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A practical and improved process for the synthesis of Hagen's gland lactones by catalytic hydro-deiodination

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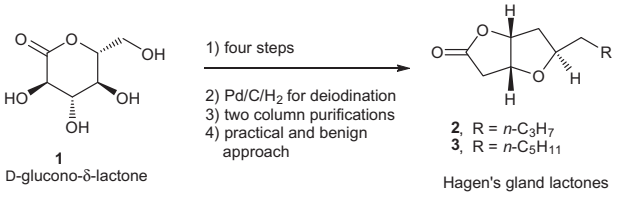
ABSTRACT

Catalytic hydro-deiodination has been efficiently employed in the development of a benign process for the synthesis of Hagen's gland lactones. The process was developed with only two column chromatographic purifications and is applicable for gram scale synthesis. No protecting groups were used in the synthesis which is an added advantage.

1. Introduction

In 1953, Hagen identified the presence of fragrant substances in the glands that originate near the abdominal tips of braconid wasps.[1a] Later, these gland secretions were studied for morphological and taxonomical properties and found to be lactone and fragrance rich.[1] The chemical analysis of these gland secretions suggested the presence of two bicyclic lactones **2** and **3**, which are known as Hagen's gland lactones (Scheme 1).[1c] These lactones are mainly from the braconid wasps, *Diachasmimorpha longicaudata* (Ashmead), *Diachasmimorpha tryoni* (Cameron), and *Diachasmimorpha arisanus*. Hagen's gland lactones are believed to be potential bio-controls in fruit fly population in Hawaii and Queensland and have been assessed for a possible role in integrated pest management strategies. The structures and relative stereochemistry of these lactones were established by extensive spectroscopic studies.[1c] The absolute stereochemistry was ascertained via the synthesis of all of the possible isomers.[1d]



Scheme 1. Development of practical and scalable process for Hagen's gland lactones synthesis.

Hagen's gland lactones have been interesting synthetic targets since their identification and there have been a few reports on their synthesis.[1d,2–8] Kitching et al.,[1d,2] reported on the first synthesis of Hagen's gland lactones and its diastereomers starting from (*R*)-(+)-ricinoleic acid and an (*R*)-epoxide. The synthetic strategy relied on the preparation of ene-1,3-diol and the construction of the bicyclic lactone via a $PdCl_2$-catalyzed oxycarbonylation–lactonization reaction.[9] Mereyala et al.[3] described two different synthetic approaches for **2** and **3** starting from D-glucose and D-mannose. A Wittig olefination-cyclization[3a,b] and a $PdCl_2$-catalyzed oxidative cyclization[3c] reaction were utilized for constructing the bicyclic lactone. Yadav et al.[4] employed a base mediated rearrangement of oxepanone epoxide, derived from (*R*)-glycidol in a divergent formal synthesis of **2** and **3**. In another method, Chakravarthy et al.[5] started from the bis-acetonide of mannofuranolactone and used SmI_2 mediated α-deoxygenation and Pd(II) mediated oxidative cyclization. An asymmetric version of oxycarbonylation–lactonization of ene-1,3-diols using palladium(II) with chiral bis(oxazoline) ligands was examined by Kapitán and Gracza.[6] Hagen's gland lactones synthesized by this approach had poor enantiomeric excess and low yields. Sartillo-Piscil et al.[7] successfully transformed 1,2-*O*-isopropylidene-α-D-xylofuranose derivative into **2** and **3** by employing stereoselective C-glycosylation and dihydroxylation–dehomologation–oxidation reactions. An enantioselective but lengthy approach to **2** and **3** by Gharpure et al.[8] was based on a diastereoselective intramolecular cyclopropanation of vinylogous carbonates, ring opening of cyclopropanes, and iodolactonization reactions. A detailed review of the literature revealed that most of the approaches involved many steps and the use of various protecting groups. However, these methods suffer from low overall yields and are not suitable for scalable processes. In connection to our interests in the development of novel synthetic strategies from the chiral pool material

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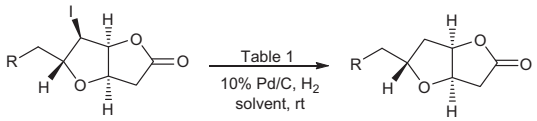
D-glucono-δ-lactone,[10] we have recently described an efficient four step synthesis of Hagen's gland lactones without using any protecting groups.[11] The strategy was based on a reliable one-pot conversion of D-glucono-δ-lactone into a β-hydoxy-γ-lactone, cross-metathesis, and iodocyclization–deiodination reactions. Due to several advantages in our own strategy, we became interested in developing a scalable process by avoiding the stoichiometric use of n-Bu_3SnH and multiple purifications. Herein we report an improved and benign process for the synthesis of Hagen's gland lactones (Scheme 1).

2. Results and discussion

In our previous synthesis of Hagen's gland lactones, all of the intermediate compounds were purified by column chromatography.[11] Considering the compatibility and high yields of reactions involving cross-metathesis, iodocyclization, and hydrogenation (foreseen), we planned to minimize the number of column purifications. This was expected to minimize the time requirement and make the process less laborious. Hence, we planned to execute the entire process with only two column chromatographic purifications. We had previously used stoichiometric amounts of toxic n-Bu_3SnH in benzene (carcinogenic) solvent for the reductive removal of iodine.[11] Although tin hydrides are very popular reagents in radical chemistry,[12] there have been serious issues associated with their toxicity. In bulk scale synthesis, disposing of the organostannane residues and product purification are major problems and necessitate special attention and handling. To address this, numerous alternatives for organostannane reagents, special work-up and purification techniques have been developed.[13] Herein in order to overcome the aforementioned problems, we planned to develop a benign process for the synthesis of Hagen's gland lactones by employing catalytic hydrogenation in the deiodination step. In the available methods for hydrodehalogenation, catalytic palladium on charcoal (Pd/C) hydrogenation plays a significant role.[14] We embarked on a strategy based on two column purifications and deiodination using catalytic hydrogenation for the synthesis of Hagen's gland lactones. This involved a one-pot conversion of **1** into **5** (first column purification) and then subjecting the latter to cross-metathesis,[15] iodocyclization,[16] and deiodination reactions to give the final products **2** or **3** (second column purification). We first decided to optimize the deiodination step by hydrogenation of pure iodolactone **4** which was synthesized by our previous strategy.[11] The optimization study is shown in Table 1. The hydrogenation of **4** using 10% palladium on charcoal under H_2 pressure (40 kg/cm^2) resulted in **2** in only 6% yield (brsm) and the bulk of the starting material was recovered (Table 1, entry 1). When the reaction was carried out with a higher catalyst loading and H_2 pressure (45 kg/cm^2) over 120 h, the deiodinated product **2** was obtained in 27% yield (brsm, entry 2). Extending the reaction time to 150 h, and increasing the catalyst loading gave the desired product **2** with improved yield (54% brsm, entry 3). Increasing the catalyst loading to 30 mg/mmol and H_2 pressure (50 kg/cm^2) gave hydro-deiodinated product **2** in 91% isolated yield (entry 4). We also studied the solvent effect on the reaction by changing the solvent to MeOH, EtOAc, *i*-PrOH, and *n*-hexane, but no significant improvement in the reaction yield (Table 1, entries 5–8) was observed. The use of 10% Pd/C (30 mg/mmol), 50 kg/cm^2 H_2 pressure in EtOH solvent were thus chosen as the optimum conditions for hydro-deiodination.

With the optimized conditions for catalytic hydro-deiodination reaction in hand, we planned to use them in the improved process for the synthesis of Hagen's gland lactones. We envisioned the structural importance of γ-lactone **5** with differentiated vicinal OH groups and γ-vinyl bonds and that it could be an important building block in natural product synthesis. In 2001, Song and Hollingsworth[17a] reported on the synthesis of γ-lactone **5** in 58% yield via a three step/one-pot process from D-glucono-δ-lactone **1**. Later, this method could not be reproduced by Brimble et al.[17b] and they obtained only 7% yield after several attempts. Recently, we have refined the one pot conversion of D-glucono-δ-lactone **1** to β-hydoxy-γ-lactone **5** in 51% yield by performing HBr/AcOH treatment at 50 °C for 1 h and with Zn dust addition at −10 °C over 1 h and then warming the mixture to room temperature over 2 h.[10,11]. This process can be reproduced on a 4 g scale with 51% yield and at a higher scale (10 g) with an average of 48% yield. The cross metathesis of β-hydoxy-γ-lactone **5** with 1-hexene using Grubbs-II catalyst gave lactone **7**, which was further subjected to cycloetherification using molecular iodine and $NaHCO_3$ in CH_3CN solvent to give iodolactone **9**. The crude iodolactone **9** was then subjected to catalytic hydro-deiodination using the optimized conditions (Table 1, entry 4) to give Hagen's gland lactone **2** in 62% yield (Scheme 2). Similarly, the cross-metathesis of **5** with 1-octene **6b** gave lactone **8** and further iodocyclization and hydro-deiodination furnished Hagen's gland lactone **3** in 43% yield. The overall conversion in this process is comparable to our earlier step-wise purification method.[11]

Table 1
Optimization of deiodination reaction under catalytic hydrogenation[a]



4 R = n-C_3H_7 **2** R = n-C_3H_7

Entry	10% Pd/C (mg/mmol)	H_2 pressure (kg/cm^2)	Solvent	Time (h)	Yield[c] (%)
1	10	40	EtOH	100	6[b]
2	15	45	EtOH	120	27[b]
3	20	45	EtOH	150	54[b]
4	30	50	EtOH	150	91
5	30	50	MeOH	150	68
6	30	50	EtOAc	150	12[b]
7	30	50	*i*-PrOH	150	75
8	30	50	*n*-hexane	150	56[b]

[a] All reactions were carried out using pure **4** (0.1 g, 0.322 mmol).
[b] Yields were based on recovered starting material **4**.
[c] Isolated yield.