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ScienceDirect
C. R. Chimie 11 (2008) 19–28
COMPTES RENDUS CHIMIE
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Free-radical and ionic routes towards hydrolytically stable and bioactive *C*-glycosyl compounds

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Received 12 February 2007; accepted after revision 19 March 2007
Available online 4 June 2007

Abstract

Photo-initiated addition of glycopyranosyl radicals to such radical acceptors as allyltributyltin, acrylonitrile, or diethyl vinylphosphonate was efficiently achieved to afford stereoselectively α-configured *C*-glycosyl compounds. With acrylonitrile or diethyl vinylphosphonate, catalytic amounts of organotin were used with $NaBH_3CN$ in excess. C-1 Sugar dihalides may be converted into the β-configured *C*-glycosyl analogues in two radical steps (C–C bond formation, reduction), or into bis-*C*,*C*-glycosides (two C–C bond forming reactions in one pot). These dihalides also opened the first access to *C*-glycodienes. *C*-Glycosyl-ethylphosphonic acids were elaborated into non-isosteric *C*-glycosyl mimics of natural sugar nucleotide diphosphates, which were evaluated as inhibitors of glycosyl transferases. In another approach, aromatic electrophilic substitution of 1,4-dimethoxybenzene by D-glycopyranosylium ions gave access to *C*-glycosyl derivatives of 1,4-dimethoxybenzene hydroquinone, and 1,4-benzoquinone. Some were found to inhibit protein tyrosine phosphatase 1B (PTP1B) and glycogen phosphorylase (GP), as shown by enzymatic and crystallographic studies. Extension of the synthetic work led to *C*-glycosyl-chromanols and *C*-glycosyl-tocopherols, which have been studied as anti-oxidants. ***To cite this article: G.-R. Chen, J.-P. Praly, C. R. Chimie 11 (2008).***

Résumé

L'addition photo-initiée de radicaux glycopyranosyl sur des accepteurs de radicaux comme l'allyltributyl étain, l'acrylonitrile, le diéthyl vinylphosphonate procède efficacement pour donner stéréosélectivement les composés α-*C*-glycosylés correspondants. Avec l'acrylonitrile et le diéthyl vinylphosphonate, l'addition s'obtient en présence de quantités catalytiques d'organo-étain et d'un excès de $NaBH_3CN$. Les C-1 dihalogéno-sucres peuvent conduire aux analogues *C*-glycosylés de configuration β en deux étapes radicalaires (formation de liaison C–C, réduction), aux bis-*C*,*C*-glycosides (création de deux liaisons C–C en un pot), ou à des *C*-glycodiènes (formation de liaison C–C, élimination). Les acides *C*-glycosyl-éthylphosphoniques ont mené à des mimes *C*-glycosylés non isostères de nucléotides sucres diphosphates naturels, qui ont été évalués comme inhibiteurs de glycosyl transférases. L'un d'eux inhibe efficacement ($IC_{50} = 40$ μM) la β-1,4-galactosyltransférase du lait de vache (β-1,4-GalT, EC 2.4.1.22). Par ailleurs, la substitution électrophile du1,4-diméthoxybenzène par des ions D-glycopyranosylium donne accès à des dérivés *C*-glycosylés du1,4-diméthoxybenzène, de la 1,4-benzoquinone et de l'hydroquinone. Certains inhibent modérément la protéine

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doi:10.1016/j.crci.2007.03.006

tyrosine phosphatase 1B (PTP1B) ou la glycogène phosphorylase (GP), comme on l'a montré par enzymologie et cristallographie. Les synthèses ont été adaptées pour conduire à des chromanols *C*-glycosylés ou à des tocophérols *C*-glycosylés, dont les propriétés antioxydantes ont été étudiées. ***Pour citer cet article : G.-R. Chen, J.-P. Praly, C. R. Chimie 11 (2008).***

Keywords: Free-radical reaction; Electrophilic substitution; Stereoselectivity/stereocontrol; *C*-Glycosyl compounds; *C*-Glycosyl aryls; Vitamin E derivatives

Mots-clés : Réaction de radicaux libres ; Substitution électrophile ; Stéréosélectivité/stéréocontrôle ; Composés *C*-glycosylés ; Aryles *C*-glycosylés ; Dérivés de la vitamine E

1. Introduction

As natural polyfunctional and chiral molecules, carbohydrates have been the subjects of intensive researches for quite a long time. They are continuously attracting much attention from synthetic chemists, in particular for designing shorter stereocontrolled routes towards oligosaccharides and other molecules of interest for glycosciences and medicine [1]. Due to the presence of various nucleophilic groups (e.g., hydroxyl, amine) in sugars, protection/deprotection strategies are generally required to prevent unwanted reactions. The search of milder and orthogonal conditions has inspired most advances, in particular for stereocontrolled glycosidations [2]. Ionic approaches were first more popular and many methods have been proposed for the generation of D-glycopyranosylium ions as reactive intermediates for glycosylation reactions, to afford *O*-, *N*-, or *S*-glycosides, among other structures. *C*-Glycosyl compounds (also frequently termed *C*-glycosides) display an anomeric carbon constitutive of an ether motif, and are, compared to common glycosides, more stable to both acid and enzyme-catalyzed hydrolysis, because of the resistance of ethers compared to acetals [3]. *C*-Glycosyl compounds, and among them *C*-glycosyl flavonoids are well represented in Nature, some of them having interesting bio-activities [4]. Therefore, their synthesis is well documented, based on a large variety of versatile approaches. Electrophilic substitution offers, in particular with electron-rich aryls, a suitable route towards *C*-glycosyl arenes with possible stereocontrol [5].

After 1980 or so [6], the synthetic potential of free-radical methods became more appreciated, thus inspiring numerous investigations of sugar-based radicals, as regard to their structure, their synthetic transformations under very mild conditions, and their participation in biological events. Our interest in radical-based transformations of sugar derivatives stems from early investigations carried out in the group of Descotes, who first reported efficient conversions of alkyl glycosides into sugar-based spiroacetals or spiro-orthoesters via, respectively, carbon, or oxygen-centered radical intermediates generated with UV or visible-light irradiation [7]. From these studies of intramolecular reactions generally based on D-*gluco* configured precursors, it was concluded that the newly created bond was established with high α-stereoselectivity. Intermolecular processes also occurred with high α-stereoselective bond formation [6], as the tri-*n*-butyltin deuteride reduction of glycosyl halides [8] or the NBS-mediated bromination of various glycosyl derivatives, as β-D-glycopyranosyl cyanides [9] or chlorides [10]. It is worth mentioning that protection of the hydroxy groups by acetylation or benzoylation proved to be suitable under the conditions promoting the aforementioned radical reactions, so that NBS-mediated bromination of 2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl chlorides afforded the corresponding 2,3,4,6-tetra-*O*-acetyl-1-bromo-β-D-glycopyranosyl chlorides in ∼65% yield [10]. Such sugar dihalides have been converted to sugar-based orthoesters [11], alkoxyazides [12], diazides [13], which allowed unprecedented ring expansions [14] or ring formation [15]. Sugar dihalides also proved to be synthetically useful for the stereocontrolled synthesis of *C*-β-D-glycosides, as described below.

This account summarizes our recent achievements in the field of *C*-glycosyl compounds, made possible with the participation, for the synthetic work, of co-tutored students from the group of Prof. Guo-Rong Chen, East China University of Science and Technology, Shanghai, PR China, as presented at 1st Chemical Workshop South China–Lyon. Other established collaborations allowed appropriate biological evaluations.

2. Radical synthesis of *C*-glycopyranosyl-alkyl compounds

In addition to ionic approaches [3], radical-based syntheses of *C*-glycopyranosyl-alkyl compounds have received considerable attention and many examples have