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Dearomatization applications of $I^{(III)}$ reagents and some unusual reactivity amongst resorcinol derived cyclohexadienones

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ABSTRACT

The oxidative dearomatization of resorcinol derivatives, which are outfitted with a lactic acid derived chiral tether, and mitigated by hypervalent iodine derivatives of PhIO, affords stable chiral cyclohexadienones as useful building blocks for the construction of many highly functionalized chiral six and seven-membered ring systems. Herein, we report a multitude of remarkable and unexpected diastereoselective transformations stemming from these cyclohexadienone adducts.

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1. Introduction

Despite many advances in asymmetric organic reaction processes, only a handful of chemical methods have emerged to provide enantiomerically enriched cyclohexadienones.[1] Few are catalytic. None are general. This is surprising because chiral cyclohexadienones offer attractive entry points to a number of complex non-racemic natural products. One needs to look no further than the early racemic syntheses of ryanodol, calicheamicinone, and ovalicin to be seduced by the utility of chiral cyclohexadienones. However, after reflecting and studying the processes that deliver these building blocks, we have come to appreciate the thorny issues of product stability and utility, which have prevented real progress. Any new dearomatization process should be judged just as much, if not more so, in these realms as in their overall diastereomeric or enantiomeric selectivity.

Diastereoselective dearomatization processes are inherently useful. In total syntheses of epoxysorbicillinol,[2] bisorbicillinol,[2] rishirilide,[3] and the cleroindicins,[4] as well as for other putative natural products,[5] we have confronted the issues of cyclohexadienone stability and subsequent utility head-on. Herein, we recount this diastereoselective dearomatization process, and report for the first time some of the remarkable reactivity we have observed amongst the resulting cyclohexadienone products.

2. The plan

Early on we speculated that a catalytic enantioselective method offered limited synthetic potential because its efficient use would be restricted by cyclohexadienone reactivity to circumstances where the target molecule contained a single stereocenter.[1] Therefore, our formulative ideas centered upon developing more utilitarian diastereoselective dearomatization processes.[6] We imagined some hypervalent $I^{(III)}$ reagent prompted oxidative dearomatization involving an unprecedented *ortho*-cyclization of a lactic acid derived tether should produce a family of sturdy cyclohexadienones capable of further regioselective and diastereoselective reactions.[7] Low yields (<70%) have long plagued the synthesis of cyclohexadienones. This stems from the reactivity of the reaction intermediates and the respective products. A workaround solution, which we were resolved to not use, has been the deployment of the oxidative dearomatization at a very early stage, when starting material is overly abundant, or very near the end, when the target compound can be easily reached. However, these solutions fail to capitalize on the malleability intrinsic to the cyclohexadienones product themselves. Fortunately, widespread use of hypervalent iodine oxidants,[8] particularly $I^{(III)}$ derivatives of iodosyl benzene (Ph–I=O),[9] have supplanted $Pb^{(IV)}$, $Tl^{(III)}$, and DDQ as oxidants. These hypervalent iodine reagents have led to

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improved yields, because these non-toxic $I^{(III)}$ reagents rarely participate in undesirable side-reactions with the intermediate phenonoxonium cation.[10]

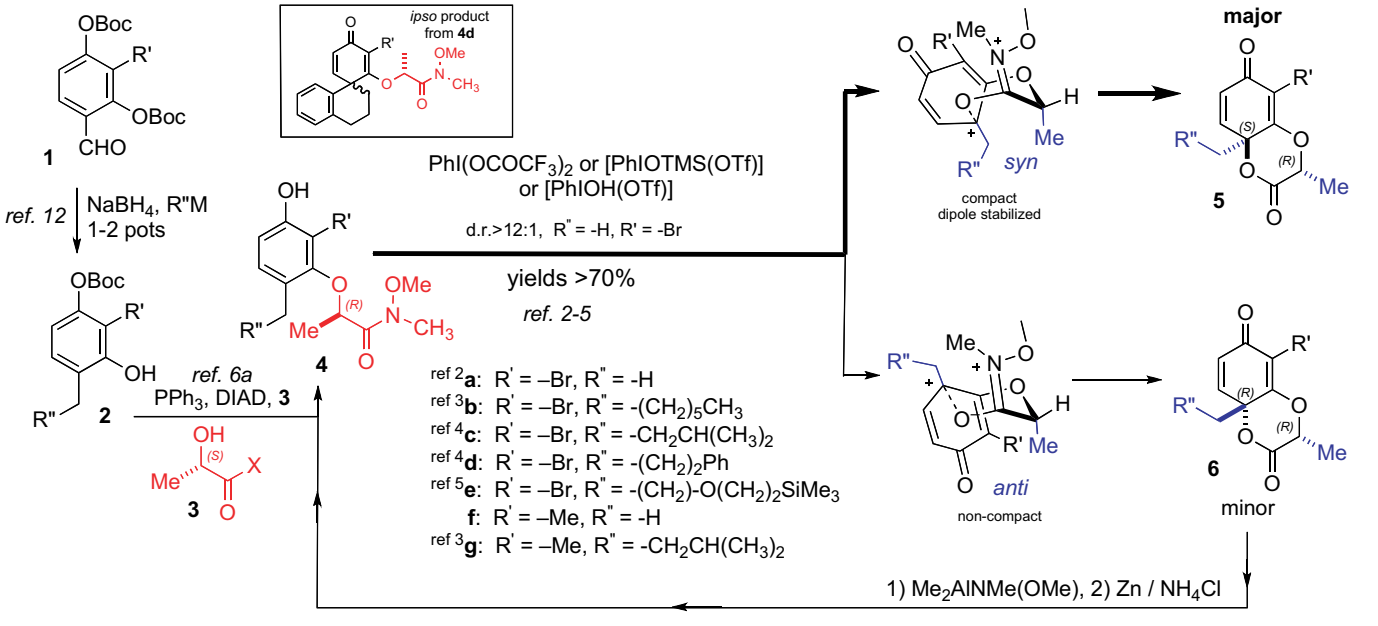
We anticipated that the δ-lactone formed by our proposed oxidation would further stabilize the cyclohexadienone so that the enone, vinylogous ester, and ketone functionality could be manipulated in both chemoselective and stereoselective manners to address a number of natural products, in spite of the inescapable fact that the cyclohexadienone product would display five trigonal sp^2 carbon atoms. We therefore set out to build several of these scaffolds so that we might determine their subsequent reactivity, which we expected to be nucleus dependent. For example, *o*-quinol derivatives are susceptible to dimerization,[1b,d] whereas their *p*-quinol counterparts succumb to single electron transfer reduction and rearomatization.[11] While none of these issues can be avoided altogether, we imagined that some electronic and structural features could be introduced into the phenol and tether functionalities to dissuade some of undesired reactivities in the resulting cyclohexadienone adduct. An added benefit of our plan was that the oxygen atom, which would be installed during the dearomatization reaction, would be already protected. This increased the efficiency of any future synthetic plans by expanding the repertoire of accessible chemical transformations and obviating the need for subsequent hydroxyl protection.

3. Diastereoselective dearomatization with $I^{(III)}$ reagents; the affects of reaction conditions and substrate substitutions on the overall yield and diastereoselectivity

Our studies have principally utilized two 2,4-dihydroxybenzaldehydes **1** (R′=–Me, –Br, Scheme 1). Some time ago, we reported a method for the straightforward conversion of these kinds of aldehydes into their corresponding 2-bromo- and 2-methyl-resorcinol derivatives **2** so as to display differing 4-alkyl substituents (**a**–**g**).[12] Before the development of our mild process, which involves *o*-quinone methide (*o*-QM) generation and consumption, these types of *mono*-protected 4-alkyl resorcinols were relatively inaccessible. The unprotected phenol product participates in an S_N2 reaction under Mitsunobu conditions with the secondary alcohol within various amides **3**, which are derived from (*S*)-methyl lactate.[13] Subsequent Boc deprotection with $ZnBr_2$ in CH_3NO_2 or in situ with aqueous LiOH at the conclusion of the Mitsunobu reaction affords the respective non-racemic mono-'protected' resorcinols **4** with enantiomeric excess of greater than 99%, demonstrated by chiral GC comparison of a derivative to a racemic standard.[6a]

Oxidation of these substrates using various $PhI^{(III)}$ species afford the corresponding lactones **5** as the major product (dr>12:1). In some instances, where the R″ substituent is fairly small (R″=–H), a minor amount (<7%) of the lactones **6** can be observed. However, this unwanted diastereomer is easily removed by column chromatography and it can even be re-introduced into the synthetic stream by formation of the corresponding Weinreb amide followed by the appropriate reduction. Given the structure of the major product, we speculate that it arises from the compact, dipole stabilized transition-state. From this transition-state, the Me– of the lactate residue, and the R″CH_2– substituent emerge on the same face (*syn*) with respect to the newly forming 1,4-di-oxygenated ring. On the other hand, for the minor diastereomer **6**, the Me– and the R″CH_2– substituent emerge on the opposite face (*anti*). The X-ray crystal structures for **5a** and *ent*-**5a** have been previously reported.[4]

After much experimentation with the oxidative dearomatization of resorcinol 4d (R″=–$(CH_2)_2$Ph), which can undergo either *ipso* or *ortho*-cyclization (Scheme 1, inset shows the *ipso* product), we believe that we have successfully ascertained the optimum combination of reagents and substituents for the formation of the desired 1,4-dioxan-2-one scaffold 5.[3] Dilute conditions (0.05 M) and very polar solvents, particularly nitromethane (CH_3NO_2), proved best in most instances. A bromine or alkyl substituent at the 2-position of the resorcinol also appeared to facilitate the dearomatization process, and increase the diastereoselectivity. Remarkably, the lactate tether motif not only resulted in diastereoselection, it also improved yields and it provided a more stable cyclohexadienone adduct than the corresponding glycolate derived tethers. In addition, we found that the transformation can be carried out at much higher concentrations (0.3 M) in methylene chloride when the oxidation is carried out with either (1.1 equiv PhIO, 0.1 equiv TMSOTf) or (1.1 equiv PhIO and 1.1 equiv TfOH).[3,5] These oxidants, which are generated in situ, prevent any undesired participation of the ligand from the hypervalent iodine species with the intermediate phenoxonium cation.[14]



Scheme 1. Diastereoselective dearomatization of resorcinol derivatives with [PhIOTMS(OTf)].