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Synthesis of C-glycosyl compounds and other natural products from levoglucosenone

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Abstract: Synthetic approaches to the analogues of the various classes of natural C-glycosyl compounds: C-glycosylflavonoids, Multustriatin, Hernandulcin, and (1-4) -C-linked disaccharides from the new carbohydrate synthon levoglucosenone are presented.

INTRODUCTION

C-glycosides [1] are naturally occurring derivatives and components on many natural compounds from the flavone, chromone, xanthone, anthrone, as well as gallic acid group. Interestingly, -glycosides are not restricted to plants. C-glycoside from the insect *Dactylopius coccus* is known as carminic acid. Polycyclic microbial metabolites with unusual C-glycosyl moieties [2-3] produced by *Streptomyces sp.* represent new types of antibiotics, kidamycicn and toromycin. Also, C-glucuronides of drugs in man [4] and other mammals [5-6] represent a new type of drug metabolite. Few *in vivo* studies concerning the formation of C-glycosyl flavonoids are reported in the literature [7]. Essentially, little is known about the enzymatic mechanisms, which lead to the formation of the C-glycoside bond. Only a single report evidenced *in vitro* formation of C-glycosides, vitexin and isovitexin during enzymatic C-glycosylation [8].

This problem still remains to be explored and detailed studies have to be undertaken to generalize the biosynthesis and possible biosynthetic pathways of particular classes of C-glycosyl derivatives. The fact that several natural compounds which contain a C-glycosidic linkage are physiologically active, (antibiotics, antitumor agents) generated an enormous interest and prompted to the intensive exploration of this new field and its synthetic chemistry. Also, this new field of C-disaccharides as nonmetabolizable, noncaloric sweeteners and potential α- or β-glucosidase inhibitors with biological activity, and as specific models for the study of the sugar metabolism is currently under extensive investigation.

RESULTS AND DISCUSSION

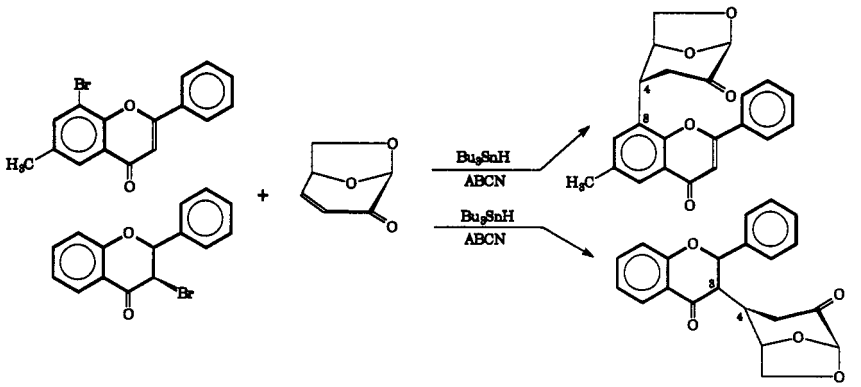
Our laboratory's continuous efforts are concentrated on strategies for the construction of different natural C-glycosyl compounds [9], their chemistry, as well as their biochemical and physiological aspects. We expanded our interest to the new analogues of C-glycosylflavonoids, and other natural products containing C-C bond between aglycon and sugar moiety (including C-disaccharides).

For our synthetic methodologies we selected the universal new carbohydrate synthon e.g. levoglucosenone (1,6-anhydro-3,4-dideoxy-α-D-*glycero*-hex-3-eno-pyranos-2-ulose) [10-13]. Levoglucosenone has the necessary functionality for further ramification and has been used extensively in the synthesis of (+ multistriatin [14], Prelog-Djerassi lactonic acid [14-15], serricornin [16] as well as tetrodotoxin [17-18].

C-Glycosylflavones

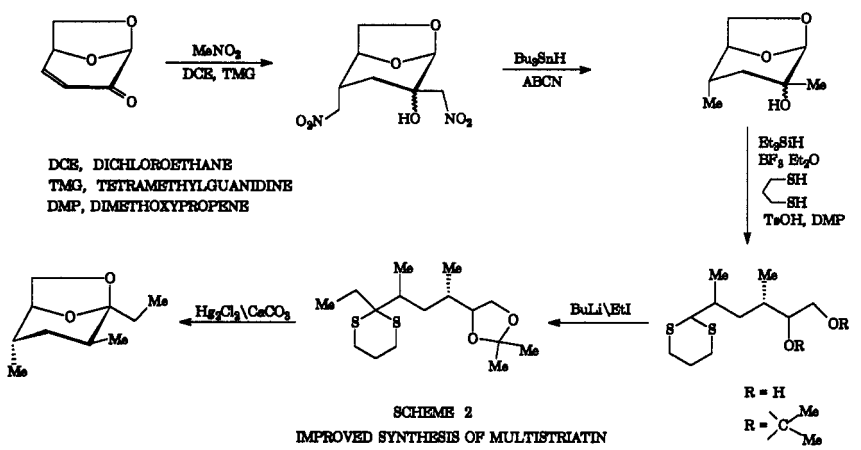
The first class of natural C-glycosyl compounds, which are under extensive investigation in our laboratory, are C-glycosylflavones [19] linked with sugar moiety either at C-8 or C-3 position. Radical coupling of 8-bromoflavone, and 3-bromoflavanone with levoglucosenone, using the tributyltin hydride methodology [20], proceeds smoothly with the formation of C-glycosides in high 82% overall yield [21]. Subsequent elaboration of the sugar moiety, by the reduction of the keto function at C-2 and

acetolysis of the 1,6-ahydro ring produced a new class of C-flavanoids.



Multistriatin

Although the synthesis of multistriatin was described [14] and Mori's approach utilizes levoglucosenone as a starting precursor [15], our improved methodology could offer a shorter approach and better yield of the final product. The approach utilizes the convenient Michael addition of nitromethane to levoglucosenone as the first, key-step according to the excellent procedure of Paton and coworkers [22-23]. Subsequent free radical removal of the nitro group with tributyltin hydride produced 2.4-disubstituted C-methyl derivative as outlined in Scheme 2. The next steps involving chain extension



SCHEME 2
IMPROVED SYNTHESIS OF MULTISTRIATIN

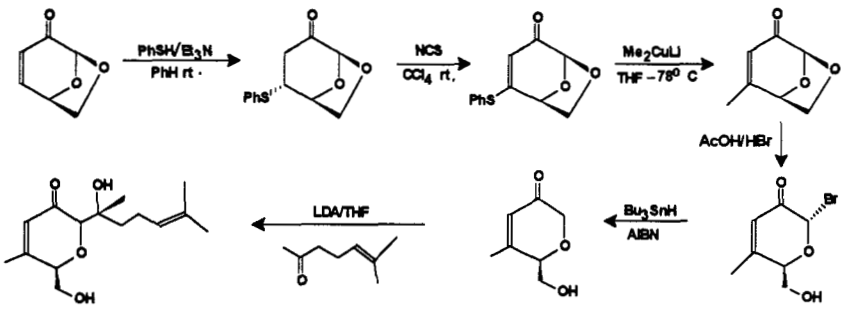
at C-1 *via* dithiane intermediate, according to the Mori methodology, allows to synthesize multistriatin in 51% overall yield. [24].

Carbohydrate Analogues of (+) Hernandulcin

The intensely sweet natural product (+) hernandulcin [24-25] (1250 times than sucrose, but with some bitterness as well as of- and after-tastes) because of its structural simplicity is an excellent model for further studies on the structure-sweetness relationship.

Hernandulcin, however is poorly soluble in water and has a slightly oily flavor. To improve solubility in water with simultaneous preservation of the sweet taste, the replacement of the cyclohexanone ring would be one of the logical choices. In conjunction to our previous studies [25-26], on the development of the new class of noncaloric sucrose substitutes (i.e.hernandulcin prototypes with carbohydrate chains at C-6) we synthesized new analogues with the sugar unit as a six member ring [27]. Our synthetic approach to this new class of analogues starts from levoglucosenone, which under

treatment with thiophenol and introduction of a Me- group at C-4, according to the method of Ebata [28] produced a C-4 adduct. The next steps, which are ring cleavage with hydrobromic acid, removal

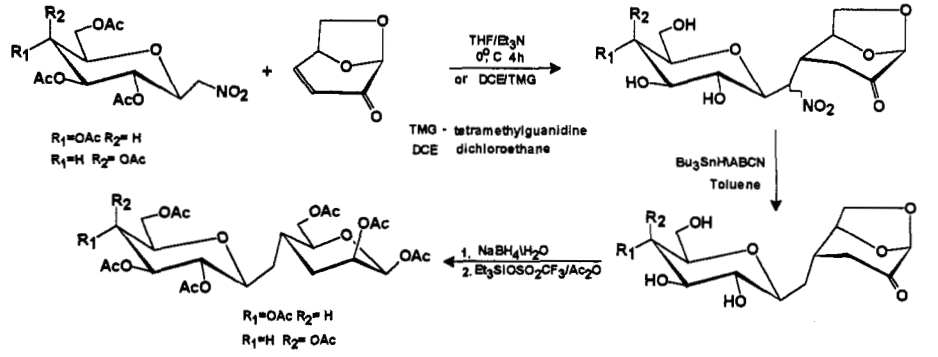


SCHEME 3

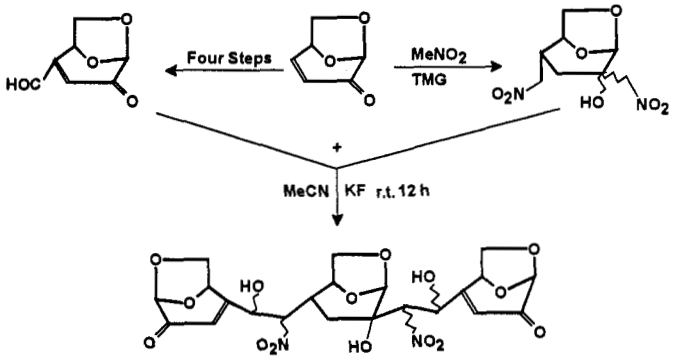
of bromine and directed aldol condensation, produced new water-soluble, carbohydrate analogues of hernandulcin in 38% yield and are outlined in Scheme 3.

C-Disaccharides

Levoglucosenone is an excellent precursor for the formation of C-C bond via coupling two sugar units



in the Michael addition reaction. The enone undergoes a mild Michael addition type reaction with various nucleophiles. Our laboratory is involved in the elaboration of levoglucosenone and its application to the synthesis C-disaccharides *via* Michael condensation of glycosyl nitronates with



levoglucosenone under strictly controlled conditions [30]. The C-trisaccharide, however was synthesized [31] *via* Henry reaction of 4-formyllevoglucosenone with the Paton adduct of nitromethane to

levoglucosenone [22-23]. These new approaches offer a convenient and simple routes to α-(1-4)-C-disaccharides and new C-linked trisaccharides. The utilization of levoglucosenone for the synthesis of other C-disaccharides with various linkages such as (1-3)- or (2-4) and (2-3) are currently under intense investigation in our laboratory.

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