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Production of enantiopure β-amino-γ-hydroxyesters from benzoic acid by a selective formal aminohydroxylation

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ABSTRACT

The enantioselective preparation of three protected β-amino-γ-hydroxyesters from benzoic acid is described. The employed synthetic methodology involves the *ipso*, *ortho cis*-dihydroxylation of benzoic acid by the mutant strain *Ralstonia eutropha* B9, followed by a selective halonium induced beta lactamization. Modification of this novel β-lactam structure by the appropriate sequence of reactions allows for the selective preparation of the aforementioned β-amino-γ-hydroxyesters in a diastereodivergent manner. The overall transformation results in a selective formal aminohydroxylation of the diene moiety of the initial *cis*-cyclohexadienediol. The synthesized products are important building blocks and will allow for the selective preparation of aminoacids, inosamines and alkaloids from benzoic acid.

cis-Cyclohexadienediols obtained by biotransformation of arenes using bacterial dioxygenases, have been widely used as starting materials for enantioselective synthesis of natural products.[1–7] Although the clear majority of synthetic examples are derived from diols obtained by the Toluene Dioxygenase enzymatic complex, dienediol **1** obtained by the *ipso*, *ortho cis*-dihydroxylation of benzoic acid by Benzoate Dioxygenase (expressed in the mutant *Ralstonia eutropha* B9) has been recently used by several research groups to produce biologically active natural products and/or advanced intermediates. (Fig. 1A)[8–24] Examples are found in the literature for the total synthesis of polyoxygenated materials from benzoic acid, such as (−)-idesolide,[10] (+)-grandifloracin,[9] piperenol B,[13] pleiogenone A[14] and, more recently, a formal approach to xylosmin and flacourtosides E and F.[20] Although the dienic system in **1** does not present any substituent to allow for the differentiation of both olefins, selective oxygenation of either center of the ring can be accomplished by selecting the appropriate sequence of reactions (osmylation, epoxidation, diol protection) as described by Myers et al. in 2001.[25]

Regarding the preparation of N-containing products, several examples are shown in the literature, such as the synthesis of inosaminoacids,[26] inosamines,[7] pyrrolidines,[12] and tetracyclines[8] from benzoic acid (Fig. 1A). In the majority of these cases, the nitrogen function is incorporated in the diene using a nitroso Diels-Alder methodology via *in situ* oxidation of hydroxamic acids (Fig. 1B), followed by a reduction of the oxazine to afford the 1,4-hydroxyamino function.[27] This methodology has the drawback of a lack in regioselectivity (which can be modulated, but not solved, by changes in the R group in **1**).

In this paper, we describe a novel protocol to accomplish a formal aminohydroxylation of the diene in **1** in a regio- and stereoselective manner. This methodology allows the preparation of three different types of protected β-amino-γ-hydroxyesters which can be used as important building blocks for the synthesis of aminoacids, inosamines, and alkaloids using benzoic acid as staring material.

We initially envisioned that an amide function in the quaternary center of **1**, could act as a nitrogen donor to produce the selective functionalization of the diene moiety through an halonium induced lactamization. In this manner, if the halonium mediated cyclization showed a preferred cycle size, regioselectivity for the nitrogen addition into the diene would be achieved. Myers et al. used a similar approach to selectively functionalize the diene using a bromolactonization protocol.[25] To follow this aim, salt **4** (obtained as the crude product of the biotransformation of benzoic acid with *Ralstonia eutropha B9*) was protected with the isopropylidene group according to a known procedure,[16] followed by a tosylamide formation by treating the carboxylic acid **5** with *p*-tosyl isocyanate followed by TEA, (Fig. 2)[28] to afford product **6** with a 70% yield. The choice of a tosylamide function as a nitrogen donor

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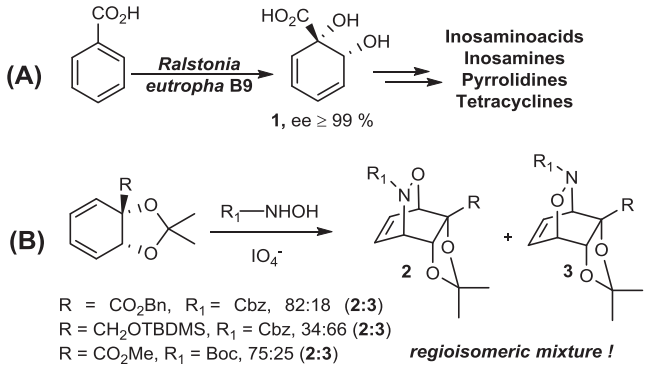

Fig. 1. A/Nitrogen containing natural products prepared from dienediol 1. B/Nitroso Diels-Alder reaction has been used to functionalize the diene moiety without complete regioselectivity.

for the halonium-mediated lactamization was based on the known preference of amides to react by the more nucleophilic O atom, while the electron withdrawing properties of the tosyl groups favors nucleophilic attack by the nitrogen.[29]

Sulfonylamide **6** was subjected to different halonium-mediated lactamization conditions as shown in Table 1, to produce β-lactams **7a** and **7b** in different ratios. For every condition the preferred isomer was **7a**, which shows that the preferred olefin for halonium addition is the one that is farther from the quaternary center (addition occurs *anti* to the bulky isopropylidene group). Halonium opening by the N-atom of the tosylamide function via a S_N2' can explain the formation of **7a**. As a first approach, reactions using iodine as the halogen source (I_2 or NIS) were performed, according to previous reports (entries 1 and 2),[30] obtaining a mixture of products which could presumably be the corresponding β -lactams, but could neither be purified nor identified, since the reaction was reversed during chromatographic column purification, recovering **6**. When using Br_2 or NBS as the halogen source, the desired products were obtained as mixtures in variable ratios depending on the polarity of the media. Reactions using polar media containing water (entries 3 and 4) gave higher proportions of **7b**, which were decreased when using acetonitrile as the sole solvent (entries 5 and 6). Best conditions were obtained upon addition of solid $NaHCO_3$, which produced an increase of yield while maintaining the selectivity (entry 6). For entry 7, where the less polar solvent mixture of toluene and dichloromethane was used, there was no reaction. When using bromine as the halogen, the reversibility of the reaction was lower than for iodine, thus allowing isolation and proper characterization of products. Nevertheless, to prevent losses of material, further reactions on **7a** were carried out using the crude reaction mixture (See Supporting information).

Table 1
Optimization conditions to produce β-lactam **7a**.

Entry	Conditions	Yield[a]	**7a**:**7b**[b]
1	I_2, aq. $NaHCO_3$ (satd.), CH_2Cl_2 (1:2)	–	–
2	NIS, aq. $NaHCO_3$ (satd.):CH_2Cl_2 (1:1)	–	–
3	Br_2, aq. $NaHCO_3$ (satd.):CH_2Cl_2 (1:2)	42	80: 20
4	NBS, H_2O:DME (1:4)	32	75: 25
5	NBS, MeCN	50	91: 9
6	NBS, MeCN, $NaHCO_3$(s)	67	91: 9
7	NBS, Toluene:CH_2Cl_2 (1:20)	–	–

[a] Determined by NMR using trichloroethylene as an internal standard.
[b] Ratio determined by NMR in the crude reaction mixture.

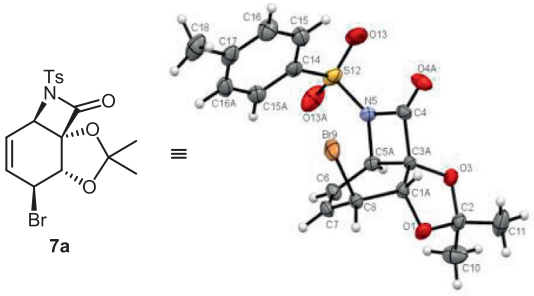

Fig. 3. β-Lactam **7a** structure resolved by X-ray diffraction. The anisotropic displacement ellipsoids are drawn at the 30% probability level (hydrogen atoms are depicted as spheres with arbitrary radii).

Structure of β-lactam **7a** was confirmed by X-ray diffraction analysis (see ORTEP diagram in Fig. 3 and Supporting information). This interesting and complex product not only allows regio- and stereoselective introduction of the nitrogen function, but also is a suitable substrate for S_N2' reactions, which will result in the selective functionalization of one of the olefins originally present in diene **6**.

With that in mind, the β-lactam **7a** was opened with different nucleophiles using KCN as catalyst, as stated previously by Palomo et al. (Fig. 4).[31,32] When using methanol, we found that the opening of the β-lactam promoted the formation of aziridine **8** with excellent yield, probably via an intramolecular S_N2' displacement of the bromine by the tosylamide group (see Fig. 4). This aziridine was opened in the allylic position by attack of water, to obtain the protected β-amino-γ-hydroxyester **9** in excellent yield Fig. 5.

Alternatively, basic hydrolysis of β-lactam **7a** produced the lactone **10**, whose formation can also be explained via an intramolecular S_N2' attack of the carboxylate function on the allyl bromide.

Transesterification of lactone **10** with sodium methoxide gave only traces of the protected β-aminoester **11**. To sort this out, a

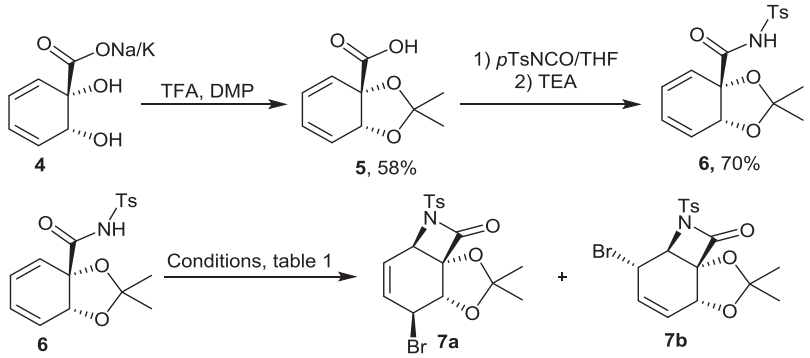

Fig. 2. Synthesis of the sulfonylamide **6** and its halogen mediated lactamization to produce β-lactams **7a** and **7b**.