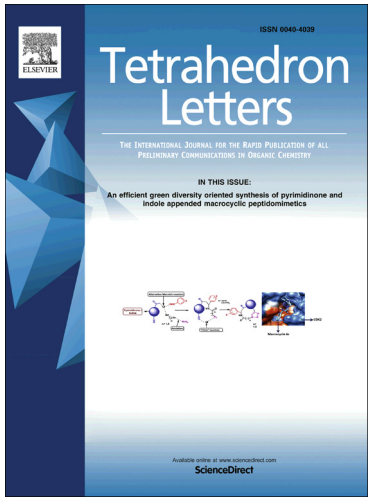

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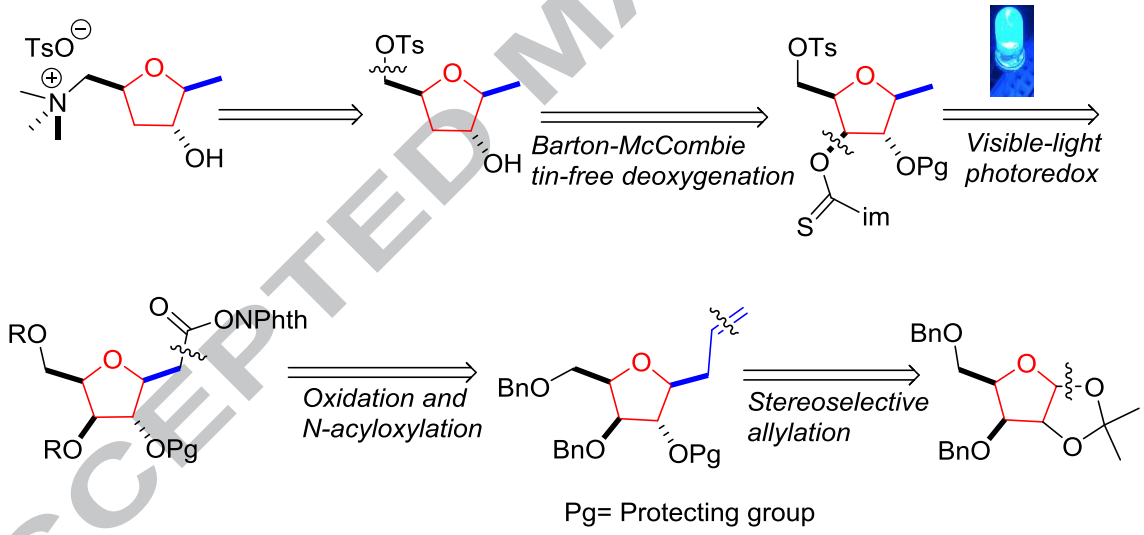
KEYWORDS Photoredox reaction, free radicals, chiron approach, *C*-glycosylation

Abstract: Starting from a 1,2-*O*-isopropylidene-D-xylofuranose derivative, a non-toxic free-radical approach for the synthesis of (+)-muscarine is reported. To this end, a stereoselective allylation reaction at the anomeric position of a respective xylofuranose derivative was employed as a new synthetic strategy for the installation of the methyl group at the C-5 position of (+)-muscarine. Accordingly, the allyl group was transformed into the methyl group in three sequential steps highlighting a blue-light photoredox decarboxylation reaction. Additionally, a tin-free Barton-McCombie deoxygenation reaction of the respective *C*-methyl glycoside allowed the completion of this free-radical approach to (+)-muscarine.

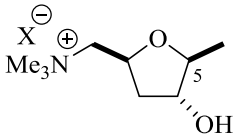


Pg= Protecting group

The (+)-muscarine is a tetrahydrofuran-derived-alkaloid isolated by Shcmiedeberg and Richard in 1869 from *Amanita Muscaria*, a mushroom that grows in autumnal woods.[1] Later, it has been isolated from other species of mushrooms, mainly of *Inocybe* and *Clitocybe* species.[2] Due to its physiological activity on the peripheral nervous system,[3] the (+)-muscarine is one of the most exciting and dangerous natural occurring alkaloids.[4] Furthermore, the best biological property of (+)-muscarine is that is a good

agonist of acetylcholine receptor (*muscarinic acetylcholine receptors*);[5] and a wide range of therapeutic properties have been suggested. Therefore, chemist´s efforts for developing new methods and synthetic strategies for preparing, not only (+)-muscarine but also all the eight possible stereoisomers, still remain in force.[6]

Figure 1. (+)-Muscarine

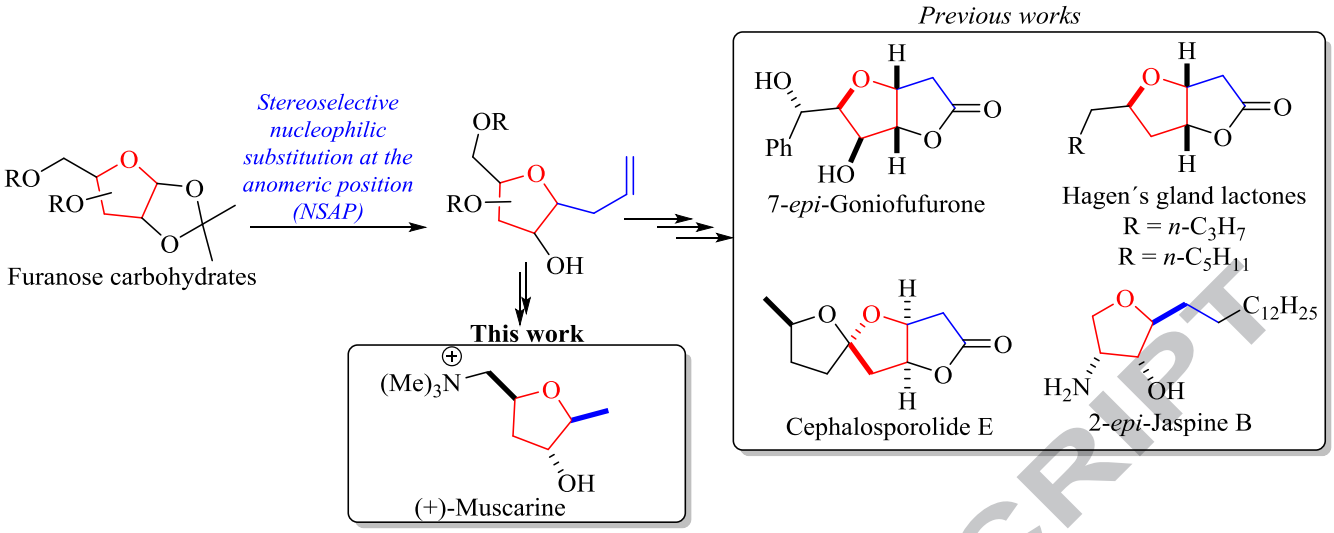


(+)-Muscarine

X = OH, halogen or Ts

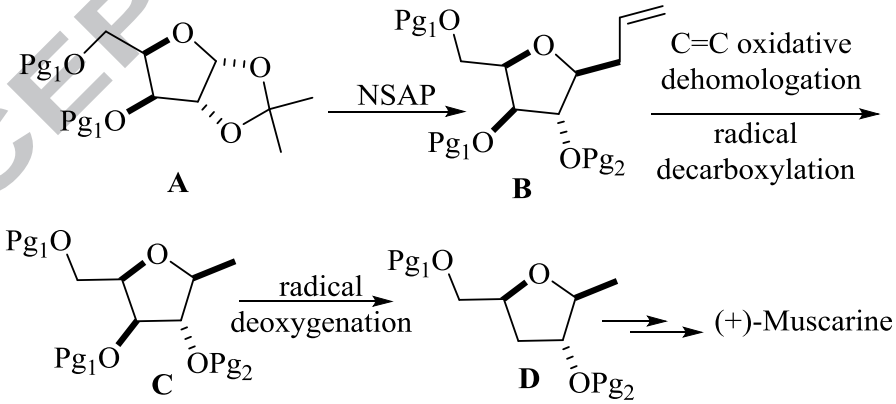
Although several syntheses to (+)-muscarine and stereoisomers have been reported, which would result in a number around 30,[7] a highly recommendable strategy is the use of the chiron approach, in which amino acids and carbohydrates are the selected starting materials.[7o-aa] From all of them, the stereoselective elaboration of the tetrahydrofuran ring with the correct stereochemistry at the C-5 center is the key step. In this regard and taking advantages from the synthetic methodology in the rapid functionalization of furanose carbohydrates to tetrahydrofuran-derived natural products via a stereoselective nucleophilic substitution at the anomeric position (NSAP),[8] we visualized the synthesis of the (+)-muscarine via the construction of the (5*S*)-methyl-tetrahydrofurane skeleton from simple xylofuranose derivative (Scheme 1).

Scheme 1. Chiron approach featuring the stereoselective functionalization of furanose carbohydrates to tetrahydrofuran-derived natural products



As shown in Scheme 1, the rational use of the NSAP reaction enabled the rapid functionalization of the allyl group into either a γ-lactone fragment of 7-*epi*-goniofufurone,[7a,c] Hagen´s gland lactones,[7b] and cephalosporolide E,[7f] or being part of the carbon chain extension of 2-*epi*-jaspine B.[7e] Now, from a furanose carbohydrate derivative (e. g., **A**), we envisaged the use of the stereoselective NSAP to form *C*-glycoside derivative **B** which would be transformed into *C*-methyl glycoside **C** via a sequential double bond oxidative dehomologation/radical decarbonylation process. Thus, the synthesis of (+)-muscarine would be practically accomplished after radical deoxygenation of **C** to **D** (Scheme 2).

Scheme 2. Synthesis plan to (+)-Muscarine

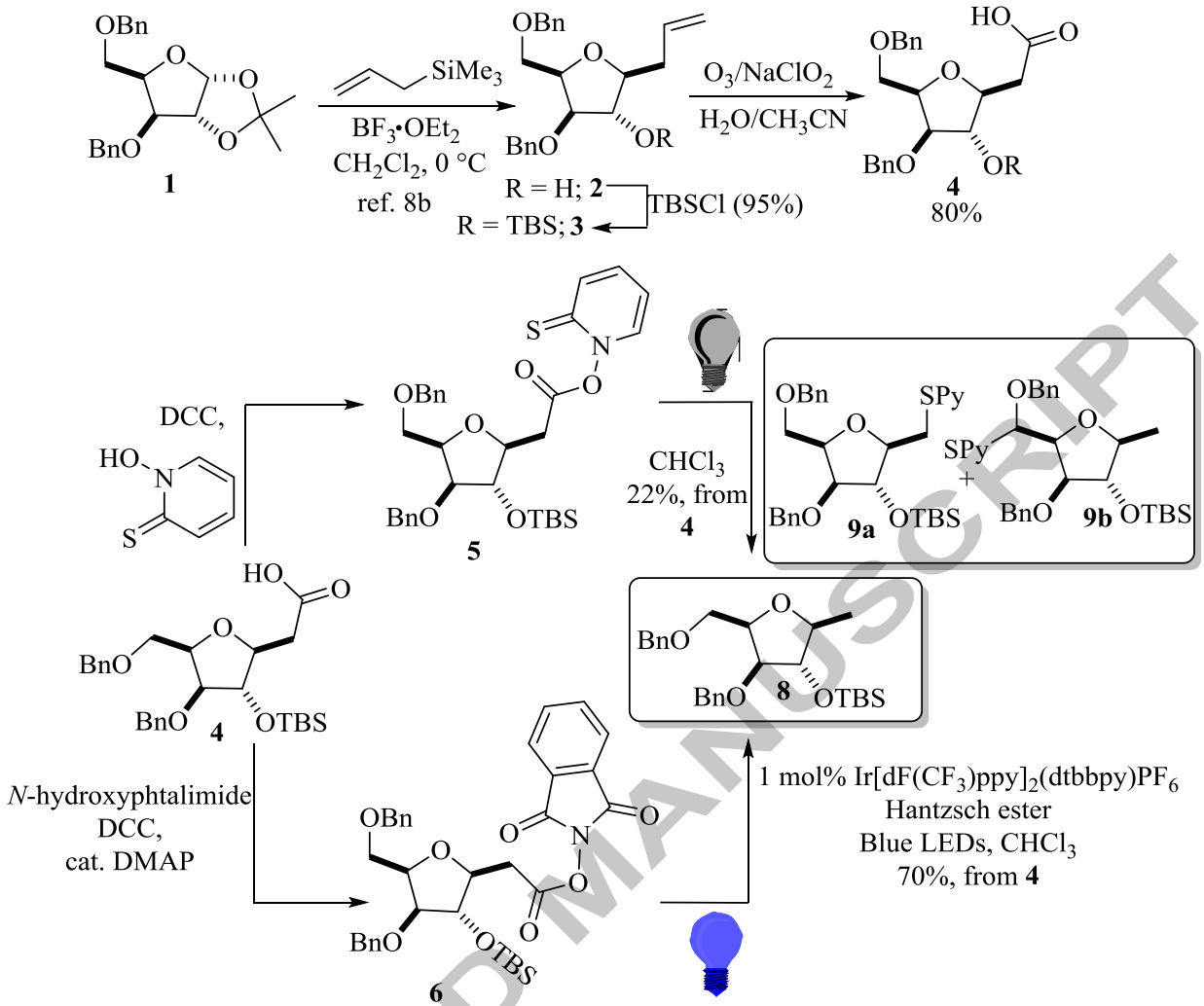


The synthesis of (+)-muscarine commenced when dibenzylated D-xylofuranose derivative **1** was treated with allyltrimethylsilane in the presence of BF_3•OEt_2 in CH_2Cl_2 at 0 °C to form *C*-glycoside **2** in

high yield.[8b,9] The high stereoselectivity can be rationalized by the Woerpel´s "inside attack" model", which predicts the formation of the 1,3-*cis*-stereoisomers in xylofuranose derivatives.[10,8e] Hydroxyl group of **2** was protected with *tert*-butyldimethylchlorosilane (TBSCl) (**3)** before to subject the double bond to an adapted ozonolysis/Pinnick oxidation to carboxylic acid **4**, which was transformed into both, ester Barton **5** with 2-mercaptopyridine *N*-oxide in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC),[11] and *N*-acyloxyphthalimida **6** with *N*-hydroxyphthalimide and DCC in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP)[12] (Scheme 3).

The ester Barton **5** was exposed to a white-light photolysis (150 W tungsten lamp)[13] for 2 h in $CHCl_3$ as solvent and hydrogen atom donor, and the expected product **8** was obtained in low yield (20%) along with two pyridyl sulfide side-products **9a** and **9b**, which we couldn´t isolate them with significant purity. Chemical yield of **8** was not considerably improved even when nBu$_3$SnH was used, albeit the presence of byproducts **9a** and **9b** was reduced.

Scheme 3. Synthesis of *C*-methyl glycoside **8** from 1,2-*O*-isopropylide-D-xylofuranose derivative **1**

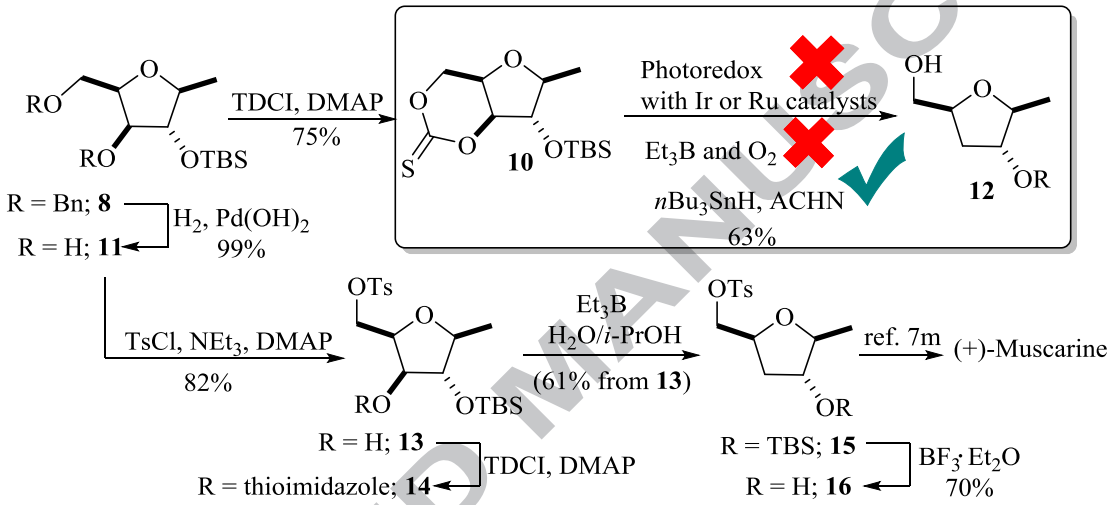


On the other hand, room temperature irradiation of *N*-acyloxyphthalimida **6** with blue-LEDs in the presence of 1 mol% of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ catalyst and two equivalents of Hantzsch ester as electron and hydrogen atom donor,[12,14] provided a clean reaction crude, which after column chromatography, yielded the desired product **8** in good yield (70% from carboxylic acid **4**). Further efforts for reaction optimization were unsuccessful; for instances, photoredox catalyst $Ru(bpy)_3(PF_6)_2$ was not effective.

Having the *C*-glycoside **8** in hands, efforts were focused on the deoxygenation at the C-3 position of **8**. An adapted Barton-McCombie-photoredox reaction of cyclic thiocarbonate **10** was explored.[15] Radical precursor **10** was prepared in two-steps from **8**. First, debenzylation reaction with H_2 and $Pd(OH)_2$ gave **11** quantitatively, which was treated with 1,1'-thiocarbonyldiimidazole (TCDI) in the presence of DMAP (Scheme 3). Unfortunately, photoredox experiments showed that cyclic

thiocarbonate **10** was unreactive with both $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and $Ru(bpy)_3(PF_6)_2$. Similar result was observed with triethylborane and oxygen. Although under classical tin-radical conditions provided the expected deoxygenated product **12** in good yield,[16] the non-toxic approach of this synthesis forced us to seek another less-contaminant strategy. Consequently, diol **11** was selectively tosylated to **13**, and then acyclic thionocarbamate **14** was prepared and exposed to radical photoredox and Et_3B/O_2 radical conditions (Scheme 4).

Scheme 4. Deoxygenation at the C-3 position and completion of the synthesis of (+)-muscarine



As for cyclic thiocarbonate **10**, photoredox catalysts were ineffective to promote radical deoxygenation of thioimidazole **14**; however, by using the Oshima´s radical conditions (Et_3B/O_2 in a H_2O/*i*-PrOH mixture),[17] deoxygenated product **15** was obtained in good yield. Subsequent removal of the silyl protecting group to **16** with BF_3•OEt_2 followed by substitution of tosyl group by triethyl amine, according to known procedure,[7m] the synthesis of (+)-muscarine was accomplished (Scheme 4).

In summary, starting from simple xylofuranose derivative, a non-toxic-free-radical approach to (+)-muscarine was developed. From which, an elegant way to elaborate the C-5 methyl group of the muscarine tetrahydrofurane skeleton from the respective *C*-allyl glycoside is highlighted. This synthesis strategy provides a new way to access to biologically important *C*-methyl glycosides.

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SUPPLEMENTARY MATERIAL

Procedures and NMR characterization of relevant products are provided.

CONFLICTS OF INTEREST

There are no conflicts to declare

ACKNOWLEDGMENTS

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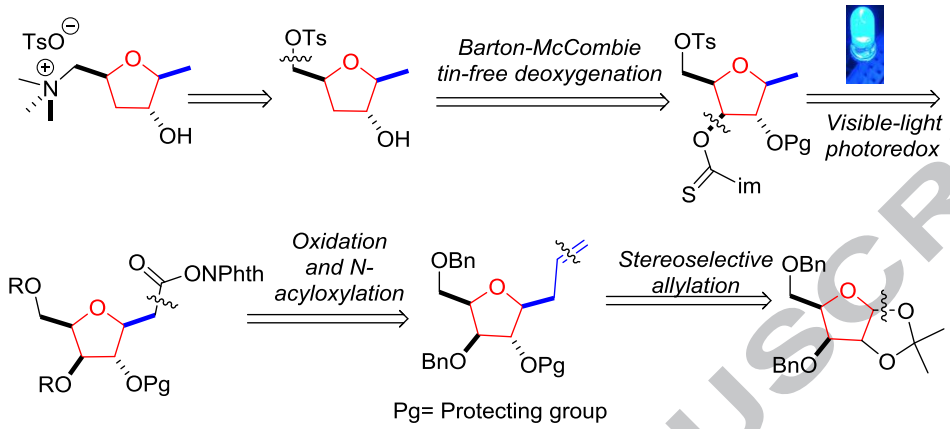

Pg= Protecting group

Highlights

- Photoredox reaction in the synthesis of a bioactive alkaloid
- New synthetic strategy to *C*-methyl glycosides
- Use of the stereoselective Nucleophilic Substitution at the Anomeric Position (NSAP).