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Stereocontrol in organic synthesis using silicon-containing compounds. Studies directed towards the synthesis of ebelactone A †

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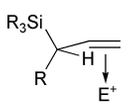
Several approaches to the synthesis of ebelactone A **2** are described, culminating in the synthesis of the benzenesulfonate of 2-epi-ebelactone A **161**. All the approaches were based on three fragments **A**, **B** and **C**, originally defined in general terms in Scheme 1, but eventually used as the aldehyde **72**, the allenylsilane **3** and the aldehyde **139**, respectively. They were joined, first **B** with **C**, and then **B+C** with **A**. In the main routes to fragments **A** and **C**, the relative stereochemistry was controlled by highly stereoselective enolate methylations **66** ⟶ **67**, **68** ⟶ **69**, and **135** ⟶ **136**, in each case *anti* to an adjacent silyl group, and by a highly stereoselective hydroboration of an allylsilane **137** ⟶ **138**, also *anti* to the silyl group. The hydroxyl groups destined to be on C-3 and C-11 were unmasked by silyl-to-hydroxy conversions **69** ⟶ **70** and **138** ⟶ **139** with retention of configuration. The stereochemistry created in the coupling of fragment **B** to **C** was controlled by the stereospecifically *anti* S_E2' reaction between the enantiomerically enriched allenylsilane **3** and the aldehyde **139**. The double bond geometry was controlled by *syn* stereospecific silylcupration **148** ⟶ **151**, and preserved by iododesilylation **151** ⟶ **152** of the vinylsilane with retention of configuration, and Nozaki–Hiyama–Kishi coupling with the aldehyde **72** gave the whole carbon skeleton **153** of ebelactone A with the correct relative configuration, all of which had been controlled by organosilicon chemistry. In the steps to remove the superfluous allylic hydroxyl, an intermediate allyllithium species **156** abstracted the proton on C-2, and its reprotonation inverted the configuration at that atom. Other routes to the fragments **A** and **C** were also explored, both successful and unsuccessful, both silicon-based and conventional, and a number of unexpected side reactions were investigated.

Introduction

A few years ago we published two series of papers describing our work on stereocontrol in organic synthesis using silicon-containing compounds. The overarching idea was that the presence of a silyl group, a large group based on an electropositive element, would substantially control the stereochemistry of electrophilic attack on a neighbouring C=C double bond in the general sense **1**.



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The first series of papers described what we learned about the scope and limitations for good stereocontrol based on this premise,[1–4] and how we made the necessary compounds,[5,6] allylsilanes and β-silylcarbonyl compounds. In between the two series, we published a full paper on the silyl-to-hydroxy conversion,[7] establishing the phenyldimethylsilyl group as a masked hydroxyl, and providing a central plank in the structure of our work. The second series of papers described how we applied what we had learned to the synthesis of a range of relatively small natural products,[8–10] culminating in a long, but stereochemically highly controlled, synthesis of nonactin.[11] These syntheses established that our methods were reasonably general, but none of them, except perhaps the last, was all that complicated. Even that synthesis involved only four stereogenic centres in the component nonactic acids, and in none of the syntheses was it difficult to work out how best to control the stereochemistry using our methods—the targets had been chosen to illustrate the methods we had developed.

While all this work was being carried out, we also selected a more substantial target molecule, one in which the best methods were not so obvious, and for which some of the relationships required that we would have to invent new solutions. Our aim was to synthesise ebelactone A **2**,[12] in which *all of the stereochemical relationships would be controlled by silicon-based methods*, and only the control of absolute configuration would use methods based on more conventional devices.

Ebelactone, with seven stereogenic centres and one double bond geometry, is not of course a particularly challenging molecule by modern standards, but our self-imposed constraint, that only silicon-based methods could be used, made it teasingly difficult. In consequence, our work on this synthesis has taken place over many years. The severity of the constraint we had imposed on ourselves held us back, but it also led us to develop new methods, and to discover which of our methods can be used most reliably in a synthesis significantly larger than those we have already published. Several offshoots of this work have been published already, for it has been remarkably productive of insights into other matters, but the work on the synthesis itself, described in full here, has only been published before in the form of lectures.[13]

We have not in fact completed the synthesis, as the story will reveal. We have however achieved one of our goals: *all of the stereochemical relationships were controlled by silicon-based methods*, strikingly well, with diastereoisomer ratios better than 95 : 5 in all but one of the relationships, and even that was an

† Electronic supplementary information (ESI) available: Experimental section. See http://www.rsc.org/suppdata/ob/b3/b316899a/

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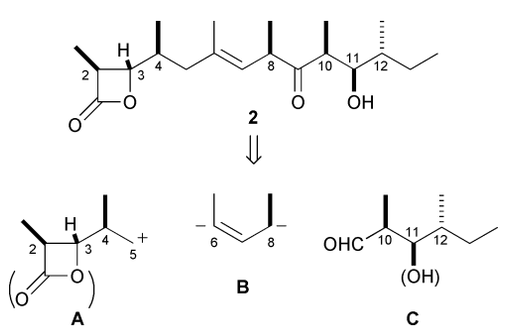
acceptable 86 : 14. We failed to complete the synthesis only because of an unexpected stumble at the last hurdle. In the meantime, two syntheses have been published, one by Paterson and Hulme, of racemic ebelactone A in 1990,[14] and enantiomerically enriched in 1995,[15] and the other by one of us in 2002,[16] using the same convergent strategy as that used here, but not using silicon to control the stereochemistry.

Strategic decisions and their basis in model work

Throughout our work, the convergent strategy has remained the same: to make three components **A**, **B** and **C**, each of which will be prepared enantiomerically enriched (Scheme 1). They will then be coupled together, first **B** with **C**, and then **A** with **B+C**. The precise structures of **A** and **C** have changed over time as a consequence of the model work described below, but the outline has not. Fragment **A** will be electrophilic at C-5, but it might be an alkyl halide or an aldehyde, and the β-lactone may well have to be protected. Fragment **C** will be electrophilic at C-9, almost certainly as an aldehyde, and the C-11 hydroxyl will either be protected or masked as a silyl group. The choice of the allenylsilane **3** for **B** has remained constant. An allenylsilane should provide the nucleophilicity at C-8, and the triple bond in the product will allow the later development of nucleophilicity at C-6. The part of the synthesis involving fragment **B** has worked well, the one unchanging feature of all our work.

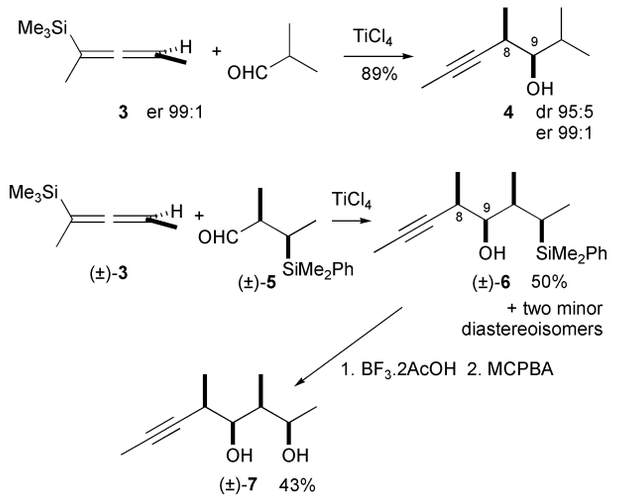


Scheme 1

The B+C coupling strategy

When we began, the stereochemistry of the S_E2' reaction of an allenylsilane had not been established. One of the first things we had to develop, therefore, was a method for making the allenylsilane **3** enantiomerically enriched to a high degree, and then show that it would react stereospecifically *anti* with aldehydes, as required for coupling fragment **B** with **C**. All this was carried out: the allenylsilane **3** was prepared in an enantiomerically highly enriched state, and it reacted with isobutyraldehyde in the presence of titanium tetrachloride to give the homopropargylic alcohol **4** with complete stereospecificity in the *anti* sense, as required for setting up the stereochemistry at C-8 (Scheme 2). This reaction also showed, as expected from analogies in the literature,[17] high selectivity for the formation of the diastereoisomer with a *syn* relationship between the substituents on C-8 and C-9. This work was complete in itself as part of our general study of the stereochemistry of the S_E2' reactions of allyl-, allenyl- and propargylsilanes, and has been published.[18]

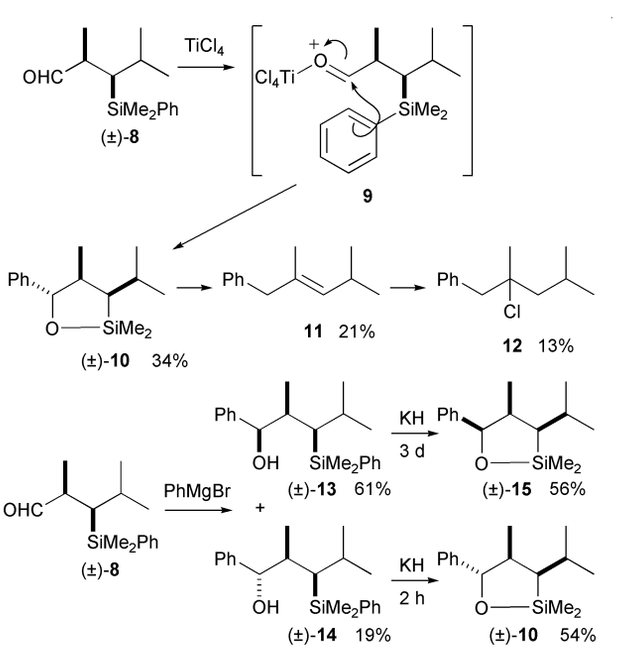
Extending this work to a model closer to the **B+C** coupling, we treated the racemic allenylsilane **3** with the racemic aldehyde **5**, and obtained one homopropargylic alcohol as the major product, almost certainly having the relative stereochemistry **6**, in spite of the racemic nature of both components (Scheme 2). This showed that our design was good as far as it went: the allenylsilane **3** and the aldehyde **5** (with the absolute configurations illustrated) are a matched pair, as of course are their enantiomers, with the formation of the *syn* isomer with respect to the relative configuration between C-8 and C-9 (ebelactone



Scheme 2

numbering) matching both the Felkin–Anh rule for the aldehyde **5** and a stereospecifically *anti* reaction for the allenylsilane **3**. The diastereoisomers are a mismatched pair, as confirmed by the relatively high yield of a single diastereoisomer in spite of the reagents being racemic. This reaction was particularly encouraging, because the silyl group in the aldehyde **5**, masking the oxygen function at C-11, was free from any possibility of inducing chelation control, and hence undermining the matched pairing. Furthermore, it contributed to the Felkin–Anh control by making the substituents on the stereogenic centre adjacent to the aldehyde group well differentiated sterically. We used the product (±)-**6** to show that the phenyldimethylsilyl group could be unmasked to give the diol (±)-**7**, in a reaction that demonstrated for the first time that the silyl-to-hydroxy conversion could be carried out in the presence of a triple bond.

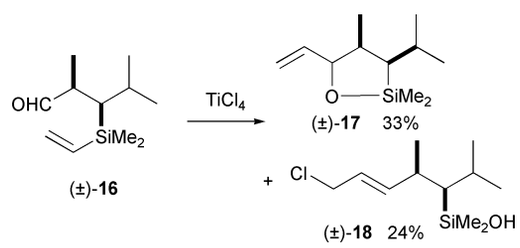
However, when we extended the model work to the aldehyde (±)-**8**, we found that the phenyl group on the silyl group attacked the aldehyde intramolecularly **9**, to give the products (±)-**10**, **11** and **12** (Scheme 3),[19] and we were unable to persuade the allenylsilane (±)-**3** to compete with this intramolecular reaction. Evidently changing the terminal methyl group to an isopropyl group had critically increased the rate of the intramolecular reaction. Intramolecular attack by a phenyl group like this is precedented,[7] as also is the rearrangement–desilyl-



Scheme 3

ation with hydride shift accelerated by the β-silyl group.[20] The stereochemistry of the attack on the aldehyde in the process **9** is interesting. To prove the stereochemistry, we treated the aldehyde (±)-**8** with phenylmagnesium bromide to give the Cram and anti-Cram products (±)-**13** and (±)-**14**, respectively, in a ratio of 76 : 24. When these compounds were treated with potassium hydride in THF, the phenyl group was ejected in a well-precedented reaction,[20,21] to give a new cyclic silyl ether (±)-**15** from the former, and the same silyl ether (±)-**10** as before. The Cram alcohol (±)-**13** gave the cyclic ether (±)-**15** much slower than the *anti*-Cram alcohol gave the ether (±)-**10**, as befits the isomer which has all the substituents *cis* on the ring being formed, and confirming the assignments based on Cram, Felkin and Anh. In the formation of the silyl ether (±)-**10** by the process **9**, the phenyl group is being delivered from the large group on the stereogenic centre adjacent to the aldehyde group, *syn* to it instead of *anti* as in the usual Felkin–Anh control seen in the intermolecular reaction giving the major product (±)-**13**.

The failure to overcome the intramolecular reaction **9** showed that we could not use a phenyldimethylsilyl group as the masked hydroxyl. We tried a vinylsilane (±)-**16** in place of the phenylsilane, since the double bond in this type of vinylsilane was expected to be an exceptionally poor nucleophile,[22] but it also underwent a similar intramolecular reaction to give the silyl ether (±)-**17** and the allyl chloride (±)-**18** (Scheme 4) faster than it reacted with the allenylsilane (±)-**3**. The syntheses of the aldehydes (±)-**5**, (±)-**8** and (±)-**16** are described in the Experimental section. †



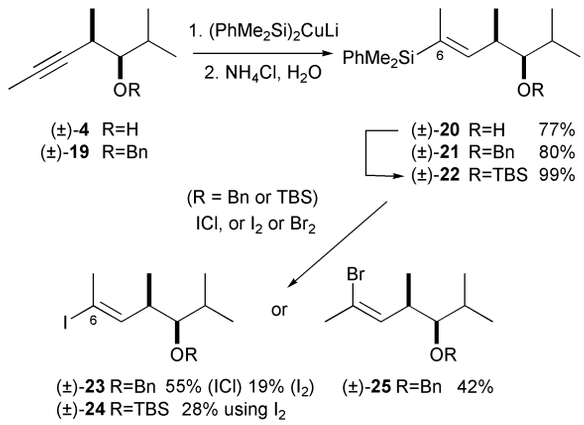
Scheme 4

Because of the ease of these intramolecular reactions, we were obliged to convert the silyl group into a hydroxyl before the coupling with the allenylsilane, and to use a *protected* hydroxyl at C-11 rather than a *masked* hydroxyl. In consequence we met the problem we had so hoped to avoid—a contribution from chelation control. Fortunately, this proved to be a relatively unimportant complication, affecting only the temporary stereogenic centre at C-9.

Creating functionality at C-6

The product of the S_E2' reaction joining together fragments **B** and **C** will be a homopropargylic alcohol, like **4**. We planned to use the triple bond to set up C-6 as a vinyl iodide, from which we would make an organometallic derivative for the coupling with fragment **A**. We knew that our silylcuprate reagent reacts stereospecifically *syn* with disubstituted acetylenes,[23] and with terminal acetylenes, the silyl group attaches itself to the terminus and the copper to the inside carbon. There was no information about the regioselectivity when the acetylene was substituted at both ends with different substituents. We therefore treated the alcohol **4** with the silylcuprate reagent, and obtained only the desired regioisomer, the vinylsilane **20** (Scheme 5). The regioselectivity was not dependent upon the presence of the free hydroxyl, because a similar silyl-cupration of the benzyl ether **19** was also completely regioselective, giving the ether **21**.

The conversion of a vinylsilane into a vinyl iodide is a well established reaction,[24] which gave the vinyl iodides (±)-**23** and (±)-**24** from the vinylsilanes (±)-**21** and (±)-**22**, with retention

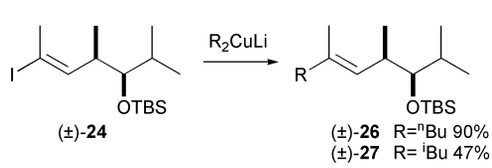


Scheme 5

of configuration, whereas bromodesilylation of the vinylsilane **21** gave the vinyl bromide (±)-**25** with, as expected, inversion of configuration (Scheme 5). These reactions in the model series were carried out with iodine monochloride, with iodine itself, and with bromine, which were all low-yielding, and suffered from more or less protodesilylation and loss of stereospecificity. Subsequently, by the time we came to the real thing, Kishi had shown that *N*-iodosuccinimide[25] was better, and we used that in the chemistry described in Scheme 31.

The A + BC coupling strategy

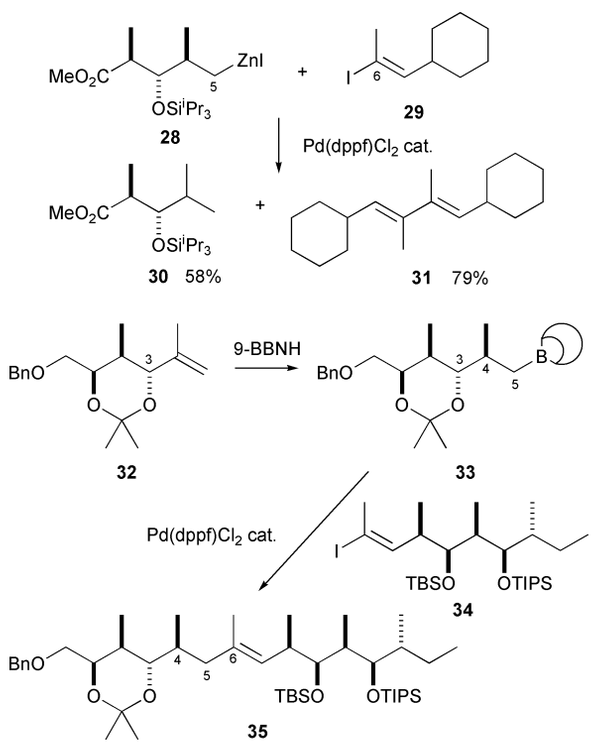
Fragment **A**, electrophilic at C-5, could be either an alkyl halide or an aldehyde. The most concise synthesis would use an alkyl halide, from which an organometallic derivative might be made, suitable for a transition metal-catalysed cross coupling with the vinyl iodide that would be fragment **B+C**. Couplings between an alkyl-metal and a vinyl halide go back to the earliest cross-couplings.[26] Thus the vinyl iodide (±)-**24** and n-butylcuprate gave the alkene (±)-**26**, and isobutylcuprate gave the alkene (±)-**27** (Scheme 6) with the correct geometry at the double bond in each case. However, at the time we began our work there were no close analogies—none with multifunctional molecules and none with a branch point adjacent to the site of coupling in the alkyl partner. Already the problem of branching was apparent in the lower yield of the alkene **27** from the isobutyl cuprate compared with the alkene **26** from the n-butyl cuprate, but in any case we were unlikely to be able to set up stoichiometrically a cuprate from a functionalised fragment **A**. Our fall-back plan therefore was to have an aldehyde group as the electrophilic site in fragment **A**, and to hope for someone to develop a cross-coupling that might allow us to use an iodide instead.



Scheme 6

In time, Negishi cross-couplings that more nearly matched our needs appeared,[27] including one very close indeed,[28] as well as Knochel's zinc-based copper-catalysed cross-couplings.[29] Even more promisingly, Suzuki couplings[30] of functional molecules, with unbranched alkyl chains[31] and with branched alkyl chains, have been reported.[32] Sadly, in our own work, we have been unsuccessful with any zinc-based methods, although they remain the most hopeful. To take just one example, the zinc reagent **28**, derived from the corresponding iodide, and the vinyl iodide **29**, as a model for fragment **B+C**, gave the ester **30** and the diene **31**, as a result of protodeiodination on the one

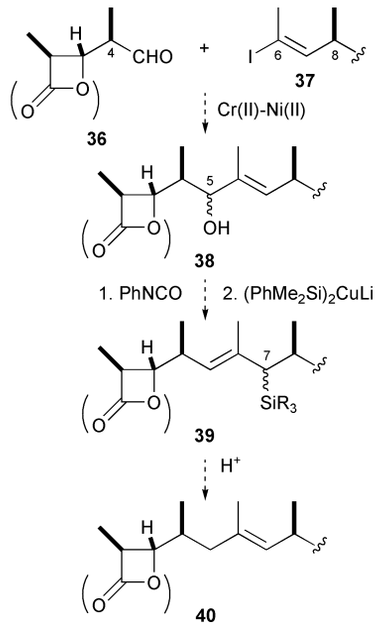
hand, and homo-coupling on the other (Scheme 7). The boron-based literature precedents, led to our only success: a Suzuki–Miyaura coupling between the borane **33** and the vinyl iodide **34**, which was a key step in the synthesis of ebelactone A published by one of us.[16] In this synthesis, the stereochemistry at C-4 was set up by hydroboration of the alkene **32**,[33,34] but this was not an option for us in the present work, because the stereochemistry would not have been controlled by silicon. Had there been a silicon in place of the oxygen atom at C-3 in the alkene **32**, the stereochemistry of the hydroboration would certainly have been in exactly the wrong sense, as we knew from our earlier work on the hydroboration of allylsilanes,[2] and as we eventually took advantage of in the hydroboration **137** ⟶ **138**. The opposite stereochemistry in the hydroboration of allylsilanes and allyl ethers is a point we have made explicitly before.[2] In the present work, we were unable to make a borane analogous to **33** by any other method, and so even though we knew that this coupling worked, we were not successful in making an appropriate starting material, although one or another of these cross-couplings must be possible with enough work.



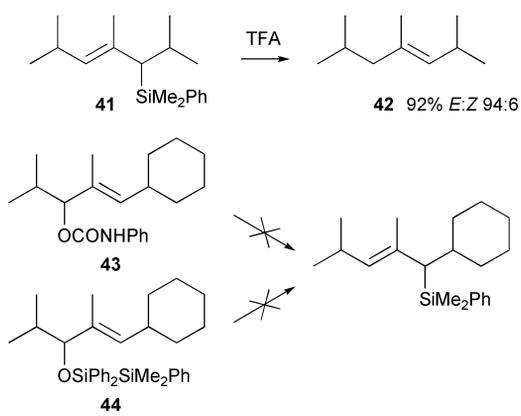
Scheme 7

Accordingly, we fell back on our original plan to use an aldehyde at C-5 **36**, but met the problem that a hydroxyl group would have to be removed from C-5 in the coupled product **38** without losing control of the double bond position or geometry (Scheme 8). This conversion does not have reliable methods in the literature, and is severely limited because it cannot use intermediate allyl cations, anions or radicals. Anticipating this problem, we developed a regiospecific synthesis of allylsilanes from allyl alcohols,[5] using a silylcuprate built onto a carbamate, in which the silyl group was cleanly moved to the allylic position at C-7 in the sense **38** ⟶ **39**, and from which a reliably regioselective protodesilylation **39** ⟶ **40** would return the double bond to its original position.

We were able to show that protodesilylation of the allylsilane **41**, which had a similar level of substitution at both ends of the allylic system to that of the allylsilane **39**, gave the *E*-double bond in the product **42** with high selectivity in the desired sense (Scheme 9), and have published this result.[3] But, in the present work, we have been unable to use our synthesis of an allylsilane



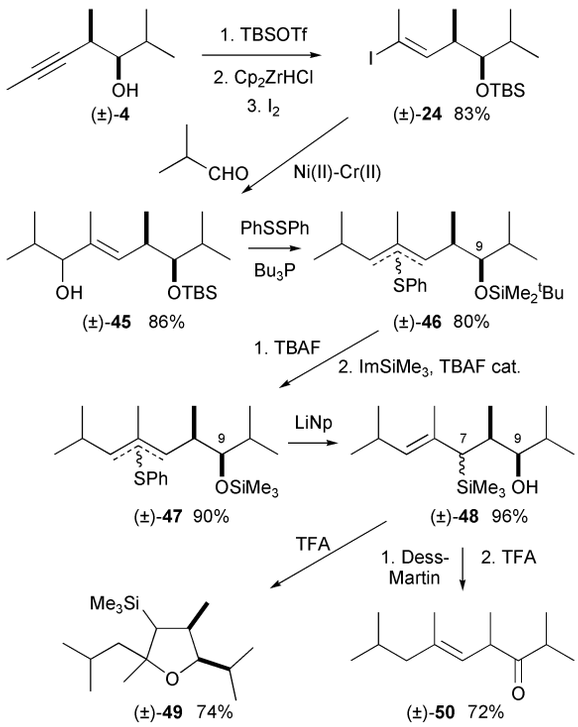
Scheme 8



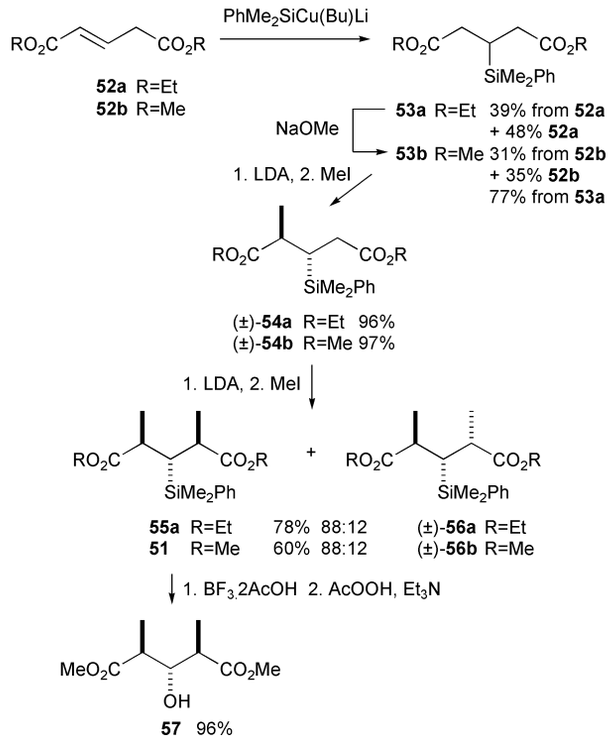
Scheme 9

in the general sense **38** ⟶ **39**. The model carbamate **43**, having a substitution pattern with branching adjacent to both ends of the allylic system, simply failed to react (Scheme 9), a limitation that had not been evident in our exploratory work with less highly substituted systems. Ito had also developed an allylsilane synthesis with the same feature of allylic shift from a secondary allylic alcohol,[35] but when we tried his method, using the silyl ether **44**, we found that it also failed to react. In both cases, we showed that the reagents were not at fault, when less highly substituted systems did work in the way that was expected of them from our own work and from Ito's.

Our third try for a model allylsilane synthesis in the sense **38** ⟶ **39** was based on the work of Brückner,[36] and was successful (Scheme 10). The allyl alcohol (±)-**45** was made by a Nozaki–Hiyama–Kishi coupling between the vinyl iodide (±)-**24** and isobutyraldehyde. The mixture of diastereoisomeric alcohols (±)-**45** gave a mixture of the regio- and stereoisomeric allyl sulfides (±)-**46**, which in turn gave the mixture of allyl sulfides (±)-**47** after an exchange of the silyl group on the C-9 oxygen (ebelactone numbering). Reduction of the allyl sulfide using lithium naphthalenide gave the corresponding allyllithium reagent, which spontaneously gave the allylsilane (±)-**48** by an intramolecular delivery of the silyl group from the oxygen on C-9 specifically to C-7. Treatment of this allylsilane with acid gave the tetrahydrofuran (±)-**49**, but oxidation of the alcohol group at C-9 before the treatment with acid allowed a clean protodesilylation to take place to give the alkene (±)-**50** with the double bond in the right place, and as a single stereoisomer.



Scheme 10



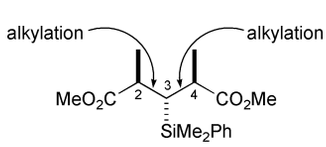
Scheme 11

The model work had now established what the three fragments will be: fragment **A** will be an aldehyde, with the β-lactone protected in some way, because the thermal conditions for the step **45** ⟶ **46** would decarboxylate a β-lactone; fragment **B** will be the allenylsilane **3** that we already had in hand; and fragment **C** will be the aldehyde with the oxygen function at C-11 protected in such a way as to minimise any contribution from chelation control in the coupling with the allenylsilane.

The syntheses of fragments A, B and C

The synthesis of fragment A

Route 1. The stereochemical relationships from C-2 to C-3 and from C-3 to C-4 are alkylation relationships—by analogy with our earlier work, the methyl groups should be introduced with *anti* stereochemistry on each side of a silyl group by enolate methylation.[1] Accordingly the *meso* diester **51** was our first target for fragment **A**. The silyl group would be a mask for the C-3 hydroxyl, and the enantiotopic ester groups would have to be differentiated in order to control the absolute stereochemistry.

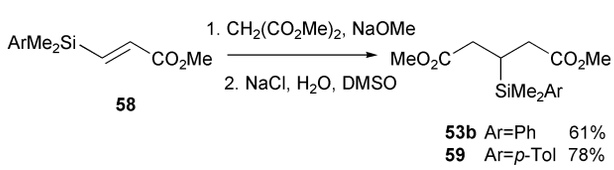


51

In our first approach, we added our silylcuprate reagent to diethyl glutaconate **52a** and to dimethyl glutaconate **52b** (Scheme 11). It is a testament to the high nucleophilicity of the cuprate reagent that we obtained any conjugate addition in competition with the easy enolate formation from these esters. In practice, on a 50 mmol scale, and using our mixed cuprate reagent in order to conserve silicon, the direct yield of the diester **53a** from the diester **52a**, which at the time was cheap and readily available, was 39%, with 48% of the starting material recoverable.

We carried out the next two steps with both diethyl and dimethyl esters, but we preferred the dimethyl ester, because it made it easier to measure the ratios of diastereoisomers in the ^{1}H NMR spectra. The first enolate methylations gave the diethyl ester (±)-**54a** and the dimethyl ester (±)-**54b** in good yield, and with only one diastereoisomer detectable in each case. The second enolate methylation was more troublesome, needed a larger excess of base, a higher dilution, and always gave a detectable amount (12%) of the alternative diastereoisomer (±)-**56a** or (±)-**56b**. The major product **55a** or **51** was a *meso* isomer (^{1}H NMR), showing that the methylations had almost certainly taken place *anti* to the silyl group, and with similar levels of diastereoselection to those we had seen in our original work on enolate methylations.[1] We confirmed the stereochemical assignment by silyl-to-hydroxy conversion of the dimethyl ester **51**, which gave the alcohol **57**. Fukui had prepared all four possible diastereoisomers of this structure using the Reformatsky reaction between methyl α-bromopropionate and 2-phenylpropanal, and converting the phenyl group into an ester. His major product was the *syn* aldol with Cram selectivity, and the diester **57** was derived from the most minor product (5%), that of the *anti* aldol, *anti*-Cram reaction.[37]

Because the price of diethyl glutaconate went up, and our use of it was inefficient, we developed a second route to the diester **53b**. Michael addition of malonate to the β-silylacrylate **58** and Krapcho demethoxycarbonylation gave the same ester **53b** in better yield (Scheme 12).



58

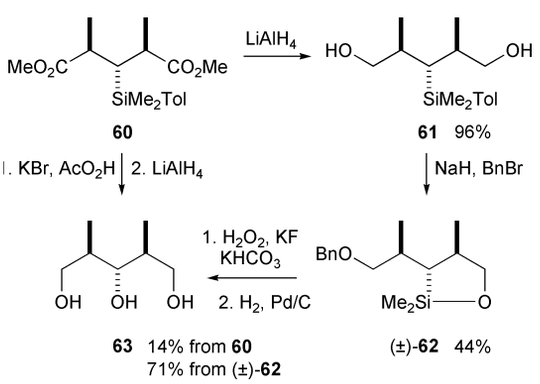
53b Ar=Ph 61%
59 Ar=*p*-Tol 78%

Scheme 12

The expected, but less than completely satisfying diastereoselectivity in the second enolate methylation **54b** ⟶ **51**, where the carbon substituent on the stereogenic centre was branched, meant that we would have to find a way to separate diastereoisomers at some stage. It was possible to separate the two esters **51** and **56b** by column chromatography, but we preferred to avoid that. We therefore repeated the preparation in Scheme 12, but used the *p*-tolyldimethylsilyl group in place of the phenyl-

dimethylsilyl group, and we also repeated the methylations like those in Scheme 11. The hope was that an intermediate in the synthesis, somewhere after the second methylation, might crystallise, just as the *p*-tolyldimethylsilyl derivative had in the first step of our synthesis of nonactin.[11]

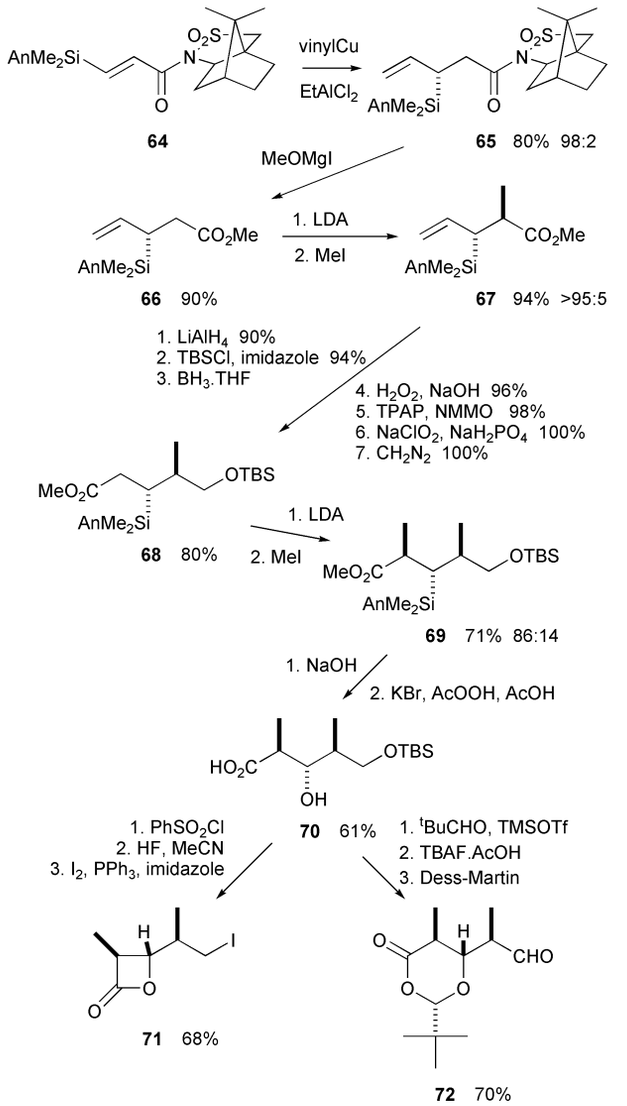
To try to differentiate the enantiotopic ester groups, we explored such reactions as the opening of the anhydride derived from the ester **51**, using achiral nucleophiles in the presence of a chiral catalyst, and using chiral nucleophiles, and we tried enzymatic resolutions. Nothing worked well, or the derivatives were not amenable to the functional group changes we needed to make later. We simply report in the Experimental section † some of the racemic compounds that we made, such as the anhydride, the mono ester and the mono amide. Our only success, and that not good enough, was first to make the diol **61** by reduction of the two ester groups with lithium aluminium hydride (Scheme 13). The diol **61** with the tolyldimethylsilyl group was crystalline, allowing us to remove the diastereoisomer left over from the second methylation, whereas the diol derived from the ester **51** was not. Silyl-to-hydroxy conversion, with protection and deprotection to make the intermediates easier to isolate, gave the triol **63**, which we also made by hydroboration–oxidation of the *tert*-butyldimethylsilyl ether of penta-1,4-dien-3-ol.[34,38]



Scheme 13

The enantiotopic hydroxymethyl groups of this compound have been differentiated by Harada and Oku,[39] by thermodynamically-controlled selective formation of one of the diastereoisomers of the acetal of (−)-menthone. Our efforts to repeat this work, and an attempt to use kinetically-controlled acetalisation,[40] although successful in making the major acetal, were not rewarded with a practical method, although others have had success with the all-*syn meso* diastereoisomer.[41]

Route 2. We turned instead to a route in which the two sides would be differentiated from the beginning. Conjugate addition of vinyl-cuprate to the β-silylacryloyl sultam **64** gave excellent diastereoselectivity in favour of the product **65** (Scheme 14). We used the anisyl group on silicon, not because the silyl-to-hydroxy conversion would be any faster (it is the rearrangement step that is rate-determining, not the removal of the aromatic ring), but because it might be more likely to give a crystalline intermediate to solve the problem of the relatively low diastereoselectivity we could expect in the second alkylation step. The first methylation **66** → **67** was highly diastereoselective, as usual when one of the substituents on the stereogenic centre is trigonal, and the second **68** → **69**, which we carried out after a short and high-yielding series **67** → **68** of functional group manipulations, was, as usual, relatively poor. We now had a system in which the two ends of the molecule were differentiated, and from the ester **69**, after saponification and silyl-to-hydroxy conversion giving the acid **70**, we were able to make two versions **71** and **72** of fragment **A**. In the event none of the intermediates crystallised, and so these products were still mixtures rich in, but not purely, the isomer illustrated.

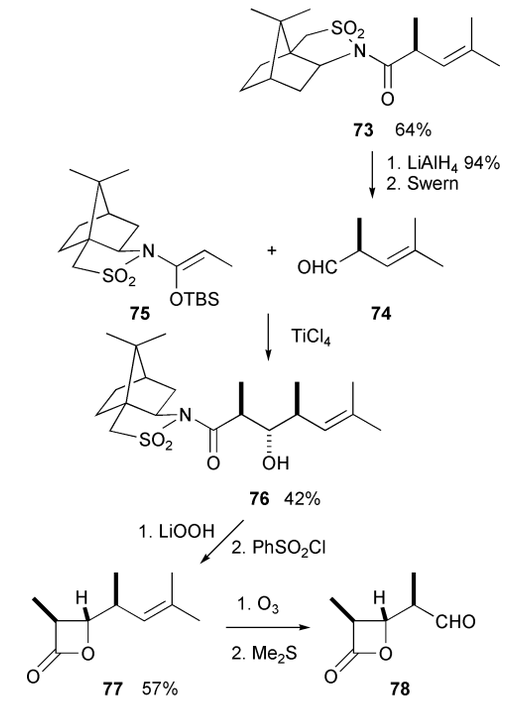


Scheme 14

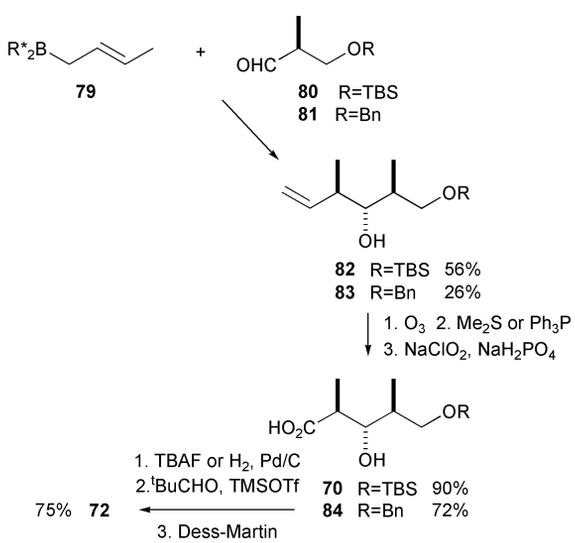
Route 3. We also developed a synthesis of another potential candidate for fragment **A**, avoiding silicon-based stereocontrol, and largely using known chemistry (Scheme 15).

Following Bloch,[42] but in the enantiomeric series to his, we made the sultam **73** based on Oppolzer's chiral auxiliary. Removal of the auxiliary, reduction and re-oxidation gave the aldehyde **74**. A Mukaiyama aldol reaction on this aldehyde, using the silyl enol ether **75** based on the enantiomer of the previous auxiliary, gave the aldol **76**. Hydrolysis and Adam lactonisation[43] gave the β-lactone **77**, ozonolysis of which gave a solution of the unstable aldehyde **78**, which we used for various unfruitful coupling reactions in the model series.

Route 4. The sequence in route 3 proved to be difficult to scale up, and even to repeat, but we found a better one. Roush crotylboration of the silyl-protected aldehyde **80** with the (*E*)-crotylboronate **79** derived from diisopropyl tartarate, is a mismatched pair, which nevertheless is known to give, by reagent control, largely the alcohol **82** (Scheme 16).[44] Alternatively, Brown crotylboration of the benzyl-protected aldehyde **81** with the (*E*)-crotylboronate based on diisopinocampheylborane **79** is known to give largely the alcohol **83**.[45,46] We repeated these reactions, well enough, but rather less well than the literature had promised. Ozonolysis gave the aldehydes and Pinnick oxidation[47] gave the hydroxy acids **70** and **84**, with the former identical to the product from the silicon-based route in Scheme 14, and the latter easily converted into the fragment **A** aldehyde **72**, with the advantage that the hydrogenolysis to



Scheme 15



Scheme 16

remove the benzyl protection gave less trouble with the acid-sensitive dioxanone ring than the selective removal of the TBS group had. These short routes confirmed the relative and absolute configuration of all the products in Scheme 14, and were also useful in providing us with material for the later stages of the synthesis. Benzyl protection, although lower-yielding in Scheme 16, was potentially better for large scale work.

The alcohol **82** was also the source of the iodide used as the precursor of the ill-fated zinc reagent **28** in Scheme 7. TIPS protection, selective removal of the TBS group, conversion of the primary hydroxyl group to the iodide, ozonolysis of the double bond, Pinnick oxidation and treatment with diazomethane gave the iodide.

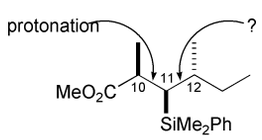
The synthesis of fragment B

Fragment **B** has always been the allenylsilane **3**. In preparation for the synthesis of ebelactone, our first approach was to develop a synthesis of allenylsilanes using the silylcuprate reagent and propargyl sulfonates,[48] in the course of which we discovered that the silylcuprate reacted not only with the product allenylsilane, but also with allenes in general, to give allyl or vinylsilanes, depending upon the structure of the allene and the reaction conditions. This powerful reaction has inspired much work since,[49] and it represents perhaps the most important of the discoveries that came from our interest in the synthesis of ebelactone. To avoid the problem, we developed instead a carbamate directed version of the same approach,[48] which was effective, but not as good as we needed for our work on the S_E2' reaction. For that, and for the ebelactone work, we extended Danheiser's[50] addition of a methyl copper reagent to a silicon-containing propargyl sulfonate. Even this reaction requires careful control to avoid the problem that alkylcuprates can racemise allenes, even though they do not add to them.[51]

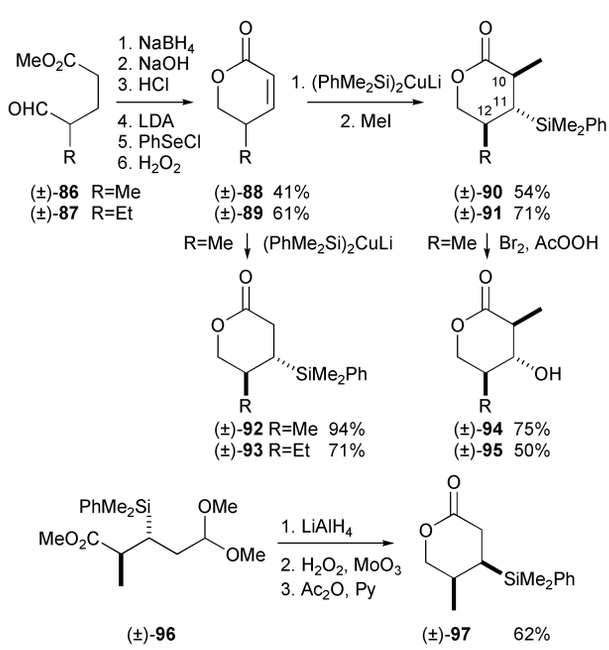
We prepared the enantiomerically enriched propargyl alcohol by reduction of 4-trimethylsilylbut-3-yn-2-one using Midland's and Brown's alpine borane,[52] which remained for many years the best reagent for this particular asymmetric reduction. We raised the enantiomeric purity by recrystallising the camphorsulfonate, and the reaction with the methyl-copper reagent proved to be highly regioselective and stereospecific in the *anti* sense. The synthesis is described in our full paper on the stereochemistry of the S_E2' reaction.[18] Noyori's catalytic asymmetric hydrogenation[53] has now overtaken alpine borane as the best method for reducing the ketone. We have used it in our more recent work, as described in the Experimental section here. †

The synthesis of fragment C

Fragment C gave us the most trouble. The stereochemical relationship between C-10 and C-11 was that achieved by protonation of an enolate,[1] but the problem of how to control the stereochemistry at C-12 was an open question **85**, with many possibilities.



Route 1. As a model sequence, we combined the enamine of propanal and methyl acrylate to make the aldehyde (±)-**86**,[54–56] from which we made, successively, the saturated lactone, and the unsaturated lactone (±)-**88** (Scheme 17). Conjugate addition of the silylcuprate reagent took place *anti* to the resident methyl group, for reasons we have explained in a preliminary com-

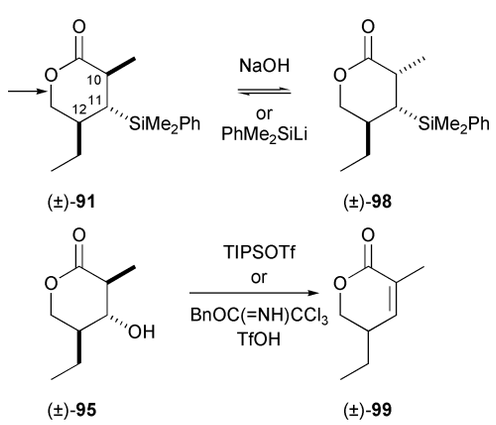


Scheme 17

munication of this part of our work devoted to stereocontrol using unsaturated δ-lactones and lactams.[57] Protonation of the intermediate enolate gave the lactone (±)-**92**, and methylation gave the lactone (±)-**90**. The introduction of the methyl group was *anti* to the resident silyl group, as we had seen earlier in the alkylation of other cyclic enolates having a β-silyl group.[58] There was no discernible trace of stereoisomers in either of these reactions. The ^{1}H NMR spectra of the lactones (±)-**90** and (±)-**92** were not helpful in confirming the relative stereochemistry. The coupling constants from the methylene protons adjacent to the oxygen atom were not very different from each other, indicating that the conformation of the ring was not a regular chair. We therefore proved the relative configuration by synthesis. First, we prepared the isomer (±)-**97** of the lactone (±)-**92**, using the ester (±)-**96** of known relative configuration,[8] and found it to be decisively different. Furthermore, with both isomers in hand, we could set a lower limit of 99.5 : 0.5 to the degree of diastereoselectivity. Second, a silyl-to-hydroxy conversion on the lactone (±)-**90** cleanly gave the known alcohol (±)-**94**.

Similarly, the enamine of butanal and methyl acrylate gave the aldehyde (±)-**87**, and reduction, lactonisation and dehydrogenation gave the unsaturated lactone (±)-**89**. Conjugate addition of the silylcuprate and methylation took place cleanly, and presumably with the same stereochemistry, to give the lactone (±)-**91**.

This route had given us the lactone (±)-**91** with, as far as we could tell, complete stereocontrol. Although the methyl group on C-10 (ebelactone numbering) had been introduced by alkylation, the relative stereochemistry corresponds to that of protonation in an open-chain compound, and so all three centres were correct for fragment **C**, provided we could remove the oxygen atom from the carbon atom attached to C-12, which we intended would become a methyl group. Unfortunately, we failed utterly in the step needed to break the C—O bond marked with an arrow in the drawing (±)-**91** in Scheme 18. Soft nucleophiles like sulfide, selenide and iodide ion, which can open lactones at the methylene carbon,[59] either failed to react, presumably because of the branching at C-12, or gave useless mixtures. We tried many reactions of this type. Attempts to open the lactone by attack at the carbonyl group instead using amide ions or hydroxide ion, and to manipulate the hydroxy amide or hydroxy acid that would have been produced, were useless, because epimerisation at C-10, giving mixtures of the lactones (±)-**91** and (±)-**98** (Scheme 18), preceded the ring opening. Similarly, even the silyllithium reagent, normally a good nucleophile with inconspicuous basic properties, merely gave a mixture of the same two lactones, and none of the diols expected from model reactions on simple δ-lactones. This last had been a promising route, for which we had prepared the ground by showing that the two hydroxyl groups in the diols produced in this way from simple lactones were well differentiated, with the primary hydroxyl easily tosylated, and

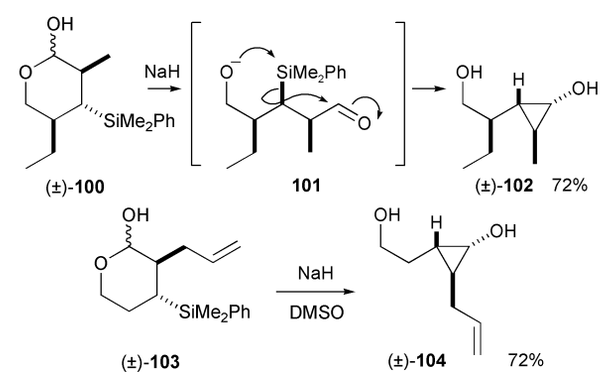


Scheme 18

the doubly α-silylated alcohol completely inert to tosylation.[60] Another possible tactic we essayed was to carry out the silyl-to-hydroxy conversion before trying to cleave the C—O bond, but the hydroxylactone (±)-**95** also proved to be susceptible to enolisation, as shown by its conversion into the unsaturated lactone (±)-**99** during our attempts to protect the hydroxyl group.

All these experiments were carried out on racemic material. Our failure to find a way through to a fragment **C**, in spite of the high level of control of relative stereochemistry, meant that we never made the enantiomerically enriched lactone **87**, in spite of having several plans in place, and a method already in the literature.[61] As it happens, we did prepare the lactone (−)-**93** in enantiomerically enriched form (Scheme 22), but we abandoned Route 1, after being deflected by an unexpected observation in the last of our attempts to deal with the problem of removing the oxygen atom in order to release a methyl group on C-12.

A diversion from Route 1. The only reaction that took place at the carbonyl group of the lactone (±)-**91**, but did not cause epimerisation at C-10, was DIBAL reduction, which gave the hemiacetal (±)-**100**. We were hopeful that we could protect the masked aldehyde function in this molecule with a Wittig reaction, in order to be free to remove the hydroxyl group. Instead, we obtained the cyclopropane (±)-**102**, whether we had a Wittig ylid present or not (Scheme 19). We have reported this work in a preliminary communication,[62] for which this is a full version. It appears that the presence of an oxyanion, five atoms away from the silicon atom, so activates it in the sense **101** that it behaves like a metal such as tin, with which cyclopropane-formation is well established, both with carbonyl electrophiles[63] and with other carbon electrophiles.[64]

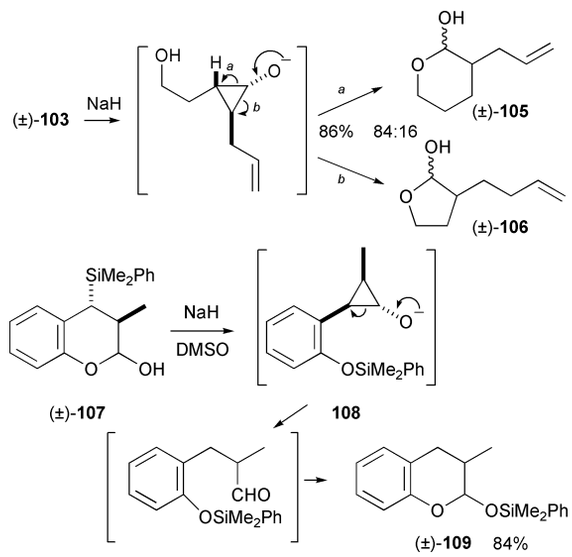


Scheme 19

Because of the presence of a stereogenic centre outside the ring, we were not able to establish with confidence the stereochemistry shown in (±)-**102**, but we were able to prove the relative stereochemistry in the analogous cyclopropane (±)-**104**, prepared from the lactol (±)-**103**. COSY and NOESY spectra were unambiguous with respect to the orientation of the three contiguous groups on the cyclopropane ring. The stereochemical event in the S_E2 reaction at the carbon carrying the silyl group is inversion of configuration, just as it is in tin-based cyclopropane-forming reactions, and we assume that it is also inversion of configuration in the formation of the cyclopropane (±)-**102**.

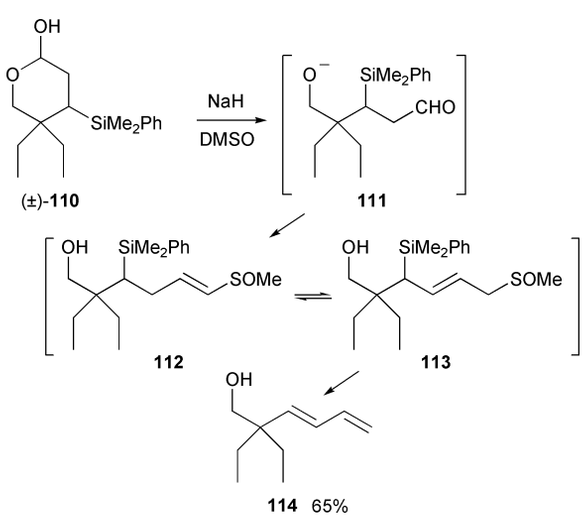
The most remarkable feature of these reactions is the mechanistic contrast they make with the reactions shown in Schemes 3 and 4. In those reactions, the Lewis acid catalysis makes the aldehyde group more *electrophilic*, and it is the phenyl and vinyl groups that attack it, as in the drawing **9**. In the cyclopropane-forming reactions in Scheme 19, the nucleophilic catalysis makes the Si–C bond more *nucleophilic*, and it is that carbon atom that attacks the aldehyde group, as in the drawing **101**.

The cyclopropane (±)-**104** was unstable to the normal ring-opening of cyclopropanols, in which one of the adjacent C–C bonds is protonated. When the reaction used to make the cyclopropanol (±)-**104** was continued for 10 hours instead of 3 hours, the products were the lactols (±)-**105** and (±)-**106** in a ratio of 84 : 16 as measured using the lactones derived from them by oxidation. The opening of the cyclopropanol ring was even easier in the cyclopropanoxide **108**, which was probably an intermediate in the reaction of the lactol (±)-**107** giving the lactol ether (±)-**109** (Scheme 20). The products (±)-**105** and (±)-**109** appear to be the result of direct removal of the silyl group, but the formation of some of the 5-membered lactol (±)-**106** shows that the pathway by opening of the cyclopropanol is more likely.



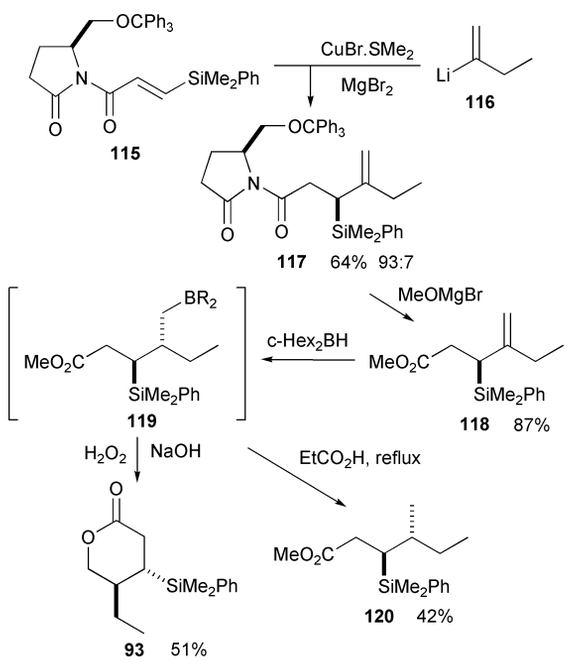
Scheme 20

Yet another limitation of the cyclopropanol-forming reaction was the reaction of the lactol (±)-**110**, which followed a completely different pathway, giving the diene **114** (Scheme 21). We surmise that this time, surprisingly in view of the Thorpe–Ingold effect that ought to have encouraged cyclopropane formation, the relatively unhindered aldehyde (±)-**111** did react with an external nucleophile, namely the dimsyl anion, and that deconjugation **112** ⟶ **113**, and either vinylogous β-elimination, or Mislow rearrangement and β-elimination, gave the diene **114**. These reactions revealed that the cyclopropanol syntheses in Scheme 19 were of limited generality. The more or less standard syntheses of the lactols (±)-**103**, (±)-**107** and (±)-**110** are described in the Experimental section.†



Scheme 21

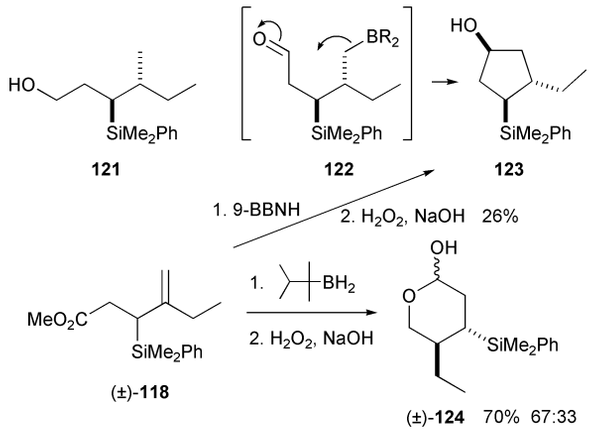
Route 2. Our second route used the β-silylacrylate **115**,[65] based on Koga's chiral auxiliary, and a copper-mediated conjugate addition of the butenyllithium reagent **116**, generated *in situ* with complete regiocontrol by a Shapiro reaction on the trisylhydrazone of 2-butanone. The product **117** was a mixture of diastereoisomers in a ratio of 93 : 7 (Scheme 22). Methoxymagnesium bromide removed the chiral auxiliary, and hydroboration of the ester **118** followed by oxidation gave the lactone **93**, by way of the borane **119**. The stereochemical control in this step was, as far as we could tell, complete, and in the desired sense, as expected from our work on the hydroboration of allylsilanes.[2] To remove the boron without introducing the recalcitrant oxygen atom, we tried two methods: iododeboronation followed by deiodination,[66] and direct protodeboronation in hot propionic acid.[67] Both methods gave the ester **120** in comparable yields, but never in better than 42% yield, and so we concentrated on the more direct protodeboronation route.



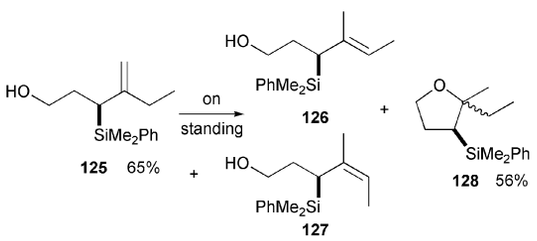
Scheme 22

Because of the risk of ester exchange during the reflux with propionic acid, we refluxed the crude product mixture in methanol with toluene-*p*-sulfonic acid to restore any acid products to their methyl esters, and found that among the byproducts were the alcohol **121** and the cyclopentanol **123** (Scheme 23). The former is unexceptional—esters are often reduced by boranes—but the latter is most unusual, implying, as it does, that the borane had reacted with an aldehyde derived from the ester in the sense **122**, which is unprecedented to the best of our knowledge with boron, although known with tin.[68] Further support for this pathway came from our unavailing attempts to find a better hydroboration–protodeboronation procedure. The reaction between the racemic ester (±)-**118** and thexylborane followed by oxidation gave the lactols (±)-**124**, showing that an aldehyde intermediate was plausible, and the reaction with 9-BBN followed by oxidation gave the same, but racemic, cyclopentanol **123**, showing that protic acid was not necessary for the C–C bond-forming step.

To avoid these pathways, we reduced the ester **118** deliberately, before attempting the hydroboration, but found that the product **125** was unstable, rapidly, and merely on standing, giving mixtures of the alcohols **126**, **127** and a pair of diastereoisomeric tetrahydrofurans **128** (Scheme 24). The last of these products provided a precedent for the formation of the alcohol **49**, and all three show how very easily and unsurprisingly[69] an allylsilane can be protonated if the cation is tertiary.



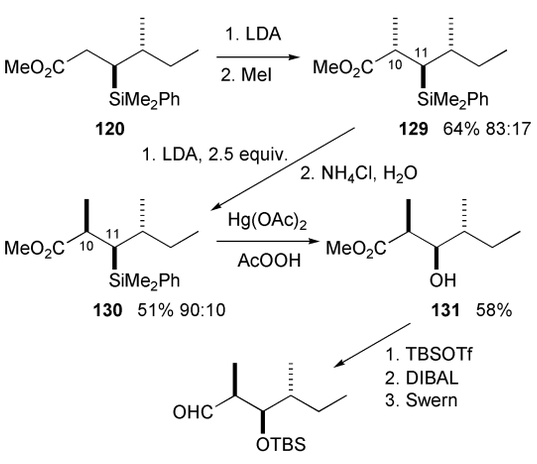
Scheme 23



Scheme 24

It seems likely, since these problems were less severe with the ester, that a protonated hydroxyl group further enhances the rate of this reaction by delivering the proton intramolecularly.

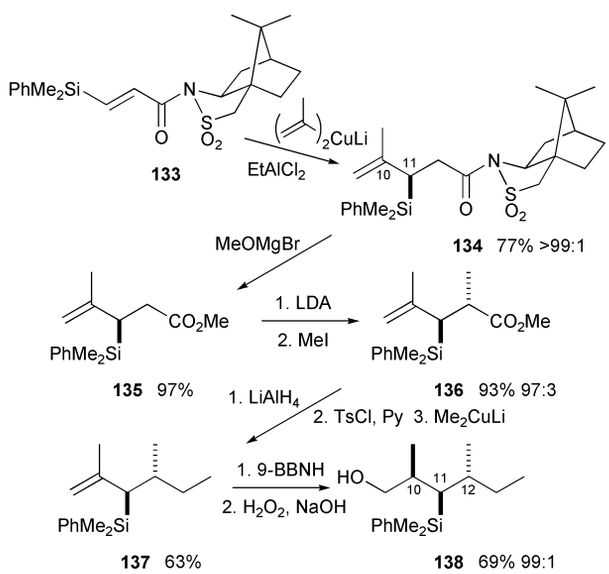
We carried on with the ester **120** and methylated the enolate to give the ester **129** selectively (83 : 17) in favour of the stereoisomer with the alkylation relationship between the substituents on C-10 and C-11 (Scheme 25). To correct the stereochemistry, we generated the enolate, and protonated it to give largely (90 : 10) the right ester **130** with the expected protonation relationship between the substituents on C-10 and C-11. In the course of model work on this step, we came across a number of unexpected consequences to using the necessarily large excess of LDA, and reported the results elsewhere.[70] We carried out the silyl-to-hydroxy conversion at this stage, and found that the ^{13}C NMR signals of the product **131** were reassuringly different from those of the two known diastereoisomers of this compound. We protected the alcohol group as its *tert*-butyldimethylsilyl ether, and reduced the ester to its aldehyde **132**, our first fragment **C**.



Scheme 25

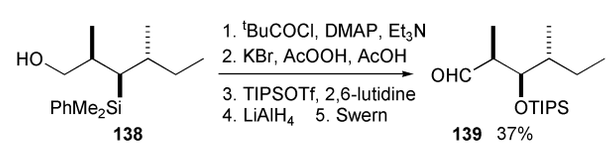
For all that this route had been successful, there were too many steps with indifferent yields. Optimisation would undoubtedly have improved some of them, but the accumulation of difficulties, notably with the Shapiro reaction at the beginning, led us to try another route.

Route 3. We began again with a conjugate addition, but this time working on the other side of the silyl group, making the bond between C-10 and C-11, instead of the bond between C-11 and C-12. We first tried the 2-propenylcuprate and the *cis*-imide based on Koga's auxiliary, the *cis*-analogue of **115**, but the best result we got was a 76 : 34 ratio of diastereoisomers. On the other hand, Oppolzer's sultam **133** gave the adduct **134** with high stereoselectivity (98 : 2 crude, easily raised to >99 : 1 by recrystallisation) in the creation of the stereocentre C-11 (Scheme 26). We actually carried out the same conjugate addition using the *Z*-isomer in the side chain attached to the enantiomeric sultam, but, although this gave the same absolute configuration at C-11, it was much less stereoselective (67 : 33). Removal of the auxiliary and methylation of the methyl ester **135** gave, again with high stereocontrol, the product **136**. We reduced the ester, and displaced the hydroxyl group as its toluene-*p*-sulfonate using methylcuprate to create the ethyl group in the product **137**. Hydroboration–oxidation, which had been so stereochemically successful in the step **118** ⟶ **120**, gave, once again with high stereocontrol, the alcohol **138**. Thus we had achieved in this route strikingly high levels of stereocontrol in all three steps, and all that remained was some functional group manipulation to convert the alcohol **138** into the aldehyde **139** which is our fragment **C**.



Scheme 26

These steps (Scheme 27) have been published in full elsewhere,[71] because working out the best way through them led us to two unexpected observations. One was that the tertiary alcohol group in the tetrahedral intermediate for a 1,3-acetyl transfer was kinetically more nucleophilic than either the primary or the secondary alcohols. This problem was solved by using the pivaloyl group instead of the acetyl.[71] The other was the discovery that all samples of TIPS triflate appear to be contaminated with the more reactive diisopropyl-n-propylsilyl triflate, and that almost every preparation of a TIPS derivative will give some, although usually very little, of the silyl ether derived from the impurity.[72] The overall yield given in Scheme 27 is from the

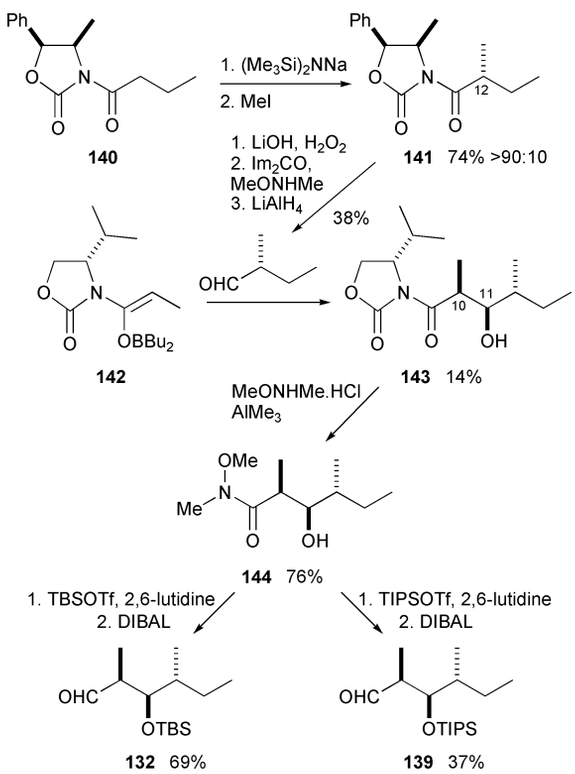


Scheme 27

definitive run with enantiomerically pure material, and is slightly different from that published (41%), which was for racemic material on a smaller scale.

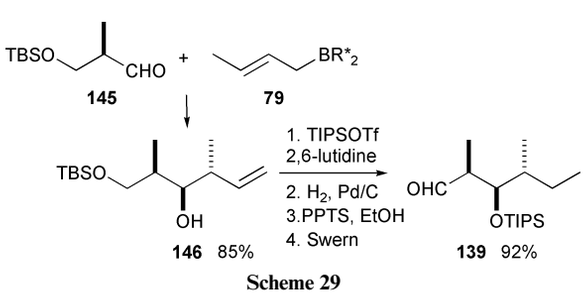
Routes 4 and 5. Concurrent with this work we also looked at two routes to fragment **C** that did not involve stereocontrol based on silicon, and relied upon known procedures.

The first was successful (Scheme 28)—it gave us the aldehydes **132** and **139**, confirming all our stereochemical assignments, and it gave us material to work with in developing the coupling procedures. The centre C-12 came from an Evans alkylation **140** → **141**, the centres C-10 and C-11 came from an Evans aldol **142** → **143**, and we protected the Weinreb amide **144** as a TBS ether and as a TIPS ether in order to show that the aldehydes **132** and **139** were the same as the aldehydes prepared by the silicon-based routes in Schemes 25 and 27.



Scheme 28

The second route not based on organosilicon chemistry was better. It was developed independently by one of us, and it provided fragment **C** in his synthesis. It also gave us material to work with in the coupling procedures that follow. Because it has been published,[16] only the outline, is included here (Scheme 29). Roush's reaction between the TBS ether of (*R*)-2-methyl-3-hydroxypropanal **145**, the enantiomer of the aldehyde **80** in Scheme 16, and the (*E*)-crotylboronate **79** derived from the same diisopropyl tartrate as before is a matched pair, which cleanly gave the homoallylic alcohol **146**. TIPS protection, hydrogenation, selective deprotection of the TBS group and Swern oxidation gave the aldehyde **139**.

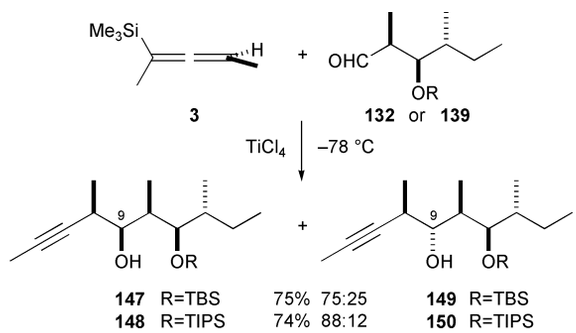


Scheme 29

Coupling the fragments and the final steps

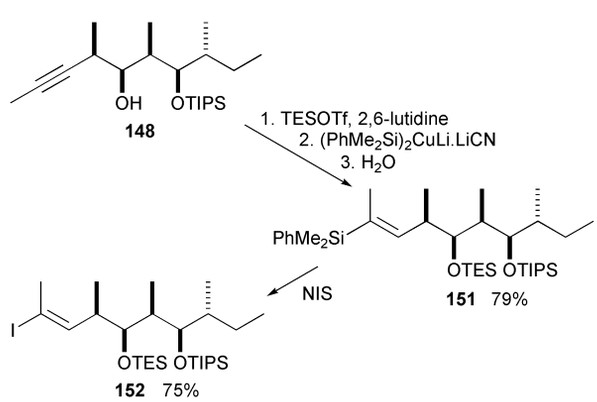
Coupling fragment B to C

We first tried the reaction of the allenylsilane **3** with the TBS ether **132**, because that was the first of the fragments **C** that we made. It gave a mixture of diastereoisomers **147** and **149** in a ratio of 75 : 25 (Scheme 30). We guessed that the problem was chelation, which the silyl ether had not quite suppressed, even though silyl ethers are sterically and electronically reluctant to support chelation.[73] Support for this explanation came when we repeated the reaction with the TIPS ether **139**, which gave a similar pair **148** and **150** but in a better ratio, typically 88 : 12. The presence of the diastereoisomer was not a serious problem, because it only differed in configuration at C-9, which will not, in the end, be a stereogenic centre. Nevertheless, we separated the isomers, in order to have clean spectra in the remaining steps.



Scheme 30

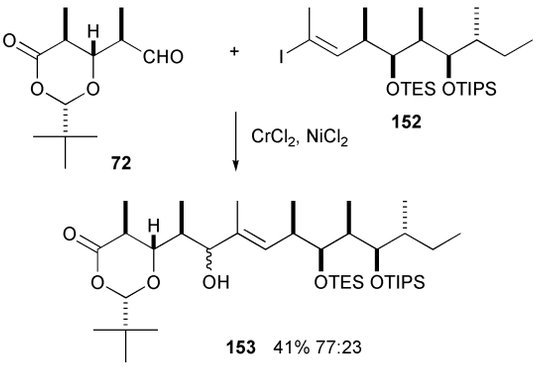
Among several other sequences, some of which are included in the Experimental section,† we carried out the silyl-cupration on the triethylsilyl ether of the alcohol **148**, which gave the expected vinylsilane **151**. Iodo-desilylation gave the (*E*)-iodide **152** (Scheme 31), and our fragment **B+C** was ready for the Nozaki–Hiyama–Kishi coupling. We chose the triethylsilyl group in anticipation of its transfer in a step like **47** → **48** in Scheme 10, where the allylsilane produced would need to undergo a clean protodesilylation like **48** → **50**. A *tert*-butyldimethylsilyl group in an allylsilane is not certain to be the electrofugal group, and furthermore it may not be transferred during the allylsilane synthesis in the step like **47** → **48**. On the other hand, a trimethylsilyl group might not survive the next few steps—a triethylsilyl group was the compromise choice, and maybe, as we shall see, an unfortunate one.



Scheme 31

Coupling fragment A to B+C

The Nozaki–Hiyama–Kishi reaction[74] between the vinyl iodide **152** and the freshly prepared aldehyde **72** gave the alcohols **153** in 41% yield based on the aldehyde, as a mixture of diastereoisomers at C-5 in a ratio of 77 : 23 (Scheme 32). In



Scheme 32

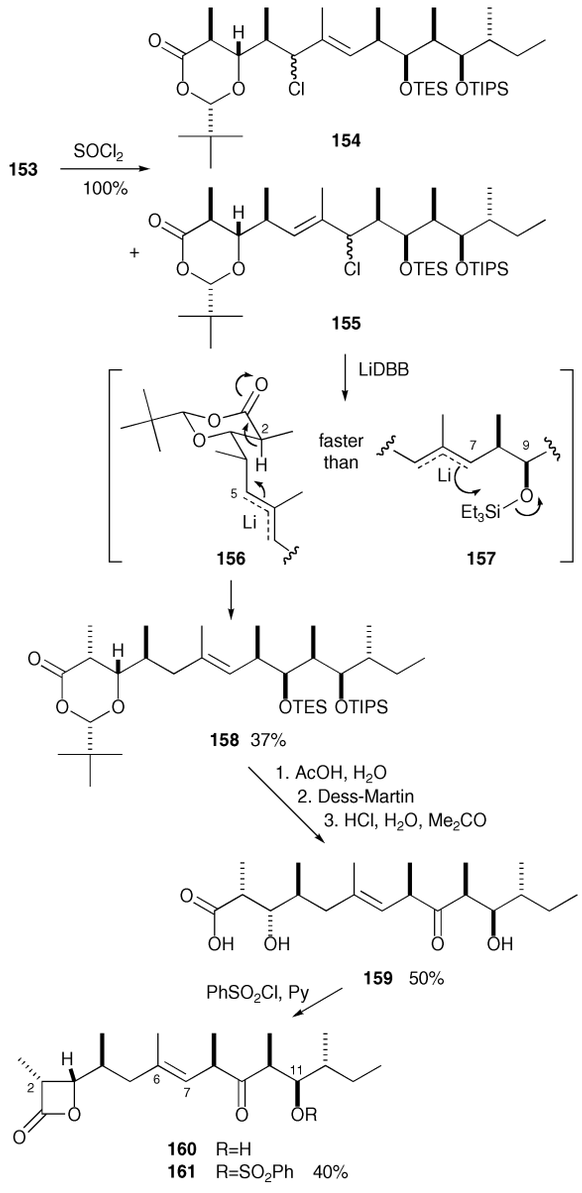
spite of much work, this was the best yield we were able to obtain, and it was only achievable with a 2.6-fold excess of the vinyl iodide, as Kishi had found with similar pairs of coupling partners.[75] Nevertheless, no other method that we tried worked at all, and so we carried forward this material, now containing the full carbon skeleton of ebelactone A.

The synthesis of 2-epi-ebelactone A and its 11-benzenesulfonate

The conditions under which the allylic alcohols (±)-**45** gave the allylic sulfides (±)-**46** failed to work with the alcohols **153**. Instead, we converted the alcohols into a mixture of four chlorides **154** and **155** using thionyl chloride. Treatment of the mixture of chlorides with lithium di-*tert*-butylbiphenyl gave the allylic lithium reagent, but instead of picking off the triethylsilyl group from the oxygen on C-9 **157**, it picked off a proton from the carbon atom C-2 **156** (arrows) (Scheme 33). On workup, the enolate derived from this proton transfer gave the lactone **158** with C-2 having an inverted configuration.

The evidence for this calamitous change of configuration is that the coupling constant between the proton on C-2 and the proton on C-3 had changed from 9.2 Hz and 9.5 Hz in the major and minor lactones **153** (and within the range 8.0–10.5 Hz for all the earlier dioxanones and the chlorides **154** and **155**) to 3.5 Hz in the product **158** (and 3.4 Hz in the two succeeding dioxanones). The larger coupling constant follows from an *axial–axial* orientation for the hydrogens on C-2 and C-3 in all the intermediates leading to, and including, the chlorides **154** and **155**, and the lower coupling constant from an equatorial orientation for the hydrogen on C-2 from the lactone **158** and thereafter. The intramolecular delivery explains the clean formation of only the correct regioisomer with respect to the double bond position between C-6 and C-7, and the stereochemistry of the protonation of the enolate corresponds to attack on the side of the ring opposite to that of both substituents. At this point we rued the choice of a triethylsilyl group to protect the C-9 hydroxyl—a trimethylsilyl group might have beaten the proton—but nothing could be done about it without a fresh start, for which we no longer had resources.

We continued by removing the triethylsilyl group, oxidising the alcohol, and removing simultaneously the TIPS and the dioxolanone protection to give the dihydroxy ketoacid **159**. Although it would not give ebelactone A, we carried out the standard Adam synthesis of the β-lactone to give 2-epi-ebelactone A **160**. However, now that the two substituents will be *cis* on the β-lactone ring, the cyclisation was substantially slower than it had been for our model compounds **71** and **77**, and slower than it had been for other people's *trans*-disposed β-lactones, including those in the syntheses of ebelactone A. As a result, while the cyclisation was taking place at the higher temperature it required (−4 °C in 50 h, compared with −20 °C in 40 h for **71**), the free hydroxyl on C-11 was benzenesulfonylated, and the major product was the benzenesulfonate **161** of 2-epi-ebelactone A. The free alcohol **160** was detectable, but could not be reliably characterised.



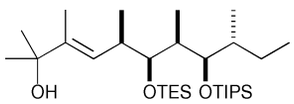
Scheme 33

Conclusions

A silyl group can be used in enolate alkylations and in the hydroboration of allylsilanes to control stereochemistry in the synthesis of the two fragments **A** and **C**. The stereospecifically *anti* S_E2' reaction of an allenylsilane was highly effective in joining fragments **B** and **C**. Finally, the double bond geometry was controlled by the *syn* silylcupration of an acetylene, and preserved from that step on.

In one sense then, we have achieved our goal of controlling all the stereochemistry using silicon. In addition, we remained inspired by Woodward's well known remark, "Of course, men make much use of excuses for activities which lead to discovery. . .we do not hesitate to advocate the case for synthesis."[76] In the event, we failed in the final steps, but we have been rewarded with his "dividend of unsought fact." In our case, this work stimulated us to find a synthesis of enantiomerically enriched allenylsilanes, and work out the stereochemistry of their reactions. We discovered the silylcupration of allenes, the high level of stereocontrol in the conjugate addition to unsaturated 6-membered ring lactones, some unexpected reactions with LDA, a problem with TIPS protection, and several intriguing pathways in organosilicon chemistry that have illuminated the details of that subject, including a remarkable but limited synthesis of cyclopropanols by γ-elimination of a β-silyl aldehyde.

We close with another curious observation that ought to herald more research. A byproduct in the Nozaki–Hiyama–Kishi reaction between the vinyl iodide **152** and the aldehyde **72** was the tertiary alcohol **162**. Nozaki–Hiyama–Kishi reactions are rarely effective with ketones,[77] and yet some nucleophilic species present in the mixture must have sought out traces of acetone inadvertently introduced when the reaction was quenched. If only such species could be prepared specifically, one of the serious limitations of the Nozaki–Hiyama–Kishi reaction might be overcome.



162 13%

Acknowledgements

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