Full paper / Mémoire

Free-radical and ionic routes towards hydrolytically stable and bioactive *C*-glycosyl compounds

Guo-Rong Chen [a], Jean-Pierre Praly [b],*

[a] *Laboratory of Advanced Materials, Institute of Fine Chemicals, East China University of Science and Technology (ECUST) 130 Meilong Road, POB 257, 200237 Shanghai, PR China*

[b] *Laboratoire de chimie organique 2, Institut de chimie et biochimie moléculaires et supramoléculaires (ICBMS), CPE Lyon, bâtiment 308, 43, boulevard du 11-Novembre-1918, Villeurbanne, F-69622, France; CNRS, UMR5246, Villeurbanne, F-69622, France; Université de Lyon, Lyon, F-69622, France; Université Lyon 1, Lyon, F-69622, France*

Abstract

Photo-initiated addition of glycopyranosyl radicals to such radical acceptors as allyltributyltin, acrylonitrile, or diethyl vinyl-phosphonate was efficiently achieved to afford stereoselectively α-configured *C*-glycosyl compounds. With acrylonitrile or diethyl vinylphosphonate, catalytic amounts of organotin were used with NaBH$_3$CN 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$_3$CN. 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 transfér-ases. 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 du 1,4-diméthoxybenzène par des ions D-glycopyranosylium donne accès à des dérivés *C*-glycosylés du 1,4-diméthoxybenzène, de la 1,4-benzoquinone et de l'hydroquinone. Certains inhibent modérément la protéine

* Corresponding author.

E-mail addresses: mrs_guorongchen@ecust.edu.cn (G.-R. Chen), jean-pierre.praly@univ-lyon1.fr (J.-P. Praly).

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).***
© 2007 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

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

been reported, thus highlighting the potential of radical methods [3,6]. These reactions generally involve reagents of the organotin type (e.g., allyl tri-*n*-butyltin, tri-*n*-butyltin hydride) transformed in the reaction into organotin products, which are toxic and difficult to remove at the purification stage. Therefore, the development of mild methods using either no organotin compounds or catalytic amounts, but affording the products with good (stereo)selectivity was worth of consideration.

### 2.1. Synthesis of alkyl C-α-D-glycosides by radical addition to alkenes

While carbon-centered glycosyl radicals add smoothly to allyl tri-*n*-butyltin in a chain reaction based on fragmentation of radical intermediates that produce the chain-carrying tri-*n*-butyltin radical [6] and *C*-glycosyl-propenes [16], the possibility for glycosyl radicals to add to other alkenes offers extended applications. Due to the ring oxygen next to the radical center, glycosyl radicals are nucleophilic and react easily with electron-poor alkenes e.g. acrylonitrile, acrylic esters, diethyl vinyl-phosphonate. The radical intermediates thus formed by addition, with (OR having) the radical center located next to an electron-withdrawing group (e.g. cyano, ester, phosphonate) are electron-poor and, being electrophilic, they react fast with tri-*n*-butyltin hydride. This step delivers the reaction product and a new tin centered-radical to continue the chain reaction. A fast addition of the glycosyl radical to the alkene is crucial for the success of C−C bond forming reaction, which can otherwise suffer from radical reduction, among other competing reactions, in particular with 2-deoxy-2-amino sugars [17]. Reports on the synthesis of *C*-glycosyl compounds by addition of glycosyl radicals to alkenes showed some

limitations, as the moderate thermal stability of glycosyl halides used as the radical precursors and the possible influence of the solvent [18]. In the quest of optimized conditions, UV-light initiation of the reaction appeared advantageous, as well as use of tri-*n*-butyltin hydride in catalytic amounts, with NaBH$_3$CN in excess. NaBH$_3$CN can reduce the tin halide (chloride, bromide) formed during the reaction so as to maintain a low concentration of tin hydride as required to continue the radical chain reaction. *t*-Butanol is the solvent of choice, due to its low absorbance at the wavelengths used and as it dissolves NaBH$_3$CN [19].

Our observations [20] clearly show (Scheme 1) that under optimized conditions at mild temperatures (30/35 °C) the addition of D-glycopyranosyl radicals to acrylonitrile [18,21] and diethyl vinylphosphonate [22] afforded efficiently the corresponding α-configured *C*-glycosyl compounds and only trace amounts of the β-anomers. With both alkenes, the recorded yields were very similar, and somehow higher than those previously reported, either with acrylonitrile (57−76%) [21], or diethyl vinylphosphonate (<44% yields in Ref. [22a]). Among the minor products isolated, we obtained both 1,5-anhydro-alditol **4** and 2-deoxy sugar **5** which resulted from the reduction of either the initial anomeric radical or that formed by 2,1-acetoxy migration [8c]. To our delight, in the absence of acrylonitrile, these reductions predominated and could be controlled tightly (Scheme 2) under simple conditions without any tin compound added: photoirradiation of **1** in *t*-BuOH in the presence of NaBH$_3$CN led in 82% yield to a 95/5 **5/4** crude mixture, while adding catalytic amounts of thiophenol prevented the radical rearrangement because of polarity reversal catalysis [8d], to afford a 98/2 mixture of **4/5** in 79% yield [20].
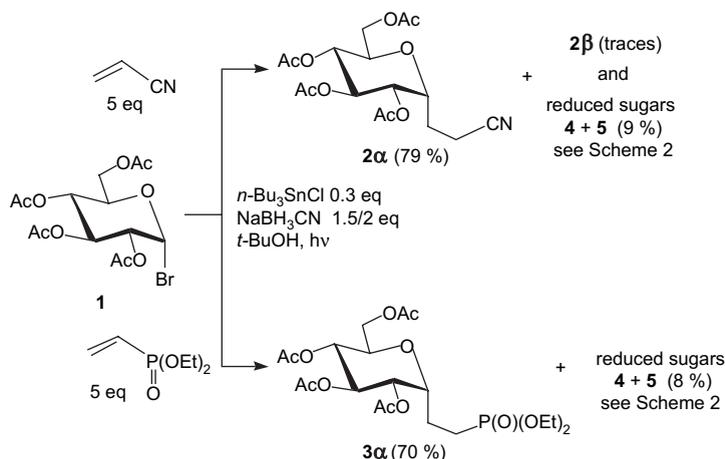
Scheme 1.
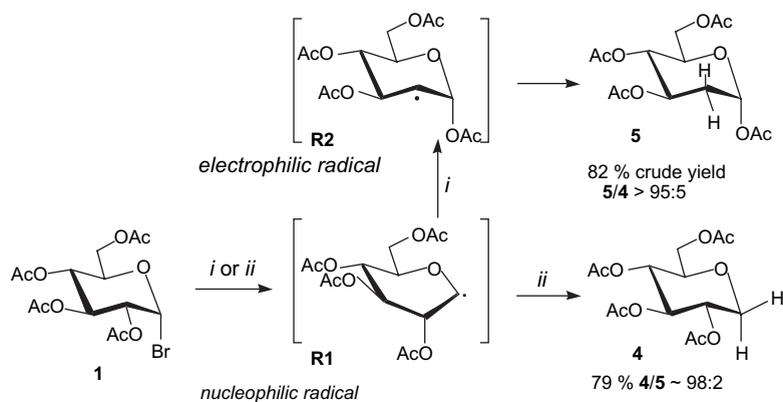
Scheme 2. *(i)* NaBH₃CN 2 equiv, *t*-BuOH, h*ν*, 0.5 h; *(ii)* NaBH₃CN 2 equiv, C₆H₅SH 10 mol%, *t*-BuOH, h*ν*, 1.75 h.

The accessibility of such *C*-glycosyl-ethylphospho-nates made possible the synthesis of *C*-glycosyl ana-logues (Scheme 3) of natural substrates of glycosyl transferases. Coupling of deprotected glycosyl ethyl-phosphonic acids with activated nucleotides (UMP-morpholidate or GMP-morpholidate) was the key step in the sequence, achieved with 10/24% yields [23]. Enzymatic evaluation with suitable glycosyl transfer-ases [24] showed that **6b** was a good inhibitor (IC₅₀ = 40 μM) of bovine milk β-1,4-galactosyltransferase (β-1,4-GalT, EC 2.4.1.22).

2.2. Stereocontrolled synthesis of C-β-D-glycosides

The aforementioned conditions applied to prepare *C*-α-D-glycosyl compounds appeared favorable to extend further the scope of radical methods. In particular, the available peracetylated sugar dihalides [10] appeared valuable substrates for the stereocontrolled synthesis of *C*-β-D-glycosyl compounds. We supposed that upon reac-tion of sugar dihalides (e.g. **9**) with tin radicals, homolysis of the C−Br axial bond should be easier as compared to the equatorial C−Cl bond (anomeric effect, BDE lower for the C−Br bond), thus leading to chlorinated anomeric radicals. Their addition to either allyl tributyltin or acrylo-nitrile/diethyl vinylphosphonate (in the presence of *n*-Bu₃SnH to reduce the so-formed radical intermediate) would lead to chlorinated *C*-glycosyl compounds. Al-though prone to hydrolysis, they could be obtained, some-times in high yield, as for **10**, apparently more stable than its D-*galacto*/D-*manno* analogues (51% and 31% isolated yield, respectively). However, radical reduction of the chlorinated *C*-glycosyl compounds with an excess of *n*-Bu₃SnH (one-pot or stepwise process) occurred as ex-pected with an α-stereoselectivity, as shown by the β-anomeric configuration of the obtained products **2β, 3β, 11** (Scheme 4). In this way, besides minor products

formed by hydrolysis, radical rearrangement, and reduc-tion, the desired β-configured anomers were obtained as the major products (38/55%) in comparable yields, inde-pendently of the sugar configuration [20,25].

2.3. Synthesis of glycodienes, bis-C,C-glycosides and spiro derivatives

Interestingly, acetylated 1-chloro-*C*-glycosyl propenes **10**, **16**, **17** (D-*gluco*, D-*galacto*, D-*manno* configurations) underwent DBU-induced elimination of hydrochloric acid, to form hitherto unprecedented (*Z*)-configured gly-codienes [25,26]. Since *C*-ketosyl compounds and bis-*C,C*-glycosides are not very common structures, with limited accessibility [27], sugar dihalides appeared candi-dates of choice for preparing under very mild conditions
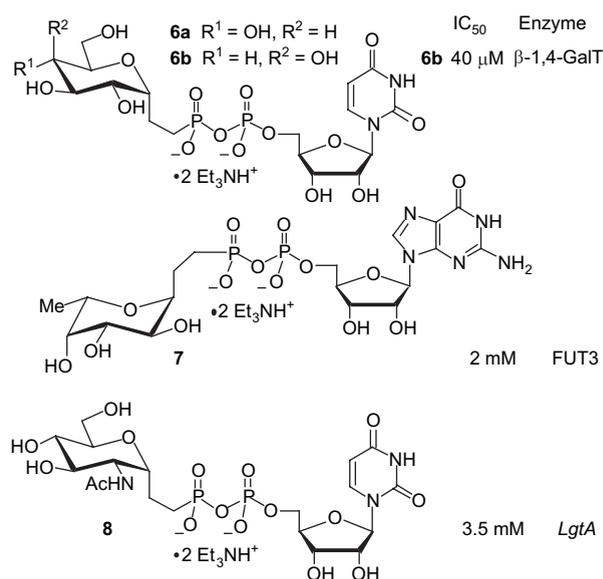
Scheme 3.
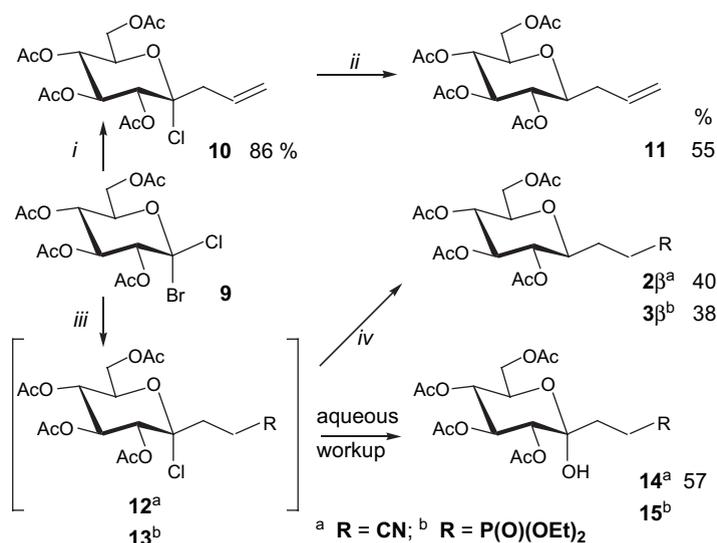
Scheme 4. *(i)* Allytributyltin 2 equiv, C_6H_6, hν; *(ii)* n-Bu$_3$SnH 2 equiv, C_6H_6, hν; *(iii)* CH_2CHCN or $CH_2CHP(O)(OEt)_2$ 5 equiv, n-Bu$_3$SnCl 0.3 equiv, $NaBH_3CN$ or Bu_4NBH_3CN 2 equiv, t-BuOH or C_6H_6, hν; *(iv)* C_6H_6, n-Bu$_3$SnH, 3/4 equiv, hν, 15 min.

bis-*C*,*C*-glycosides having two allyl residues (Scheme 5). Applying to **9** and related sugar dihalides the C—C bond forming conditions with excess of allyltributyltin led in moderate yield to the desired bis-*C*,*C*-glycosides, which were converted efficiently by the ring-closing metathesis reaction with Grubb's catalyst to D-*gluco*, D-*galacto*, and D-*manno* glycosyl-spiro-cyclopentenes [28]. The new structures prepared were deacetylated readily.

3. *C*-Glycosyl-hydro(benzo)quinones and derivatives

Because of their natural occurrence and due to the existence of several synthetic approaches to *C*-glycosyl arenes, such compounds are well documented, in particular as phenol or polyphenol (resorcinol, phloroglucinol) derivatives [5]. Within a project focusing on *C*-glycosyl compounds with potential antithrombotic activities [29], we noticed that *C*-glycosyl derivatives derived from hydro(benzo)quinones are poorly known, except for the early investigation reported by Kalvoda [30], who mainly described furanosides of hydroquinone and *C*-ribofuranosyl derivatives of dimethoxybenzenes and hydro(benzo)quinone. While the O→C rearrangement of hydroquinone glycosides to *C*-glycosides appears to be unprecedented, scattered reports described the synthesis of *C*-glycosyl derivatives of hydroquinone and analogues based on carbene or radical intermediates. Considering that *C*-glycosyl aryls are stable molecules prone to various chemical modifications that may lead to bioactive structures [31], we decided to focus our

efforts on the synthesis of *C*-glycopyranosyl aryls by electrophilic substitution of 1,4-dimethoxybenzene [32]. The so-obtained molecules could be converted into a variety of stable *C*-glycosyl derivatives interesting for both chemical modifications and bioactivities. Initially, we planned to synthesize glucose-based molecules for biological evaluation as glycogen phosphorylase (GP) inhibitors [33] for study in the frame of an established collaboration [34].

3.1. *Synthesis of C-glycosyl-hydro(benzo)quinones*

As mentioned before, *C*-glycosyl-hydro(benzo)quinones are simple structures which are poorly known,
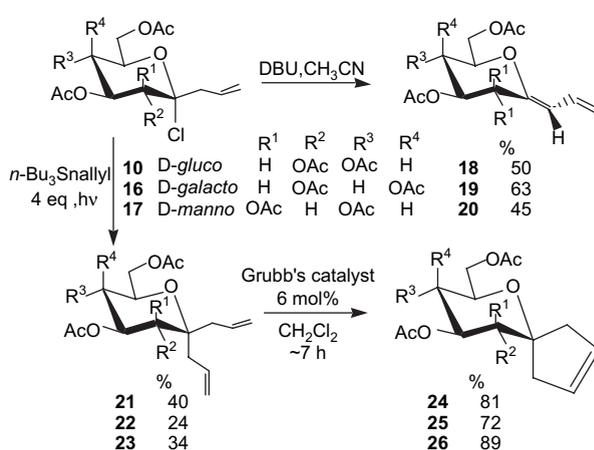
Scheme 5.

except for one report by Kalvoda, who studied a route based on electrophilic substitution of dimethoxybenzene by glycofuranosyl cations followed by oxidation and reduction [30]. Electrophilic substitution of 1,4-dimethoxybenzene with glycopyranosylium ions [32] followed by oxidation and reduction was therefore investigated [35]. The coupling reaction of glycopyranosyl cations and 1,4-dimethoxybenzene can be promoted by SnCl$_4$ and various salts, in particular F$_3$CCOOAg in CH$_2$Cl$_2$ as solvent [32]. In order to optimize, in terms of yield and β-stereoselectivity, such a *C*-glycosylation applied to **27** and **28**, we found that the reaction temperature was critical. So as to shift equilibria towards the thermodynamically favoured β-anomers within a reasonable time, mild heating to 25/30 °C was applied for 4/5 h, resulting in reproducible yield of the desired compounds (D-*gluco*: 69%; D-*galacto*: 81%). Oxidation with ceric ammonium nitrate (CAN) afforded cleanly the corresponding glycosyl-benzoquinones (Scheme 6) whose deacetylation proved to be unselective, except for the unexpected formation of chlorinated hydroquinone derivatives on stirring in MeOH acidified with AcCl. Therefore, in view of preparing deprotected glycopyranosyl-benzoquinones **37**, **38** for biological evaluations, the oxidation, reduction and deacetylation steps were combined in different sequences: (a) the dimethoxy derivatives **29β** and **30β** were deacetylated, then oxidized (CAN); (b) the benzoquinones **31**, **32** were reduced, deacetylated, then oxidized, either by Ag$_2$O or by PhI(OAc)$_2$. This afforded deacetylated glycopyranosyl benzoquinones which were tested without delay, because of their limited stability.

3.2. Synthesis of C-glycosyl-chromanols and C-glycosyl-tocopherols

Among free-radical scavengers and antioxidants, vitamin E is well known, particularly because α-tocopherol is the more abundant and the more effective dietary antioxidant, with some industrial importance. Its structure makes it essentially lipophilic. Modified analogues with polar residues have been prepared, and shown to dissolve in polar solvents, sometimes in water, as it is the case of tocopheryl oligosaccharides. However, such *O*-glycosides have no free phenoxy group and they are dependent on in vivo deglycosidation to exert antioxidant properties. This problem does not exist in the case of *C*-glycosyl-tocopherols. To test their synthesis, hydroquinone **39** was reacted with racemic phytol in the presence of ZnCl$_2$. Because both phenoxy groups could participate in cyclization, this attempt afforded a mixture of glycosylated
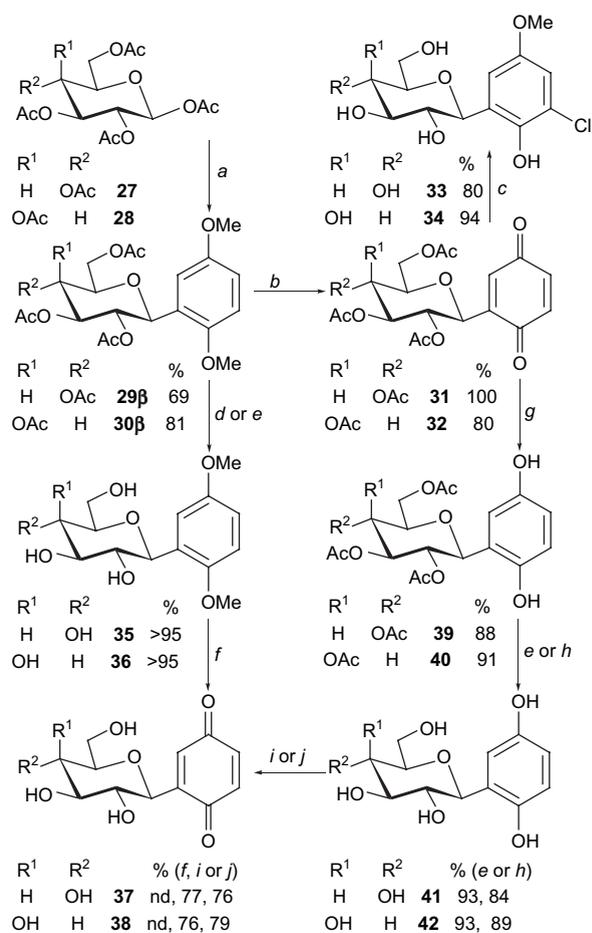
Scheme 6. (a) **5** or **6**, *p*-Dimethoxybenzene 2 equiv, SnCl$_4$ 3 equiv, CF$_3$CO$_2$Ag 1.5 equiv, CH$_2$Cl$_2$, 20–25 °C, ∼ 5 h; (b) CAN 3 equiv, CH$_3$CN/H$_2$O, 1:1 or 2:3, 25 min; (c) MeOH containing 0.5% AcCl, 1 week, rt; (d) MeOH/NEt$_3$/H$_2$O, 8:1:1, rt, 10/12 h; (e) for **29β/30β** or **39/40**, respectively, 0.1 M or 0.033 M MeONa in MeOH, rt, ∼ 2 h; (f) CAN 3 equiv, H$_2$O, rt, 30 min; (g) NaBH$_4$ 2 equiv, EtOAc, rt, 30 min; (h) MeOH containing 1% AcCl, 5 days, rt; (i) Ag$_2$O (8 equiv with **41**, oxidation almost complete; 3 equiv with **42**, ∼95% conversion), 2-propanol, rt, 2 h; (j) PhI(OAc)$_2$ 1.5 equiv, MeOH, rt, 40 min; (nd) not determined.

compounds, which proved to be difficult to resolve by chromatography. To avoid such unselective annelations, defined glycosylated dimethylhydroquinones were prepared, and syntheses were adapted to isomeric *o*-, *m*-, and *p*-dimethyl-1,4-dimethoxybenzenes (Schemes 7 and 8). The first one was prepared from commercially available *o*-dimethylhydroquinone by methylation, while high-yielding three-step sequences (oxidation with Fremy's salt, reduction, methylation) applied to 2,6-, or 2,5-dimethylanisole led, respectively, to the other precursors. While the electrophilic substitution of *o*-, and *m*-dimethyl-1,4-dimethoxybenzenes with glucopyranosyl cation was effective (67 and 74% yield,
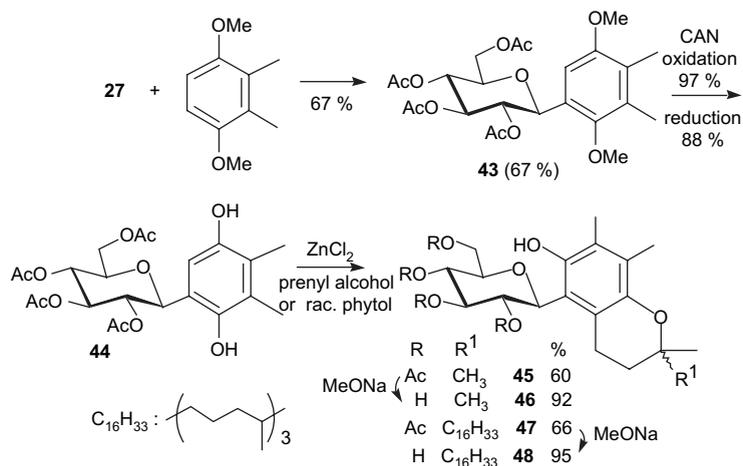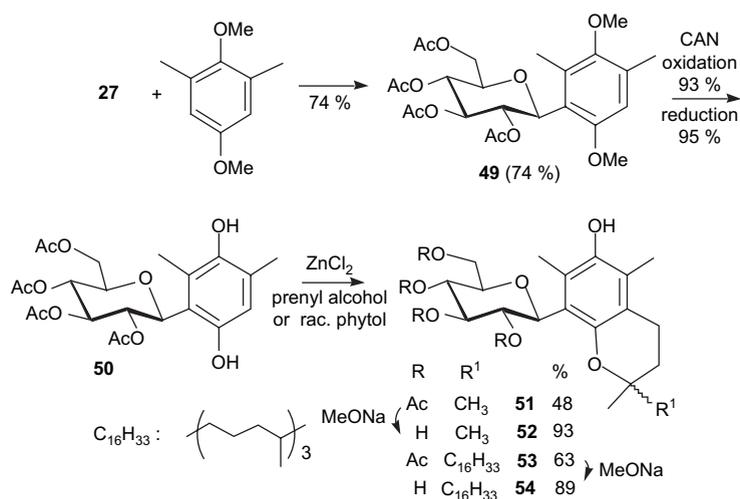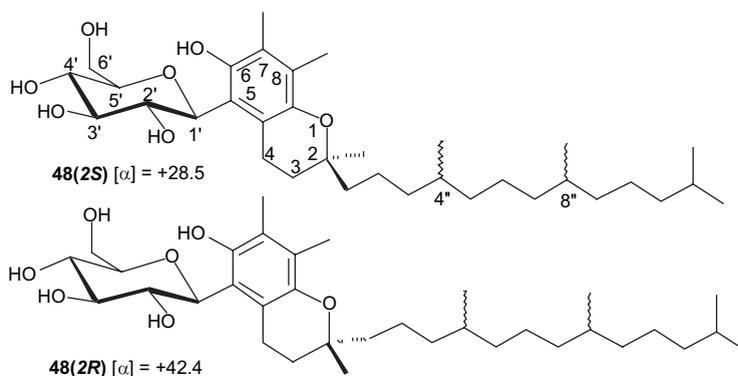
Scheme 7.

respectively), use of the *para* isomer afforded an α/β anomeric mixture of *C*-glucosyl compounds in <17% yield, thus hampering the next steps. The rest of the sequence [CAN oxidation, reduction, annelation with 3-methyl-2-buten-1-ol (prenyl alcohol) or racemic phytol] applied to **44** and **50** was straightforward, as were the final deacetylations under Zemplén conditions, so that various *C*-glucopyranosyl chromanol derivatives were obtained. With racemic phytol, these sequences afforded mixtures of diastereoisomers, with an *R* or *S* configuration at C2, C″4, and C″8 (Scheme 9), as evidenced by examination of high-field NMR spectra. In the case of deacetylated compound **48**, column chromatography allowed the separation of the 2*R* and 2*S* diastereoisomers (Scheme 9).

3.3. Biological evaluation: preliminary tests

The prepared molecules were subjected to different tests. *C*-Glycopyranosyl-hydro(benzo)quinones were assayed as protein tyrosine phosphate 1B (PTP1B) inhibitors [36], the main reason being that several quinones are known to inhibit PTP1B via a specific mechanism [36b]. Being responsible for the dephosphorylation of the insulin receptor, a process which turns off the insulin signaling cascade, PTP1B is considered as a promising target in therapeutic approaches towards non-insulino-dependent diabetes (type-2 diabetes) [37]. Deacetylated D-glucopyranosyl-hydro(benzo)quinones were also tested as glycogen phosphorylase (GP) inhibitors. Since GP catalyzes

Scheme 8.

48(2S) [α] = +28.5

48(2R) [α] = +42.4

Scheme 9.

glycogen depolymerization, it was assumed that glucose-based molecules could fit the enzyme active site, while the aglycon could establish stabilizing non-covalent interactions at its vicinity, with the result of competitive inhibition [33,34]. Finally, the glycosyl-chromanols and glycosyl-tocopherols were investigated with the expectation that their structural features (type of substitution, free or acetylated sugar ring, Me versus the $C_{16}H_{33}$ chain) will modulate their expected antioxidant properties.

3.3.1. Inhibition of PTP1B

C-Glycopyranosyl-benzoquinones proved to be irreversible inhibitors of PTP1B in vitro, as found by Prof. Jia Li, Chinese National Center for Drug Screening, Shanghai Institute of Materia Medica, Shanghai, PR China [38]. The acetylated β-D-glucosyl-benzoquinone **31** was the best inhibitor of PTP1B ($IC_{50} = 4.8$ μM), as compared to the deacetylated D-*gluco* and D-*galacto* analogues **37** and **38** ($IC_{50} = 25.6$ and 24.3 μM, respectively). Unfortunately, other analogues such as β-D-glucopyranosyl-naphthoquinones showed no activity in these tests. Ongoing efforts are pursued to explore in more detail such an interesting inhibition, having in mind, however, that potent molecules or leads suitable for pharmaceutical development should be bioavailable intracellularly, with a high selectivity to PTP1B compared to other phosphatases, among other criteria [36].

3.3.2. Inhibition of glycogen phosphorylase

Enzymatic evaluations of **35**, **37**, and **39** against GP showed modest inhibitions for **37** and **39** with Ki = 3.8 and 2.6 mM, respectively, while **35** had no activity. However, after soaking the crystals of GP in the presence of **37** and **39** as ligands, it was possible to achieve the crystal structure analysis of the obtained ligand–enzyme complexes. The β-D-glucosyl-hydro(benzo)quinones

were found to bind at the enzyme active site [35b]. Even though the measured inhibitions were modest, such molecules represent a new type of GP inhibitors with specific features associated to the *C*-glycosyl arene linkage (stability, conformers with restricted rotation). In the quest of more active molecules, our ongoing efforts focus on synthetic modifications of the aglycon moiety.

3.3.3. C-glycosyl-tocopherols as antioxidants

As noted before, the naturally occurring tocopherols and tocotrienols (vitamin E), with a phenoxy group and C_{16} alkyl chains (saturated or not), are major lipophilic antioxidants, among other species from the diet, which act in connection with the hydrophilic ascorbic acid (vitamin C) [39]. Because of the biological importance of free radicals, as regard to normal processes, damages to biomolecules and tissues or aging, this field is the focus of intensive researches. While a better insight into the phenomena is still necessary [40], the idea that free radicals contribute to health has reached a consensus (French paradox, beneficial effects of tea). As a consequence, the food and health companies are strongly involved in basic research and in the development of improved products, which may incorporate supplements, as nutraceutics.

The obtained glycosylated chromanol and tocopherol analogues were evaluated as antioxidants by Galland [41] at the University of Avignon (France) under the supervision of Dangles [42]. The observations collected in the case of the linoleic acid peroxidation point to antioxidant activities lower than that of tocopherol, as shown by the following the sequence: α-tocopherol > **51** ≈ **54** > **53** > **52** > **45** > **47** > **48** > **46**. The synthetic data and a detailed analysis of the antioxidant properties will be reported in a forthcoming article, in preparation [43].

Acknowledgements

References

[1] (a) E. Beat, G.W. Hart, P. Sinaÿ (Eds.), Carbohydrates in Chemistry and Biology, vol. 1−4, Wiley-VCH, Weinheim, 2000;
(b) B. Fraser-Reid, K. Tatsuta, J. Thiem (Eds.), Glycoscience: Chemistry and Chemical Biology, vol. 1−3, Springer, Berlin, 2001;
(c) C.-H. Wong (Ed.), Carbohydrate-based Drug Discovery, vol. 1−2, Wiley-VCH, Weinheim, 2003;
(d) C.A. Bewley (Ed.), Protein−Carbohydrate Interactions in Infectious Diseases, RSC Publishing, London, 2006.

[2] D.E. Levy, P. Fügedi (Eds.), The Organic Chemistry of Sugars, CRC Press, Taylor & Francis Group, Boca Raton, 2006.

[3] (a) M.H.D. Postema, *C*-Glycoside Synthesis, CRC Press, Boca Raton, 1995;
(b) D.E. Levy, C. Tang, The Chemistry of *C*-Glycosides, Pergamon, Oxford, 1995;
(c) J.-M. Beau, T. Gallagher, Top. Curr. Chem. 187 (1997) 1;
(d) F. Nicotra, Top. Curr. Chem. 187 (1997) 55;
(e) Y. Du, R.J. Linhardt, I.R. Vlahov, Tetrahedron 54 (1998) 9913;
(f) M.H.D. Postema, D. Calimente, in: P.G. Wang, C.R. Bertozzi (Eds.), Glycochemistry, Marcel Dekker, New York, 2001, p. 77 (Chap. 4);
(g) D.E. Levy, in: D.E. Levy, P. Fügedi (Eds.), The Organic Chemistry of Sugars, CRC Press, Taylor & Francis Group, Boca Raton, 2006, p. 269.

[4] (a) M. Jay, in: J.B. Harborne (Ed.), The Flavonoids: Advances in Research Since 1986, Chapman and Hall, London, 1994, p. 57;
(b) M. Jay, M.-R. Viricel, J.-F. Gonnet, in: Ø.M. Andersen, K.R. Markham (Eds.), Flavonoids: Chemistry, Biochemistry and Applications, CRC Press, Taylor & Francis Group, Boca Raton, 2006, p. 857.

[5] (a) C. Jaramillo, S. Knapp, Synthesis (1994) 1;
(b) K. Suzuki, T. Matsumoto, in: S. Hanessian (Ed.), Preparative Carbohydrate Chemistry, Marcel Dekker Inc, New York, 1997, p. 527;
(c) K.A. Parker, in: R. Roy (Ed.), Glycomimetics: Modern Synthetic Methodologies, ACS Symposium Series 896, 2005, p. 93.

[6] (a) B. Giese, Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds, Pergamon Press, Oxford, 1986;
(b) Houben-Weyl, in: M. Regitz, B. Giese (Eds.), Methoden der Organischen Chemie, C-Radikale, Band E 19a, Parts 1 and 2, Georg Thieme Verlag, Stuttgart, 1989;
(c) B. Giese, H.-G. Zeitz, in: S. Hanessian (Ed.), Preparative Carbohydrate Chemistry, Marcel Dekker Inc, New York, 1997, p. 507;
(d) H. Abe, S. Shuto, A. Matsuda, J. Am. Chem. Soc. 123 (2001) 11870;
(e) Y. Guindon, M. Bencheqroun, A. Bouzide, J. Am. Chem. Soc. 127 (2005) 554.

[7] (a) G. Descotes, J. Carbohydr. Chem. 7 (1988) 1;
(b) G. Descotes, Top. Curr. Chem. 154 (1990) 39;
(c) M. Sannigrahi, Tetrahedron 55 (1999) 9007.

[8] (a) J.-P. Praly, Tetrahedron Lett. 24 (1983) 3075;
(b) B. Giese, J. Dupuis, Tetrahedron Lett. 25 (1984) 1349;
(c) J.-P. Praly, Adv. Carbohydr. Chem. Biochem. 56 (2000) 65;
(d) Y. Cai, B.P. Roberts, J. Chem. Soc. Perkin Trans. 2 (2002) 1858 (and references therein).

[9] L. Somsák, R.J. Ferrier, Adv. Carbohydr. Chem. Biochem. 49 (1991) 37.

[10] (a) J.-P. Praly, L. Brard, G. Descotes, L. Toupet, Tetrahedron 45 (1989) 4141;
(b) J.-P. Praly, J.-C. Brendlé, J. Klett, F. Péquery, C.R. Chimie 4 (2001) 611.

[11] J.-P. Praly, Z. El Kharraf, P.-J. Corringer, L. Brard, G. Descotes, Tetrahedron 46 (1990) 65.

[12] J.-P. Praly, C. Di Stéfano, M.-N. Bouchu, Z. El Kharraf, R. Faure, G. Descotes, Tetrahedron 49 (1993) 9759.

[13] J.-P. Praly, F. Péquery, C. Di Stéfano, G. Descotes, Synthesis (1996) 577.

[14] (a) J.-P. Praly, C. Di Stéfano, G. Descotes, R. Faure, Tetrahedron Lett. 35 (1994) 89;
(b) C. Di Stéfano, G. Descotes, J.-P. Praly, Tetrahedron Lett. 35 (1994) 93.

[15] (a) J. Kovács, I. Pintér, M. Kajtár-Peredy, J.-P. Praly, G. Descotes, Carbohydr. Res. 279 (1995) C1;
(b) J. Kovács, I. Pintér, M. Kajtár-Peredy, G. Argay, A. Kálmán, G. Descotes, J.-P. Praly, Carbohydr. Res. 316 (1999) 112.

[16] G.E. Keck, E.J. Enholm, J.B. Yates, M.R. Wiley, Tetrahedron 41 (1985) 4079.

[17] (a) R. SanMartin, B. Tavassoli, K.E. Walsh, D.S. Walter, T. Gallagher, Org. Lett. 2 (2000) 4051;
(b) T. Wakabayashi, M. Shiozaki, S.-i. Kurakata, Carbohydr. Res. 337 (2002) 97;
(c) V.R. Bouvet, R.N. Ben, J. Org. Chem. 71 (2006) 3619.

[18] B. Giese, J. Dupuis, M. Leising, M. Nix, H.J. Lindner, Carbohydr. Res. 171 (1987) 329.

[19] (a) J.C. López, B. Fraser-Reid, J. Am. Chem. Soc. 111 (1989) 3450;
(b) J. Brunckova, D. Crich, Q. Yao, Tetrahedron Lett. 35 (1994) 6619;
(c) J.C. López, A.M. Gómez, B. Fraser-Reid, J. Org. Chem. 60 (1995) 3871.

[20] J.-P. Praly, A.S. Ardakani, I. Bruyère, C. Marie-Luce, B.B. Qin, Carbohydr. Res. 337 (2002) 1623.

[21] S.K. Readman, S.P. Marsden, A. Hodgson, Synlett (2000) 1628.

[22] (a) H.-D. Junker, W.-D. Fessner, Tetrahedron Lett. 39 (1998) 269;
(b) H.-D. Junker, N. Phung, W.-D. Fessner, Tetrahedron Lett. 40 (1999) 7063.

[23] S. Vidal, I. Bruyère, A. Malleron, C. Augé, J.-P. Praly, Bioorg. Med. Chem. 14 (2006) 7293.

[24] (a) P. Compain, O.R. Martin, Bioorg. Med. Chem. 9 (2001) 3077;
(b) P. Compain, O.R. Martin, Curr. Top. Med. Chem. 3 (2003) 541;
(c) C. Breton, L. Snajdrova, C. Jeanneau, J. Koca, A. Imberty, Glycobiology 16 (2006) 29R.

[25] (a) J.-P. Praly, G.-R. Chen, J. Gola, G. Hetzer, C. Raphoz, Tetrahedron Lett. 47 (1997) 8185;
(b) J.-P. Praly, G.-R. Chen, J. Gola, G. Hetzer, Eur. J. Org. Chem. (2000) 2831.

[26] (a) C. Taillefumier, Y. Chapleur, Chem. Rev. 104 (2004) 263;
(b) W.-B. Yang, Y.-Y. Yang, Y.-F. Gu, S.-H. Wang, C.-C. Chang, C.-H. Lin, J. Org. Chem. 67 (2002) 3773;
(c) S.S. Verma, N. Dwivedi, B.K. Singh, R.P. Tripathi, Carbohydr. Res. 341 (2006) 1930.

[27] (a) A.M. Gómez, M. Casillas, S. Valverde, J.C. López, Tetrahedron, Asymmetry 12 (2001) 2175;
(b) A.M. Gómez, C. Uriel, S. Jarosz, S. Valverde, J.C. López, Tetrahedron Lett. 43 (2002) 8935;
(c) A.M. Gómez, C. Uriel, S. Jarosz, S. Valverde, J.C. López, Eur. J. Org. Chem. (2003) 4830;
(d) T. Yamanoi, Y. Oda, Heterocycles 57 (2002) 229;
(e) F. Goursaud, F. Peyrane, A. Veyrières, Tetrahedron 58 (2002) 3629;
(f) W.-C. Haase, M. Nieger, K.H. Dötz, J. Organomet. Chem. 684 (2003) 153;
(g) A.M. Gómez, C. Uriel, S. Valverde, J.C. López, Org. Lett. 8 (2006) 3187.

[28] (a) G.-R. Chen, Z. Fei, X.-T. Huang, Y.-Y. Xie, J.-L. Xu, J. Gola, M. Steng, J.-P. Praly, Eur. J. Org. Chem. (2001) 2939;
(b) M.K. Gurjar, S.V. Ravindranadh, S. Karmakar, Chem. Commun. (2001) 241;
(c) P.A.V. van Hooft, F. El Oualid, H.S. Overkleeft, G.A. van der Marel, J.H. van Boom, M.A. Leeuwenburgh, Org. Biomol. Chem. 2 (2004) 1395.

[29] (a) M. Baudry, V. Barberousse, G. Descotes, R. Faure, J. Pires, J.-P. Praly, Tetrahedron 54 (1998) 7431;
(b) M. Baudry, V. Barberousse, G. Descotes, J. Pires, J.-P. Praly, Tetrahedron 54 (1998) 7447;
(c) M. Baudry, V. Barberousse, Y. Collette, G. Descotes, J. Pires, J.-P. Praly, S. Samreth, Tetrahedron 54 (1998) 13783;
(d) Y. Collette, K. Ou, J. Pires, M. Baudry, G. Descotes, J.-P. Praly, V. Barberousse, Carbohydr. Res. 318 (1999) 162;
(e) L. Mignon, C. Goichot, P. Ratel, G. Cagnin, M. Baudry, J.-P. Praly, B. Boubia, V. Barberousse, Carbohydr. Res. 338 (2003) 1271.

[30] L. Kalvoda, Collect. Czech. Chem. Commun. 38 (1973) 1679.

[31] S. Satoh, M. Shimojima, K. Ito, T. Kuribayashi, Annu. Rep. Sankyo Res. Lab. 54 (2002) 85.

[32] (a) T. Kuribayashi, N. Ohkawa, S. Satoh, Tetrahedron Lett. 39 (1998) 4537;
(b) T. Kuribayashi, Y. Mizumo, S. Gohya, S. Satoh, J. Carbohydr. Chem. 18 (1999) 371.

[33] (a) N.G. Oikonomakos, Curr. Protein Pept. Sci. 3 (2002) 561;
(b) L. Somsák, V. Nagy, Z. Hadady, T. Docsa, P. Gergely, Curr. Pharm. Des. 9 (2003) 1177;
(c) L. Somsák, V. Nagy, Z. Hadady, N. Felföldi, T. Docsa, P. Gergely, in: A.B. Reitz, Atta-ur-Rahman (Eds.), Frontiers in Medicinal Chemistry, vol. 2, Bentham Science Publishers, 2005, p. 253.

[34] (a) N.G. Oikonomakos, M. Kosmopoulou, S.E. Zographos, D.D. Leonidas, E.D. Chrysina, L. Somsák, V. Nagy, J.-P. Praly, T. Docsa, B. Toth, P. Gergely, Eur. J. Biochem. 269 (2002) 1684;
(b) M. Benltifa, S. Vidal, D. Gueyrard, P.G. Goekjian, M. Msaddek, J.-P. Praly, Tetrahedron Lett. 47 (2006) 6143;
(c) M. Benltifa, S. Vidal, B. Fenet, M. Msaddek, P.G. Goekjian, J.-P. Praly, A. Brunyánszki, T. Docsa, P. Gergely, Eur. J. Org. Chem. (2006) 4242.

[35] (a) J.-P. Praly, Li He, B.B. Qin, M. Tanoh, G.-R. Chen, Tetrahedron Lett. 46 (2005) 7081;
(b) Li He, Y.Z. Zhang, M. Tanoh, G.-R. Chen, J.-P. Praly, E.D. Chrysina, C. Tiraidis, M. Kosmopoulou, D.D. Leonidas, N.G. Oikonomakos, Eur. J. Org. Chem. (2007) 596.

[36] (a) N.K. Tonks, FEBS Lett. 546 (2003) 140;
(b) L. Bialy, H. Waldmann, Angew. Chem. Int. Ed. 44 (2005) 3814;
(c) S. Lee, Q. Wang, Med. Res. Rev. (2006). doi:10.1002/med20079 (published on line 12 October 2006).

[37] S.A. Ross, E.A. Gulve, M. Wang, Chem. Rev. 104 (2004) 1255.

[38] (a) R.M. Chen, L.-H. Hu, T.Y. An, J. Li, Q. Shen, Bioorg. Med. Chem. Lett. 12 (2002) 3387;
(b) Y.-F. Li, L.-H. Hu, F.-C. Lou, J. Li, Q. Shen, J. Asian Nat. Prod. Res. 7 (2005) 13.

[39] (a) C. Schneider, Mol. Nutr. Food Res. 49 (2005) 7;
(b) E. Niki, Oxidative Stress and Disease: Molecular Interventions in Lifestyle-Related Diseases, vol. 21 CRC Press, Boca Raton, 2006, p. 217.

[40] M. Afri, B. Ehrenberg, Y. Talmon, J. Schmidt, Y. Cohen, A.A. Frimer, Chem. Phys. Lipids 131 (2004) 107.

[41] S. Galland, PhD thesis, University of Avignon, France, 11 December 2006.

[42] (a) M. Roche, C. Dufour, N. Mora, O. Dangles, Org. Biomol. Chem. 3 (2005) 423;
(b) O. Dangles, C. Dufour, in: Ø.M. Andersen, K.R. Markham (Eds.), Flavonoids: Chemistry, Biochemistry and Applications, CRC Press, Taylor & Francis Group, Boca Raton, 2006, p. 443.

[43] L. He, S. Galland, C. Dufour, O. Dangles, G.-R. Chen, J.-P. Praly, Chem. Eur. J., in preparation.