Hypervalent Iodine and Carbohydrates – A New Liaison☆

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Received June 18, 1998

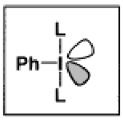
Keywords: Carbohydrates / Glycals / Hypervalent iodine / Glycosylation

Synthetic applications of hypervalent iodine reagents in the oxidation state +3 in relation to unsaturated carbohydrates are reviewed. By using the Koser reagent or its bis(azido) derivative, fully protected glycals are oxidatively deblocked in the allylic position. The reaction furnishes carbohydrate-derived 2,3-dihydro-4*H*-pyranones, which serve as starting materials for the preparation of *C*-saccharides, glycosyl stannanes or thromboxane A_2-analogues. Alternatively, iodine(III) reagents can be used to oxidize halide anions. The halogen-ate complexes thus generated behave like synthetic equivalents of acyl hypobromite and iodite, respectively, or halogen azides, which can all add to alkenes, including glycals, under very mild conditions.

Introduction

Organic compounds of polycoordinated iodine have long been known. In fact, Willgerodt[1][2] reported the first preparation of $PhICl_2$ from iodobenzene and ICl_3 as early as 1886. However, it is only recently that iodine compounds in the oxidation state +3 have gained synthetic and mechanistic significance, as described in several excellent reviews[3]. Two reasons can be given for this revival of interest. In the late 1960s, the new theory of hypervalency helped in the understanding of the nature of the bonding in hypervalent iodine reagents. For example, hypervalent iodine reagents in the oxidation state +3 ($PhIL_2$ **1**; iodanes) commonly contain a strong I−C σ-bond occupying the equatorial position of a trigonal bipyramid and two weaker bonds to two axially located ligands (L) in a three-center, 4-electron bond. Therefore, chemical reactivity is usually observed in the vicinity of the latter substructure. Secondly, the development of various new hypervalent iodine(V) reagents, of which the Dess-Martin reagent is the most prominent example[4], as well as of iodine(III) compounds such as **2a−f**[5] drew the attention of a broader scientific community to these reagents. More than 30 distinct classes of polyvalent organic iodine compounds are now known.

Scheme 1. Selected examples of iodine(III) compounds



1

$PhI(OAc)_2$	**2a**	$PhI(O_2CCF_3)_2$	**2d**
$PhI(OH)OTs$	**2b**	$PhI(CN)_2$	**2e**
$PhI(N_3)_2$ / $PhI(OAc)N_3$	**2c**	$PhI{=}C(CO_2Me)_2$	**2f**

Due to the two weakly bound ligands attached, the central iodine atom in iodine(III) reagents exhibits strong electrophilic character. The reactivity patterns of iodanes **1** may be rationalized in terms of this electrophilicity and are out-

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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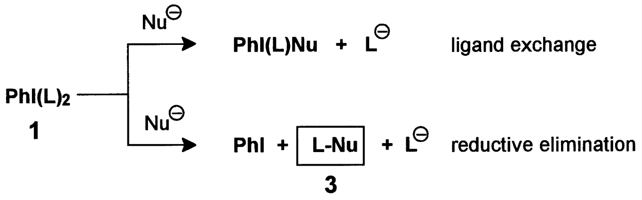
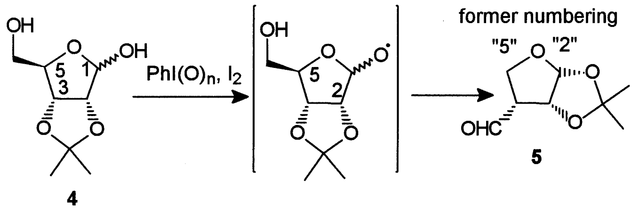
lined in Scheme 2. Ligand exchange reactions (route 1) and reductive elimination of two ligands on the central iodine atom (route 2) are the common reaction pathways followed by this class of reagents. In most cases, reactions of **1** with nucleophiles are terminated by the reductive elimination process, affording final products **3** containing a combination of L and Nu[6]. Due to this behaviour, compounds like **1** are occasionally termed "nonorganometallic" reagents.

Scheme 2. Reactivity patterns of iodine(III) reagents



Although the chemistry of hypervalent iodine has witnessed a renaissance since the 1970s, there have been only very few instances of the application of these reagents in cases of multifunctional and complex nucleophiles or in natural product synthesis[7], where, in addition to stereo- and regiospecificity, chemoselectivity is also a major concern. Applications in the field of carbohydrates are particularly rare. In some cases, iodine(III) reagents like PhI-$(O_2CCF_3)_2$ have been employed as promotors in glycosidation reactions of thioglycosides[8]. An intriguing ring-contraction reaction of carbohydrates mediated by iodine(III) was developed by Suárez and co-workers[9] and others[10], which was later utilized by the Danishefsky group for constructing the C28−C42 segment of rapamycin (Scheme 3)[11]. Thus, under radical conditions, furanose **4** can be cleanly converted into the heterocyclic derivative **5**, which contains one less carbon and is blocked at the anomeric center. This method is widely applicable, working equally well with other starting compounds of various ring sizes. These results illustrate how iodine(III) reagents can efficiently be used to selectively perform transformations on carbohydrates that would otherwise be difficult to achieve.

Scheme 3. The Suárez oxidation of lactols



Investigation into the use of hypervalent iodine reagents in carbohydrate chemistry has been an ongoing concern in these laboratories for some time now. This brief review focusses on efforts made to use these reagents for improving known processes in carbohydrate chemistry and, perhaps more interestingly, to perform new oxidative transformations in this field.

Iodine(III)-Promoted Direct Oxidation of Glycals

Glycals are very versatile carbohydrate-derived cyclic building blocks, which due to the nucleophilicity of the electron-rich enol ether double bond were anticipated to be ideally suited for reactions with iodanes, such as the Koser reagent **2b**[11]. As shown for tri-*O*-acetyl-D-galactal **6**, oxidative regioselective deblocking at C-3 takes place in the presence of **2b** and powdered molecular sieves (3 Å) (Scheme 4). This unusual transformation[12] furnishes 2,3-dihydro-4*H*-pyran-4-one **7**[13], a member of a relatively unexplored class of highly functionalized chiral building blocks for which few versatile accesses from carbohydrates had hitherto been known[14].

Scheme 4. Iodine(III)-promoted oxidative allylic deblocking of tri-*O*-acetyl-D-galactal

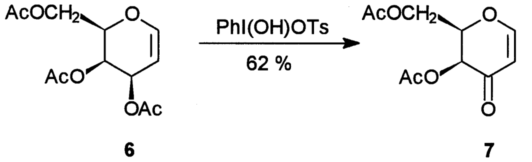
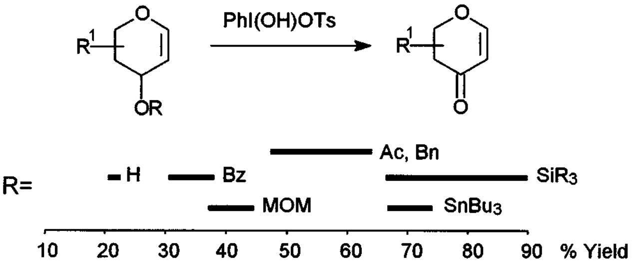


Figure 1. Protective group R dependence of yields in the iodine(III)-promoted oxidation of glycals

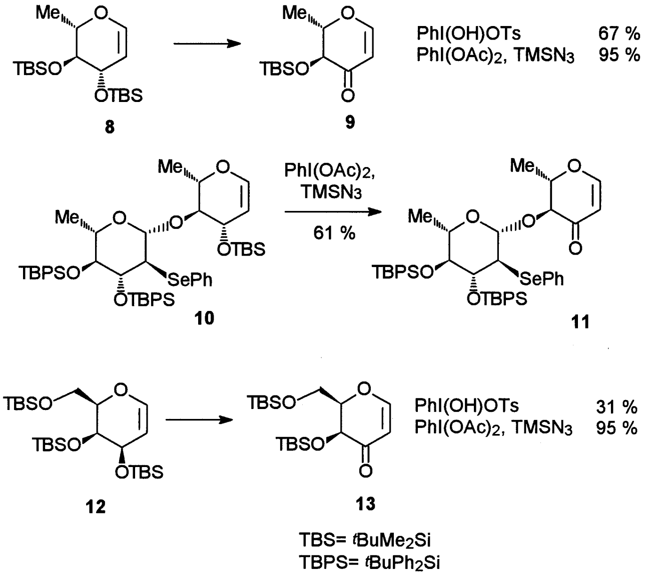


This oxidation process can be applied to a wide range of differently O-3 protected glycals with varying efficiencies (Figure 1). Thus, the ketone functionality can be elaborated from diverse precursors including alcohols, esters, acetals, and ethers, and especially well from 3-*O*-silylated glycals. The oxidation is independent of the relative stereochemistry of the alcohol starting material as well as insensitive to the nature and number of protecting groups on remaining stereocenters, making this transformation a very general oxidation method in glycal chemistry[15].

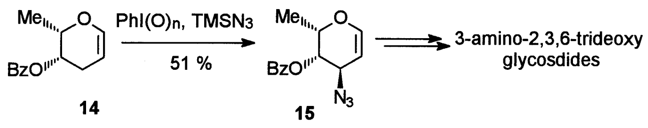
Other iodine(III) reagents such as **2a**, **2d**, PhI(OMe)OTs, or $(PhIO)_n$ in the presence of different Lewis acids do not promote this oxidation. However, the reagent system $PhI(OAc)_2/TMSN_3$ (**2c** is formed as the active agent) gives improved yields of 3-*O*-silylated glycals **8**, **10** and **12** (Scheme 5)[16]. Other protecting groups on O-3 lead only to poor yields of enones or do not react at all. Reaction with disaccharide **10** is particularly noteworthy as the high-yielding transformation to enone **11** occurs in the presence of the oxidation-labile phenylselenyl group.

3-Deoxy glycals exhibit a slightly different behaviour, as these substrates do not have a polarized C−O bond in the allylic position. Thus, in situ preparation of **2c** in the pres-

Scheme 5. Allylic oxidative deblocking of glycals using the reagent system **2a**/$TMSN_3$



Scheme 6. Allylic azidation of 3-deoxyglycal **14**



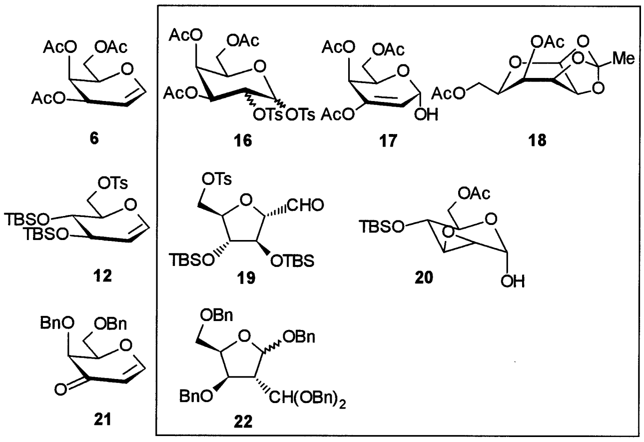
ence of glycal **14** stereoselectively affords 3-azido-3-deoxy glycal **15** (Scheme 6)[17]. These azido glycals are valuable intermediates en route to 3-amino-2,3,6-trideoxy glycosides[18]. For example, the C-4 epimer of **15** is an important precursor of daunosamine, a constituent of many anthracycline antitumor agents[19].

Studies on the Mechanism

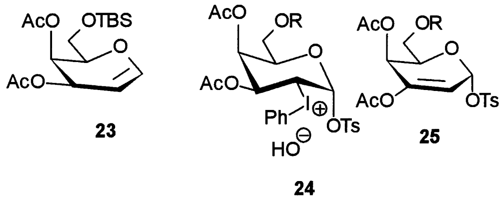
Along with the well-documented iodine(III)-promoted oxidation of triisopropylsilyl enol ethers described by Magnus and co-workers[20][21], this type of allylic oxidation illustrates a unique reactivity pattern of polycoordinated iodine compounds. A mechanistic rationale for these allylic oxidations has been proposed by this group[13b][22] and by Magnus et al.[21]. As many iodine(III)-promoted reactions are thought to proceed via unstable intermediates, often alkylphenyliodonium species, detailed studies on their mechanisms are scarce. In addition, it is often unclear as to whether this kind of iodine(III) chemistry proceeds via ionic or radical pathways.

The identification of by-products helped in gaining mechanistic insights into the allylic oxidation of cyclic enol ethers such as glycals. Figure 2 lists starting materials **6**, **12**, and **21** as well as the most relevant by-products necessary for describing the mechanism. In some cases, these by-products are only formed in very small amounts besides the desired 2,3-dihydro-4*H*-pyran-4-ones[22]. Apart from simple monosaccharides, such as *vic*-bis(tosyloxy)pyran **16**, rare enopyranose **17**, orthoester **18** and oxirane **20**, various unusual ring-contracted tetrahydrofurans such as **19** and **22** were also isolated. Furthermore, efforts were made to track, isolate and characterize the possible intermediates of this oxidation process. It was reckoned that enopyranose **17** might have been a possible precursor of enone **7**. However, it was in fact only instantaneously transformed into enone **7** under strongly acidic conditions (CH_2Cl_2, TFA), whereas TsOH in acetonitrile as well as aqueous bicarbonate solution proved to be ineffective reagent systems for promoting this conversion.

Figure 2. By-products formed in the iodine(III)-promoted oxidation of selected glycals



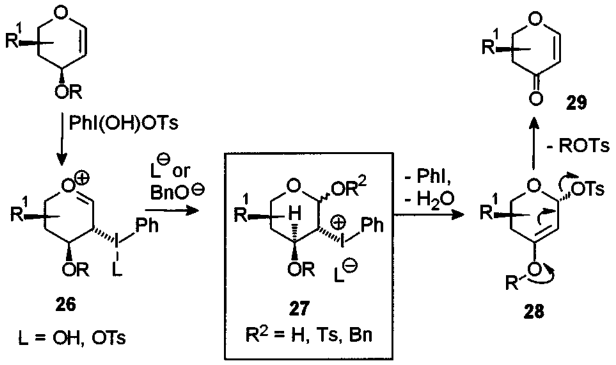
To obtain more structural evidence on possible intermediates, oxidation of galactals **6** and **23** was studied in NMR tubes. The two starting materials reacted at different rates, which allowed the collection of analytical data for both the relevant intermediates. In the first step, galactals **6** and **23** were stereoselectively converted into the primary intermediate, the alkylphenyliodonium species **24**[23]. Once formed, it rapidly underwent further reaction to enopyranosyl tosylate **25**. This further supports the notion that **17** is not an intermediate on the main route, but is formed in the course of a side reaction.



A mechanism that is consistent with all the above data, observations and stereochemical results is outlined in Schemes 7a and 7b.

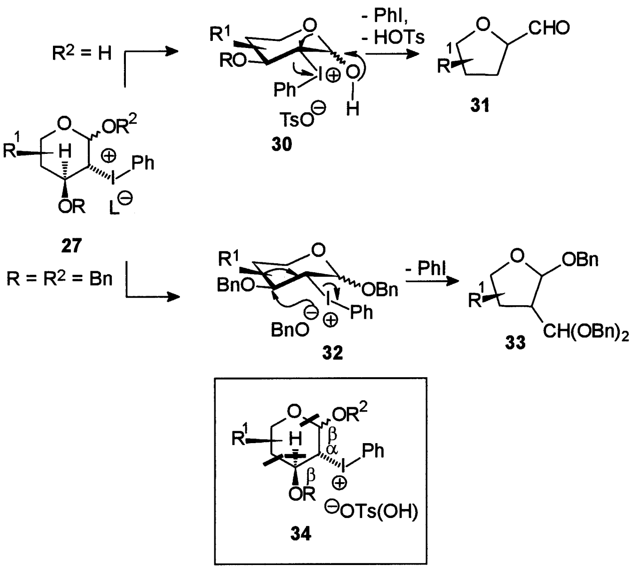
The oxidation is initiated by electrophilic attack of the hypervalent iodine reagent at the α-face of the glycal, and subsequent trapping of the intermediate oxonium ion **26** with an external nucleophile gives the 2-phenyliodonium pyranoses **27**. In most cases, the tosyloxy ligand is incorporated, whereas in cases of per-*O*-benzylated glycals, the benzyloxy group can serve as the nucleophile. This highly

Scheme 7a. Proposed mechanism of the iodine(III)-promoted allylic oxidative deblocking of glycals − part I



reactive primary intermediate usually undergoes reductive elimination of PhI, typically in a *cis*-fashion, to give enopyranoses **28**, which are rapidly transformed into 2,3-dihydro-4*H*-pyran-4-ones **29** upon aqueous hydrolysis (Scheme 7a).

Scheme 7b. Proposed mechanism of the iodine(III)-promoted allylic oxidative deblocking of glycals − part II



Besides this main pathway, two alternative routes may be operative, leading to tetrahydrofurans (Scheme 7b). Thus, when R^2 = H, intermediate **30** undergoes ring-contraction by a stereoselective backside attack of the ring oxygen atom O-5 on the nucleo*fugic* organoiodine substituent at C-2, to afford tetrahydrofurfural **31**. In contrast, when per-*O*-benzylated glycals are transformed into 2,3-dihydro-4*H*-pyran-4-ones **29** by oxidative deblocking, benzyl alcohol is liberated, which can efficiently compete for oxonium ion **26**, affording benzyl glycoside **32**. The latter undergoes ring-contraction resulting in tetrahydrofuran **33**. The common feature of all of these oxidative routes is the cleavage of the β,γ bond relative to the carbon−iodine bond of the intermediate alkylphenyliodonium species **34**. Preference for one or other of these different routes is determined by the conformation of the glycal and the nature of the nucleophiles present.

Synthetic Applications of Carbohydrate-Derived 2,3-Dihydro-4*H*-pyran-4-ones

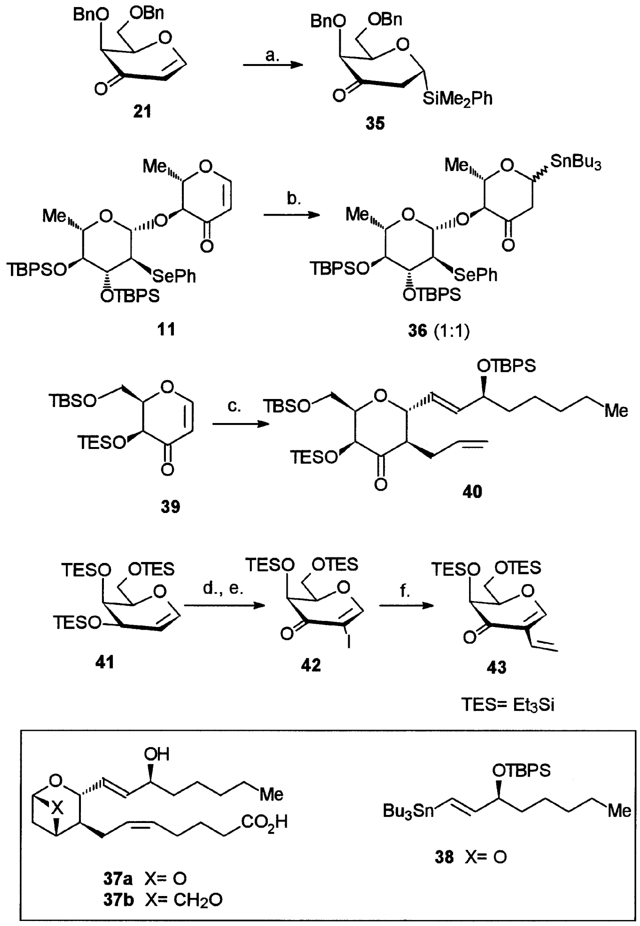
Carbohydrate-derived 2,3-dihydro-4*H*-pyran-4-ones, though not frequently employed in natural product synthesis[24], are versatile chiral building blocks. The enone functionality is a very appealing structural element as it is set up for a wide range of further synthetic manipulations[25], in particular for 1,4-additions of C-nucleophiles, ultimately leading to *C*-glycosides[26]. Scheme 8 depicts some representative examples worked on in these laboratories. Enones such as **21** react smoothly with silyl cuprates[27] affording glycosylsilylane **35**, thereby introducing a masked hydroxy group at the anomeric center. Tributylstannyllithium adds in a 1,4-fashion to 2,3-dihydro-4*H*-pyran-4-ones such as disaccharide **11**, affording glycosyl stannanes **36**. Studies by Sinaÿ and co-workers[28] and later by Kessler and Vasella et al.[29][30] showed that these compounds are ideal precursors of anomeric lithio derivatives and hence of *C*-glycosides. Both research groups confirmed that these anomeric anionic species are configurationally stable and react with electrophiles with retention of configuration. In addition to heteroatom-stabilized anions, suitable carbanions react equally well with these carbohydrate-derived 2,3-dihydro-4*H*-pyran-4-ones. In fact, they should be ideal chiral precursors for constructing stable thromboxane A_2 **37a** (TXA_2) analogues[31]. Thus, enone **39** was coupled with the vinyl cuprate derived from vinylstannane **38**[32]. The intermediate enolate was directly trapped with allyl iodide to stereoselectively furnish pyranone **40**[33]. This multi-component reaction is the key step of a synthetic approach developed for stable thromboxane A_2 (TXA_2) analogues such as **37b**[34].

Furthermore, hypervalent iodine reagents in the oxidation state +3 have been employed in a multi-step procedure that involved an efficient transformation of glycal **41** into 2,3-dihydro-5-iodo-4*H*-pyran-4-one **42** in one of the steps[33]. In analogy to work by Evans and co-workers[35], it was found that this vinyl iodide could be alkylated under Stille reaction conditions furnishing diene **43**.

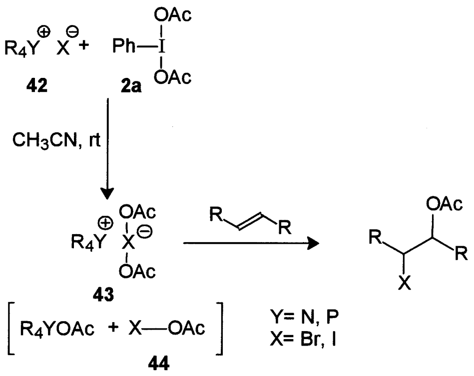
Halogen−ate Reagents Derived from Iodine(III) Precursors

Surveying the literature on synthetic applications of hypervalent iodine reagents in the oxidation state +3, it becomes apparent that the electrophilicity of these reagents has most commonly been exploited in reactions with carbon nucleophiles such as electron-rich alkenes and arenes[3]. In contrast, heteroatoms have rarely found use as nucleophiles to date[36]. Recently, an investigation was initiated in these laboratories concerned with ligand transfer reactions from iodine(III) onto halide anions[37]. As was first pointed out by Doleschall and Tóth[38], the species generated under these conditions are believed to be halogen-ate complexes[39]. Apart from their use as a source of iodine radicals[40][41] these new reagents had not been exploited in organic synthesis.

Scheme 8. Synthetic applications of carbohydrate-derived 2,3-dihydro-4*H*-pyranones; a) $Me_2PhSiLi$, CuCN, MeLi, THF, 0°C, 20 min, then −40°C and addition of **21**, −23°C, 30 min, 98%; b) Bu_3SnLi, THF, −78°C to −50°C, 2 h, 43%; c) **38**, MeLi, CuCN, THF, −30°C, 1 h, then addition to **39**, −78°C to −50°C, 3 h, then addition of $ICH_2CH=CH_2$, −78°C to −20°C 15 h, 58%; d) $PhI(OAc)_2$ (2 equiv.), $TMSN_3$ (4 equiv.), CH_2Cl_2, 0°C to r.t., 1 h; e) pyr. (5 equiv.), then addition of $PhI(OAc)_2$ (3 equiv.), TMSI (6 equiv.), CH_2Cl_2, r.t., 12 h, 61% for two steps; f) $Bu_3SnCH=CH_2$, $Pd(Ph_3)_4$ (0.05 equiv.), toluene, 65°C, 2.5 h, 89%.

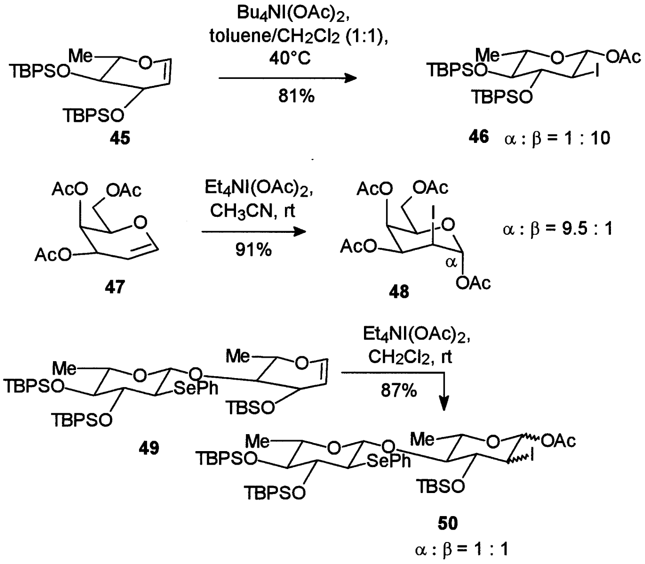


Scheme 9. Iodine(III)-initiated preparation of diacetoxy−halogen−ate complexes



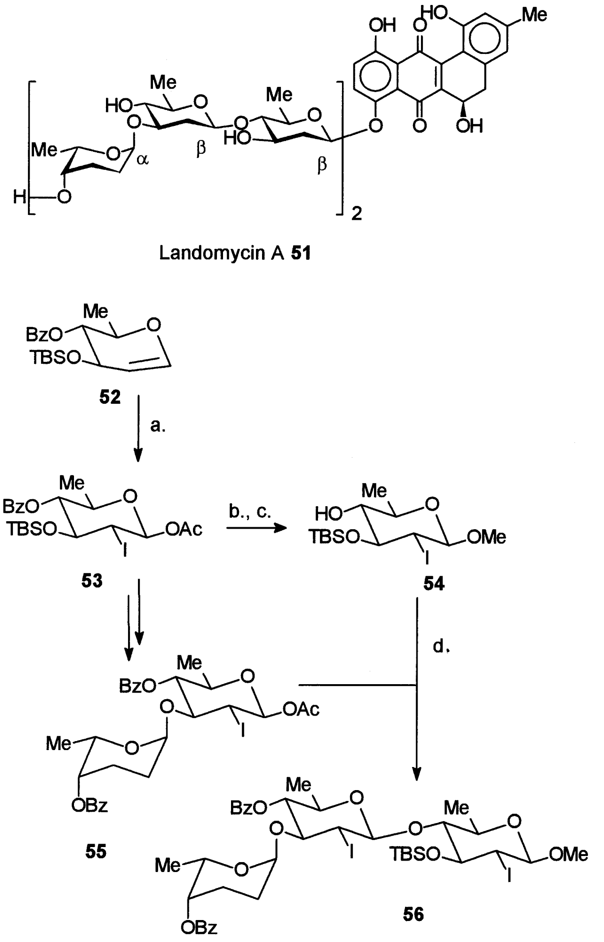
The diacetoxy salts **43** are conveniently prepared by treating ammonium or phosphonium halides **42** with (diacetoxy)iodobenzene **2a** (Scheme 9). Chemically, these brown, amorphous salts behave like acetyl hypobromite or acetyl hypoiodite **44**, respectively. The latter has never been isolated, but has been postulated as an intermediate in various reactions[42]. These salts efficiently add to alkenes to give α-halo acetates (Scheme 9)[43]. Using glycals, 2-halo glycosyl acetates are formed, which are ideal glycosyl donors for use in the construction of 2-deoxy glycosides[44]. Typically, the reaction of an electrophile with glycals in the presence of a glycosyl acceptor preferentially furnishes a *trans* diaxial 1,2-addition product, leading to 2-deoxy-α-glycosides[45]. In order to obtain access to 2-deoxy-β-glycosides, for which no reliable synthesis has yet been developed, the electrophile and nucleophile need to add in a *trans* diequatorial mode. This can be achieved if a glycal such as **45**, bearing bulky electron-donating silyl protecting groups, is employed in the iodoacetoxylation reaction[46]. In an apolar solvent such as toluene in the presence of a catalytic amount of TMSOTf, only the 1,2-diequatorial addition product **46** is formed (Scheme 10)[47]. In contrast, the use of polar solvents and ester or benzyl protection on glycal **47** favours *trans* diaxial addition of halonium ion and acetate, thereby furnishing **48** as the major isomer. Dichloromethane is a borderline case and usually leads to 1:1 mixtures, as exemplified by the conversion of glycal **49** into disaccharide **50**. Using this method, both bromine and iodine can be introduced at C-2, which is necessary for exerting stereocontrol in the next step, i.e. the glycosidation.

Scheme 10. Haloacetoxylations of selected glycals



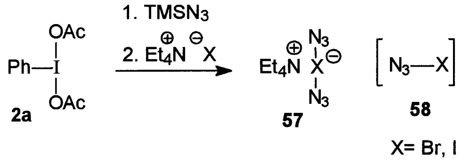
As part of an ongoing interest in the class of angucyclin antibiotics[48], the use of this reagent system for the construction of the oligosaccharide chain of landomycin A (**51**) was envisaged[49][50]. Landomycin A exhibits a broad spectrum of antitumor activity, where the length of the carbohydrate chain effects its cytostatic activity[51]. A unique feature of the hexasaccharide portion of **51** is its dimeric structure, each monomer consisting of a trisaccharide constructed of one L-rhodinose and two D-olivose units. The starting point of the synthesis was the iodoacetoxylation of glycal **52** in toluene, which afforded glycosyl acetate **53** as the major product (α-*manno*/β-*gluco* = 1:2). The isomers were easily separated by column chromatography (Scheme 11). The required product was converted in two steps into disaccharide **55**. Parallel to this sequence, methyl β-glycoside **54** was prepared from **53** in two steps in 69% overall yield[52], and was then directly transformed into trisaccharide **56**.

Scheme 11. Synthesis of the trisaccharide monomer of landomycin A; a) Bu_4NI, $PhI(OAc)_2$, $TMSOTf_{cat}$, toluene, 0°C, 12 h, 93% for both addition products; b) MeOH, TMSOTf, Et_2O, −20°C, 12 h; c) Na, MeOH, r.t., 24 h, 69% for 2 steps; d) TMSOTf, Et_2O, r.t., 24 h, 23%.



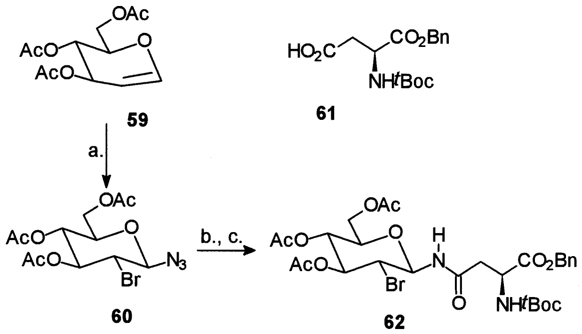
As is apparent from Scheme 9, formation of halogen−ate complexes **43** is achieved by ligand transfer from the hypervalent iodine(III) reagent onto halide anions. Instead of acetate, azide can be transferred equally well (Scheme 12). This method furnishes halogen azide like species **57** under much milder conditions than conventionally employed procedures originally developed by Hassner et al.[53]. In effect, synthetic equivalents of iodine and bromine azides **58** are generated at low temperatures in different solvents.

Scheme 12. Preparation of synthetic equivalents of halogen azides



Thus, 2-halo-2-deoxy-β-glucosyl azide **60** is formed preferentially upon treatment of glucal **59** with the reagent system bis(azido)iodobenzene **2c** (generated from **2a** and $TMSN_3$) and ammonium bromide[54]. This glucosyl azide was efficiently reduced to the corresponding glucosyl amine and coupled with aspartic acid ester **61** to afford 2-deoxyglucosyl aspartate **62**.

Scheme 13. Iodine(III)-initiated azidobromination of tri-*O*-acetyl glucal **59** and synthesis of a simple 2-deoxy glycopeptide; a) Et_4NBr, **2a**, CH_2Cl_2, r.t., 12 h, 29%; b) PtO_{2cat}, H_2, EtOAc, r.t., 24 h; c) **61**, IIDQ, CH_2Cl_2, r.t., 24 h, 82% for 2 steps.



Conclusion

In summary, it has been established that hypervalent iodine reagents in the oxidation state +3 and derived halogen−ate(I) complexes can be advantageously applied in the promotion of unique and new transformations in carbohydrate chemstry. The number of hypervalent iodine reagents will undoubtedly increase further in the near future, as will the importance of these reagents for oxidative transformations of natural products, including carbohydrates.

The work reviewed here was generously supported by the *Deutsche Forschungsgemeinschaft* (including SFB 416), the *Deutsche Akademische Austauschdienst* (DAAD), and the *Fonds der Chemischen Industrie.* Additional support by *AnalytiCon AG* (Potsdam), *Chemetall GmbH* (Langelsheim), *Degussa AG* (Frankfurt), and *Hoechst AG* (Frankfurt) is gratefully acknowledged. I particularly thank Prof. *Md. Abul Hashem* (Dhakar, Bangladesh), Dr. *Jan Harders*, Dr. *Lars Rose*, and *Monika Ries* for the creativity and skill in their intellectual and preparative work.

[☆] Dedicated to Professor *Wolfgang Steglich* on the occasion of his 65th birthday.

[1] C. Willgerodt, *J. Prakt. Chem.* **1886**, *43*,154−160.

[2] First exhaustive coverage of polycoordinated iodine compounds by C. Willgerodt, *Die organischen Verbindungen mit mehrwertigem Jod*, Enke, Stuttgart, **1914**.

[3] Reviews: [3a] A. Varvoglis, *Synthesis* **1984**, 709−726. − [3b] R. M. Moriarty, R. K. Vaid, G. F. Koser, *Synlett* **1990**, 365−383. − [3c] A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*, Verlag Chemie, New York, Weinheim, Cambridge, **1992**. − [3d] A. Varvoglis, *Chim. Chron., New Ser.* **1995**, *24*, 3−55. − [3e] P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123−1178. − [3f] A. Varvoglis, *Hypervalent Iodine in Organic Synthesis*, Acadamic Press, San Diego, London **1997**.

[4] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

[5] A. Kirschning, *J. Prakt. Chem.* **1998**, 184−186

[6] For reviews on ligand coupling reactions, see: [6a] S. Oae, Y. Uchida, *Acc. Chem. Res.* **1991**, *24*, 202−208. − [6b] S. Oae, *Croat. Chem. Acta* **1986**, *59*, 129−151.

[7] [7a] C. B. Saitz, J. A. Valderrama, R. Tapia, F. Farina, M. C. Paredes, *Synth. Commun.* **1992**, *22*, 955. − [7b] A. M. Turuta, A. V. Kamernitzky, T. M. Fadeeva, A. V. Zhullin, *Synthesis* **1985**, 1129−1131. − [7c] C. Szántay, G. Blaskó, M. Bárczai-Beke, P. Péchy, G. Dörnyei, *Tetrahedron Lett.* **1980**, *21*, 3509−3512.

[8] For iodine(III) reagents as glycosidation promoters: [8a] S. Caddick, W. B. Motherwell, J. A. Wilkinson, *J. Chem. Soc., Chem. Commun.* **1991**, 674−675. − [8b] K. Fukase, A. Hasuoka, I. Kinoshita, S. Kusumoto, *Tetrahedron Lett.* **1992**, *33*, 7165−7168. − [8c] K. Fukase, I. Kinoshita, T. Kanoh, Y. Nakai, A. Hasuoka, S. Kusumoto, *Tetrahedron* **1996**, 52, 3897−3904. − [8d] K. Fukase, Y. Nakai, T. Kanoh, S. Kusumoto, *Synlett* **1998**, 84−86.

[9] [9a] P. de Armas, C. G. Francisco, E. Suárez, *Angew. Chem.* **1992**, *104*, 746−748; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 772−774. − [9b] C. G. Francisco, R. Freire, M. S. Rodríguez, E. Suárez, *Tetrahedron Lett.* **1995**, *36*, 2141−2144. − [9c] C. G. Francisco, C. C. González, E. Suárez, *Tetrahedron Lett.* **1996**, *37*, 1687−1690. − [9d] C. G. Francisco, C. González, E. Suárez, *J. Org. Chem.* **1998**, *63*, 2099−2109.

[10] J. Inanaga, Y. Sugimoto, Y. Yokoyama, T. Hanamoto, *Tetrahedron Lett.* **1992**, *33*, 8109−8112.

[11] C. M. Hayward, M. J. Fisher, D. Yohannes, S. J. Danishefsky, *Tetrahedron Lett.* **1993**, *34*, 3989−3402.

[12] G. F. Koser, R. H. Wettach, J. M. Troup, B. A. Frenz, *J. Org. Chem.* **1976**, *41*, 3609−3611.

[13] [13a] A. Kirschning, G. Dräger, J. Harders, *Synlett* **1993**, 289−290. − [13b] A. Kirschning, *J. Org. Chem.* **1995**, *60*, 1228−1232.

[14] [14a] S. Czernecki, K. Vijayakumaran, G. Ville, *J. Org. Chem.* **1986**, *51*, 5472−5475. − [14b] H. Paulsen, H. Bünsch, *Chem. Ber.* **1978**, *111*, 3484−3496. − [14c] V. Bellosta, R. Benhaddou, S. Czernecki, *Synlett* **1993**, 861−862. − [14d] S. Czernecki, C. Leteux, A. Veyrières, *Tetrahedron Lett.* **1992**, *33*, 221−224. − [14e] M. Fétizon, D. D. Khac, N. D. Tho, *Tetrahedron Lett.* **1986**, *27*, 1777−1780. − [14f] B. Fraser-Reid, B. J. Carthy, N. L. Holder, M. Yunker, *Can. J. Chem.* **1971**, *49*, 3038−3045. − [14g] J. M. J. Tronchet, J. Tronchet, A. Birkhäuser, *Helv. Chim. Acta* **1970**, *53*, 1489−1490. − [14h] P. M. Collins, *Carbohydr. Res.* **1969**, *11*, 125−128.

[15] For related oxidations using NBS, see: A. Bouillot, D. Do Khac, M. Fétizon, F. Guir, Y. Memoria, *Synth. Commun.* **1993**, *23*, 2071−2081.

[16] A. Kirschning, J. Harders, L. Rose, unpublished results

[17] A. Kirschning, S. Domann, G. Dräger, L. Rose, *Synlett* **1995**, 767−769.

[18] [18a] K. Heyns, R. Hohlweg, *Chem. Ber.* **1978**, *111*, 1632−1645. − [18b] R. D. Guthrie, R. W. Irvine, J. D. Jenkins, *Aust. J. Chem.* **1980**, *33*, 2499−2508. − [18c] J. Boivin, A. Montagnac, C. Monneret, M. Pais, *Carbohydr. Res.* **1980**, *85*, 223−242. − [18d] K. Heyns, J. Feldmann, D. Hadamczyk, J. Schwentner, J. Thiem, *Chem. Ber.* **1981**, *114*, 232−239.

[19] Extensive coverage on anthracycline antibiotics: U. Gräfe, in *Biochemie der Antibiotika: Struktur, Biosynthese, Wirkmechanismus*, Spektrum Akademischer Verlag, Heidelberg, Berlin, New York **1992**.

[20] P. Magnus, M. B. Roe, *Tetrahedron Lett.* **1996**, *37*, 303−306.

[21] [21a] P. Magnus, J. Lacour, P. A. Evans, M. B. Roe, C. Hulme, *J. Am. Chem. Soc.* **1996**, *118*, 3406−3418. − [21b] P. Magnus, J. Lacour, *J. Am. Chem. Soc.* **1992**, *114*, 3993−3994. − [21c] P. Magnus, J. Lacour, *J. Am. Chem. Soc.* **1992**, *114*, 767−769.

[22] [22a] J. Harders, A. Garming, A. Jung, V. Kaiser, H. Monenschein, M. Ries, L. Rose, K.−U. Schöning, T. Weber, A. Kirschning, *Liebigs Ann./Recueil* **1997**, 2125−2132. − [22b] A. Kirschning, *Liebigs Ann. Chem.* **1995**, 2053−2056.

[23] At present, very few NMR data for alkylphenyliodonium species are available. For NMR studies on these compounds and related iodine(III) species, see: [23a] A. R. Kratritzky, J. K. Gallos, H. D. Durst, *Magn. Reson. Chem.* **1989**, *27*, 815−822. − [23b] T. Umemoto, Y. Gotoh, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3307−3313. − [23c] G. A. Olah, M. R. Bruce, *J. Am. Chem. Soc.* **1979**, *101*, 4765−4766.

[24] [24a] R. Benhaddou, S. Czernecki, G. Ville, *J. Org. Chem.* **1992**, *57*, 4612. − [24b] T. E. Goodwin, N. M. Rothman, K. L. Salazar, L. S. Shannon, *J. Org. Chem.* **1992**, *57*, 2469. − [24c] M. Takiya, M. Ishii, K. Shibata, Y. Mikami, O. Mitsunobu, *Chem. Lett.* **1992**, *11*, 1917. − [24d] T. Kaufmann, W. Klaffke, C. Philip, J. Thiem, *Carbohydr. Res.* **1992**, *207*, 33. − [24e] V. Bellosta, S. Czernecki, *Carbohydr. Res.* **1992**, *171*, 279. − [24f] T. E. Goodwin, C. M. Crowder, R. B. White, J. S. Swanson, F. E. Evans, W. L. Meyer, *J. Org. Chem.* **1992**, *48*, 376.

[25] Reviews: [25a] N. L. Holder, *Chem. Rev.* **1982**, *82*, 287−332. − [25b] F. W. Lichtenthaler, in *Modern Synthetic Methods* (Ed.: R. Scheffold), *Vol. 6*, VHCA, **1992**.

[26] [26a] M. H. D. Postema, *C−Glycoside Synthesis*, CRC Press, Boca Raton, Ann Arbor, London, Tokyo, **1995**. − [26b] M. H. D. Postema, *Tetrahedron* **1992**, *48*, 8545−8599.

[27] A. Kirschning, J. Harders, *Synlett* **1996**, 772−774.

[28] [28a] P. Lesimple, J.-M. Beau, P. Sinaÿ, *Carbohydr. Res.* **1987**, *171*, 289−300. − [28b] P. Lesimple, J.-M. Beau, P. Sinaÿ, *J. Chem. Soc., Chem. Commun.* **1985**, 894−895.

[29] [29a] O. Frey, M. Hoffmann, H. Kessler, *Angew. Chem.* **1995**, *107*, 2194−2195; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2026−2028. − [29b] M. Hoffmann, H. Kessler, *Tetrahedron Lett.* **1994**, *35*, 6067−6070. − [29c] V. Wittman, H. Kessler, *Angew. Chem.* **1993**, *105*, 1138−1140; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1091−1093. − [29d] J.-M. Lancelin, L. Morin-Allory, P. Sinaÿ, *J. Chem. Soc., Chem. Commun.* **1984**, 355−356.

[30] O. Frey, M. Hoffmann, V. Wittmann, H. Kessler, P. Uhlmann, A. Vasella, *Helv. Chim. Acta* **1994**, *77*, 2060−2069.

[31] For a recent review on carbohydrate-based syntheses of thromboxane compounds refer to: I. Pelyvás, J. Thiem, Z. G. Tóth, *J. Carbohydr. Chem.* **1998**, *17*, 1−26.

[32] A. Kirschning, J. Harders, *Tetrahedron* **1997**, *53*, 7867−7876.

[33] J. Harders, Ph. D. thesis, Technical University of Clausthal, **1998**.

[34] It has been shown that **37b** exhibits TXA$_2$ agonist activity without showing antagonist effects. Furthermore, it is able to inhibit thromboxane synthase: T. K. Schaaf, D. L. Bussolotti, M. J. Parry, E. J. Corey, *J. Am. Chem. Soc.* **1981**, *103*, 6502−6505.

[35] P. A. Evans, T. D. Nelson, T. Manangan, *Synlett* **1997**, 968−970.

[36] [36a] D. G. Ray III, G. F. Koser, *J. Am. Chem. Soc.* **1990**, *112*, 5672−5673. − [36b] C. Srinavasan, A. Chellamani, P. Kuthalingam, *J. Org. Chem.* **1982**, *47*, 428−431.

[37] [37a] A. Kirschning, C. Plumeier, L. Rose, *J. Chem. Soc., Chem. Commun.* **1998**, 33−34. − [37b] A. Kirschning, Md. A. Hashem, A. Jung, M. Ries, *Synlett* **1998**, 195−197.

[38] G. Doleschall, G. Tóth, *Tetrahedron* **1980**, *36*, 1649−1665.

[39] For studies on dialkyl− and diphenyl−halogen−ate complexes, see: [39a] V. Schulze, M. Brönstrup, V. P. W. Böhm, P. Schwerdtfeger, M. Schimeczek, R. W. Hoffmann, *Angew. Chem.* **1998**, *110*, 869−871; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 824−826. − [39b] H. J. Reich, D. P. Green, N. H. Phillips, *J. Am. Chem. Soc.* **1991**, *113*, 1414−1416 and references cited therein.

[40] C. Szántay, G. Blaskó, M. Bárczai-Beke, P. Péchy, G. Dörnei, *Tetrahedron Lett.* **1980**, *21*, 3509−3512.

[41] P. de Armas, J. I. Concepción, C. G. Francisco, R. Hernández, J. A. Salazar, E. Suárez, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 405−411.

[42] Acetyl hypoiodite has never been isolated, but has been postulated as an intermediate in the Hunsdiecker and Simonini reactions, as well as in the thermal decomposition of diacyl iodobenzenes: [42a] A. Simonini, *Monatsh. Chem.* **1892**, *13*, 320−325. − [42b] J. E. Leffler, L. J. Story, *J. Am. Chem. Soc.* **1967**, *89*, 2333−2338.

[43] A related and very versatile iodine(III)-induced addition reaction to enol ethers including glycals using the reagent system (PhSe)$_2$, PhI(OAz)$_2$, and NaN$_3$ has been studied by: [43a] M. Tingoli, M. Tiecco, D. Chianelli, R. Balducci, A. Temperini, *J. Org. Chem.* **1991**, 56, 6809−6813. − [43b] F. Santoyo-González, F. G. Calvo-Flores, P. García-Mendoza, F. Hernández-Mateo, J. Isac-García, R. Robles-Díaz, *J. Org. Chem.* **1993**, *58*, 6122−6125. − [43c] S. Czernecki, D. Randriamandimby, *Tetrahedron Lett.* **1993**, *34*, 7915−7918.

[44] [44a] A. Kirschning, A. Bechthold, J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 1−84. − [43b] J. F. Kennedy, C. A. White, *Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology*, Ellis Horwood, Chichester, **1983**.

[45] [45a] S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1482−1522; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380−1419. − [45b] K. Toshima, K. Tatsatu, *Chem. Rev.* **1993**, *93*, 1503. −

[45c] J. Thiem, W. Klaffke, *Top. Curr. Chem*. **1990**, *54*, 285−332.

[46] L. Rose, Ph. D. thesis, Technical University of Clausthal, **1998**.

[47] Similar conditions seem to govern the stereochemical outcome of the formal addition of phenylselenyl acetate to glycals: M. Perez, J. −M. Beau, *Tetrahedron Lett*. **1989**, *30*, 75−78.

[48] For a recent review on angucycline antibiotics, see: J. Rohr, K. Krohn, *Top. Curr. Chem*. **1997**, *108*, 127−195.

[49] [49a] T. Henkel, J. Rohr, J. Beale, L. Schwenen, *J. Antibiot*. **1990**, *43*, 492−503. – [49b] S. Weber, C. Zolke, J. Rohr, J. Beale, *J. Org. Chem*. **1994**, *59*, 4211−4214.

[50] Recently, the synthesis of the hexasaccharide fragment has been accomplished by: Y. Guo, G. A. Sulikowski, *J. Am. Chem. Soc.* **1998**, *120*, 1392−1397.

[51] J. Rohr, S. −E. Wohlert, C. Oelkers, A. Kirschning, M. Ries, *J. Chem. Soc., Chem. Commun*. **1997**, 973−974.

[52] A. Kirschning, G. Dräger, M. Ries, unpublished results.

[53] [53a] A. Hassner, F. Boerwinkle, *J. Am. Chem. Soc*. **1968**, *90*, 216−218. – [53b] F. Boerwinkle, A. Hassner, *Tetrahedron Lett*. **1968**, 3921−3924. – [53c] A. Hassner, F. Boerwinkle, *Tetrahedron Lett*. **1969**, 3309−3312.

[54] A. Kirschning, Md. A. Hashem, M. Monenschein, L. Rose, K.-U. Schöning, *J. Org. Chem*., submitted for publication.

[O98272]