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The first total synthesis of (±)-annosqualine by means of oxidative enamide–phenol coupling: pronounced effect of phenoxide formation on the phenol oxidation mechanism

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Abstract—The first total synthesis of a spiro-isoquinoline alkaloid, (±)-annosqualine, was established by employing an enamide–phenol coupling of a 1-methylene-1,2,3,4-tetrahydroisoquinoline derivative with a hypervalent iodine reagent, where the formation of the phenoxide was recognized to be an essential step for the reaction of the phenolic hydroxyl group with the hypervalent iodine reagent leading to the formation of the desired product.

Annosqualine **1**, a novel isoquinoline alkaloid with an unprecedented skeleton bearing a spirocyclohexadienone function, was isolated from the stems of *Annona squamosa* in 2004 as a minor component, and was supposed to be a biogenetic precursor of protoberberine and oxoprotoberberine alkaloids.[1] Although the structure of **1** was elucidated spectroscopically, its synthesis and biological activity have not been studied yet (Fig. 1).

Recently, we have developed a facile synthetic procedure for a proaporphine alkaloid, (±)-stepharine, where an oxidative enamide–phenol coupling of an isoquinoline derivative with a hypervalent iodine reagent, iodobenzene diacetate (PIDA) in trifluoroethanol (TFE) leading to the formation of a spirocyclohexadienone moiety, was involved as the key step[2] (Fig. 2).

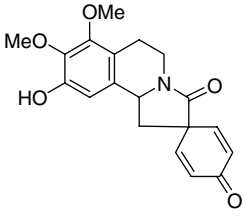

Figure 1. Structure of annosqualine **1**.

In relation to a project directed at the synthesis of biologically active natural products by employing aromatic oxidation with a hypervalent iodine reagent,[3–5] we are interested in establishing a concise synthesis of the unique isoquinoline alkaloid, annosqualine **1**. Prior to the synthesis of the natural product, we decided to investigate efficient and mild reaction conditions for the oxidation of a readily available enamide **5** as follows (Scheme 1).

Condensation of the known 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride **3** with 4-(*tert*-butyldimethylsilyloxy)benzoyl chloride **2**, prepared from 4-(*tert*-butyldimethylsilyloxy)benzoic acid,[6] afforded enamide **4**. Since an attempted isolation of the phenolic enamide **5**, derived from **4** by desilylation with

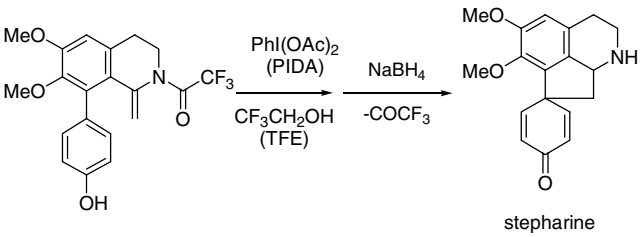

Figure 2. Our previous synthesis of proaporphine alkaloid.

Keywords: Annosqualine; Spiro-isoquinoline alkaloid; Iodobenzene diacetate; Enamide–phenol coupling; Phenoxide formation.
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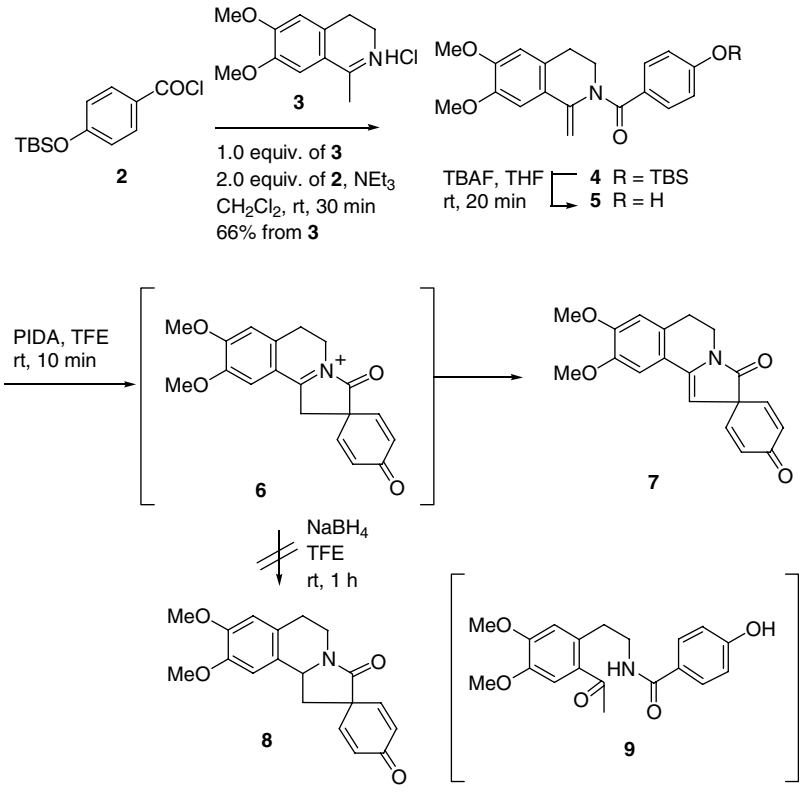

Scheme 1. Preparation of enamide **4** and its conversion to **7**.

tetrabutylammonium fluoride (TBAF) in tetrahydrofuran, resulted in the easy formation of the hydrolysis product **9**, the crude enamide **5**, obtained from the above reaction mixture by evaporation of the solvent, was subjected to oxidation without further purification.

First, we investigated the oxidation of **5** with the use of PIDA as the oxidant, in TFE at room temperature, and subsequent reduction of the presumed intermediate **6** with sodium borohydride in a one-pot procedure according to our previous procedure;[2] however, none of the desired product **8** could be isolated under these reaction conditions producing only decomposed products. However, we were pleased to be able to isolate enamide **7** by careful examination of the reaction mixture when this oxidation was conducted under the same reaction conditions, without further treatment of an intermediate with sodium borohydride, although the yield was lower than 10%. Encouraged by this result, we next focused our attention on searching for optimal conditions for the oxidation, in which we decided to isolate spiro-enamide **7** instead of its one-pot conversion to **8** by subsequent reduction.

It is well recognized that the use of a solvent with less nucleophilicity gives better result in an oxidative phenolic coupling. Thus, a similar oxidation of **5** with PIDA was carried out in hexafluoroisopropanol (HFIP) as the solvent,[7] instead of TFE; however, the desired spiro-enamide **7** was again obtained in a trace amount. At this point, we had to figure out the reason why the oxidation of **5** did not proceed smoothly to give the desired product, compared to our previous work,[2] where the oxidation gave the desired product in 90% yield. As for this reason, we thought that there are two reactive sites against the oxidant (PIDA), in the starting compound **5**, a phenolic oxygen and an enamide carbon, which might make the oxidation troublesome. Although two reactive sites were also present in the starting material of our proaporphine synthesis, the enamide nitrogen of the starting isoquinoline was protected with a trifluoroacetyl group, a strong electron-withdrawing group, which might diminish the reactivity of the enamide carbon with the oxidant to afford the desired product in high yield. To prove this hypothesis, we decided to add a base to the starting enamide prior to its further oxidation, since generation of the phenoxide by addition of a base would be expected to increase its reactivity against an oxidant. Thus, the starting enamide **5** was treated with 1.0 equiv of *n*-butyllithium in HFIP at 0 °C,[8] and the resulting mixture was reacted with 1.0 equiv of PIDA at room temperature to give the desired spiro-enamide **7** in 38% yield. When this reaction was carried out in the presence of 2.0 equiv of *n*-butyllithium, the yield was improved to 78%. The results obtained are summarized in Table 1.

It is noteworthy that the reaction temperature for the preparation of the phenoxide would be required to be below 4 °C due to the instability of the starting enamide.[9] Moreover, HFIP was obviously better than TFE as the solvent in this reaction. The necessity of 2 equiv of *n*-butyllithium would be attributed to trapping of acetic acid generated from the reagent during the reaction process, in addition to the formation of the phenoxide to increase its reactivity against the oxidant.