM CHLOROBENZENE TO A CARBOHYDRATE IN TWO STEPS. A NEW CHEMOENZYMATIC SYNTHESIS OF 2,3-*O*-ISOPROPYLIDENE-D-ERYTHRURONOLACTONE

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Dedicated to Professor Otto Wichterle on the occasion of his 80th birthday.

Controlled oxidation of chloroepoxide *V* with two equivalents of sodium periodate furnished 2,3-*O*-isopropylidene-D-erythruronolactone (*I*) in 63% yield. This procedure was augmented by combining the protection of diol *III*, the oxidation of acetonide *IV* to *V*, and the subsequent oxidative cleavage to *I* into one operation which yielded, on medium scale, the title lactone in 51% yield. Detailed procedure of preparation and physical constants are provided for lactone *I*.

The microbial oxidation of aromatic hydrocarbons to corresponding homochiral cyclohexadiene diols with mutant strains of *Pseudomonas putida*, discovered in the late 1960's by Gibson[1], opened new horizons in syntheses of chiral oxygenated compounds[2]. The utility of these versatile synthons is reinforced by their use in enantiocontrolled syntheses described in several recent reviews[3–5]. In the carbohydrate field the utility of these metabolites has recently been expressed in the preparation of cyclitols[6,7] as well as four- and five-membered sugars such as protected L-erythrose and its enantiomer[8,9], protected L-erythrolactone[9], and protected L-ribonic γ-lactone[10]. 2,3-*O*-Isopropylidene-D-erythruronolactone (*I*) is a versatile chiral synthon that has been used in many enantioselective syntheses including the preparation of pyrrolizidine alkaloids[9], prostaglandin intermediates[11,12], and specionin[13]. Recently, compound *I* appeared to be of particular interest as the key intermediate in the synthesis of dipeptide renine inhibitor, dihydroxyethylene isostere *II* (refs[14,15]). The known methods for the preparation of *I* starting from ribonolactone[16], chlorobenzene[8,9], and D-gulonolac-

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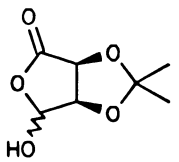
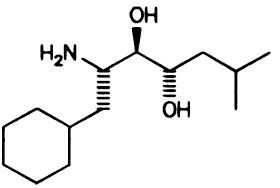
tone[17,18] (with cyclohexylidine as a protecting group) have been reviewed, and a new concise and scaleable procedure that appears to be effective in both cost and the use of an environmentally acceptable protocol has been developed. In this manuscript we provide the details of a two-step procedure for the preparation of *I* from 1-chloro-2,3-dihydroxycyclohexa-4,6-diene (*III*) obtained by microbial oxidation of chlorobenzene.



I



II

EXPERIMENTAL

The optical rotation data were measured in chloroform (*c* 1) with a Perkin Elmer 241 Polarimeter, melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus. The TLC system used throughout was MeOH–$CHCl_3$ (1 : 9).

2,3-*O*-Isopropylidene-D-erythruronolactone (*I*)

A) The mixture of chloroepoxide[6] *V* (10.0 g, 42.3 mmol), water (200 ml), and $NaIO_4$ (19.0 g, 88.8 mmol) was stirred at ambient temperature for 4 h, while slight stream of argon was bubbled through. After the reaction was complete, pH was adjusted to 7.5 (5 M NaOH), and the mixture was extracted with ethyl acetate (3 ×). Water layer was acidified to pH 2 (6 M HCl); the solution was quickly saturated with NaCl and extracted with ethyl acetate (6 ×). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give crystalline product, (4.63 g, 63%), m.p. 82 – 90 °C. Recrystallization (toluene/hexane; (5.5 ml/g)/(4 ml/g), 85% recovery) afforded pure *I* as colorless crystals with m.p. 101 – 103 °C and $[\alpha]_D^{25}$ +31°. Literature[9]: m.p. not given, $[\alpha]_D^{25}$ –60° (*c* 1, $CHCl_3$); see discussion for the explanation of this discrepancy.

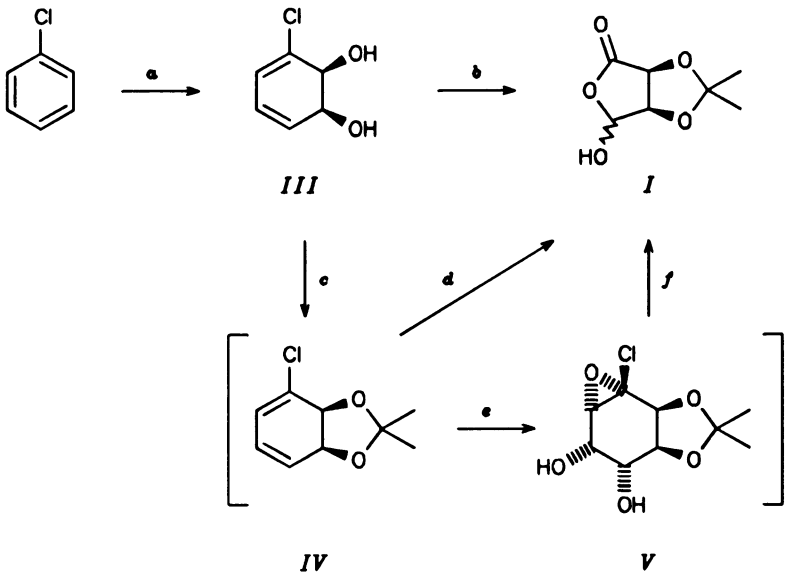
B) The mixture of chlorobenzene diol* *III* (10.0 g, 68.2 mmol), acetone (100 ml), 2,2-dimethoxypropane (22.6 ml, 184.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.80 g, 0.42 mmol) was stirred for 20 min at ambient temperature. The resulting solution was cooled to 0 °C and added dropwise over a period of 15 min to a mixture of $KMnO_4$ (24.8 g, 156.9 mmol), $MgSO_4$ (14.0 g, 116.0 mmol), acetone (150 ml) and water (400 ml), precooled to –12 °C. The temperature of the reaction mixture was maintained bellow 0 °C by controlling the rate of addition. Excess permanganate was titrated with saturated solution of $NaHSO_3$, and the mixture was stirred at 0 °C for 10 min and then filtered. To the resulting, slightly yellow solution was added $NaIO_4$ (38.2 g, 178.6 mmol),

* For the preparation of diol *III* on a laboratory scale see ref.[19]. For commercial availability consult the following sources: Genencor International, Inc., South San Francisco, CA; ICI Fine Chemicals, Manchester, U.K.; Enzymatix, Cambridge, U.K. and Janssen Chimica, Geel, Belgium.

and the mixture was stirred at ambient temperature for 2 h (at the end of the reaction, pH of the mixture was 3 – 4). The pH was adjusted to 7.5 (5 M NaOH), the mixture was extracted with ethyl acetate (4 ×), saturated with NaCl and acidified to pH 2 (HCl 1 : 1). Extraction with ethyl acetate (10 ×), drying of the combined extracts over $MgSO_4$, and evaporation furnished 6.0 g (51%) of the oily product, which turned to crystals identical with the crude product obtained above.

RESULTS AND DISCUSSION

The literature[8,9,16] contains two syntheses of *I*, but the various accounts differ in its full characterization. For example, Beer et al.[16] report specific optical rotation of –54.6° (*c* 1.25, $CHCl_3$) and m.p. of 103 – 104 °C, while our previous paper[9] reports $[\alpha]_D^{25}$ of –60° (*c* 1, $CHCl_3$) but does not report the melting point. This discrepancy was puzzling, initially ascribed to the varying proportions of anomers, and we set out to provide a reliable set of physical constants in addition to an improved synthesis. Thus, subsequent repetition of this work, both in our laboratories and at Genencor International,

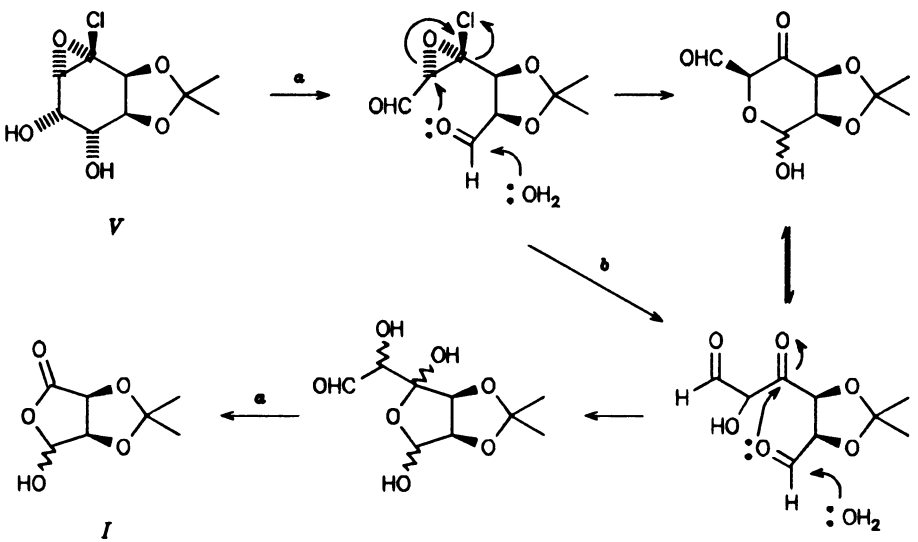


a ***Pseudomonas putida***; ***b*** overall yield 51%; ***c*** 2,2-dimethoxypropane, ***p***-toluenesulfonic acid, yield 95%; ***d*** 1. ozone, 2. dimethyl sulfide, yield 73%; ***e*** $KMnO_4$, $MgSO_4$, yield 60%; ***f*** $NaIO_4$, yield 63%

SCHEME 1

revealed consistent optical rotations of recrystallized samples (toluene/hexane or ethyl acetate/hexane) above +30°. Pure hydroxylactone *I* with m.p. of 104 – 104.5 °C (butyl acetate/hexane) showed the rotation of +32.6°. No anomeric equilibrium has been detected in the NMR spectra of pure samples of *I*, nor have NMR data on the anomeric composition of a fully deprotected sample been obtained. We do not have an adequate explanation for the difference in optical rotation data. Our earlier paper[9] clearly reported an erroneous value and described the compound as the L- rather than D-enantiomer; however, the title compound has been converted to a number of known substances, therefore its absolute stereochemistry, enantiomeric composition, and purity is without question[8 – 15].

Recently we have reported that the oxidation of chlorobenzene diol acetonide (*IV*) with permanganate[6] yielded the unusual chloroepoxide *V* (Scheme 1). Among other interesting transformations[20], this compound now proved to be an useful intermediate in the synthesis of erythruronolactone *I* via a unique oxidation of the diol-chloroepoxide moiety with periodate (Scheme 1). Initial study showed that no more than 2 eqs of periodate are necessary for complete oxidation of chloroepoxide *V* while lesser



SCHEME 2

amounts of periodate led to the recovery of starting material. No intermediate was observed during monitoring of these reactions by TLC. Larger amounts of periodate did not increase the yield, nor change the amount of byproducts, which were separated by extraction of basified reaction mixtures with ethyl acetate. The proposed oxidative degradation of *V* to *I* is depicted in Scheme 2. Although speculative, it explains the formation of lactone *I* through intermediates analogous to those invoked in the breakdown of ozonides derived from ozonolysis[9] of *IV* and related compounds[12].

On a 10 g scale the oxidation furnished erythruronolactone *I* with a crude yield higher than 60% and purity comparable, if not superior, to the product obtained previously by ozonolysis[9] of diene *IV*. The ease of this preparation and the good quality of the product prompted us to investigate a more direct preparation without the isolation of intermediates *IV* and *V*. Thus, the reaction sequence of protection and both permanganate and periodate oxidation of the chlorobenzene diol *III* (10 g scale preparation) was realized as a one-pot sequence with an overall yield higher than 50%.

The crude yield of *I* from optimized discontinuous ozonolysis[21] of *IV* is in the range of 70 – 75% on a 20 g scale. As a result, a technologically arduous and environmentally hazardous oxidation of diene with ozone was replaced by a more easily manageable procedure that uses significantly less toxic reagents and has good potential for further optimization.

This work was supported by Genencor International, Inc., TDC Research, Inc., and Jeffress Trust Fund.

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