Desymmetrisation of Dienylsilanes. Stereoselective Access to Cyclitols and Carba-Sugars

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Werner Prize Winner 1997

Abstract. The diastereo- and enantioselective functionalisation of 1,4-cyclohexadienylsilanes using Sharpless asymmetric dihydroxylation and aminohydroxylation offers a straightforward access to various classes of potent inhibitors of glycosidases. The scope and limitation of this desymmetrisation method is illustrated here with the synthesis of various conduritols, carba-sugars and carba-C-disaccharides.

1. Introduction

Cyclitols and structurally related compounds have received increased amounts of attention, recently, due to their wide range of biological activities, for instance as antibiotics, e.g., amino-cyclitols [1] (Scheme 1) which are found in several complex aminoglycoside antibiotics (streptomycin, kanamycin and arbekacin), but also as antidiabetes and anticancer agents [2]. The important synthetic efforts directed towards cyclitols and similar structures have also been stimulated by the recognition that natural and synthetic cyclitols could efficiently inhibit glycosidases and glycosyltransferases, oligosaccharide-processing enzymes [3] (e.g., conduritol-B epoxide, an irreversible inhibitor). The synthesis of sugar mimics such as conduritols and carba-sugars (Scheme 1) has been addressed several times in the past [4], with the most efficient approach being the microbial oxidation of arenes [5]. We recently proposed an alternative and general strategy directed towards the synthesis of different classes of potential inhibitors of glycosidases, using catalytic, diastereo- and enantioselective transformations of dienylsilanes 2, which are readily available from the corresponding arylsilanes [6]. While desymmetrisation of meso-compounds [7] or symmetrical bifunctional substrates [8] has been well documented in acyclic series, we noticed that it had never been applied to cyclic systems such as 1. Anticipating that 1 might be too tedious to prepare, we turned our attention to the known and reasonably stable dienylsilane 2 [9]. The latter can be considered as synthetically equivalent to 1, since the SiR₃ group can be oxidatively converted into the corresponding OH group, with retention of configuration at the carbon centre [10]. It is also noteworthy that dienylsilanes can be regarded as symmetrical double allylsilanes. Consequently, we reasoned that the chemistry developed with simple chiral allylsilanes [11] might be applied to this particular case, providing that the aromatisation process [9] was slower than the double-bond functionalisation. We thus decided to investigate asymmetric dihydroxylation [12] and epoxidation [13] of substrates such as 2, speculating that electrophilic reagents (E⁺*) involved in these processes would be able to differentiate the two enantiomeric double bonds, affording in one step homochiral synths which could be elaborated

Scheme 1
further into the desired sugar mimics
(Scheme 2). Based on literature precedent
[11], we also assumed that the approach of
asymmetric reagents, E\(^+\), onto the \(\pi\)-system of the dienylsilane would occur \textit{anti}
relative to SiR\(_3\) both for steric and elec-
tronic reasons; the silicon group thus con-
trolling efficiently the diastereofacial se-
lectivity. This concept of desymmetrisa-
tion of dienylsilanes is illustrated below
with the total synthesis of various cycli-
tols, such as conduritols, carba-sugars,
amino-carba-sugars and carba-C-disaccha-
rides.

2. Total Synthesis of (+)-Conduritol-E
(11) and (−)-Patitantin (14)

We first investigated the preparation
of dienylsilanes using the \textit{Birch} reduction
of arylsilanes [14]. Commercially avail-
able PhMe\(_2\)SiCl(3) [15] was selected as the
best candidate for the \textit{Birch} reduction since the
hydrolysis of the Si-Cl bond after reduction would provide a silanol, which
could be easily converted into an OH
group using the \textit{Tamao-Kumada} oxida-
tion [10]. We were pleased to find that the
\textit{Birch} reduction, using finely powdered
lithium (30–60 mesh), gave the desired silanol 5 in 77% yield after distilla-
tion (Scheme 3). This was surprising since this reaction is known to occur readily using
electrochemical reduction but with low yields using metal-ammonia reduction, due
to extensive desilylation of the cyclohexa-
dienylsilane [14b, c]. In our case, the re-
duction probably occurred on the more
reactive silylamine 4 formed by reaction
between the chlorosilane and ammonia.
We also observed that dilution with ether
prior to workup minimised the formation
of the undesired siloxane (Scheme 4).

We also investigated the desymmetrisation
process of dienylsilanes (Scheme 2). Based on
literature precedent [11], we also assumed that the approach of
asymmetric reagents, E\(^+\), onto the \(\pi\)-system of the dienylsilane would occur \textit{anti}
relative to SiR\(_3\) both for steric and elec-
tronic reasons; the silicon group thus con-
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tion of dienylsilanes is illustrated below
with the total synthesis of various cycli-
tols, such as conduritols, carba-sugars,
amino-carba-sugars and carba-C-disaccha-
rides.

\begin{align*}
\text{SiMe}_2\text{Cl} & \rightarrow \text{NH}_3 \quad \text{SiMe}_2\text{NH}_2 \\
3 & \rightarrow 4 \\
\text{SiMe}_2\text{OH} &
\end{align*}

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\text{SiMe}_2\text{Cl} & \rightarrow \text{NH}_3 \\
3 & \rightarrow 4 \\
\text{SiMe}_2\text{OH} &
\end{align*}

\begin{align*}
\text{SiMe}_2\text{OH} & \rightarrow \text{OH} \\
6 & \rightarrow 98\% \text{ d.e.}
\end{align*}

Limitation of the actual AD process in
these cases [12]. The diol 6 was then
protected as an acetonide, leading con-
comitantly to the conversion of the silanol
moiety into the corresponding silyl me-
thy ether 7 (Scheme 5). Oxidation of the
C-Si bond was then carried out using
standard \textit{Tamao-Kumada} conditions to
afford the allylic alcohol 8. The fourth OH
group of conduritol-E was then introduced
using the Sharpless asymmetric epoxidation [13a] with the idea of raising the enantiomeric purity through kinetic resolution. Epoxidation with (−)-DET as a chiral ligand effectively afforded, after 8 h, the epoxide 9 in 80% yield as a single diastereomer with 90% e.e. [18]. Treatment of 9 with LDA [19] then led to the formation of the desired allylic alcohol 10 which was deprotected to afford, after one recrystallisation, enantiomerically pure (+)-conduritol-E (11) in 30% overall yield starting from PhMe2SiCl (3) [20]. We have thus achieved the enantioselective synthesis of a cyclitol having four stereo
genetic centres in only seven steps from an aromatic precursor, demonstrating that our methodology may compete efficiently with the microbial oxidation approach in terms of efficiency and cost. To further illustrate the potential of our method, we then carried out the total synthesis of (−)-palitantin (14), an antibiotic isolated from Penicillium palitans [21]. The synthesis started with the unsaturated ketone 12, readily available by Swern oxidation of the allylic alcohol 8. The carbon chains at C(2) and C(3) were then introduced using a one-pot cuprate addition-aldo
disation sequence (Scheme 6) [22]. Whereas the 1,4-addition of the higher-order dienyl cuprate was found to occur exclusively anti relative to the acetamide group, the aldo
disation using monomeric formaldehyde was not as selective and resulted in the formation of a 6:4 mixture of the cis- and trans-cyclohex
anones 13a and 13b, which were separated by chromatography and treated inde
dependently. Deprotection of the trans-isomer 13b gave directly the (−)-enantiomer 14 of the natural product, in enantiomer
cally pure form after one recrystallisation.

In parallel, the (−)-isomer 13a was con
tverted into a triyl derivative, then isomer
is ed under basic conditions [23] before being fully deprotected, which leads to 14. Viewed together, both routes afforded (−)- palitantin (14) in 15% overall yield and only ten steps from PhMe2SiCl (3) [24].

3. Access to Amino-Cyclitols and Analogues – Sharpless Aminohydroxylation

We next investigated the synthesis of amino-cyclitols, aglycon moieties of sev
eral antibiotics, starting from the homo
cyclic synthon 9. Surprisingly, ring opening of the epoxide [25], using either BnNH2 or Na3, resulted in the formation of a mixture of regioisomers 15a/16a and 15b/ 16b, respectively, which could not be separated by chromatography (Scheme 7).
This was in sharp contrast to our own observations [26] where treatment of 9 with oxygenated nucleophiles (H2O under basic or acidic catalysis) provided a single regioisomer 17 [27], finally obtained enan
tiomerically pure after one recrystallisation. The problem of regioselectivity could, however, be circumvented by simply tether
ing the nitrogen nucleophile onto the allylic alcohol function. The tosyl carbamate was selected as the best candidate since it is known from literature that with such ambident nucleophiles, reaction at the nitrogen centre is usually preferred [28]. This approach is illustrated here with a short synthesis of (−)-conduramine-E (21). The carbamate 18, prepared from the corresponding alcohol 8, was treated using standard 5-exo-trig iodocarbalation conditions to afford 19 as a single diaste
tereomer (Scheme 8). Reaction of crude 19 with DBU then led to the conduramine skeleton (i.e., 20). The protective groups were removed via a three-step sequence carried out without purification of the interme
diates. Deprotection of the tosyl group (naphthalene/Na) [29], followed by saponification of the oxazolidinone and removal of the acetamide at acidic conditions led quantitatively to the free conduramine-E (21), isolated as its tetraacetate form in 23% overall yield from PhMe2SiCl (3). Whereas the overall yield was rather satisfying, we observed that the optical rotation of 21 did not match that of the literature [30] even after recrystallisation of 20 and 22. This was, however, not too surprising since the improvement of enan
tiomer purity by simple recrystallisation is rather exceptional when starting from 65% e.e. (i.e., see synthesis of 14). Fortunately, at about the same time, Sharpless...
and coworkers reported on an asymmetric version of their olefin aminohydroxylation process (AA) [31], using conditions which parallel those employed for the dihydroxylation. We realised that this process could also be applied to our dienyl system which would represent a simple way of introducing both the amino and the hydroxy group present in amino-cyclitols. As for the AD process, we anticipated that diastereofacial selectivity would be controlled by the silicon group. On the other hand, we had no information as to the regioselectivity of the AA process on allylsilanes. Our first attempt was carried out on dienylsilane 5 using EtO2CNCINa as nitrogen and oxidant source. We were pleased to find that the reaction afforded the desired carbamate 23, having the nitrogen substituent β to the silicon group, in good yield and more importantly with complete diastereo- and regioselectivity (within the limits of H-NMR detection) (Scheme 9). The relative configuration of 23 was unambiguously assigned using H-NMR and X-ray structure determination of the corresponding alcohol 25, prepared through oxidation of the C-Si bond and protection of the hydroxy-carbamate 24. It is important to note that the protection is also regioselective involving only those groups which are cis to each other. The enantioselectivity measured from the Mosher ester of 25 indicated an e.e. of 70% using (DHQ)2PYR as a chiral ligand. It is also worth mentioning that the absolute configuration of 23 (and therefore of 25), determined through chemical correlation ([6b], is identical to that of the diol 6 prepared using the same chiral ligand. More significantly, a single crystallisation afforded the enantiomerically pure allylic alcohol 25, thus suitable for further elaboration into various amino-cyclitols. As an example, 25 was treated with m-CPBA leading, with high levels of diasterecontrol, to the syn-epoxide 26 (Scheme 10). The diastereofacial selectivity was rationalised invoking both the syn-directing effect [32] of the allylic alcohol and the steric hindrance of the oxazolidine ring (anti). Compound 26 was then deprotected using LDA, as described above, to afford 27 which can be regarded as an advanced precursor of fortamine (28), the aglycon part of the fortimicin antibiotics [31]. In parallel, the carbamate 29, prepared from 25, was used to access the aglycon part of the streptomycin class of antibiotics [1][34], possessing a typical 1,3-diamino moiety. Iodocarbamation of 29, using standard conditions [28], thus led to the oxazolidinone 30 as a single diastereomer, which on treatment with DBU afforded the amino-cyclitol 31 in 40% overall yield from 25 (Scheme 11). As observed during the synthesis of conduramine-E (21, Scheme 8), iodocarbamation occurred syn relative to the allylic alcohol [32] with the nitrogen and the iodine adding anti across the double bond. Finally, we demonstrated that amino-carba-sugars were also accessible in a straightforward manner through radical function-
alisation of the alcohol 25 [35]. The CH₂OH group was thus efficiently introduced through a tin-mediated 5-exo-trig radical cyclisation of the bromomethylsilyl ether 32 which gave the cyclic siloxane 33 as a single diastereomer with the configuration as shown (Scheme 12). Tamao-Kumada oxidation of the C–Si bond then revealed the diol system of 34 which was isolated enantiomerically pure in 75% overall yield from 25 (39% from PhMe₂SiCl (3)). These few examples thus demonstrate the efficiency of our methodology to prepare amino-cyclitol in a rapid manner with high stereocontrol and overall yield. The modest enantioselectivity observed during the AA process (as with the previous AD process) was improved by crystallisation of the early building block 25. A similar solution might also be applied to dihydroxylation products.

4. A New Access to Carba-Sugars and Carba-C-Disaccharides

In the last part of this review, we will present our recent results on the synthesis of carba-sugars and analogues based on the desymmetrisation of dienyilsilanes [6c, d]. The term carba-sugar has been given to compounds having the same structure and substitution pattern as that of the parent carbohydrates, but possessing an endocyclic methylene group instead of an oxygen, which makes them hydrolytically more stable than the corresponding sugars (Scheme 13) [36]. It was soon recognised that with these features, carba-sugars could possess attractive biological activities. This proved indeed to be the case since some of them were found to be active as antibiotics, inhibitors of glucose-stimulated insulin release and, more recently, as inhibitors of glycosidases [37]. Two different routes were devised to prepare these substrates, both relying on an early desymmetrisation of the dienyilsilane precursor 2, but differing only in the stereoselective introduction of the CH₂OH group at C(5) (Scheme 13). In the first approach, the CH₂OH group was introduced through a cyclopropanation followed by an electrophile-mediated cyclopropane ring-opening sequence [38]. It was assumed that cyclopropanation of the chiral allylsilane moiety would occur anti relative to the silicon group [11] and that the ring opening in 35 with concomitant desilylation (SiR₂ as a proton equivalent) would be regioselective [39], thus leading to the desired cis-1,5-configuration. In the second approach, the silicon group would be oxidised (SiR₃ as a hydroxy equivalent) with retention of configuration at C(3) [10], leading to an alcohol which would serve as a precursor for a [2,3]-Wittig rearrangement [40] (i.e., through 36), thus affording the complementary diastereomer having the trans-1,5-relationship.

The dienyilsilane 38, prepared from the arylsilane 37, was used instead of silanol 5 since we thought it would be more able to survive the rather harsh cyclopropanation conditions. As above, Sharpless asymmetric dihydroxylation on 38 afforded the desired anti-diol as a single diastereomer with 71% e.e. (measured from the ¹H-NMR of the bis-Mosher ester; Scheme 14). The diol was then protected as its dibenzyl ether 39 and treated using Furukawa cyclopropanation conditions [41] to

**Scheme 11. Synthesis of a Precursor of Streptomycins Aglycons**

**Scheme 12. Synthesis of Amino-Carba-Sugars**

**Scheme 13. Approach Towards the Carba-Sugar Synthesis**

**Scheme 14**
give the cyclopropane 40 in good yield with complete diastereoselectivity. As expected, NMR studies showed unambiguously that cyclopropanation had taken place anti relative to the silicon group [11]. With the cyclopropane in hand, we then investigated the electrophilic cyclopropane ring opening and found that, in contrast to recent studies in our group [39], mercury or NBS in acetonitrile gave the desired homoolylic halides 41a, b having the required cis-1,5-configuration in good yields [42]. Functionalisation of these halides then revealed to be far more troublesome than we had expected at first. For instance, treatment of iodide 41b with several nucleophiles (H₂O, N₂) invariably led to the elimination product, probably as a result of the relative acidity of the allylic proton at C(5). We first tried to solve this problem by functionalising the double bond prior to the conversion of the C-X bond into the corresponding C-OH bond. Thus, 41a was converted (with >98% d.e.) into the desired anti-diol, which was protected as its acetone 42, and treated under neutral nucleophilic conditions [43] (Scheme 15).

Unfortunately, the fastest nucleophilic displacement of the bromide by the neighboring benzyloxy group at C(1) led to the exclusive formation of the anhydro-carba-sugar 43 [44]. Functionalisation of 41a, b was finally achieved using once more the oxidative unmasking of a silicon group (i.e., PhMe₂Si). Treatment of 41b with t-BuLi, in the presence of PhMe₂SiCl (3) [45], at low temperature led to an iodine-lithium exchange which was followed by a rapid trapping of the lithio species by the silicon electrophile (internal quench) to give the homoallylsilane 44 in 80% yield (Scheme 16). The double bond was then osmylated (anti relative to the benzyloxy groups) and the silicon group oxidised using Fleming’s conditions [40] affording the triol 45 as a single diastereomer. Compound 45 was acetylated and the benzylic groups removed by hydrogenolysis to give after acetylation pseudo-β-L-altropyranose pentaacetate (46) in 23% overall yield and eleven steps from PhMe₂Si(t-Bu) [37] [46].

Again, as experienced with conduramine-E (21), the optical rotation did not match exactly that of the enantiomerically pure product [6c] [47].

The second carba-sugar, possessing the trans-1,5-configuration, was obtained starting from tributyltinmethyl ether 47 prepared in one step from 8 (65% e.e.) (Scheme 17). Tin-lithium exchange was carried out with BuLi at -60°, and the Wittig rearrangement [40] took place in 12 h at -60° to afford the homoallic alcohol 48. As expected, the transfer of the hydroxymethyl group had occurred syn relative to the original alcohol function, but surprisingly in moderate yield. Acetylation of 48 followed by osmylation led to the diol 49 as a single diastereomer; the approach of the osmium reagent occurring anti relative to the acetoneide. Deprotection of the acetoneide followed by complete acetylation finally produced the pseudo-α-D-galactopyranose pentaacetate (50) in ten steps and 20% overall yield from PhMe₂SiCl (3) [48].

In the last part, we will describe a short access to carba-C-disaccharides such as 51, another class of potent glycosidase inhibitors, using functionalisation of dienylsilanes. Our approach was based on a coupling reaction between a carba-sugar and a sugar moiety as the key step, assum-
ing that this nucleophilic addition process would occur with retention of configuration at the anomeric centre C(1') [49]. The carba-sugar fragment would be introduced as an aldehyde such as 53 and the sugar unit through its lithio derivative 52. As illustrated in Scheme 18, the carba-sugar unit should be available using an approach similar to that used for the synthesis of the pseudo-β-L-altropyranose 46 (Scheme 16). The aldehyde would be prepared from the corresponding ester 54, itself prepared by hydrogenation of the corresponding aldehyde, which was then treated with CsF in acetonitrile, producing the desired ester 57 in good yield. Osmylation of the double bond using OsO₄/NMO occurred diastereoselectively (> 98% d.e.) to afford the anti-diol which was directly protected as an acetonide. The ester group was then converted through Li/AlH₃ reduction and Swern oxidation of the resulting alcohol to afford the desired aldehyde 58 (58% overall yield from 39). Reaction between the glycosyl-lithium, generated in situ from the stannyl intermediate 59 [49a], and the aldehyde 58 afforded a 80:15:5 mixture of three diastereomers 60a-c, 60a and 60c, which could not be separated by chromatography, were thus subjected directly to pyridinium-dichromate oxidation to afford a single ketone [49a]. This indicates that 60a and 60c are epimers at C(7) and are produced from the major enantiomer of 58. The third diastereomer 60b (not represented) was produced in a 15% amount from the minor enantiomer of 58, which mirror, the enantiomeric excess estimated for allylsilane 39. 1H-NMR finally demonstrated, that, as expected, retention of configuration at the anomeric centre C(1') had occurred during the nucleophilic process. We have thus prepared a carba-C-disaccharide having nine configurationally defined stereogenic centres in only eleven steps and 23% overall yield from PhMe₂Si(t-Bu) (37). Our approach is flexible since both the nature of the carba-sugar and the sugar units can be varied. The (3)=C(4) bond in 57 can be functionalised using other electrophiles than OsO₄ and the substituents and the configuration of the sugar moiety can also be varied allowing access to numerous other carba-C-disaccharides.

**Conclusion**

We have presented a brief outline of our most recent research in the field of desymmetrisation of dienylsilanes. Several points deserve comment and are summarised below. Our approach uses cheap and/or easily available starting materials which can all be generated from bromobenzene [15]. Direct comparisons with microbial oxidation of similar arenes [5] can be made and show that our methodology is competitive with the latter in terms of cost and efficiency. The dienylsilanes are rapidly converted into synthons of high value with excellent diastereoccontrol and reasonable enantiocontrol using exclusively catalytic enantioselective processes. Both enantiomers are also readily available by changing only the nature of the chiral ligands, which is easily achieved since Sharpless catalysts are now all commercially available. This is a major advantage if one compares our method with microbial oxidation. The other important feature of our approach is the high level of diastereoccontrol which can only be attained because of the presence of the sterically demanding silicon group. The SiR₃ group is the key element of the strategy ensuring complete diastereoccontrol in every single electrophilic process before being used
either as a proton or as an hydroxy equivalent. These preliminary results have thus paved the way for a future extension of the concept of desymmetrisation of cyclohexadienyl substrates. However, more investigations will be necessary to improve the enantioselectivity during asymmetric dihydroxylation, which sometimes hampers the value of the methodology. Such a drawback will hopefully be circumvented with the discovery of new and more efficient chiral ligands [51].

I would like to thank my coworkers, whose names appear in the list of references for their contributions to this work, and particularly Dr. Rémy Angelaud, who efficiently turned the concept of desymmetrisation of dienyl substrates. However, more investigations will be necessary to improve the enantioselectivity during asymmetric dihydroxylation, which sometimes hampers the value of the methodology. Such a drawback will hopefully be circumvented with the discovery of new and more efficient chiral ligands [51].

Received: January 2, 1998

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