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Syntheses of 1,2-annulated and 1-spiroannulated carbohydrate derivatives: Recent developments

Shahid I. Awan, Daniel B. Werz *

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstr. 2, 37077 Göttingen, Germany

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ABSTRACT

A variety of different strategies has been used for the 1,2-annulation and the 1-spiroannulation of further rings to monosaccharides. This short review presents some recent methods to access such structures involving radical chemistry, cycloadditions, Michael reactions and metal-catalyzed transformations.

1. Introduction

Carbohydrates are of crucial importance for a plethora of molecular recognition events.[1] With the high density of functional groups[2] they play an important role in signalling, as an attachment point for bacteria, viruses and antibodies.[3] Processes such as inflammation and cancer metastasis are also modulated by this class of biomolecules.[4] Synthetic carbohydrates and carbohydrate mimetics[5] are often applied to investigate these processes. Therefore, numerous efforts have been made to access natural highly complex carbohydrates in a reliable and effective manner.[6] Whereas protecting group strategies and glycosylation methods dominate the field of oligosaccharide synthesis, a variety of different reactions has been employed for the preparation of carbohydrate mimetics. In contrast to oligosaccharides which are prone to enzymatic degradation in the organism, carbohydrate mimetics have raised considerable interest because of their stability and the resulting possibilities as glycosidase inhibitors.[7] The most common modifications with respect to the linkage between two monosaccharide units are S-glycosides,[8] N-glycosides[9] and C-glycosides.[10] This nomenclature means that the anomeric oxygen of a glycosidic linkage is replaced by a sulfur, a nitrogen or a carbon atom (with further residues if needed), respectively. However, also the ring system itself can be modified leading to carba-, thia- and iminosugars. Especially, the latter have developed as useful tools for the investigation of glycosidases.[11] Another class of carbohydrate mimetics consists of annulated and spiroannulated ring systems to the original sugar core. By using this kind of modification one tries to mimic the transition state geometry of glycosidases or glycosyltransferases. In this short review, we will limit ourselves mostly to results obtained in the last decade which deal with the 1,2-annulation and 1-spiroannulation. The 1,2-annulated and 1-spiroannulated core or substructures thereof found in many natural products show distinct, compelling biological activities.[12] Due to space constraints we will only review annulations with a ring size larger than 4,[13] we will not review the biological activity of these compounds even if their biological behaviour (mostly enzyme inhibition) has been elucidated and might be highly interesting.

2. [1,2]-Annulated carbohydrate derivatives

A [1,2]-annulation of a further ring to a carbohydrate moiety commonly requires some prerequisites to facilitate its attachment. Glycals such as **1** with its electron-rich double bond or modified glycals such as 2-nitroglycals **2**, 2-bromoglycals **3** or glycal epoxides **4** set the stage for radical processes, electrophilic additions, Michael additions, Pd-catalyzed reactions or nucleophilic attacks (Fig. 1).

2.1. Glycals as starting materials

The Linker group developed several radical reactions in which the electron-rich double bond of glycals is attacked by radicals.[14] Mainly 2-branched carbohydrate derivatives were obtained. However, using appropriate radical sources such as radicals derived from the ethyl ester of nitroacetic acid **6** an annulation to **7** and

* Corresponding author. Tel.: +49 551 393251; fax: +49 551 399476.
E-mail address: dwerz@gwdg.de (D.B. Werz).

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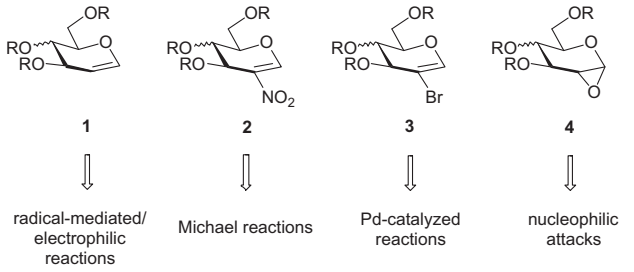


Figure 1. Different glycal derivatives **1**–**4** used for different type of reactions to annulate a further ring.

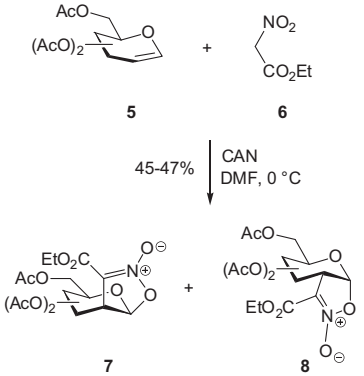
8 occurred.[15] The radicals are commonly formed by the action of base and cerium(IV) ammonium nitrate (CAN). In this case the intermediary anomeric radical was converted to the corresponding cation by further CAN oxidation. The bicyclic isoxazoline N-oxide is the result of an attack by the nitro group to the positively charged anomeric carbon (Scheme 1). These heterocyclic compounds can be further used to access glycosylated glycine derivatives. A variety of different peracetylated glycals such as glucal, galactal, xylal, arabinal, maltal and lactal were employed as starting materials. Recently, also malonic ester under the action of manganese(III) acetate served as starting material to yield carbohydrate-based butyrolactones.[16]

Thiem and co-workers treated glucals with *N*-iodosuccinimide (NIS). The corresponding 2-iodo-2-deoxy mannopyranosyl derivative **10** was formed in a stereoselective fashion (Scheme 2).[17] Dehalogenation by Bu_3SnH yielded compound **11**. After protecting group exchange the fully silylated compound was irradiated by UV light affording a bicyclic azepindione **12** and a tricyclic aminal **13**. The latter was further converted to sugar-alkaloid conjugates.

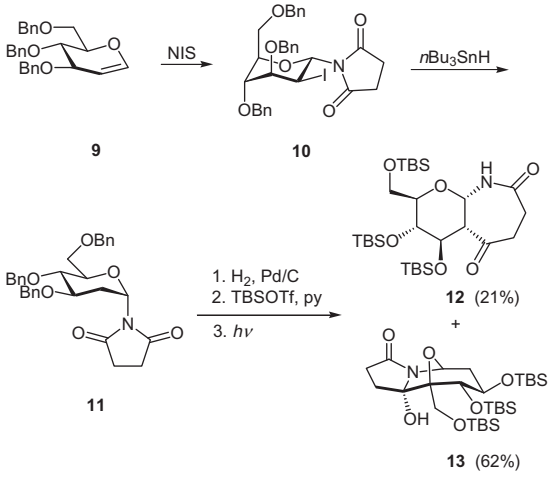
2.2. 2-Nitroglycals as starting materials

2-Nitroglycals can either be used as Michael acceptors or as highly reactive dienophile.[18] For the synthesis of sugar-derived oxazines Schmidt made use of the electron-accepting power of the nitro-substituted double bond.[19] With the lactic acid esters **15** and **16**, respectively, a Michael addition occurred to afford the glycosidated lactic acid ester derivatives **17** and **18** (Scheme 3). Standard procedures that converted the nitro moiety into an amine (reduction by Raney-Ni) paved the way for the final annulation of the oxazine moiety in **19** and **20**. *Galacto*-configurations allowed a better stereocontrol than the respective *gluco*-configured starting materials.

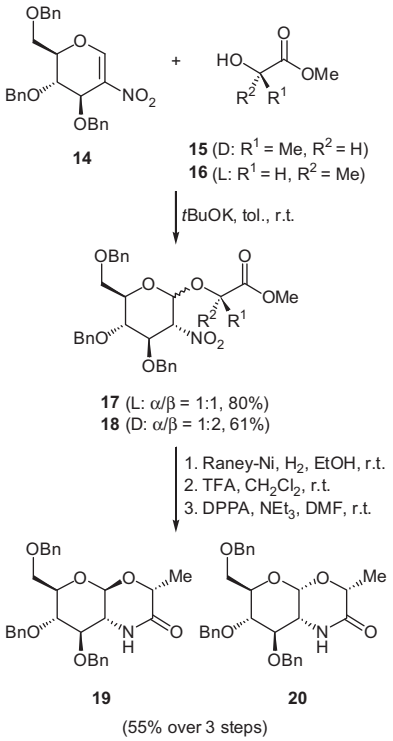
The Michael system of nitroglycals was also utilized to add other oxygen electrophiles to the pseudoanomeric position and to trap the developing negative charge at position 2 by



Scheme 1. Radical-mediated reaction to annulate isoxazoline N-oxides.[15]



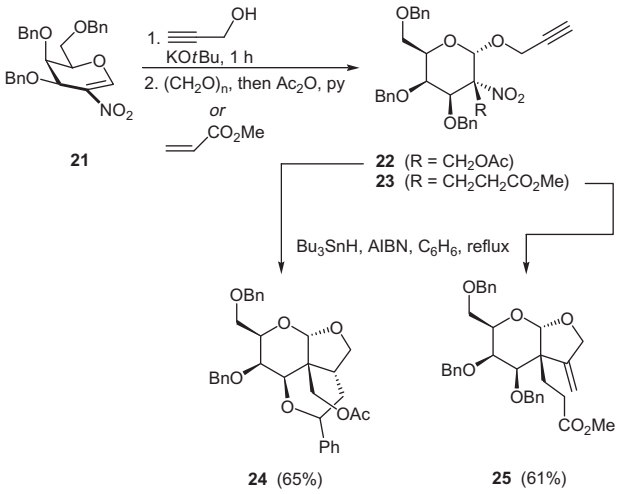
Scheme 2. NIS addition to glycals followed by dehalogenation and irradiation.[17]



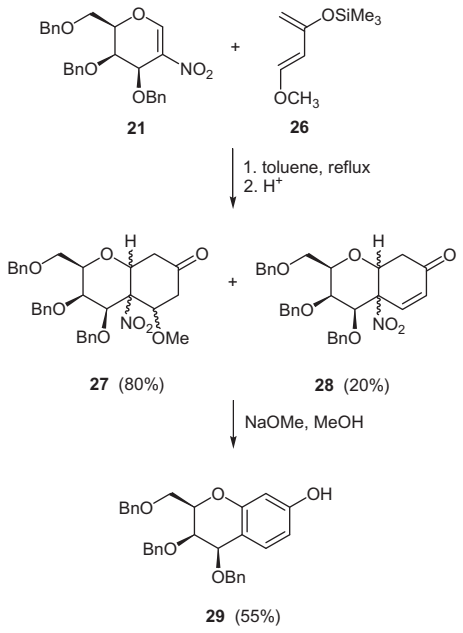
Scheme 3. Lactic acid ester as nucleophile in a Michael addition.[19]

electrophiles. Vankar and co-workers constructed in such a way 2-C-branched glycosides **22** and **23** (Scheme 4).[20] When treating these compounds with Bu_3SnH and AIBN, a tertiary radical was generated at C-2 which could trap the triple bond of the tethered propargyl group intramolecularly. Depending on the residue the emerging sp^2-centered radical could even react further with an adjacent benzyl group to afford a tricyclic system **24**.

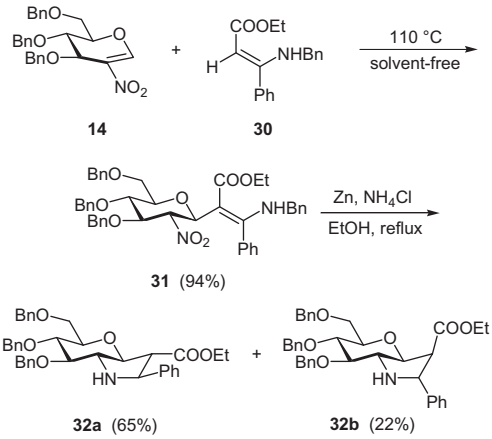
Schmidt and co-workers studied Diels–Alder reactions of 2-nitroglycals for the synthesis of benzopyran derivatives.[21] The perbenzylated derivative **21** was reacted with electron-rich Danishefsky's diene **26** to afford after appropriate acidic work-up the bicyclic intermediates **27** and **28** (Scheme 5). Upon treatment with sodium methoxide at 50 °C the latter two compounds were prone to elimination of HNO_2. As a result the benzannulated compound **29**, a chromane derivative, was formed.



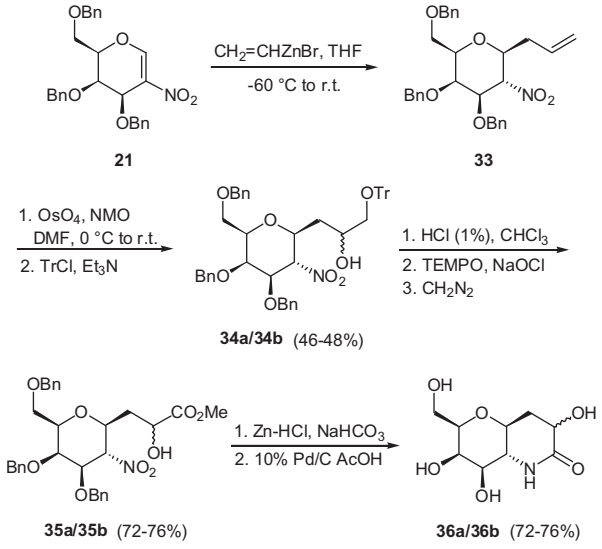
Scheme 4. Michael addition followed by radical-mediated ring-closure.[20]



Scheme 5. Chroman formation using 2-nitrogalactal **21**.[21]



Scheme 6. Synthesis of sugar-derived pyrrolidines **32** by Michael addition to 2-nitroglycals.[22]

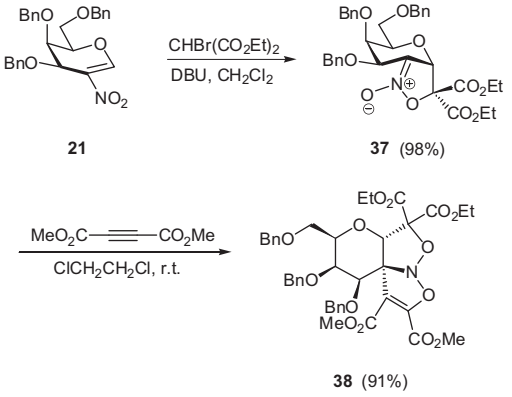


Scheme 7. Organometallic attack to the Michael system and lactam formation.[23]

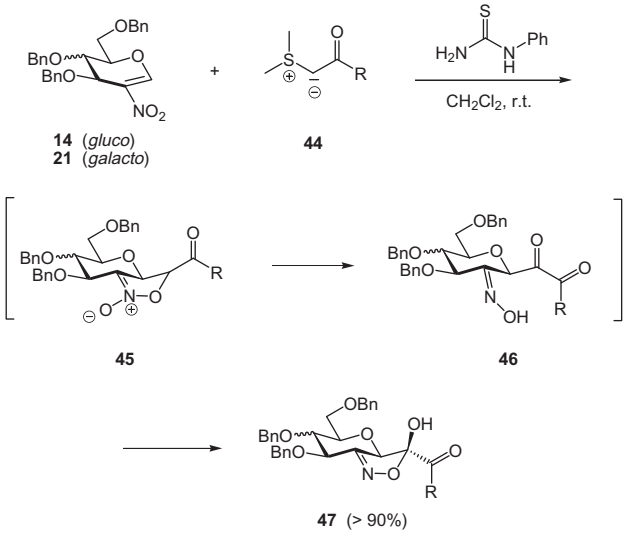
For Michael additions to 2-nitroglycals not only heteroatom-substituted nucleophiles, but also carbon nucleophiles can be used. For instance, Huang's research group developed a procedure that ensured a Michael-type addition of enamino esters such as **30** to 2-nitroglucal **14** (Scheme 6).[22] Interestingly, this reaction delivered corresponding C-glycosides even under solvent-free conditions. Novel carbohydrate-annulated pyrrolidines such as **32a/32b** were formed through a sequence of reactions induced by zinc and ammonium chloride in refluxing ethanol (reduction of the nitro group, followed by intramolecular cyclization along with the elimination of the amino group).

Also organometallic species such as zinc organyls or Grignard reagents were used as nucleophiles for the Michael addition to 2-nitrogalactals. As products *C*-allyl galactosides were formed. Vankar and co-workers used a sequence of different reactions to prepare annulated piperidinone derivatives **36a/36b**.[23] The approach includes a dihydroxylation with catalytic amounts of OsO_4 and *N*-methylmorpholin-N-oxide (NMO) resulting in an inseparable mixture of diastereoisomers (Scheme 7). However, they could be separated as their trityl derivatives **34a/34b** after protection of their primary hydroxyl group. Removal of the trityl group, oxidation with TEMPO and sodium hypochlorite afforded α-hydroxy acids which in turn were converted to the respective methyl esters **35a/35b** by the action of diazomethane. Zinc-mediated reduction of the nitro group was followed by cyclization to furnish the bicyclic lactams. Global deprotection by hydrogenolysis provided the fully hydroxylated lactams **36a/36b** (Scheme 7). Similar to the above-mentioned protocol *C*-vinyl galactosides were transformed in the respective pyrrolidine analogues. The free amino group was employed as a nucleophile; whereas the hydroxyl groups were converted to mesyl esters being excellent leaving groups.

Recently, Yu and co-workers investigated the formation of sugar-fused isoxazoline N-oxide **37** via a condensation of 2-nitrogalactal **21** with bromomalonate in the presence of DBU.[24] The sequence consists of the attack of a carbanion to the Michael system followed by a nucleophilic substitution of the bromide by the oxygen of the nitro group (Scheme 8). The resulting nitrone set the stage for further annulations. Different types of alkene and alkyne dipolarophiles were employed. The stereochemical



Scheme 8. Formation of carbohydrate-derived nitroso acetal **38**.[24]



Scheme 10. Isoxazoline formation starting with 2-nitroglycals.[26]

outcome (configuration at C-2) was highly dependent on the type of dipolarophile. Olefins led to the reversed facial selectivity in comparison to acetylenes. As a result nitroso acetals with three fused rings such as **38** were obtained in good yields.

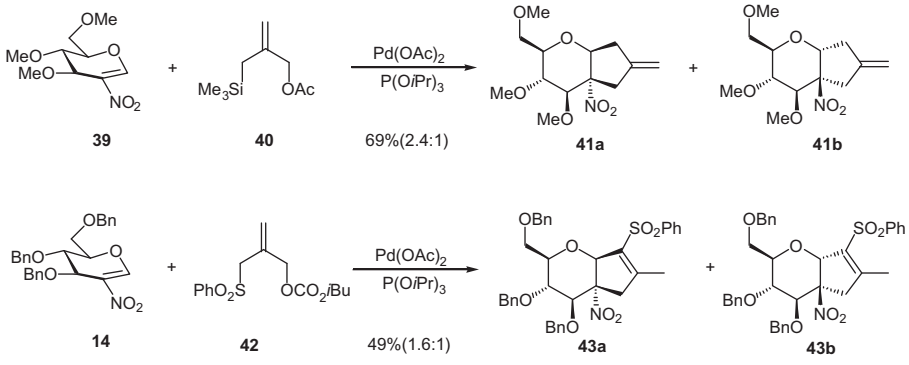
A Pd-catalyzed [3+2]-cycloaddition between 2-nitroglycals and allyl acetates such as **40** to furnish the bicyclic structures **41a** and **41b** was employed by Holzapfel et al.[25] The facial selectivity in this transformation to afford the annulated 5-membered ring is only moderate (2.4:1) (Scheme 9). In this case, elimination of HNO_2 does not take place because there is no aromatic stabilization. Similar experiments were performed with the allylic carbonate **42** providing the bicycles **43a** and **43b** in 49% overall yield with a facial selectivity of 1.6:1.

Isoxazolines annulated to carbohydrate moieties were recently prepared by Liu et al. The key reaction was a [4+1]-cycloaddition between 2-nitroglycals **14** or **21** and sulfur ylides **44** followed by a subsequent rearrangement (Scheme 10).[26] 1-Phenylthiourea served as catalyst; the carbohydrate-derived isoxazolines **47** were obtained in very good yields and excellent diastereoselectivities. A hypothetical mechanism for this transformation is also depicted in Scheme 10. At the outset of the reaction, phenylurea activates the Michael system, the carbon of the ylide attacks C-1. Dimethyl sulfide acts as a leaving group when the 5-membered ring in **45** is formed. Enolization, subsequent ring-opening to **46** and a further ring-closure formed a hemiacetal-oxazoline type structure **47**. The preference of the (*R*)-isomer over the (*S*)-isomer might be due to (i) less steric interactions of the carbonyl group with the pyran ring and (ii) formation of a hydrogen bond with pyran oxygen. These isoxazolines might serve as useful starting materials for *C*-glycosidic gluco- or galactosamines.

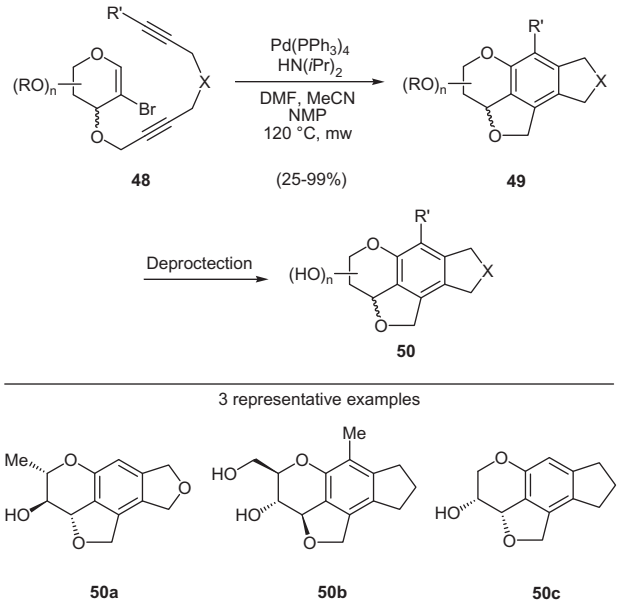
2.3. 2-Bromoglycals as starting materials

In contrast to 2-nitroglycals which have been extensively used as Michael acceptors (vide supra) 2-bromoglycals open the possibility to perform Pd-catalyzed reactions to annulate a further ring system. The respective bromoglycals are easily obtained by an addition–elimination sequence: Bromine is added to the electron-rich olefinic double bond of the glycal and HBr is eliminated by the action of DBU.[27] Due to the better stabilization of the positive charge next to the endocyclic oxygen only the 2-substituted regioisomer is generated. The bond between the sp^2-hybridized carbon and the Br atom is prone to an oxidative addition of an appropriate Pd(0) species, respective alkyne units in the neighborhood might lead to carbopalladation and cyclization reactions.

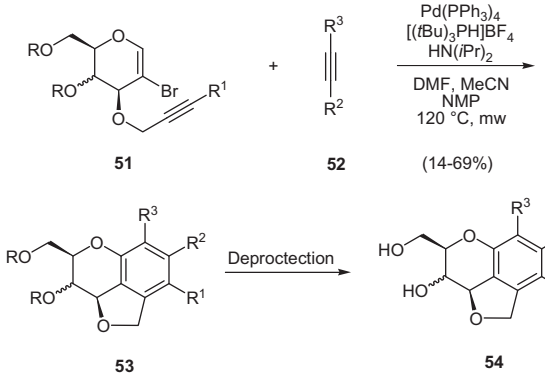
Our group used precursors of type **48** in which a diyne chain is attached to the 3-hydroxyl of a 2-bromoglycal (Scheme 11).[28] Under the influence of Pd(0) a domino reaction took place: after the oxidative addition of the Pd(0) species into the C–Br bond of the respective bromoglycal two intramolecular carbopalladation reactions of the Pd species to the respective triple bonds occur, generating a triene. The final cyclization step affording the benzene unit in **49** may either be either regarded as electrocyclic 6 π electron ring-closure followed by the subsequent release of the catalytic species or as Heck-type addition to the endocyclic double bond. A variety of different diyne chains and different bromoglycals derived from galactose, glucose, rhamnose and arabinose were



Scheme 9. [3+2]-Cycloaddition to access bicyclic structures **41** and **43**.[25]

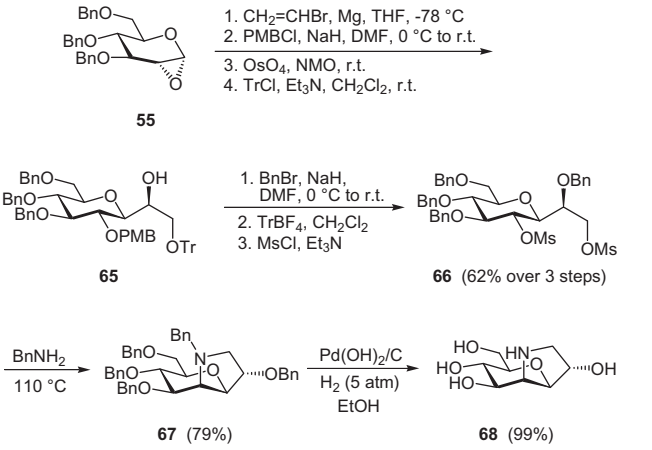


Scheme 11. Preparation of carbohydrate-derived chromans **50** via a Pd-catalyzed domino approach.[28]



Scheme 12. Intermolecular variant with an external alkyne leading to carbohydrate-derived chromans **53**.[29]

utilized to generate a library of highly substituted sugar-derived chroman systems. In order to regenerate the native hydroxyl group pattern of the carbohydrate core respective protecting groups were cleaved to furnish **50**.

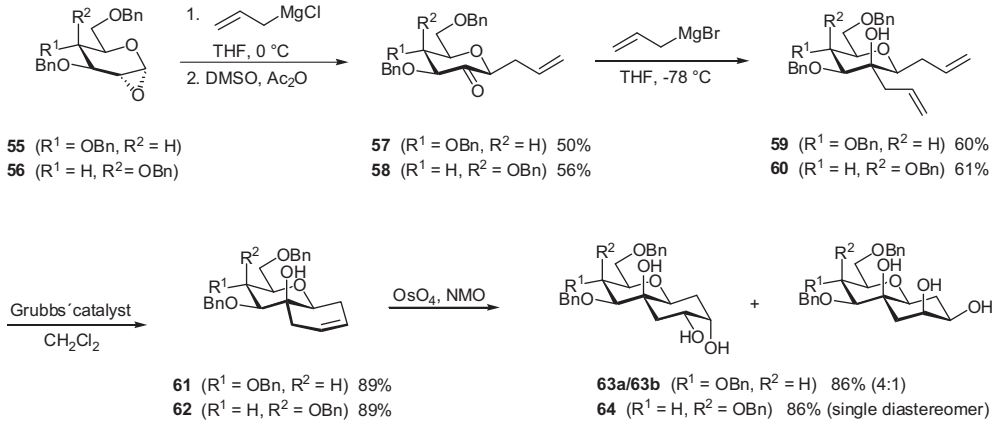


Scheme 14. Pyrrolidine-sugar hybrid **68** by double nucleophilic substitution.[34]

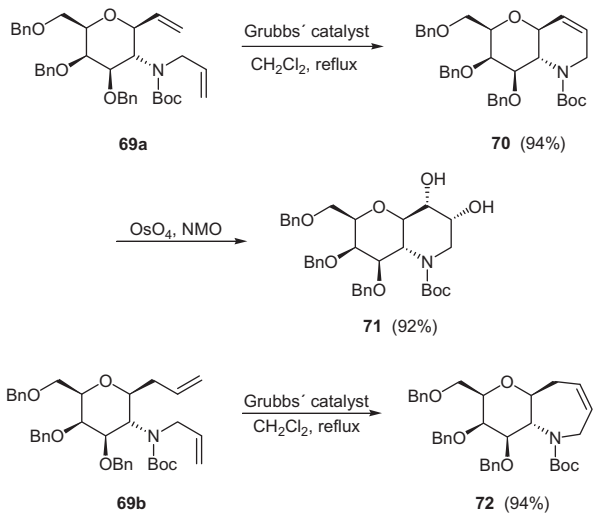
Very recently also an intermolecular variant of this reaction was developed (Scheme 12).[29] However, a large excess of the second alkyne **52** was a prerequisite for a successful outcome of this reaction sequence. Advantageous to this approach are the more easily available starting materials **51** and a more flexible substitution pattern of the chroman **54**. The best results regarding regioselectivity are obtained with symmetrical alkynes. However, when trimethylsilylacetylene was employed it gave derivatives with the trimethylsilyl substituent in *ortho* position to the pyran ring.

2.4. Glycal epoxides as starting materials

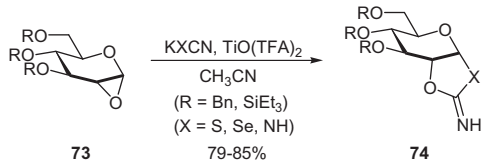
Glycal epoxides open unique possibilities for the functionalization of carbohydrates. These acetal epoxides which are commonly produced by the action of dimethyldioxirane (DMDO)[30] are highly reactive compounds; their three-membered ring is easily opened by a variety of nucleophiles. Often they are used as building blocks in oligosaccharide assembly[31] or in the preparation of glycosyl thioethers or phosphates.[32] But also carbon nucleophiles are able to open the respective epoxide. For instance, a Grignard reagent was used to obtain the 1-*C*-allyl glycoside in a stereoselective fashion (Scheme 13).[33] The emerging 2-hydroxyl group was oxidized to the ketones **57** and **58**, respectively, and subsequently subjected to another Grignard reaction providing the tertiary alcohols **59** and **60**. Ring-closing metathesis of the dienes by using the first generation Grubbs' catalyst afforded the bicyclic compounds **61** and **62** in high yields. The double bond could be further transformed (e.g., by OsO_4 in the presence of NMO).



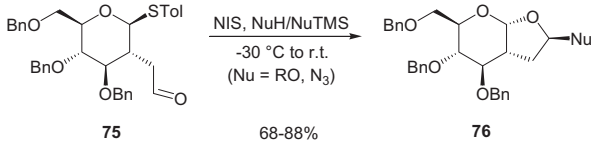
Scheme 13. Addition of Grignard reagents to glycal epoxides and further transformation to bicyclic compounds **63** and **64**.[33]



Scheme 15. Ring-closing metathesis approach to annulated piperidines.[35]



Scheme 16. Ring-enlargement of glycal epoxides by inorganic anions to afford compounds such as **74**.[36]



Scheme 17. 2-Branched glycosyl sulfides for the annulation of a 5-membered ring.[37]

Instead of oxidizing the 2-hydroxyl that has been generated in the addition of carbon nucleophiles to glycal epoxides it can also be converted into an appropriate leaving group (Scheme 14).[34] Combined with a leaving group at the terminal position of the carbon chain attached to position 1 nucleophiles such as amines led to ring formation. By such an approach pyrrolidine-sugar hybrids such as **68** being moderate glycosidase inhibitors were accessed in very good yields.

A metathesis-based approach (as shown in Scheme 13) was also utilized for piperidines annulated to the sugar core.[35] The two terminal double bonds in **69a** set the stage for the ring-closing metathesis (Scheme 15). By using allyl residues (in **69b**) in contrast to vinyl residues (as in **69a**) attached to the pseudoanomeric center also annulated seven-membered ring systems such as **72** were in reach.

Also several bidentate inorganic anions were successfully employed to enlarge the three-membered epoxide ring in **73**. A concise method for the synthesis of *cis*-1,2-fused 1,3-oxathiolane-, 1,3-oxaselenolane- and 1,3-oxazolidine-2-imine carbohydrate derivatives was described by Castillón and co-workers.[36] The synthesis proceeds with the reaction of 1,2-anhydrosugars with KSCN for thio-, KSeCN for seleno-, and NaNHCN for 1,3-oxazolidine-2-imine derivatives (Scheme 16). The use of $TiO(CF_3COO)_2$ as a catalyst proved to be crucial for a successful outcome; derivatives with *gluco*-, *galacto*- and *altro*-configurations were prepared.

2.5. Glycosyl donors as starting materials

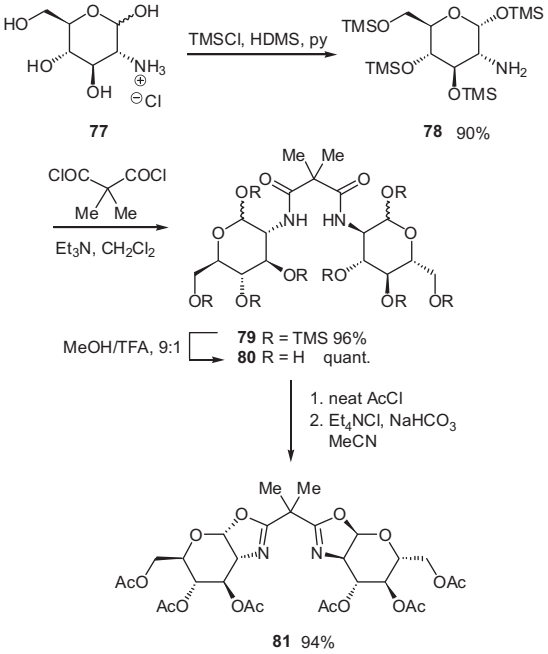
Not only glycal epoxides, but also glycosyl donors such as thioethers were used for the [1,2]-annulation. The Shao group has recently reported an effective route for the synthesis of 2-substituted perhydro[2,3-*b*]pyran derivatives **76**.[37] A glycosyl sulfide equipped at position 2 with a chain terminated by an aldehyde was activated with NIS (Scheme 17). The thiophilic reagent attacked the sulfur, and the positive charge at the anomeric center was trapped by the highly nucleophilic oxygen of the aldehyde giving rise to a positive charge inside the five-membered ring. The latter is trapped either by alcohols or trimethylsilyl azide to yield bicycles **76** in moderate to good yields.

A number of carbohydrate based bis(oxazoline) and bis(thiazoline) ligands were prepared by the Boysen research group.[38] Per-*O*-trimethylsilyl derivative **78** easily obtained from the parent glucosamine hydrochloride **77** was reacted with dimethylmalonyl dichloride to produce bis(amide) **79**. After removal of the trimethylsilyl groups, the anticipated cyclization to bis(oxazoline) was achieved under basic conditions (Scheme 18). Ligands of type **81** were used for metal-catalyzed asymmetric reactions.

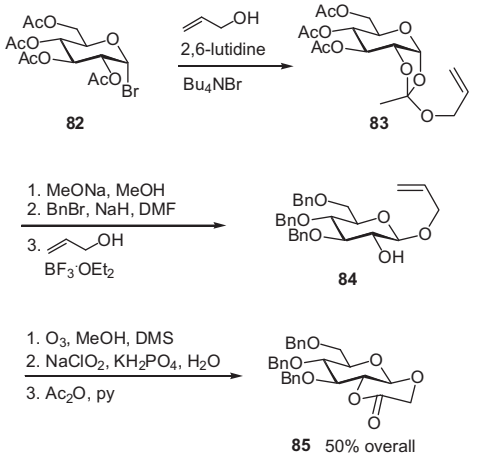
The group of Queneau has reported the synthesis of carboxymethyl-glycoside lactones (CMGLs).[39] The attack of allylic alcohol at per-*O*-acetylated bromo sugars of type **82** gave orthoester **83**. The acetates were converted into benzyl groups and an anomeric allyl protecting group was installed. Finally, under oxidative conditions (ozonolysis) lactone **85** was formed (Scheme 19). Carboxymethyl-glycoside lactones (CMGLs) can be further used as synthons in the synthesis of complex molecules.

2.6. C–H Activation

Most of the examples discussed above relied on functionalized or unfunctionalized double bonds between the carbon atoms 1 and 2 of the six-membered ring. However, the advances in the functionalization of C–H groups have not stopped in front of carbohydrate chemistry. Recently, the Lecourt lab has developed a synthetic route to bicyclic ketopyranosides based on a carbene-mediated activation of the anomeric C–H bond of glycosides.[40] In

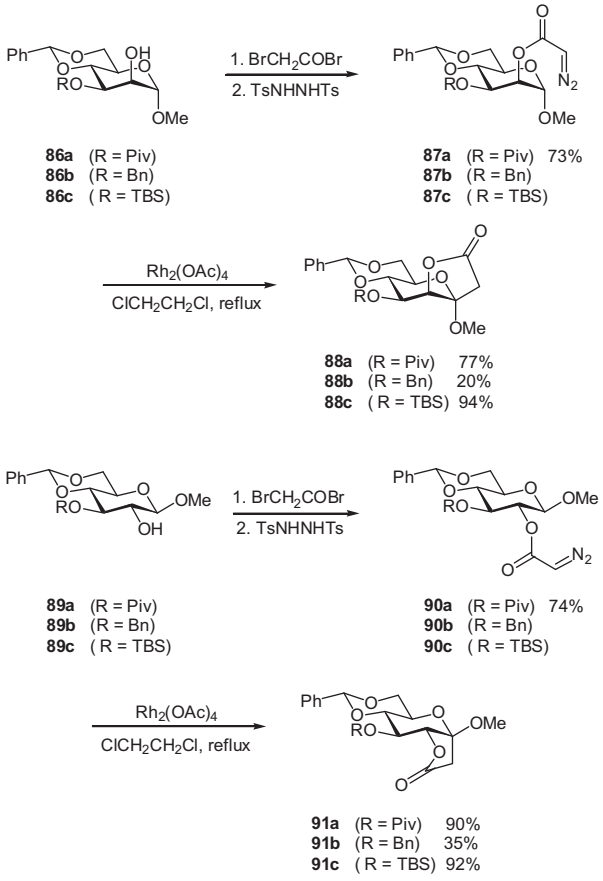


Scheme 18. Synthesis of carbohydrate based bis(oxazoline) ligands.[38]



Scheme 19. Carboxymethyl-glycoside lactone formation under oxidative conditions.[39]

a first step the 2-hydroxyl group of **86** and **89**, respectively, was protected by bromoacetate which was converted via the bis-tosylated hydrazine into the respective diazo compounds **87** and **90**. A Rh(II) salt catalyzed the decomposition of **87** and **90** to the corresponding carbenes. These electron-deficient species insert into the activated C–H bond at the anomeric position; as a result a C–C bond is formed and [5,6]-bicyclic structures **88** and **91** are generated (Scheme 20).



Scheme 20. C–H Activation at the anomeric center to access bicyclic ketopyranosides **88** and **91**.[40]

3. 1-Spiroannulated carbohydrate derivatives

A 1-spiroannulation of a carbohydrate moiety commonly requires some prerequisites. Modified glycals such as **92–95** set the stage for carbene insertions or 1,3-dipolar cycloaddition reactions, Pd-catalyzed reactions, Michael additions and radical processes (Fig. 2).

3.1. 1Carbene insertions and 1,3-dipolar cycloaddition reactions

Exocyclic glycals that are obtained from the corresponding lactones consist of a highly electron-rich enol ether. With such a system [2+1]- and [3+2]-cycloaddition reactions have been performed. Results are spiroannulated three- and five-membered rings, respectively. In our research group sugar-derived [5.n]-spiroketals **98** and **99** were synthesized by a three-step sequence consisting of cyclopropanation, reduction and oxidation (Scheme 21).[41] Cu- or Rh-catalyzed cyclopropanations using diazo ethyl acetate were shown to proceed smoothly when enol ether systems are employed.[42] The esters of type **97** that were formed in this reaction were converted by lithium aluminium hydride into the corresponding alcohols. Oxidation by IBX[43] was followed by a subsequent ring-enlargement of the donor-acceptor-substituted cyclopropane affording a five-membered cycle. The rearrangement could be

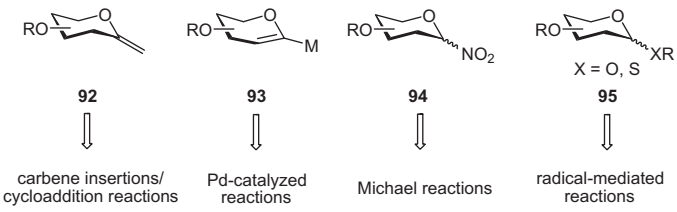
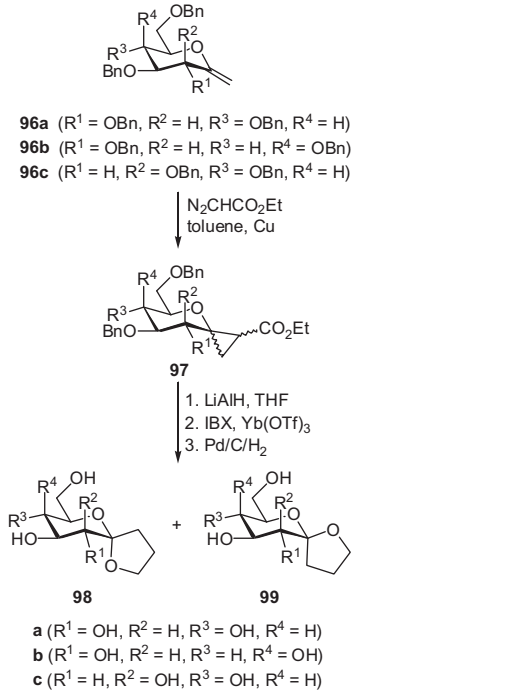
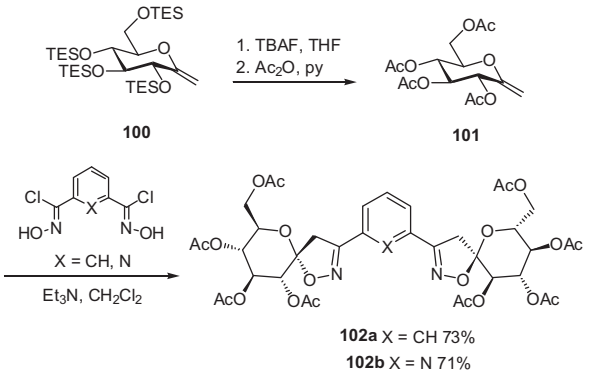


Figure 2. Different glycal derivatives **92–95** used for different types of 1-spiroannulation reactions.



Scheme 21. Three-step sequence from exocyclic glycals **96** to sugar-derived spiroketals **98/99**.[41]

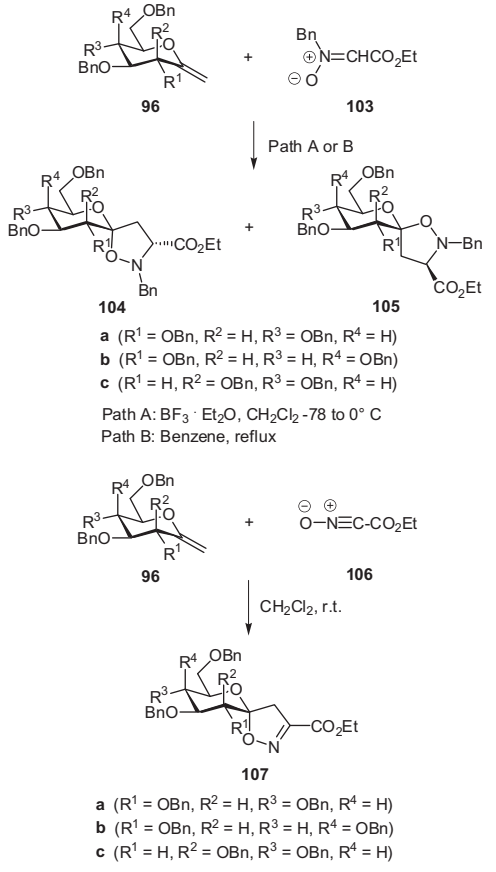


Scheme 22. Synthesis of glucose-based bis(spiroisoxazoline) ligands via 1,3-dipolar reactions.[44]

facilitated by the action of $Yb(OTf)_3$. Finally hydrogenolysis gave deprotected spiroketals **98** and **99**, respectively.

Vidal et al. also have utilized 1,3-dipolar cycloaddition reactions to synthesize glucose-based bis(spiroisoxazoline) ligands (Scheme 22).[44] The synthetic route involved the formation of acetylated exocyclic glucal **101**. The 1,3-dipolar cycloaddition reaction was performed by invoking the bis(nitrile oxides) in situ from bis(carboximidoyl) chlorides in the presence of dipolarophile **101** to afford the desired products **102a** and **102b** depending upon the nature of the aromatic core.

A [3+2]-cycloaddition reaction was used by Ikegami and coworkers to access spiro-annulated isoxazolidines **104** and **105**.



Scheme 23. [3+2]-Cycloadditions to access spiroannulated isoxazolidines **104/105** (top) and isoxazolines **107** (bottom).[45]

Exocyclic enol ethers **96** and nitrones **103** were used as starting materials (Scheme 23, top). When *gluco*- and *galacto*-configured building blocks were employed under optimized conditions using $BF_3{\cdot}OEt_2$ (Scheme 23, Path A), a mixture of α and β-anomeric ketosyl spiro-isoxazolines was obtained, with the α-isomer as predominant product. Refluxing the reaction mixture in benzene (Scheme 23, Path B), an increase in β-selectivity was observed in case of the *manno*-configuration, owing to presence of the axial 2-hydroxyl group. In another type of 1,3-dipolar cycloaddition 1-methylene glycosides **96** were reacted with nitrile oxides **106** to furnish the α-isomer of a spiro-annulated isoxazoline as the only product (Scheme 23, bottom).[45] Similar work was also performed with aryl-substituted nitrile oxides.[46]

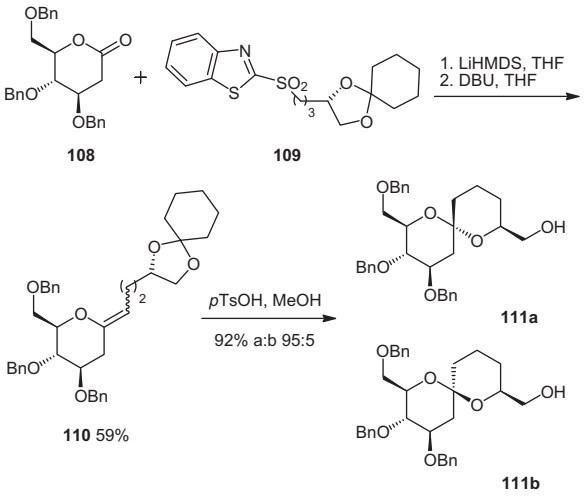
3.2. Acid-induced ring-closing reactions

The group of Gueyrard and Goekjian has effectively functionalized *exo*-glycals to [5.6]- and [6.6]-spiroketals under acidic conditions. Condensation of benzothiazol-2-yl sulfone **109** with sugar lactone **108** formed *exo*-glycal **110** in 59% yield. *p*-Toluenesulfonic acid in methanol mediated the spirocyclization of the enol ether **110** to afford the [6.6]-spirocyclic compound **111a** as a single diastereoisomer in high yield (Scheme 24).[47]

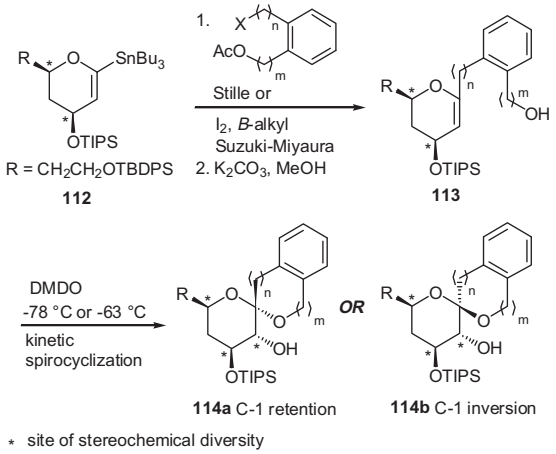
Benzannulated spiroketals, due to their presence in natural products are of immense importance. The Tan research group has utilized stereoselective *anti*-epoxidation followed by spirocyclization to synthesize benzannulated spiroketals. The starting materials, stannylated glycals **112** were functionalized at C-1 either by Stille cross-couplings or via conversion to the glycal iodides followed by *B*-alkyl Suzuki–Miyaura cross-coupling. $Ti(Oi\text{-}Pr)_4$ catalyzed the kinetically controlled spirocyclization, led to the formation of **114a** with retention of configuration at C-1, while inversion products such as compound **114b** were obtained by using AcOH (Scheme 25).[48]

3.3. C–H Activation

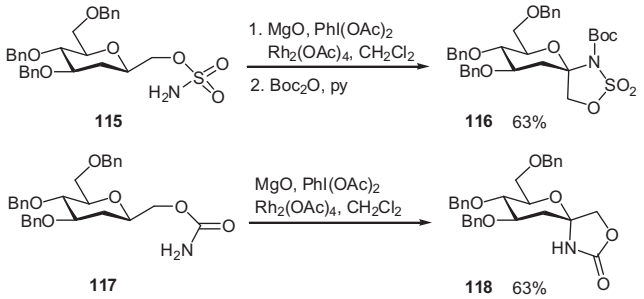
Compain et al. has reported an intramolecular metal-catalyzed amination of pseudo-anomeric C–H bonds in C-glycosides (Scheme 26).[49] The oxidative conversion of sulfamate ester **115** and carbamate **117** gave the bicyclic compounds **116** and **118**. The amination reaction of the sulfamate esters strongly depends on the anomeric configuration.



Scheme 24. Synthesis of [5.5]-spirocyclic compound **111a** under acidic conditions.[47]



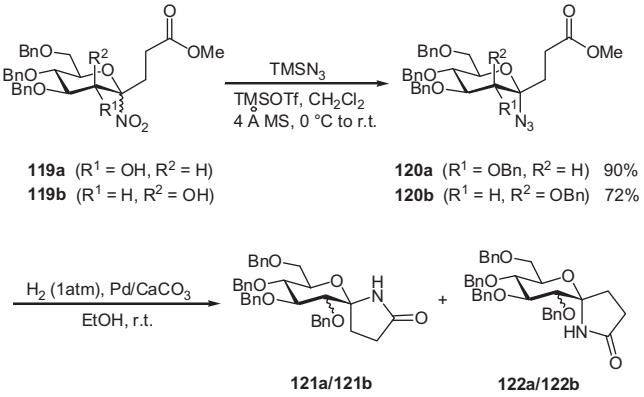
Scheme 25. Benzannulated spiroketal formation via kinetic spirocyclization.[48]



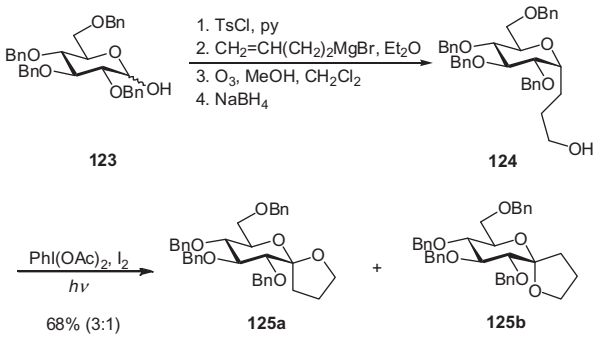
Scheme 26. Intramolecular metal-catalyzed amination.[49]

3.4. Other ring-closing reactions

Due to their facile accessibility also 1-substituted nitro derivatives of sugars have become versatile intermediates for carbohydrate-derived spiro compounds.[50] Several pharmacologically important natural products contain a spiroaminal motif that is generated from appropriately functionalized nitro compounds in a facile fashion. Vankar and co-workers used nitro derivatives to attach a further residue at C-1 by a Michael addition to afford **119a/119b**, followed by a transformation to the respective azido esters **120a/120b** using $TMSN_3$ and TMSOTf (Scheme 27).[51] After reduction of the azido group under an atmosphere of hydrogen and $Pd/CaCO_3$ as catalyst an instantaneous cyclization took place to furnish the spiroaminals **121** and **122** (in a 1:1 isomeric ratio).



Scheme 27. Spiroaminal formation starting with 1-nitro glycosides **119**.[51]



Scheme 28. Spiroketal formation via a radical pathway.[52]

It is envisioned that first the azido group is reduced to the free amine which undergoes tautomerization, escorted by pyranose ring-opening to result a free alcohol and an imine. Thus, the two diastereomeric spiroaminals **121** and **122** resulted from the re-closure of the pyranose ring. Deprotection led to the fully hydroxylated compounds.

The Suárez research group presented a convenient methodology for the synthesis of spiroketals by using an oxidation of the anomeric carbon.[52] First of all, a homoallyl C-glycoside was built up, followed by an ozonolysis of the terminal double bond and subsequent reductive work-up to afford **124**. (Diacetoxyiodo)benzene in the presence of iodine under irradiation was able to oxidize the anomeric center and led to alkoxy radicals which combined with each other furnishing a five-membered ring (Scheme 28). Unfortunately, this method did not conserve the configuration at the anomeric center: a mixture of the two diastereomers **125a** and **125b** in a ratio of 3:1 was obtained.

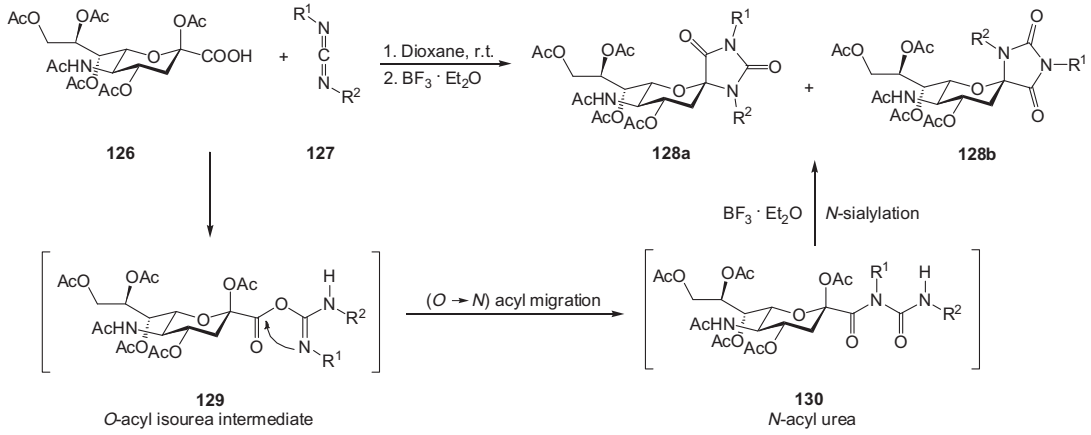
Due to their importance in pharmaceutical chemistry[53] spirohydantoins based on sialic acid were recently synthesized. Key was a one-pot sequential reaction of peracetylated sialic acid **126** and carbodiimides **127** (Scheme 29).[54] In a first step an *O*-acyl isourea intermediate **129** was generated that underwent an (*O*→*N*) acyl migration leading to the respective *N*-acyl urea. In the final step BF_3-etherate initiated the N-sialylation leading after ring-closure to **128a** and traces of **128b**. Due to the anomeric effect excellent α-selectivity was obtained.

Glucose-derived spirohydantoins were accessed by a partial hydrolysis of the cyanide group in **131** mediated by the action of $TiCl_4$.[55] The Br substituent was exchanged by cyanate or thiocyanate anions, respectively. Thus, so obtained intermediates cyclized immediately to the [5.6]-spiro derivatives (Scheme 30). Saponification led to the fully hydroxylated compounds **133** and **134**. If thiocyanate anions were used, the only cyclized product which was observed was **134**; an analogous sulfur-containing compound (similar to **133**) was not detected.

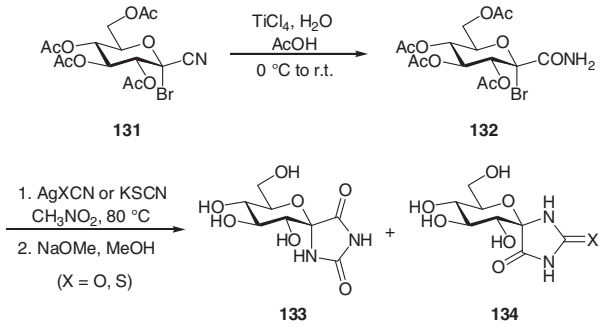
Another type of 5-membered carbohydrate-derived spiro compounds, spiro-oxathiazoles, were prepared by Somsák, Praly and co-workers.[56] The synthesis commenced with the formation of hydroximothioates **136** by utilizing a chlorinated aryl oxime and the respective thiol **135** (Scheme 31). A radical process initiated by NBS led to the anticipated ring-closure. Commonly, a mixture of epimers was obtained with a predominance of the (1*S*)-configured compound. Hydrolysis afforded the fully hydroxylated glucose core of **137**. These compounds have shown to be potent inhibitors of glycogen phosphorylase.

4. Conclusion and outlook

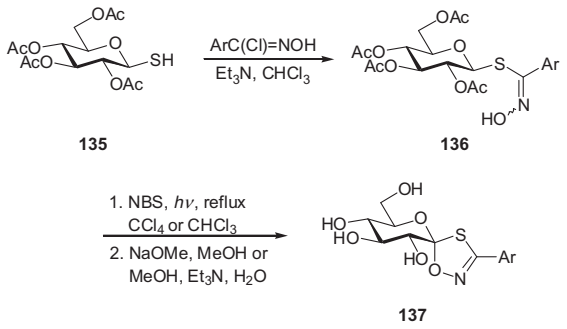
Numerous methods to create 1,2-annulated and 1-spiroannulated carbohydrate derivatives have been developed during the last



Scheme 29. Sialyl spirohydantoins by domino condensation, (*O*→*N*) acyl migration and intramolecular N-sialylation.[54]



Scheme 30. Spirohydantoin formation with cyanates and thiocyanates.[55]



Scheme 31. Spiro-oxathiazole formation starting from glucosyl thiol **135**.[56]

decades. Key to 1,2-annulation is commonly a modified or unmodified glycal. The electron-rich enol ether system of the latter can be either attacked by radicals or by electrophiles. Electron-poor 2-nitro-substituted glycals are Michael systems and are prone to nucleophilic attack. A Br substituent in position 2 of the double bond sets the stage for Pd-catalyzed domino reactions in order to annulate a further ring. The well-known glycal epoxides—easily available from the respective glycals by dimethyldioxirane—are ideal starting materials for the functionalization with carbon or heteroatom nucleophiles. The recent use of C–H activation for a 1,2-annulation demonstrates that modern methods might facilitate previously rather difficult syntheses. The methods employed for the synthesis of 1-spiroannulated carbohydrate derivatives are even more diverse than for the 1,2-annulation. Exocyclic glycals are often common starting materials paving the way for carbene insertions and cycloaddition reactions. However, also radical-initiated processes involving the abstraction of the anomeric hydrogen are often the method of choice.

A facile access to 1,2-annulated and 1-spiroannulated carbohydrate derivatives is of utmost importance. It will help to complete our understanding of a variety of glycosidases and glycosyltransferases. Several of these derivatives mimic in some ways a transition state geometry and show a stronger binding to the respective enzyme than the natural carbohydrate, thus functioning as potent glycosidase or glycosyltransferase inhibitors.

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References and notes

1. (a) Varki, A. *Glycobiology* **1993**, *3*, 97; (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683; (c) Seeberger, P. H.; Werz, D. B. *Nature Rev. Drug Discov.* **2005**, *4*, 751; (d) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321; (e) Werz, D. B.; Seeberger, P. H. *Chem. Eur. J.* **2005**, *11*, 3194; (f) Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046.
2. An overview of the tentative number of structures and the diversity of mammalian and bacterial glycomes is provided: Werz, D. B.; Ranzinger, R.; Herget, S.; Adibekian, A.; von der Lieth, C.-W.; Seeberger, P. H. *ACS Chem. Biol.* **2007**, *2*, 685; (b) Herget, S.; Toukach, P. V.; Ranzinger, R.; Hull, W. E.; Knirel, Y. A.; von der Lieth, C.-W. B. M. C. *Structural Biol.* **2008**, *8*, 35; (c) Adibekian, A.; Stallforth, P.; Hecht, M.-L.; Werz, D. B.; Gagneux, P.; Seeberger, P. H. *Chem. Sci.* **2011**, *2*, 337; (d) Laine, R. A. *Glycobiology* **1994**, *4*, 759.
3. (a) Disney, M. D.; Seeberger, P. H. *Chem. Biol.* **2004**, *11*, 1701; (b) Tamborrini, M.; Werz, D. B.; Frey, J.; Pluschke, G.; Seeberger, P. H. *Angew. Chem.* **2006**, *118*, 6731. *Angew. Chem. Int. Ed.* **2006**, *45*, 6581–6582; (c) Almant, M.; Moreau, V.; Kovensky, J.; Bouckaert, J.; Gouin, S. G. *Chem. Eur. J.* **2011**, *17*, 10029; (d) Oberli, M. A.; Tamborrini, M.; Tsai, Y.-H.; Werz, D. B.; Horlacher, T.; Adibekian, A.; Gauss, D.; Möller, H. M.; Pluschke, G.; Seeberger, P. H. *J. Am. Chem. Soc.* **2010**, *132*, 10239.
4. Danishefsky, S. J.; Allen, J. R. *Angew. Chem.* **2000**, *112*, 882. *Angew. Chem. Int. Ed.* **2000**, *39*, 836.
5. Reviews on carbohydrate mimetics: (a) Koester, D. C.; Holkenbrink, A.; Werz, D. B. *Synthesis* **2010**, 3217; (b) Sears, P.; Wong, C.-H. *Angew. Chem.* **1999**, *111*, 2446. *Angew. Chem. Int. Ed.* **1999**, *38*, 2300; (c) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443; (d) Wong, C.-H. *Acc. Chem. Res.* **1999**, *32*, 376; (e) Ernst, B.; Magnani, J. L. *Nat. Rev. Drug Discovery* **2009**, *8*, 661.
6. Several representative examples: (a) Walvoort, M. T. C.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2010**, *75*, 7990; (b) Iwayama, Y.; Ando, H.; Ishida, H.; Kiso, M. *Chem. Eur. J.* **2009**, *15*, 4637; (c) Werz, D. B.; Castagner, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2007**, *129*, 2770; (d) Werz, D. B.; Seeberger, P. H. *Angew. Chem.* **2005**, *117*, 6474. *Angew. Chem. Int. Ed.* **2005**, *44*, 6315–6318; (e) Oberli, M. A.; Bindschädler, P.; Werz, D. B.; Seeberger, P. H. *Org. Lett.* **2008**, *10*, 905.
7. (a) Heightman, T. D.; Vasella, A. T. *Angew. Chem.* **1999**, *111*, 794. *Angew. Chem. Int. Ed.* **1999**, *38*, 750–770; (b) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.

8. For an overview of S-glycosides: Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160.
9. Selected examples of *N*-glycosides: (a) Libnow, S.; Hein, M.; Langer, P. *Synlett* **2009**, 221; (b) Driller, K. M.; Libnow, S.; Hein, M.; Harms, M.; Wende, K.; Lalk, M.; Michalik, D.; Reinke, H.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 4218; (c) Wang, W.; Rattananakin, P.; Goekjian, P. G. *J. Carbohydr. Chem.* **2003**, *22*, 743.
10. (a) Koester, D. C.; Leibeling, M.; Neufeld, R.; Werz, D. B. *Org. Lett.* **2010**, *12*, 3934; (b) Chen, C.-L.; Sparks, S. M.; Martin, S. F. *J. Am. Chem. Soc.* **2006**, *128*, 13696; (c) Dondoni, A.; Marra, A.; Mizuno, M.; Giovannini, P. P. *J. Org. Chem.* **2002**, *67*, 4186; (d) Postema, M. H. D.; Piper, J. L.; Komanduri, V.; Liu, L. *Angew. Chem.* **2004**, *116*, 2975. *Angew. Chem. Int. Ed.* **2004**, *43*, 2915.
11. (a) Compain, P.; Martin, O. R. *Iminosugars – from synthesis to therapeutical applications*; John Wiley & Sons: Hoboken, 2007; (b) Cren, S.; Wilson, C.; Thomas, N. R. *Org. Lett.* **2005**, *7*, 3521; (c) McDonnell, C.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *J. Org. Chem.* **2004**, *69*, 3565.
12. (a) Aho, J.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406; (b) Brasholz, M.; Sörgel, S.; Azap, C.; Reißig, H.-U. *Eur. J. Org. Chem.* **2007**, 3801; (c) Stierle, A. A.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357; (d) Rateb, M. E.; Houssen, W. E.; Schumacher, M.; Harrison, W. T. A.; Diederich, M.; Ebel, R.; Jaspars, M. *J. Nat. Prod.* **2009**, *72*, 1471; (e) Kim, J.-H.; Huang, F.; Ly, M.; Linhardt, R. J. *J. Org. Chem.* **2008**, *73*, 9497; (f) Yuan, X.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393.
13. An overview of 1,2-cyclopropanated carbohydrates: Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165.
14. (a) Linker, T.; Hartmann, K.; Sommermann, T.; Scheutzow, D.; Ruckdeschel, E. *Angew. Chem.* **1996**, *108*, 1819; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1730; (b) Linker, T.; Sommermann, T.; Kahlenberg, F. *J. Am. Chem. Soc.* **1997**, *119*, 9377; (c) Linker, T.; Schanzenbach, D.; Elamparuthi, E.; Sommermann, T.; Fudickar, W.; Gyóllai, V.; Somsák, L.; Demuth, W.; Schmittel, M. *J. Am. Chem. Soc.* **2008**, *130*, 16003.
15. (a) Sommermann, T.; Kim, B. G.; Peters, K.; Peters, E.-M.; Linker, T. *Chem. Commun.* **2004**, 2624; (b) Elamparuthi, E.; Kim, B. G.; Yin, J.; Maurer, M.; Linker, T. *Tetrahedron* **2008**, *64*, 11925.
16. Yousuf, S. K.; Mukherjee, D.; Mallikharjunrao, L.; Taneja, S. C. *Org. Lett.* **2011**, *13*, 576.
17. Sowa, C.-E.; Thiem, J. *Carbohydr. Res.* **2011**, *346*, 1546.
18. Schmidt, R. R.; Vankar, Y. D. *Acc. Chem. Res.* **2008**, *41*, 1059.
19. Khodair, A. I.; Pachamuthu, K.; Schmidt, R. R. *Synthesis* **2004**, 53.
20. Kancharla, P. K.; Vankar, Y. D. *J. Org. Chem.* **2010**, *75*, 8457.
21. Pachamuthu, K.; Schmidt, R. R. *Synlett* **2003**, 1355.
22. Zhang, T.; Yu, C.-Y.; Huang, Z.-T.; Jia, Y.-M. *Synlett* **2010**, 2174.
23. Jayakanthan, K.; Vankar, Y. D. *Tetrahedron Lett.* **2006**, *47*, 8667.
24. Zhang, Q.; Sun, J.; Zhang, F.; Yu, B. *Eur. J. Org. Chem.* **2010**, 3579.
25. Holzapfel, C. W.; van der Merwe, T. L. *Tetrahedron Lett.* **1996**, *37*, 2307.
26. Cai, S.; Xiang, S.; Zeng, J.; Gorityala, B. K.; Liu, X.-W. *Chem. Commun.* **2011**, *47*, 8676.
27. Yoshimoto, K.; Kawabata, H.; Nakamichi, N.; Hayashi, M. *Chem. Lett.* **2001**, *30*, 934.
28. (a) Leibeling, M.; Koester, D. C.; Pawliczek, M.; Schild, S. C.; Werz, D. B. *Nat. Chem. Biol.* **2010**, *6*, 199; (b) Leibeling, M.; Koester, D. C.; Pawliczek, M.; Kratzert, D.; Dittrich, B.; Werz, D. B. *Bioorg. Med. Chem.* **2010**, *18*, 3656; (c) Young, D. W. *Nat. Chem. Biol.* **2010**, *6*, 174.
29. Leibeling, M.; Milde, B.; Kratzert, D.; Stalke, D.; Werz, D. B. *Chem. Eur. J.* **2011**, *17*, 9888.
30. (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661; (b) Düfert, A.; Werz, D. B. *J. Org. Chem.* **2008**, *73*, 5514; (c) Alberch, L.; Cheng, G.; Seo, S.-K.; Li, X.; Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2011**, *76*, 2532.
31. Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5693.
32. Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211.
33. Doddi, V. R.; Kancharla, P. K.; Reddy, Y. S.; Kumar, A.; Vankar, Y. D. *Carbohydr. Res.* **2009**, *344*, 606.
34. Doddi, V. R.; Kokatla, H. P.; John Pal, A. P.; Basak, R. K.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 5731.
35. Reddy, B. G.; Vankar, Y. D. *Angew. Chem.* **2005**, *117*, 2037; *Angew. Chem. Int. Ed.* **2005**, *44*, 2001.
36. Castilla, J.; Marín, I.; Matheu, M. I.; Díaz, Y.; Castillón, S. *J. Org. Chem.* **2010**, *75*, 514.
37. Ma, X.; Tian, Q.; Tang, Q.; Zhao, J.; Shao, H. *Org. Lett.* **2011**, *13*, 4276.
38. (a) Minuth, T.; Irmak, M.; Groschner, A.; Lehnert, T.; Boysen, M. M. K. *Eur. J. Org. Chem.* **2009**, 997; (b) Irmak, M.; Boysen, M. M. K. *Adv. Synth. Catal.* **2008**, *350*, 403; (c) Irmak, M.; Groschner, A.; Boysen, M. M. K. *Chem. Commun.* **2007**, 177; (d) Irmak, M.; Lehnert, T.; Boysen, M. M. K. *Tetrahedron Lett.* **2007**, *48*, 7890.
39. (a) Listkowski, A.; Ing, P.; Cheaib, R.; Chambert, S.; Doutheau, A.; Queneau, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 2201; (b) Cheaib, R.; Listkowski, A.; Chambert, S.; Doutheau, A.; Queneau, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1919; (c) Trombotto, S.; Danel, M.; Fitremann, J.; Bouchu, A.; Queneau, Y. *J. Org. Chem.* **2003**, *68*, 6672.
40. Boultadakis-Arapinis, M.; Lemoine, P.; Turcaud, S.; Micouin, L.; Lecourt, T. *J. Am. Chem. Soc.* **2010**, *132*, 15477.
41. Brand, C.; Rauch, G.; Zanoni, M.; Dittrich, B.; Werz, D. B. *J. Org. Chem.* **2009**, *74*, 8779.
42. (a) Schneider, T. F.; Kaschel, J.; Dittrich, B.; Werz, D. B. *Org. Lett.* **2009**, *11*, 2317; (b) Schneider, T. F.; Kaschel, J.; Awan, S. I.; Dittrich, B.; Werz, D. B. *Chem. Eur. J.* **2010**, *16*, 11276; (c) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848.
43. For an overview of IBX-mediated oxidations: Duschek, A.; Kirsch, S. F. *Angew. Chem.* **2011**, *123*, 1562. *Angew. Chem. Int. Ed.* **2011**, *50*, 1524.
44. Goyard, D.; Telligmann, S. M.; Goux-Henry, C.; Boysen, M. M. K.; Framery, E.; Gueyrard, D.; Vidal, S. *Tetrahedron Lett.* **2010**, *51*, 374.
45. (a) Li, X.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Heterocycles* **2003**, *59*, 547; (b) Li, X.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Tetrahedron Lett.* **2004**, *45*, 4123; (c) Benltifa, M.; Vidal, S.; Gueyrard, D.; Goekjian, P. G.; Msaddek, M.; Praly, J.-P. *Tetrahedron Lett.* **2006**, *47*, 6143.
46. Benltifa, M.; Hayes, J. M.; Vidal, S.; Gueyrard, D.; Goekjian, P. G.; Praly, J.-P.; Kizilis, G.; Tiraidis, C.; Alexacou, K.-M.; Chrysina, E. D.; Zographos, S. E.; Leonidas, D. D.; Archontis, G.; Oikonomakos, N. G. *Bioorg. Med. Chem.* **2009**, *17*, 7368.
47. Corbet, M.; Bourdon, B.; Gueyrard, D.; Goekjian, P. G. *Tetrahedron Lett.* **2008**, *49*, 750.
48. (a) Liu, G.; Wurst, J. M.; Tan, D. S. *Org. Lett.* **2009**, *11*, 3670; (b) Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 1792.
49. Toumieux, S.; Compain, R.; Martin, O. R. *Tetrahedron Lett.* **2005**, *46*, 4731.
50. Somsák, L. *Chem. Rev.* **2001**, *101*, 81.
51. (a) John Pal, A. P.; Vankar, Y. D. *Tetrahedron Lett.* **2010**, *51*, 2519; (b) John Pal, A. P.; Kadigachalam, P.; Mallick, A.; Doddi, V. R.; Vankar, Y. D. *Org. Biomol. Chem.* **2011**, *9*, 809.
52. Martín, A.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1995**, *36*, 4489.
53. (a) Thenmozhiyal, J. C.; Wong, P. T. H.; Chui, W. K. *J. Med. Chem.* **2004**, *47*, 1527; (b) Hah, S. S.; Kim, H. M.; Sumbad, R. A.; Henderson, P. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 627; (c) Carmi, C.; Cavazzoni, A.; Zuliani, V.; Lodola, A.; Bordi, F.; Plazzi, P. V.; Alfieri, R. R.; Petronini, P. G.; Mor, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4021.
54. Zhang, D.; Ye, D.; Feng, E.; Wang, J.; Shi, J.; Jiang, H.; Liu, H. *J. Org. Chem.* **2010**, *75*, 3552.
55. (a) Somsák, L.; Kovács, L.; Tóth, M.; Ősz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843; (b) Somsák, L.; Nagy, V. *Tetrahedron: Asymmetry* **2000**, *11*, 1719.
56. (a) Nagy, V.; Benltifa, M.; Vidal, S.; Berzsényi, E.; Teilhet, C.; Czifrák, K.; Batta, G.; Docsa, T.; Gergely, P.; Somsák, L.; Praly, J.-P. *Bioorg. Med. Chem.* **2009**, *17*, 5696; (b) Somsák, L.; Nagy, V.; Vidal, S.; Czifrák, K.; Berzsényi, E.; Praly, J.-P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5680.