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Towards the First Synthesis of Salvianolic Acid F : An Unexpected Intramolecular Diels-Alder Cyclisation

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Abstract:

The reaction of tetramethylsalvianolic acid F **3** with BBr_3 led to the expected salvianolic acid F **2** in 10% yield. **2** underwent Diels-Alder cyclisation to **5** or cyclisation to benzofuran **6** depending on the reaction conditions.

Keywords : Dealkylation, Diels-Alder reaction

During the last 15 years, several water-soluble phenolic acids have been isolated from species of the genus *Salvia*[1]. The first of them, named salvianolic acid A **1**, has been widely studied and numerous biological properties have been found (antitumoral[2], antiinflammatory[3] activities, gastric H^+,K^+-ATPase[4] inhibition, peroxidative damage to biomembranes inhibition[5] and antioxidant properties[6-7]). Attempts at synthesizing **1** and the related natural product salvianolic acid F **2** have resulted in the obtention of the polymethylated derivatives[8-9]. However, the authors presumed that the removal of the protective groups probably would lead to the destruction of the" fragile system ".

In the course of our own programme devoted to the total synthesis of salvianolic acid A, we embarked in a systematic study on which tetramethyl salvianolic acid F **3** was treated with BBr_3 under different conditions of temperature, and we present herein our preliminary results.

All reactions were performed in dichloromethane and quenched by water after 30 min. Under these conditions, **3** gave the Diels-Alder demethylated adduct **5** in high yield(entry 1). Since the Diels-Alder cyclisation proved to be an extremely favorable process at room temperature, several attempts were next performed at lower temperatures.

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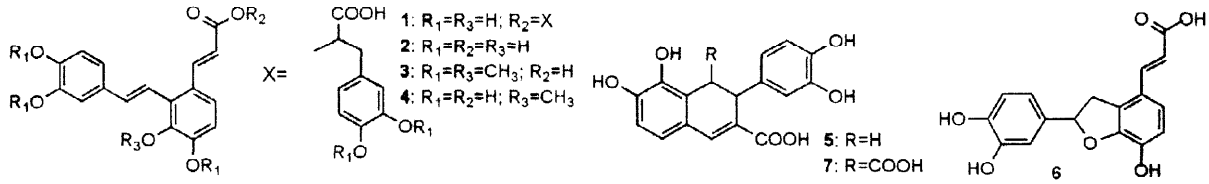

Table 1

Treatment of **3** with BBr_3

Entry	Temperature	BBr_3 (eq.)	Yield in isolated product
1	20	10	**5** (95%)
2[a]	-20	"	**5** (63%), **6** (27%)
3	-40	20	**4** (30%)[b]
4	"	10	**2** (10%), **4** (30%)

a. In this case, the percentages have been calculated from the ^1H nmr spectra of the crude product.

b. From the ^1H nmr spectrum of the crude product, **4** appeared to be the major product (up to 80%) . However, we were unable to isolate more than 30% of **4** after separation by column chromatography.

Working at –20°C, the Diels-Alder cyclisation was slower and a competitive heterocyclisation leading to the formation of benzofuran **6** occurred (entry 2).

Still lowering the temperature (-40°C)(entry 3) suppressed the formation of **5** and **6**. Instead, only the monomethylated salvianolic acid F **4** was isolated. The position of the residual methyl group has been determined by nOe's experiments. As expected, the most exposed methoxy groups were the most reactive. Using a large excess of BBr_3 (20eq)(entry 4), allowed us to isolate the targeted salvianolic acid F **2** in a low yield, beside **4** as a major product.

These last results highlight the difficulties of obtaining the desired product **2**, which seems to be very reactive and particularly prone to cyclisation under acidic conditions. The facile Diels-Alder cyclisation of the E,E-styryl caffeic acid moiety may be applied as the key step for the synthesis of type **7** neolignan isolated from *Mentha haplocalyx*[11].

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