Stereocontrol in organic synthesis using silicon compounds

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Abstract—A stereogenic centre carrying a silyl group, a carbon substituent, and a hydrogen atom adjacent to a double bond (**1**) induces highly diastereoselective attack by electrophiles. The reasons for the effectiveness of this combination and its limitations are discussed, and illustrated by electrophilic substitution reactions (**3**) and the hydroboration (**4**) of allylsilanes, and enolate alkylations of esters having a β-silyl group (**5**). Studies directed towards the synthesis of ebelactone-a (**17**) illustrate how well and with what versatility the silyl group can control relative stereochemistry.

INTRODUCTION

We have been engaged for several years in a study of stereocontrol using silicon-containing compounds. The essence of the method is to use an electrophilic reaction on a double bond adjacent to a stereogenic centre carrying a silyl group, a carbon group, and hydrogen (**1**) (ref. 1). We suggest, in outline, that this relatively good, genuinely open-chain stereocontrol stems from the sum of four mutually supporting influences. (i) The lowest energy conformation is


1   **2**
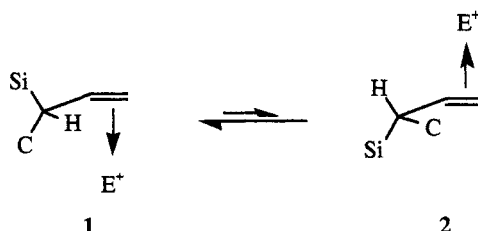
usually well controlled to be close to that depicted in **1**, because only the hydrogen atom comfortably eclipses (or partly eclipses) the double bond. (ii) The lowest energy conformation is also likely to be close to the reactive conformation, because the Si-C bond is able to overlap with the π-bond, activating it towards electrophilic attack. (iii) The top and bottom surfaces of the π-bond are well differentiated: the silyl group is large relative to most carbon groups, and (iv) electronically the polarisation of the Si-C bond will also encourage attack by electrophiles from the lower surface of the π-bond. The only serious limitation that has emerged so far arises when the stereogenic centre has as its carbon substituent only a small group like methyl, and when this coincides with the substituent on the double bond *cis* to the stereogenic centre being no larger than a hydrogen atom. In this situation, the alternative conformation (**2**) is well populated, and attack on it will take place on the upper surface. Examples of this problem can be found in osmylation and epoxidation reactions (ref. 2), in a nitrile oxide cycloaddition (ref. 3), and in a Simmons-Smith reaction (ref. 4), all of which show an approximately 2:1 preference for reaction to take place in the sense (**2**). However, although hydroboration with diborane is similarly unselective, hydroboration with 9-BBN is very selective in the sense (**1**)(ref. 5). Diels-Alder cycloadditions are very selective in the sense (**1**) with *N*-phenylmaleimide but in the sense (**2**) with dimethyl acetylenedicarboxylate (ref. 6). When the substituent on the stereogenic centre is larger than methyl and/or when the substituent *cis* to the stereogenic centre is larger than a hydrogen atom, these reactions become relatively well behaved in the sense (**1**)(refs. 2,4,5). Of course, we cannot be certain that attack in the sense (**1**) actually takes place in this conformation, anymore than we can be certain that attack taking place in the sense (**1**) takes place in that conformation. We are currently investigating this point by examining in detail the stereochemistry of the electrophilic substitution of allylsilanes, but for the moment, it seems reasonable to assume that this is where the problem lies.

In spite of this limitation, stereochemical control based on this one idea can be applied in several different ways with correspondingly different outcomes. In this lecture I want to demonstrate how we have used it, in each of its manifestations, in an incomplete synthesis of ebelactone-a, which has seven stereogenic centres and a trisubstituted double bond. Our major claim with this work is that we shall be able to control all of the stereochemical problems with this single device.

The three aspects of this method of stereocontrol that we have used are: the transposition of chiral information from C-1 to C-3 in electrophilic substitution reactions of allylsilanes (3)(refs. 2,3,7,8), the setting up of stereogenic centres with a 1,3 relationship using the hydroboration of allylsilanes (4)(ref. 5), and the setting up of stereogenic centres

3   **4**   **5**   **6**
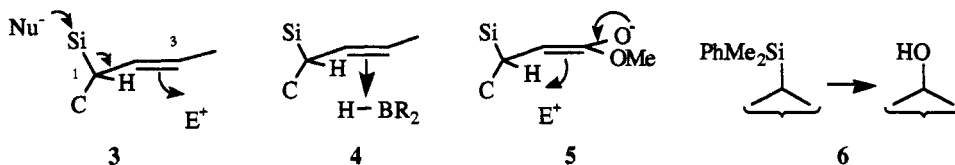
with a 1,2 relationship by the alkylation of enolates having a β-silyl group (5)(refs. 9,10). To these three methods, we add the possibility of converting a phenyldimethylsilyl group into a hydroxyl with retention of configuration (6)(ref. 11). Perhaps most striking about these methods of stereocontrol is the sense in which the word "control" really means control: with each of them, we are able to control relative stereochemistry in whichever sense is wanted. In the electrophilic subtitution of an allyl silane (3), a stereospecifically *anti* reaction allows, in principle, the new centre to be created in either sense by three methods: (i) control of the absolute configuration of the stereogenic centre, which is then relayed to the new centre, (ii) choice of which group shall be resident on C-3 of the allylsilane unit and which shall be the electrophile E⁺, and (iii) choice of double bond geometry. The last method also works for the hydroboration reaction (4), where we have demonstrated that the *E*-allylsilane (7) gives the 1,3-diol derivative (8)

7   96% >95:5   **8**   71%

9   79% >95:5   **10**   74%
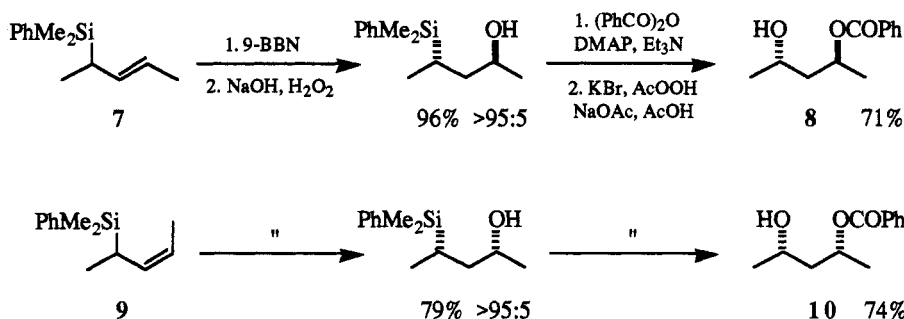
with an *anti* relationship of substitutents on the carbon chain, and the Z-allylsilane (9) gives the 1,3-diol derivative (10) with a *syn* relationship (ref. 5). Furthermore, we have shown that the electrophilic attack on enolates (5) is also

**11**   **12** 97:3 88%   **13** 84%

14   **15** 91:9   **16** 63%
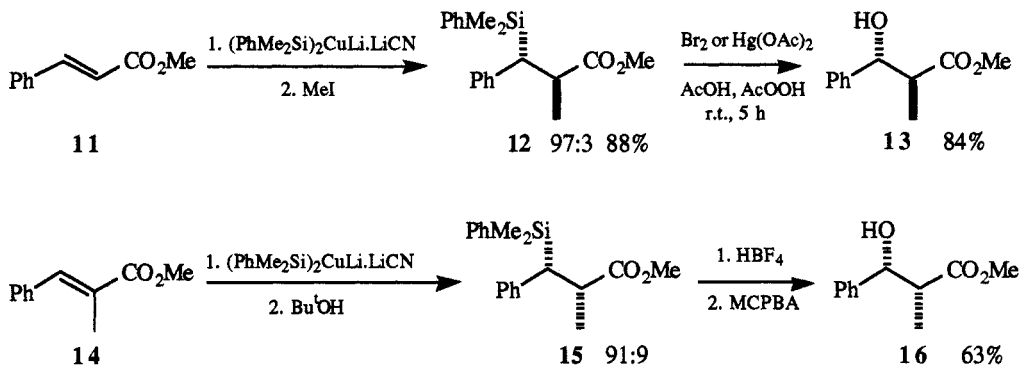
amenable to control in either sense, since alkylation of an enolate (11 → 12) gives the *anti* relationship of substituents, whereas protonation of the enolate (14 → 15) gives the *syn* relationship (ref. 9). In each case, the conversion of the silyl to the hydroxy group gives β-hydroxy esters (13 and 16, respectively)(refs. 11 and 12).

## EBELACTONE-A

Ebelactone-a (17)(ref. 13) is an esterase inhibitor, but from the synthetic point of view it presents a much more substantial challenge than the targets that we have tackled hitherto, such as tetrahydrolipstatin (ref. 14). Although incomplete, our work on the synthesis of ebelactone-a has led us to seek and find solutions to all the stereochemical

problems. Our approach has been to divide the molecule into three parts, two electrophilic fragments (**18** and **20**) and one doubly nucleophilic fragment (**19**). The left-hand electrophile (**18**) might be derivable from a *meso* diester (**23**),
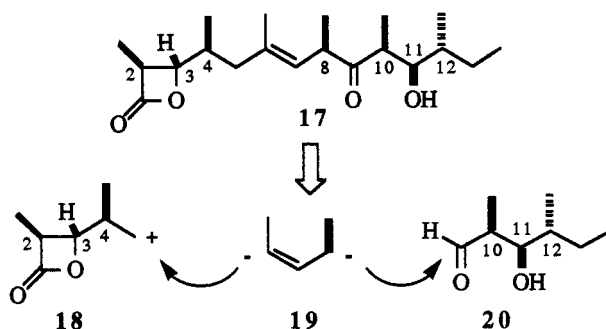
if the diastereotopic ester groups can be differentiated in some way. Since there are several methods for dealing with this sort of problem, we have not looked at it yet, but have concentrated simply on setting up the three stereogenic centres with the appropriate relationship, which is that of an alkylation reaction, as in the model sequence (**11** → **12**). The first methylation step (**21** → **22**) was very highly diastereoselective, and the second (**22** → **23**) was less so, but
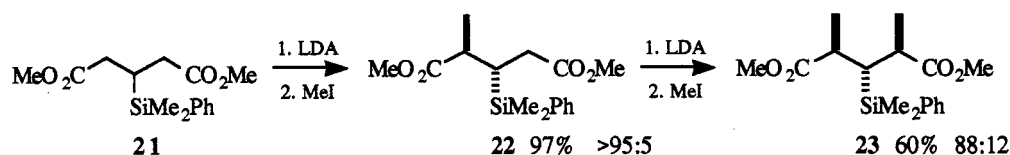

the diester (**23**) gave a crystalline anhydride (**24**), which was clearly a *meso* compound. There was some risk that these reactions might have induced epimerisations α to the ester groups, leading to the, presumably more stable, all-*trans meso* anhydride. However, no epimerisations had taken place in this transformation, as was readily apparent when we converted the minor component of the second alkylation step into the corresponding anhydride, which was
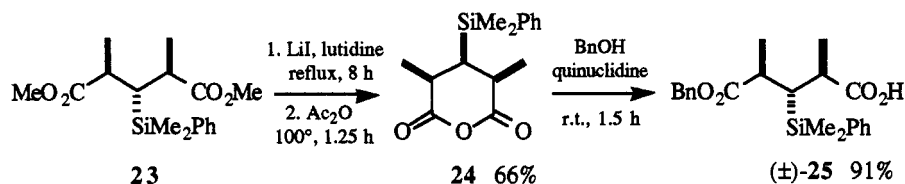

clearly different from the anhydride (**24**). As a model reaction for the differentiation of the two carbonyl groups, we opened the anhydride (**24**) with benzyl alcohol to give the racemic mono-ester (**25**), which could be selectively reduced at the carboxylic acid group using borane:THF to give the corresponding primary alcohol. It is easy to imagine how this or some related reaction can be used to enter the optically active series, and how an aldehyde or halide derived from the alcohol might function as the component (**18**).

Turning to the other electrophilic component (**20**), we can see a hydroxy group β to a carbonyl group, with the stereogenic centres C-10 and C-11 related in the sense of the protonation sequence (**14** → **15**), but the other pair, C-11 and C-12, present a new problem with many possible solutions. Our first efforts in this direction were stereochemically very successful: conjugate addition of our silyl-cuprate reagent to the unsaturated lactone (**26**), followed by alkylation, gave only, as far as we could tell, the lactone (**27**)(ref. 15). Although the C-10 centre has been put in by alkylation not protonation, it is in the correct sense, because alkylation is taking place in a cyclic structure constrained to have the conformation (**2**). Unfortunately, we have been unable, so far, to reduce this lactone
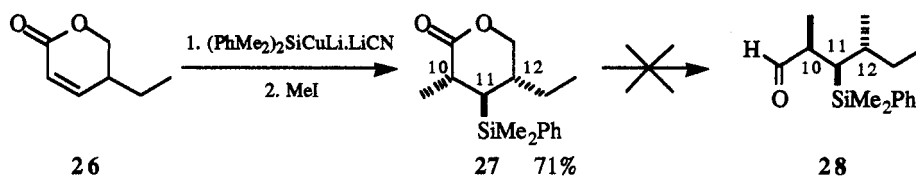

to the aldehyde (**28**). In particular, the methylene group adjacent to the oxygen atom is too hindered to be attacked by any of the powerful nucleophiles like selenide, that normally open lactones by alkyl-oxygen cleavage (ref. 16), and approaches based on reduction of the lactone carbonyl have been similarly unfruitful.

To solve this problem, we turned to hydroboration: as well as giving 1,3 control in the sense (7 → 8) and (9 → 10), we already knew that it could be used to control 1,2-related centres. Thus the hydroboration-oxidation (29 → 30)
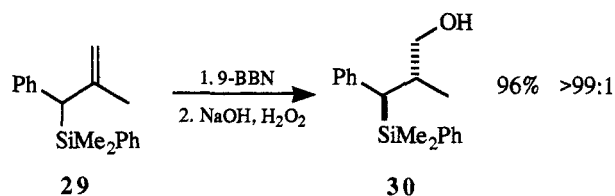
was highly diastereoselective (ref. 5), and we now find that the model allylsilane (31) undergoes hydroboration-oxidation with similar selectivity giving only the lactone (33). We can confidently extrapolate this reaction to a substrate having an ethyl group in place of the methyl, but we still face the problem of avoiding the formation of a lactone. We really want the boron atom in the hydroboration product (32) to be replaced by a proton, not an oxygen
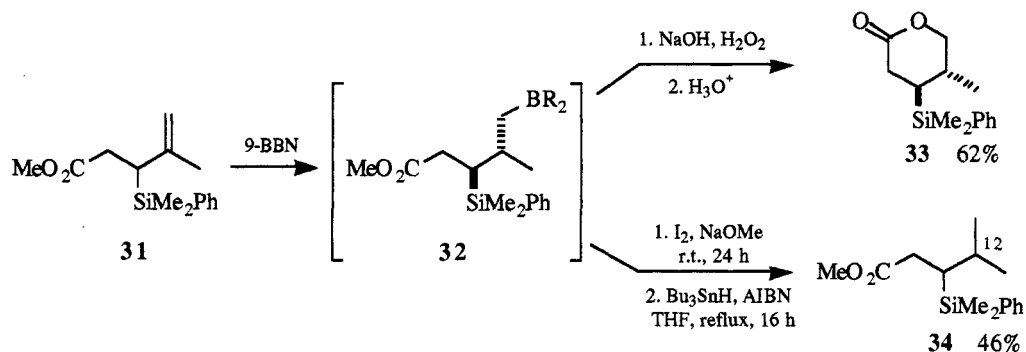

atom. Although this kind of process is well known using acids like propionic acid, we have had more success with a two step sequence: iododeboronation (ref. 17) followed by reduction of the iodide (ref. 18) giving the ester (34). This particular compound no longer has a stereogenic centre at C-12, but the sequence (31 → 34) is a good model for the problem that we want to solve. Furthermore, we already know that absolute control of the stereochemistry at C-11 will be fairly easy, since the conjugate addition reaction (35 → 36) is substantially selective in the sense we want, which happens to be epimeric to the result we had in the tetrahydrolipstatin synthesis. Once again, we are able to emphasise that each of our methods is able to give either epimeric relationship; in this case control from the choice of
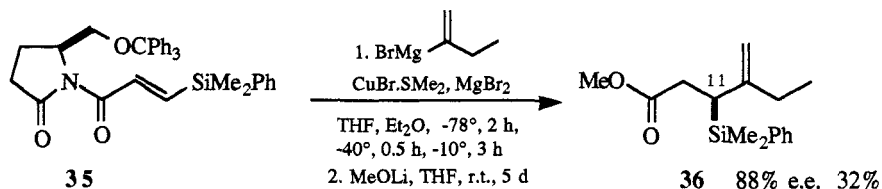
double bond geometry in the enone precursor (cis in the tetrahydropipstatin synthesis and trans in 35) leads to control in the absolute configuration of the silicon-substituted stereogenic centre. With the method for controlling the C-11 and C-12 relationship settled, we can now look ahead to the C-11 and C-10 relationship. Normally, since this is a "protonation relationship" in the sense of the reaction (14 → 15), we would control it easily by having the methyl group on C-10 already in the molecule when we do the conjugate addition. This is not possible here, because a substituent on this carbon in 35 would interfere with the absolute stereocontrol. One might consider introducing the methyl group by alkylation of the ester (36). This would have exactly the wrong stereochemistry, but regenerating the enolate and protonating it under kinetic control should correct the stereochemistry. Unfortunately, we have so far been unable to generate an ester enolate when there is a substituent at the α position, and we will have to use a

sequence that we set up some time ago (refs. 10,19) precisely to solve this kind of problem. Methylenation of the β-silylbutyrate ester (37) by several methods gave the ester (38), and phenylthio conjugate addition-protonation gave
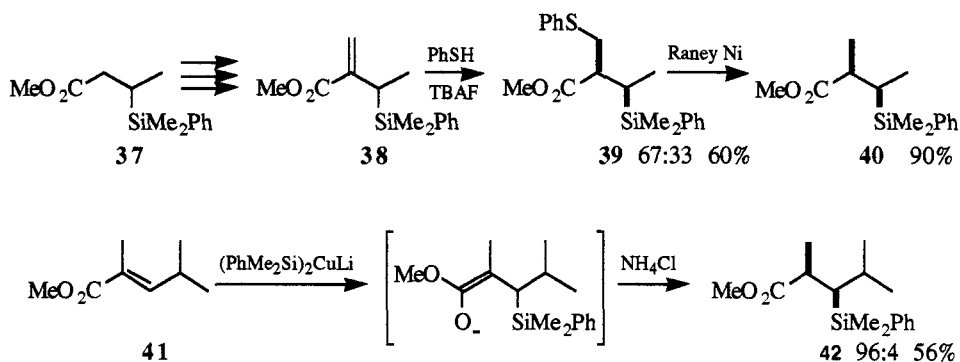
the ester (39), although in this case only with low stereoselectivity in the protonation sense. However, we know that protonation of an enolate with a methyl group on the stereogenic centre is less selective than with larger groups; protonation with an isopropyl group on the stereogenic centre (41 → 42) (ref. 9), for example, gives very high selectivity, which augurs well for what we will be wanting to do in the ebelactone synthesis.

We now come to the central and most intriguing problem: how to join the three pieces together, and what will be the doubly nucleophilic synthon (19)? Our plan here is to use an optically active allenylsilane (45), which will react in the general sense (3), *anti* to the silicon, to set up the correct absolute configuration at the isolated stereocentre C-8. We have already established how best to prepare this type of allenylsilane (ref. 20), and we have now used the method in the optically active series, starting from the known propargyl alcohol (43)(ref. 21), to prepare the allenylsilane (45). To improve the enantiomeric purity of the propargyl starting material, we have used the sulphonate
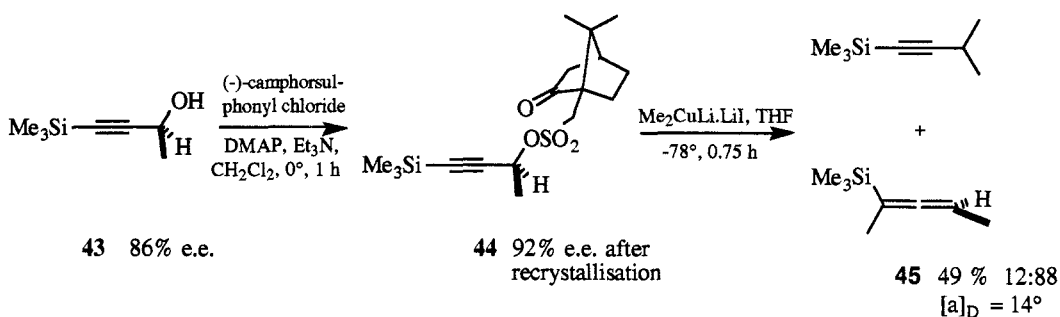
ester (44), which crystallises, but we are still left with some uncertainty about the optical purity of the allenylsilane. The problem is that cuprates, although they are known (ref. 22) to react in a stereospecifically *anti* manner, are also known (ref. 23) to racemise allenes, and there is no direct and easy way by which we can tell what the optical purity of our allene is. The best we have been able to do is to treat the allenylsilane (45) with isobutyraldehyde and a Lewis acid, and to measure the optical purity of the product (46), which proved to be less (60% e.e.) than that of the sulphonate (44)(92% d.e.) from which it had been prepared. However, the diastereoselectivity for the formation of the product (46), assigned by analogy with Danheiser's work (ref. 24), with the substituents *syn* on the backbone
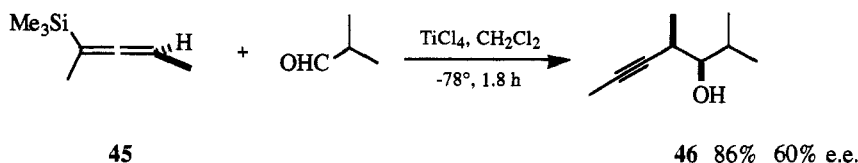
rather than *anti*, is high, and this has further consequences in our favour. When we come to combine the allenylsilane (45) with the aldehyde (29), the temporary stereogenic centre C-9 will be controlled from both

components in the same sense: the allenylsilane will react in the same sense as in the model series (**45 → 46**), and the *syn* relationship between C-9 and C-10 in the product (**47**) corresponds to that expected of attack on the aldehyde in
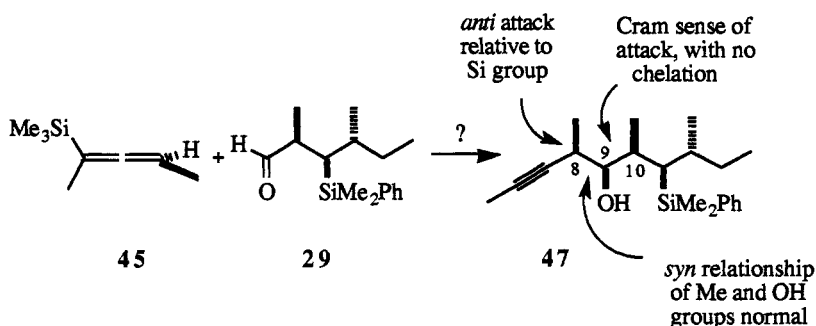
the sense of Cram's rule. This means that, although the stereochemistry of C-9 itself is unimportant, the two components are matched—they will reinforce each other's stereochemical preferences. We can expect a particularly clean reaction when we come to do it, and any enantiomeric impurity in our allene may be less important than it would

otherwise be, because the enantiomer of the allene (**45**) will not react as efficiently with the aldehyde (**29**). As a check on this point, we have carried out the model reaction (**45 + 48 → 49**), in which *both components were racemic*, an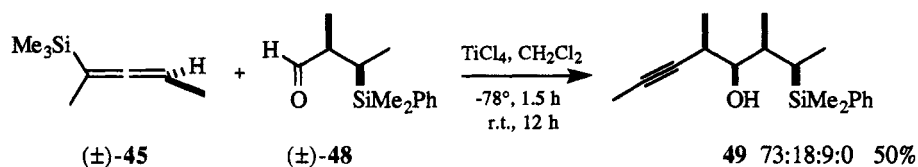d obtained, to be sure, a mixture of diastereoisomers, but with *one major component* (**49**) making up 73% of the mixture.

The success of this operation is dependent upon the phenyldimethylsilyl group masking the C-11 hydroxy group until this step is complete. If the hydroxy group is already unmasked, it will induce chelation control in the step (**45 + 29**) and the two components would then be stereochemically mismatched. However, looking ahead, there will be a problem in converting the silyl group to a hydroxy once the C-6,C-7 double bond is in place, because that reaction is dependent upon an electrophile's attacking the phenyl group on the silicon faster than it attacks anything else. A disubstituted and especially a trisubstituted double bond would be more nucleophilic than a silylated benzene ring, and will defeat our efforts. The unmasking must be the next step. We have found that a triple bond is capable of surviving the unmasking (**49 → 50**), but here we can take advantage of the presence of the C-9 hydroxy group to
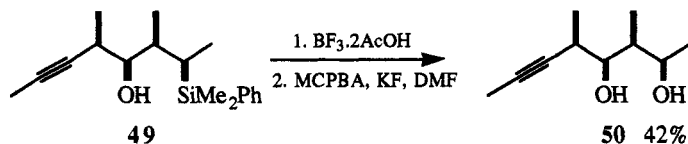
remove the phenyl group under mild conditions. In the benzylation step in our tetrahydrolipstatin synthesis (ref. 14), we had found it necessary to use acid-catalysed conditions, because of the easy loss of the phenyl group when we used sodium hydride. Now we shall be able to use sodium hydride deliberately, and the only problem then is to preserve the distinction between the two hydroxy groups before the migration of C-11 from silicon to oxygen takes place. As a model for this step, we have carried out the sequence (**51 → 52 → 53**). This leaves the problem of

creating the second of the nucleophilic centres, in order to join the two fragments (**18** and **19**). Our plan here is to carry out a silyl-cupration of the triple bond of a suitably modified and protected version of the alcohol (**47**). We

know that disubstituted triple bonds react stereoselectively *syn* with our silyl-cuprate reagent (ref. 25), and we have now tested the regioselectivity of this reaction when the two ends of the acetylene are as substantially different as they will be here—the silyl ether (54) of the acetylenic alcohol (46) reacts very selectively to place the silyl group at the

methyl-substituted end of the bond, and the product (55) reacts with iodine to give the iodide (56), in a reaction that is far from satisfactory as yet, since we get a large amount of protodesilylation, whether we protect the alcohol group or not, but is stereospecific in giving retention of double bond geometry. A vinyl iodide is obviously a suitable precursor for an organometallic nucleophile, but there are not too many ways of using a vinyl-metal to make a bond with an alkyl halide. The alternative, to use the intermediate (18) as the nucleophile, provides several methods, and we have carried out the conversion of the iodide (57) to the alkene (58) as a model for such a procedure, but we are

not sanguine about this idea—it will probably not be easy to create a nucleophilic species out of the "real" reagent corresponding to 18; there will surely be too many problems of protection for the β-lactone group. Accordingly, we have to face the prospect that the organometallic nucleophile corresponding to the sum of the components (19 and 20) may have to be treated with an aldehyde in a reaction of the type (59 + 60 → 61), whereupon we face a new

problem: how to convert the allylic alcohol (61) to the alkene (62), with retention of the position of the double bond, and the selective formation (or retention) of the *E* configuration. Once again, we have developed a model sequence that solves precisely this problem using silicon chemistry. Trisubstituted double bonds are selectively set up in the sense that we want here by the protodesilylation of allylsilanes, as in the reaction (63 → 64), when the substituent on

the stereogenic centre carrying the silyl group is branched (ref. 26). Furthermore, we have a method by which an unsymmetrical allylic alcohol can reliably give the allylsilane with the necessary allylic shift in functionality, if we use the urethane-cuprate protocol (ref. 27), as illustrated in the reaction (65 → 66 → 67).

With all the methods in place, we have now to put them into practice; perhaps I can finish by summarising the methods by which the stereocontrol will be achieved, if all goes according to plan! The single diagram (68) says it

all, but I should like to emphasise that all of the methods that we plan to use could be adapted to give the opposite stereochemical outcome. Although reactions with high levels of stereoselectivity or stereospecificity are now common, stereo*control,* in the sense that I have illustrated it in this lecture, is rare.

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