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On the basis for regioselective oxidation within a tetragalloylpyranose substrate

Ken S. Feldman* and Kendra L. Hunter

Department of Chemistry, The Pennsylvania State University, University Park, PA 16802 USA

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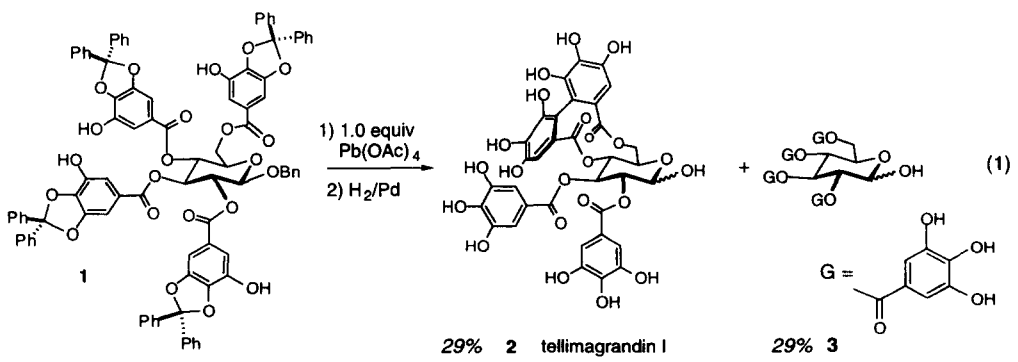
Abstract:

Lead (IV)-mediated oxidation of a benzyl 2,3,4,6-tetragalloylglucopyranoside leads only to coupling at the O(4)/O(6) galloyls. Competitive oxidation experiments with a series of positionally distinct phenolic galloyl analogs furnishes evidence that this unexpected regioselectivity stems from preferential oxidation at the O(6) galloyl ring. Companion studies with electronically dissimilar analogs provide support for a through-space component to O(6) galloyl oxidation selectivity in addition to steric and inductive influences.

Keywords: oxidation; regioselective; electronic effects

Progress in the synthesis of ellagitannin natural products[1] depends on the continuing development of methodology for the stereo- and regioselective coupling of galloyl esters appended to a glucopyranose core. A particularly striking resolution of both selectivity issues can be found in the Pb(OAc)4-mediated oxidation of the tetragalloylated substrate **1** to afford tellimagrandin I (**2**) (following hydrogenolytic debenzylation) as the only coupled material, eq. (1).[2] The stereoselectivity of this transformation has been addressed earlier,[1b,2] but the basis for the unexpectedly high level of regioselectivity remained a matter of speculation. Subsequent studies designed to probe the origins of the regioselectivity upon oxidative coupling within **1** have been conducted, and the results of these studies point to an explanation for this observation, as described below.



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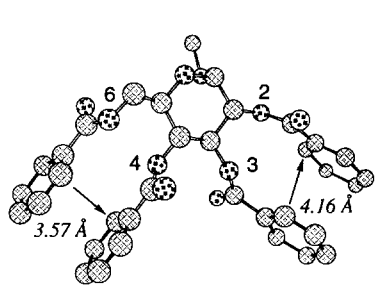
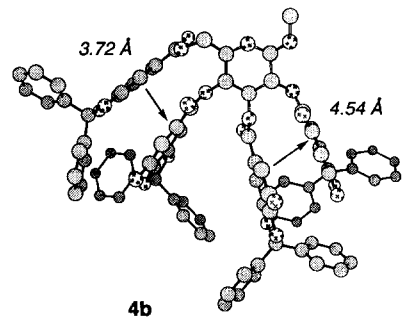
Conformational analysis of the computationally simple model compound methyl 2,3,4,6-tetrabenzoylglucopyranoside revealed that the O(4)/O(6) and O(2)/O(3) benzoyl rings were paired in the "global" minimum energy conformer **4a**.[3] Similar analysis of the more realistic *O*-1-methyl ether analog of **1** led to an analogous conformation of the "global" minimum, **4b**.[3] Thus, a simple ground state conformer model of oxidative coupling reactivity would suggest that while reaction might be observed between these proximal pairs, the prospects for O (3)/O(4) galloyl coupling were greatly diminished. However, deciding between O(4)/O(6) and O(2)/O(3) galloyl coupling, both of which have been observed experimentally,[4] is not obvious based upon this model. The likely irreversibility of Pb(IV)-mediated phenol oxidation (Wessely oxidation)[5] refocuses the regioselectivity question on the relative oxidation potential of the different galloyl rings, as it follows that the most readily oxidized ring will determine the position of biaryl formation.



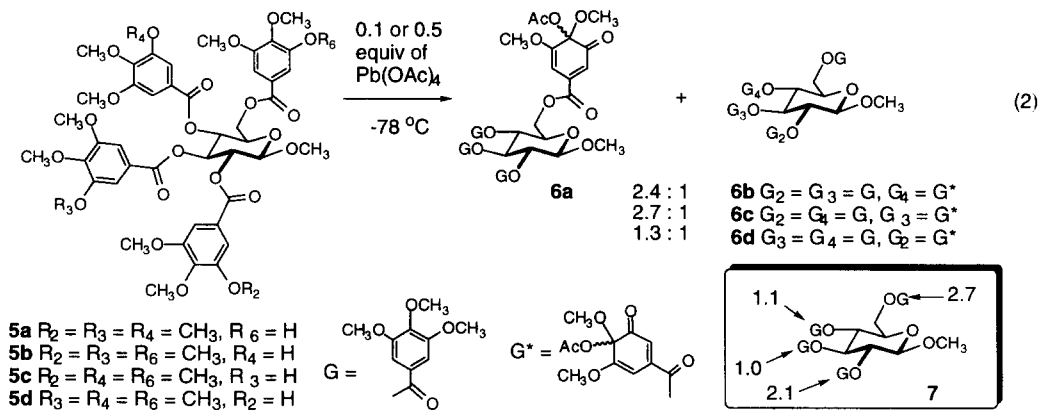
4a



4b

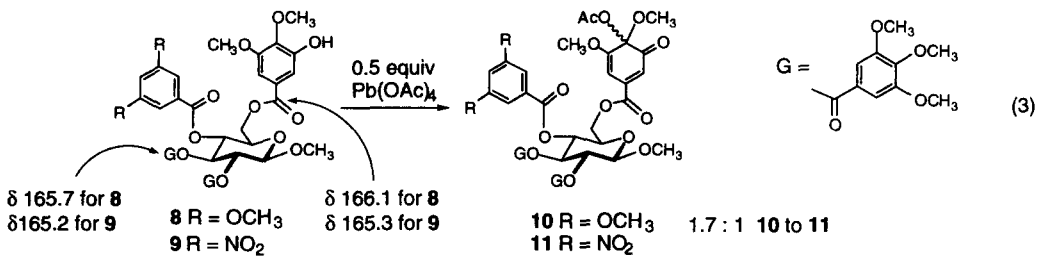
Competitive galloyl oxidation experiments in a model system were conducted to probe this relationship between pyranose ring position and facility of oxidation of the phenolic ring, eq. (2). In each of three independent experiments, an equimolar mixture of **5a** and either **5b**, **5c**, or **5d** were treated with a deficiency of $Pb(OAc)_4$ (both 0.1 and 0.5 equivalents of Pb per phenol were examined, with little difference in product ratio). In all cases, high yields of orthoquinone monoketal product (> 90 % based on $Pb(OAc)_4$) were obtained. A control experiment (1 equiv each of **5a**, **6c**, and HOAc in $CDCl_3$ remained unchanged at rt over 1 h) indicated that kinetic control of acetate delivery prevailed. The ratios of the O(6)-galloyl oxidized product **6a** to the O(2)-, O(3), or O(4) oxidized products **6b**, **6c**, or **6d**, respectively, allowed direct assessment of the relative reactivity of a galloyl phenol at each pyranose ring position. Thus, a galloyl ring at

O(6) appears to be measurably more susceptible to $Pb(OAc)_4$-mediated oxidation than the identical rings at O(4), O(3), or O(2). These results can be normalized to the intrinsic reactivity rankings shown in the composite structure **7**. The inherent preference for O(6) galloyl oxidation within **7** is consistent with the observation that galloyl coupling proceeds exclusively at the O(6)/O(4) juncture in substrate **1**.



(2)

It is interesting to note that this pattern of oxidation propensity exactly mirrors the relative rates of glucopyranoside hydroxyl acylation and therefore may, in part, simply reflect the interplay between steric accessibility and inductive electronic deactivation by the electron depleted pyranose ring as felt by each of the oxygen atoms.[6] However, the results of the experiment depicted in eq. (3) suggest that an additional *through-space* electronic contribution to the observed oxidation selectivity cannot be discounted. Oxidation of an equimolar mixture of **8** and **9** with a limiting amount of the lead reagent again furnished the monooxidized products **10** and **11** in good yield, but in this case oxidation of the more electron rich substrate **8** was favored by 1.7:1. Thus, it is not implausible that this through-space effect, manifested perhaps as transition state anchimeric stabilization of the burgeoning electron deficiency in one ring by the adjacent ring, might be operational. The closer proximity of the O(4)/O(6) pair compared with the O(2)/O(3) pair (cf. **4a** and **4b**) may differentially enhance this interaction at the former locus and contribute to the observed preference for O(6) galloyl oxidation. The comparable ^{13}C NMR signals for the flanking carbonyls at O(3) and O(6) argue against the incursion of a through-bond inductive effect due to the dissimilar electronic character of the aroyl rings at O(4) in these substrates.



(3)

The overall picture emerging for the basis of the coupling regioselectivity observed within the tetragalloylated substrate **1** cites initial oxidation of the O(6)-galloyl ring as a consequence of 1) its position on a relatively sterically accessible and relatively electron rich (or less electron depleted) carbon of the glucopyranose framework, and 2) the possible benefit of through-space electronic interactions with the adjoining O(4) galloyl ring. The relatively modest selectivities observed in the model system **5** compared to the higher selectivity implied in eq. (1) may point to an unanticipated role of the nucleophile in the rate-determining step of the Wessely oxidation.[5] Whether this model can be extrapolated to other polygalloyl glucopyranose systems, including those involved in ellagitannin biosynthesis, remains unknown.

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