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A new 20-membered macrocyclic dilactam: an unexpected product of a tri-*n*-butyltin hydride-mediated radical reaction ☆

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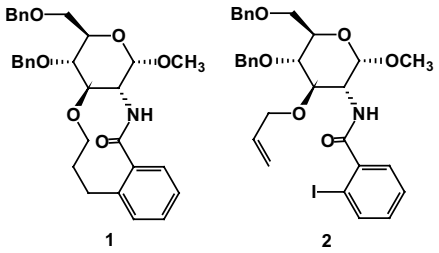
Abstract—The tri-*n*-butyltin hydride-mediated reaction of methyl 3-*O*-allyl-4,6-di-*O*-benzyl-2-deoxy-2-(2-iodobenzoylamino)-α-D-glucopyranoside affords an unexpected benzomacrodilactam. The structure of this new 20-membered macrocyclic dilactam has been elucidated by electrospray mass and tandem mass spectrometry (ESI-MS/MS) and by ^{1}H, ^{13}C NMR spectroscopy, COSY, TOCSY, HMQC and HMBC experiments.

In continuing studies[1–4] of Bu_3SnH-mediated radical cyclizations, we have applied unsaturated organohalides to synthesize lactones and lactams, most particularly benzomacrolactams from *ortho*-iodobenzamides bearing a side allyloxy group.[1–3] These studies confirmed that 12- and 11-*endo* cyclizations are preferred over the corresponding 11- and 10-*exo* cyclizations, in agreement with both the general guideline for radical macrocyclization that states that '*endo* cyclization modes are favored'[5] and with other experimental results on macrocyclization.[6–12] But in contrast with the larger ones, small macrocycles (10–12 membered) are known to be extremely difficult (if not impossible) to synthesize.[13,14] It was therefore important to find that, by an *endo*-selective intramolecular attack of an aryl radical to an unsaturated carbon–carbon bound, a 10-membered ring lactam could be obtained in 45% yield.[14] We have also shown that a sugar unit in the *ortho*-iodobenzamides aids the 11-*endo* aryl radical cyclizations.[1,2] Based on these encouraging results, we decided to test the Bu_3SnH-mediated 10-*endo* radical cyclization reaction with methyl 3-*O*-allyl-4,6-di-*O*-benzyl-2-deoxy-2-(2-iodobenzoylamino)-α-D-glucopyranoside (**2**) as a route to synthesize the 10-membered benzomacrolactam **1**.



The iodobenzamide **2** was prepared from D-glucosamine hydrochloride (**3**) in six conventional synthetic steps (Scheme 1): reaction of **3** with 2-iodobenzoyl chloride,[15] treatment of **4** with methanol in the presence of acidic resin (IR-120), protection of the C-4 and C-6 hydroxy groups of methyl glycoside **5** as benzylidene acetal,[16] treatment of **6** with allyl bromide under phase transfer catalyst,[17] removal of benzylidene group under mild

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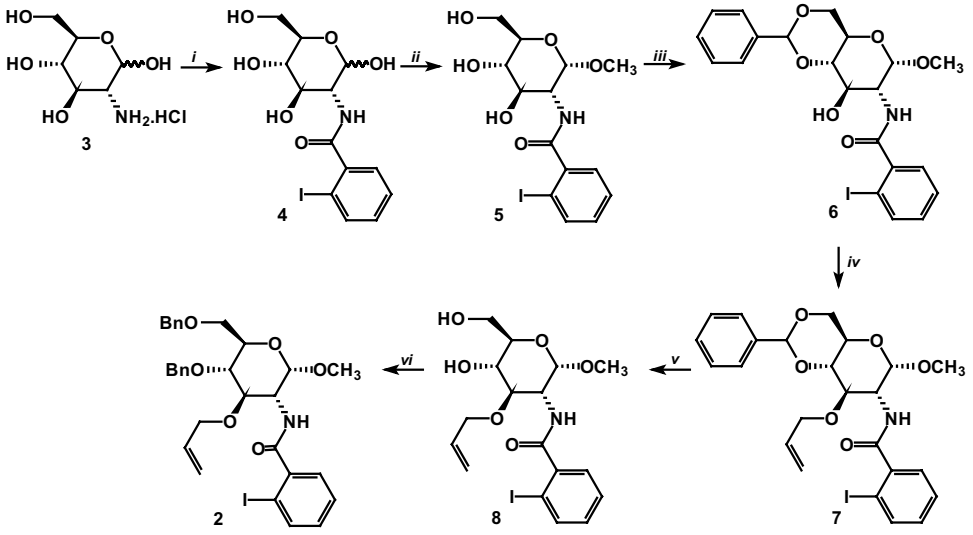
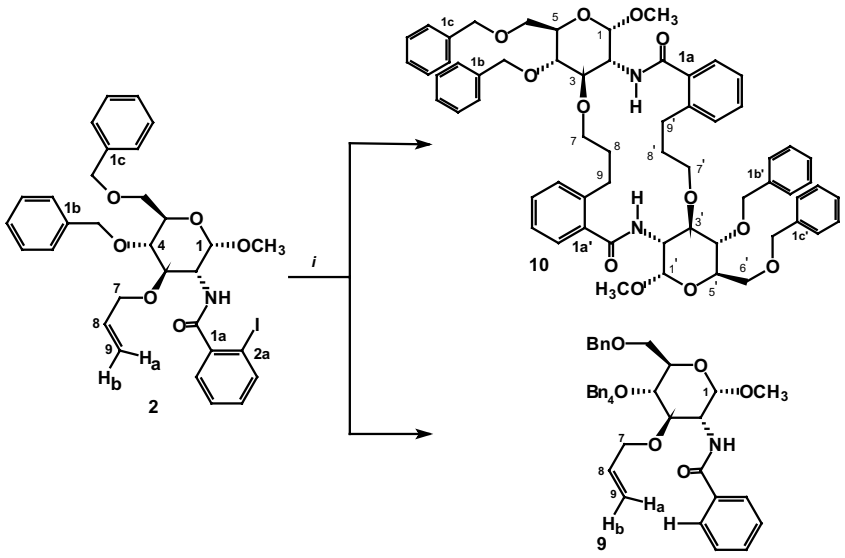


Scheme 1. Reagents, conditions and yields: (i) 6 equiv $NaHCO_3$ (aq), 1.5 equiv 2-iodobenzoyl chloride (acetone), 0 °C 3 h, 25 °C rt, 73%; (ii) anhydrous methanol, IR-120 resin (cat.), reflux, 58%; (iii) 13.4 equiv benzaldehyde, 2 equiv $ZnCl_2$, rt, 64%; (iv) 0.5 equiv Bu_4NBr, 10% aq NaOH, CH_2Cl_2, 2.0 equiv allyl bromide, rt, 76%; (v) acetone, aqueous HCl (cat.), reflux, 73%; (vi) 3.5 equiv KOH, 8 equiv BnCl, 80 °C, **2** 25%, **8** 50%.

acidic conditions[18] and O-benzylation of hydroxy groups at C-4 and C-6[19] of **8**.

The benzamide **2** was submitted to the recommended Bu_3SnH-mediated reaction conditions.[13,20,21] A mixture of Bu_3SnH (1.5 equiv) and AIBN (catalytic amount) in nitrogen-saturated anhydrous benzene was added over 1 h to a solution of **2** in nitrogen-saturated anhydrous benzene maintained at 80 °C to give a reaction mixture 0.012 mol L^{-1} in Bu_3SnH. After addition was completed, the reaction mixture was heated under reflux for an hour. Solvent removal and column chromatography on silica gel of the crude product provided two main products. The minor product (27% yield) was readily identified from its ^1H NMR data as the uncyclized reduced product: methyl 3-*O*-allyl-4,6-di-*O*-benzyl-2-benzoylamino-2-deoxy-α-D-glucopyranoside **9** (Scheme 2). The NMR and MS data of the major product were found, however, to be incompatible with the structure of the expected macrolactam **1**. A detailed analysis of the MS and NMR data, as discussed below, allows us to identify this major product (40% yield) as the interesting, new 20-membered benzomacrodilactam **10**[22] (Scheme 2).

MS analysis: Mass (MS) and tandem mass spectrometry (MS/MS) with electrospray ionization (ESI) has been incorporated into the major techniques particularly for the structural characterization of large and/or more polar molecules.[23] We have therefore use these MS techniques for the structural characterization of the unknown, unexpected product. The ESI-MS spectrum in the positive ion mode of a methanolic solution of the major product shows an ion of m/z 1035.624 (m/z



Scheme 2. Reagents, conditions and yields: (i) 1.5 equiv Bu_3SnH, AIBN (cat.), benzene, reflux, **9** 27% **10** 40%.

1035.5001 calculated for $C_{62}H_{70}N_2O_{12}+H^+$), which displays a m/z ratio and an isotopic distribution that matches that of the protonated molecule of a *dimer of lactam* **1** ($2\times C_{31}H_{35}NO_6$). The ESI-MS/MS spectrum of the protonated molecule (MH^+) is also very indicative of dimerization since it shows that MH^+ dissociates to a great extent by '*in-half*' breaking, that is, by loosing a neutral molecule of $C_{31}H_{35}NO_6$ composition (517 u, likely a neutral molecule of the monomeric lactam **1**) to form a fragment ion of m/z 518 with a $[C_{31}H_{35}NO_6+H]^+$ composition. The ESI-MS and ESI-MS/MS data indicates therefore that a dimer of **1** has been formed, likely the new 20-membered benzomacrodilactam **10**.

NMR analysis: The ^1H and ^{13}C NMR data of the major product, likely **10**, reveals the presence of two carbohydrate moieties, two metoxy groups, two amide carbonyl, two amide hydrogen, six phenyl and twelve sp^3 metylenes, eight of them bearing an oxygen atom (two of sugar unit, four benzyloxy groups and two methylene deriving from allyloxy group). These NMR data, similarly to the ESI-MS data, suggests the molecule to display a dimeric structure. The 20-membered ring is suggested by the presence of four sp^3 methylene groups, which are not bounded to a heteroatom. Connectivity studies by COSY, TOCSY, HMQC and HMBC experiments enabled us to depict the structure of **10** in detail.

We proposed that lactam **10** could have been formed by an initial unusual intermolecular radical reaction followed by a 20-*endo* cyclization process. We believe that an intermolecular reaction is favored in this case owing to the known constraints associated with 10-ring closure.[13,14] Bu_3SnH-mediated intermolecular addition of aryl radicals to the double bound of alkenes has been reported,[24] which could support the unusual bimolecular addition of aryl radical of **2** to sp^2 terminal carbon of allyloxy group of another molecule of **2**. This preferential intermolecular attack, instead of that to benzene to form the fully aromatized product as a consequence of deproportionation or oxidation of the intermediate cyclohexenyl radical,[25] can be explain by assuming that the rate constant of the former reaction is smaller based on the rate constants for the reactions of phenyl radicals to benzene (4.5×10^5) and cyclohexene (2.8×10^8).[26]

In summary, Bu_3SnH-induced aryl radical cyclization of *ortho*-allyloxyiodobenzamide **2** fails to proceeds through a 10-*endo* mode, which we expected to afford the 10-membered lactam **1**. Instead, **2** forms predominantly the macrolactam **10**, as indicated by MS and NMR analysis. Formation of the new 20-membered macrocycle dilactam **10** shows the potential of Bu_3SnH-mediated aryl radical cyclization in the synthesis of macrocycles incorporating large rings and polyfunctional groups.

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