CHIMIA 52 (1998) Nr. 3 (März)

Chimia 52 (1998) 104–111

ISSN 0009–4293

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

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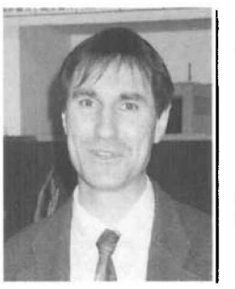
Werner Prize Winner 1997

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.

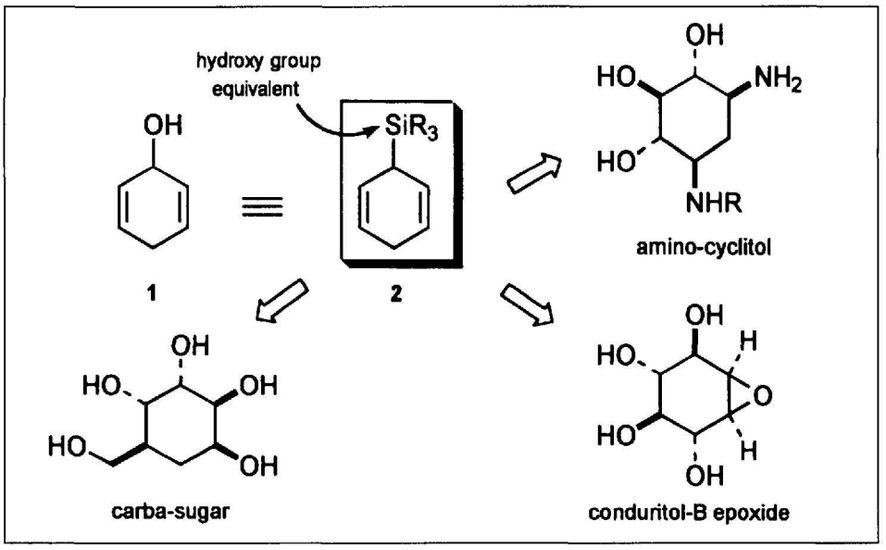


Yannick Landais was born in Angers, France, in 1962. He received his Ph.D. in 1988 from the University of Orsay (Paris XI) under the guidance of Dr. *Jean-Pierre Robin*. He was subsequently awarded a EEC fellowship and carried out postdoctoral work with Dr. *Ian Fleming* at Cambridge University (UK) (1988–1990), where he was exposed for the first time to organosilicon chemistry. He was then appointed as a 'Maître-assistant' at the university of Lausanne (CH) (1990–1997) before he moved to the University of Bordeaux-I (F) in 1997, where he is currently Professor for organic chemistry. His research interests are in synthetic organic chemistry, asymmetric synthesis, with a special emphasis on the use of the silicon group as a tool for stereocontrol in total synthesis of natural products.

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 SiR_3 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 enantiotopic double bonds, affording in one step homochiral synthons which could be elaborated

Scheme 1



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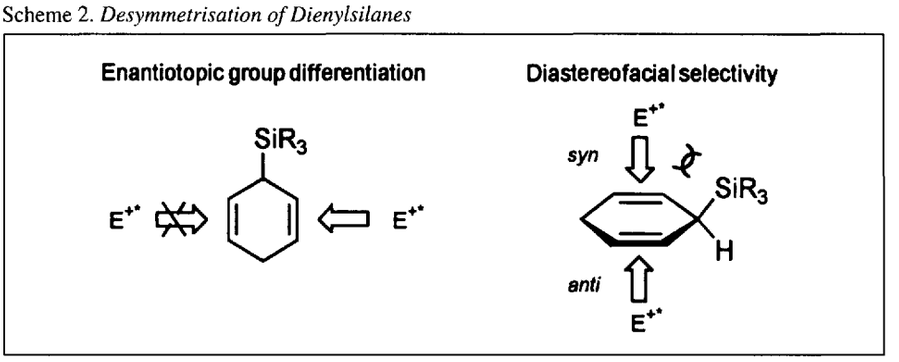
further into the desired sugar mimics (*Scheme 2*). Based on literature precedent [11], we also assumed that the approach of asymmetric reagents, E^{+*}, onto the π-system of the dienylsilane would occur *anti* relative to SiR_3 both for steric and electronic reasons; the silicon group thus controlling efficiently the diastereofacial selectivity. This concept of desymmetrisation of dienylsilanes is illustrated below with the total synthesis of various cyclitols, such as conduritols, carba-sugars, amino-carba-sugars and carba-*C*-disaccharides.

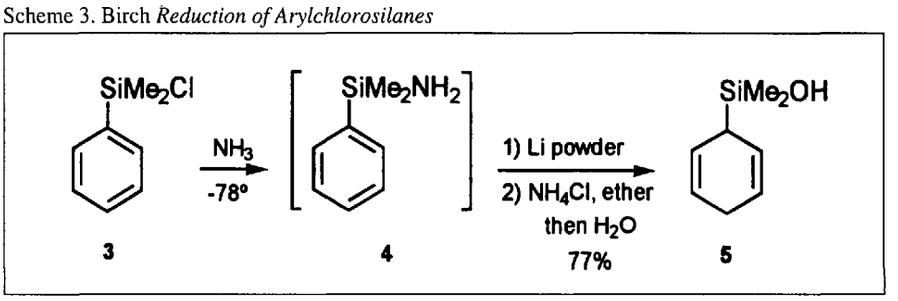
Scheme 2. *Desymmetrisation of Dienylsilanes*



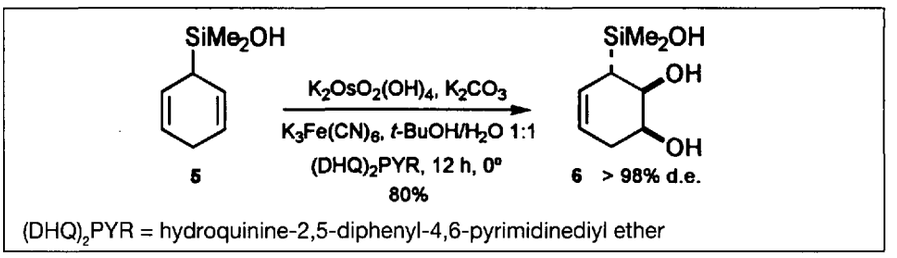
2. Total Synthesis of (+)-Conduritol-E (11) and (–)-Palitantin (14)

We first investigated the preparation of dienylsilanes using the *Birch* reduction of arylsilanes [14]. Commercially available $PhMe_2SiCl$ (**3**) [15] was selected as the best candidate for the *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 *Tamao-Kumada* oxidation [10]. We were pleased to find that the *Birch* reduction, using finely powdered lithium (30–60 mesh), gave the desired silanol **5** in 77% yield after distillation (*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 cyclohexadienylsilane [14b, c]. In our case, the reduction 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 (< 5–10%) which is easily removed by distillation. With our first dienylsilane in hand we then investigated the desymmetrisation process. *Sharpless* and *Jacobsen* epoxidations [13] gave either no reaction or simply aromatisation of **5**. Fortunately, *Sharpless* asymmetric dihydroxylation (AD process [12]) afforded cleanly the desired diol **6** in 80% yield after 12 h at 0° (*Scheme 4*). We noticed that a longer reaction time led to a lower yield, due to the formation of a tetrol as a result of the dihydroxylation of the second double bond [16]. As expected, dihydroxylation took place *anti* relative to the silicon group with the best enantioselectivities (*i.e.*, 65% e.e.) obtained with the chiral ligand $(DHQ)_2PYR$ [17]. These moderate enantioselectivities parallel those obtained by *Sharpless* and coworkers with (*Z*)- and cyclic olefins and point out the limitation of the actual AD process in these cases [12]. The diol **6** was then protected as an acetonide, leading concomitantly to the conversion of the silanol moiety into the corresponding silyl methyl ether **7** (*Scheme 5*). Oxidation of the C–Si bond was then carried out using standard *Tamao-Kumada* conditions to afford the allylic alcohol **8**. The fourth OH group of conduritol-E was then introduced

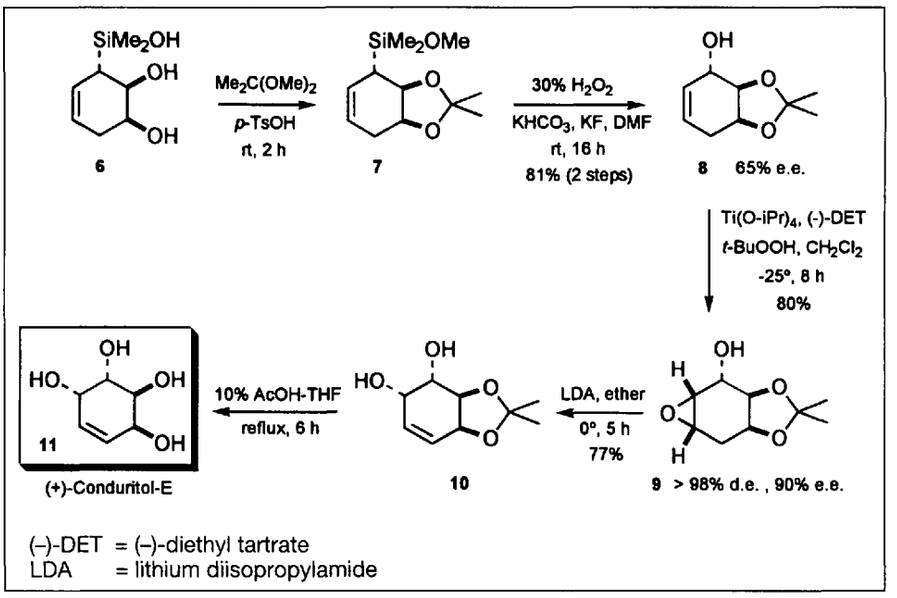
Scheme 3. Birch *Reduction of Arylchlorosilanes*



Scheme 4



Scheme 5. *Total Synthesis of (+)-Conduritol-E* (**11**)



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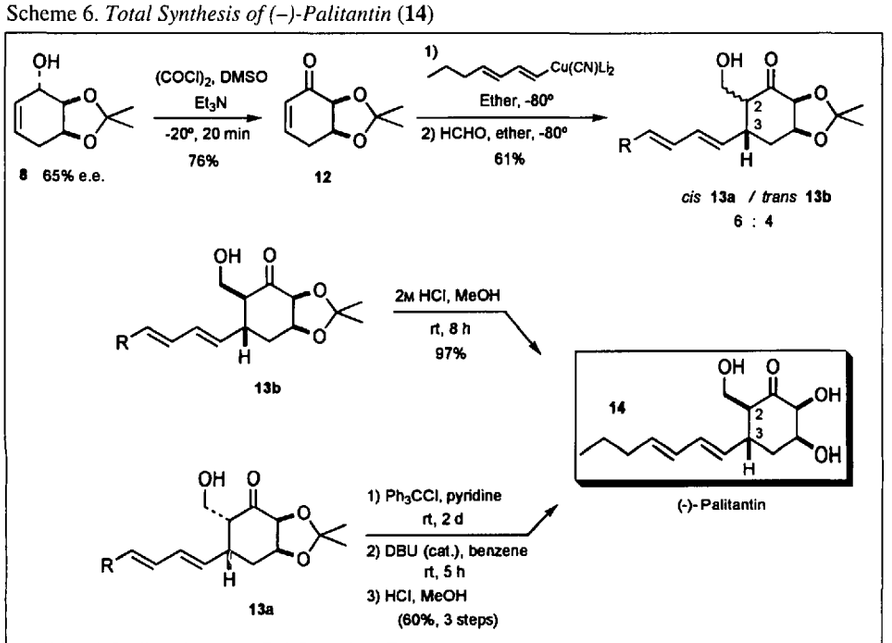
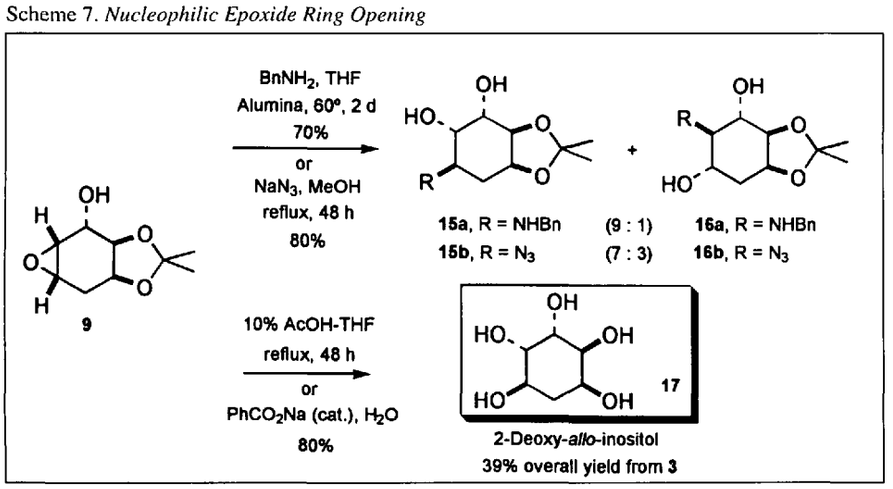
using the *Sharpless* asymmetric epoxidation [13a] with the idea of raising the enantiomeric purity through kinetic resolution. Epoxidation with (–)-DET as a chiral ligand effectively afforded, after 8 h, the epoxide **9** in 80% yield as a single diastereomer with 90% e.e. [18]. Treatment of **9** with 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 $PhMe_2SiCl$ (**3**) [20]. We have thus achieved the enantioselective synthesis of a cyclitol having four stereogenic 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 *Penicillum 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-aldolisation sequence (*Scheme 6*) [22]. Whereas the 1,4-addition of the higher-order dienyl cuprate was found to occur exclusively *anti* relative to the acetonide group, the aldolisation using monomeric formaldehyde was not as selective and resulted in the formation of a 6:4 mixture of the *cis*- and *trans*-cyclohexanones **13a** and **13b**, which were separated by chromatography and treated independently. Deprotection of the *trans*-isomer **13b** gave directly the (–)-enantiomer **14** of the natural product, in enantiomerically pure form after one recrystallization.

Scheme 6. *Total Synthesis of (–)-Palitantin* (**14**)



Scheme 7. *Nucleophilic Epoxide Ring Opening*



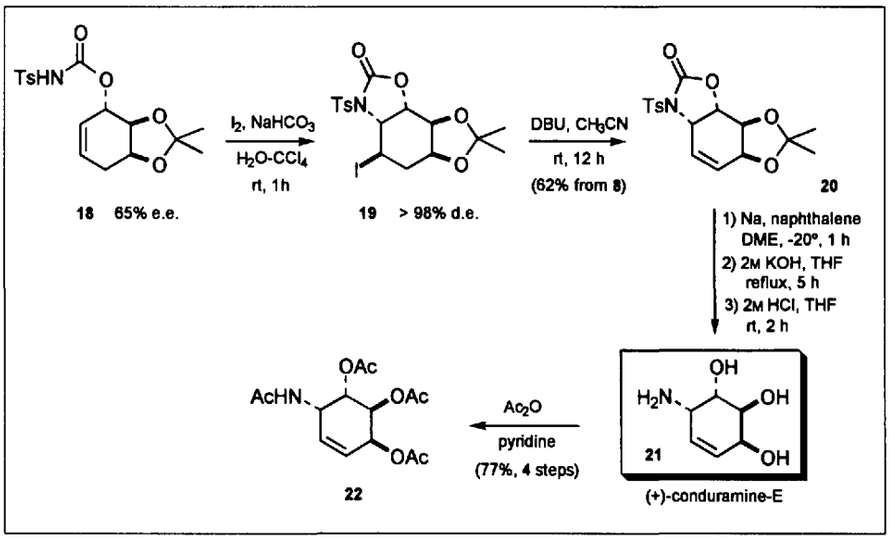
In parallel, the *cis*-isomer **13a** was converted into a trityl derivative, then isomerised under basic conditions [23] before being fully deprotected, which leads to **14**. Viewed together, both routes afforded (–)-palitantin (**14**) in 15% overall yield and only ten steps from $PhMe_2SiCl$ (**3**) [24].

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

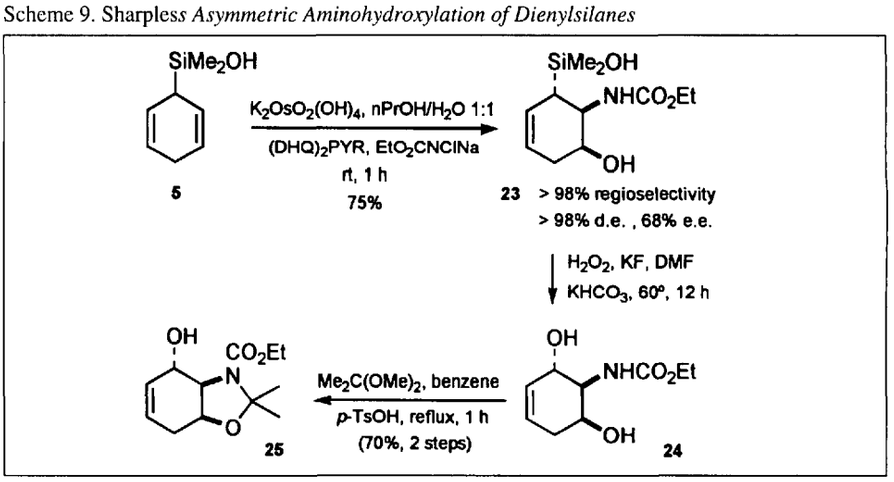
We next investigated the synthesis of amino-cyclitols, aglycon moieties of several antibiotics, starting from the homochiral synthon **9**. Surprisingly, ring opening of the epoxide [25], using either $BnNH_2$ or NaN_3, resulted in the formation of a mixture of regioisomers **15a/16a** and **15b/16b**, 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 (H_2O under basic or acidic catalysis) provided a single regioisomer **17** [27], finally obtained enantiomerically pure after one recrystallisation. The problem of regioselectivity could, however, be circumvented by simply tethering 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* iodocarbamation conditions to afford **19** as a single diastereomer (*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 intermediates. Deprotection of the tosyl group (naphthalene/Na) [29], followed by saponification of the oxazolidinone and removal of the acetonide at acidic conditions led quantitatively to the free conduramine-E (**21**), isolated as its tetraacetate form in 23% overall yield from $PhMe_2SiCl$ (**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 enantiomeric 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 $EtO_2CNClNa$ 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 ^{1}H-NMR detection) (*Scheme 9*). The relative configuration of **23** was unambiguously assigned using ^{1}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 diastereocontrol, 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 deprotonated 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 [33]. 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-

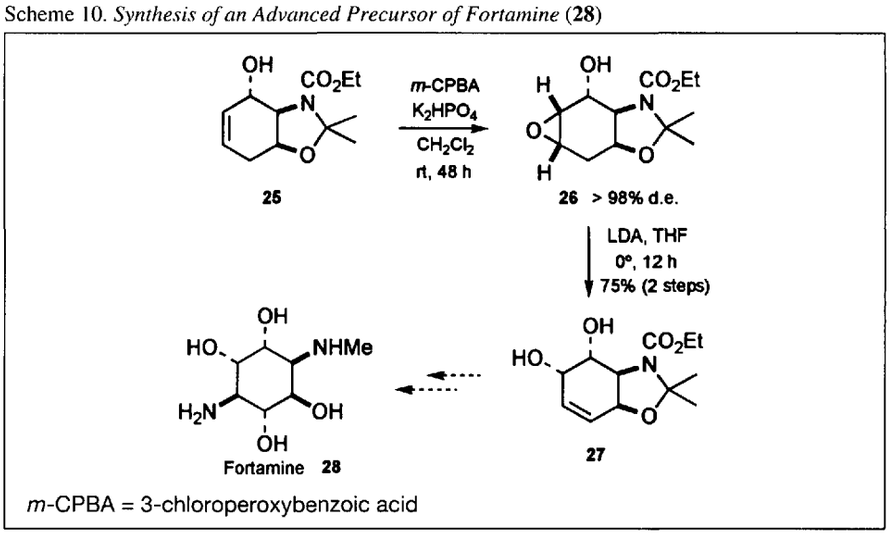
Scheme 8. *Total Synthesis of (+)-Conduramine-E* (**21**)



Scheme 9. Sharpless *Asymmetric Aminohydroxylation of Dienylsilanes*

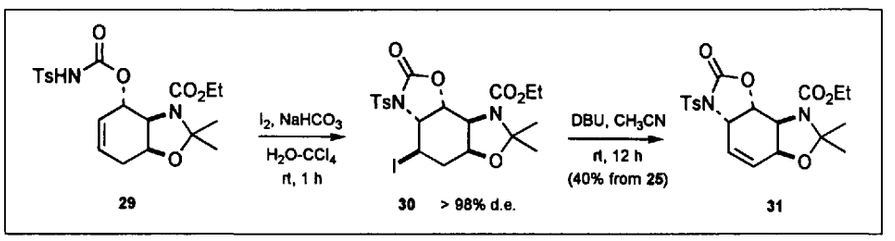


Scheme 10. *Synthesis of an Advanced Precursor of Fortamine* (**28**)

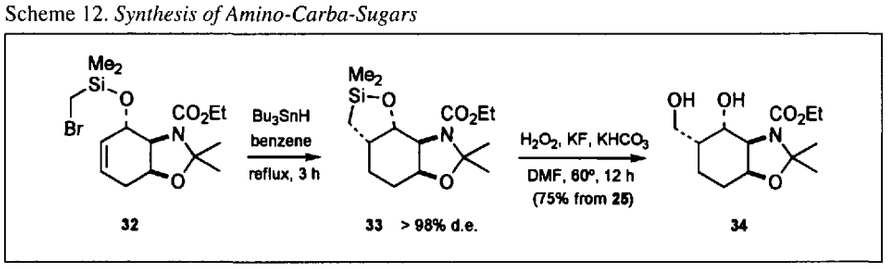


alisation of the alcohol **25** [35]. The CH_2OH group was thus efficiently introduced through a tin-mediated 5-*exo-trig* radical cyclisation of the bromomethylsilyl ether **32** which gave the cyclic siloxane **33** as a single diastereomer with the configuration as shown (*Scheme 12*). *Tamao-Kumada* 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 $PhMe_2SiCl$ (**3**)). These few examples thus demonstrate the efficiency of our methodology to prepare amino-cyclitols 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.

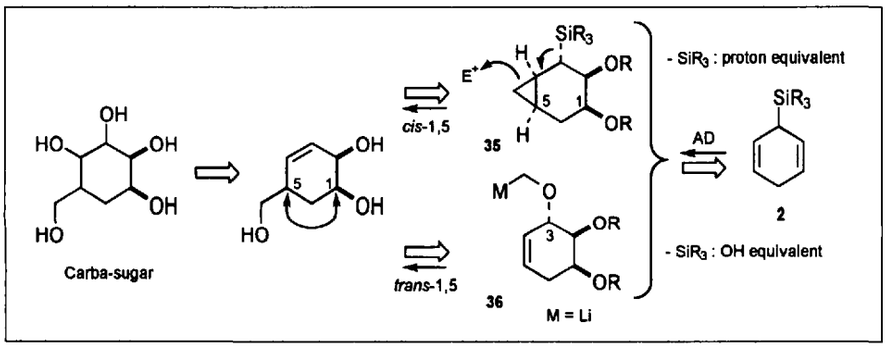
Scheme 11. *Synthesis of a Precursor of Streptomycins Aglycons*



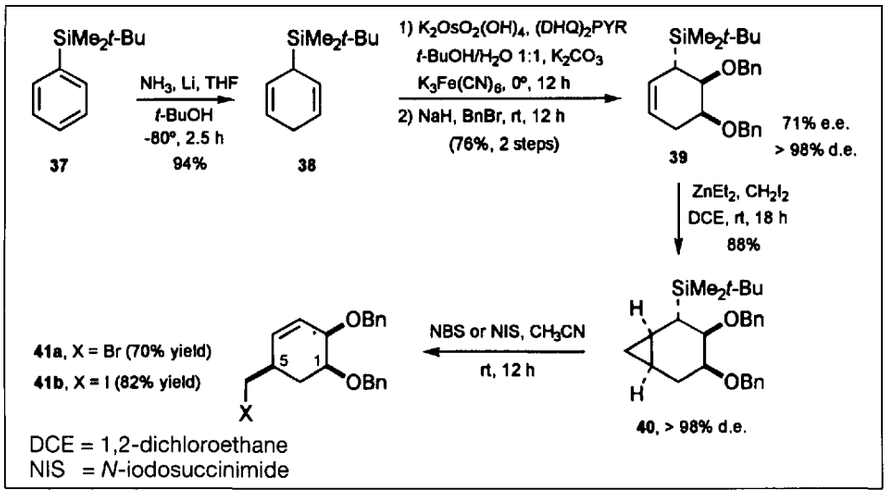
Scheme 12. *Synthesis of Amino-Carba-Sugars*



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



Scheme 14



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 dienylsilanes [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 dienylsilane precursor **2**, but differing only in the stereoselective introduction of the CH_2OH group at C(5) (*Scheme 13*). In the first approach, the CH_2OH 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 (SiR_3 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 (SiR_3 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 dienylsilane **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 ^{1}H-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

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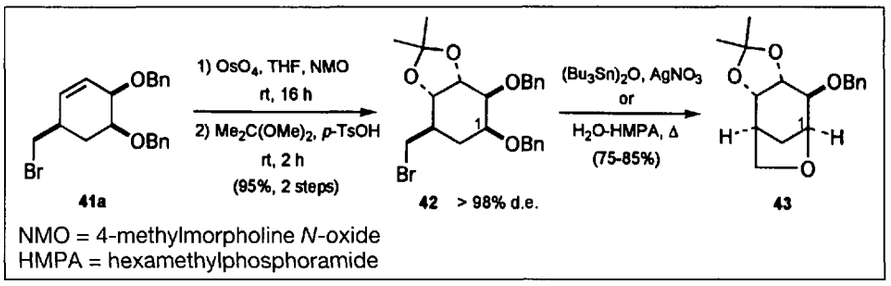
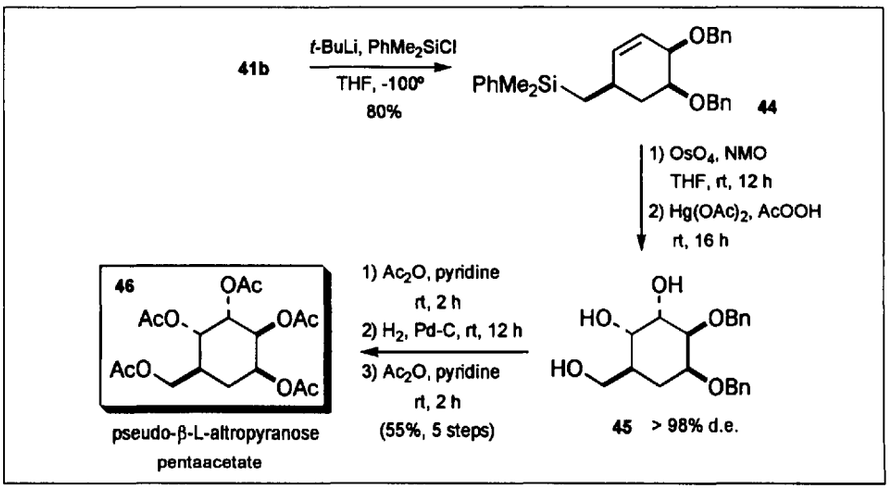
give the cyclopropane **40** in good yield with complete diastereocontrol. As expected, NMR studies showed unambiguously that cyclopropanation had taken place *anti* relative to the silicon group [11]. With the cyclopropane in hand, we then investigated the electrophilic cyclopropane ring opening and found that, in contrast to recent studies in our group [39], mercury salts were not suitable as electrophiles leading to low and irreproducible yields. Fortunately, it was finally found that NIS or NBS in acetonitrile gave the desired homoallylic 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 (H_2O, N_3^-) 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 acetonide **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.*, $PhMe_2Si$). Treatment of **41b** with *t*-BuLi, in the presence of $PhMe_2SiCl$ (**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 [10] affording the triol **45** as a single diastereomer. Compound **45** was acetylated and the benzyl groups removed by hydrogenolysis to give after acetylation pseudo-β-L-altropyranose pentaacetate (**46**) in 23% overall yield and eleven steps from $PhMe_2Si$(*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

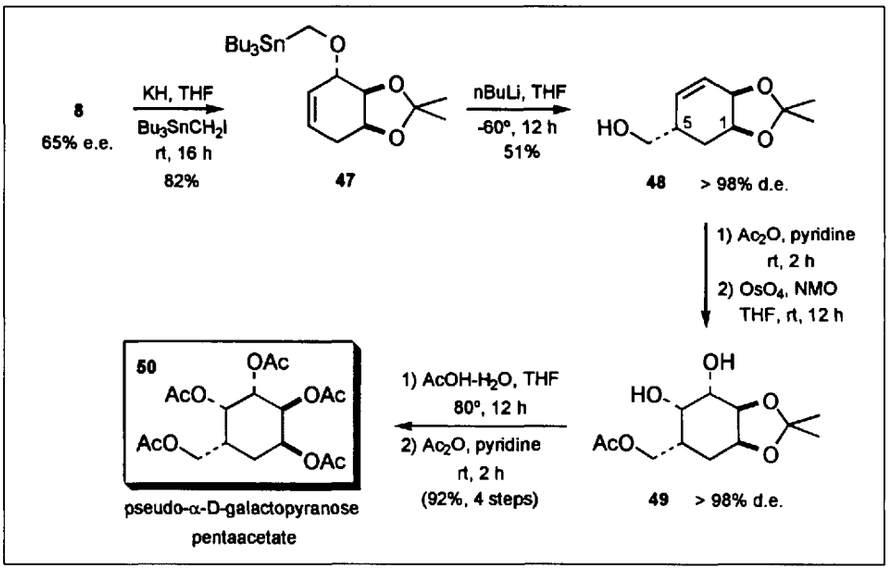
Scheme 15. *Synthesis of the Anhydro-Carba-Sugar* **43**



Scheme 16. *Total Synthesis of Pseudo-β-L-Altropyranose Pentaacetate* (**46**)



Scheme 17. *Total Synthesis of Pseudo-α-D-Galactopyranose Pentaacetate* (**50**)



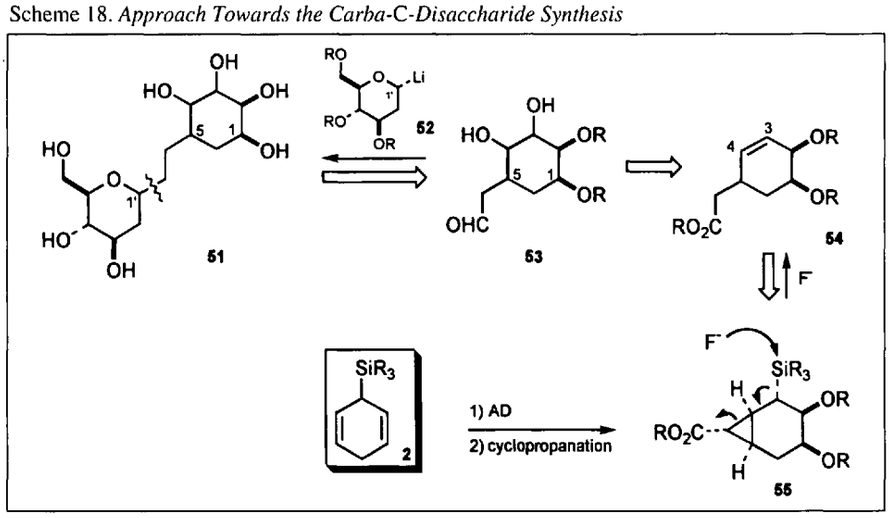
[2,3]-*Wittig* rearrangement [40] took place in 12 h at –60° to afford the homoallylic alcohol **48**. As expected, the transfer of the hydroxymethyl group had occurred *syn* relative to the original alcohol function, but surprisingly in moderate yield. Acetylation of **48** followed by osmylation led to the diol **49** as a single diastereomer; the approach of the osmium reagent occurring *anti* relative to the acetonide. Deprotection of the acetonide followed by complete acetylation finally produced the pseudo-α-D-galactopyranose pentaacetate (**50**) in ten steps and 20% overall yield from $PhMe_2SiCl$ (**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-

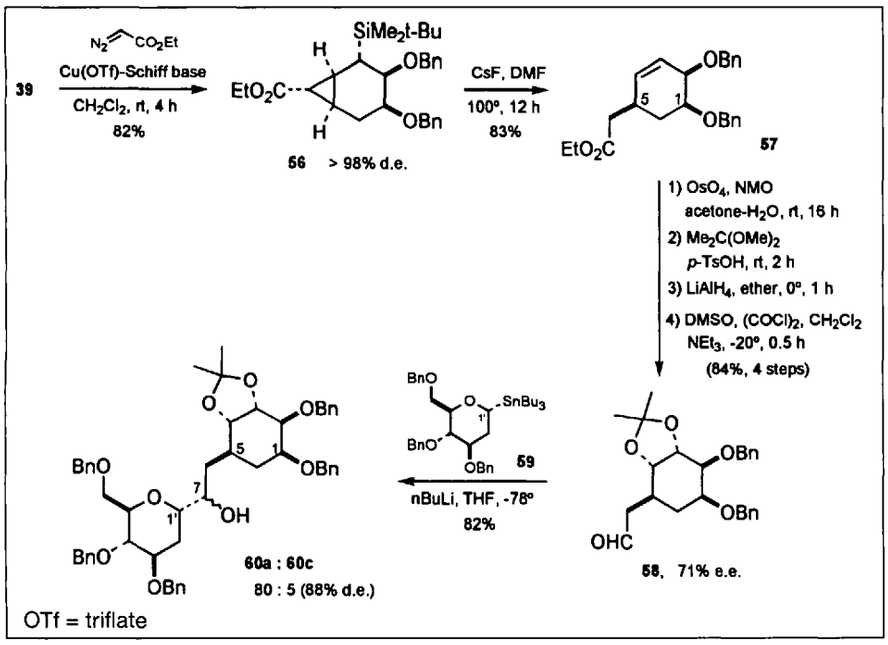
ing that this nucleophilic addition process would occur with retention of configuration at the anomeric centre C(1') [49]. The carba-sugar fragment would be introduced as an aldehyde such as **53** and the sugar unit through its lithio derivative **52**. As illustrated in *Scheme 18*, the carba-sugar 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 cyclopropane ring opening of the suitable functionalised cyclopropane **55**. As the cyclopropane ring is substituted with an activating group, nucleophilic displacement of the silicon group should assist the cyclopropane ring opening [50], generating the C(3)=C(4) bond. As before, the silicon group was expected to control the diastereofacial approach of the reagents during the dihydroxylation-cyclopropanation sequence, thus ensuring the relative *cis*-configuration between C(1) and C(5).

The synthesis started with the allylsilane **39** which was cyclopropanated using Cu(I)OTf and ethyl diazoacetate leading to **56** as a single diastereomer (*Scheme 19*), which was then treated with CsF in acetonitrile, producing the desired ester **57** in good yield. Osmylation of the double bond using OsO_4/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 $LiAlH_4$ 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**. ^{1}H-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 $PhMe_2Si(t\text{-}Bu)$ (**37**). Our approach is flexible since both the nature of the carba-sugar and the sugar units can be varied. The C(3)=C(4) bond in **57** can be functionalised using other electrophiles than OsO_4, and the substituents and the configuration of the sugar moiety can also be varied allowing access to numerous other carba-C-disaccharides.

Scheme 18. *Approach Towards the Carba-C-Disaccharide Synthesis*



Scheme 19. *Total Synthesis of a Carba-C-Disaccharide*



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 diastereocontrol 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 diastereocontrol which can only be attained because of the presence of the sterically demanding silicon group. The SiR_3 group is the key element of the strategy ensuring complete diastereocontrol 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 dienylsilanes into reality at the bench. I would also like to thank Prof. *P. Vogel* for his help during these few years in Lausanne. I am also grateful to Dr. *Pascal Dumy* for his advice concerning NMR structure determination and Dr. *Simon Ainge* for correction of the manuscript. The Swiss National Science Foundation, the Office Fédéral de l'Education et de la Science (COST D2) and the Fondation Agassiz are gratefully acknowledged for financial support.

Received: January 2, 1998

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