Polish J. Chem., **78**, 881–901 (2004) **REVIEW ARTICLE**

Enantiomerically Pure Carbocyclic Derivatives from Sugar Allyltins

by S. Jarosz

Institute of Organic Chemistry, Polish Academy of Sciences
Kasprzaka 44/52, 01-224 Warszawa (e-mail: sljar@icho.edu.pl)

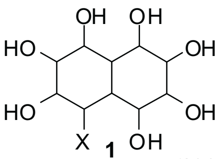
(Received April 2nd, 2004; revised manuscript April 23rd, 2004)

The concise approach to enantiomerically pure, highly oxygenated carbobicyclic derivatives from sugar allyltins as well as the preparation of these sugar organometallics is reviewed.

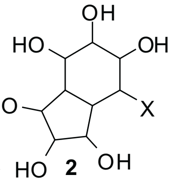
Key words: allyltin derivatives, carbocyclic derivatives, synthesis, sugars

1. Introduction

Monocyclic analogues of simple sugars such as: cyclitols [1], and carbasugars [2] play an important role in biological processes. Much less is known about bicyclic analogues, their synthesis and biological activity. Recently it was reported, that highly oxygenated, although racemic, derivatives of bicyclo[4.4.0]decane **1** and bicyclo [4.3.0]nonane **2** possess interesting biological properties. For example one of the ***racemic*** stereoisomers of **1** showed potent and selective α-glucosidase inhibition at the μM concentration against the α- and β-glucosidases [3]. The problem lays, however, in the preparation of individual diastereoisomers as single enantiomers. One of the most convenient methods for the synthesis of enantiomerically pure compounds is undoubtedly the '*chiron approach*' [4], the use of readily available optically pure natural products such as sugars, aminoacids, terpenes *etc.* as starting materials. Retrosynthetic analysis shown in Fig. 1 revealed that the direct precursors of (optically pure) compounds **1** and **2** can be the bicyclic derivatives **3** and **4** respectively.



1



2

racemic

Such precursors might be obtained from the trienes **5** and **6**, and these trienes should result from the dienoaldehyde **7**. The preparation of such dienoaldehyde from sugars was, therefore, the first synthetic target faced by us.

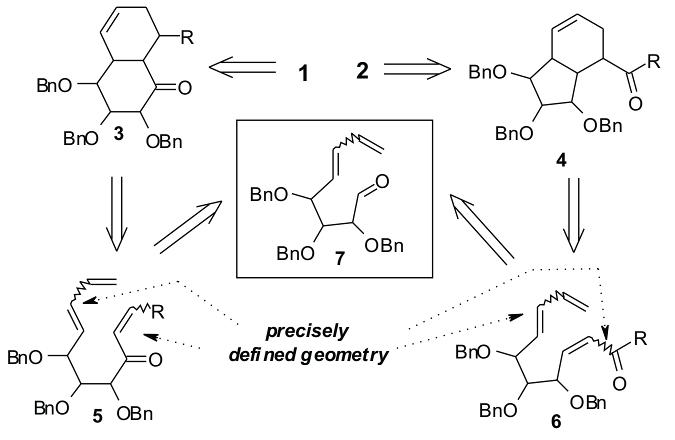


Figure 1. Retrosynthetic analysis for the preparation of optically pure carbobicycles.

In the end of 80's Herczegh [5] reported on the synthesis of carbobicyclic compounds from sugar chirons using the standard methodology (Fig. 2). Serious problem consisted, however, in the preparation of geometrically pure diene **8**, direct precursor of **9** and then **10**.

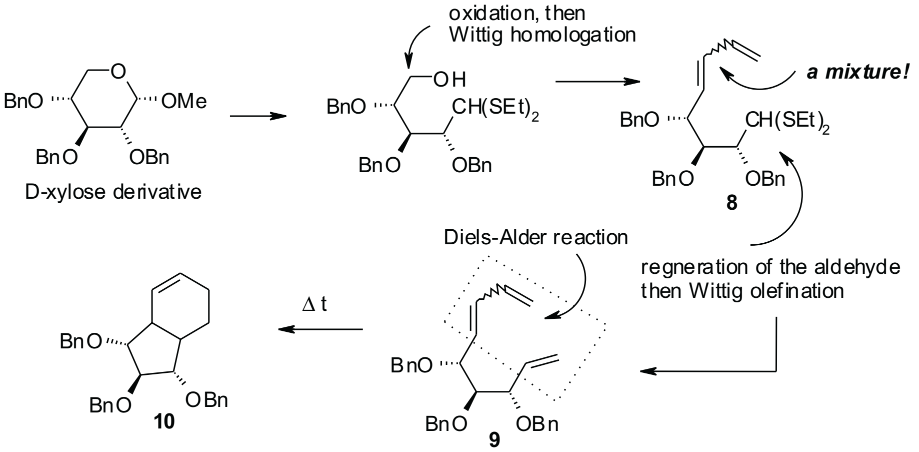
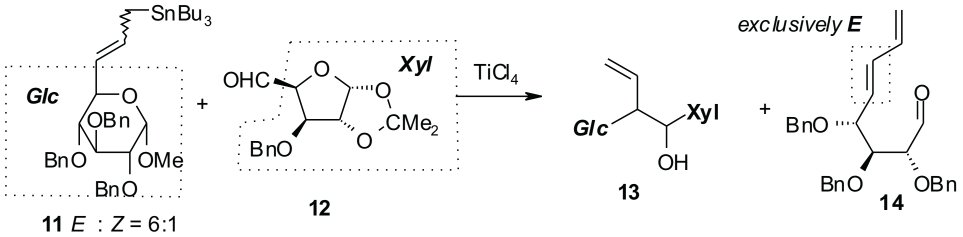


Figure 2. Synthesis of carbocycles from simple sugars by Herczegh.

In our concept, the synthesis of the triene of type **5** and **6** with ***the precisely defined*** geometry across the double bonds was crucial. Such derivatives should undergo highly stereoselective and predictable cyclization [6] providing the bicyclic derivatives of desired structure.

During the study on higher sugar synthesis we have found, that sugar allyltin derivatives undergo a fragmentation in the presence of Lewis acids. When organometallic **11** reacted with aldehyde **12** in the presence of titanium tetrachloride, besides the expected homoallylic alcohol **13**, the dienoaldehyde **14** with the *E*-geometry across the internal double bond was formed [7]. This product surely resulted from a controlled fragmentation of sugar allyltin **11**.



This rather unexpected observation led us to a conclusion that sugar allyltins are excellent precursors of dienoaldehydes having the precisely defined geometry across the internal double bond. We elaborated the convenient route to such dienes from sugar allyltins [8].

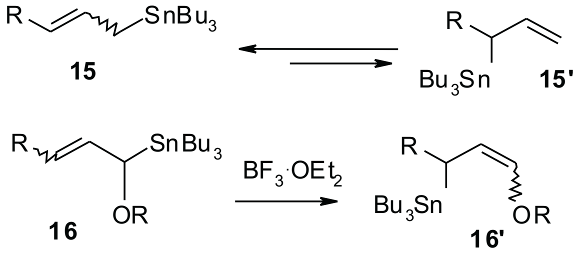
In this article preparation of sugar allyltin derivatives and their application in stereocontrolled synthesis of highly oxygenated, enantiomerically pure carbobicyclic compounds will be reviewed.

2. Synthesis of sugar allyltin derivatives

2.1. General remarks on the preparation and reactivity of organotin derivatives

Organotin chemistry has a long history. First organotin compound was synthesized more than 150 years ago by Farkland [9], who obtained diethyl diiodotin (Et_2SnI_2) in reaction of ethyl iodide with metallic tin. A number of simple and mixed tetraalkyltin derivatives was obtained by reaction of Grignard reagents with $SnCl_4$ by Pope and Peachey [10] a century ago; this reaction became soon a standard method for the preparation of alkyl- and aryltin derivatives. The real interest, however, in organotin chemistry started in mid 1960's when Kuivila [11] discovered, that trialkyltin hydrides reacted with alkyl halides according to a radical-chain mechanism involving short-lived triallyltin radicals. Further work of Barton [12] led to discovery of a very synthetically important method of deoxygenation of secondary alcohols *via* their conversion into xanthates followed by reaction with tributyltin hydride. Nowadays organotin derivatives are important synthetic intermediates; their utility and synthesis are described in numerous monographs [13,14,15,16].

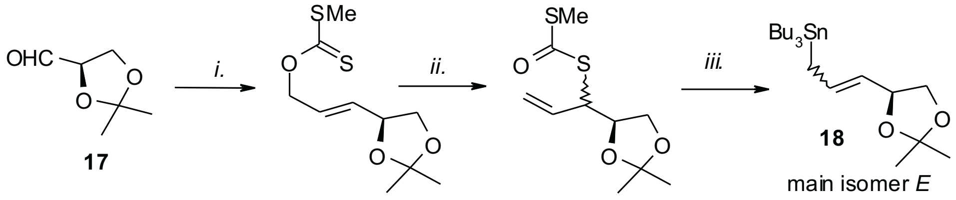
The C–Sn bond is covalent, what makes organotin compounds stable enough to be isolated in a pure form. Their stability is so high that for introduction of some functional groups the activation of the Sn–C bond is required [14]. Tin atom is more electropositive than the carbon, so organostannanes exhibit the reactivity as carbanion or radical. The strength of the C–Sn bond is dependent on the nature of organic substituent and can be arranged in the following order [17]: allyl ~ benzyl < indenyl < ethynyl < phenyl ~vinyl < alkyl. Since the Sn–allyl bond is weaker than C–alkyl bond, allylic stannanes of the general formula $(Alkyl)_3SnCR_2CR{=}CR_2$ might be regarded as convenient sources of a C_3 (allyl) fragment. The dissociation energy of C–Sn linkage in allyltins [18] is similar to the strength of the Sn–H bond, so this linkage is easily split into alkyltin and allyl radicals. The allylation of organic compounds under radical conditions has found, therefore, a wide application in organic synthesis since the beginning of seventies [19]. Important feature of this method is the compatibility of radical allylation with the presence of various functional groups present in alcohols, acetals, esters, oxiranes, ketones and even aldehydes [20]. Preparation of allyl *C*-glycosides may serve as an example [21] of this method. No wonder, therefore, that allyltin derivatives are one of the most useful classes of synthetic intermediates among organic stannanes.



Generally, two main classes of these derivatives should be considered: *i.* allyltins, in which the only heteroatom placed directly at the allylic system is the tin atom (compounds **15** and **15**′) and *ii.* alkoxy-allyltins (**16** and **16**′). Primary allyltin derivatives **15** are more thermodynamically stable than secondary ones; the latter isomerize easily to **15** in the presence of even mild Lewis acid [22]. α-Alkoxyallyltins **16** on treatment with non-chelating strong Lewis acids (preferably boron trifluoride etherate) isomerize to γ-alkoxy-derivatives **16**′ [23]; this is one of the most useful methods of the preparation of such compounds. This paper will deal only with compounds of type **15** and **15**′. Moreover, it will be limited to derivatives in which the substitutent R is a sugar unit. Such organization of the presentation results from the high synthetic potential of sugar allyltins in the preparation of optically pure complex carbocyclic products. The methodology presented here can be complementary to other 'standard' methods of the synthesis of enantiomerically pure carbocycles.

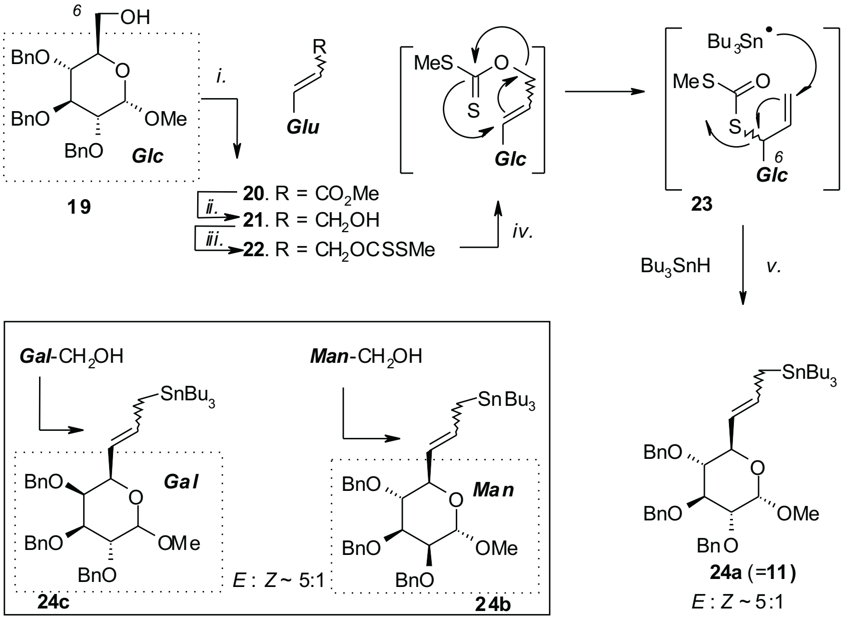
2.2. Preparation of allyltin derivatives of simple monosaccharides by a 'xanthate' reaction

Although a number of methods can be used for the preparation of allyltin derivatives [13,15,24,25], they are hardly applicable to sugars. Most of the methods do not afford any sugar allyltins and quite often lead to decomposition of sugar substrates [15]. The most reliable and reproducible processes are radical reactions *e.g.* reactions of the allylic derivatives with stannyl radicals. Usually sulfur derivatives, such as thiocarbonates [25], sulfones [26], aryl sulfides [27] *etc.* are used as allyl components. One of the most convenient methods consists of the conversion of allylic alcohols into xanthates followed by a thermal [3,3] rearrangement into thiocarbonates and subsequent reaction with Bu$_3$SnH, what leads finally to allyltins usually as a mixture of geometrical isomers. This method proposed by Ueno and coworkers [25] was applied by Mortlock and Thomas [28] in the first synthesis of sugar allyltin derivative **18** from 2,3-*O*-isopropylidene-D-glyceraldehyde (**17**; Scheme 1).



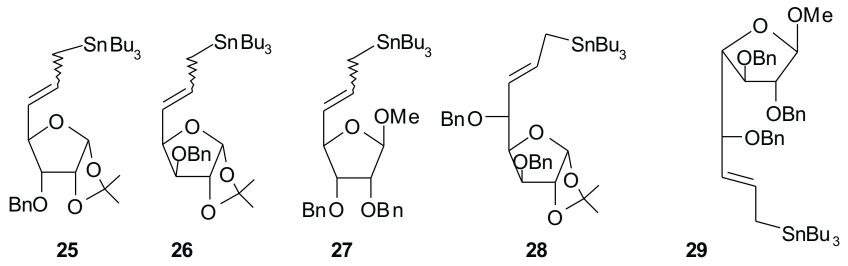
Scheme 1. *i*. 1. $Ph_3P=CHCO_2Me$; 2. DIBAL-H; 3. $NaH/CS_2/MeI$; *ii*. 80°C; *iii*. Bu_3SnH

We applied the same methodology for the preparation of more complex allyltins as shown in Scheme 2 [8]. The important feature of this methodology was formation of a mixture of sugar allyltins **24** with the *E*-isomer highly predominating ***regardless*** of the geometry across the double bond in starting allyl alcohol. As we proved, a mixture of the same composition of the *E/Z* isomers was obtained either from the pure *E* or pure *Z* or a 1:1 mixture of both isomers [29].



Scheme 2. *i*. 1. $(COCl)_2$, DMSO, Et_3N, 2. $Ph_3P=CHCO_2Me$, 80%; *ii*. DIBAL-H, –23°C, 80%; *iii*. 1. THF, NaH, 30 min. 2. CS_2, 2 h, 3. MeI, 2 h; *iv*. toluene, 110°C, 2 h; *v*. toluene, 110°C, 0.5 h.

Derivatives of furanoses can be prepared in the same way. Several examples of furanos-allyltins prepared by us [30] are presented in Fig. 3.



25 26 27 28 29

Figure 3. Examples of furanos-derived primary sugar allyltins prepared by a 'xanthate' methodology.

Although this method is reproducible and provides sugar allyltins in good yields, it has one main limitation. The allyltins obtained by the 'xanthate' methodology are always mixtures of geometrical isomers with the *E*-one strongly predominated ***regardless*** of the configuration across the double bond in starting allylic alcohol. For many synthetic purposes (*e.g.* for reaction with aldehydes under high pressure or high temperature leading to homoallylic alcohols [24]) the pure geometrical isomers are required. The accessibility to the *Z*-sugar allyltin is very limited by the 'xanthate' method.

2.3. Preparation of sugar allyltins by reaction reaction with tributyltin cuprate (Bu_3SnCu)

Pure geometrical isomers of sugar allyltins may be prepared by reaction of the corresponding allylic derivatives with tin nucleophiles, represented by tributyltin cuprate ('Bu_3SnCu') [31], tributyltin lithium (Bu_3SnLi) [14,32] or tributyltin sodium (Bu_3SnNa) [33]. These nucleophiles can react either in an S_N2 or S_N2' mode (Fig. 4-I). All these reagents were tested in reaction with sugar allylic bromides (X = Br), and mesylates (X = OMs). Only tributyltin cuprate reacted satisfactorily with sugar allylic derivatives; the other two compounds either did not react at all or caused decomposition of the starting material [34].

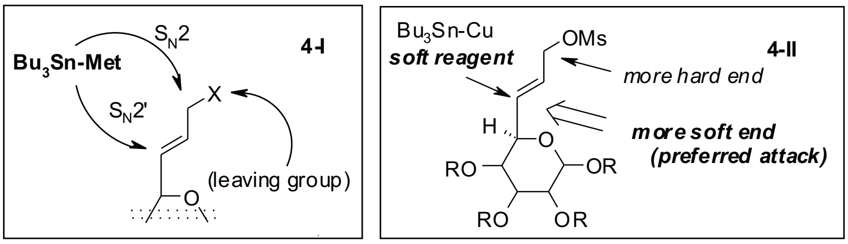
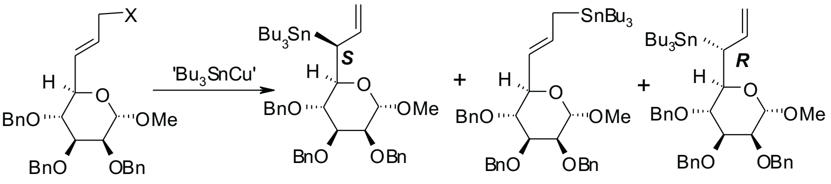


Figure 4. Regioselectivity of formation of sugar allyltins.

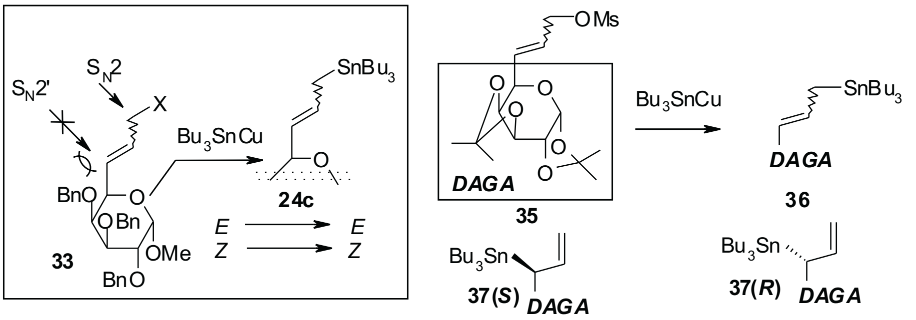
Tributyltin cuprate is a very soft nucleophile. One can expect, therefore, that the regioselectivity of the reaction with sugar electrophiles should depend on the nature of the leaving group (substituent X). If this leaving group has a soft character (*e.g.* iodine) the S_N2 process should dominate; if X is hard (*e.g.* X=OMs; Fig. 4-II) the secondary allyltin (from the S_N2' reaction) should be formed as the main product. Indeed, reaction of Bu_3SnCu with derivatives of methyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-6,7-dideoxy-oct-7(*E*)-eno-pyranoside (**30a–d**) fully confirmed our assumption (Fig. 5). The highest yield of the secondary derivative **31** was obtained in reaction of **30d** with the 'hard end'. Moreover, only one stereoisomer of secondary allyltin was formed, to which the (***S***)-configuration at the newly created stereogenic center was assigned [34].



	31(*S*)	**32**	**31(*R*)**
30a. X = Cl	50%	2%	0%
30b. X = Br	30	16	traces
30c. X = I	*18*	*20*	*0*
30d. X = OMs	***57.5***	***2.5***	***0***

Figure 5. Reaction of sugar allylic derivatives with metallated tributyltin reagents.

The galactose derivatives represent a special case. Because of the strong shielding of the C-6 center in **33** (Fig. 6) the S_N2' process is rather unlikely [29].



35(*E*) ⟶ **36(*E*)**

35(*Z*) ⟶ **36(*Z*)** + **37(*S*)**+ **37(*R*)** in the ratio: 50:8:5

Figure 6. Reaction of allylic derivatives of galactose with Bu_3SnCu.

Situation is slightly different for diacetonogalactose derivatives. Mesylate (***E***)**-35** reacted with Bu_3SnCu to afford only the primary organometallic derivative (***E***)**-36**, while the *Z*-isomer upon treatment with the same reagent furnished – besides the primary product (***Z***)**-36** – also the secondary isomers **37** in small yields. It is worth to mention, that these secondary sugar allyltins were formed in comparable amounts [35]. This method can be applied also for other sugar electrophiles. The furanose derivatives of sugars provided secondary allyltins on reaction with (Bu_3SnCu). It is very interesting that the configuration of the regioisomer formed in this process ***was not dependent*** on the geometry of starting allylic mesylate. From both geometrical isomers (***E***)-**38** and (***Z***)-**38** the same derivative **40** with the (***S***)-configuration at the C5 was obtained [35]!

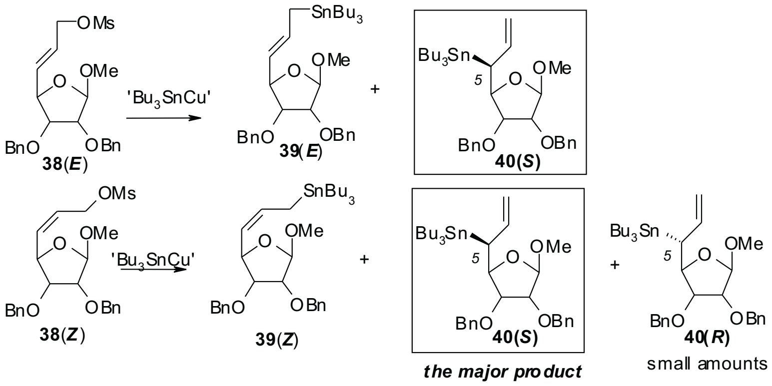


Figure 7. Reaction of allylic derivatives of furanoses with Bu_3SnCu.

Another class of sugar allyltins (represented by **42** and **43** in Fig. 8) was prepared by Marshall and Elliott [36], by the S$_N$2′ addition of Bu_3SnCu to the α,β-unsaturated sugar aldehyde **41**, followed by trapping the intermediate with silyl chloride. These organometallic derivatives were further used in the synthesis of higher carbon sugars.

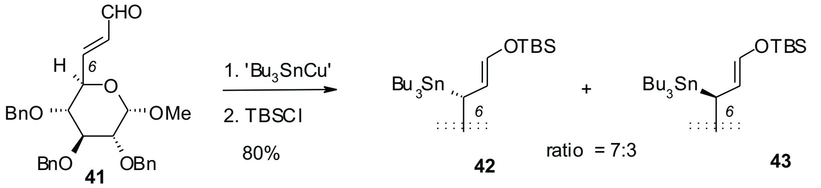


Figure 8. Synthesis of sugars alkoxyallyltins by Marshall and Elliott.

3. Controlled fragmentation of sugar allyltins

3.1. Fragmentation induced with a Lewis acid

Sugar allyltins are convenient precursors of highly oxygenated dienoaldehydes, which are formed by a controlled fragmentation. We observed this unusual rearrangement, while working on the synthesis of higher carbon sugars by a coupling of the primary sugar allyltins with sugar aldehydes catalyzed with titanium tetrachloride [7]. Optimization of this method was done by replacement of $TiCl_4$ with zinc chloride, and this method became now a standard preparation in our laboratory le-

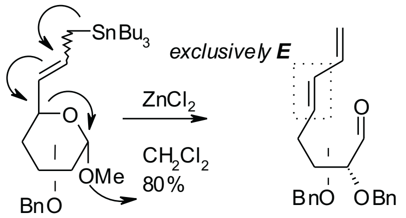
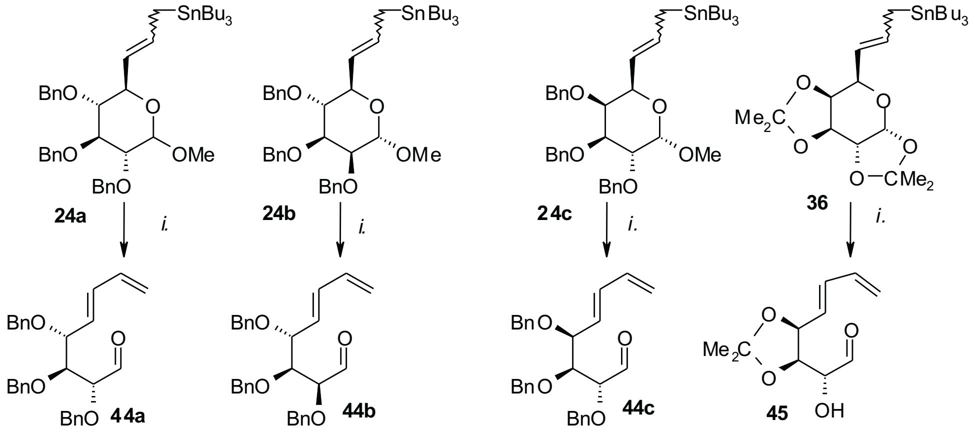


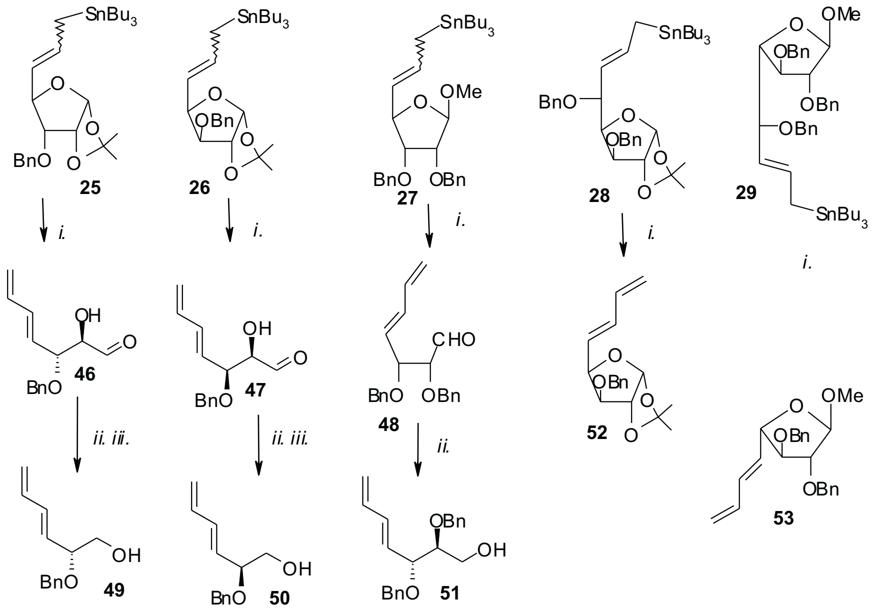
Figure 9. Preparation of dienoaldehydes by a controlled decomposition of sugar allyltins.

ading to highly oxygenated enantiomerically pure dienoaldehydes with the *E*-configuration across the internal double bond (Fig. 9) [8,30].



Scheme 3. *i*. $ZnCl_2$, CH_2Cl_2, room temperature, 1 h, 80%.

Several dienoaldehydes **44a–c** [8], and **45** [37] derived from homologated D-glucose (**24a**), D-mannose (**24b**) and D-galactose (**24c** and **36**) were obtained in good yields (Scheme 3) by this method. This method can be also applied for the conversion of furanose allyltins into the dienes [30] (Scheme 4).



Scheme 4. *i*. $ZnCl_2$; *ii*. $NaBH_4$; *iii*. $NaIO_4$ then $NaBH_4$.

A number of different highly oxygenated sugar-derived dienes **46–53** were prepared in high yields and with very high stereoselectivity by this simple method [30].

3.2. Thermal stability of sugar allyltins

The behavior of sugar allyltins at high temperature is interesting. While the primary isomers were stable up to 214°C (boiling trichlorobenzene), the secondary derivatives underwent fragmentation in boiling xylene (140°C) with elimination of the stannyl moiety providing the product identified as dienoaldehyde, but with the *Z*-geometry across the internal double bond [34]. This observation opened a new, very interesting possibility in stereocontrolled organic synthesis of highly oxygenated carbobicyclic derivatives in enantiomerically pure form (described in chapter 5). While fragmentation of the primary isomers with Lewis acid provided the *E*-dienes as the only products [34,38] (Scheme 4), thermal decomposition of the secondary ones gave the *Z*-dienes. Both geometrical isomers (*E* or *Z*) of dienoaldehydes, therefore, are easily available in pure form, either by treatment of the primary sugar allyltin with zinc chloride (→ *E* regardless of the geometry of starting allyltin), or by a controlled thermal fragmentation of a secondary organometallics (only one stereoisomer formed in reaction of sugar allylic mesylates with Bu_3SnCu). Interestingly, this secondary isomer decomposed to the *E*-diene upon treatment with $ZnCl_2$ [34]. The basic idea of this methodology is presented in Fig. 10.

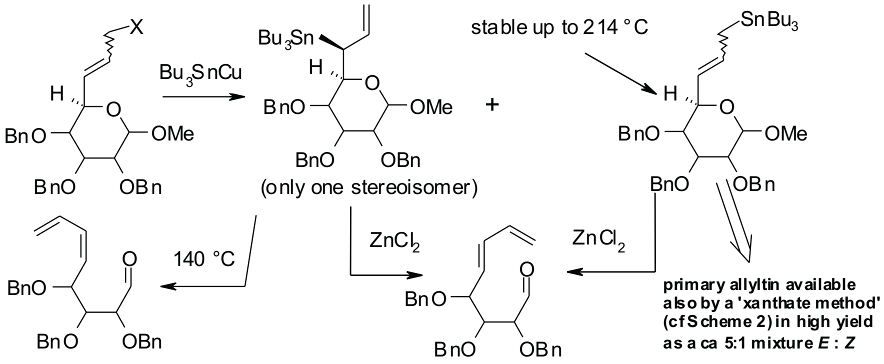


Figure 10. Behavior of sugar allyltins at high temperature and in the presence of $ZnCl_2$.

Several *Z*-dienoaldehydes were prepared form secondary sugar allyltins – the exclusive (or major) products of the reaction of sugar allylic mesylates with BuSnCu [34] (Fig. 11).

This very interesting and useful behavior of sugar allyltins needs explanation. We do not know yet the mechanism of fragmentation induced with a Lewis acid leading to the *E*-dienes regardless of the configuration of starting allyltin. But a highly stereoselective thermal fragmentation of the secondary isomers can be explained assuming the concerted process of the elimination of the stannyl moiety.

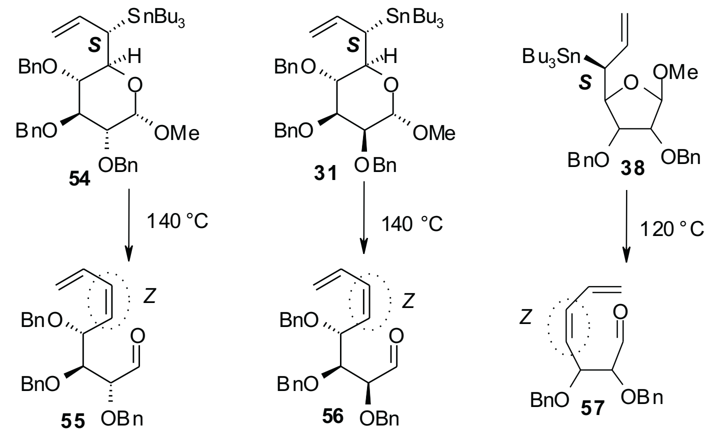


Figure 11. Thermal fragmentation of secondary sugar allyltins.

3.2.1. Mechanism of thermal fragmentation of secondary sugar allyltins and determination of their absolute configuration

One may postulate either *anti* (E2) or *syn* elimination (both are concerted) or, eventually, the radical mechanism of this fragmentation reaction. The latter (Fig. 12) will require cleavage of the carbon–oxygen bond under radical conditions; such process, although not common, is known [39]. To check if radicals are involved in fragmentation of secondary sugar allyltin derivatives, compound **31**was heated at 140°C in the presence of Bu_3SnH and in a separate experiment with $(Bu_3Sn)_2$. ***No formation*** of either a reduced product **57** or a primary (*Z* or *E*) allylstannane **24b** (which is stable up to at least 214°C) was noted, what rather excluded the radical mechanism of fragmentation.

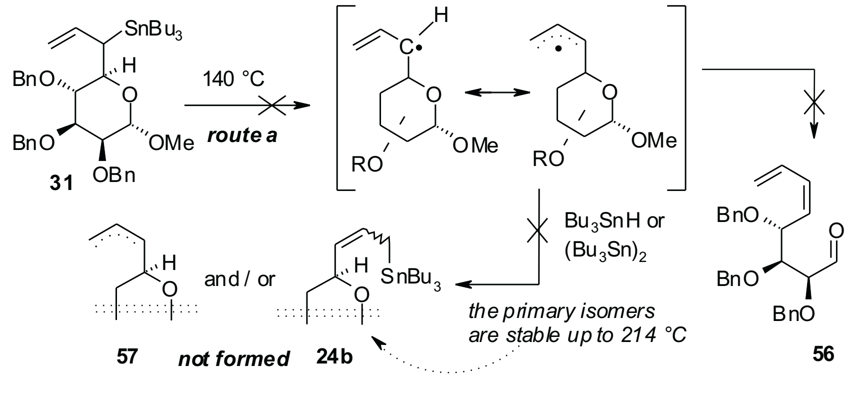


Figure 12. The (excluded) radical mechanism of decomposition of **31**.

At least, two other possible mechanisms of such elimination are possible (concerted: *anti* or *syn*). If the process of a controlled fragmentation of secondary sugar allyltins proceeds according to one of them, both stereoisomeric organometallics (*e.g.* **31**) differing in the configuration at the stereogenic center bearing the stannyl group, should decompose to dienoaldehydes with the ***opposite*** configurations across the internal double bond. Although in reaction of sugar allyl mesylates with Bu_3SnCu only one stereoisomer is formed we were able to isolate traces of the opposite isomer from reaction of **30d** (cf Fig. 5). Heating of both isomers in boiling xylene (140°C) indeed resulted in formation of the *Z*-diene **56** from the main isomer **31(*S*)** and the *E*-dienoaldehyde **44b** from the minor one (obtained in < 1% yield in reaction of the corresponding mesylate with Bu_3SnCu) stereoisomer [34] (Fig. 13).

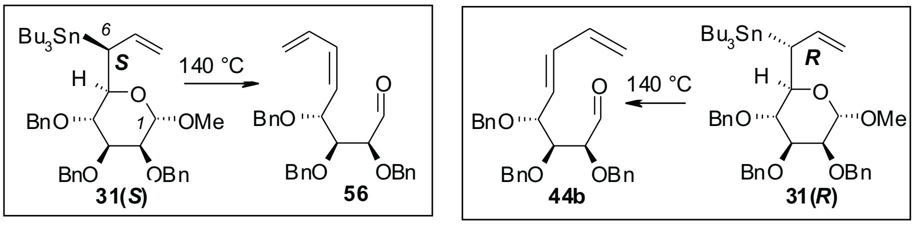


Figure 13. Thermal decomposition of ***isomeric*** secondary sugar allyltins.

This result pointed unequivocally on the concerted mechanism of this thermal fragmentation, but the question was, which one: *syn* or *anti*. We suggest, that more likely was the *anti*-(E2) elimination as shown in Fig. 14, which is consistent with the literature data [40] proposed for thermal fragmentation of β-stannylalcohols and β-stannylesters.

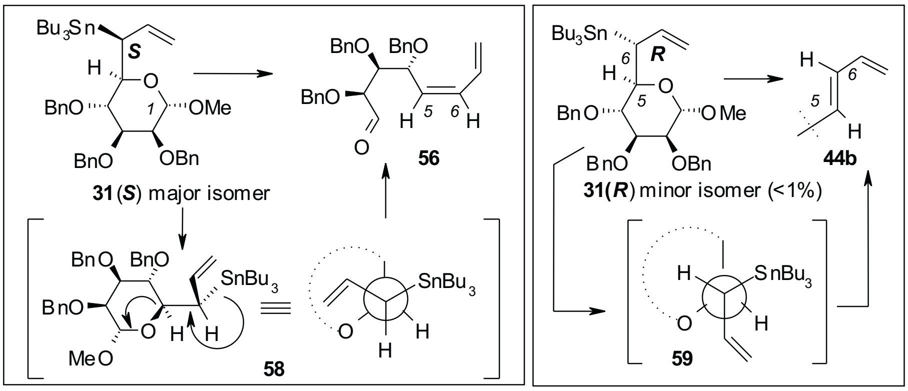
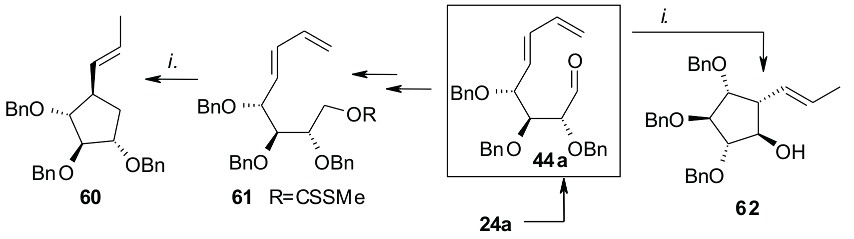


Figure 14. Stereochemical models for the controlled decomposition of secondary sugar allyltins.

The knowledge of the mechanism of this process would enable also to determine the configuration at the secondary stereogenic center bearing the stannyl group. Determination of the configuration of tin derivatives is not trivial, however, their structure may be often deduced from the products of their controlled fragmentation [41] if the mechanism of such process is known. If we assume the *anti*-elimination mode, as shown in Fig. 14, the C6(*S*)-configuration can be safely assigned to the main isomer **31** and the C6(*R*) to the product which is formed in less than 1% yield in reaction of **30b** with Bu_3SnCu.

4. Synthesis of monocarbocyclic derivatives from sugar-derived dienoaldehydes

The dienoaldehydes obtained can serve as precursors of monocyclic as well as bicyclic, highly oxygenated derivatives. Since the chemistry of monocyclic analogues are very well explored [1,2,42] we tested only one type of reaction for the preparation of cyclopenanes as shown in Scheme 5 [43].



Scheme 5. *i*. Bu_3SnH/AIBN.

Aldehyde **44a** (obtained by a controlled fragmentation of a D-*gluco* configurated allyltin **24a** (*c.f.* Scheme 3) was treated with tributyltin hydride under radical conditions to afford cyclopentane **62** as a single stereoisomer, although in moderate yield [43]. Alternatively, conversion of the aldehyde **44a** into the xanthate **61** followed by radical cyclization gave compound **60** [43].

5. Synthesis of carbobicyclic derivatives from sugar allyltins

In this chapter the approach to highly oxygenated bicyclo[4.3.0]nonene and bicyclo[4.4.0]decene derivatives from sugar allyltins will be presented. The general idea is shown in Fig. 15.

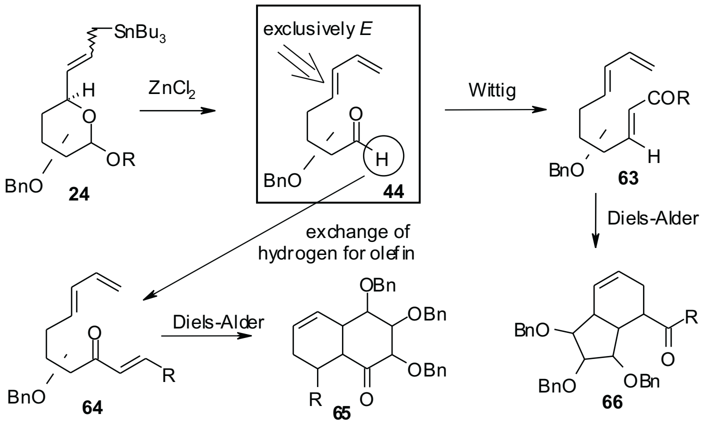
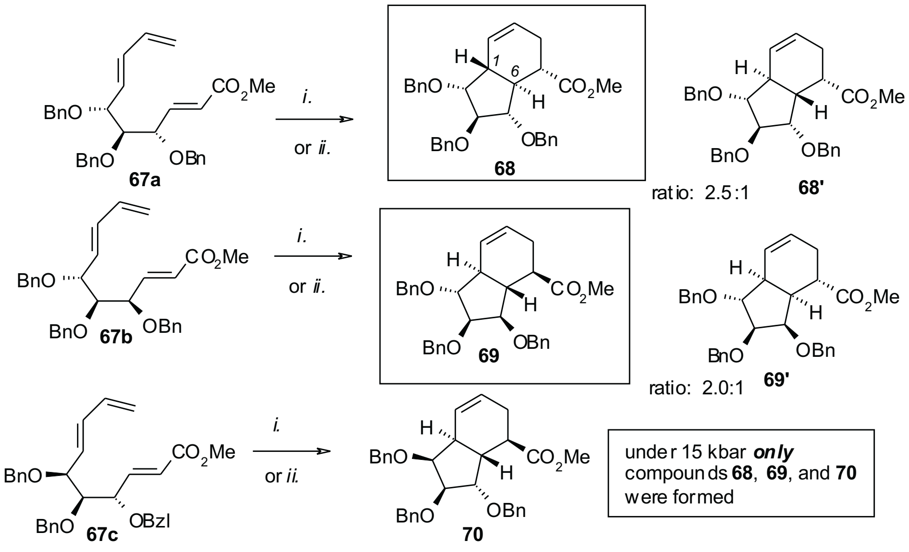


Figure 15. Synthesis of highly oxygenated perhydroindanes and decalines from of sugar allyltins.

The primary sugar allyltin (**24**) is converted into the dienoaldehyde **44** with the *E*-geometry across the internal double bond (*c.f.* Scheme 3). The Wittig homologation should afford the triene **63**, cyclization of which should lead to bicyclo[4.3.0]nonene **66**. Alternatively, the hydrogen atom in this aldehyde **44** could be replaced by a (substituted) vinyl function providing (regioisomeric to **63**) triene **64**, which would cyclize to bicyclo[4.4.0]decene **65**. The synthetic plan was designed for *E*-aldehyde **44**, however, the *Z*-aldehydes are also readily available (*c.f.* Fig. 11) what will allow to synthesize different stereoisomers of **65** and **66** by this methodology.

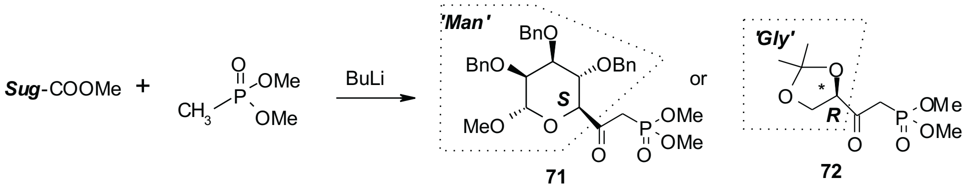
5.1. Synthesis of bicyclo[4.3.0]nonenes

The first synthesis of these bicyclic derivatives was performed by us in 1997 [44]. The corresponding dienoaldehydes **44a–c** (*c.f.* Scheme 3) were reacted with the simplest stabilized Wittig reagent ($Ph_3P{=}CHCO_2Me$) to afford the trienes **67a–c** (Scheme 6). Cyclization to the bicyclic derivatives was induced either by aluminum trichloride or high pressure. Reaction under high pressure was highly stereoselective and provided single stereoisomers, while in a catalyzed process a mixture of isomers were obtained from the D-*xylo*- (**67a**) and D-*lyxo*- (**67b**) trienes. The junction between both ring was *trans*- what resulted form the *endo*-transition state of this intramolecular Diels-Alder reaction (Scheme 6).



Scheme 6. *i.* $AlCl_3$ (78–85%); *ii.* 15 kbar (*ca* 80% yield in each case).

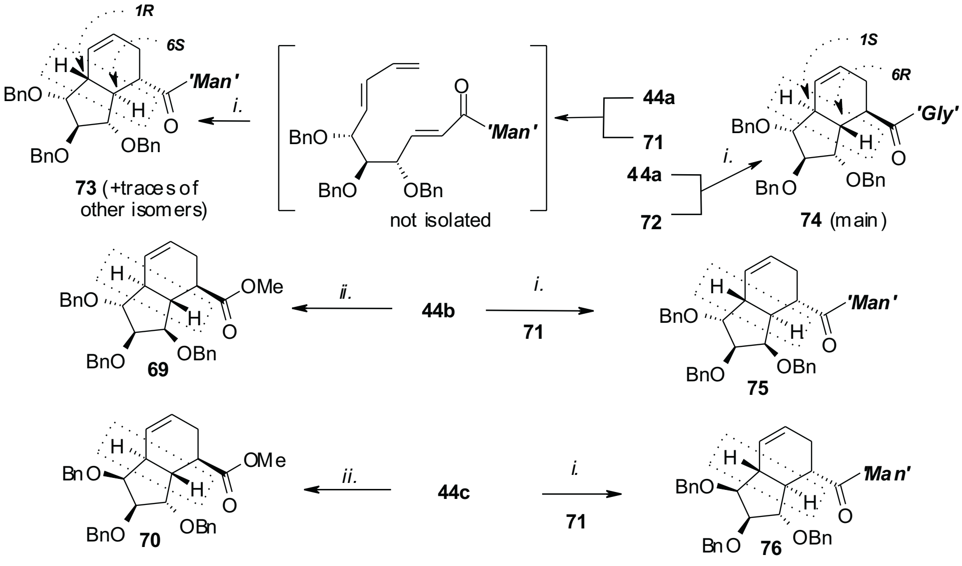
Can the absolute configuration at the ring junction (*i.e.* at C1 and C6) be changed? To test this possibility we reacted the trienes not with achiral Wittig reagent (Ph_3PCHCO_2Me), but with chiral one, $Ph_3P{=}CHCOR^*$. Synthesis of such sugar derived Wittig type reagents is presented in Scheme 7.



Scheme 7. *i*. BuLi, THF, –78°C, 80–90%.

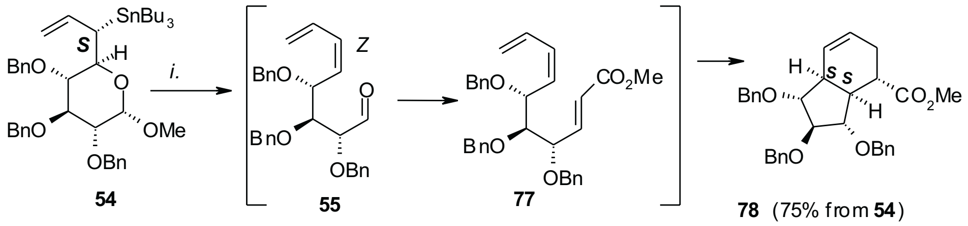
The corresponding methyl uronate (derived from D-mannose or D-glyceraldehyde) upon reaction with dimethyl methylphoshonate anion afforded in high yield the phosphonates **71** [45] (with the *S*-configuration at the neighboring center and **72** [46] (the *R*-configuration).

Reaction of D-*xylo*-dienoaldehyde **44a** with the phosphonate **71** gave compound **73** with the 1(*R*),6(*S*) configuration, while the phosphonate **72** upon the same process gave the bicycle **74** with the opposite configurations at these two stereogenic centers. The same tendency was observed for dienoaldehydes **44b** and **44c**. The configuration of these two centers can be changed, although still the relative geometry is *trans* [46] (Scheme 8).



Scheme 8. *i*. toluene, K_2CO_3, 18-crown-6, room temp.; *ii*. 1. $Ph_3P{=}CHCO_2Me$; 2. cyclization.

Thus, the desired bicylo[4.3.0]nonene system is available by a proper choice of the reactants. The *E*-dienoaldehydes **44** reacted with the Wittig type reagents to afford trienes, which undergo the intramolecular Diels-Alder reaction (IMDA) providing the *trans* perhydroindenes [46]. This is the result of the preferred *endo*-transition state of the IMDA process. Having in hand also the *Z*-dienoaldehydes, we applied them for the preparation of the bicycles with the *cis*-relative configuration between the 6- and 5-membered rings [47] (Scheme 9).



Scheme 9. *i.* boiling xylene (140°C), $Ph_3P{=}CHCO_2Me$, 2 h.

When secondary sugar allyltin **54** was thermally decomposed in the presence of the simplest stabilized phosphorane ($Ph_3P{=}CHCO_2Me$), the *Z*-dienoaldehyde formed (**55**) was converted into the triene **77**, which underwent spontaneous IMDA reaction to the *cis*-bicycle **78** [47].

5.2. Synthesis of bicyclo[4.4.0]decenes

During the synthesis of higher carbon sugars we developed the methodology of a coupling of two sugar sub-units *via* a Wittig type methodology. Sugar phosphoranes [48,49] **79** or phosphonates [45,49] **80** can be used as olefinating reagents to provide the α,β-unsaturated enones in good yields (Fig. 16).

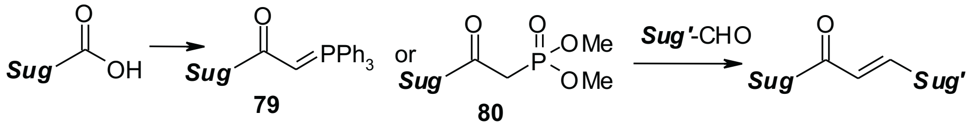
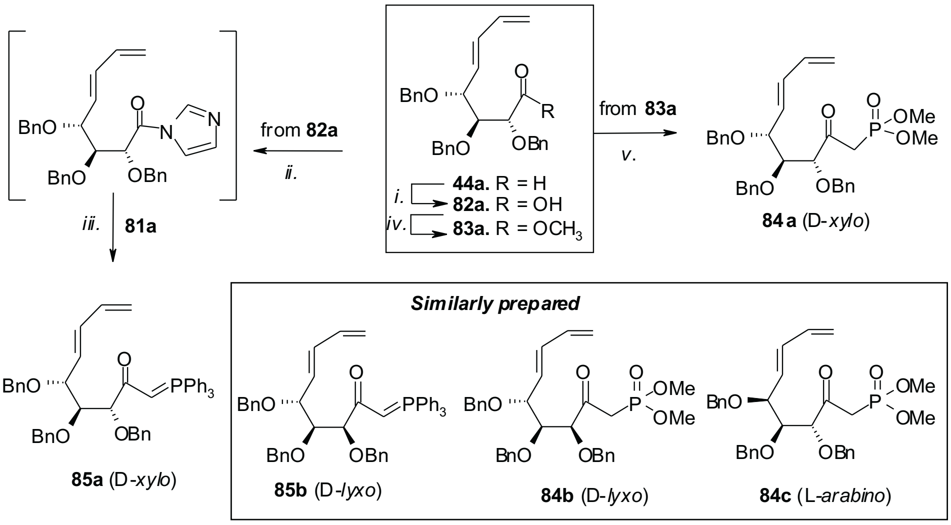


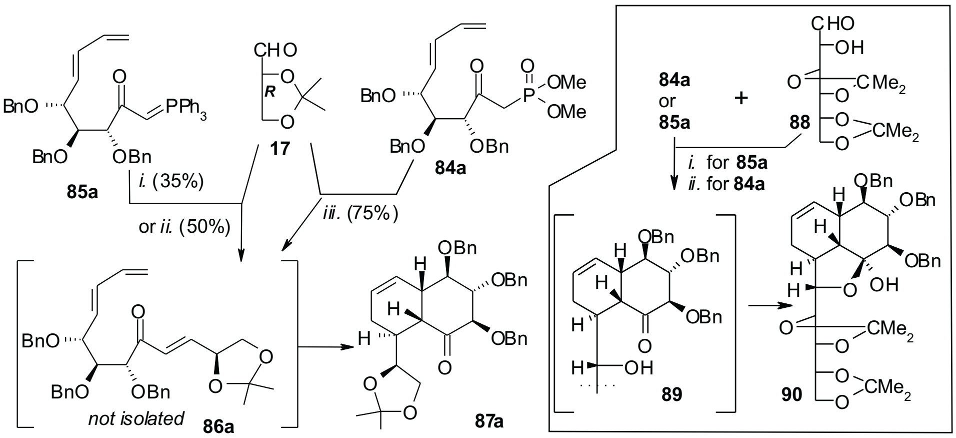
Figure 16. Preparation of higher carbon sugars by a Wittig type methodology.

This methodology was applied for conversion of the dienoaldehydes into the corresponding trienes and is presented in Scheme 10 (exemplified by the synthesis of the Wittig-type reagents with the D-*xylo*-configuration from the aldehyde **44a**).

Aldehyde **44a** was oxidized to an acid **82a**, which can be further transformed into the methyl ester **83a**. The synthesis of the Wittig reagent **85a** was realized by conversion of the acid into the imidazolide **81a** and reaction with the 3 equiv. of $Ph_3P{=}CH_2$ [50]. The phosphonate reagent **84a** was prepared in much higher yield (86% *vs.* 55% of the phosphorane) by reaction of the methyl ester **83a** with dimethyl methylphosphonate anion [51]. Both reactive intermediates were precursors of the olefins; the goal faced by us – replacement of the hydrogen atom in aldehyde **44** with an olefinic function – was therefore achieved. Both Wittig-type reagents were used for the synthesis of the sugar-derived trienes. The model reaction with 1,2-*O*-isopropylidene-D-glyceraldehyde (**17**) is shown in Scheme 11. Phosphorane **85a** was extremely



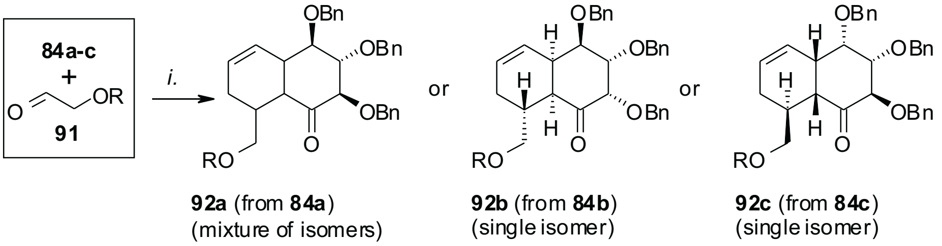
Scheme 10. *i.* Jones' oxidation; *ii.* N,N-carbonyl diimidazole, benzene, r.t. 15 min.; *iii.* $Ph_3P=CH_2$, (3 equiv.), benzene r.t. 2 h. 55% from **44a**; *iv.* CH_2N_2; *v.* $MeP(O)(OMe)_2$; BuLi, THF, 15 min., 86%.



Scheme 11. *i.* xylene, reflux; *ii.* toluene, 10 kbar; *iii.* K_2CO_3, 18-crown-6, toluene, r.t.

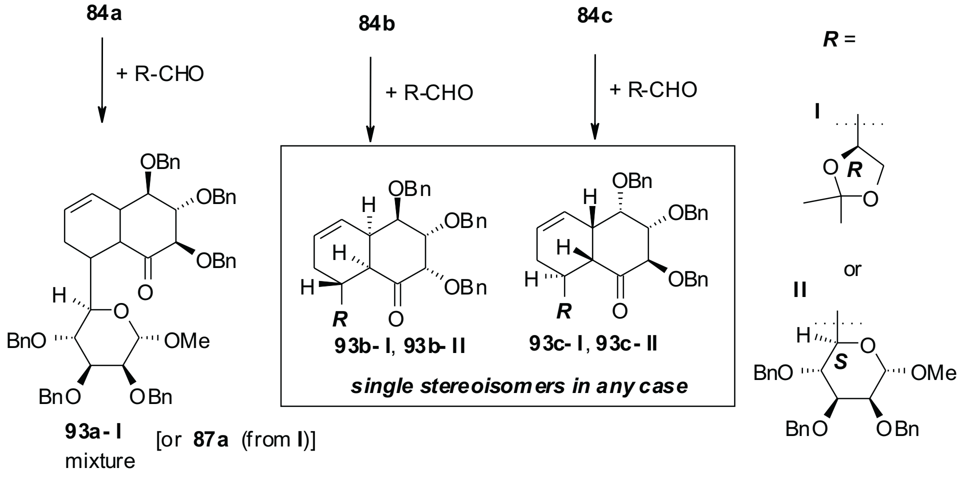
unreactive, and the procees can be conducted only at high temperature (boiling xylene) or under high pressure (10 kbar). The triene **86a** formed under these conditions cyclized *in situ* providing the bicyclic derivative **87a** as single stereoisomer [50]. The yield of this tandem reaction was not, however, very impressive and varied from 35% (at 140°C) to 50% (10 kbar). Calculating also the rather low yield in the synthesis of phosphorane **85a** (55% yield from **44a**), the overall yield of **87a** is very low (19–27%). Much more efficient is the reaction of the phosphonate **84a** with the aldehyde performed under mild phase transfer conditions (K_2CO_3/toluene/18-crown-6, room temp.), which afforded the same bicycle **87a** in 75% yield (overall calculated on **44a** is 65%) [51].

This reaction was also applied for the preparation of derivative **90**, obtained in a moderate yield from phosphorane **85a** and aldehyde **88** and in good yield from phosphonate **84a** and **88** [50,51]. Further studies were performed using the phosphonates **84** instead of classical Wittig reagents **85**. First, we reacted the corresponding phosphonates **84** with the simplest achiral sugar like aldehyde **91** (Scheme 12).



Scheme 12. *i*. K_2CO_3, 18-crown-6, toluene, r.t.

Reaction of the phosphonates **84a–c** with **91** under the mild phase transfer conditions provided the corresponding trienes, which underwent spontaneous cyclization to **92**. When the same reaction was conducted with chiral aldehydes (derivatives of the D-mannose and D-glyceraldehyde; see Scheme 13) the corresponding bicycles **93** were formed in high yields. As may be seen from Schemes 12 and 13, the configuration at the ring junction does not depend on the configuration of the aldehyde used [achiral **91**, or chiral: mannose (α-*S*) and D-glyceraldehyde (α-*R*) derivatives].



Scheme 13. *i*. K_2CO_3, 18-crown-6, toluene, r.t.

This results can be explained by the *endo* transition state of the IMDA process which is exemplified by the cyclization of the triene **94** (obtained from phosphonate **84b**) [51]. As may be seen in Fig. 17 the stereogenic centers of the aldehyde are too distant to influence the steric course of this IMDA process.

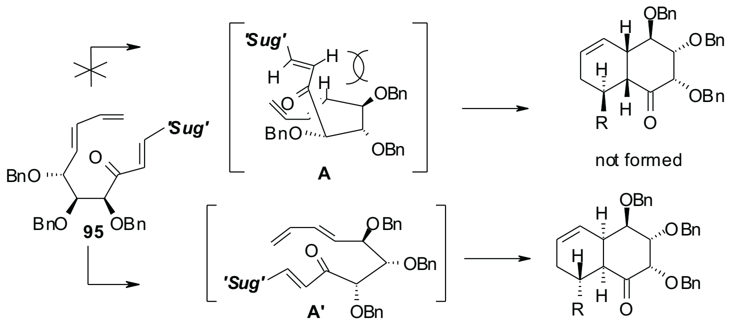


Figure 17. Stereochemical models of cyclization of triene **95**.

6. Perspectives

Enantiomerically pure carbobicyclic derivatives are available from sugar allyltins. These organometallics can be easily prepared either by a xanthate methodology or by reaction of properly activated sugar allylic derivatives (*e.g.* mesylates) with tri-(butyl)tin cuprate. The allyltins undergo a controlled fragmentation either to the *E*- or Z-dienoaldehyes, which can be further converted into the bicyclic, highly oxygenated derivatives. The highly stereoselective preparation of such bicycles involves simple and well defined transformations (Wittig-type and Diels-Alder reactions).

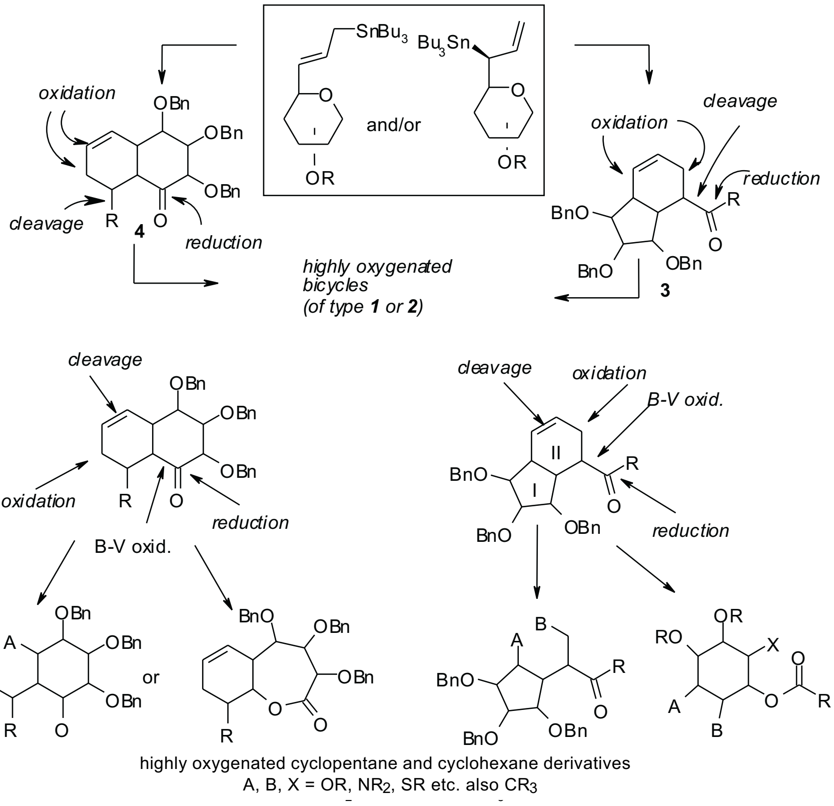


Figure 18. A concise approach to highly oxygenated carbocyclic and carbobicyclic derivatives from sugar allyltins.

The ready access to such derivatives opens a convenient an useful route to both: mono- and bicyclic highly oxygenated derivatives in enantiomerically pure form (Fig. 18). We already proved that osmylation of compounds of type **3** [44] and **4** [52] is highly stereoselective, but epoxidation process provides usually a mixture of stereoisomers in comparable amounts [52]. Further study on the conversion of **3** and **4** into highly oxygenated bicyclic and monocyclic derivatives are in progress.

Acknowledgments

This work was supported by a Grant **4 T09A 107 23** from the Polish State Committee for Scientific Research, which is gratefully acknowledged.

REFERENCES

1. Brammer L.E. and Hudlicky T., *Tetrahedron:Asymmetry,* **9**, 2011 (1998) and references therein.
2. Suami T. and Ogawa S., *Adv. Carbohydr. Chem., Biochem.,* **48**, 22 (1990); Gomez A.M., Danelon G.O., Valverde S. and Lopez J.C., *J. Org. Chem.*, **63**, 9626 (1998) and references therein.
3. Mehta G. and Ramesh S.S., *Chem. Commun.,* 2429 (2000); Mehta G. and Ramesh S.S., *Tetrahedron Lett.,* **42**, 1987 (2001).
4. Hanessian S., *Total Synthesis of Natural Products: The Chiron Aproach*, Pergamon Press, New York, (1983); Fraser-Reid B., *Acc. Chem. Res.*, **29**, 57 (1996) and references therein.
5. Herczegh P., Zsely M., Szilagyi L., Bajza I., Kovacs A., Batta G. and Bognar R., *Cycloaddition Reactions in Organic Chemistry,* 112 (ACS Symposium Series **494**, Guiliano R.M. Edition 1992) and references therein.
6. Pindur U., Lutz G. and Otto Ch., *Chem. Rev.*, **93**, 741 (1993); Roush W.R., Koyama K., Curtin, M.L. and Moriarty K.J., *J. Am. Chem. Soc.*, **118**, 7502 (1996); Shiina J. and Nishiyama Sh., *Tetrahedron*, **59**, 6039 (2003).
7. Jarosz S. and Fraser-Reid B. *J. Org. Chem.*, **54**, 4011 (1989).
8. Kozłowska E. and Jarosz S., *J. Carbohydr. Chem.*, **13**, 889 (1994).
9. Farkland E., *J. Chem. Soc.,* **2**, 263 (1849).
10. Pope W.J. and Peachey S.J., *Proc. Chem. Soc.,* **19**, 290 (1903).
11. Kuivila H.G., Menapace L.W. and Warner C.R., *J. Am. Chem. Soc.,* **84**, 3584 (1962); Kuivila H.G., *Adv. Organomet. Chem.,* **1**, 47 (1964).
12. Barton D.H.R. and McCombie S.W., *J. Chem. Soc., Perkin Trans. 1,* 1574 (1975); Barton D.H.R. and Motherwell W.B., in *Organic Synthesis Today and Tomorrow,* (Trost B.M. and Hutchinson C.R. Eds, Pergamon, Oxford, 1981).
13. Giese B., "*Radicals in Organic Synthesis: Formation of a Carbon-Carbon Bond*", Pergamon Press, New York (1986); Pereyre M., Quintard J.-P., Rahm A., "*Tin in Organic Synthesis*", Butterworth: London (1987); Mikołajczyk M., Drabowicz J. and Kiełbasiński P. in *Houben-Weyl, Methods in Organic Chemistry,* vol. E21, chapter D10; Thomas E.J., in *Houben-Weyl, Methods in Organic Chemistry,* vol. E21, p.1508; Davies A.L. *"Organotin Chemistry"*, VCH, Weinheim, New York (1997); *see also: Encyclopedia of Reagents for Organic Synthesis* (Wiley & Sons Ed. 1995; Editor-in-Chief, Paquette, L.), *vol 7,* pp. 5000 – 5039 *and references therein*.
14. Sato T., *Synthesis,* 259 (1990).
15. Jarosz S. and Kozłowska E., *Polish J. Chem.*, **72**, 815 (1998).
16. Jarosz S. and Zamojski A., *Curr. Org. Chem.,* **7**, 13 (2003).
17. Gielen M., *Acc. Chem. Res.*, **6**, 198 (1973).
18. Neumann W.P., *Angew. Chem. Int. Ed. Engl.*, **8**, 287 (1969); Kawakami K. and Kuivila H.G., *J. Org. Chem.*, **34**, 1502 (1969).
19. Kosugi M., Kurino K., Takayama K. and Migita T., *J. Organometal. Chem.*, **56**, C11 (1973).

20. Grignon J., Servens C. and Pereyre M., *J. Organometal. Chem.*, **96**, 225 (1975); Keck G.E. and Yates J.B., *J. Am. Chem. Soc.*, **104**, 5829 (1982); Kosugi M., Arai H., Yoshino A. and Migita T., *Chem. Lett.*, 795 (1978).
21. Keck G.E., Enholm E.J. and Kachensky D.F., *Tetrahedron Lett.,* **25**, 1867 (1984).
22. Verdone J.A., Mangravite J.A., Scarpa N.M. and Kuivila H.G., *J. Am. Chem. Soc.,* **97**, 843 (1975).
23. Quintard J.P., Elissondo B. and Pereyre M., *J. Org. Chem.,* **48**, 1559 (1983); Naruta Y. and Maruyama K., *J. Chem. Soc., Chem. Comm.,* 1264 (1983).
24. Yamamoto Y., Yatagi H., Ishihara Y., Maeda N. and Maruyama K., *Tetrahedron*, **40**, 2239 (1984); Yamamoto Y., *Acc. Chem. Res.*, **20**, 243 (1987); Yamamoto Y. and Asao N., *Chem. Rev.*, **93**, 2207 (1993); Sumida Sh-i., Ohga M., Mitani J. and Nokami J., *J. Am. Chem. Soc.,* **122**, 1310 (2000) and references therein.
25. Ueno Y. and Okawara M., *J. Am. Chem. Soc.*, **101**, 1893 (1979); Ueno Y., Aoki S. and Okawara M., *J. Am. Chem. Soc.*, **101**, 5454 (1979); Ueno Y., Sano H. and Okawara M., *Synthesis*, 1011 (1980).
26. Ueno Y., Ohta M. and Okawara M., *J. Organomet. Chem*., **197**, C1 (1980).
27. Keck G.E., Palani A. and McHardy S.F., *J. Org. Chem.*, **59**, 3113 (1994).
28. Mortlock S.V. and Thomas E.J., *Tetrahedron Lett.,* **29**, 2479 (1988).
29. Jarosz S., *Tetrahedron*, **53**, 10765 (1997).
30. Jarosz S., Skóra S. and Szewczyk K., *Tetrahedron: Asymmetry,* **11**, 1997 (2000).
31. Lipshutz B.H., Ellsworth E.L., Dimock S.H. and Reuter D.C., *Tetrahedron Lett*., **30**, 2065 (1989).
32. Seyferth D. and Jula T.F., *J. Organometal. Chem*., **66**, 195 (1974); Seyferth D. and Mammarella R.E., *J. Organometal. Chem*., **177**, 53 (1979).
33. Jones C.H.W., Jones R.G., Parington P. and Roberts R.M.G., *J. Organomet. Chem*., **32**, 201 (1971).
34. Jarosz S., Szewczyk K. and Zawisza A., *Tetrahedron: Asymmetry*, **14**, 1715 (2003).
35. Jarosz S., Szewczyk K. and Zawisza A., *Polish J. Chem*, **77**, 985 (2003).
36. Marshall J.A. and Elliott L.M., *J. Org. Chem.,* **61**, 4611 (1996).
37. Jarosz S., unpublished results.
38. Jarosz S. and Szewczyk K. *Tetrahedron Lett.,* **42**, 3021 (2001).
39. Roberts B.P. and Smits T.M., *Tetrahedron Lett.*, **42**, 137 (2001); Huyser E.S. and Garcia Z., *J. Org. Chem*., **27**, 2716 (1962).
40. Jousseaume B., Noiret N., Pereyre M. and Frances J.M., *J. Chem. Soc. Chem. Comm.,* 739 (1992); Jousseaume B., Noiret N. and Pereyre M., *Organometallics*, **11**, 3910 (1992).
41. Krief A., Provins L. and Dumont W., *Angew. Chem. Int. Ed.,* **38**, 1946 (1999).
42. Gomez A.M., Moreno E., Valverde S. and Lopez J.C., *SYNLETT,* 891 (2002) and references therein.
43. Mach M. and Jarosz S., *Polish J. Chem.,* **71**, 936 (1997).
44. Jarosz S., Kozłowska E. and Jeżewski A., *Tetrahedron,* **53**, 10775 (1997).
45. Jarosz S. and Mach M., *J. Chem. Soc., Perkin Trans. 1,* 3943 (1998).
46. Jarosz S. and Skóra S., *Tetrahedron: Asymmetry,* **11**, 1425 (2000).
47. Jarosz S., Szewczyk K. and Zawisza A., *Tetrahedron: Asymmetry*, **14**, 1709 (2003).
48. Jarosz S., Mootoo D. and Fraser-Reid B., *Carbohydr. Res*., **147**, 59 (1986).
49. Jarosz S., *Tetrahedron Lett*., **34**, 7655 (1994).
50. Jarosz S., *J. Chem. Soc., Perkin Trans. 1,* 3579 (1997).
51. Jarosz S. and Skóra S., *Tetrahedron: Asymmetry,* **11**, 1433 (2000).
52. Jarosz S. and Skóra S., *Tetrahedron: Asymmetry,* **12**, 1651 (2001).