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Radicals and Carbohydrates: A Grand Alliance

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Dedicated with admiration and gratitude to *Professor Andrea Vasella* on the occasion of his 80th birthday

Abstract: This review describes applications of radical reactions developed in the authors' laboratory for the modification of carbohydrates. It focuses on tin-free variation on the Barton-McCombie deoxygenation; on reductive de-iodination; on intermolecular radical additions of xanthates; on allylations and vinylations of xanthates and iodides, with emphasis on allylations using allylic alcohols activated as fluoropyridyl ethers; and, finally, on the synthesis of mercaptosugars.

Keywords: deoxygenations • xanthates • iodides • radical additions • allylations

Introduction

Reduction of carbohydrates

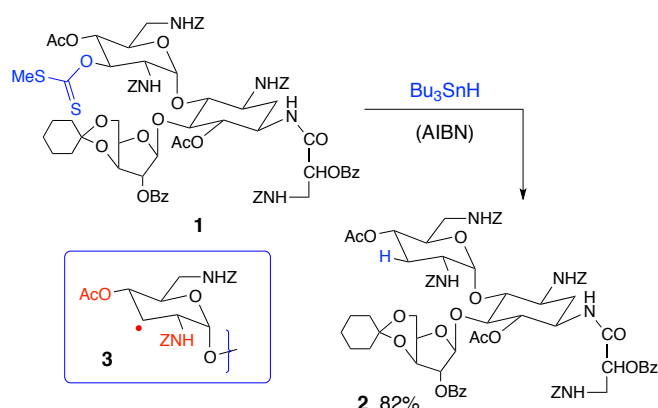
Carbon-carbon bond formation

Allylations and vinylations

Conclusion

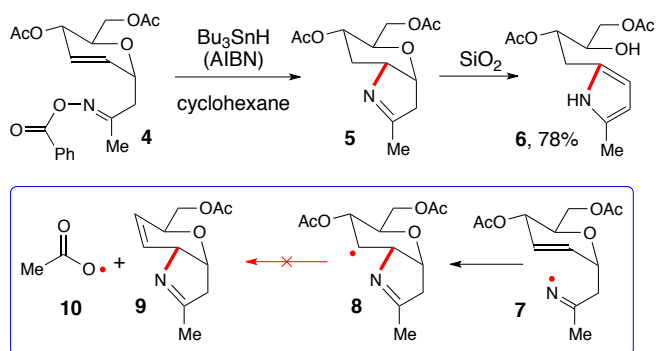
Introduction

The main defining moment of the alliance of radical chemistry and carbohydrates can be traced to the discovery of the Barton-McCombie deoxygenation, published in 1975 [1-3]. Indeed, this powerful deoxygenation process was initially developed in response to an industrial need to selectively modify complex biologically active glycosides in order to modulate their pharmacological profile, but it rapidly found widespread applications in all fields of organic synthesis. The early, spectacular, example in Scheme 1 from the Central Research Laboratories of Sankyo in Japan is an apt illustration of the tremendous opportunities offered by this chemistry [4]. Even now, nearly 50 years later, the conversion of trisaccharide **1** into deoxygenated analogue **2** would be highly challenging to accomplish by other methods. One of the main reasons this transformation is possible derives from the normal absence of eliminations, rearrangements, and other unwanted side-reactions once the intermediate carbon radical is generated. Thus, in the present case, intermediate radical **3** does not suffer β -fragmentation of either the neighboring acetate or carbamate groups colored in red. This contrasts strongly with any hypothetical ionic intermediate, such as an anionic or a cationic species, which would suffer rapid β -elimination, skeletal rearrangement, or neighboring group participation. Another considerable advantage is the general tolerance of radicals for polar groups, such as alcohols, esters, amides, and carbamates, which are ubiquitous in carbohydrates [5-7].



Scheme 1. A spectacular example of a Barton-McCombie deoxygenation.

The disclosure of the Barton-McCombie deoxygenation ushered an explosive growth in the incorporation of radical based transformations in synthetic planning in general and contributed significantly to the modification and use of carbohydrates as readily available, inexpensive chiral raw materials in particular [7,8]. Over the years, thousands of transformations involving radical intermediates have been applied to carbohydrates and the field is far too broad to be covered in a short article. The present review will therefore be limited to applications of methods developed in our laboratory to the modification of carbohydrates. For instance, as part of our study of processes for the generation and capture of nitrogen radicals, we reported the formation of pyrrole **6** from oxime benzoate **4** by ring-closure of iminyl radical **7** [9]. This is an instructive example because it illustrates further the stark difference between homolysis and heterolysis of carbon-oxygen bonds. Intermediate **8** from the cyclization step does not undergo any *homolytic* β -elimination of the high energy acetoxy group to give unsaturated dihydropyrrole **9** and an acetoxy radical **10**. In contrast, the primary cyclized product **5** suffers a facile *heterolysis* of the carbon-(anomeric) oxygen bond to produce pyrrole **6** upon mere contact with silica. The question of homolysis of carbon-oxygen bonds will be discussed later in connection with a radical allylation procedure we devised.

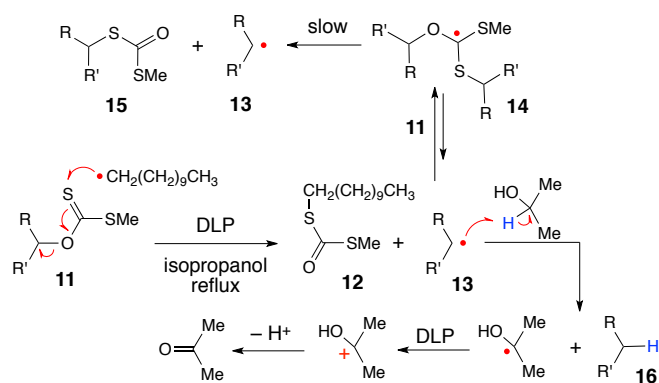


Scheme 2. An iminyl radical route to a glucose derived pyrrole.

Reduction of carbohydrates

From the practical standpoint, the Barton-McCombie deoxygenation suffers from a few shortcomings. The original process employs tri-*n*-butyltin hydride, a relatively expensive and toxic reagent that does not keep well, and the variable quality of the commercial samples can result in irreproducible yields. More seriously, removal of tin residues from the product to levels acceptable for the pharmaceutical industry is a nightmare, especially in large scale work. Unsurprisingly, there is hardly any application of stannanes to the manufacture of medicines. Another drawback is the formation of obnoxious volatile sulfur derivatives such as sulfur oxysulfide and methyl mercaptan upon workup. This could be a serious nuisance when operating on more than a few grammes. Silicon based reagents, most notably tris(trimethylsilyl)silane [10], solve the toxicity and purification problems but do not overcome the stench of the co-products and are prohibitively expensive, thus limiting their application in industry. Hypophosphorus salts, introduced later by Barton [11], are inexpensive and ecologically benign, but do not circumvent the odor problem.

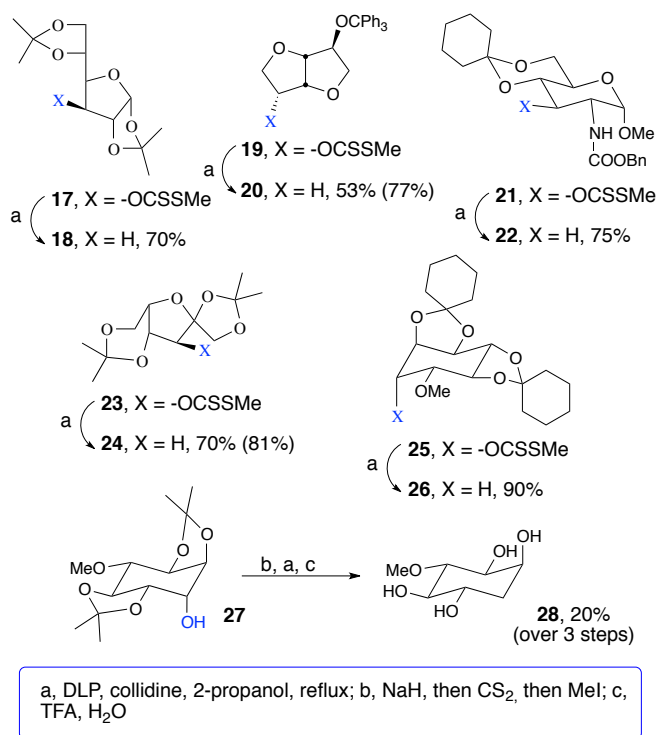
We devised a simple variation on the Barton-McCombie deoxygenation that solves most of the problems associated with the scale-up of the process. It exploits the difference in radical stabilities and the large difference in reaction rates between the fast radical addition to the thiocarbonyl of the xanthate and the much slower hydrogen atom abstraction from isopropanol [12]. In practice, it merely consists in gradually adding a stoichiometric amount of di-lauroyl peroxide (DLP, also sold under lauroyl peroxide, Laurox[®] or Luperox[®]) to a refluxing solution of the xanthate in 2-propanol. Thus, as outlined in Scheme 3, DLP decomposes upon heating to generate reactive primary undecyl radicals, which rapidly react with starting xanthate **11** by an addition-fragmentation process to produce dithiocarbonate **12** and secondary radical **13**. This process is favorable because a thiocarbonyl is replaced by the more stable carbonyl and secondary radical **13** is more stable than the primary undecyl radical derived by thermolysis of the DLP. Furthermore, the reaction of the undecyl radical with xanthate **11** is faster than hydrogen abstraction from the isopropanol, even though the latter is the solvent.



Scheme 3. Deoxygenation using 2-propanol as the source of hydrogen atoms.

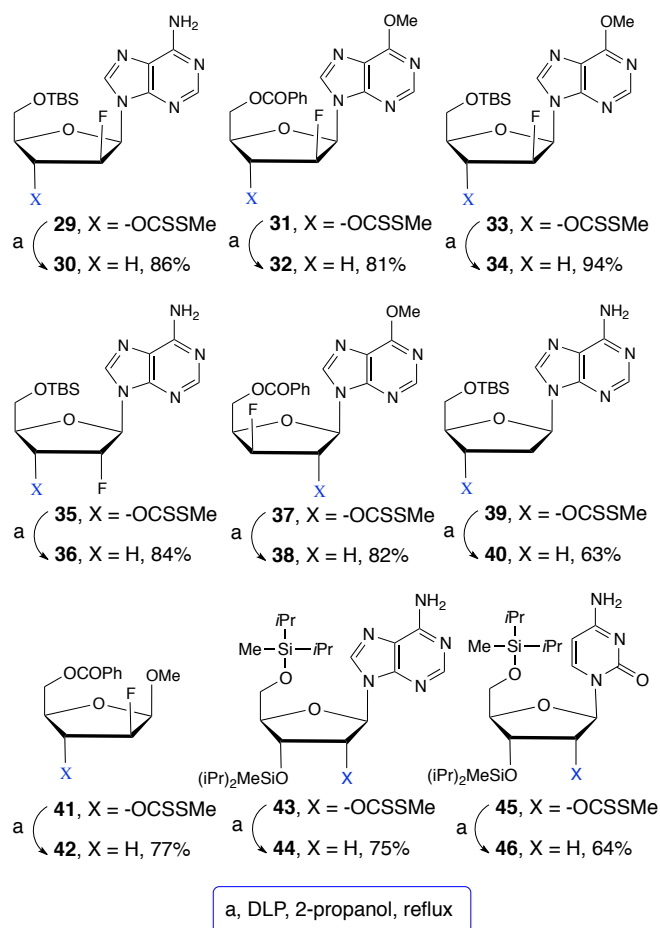
Once secondary radical **13** is produced, it reacts in turn rapidly with starting xanthate **11** to give intermediate **14**. However, the reverse reaction is much faster than the β -scission of the carbon-oxygen bond to give radical **13** and dithiocarbonate **15**. This is because the same radical **13** is produced in this addition-fragmentation, so the driving force is significantly weaker in comparison with the analogous reaction of undecyl radicals with xanthate **11**. Since radical **13** is not rapidly consumed by the pathway leading to dithiocarbonate **15**, it is now able to abstract the tertiary hydrogen from 2-propanol to give deoxygenated product **16** and a ketyl radical. The latter is oxidized to the corresponding cation by electron transfer to the DLP and loss of a proton finally gives acetone. DLP is therefore both an initiator for the radical sequence and a stoichiometric oxidant. The co-products of this deoxygenation are lauric acid and dithiocarbonate **12**. All the sulfur in the initial xanthate is thus captured as the essentially odorless, non-polar compound **12**. DLP is a non-toxic, non-hazardous, and very inexpensive commodity reagent derived from coconut oil.

Examples of deoxygenations of carbohydrates using this method are displayed in Scheme 4 [12, 13]. Collidine has been added in these cases to neutralize the lauric acid produced and prevent premature hydrolysis of the acid-labile ketal protecting groups. The yields are generally good and comparable to those obtained using tri-*n*-butyltin hydride (values in parentheses refer to yields based on recovered starting material, throughout this review). Compounds **26** and **28** are cyclitols but have been included because of their similarity with carbohydrates. The latter example was taken from a study by Painter and Loomes and their co-workers [13].



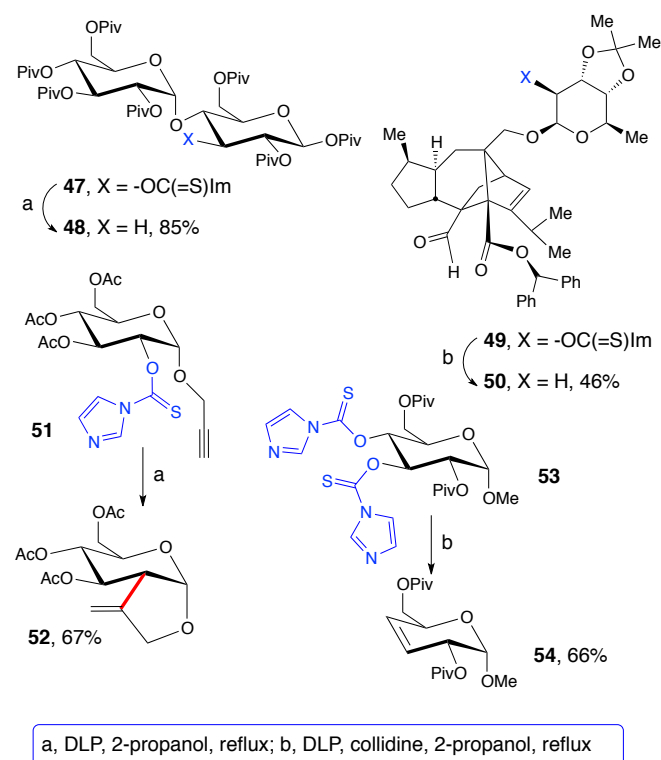
Scheme 4. Deoxygenation of carbohydrates with DLP/2-propanol.

Marquez and co-workers applied this deoxygenation procedure to a series of nucleosides pictured in Scheme 5 [14]. In these examples, no collidine was necessary since there are no acid-sensitive protecting groups. By using deuterated 2-propanol, the deuterated analogues of deoxygenated products **32** and **36** could be prepared. Not unexpectedly, the abstraction of deuterium took place mostly from the less hindered α -face (approximately 9:1). Interestingly, deprotection of the primary alcohol in compound **30** gives lodenosine, at the time a promising antiretroviral agent in phase II clinical studies for the treatment of AIDS. The deoxygenation of its xanthate precursor **29** using DLP/2-propanol could be accomplished on multi-hundred grammes scale and provided heavy metal-free samples of lodenosine suitable for biological testing.



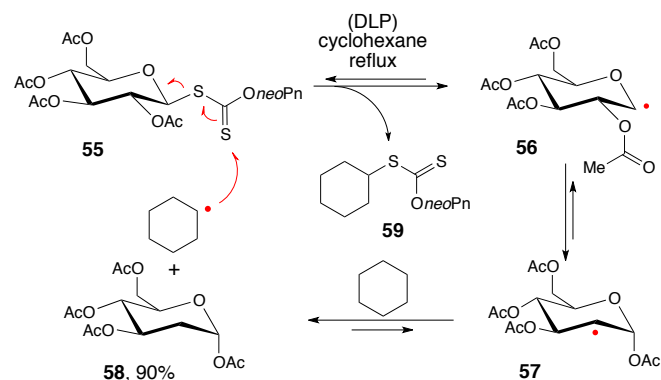
Scheme 5. Deoxygenation of nucleosides with DLP/2-propanol.

As in the original Barton-McCombie deoxygenation, the xanthate can be replaced by a thiocarbonylimidazolide. This alternative group is often more convenient to introduce on complex structures than a xanthate. Four illustrative examples are depicted in Scheme 6 [15]. The first concerns the synthesis of perbenzoylated deoxymaltose **48**, whereas the second, **50**, is a more heavily functionalized sordarin derivative studied in collaboration with GSK. The moderate yield in the latter case is in fact comparable to that obtained using tri-*n*-butylstannane. The third transformation is an instance where the intermediate carbon radical is captured by an internal alkyne to produce tetrahydrofuran **52**. Finally, in accord with earlier observations on the Barton-McCombie deoxygenation [2], vicinal bis(thiocarbonyl imidazolide) **53** furnished alkene **54**. This is a useful transformation that deserves greater attention from the synthetic community.



Scheme 6. Deoxygenation of thiocarbonyl imidazolides (Im = imidazolyl).

The DLP/2-propanol system is not limited to the deoxygenation of carbohydrates; however, the ubiquitous presence of electron-attracting C—O bonds, especially esters, next to the radical center facilitates the process because of matching polarities. We accidentally discovered a dramatic manifestation of polar effects when, in an attempt to prepare 2-xanthyl glucose (see Scheme 21 below), we subjected xanthate **55** to the action of DLP in refluxing cyclohexane and obtained an excellent yield of 2-deoxyglucose peracetate **58** (Scheme 7) [16]. A very small amount (<5%) of DLP was sufficient to drive the reaction to completion. (Throughout the present article, placing the DLP in parentheses indicates the use of sub-stoichiometric amounts of the peroxide).

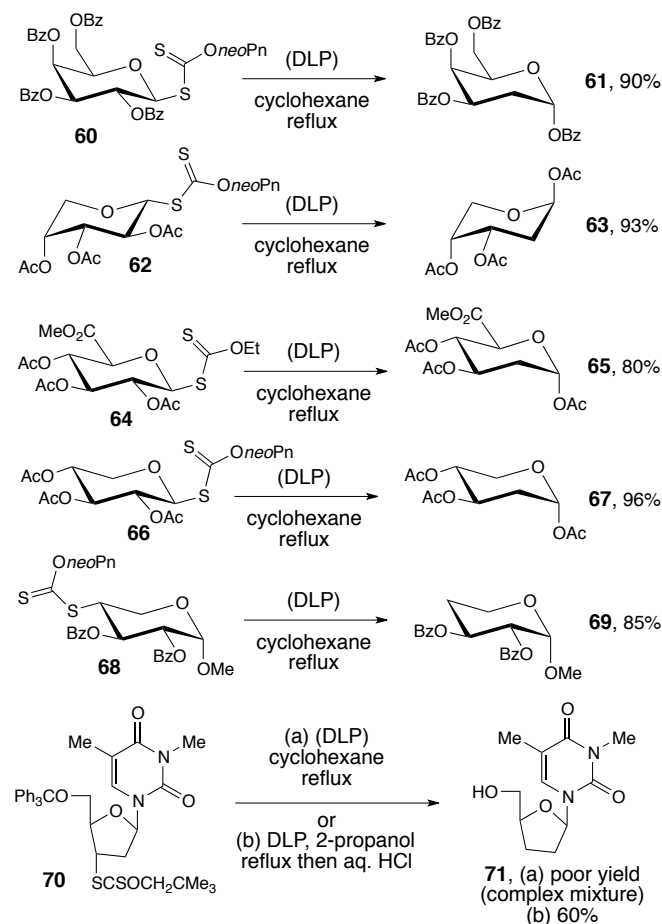


Scheme 7. Synthesis of 2-deoxyglucose (*neoPn* is neopentyl).

Thus, initiation by the undecyl radicals from the DLP generates a small amount of anomeric radical **56**, which is in equilibrium with isomeric radical **57**. This unusual 1,2-shift of an anomeric ester is well known [17]. Radical **57** has an electrophilic character, because of the two flanking acetate groups, but it is not thermodynamically stabilized. It is thus capable of rapidly

abstracting a hydrogen from the relatively electron-rich cyclohexane, even though the difference in C—H bond energies is small. This produces 2-deoxyglucose peracetate **58** and a cyclohexyl radical to propagate the chain process.

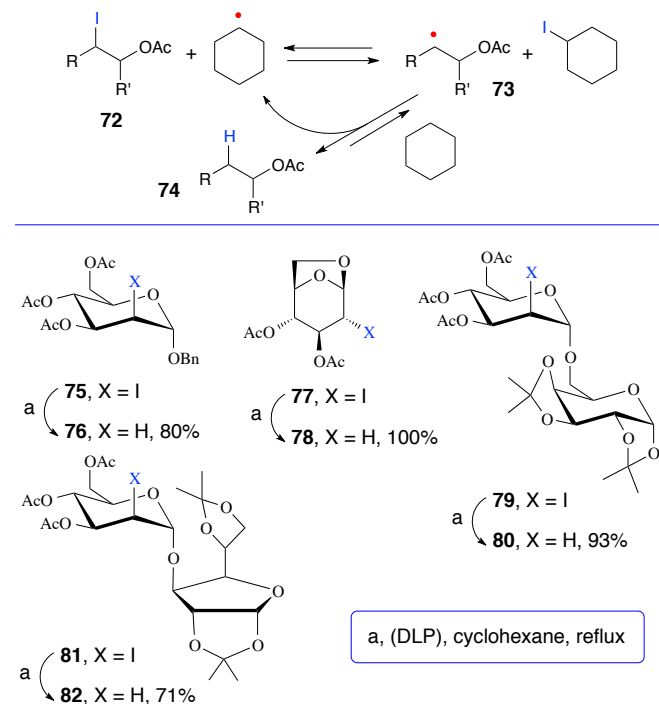
This practical, efficient, and inexpensive method for accessing 2-deoxyglucose is easily extended to other substrates, as shown by the transformations in Scheme 8 [16]. The first four, **61**, **63**, **65**, and **67** involve a similar migration of the ester group to the anomeric position, with the initial configuration being preserved in the product, as can be seen by comparing the stereochemistry of the ester in the 2-position in the starting xanthate with the configuration of the anomeric carbon in the product. In the reduction of xanthate **68** into 4-deoxy-xylose derivative **69**, no ester migration occurs as there is no driving force in its favor. In the last example, **70**, lacking strongly electron-attracting groups to provide the intermediate carbon radical with enough electrophilic character, only a complex mixture is observed. To accomplish the dexanthylation in this case, 2-propanol and a stoichiometric amount of peroxide have to be employed [conditions (b)], in the same way as for the deoxygenation discussed above [18]. The reduced product **71** was isolated after *in situ* removal of the trityl protecting group.



Scheme 8. Further examples of deoxyglucose.

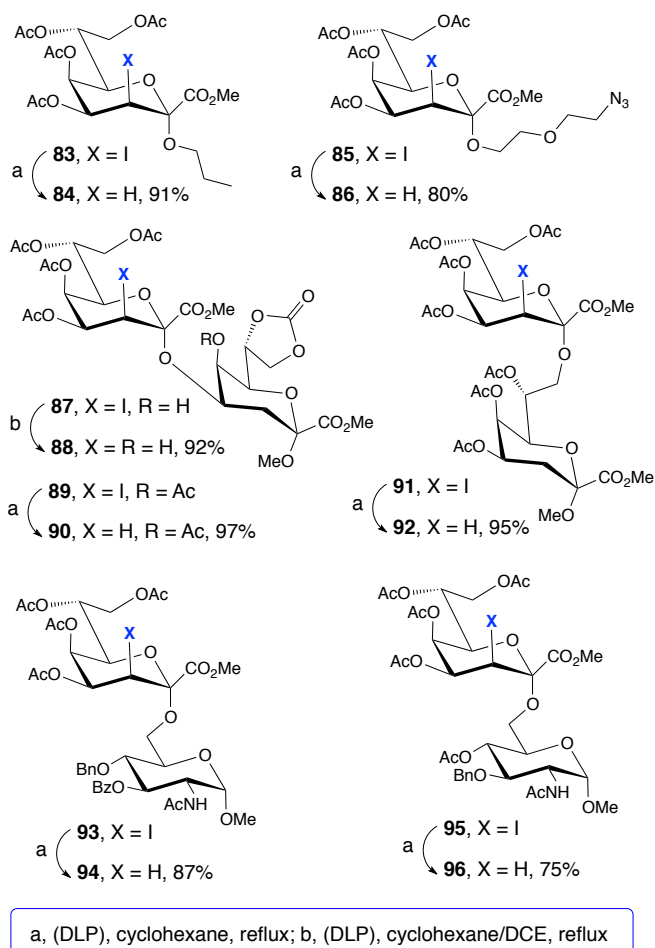
In a similar way to xanthates, iodides undergo rapid and reversible exchange of iodine atoms with radicals, with the important difference that this is a one-step process and not two-step addition-fragmentation with an

identifiable intermediate. Nevertheless, the existence of this fast exchange allows a similar reductive de-iodination of iodides **72** into **74** using cyclohexane as the source of hydrogen atoms, as long as the intermediate carbon radical **73** possesses sufficient electrophilic character due to the presence of inductively electron-withdrawing neighboring groups, such as esters, that do not provide thermodynamic stabilization (through conjugation, for instance), as outlined in Scheme 9 [19]. The examples presented in the same Scheme give an idea of the synthetic possibilities [19].

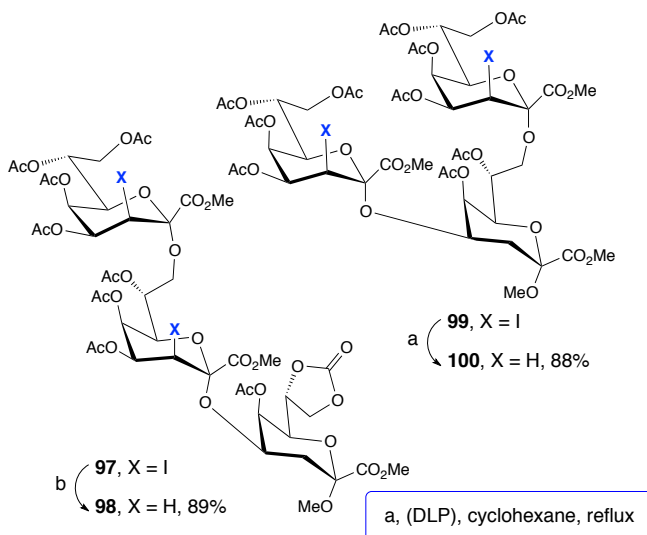


Scheme 9. Reductive deiodination using cyclohexane as the source of hydrogen atoms.

It is important to point out that the presence of the iodine in the substrate is most frequently the result of an iodolactonization or an iodoetherification of an electron rich alkene, as can be gauged by a closer examination of the compounds in Scheme 9. The latter process represents a major route for assembling sugar units and the ability to remove the iodine under mild conditions acquires a special importance. Numerous additional, more complex examples are assembled in Schemes 10–12. These have been taken from the subsequent studies by the groups of Kosma [20–22] (Schemes 10 & 11) and Wan [23] (Scheme 12). The tolerance for the presence of a free hydroxy group is exemplified by the reduction of iodide **87** into disaccharide **88**. The transformations in Scheme 11 concern diiodides of trisaccharides, which also proceeds in high yield.



Scheme 10. Further examples of deiodinations.

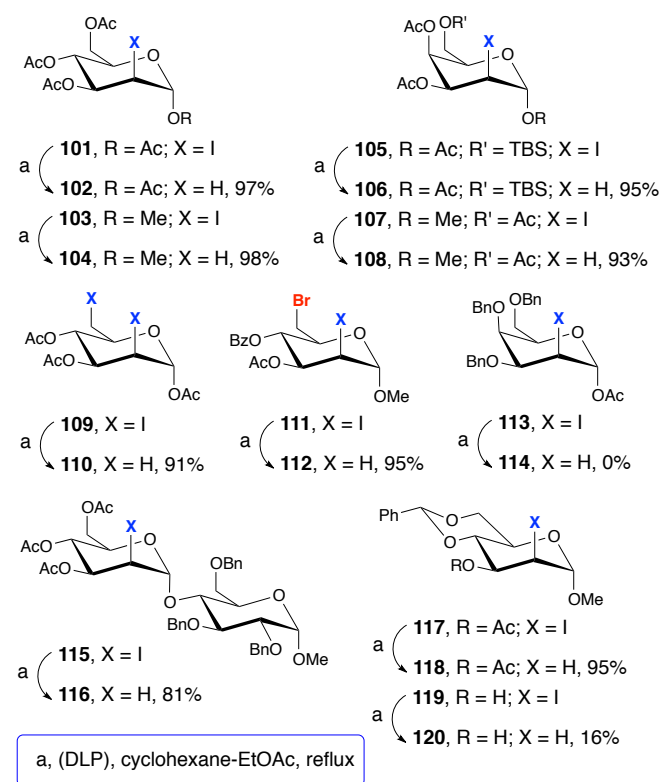


Scheme 11. Deiodination of trisaccharides.

In some cases, cyclohexane is a poor solvent for the substrate. Wan and co-workers found that mixtures of cyclohexane and ethyl acetate are equally efficient (Scheme 12) [23]. Interestingly, diiodide **109** containing a primary iodide could be efficiently reduced into iodine-free derivative **110**. The bromiodide analogue **111** could be selectively reduced to give bromide **112** in excellent yield. The importance of the presence of sufficiently strong electron-attracting, non-stabilizing groups next to the radical center is

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underscored by examples **117** and **119**. Replacing the acetate in the former by a free hydroxy group in the latter causes a dramatic drop in the yield of the corresponding products **118** and **120**, from 95% to 16%, respectively.

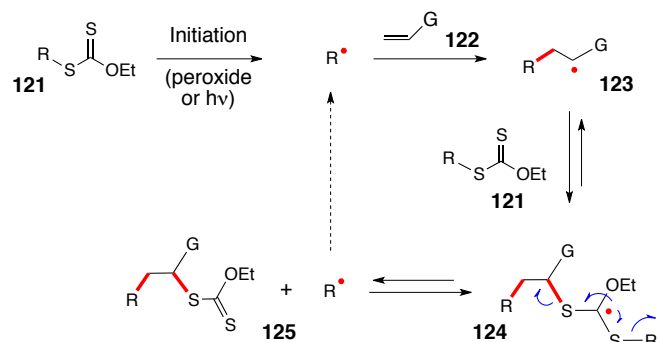


Scheme 12. Further examples of deiodinations with cyclohexane/EtOAc.

Radical additions involving carbohydrates

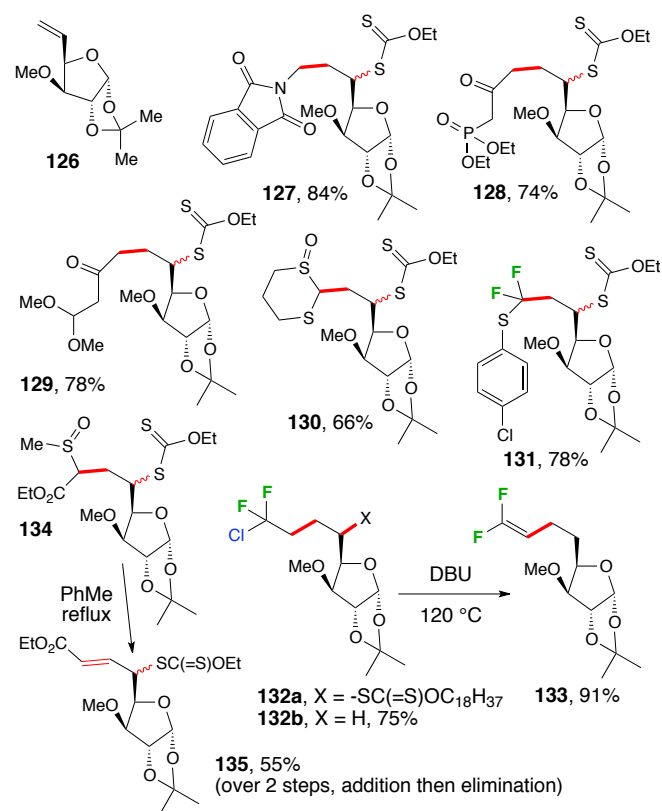
Our interest in xanthates stemmed from the discovery that, under appropriate conditions, it is possible to perform intermolecular additions to even unactivated alkenes, according to the simplified radical chain mechanism depicted in Scheme 13 [24-26]. More generally, xanthates and related dithiocarbonyl derivatives, such as dithioesters, dithiocarbamates and trithioesters, constitute a means to perform radical transformations that are too slow to be accomplished by more conventional methods. In the addition to alkenes, xanthate **121** and alkene **122** react to give adduct **125**, where a new carbon-carbon bond and a new carbon-sulfur bond have been created. This reaction has several unique features. The *effective lifetime* of R^\bullet and adduct radical **123** is significantly lengthened, because their reaction with any xanthate in the medium is *fast and reversible*. Furthermore, the *absolute concentration* of these radicals is considerably lowered because they are most of the time *reversibly* stored in the form of rather unreactive semi-persistent intermediates such as **124**. Radicals R^\bullet and **123** are in equilibrium through intermediate **124**, and this allows the regulation of their *relative concentration*. Thus, by selecting the reacting partners in such a manner that the initial radical R^\bullet is more stable than adduct radical **123**, the equilibrium between the two will favor the former, and the undesired formation of oligomers by further addition of radical **123** to alkene **122** will be slowed down. This is a critical observation to constantly keep in mind, even if polar effects can be important in certain circumstances. The actual

mechanistic manifold is more sophisticated and subtle. The interested reader is directed to references where a more detailed discussion is presented [24-26].



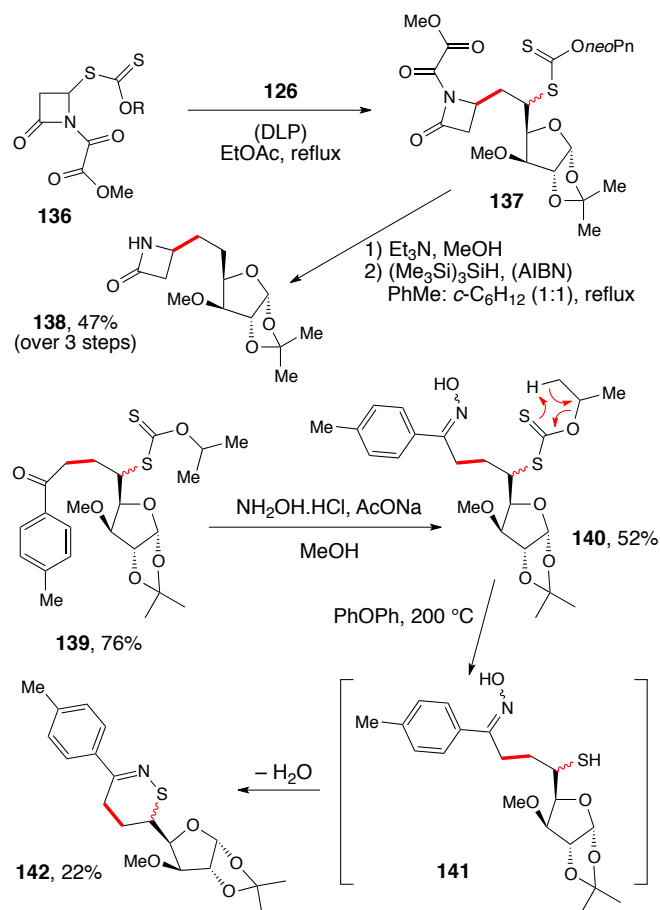
Scheme 13. The addition of a xanthate to an alkene, a simplified mechanism.

From the standpoint of carbohydrates, the radical addition-transfer of xanthates can be applied in many ways. For instance, the alkene partner could be part of the carbohydrate, as shown by the addition of a variety of xanthates to glucofuranose derived alkene **126** (Scheme 14). The new bonds formed are colored in red. In this manner numerous functional groups could be introduced, a phthalimido-protected methylamino unit as in **127** [27]; a phosphonylketone as in **128** [28]; a selectively protected ketoaldehyde as in **129** [29]; a dithiane mono-oxide as in **130** [30]; a difluoromethylsulfide as in **131** [31]; chlorodifluoromethyl motif as in **132a**, from which the xanthate can be reduced off using $(\text{Me}_3\text{Si})_3\text{SiH}$ and the chlorine eliminated from **132b** by treatment with DBU to give finally difluorovinyl derivative **133** [32]; a sulfoxide ester **134**, which can be directly thermolyzed in refluxing toluene to give unsaturated methyl ester **135** [33]. In this Scheme, and in the rest of this article, the diastereoisomeric ratio is approximately 1:1, unless indicated otherwise.



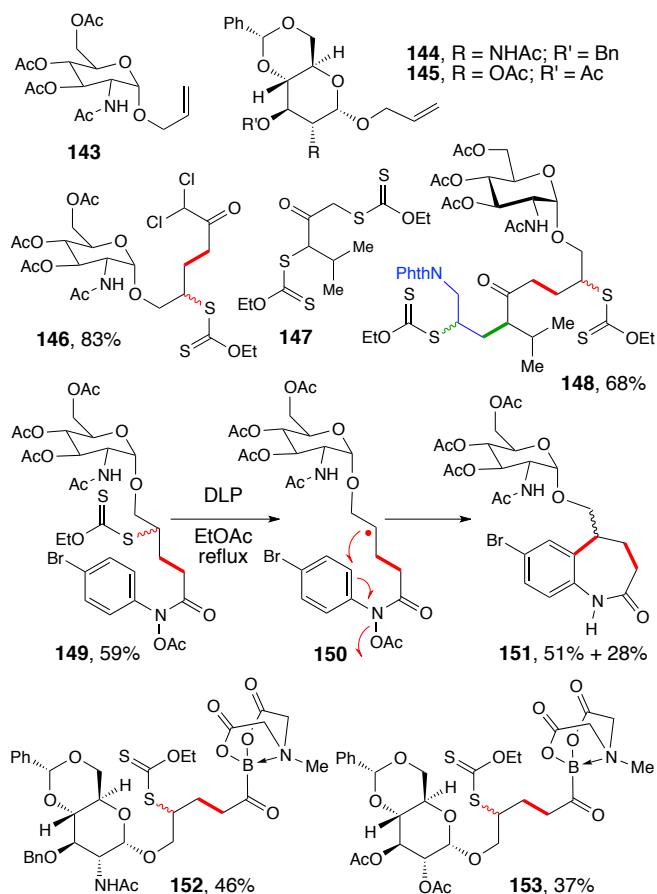
Scheme 14. Additions of xanthates to alkene **126**.

Two additional examples are presented in Scheme 15. In the first, addition of β -lactam xanthate **136** to alkene **126** gives adduct **137**, from which the oxalyl group can be removed and the xanthate reduced off with tris(trimethylsilyl)silane to furnish unusual β -lactam **138** without harm to the fragile β -lactam moiety [34]. In the second, adduct **139** obtained by addition of a *p*-methylphenacyl xanthate to the same olefin **126**, is converted into the corresponding oxime **140** which was then heated in diphenyl ether at 200 °C. Under these conditions, the *O*-isopropyl xanthate undergoes the classical Chugaev elimination to give thiol **141**, which spontaneously cyclizes onto the oxime to give dihydrothiazine **142** in modest yield [35]. Dihydrothiazines constituted a virtually unknown class of heterocycles before this route was uncovered.



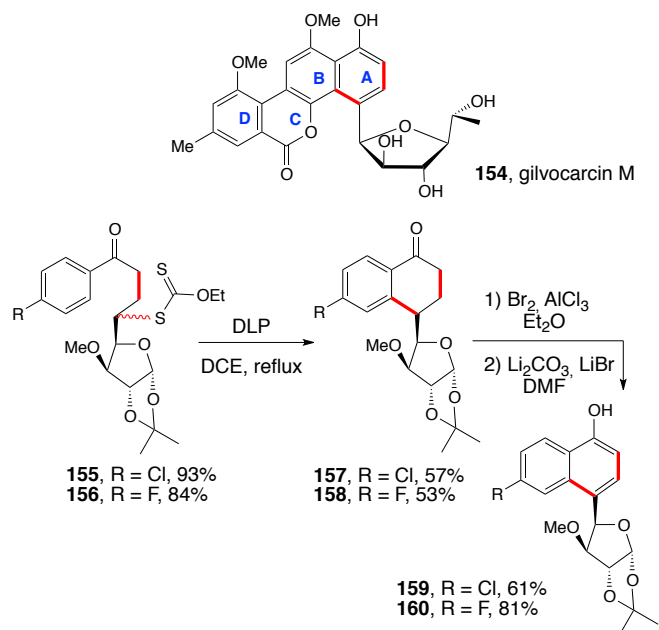
Scheme 15. Carbohydrate β -lactam and dihydrothiazine.

Additions to carbohydrate alkenes **143-145** are shown in Scheme 16. Compound **146** arises from addition of *S*-dichloroacetyl xanthate to allyl 2-acetamido-2-deoxy- α -D-glucopyranoside **143** [36]. Adduct **148** is more complicated as it results from two radical additions starting with dixanthate **147** [37]. This reagent was first made to react with *N*-allylphthalimide from the more substituted side (green bonds) and then with allyl *N*-acetylglucosamine **143** from the other side of the ketone (red bonds). The regioselectivity in the radical additions is controlled by the relative stabilities (secondary vs primary) of the carbon radicals on either side of the ketone. In the case of adduct **149** to the same alkene **143**, further treatment with DLP regenerates the intermediate radical **150**, which now is forced to attack the aromatic ring with concomitant rupture of the weak N—O bond. The result is the formation of the unusual benzazepinone **151**, as a separable mixture of two epimers in high combined yield [38]. Finally, examples **152** and **153** correspond to the addition of an acetyl(MIDA) radical generated from the corresponding xanthate to alkenes **144** and **145** (MIDA = *N*-methyliminodiacetyl) [39].



Scheme 16. Further examples of xanthate additions.

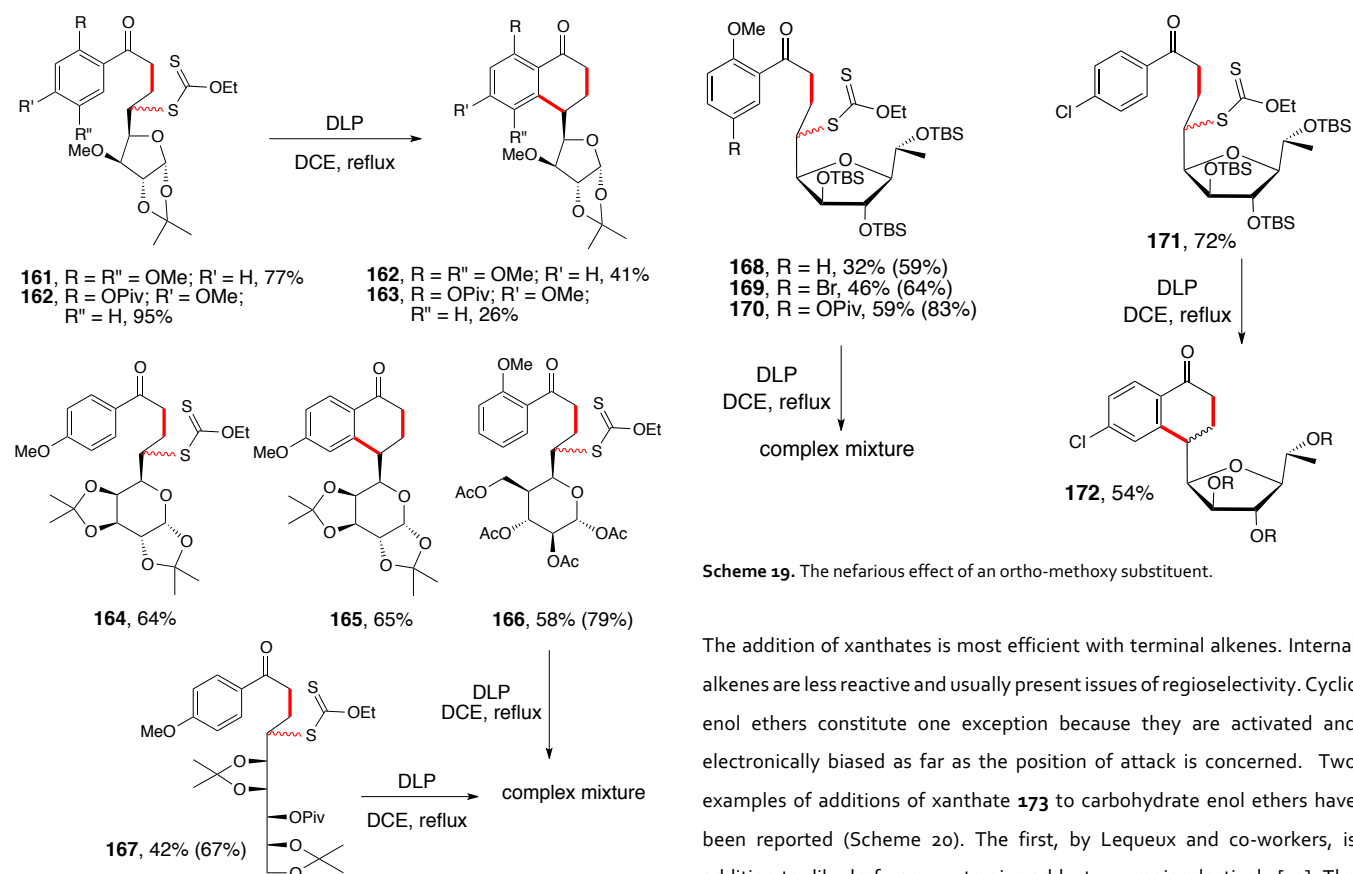
The ability of accomplishing a ring closure onto an aromatic ring under conditions that preserve the integrity of the carbohydrate moiety, as illustrated by the conversion of xanthate **149** into benzazepinone **151**, provides a basis for a strategy to synthesize certain natural compounds such as gilvocarcin M **154** (Scheme 17). In a model study, adducts **155** and **156** of *p*-Cl- and *p*-F-phenacyl xanthates to alkene **126** were cyclized into the corresponding tetralones **157** and **158** and then converted into naphthols **159** and **160** by a classical sequence of bromination and base induced elimination [40].



Scheme 17. Model studies for the total synthesis of gilvocarcin M.

Further model studies were unfortunately not as promising due to the need to place a methoxy group corresponding to the one present in ring B of Gilvocarcin M **154**. As shown in Scheme 18, a number of substituted phenacyl adducts to alkene **126** and other carbohydrate alkenes were prepared and their cyclization into the respective tetralones examined [40]. Whereas the dimethoxy and methoxy-pivaloxy derivatives **161** and **162** did indeed cyclize into tetralones **162** and **163**, the yields were a little disappointing, especially in the case of the latter. The nefarious influence of an *ortho*-methoxy substituent was also evident in the case of adducts **164** and **166**. The former cyclized normally to give tetralone **165**, whereas the latter resulted in a complex mixture under the same conditions. A complex mixture was also produced with compound **167** with an open chain carbohydrate appendage.

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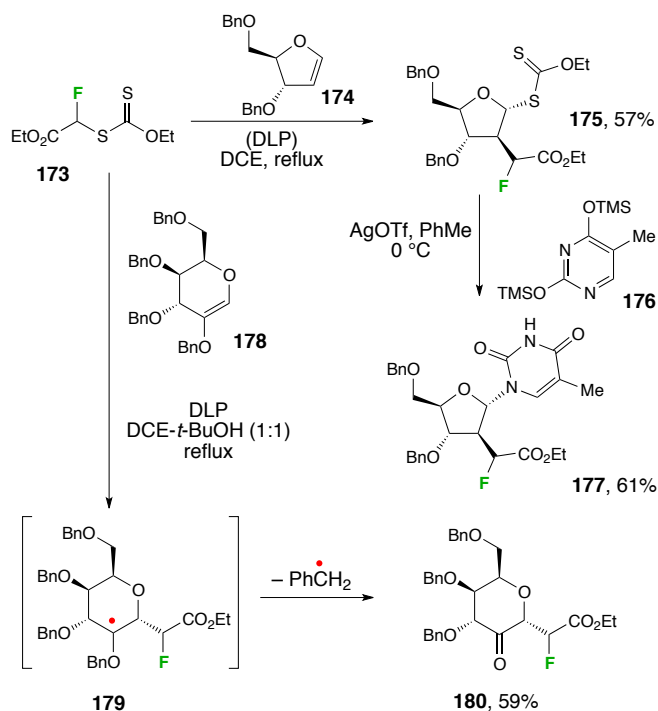


Scheme 18. Further model studies for the total synthesis of gilvocarcin M.

These observations were again confirmed with adducts **168-171** possessing the carbohydrate attachment actually present in gilvocarcin M **154** (Scheme 19) [41]. The first three, **168-170**, containing an *ortho*-methoxy substituent failed to furnish the desired cyclized products, in contrast to the *para*-chloro xanthate **171**, which afforded the expected tetralone **172**. While these preliminary results did not bode well for this approach to gilvocarcin M **154**, we later found in another context that an *ortho*-hydroxy substituent in fact favors the cyclization to a tetralone [42]. The hydrogen bonding between the hydroxy group to the ketone oxygen freezes the conformation of the side chain in a manner propitious for ring closure. At the same time, the hydrogen bonding lowers the rate of abstraction of the phenolic hydrogen, thus limiting unwanted side-reactions. There is therefore a path to salvage this synthetic strategy to gilvocarcin M **154**, for example by replacing the methoxy group in **170** with a free OH, but we have not yet had the opportunity to implement it.

Scheme 19. The nefarious effect of an *ortho*-methoxy substituent.

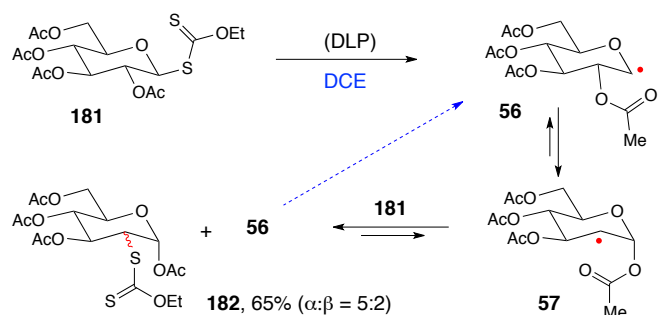
The addition of xanthates is most efficient with terminal alkenes. Internal alkenes are less reactive and usually present issues of regioselectivity. Cyclic enol ethers constitute one exception because they are activated and electronically biased as far as the position of attack is concerned. Two examples of additions of xanthate **173** to carbohydrate enol ethers have been reported (Scheme 20). The first, by Lequeux and co-workers, is addition to dihydrofuran **174** to give adduct **175** regioselectively [43]. The xanthate at the anomeric position was then used to introduce a thymine by a variation on the Vorbrüggen's method to provide nucleoside **177**. The second is from the group of Leclerc and Pannecoucke, who used enol ether **178** as the olefinic partner [44]. Intermediate adduct radical **179** extrudes a stabilized benzylic radical to give ketone **180**. Another, non-mutually exclusive possibility to form ketone **180** is via oxidation of electron-rich radical **179** into the corresponding cation by electron transfer to the DLP, which in both cases has to be used in stoichiometric amounts, followed by reaction with water (or lauric acid followed by hydrolysis upon workup).



Scheme 20. Additions to cyclic enol ethers.

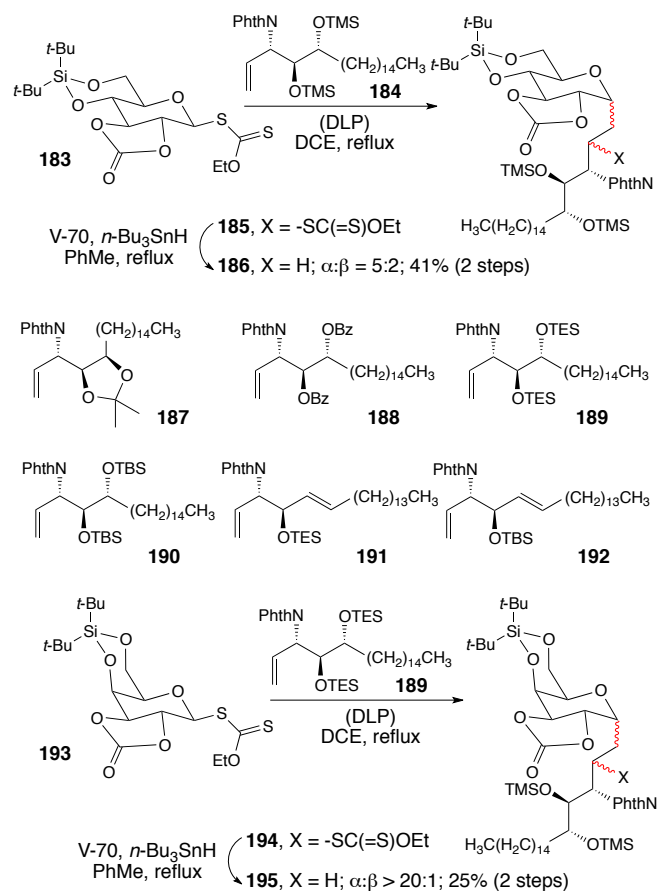
In the preceding examples, the alkene is part of the carbohydrate partner. It is of course also possible to have the xanthate moiety attached to the carbohydrate and use it to create new carbon-carbon bonds. The most interesting is to have the xanthate at the anomeric position, as this would lead to a somewhat stabilized radical that is more stable than the adduct radical resulting from the addition to a monosubstituted terminal alkene. As stated in connection with the general mechanistic discussion of the xanthate addition outlined in Scheme 13, the initial radical R^\bullet must be more stable than adduct radical **123**, neglecting possible polar effects.

The one complication arises from the presence of an ester at C-2 which undergoes a 1,2 shift, as previously shown in Scheme 7. In cyclohexane as the solvent, a clean hydrogen atom transfer is observed resulting in the efficient production of 2-deoxy-sugars (Scheme 8). However, as found in the group of Usui and Hirai [45], when dichloroethane (DCE) is the solvent, the hydrogen atom transfer is slower because of polarity mismatch and exposure of the ethyl analogue **181** of xanthate **55** now furnishes isomeric xanthate **182** (Scheme 21). Thus, treatment of xanthate **181** with DLP in DCE generates the same radicals **56** and **57**, with the equilibrium favoring the latter. Reversible transfer of the xanthate group then furnishes the observed product **182**.



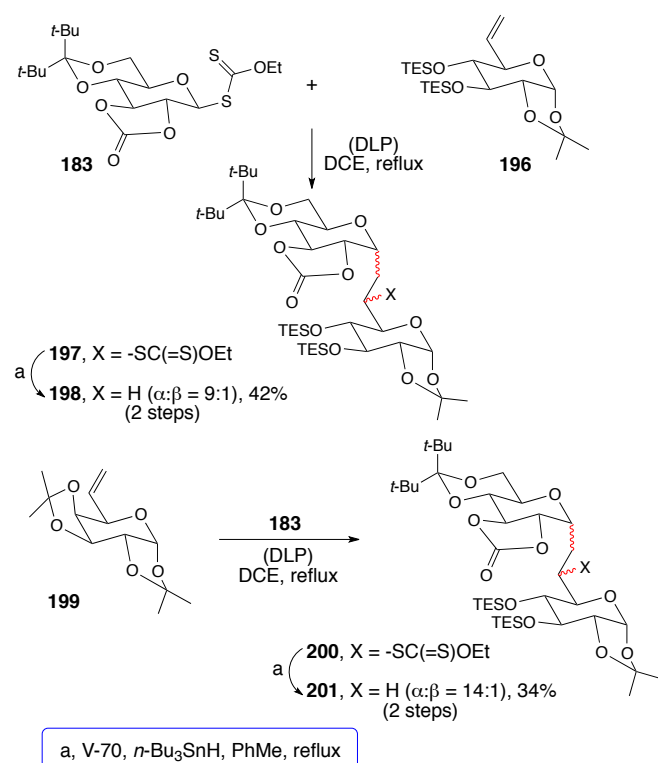
Scheme 21. Synthesis of 2-xanthyl sugars.

To circumvent this unwanted radical isomerization, the acetate was replaced with a cyclic carbonate, as in **183**, which cannot undergo the formal 1,2-shift from the C-2 to the anomeric position (Scheme 22). In this case, normal radical additions could be performed to access α -glucoceramide **186** by reaction with alkene **184** followed by reductive removal of the xanthate group from the intermediate adduct **185** [46]. The same two-step sequence was applied to alkenes **187-192**, providing the corresponding protected α -glucoceramides in comparable yield. α -Galactoceramides can be prepared by starting with xanthate **193**, as illustrated by its addition to alkene **189** to give compound **195** after dexanthylation of intermediate **194**. The $\alpha:\beta$ ratio is significantly better in this case, as it is $>20:1$. These derivatives are C-analogues of the natural O-glycosylceramides, such as the agelasphins [46].



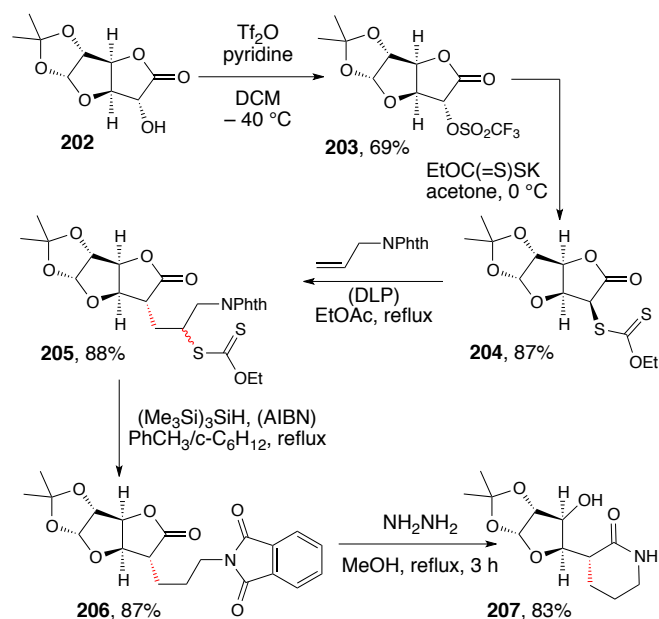
Scheme 22. Synthesis of α -gluco- and α -galacto-ceramide, C-analogues of natural O-glycosylceramides.

By using carbohydrate alkenes, the same group constructed a number of CH₂-linked disaccharides [45]. Two examples are displayed in Scheme 23 involving glucose derived xanthate **183**. Its addition to glucose and galactose derived alkenes **196** and **199** gives rise to CH₂-linked disaccharides **198** and **201** after removal of the xanthate group from intermediate adducts **197** and **200** respectively. In both cases, the selectivity for the α -isomer is high.



Scheme 23. Synthesis of CH₂-linked disaccharides.

The xanthate group can also be positioned elsewhere on the carbohydrate framework, so long as the derived radical is more stable than the adduct radical generated in the addition to the alkene. This is most conveniently accomplished by placing a carbonyl group on the adjacent carbon. The resulting radical is thus stabilized and, at the same time, acquires a certain electrophilic character that is complementary to the mild nucleophilic nature of the unactivated alkene. This polarity matching is often reflected in a faster reaction rate and a higher chemical yield. One example is pictured in Scheme 24 involving xanthate **204**, obtained from glucuronic lactone **202** by substitution of its triflate **203** with potassium *O*-ethyl xanthate [47]. Its addition to *N*-allylphthalimide gives a high yield of adduct **205**, with the new C–C bond being formed exclusively from the less hindered α -face. Reductive removal of the xanthate furnishes lactone **206** and deprotection of the amine induces spontaneous ring closure into lactam **207**.

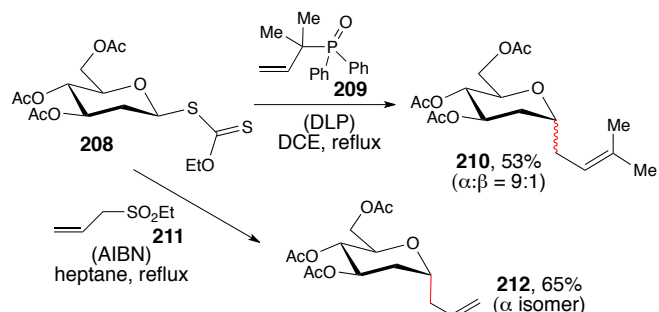


Scheme 24. Synthesis of a lactam from a glucuronic lactone.

Allylations and vinylations of carbohydrates

A special case of carbon–carbon bond formation concerns allylations and vinylations using alkene partners possessing a “leaving group” that can be cleaved by homolysis. One example is the prenylation of 2-deoxyglucose xanthate **208** using dimethylallyl phosphine oxide **209** to give mostly α -dimethylallyl deoxyglucose derivative **210** (Scheme 25) [48]. The addition–fragmentation of the intermediate anomeric radical liberates a diphenylphosphinoyl radical [Ph₂P•(=O)] which propagates the chain process. The chain propagation is, however, not very efficient and a substantial proportion of DLP has to be used.

Sulfonyl radicals are better “leaving groups”. By placing an ethylsulfonyl group on the allyl motif, the departing ethylsulfonyl radical undergoes an α -scission to produce sulfur dioxide and a reactive ethyl radical that easily propagates the chain (EtSO₂• → SO₂ + Et•) [49]. Thus, reaction of the same 2-deoxyglucose xanthate **208** with allyl ethylsulfone **211** furnishes allyl derivative **212** (Scheme 25) [49].

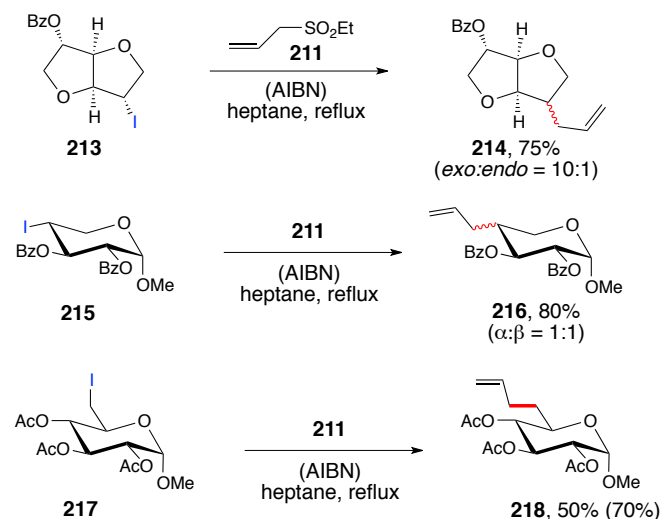


Scheme 25. Allylations with dimethylallyl diphenylphosphine oxide and allyl ethylsulfone.

This transformation is not limited to xanthates. As mentioned above, iodides also exchange readily with carbon radicals (Scheme 9), and the primary ethyl radicals generated by α -scission of ethylsulfonyl radicals

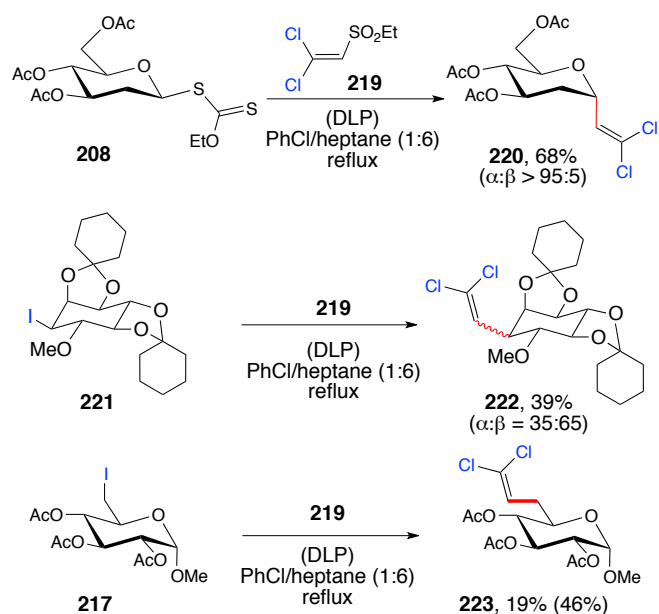
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rapidly attack a sugar iodide to produce the more stable secondary radical in the case of iodides **213** and **215** (Scheme 26). Addition–fragmentation on allyl ethylsulfone **211** affords allylated products **214** and **216**, respectively [50]. The exchange of iodine atoms with primary 6-iodoglucose triacetate **217** is essentially thermoneutral and not as efficient. Allylation leading to compound **218** is, not unexpectedly, somewhat sluggish.



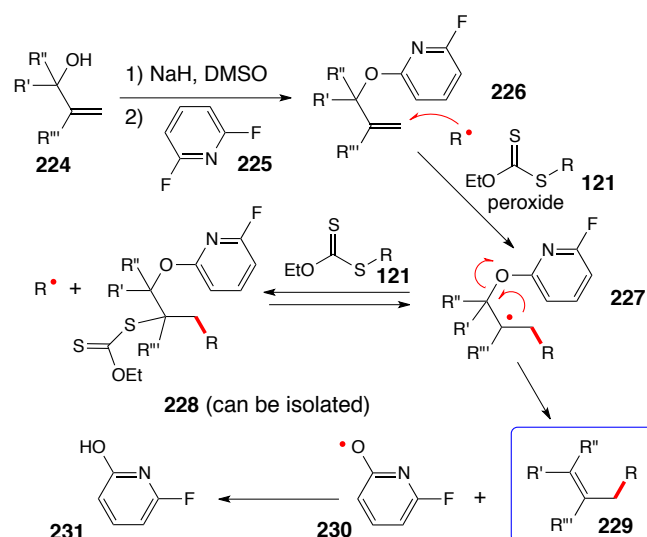
Scheme 26. Allylations of carbohydrate iodides with allyl ethylsulfone.

Vinylation of xanthates and iodides is also possible using suitable vinylsulfones such as **219** (Scheme 27). Because of steric shielding by the two chlorines, the attack of the carbon radical takes place on the carbon bearing the sulfone group and is followed by β -scission of the ethylsulfonyl radical. In this manner, dichlorovinyl derivatives **220**, **222**, and **223** were prepared, with the last, derived from primary iodide **217**, being obtained in poor yield for the same reason as for **218** [51]. Note also that compounds **221** and **222** are cyclitols and not strictly carbohydrates. The dichlorovinyl moiety is a particularly useful appendage. It can be converted into an alkyne by the powerful Corey-Fuchs reaction [52] and both chlorines can be used to generate new C–C bonds by transition metal catalyzed couplings [53].



Scheme 27. Vinylation of carbohydrate xanthates and iodides.

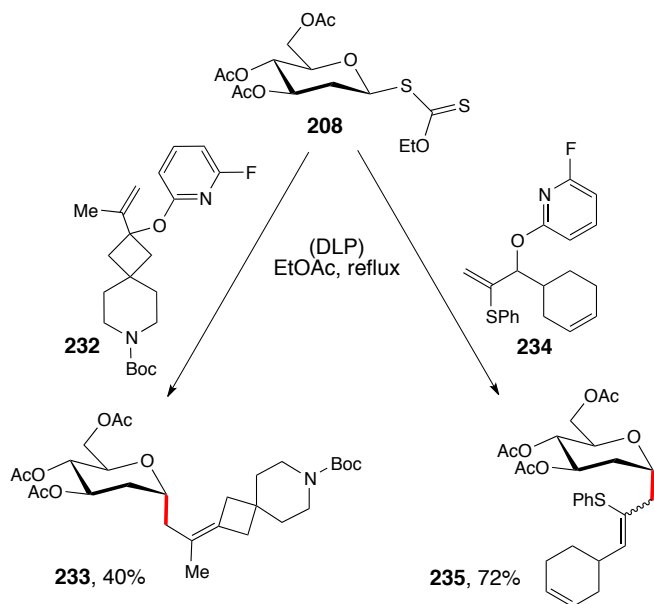
A much more powerful allylation system was uncovered when it was found that fluoropyridyloxy derivatives **226** of allylic alcohols can undergo a radical addition–fragmentation process when associated with the relatively long lifetime of radicals generated through the degenerative exchange of xanthates (Scheme 28) [54, 55]. As stated in the introduction, one of the main advantages of radical processes is the general absence of β -scission of C–O bonds. Nevertheless, the ability to accomplish such a fragmentation opens up numerous synthetic opportunities, a few of which will be presented in the following schemes.



Scheme 28. Allylic alcohols as allylating agents.

Thus, radical **R•** derived from xanthate **121** adds to the alkene in **226**. The resulting adduct **227** exchanges rapidly a xanthate by reacting with the starting xanthate **121** to give compound **228**, which can be isolated in certain instances [54]. However, this exchange is reversible and radical **227** is continuously regenerated and ultimately undergoes the desired, albeit relatively slow, fragmentation to give alkene **229** and fluoropyridoxyl

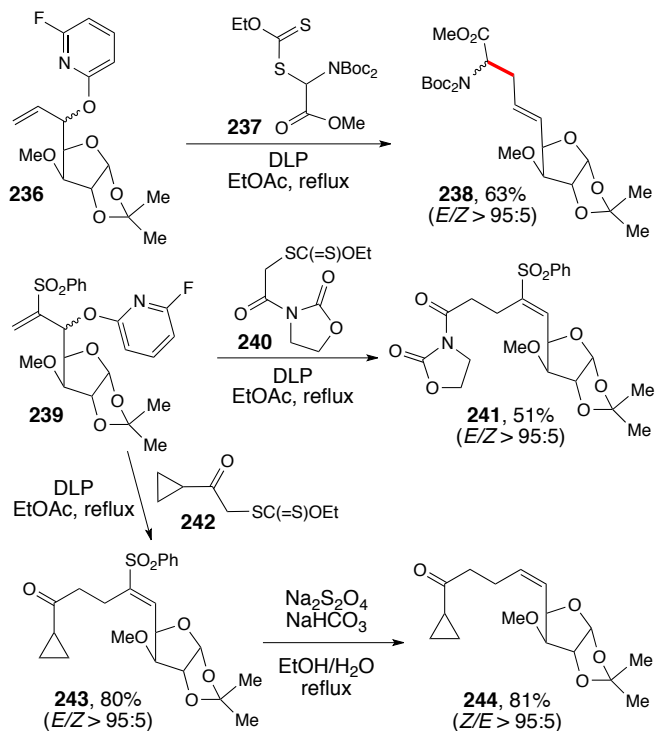
radical **230**. The latter evolves finally into fluoropyridinol **231** by a mechanism that will not be discussed here [55]. Stoichiometric amounts of DLP are required since this transformation is not a chain process. The synthetic power of this method derives from the broad availability of the starting allylic alcohols **224**, the numerous functional xanthates **121** that can be used, and the modularity and functional group compatibility of this chemistry. Since the allylic alcohols **224** are most often prepared by addition of a vinylmetal reagent to aldehydes or ketones ($R'R''C=O$), the overall transformation can be viewed as the formal equivalent of the classical Wittig olefination with a few advantages, namely a greater tolerance for base-sensitive groups and a much easier access to tetrasubstituted alkenes. Indeed, both the addition and fragmentation steps are favored when R' , R'' , and $R''' \neq H$. These advantages will become obvious upon inspection of the examples in the following schemes. Thus, reaction of anomeric xanthate **208** with activated allylic alcohol **232** produces tetrasubstituted alkene **233** (Scheme 29) [56]. The moderate yield reflects the strain of the cylobutylidene structure and the consequent slower fragmentation step. Nevertheless, access to such a compound by a Wittig olefination would be particularly hard. Reaction with vinylsulfide **234** affords the corresponding C-glycoside **235** [57]. In both cases, the α -isomer is practically the exclusive product.



Scheme 29. Examples of allylation of 2-deoxyglucose derived xanthate.

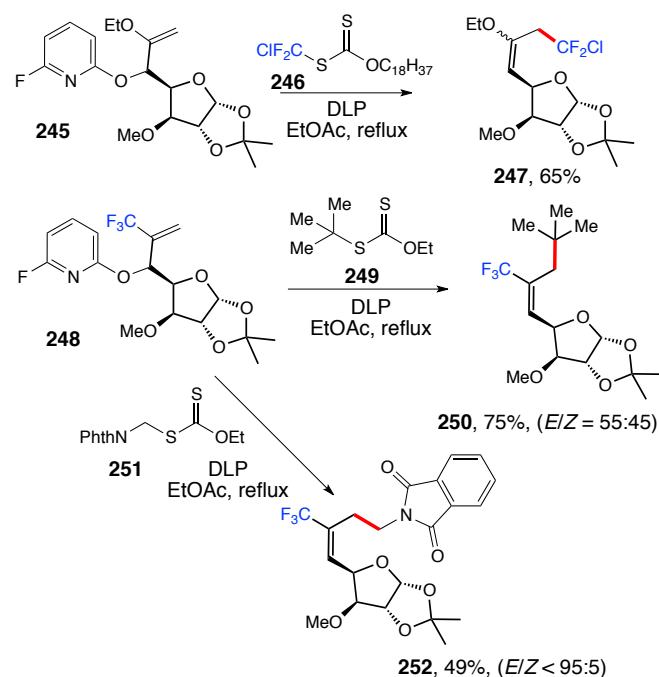
The activated allylic partner can be part of the carbohydrate, as illustrated by the transformations starting with glucofuranose derived compounds **236** and **239** in Scheme 30. Reaction of the former with xanthate **237** leads to protected aminoacid **238** with a high degree of selectivity for the E geometrical isomer [54]. A similar strong preference for the E isomer was observed on reaction of the latter with xanthates **240** and **242** to give vinyl sulfones **241** and **243**, respectively [58]. The advantage of placing the sulfone group, apart from providing an electrophilic alkene capable of participating in various conjugate additions with nucleophilic reagents, is the possibility of reductively removing it with retention of configuration

using sodium dithionite (the Julia desulfonation). This is exemplified by the conversion of vinylsulfone **243** into Z -alkene **244** [58]. Thus, both E and Z alkenes are accessible through this chemistry.



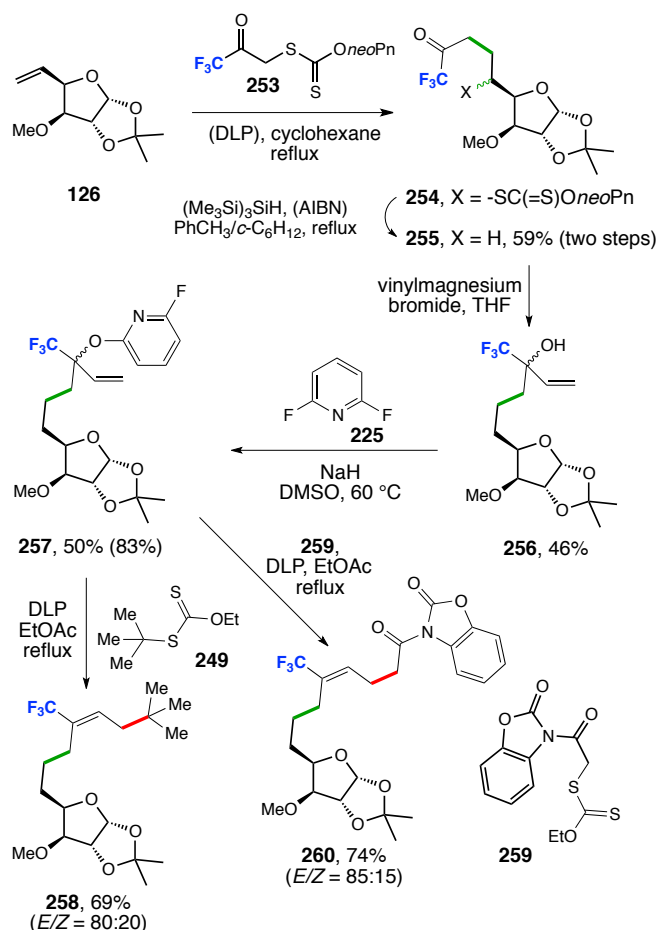
Scheme 30. Synthesis of E and Z carbohydrate alkenes.

The examples in Scheme 31 illustrate the synthesis of fluorinated alkenes. The first transformation involves the reaction of xanthate **246** with enol ether **245** to give chlorodifluoromethyl enol ether **247** [32]. Xanthate **246** is the same one employed to prepare compound **132a** in Scheme 14. The long octadecyl appendage replacing the ubiquitous ethyl is to avoid having to handle a volatile and possibly obnoxious reagent. In principle, the chlorine could similarly be eliminated with base to furnish a difluorodiene and the enol ether moiety could be hydrolyzed into the corresponding ketone. Alternatively, the fluorinated group can be placed on the alkene partner, as shown by the reaction of compound **248** with xanthates **249** and **251** to give trifluoromethylalkenes **250** and **252** possessing a t -butyl group and a protected primary amine, respectively [59]. Note that in these two products, the trifluoromethyl group is *proximal* to the newly formed C–C bond colored in red.



Scheme 31. Synthesis of chlorodifluoro- and trifluoro-methyl alkenes.

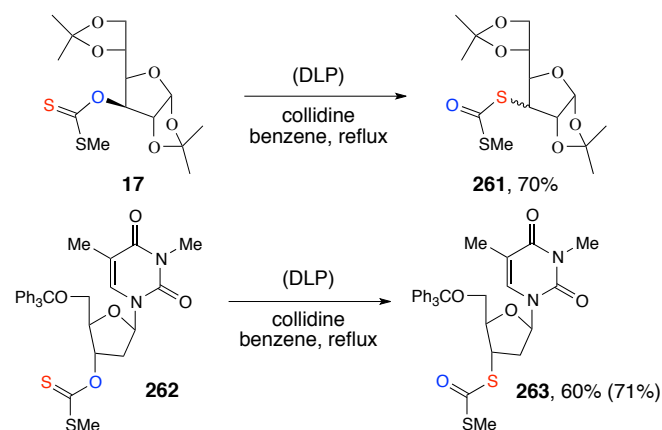
The sequence in Scheme 32 underscores the enabling power of this radical chemistry of xanthates for the modular creation of C–C bonds. The addition of xanthate **253** to alkene **126** and reductive removal of the xanthate from adduct **254** affords trifluoromethylketone **255** [59]. Addition of vinylmagnesium bromide and activation of the resulting allylic alcohol **256** by reaction with 2,6-difluoropyridine **225** gives alkene **257**. This key intermediate then reacts with xanthates **249** and **259** to furnish trifluoromethyl alkenes **258** and **260**, respectively, where two new bonds, colored in green and red, have been created by intermolecular radical additions [59]. Note that the bonds in red in the final products are now *distal* to the trifluoromethyl group.



Scheme 32. Further examples of trifluoromethyl alkenes.

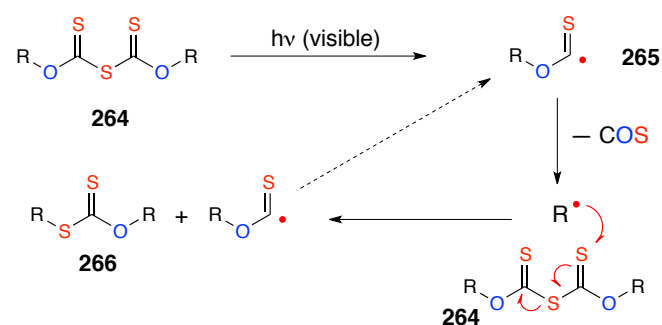
Concluding remarks

The foregoing examples give a glimpse of the synthetic possibilities in the carbohydrate field enabled by radical chemistry developed in our research group. Much more can still be done. For instance, in the mechanistic manifold in Scheme 3, a rationale is provided for the use of DLP and 2-propanol to replace the stannane in the Barton-McCombie deoxygenation. Implicit in this explanation is that the rate of hydrogen abstraction from the 2-propanol solvent to give alkane **16** is greater than rupture of the C–O bond in intermediate **14** to give dithiocarbonate **15**. However, by switching from 2-propanol to benzene (or another solvent with strong C–H bonds) and operating under concentrated conditions, then it becomes possible to favor the formation of dithiocarbonate **15**, where a C–O bond has been replaced by a C–S bond through a radical chain process. The feasibility of this variant is exemplified by the two examples in Scheme 33 [12]. Thus, xanthate **17**, which in 2-propanol is cleanly deoxygenated into compound **18** (Scheme 4), is now isomerized into dithiocarbonate **261** when benzene is employed as the solvent. Similarly, nucleoside xanthate **262** is converted into dithiocarbonate **263**. In this case, only the α -epimer is formed because the upper β -face is completely shielded sterically.



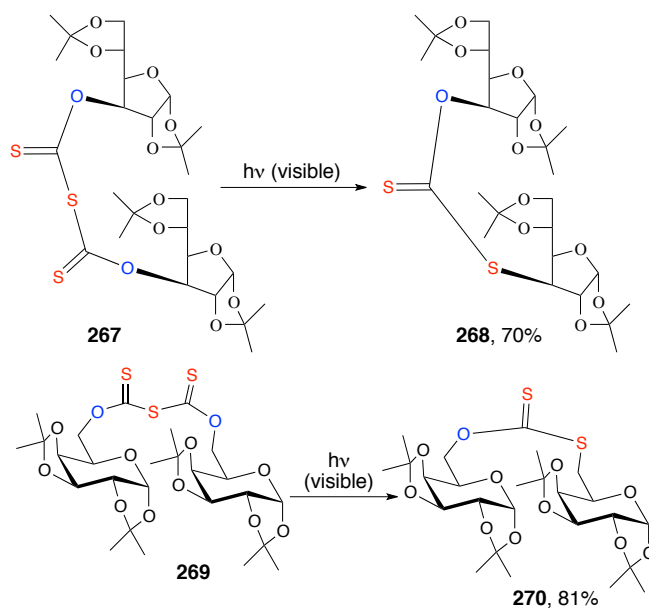
Scheme 33. O- to S-Rearrangement of xanthates.

Another method for exchanging C–O with C–S bonds exploits a little-known reaction of xanthic anhydrides we uncovered some time ago and outlined in Scheme 34 [60]. Xanthic anhydrides **264** are yellow substances that absorb visible light and are transformed into xanthates **266** by extrusion of a molecule of carbon oxysulfide from the intermediate alkoxy carbonyl radicals **265**. The reaction is most simply accomplished by irradiating a refluxing toluene solution of the xanthic anhydride with a tungsten filament lamp until discharge of the yellow color (5–60 minutes). On small scale, the heat from the lamp is usually sufficient to bring the solution to the boiling point. The visible light thus acts simply as the initiator.



Scheme 34. Visible light induced transformation of xanthic anhydrides.

Two examples are displayed in Scheme 35 [60]. Glucose and galactose derived xanthic anhydrides **267** and **269** are converted in good yield into xanthates **268** and **270**, respectively. These compounds were previously prepared in modest yield by UV irradiation of the corresponding bis-xanthates in a non-chain process [61]. The main drawback of this transformation is that only half the C–O bonds in the starting carbohydrate are exchanged with C–S bonds; however, this can be compensated by a significant gain in stereoselectivity due to steric bulk of the sugar substituents on either side of the xanthic anhydride. For instance, xanthate **261** in Scheme 33 is obtained as an approximately 1:1 mixture of epimers whereas xanthate **268** in Scheme 35 is formed as solely the β -isomer. In any case, both approaches are useful for the synthesis of mercapto-carbohydrates that cannot be easily obtained by more classical ionic methods.



Scheme 35. Examples of visible light induced transformation of xanthic anhydrides.

It is also worth emphasizing the potential applications of the addition of xanthates to allyl glycosides in various biological contexts. This addition allows the attachment of a variety of functional groups to the carbohydrate moiety as well as a xanthate group. The latter can then be cleaved to furnish the corresponding thiol. Indeed, the radical thiol-ene additions to allyl glycosides have been used extensively for the introduction of spacer functions for subsequent conjugation to proteins [62].

In summary, it is hoped that the transformations described in this brief overview will encourage further applications of these radical processes that are inexpensive, metal-free, ecologically benign, scalable, and tolerant of most functional groups. In particular, no organotin reagents are involved. As stated above in the section on reduction, removal of tin residues to reach levels sufficiently low to be acceptable to the pharmaceutical industry is an almost impossible task, especially when operating on a large scale [63].

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Biographical sketches :



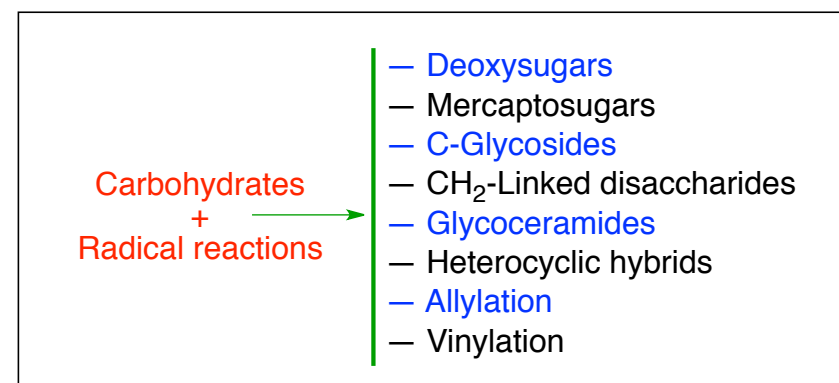
Dr Béatrice Sire (née Quiclet) obtained her MSc in biochemistry in 1976 from Université Paris-Sud, Orsay, France. She then completed her PhD thesis in 1980 at the same university under the supervision of Dr Stéphane Géro, working on the synthesis of pseudo-disaccharides related to the aminoglycoside antibiotics. In 1981, she obtained a position as a Chargée de Recherches at the CNRS within the research group of Dr Stéphane Géro at the Institut de Chimie des Substances Naturelles (ICSN) in Gif-sur-Yvette. Where she also collaborated with Professor Sir Derek Barton. In 1993, she joined the group of Professor Samir Z. Zard, first at the ICSN, then at Ecole Polytechnique.



Dr Samir Z. Zard was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, Orsay, France, where he received his doctorate under the supervision of Professor Sir Derek Barton in 1983. His main research concerns the study and development of new reactions and processes, with a special interest in radicals, organosulfur derivatives, alkynes, and nitro compounds. In addition to a number of academic awards, he received in 2007 the Croix de Chevalier de la Légion d'Honneur.

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Radical chemistry developed in the authors laboratory involving xanthates and iodides allows numerous metal-free transformations of carbohydrates.