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Toward a 'reagent-free' synthesis

Tandem enzymatic and electrochemical methods for increased effective mass yield (EMY)†

Tomas Hudlicky,* Dean A. Frey, Lukasz Koroniak,‡ Christopher D. Claeboe and Larry E. Brammer Jr.

Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA

Received 19th February 1999

Published on 01 January 1999. Downloaded on 22/01/2017 07:06:14.

Summary

Several synthetic pathways to cyclohex-5-ene-1*R*,2*S*,3*R*,4*R*-tetrol (conduritol C) and cyclohex-5-ene-1*S*,2*R*,3*R*,4*R*-tetrol (conduritol F) are compared; each is analyzed for effectiveness of waste minimization. The latest synthesis, reported in this manuscript, combines enzymatic transformations with electrochemical methods. The concept of "effective mass yield" (EMY) is defined and illustrated.

Introduction

The definition of efficiency with respect to organic synthesis varies according to the source or the focus of a pertinent activity. For example, academic researchers define efficiency (of a total synthesis) in terms of overall chemical yield and/or brevity of design.[1] A process chemist, on the other hand must also be concerned with generation of bulk waste (organic and inorganic) and the ratio of such weight to that of the desired product. Finally, the economics of cost and energy expenditures all enter into consideration for compounds about to enter the market place. Of the various definitions, Wender's covers most of these issues: '*the ideal synthesis . . . may be defined as one in which the target molecule is prepared from readily available starting materials in one simple, safe, environmentally-acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.*'[2] Sheldon defines the efficiency and environmentally benign nature of a synthesis in terms of an environmental factor or *E*-factor: the ratio of the mass of byproducts to the mass of the product.[3] At the same time he considers the stoichiometry of the reaction (*i.e.* catalysis) as a contributing factor to the overall efficiency.[4] The concept of 'atom economy' has been advanced by Trost,[5] and it has also been addressed by Sheldon in a recent review.[6]

In this manuscript we compare several approaches to conduritols and provide 'effective mass yield,' which we define as the percentage of the mass of desired product relative to the mass of all non-benign materials used in its synthesis. It can be approximated as $1/E$ where E is as defined by Sheldon,[3] with one additional consideration: those byproducts, reagents or solvents that have no known environmental risk associated with them (for example, water, low-concentration saline, dilute ethanol, autoclaved cell mass, *etc.*) do not enter into the calculations. A qualitative attempt at such a classification was made by Sheldon (environmental quotient or EQ).[3] By looking at the percentages of effective mass yield (EMY) for several synthetic pathways, one sees that neither atom economy, brevity nor chemical yields by themselves provide an accurate picture of the overall processes with respect to the total waste component.

Results and discussion

Several conduritol syntheses (Schemes 1–3) are analyzed for effective mass yield: Weinreb's classical synthesis,[7] a preparation that utilizes an enzymatic step,[8,9] and one in which electrochemistry has been employed.[10] These three preparations are compared for relative efficiency in terms of overall chemical yield (as reported), Sheldon's *E* value, and the effective mass yield (EMY). The weights of autoclaved cell masses, water, ethanol, methanol, and acetic acid are not taken into account because of their nontoxicity in the environment.[11] The EMY values are therefore calculated without the masses of these solvents. It follows that nonhazardous solvents should be used in all synthetic ventures to maximize EMY values.

Green Context

This paper describes a new synthetic route to conduritols C and F, based on a combination of enzymatic dihydroxylation and electrochemical reduction. In comparing this new approach to earlier syntheses, the author proposes a new measure of 'environmental friendliness'—effective mass yield, defined as the 'mass of desired product compared to the mass of all non-benign materials used in its synthesis'. This approach augments and complements Sheldon's *E*-factor and environmental quotient. *DJM*

† Supplementary data available: effective mass yield calculations. For direct electronic access see http://www.rsc.org/suppdata/gc/1999/57/, otherwise available from the British Library (BLDSC, No. SUP 57506, 2 pp.) or the RSC Library. See Author Guidelines (inside back cover, or http://www.rsc.org/greenchem).

‡ Undergraduate Research Participant, present address: Adam Mickiewicz University, Chemistry Department, 60-780 Poznan, Poland.

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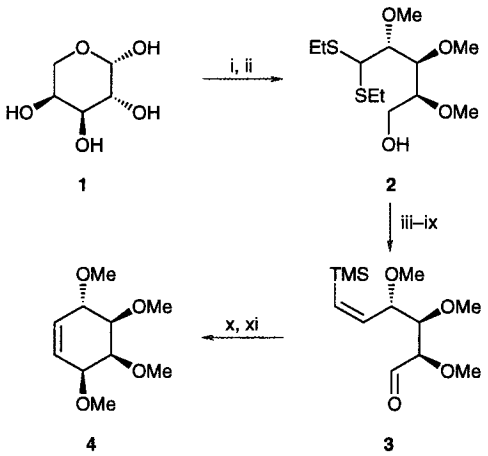
In the classical synthesis, Scheme 1, standard synthetic operations are used to convert arabinose to the final product.[7] It should be noted, however, that the tetramethyl derivative of conduritol C (**4**) requires deprotection (BBr_3/CH_2Cl_2), with uncertain outcome, as the transformation was not performed by the authors. Even a successful deprotection would reduce the calculated yield. Scheme 1 shows the mass ratios for this preparation.

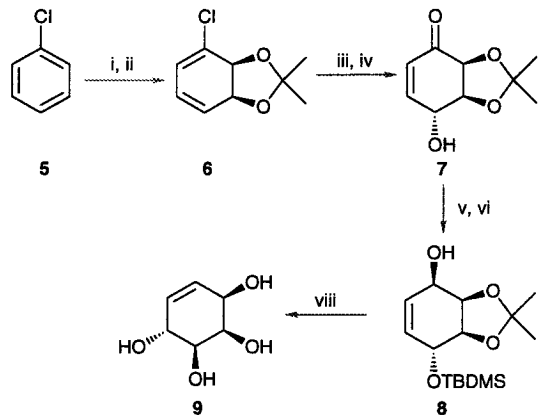


Scheme 1. Overall yield = 8.8%; E = 625; EMY = 0.16%. *Reagents and conditions*: i, $(CH_3O)_2SO_2$, NaOH, H_2O; ii, EtSH, HCl; iii, *tert*-butyldimethylsilyl chloride, imidazole, 4-dimethylaminopyridine, dimethoxyethane; iv, $HgCl_2$, HgO, acetone–H_2O; v, PPh_3, CBr_4, CH_2Cl_2, Et_3N; vi, *n*-BuLi, TMEDA, THF, TMSCl; vii, Pd($BaSO_4$), pyridine; viii, HOAc–H_2O (2:1); ix, dimethyl sulfoxide, $(COCl)_2$, CH_2Cl_2, Et_3N; x, $SnCl_4$, CH_2Cl_2; xi, AgO, MeI.

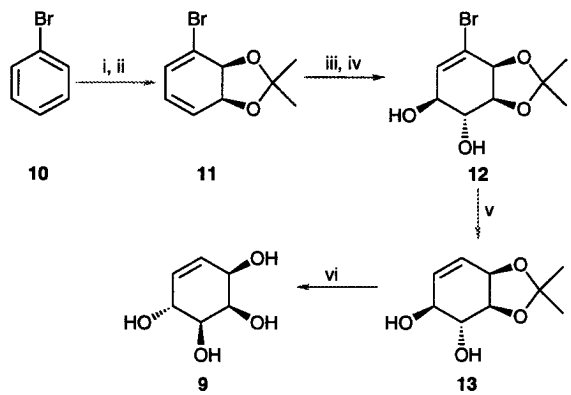
The syntheses of conduritols F[8] and C[9] from arene *cis*-dihydrodiols obtained by enzymatic oxidation of halobenzenes with *E. coli* JM109 (pDTG601) have been accomplished in our laboratories.[12] In an effort to incorporate environmentally benign protocols that utilize less reagent and solvent mass to achieve the syntheses, we have investigated alternative methods for the epoxidation of C4–C5 olefin and for the reduction of vinyl halides at C1. For example, in our earlier synthesis of conduritol F,[8] the oxidative functionalization at C4–C5 (*m*-chloroperbenzoic acid; methylene chloride) was followed by reduction of the vinyl halide (tri-*n*-butyltin hydride, AIBN), to the protected conduritol F. Similar chemistry was also used to attain conduritol C (**9**), as shown in Scheme 2.

In the 'green' synthesis of conduritol F, the epoxidation with *m*-chloroperbenzoic acid in methylene chloride has been replaced with either bromohydrin generation or environmentally friendly carbodiimide-promoted olefin epoxidation with aqueous hydrogen peroxide to form the *anti*-epoxide, as reported by Majetich *et al.*[13] The tri-*n*-butyltin hydride reduction of vinyl halide **12** was replaced with an electrochemical reduction, which we have developed in our laboratory,[10] to give a 60% yield of the protected conduritol F.

Although our conventional synthesis of conduritol C[9] (Scheme 2) is the shortest on record, it still contains a number of environmentally "unfriendly" chemical transformations. The EMY value for this synthesis is comparable to that of the completely chemical preparation. When the enzymatic step in the latest preparation (Scheme 3) was augmented with electrochemical reduction rather than traditional tri-*n*-butyltin hydride-mediated dehalogenation, the component of byproduct mass was further reduced, indicated in an increased EMY value.



Scheme 2. Overall yield = 26.9%; E = 1125; EMY = 0.12%. *Reagents and conditions:* i, *E. coli* JM109 (pDTG601A); ii, 2,2-dimethoxypropane, acetone, *p*-TsOH; iii, O_2, tetraphenylporphine, CCl_4, $h\nu$; iv, thiourea, MeOH; v, *tert*-butyldimethylsilyl chloride, dimethyl formamide; vi, L-Selectride, THF; vii, HCl, H_2O.



Scheme 3. Overall yield = 23.9%; E = 391; EMY = 2.39%. *Reagents and conditions:* i, *E. coli* JM109 (pDTG601A); ii, 2,2-dimethoxypropane, acetone, *p*-TsOH; iii, 1,3-dibromo-5,5-dimethylhydantoin, H_2O–acetone; iv, NaOH, H_2O–dimethoxyethane, heat; v, e^-, MeCN, Et_4NBr; vi, NaOBz, H_2O.

In order to determine the overall efficiency of the syntheses, effective mass yields were calculated[14] for conventional and 'green' syntheses of conduritol C, as shown in Schemes 1 and 2. Effective mass yield accounts for not only atom economy,[5] (*i.e.*, 'how much of the reagent mass ends up in the product'), but also those materials such as solvents and reagents that do not contribute to the mass of accumulated byproducts. Hence effective mass yield is a more accurate representation of (desired) mass expressed as a percent of the total mass of materials used in manufacturing.

Acknowledgements

We thank Prof. David T. Gibson (Uuniversity of Iowa) for providing us with a sample of *E. coli* JM109 (pDTG601A), Prof. Angela S. Lindner (University of Florida) for her assistance with environmental issues, Dr. Mary Ann Endoma for her assistance with the biotransformation experiments, Dr. Gabor Butora for his assistance with electrochemical eperiments, and Dr. Ion Ghiriviga for NMR support. Financial support by TDC Research Foundation (Fellowship to L. K. and C. D. C.), National Science Foundation (CHE-9615112), and US Environmental Protection Agency (R826133) is gratefully acknowledged.

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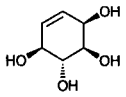

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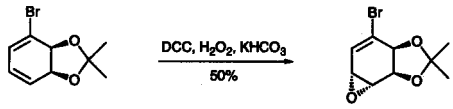

14 All calculations are shown in tabular form in the Supplementary Material, (see footnote †).

Paper 9/01397K