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A novel β-D-glycosyl carbamate forming reaction

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Abstract

The synthesis and use of a novel and versatile 1-β-*O*-D-glycosyl active carbamate is described. This active carbamate is prepared from an in situ generated isocyanate and is used to prepare 1-β-*O*-D-glycosyl carbamates of multi-functionalized primary or secondary amines in high yield and with 100% β-diastereoselectivity. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

In an attempt to couple the carboxylic acid group of **1a** to the amino group of daunorubicin **2** using the BOP coupling reagent, instead of the expected amide product, carbamate **3a** was obtained in 89% yield together with 6(5*H*)-phenanthridinone (**4**) (Scheme 1). Variation of the peptide coupling reagent, solvent and base did not lead to the desired product; in all cases β-D-glucuronyl carbamate **3a** was isolated.[1] This unexpected reaction sequence was also followed for the galactosyl analogue leading to daunorubicin-β-D-galactosyl carbamate **3b**. In the literature, comparable examples of the present 1-β-*O*-D-glycosyl carbonyl-transfer reaction with phenanthridinone **4** acting as a leaving group have not been reported.

As reported earlier by us, glycosyl carbamates can be prepared by the addition reaction of an anomeric hydroxyl group of a glycosyl donor to an isocyanate.[2] This was found to proceed with high β-diastereoselectivity and was used in our work on anthracycline prodrugs.[3] In the specific case of daunorubicin **2** however, the 3′-amino group could not be converted to an isocyanate group in order to react with glycosyl donor **9** (Scheme 3) and yield **3**, because the 4′-hydroxy reacted with the 3′-isocyanate group to form cyclic carbamate **5** (Scheme 1).

The unexpected sequence depicted in Scheme 1 can be rationalized as follows (see Scheme 2). The coupling reagent (i.e. BOP) activates the carboxylic acid **1** in the normal manner. Then an

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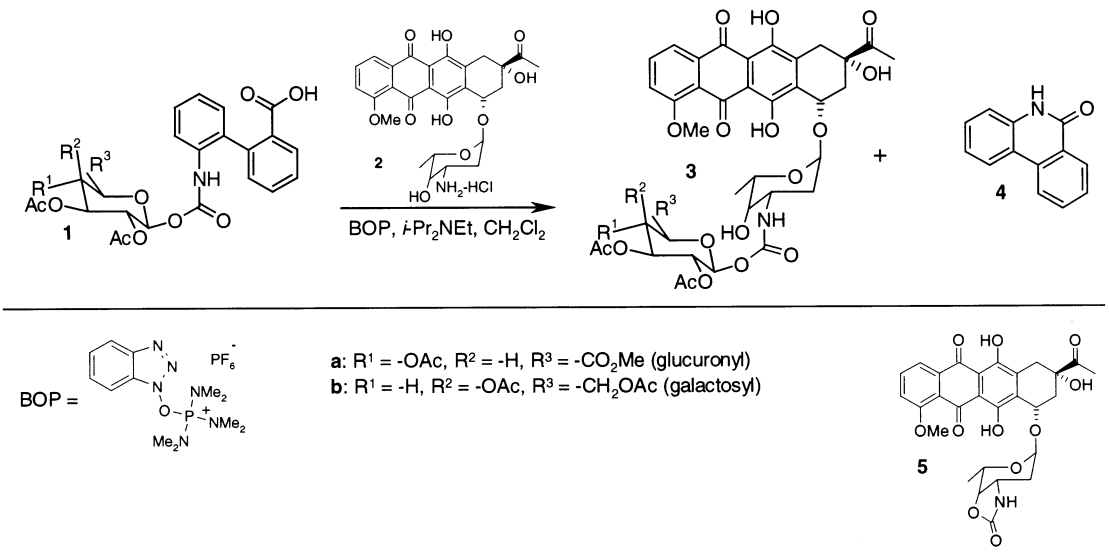
intramolecular reaction with the carbamate nitrogen takes place to give the *N*-phenanthridinone *O*-β-D-glucuronyl carbamate **6**. The phenanthridinone moiety serves as a leaving group in the subsequent reaction of **6** with daunorubicin **2** to give compound **3** and phenanthridinone **4**.

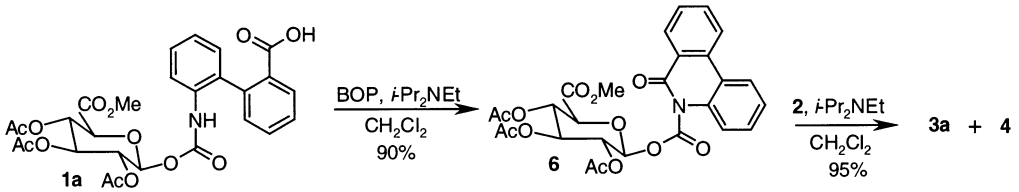


Scheme 1.

Unequivocal evidence for this mechanism was obtained by a reaction of **1a** with coupling reagent BOP in the absence of a nucleophilic amine. This reaction led to the high yield formation of compound **6** (90%). An independent reaction of active carbamate **6** with daunorubicin **2** led to carbamate **3a** and phenanthridinone **4**.

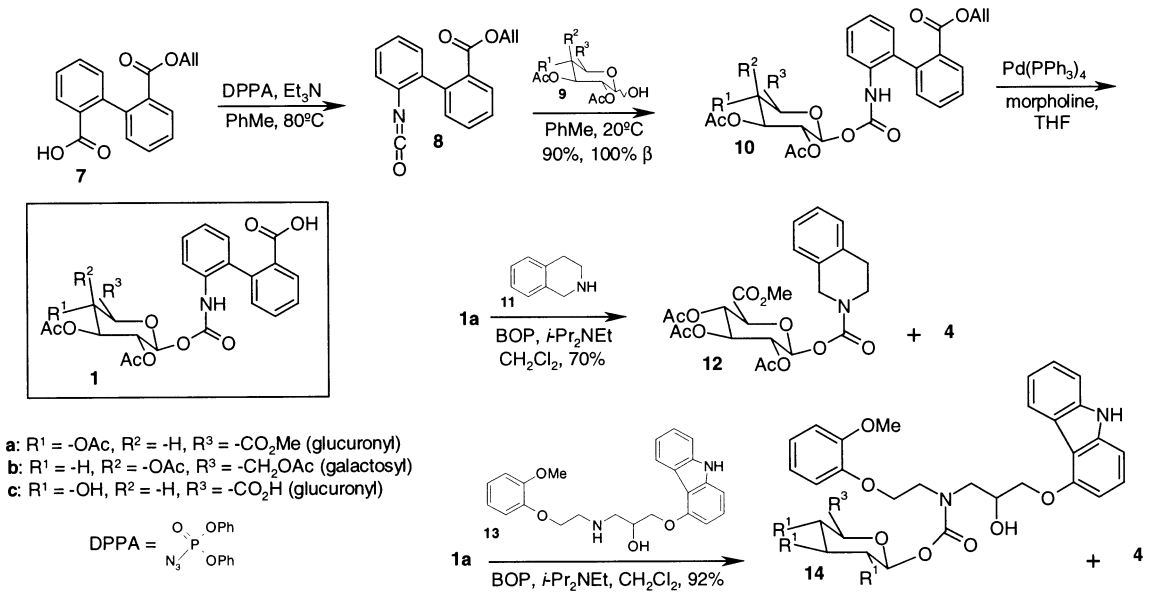
2. Application of the novel transfer reaction

Application of the reaction to the synthesis of β-D-glucuronyl carbamates of primary or secondary amines is of interest because these β-D-glucuronyl carbamates are well known metabolites[4] of drugs containing a primary[5] or a secondary[6] amino group respectively. Synthesis of these metabolites, however, is not always straightforward: (a) Other nucleophilic groups in the substrate molecule (e.g. –OH, –NHR, $-CO_2H$) can impede isocyanate formation by reaction with it (see e.g. by-product **5**). (b) An isocyanate group cannot be formed from a secondary amine. (c) When glycosyl donor **9** is reacted with a chloroformamide prepared from a secondary amine, principally α- and not β-D-glucuronyl carbamates are formed. Our new synthetic route to β-D-glucuronyl carbamates avoids these problems.



Scheme 2.

The novel β-D-glycosyl carbamate forming reaction was first tested in a model system (Scheme 3). When 1,2,3,4-tetrahydroisoquinoline **11** was reacted with *N*-2-biphenyl-2′-carboxylic acid *O*-(methyl 2,3,4-tri-*O*-acetyl β-D-glucuronyl) carbamate (**6**, Scheme 2), the β-D-glucuronyl carbamate **12** was obtained in 70% yield.



Scheme 3.

Furthermore, using our new method, synthesis of the protected precursor **14a** of the metabolite **14c** of the anti-hypertensive drug carvedilol **13**[7] was successfully achieved in 92% yield from (±)-carvedilol (Scheme 3). Metabolite **14c** had previously been prepared in vitro using dog and rat liver microsomes[8] for use as a reference compound.

Glucuronyl carrier **1** was prepared from **10** (previously prepared by us[2] from **7** and **9**) in 93% by a palladium(0) mediated allylester demasking reaction (Scheme 3).

In conclusion, the preparation of *N*-daunorubicinyl- and *N*-carvediloyl *O*-β-D-glucuronyl carbamates **3a** and **14a**, respectively, exemplifies the value of the present novel reaction in the preparation β-D-glucuronyl carbamates of relatively complicated primary and secondary amines.

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