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A facile method for steroid labeling by heavy isotopes of hydrogen

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ABSTRACT

A new catalytic enantiospecific approach to the synthesis of epibrassinosteroids (and other polyhydroxylated steroids) regiospecifically labeled by heavy isotopes of hydrogen is reported. Chlorocarbonate, efficiently synthesized from α-hydroxy ketone by a reaction with triphosgene, undergoes reductive tritium dechlorination catalyzed by the [Pd^0]/Et_3N system, providing 24-[3β-^{3}H]epicastasterone and 24-[3β-^{3}H]epibrassinolide, respectively, in good yield and with high specific activity (5.8 Ci/mmol; 20% tritium enrichment per molecule).

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1. Introduction

Brassinosteroids (BRs) are small organic polyhydroxylated sterol phytohormones with a close structural resemblance to animal and insect steroid hormones. They occur at low levels throughout the plant kingdom and were first isolated and characterized from the pollen of *Brassica napus* (Brassinolide) in 1979.[1] More than 70 of these plant growth regulators have been discovered so far.[2] Recently, Strnad et al. have published the first evidence that some natural BRs induce cell-growth-inhibitory responses in several human cancer cell lines without affecting normal non-tumor cell growth (BJ fibroblasts).[3] Only those containing 2α, 3α- and 22*R*, 23*R*-diol functions and a lactone or ketone moiety in ring B exhibited high biological activity (Fig. 1). Studies on the mechanism of action of biologically active compounds on the molecular level require the labeling of these substances by the radionuclide ^{3}H. Only one example of such synthesis has been published.[4] However, 24-[5,7-^{3}H]epibrassinolide, prepared by a base-catalyzed exchange with tritiated water, had very low specific activity (6.3 mCi/mmol); moreover, the product was labeled on the exchangeable position. A general method providing [^{3}H]-labeled BRs in high specific activity is seriously missing. We have recently published a short paper paving the way for the synthesis of a suitable synthetic precursor for the introduction of a deuterium label onto 24-epibrassinolide.[5] A detailed study establishing a robust method for the synthesis of BRs regio- and enantio-specifically labeled by deuterium/tritium is reported in this paper.

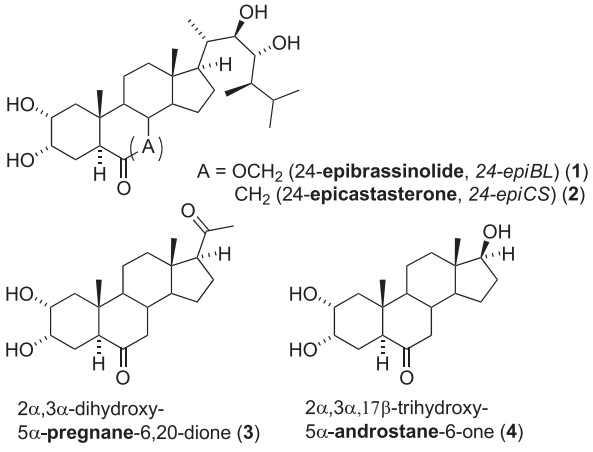

Fig. 1. 24-epiBL (**1**) is the 24-(*R*)-Epimer of the first isolated brassinosteroide, 24-epiCS (**2**) and its pregnane (**3**) and androstane (**4**) 2,3-dihydroxy analogs.

2. Results and discussion

The creation of a reducible double bond on the BRs skeleton seemed to be the most feasible strategy for transformation of starting materials **2**–**4** into suitable synthetic precursors for a labeling step. We have recently reported the conversion of a vicinal

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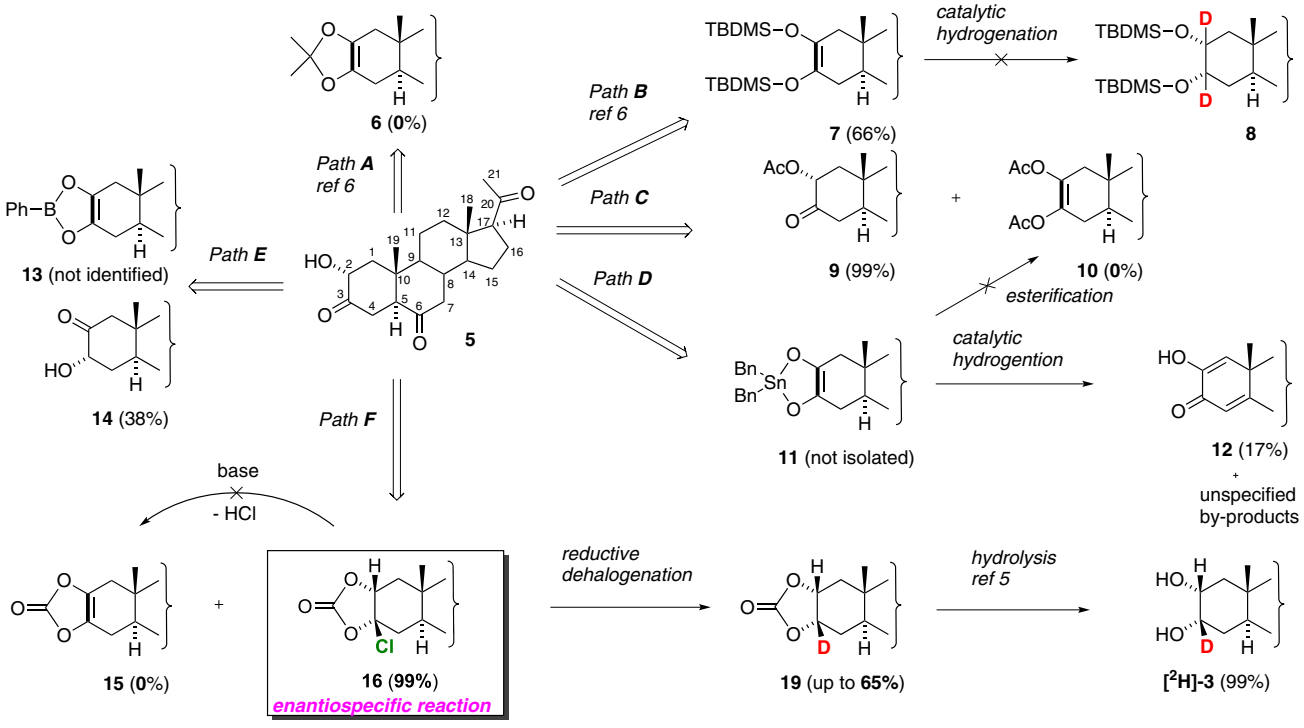
2α, 3α-diol **3** to the appropriate α-hydroxy ketone **5** by oxidation with freshly generated dimethyldioxirane.[5,6] An endiol form of such an α-hydroxy ketone seemed to be a proper substrate for variable synthetic transformations leading to an appropriate bis-substituted endiol. Such a synthetic precursor would provide a distinct opportunity for reductive catalytic tritiation yielding BRs with high specific activity. The closest *synthon*-analogs to an endiol, vicinal alcohols, offer various synthetic transformations. The most feasible approaches we had decided to try with our substrate; for instance the conversions into silylethers, carboxyesters as well as to 1,3-dioxole, 1,3-dioxoborole and 1,3,2-dioxastannolene ring formation. Since the amount of BRs is limited, we have carried out the model study on a commercially available acyloin, a benzoin.

Jadhav et al. have reported the isopropylidation of an in situ generated α-hydroxy ketone of 9,10,12-trihydroxyoctadecanoate into the appropriate isopropylidenedioxy-9-ene derivative by acid-catalyzed ring formation.[7] In our recent experiments, following this procedure on BRs substrate, diol **3** did not yield the desired product **6**.[6] The conversion of the acyloin **5** into an appropriate isopropylidenedioxy derivative under various different conditions including a reaction with 2,2-dimethoxypropane or acetone catalyzed with *p*-TsOH,[8–10] $CuCl_2$,[11,12] or $FeCl_3$[13] respectively, failed too, both with the steroid **5** (Scheme 1; Path A) and benzoin substrate.

either; in that case, only desilylation was observed. The two sterically demanding TBDMS groups make the double bond inaccessible for hydrogenation on solid catalysts.

The other potential transformation—the esterification of the enolform of **5** (Scheme 1; Path C) by Ac_2O catalyzed by *p*-TsOH or DMAP was not successful even when left to react up to 7 days at 130 °C. Only monoacetate **9** was always isolated in quantitative yield. Davies and Hawari reported the synthesis of acetyldiolates through in situ generation of organotinenediolates.[14] Following this procedure in our laboratory with the employment of 3,6,20-trione **5** and dibuthyltindimethoxide (1 equiv) in CD_3OD, a quick disappearance of the hydrogen signal of the C2 position was observed by ^1H NMR, which corroborated the formation of the 1,3,2-dioxostanollene derivative **11** (Scheme 1; Path D). Unfortunately, the addition of acetic anhydride into the reaction mixture of **11** did not yield the desired bis-ester **10**. The catalytic hydrogenation of the organotin enediolate **11** was carried out by deuterium gas catalyzed with Pd/C 10%. Regrettably, a complex mixture was formed and the major product, an unexpected 1,4-diene-2-hydroxy-3-ketone **12**, was isolated.

The formation of the cyclic boronic ester of **13** could be another simple way to generate a double bound on the BRs scaffold (Scheme 1; Path E). Indeed, the initial reaction of benzoin and phenylboronic acid (1 equiv) with azeotropic distillation of the



Scheme 1. The studied pathways to create a synthetic precursor for introduction of deuterium/tritium onto BRs skeleton.

The alternative transformation of acyloin **7** into O-substituted endiol is provided by O-silylation (Scheme 1; Path B). The reaction of acyloin **5** with trimethylsilyl triflate (TBDMSOTf) gave a very stable 2,3-bis(*tert*-butyldimetylsilyloxy)-5α-pregn-2-ene-6,20-dione (**7**) in a 66% yield.[6] Such a substituted endiol was subjected to catalytic hydrogenation by carrier-free deuterium gas. Heterogenic reduction catalyzed by transition metals such as 10–30% Pd/C, $PdO/BaSO_4$, PtO_2, nanoRh/AlO(OH) and Rh/alumina carried out at a low pressure of deuterium gas (800 mbar) and at room temperature unfortunately did not yield any desired bis-silylated diol **8** even after overnight reaction. Hydrogenation catalyzed by the Crabtree catalyst did not lead to a reduction of the double bond

generated H_2O from the reaction mixture provided a 2,4,6-triphenyl-1,3-dioxoborole-2-ene[15,16] in high yield (79%). Unfortunately, analogous reaction conditions set for acyloin **5** led only to isomerisation and both α-hydroxyl ketones **5** and **14** were isolated in the ratio 62:38, respectively. The isolation of 2,6,20-trione **14** makes us assume the formation of fairly unstable 1,3-dioxoborole **13**, which unfortunately tends to decompose back to the starting 3,6,20-trione **5** and its regiomer 2,6,20-trione **14**.

In order to synthesize the vinylene carbonate derivate of **5** we decided to follow Hiyama's procedure. He reported the thermal dehydrochlorination of 4,5-disubstituted 4-chloro-1,3-dioxolan-2-

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