Enantioselective Hydrosilylation Of Prochiral Alkenes Using Homochiral Thiols As Polarity-Reversal Catalysts

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for the Degree of
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Muhammed Bodrul Haque

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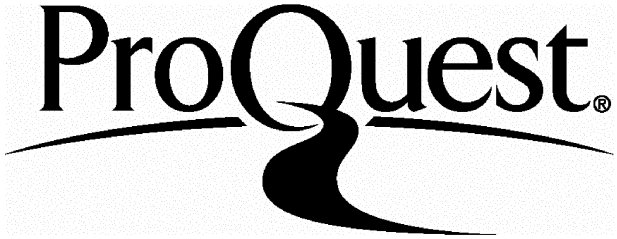
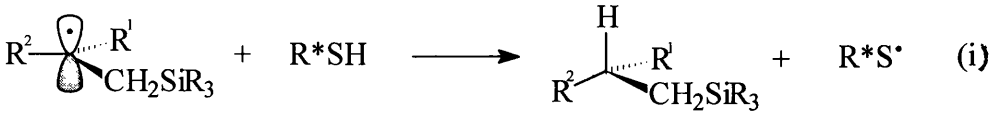
Christopher Ingold Laboratories
Department of Chemistry
University College London
London WC1H OAJ



To My Parents

Abstract

It has been shown that the radical-chain hydrosilylation of alkenes by simple triorganosilanes is promoted by thiols, which behave as polarity-reversal catalysts. The radical-chain hydrosilylation of alkenes of the type $H_2C=CR^1R^2$, catalysed by small amounts of homochiral thiol (R*SH), affords functionalised organosilanes in moderate to high enantiomeric purity by a mechanism which involves enantioselective hydrogen-atom transfer from the homochiral thiol to a prochiral β-silylalkyl radical [eqn. (i)].



(i)

First, hydrosilylations of acyclic prochiral alkenes were investigated, then the corresponding reactions of cyclic prochiral alkenes were studied. All hydrosilylation reactions were first carried out using achiral thiol catalysts and then with homochiral thiols. All the homochiral thiols investigated were derived from naturally-occurring homochiral molecules and a number of new enantiomerically-pure thiols have been prepared. The functionalised organosilanes obtained, could be oxidatively desilylated to give functionalised alcohols and other functionalised derivatives.

The enantiomeric excesses were generally low at the beginning of this project, but progressively increased as more was understood about the important factors leading to higher enantioselectivities. Enantiomeric excesses of up to 95 % could be obtained in one-pot reactions at 60 °C when using sterically-hindered cyclic prochiral alkenes with the bulky triphenylsilane and catalysed by homochiral monosaccharide carbohydrate thiols. The enantiomeric purities were generally determined by chiral-stationary-phase HPLC analysis, otherwise by ^1H NMR analysis using homochiral shift reagents.

Enantioselective atom abstraction reactions are relatively rare and the selectivities obtained in the present work are the highest obtained to date. Furthermore, high enantioselectivities can be achieved at relatively high temperature (60 °C).

Acknowledgements

I would like to thank my supervisor Dr. B.P. Roberts for all the help and advice throughout the project. I would also like to thank the members of the group past and present for making life in the lab pleasant (most of the time). A big thank you goes to all the people in the Department for their time when pointing me in the right direction, especially Dr. H.-S. Dang for useful tips and some initial advice on operating the NMR spectrometers, Steve Corker for help with the HPLC instruments and Dr. J. Cai for his help and advice when I first started. Finally, thank you to my parents for their support for the duration of my studies.

Abbreviations

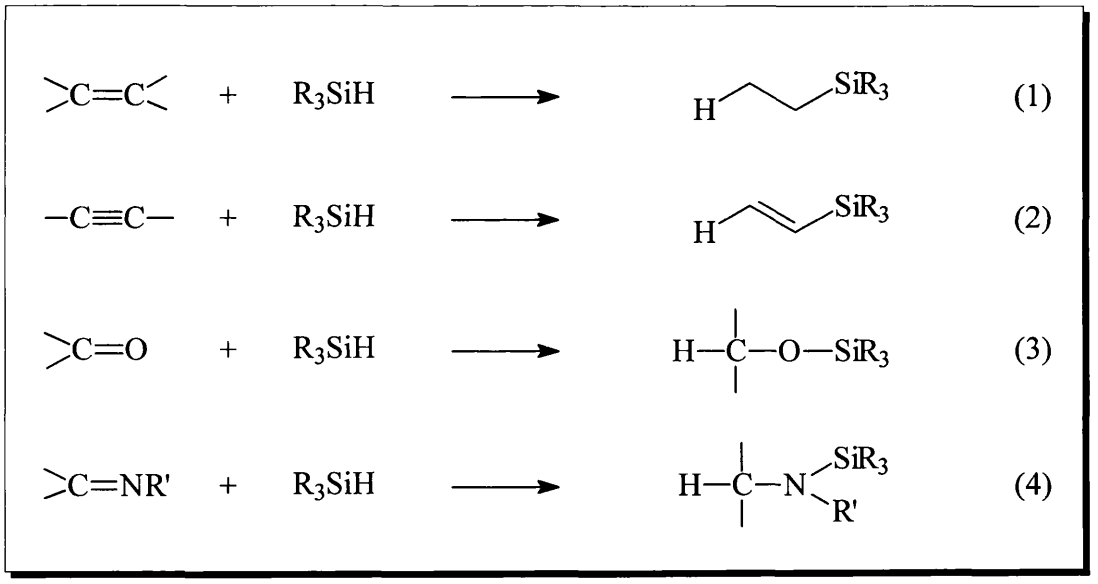
Ac	acetyl
ACHN	azobiscyclohexanecarbonitrile
AIBN	azobisisobutyronitrile
ATPH	aluminium tris(2,6-diphenylphenoxide)
DEAD	diethyl azodicarboxylate
Dibal-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
ether	diethyl ether
HPLC	high performance liquid chromatography
HMPA	hexamethylphosphoramide
IPA	isopropyl alcohol
LDA	lithium diisopropylamide
petroleum	petroleum spirit 40-60 °C
Piv	pivaloyl
PRC	polarity-reversal catalysis
NMR	nuclear magnetic resonance
RT	retention time
TBAF	tetra-*n*-butylammonium fluoride
TBHN	di-*tert*-butyl hyponitrite
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl (trifyl)
TfO	trifluoromethanesulfonate (triflate)
tlc	thin layer chromatography
TTMSS	tris(trimethylsilyl)silane
Ziram	zinc *N*,*N*-dimethyldithiocarbamate

Contents

Introduction

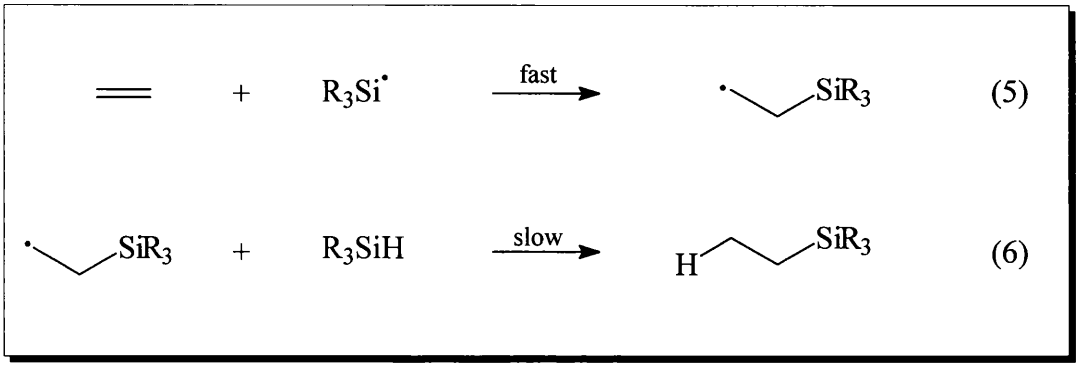
Organosilicon compounds play an important role in organic synthesis.[1] They have a variety of uses, including silicon-containing perfumes, medicines, adhesives and have been used in the pharmaceutical industry.[2] After oxygen, silicon is the most abundant element in the Earth's crust (28 % by weight).[3] Two important types of reaction first observed involving silicon, (a) the direct synthesis of halosilanes which was first reported in 1945[4] and (b) hydrosilylation, were first observed many years ago.

Hydrosilylation is the name given to the reaction in which a hydrosilane (*e.g.* R_3SiH) adds to an unsaturated compounds such as an alkene, alkyne, ketone or imine [eqns. (1)-(4)] to give an alkylsilane, vinylsilane, alkoxysilane or aminosilane, respectively.[5] The hydrosilylation of alkenes [eqn. (1)] is an important method for the



formation of Si-C bonds.[2] This hydrosilylation reaction can proceed by a radical-chain mechanism or under the influence of various transition-metal complexes as catalysts.[3] Of these rhodium, palladium and platinum complexes are most frequently used. Hexachloroplatinic acid, H_2PtCl_6, is the classic example of such a catalyst for hydrosilylation and functions with a wide variety of silanes and substrates. The transition-metal-complex catalysed hydrosilylation was first reported in 1957.[6]

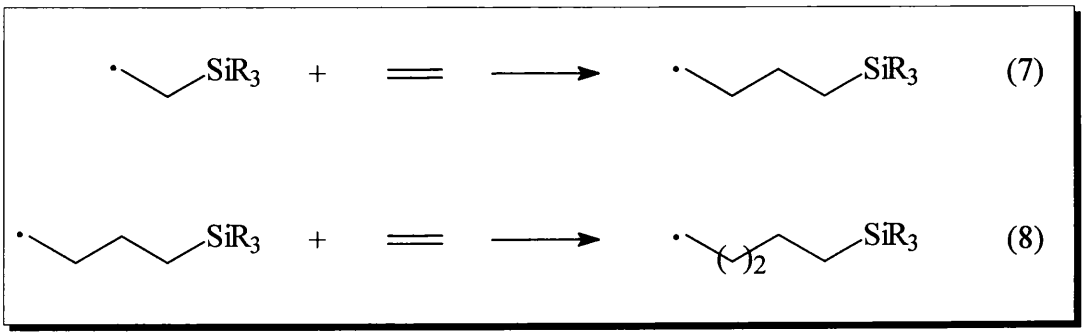
Radical-chain hydrosilylation of alkenes



Radical-chain hydrosilylation of alkenes were first described in several reports in 1947 in which the reaction was promoted by peroxides, UV light, high-energy irradiation or heat (~ 300 °C).[7] The general rule for radical-chain addition of the reagent R_3SiH to an alkene is anti-Markovnikov addition. This regioselectivity is the result both of higher stability of the adduct radical and a less congested pathway which favours addition of $R_3Si^{\bullet}$ to the less alkylated end of the double bond.[3]

Aspects of the radical-chain process

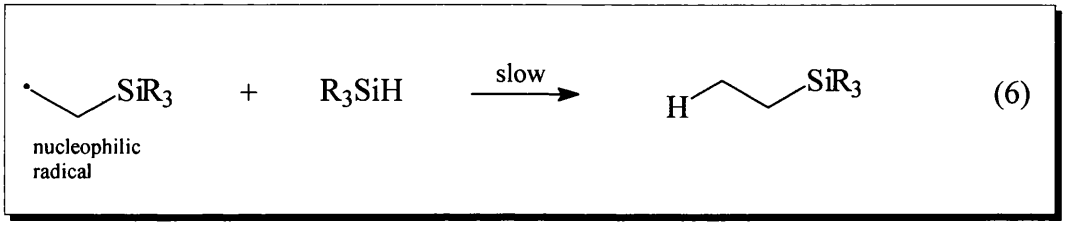
In the past, radical-chain hydrosilylation of alkenes using trialkylsilanes has been considered not very useful in synthesis. Problems can arise from the β-silylalkyl radical adding to the alkene which can lead to telomerisation of the latter [eqns. (7) and (8)].[8]



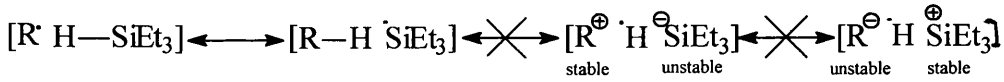
The addition of a silyl radical to the double bond is facile [eqn. (5)], but the hydrogen-atom abstraction step [eqn. (6)] is relatively slow at moderate temperatures. For example, the attempted reaction between triethylsilane and oct-1-ene at 40 °C, initiated by the UV photolysis of di-*tert*-butylperoxide (DTBP), gave no triethyloctylsilane,[8a] and

only a 15 % yield of Et_3SiOct was obtained after triethylsilane, oct-1-ene and DTBP in the molar portions 5:5:1 had been heated at 110 °C for 96 h.[8b] At both temperatures, the addition of $Et_3Si^{\bullet}$ to the alkene [eqn. (5)] is known to be fast and irreversible.[9] However, a 90 % yield of Pr_3SiOct could be obtained from radical addition of Pr_3SiH to oct-1-ene by slowly dropping a mixture of the alkene (1 mol) and DTBP (0.2 mol) onto the silane (6 mol) heated at 140 °C.[8b]

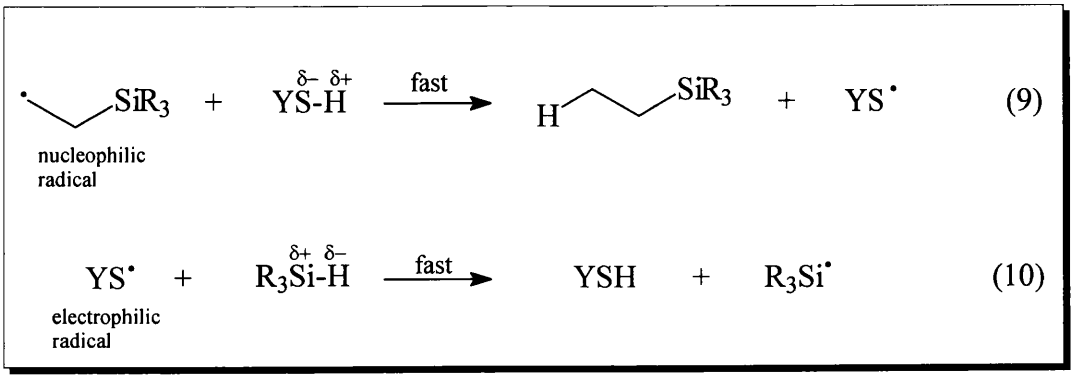
Thiols as polarity-reversal catalysts



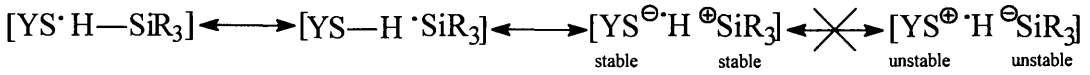
On closer inspection, the slowness of the hydrogen-atom transfer step [eqn. (6)] can be attributed to the unfavourable polar effects which operate in the transition state for abstraction of *electron-rich* hydrogen from the silane by the *nucleophilic* β-silylalkyl radical.[10]



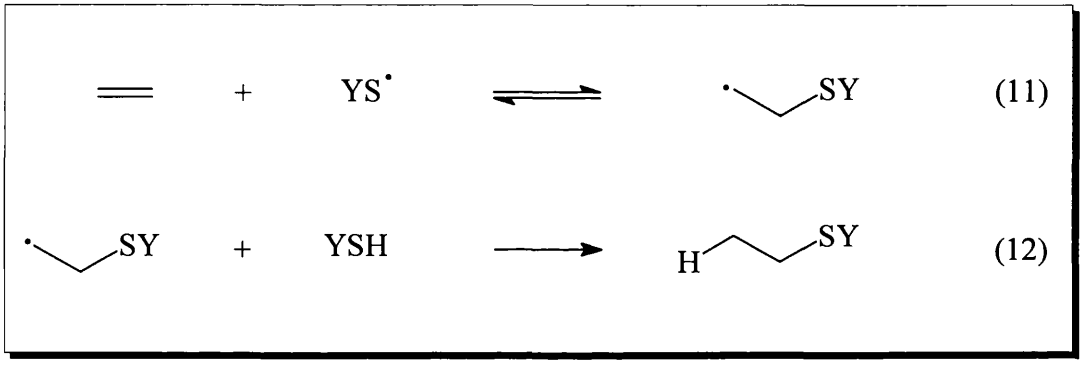
It has been shown that reactions of the type (6) can be promoted by small amounts of thiol (YSH) which act as *polarity-reversal catalysts*, such that the slow direct abstraction is replaced by the cycle of reactions (9) and (10).[11]



Both these reactions benefit from favourable polar effects, because the thiyl radical is *electrophilic* and the sulfhydryl hydrogen atom is *electron-deficient*. Polar effects will facilitate the hydrogen transfer reaction (10) by stabilising the transition state.



Hence, it would be expected that thiols will catalyse the radical-chain hydrosilylation of alkenes by trialkylsilanes, provided that possible competing radical-chain addition of the thiol to the alkene can be suppressed [eqns. (11) and (12)]. The



known ready reversibility of the addition of thiyl radicals to alkenes[12] should help to favour the desired reaction.

Hydrosilylation of alkenes using thiols as polarity-reversal catalysts

Previous experiments have shown how ineffective hydrosilylation reactions are in the absence of thiol.[11] For example, when a solution in hexane (6.0 cm^3) containing oct-1-ene (10 mmol), triethylsilane (20.0 mmol), tridecane (2.0 mmol), and di-*tert*-butyl hyponitrite (TBHN; 0.5 mmol) as initiator was heated at 60 °C for 2 h under an atmosphere of nitrogen, GLC analysis of the reaction mixture (using the tridecane as internal reference) showed only a trace amount of Et_3SiOct had been formed (< 1% yield based on octene). However, when the experiment was repeated and *tert*-dodecanethiol (0.5 mmol) was added in one portion when the temperature of the reaction mixture had reached 60 °C, the yield of Et_3SiOct increased to *ca.* 40 %. It would be predicted that the yield of Et_3SiOct should be improved by adding the thiol slowly during the reaction,

rather than in one single portion. This is suggested when considering the reactions (9)-(12), because competitive (and overall irreversible) addition of thiol to the alkene should then be suppressed. Using this procedure, under otherwise identical conditions, when the thiol in hexane (1.0 cm^3) was added over a period of 1.8 h (with the aid of syringe pump), the yield of Et_3SiOct was increased to *ca.* 60 %.

Thiols clearly catalyse radical-chain hydrosilylation of alkenes. In addition, because the kinetics and thermodynamics of reactions (9)-(12), especially those of reactions (10) and (11), will change in response to the electronic and steric properties of the group Y, the efficiency of thiol-catalysed alkene hydrosilylation could depend markedly on the nature of the thiol.[10b]

Other applications of polarity-reversal catalysis (PRC) by thiols

The principle of PRC by thiols has been widely used in several types of radical reactions. In addition to the hydrosilylation of alkenes using PRC by thiols,[11] reduction of alkyl halides, diakyl sulphides and *O*-alkyl-*S*-methyldithiocarbonates (xanthates) to alkanes using triethylsilane and thiols has also been reported.[10b]

Silanes as reducing agents with PRC by thiols

Alkyl halides can be reduced to alkanes by homolytic or heterolytic means. Radical-based reductions have the advantage of being less susceptible to steric effects and the formation of rearranged products than the heterolytic routes[13] in which the carbocationic intermediate R^+ is often formed.

The usual method of homolytic hydrodehalogenation uses Bu_3SnH[14] and involves the radical-chain mechanism generalised in reactions (13) and (14). However,

$$Bu_3Sn^{\bullet} + R\text{-}X \rightarrow Bu_3Sn\text{-}X + R^{\bullet} \quad (13)$$

$$R^{\bullet} + Bu_3Sn\text{-}H \rightarrow R\text{-}H + Bu_3Sn^{\bullet} \quad (14)$$

organotin compounds are toxic and are often difficult to remove completely from the desired reaction product, as well as being rather costly and presenting disposal problems. Simple, low molecular weight trialkylsilanes (especially Et_3SiH) would be very acceptable alternatives, through the propagating cycle of reactions (15) and (16).

$$Et_3Si^{\bullet} + R\text{-}X \rightarrow Et_3Si\text{-}X + R^{\bullet} \quad (15)$$

$$R^{\bullet} + Et_3SiH \rightarrow R\text{-}H + Et_3Si^{\bullet} \quad (16)$$

However, although reaction (15) is generally more exothermic and faster than its tin counterpart [reaction (13)], reaction (16) is relatively slow at moderate temperatures, because of the greater strength of the Si-H bond (397 kJ mol^{-1}) compared with the Sn-H bond (310 kJ mol^{-1}).

Polar factors are unfavourable for reaction (16), because a nucleophilic alkyl radical is being called upon to abstract an electron-rich hydrogen atom. As stated before, thiols catalyse this overall reaction, because in their presence it is replaced by the cycle of reactions (17) and (18).

$$R^{\bullet} + YSH \rightarrow RH + YS^{\bullet} \quad (17)$$

$$YS^{\bullet} + Et_3SiH \rightarrow YSH + Et_3Si^{\bullet} \quad (18)$$

Thiyl radicals are *electrophilic* and both reactions (17) and (18) benefit from favourable charge-transfer interactions in the transition state. The reductions of 1- or 2-bromooctane and dioctylsulphide by triethylsilane and *tert*-dodecanethiol as polarity-reversal catalyst gave the corresponding alkanes in >90 % and 73 % yields, respectively.[10b,14]

Tris(trimethylsilyl)silane (TTMSS) has been shown recently to act as an efficient reducing agent for alkyl halides,[15] because the Si-H bond in $(Me_3Si)_3SiH$ is appreciably weaker than that in Et_3SiH (331 $kJmol^{-1}$ compared with 397 $kJmol^{-1}$).[16] These TTMSS reductions might also be promoted by thiols *via* PRC, because thiyl radicals should abstract hydrogen from TTMSS even more readily than from Et_3SiH.

The reduction of alcohols (R-OH → R-H) by the reaction of their xanthate esters with Et_3SiH[10b,17] can also be the subject of PRC by thiols [eqn. (19)]. This reaction makes a non-toxic alternative to the Barton-McCombie reaction which proceeds by a radical-chain mechanism using Bu_3SnH [eqn. (20)].[18] For example, octane (63 %) was

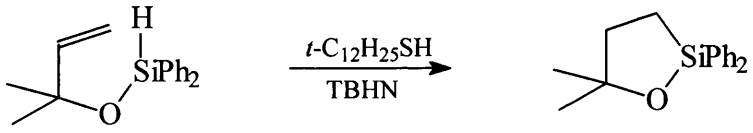
$$ROC(S)SMe + Et_3SiH \rightarrow RH + Et_3SiSC(O)SMe \quad (19)$$

$$ROC(S)SMe + Bu_3SnH \rightarrow RH + Bu_3SnSC(O)SMe \quad (20)$$

obtained from the reduction of 2-octyl xanthate using Et_3SiH in the absence of thiol catalyst. However, in the presence of thiol catalyst (t-$C_{12}H_{25}SH$, 2 mol%), octane was obtained with a 92 % yield. It seems likely that traces of thiol catalyst are actually present in the xanthate-silane system even when thiol is not purposely added.

Intramolecular hydrosilylation using PRC by thiols

Cyclisation of alkenyloxysilanes that contain terminal double bond are subject to PRC by thiols.[19] For example, when diphenyl(2-methylbut-3-eneyl-2-oxy)silane was heated for 3 h under an atmosphere of nitrogen with TBHN initiator (5 mol %), t-$C_{12}H_{25}SH$ (5 mol%) (TBHN and t-$C_{12}H_{25}SH$ were added in two equal portions) in hexane as solvent, 2,2-diphenyl-5,5-dimethyl-1-oxa-2-silacyclopentane was produced in 95 % yield [eqn. (21)]. In the absence of thiol catalyst, no cyclic product was formed.



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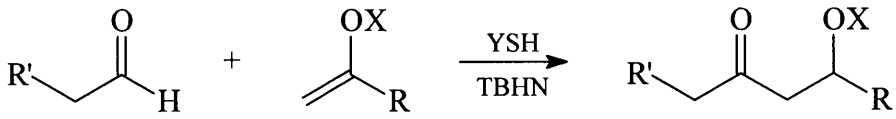
Further applications of PRC by thiols

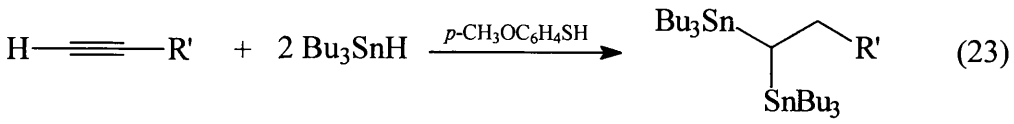
Thiols are able to catalyse the radical-chain addition of primary aldehydes to enol esters and to silyl enol ethers to give aldol derivatives [eqn. (22)] in good yields under



(22)

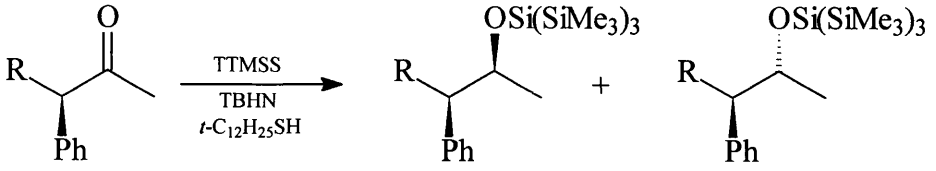
mild conditions.[20] When the silane, R_3SiH is replaced by a primary aldehyde an analogous mechanism involving PRC affords new C-C bonds. This reaction is known as hydroacylation and is a homolytic version of the aldol condensation.

Ratier and co-workers[21] reported that double hydrostannylation reactions of terminal alkynes occurred by a radical mechanism in the presence of aryl thiols, which act as polarity-reversal catalysts [eqn. (23)]. Giese and co-workers[22] described the



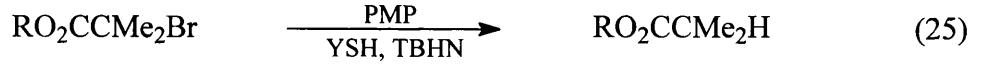
(23)

hydrosilylation of ketones by TTMSS in the presence of *tert*-dodecanethiol and TBHN as part of their investigations into homolytic 1,2-asymmetric inductions in acyclic systems [eqn. (24)]. Wayner and co-workers[23] made use of PRC by thiols in the reduction of



(24)

electron-deficient α-bromoesters using 1,2,2,6,6-pentamethylpiperidine (PMP) with TBHN as initiator [*e.g.* eqn. (25)]. *tert*-Butoxyl radicals derived from the initiator



(25)

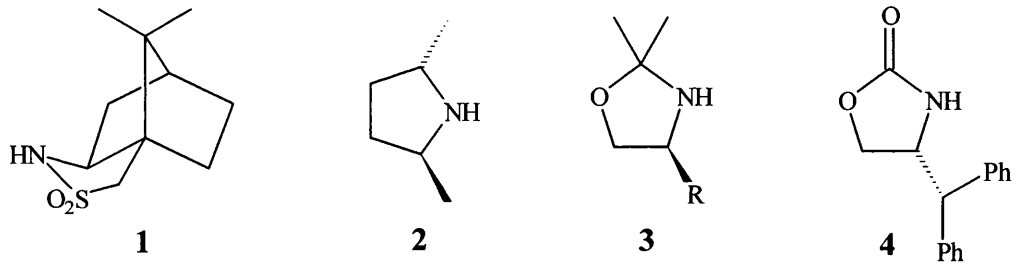
abstract hydrogen from the *N*-methyl group of PMP to give an α-aminoalkyl radical that subsequently transfers an electron to the bromoester. Following loss of Br^-, the α-alkoxycarbonylalkyl radical abstracts hydrogen from the thiol, which is regenerated by abstracting hydrogen from PMP to propagate the radical-chain cycle.

Stereoselective radical reactions

Radical-chain reactions have been proven to be effective in organic synthesis[24] and the control of stereochemistry in intermolecular reactions of acyclic free radicals is a topic of current interest in this area of research.[25] Three main approaches to stereoselective radical reactions have been the use of chiral auxiliaries, the use of chiral Lewis acids and chirality transfer using a stereogenic centre adjacent to the radical centre, known as 1,2-asymmetric induction.

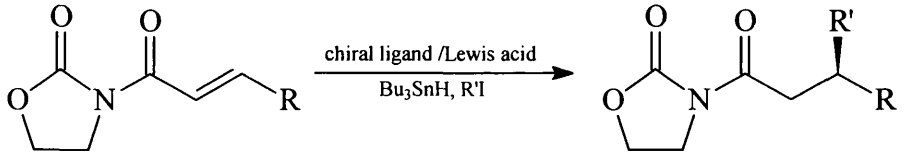
Chiral auxiliaries used in stereoselective radical reactions include Oppoltzer's camphor sultam **1**,[26] the C_2-symmetrical *trans*-2,5-dimethylpyrrolidine **2**[27] and

oxazolidine-derived auxiliaries **3**.[28] Diastereoselectivities >25:1 (for **1**) to >80:1 (for **3**)



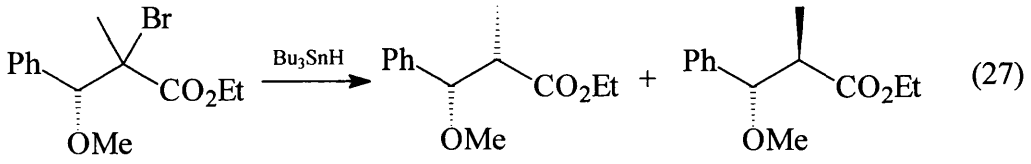
1 **2** **3** **4**

have been achieved. 4-(Diphenylmethyl)-2-oxazolidinone **4** has been used in conjunction with achiral Lewis acids to give distereoselectivities of up to 71:1.[29] Chiral bidentate ligands have also been used with Lewis acids in oxazolidinone-mediated enantioselective conjugate radical additions giving up to 90 % enantiomeric excess (ee) [eqn. (26)].[30]



(26)

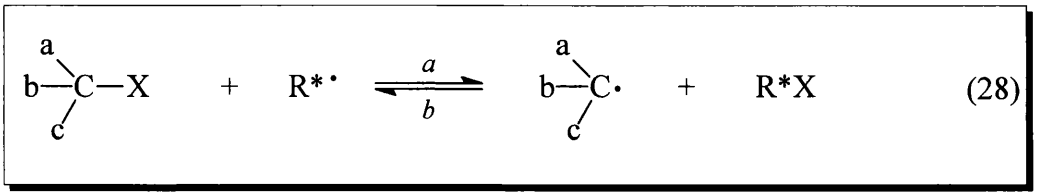
There are a number of reports of the use of Lewis acids to promote diastereoselective processes involving acyclic radicals.[31] Lewis acids have been used in conjunction with 1,2-asymmetric induction approaches as well.[32] 1,2-Asymmetric induction approaches, for example the reduction of α-bromoesters [eqn. (27)], can work effectively in the absence of Lewis acids giving up to 97:3 diastereoselectivity ratios.[33] In other examples, ratios of up to 99:1 have been achieved.[34]



(27)

Enantioselective radical reactions

Enantioselective radical-chain atom-transfer processes are challenging and are particularly uncommon. Unlike diastereoselective radical processes, only a few examples can be found in the chemical literature. Enantioselective atom transfer from and to carbon, mediated by a homochiral radical R*• and the closed-shell molecule abcCX, is generalised in eqn. (28). This reaction can occur in both directions and proceeds through



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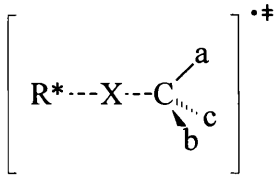
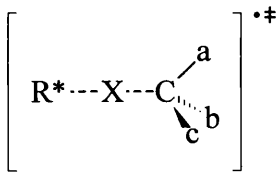
the diastereoisomeric pair of transition states **5a** and **5b**. The energy difference between



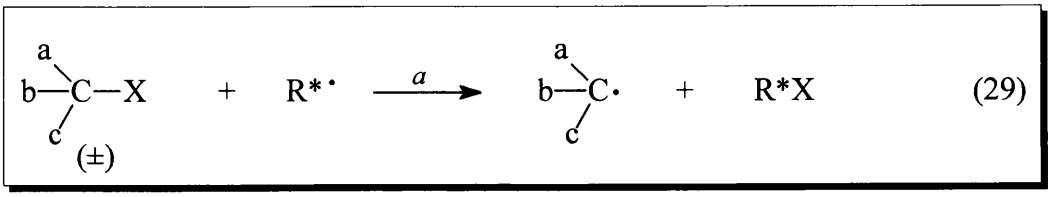
5a



5b

these two transition states determines the enantioselectivity of the transfer of the atom (or group) X. In the case of enantioselective hydrogen-atom transfer reactions, X = H, enantioselective atom-transfer processes have been reported in both forward and reverse directions.

Direction *a*. Kinetic resolution



(29)

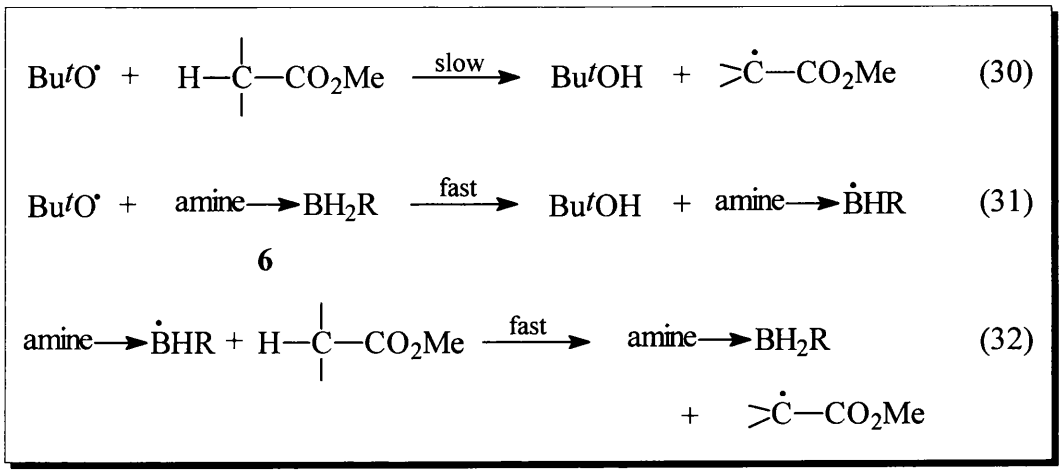
Enantioselective atom transfer processes like reaction (29) can be used to bring about kinetic resolution. It is possible to partially resolve a racemic compound of the

type XCabc as long as there is a significant difference in energy between the two diastereoisomeric transition states (**5a** and **5b**) during abstraction of atom X by homochiral radical R*•. If a deficiency of R*• is generated, then the compound XCabc remaining should be enriched with the enantiomer which reacts more slowly.

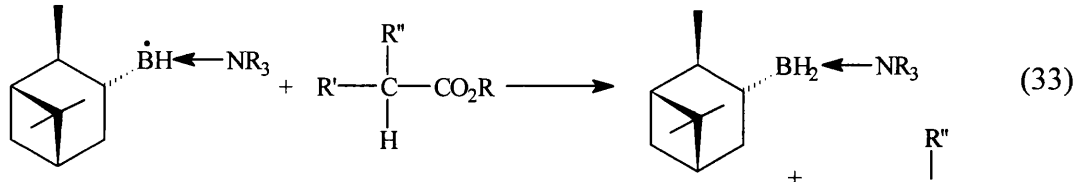
In 1977, Hargis and Hsu[35] showed that the 2-phenyl-2-butoxyl radical abstracts benzylic hydrogen enantioselectively from 2-phenylbutane with modest selectivity. Perkins and his co-workers[36] have reported enantioselective transfer of hydrogen to homochiral acyl nitroxides from benzoin and from α-phenyl alcohols. Tanner and Kharrat[37] have reported up to 67 % ee when a homochiral dihydronicotinamide donates hydrogen to the radical anion of a prochiral ketone.

Catalytic kinetic resolution: enantioselective hydrogen-atom abstraction by homochiral amine-boryl radicals

For sometime, there has been an interest within our group in enantioselective hydrogen-atom transfer in connection with the applications of polarity-reversal catalysis of radical reactions. It has been shown previously that the slow abstraction of electron-deficient hydrogen atoms by electrophilic alkoxyl radicals can be promoted by amine-borane complexes which act as "donor" *polarity-reversal catalysts*.[38] For example, *tert*-butoxyl radicals abstract hydrogen relatively slowly from an α-C-H group in an ester [eqn. (30)], because of adverse polar effects which operate in the transition state. However, in the presence of amine-borane **6**, the single-step reaction (30) is replaced by the catalytic cycle of reactions (31) and (32), both of which benefit from favourable charge-transfer interactions in the transition state.



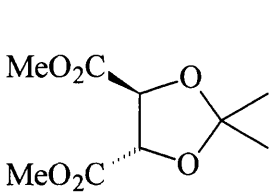
Hence, the overall process of hydrogen abstraction could be made enantioselective by using homochiral amine-boryl radicals *e.g.* those of the type **7**. These would abstract hydrogen enantioselectively from the electron-deficient α-C-H group of a chiral ester **8** [eqn. (33)], therefore making overall hydrogen-atom transfer to $Bu^tO^\bullet$ enantioselective.[39]



(33)

7 **8** **9**

Although the observed enantioselectivities were generally not large, for some systems investigated the selectivity was sufficient to enable effective *catalytic* kinetic resolution of **8**, during which the amine-boryl radical **7** is regenerated from the amine-borane **9** by hydrogen-atom transfer to the *tert*-butoxyl radical. For example, it has been shown that the (*S*,*S*)-enantiomer **10** of dimethyl 2,3-*O*-isopropylidene tartrate is 21 times more reactive than the (*R*,*R*)-enantiomer towards the amine-boryl radical **11** at -85 °C.[39b] When di-*tert*-butyl peroxide was photolysed in the presence of the racemic tartrate and a catalytic amount of the amine-borane **12**, the tartrate that remained after 75 % had been consumed showed a 97 % ee in favour of the (*R*,*R*)-ester.[39c]



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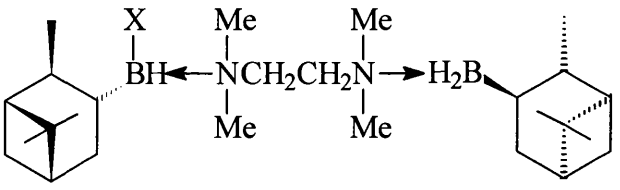


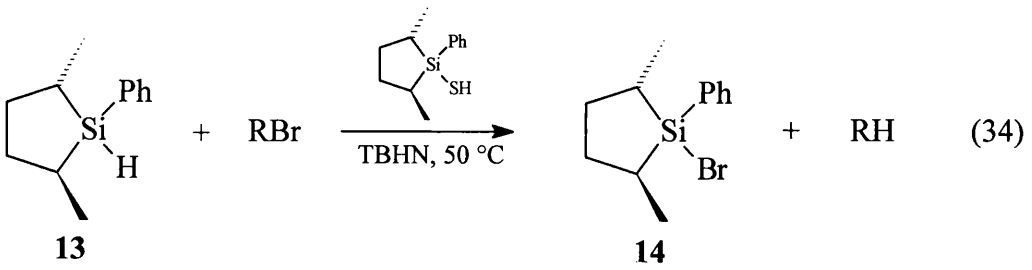
11 X = unpaired electron

12 X = H

Enantioselective hydrogen-atom abstraction by homochiral silanethiyl radicals

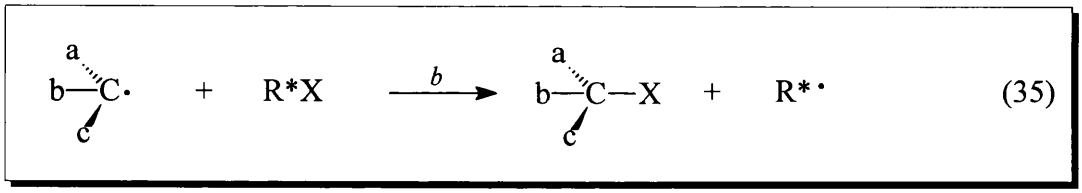
The principle of polarity-reversal catalysis has also been applied in reactions of the C_2-symmetric homochiral (2*S*,5*S*)-*trans*-2,5-dimethyl-1-phenyl-1-silacyclopentane-1-

thiyl radicals. These abstract hydrogen enantioselectively from silicon in racemic *trans*-2,5-dimethyl-1-phenyl-1-silacyclopentane **13** to bring about kinetic resolution of the latter.[40] The enantiomerically enriched silyl radicals produced are trapped by an alkyl bromide to give optically active bromosilanes **14** [eqn. (34)].



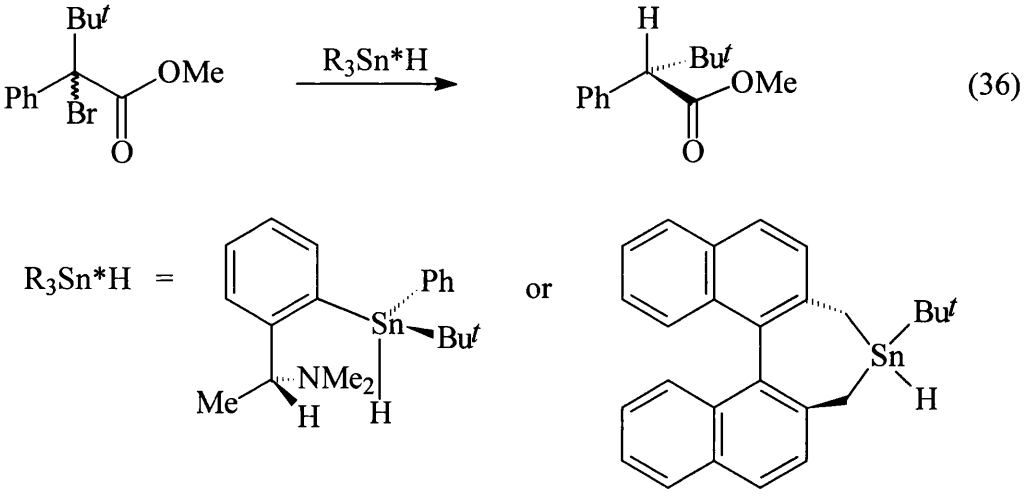
13 **14**

Direction *b*. Transfer of chirality to prochiral radicals



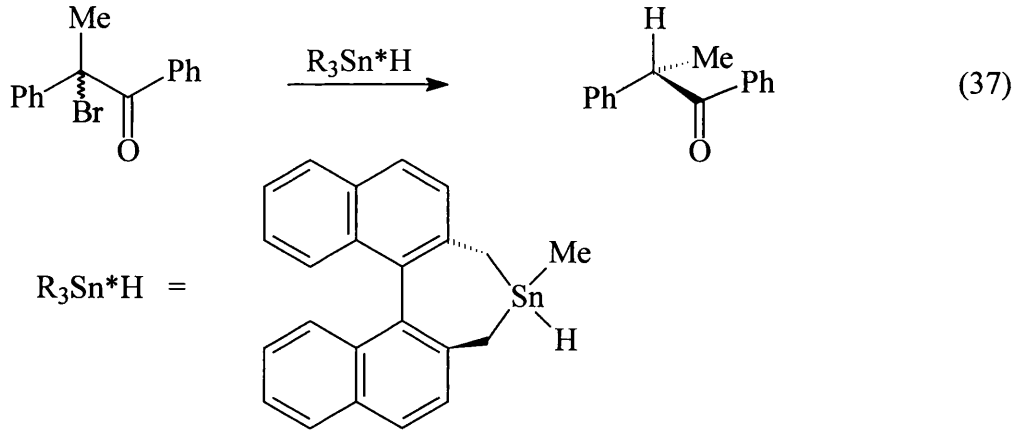
The diastereoisomeric transition states **5a** and **5b** can be approached from the direction shown in eqn. (35). Here, the homochiral reagent R*X is able to attack at the *Re* and *Si* faces of the prochiral radical abcC$^{\bullet}$. As before, practically useful enantioselectivity is only possible if there is a large difference in energy between the two transition states.

Metzger and co-workers reported enantioselective hydrogen-atom transfer from a homochiral tin hydride in the reduction of α-bromoesters to esters [eqn. (36)].[41] In their studies, two types of homochiral tin hydrides were investigated. The first homochiral tin hydride contained a chiral 2-[(1-dimethylaminoalkyl)phenyl] (DAAP) ligand and the second was derived from the C_2-symmetric binapthyl group. The enantioselective reduction of the α-bromoester occurs via the prochiral radical with up to 25 % ee when using the DAAP ligand containing tin hydride and a 52 % ee with the binapthyl containing tin hydride at -78 °C. The DAAP ligand containing tin hydride was used as a diastereomeric mixture which could be responsible for the lower ee observed. The



enantioselectivity decreased with increasing temperature (32 % ee at -10 °C and 28 % ee at 24 °C). The homochiral tin hydride reagent was used in stoichiometric amounts but was used in a catalytic amount in the presence of sodium cyanoborohydride to give the same ee (28 %) at 24 °C.

Curran and Nanni reported the reduction of α-bromoketone to ketones also using a homochiral tin hydride [eqn. (37)].[42] The homochiral tin hydride like in Metzger's

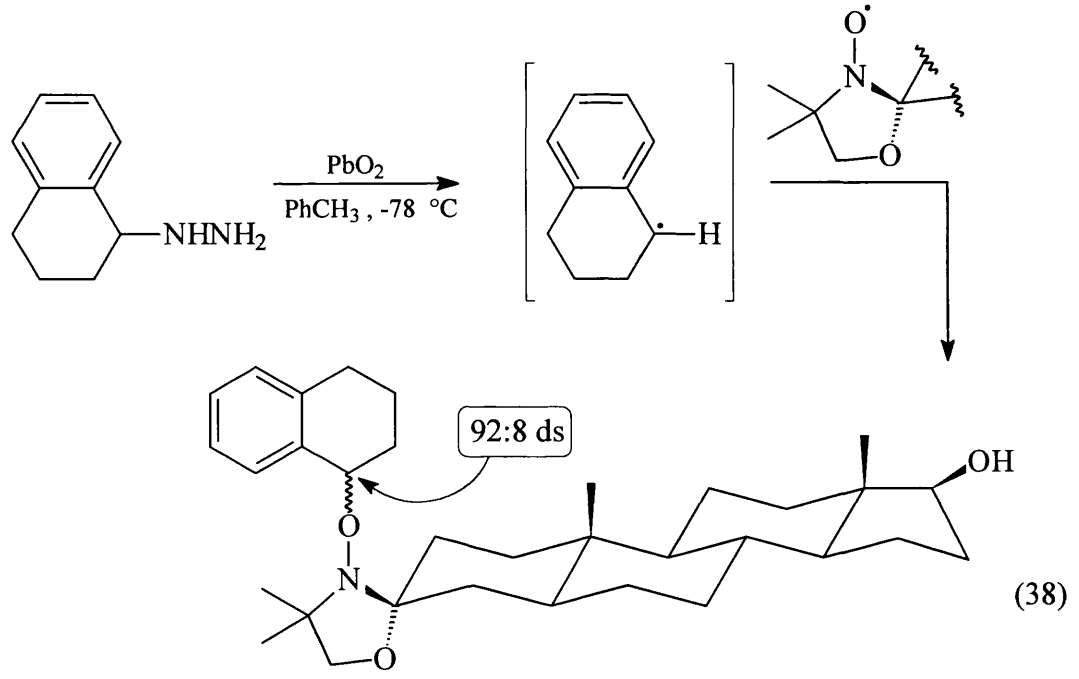


studies, also contained the binapthyl substituent but was prepared by an alternative route. The α-bromoketone was reduced via the prochiral radical to give the ketone with up to 41 % ee and a 30 % yield at -78 °C. The enantioselectivity decreased with increasing temperature like in Metzger's studies. These reactions required large amounts of the homochiral tin reagent and initiator with long reaction times. Both Metzger and Curran

report that the binapthyl containing homochiral tin reagent readily decomposed in air and therefore had to be carefully stored or freshly prepared before its use. In both studies, steric effects would be important in the transition state during the hydrogen-atom transfer from the tin hydride to the prochiral radical.

Examples of other homochiral tin hydride reagents used have also been reported. These include the reduction of acetophenone with a triorganotin hydride containing a (-)-menthyl ligand[43] and the reduction of chloroalkanes to alkanes with up to 32 % ee.[44]

Braslau and co-workers have described the coupling of homochiral nitroxyl radicals to prochiral carbon radicals [eqn. (38)].[45] The prochiral radicals were generated

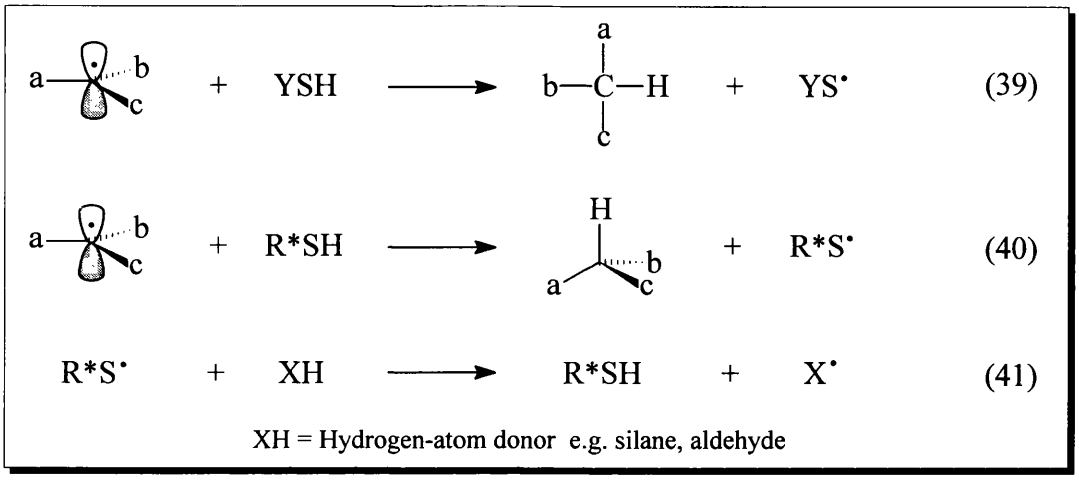


(38)

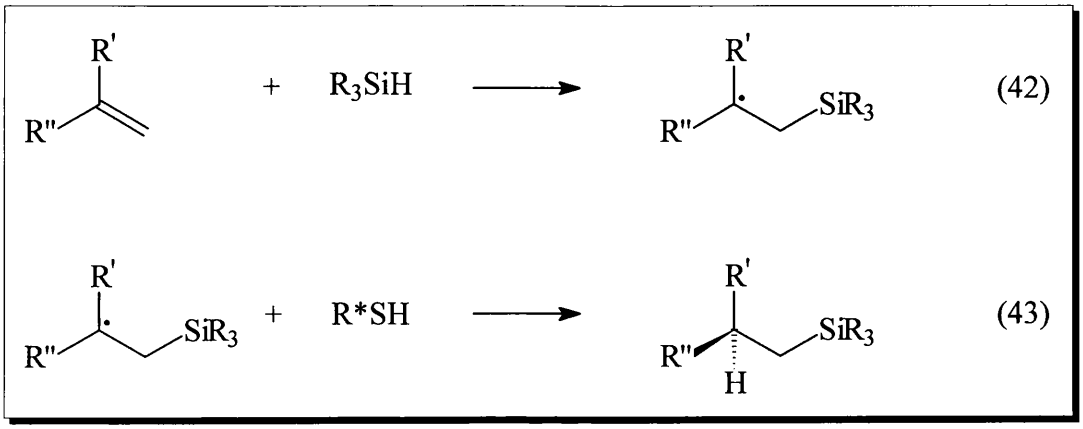
from alkyl hydrazines under mild oxidative conditions with lead dioxide in toluene at -78 °C. Initial coupling reactions were carried out with achiral nitroxyl radicals and then was carried out with acyclic homochiral nitroxyl radicals derived from camphor which gave up to a 63:37 ratio of diastereomers. However, from their studies, Braslau found that cyclic homochiral nitroxyl radicals like the steroidal doxyl radical, which are conformationally restrained nitroxyl radicals gave better selectivity. The coupling reactions with the doxyl radical gave up to a 92:8 ratio of diasteroisomers and up to an 80 % yield.

Catalytic transfer of chirality to prochiral radicals

Homochiral thiols might be used as polarity reversal catalysts in asymmetric synthesis. Here the achiral thiol YSH employed previously in the fast hydrogen-atom abstraction reaction with a nucleophilic prochiral radical abcC$^{\bullet}$ [eqn. (39)], would be replaced by a homochiral thiol R*SH, in the catalytic cycle of reactions (40) and (41). The product formed by this sequence should be optically active to some extent.

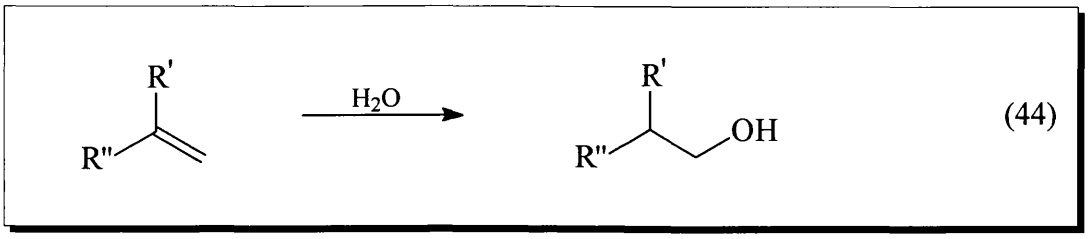


Therefore, in principle, prochiral radicals generated from the reduction of *tert*-halides (abcCHal) and those involved in hydroacylation or hydrosilylation of prochiral alkenes can all be made to react with homochiral R*SH in enantioselective hydrogen-atom transfer radical processes.[10b,20] Homochiral thiols have been used for enantioselective intramolecular cyclization of alkenyloxysilanes with modest selectivities.[19] However, in the present work, preliminary experiments have shown good results for enantioselective radical-chain additions of hydrosilanes to prochiral alkenes, using homochiral thiols as polarity-reversal catalysts [eqn. (42) and (43)].[46]



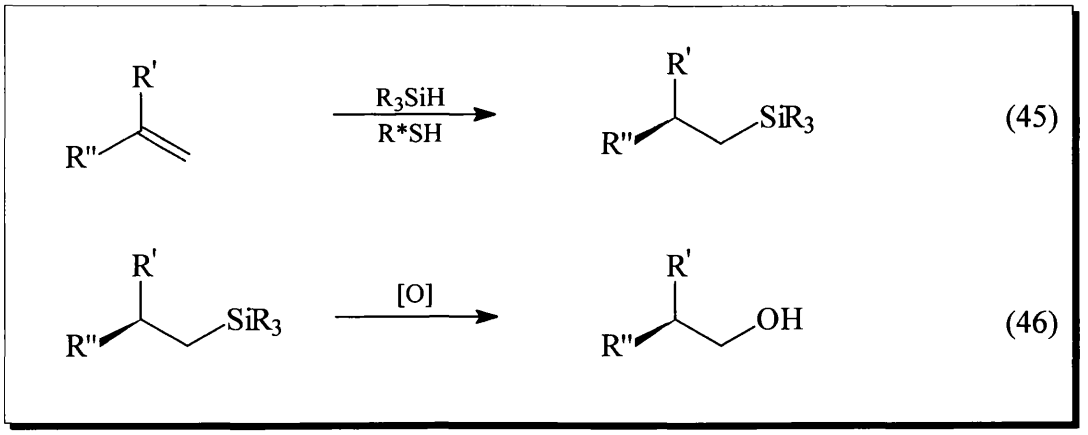
In this general way, it should be possible to prepare relatively large quantities of optically active products using small quantities of recycleable homochiral thiols as catalysts.

Desilylation. Oxidative cleavage of the carbon-silicon bond



(44)

The above transformation [eqn. (44)] can be achieved in two steps. The usual method employed is the heterolytic process of hydroboration followed by oxidation. A useful alternative to this procedure is the hydrosilylation of the alkene, followed by the oxidative cleavage of the C-Si bond [eqns. (45) and (46)] to form the alcohol.

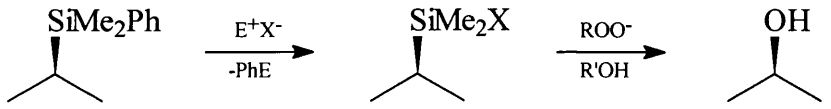


(45)

(46)

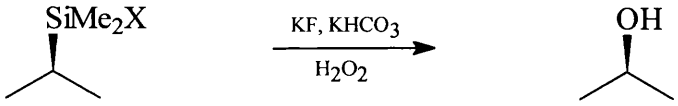
The silyl group in this type of transformation is behaving as a *masked* hydroxy group which has different properties to a hydroxy group or a conventionally-protected hydroxy group. The silicon group is neutral and does not possess a lone pair of electrons which could co-ordinate undesirably to any incoming Lewis acids or electrophiles in a multi-step synthesis. It acts as an electropositive substituent in the molecule, when compared to an electronegative hydroxy group, and also has a substantially larger steric influence, thus making it a powerful tool in synthetic chemistry.

There are two main methods for the oxidative cleavage of a C-Si bond to a C-OH bond. These are the Fleming reaction and the Tamao reaction, both of which occur under mild conditions and with retention of configuration at the carbon centre. The Fleming oxidative cleavage of dimethylphenylsilyl groups [eqn. (47)] can be brought about by three main methods,[47] all of which have two basic steps in common. The first method involves protodesilylation, which removes a phenyl ring from the silicon atom, followed by oxidation of the remaining silicon moiety using peracids or hydrogen peroxide. The second method uses mercuric acetate for the dephenylation, followed by oxidation with peracetic acid. The third method uses bromine instead of mercuric acetate and the second and third methods can be carried out as one-pot procedures.



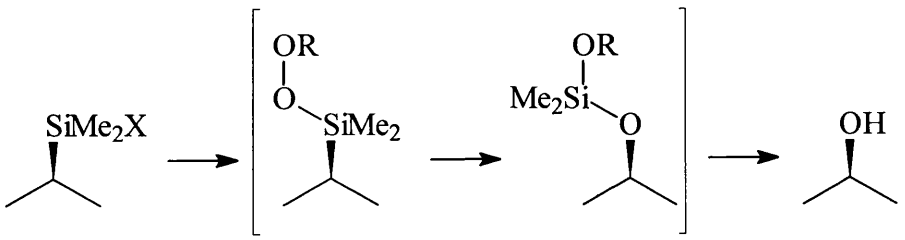
(47)

The Tamao oxidative cleavage [eqn. (48)] is an efficient method provided the group X is RO, R_2N, Hal or H.[48] However, both the Fleming and Tamao oxidation



(48)

cleavages are thought to occur through similar reaction intermediates and the process is simplified in eqn. (49). There are several modifications of both the Fleming and Tamao reactions which have been reported recently in a comprehensive review.[49] Therefore, it should be possible to find an oxidation condition which would be compatible with the various functionality that might be present within the molecule.



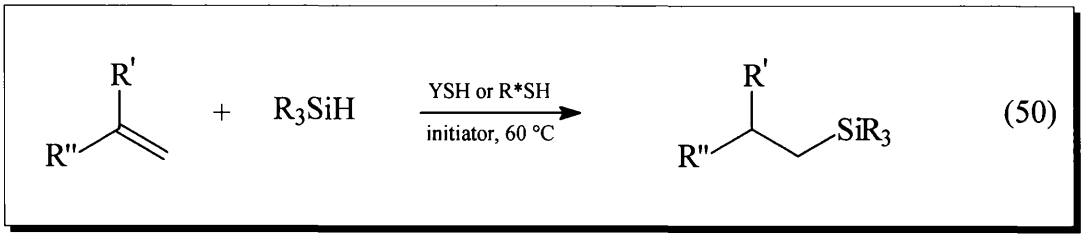
(49)

Aims of the project

The aims of the project can then be summarised as follows.

1. To prepare all unavailable starting materials required including initiators, prochiral alkenes and thiols.
2. To carry out the hydrosilylation of prochiral alkenes using achiral thiols to confirm that these act as polarity reversal catalysts and promote the reactions.
3. To use homochiral thiols as catalysts and to determine the extent of asymmetric induction in the hydrosilylation products.
4. To understand the basic principles of the thiol-catalysed hydrosilylation of alkenes in order to improve enantioselectivities.
5. To carry out oxidative cleavage of the carbon-silicon bond in the adducts in order to convert them to alcohols and other silicon-free products.

Results and Discussion



(50)

In order to investigate the above reaction [eqn. (50)], it was first necessary to find suitable prochiral alkenes, silanes and thiols. All the hydrosilylations were first carried out using achiral thiols, YSH to determine the effectiveness of the catalytic process by thiols and thus racemic silane adducts were obtained. They were then carried out with homochiral thiols, R*SH. The homochiral group R* attached to the thiol R*SH is responsible for the overall degree of chiral induction achieved in the silane adducts produced and hence different types of optically pure thiols were investigated in initial experiments. The optical purities of these products could be determined by using homochiral NMR shift reagents and/or by chiral-stationary-phase HPLC analysis.

The first aim of the project was to prepare starting materials which were unavailable commercially. All the silanes and achiral thiols were commercially available, but the majority of the homochiral thiols had to be prepared. The prochiral alkenes and homochiral thiols were prepared throughout the project and will be discussed at appropriate places.

Preparation of di-*tert*-butyl hyponitrite (TBHN) initiator

$$NaON{=}NONa + 2\ Bu^tBr \xrightarrow{ZnCl_2} Bu^tON{=}NOBu^t \qquad (51)$$

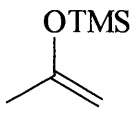
TBHN was prepared by the zinc chloride-catalysed reaction between sodium hyponitrite and *tert*-butyl bromide [eqn. (51)] as described by Mendenhall.[50] It was first prepared by Kiefer and Traylor[51] in 1966 and is a stable solid which decomposes readily with a half-life of about 55 min at 60 °C to give nitrogen and *tert*-butoxyl radicals. These *tert*-butoxyl radicals are known to abstract hydrogen rapidly from both silanes and thiols to generate chain-carrying radicals [eqn. (52)-(54)].

$$Bu^tON{=}NOBu^t \rightarrow 2Bu^tO^\bullet + N_2 \quad (52)$$

$$Bu^tO^\bullet + R_3SiH \rightarrow Bu^tOH + R_3Si^\bullet \quad (53)$$

$$Bu^tO^\bullet + YSH \rightarrow Bu^tOH + YS^\bullet \quad (54)$$

Preparation of acyclic prochiral alkenes



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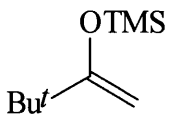

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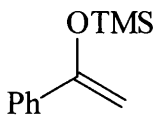

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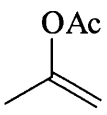

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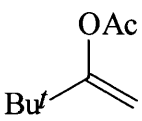

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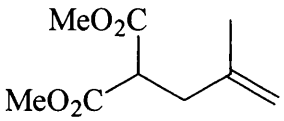

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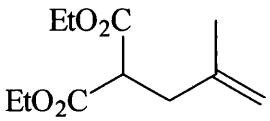
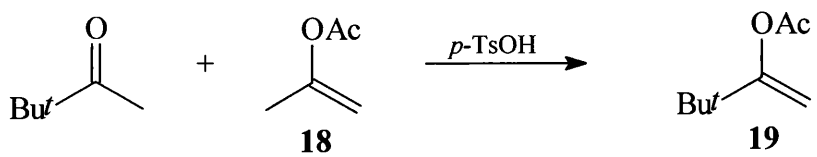


21

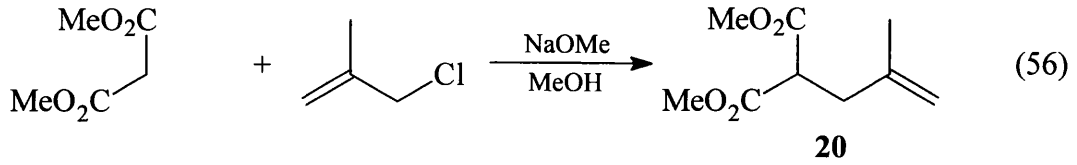
The acyclic prochiral alkenes **15-21** were chosen for the initial hydrosilylation reactions. These enol acetate, silyl enol ethers and malonate derived alkenes have substituents of varying steric demands and should help to determine the importance of such groups (bulky or non-bulky) at the radical centre during hydrogen-atom transfer when using achiral or homochiral thiols. The alkenes **15-18** were available from the Aldrich Chemical Company and **19-21** had to be prepared.

3,3-Dimethyl-2-acetoxybut-1-ene **19** was prepared by the method outlined by House *et al.*[52] This involved the heating of pinacolone and isopropenyl acetate **18** with *p*-toluenesulphonic acid, which was used as an acid catalyst [eqn. (55)]. The reaction was carried out under an atmosphere of nitrogen using a distillation apparatus in order to continuously remove volatile materials boiling below 90 °C (mainly acetone).



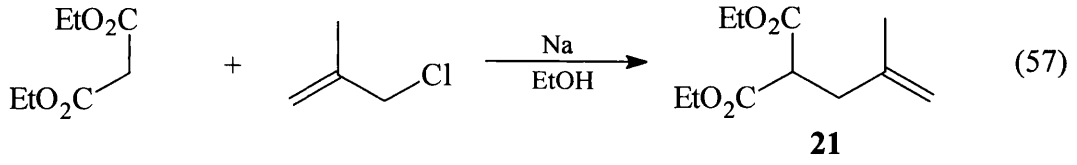
18 **19** (55)

The preparations of dimethyl (2-methallyl)malonate **20** and diethyl (2-methallyl)malonate **21** were first attempted using sodium hydride as the base to form the enolate ions from the corresponding malonate, then adding methallyl chloride with stirring at room temperature.[53] However, this proved to be unsuccessful for both alkenes and therefore **20** was made using sodium methoxide as the base with methanol as solvent, followed by the addition of methallyl chloride with heating to reflux [eqn. (56)].



20 (56)

The alkene **21** was prepared by a similar procedure except using sodium ethoxide as the base which was generated *in situ* from sodium metal and ethanol solvent [eqn. (57)].[54]

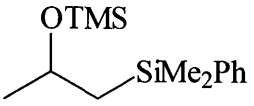


21 (57)

Hydrosilylation of acyclic prochiral alkenes using *tert*-dodecanethiol as catalyst

The radical-chain hydrosilylations of the acyclic prochiral alkenes **15-21** were carried out at 60 °C using TBHN as initiator and *t*-$C_{12}H_{25}SH$ as the thiol catalyst. For these experiments, three silanes were investigated, Et_3SiH, $PhMe_2SiH$ and Ph_2MeSiH. Triethylsilane was used as solvent, because it is volatile and easily removed by evaporation after the reaction has completed. Hexane was used as solvent for the addition of $PhMe_2SiH$ and Ph_2MeSiH with a small molar excess of the arylsilane. *tert*-Dodecanethiol (5 mol% based on alkene) was added in hexane solution slowly over 2 h with the aid of a syringe pump. Previous work has shown that the slow addition of the thiol increases the yield of the hydrosilylation product, probably by disfavouring addition of the thiol across the C=C double bond of the alkene.[12] After all the thiol had been added, the reaction mixture was heated for a further 30 min. The silane adducts **22-**

34 can be purified by flash-column chromatography on silica gel without a prior aqueous work-up.



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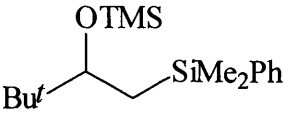

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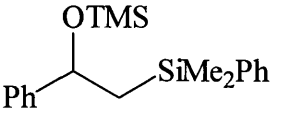

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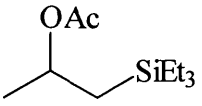

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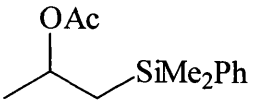

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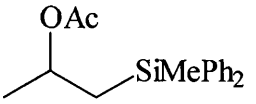

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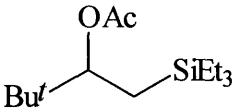

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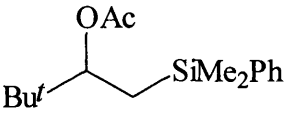

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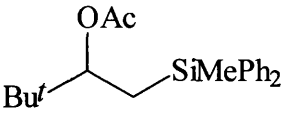

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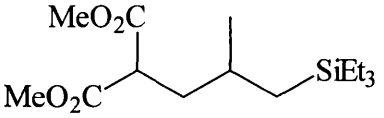

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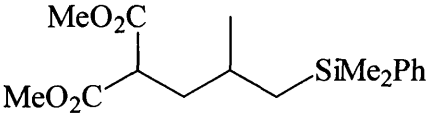

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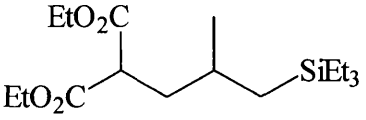

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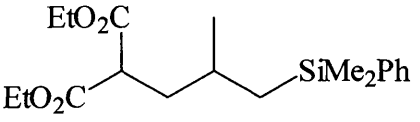

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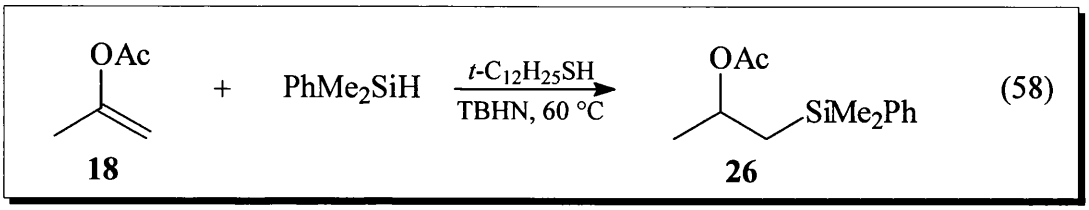
Standard experimental procedure



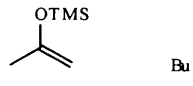
The hydrosilylation reaction (58) will be used to illustrate the general experimental procedure adopted. A stirred solution in hexane (3.0 cm^3) containing isopropenyl acetate **18** (5.0 mmol), dimethylphenylsilane (6.5 mmol) and TBHN (0.25 mmol) as initiator was heated at 60 °C under an atmosphere of nitrogen. *tert*-Dodecanethiol (0.25 mmol) in hexane (1.0 cm^3) was added over a period of 2 h (with the aid of a syringe pump). The reaction mixture was heated for a further 30 min and then allowed to cool to room temperature. The solvent was removed under reduced pressure and the alkyldimethylphenylsilane adduct **26** (1.10 g, 93 %) was isolated by flash-column chromatography using petroleum-ether (19:1) as eluent (petroleum refers to petroleum spirit (40-60 °C) and ether refers to diethyl ether).

All hydrosilylations of alkenes carried out using *tert*-dodecanethiol as catalyst are summarised in Table 1.

Table 1: Hydrosilylation of acyclic prochiral alkenes using *t*-$C_{12}H_{25}SH$ as catalyst[a]

Entry	Alkene	Silane[b]	Product[c]	Yield (%)
1	**15**	$PhMe_2SiH$	**22**	88
2	**16**	$PhMe_2SiH$	**23**	85
3	**17**	$PhMe_2SiH$	**24**	<1
4	**18**	Et_3SiH	**25**	98
5	**18**	$PhMe_2SiH$	**26**	93
6	**18**	$PhMe_2SiH$	**26**	<1[d]
7	**18**	Ph_2MeSiH	**27**	99
8	**19**	Et_3SiH	**28**	84
9	**19**	$PhMe_2SiH$	**29**	90
10	**19**	Ph_2MeSiH	**30**	98
11	**20**	Et_3SiH	**31**	96
12	**20**	$PhMe_2SiH$	**32**	90
13	**21**	Et_3SiH	**33**	92
14	**21**	$PhMe_2SiH$	**34**	82

a. All reactions were carried out using 5 mmol of alkene at 60 °C for 2.5 h under nitrogen. *tert*-Dodecanethiol (0.05 equiv.) in hexane (1.0 cm^3) was added by a syringe over a period of 2 h and TBHN (0.05 equiv.) was used as initiator. *b.* The silane was used in excess. Et_3SiH (6 equiv.) was used as solvent and hexane (3.0 cm^3) was used as solvent when using $PhMe_2SiH$ or Ph_2MeSiH (1.3 equiv.). *c.* All products were purified by flash-column chromatography [eluent: neat petroleum followed by petroleum-ether (19:1)]. The structures of all alkenes and products are shown below. *d.* No thiol was added in this reaction.



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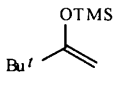

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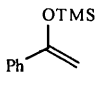

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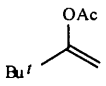

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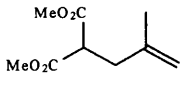

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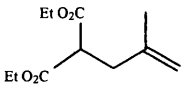

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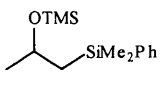

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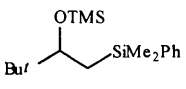

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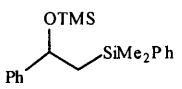

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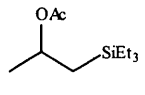

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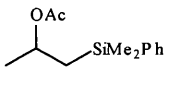

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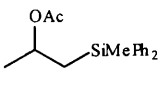

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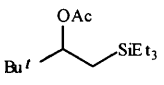

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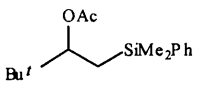

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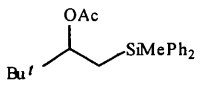

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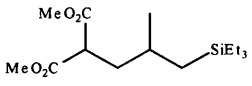

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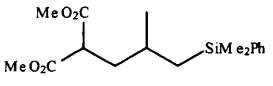

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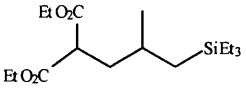

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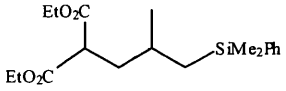
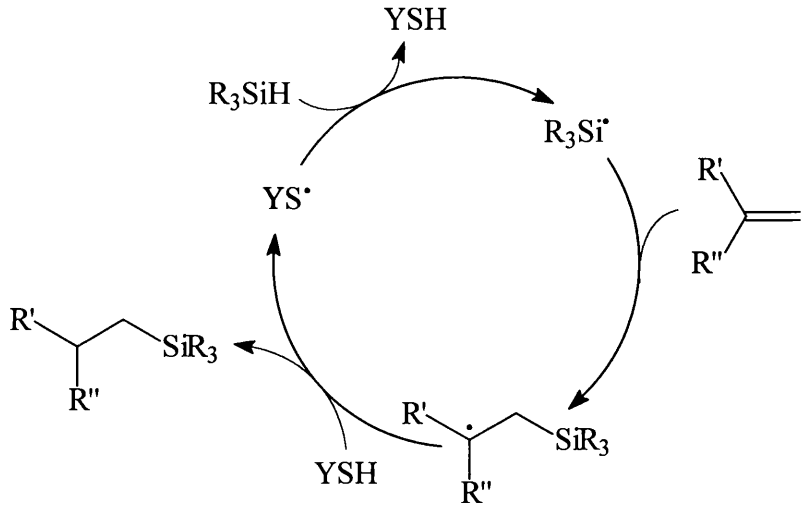


34

As the results indicate, *t*-$C_{12}H_{25}SH$ is an efficient polarity-reversal catalyst for the hydrosilylation of the acyclic prochiral alkenes chosen. Apart from alkene **17**, all the yields were quantitative. The β-silylalkyl radical formed from the rapid addition of silyl radicals to the alkenes will be nucleophilic in character and hence the abstraction of hydrogen from *t*-$C_{12}H_{25}SH$ will also be relatively fast, due to favourable polar effects operating in the transition state. The nucleophilic character of these β-silylalkyl radicals is due to the presence of a β-C-Si bond and also to the oxygen atom directly attached to the radical centre. It could be envisaged that the presence of bulky groups in the sterically hindered β-silylalkyl radicals obtained from the alkenes **16** and **19-21** might retard abstraction of hydrogen from the thiol, but as the high yields indicate, the thiol is able to approach the β-silylalkyl radical and make an efficient hydrogen-atom transfer without being affected by steric hindrance.

When reaction (58) was repeated in the absence of the thiol catalyst, under otherwise identical conditions, ^1H NMR analysis of the crude product mixture showed a trace amount (< 1 %) product (entries 5 and 6). Therefore, the radical-chain addition of silanes to alkenes using thiols as catalysts proceeds through the propagation sequence illustrated in Scheme 1.



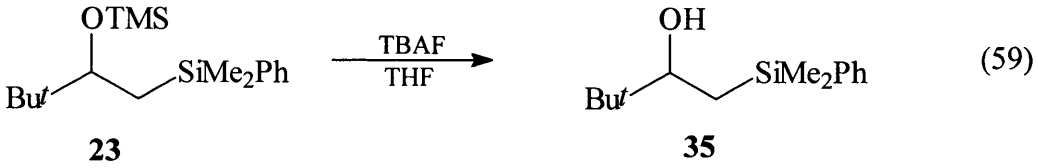
Scheme 1

When triethylsilane is used in a large excess, the equilibriuim:

$$YS^{\bullet} + Et_3SiH \rightleftharpoons YSH + Et_3Si^{\bullet}$$

will be shifted in the favourable right-hand-side direction and the efficiency with which $YS^{\bullet}$ is converted into $Et_3Si^{\bullet}$ is increased. All the silane adducts were obtained as colourless oils.

When the silane adduct **23** was treated with a solution of tetra-*n*-butylammonium fluoride (TBAF) in moist THF at room temperature for 2-3 h, the TMS group was hydrolysed to give the β-hydroxysilane **35** [eqn. (59)]. This reaction also indicates the strength of the Si-C bond in comparison to the Si-O bond under the conditions employed.

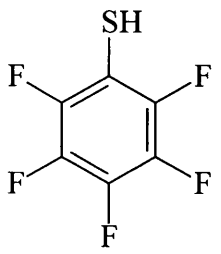


23 **35** (59)

β-Hydroxysilanes like **35** play a role as intermediates in the Peterson olefination reaction.[55]

Hydrosilylation of acyclic prochiral alkenes using other potential catalysts

Other achiral thiols apart from t-$C_{12}H_{25}SH$ were investigated and these thiols had a range of groups attached to the SH moiety. The achiral thiols (or thiol precursors) used were pentafluorothiophenol **36**, perfluorohexane-1-sulphenyl chloride **37** and methyl thioglycolate **38**. The amino acids L-cysteine **39** and L-cysteine ethylester hydrochloride **40** were also examined and although these thiols are homochiral, the chiral centre is some distance away from the SH group such that these thiols would be expected to behave like



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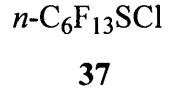

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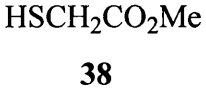

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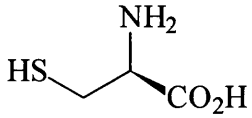

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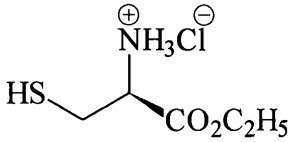

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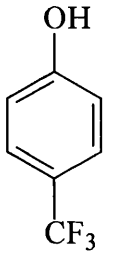

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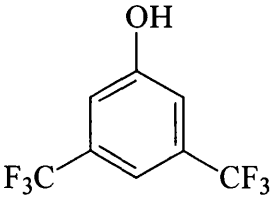
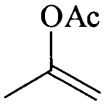


42

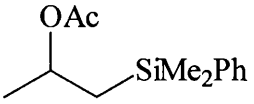
achiral thiols and give little stereoinduction in the hydrosilylation product. The sulphenyl chloride **37** has been shown to be reduced by silanes to give the corresponding thiol[11] and this will occur *in situ* for the reaction described here [eqn. (60)]. The two substituted phenols **41** and **42** were also investigated as possible catalysts.

$$n\text{-}C_6F_{13}SCl + PhMe_2SiH \rightarrow n\text{-}C_6F_{13}SH + PhMe_2SiCl \qquad (60)$$

The hydrosilylation of isopropenyl acetate **18** with $PhMe_2SiH$ was used as the standard reaction to investigate all the above potential catalysts [eqn. (61)]. The standard



18 + $PhMe_2SiH$ $\xrightarrow[\text{TBHN, 60 °C}]{\text{YSH or ArOH}}$



26 (61)

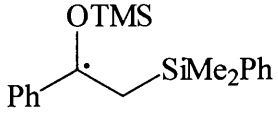
reaction conditions were employed as previously described when using *t*-$C_{12}H_{25}SH$ as catalyst. The thiols **39** and **40** were not soluble in hexane and therefore DMF was used as the solvent. The product was obtained in less than 1 % yield when using the thiols **36-40** as catalysts, apart from methyl thioglycolate **38** which gave a yield of 75 % of the desired silane adduct. In comparison, a 93 % yield was obtained from this experiment when using *t*-$C_{12}H_{25}SH$ as catalyst (entry 5, Table 1). The thiol **36** was not an effective catalyst probably because $C_6F_5S^{\bullet}$ cannot abstract hydrogen effectively from the silane. The β-silylalkyl radical should abstract hydrogen from the thiol efficiently as the SH bond in this thiol will be relatively weak, due to the unpaired electron in the thiyl radical delocalising into the π-system of the benzene ring. The thiol generated from **37** probably has the strongest SH bond and therefore the β-silylalkyl radical cannot abstract hydrogen

from this thiol efficiently. It is unclear why the cysteine derivatives **39** and **40** do not function as efficient catalysts.

Interestingly, when **37** was employed as catalyst for the hydrosilylation of the silyl enol ether **16** in the same concentration as the standard hydrosilylation reaction, a mixture of the adduct **23** and hydroxysilane **35** was obtained, as determined by ^{1}H NMR analysis. The TMS group could only be removed when using TBAF as stated earlier. The partial hydrolysis of **23** may have occurred because of the presence of phenyldimethylchlorosilane ($PhMe_2SiCl$) which can be generated *in situ* during the reaction.

It was anticipated that the O-H bond in the phenol derivatives **41** and **42**, with strong electron-withdrawing groups present on the ring, might be strong enough for these compounds to act as efficient catalysts. Polar effects could also be very favourable because the hydroxyl hydrogen will be electron deficient. However, when **41** and **42** were used as catalysts in the standard reaction (61), no silane adduct was obtained with either phenol derivative.

The hydrosilylation of the acetophenone-derived the silyl enol ether **17** indicated a <1 % yield of product (entry 3, Table 1). This reaction was repeated using a mixture of thiol **36** (1 mol%) and *t*-$C_{12}H_{25}SH$ (10 mol%) as catalysts. Here, it was hoped that the β-silylalkyl radical adduct would abstract hydrogen from the thiol **36**. The thiyl radical generated $C_6F_5S^{\bullet}$ would then abstract hydrogen from the second thiol (*t*-$C_{12}H_{25}SH$), which in turn would be able to abstract hydrogen from the silane. However, no improvement in the yield of product **24** was obtained. A probable reason for the failure of this reaction is that the benzylic radical **42** formed by the addition is highly stabilised because of conjugation of the unpaired electron with the phenyl ring, making it unable to abstract hydrogen effectively from *t*-$C_{12}H_{25}SH$.



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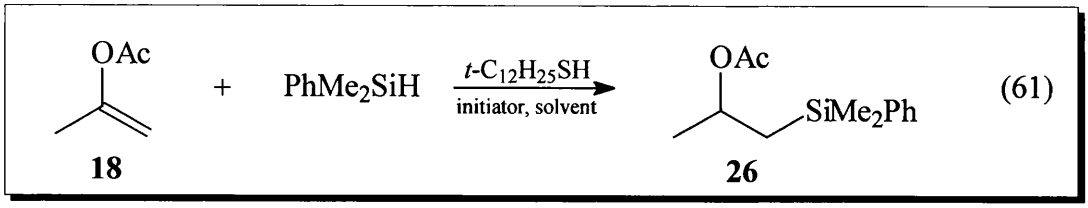
Initiator and solvent effects on the standard reaction



So far, the preliminary experiments show that *t*-$C_{12}H_{25}SH$ and methyl thioglycolate are effective thiol catalysts. Next, it was decided to investigate different initiators and solvents on the standard reaction (61). Although TBHN is conveniently prepared in one step by Medenhall's method,[50] it would also be an advantage to use commercially- available initiators. Changing the solvent would be an important factor as new thiols and alkenes investigated in the future might not be soluble in hexane. The results from these reactions are shown in Table 2, along with that obtained using TBHN in hexane solvent for comparison.

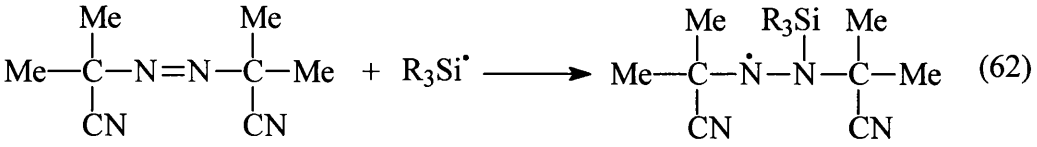
Table 2: Hydrosilylation of isopropenyl acetate **18** with $PhMe_2SiH$ using *t*-$C_{12}H_{25}SH$ as catalyst[a]

Entry	Initiator[b]	Solvent	Yield (%)
1	TBHN	hexane	93
2	TBHN	DMF	40
3	AIBN	benzene	42
4	AIBN	dioxane	35
5	AIBN	cyclohexane	39
6	ACHN	cyclohexane	<1

a. Reaction (61) was carried out according to the method as described in Table 1. *b*. Reactions using AIBN and ACHN (entries 3-6) as initiators were carried out at 80 °C (bath temperature).

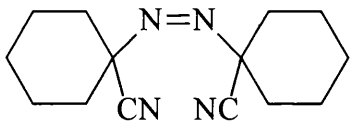
The commonly-used commercially-available initiator azobisisobutyronitrile (AIBN) **43** was investigated with different solvents. As the results indicate, the maximum yield of silane adduct obtained was 42 % (entries 3-6). A probable reason for the unsuitability of AIBN for these types of radical reactions is because silyl radicals add to the azo compound [eqn. (62)] to give relatively long-lived hydrazyl radicals which

inhibit the reactions by scavenging the chain-carrying radicals. Of course, TBHN is also



43 (62)

an azo compound, but in this case the hydrazyl radical adduct is probably unstable and may decompose to give $Bu^tO^{\bullet}$. The next initiator to be investigated was azobiscyclohexanecarbonitrile (ACHN) **44**.[56] ACHN was found to be an inefficient



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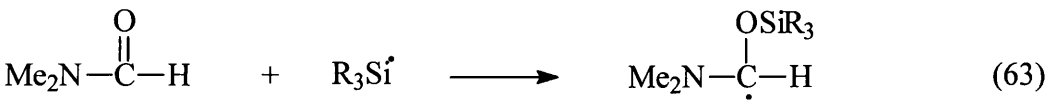
initiator for these types of radical reactions at 80 °C.

Changing the solvent had a minimal effect on the AIBN-initiated reactions (entries 3-5). A substantial effect is observed in the TBHN-initiated reactions on moving from the non-polar hexane to the dipolar aprotic solvent DMF (entries 1 and 2). However, this could be due to silyl radicals adding to C=O group of the DMF molecule [eqn. (63)].

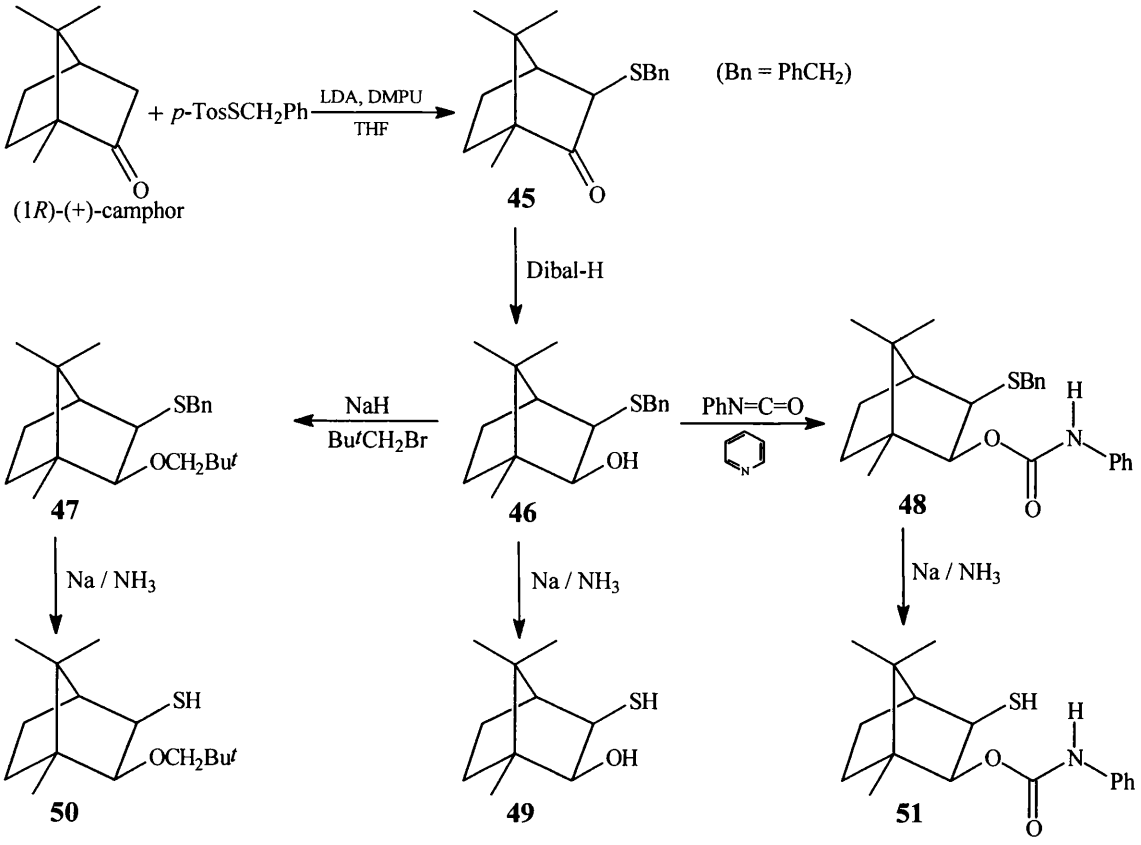


(63)

Preparation of thiols derived from camphor and from menthol

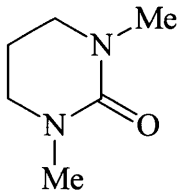
Homochiral thiols were generally not available from commercial sources and therefore had to be synthesised. Homochiral thiols initially investigated were derived from the natural products camphor and menthol.

The camphor-derived thiols **49-51** were prepared according to the reactions shown in Scheme 2.[57]



Scheme 2

(+)-Camphor was first *exo*-sulphenylated at the 3-position, using LDA with HMPA followed by benzyl thiotosylate in THF to obtain the ketone **45**, which was then reduced using Dibal-H in THF to give the *exo*-alcohol **46**. In a slight modification to the literature procedure, DMPU **52** was used as a non-toxic alternative to HMPA **53**.



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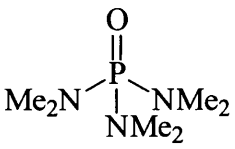

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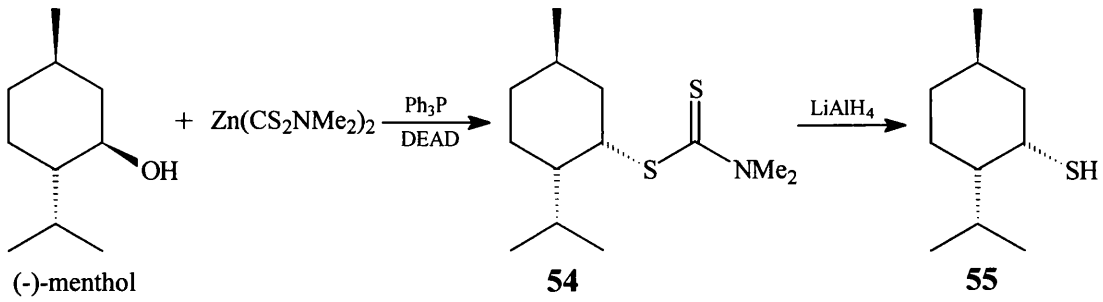
In addition, the authors report the use of $NaBH_4$ in anhydrous methanol as a cheaper alternative to Dibal-H for the reduction of ketone **45** to alcohol **46**, but this was not used in the present work.

The alcohol **46** is the common intermediate for the preparation of all three camphor-derived thiols. Alcohol **46** can be directly debenzylated with sodium in liquid ammonia to give the thiol **49**. Otherwise, the alcohol **46** was treated with sodium hydride and then with neopentyl bromide in refluxing *N*-methylpyrrolidin-2-one to give the neopentyl ether **47**, which was then debenzylated using the sodium/liquid ammonia reaction in the presence of *t*-butanol to give the thiol **50**. When the alcohol **46** was treated with sodium hydride and phenyl isocyanate in refluxing pyridine, the carbamate **48** was obtained, which could be debenzylated by the sodium/liquid ammonia procedure to give the thiol **51**.

The thiols **50** and **51** were easily purified, but thiol **49** had to be purified several times by flash-column chromatography because an impurity had virtually the same R_f value as the thiol. In addition, this thiol **49** also 'tailed' on the tlc plate. The possible impurities present could have been isomers of the thiol **49**, the corresponding disulphide or camphanol where the sulphur atom has been completely removed from the camphor skeleton. This could arise during the debenzylation step if excess of sodium is used.

The (1*R*,2*S*,5*R*)-(-)-menthol derived thiol, (+)-neomenthane-3-thiol **55** has been prepared by several different methods.[58] In this present work, the thiol **55** was prepared by the reduction of (1*S*,2*S*,5*R*)-(+)-neomenthyl *N*,*N*-dimethyldithiocarbamate **54**[59] according to the method of Aggarwal *et al.*[60] and is illustrated in Scheme 3.



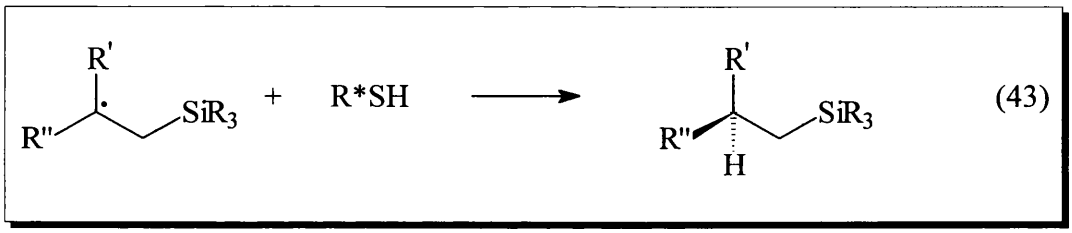
Scheme 3

Here, the (-)-menthol is converted to the carbamate **54** with inversion of stereochemistry by a Mitsonubu-type reaction using diethyl azodicarboxylate (DEAD) and triphenylphosphine, with stirring at room temperature. Zinc *N*,*N*-dimethyldithiocarbamate (Ziram) is used as the primary source of sulphur. Zinc salts like

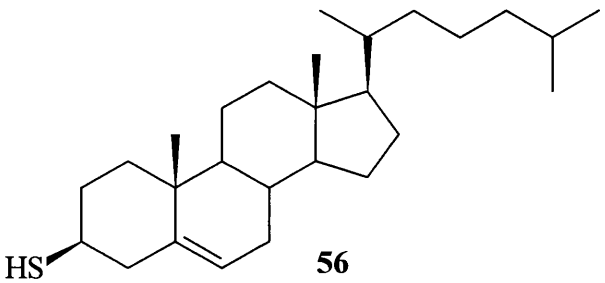
Ziram are inexpensive and have been shown to behave as efficient nucleophilic reagents under mild conditions. The thiocarbamate **54** is reduced with $LiAlH_4$ to give the desired thiol **55** as a colourless oil, after purification by flash-column chromatography.

Enantioselective hydrosilylation of acyclic prochiral alkenes using homochiral thiols as catalysts

The acyclic prochiral alkenes chosen for this study all show high yields for hydrosilylation reactions using achiral *t*-$C_{12}H_{25}SH$ as catalyst. Therefore, it was decided to investigate the enantioselectivities obtained when homochiral thiols were used as catalysts. Here, the prochiral β-silylalkyl radical generated would abstract hydrogen enantioselectively from the homochiral thiol [eqn. (43)].



The enantiomeric excess (ee) of these products was to be determined either by chiral-stationary-phase HPLC analysis or by using the homochiral NMR shift reagent $Eu(hfc)_3$ {europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]}. The acyclic prochiral alkenes chosen for this study were **18**, **19** and **21**. All the hydrosilylations were carried out using dimethylphenylsilane to give the silane adducts **26**, **29** and **34**. The homochiral thiols used were the camphor-derived thiols **49** and **50** and the commercially-available thiols, thiocholesterol **56** and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **57**. All the reactions were carried out following the same standard procedure described previously and the results for this section are summarised in Table 3.



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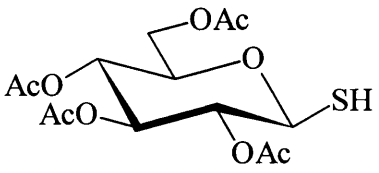

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Table 3: Enantioselective hydrosilylation of acyclic prochiral alkenes with $PhMe_2SiH$ using homochiral thiols as catalysts[a]

Entry	Alkene	Product	Thiol catalyst[b]	Isolated yield (%)	Product ee (%)[c]
1	**18**	**26**	**49**	33	3
2	**18**	**26**	**50**	72	1
3	**18**	**26**	**56**	94	3
4	**18**	**26**	**57**	94	3
5	**19**	**29**	**49**	55	3
6	**19**	**29**	**50**	74	7
7	**19**	**29**	**56**	62	5
8	**19**	**29**	**57**	87	3
9	**21**	**34**	**49**	60	4
10	**21**	**34**	**49**[d]	50	12
11	**21**	**34**	**50**	54	13
12	**21**	**34**	**56**	82	10
13	**21**	**34**	**57**	41	4

a. All reactions were carried out on a 5 mmol scale of alkene. The alkene (5 mmol), $PhMe_2SiH$ (1.3 equiv.), TBHN (0.05 equiv.) and hexane or dioxane (3.0 cm^3) were placed in a flask and stirred and heated at 60 °C (bath temp.) under an atmosphere of nitrogen. The homochiral thiol (0.05 equiv.) in hexane or dioxane (1.0 cm^3) was added by a syringe over a 2 h period. The reaction mixture was left to stir for a further 30 min at 60 °C. After removal of solvent under reduced pressure, the crude product was purified by flash-column chromatography [eluent: neat petroleum followed by petroleum-ether (19:1)]. *b*. Hexane was used as solvent with the thiols **49** and **50**; dioxane was used as solvent with the thiols **56** and **57**. *c*. The enantiomeric excesses of the products **26** and **29** were determined by using homochiral NMR shift reagent [Eu(hfc)$_3$]. The ee of the product **34** was determined by chiral-stationary-phase HPLC analysis using a Chiralcel-OJ column (Daicel Chemical Industries). *d*. All the thiol was added at the beginning of the reaction.

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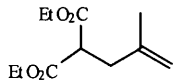

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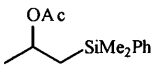

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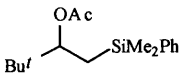

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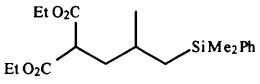

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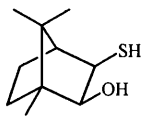

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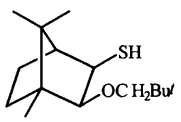

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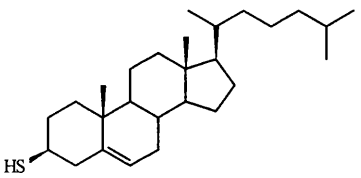

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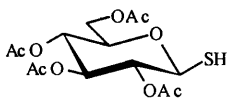

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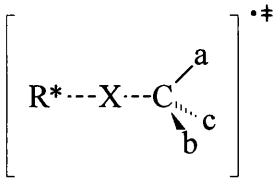
The three prochiral alkenes chosen were expected to give a wide range of enantioselectivities with the homochiral thiols used. These homochiral thiols are all derived from naturally-occurring homochiral molecules (*i.e.* terpenes, steroids and sugars). As the results shown in Table 3 indicate, the enantioselectivities were low (1-13 % ee), but as expected, the best results were obtained with the most sterically hindered alkenes and thiols (entries 10-12). It was thought that the prochiral alkene **19** would give moderately high chiral discrimination during enantioselective hydrogen abstraction between the two enantiotopic faces of the prochiral radical generated, but this was not the case. One of the main reasons for the low enantiomeric excesses could be that the reaction temperature (60 °C) was rather high. The temperature employed in any type of enantioselective reaction is usually below 0 °C. The glucose thiol **57** did not give any good enantiomeric excesses because it was the least sterically hindered thiol employed. The enantioselectivity obtained with the camphor-derived thiol **49** increased when it was all added at the beginning of the experiment, which also resulted in a slight reduction in the yield (entries 9 and 10).

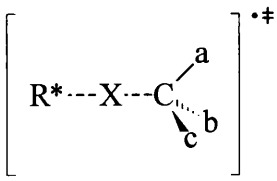
Another interesting point is the comparison of yields obtained between the two camphor-derived thiols **49** and **50**. In each case, **49** which contains the free OH group always gave the lower yields (except for alkene **21**, which gave a similar yield) when compared to the sterically-hindered neopentylether-containing thiol **50**. This result may indicate that hydrogen bonding is occurring to **49** and that this is affecting the yield of enantioselective hydrogen-atom transfer from the thiol group. When the possibility of hydrogen-bonding is removed (as in **50**), hydrogen-atom transfer is more efficient. The results obtained with thiocholesterol **56** and the thiol **50** indicate the importance of steric hindrance in these types of enantioselective reactions.

Consideration of cyclic prochiral alkenes

As previously mentioned, a large ee can only be achieved if there is a relatively large difference in energy between the two transition states (**5a** and **5b**). One approach to

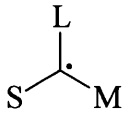


5a



5b

encourage such a difference in energy between the two transition states is to have large (L), medium (M) and small (S) groups attached to the radical centre **58**. In this way, the



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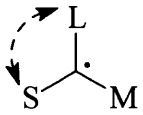
incoming homochiral thiol, R*SH should be able to distinguish between the two enantiotopic faces of the prochiral radical and thus deliver the hydrogen atom enantioselectively. However, acyclic radicals do not have fixed conformations and are free to rotate hence making discrimination between the two enantiotopic faces more difficult. This would suggest that cyclic radicals, which lack the conformational mobility of the acyclic systems, are more likely to give large differences in energy between the two distereoisomeric transition states. Therefore, with the aid of L, M and S groups attached to the radical centre, the largest enantiomeric excesses should be achieved when the prochiral radical is a conformationally constrained cyclic radical of the type **59**. The interactions between the groups L, M, S and R* of the thiol could be purely steric in

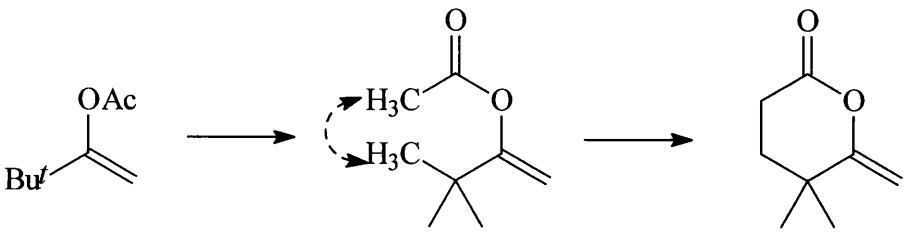


cyclization could be between any of the three groups

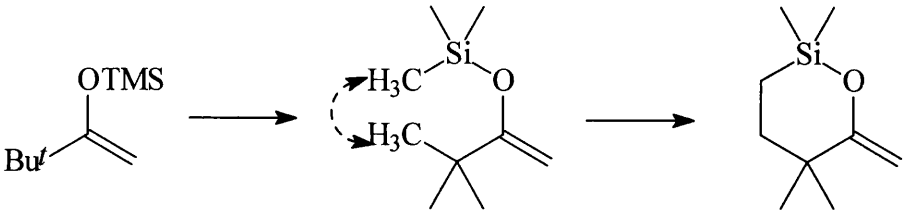
59

origin or be a combination of steric and bonding interactions (*e.g.* H-bonding, chelation linking) or have an electrostatic origin.

The enol acetate and silyl enol ethers both gave good yields in hydrosilylation reactions. Therefore, if the cyclic versions of these compounds are used, it might still be possible to achieve good yields, but with better enantioselectivities. For example, alkenes **16** and **19** can be "cyclized" to give prochiral alkenes **60** and **61** (Scheme 4).



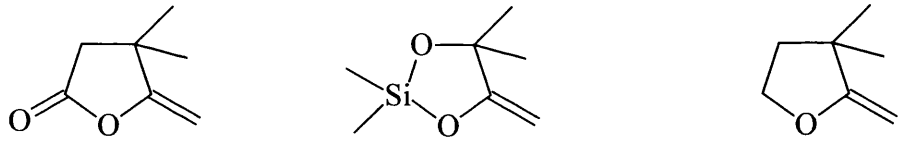
19 **60**



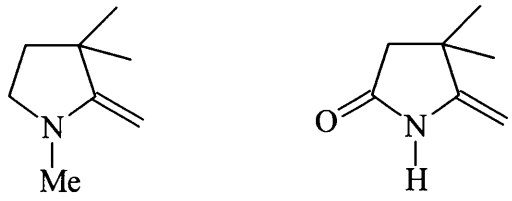
16 **61**

Scheme 4

Five-membered ring versions of **60** and **61** might provide a more rigidly fixed conformation than their six membered ring counterparts.



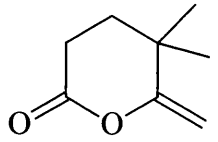
62 **63** **64**



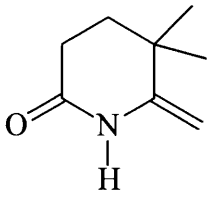
65 **66**

The oxygen atom in **62** can be replaced by N-H to give alkene **66**. If desired, a large bulky substituent could be attached to the nitrogen atom and this could lead to an overall increase in the 'steric chirality' (size difference between the L, M and S groups). The cyclic prochiral alkenes **60-66** (except **61**) are known compounds. However, some of these alkenes were difficult to prepare or required many steps to synthesize.[61] Hence, alkene **60** and other cyclic prochiral alkenes were investigated first.

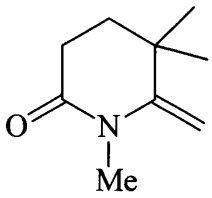
Preparation of cyclic prochiral alkenes



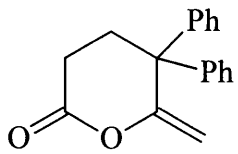
60



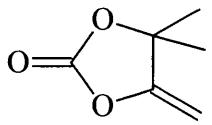
67



68



69



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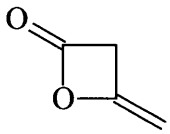
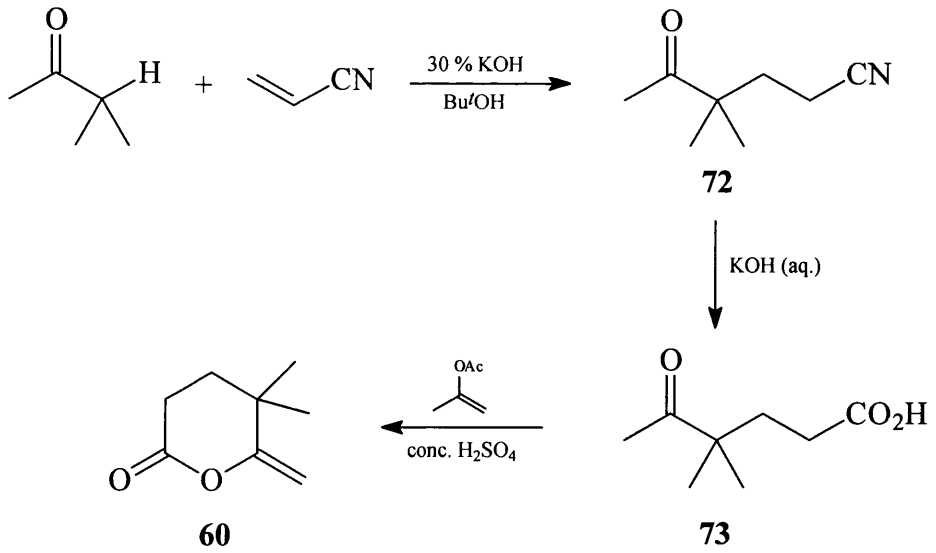


71

The cyclic prochiral alkenes **60** and **67-70** were all conveniently prepared in relatively few steps, with high yields. The δ-methylene lactone **60** was prepared according to the method as described by Shusherina *et al.* and is illustrated in Scheme 5.[62]



72

73

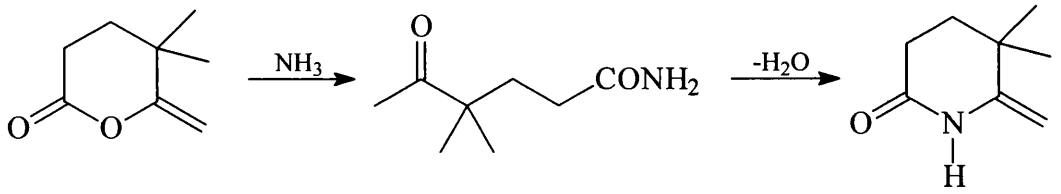
60

Scheme 5

The synthesis begins with the reaction between methyl isopropyl ketone and acrylonitrile to form the ketonitrile intermediate **72**, which was then hydrolysed using dilute KOH to form the ketoacid **73** quantitatively. The authors report that the hydrolysis is not as effective when using dilute or concentrated aqueous acid. The ketoacid **73**

undergoes dehydration using acetyl chloride to form the lactone **60**. However, the dehydration using acetyl chloride was sometimes irreproducible, because the lactone would hydrolyse back to the ketoacid during a basic wash with dilute $NaHCO_3$ in the work-up on account of local build-up of acid arising from the acyl chloride. An alternative to this type of dehydration reaction is the acid-catalysed dehydration reaction using isopropenyl acetate. This method worked efficiently and reproducibly and was used for the preparation of alkene **19** [eqn. (55)] and lactone **69** (Scheme 8). The reaction was carried out with continuous removal of the by-products boiling below 70 °C (mainly acetone) by slow distillation over a period of 2-3 h.

The δ-methylene lactam **67** was prepared from the lactone **60** and is illustrated in Scheme 6.[62] A major modification to the authors preparation was to use liquid ammonia

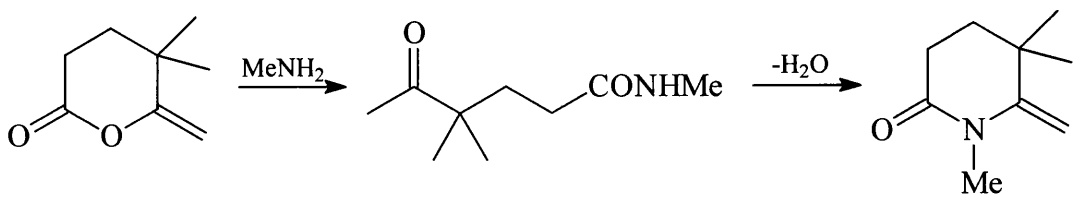


60 **74** **67**

Scheme 6

to form the ketoamide intermediate **74** rather than 0.880 aqueous ammonia, since the latter resulted in extreme contamination of the amide by the corresponding acid. This ketoamide **74** was then azeotropically dehydrated using toluene and a Dean-Stark apparatus. The lactam **67** can be recrystallized from CH_2Cl_2 / hexane.

The *N*-methyl δ-methylenelactam **68** was prepared in a similar way using methylamine in place of ammonia (Scheme 7). It was found that the ketoamide

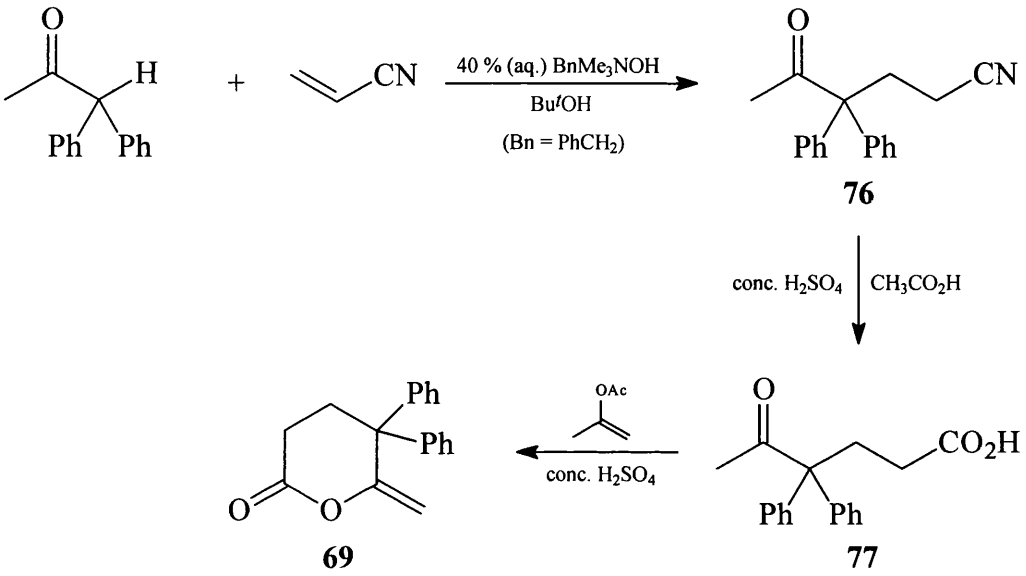


60 **75** **68**

Scheme 7

intermediate **75** dehydrated forming the lactam **68** during simple distillation under reduced pressure (0.02 Torr). Therefore, the Dean-Stark dehydration step was not necessary.

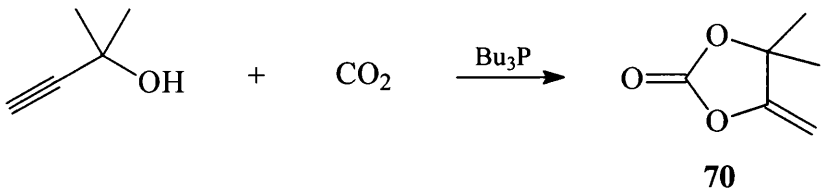
The diphenyl-substituted lactone **69** was prepared according to the method as described by Cragoe *et al.*[63] and is illustrated in Scheme 8. This procedure is similar to



Scheme 8

that described by Shusherina *et al.*[62] for the preparation of lactone **60**, except that the ketonitrile **76** is hydrolysed using concentrated acid to form the ketoacid **77**.

The preparation of the cyclic carbonate **70** is illustrated in Scheme 9.* The alkene **70** is conveniently prepared in one step, stirring the alkynol and tributylphosphine for 20h

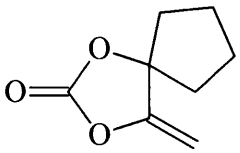


70

Scheme 9

at 100 °C under CO_2 pressure.[64] The authors also report the preparations of two other

* I would like to thank Dr. H.-S. Dang for preparing the alkene **70**.



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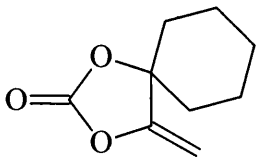
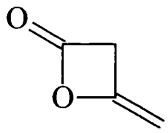


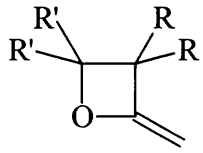
79

similar alkenes (**78** and **79**) which have spirocyclic functions replacing the *gem*-dimethyl groups. Although **78** and **79** were not prepared, these rigid spirocyclic groups could provide more steric control in the transition state than the *gem*-dimethyl groups.

The final cyclic prochiral alkene to be investigated, diketene **71** was commercially available. This alkene was not expected to give a product with a high ee because it did



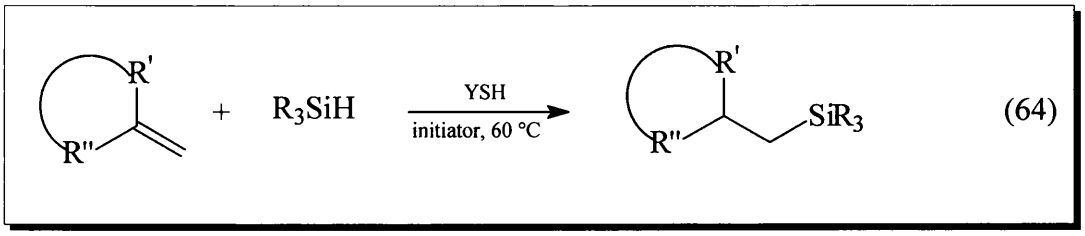
71



80

not possess the sterically-hindering *gem*-dimethyl or *gem*-diphenyl groups as do the other cyclic prochiral alkenes. Nevertheless, it was the only four membered ring containing alkene to be investigated and could still provide with some valuable information. A method for the preparation of sterically-hindered four-membered-ring-containing alkenes of the type **80** have been reported[65] and these alkenes could be investigated in the future.

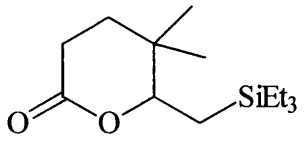
Hydrosilylation of cyclic prochiral alkenes using achiral thiols



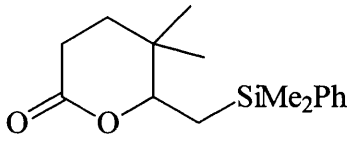
(64)

The hydrosilylation of cyclic prochiral alkenes using achiral thiols was investigated [eqn. (64)]. The two main achiral thiols used for these experiments were

tert-dodecanethiol and triphenylsilanethiol. Hydrosilylation experiments were also carried out using dioxane as solvent in place of hexane. In some experiments, a mixture of these two solvents were used. All the experiments follow the same standard procedure, as described previously, except that the thiol was no longer added over a 2 h period and was all added at the beginning of the reaction along with the other starting materials. This is because initial experiments with lactone **60** showed that there was no substantial effect on the yield whether the thiol was added at the beginning or over a 2 h period. Hence, the overall addition of thiol across the double bond is not favoured for these alkenes. The silane adducts **81-91** were obtained from these experiments and all the results are summarised in Table 4.



81



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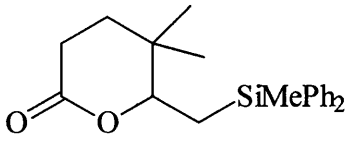

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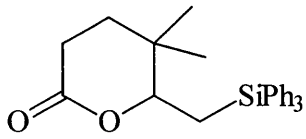

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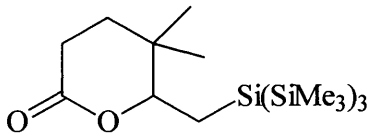

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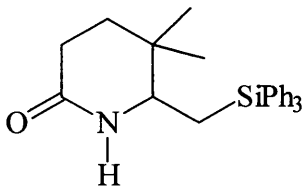

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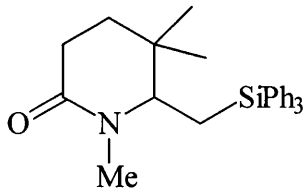

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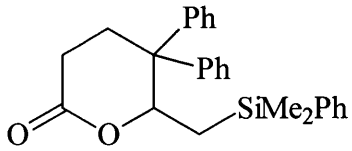

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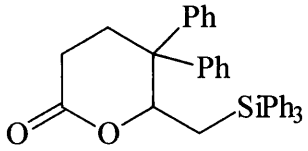

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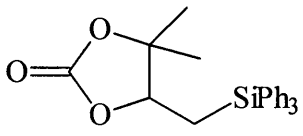

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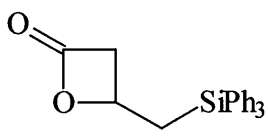
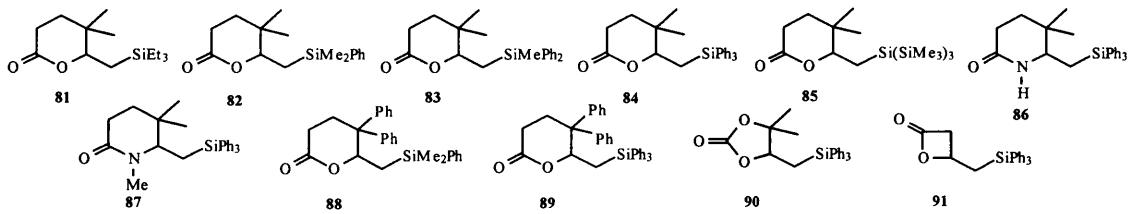


91

Table 4: Hydrosilylation of cyclic prochiral alkenes using achiral thiols as catalyst[a]

Entry	Alkene	Silane	Solvent[b]	Thiol catalyst	Product	Yield (%)[c]
1	**60**	Et_3SiH	-	t-$C_{12}H_{25}SH$	**81**	30 (60)
2	**60**	$PhMe_2SiH$	hexane	t-$C_{12}H_{25}SH$	**82**	75
3	**60**	$PhMe_2SiH$	hexane	$HSCH_2CO_2Me$	**82**	93
4	**60**	Ph_2MeSiH	hexane	t-$C_{12}H_{25}SH$	**83**	85
5	**60**	Ph_3SiH	hexane	t-$C_{12}H_{25}SH$	**84**	54 (63)
6	**60**	Ph_3SiH	hexane	Ph_3SiSH	**84**	(> 90)
7	**60**	Ph_3SiH	dioxane	Ph_3SiSH	**84**	(> 90)
8	**60**	$(Me_3Si)_3SiH$	hexane	t-$C_{12}H_{25}SH$	**85**	60
9	**60**	$(Me_3Si)_3SiH$	hexane	t-$C_{12}H_{25}SH$	**85**	74[d]
10	**60**	$(Me_3Si)_3SiH$	hexane	-	**85**	44
11	**67**	Ph_3SiH	hex + diox[e]	Ph_3SiSH	**86**	65 (74)
12	**67**	Ph_3SiH	hex + diox[e]	t-$C_{12}H_{25}SH$	**86**	(40)
13	**68**	Ph_3SiH	hexane	t-$C_{12}H_{25}SH$	**87**	33 (50)
14	**69**	$PhMe_2SiH$	hex + diox[f]	Ph_3SiSH	**88**	65 (80)
15	**69**	Ph_3SiH	hex + diox[f]	Ph_3SiSH	**89**	33
16	**69**	Ph_3SiH	hex + diox[f]	t-$C_{12}H_{25}SH$	**89**	15
17	**69**	Ph_3SiH	hex + diox[f]	n-$C_{12}H_{25}SH$	**89**	25
18	**70**	Ph_3SiH	hexane	t-$C_{12}H_{25}SH$	**90**	30 (50)
19	**71**	Ph_3SiH	dioxane	t-$C_{12}H_{25}SH$	**91**	37 (> 90)
20	**71**	Ph_3SiH	dioxane	-	**91**	(< 5)

a. All reactions were carried out on a 2.5 or 5 mmol scale of alkene and all follow the same general procedure. The alkene, thiol (0.05 equiv.), TBHN (0.05 equiv.) and silane (1.3 equiv.) in solvent were placed in a flask and stirred and heated at 60 °C (bath temp.) for 2.5 h under nitrogen. The reaction mixture was then cooled and concentrated *in vacuo* and the crude product remaining was purified by flash-column chromatography. No solvent was used with Et_3SiH (6 equiv.) as the silane. *b*. 4.0 cm^3 of solvent was used in the reactions; 6.0 cm^3 of solvent was used with alkene **69**. *c*. Isolated yields are given and yields determined by ^1H NMR analysis before purification are shown in the parentheses. *d*. t-$C_{12}H_{25}SH$ (0.1 equiv.) was used as catalyst. *e*. Hexane (2.0 cm^3) + dioxane (2.0 cm^3). *f*. Hexane (5.0 cm^3) + dioxane (1.0 cm^3).



The majority of the results obtained for the hydrosilylation of cyclic prochiral alkenes were satisfactory. Triethylsilane did not give good yields for the hydrosilylation of the lactone **60** and therefore the arylsilanes were mainly investigated. The three achiral thiols, *tert*-dodecanethiol, triphenylsilanethiol and methylthioglycolate were all efficient catalysts in these hydrosilylation experiments. Both hexane and dioxane solvents produced good yields for the hydrosilylation of the lactone **60** (entries 6 and 7). Some of the hydrosilylation experiments were carried out in a hexane and dioxane mixed solvent system (entries 12-18). These mixed solvent systems remain consistent with experiments discussed later, where the achiral thiol catalyst is replaced by a homochiral thiol catalyst and hence, would allow a direct comparison on catalytic efficiency between the achiral and homochiral thiols (based on the yields of the silane adduct obtained). The homochiral thiols were generally sparingly soluble in hexane which was the solvent of choice for enantioselective hydrosilylation experiments.

The hydrosilylation of lactone **60** with tris(trimethylsilyl)silane (TTMSS) gave an important set of results. TTMSS has a weak Si-H bond[16] and therefore a thiol catalyst might not be required because the β-silylalkyl radical would abstract hydrogen directly from the TTMSS. As the results indicate, in the absence of a thiol catalyst, a 44 % yield in product **85** is obtained (entry 11). Usually, about a 1 % yield in silane adduct was obtained in the absence of a thiol catalyst when using any of the other silanes. However, it was anticipated that the addition of TTMSS to the lactone **60** would still be subject to thiol catalysis, because unfavourable polar effects still operate in the transition state for direct abstraction of hydrogen from TTMSS. When *tert*-dodecanethiol (5 mol%) was added, the yield increased from 44 to 60 % and when 10 mol% of the thiol was used, the yield further increased to 74 % (entries 9 and 10). These results demonstrate the effectiveness of polarity-reversal catalysis by thiols even when thiol is not strictly necessary for the reaction to take place.

The lactams **67** and **68** gave lower yields of silane adducts than the lactone **60**. The silane adduct **88** formed from the hydrosilylation of the diphenyl lactone **69** with $PhMe_2SiH$ was difficult to purify by flash-column chromatography because the adduct had a similar polarity to the parent lactone **69**. The yields obtained for the silane adduct **89**, formed by the hydrosilylation of **69** with Ph_3SiH, was low possibly due to adverse steric interactions. Here, the phenyl rings surround the radical centre, thus making

hydrogen-atom transfer more difficult. This is supported by comparing the yields obtained using *n*-dodecanethiol and *t*-dodecanethiol as catalysts (entries 17 and 18). The silane adduct **91** obtained from alkene **71** decomposed on silica gel during flash-column chromatography and therefore was purified by recrystallization.

Enantioselective hydrosilylation of cyclic prochiral alkenes using homochiral thiols

The lactone **60** was used in preliminary experiments for these investigations and the silanes used were $PhMe_2SiH$, Ph_2MeSiH and Ph_3SiH. The largest ee would be expected when using Ph_3SiH, because this is the bulkiest silane. In a typical experiment, the homochiral thiol (5 mol % based on the alkene) was added at the beginning of the reaction with all the other starting materials, because the addition of thiol across the double bond of the alkene is evidently slow. The products obtained were easily purified by flash-column chromatography and the ee of the product was determined by chiral-stationary-phase HPLC analysis using Chiralcel-OD and Chiralcel-OJ columns (Daicel Chemical Industries). The results are summarised in Table 5.

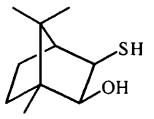
Table 5: Enantioselective hydrosilylation of lactone **60** at 60 °C using homochiral thiols as catalysts[a]

Entry	Silane	Solvent	Thiol catalyst	Product	Yield (%)[b]	Product ee (%)[c]
1	$PhMe_2SiH$	hexane	**50**	**82**	26 (48)	2
2	$PhMe_2SiH$	dioxane	**51**	**82**	40	6
3	$PhMe_2SiH$	hexane	**55**	**82**	39	3
4	$PhMe_2SiH$	dioxane	**56**	**82**	47	7
5	$PhMe_2SiH$	dioxane	**57**	**82**	74	16
6	$PhMe_2SiH$	hexane	**57**	**82**	52	23
7	$PhMe_2SiH$	DMF	**57**	**82**	20	8
8	Ph_2MeSiH	hexane	**49**	**83**	<1	-
9	Ph_2MeSiH	hexane	**50**	**83**	<1	-
10	Ph_2MeSiH	dioxane	**51**	**83**	76	10
11	Ph_2MeSiH	hexane	**55**	**83**	69	1
12	Ph_2MeSiH	dioxane	**56**	**83**	40	4

Table 5 - Continued

Entry	Silane	Solvent	Thiol catalyst	Product	Yield (%)[b]	Product ee (%)[c]
13	Ph_2MeSiH	dioxane	**57**	**83**	78	26
14	Ph_2MeSiH	hexane	**57**	**83**	65 (80)	32
15	Ph_3SiH	hexane	**49**	**84**	6	6
16	Ph_3SiH	dioxane	**51**	**84**	60 (78)	10
17	Ph_3SiH	hexane	**55**	**84**	36	3
18	Ph_3SiH	dioxane	**56**	**84**	33	3
19	Ph_3SiH	dioxane	**57**	**84**	63	40[d]
20	Ph_3SiH	hexane	**57**	**84**	72 (80)	50[e]

a. General procedure: The lactone **60** (5 mmol), silane (1.3 equiv.), TBHN (0.05 equiv.), thiol (0.05 equiv.) and solvent (4.0 cm^3) were placed in a flask and stirred and heated at 60 °C for 2.5 h under an atmosphere of nitrogen. The reaction mixture was then cooled, concentrated *in vacuo* and purified by flash-column chromatography. *b*. The isolated yields are shown and the yields determined by ^1H NMR analysis before purification are shown in the parentheses. *c*. Determined by chiral-stationary-phase HPLC analysis using a Daicel Chemical Industries Chiralcel-OJ column for **82** and **83** and a Chiralcel-OD column for **84**. With the thiols **55** and **56** as catalysts, the enantiomer present in excess was eluted second; for the remaining thiol catalysts, the predominant enantiomer was eluted first. *d*. For 40 % ee material, $[\alpha]_D^{20} = -31.3°$ (c = 1.48, $CHCl_3$). *e*. For 50 % ee material, $[\alpha]_D^{20} = -38.8$ (c = 1.82, $CHCl_3$).



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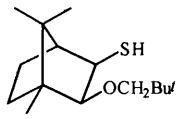

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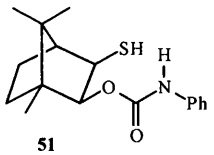

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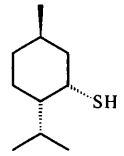

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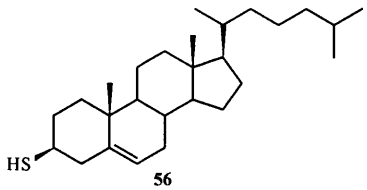

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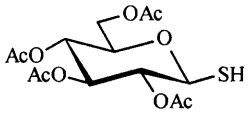

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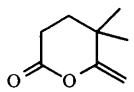

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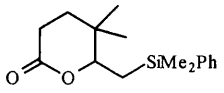

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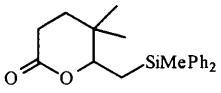

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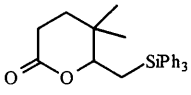


84

Within the accuracy of the determinations, an ee of 3 % or below should be regarded as racemic. The menthol-derived thiol **55** did not produce any large enantiomeric excesses although yields were generally high. The camphor-derived thiols **49**, **50** and **51** produced poor yields and enantioselectivity. It was anticipated that the

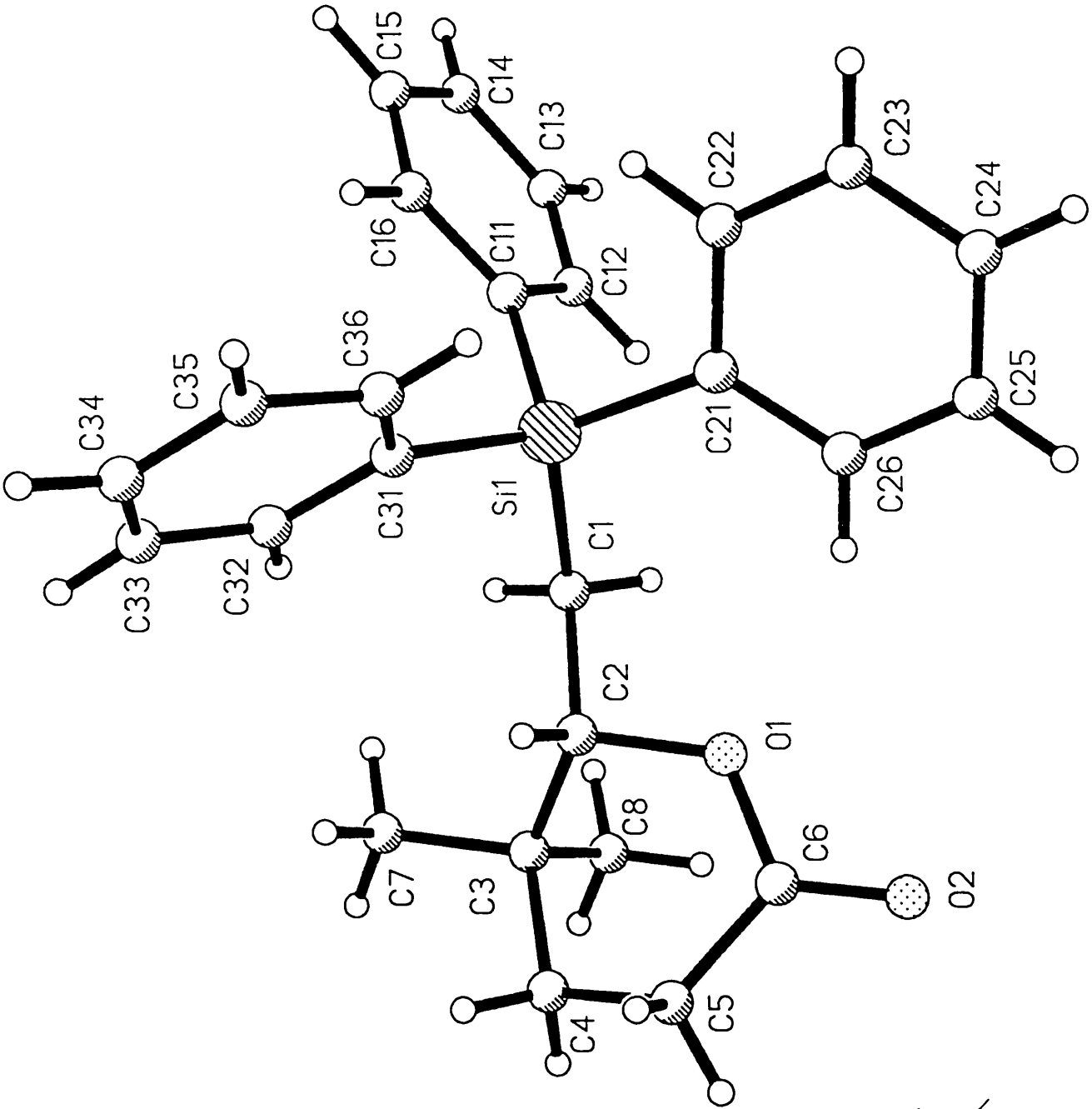
sterically-hindered thiol catalyst thiocholesterol **56** would produce the best enantioselectivity in these experiments, as it did for hydrosilylation of the acyclic alkenes (see Table 3). However, as the results indicate, both the yield and enantioselectivity were low when using this thiol.

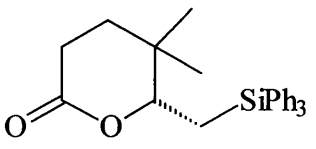
The best yields and enantioselectivities were obtained when using the commercially-available thiol **57** derived from glucose. The high enantioselectivity obtained with this sugar thiol catalyst was not expected as this thiol gave the lowest enantioselectivities for the hydrosilylation of acyclic alkenes (see Table 3). Thiol **57** is not as sterically hindered as thiocholesterol **56** or the camphor derived thiols **49-51** but nevertheless it gave up to 50 % ee (entry 20). As expected, the size of the silane played an important role in increasing the enantioselectivity (entries 19 and 20) which was largest for addition of Ph_3SiH. It could also be possible that favourable electrostatic interactions occur in the transition state for the hydrogen transfer between the thiol and the β-silylalkyl radical to produce these moderately high enantioselectivities. Support for this suggestion is provided by the increase in enantiomeric excesses observed on changing the solvent from dioxane to hexane. When using DMF as the solvent, the ee and yield both decreased when compared to dioxane and hexane (entries 5-7). Although the glucose thiol **57** is sparingly soluble in hexane at room temperature, all the thiol did dissolve in the reaction mixture at 60 °C. For these reactions hexane, the adduct **84** came out of solution towards the end of the reaction and care was taken to recover all the product for the determination of the ee. Considering the simplicity of the procedure and the preliminary nature of this work, the moderate degree of asymmetric induction obtained using the glucose thiol **57** as catalyst is encouraging.

The adduct **84** (50 % ee) could be upgraded to the enantiopure material $\{[\alpha]_D^{22} = -77.5\ °(c = 1.78, CHCl_3)\}$ by recrystallization from a mixture of hexane and benzene (2:1). This (*R*)-enantiomer was eluted first during chiral-stationary-phase HPLC analysis using a Chiralcel-OD column [hexane-isopropylalcohol (99:1) eluent]. X-ray crystallographic analysis of the enantiopure adduct **84** shows that the absolute configuration at the chiral centre is *R*.*

* I would like to thank Dr. Tocher for carrying out the X-ray crystallographic analysis.

X-ray structure of adduct 84

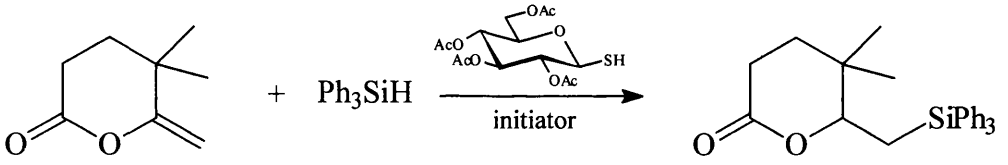




84

Improvement of enantioselectivity

Two approaches which might be considered to improve the enantioselectivity would be to lower the reaction temperature or to carry out the reactions in the presence of Lewis acids. A Lewis acid combined with a low temperature has been used as a popular method in stereoselective free-radical reactions.[31] In these hydrosilylation reactions, it might also be possible to improve the enantioselectivity by increasing the thiol catalyst concentration, because it is possible that not all the β-silylalkyl radicals are trapped by thiol at low concentrations. All the experiments in this section were carried out using lactone **60** and Ph_3SiH with the glucose-derived thiol **57** as catalyst [eqn. (65)].



60 **84** (65)

Increasing thiol concentration

For these experiments, the thiol concentration was increased from 5 mol % to 10 mol % in hexane solvent, still allowing the reaction to remain truly catalytic. When thiol **57** (10 mol %) was used for reaction (65), the silane adduct **84** was obtained in 70 % isolated yield and 54 % ee. Under the same conditions but with 5 mol % thiol, the isolated yield was 72 % and the ee was 50 %. When the experiment was repeated using Ph_2MeSiH, again no significant improvement in ee was observed. Therefore, no significant improvement in ee is obtained by increasing the thiol concentration.

Low temperature hydrosilylation reactions

There is the potential for the design of radical-chain hydrosilylation reactions that are efficient at lower temperatures when enantioselectivity should be enhanced. The reaction (65) is ideal for low temperature investigations as it already gives 50 % ee at 60 °C which should improve with the lowering of the temperature. The initial temperature investigated for reaction (65) was 45 °C in conjunction with TBHN (5 mol %) and an increased reaction time of about 12 h (the half-life of TBHN is *ca.* 7.1 h at 45 °C). However, the ee obtained from this reaction remained at 50 %, although the

yield was lowered from quantitative to 48 %. Experiments at room temperature and below would have required photochemical initiation using UV light and di-*tert*-butyl peroxide (DTBP) initiator which also generates *tert*-butoxyl radicals. Photochemical initiation is very versatile for a wide range of temperatures, but problems could arise when estimating the extent of exposure to UV light. Too little light and the reaction may not proceed, too much light and the product may degrade. To overcome this problem, the wavelength of the light can be changed easily by using different types of UV lamps. Three types of UV lamps are readily available; sunlamps, grow-bulbs and medium-pressure mercury lamps with quartz envelopes. Of these, the mercury lamp emits the largest amount of short-wavelength UV radiation and the sunlamp the least. An alternative method of low temperature initiation available involves the use of a trialkylborane in the presence of oxygen. However, trialkylboranes (R_3B) are known to react with thiols (YSH) by a radical-chain mechanism to give R_2BSY and RH.

The first UV/DTBP-initiated version of reaction (65) was carried out at room temperature using a 160 watt medium-pressure mercury lamp and the reaction time was decreased from the standard 2.5 h to 1 h. A typical procedure involved 2.5 mmol of the lactone **60** which was placed in a quartz flask with Ph_3SiH (1.3 equiv.), thiol **57** (0.05 equiv.), DTBP (4 equiv.) and dioxane (2.0 cm^3) as solvent. The reaction mixture was irradiated with UV light from the lamp at a distance of *ca.* 1 cm and stirred in a water bath for 1 h. Usually, the water bath temperature would increase by 5-10 °C from the initial temperature and therefore a water bath with a continuos flow of tap water was used. After 1 h stirring, the solvent was evaporated under reduced pressure and the crude material was purified by flash-column chromatography. The adduct **84** was obtained with a 58 % yield and 37 % ee. This experiment shows a similar ee as the TBHN-initiated reaction at 60 °C (40 % ee obtained in dioxane solvent) but with a lower yield which is probably due to the reduced reaction time. When this reaction was repeated at 0 °C, a 54 % yield of adduct **84** was obtained with a 15 % ee. The reduction in ee with decreasing temperature is the opposite of the expected trend. However, when the reaction was repeated in the *absence* of the thiol **57** at 0 °C a 30 % yield of adduct **84** was obtained.

Many different permutations of slow addition of starting materials were carried out. For example, one third of the Ph_3SiH was added initially, followed by slow addition

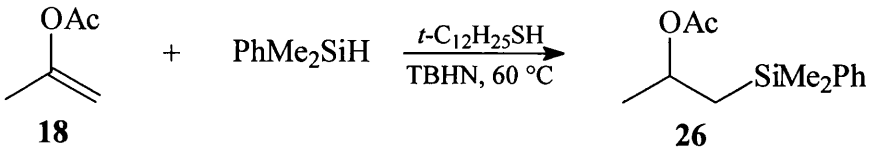
of the remaining two thirds. Alternatively, a mixture of lactone **60** and silane was added slowly to the reaction mixture. However, none of these different modes of addition increased the ee of the product, either at 0 °C or at room temperature. The best results came from using 10 mol % glucose thiol **57** as catalyst, added over a period of 45 min at room temperature which gave the adduct **84** in 71 % yield and with a 55 % ee. This result is very similar to that obtained from the TBHN-initiated reaction at 60 °C. Therefore, the UV/DTBP-initiated reaction has the advantage of being carried out at room temperature with a shorter reaction time period, but has the added experimental complications associated with photochemical processes.

Interestingly, instead of the slow addition of thiol to the reaction mixture, when the lactone **60** in hexane or dioxane solvent was added slowly over a period of 45 min to a reaction flask containing all the remaining starting materials for reaction (65), the yield of adduct **84** was 70 % but the product was racemic. This same result was reproduced with 10 mol % thiol catalyst and was also obtained in any experiment where the thiol **57**, Ph_3SiH and DTBP were present together before the addition of lactone. This result suggests that **57** is being converted to an achiral thiol before the hydrosilylation of **60** takes place. It seemed likely that Ph_3SiSH could be generated from a radical reaction between Ph_3SiH and the glucose thiol **57** initiated by DTBP, since in previous experiments (Table 4) Ph_3SiSH had been shown to act as an efficient catalyst for this hydrosilylation reaction.

These reactions show the necessity of adding the starting materials in the correct order if a slow addition mode is being employed. The low temperature hydrosilylation experiments were not pursued, although it may still be possible to achieve better enantioselectivity if the correct conditions can be found.

Lewis acid-mediated hydrosilylation reactions

After the moderately successful low temperature approach to radical-chain hydrosilylations of alkenes, it was decided to focus on possible Lewis acid-mediated reactions. An initial investigation on the hydrosilylation reaction (61) showed promising results.

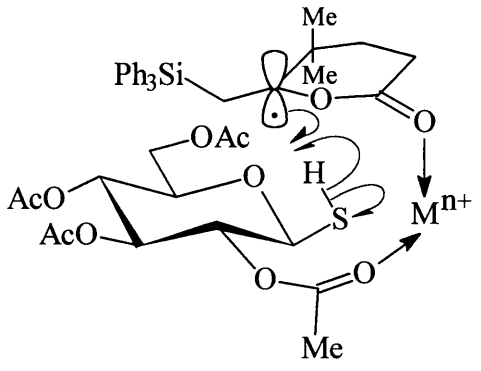


18 **26** (61)

Here, the thermally-initiated (TBHN, 60 °C) hydrosilylation of isopropenyl acetate **18** with $PhMe_2SiH$ using *t*-$C_{12}H_{25}SH$ as catalyst gave the adduct **26** in 93 % yield using hexane as solvent (Table 2). With DMF solvent, a 40 % yield of adduct **26** was obtained. However, this 40 % yield could be increased to 86 % when $LiBF_4$ (1 equiv. based on alkene) was present initially in the reaction mixture. It is possible that Lewis acidic Li^+ complexes to the alkene **18** making it more electrophilic and thus more reactive towards addition of the nucleophilic silyl radicals. Lithium tetrafluoroborate is a mild Lewis acid, but was used in these hydrosilylation reactions with caution because it has been used as a flouride source for the cleavage of silyl ethers.[66] However, the cleavage of the Si-C bond was not observed in any of the reactions in which $LiBF_4$ was used.

Effects of Lewis acids on enantioselective reactions

Enantioselectivity in the hydrosilylation of lactone **60** using the glucose thiol **57** as catalyst might be improved by making use of Lewis acid complexation. Here, the Lewis acid might bridge reversibly between the thiol and the β-silylalkyl radical to give a loose complex **92**, thus rendering hydrogen-atom transfer effectively intramolecular and



92

thereby hopefully increasing enantioselectivity. Preliminary experiments with the lactone **60** and $PhMe_2SiH$ using $LiBF_4$ (1 equiv.) as the Lewis acid in DMF solvent showed only

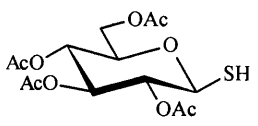
5-10 % yield of the adduct **82** by ^{1}H NMR analysis of the crude product. The ^{1}H NMR spectrum also indicated a large amount of the hydrolysis product of the lactone **60** (the ketoacid **73**, see Scheme 4). A possible reason for this hydrolysis is that the Lewis acid complexes to the lactone, thus promoting its hydrolysis by trace amounts of moisture. Lithium tetrafluoroborate has been shown to promote the hydrolysis of acetals in wet acrylonitrile.[66]

To ensure effective Lewis acid-promoted hydrosilylation reactions, it should be possible for the Lewis acid to be present in high concentrations and not to destroy the reactants, initiator or the catalyst (or epimerise it). Also, aprotic dipolar solvents like DMF should be avoided because the Lewis acid will bind to the aprotic solvent rather than to the reactants and/or intermediates. Another important factor that should be considered is that any Lewis-acidic metal cation must not be too thiophilic (sulphur loving) because the SH group of the catalyst must be left intact. The lanthanides might be ideal Lewis acids because these metals are oxophilic rather than thiophilic.[67] All the results obtained using lanthanide complexes and other Lewis acids are shown in Table 6. Reactions in the absence of Lewis acids are shown for comparison.

Table 6: Lewis acid-mediated enantioselective hydrosilylation of prochiral cyclic alkenes **60** and **67** with Ph_3SiH using the homochiral thiol **57** as catalyst.[a]

Entry	Product	Lewis acid [b]	Isolated yield (%)	Product ee (%) [c]
1	**84**	-	63	40
2	**84**	$Eu(fod)_3$	82	42
3	**84**	$Yb(OTf)_3$	71	39
4	**84**	$La(OTf)_3$	79	41
5	**84**	$Zn(OTf)_2$	71	39
6	**84**	$Mg(OTf)_2$	80	43
7	**84**	$Y(OTf)_3$	63	39
8	**84**	$Er(OTf)_3$	68	38
9	**84**	$Sc(OTf)_3$	60	37
10	**84**	$ZnCl_2$	77	35
11	**86**	-	42	29
12	**86**	$Yb(OTf)_3$	61	33

a. All the reactions using Lewis acids all follow the same basic procedure: The alkene **60** or **67** (2.5 mmol), Ph_3SiH (1.3 eqiuv.), TBHN (0.05 equiv.), thiol **57** (0.05 equiv.), Lewis acid (0.1 equiv.) and dioxane (4.0 cm^3) were placed in a flask and heated at 60 °C for 2.5 h under nitrogen. After the removal of the solvent, the crude product was purified by flash-column chromatography. *b.* All the Lewis acids (10 mol %) were > 90 % soluble in the reaction mixture, except $Eu(fod)_3$ [europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-ocatanedionate)] (entry 2) which was essentially insoluble. *c.* The product enantiomeric excesses were determined by chiral-stationary-phase HPLC analysis using Daicel Chemical Industries columns (Chiralcel-OD column for **84** and Chiralpak-AD column for **86**).



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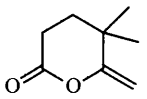

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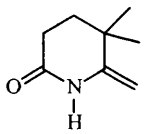

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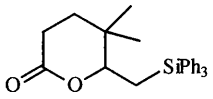

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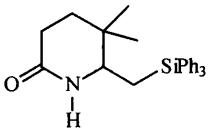

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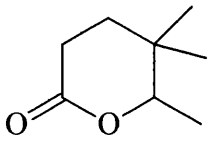
All the above reaction mixtures containing Lewis acids were > 90 % homogenous, except when using $Eu(fod)_3$ which remained heterogenous throughout the entire reaction. As indicated by the results in Table 6, the yields were generally high, but no significant increase in ee was observed. The Lewis acids were all hygroscopic and care was taken to ensure that moisture was excluded at all stages. Only 10 mol % Lewis

acid was used in these experiments, because these Lewis acids have high molecular weights and hence large concentrations were not practical. In addition, when it was possible to increase the concentration of the Lewis acid for experiments using lactone **60**, the lactone **60** was found to undergo hydrolysis to the ketoacid **73** or the double bond would reduce to give the corresponding alkane. For example, when $Yb(OTf)_3$ (1 equiv. based on alkene) was present in a reaction mixture containing lactone **60**, Ph_3SiH and the thiol **57** in dioxane solvent, no adduct **84** was formed. ^1H NMR analysis of the crude mixture indicated the presence of the ketoacid **73** and the reduced lactone **124**, in addition to other unidentified compounds. A similar result was obtained when using 1 equivalent of $Er(OTf)_3$.



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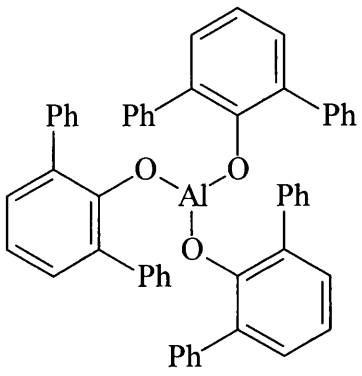
The only encouraging result obtained using Lewis acids was the improvement in the yield of the adduct **86**. Here, in the absence of the Lewis acid, the lactam **67** reacts with Ph_3SiH to give the adduct **86** in 42 % yield while this is increased to 61 % in the presence of $Yb(OTf)_3$ (0.1 equiv.); however, the ee remains similar.

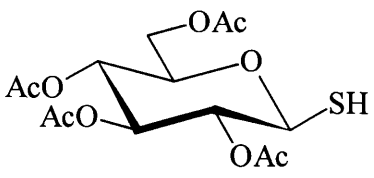
Using ATPH as Lewis acid

Aluminium salts are commonly used as Lewis acids in organic reactions. A novel aluminium-based Lewis acid, aluminium tris(2,6-diphenylphenoxide) (ATPH) **93** has been used in intramolecular radical cyclizations with great effect.[68] Here, the aryloxy substituents form a chiral pocket in which the aluminium atom lies in the centre at the



93

base. It might be possible to use ATPH in conjunction with β-silylalkyl radicals to block one of the enantiotopic faces and promote enantioselective hydrogen-atom transfer from a chiral thiol catalyst. The ATPH was generated *in situ* by reacting 2,6-diphenylphenol with trimethylaluminium. The cyclic prochiral alkenes **60**, **67** and **68** were chosen for this study, along with Ph_3SiH and the glucose thiol **57** as the catalyst.



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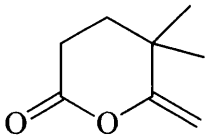

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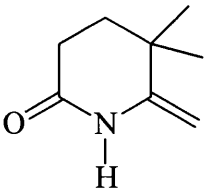

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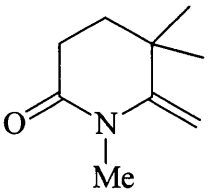
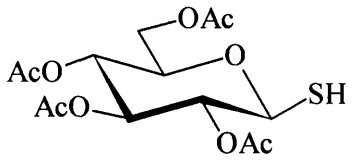


68

A typical procedure was as follows. 2,6-Diphenylphenol (1.85 g, 7.5 mmol), in benzene (10.0 cm^3) was placed in a flask and trimethylaluminium (2 M soln. in hexane) (1.25 cm^3, 2.5 mmol) was added carefully dropwise with stirring and the resultant yellow solution was stirred for 30 min at room temperature. All the remaining reagents, lactone **60** (0.35 g, 2.5 mmol), Ph_3SiH (0.85 g, 3.25 mmol), thiol **57** (0.05 g, 0.13 mmol), and TBHN (0.02 g, 0.13 mmol) were added to the flask and the reaction mixture was heated at 60 °C for 2.5 h under nitrogen. However, ^1H NMR analysis of the reaction product after removal of solvent indicated no adduct had been formed or starting lactone remaining. Once the ATPH was generated and the remaining reagents were added to the flask, a white precipitate was always formed after the addition of the alkene.

Homochiral carbohydrate-derived thiols

The Lewis acid and low temperature-mediated hydrosilylation reactions were moderately successful under the conditions employed. The combination of Lewis acid and low temperatures was not investigated. It was then decided to investigate other homochiral thiols as catalysts. The glucose derived thiol **57** showed the best enantiomeric excesses in hydrosilylations of **60** and therefore other related carbohydrate thiols **94-100** were synthesized.



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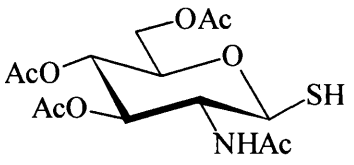

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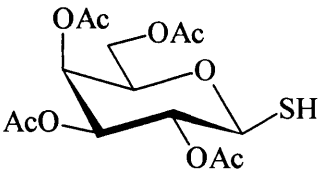

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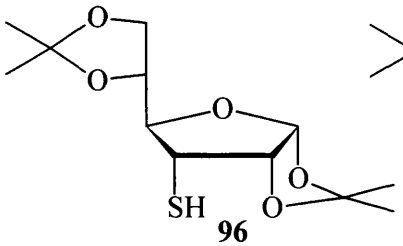

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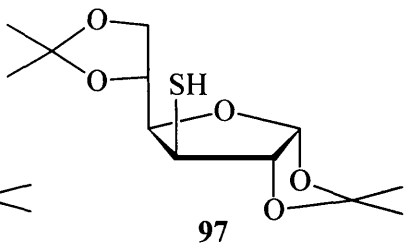

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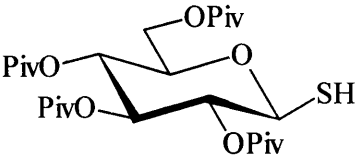

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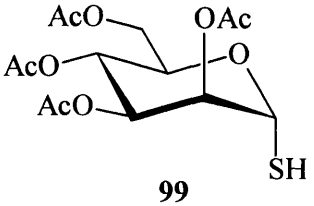

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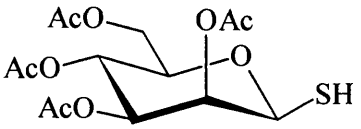
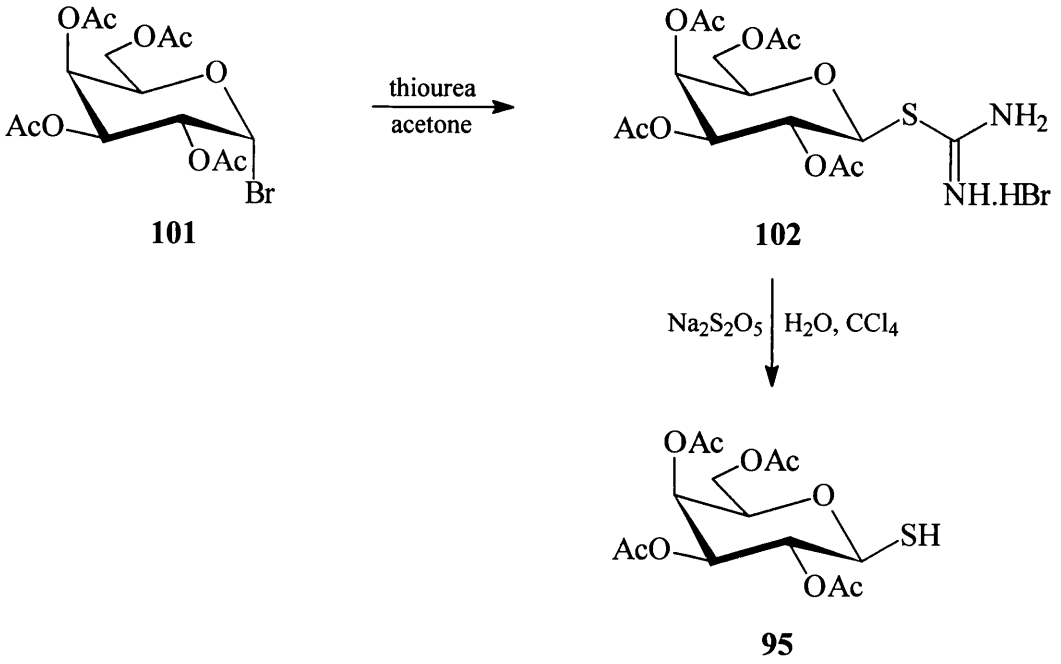


100

It was thought that the OAc group α to the SH group was mainly responsible for the moderately large enantioselectivities so far obtained, because of electrostatic and/or steric interactions. If electrostatic interactions are important, then the thiol **94** might give different results due to the difference in electronegativity of the NHAc group. If steric interactions are dominant, use of the more sterically hindered thiol **98**, with the *O*-pivalate groups [Piv- = Bu^{t}C(O)-] should give better enantioselectivities. The mannose thiol **100** should provide a very useful comparison with the glucose thiol **57**. Thiols **57** and **94** are commercially available, whereas the remaining carbohydrate thiols (except **98** and **100**) were known literature compounds. Thiols **98** and **100** are new compounds which were prepared by similar methods to those in the literature.

Preparation of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose 95

The galactose-derived thiol **95** was prepared according to the method illustrated in Scheme 10.[69] This method follows a standard procedure by which most of the sugar thiols are prepared and the details of the general experimental procedures for the preparation of all intermediates are well known.[70]



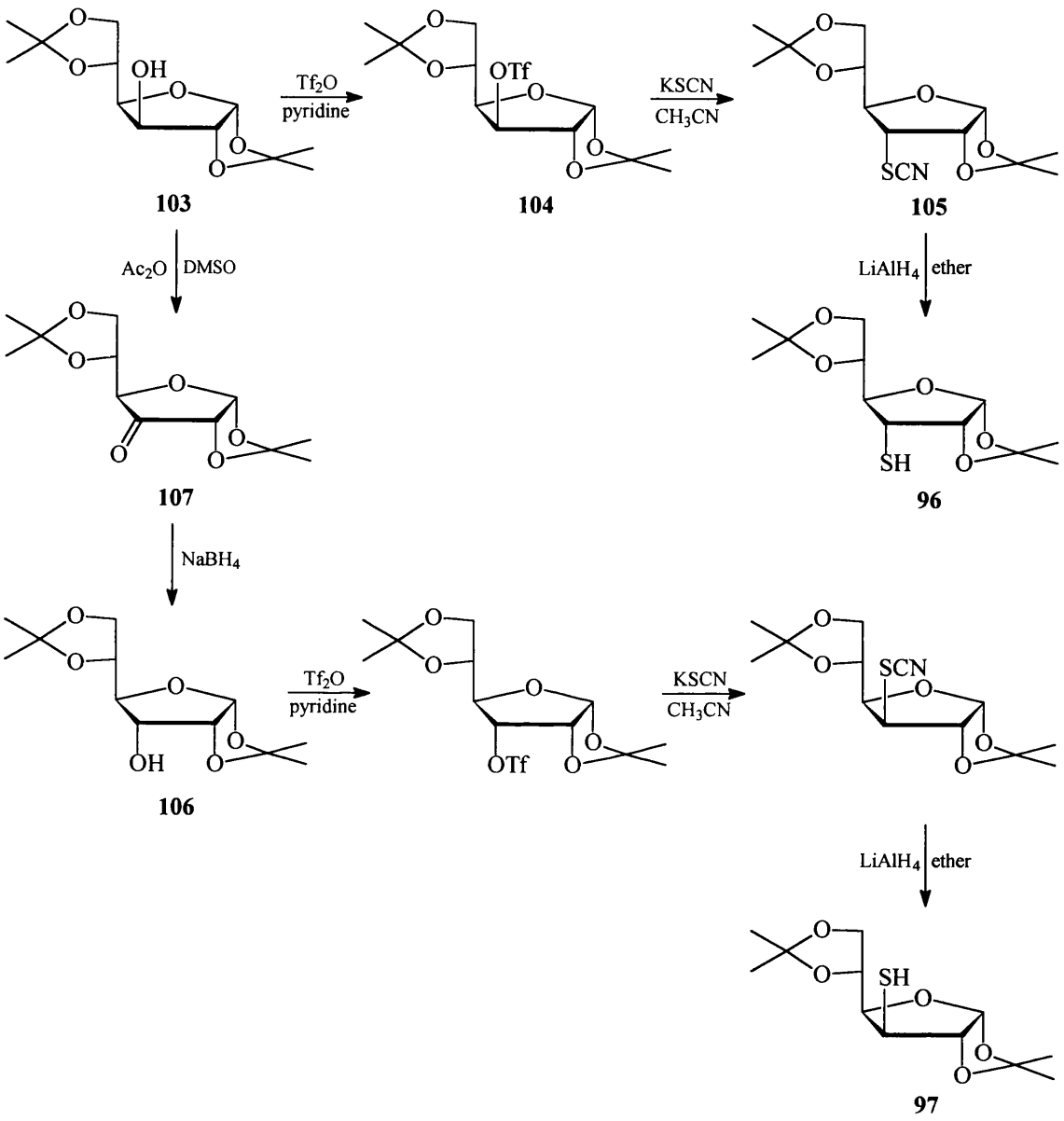
101 **102** **95**

Scheme 10

The bromosugar **101** is commercially available, hence allowing the preparation of **95** to be carried out in two steps. The intermediate **101** can be prepared in two steps from D-galactose. The reactions shown in Scheme 10 are carried out at reflux temperatures with short reaction times. The hydrobromide salt **102** is reduced by sodium metabisulphite in CCl_4 and water to give **95** which was recrystallized from benzene. This reduction step could also be carried out using potassium metabisulphite instead of sodium metabisulphite and $CHCl_3$ instead of CCl_4. The galactose thiol **95** should give a useful comparison with the glucose thiol **57**, because it has an identical structure apart from the axial OAc group on the C-4 position. This group is far from the SH group where hydrogen-atom transfer takes place and therefore, it would be predicted that **95** would give similar results to **57** when used as catalyst.

Preparation of glucofuranose and allofuranose-derived thiols 96 and 97

The isopropylidene protected glucofuranose and allofuranose thiols **96** and **97**

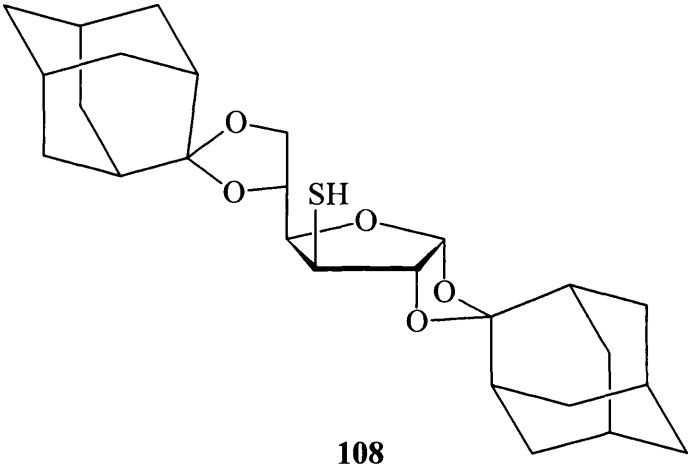


Scheme 11

were prepared by the same method which is illustrated in Scheme 11.[71] Here, isopropylidene protected glucose **103** is the common starting material for both the thiols. For the preparation of the thiol **96**, **103** is converted to the triflate **104**,[72] which is then caused to react with potassium thiocyanate in refluxing acetonitrile to give the thiocyanate **105**. The attack by the thiocyanate nucleophile on the triflate **104** does not proceed efficiently because of steric hindrance. Nevertheless, the **105** is then reduced by $LiAlH_4$ to give the isopropylidene protected allose thiol **96**. The isopropylidene protected

glucose thiol **97** is prepared by a similar procedure except starting from the allofuranose **106**, which is conveniently prepared in two steps according to the method of Sowa and Thomas.[73] Here, **103** is oxidised to the ketone by a Swern-type procedure using dimethyl sulphoxide in acetic anhydride. The ketone can then be reduced stereospecifically to the allofuranose **106** using $NaBH_4$.

The thiols **96** and, especially, **97** could give high enantioselectivity as catalysts because the SH groups are in sterically-hindered enviroments. If **97** proves to be a good catalyst, then more sterically hindered thiols like **108** could be employed. Thiols of the

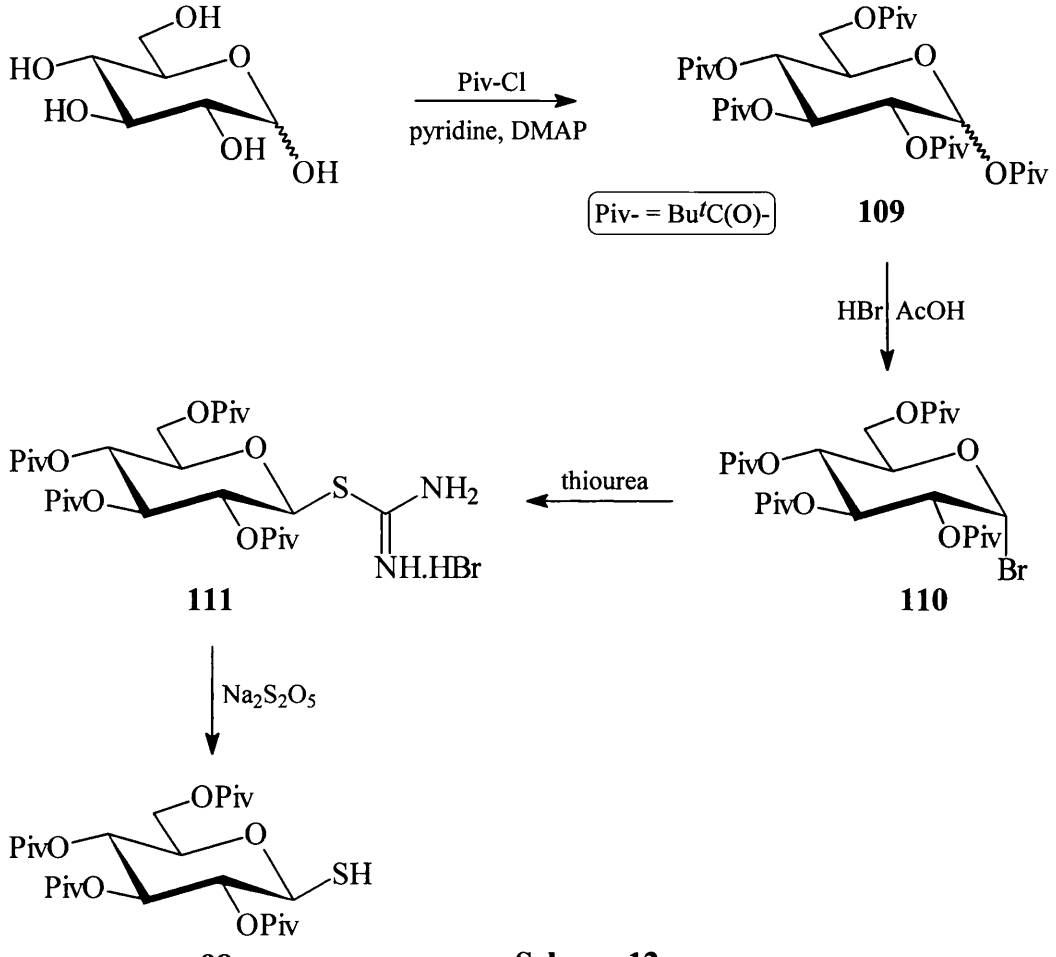


108

type **97** and **108** have been used as chiral ligands for metal-catalysed enantioselective synthesis.[74]

Preparation of 2,3,4,6-tetra-*O*-pivaloyl-1-thio-β-D-glucopyranose 98

The pivalate-containing glucose thiol **98** is a new compound which was prepared according to the standard literature procedures adopted for preparing the analogous acetate protected glucose thiol **57**.[70] It was envisaged that the pivalate groups would provide more steric hindrance than the acetate groups and thus if steric interactions are important hydrogen-atom transfer should be more enantioselective. The preparation of **98** is illustrated in Scheme 12. The α-bromosugar **110** was prepared according to literature methods.[75] Here, D-glucose was pivalated using pyridine and pivaloyl chloride

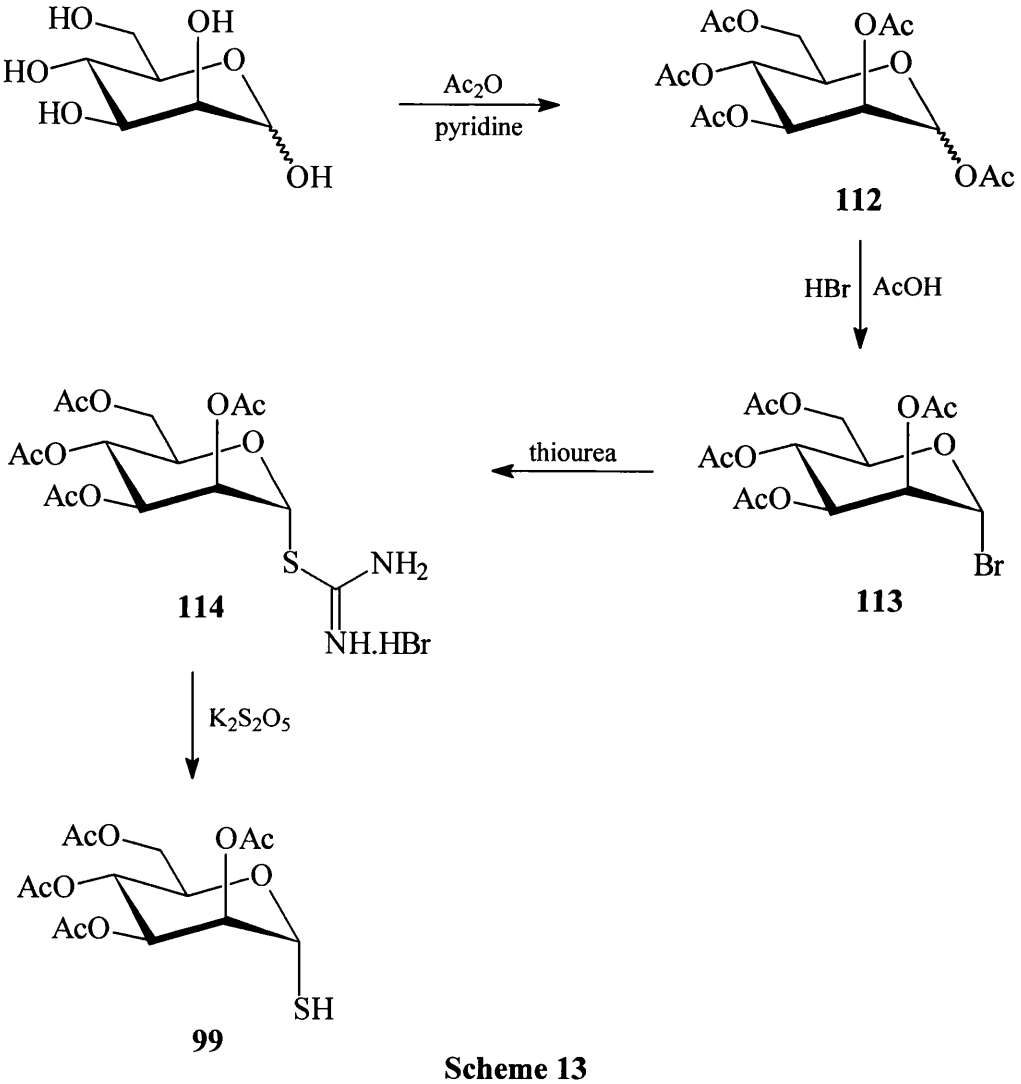


Scheme 12

with stirring for 5 days. However, when a catalytic amount of 4-dimethylaminopyridine (DMAP) was added quantitative yields of **109** were obtained after stirring overnight. The pentapivalate **109** was brominated using a solution of HBr (40 % in AcOH) to give solely the α-bromosugar **110** which was heated under reflux in acetone with thiourea to give the hydrobromide salt **111**. The thiol **98** was obtained by reduction of **111** with sodium metabisulphite ($Na_2S_2O_5$).

Preparation of α- and β-mannose thiols 99 and 100

2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-mannopyranose **99** was prepared according to literature methods as illustrated in Scheme 13.[76]

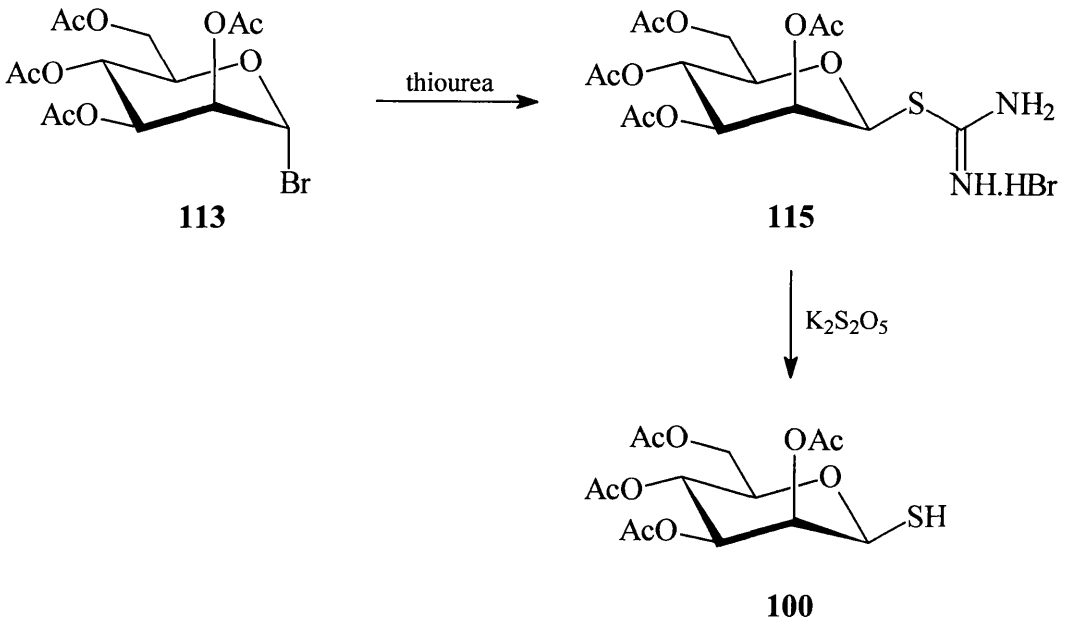


Scheme 13

The α-mannose thiol **99** was prepared by acetylating D-mannose to give a mixture of acetylated anomers **112** which, on bromination using a solution of HBr (40 % in AcOH), gives solely the α-bromosugar **113**. This α-bromosugar **113** was then caused to react with thiourea to give the hydrobromide salt **114**, which then could be reduced to give the desired thiol **99**.

However, when the above synthesis (Scheme 13) was carried out initially, all the products from each step were taken through to the next step without any prior purification. It was only during the purification of **99**, that it was noticed that the β-mannose thiol **100** (2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranose) was also produced from the same experiment. This thiol was presumably produced by attack of the sulphur nucleophile (thiourea) on the more sterically hindered face in the presence of the usual neighbouring group participation effect by the adjacent acetate group. The

mixture of α- and β-hydrobromide salts (**114** and **115**) were then reduced to give the desired thiols **99** and **100** (see also Scheme 14).



113 **115** **100**

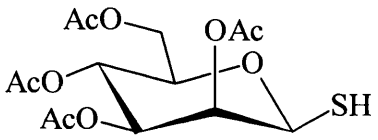
Scheme 14

^{1}H NMR analysis of the crude material after the reduction step, indicated that a large amount of polymeric material had been produced in addition to the thiols **99** and **100**. Conveniently, these three compounds can be separated without performing any difficult chromatography. It was found that the β-mannose thiol **100** could be isolated first from the crude mixture by simply dissolving this mixture in a slight excess of absolute ethanol and then placing in the freezer at -20 °C for 4-5 days. This causes the β-mannose thiol **100** to precipitate (> 90 % pure) which then could be recrystallized from absolute ethanol to give **100** as white needle-like crystals. The remaining crude mixture (containing the α-mannose thiol **99** and polymer) can be diluted with CCl_4 and cooled to 5 °C for a few hours. This causes the polymer to precipitate which can be removed by filtration and the filtrate is then concentrated *in vacuo* to give the α-mannose thiol **99** (90 % pure) which can be easily purified by flash-column chromatography.

Subsequently, if the α-bromosugar **113** is purified before carrying out the next step, by ensuring that all the AcOH is removed either by a base wash or by pumping under reduced pressure (0.1 Torr), then no polymeric material is obtained.

The β-mannose thiol **100** has not been reported previously in the literature and, as in these experiments it was isolated before the α-mannose thiol **99**, it was therefore not identified initially. Like for most of the carbohydrate thiols prepared, no NMR data was available for **99** to permit a direct comparison with **100**. The thiol **99** is reported in the literature simply as a 'colourless oil' {$[\alpha]_D^{20}$ = + 84.5 °(c = 1, MeOH)}.[76a] The β-mannose thiol **100** is a crystalline solid of m.p. 161-162 °C {$[\alpha]_D^{20}$ = – 29.7 °(c = 0.78, $CHCl_3$)}. The structure of the β-mannose thiol **100** was confirmed by X-ray crystallographic analysis.*

These thiols **99** and **100** should provide useful results in comparison with the glucose thiol **57** to determine the importance of axial and equitorial substituents in controlling the enantioselectivity of hydrogen-atom transfer.



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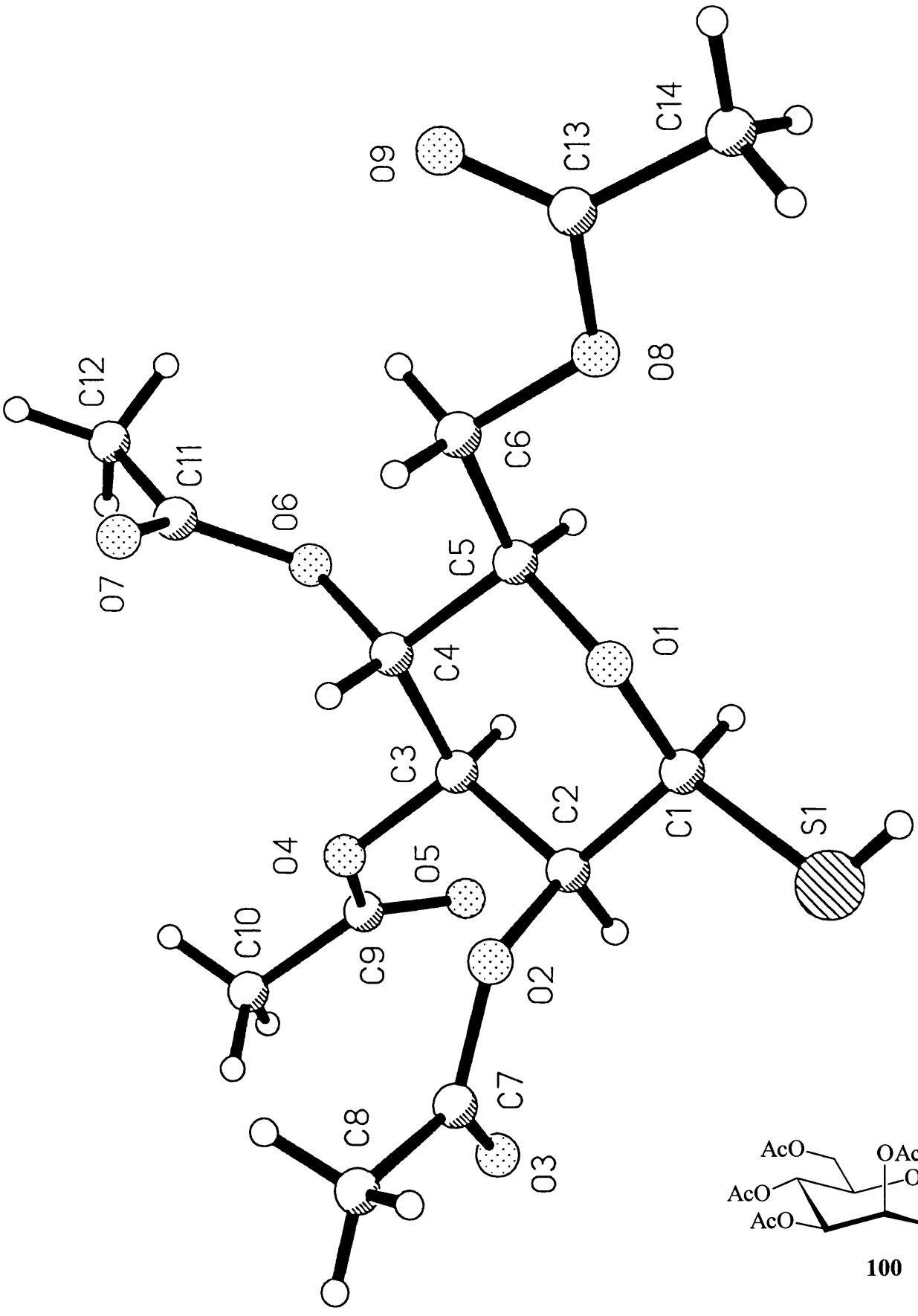
* I would like to thank Dr. Tocher for carrying out the X-ray crystallographic analysis.

X-ray structure of the β-mannose thiol 100



100

Enantioselective hydrosilylations using homochiral carbohydrate thiols as catalysts

Earlier experiments with lactone **60** and Ph_3SiH, using the glucose thiol **57** as catalyst, showed good enantiomeric excesses. In order to investigate how the structure of the monosaccharide residue influences enantioselectivity, other homochiral monosaccharide carbohydrate thiols were prepared and studied as catalysts for the hydrosilylation of cyclic prochiral alkenes. With the selection of homochiral carbohydrate thiols, it was hoped to identify the role of the groups adjacent to the thiol moiety. These adjacent groups could provide favourable electrostatic or hydrogen-bonding interactions as in thiol **94** or steric interactions as in thiol **98**. Switching the 2-substituent into the axial position, as in thiols **99** and **100**, could also be investigated.

For these studies, all the reactions were carried out on a 2.5 mmol scale of cyclic prochiral alkene. All reactions required more solvent than the original hydrosilylation reactions, because the reagents in these experiments had larger molecular weights. In some experiments, the larger solvent volume helped to allow efficient stirring of the reaction mixture, which became increasingly turbid due to the product crystallizing out of solution over the reaction time. The larger volume of solvent did not reduce either the yield or the enantioselectivity. Hexane produced higher enantiomeric excesses than dioxane when used as solvent and therefore, whenever possible hexane was used, otherwise a mixture of hexane and a minimum amount of dioxane was employed to keep the reaction mixture homogenous. Benzene solvent was investigated as a potential replacement to the hexane-dioxane mixed solvent system. The majority of the experiments were carried out using Ph_3SiH (all the thiol was added at the beginning of the experiment). The enantiomeric excesses were determined by chiral-stationary-phase HPLC analysis except for adduct **85**, which was determined by ^1H NMR analysis using a homochiral shift reagent; the results are summarised in Table 7.

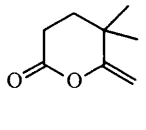
Table 7: Enantioselective hydrosilylation of cyclic prochiral alkenes using homochiral carbohydrate thiols as catalysts[a]

Entry	Alkene	Silane	Solvent[b]	Thiol	Product	Yield (%)[c]	Product ee (%)[d]
1	**60**	Ph_3SiH	dioxane	**57**	**84**	63	40
2	**60**	Ph_3SiH	hexane	**57**	**84**	72 (80)	50
3	**60**	Ph_3SiH	benzene	**57**	**84**	84	43
4	**60**	Ph_3SiH	hex-diox	**94**	**84**	68	15
5	**60**	Ph_3SiH	hex-diox	**94**[e]	**84**	67	30
6	**60**	Ph_3SiH	hexane	**95**	**84**	79	40
7	**60**	Ph_3SiH	hexane	**96**	**84**	81	6
8	**60**	Ph_3SiH	hexane	**97**	**84**	88	9
9	**60**	Ph_3SiH	hexane	**98**	**84**	77	44
10	**60**	Ph_3SiH	hexane	**99**	**84**	79	3
11	**60**	Ph_3SiH	hexane	**100**	**84**	84	76
12	**60**	Ph_3SiH	benzene	**100**	**84**	82	60
13	**60**	Ph_3SiH	benzene	**100**[f]	**84**	80	54
14	**60**	$(Me_3Si)_3SiH$	hexane	**57**[g]	**85**	92	47
15	**60**	$(Me_3Si)_3SiH$	hexane	**100**	**85**	91	55
16	**67**	Ph_3SiH	hex-diox	**57**	**86**	31 (45)	29
17	**67**	Ph_3SiH	hex-diox	**94**	**86**	25 (35)	9
18	**67**	Ph_3SiH	hex-diox	**100**	**86**	33 (40)	41
19	**67**	Ph_3SiH	hex-diox	**51**[h]	**86**	68	5
20	**68**	Ph_3SiH	hexane	**57**	**87**	43	5
21	**68**	Ph_3SiH	hexane	**100**	**87**	48	5
22	**69**	$PhMe_2SiH$	hex-diox	**100**	**88**	60 (80)	73
23	**69**	Ph_3SiH	dioxane	**57**	**89**	88	80
24	**69**	Ph_3SiH	hexane	**57**	**89**	58	88
25	**69**	Ph_3SiH	benzene	**57**	**89**	92	86
26	**69**	Ph_3SiH	hex-diox	**57**	**89**	93	87
27	**69**	Ph_3SiH	hex-diox	**95**	**89**	96	84

Table 7 - Continued

Entry	Alkene	Silane	Solvent[b]	Thiol	Product	Yield (%)[c]	Product ee (%)[d]
28	**69**	Ph_3SiH	hex-diox	**98**	**89**	97	87
29	**69**	Ph_3SiH	hex-diox	**99**	**89**	92	5
30	**69**	Ph_3SiH	hex-diox	**100**	**89**	90	95
31	**69**	Ph_3SiH	benzene	**100**	**89**	95	93
32	**70**	Ph_3SiH	hexane	**57**	**90**	96	31
33	**70**	Ph_3SiH	hexane	**100**	**90**	76	55
34	**71**	Ph_3SiH	hex-diox	**57**	**91**	35 (57)	5

a. The same procedure as described in Table 5. *b*. Between 4.0 and 6.0 cm^3 of solvent used. For entries 4 and 5, hexane (3.5 cm^3) and dioxane (0.5 cm^3) used as solvent. For alkene **67**, hexane (4.0 cm^3) and dioxane (0.5 cm^3) used as solvent. For alkene **69**, hexane (5.0 cm^3) and dioxane (1.0 cm^3) was used as solvent. For alkene **71**, hexane (3.0 cm^3) and dioxane (1.0 cm^3) used as solvent. *c*. Isolated yields are shown with yields determined by ^1H NMR analysis before purification shown in the parentheses. *d*. The methods for ee determination are shown in Table 8. *e*. The thiol in a mixture of hexane (0.5 cm^3) and dioxane (0.5 cm^3) was added over a 2 h period. *f*. 1 mol % thiol catalyst was used. *g*. Identical results were obtained when using 5 or 10 mol % thiol **57** as catalyst. *h*. This thiol is not carbohydrate-derived.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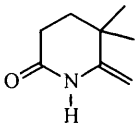
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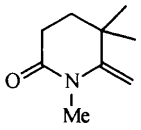
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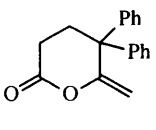
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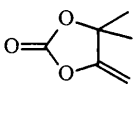
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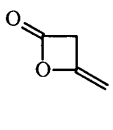
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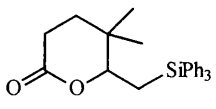
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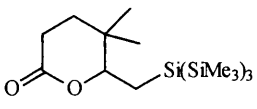
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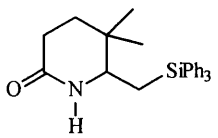
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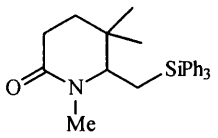
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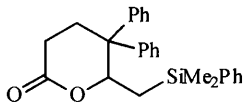
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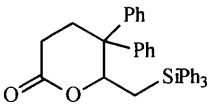
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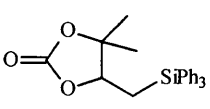
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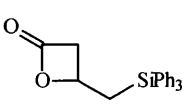
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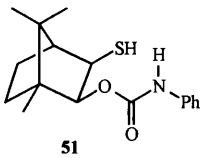
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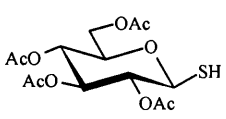
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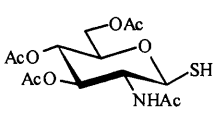
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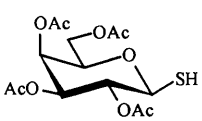
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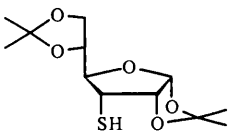
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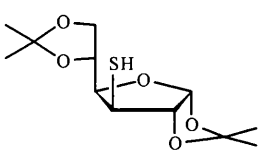
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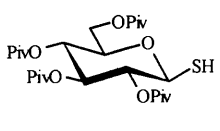
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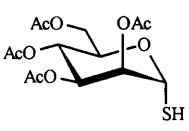
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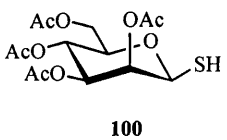

100

As the results indicate, the homochiral carbohydrate thiols gave the best results, in terms of both yield and enantioselectivity, of all the thiols investigated in this present work. The glucofuranose and allofuranose thiols **96** and **97** did not produce high enantiomeric excesses. The β-mannose thiol **100** produced the best results as catalyst.

For the hydrosilylation of lactone **60** using **100** as catalyst, the adduct **84** was obtained with a 84 % yield and 76 % ee (entry 11). The ee was lowered in benzene solvent and was further reduced when 1 mol % thiol **100** was used as catalyst. Therefore, it appears that 5 mol % is the ideal amount of thiol catalyst since, in previous experiments, 10 mol % of thiol **57** gave the same results as obtained with 5 mol % catalyst. Hexane is generally the best solvent for hydrosilylation of lactone **60**.

Comparison of the remaining pyranose thiols indicates the important factors required to produce good enantioselectivity. It was suggested earlier that the C-2 substituent on the pyranose thiols (adjacent to the SH group) played an important electrostatic or steric role for achieving enantioselective hydrogen-atom transfer. Comparison could be made between thiols **57** and **94**, which have equatorial *O*-acetyl and *N*-acetyl groups attached at the 2-position. The amide thiol **94** gives an appreciably lower ee (30 %) than that obtained with the acetate thiol **57** (50 %) (entries 1-5). The best ee obtained with catalyst **94** was when this thiol was added over a 2 h period.

The structures of the glucose thiol **57** and the galactose thiol **95** are the same except the galactose thiol has an axial *O*-acetyl group on C-4. It was thought that this group was relatively far from the SH group and therefore should have little effect on the enantioselective hydrogen-atom transfer. However, a 40 % ee was obtained with the galactose thiol catalyst as compared to the 50 % ee for the same reaction using the **57** as catalyst (entries 2 and 6). 1,3-Diaxial interactions occuring in the galactose thiol **95** might alter the structure of this thiol in the region of the SH group.

If steric interactions associated with the thiol catalyst are an important factor, then the pivalate-protected glucose thiol **98** might give better results than the acetate **57**. However, as the results indicate (entries 2 and 9), no improvement to the ee was achieved. As stated, the best ee obtained for the adduct **84** was obtained was when the β-mannose thiol **100** was used as catalyst. Here, the C-2 axial *O*-acetyl group in the β-mannose thiol **100** leads to a 76 % ee for adduct **84**, as compared to the C-2 equatorial *O*-acetyl group for the glucose thiol **57**, which leads to a 50 % ee (entries 2 and 11).

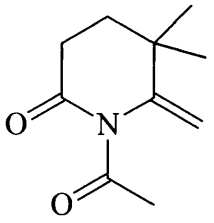
Interestingly, when the α-mannose thiol **99** was used as catalyst, the adduct **84** was obtained virtually racemic (3 % ee, entry 10). This thiol **99** has the same structure as the high ee producing β-mannose thiol **100**, except that the SH group is in an axial position. Therefore, the axial/equatorial positioning of the thiol and *O*-acetyl groups (especially adjacent to the SH group) are important in determining the effectiveness of enantioselective hydrogen-atom transfer.

An important point needs to be made on the handling of the adduct **84**. After **84** was purified by flash-column chromatography, some of the solid adduct was found to 'stick' to the side of the flask and coat it, while the remaining adduct was a free-moving solid. If the ee is determined separately for the free moving solid and for the material adhering to the walls of the flask, it is found that the free moving solid has a greater ee. For example, in one experiment the total adduct **84** obtained after purification, had an overall 47 % ee, while the free moving solid in the flask had a 51 % ee and the material adhering to the side had an 11 % ee. Therefore, care must be taken when determining the ee.

The adduct **85** derived from lactone **60** and TTMSS was isolated in quantitative yield and a 54 % ee when using **100** as catalyst. The quantitative yields of adduct **85** obtained by using homochiral carbohydrate thiols also indicates the efficiency of these compounds as catalysts (entries 14 and 15). As previously shown in Table 4, in the *absence* of thiol catalyst, adduct **85** was isolated in 44 % yield and in 74 % yield in the presence of *t*-$C_{12}H_{25}SH$ (10 mol %) (entries 10 and 11, Table 4). TTMSS has a relatively weak Si-H bond and therefore can act as a hydrogen-atom donor, but (of course) leads to racemic adduct **85**. In the case of the carbohydrate thiols **57** and **100**, these catalyst are evidently better hydrogen-atom donors than TTMSS because the yields of adduct **85** obtained are much greater and the products are optically active.

For hydrosilylations of the lactams **67** and **68**, the yields and enantiomeric excesses were generally lower (especially for **68**) than those obtained for the lactone **60**. It was originally thought that the N-H lactam **67** would give similar results to lactone **60** because the O and N-H groups are similar in size and also have similar electronic effects. Unlike the O group, the N-H group could be made larger by replacing the hydrogen with a bigger substituent which might lead to higher enantiomeric excesses than lactone **60**. However, this was not the case with an *N*-methyl substituent (*i.e.* lactam **68**) was present.

The enantiomeric excesses of the lactam **68** were virtually racemic (entries 20 and 21). If lactam **67** was acetylated, then the resultant lactam **116** might produce better results. If **116** proves to be better than the lactams **67** and **68**, as regards yields and



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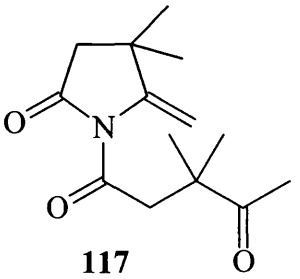
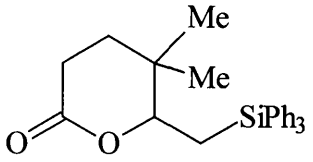


117

enantioselectivities, then the lactam **117** [61e] could provide better enantioselectivity. The lactams **116** and **117** should provide useful information as to the importance of size and electronic properties of groups attached to nitrogen and adjacent to the radical centre involved in the (enantioselective) hydrogen-atom transfer.

Hydrosilylations of the diphenyl lactone **69** were carried out using $PhMe_2SiH$ and Ph_3SiH. With $PhMe_2SiH$, the adduct **88** was isolated in 60 % yield and 73 % ee when using thiol **100** as catalyst (entry 22). Interestingly, the ee obtained was similar to that obtained for adduct **84** with thiol **100** (entry 11). These adducts are structural isomers.



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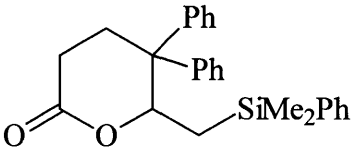

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Adduct **88** was difficult to purify by flash-column chromatography using standard silica gel because it had similar polarity to the starting diphenyl lactone **69**.

The majority of hydrosilylation reactions of lactone **69** were carried out using Ph_3SiH. The adduct **89** was generally isolated in high yields and enantioselectivities with the homochiral carbohydrate thiol catalysts. When **57** was used as catalyst, the hydrosilylation reaction was carried out in dioxane, hexane and benzene solvent (entries 23-25). As before, the reaction in hexane solvent produced the best ee (88 %),

but the yield was only about 60 %, probably due to low solubility of the lactone **69** in hexane. The best solvent system apart from benzene was a mixture of hexane and dioxane (5:1) which produced a 93 % yield and 87 % ee (entry 26). This solvent system was used in the majority of the experiments using lactone **69**. The glucose thiol **57**, galactose thiol **95** and the pivalate-protected glucose thiol **98** all produced similar near-quantitative yields and optical purities (~87 % ee) of adduct **89** when used as catalysts (entries 26-28). The pivalate- and acetate-protected glucose thiols **57** and **98** gave identical enantiomeric excesses even though there is a significant difference in bulk between these catalysts. The mannose thiols **99** and **100** produced strongly contrasting results (entries 29 and 30). When α-mannose thiol **99** was used as catalyst, the adduct **89** was obtained with a quantitative yield and a 5 % ee, while the β-mannose thiol **100** produced the largest ee obtained in this work (95 % ee) and a near-quantitative yield. These contrasting results are similar to those obtained for adduct **84** with these thiols.

The adduct **90** from the hydrosilylation of alkene **70** with Ph_3SiH was produced in quantitative yields and moderate enantiomeric excesses (entries 32 and 33). It is possible that hydrosilylation of the spirocyclic alkenes **78** and **79** (p. 42) might give larger enantiomeric excesses than obtained with alkene **70**, because the spirocyclic groups could provide more steric hindrance than the *gem*-dimethyl groups.

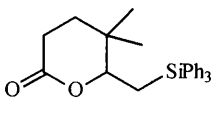
The hydrosilylation of diketene **71** produced a low isolated yield and ee. The adduct **91** was difficult to purify as it decomposed on silica gel during flash-column chromatography. The ee was not expected to be high because diketene does not have a bulky group adjacent to the prochiral centre and the 'steric asymmetry' in the region of the radical centre is very small. Therefore, it is likely that alkenes of the type **80** (p. 42) should give larger enantiomeric excesses.

A summary of the ee determinations and optical rotations of some of the silane adducts obtained are shown in Table 8.

Table 8: A summary of the determinations of enantiomeric excess and optical rotation

Entry	Product	ee (%)	column for HPLC[a]	eluent: IPA (%)[b]	major enantiomer	$[\alpha]_D$ (c,$CHCl_3$)[c]
1	**84**	40	Chiralcel-OD	1	1st eluted (*R*)	-31.3° (1.48)
2	**84**	50	Chiralcel-OD	1	1st eluted (*R*)	-38.8° (1.82)
3	**84**	100	Chiralcel-OD	1	1st eluted (*R*)	-77.5° (1.78)
4	**84**	76	Chiralcel-OD	1	1st eluted (*R*)	-60.0° (1.38)
5	**84**	60	Chiralcel-OD	1	1st eluted (*R*)	-47.1° (1.43)
6	**85**[d]	47	-	-	-	-29.7° (1.16)
7	**85**[d]	55	-	-	-	-35.7° (1.23)
8	**86**	29	Chiralpak-AD	10	2nd eluted	-16.9° (0.66)
9	**87**	5	Chiralpak-AD	5	2nd eluted	-
10	**88**	73	Chiralcel-OD	4	1st eluted	-
11	**89**	80	Chiralcel-OD	10	1st eluted	-158.7 (1.20)
12	**89**	95	Chiralcel-OD	10	1st eluted	-187.9 (1.21)
13	**89**	98	Chiralcel-OD	10	1st eluted	-193.8° (1.21)
14	**89**	68	Chiralcel-OD	10	1st eluted	-134.9° (1.18)
15	**90**	31	Chiralcel-OD	10	1st eluted	-13.1° (1.35)
16	**90**	55	Chiralcel-OD	10	1st eluted	-24.0° (1.24)
17	**91**	5	Chiralcel-OD	20	1st eluted	-

a. Both the columns used in chiral-stationary-phase HPLC analysis are available from Daicel Chemical Industries. *b*. The % isopropyl alcohol (IPA) in hexane was used with a flow rate of 1.0 cm^3min^{-1} at 254 nm (except for **88**, flow rate: 0.5 cm^3min^{-1}). Retention times are as follows, **84**: 12 and 13 min; **86**: 7 and 11 min; **87**: 7 and 9 min; **88**: 16 and 17 min; **89**: 7 and 10 min; **90**: 7 and 8 min; **91**: 10 and 13 min. *c*. All optical rotations were carried out in $CHCl_3$ and concentrations are shown in the parentheses. *d*. The ee for **85** was determined by ^1H NMR analysis using homochiral [$Eu(hfc)_3$] shift reagent.



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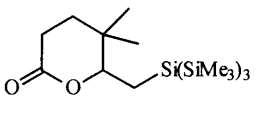

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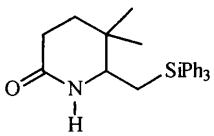

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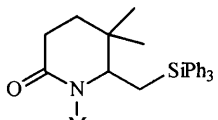

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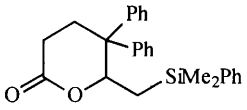

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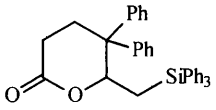

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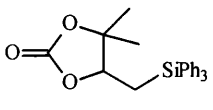

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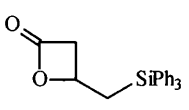

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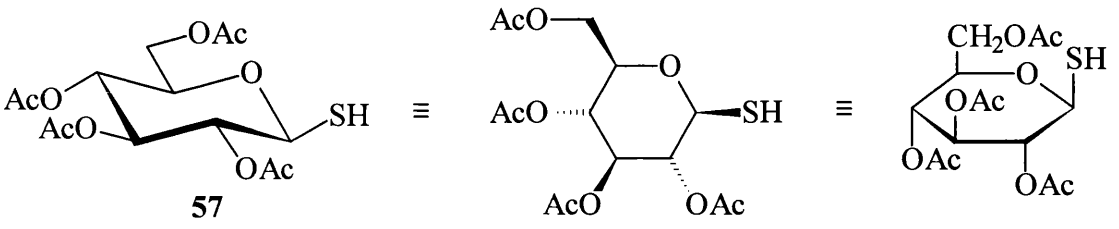
Factors governing enantioselectivity for homochiral carbohydrate thiols

From these radical-chain hydrosilylation reactions of prochiral cyclic alkenes, it can be seen that the β-mannose thiol **100** produced the best results as catalyst. Although all the pyranose-derived homochiral carbohydrate thiols have similar structures, the specific shape of **100** allows the higher enantioselectivities (up to 95 % ee) to be achieved. It is thought that the adjacent OAc group to SH group play an important role through steric or electronic interactions. However, it still is not clear why this thiol is the



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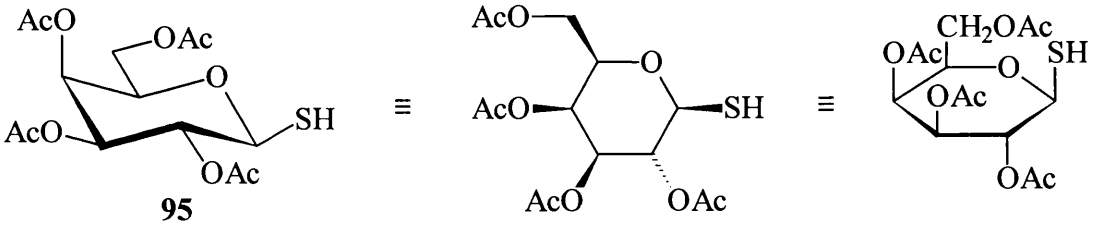

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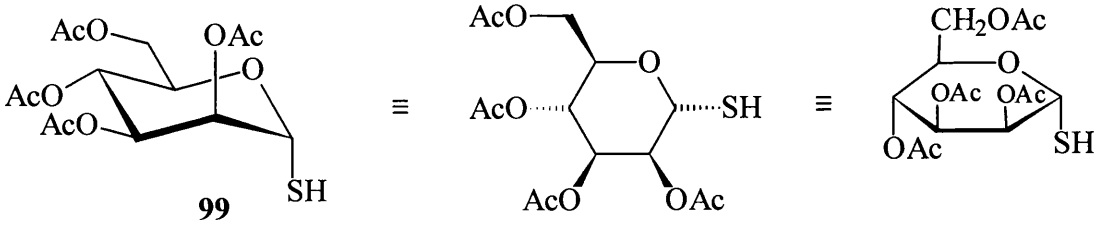
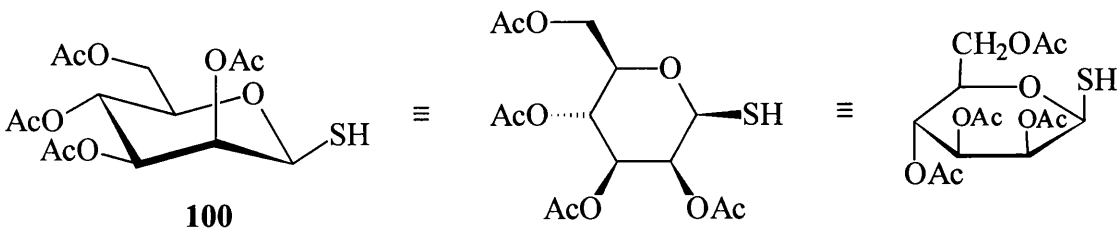


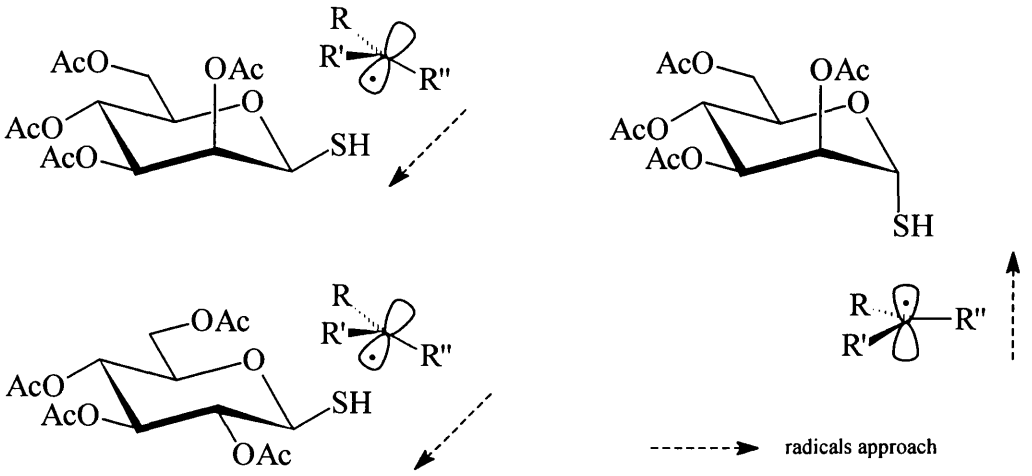
99



100

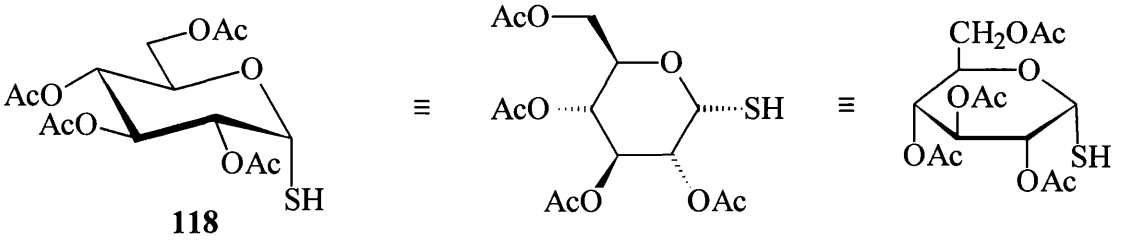
most effective. When a comparison is made between the glucose thiol **57**, galactose thiol **95** and the two mannose thiols **99** and **100**, it can be deduced that when the SH group is

equatorial, as in **57**, **95** and **100**, a high ee could be obtained. A possible reason for this is that the prochiral radical's approach to the thiol is partially hindered by the adjacent OAc group. In the case of the β-mannose thiol **100**, the adjacent OAc group is in an axial position (and therefore *cis* to the SH group), which causes more steric hindrance than an equatorial OAc group (Scheme 15). In the case of the α-mannose thiol **99**, the adjacent



Scheme 15

axial OAc group (which is *trans* to the SH group) provides no form of steric or electronic interaction with an approaching prochiral radical during enantioselective hydrogen-atom transfer, thus leading to low enantiomeric excesses (Scheme 15). To help understand the importance of the group adjacent to the SH moiety, the α-glucose thiol **118**[77a] could be prepared and investigated, as the adjacent OAc group should provide more steric hindrance and thus give larger enantiomeric excesses.

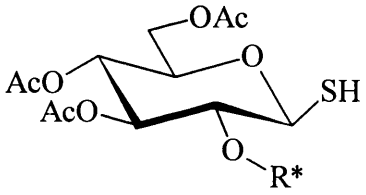


118

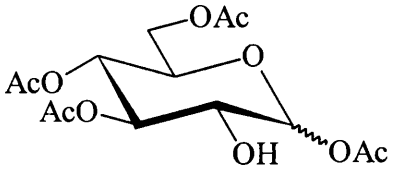
The pivaloyl-protected glucose thiol **98** was expected to provide more steric hindrance and therefore better enantioselectivity than the acetate protected glucose thiol

57. However, the enantiomeric excesses and yields obtained from these thiols were essentially identical. This suggests that because both the pivalate and acetate groups (adjacent to the SH group) are able to rotate fairly freely, they provide a similar amount of steric hindrance.

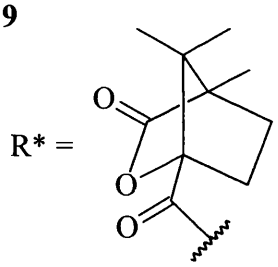
The glucose-derived thiol **119** could provide more steric hindrance and an increase in chirality in the region of the SH group because the camphanate group is larger and is also homochiral. Thiol **119** would be prepared in a similar way to the other homochiral carbohydrate thiols, but using the tetraacetate **119a**[77b] as a precursor. This tetraacetate **119a** could also be used to prepare other derivatives similar to **119**.



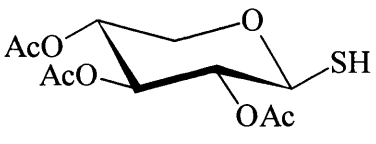
119



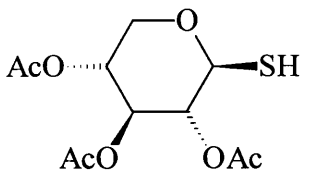
119a

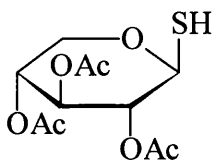


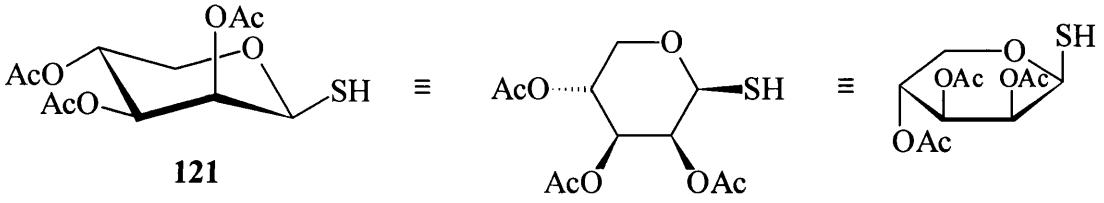
Another group that needs to be investigated, is the primary OAc group. Of the four acetate-protected thiols used in the hydrosilylation reactions, the three thiols which produced high enantiomeric excesses (*i.e.* **57**, **95** and **100**) have the equatorial SH group *cis* to the primary OAc group. This primary OAc group is further away from the SH group than the C-2 OAc group and therefore might not play an important role during enantioselective hydrogen-atom transfer. To confirm this, the thiols **120** and **121** which do not contain the primary OAc group, could be prepared and investigated.[77c] If the



120

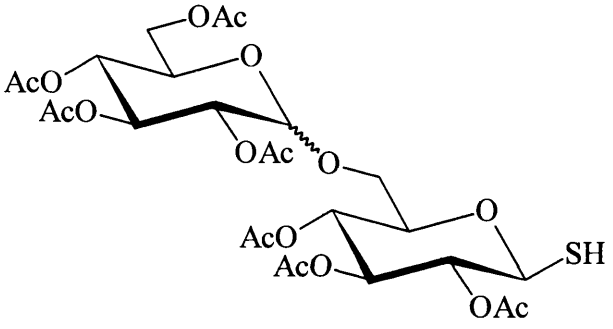




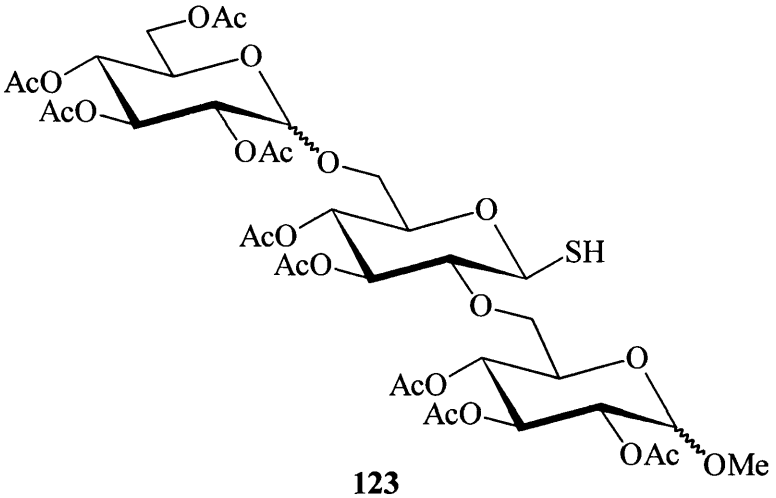


121

primary OAc group does play an important role during enantioselective hydrogen-atom transfer, then larger groups could be attached at this position. For example, disaccharide or trisaccharide derived thiols **122** and **123** could be investigated. An ideal thiol catalyst



122



123

for enantioselective radical-chain hydrosilylations would be one which produces high enantioselectivity during hydrogen-atom abstraction for both acyclic and cyclic systems and oligosaccharide-derived thiols might be used as such general catalysts. Thiol-functionalised cyclodextrins could also be investigated. Some of these thiols are currently being investigated within our group.

Control experiments

In this present work, many control experiments were carried out and will be highlighted in this section. It was important to ensure that no unwanted side reactions, moisture and other undesirable factors were unnecessarily affecting the radical-chain hydrosilylation reactions.

General points

The initial control experiments focused on proving the radical-chain and thiol-catalysed nature of these reactions. As previously stated, some of the hydrosilylation reactions were carried out in the absence of initiator or thiol. For example, when the hydrosilylation of isopropenyl acetate **18** with $PhMe_2SiH$ [eqn. (61)] was carried out in the absence of initiator, only a small amount (< 1 %) of the adduct **26** was obtained, thus proving the radical-chain nature of the reaction. A similar amount (< 1 %) of silane adduct **26** was obtained when the reaction was carried out in the absence of the thiol catalyst (but in the presence of initiator), hence indicating the thiol-catalysed nature of this reaction. A few other achiral thiols, such as pentafluorothiophenol **36**, were also investigated as potential catalysts but were found to be ineffective, as were phenol derivatives which, like thiols, have electron-deficient hydrogen.

The importance of a large group (such as a *gem*-dimethyl group) adjacent to the radical centre in the β-silylalkyl radical for obtaining high enantiomeric excesses was indicated by the experiments carried out with diketene **71**. Diketene, which does not have a large adjacent group produced the silane adduct with a low ee when reacted with Ph_3SiH (entry 34, Table 7).

Other factors which were investigated included changing the solvent, solvent volumes and the effects of moisture on the hydrosilylation reaction. In general, it was found that less polar solvents give the best results in terms of enantioselectivity. These hydrosilylation reactions were not affected by solvent dilution. For example, 2.5 mmol-scale alkene reactions usually involved 2.0 cm^3 of solvent, but when the solvent volume was increased to 4.0 cm^3, no change in the yield or ee was observed, although increasing the solvent volume allowed more effective stirring of heterogenous reaction mixtures.

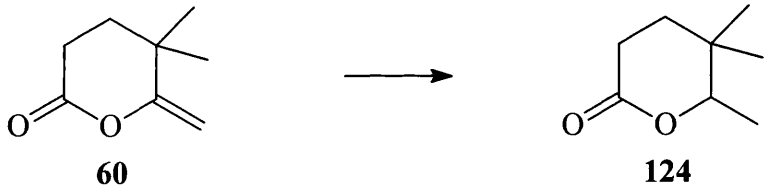
The hydrosilylation of lactone **60** with $PhMe_2SiH$ was carried out in the presence of water (0.5 equiv. based on **60**) using t-$C_{12}H_{25}SH$ as catalyst. The presence of this

water had a detrimental effect on the reaction and the silane adduct **83** was only obtained in 17 % yield. Normally all reactions were carried out in the complete absence of water.

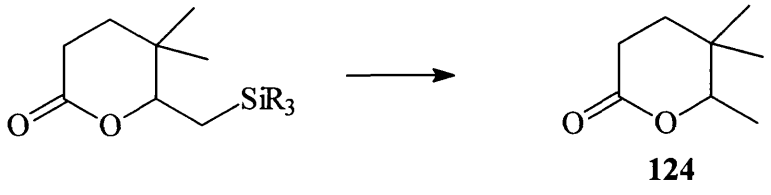
Similar reactions were carried out in the presence of ethanol. Here, the hydrosilylation of isopropenyl acetate **18** with $PhMe_2SiH$ using *t*-$C_{12}H_{25}SH$ as catalyst [eqn. (61)] was carried out in the presence of EtOH. It was thought that the presence of hydroxylic solvents might not be appropriate because of unwanted hydrogen bonding to the alkene or to the catalyst. However, in the presence of a small amount of EtOH (0.25 equiv. based on **18**) a 93 % yield of silane adduct **26** was obtained and a 70 % yield of **26** was obtained in the presence of 1.25 equiv. (based on **18**) of EtOH.

Side reactions

During a few hydrosilylation reactions of lactone **60**, a by-product was detected and isolated in very low yields; this by-product was the lactone **124**. This lactone could have been produced either by the simple reduction of the starting lactone **60** [eqn. (68)] or by the cleavage of the C-Si bond of the silane adduct [eqn. (69)]. Therefore, experiments were carried out to determine how this undesired compound had arisen. Lactone **124** was obtained in 5-7 % yield (as indicated by ^1H NMR analysis) in some hydrosilylation experiments.



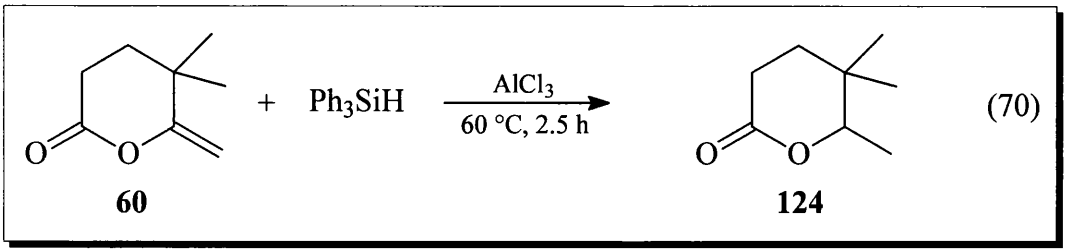
60 **124** (68)



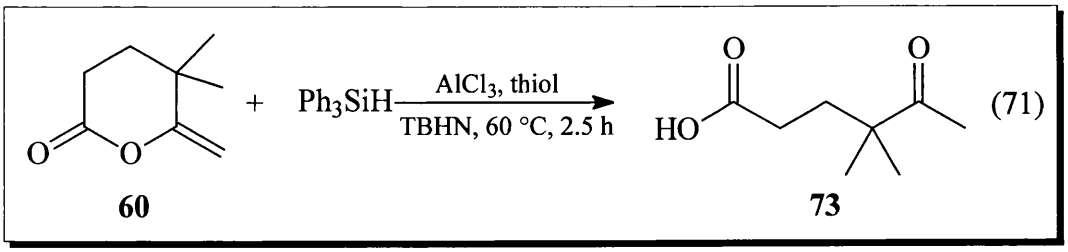
124 (69)

Lactone **124** was not always produced and appeared in only a very few hydrosilylation reactions, especially those involving Lewis acids (but still in low yield). A control experiment was carried out in the absence of thiol and initiator, but presence of $AlCl_3$. When the lactone **60** (0.35 g, 2.5 mmol) was stirred at 60 °C in the presence of

$AlCl_3$ (0.33 g, 2.5 mmol) and Ph_3SiH (0.85 g, 3.3 mmol) in dioxane (4.0 cm^3) for 2.5 h under nitrogen, the lactone **124** was isolated in 30 % yield [eqn. (70)]; *ca.* 70 % of the lactone **60** remained unchanged. In this reaction, the silane acts as a reducing agent promoted by Lewis acids.[78]



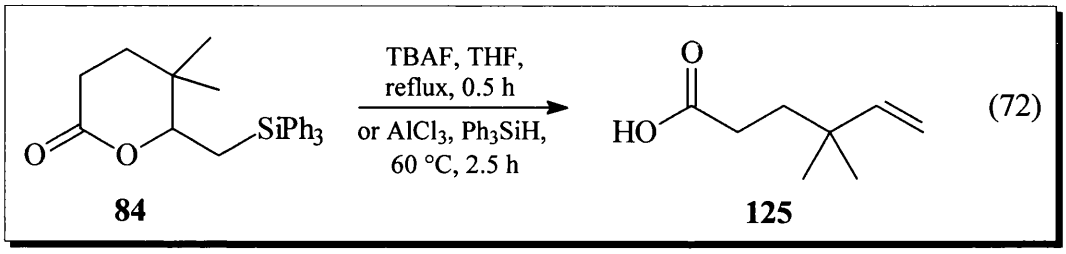
When the radical-chain hydrosilylation of lactone **60** with silane was carried out in the presence of a large concentration of Lewis acid (1 equiv. based on **60**) like $AlCl_3$ under the usual conditions, no silane adduct was ever formed. None of the starting lactone **60** remains at the end of the reaction, and a large amount of ketoacid **73** (hydrolysed lactone **60**) was formed [eqn. (71)]. It was thought that the lactone **60** remaining at the end of the reaction might have hydrolysed during the aqueous work-up, but this was not observed for reaction (70) where any unreacted lactone **60** remained unchanged after a similar aqueous work-up. Additionally, from this reaction, a small amount (3-5 %) of the lactone **124** was also obtained.



Attempts were made to produce the lactone **124** by cleavage of the C-Si bond. This cleavage might occur by a radical-chain mechanism involving some of the reagents used in the hydrosilylation reaction itself. A reaction was carried out in which the silane adduct **84** (1 equiv.) was stirred with TBHN initiator (0.05 equiv.) and *t*-$C_{12}H_{25}SH$ (0.05 equiv.) in dioxane solvent (4.0 cm^3) for 2.5 h at 60 °C. However, no lactone **124** was formed. No lactone was formed when Ph_3SiH (1.3 equiv.) was also present in

addition to the thiol.

Heterolytic pathways were then explored. Initial attempts involved stirring the silane adduct **84** with water (1 equiv.) and an acid catalyst (*p*-TsOH) in dioxane at 60 °C. In another experiment, Ph_3SiH was also present, but in none of these reactions was **124** formed. The silane adduct **84** (2.0 g, 5.0 mmol) was then stirred at room temperature with TBAF (1.0 M soln. in THF, 10 cm^3, 10 mmol) in CH_2Cl_2 (20 cm^3), but no reaction occurred. When this reaction with TBAF was repeated in refluxing THF for 30 min, **124** was not produced, but instead a Peterson elimination took place to give the alkene **125** in



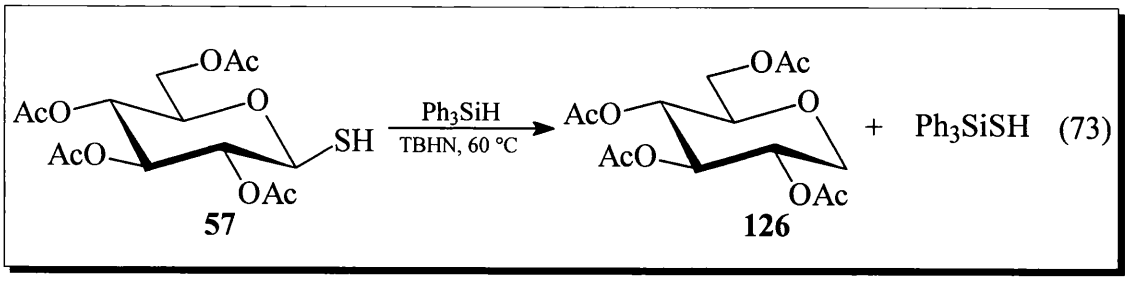
84 **125** (72)

55 % yield [eqn. (72)]. This alkene was also produced when the silane adduct **84** was stirred with Ph_3SiH and $AlCl_3$ in dioxane at 60 °C for 2.5 h in the same quantities employed for the reduction of lactone **60** [eqn. (70)].

Desulphurization of thiol catalysts

Another area of concern, which first became apparent during the DTBP-initiated low-temperature reactions, was the possibility of the *in situ* generation of racemic thiol. For example, when the lactone **60** (1 equiv.) in dioxane was added by syringe over a 30 min period to a stirred solution of Ph_3SiH (1.3 equiv.), glucose thiol **57** (0.05 equiv.) and DTBP (1 equiv.) in dioxane at room temperature, during exposure of the reaction mixture to UV light, the silane adduct **84** obtained was racemic. However, when the glucose thiol **57** in dioxane was added by syringe over 30 min to the lactone **60**, the silane adduct **84** was obtained with a 40 % ee. This is similar to the ee obtained when using **57** as catalyst under thermal conditions.

An experiment was carried out to determine whether a reaction occurs between the glucose thiol and Ph_3SiH in the presence of initiator [eqn. (73)]. When a solution of



the glucose thiol **57** (364 mg, 1.0 mmol), Ph_3SiH (313 mg, 1.2 mmol) and TBHN (8.70 mg, 0.05 mmol) in dioxane (2.0 cm^3) was stirred at 60 °C for 2.5 h under an atmosphere of nitrogen, the desulphurized thiol **126** was obtained in 91 % yield after purification by flash-column chromatography. The structure of the desulphurized glucose thiol **126** was confirmed by ^1H NMR.[79] Triphenylsilanethiol (Ph_3SiSH) will also be generated from this radical-chain reaction. When this reaction was repeated in the absence of TBHN initiator under otherwise identical conditions, no reaction takes place, hence indicating the radical-chain nature of the process.

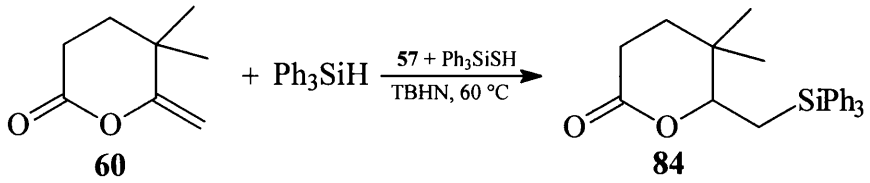
This simultaneous desulphurization of homochiral thiol and generation of achiral thiol is presumably responsible for the generation of racemic silane adduct **84** in the previously-mentioned photochemical reaction. The generation of achiral thiol might also be responsible for some of the very low enantiomeric excesses obtained with some of the other homochiral thiols. Less polar solvents like hexane might help to reduce this radical desulphurization reaction, because some thiols, like **57**, are sparingly soluble in hexane. Radical-chain desulphurization has also been carried out using Bu_3SnH in the presence of AIBN initiator.[24e]

Mixed thiol catalysis

As a result of the potential desulphurization of homochiral thiol accompanied by the *in situ* generation of achiral thiol, investigations of hydrosilylation reactions using a mixture of homochiral and achiral thiol catalysts were carried out. For these experiments, Ph_3SiH was used in conjunction with three prochiral cyclic alkenes; the glucose thiol **57** (2.5 mol %) together with achiral Ph_3SiSH (2.5 mol %) were used as catalysts. All the reactions followed the same standard procedure as described previously in Table 7. The results obtained show which of the two thiols has the greater influence.

The first hydrosilylation reaction investigated was with the lactone **60** in dioxane

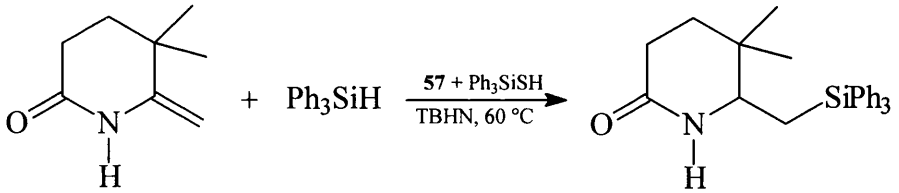
solvent [eqn. (74)] and the silane adduct **84** was obtained in 80 % yield with a 30 % ee.



60 **84** (74)

The same result was obtained using hexane as solvent. Adduct **84** was obtained in quantitative yields with both catalysts when used separately and with a 50 % ee (hexane solvent) and 40 % ee (dioxane solvent) with **57** as catalyst. With the thiol mixture, the glucose thiol **57** is clearly the more efficient catalyst because a 30 % ee was obtained. However, the drop in ee indicates that the Ph_3SiSH has a significant influence, especially in hexane solvent.

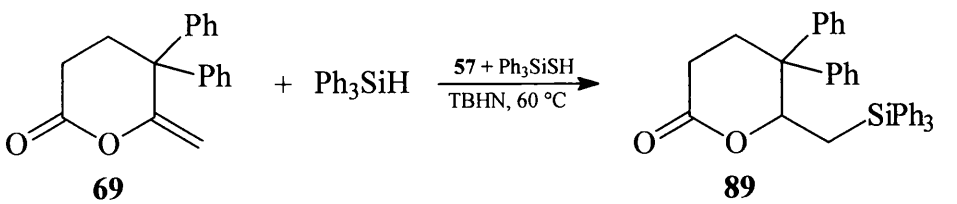
For the hydrosilylation of lactam **67** [eqn. (75)], the adduct **86** was obtained in 70 % yield and 6 % ee. Triphenylsilanethiol was the more efficient catalyst in this



67 **86** (75)

experiment, because the adduct obtained has a very low ee, although the yield is high. When the glucose thiol **57** alone was used as catalyst for this hydrosilylation under otherwise identical conditions, the adduct **86** was obtained in 31 % yield and 29 % ee.

The hydrosilylation of lactone **69** was also carried out in the presence of the mixed thiol catalysts in dioxane solvent [eqn. (76)]. The silane adduct **89** was obtained

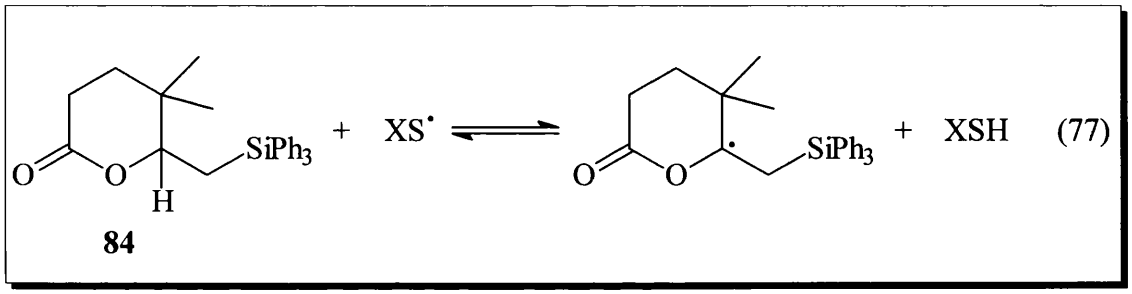


69 **89** (76)

in 79 % yield and 69 % ee. This result compares to the 88 % yield and 80 % ee obtained when the glucose thiol **57** alone was used as catalyst. The greater influence and efficiency of the glucose thiol **57** catalyst was expected because Ph_3SiSH is a poor catalyst for this hydrosilylation reaction (see Table 4).

Racemization of silane adducts

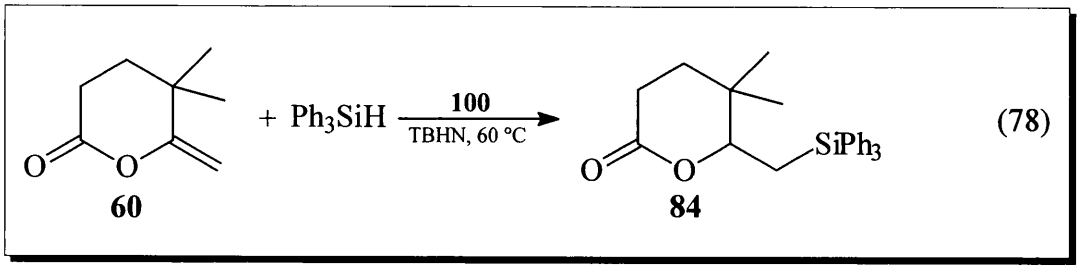
Another experiment was concerned with whether the hydrogen-atom transfer from the thiol to the prochiral radical was reversible under the reaction conditions [eqn. (77)]. If this were to happen, then a reduction of ee would occur below the value that would be obtained in the absence of reversibility. For these experiments, the enantiopure (*R*)-silane



adduct **84** (1.0 g, 2.5 mmol) was stirred with a solution of TBHN (0.022 g, 0.125 mmol), thiol (0.125 mmol) in benzene (4.0 cm^3) at 60 °C for 2.5 h under nitrogen. The crude product remaining was analysed by ^1H NMR spectroscopy to determine how much adduct **84** remained; it was isolated by flash-column chromatography and chiral-stationary-phase HPLC to determine whether any reduction of ee had occurred.

Two thiols were investigated in these experiments; Ph_3SiSH (5 mol %) and the glucose thiol **57** (5 mol %). The adduct **84** was retrieved in quantitative yields and 100 % ee when either thiol was present.

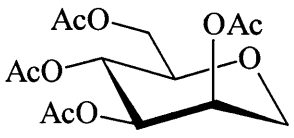
Large-scale hydrosilylation reaction



A hydrosilylation reaction was carried out to determine whether the asymmetric synthesis of **84** could be readily scaled up. The hydrosilylation of lactone **60** with Ph_3SiH using the β-mannose thiol **100** as the thiol catalyst was used for this experiment [eqn. (78)], chosen because the adduct **84** was obtained in quantitative yields and 76 % ee (hexane solvent) in the small scale reaction (2.5 mmol scale).

The large-scale hydrosilylation of lactone **60** was carried out on a 75 mmol scale (10.5 g of lactone **60**) in hexane solvent. The adduct **84** crystallizes out of the hexane solution during the 2.5 h reaction time period and at the end of the reaction, the majority (64 % yield) of the silane adduct (100 % ee) could be recovered by simple filtration and washed with hexane. The filtrate was concentrated *in vacuo* and the residue was purified by flash-column chromatography to give the remaining silane adduct **84** (14 % yield) with an ee of 17.5 % in favour of the (*S*)-enantiomer (overall yield 78 %, overall ee 74 %).

From this reaction, the thiol **100** catalyst could not be recycled and only the desulphurized thiol **127** was isolated. To prevent this desulphurization from occurring in



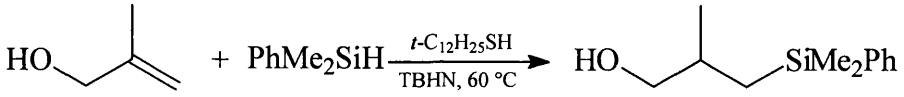
127

future experiments and hence re-isolating the thiol **100** catalyst, Ph_3SiH should not be used in excess. The structure of **127** was confirmed by ^1H NMR analysis.[80]

Hydrosilylation of miscellaneous alkenes

The experiments detailed in this section were carried out to investigate the hydrosilylation reaction on a variety of alkenes. All the hydrosilylation reactions followed the same procedure and the thiol catalyst (t-$C_{12}H_{25}SH$) was added by a syringe over a 2 h period.

The hydrosilylation of methallyl alcohol **128** with $PhMe_2SiH$ was carried out [eqn. (79)]. For this experiment, methallyl alcohol **128** (5.0 mmol),

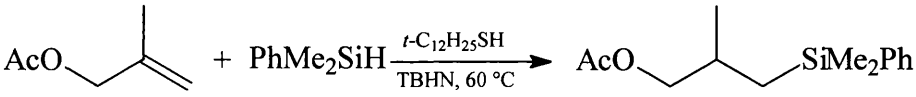


(79)

128 **129**

$PhMe_2SiH$ (6.5mmol) and TBHN (5 mol %) in hexane (4.0 cm^3) was stirred at 60 °C. *tert*-Dodecanethiol (5 mol %) in hexane (1.0 cm^3) was added over a 2 h period and then the reaction was left to stir for a further 0.5 h. At the end of the reaction, no silane adduct **129** was formed. A reason for this could be that the thiyl radical adds across the C=C double bond even though the thiol was added over a 2 h period.

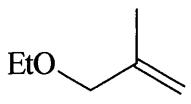
However, when the same reaction was carried out with methallyl acetate **130**[81] [eqn. (80)], the adduct **131** was isolated with a ~70 % yield. It is unclear why the



(80)

130 **131**

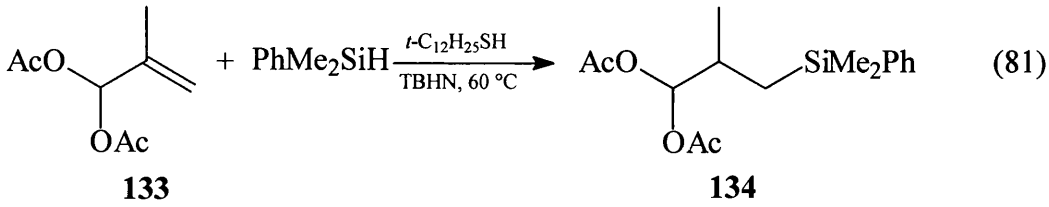
acetate-protected alcohol readily undergoes hydrosilylation. A hydrosilylation reaction with the ethoxide protected methallyl alcohol **132**[82] may be informative, because the CH_2O group in **132** should be as reactive towards hydrogen as that in **128**, but **132** lacks



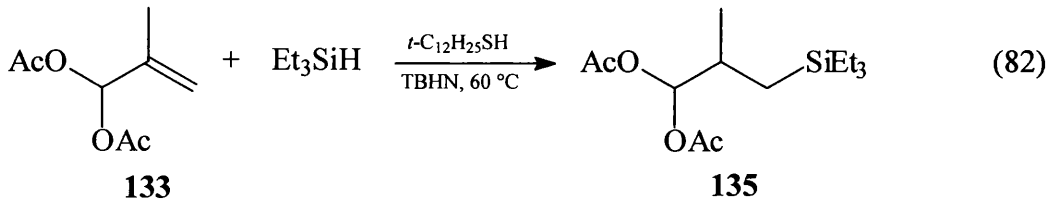
132

the hydroxyl group present in the latter. The CH_2O group in **130** is likely to be less reactive towards abstraction of hydrogen than those in **128** and **130**.

Another acyclic prochiral alkene used in these hydrosilylation experiments was 2-methyl-2- propen-1,1-diol diacetate **133**. This alkene was hydrosilylated with $PhMe_2SiH$ [eqn. (81)] and Et_3SiH [eqn. (82)]. Both the silane adducts **134** and **135** were isolated in ~30 % yields, lower than expected.

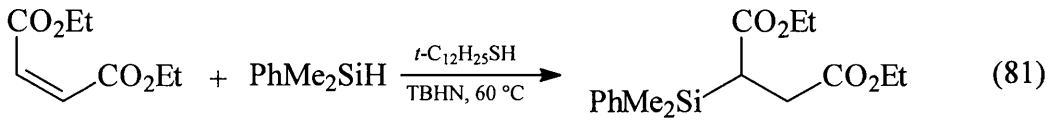


133 **134** (81)



133 **135** (82)

Alkenes with electron-withdrawing groups had not been investigated in this work. Therefore, the hydrosilylation of diethyl maleate **136** with $PhMe_2SiH$ catalysed by *t*-$C_{12}H_{25}SH$, following the usual procedure, was carried out [eqn. (83)]. Alkenes with

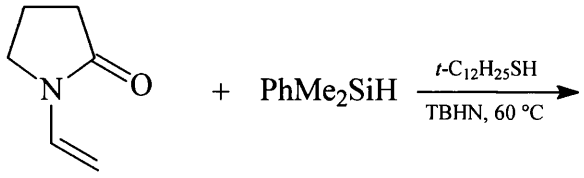


136 **137** (81)

electron-withdrawing groups should favour the silyl addition step because of favourable polar effects in the transition state. The silane adduct **137** was not isolated, but was identified by ^1H NMR analysis which indicated a yield of ~37 %. It was thought that a Lewis acid might help improve the yield, but when $LiBF_4$ (1 equiv. based on alkene) was added using DMF as solvent, no silane adduct was formed.

The hydrosilylation of *N*-vinyl pyrrolidinone **138** with $PhMe_2SiH$ was carried out following the usual procedure [eqn. (84)]. *N*-Vinyl pyrrolidinone is a polar alkene

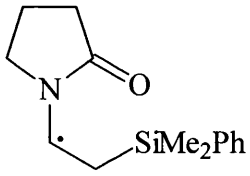
relatively insoluble in hexane, hence dioxane was used as solvent for this reaction.



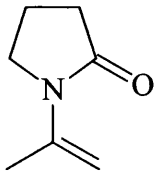
(84)

138 **139**

However, no silane adduct **139** was obtained, but instead an uncharacterised polymer was formed. This polymer was probably derived from the secondary β-silylalkyl radical **140**, which is more reactive than the usual tertiary radicals generated from all the other



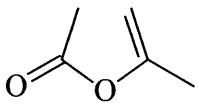
140



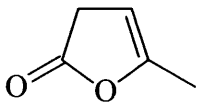
141

hydrosilylation experiments, and adds to the starting alkene. When this hydrosilylation reaction was carried out in the absence of the thiol catalyst under otherwise identical conditions, only this same polymer was generated. To reduce polymer formation the alkene **138** was added by syringe over a 2 h period (instead of the *t*-$C_{12}H_{25}SH$) which was all present initially. However, the polymer was still formed. The only way adduct could be obtained was to use hexane as solvent instead of dioxane. The alkene **138** appeared to be immiscible with hexane, even at 60 °C. In this way, the alkene concentration was further reduced and therefore favouring product formation by reaction of **140** with the thiol rather than with the starting alkene. The silane adduct **139** was isolated in 53 % yield under these conditions. An alkene that should not undergo polymerisation is 1-(1-methylethenyl)-2-pyrrolidinone **141**[83] and therefore should be investigated in future experiments.

The final alkene investigated was α-angelicalactone **142**, a cyclic version of isopropenyl acetate **18** and the only trisubstituted alkene to be studied in this work. $PhMe_2SiH$ was used as the silane in dioxane solvent and the reaction followed the usual

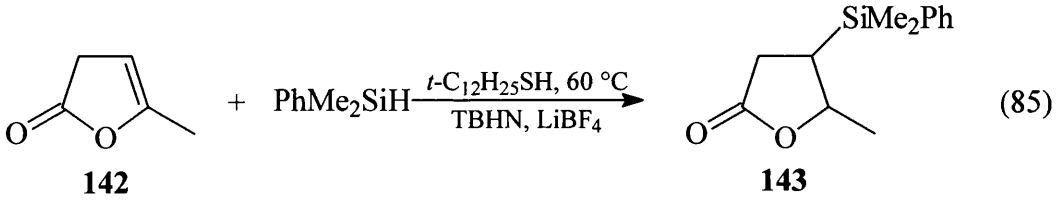


18



142

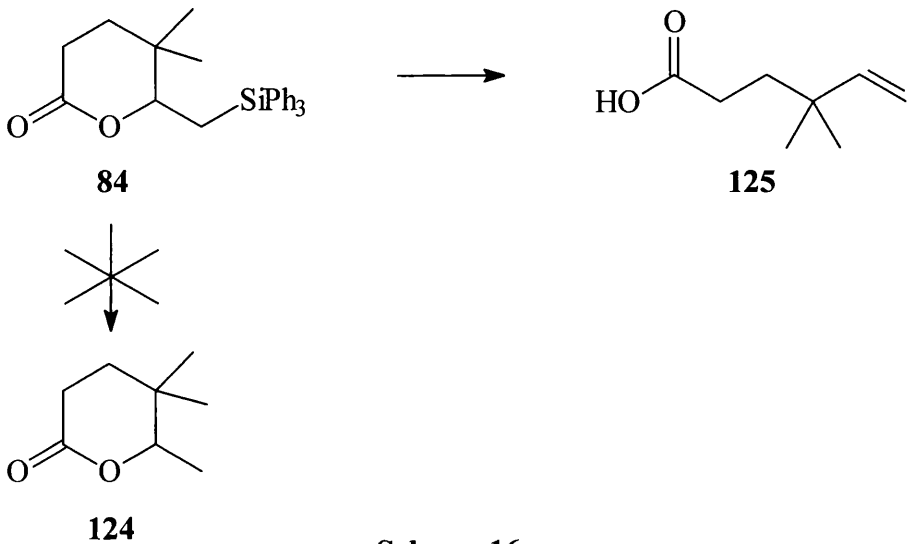
procedure [eqn. (85)]; the adduct **143** was isolated in ~10 % yield. This yield was increased slightly to ~20 % by adding $LiBF_4$ (1 equiv. based on alkene) when using DMF or sulpholan as solvent. Adduct **143** was obtained as *cis*- and *trans*-isomers, which were not isolated separately, but ^1H NMR analysis indicated that the *cis*-isomer was formed as the major product (*cis*: *trans* = *ca.* 2:1).



142 **143** (85)

Desilylation

The majority of the desilylation reactions were carried out on the silane adduct **84**. Initial attempts to desilylate adduct **84** using TBAF in refluxing THF or $AlCl_3$ and Ph_3SiH in dioxane at 60 °C were unsuccessful and instead produced only the Peterson elimination product **125** (Scheme 16) . Therefore, caution was required in any type of desilylation reaction on adduct **84**, which is prone to Peterson elimination. The silane

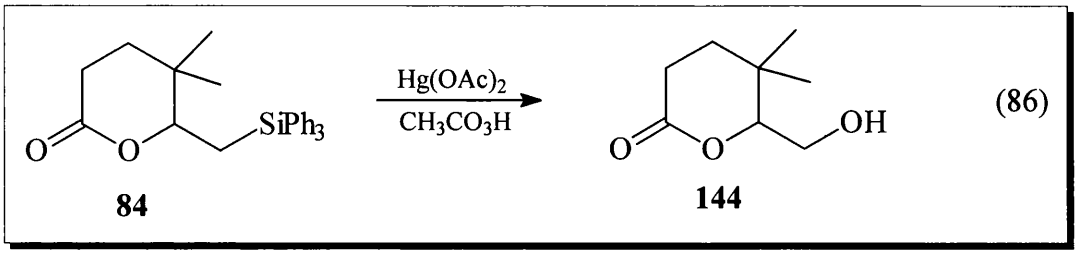


84 **125**

124

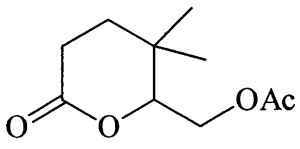
Scheme 16

adducts obtained from this work are most suited to the Fleming oxidation reaction [eqn. (47)].[47] The first Fleming method which was attempted used mercury acetate and peracetic acid [eqn. (86)]. Here, the mercury acetate removes a phenyl ring from the silicon atom, followed by oxidation of the remaining silicon moiety by peracetic acid.



84 **144** (86)

When the enantiopure (*R*)-adduct **84** (0.50 g, 1.25 mmol) was stirred at room temperature (after initial cooling in an ice-bath) with $Hg(OAc)_2$ (0.42 g, 1.31 mmol) in peracetic acid (40 % in AcOH, 10 cm^3, 65 mmol) and monitored by tlc and ^1H NMR analysis, ~70 % of adduct **84** still remained after 2 days. A similar amount still remained even after stirring the heterogeneous reaction mixture for 7 days. In Fleming's work, 1 equiv. of $Hg(OAc)_2$ was used in the desilylation of $SiMe_2Ph$ adducts.[47b] Therefore, the above reaction was repeated in the presence of a larger amount of $Hg(OAc)_2$ (1.31 g, 4.13 mmol, 3.3 equiv.). After 2 days, no adduct **84** remained in the reaction mixture, however, apart from the alcohol **144** being produced, a moderate amount (30 %) of the Peterson alkene **125** was also produced. To minimise the amount of **125** being obtained, $Hg(OAc)_2$ was added in 3 equal portions (1.1 equiv.) every 2 days. This slightly modified procedure produced no **125**, but due to the prolonged reaction time, about half of the alcohol **144** was converted to the acetate **145**. The combined yields of **144** and **145** isolated from this experiment



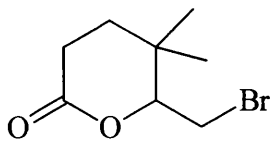
145

was 63 %. In a separate experiment, the acetate **145** was isolated in 48 % yield starting with racemic silane adduct **84**. In this experiment, the alcohol **144** was not isolated

because it was not identified at the time. These relatively high yields obtained were only possible in the absence of the aqueous work-up recommended by Fleming.[47b] The aqueous work-up causes the alcohol **144** to decompose and therefore the excess peracetic acid was cautiously removed by co-evaporation with toluene *in vacuo*. Chiral-stationary-phase HPLC analysis of the two products confirms that the desilylation occurred with retention of configuration at the chiral centre.

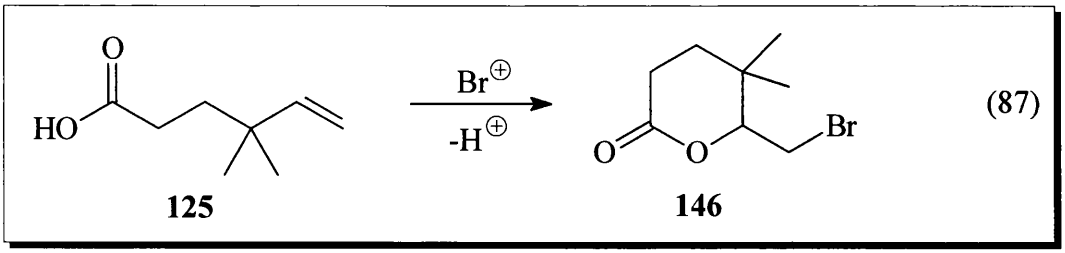
Another Fleming method which was investigated employed bromine instead of mercury acetate as the electrophile. In this reaction, sodium acetate (10 % of peracetic acid) was be added as a buffer, but from these experiments, the results obtained were identical to those in the absence of sodium acetate. In a typical experiment, the adduct **84** (0.5 g, 1.25 mmol) was stirred with bromine (0.30 g, 1.88 mmol), peracetic acid (40 % in AcOH, 10 cm^3, 65 mmol), glacial acetic acid (3 cm^3) and sodium acetate (1 g) (optional) for 1 day. Indications by tlc shows that the reaction could be over within 7-8 h. The yields obtained from this experiment were generally lower (overall 20-30 %). The alcohol **144** was being produced in a greater amount than the acetate **145** (about 2:1, respectively) which could be due to the shorter reaction time period.

In another Fleming method,[47b] KBr (4 equiv.) was used instead of Br_2, but the yield of product still remained low. This has some advantage over the Br_2 method because no acetate **145** was formed however long the reaction time was. Interestingly, no Peterson alkene **125** is generated even with large concentrations of KBr or Br_2.



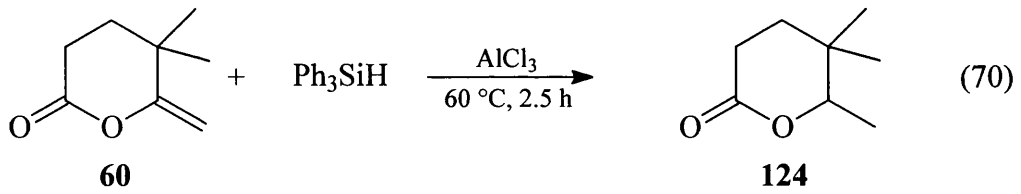
146

However, a large amount of the bromide **146** was generated. Chiral-stationary-phase HPLC analysis of this bromide always indicated a racemic compound, even when starting with enantiopure (*R*)-silane adduct **84**. The alcohol **144** and acetate **145** were always obtained with complete retention of configuration at the chiral centre. Therefore, it appears that the bromide **146** was produced *via* the Peterson alkene **125** [eqn. (87)]. This also explains why the alkene **125** was never obtained. One possible way to confirm this

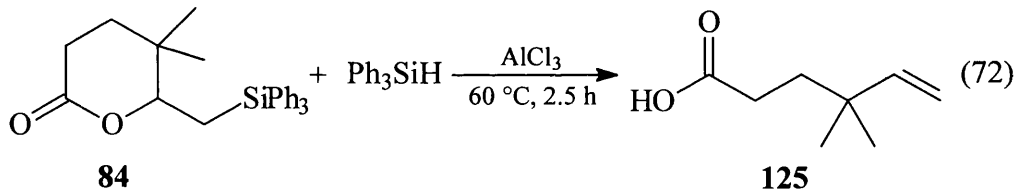


125 146 (87)

would be to react **125** with *N*-bromosuccinimide. A similar reaction might also explain how the lactone **124** could be generated from the silane adduct **84** [eqn. (69)]. As previously mentioned, the lactone **60** could be reduced in the presence of a Lewis acid such as $AlCl_3$, and Ph_3SiH [eqn. (70)]. It was thought that the desilylation of the silane

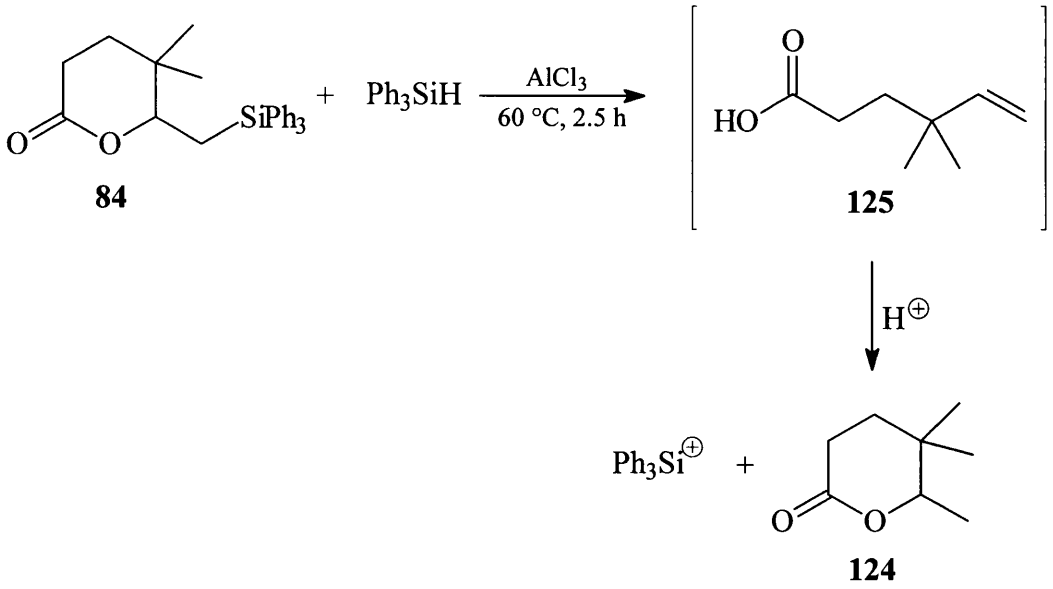


60 **124** (70)



84 **125** (72)

adduct **84** would also produce lactone **124** when using $AlCl_3$ and Ph_3SiH, but instead the Peterson alkene **125** was formed [eqn. (72)]. Acid-catalysed cyclisation of the ketoacid might occur in the presence of silane to give the lactone **124** (Scheme 17).



84 **125** **124**

Scheme 17

Although some problems do arise from the Br_2 and KBr mediated reactions, the $Hg(OAc)_2$ method works well and gives a high conversion of the silane adduct to alcohol and acetate. Many modifications of the Fleming oxidation reaction have been reported and these should be investigated in future experiments.

Experimental

X-Ray crystallography

Data were collected on a Nicolet R3mV diffractometer at 20 °C using graphite-monochromated Mo-K_α radiation. Three standard reflections were monitored throughout the data collection and these showed no variation with time. The data were corrected for Lorentz and polarisation effects. The structures were solved by direct methods (SHELXL-86)[84] and developed using alternating cycles of least-squares refinement and difference-fourier synthesis (SHELXL-93).[85] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in idealised positions and assigned a common isotropic thermal parameter.

Crystal data for (*R*)-(-)-5,5-dimethyl-6-triphenylsilylmethyltetrahydropyran-2-one 84 $C_{26}H_{28}O_2Si$, M = 400.6, orthorhombic, space group $P2_12_12_1$, a = 9.779(2), b = 11.404(2), c = 20.049(4) Å, U = 2236 Å^3, (by least-squares refinement of diffractometer angles for 17 reflections in the range 16 < 2θ < 24°, λ= 0.71073 Å), Z = 4, F(000) = 856, D_c = 1.19 g cm^{-3}, μ(Mo-K_α) = 1.24 cm^{-1}, colourless block 0.70 x 0.25 x 0.22 mm. Full matrix least-squares refinement on 262 parameters gave R = 0.0471 (R_w = 0.1178) for 2784 independent reflections [$I > 2\sigma(I)$] and R = 0.0626 (R_w =0.1339) for all 3441 independent reflections in the range 5 ≤ 2θ 50°. The absolute configuration was determined using SHELXL-93 precedures [absolute structure parameter = -0.2(2)]. The final electron density map was featureless with the largest peak 0.25 e Å^{-3}.

Crystal data for 2,3,4,6-tetra-O-acetyl-1-thio-β-D-mannopyranose 100. $C_{14}H_{20}O_9S$, M = 364.4, monoclinic, space group $P2_1$, a = 9.701(2), b = 8.654(3), c = 11.331(3) Å, U = 943 Å^3, (by least-squares refinement of diffractometer angles for 25 reflections in the range 16 < 2θ < 25°, λ= 0.71073 Å), Z = 2, F(000) = 384, D_c = 1.28 g cm^{-3}, μ(Mo-K_α) = 2.12 cm^{-1}, colourless plate 0.76 x 0.72 x 0.14 mm. Full matrix least-squares refinement on 218 parameters gave R = 0.0497 (R_w = 0.1198) for 1414 independent reflections [$I > 2\sigma(I)$] and R = 0.0721 (R_w =0.1488) for all 1775 independent reflections in the range 5 ≤ 2θ 50°. The absolute configuration was determined using SHELXL-93 precedures [absolute structure parameter = 0.03(6)]. The final electron density map was featureless

with the largest peak 0.28 e $Å^{-3}$.

General procedures

All NMR spectra were recorded using a Varian VXR-400 (400 MHz for ^1H), XL-200 (200 MHz for ^1H) or a Bruker AC 300 (300 MHz for ^1H) instrument; the solvent was $CDCl_3$. In some experiments, tetramethylsilane was present as an internal standard; otherwise chemical shifts are quoted relative to the residual proton in deuteriochloroform (δ_H 7.25). Coupling constants *J* are given in Hz. NMR data recorded using the Varian XL-200 MHz and the Bruker AC-300 MHz instruments will be indicated as such; otherwise all NMR data reported were recorded using the Varian VXR-400 instrument.

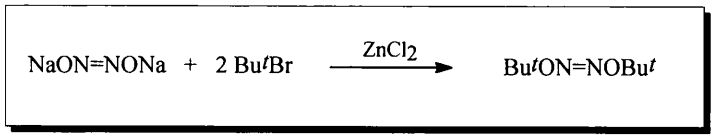
Infrared (IR) spectra were recorded on Perkin Elmer 983G or FT-IR 1600 spectrometers as liquid films or Nujol mulls, using KBr plates. Only the major peaks are reported (in cm^{-1}) for the IR spectra. Mass spectra were obtained using EI (electron impact) ionisation on a VG 7070H and positive APCI (atmospheric pressure chemical ionisation) on a Micromass Quattro LC instruments at University College. Only the major peaks are reported with the (%) population of fragments given in the parentheses.

Elemental analyses were performed by the University College Chemistry Department Microanalytical Service. Melting points were determined in capillary tubes using a Büchi Model 510 melting point appparatus or a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using an AA Series Polaar 2000 automatic polarimeter instrument by Optical Activity Ltd using a 1 dm pathlength cell.

All reactions were performed using oven dried glassware under an atmosphere of nitrogen or argon, unless otherwise stated. All solvents and reagents were purified by standard methods. Petroleum refers to the fraction b.p. 40-60 °C and ether implies diethyl ether. HPLC grade (>95 %) hexane was used in all the hydrosilylation experiments.

The progress of reactions was monitored by thin-layer chromatography, which was performed on Merck Kieselgel 60 F_{254} aluminium-backed pre-coated plates. Detection was first made by ultraviolet light (254 nm), then with iodine or charring with anisaldehyde stain which was prepared from anisaldehyde (8.0 cm^3), conc. H_2SO_4 (8.0 cm^3), glacial acetic acid (8.0 cm^3) in absolute ethanol (350 cm^3). Flash chromatography was performed by using Merck Kieselgel 60 (230-400 mesh).

Di-*tert*-butyl hyponitrite (TBHN)[50]

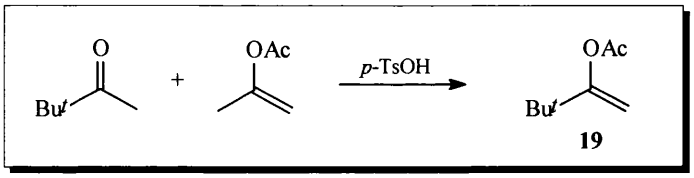


A stirred solution of anhydrous zinc chloride (2.5 g, 20 mmol) and *tert*-butyl bromide (13.0 g, 95 mmol) in dry ether (11 cm^3) under an atmosphere of nitrogen was cooled to 0 °C in an ice-bath. Sodium hyponitrite (2.0 g, 24 mmol) was added in a single portion and the mixture was further stirred for 30 min at 0 ° C, then stoppered and placed in a fridge at 4 °C overnight. After removal of the precipitated NaBr by filtration through Celite, the organic filtrate was washed with water (2 x 10 cm^3), with brine (10 cm^3) and dried over $MgSO_4$. The solvent and most of the excess *tert*-butyl bromide was evaporated under reduced pressure and the residual semi-solid was recrystallized from methanol to afford the product as a white crystalline solid (1.2 g, 41 %), m.p. 80-81 °C (lit.[51] m.p. 82 °C).

δ_H : 1.36 (9H, s, Bu^t).

Preparation of prochiral acyclic alkenes

2-Acetoxy-3,3-dimethylbutene 19[52]

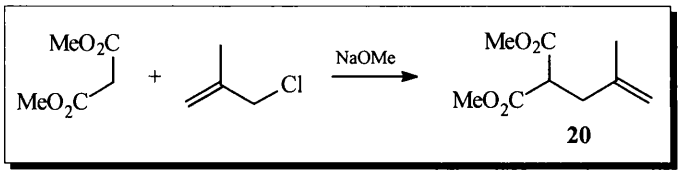


A stirrred solution of pinacolone (38.1 g, 380 mmol), isopropenyl acetate (78.1 g, 780 mmol) and *p*-toluenesulphonic acid (2.3 g, 12.2 mmol) was heated below reflux for 24 h under nitrogen, ensuring that materials boiling below 90 °C were continuously removed by distillation. The resulting mixture was diluted with petroleum (100 cm^3) and then poured into saturated aqueous $NaHCO_3$ (100 cm^3). Solid $NaHCO_3$ was added to make the solution neutral (litmus). The organic layer was washed with brine (2 x 100 cm^3), dried over $MgSO_4$ and then the solvent was evaporated under reduced pressure. The crude material was distilled under reduced pressure to afford the product as a colourless oil (21.5 g, 40 %), b.p. 44-45 °C/14 Torr (lit.[52] b.p. 140-141°C).

δ_H : 1.05 (9H, s, Bu^t), 2.13 (3H, s, $COCH_3$), 4.59 (1H, d, *J* 2.0, vinyl CH), 4.83 (1H, d, *J* 1.99, vinyl CH).

δ_C : 21.0, 27.7, 36.0, 99.0, 162.5, 169.1.

Dimethyl (2-methylallyl)malonate 20



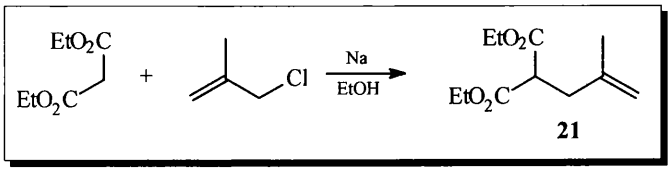
Dimethyl malonate (46.8 g, 0.35 mol) was added to a solution of sodium methoxide (95%, Aldrich) (20.1 g, 0.35 mol) in methanol (200 cm^3) and stirred for 20 min at room temperature. This reaction mixture was then cooled to 0 °C, methallyl chloride (32.8 g, 0.35 mol) was added and the mixture was then heated under reflux for 2 h. A white precipitate was formed during this time. After 2 h, the reaction mixture was allowed to cool to room temperature and diluted with ether (100 cm^3). The ether layer was washed successively with water (100 cm^3), saturated brine (100 cm^3) and dried over $MgSO_4$. The crude product was distilled under reduced pressure (40.1 g, 60 %), b.p. 40 °C/0.01 Torr. Found : C, 57.76; H, 7.56. $C_9H_{14}O_4$ requires C, 58.05; H, 7.58 %.

δ_H : 1.73 (3H, s, CH_3), 2.6 (2H, d, *J* 7.9, CH_2), 3.61 (1H, t, *J* 7.8, CH),
3.72 (6H, s, CO_2Me), 4.70 (1H, brs, vinyl CH), 4.77 (1H, brs, vinyl CH).

δ_C : 22.3, 36.6, 50.3, 52.6, 112.4, 141.6, 169.5.

The product was difficult to purify by distillation, but the yield based on the ^1H NMR spectrum of the crude material was 80 %.

Diethyl (2-methylallyl)malonate 21



Sodium (4.6 g, 0.2 mol) was cut into small pieces and carefully added to absolute ethanol (180 cm^3). When all the sodium had dissolved, the solution was cooled to 0 °C diethyl malonate (73.6 g, 0.46 mol) was added dropwise and the mixture was then stirred for 20 min. Methallyl chloride (41.7 g, 0.46 mol) was added dropwise and the solution was stirred and heated under reflux for 2 h. During this time, a white precipitate (NaCl) was formed. The apparatus was arranged for distillation and, ethanol (150 cm^3) was removed by distillation. The remaining mixture was diluted with ether (100 cm^3) and washed

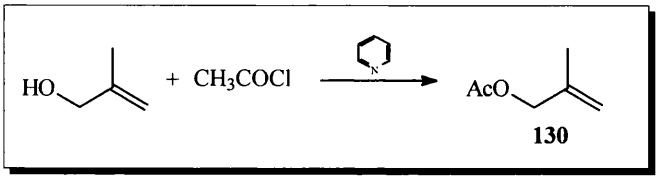
successively with water (100 cm^3), saturated brine (100 cm^3) and dried over $MgSO_4$. The solvent was evaporated and the residual oil was purified by distillation under reduced pressure to afford the product as a colourless oil (47.0 g, 48 %),

b.p. 54-56 °C/0.4 Torr (lit.[53] b.p. 82-86 °C/1.0 Torr).

δ_H : 1.22 (3H, apparent t, *J* 7.1, CO_2Et), 1.71 (3H, s, CH_3),
2.58 (2H, d, *J* 7.86, CH_2), 3.54 (1H, t, *J* 7.8, CH), 4.15 (2H, q, *J* 7.1, CO_2Et),
4.69 (1H, brs, vinyl CH), 4.75 (1H, brs, vinyl CH).

δ_C : 14.0, 22.2, 36.4, 50.4, 61.3, 112.2, 141.6, 169.0.

Methallyl acetate 130[80]



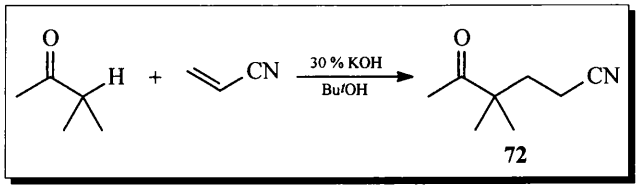
130

A solution of methallyl alcohol (17.1 g, 0.23 mol) in pyridine (50 cm^3) was cooled to 5 °C and then acetyl chloride (13.4 g, 0.17 mol) was added dropwise. The resulting mixture was stirred for 15 min and then poured into water (40 cm^3) and extracted with ether (3 x 40 cm^3). The combined ether layers were washed with 2 M HCl (3 x 30 cm^3) and then dried over $MgSO_4$. Careful removal of the solvent under reduced pressure afforded the crude material as a yellow oil which was purified by distillation to afford the product as a colourless oil (11.4 g, 59 %), b.p. 123-124 °C (lit.[80] b.p. 123-124 °C).

δ_H : 1.74 (3H, s, CH_3), 2.08 (3H, s, Ac), 4.47 (2H, s, CH_2), 4.91 (1H, s, vinyl CH),
4.96 (1H, s, vinyl CH).

Preparation of prochiral cyclic alkenes

4,4-Dimethyl-5-oxohexanenitrile 72[62]



72

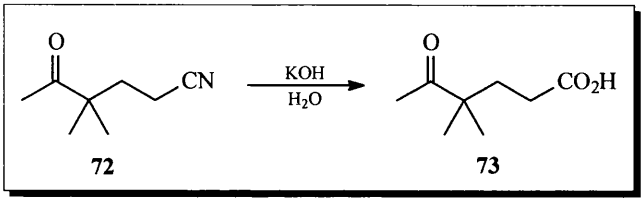
To a stirred solution of 3-methylbutan-2-one (21.5 g, 0.25 mol), *t*-butyl alcohol (2.2 g, 0.03 mol) and 30 % KOH in MeOH solution (6.0 cm^3) under an atmosphere of nitrogen, acrylonitrile (15.9 g, 0.3 mol) was added dropwise over 30 min, ensuring the

reaction temperature did not exceed 40 °C (using an ice-bath). The reaction mixture was stirred for a further 4 h at room temperature, then was purified by distillation under reduced pressure to afford the product as a colourless oil (21.4 g, 62 %),

b.p. 70 °C/0.2 Torr (lit.[62] b.p. 126-127 °C/15.0 Torr).

δ_H: 1.16 (6H, s, CMe_2), 1.87 (2H, m, $C\underline{H}_2CMe_2$), 2.12 (3H, s, CH_3),
2.25 (2H, m, CH_2CN).

4,4-Dimethyl-5-oxohexanoic acid 73[62]

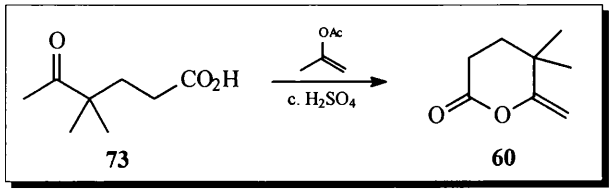


72 73

A stirred solution of the ketonitrile **72** (21.4 g, 0.15 mol) and potassium hydroxide pellets (29.0 g, 0.53 mol) in water (140 cm^3) was heated under reflux for 2-3 h until evolution of ammonia had ceased. After cooling, the reaction mixture was acidified with conc. HCl, then extracted with ether (3 x 75 cm^3). Combined ether extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the product as a white solid (23.5 g, 99 %). Before acidification, the reaction mixture was washed with ether (75 cm^3) and discarded, to remove any organic impurities, (lit.[62] m.p. 46-47 °C).

δ_H: 1.13 (6H, s, CMe_2), 1.85 (2H, m, $C\underline{H}_2CMe_2$), 2.13 (3H, s, CH_3),
2.25 (2H, m, CH_2CO_2).

5,5-Dimethyl-6-methylenetetrahydropyran-2-one 60



73 60

The ketoacid **73** (200 g, 1.27 mol), isopropenyl acetate (380 g, 3.80 mol), and conc. H_2SO_4 (3-4 drops) were placed in a flask which was arranged for distillation and fitted with a short vigreux column. The mixture was stirred and heated so that slow distillation occurred and the material boiling at 55-59 °C (~ 200 cm^3) was collected over 2.5 h. The reaction mixture was transferred to a high vacuum distillation apparatus and the crude product was distilled to give the pure product as a colourless oil (125 g, 70 %),

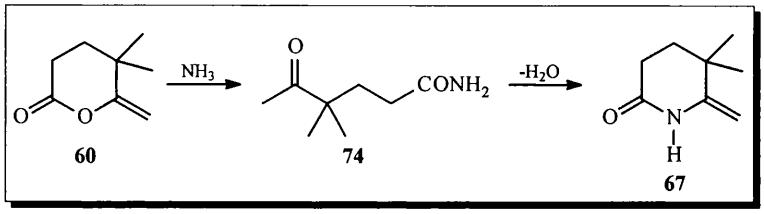
b.p. 42-44 °C/0.1 Torr (lit.[62] b.p. 95-96 °C/10 Torr).

m/z (EI) 140 (M^+, 54), 112 (M^+-CO, 36), 96 (M^+-CO_2, 53), 70 (59), 44 (CO_2^+, 100).

δ_H: 1.20 (6H, s, CMe_2), 1.68 (2H, t, *J* 7.2, $C\underline{H}_2CMe_2$), 2.64 (2H, t, *J* 7.2, CH_2CO), 4.34 (1H, d, *J* 2.0, vinyl CH), 4.62 (1H, d, *J* 2.0, vinyl CH).

δ_C: 25.9, 27.1, 31.8, 32.6, 91.2, 163.2, 167.8.

5,5-Dimethyl-6-methylenepiperidin-2-one 67[62]



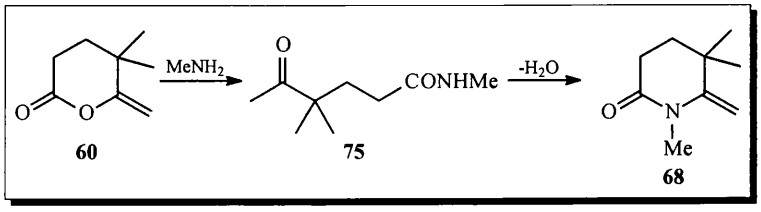
Using a dry ice condenser, liquid ammonia (20 cm^3) was added to a flask containing the lactone **60** (20.0 g, 0.14 mol) with stirring at room temperature. The mixture instantaneously became a white solid. After the evaporation of ammonia, the unpurifed ketoamide **74** was azeotropically dehydrated using a Dean-Stark apparatus with toluene as solvent. The toluene was then evaporated under reduced pressure and the solid residue remaining was recrystallized from CH_2Cl_2 / hexane to afford the product as white flaky crystals (15.7 g, 80 %), m.p. 108-109 °C (lit.[62] m.p. 108-109 °C).

m/z (APCI) 173 (3), 172 (9), 158 (6), 141 (M^++2, 17), 140 (M^++1, 100), there are very few fragments below and above the M^+ ion.

δ_H: 1.15 (6H, s, CMe_2), 1.59 (2H, t, *J* 6.8, $C\underline{H}_2CMe_2$), 2.44 (2H, t, *J* 6.8, CH_2CO), 4.12 (1H, d, *J* 1.1, vinyl CH), 4.25 (1H, d, *J* 1.1, vinyl CH), 8.91 (1H, brs, NH).

δ_C: 27.0, 28.6, 32.3, 33.4, 89.5, 150.1, 171.0.

***N*-Methyl-5,5-dimethyl-6-methylenepiperidin-2-one** or **1,5,5-trimethyl-6-methylenepiperidin-2-one 68**



Using a dry ice condenser, methylamine (15 cm^3) was added to a flask containing the lactone **60** (15.0 g, 0.11 mol) with stirring at room temperature. The mixture was stirred

at room temperature until all excess methylamine had evaporated (2-3 h). The unpurified ketoamide **75** should then be azeotropically dehydrated using a Dean-Stark apparatus with toluene as solvent. The unpurified ketoamide **75** also undergoes spontaneous dehydration to afford the product as a colourless oil (14.1 g, 86%) when distilled under reduced pressure using a short-path apparatus (b.p. 50 °C/0.02 Torr).

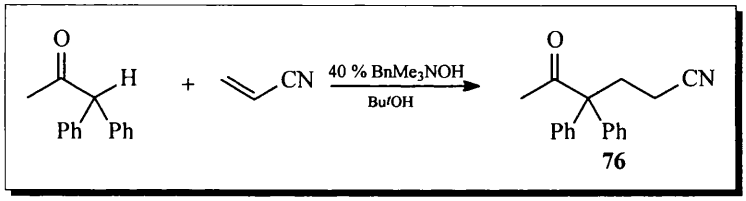
Found : C, 70.22; H, 9.86; N, 9.23. $C_9H_{15}NO$ requires C, 70.55; H, 9.87; N, 9.14 %.

m/z (APCI) 176 (M^++ Na, 1), 173 (8), 172 (49), 155(M^++2, 35), 154 (M^++1, 100), 141 (15).

δ_H : 1.13 (6H, s, CMe_2), 1.58 (2H, t, *J* 7.0, CH_2CMe_2), 2.50 (2H, t, *J* 7.0, CH_2CO), 3.10 (3H, s, NMe), 4.30 (2H, s, vinyl CH).

δ_C : 27.7, 29.4, 31.0, 33.2, 33.9, 90.2, 154.2, 169.2.

4,4-Diphenyl-5-oxohexanenitrile 76[63]



76

To a stirred solution of 1,1-diphenylacetone (25.0 g, 0.12 mol), *t*-butyl alcohol (81.0 cm^3) and a solution of 40 % aqueous benzyltrimethylammonium hydroxide (2.0 cm^3) under an atmosphere of nitrogen, acrylonitrile (7.6 g, 0.14 mol) was added dropwise over 30 min, ensuring the reaction temperature did not exceed 30 °C (using an ice-bath). The reaction mixture was stirred for a further 2 h at room temperature, followed by stirring at 38-45 °C for 1 h ensuring that the reaction mixture is weakly basic by adding more catalyst (universal indicator paper). It was then cooled, neutralized with conc. sulphuric acid and the solid which had separated during the reaction was filtered and dried under reduced pressure to afford the product (28.2 g, 88 %),

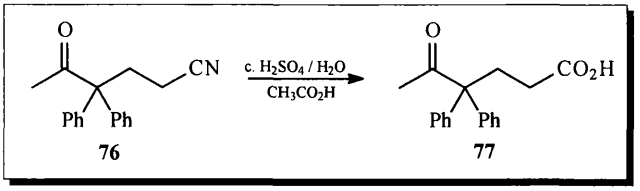
(lit.[63] m.p. 113-115 °C).

300 MHz ^{1}H NMR

δ_H : 2.00-2.04 (2H, m, CH_2CPh_2), 2.02 (3H, s, CH_3), 2.69 (2H, m, CH_2CN), 7.27-7.45 (10 H, m, Ph).

If desired, the crude product can be recrystallized from isopropanol.[63]

4,4-Diphenyl-5-oxohexanoic acid 77[63]

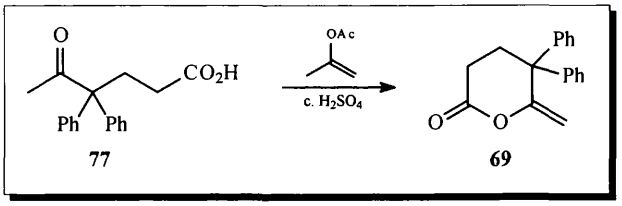


A stirred solution of the ketonitrile **76** (28.2 g, 0.11 mol), conc. H_2SO_4 (41 cm^3), water (55 cm^3) and glacial acetic acid (182 cm^3) was heated for 1.5 h under reflux during which time the solid nitrile dissolved. After cooling the reaction mixture, water (720 cm^3) was added with stirring which caused the product to crystallize out of solution. The product was separated by filtration, washed with water and dried to afford the acid as a white solid (29.1 g, 93 %), (lit.[63] m.p. 137.5-139 °C).

300 MHz ^{1}H NMR

δ_H: 2.08 (3H, s, Me), 2.10 (2H, m, CH_2CPh_2), 2.66 (2H, m, CH_2CO_2)
3.61 (1H, brs, OH), 7.14-7.43 (10H, m, Ph).

5,5-Diphenyl-6-methylenetetrahydropyran-2-one 69[63]



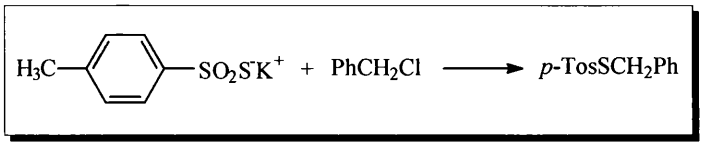
The ketoacid **77** (30.2 g, 0.12 mol), isopropenyl acetate (36.0 g, 0.36 mol) and conc. H_2SO_4 (2-3 drops) were placed in a flask which was arranged for distillation and fitted with a short vigreux column. The mixture was heated so that slow distillation occurred and the material boiling at 55-59 °C (~ 25 cm^3) was collected over 2.5 h. The reaction mixture was transferred to a high vacuum (0.02 Torr) distillation apparatus to remove volatile impurities at room temperature. The solid residue remaining was recrystallized from CH_2Cl_2/hexane or EtOAc/hexane to afford the pure product as a white crystalline solid. (19.2 g, 61 %), m.p. 137-138 °C (lit.[63] m.p. 138.5-139.5 °C).

δ_H: 2.55 (2H, t, *J* 6.8, CH_2CPh_2), 2.75 (2H, t, *J* 6.8, CH_2CO_2),
3.90 (1H, d, *J* 1.8, vinyl CH), 4.99 (1H, d, *J* 1.8, vinyl CH),
7.20-7.37 (10H, m, CPh_2).

δ_C: 28.4, 29.9, 51.4, 99.1, 127.4, 128.2, 128.6, 142.1, 160.4, 167.3.

Preparation of camphor-derived homochiral thiols[57]

Benzyl thiotosylate



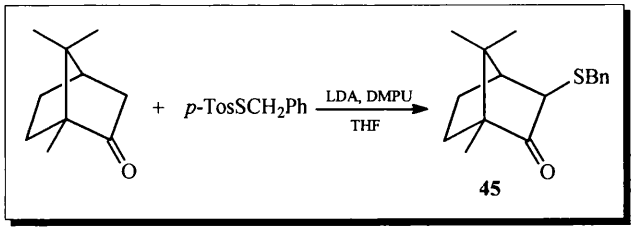
To a stirred solution of potassium thiotosylate (22.6 g, 0.10 mol) in DMF (500 cm^3) under an atmosphere of nitrogen was added benzyl chloride (12.7 g, 0.10 mol) at room temperature. The resultant mixture was stirred for 72 h. It was then quenched with water (100 cm^3) and extracted with ether (3x 200 cm^3). The combined ether extracts were washed with sat. $NaHCO_3$ and then dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude material was recrystallized from methanol to afford the product as colourless crystals (23.2 g, 84 %), m.p. 59-60 °C (lit.[57] m.p. 57-60 °C).

δ_H: 2.44 (3H, s, CH_3), 4.26 (2H, s, SCH_2Ph), 7.25 (5H, m, Ph),
7.28 (2H, d, *J* 8.2, ArH-2 and H-6), 7.73 (2H, d, *J* 8.2, ArH-3 and H-5).

δ_C: 21.6, 40.2, 126.9, 128.7, 129.0, 129.7, 133.6, 141.9, 144.6.

No NMR data was available in the literature.

(1*R*,3*R*)-3-(Benzylthio)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one or **(1*R*,3*R*)-3-(benzylthio)camphor 45**



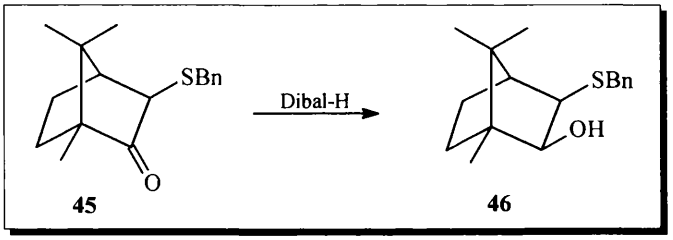
To a stirred solution of LDA (2.0 M soln. in heptane/THF, Aldrich) (32.5 cm^3, 65 mmol) in THF (118 cm^3) at -78 °C under an atmosphere of nitrogen was added (1*R*)-(+)-camphor (9.9 g, 65 mmol) in THF (118 cm^3). The solution was left to stir for 1.5 h at -78 °C, followed by the slow addition of DMPU (25.0 g, 195 mmol) and benzyl thiotosylate (20.0g, 72 mmol) in THF (150 cm^3) *via* a cannula, maintaining the reaction temperature at -78 °C. Stirring was continued for another 2 h. The reaction mixture was quenched at -78 °C with sat. NH_4Cl (150 cm^3) and washed with ether (3 x 120 cm^3). The combined ether layers were washed successively with 2 M HCl (3 x 120 cm^3), sat. $NaHCO_3$ (3 x 120 cm^3) and sat. brine (80 cm^3) and then dried over $MgSO_4$. The solvent

was evaporated under reduced pressure to give a yellowish solid which was recrystallized from ethyl acetate-petroleum, to afford the product as a white crystalline solid (11.3 g). The filtrate was concentrated and purified by flash-column chromatography [petroleum-ether (30:1)], to afford further product (3.8 g) as a white solid (total yield : 15.1 g, 85 %), m.p. 73-74 °C (lit.[57] m.p 73-75 °C).

δ_H: 0.89 (3H, s, Me), 0.93 (3H, s, Me), 0.99 (3H, s, Me), 1.23 (1H, m), 1.42 (1H, m), 1.61 (1H, m), 1.94 (2H, m), 2.75 (1H, s, CHS), 3.93 (1H, d, *J* 13.2, CH_2Ph), 4.02 (1H, d, *J* 13.2, CH_2Ph), 7.25-7.37 (5H, m, Ph).

The product could be taken through to the next step without further purification.

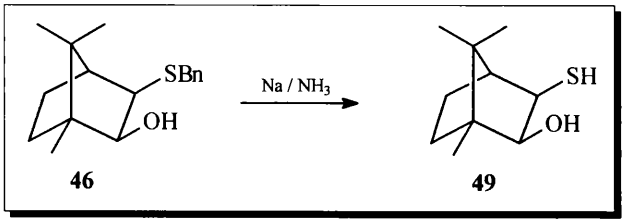
(1*R*,2*S*,3*R*)-3-(Benzylthio)-1,7,7-trmethylbicyclo[2.2.1]heptan-2-ol or **(1*R*,2*S*,3*R*)-3-(benzylthio)camphanol 46**



To a stirred solution of the ketone **45** (1.0 g, 3.7 mmol) in CH_2Cl_2 (20 cm^3) at room temperature under an atmosphere of nitrogen was added dropwise Dibal-H (1.5 M soln. in toluene) (3.9 cm^3, 5.9 mmol) over a period of 5 min. The mixture was stirred at room temperature for 2 h. It was then quenched with sat. NH_4Cl (20 cm^3) and extracted with ether (3 x 20 cm^3). The combined ether extracts were washed successively with 2 M HCl (2 x 30 cm^3), sat. $NaHCO_3$ (2 x 30 cm^3) and sat. brine (30 cm^3) and then dried over $MgSO_4$. After solvent removal under reduced pressure, the crude material was purified by flash-column chromatography [eluent: petroleum followed by petroleum-ether (97:3)] to afford the product as a colourless oil (0.89 g, 87 %).

δ_H: 0.76 (3H, s, Me), 0.94 (3H, s, Me), 1.00 (3H, s, Me), 1.03 (2H, m), 1.46 (1H, m), 1.74 (1H, m), 1.81 (1H, d, *J* 4.3, H-4), 2.68 (1H, d, *J* 4.3, OH), 2.95 (1H, d, *J* 7.6, CHS), 3.48 (1H, dd, *J* 7.5 and 4.0, C<u>H</u>OH), 3.70 (1H, s, CH_2Ph), 7.26-7.35 (5H, m, Ph).

(1*R*,2*S*,3*R*)-3-(Mercapto)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol or **(1*R*,2*R*,3*R*)-3-(mercapto)camphanol 49**



To a stirred solution of the camphanol **46** (10.7 g, 39 mmol) in ammonia (100 cm^3) at -78 °C (liquid ammonia was added to three neck flask using a dry ice condenser) was added sodium (4.0 g, 170 mmol) which was carefully cut into small pieces. The blue-coloured solution was left to stir for 1 h and then quenched with sat. NH_4Cl (100 cm^3). The reaction mixture was allowed to warm up to room temperature, then acidified (litmus) with conc. HCl and extracted with ether (3 x 100 cm^3). The combined ether layers were washed successively with sat. $NaHCO_3$ (3 x 50 cm^3) and sat. brine (50 cm^3) and then dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude material was purified by flash-column chromatography [eluent: petroleum-ether (95:5)] to afford the product as a white solid (6.4 g, 88 %),

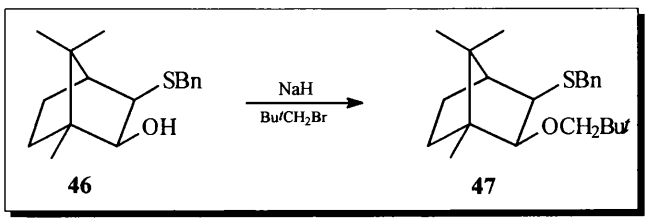
m.p.130-131 °C (lit.[57] m.p.131-132 °C).

$[\alpha]_D^{19}$ = + 1.0 ° (c = 0.97, $CHCl_3$) {lit.[57] $[\alpha]_D^{20}$ = + 5.1 ° (c = 1.18, $CHCl_3$)}.

δ_H: 0.77 (3H, s, Me), 0.95 (3H, s, Me), 1.07 (3H, s, Me), 1.00-1.15 (2H, m), 1.47 (1H, m), 1.71 (1H, d, *J* 9.6, SH), 1.75 (1H, m), 1.81 (1H, d, *J* 4.2, H-4), 2.50 (1H, brs, OH), 3.25 (1H, dd, *J* 9.6 and 7.6, CHS), 3.56 (1H, d, *J* 7.6, C<u>H</u>OH).

δ_C: 11.8, 21.4, 21.6, 29.0, 33.3, 47.2, 48.4, 49.6, 54.2, 79.3.

(1*R*,2*S*,3*R*)-3-(Benzylthio)-2-neopentoxy-1,7,7-trimethylbicyclo[2.2.1]heptane 47

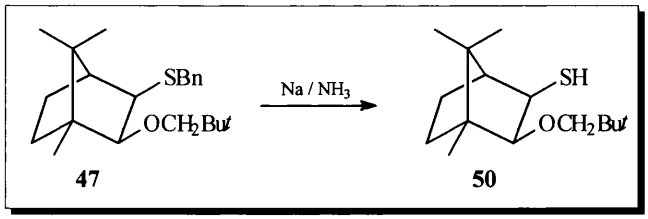


To a stirred solution of the camphanol **46** (0.80 g, 2.91 mmol) in *N*-methylpyrrolidinone (2.0 cm^3) was added oil-free sodium hydride (0.23 g, 9.6 cm^3) (sodium hydride was washed with petroleum to remove the mineral oil) in *N*-methylpyrrolidinone (2.0 cm^3) at

room temperature. The mixture was stirred and heated to about 130 °C (bath temp.) then neopentyl bromide (1.32 g, 8.7 mmol) was added slowly and the resultant mixture was stirred for a further 10 h at 130 °C under an atmosphere of nitrogen (the reaction mixture was initially green, then became dark brown, then light brown towards the end of the reaction). The reaction mixture was poured into sat. $NaHCO_3$ (5.0 cm^3), extracted with CH_2Cl_2 (10 cm^3) and the extract was washed with 2 M HCl (3 x 10 cm^3). The acid washings were combined and washed with CH_2Cl_2 (3 x 10 cm^3). The organic layers were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash-column chromatography [eluent: petroleum-ether (30:1)] to afford the product as a colourless oil (0.95 g, 94%).

δ_H: 0.75 (3H, s, Me), 0.87 (3H, s, Me), 0.80-1.00 (2H, m), 0.92 (9H, s, Bu^t), 1.18 (3H, s, Me), 1.43 (1H, m), 1.68 (1H, m), 1.73 (1H, d, *J* 3.9, H-4), 2.80 (1H, d, *J* 7.8, CHS), 2.90 (1H, d, *J* 7.8, OCH_2), 3.17 (1H, d, *J* 7.8 and 4.0, OCH), 3.38 (1H, d, *J* 7.8, OCH_2), 3.67 (1H, d, *J* 13.2, CH_2Ph), 3.72 (1H, d, *J* 13.2, CH_2Ph), 7.20-7.35 (5H, m, Ph).

(1*R*,2*S*,3*R*)-3-(Mercapto)-2-neopentoxy-1,7,7-trimethylbicyclo-[2.2.1]heptane 50



47 **50**

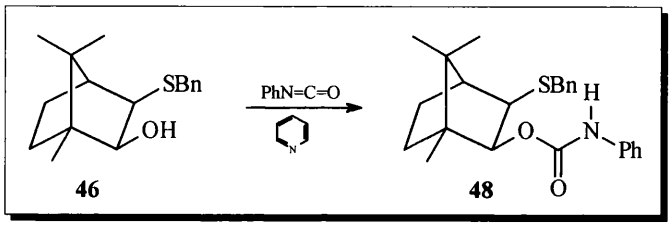
A solution of the neopentyl ether **47** (0.94 g, 2.7 mmol) and *t*-butanol (0.80 g, 10.8 mmol) in THF (10 cm^3) was added slowly to a solution of sodium (0.38 g, 17.0 mmol) in liquid ammonia (10 cm^3) at -84 °C (petroleum and dry ice). The blue solution was stirred for 30-40 min and then quenched with methanol (5.0 cm^3) followed by sat. NH_4Cl (30 cm^3). The reaction mixture was allowed to warm to room temperature and then extracted with hexane (3 x 30 cm^3). The hexane extracts were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash-column chromatography [eluent: petroleum-ether (20:1)] to afford the product as a colourless oil (0.58 g, 84 %).

$[\alpha]_D^{20}$ = - 53.8 ° (c = 1.88, $CHCl_3$) {lit.[57] $[\alpha]_D^{20}$ = - 70.4 ° (c = 1.98, $CHCl_3$)}.

δ_H: 0.77 (3H, s, Me), 0.91 (3H, s, Me), 0.80-1.00 (1H, m), 0.94 (9H, s, Bu^t), 1.02 (1H, d, *J* 8.6, SH), 1.20 (3H, s, Me), 1.40-1.53 (1H, m), 1.63-1.76 (1H, m), 1.70 (1H, d, *J* 2.0, H-4), 1.85 (1H, m), 2.96 (1H, d, *J* 7.9, OCH_2), 3.17-3.23 (2H, m, SCH and OCH), 3.44 (1H, d, *J* 7.9, OCH_2).

δ_C: 12.2, 21.4, 21.6, 27.0, 28.7, 32.8, 33.5, 47.3, 47.9, 50.6, 55.4, 83.8, 88.7.

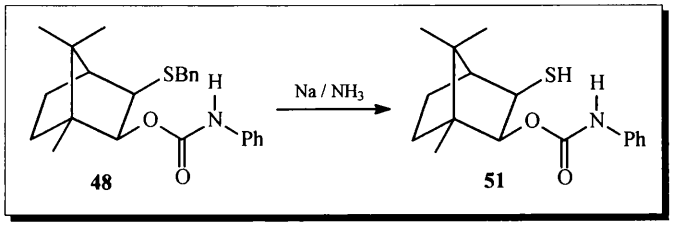
(1*R*,2*S*,3*R*)-3-(Benzylthio)-2-(*N*-phenylcarbamoyl)oxo-1,7,7-trimethylbicyclo[2.2.1]heptane 48



To a stirred solution of the camphanol **46** (1.21 g, 4.37 mmol) in pyridine (2.0 cm^3) was added phenyl isocyanate (0.50 g, 4.15 mmol) at room temperature. The mixture was heated under reflux for 1 h and then allowed to cool to room temperature. Water (20 cm^3) and CH_2Cl_2 (10 cm^3) were added and the organic layer was separated and washed with 2 M HCl (3 x 30 cm^3). The acid washings were combined and extracted with CH_2Cl_2 (3 x 30 cm^3). The combined organic layers were dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The crude material was purified by flash-column chromatography [eluent: petroleum-ether (10:1)] to afford the product as a yellow oil (1.65 g, 95 %).

δ_H: 0.78 (3H, s, Me), 0.88 (3H, s, Me), 1.08 (3H, s, Me), 0.80-1.25 (2H, m), 1.49-1.75 (2H, m), 1.80 (1H, d, *J* 4.1, H-4), 2.95 (1H, d, *J* 7.5, CHS), 3.73 (2H, s, CH_2Ph), 4.86 (1H, d, *J* 7.5, CHO), 6.68 (1H, brs, NH), 7.07 (1H, t, *J* 8.1, ArH), 7.10-7.38 (7H, m, Ph).

(1*R*,2*S*,3*R*)-3-(Mercapto)-2-(*N*-phenylcarbamoyl)oxo-1,7,7-trimethylbicyclo[2.2.1]heptane 51



A solution of the phenyl carbamate **48** (1.65 g, 4.2 mmol) in dry ether (16 cm^3) was added slowly to a stirred solution of sodium (0.63 g, 27.5 mmol) in ammonia (17 cm^3) at -78 °C. The resultant blue solution was stirred for 10 min then quenched with methanol (10 cm^3) followed by sat. NH_4Cl (30 cm^3). The reaction mixture was allowed to warm to room to temperature and then extracted with EtOAc (3 x 20 cm^3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash-column chromatography [eluent: petroleum-ether (20:1)] to afford the product as a white crystalline solid (1.12 g, 87 %), m.p. 105-106 °C (lit.[57] m.p. 106-107 °C).

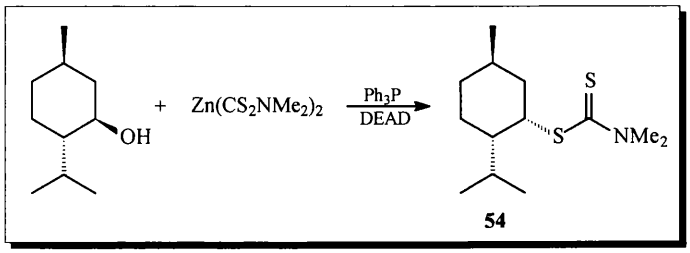
$[\alpha]_D^{20}$ = + 83.5 ° (c = 0.98, $CHCl_3$) {lit.[57] $[\alpha]_D^{25}$ = + 86.9 ° (c = 1.08, $CHCl_3$)}.

δ_H: 0.84 (3H, s, Me), 0.94 (3H, s, Me), 1.17 (3H, s, Me), 1.15-1.30 (1H, m), 1.70-1.84 (2H, m), 1.88 (1H, d, *J* 8.1, SH), 3.35 (1H, dd, *J* 8.1 and 7.5, C<u>H</u>SH), 4.77 (1H, d, *J* 7.5, CHO), 6.71 (1H, brs, NH), 7.06 (1H, t, *J* 7.8, Ph), 7.31 (2H, t, *J* 7.8, Ph), 7.42 (2H, d, *J* 7.8, Ph).

δ_C: 11.7, 21.15, 21.4, 28.6, 33.3, 46.3, 47.8, 49.5, 54.4, 82.3, 118.9, 123.5, 129.0, 137.9, 153.3.

Preparation of the menthol derived thiol[58-60]

(1*S*,2*S*,5*R*)-(+)-Neomenthyl *N*,*N*-dimethyldithiocarbamate 54[59-60]

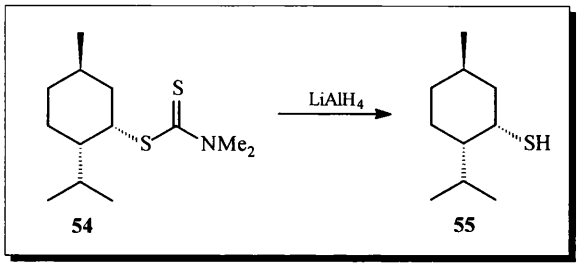


54

A stirred solution of (1*R*,2*S*,5*R*)-(-)-menthol (3.0 g, 19 mmol), zinc *N*,*N*-dimethyl dithiocarbamate (5.9 g, 19 mmol) and triphenylphosphine (13.1 g, 50 mmol) in dry toluene (31.0 cm^3) was cooled to 0 °C and protected from the light. To this mixture, diethyl azodicarboxylate (DEAD) (9.4 g, 54 mmol) was added slowly and then the mixture was allowed to warm to room temperature. The reaction mixture was left to stir overnight, most of the toluene was removed under reduced pressure and the residue was purified by flash-column chromatography [eluent: neat petroleum followed by petroleum-

ether (9:1)] to afford the product as a pink crystalline solid (3.5 g, 72 %),
m.p. 90-91 °C (lit.[59a] m.p. 90-91 °C).
200 MHz NMR,
δ_H: 0.82 (3H, s, Me), 0.84 (3H, s, Me), 0.88 (3H, s, Me), 1.10-2.11 (9H, m),
3.34 (3H, brs, NMe^A), 3.51 (3H, brs, NMe^B), 4.46 (1H, m, CHS).

(1*S*,2*S*,5*R*)-(+)-Neomenthane-3-thiol 55[59-60]

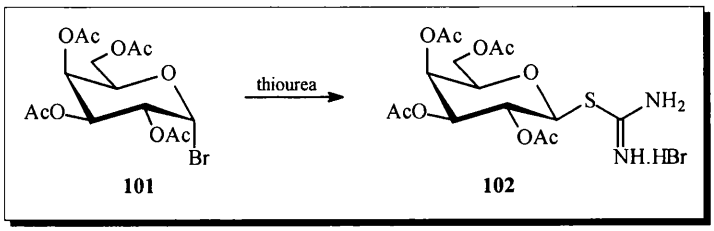


54 55

A stirred solution of the dithiocarbamate **54** (3.5 g, 13 mmol) and lithium aluminium hydride (1.3 g, 33 mmol) in dry ether (148 cm^3) was heated under reflux overnight. The reaction mixture was quenched by cooling the flask in an ice-bath and adding ether (50 cm^3) and sat. Na_2SO_4 while stirring. Once the evolution of gasses had ceased, the white residue was filtered and the filtrate was dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude material was purified by flash-column chromatography [eluent: neat petroleum] to afford the product as a colourless oil (1.73 g, 77 %), $[\alpha]_D^{25}$ = + 52.6 ° (c = 1.66, $CHCl_3$).
{lit.[58a] $[\alpha]_D^{20}$ = + 53.2 ° (c = 1.36, $CHCl_3$) and $[\alpha]_D^{20}$ = + 53.9 ° (c = 1.85, $CHCl_3$)[58e]}.
δ_H: 0.84 (3H, d, *J* 6.5, Me), 0.87 (3H, d, *J* 1.7, Me), 0.89 (3H, d, *J* 1.8, Me),
1.01 (1H, m), 1.20 (1H, d, *J* 7.0, SH), 1.27-1.83 (8H, m), 3.48 (1H, m,C<u>H</u>SH).
δ_C: 20.4, 20.9, 22.2, 24.2, 26.0, 30.3, 35.3, 40.2, 44.0, 48.3.

Preparation of homochiral carbohydrate thiols

Hydrobromide salt 102[69]

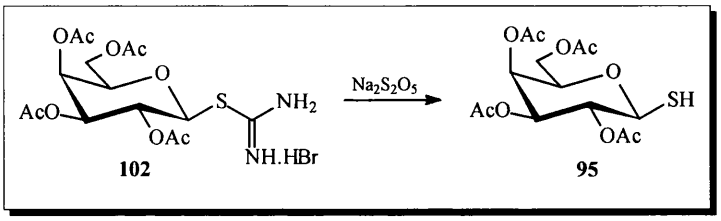


101 102

A stirred solution of 2,3,4,6-tetra-*O*-acetyl-α-galactopyranosyl bromide **101** (Aldrich)

(27.5 g, 67 mmol) and thiourea (5.1 g, 67 mmol) in dry acetone (27 cm^3) was heated under reflux for 15 min. After cooling of the mixture, the solvent was evaporated under reduced pressure and the crude product was taken through to the next step without any further purification. If desired, the crude material could be recrystallized from acetone.[69]

2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-galactopyranose 95[69]



102 **95**

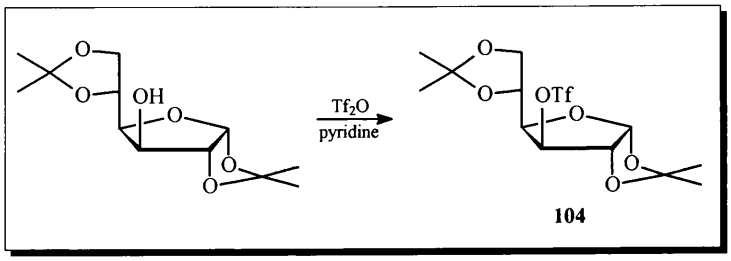
To a vigorously stirred solution of sodium metabisulphite (12.5 g, 66 mmol) in water (50 cm^3) at 85 °C, was added the hydrobromide salt **102** (32.0 g, 66 mmol) in CCl_4 (63 cm^3). The resultant mixture was heated under reflux for 10-15 min then cooled. The layers were separated and the organic layer was washed successively with water (40 cm^3) and sat. brine (40 cm^3) and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material was recrystallized from benzene to afford the product as a white solid (5.3 g, 22 %), m.p. 86-88 °C (lit.[69b] m.p. 86.5-88 °C).

$[\alpha]_D^{19}$ = + 38.0 ° (c = 2.62, $CHCl_3$) {lit.[69b] $[\alpha]_D^{19}$ = + 32.0 ° (c = 3.5, $CHCl_3$)}.

δ_H: 1.93 (3H, s, Ac), 2.00 (3H, s, Ac), 2.04 (3H, s, Ac), 2.12 (3H, s, Ac), 2.33 (1H, d, *J* 10.0, SH), 3.91 (1H, td, *J* 6.6 and *ca.* 1.1, H-5), 4.08 (2H, d, H-6), 4.49 (1H, t, *J* 9.9, H-1), 4.97 (1H, dd, *J* 10.1 and 3.2, H-3), 5.13 (1H, t, *J* 10.0, H-2), 5.38 (1H, dd, *J* 3.3 and *ca.* 1.1, H-4). This analysis was confirmed by ^1H-^1H decoupling experiments.

δ_C: 20.5, 20.7 (2C), 20.8, 61.4, 67.2, 70.8, 71.5, 74.9, 79.1, 169.8, 170.0, 170.1, 170.4.

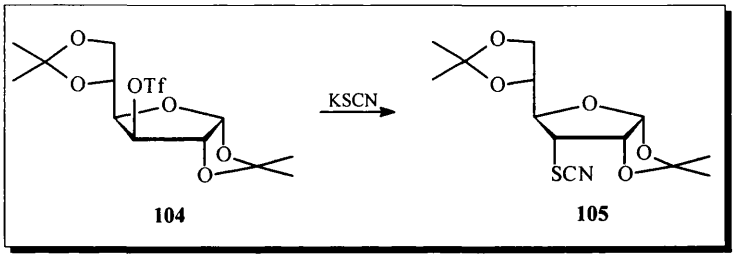
1,2:5,6-Di-*O*-isopropylidene-3-*O*-trifyl-α-D-glucofuranose 104[71, 72]



104

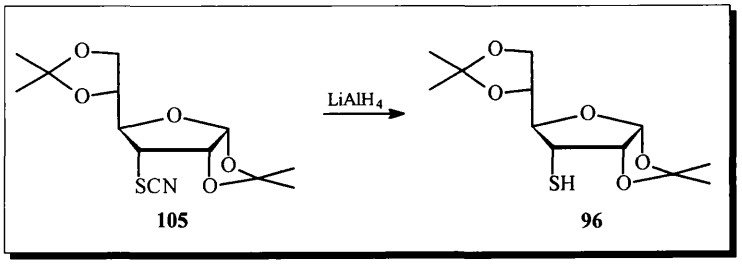
To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (Aldrich, 6.0 g, 24 mmol), dry pyridine (7.5 cm^3, 92 mmol) in dry CH_2Cl_2 (240 cm^3) at -15 °C under nitrogen was added dropwise trifluoromethanesulphonic anhydride (triflic anhydride) (7.3 g, 26 mmol). The resultant mixture was stirred at -15 °C for 1.5 h then poured into a mixture of ice (15 g) and $NaHCO_3$ (5 g). Once the ice had melted, the two layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 70 cm^3). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure, then co-evaporated with toluene (3 x 20 cm^3). The crude material was taken through to the next step without any further purification.

3-*S*-Cyano-1,2:5,6-di-*O*-isopropyidene-3-thio-α-allofuranose 105[72, 74]



A solution of the crude triflate **104** (9.4 g, 24 mmol) and potassium thiocyanate (21.7 g, 220 mmol) in dry acetonitrile (130 cm^3) was heated under reflux for 36 h under an atmosphere of nitrogen. It was then cooled to room temperature and the acetonitrile was removed under reduced pressure. The resultant residue was diluted with water (150 cm^3), extracted with CH_2Cl_2 (3 x 70 cm^3) and the combined extracts were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material obtained was taken through to the next step without any further purification.

1,2:5,6-Di-*O*-isopropylidene-3-thio-α-D-allofuranose 96[72, 74]



A stirrred solution of the crude thiocyanate **105** (3.8 g, 13 mmol) and lithium aluminium hydride (5.5 g, 150 mmol) in dry ether (200 cm^3) was heated under reflux for 1 h under an atmosphere of nitrogen and then cooled to room temperature. The mixture was

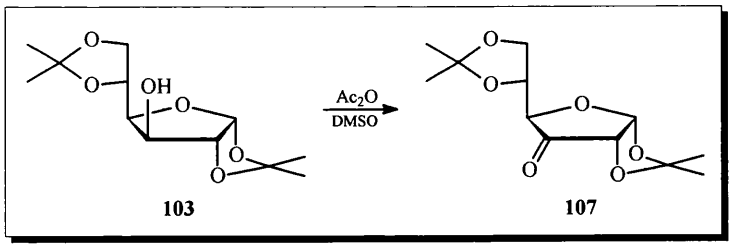
quenched by slow addition of EtOAc (20 cm^3), followed by water (20 cm^3) and 2 M acetic acid (200 cm^3). The ether layer was separated and the aqueous layer was extracted with ether (2 x 200 cm^3). The combined ether layers were washed with water (200 cm^3) and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography [eluent: petroleum-ether (9:1) followed by petroleum-ether (7:1)] to afford the product as a colourless oil (0.75 g, 21 %).

IR (liq. film) : 2980, 2582(w), 1450, 1390, 1140 cm^{-1} [lit.[72] 2600 cm^{-1} (SH)].

δ_H: 1.33 (3H, s, Me), 1.35 (3H, s, Me), 1.46 (3H, s, Me), 1.52 (3H, s, Me), 2.06 (1H, d, *J* 9.6, SH), 3.01 (1H, td, *J* 9.7 and 4.8, H-3), 3.93 (1H, dd, 9.8 and 3.9, H-4), 4.04 (1H, dd, *J* 8.5 and 7.1, H^A-6), 4.16 (1H, dd, *J* 8.5 and 6.0, H^B-6), 4.32 (1H, m, H-5), 4.62 (1H, t, *J* 4.2, H-2), 5.80 (1H, d, *J* 3.7, H-1). This analysis was confirmed by ^1H-^1H decoupling experiments.

δ_C: 25.1, 26.4, 26.5, 26.6, 41.1, 65.6, 75.7, 81.8, 83.0, 104.0, 109.9, 112.0.

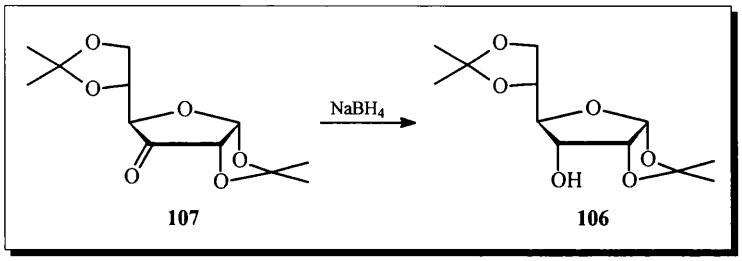
1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose 107[73]



103 107

To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (10.0 g, 38 mmol) in DMSO (115 cm^3) was added acetic anhydride (77 cm^3). The mixture was left to stir for 24 h at room temperature, after which time the mixture was distilled at room temperature under reduced pressure (0.02 Torr) to remove unreacted acetic anhydride, DMSO and dimethyl sulphide. After the removal of these materials, the crude material was taken through to the next step without any further purification.

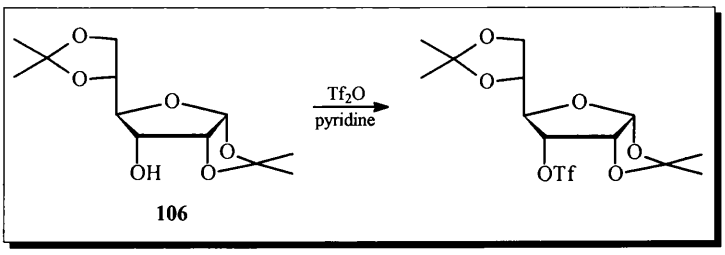
1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose 106[73]



To a stirred solution of the crude ketone **107** (9.8 g, 38 mmol) in aqueous (70 %) ethanol (220 cm^3) at 0 °C was added sodium borohydride (10.0 g, 266 mmol) and the mixture was stirred for 30 min at 0 °C. The mixture was quenched with water (200 cm^3) and then extracted with EtOAc (8 x 200 cm^3). A small amount of sodium chloride was added to promote the separation of the organic and aqueous layers. The combined organic layers were dried over $MgSO_4$, then the solvent was evaporated under reduced pressure and the residue was pumped at 0.02 Torr to remove final traces of volatile material. The crude material was recrystallized from benzene/hexane to afford the product as a white solid (5.6 g, 56 %), m.p. 76-77 °C (lit.[73] m.p. 77-78 °C).

δ_H: 1.35 (3H, s, Me), 1.36 (3H, s, Me), 1.44 (3H, s, Me), 1.56 (3H, s, Me), 2.54 (1H, d, *J* 9.0, OH), 3.82 (1H, dd, *J* 9.0 and 4.0, H-4), 4.03 (3H, m, H-6 and H-3), 4.28 (1H, q, *J* 4.0, H-5), 4.59 (1H, t, *J* 4.0, H-2), 5.78 (1H, d, *J* 3.6, H-1).

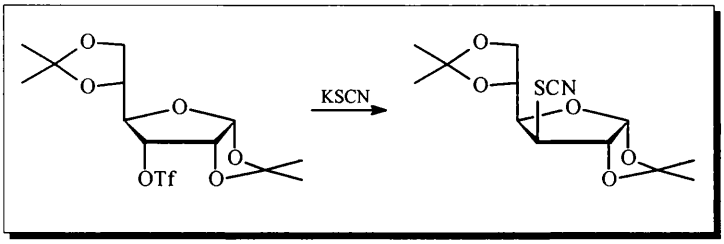
1,2:5,6-Di-*O*-isopropylidene-3-*O*-trifyl-α-D-allofuranose[71, 72]



To a stirred solution of the D-allose **106** (5.9 g, 21 mmol), dry pyridine (6.7 cm^3, 84 mmol) in dry CH_2Cl_2 (200 cm^3) at -15 °C under an atmosphere of nitrogen was added dropwise triflic anhydride (6.7 g, 24 mmol). The resultant mixture was stirred at -15 °C for 1.5 h then poured into a mixture of ice (15 g) and $NaHCO_3$ (5 g). Once the ice had melted, the two layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 70 cm^3). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure then azeotroped with toluene (3 x 20 cm^3). The crude

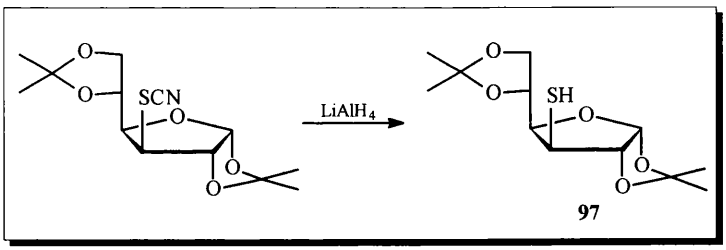
material was taken through to the next step without any further purification.

3-*S*-Cyano-1,2:5,6-di-*O*-isopropyidene-3-thio-α-glucofuranose[72, 74]



A solution of the crude D-allose triflate (8.4 g, 21mmol) and potassium thiocyanate (8.3 g, 86 mmol) in dry acetonitrile (130 cm^3) was heated under reflux for 20 h under an atmosphere of nitrogen. It was then cooled and the acetonitrile was evaporated under reduced pressure. The resultant residue was diluted with water (150 cm^3), extracted with CH_2Cl_2 (3 x 70 cm^3) and the combined extracts were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material obtained was taken through to the next step without any further purification.

1,2:5,6-Di-*O*-isopropylidene-3-thio-α-D-glucofuranose 97[72, 74]



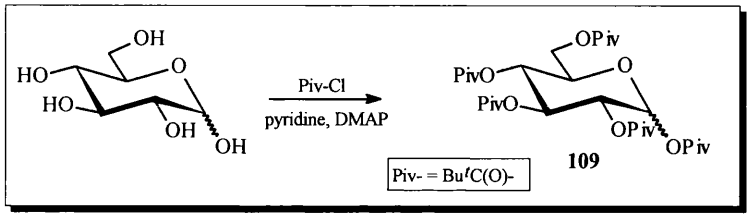
A solution of the crude D-glucose thiocyanate (4.4 g, 15 mmol) and lithium aluminium hydride (4.0 g, 105 mmol) in dry ether (180 cm^3) was heated under reflux for 1 h under an atmosphere of nitrogen and then cooled to room temperature. The mixture was quenched by slow addition of EtOAc (20 cm^3), followed by water (20 cm^3) and 2 M acetic acid (180 cm^3). The ether layer was separated and the aqueous layer was extracted with ether (2 x 200 cm^3). The combined ether layers were washed with water (200 cm^3) and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material was purified by flash-column chromatography [eluent: petroleum-ether (9:1) followed by petroleum-ether (7:1)] to afford the product as a colourless oil (1.1 g, 27 %).

IR (liq. film) : 2980, 2580(w), 1450, 1380, 1220 cm^{-1} [lit.[72] 2600 cm^{-1} (SH)].

δ_H: 1.29 (3H, s, Me), 1.34 (3H, s, Me), 1.40 (3H, s, Me), 1.49 (3H, s, Me), 1.47 [1H, d (overlapping with Me singlet, SH], 3.53 (1H, dd, *J* 8.4 and 3.7, H-3), 3.99 (1H, dd, *J* 8.7 and 4.7, H^A-6), 4.10-4.20 (2H, m, H^B-6 and H-4), 4.31 (1H, ddd, *J* 11.2, 7.7 and 3.4, H-5), 4.61 (1H, d, *J* 3.4, H-2), 5.85 (1H, d, *J* 3.6, H-1).

δ_C: 25.2, 26.2, 26.6, 26.9, 45.3, 67.7, 74.1, 80.0, 87.5, 104.7, 109.5, 112.1.

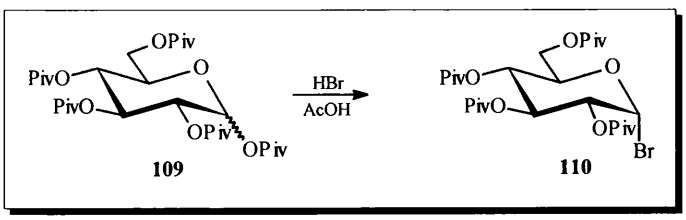
Penta-*O*-pivaloyl-β-D-glucose 109



To a stirred solution of pivaloyl chloride (97.9 g, 830 mmol) and dry pyridine (100 cm^3) in dry $CHCl_3$ (165 cm^3) at room temperature was added D-glucose (24.0 g, 133 mmol) in portions over 30 min. The mixture was heated under reflux for 3 h and then cooled to room temperature. DMAP (1.0 g, 8.30 mmol) was added to the mixture and this was left to stir at room temperature overnight. The pyridinium hydrochloride was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was diluted in ether (400 cm^3) and washed successively with 2 M HCl (250 cm^3), water (100 cm^3) and sat. brine (100 cm^3), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude product as a white solid (75.2 g, 94 %). In this experiment, ^{1}H NMR spectrum indicated >90 % purity for the product, (lit.[75] m.p. 156-158 °C). If desired, the product can be recrystallized from ethanol.[75]

δ_H: 1.12 (9H, s, CMe_3), 1.14 (9H, s, CMe_3), 1.16 (9H, s, CMe_3), 1.18 (9H, s, CMe_3), 1.21 (9H, s, CMe_3), 3.80-3.89 (1H, m, H-5), 4.13 (2H, apparent d, *J* 3.5 H-6), 5.10-5.40 (3H, m, H-2, H-3, H-4), 5.71 (1H, d, *J* 7.7, H-1).

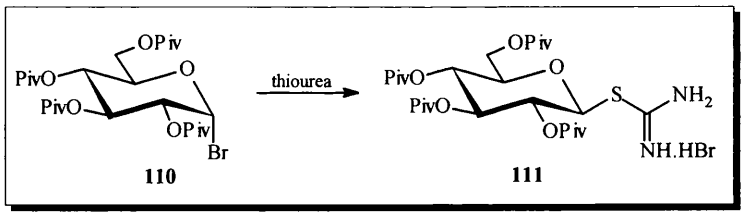
2,3,4,6-Tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide 110[75]



To a stirred solution of penta-*O*-pivaloyl-β-D-glucose **109** (35.0 g, 58 mmol) in dry CH_2Cl_2 (64 cm^3) at 0 °C under an atmosphere of nitrogen was added HBr (30 % in AcOH, 64 cm^3) dropwise. The mixture was stirred for 1 h and then placed in a fridge at 4 °C for 12 h. It was then warmed to room temperature and co-evaporated with toluene (400 cm^3), followed by co-evaporation with ether (200 cm^3). The residue was diluted with ether (200 cm^3) and washed successively with sat. $NaHCO_3$ (100 cm^3), water (100 cm^3) and sat. brine (100 cm^3), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude product as a white solid (34.7 g) which was taken through to the next step without any further purification. In this experiment, the ^1H NMR spectrum indicated >95 % purity for the product, (lit.[75] m.p. 142-144 °C). If desired, the product can be recrystallized from ethanol.[75]

δ_H: 1.14 (9H, s, CMe_3), 1.18 (9H, s, CMe_3), 1.19 (9H, s, CMe_3), 1.22 (9H, s, CMe_3), 4.03-4.30 (3H, m, H-5, H-6), 4.80 (1H, dd, *J* 9.7 and 4.2, H-1), 5.20 (1H, t, *J* 4.2, H-4), 5.64 (1H, t, *J* 4.2, H-3), 6.52 (1H, d, *J* 4.2, H-1).

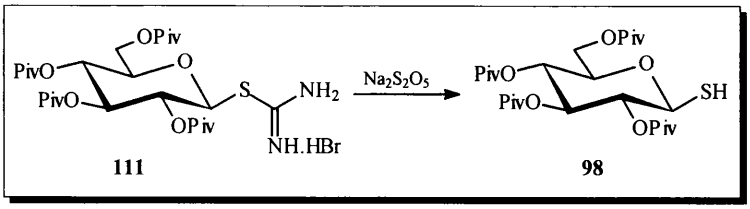
Hydrobromide salt 111



A stirred solution of 2,3,4,6-tetra-*O*-pivaloyl-α-glucopyranosyl bromide **110** (33.6 g, 58 mmol) and thiourea (4.4 g, 58 mmol) in dry acetone (24 cm^3) was heated under reflux for 40 min. After the mixture had cooled, the solvent was evaporated under reduced pressure. The crude material was taken through to the next step without any further purification.

δ_H: 1.12 (9H, s, CMe_3), 1.17 (9H, s, CMe_3), 1.19 (9H, s, CMe_3), 1.24 (9H, s, CMe_3), 4.02-4.19 (2H, m, H-6), 4.32-4.38 (1H, br.d, H-5), 5.12-5.51 (4H, m, H-4, H-3, H-2, H-1).

2,3,4,6-Tetra-*O*-pivaloyl-1-thio-β-D-glucopyranose 98



111 98

To a stirred solution of the hydrobromide salt **111** (37.0 g, 56 mmol) in CCl_4 (73 cm^3) at 70 °C was added sodium metabisulphite (10.7 g, 56 mmol) in water (43 cm^3). The resultant mixture was heated under reflux for 1 h, then allowed to cool. The layers were separated and the organic layer was washed successively with water (40 cm^3) and sat. brine (40 cm^3) then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was recrystallized from EtOH (or MeOH) to afford the product as a white solid (16.1 g, 54 %), m.p. 115-116 °C.

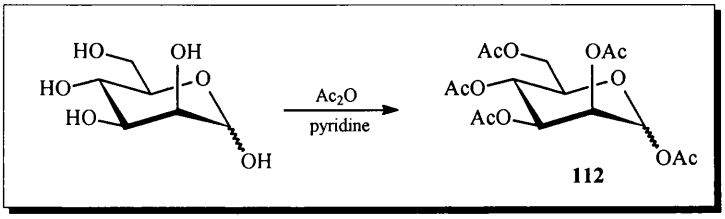
$[\alpha]_D^{20}$ = + 18.8 ° (c = 1.18, $CHCl_3$) and $[\alpha]_D^{20}$ = + 18.8 ° (c = 1.14, $CHCl_3$) (two experiments). *m/z* (APCI) 555 (M^++ Na, 10), 533 (M^++1, 9), 500 (M^+-SH, 23), 499 (79), 431 (M^+-OPiv, 9), 397 (29), 227 (30), 211 (100), 85 (Piv^+, 61).

Found : C, 58.27; H, 8.31. $C_{26}H_{44}O_9S$ requires C, 58.62; H, 8.33 %.

δ_H: 1.09 (9H, s, CMe_3), 1.12 (9H, s, CMe_3), 1.16 (9H, s, CMe_3), 1.21 (9H, s, CMe_3), 2.23 (1H, d, *J* 10.0, SH), 3.72 (1H, ddd, *J* 10.1, 4.9 and 1.9, H-5), 4.08 (1H, dd, *J* 12.5 and 4.9, H^A-6), 4.17 (1H, dd, *J* 12.5 and 1.9, H^B-6), 4.52 (1H, apparent t, *J ca.* 9.7, H-1), 4.98 (1H, t, *J* 9.4, H-2), 5.15 (1H, apparent t, *J ca.* 9.8, H-4), 5.27 (1H, t, *J* 9.4, H-3). This analysis was confirmed by ^1H-^1H decoupling experiments.

δ_C: 27.0, 27.0(7), 27.1(0), 27.1(3), 38.7(0), 38.7(3) (2C), 38.9, 61.8, 67.5, 73.0, 73.5, 76.8, 79.0, 176.3, 176.8, 177.1, 178.0.

Penta-*O*-acetyl-D-mannose 112[76]

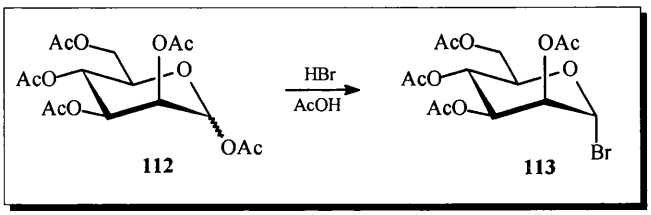


112

To a stirred solution of D-mannose (10.0 g, 56 mmol) in pyridine (40 cm^3) was added acetic anhydride (35.7 g, 350 mmol) and the mixture was stirred overnight at room

temperature. It was concentrated *in vacuo,* then co-evaporated with toluene (3 x 30 cm^3) and diluted with ether (40 cm^3). The ether layer was washed successively with water (40 cm^3) and sat. brine (40 cm^3), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude material as a syrup, which was taken through to the next step without any further purification.

2,3,4,6-Tetra-*O*-acetyl-α-D-mannosyl bromide 113[76]

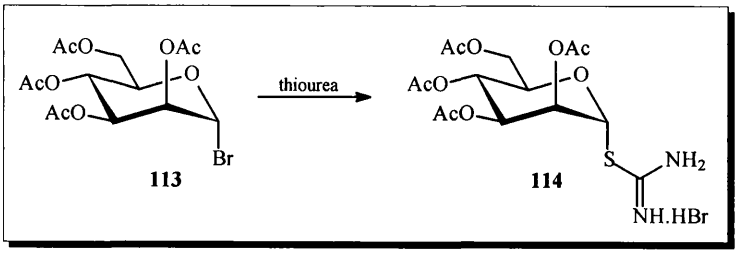


112 **113**

To a stirred solution of penta-*O*-acetyl-D-mannose **112** (21.9 g, 56 mmol) in dry CH_2Cl_2 (50 cm^3) under an atmosphere of nitrogen, was added dropwise HBr (30 % in AcOH, 62 cm^3) and the mixture was stirred overnight at room temperature. It was then co-evaporated with toluene (200 cm^3) followed by co-evaporation with ether (200 cm^3) under reduced pressure. The residue was diluted with ether (200 cm^3) and washed successively with sat. $NaHCO_3$ (100 cm^3), water (100 cm^3) and sat. brine (100 cm^3), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude product as a white solid (21.3 g), which was taken through to the next step without any further purification. In this experiment, the ^1H NMR spectrum indicated >95 % purity for the product. If desired, the product can be recrystallized from ethanol.[76]

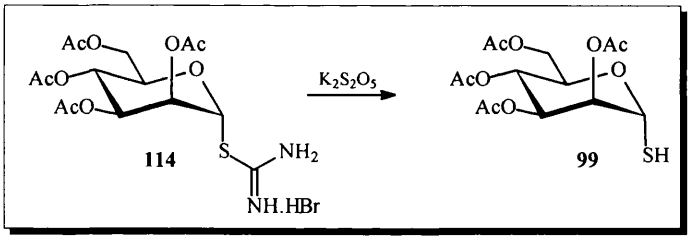
δ_H: 2.01 (3H, s, Ac), 2.07 (3H, s, Ac), 2.10 (3H, s, Ac), 2.17 (3H, s, Ac),
4.13 (1H, dd, *J* 12.4 and 2.2, H^A-6), 4.22 (1H, ddd, *J* 10.1, 4.9 and 2.2, H-5),
4.33 (1H, dd, *J* 12.4 and 4.9, H^B-6), 5.37 (1H, t, *J* 10.1, H-4),
5.44 (1H, dd, *J* 3.4 and 1.6, H-2), 5.71 (1H, dd, *J* 10.1 and 3.4, H-3),
6.29 (1H, s, H-1).

2-*S*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide 114[76]



A stirred solution of 2,3,4,6-tetra-*O*-acetyl-α-mannnosyl bromide (21.3 g, 52 mmol) and thiourea (5.9 g, 78 mmol) in dry acetone (30 cm^3) was heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the crude product was taken through to the next step without any further purification. The crude product could be recrystallized from water.[76]

2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-mannopyranose 99[76]



A solution of the hydrobromide salt **114** (25.3 g, 52 mmol) and potassium metabisulphite (11.6 g, 52 mmol) in CCl_4 (50 cm^3) and water (45 cm^3) was heated under reflux for 30 min. The mixture was then cooled to room temperature. The layers were separated and the organic layer was washed successively with water (40 cm^3) and sat. brine (40 cm^3), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure (15 Torr) and then under high vacuum (0.02 Torr). From this reaction, the β-mannose thiol **100** and a polymeric by-product were also produced and were isolated first (as discussed in the next experiment). The crude material remaining was purified by flash-column chromatography [eluent: petroleum-ether (2:1), followed by petroleum-ether (1:1)] to afford the product **99** as a colourless oil (2.0 g, 10 %),

$[\alpha]_D^{20}$ = + 78.6 ° (c = 0.77, $CHCl_3$) {lit.[76] $[\alpha]_D^{20}$ = + 84.5 ° (c = 1, MeOH)}.

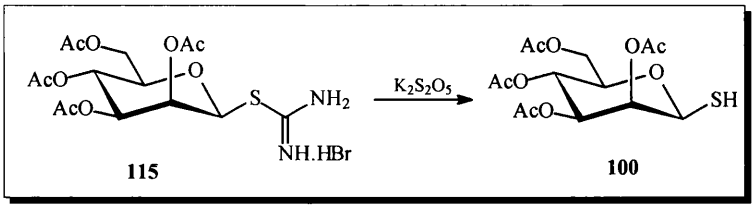
Found : C, 46.54; H, 5.54. $C_{14}H_{20}O_9S$ requires C, 46.15; H, 5.53 %.

δ_H : 1.99 (3H, s, Ac), 2.05 (3H, s, Ac), 2.09 (3H, s, Ac), 2.15 (3H, s, Ac),
2.29 (1H, d, *J* 6.9, SH), 4.10 (1H, dd, *J* 12.2 and 2.0, H^A-6),

4.29 (1H, dd, *J* 12.2 and 5.0, H^B-6), 4.35 (1H, m, H-5),
5.31 (3H, m, H-2, H-3 and H-4), 5.55 (1H, d, *J* 6.9, H-1). This analysis was confirmed by ^{1}H-^{1}H decoupling experiments.

δ_C: 20.6(0), 20.6(4), 20.7, 20.8, 62.1, 66.0, 68.5, 69.6, 71.8, 76.9, 169.6, 169.8, 169.9, 170.6.

2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-mannopyranose 100



During the reaction between the α-bromosugar **113** and thiourea, 2-*S*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide **115** was evidently also formed in addition to the hydrobromide salt **114** and possibly a polymeric by-product. However this crude mixture was taken through to the next step (reduction by potassium metabisulphite) without any purification. At the end of this reduction step, the crude material remaining after the work-up, was dissolved in a slight excess of ethanol and placed in a freezer at -15 °C for 4-5 days. This causes the β-mannose thiol **100** to precipitate and was removed by filtration and then recrystallized from ethanol to afford the product **100** as white-needle like crystals (1.4 g, 7 %), m.p. 161-162 °C, $[\alpha]_D^{19}$ = -29.7 ° (c = 0.78, $CHCl_3$).

Found : C, 46.30; H, 5.50. $C_{14}H_{20}O_9S$ requires C, 46.15; H, 5.53 %.

m/z (APCI) 387 (M^++ Na, 12), 365 (M^++1, <1), 331 (M^+-SH, 17), 170 (9), 169 (100), 127 (12), 109 (47).

δ_H: 1.96 (3H, s, Ac), 2.02 (3H, s, Ac), 2.08 (3H, s, Ac), 2.22 (3H, s, Ac),
2.52 (1H, d, *J* 9.8, SH), 3.69 (1H, ddd, *J* 10.0, 5.4 and 2.4, H-5),
4.10 (1H, dd, *J* 12.4 and 2.4, H^A-6), 4.22 (1H, dd, 12.4 and 5.4, H^B-6),
4.87 (1H, dd, *J* 9.8 and 1.2, H-1), 5.05 (1H, dd, *J* 10.1 and 3.5, H-3),
5.20 (1H, t, *J* 10.1, H-4), 5.42 (1H, dd, *J* 3.4 and 1.1, H-2). This analysis was confirmed by ^{1}H-^{1}H decoupling experiments.

δ_C: 20.6(0), 20.6(2), 20.7, 20.8, 62.6, 65.2, 71.6, 72.0, 76.4, 76.9, 169.6, 170.0, 170.1, 170.7.

The ethanolic filtrate remaining (after the isolation of **100**) was concentrated under reduced pressure and the solid residue remaining was diluted with CCl_4. The polymeric impurity was insoluble in CCl_4 and therefore could be discarded by filtration on a sintered funnel (and washed with further amounts of CCl_4). The CCl_4 washings (containing the α-mannose thiol **99**) were concentrated under reduced pressure. The residue remaining was purified by flash-column chromatography [eluent: petroleum-ether (2:1), followed by petroleum-ether (1:1)] to obtain the α-mannose thiol **99**. The proportion of the hydrobromide salt **115** was not increased significantly by using 2 equivalents of thiourea in the reaction with the α-bromosugar **113**.

Hydrosilylation of prochiral acyclic alkenes using achiral thiols as catalysts

All experiments were carried out under an atmosphere of nitrogen. Experiments were carried out with 5 mmol of alkene, 5 mol % thiol and 5 mol % initiator and all follow the same basic procedure.

General procedure

A stirred solution of the alkene (5.0 mmol), TBHN (44 mg, 0.25 mmol) and the arylsilane (6.5 mmol) in hexane (3.0 cm^3) was placed in a 25 cm^3 flask fitted with a short reflux condenser, equipped at the top with a septum inlet and a nitrogen by-pass bubbler. The flask was immersed in an oil bath equilibrated at 60 °C and *tert*-dodecanethiol (50 mg, 0.25 mmol) in hexane (1.0 cm^3) was added over 2 h to the stirred solution *via* a syringe pump and a fine Teflon tube passed through the septum. After the addition, the reaction mixture was heated for a further 30 min. It was then allowed to cool to room temperature, the solvent was evaporated under reduced pressure and the residue was purified by flash-column chromatography [eluent: neat petroleum, followed by petroleum-ether (19:1)].

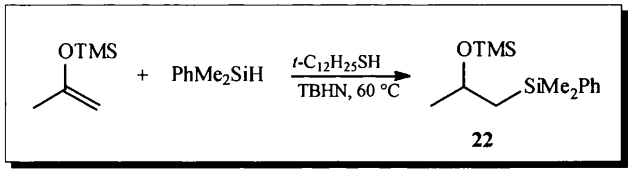
Hydrosilylation of prochiral acyclic alkenes using triethylsilane

All experiments were carried out under an atmosphere of nitrogen. Experiments were carried out with 5 mmol of alkene, 5 mol % thiol and 5 mol % initiator and all follow the same basic procedure. Triethylsilane was used as solvent and no hexane was present.

General procedure

A stirred solution of alkene (5.0 mmol), TBHN (44 mg, 0.25 mmol) and triethylsilane (3.5 g, 30 mmol) were placed in a 25 cm^3 flask fitted with a short reflux condenser, equipped at the top with a septum inlet and a nitrogen by-pass bubbler. The flask was immersed in an oil bath equilibrated at 60 °C and *tert*-dodecanethiol (50 mg, 0.25 mmol) in hexane (1.0 cm^3) was added over 2 h to the stirred solution *via* a syringe pump and a fine Teflon tube passed through the septum. After the addition, the reaction mixture was heated for a further 30 min. It was then allowed to cool to room temperature, the solvent was evaporated under reduced pressure and the residue was purified by flash-column chromatography [eluent: neat petroleum, followed by petroleum-ether (19:1)].

1-Triethylsilyl-2-trimethylsiloxypropane 22



The product was obtained as a colourless oil (1.17 g, 88 %).

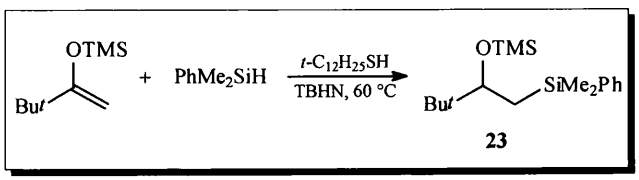
Found : C, 63.02; H, 9.87. $C_{14}H_{26}OSi_2$ requires C, 63.09; H, 9.83 %.

m/z (APCI) 267 (M^++1, 7), 237 (70), 223 (M^+-SiMe, 53), 208 (M^+-$SiMe_2$, 45), 177 (M^+-OTMS, 10), 163 (100), 149 (M^+-CH_2SiPh, 40), 135 ($PhMe_2Si^+$, 83).

δ_H : 0.05 (9H, s, OTMS), 0.30 (3H, s, $SiMe_2$), 0.31 (3H, s, $SiMe_2$), 1.10 (1H, dd, *J* 14.6 and 7.3, $SiCH^A$), 1.14 (3H, d, *J* 6.1, CH_3), 1.17 (1H, dd, *J* 10.3 and 6.1, $SiCH^B$), 4.01 (1H, m, CH), 7.35 (3H, m, Ph), 7.51 (2H, m, Ph).

δ_C : -2.2, -1.8, 0.3, 26.9, 28.0, 28.4, 66.7, 127.7, 128.8, 133.5.

3,3-Dimethyl-1-dimethylphenylsilyl-2-trimethylsiloxybutane 23



The product was also distilled under reduced pressure to afford the product as a colourless oil (1.48 g, 96 %), b.p. 92 °C/0.03 Torr.

Found : C, 66.15; H, 10.58. $C_{17}H_{32}OSi_2$ requires C, 66.16; H, 10.45 %.

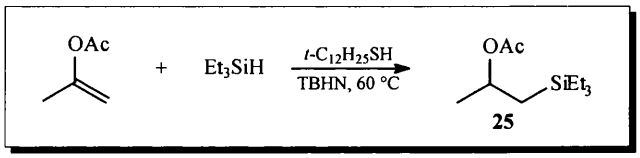
m/z (EI) 251 (M^+-Bu^t, 40), 159 (M^+-CH_2SiMe_2Ph, 53), 135 ($PhMe_2Si^+$, 100), 73 (Me_3Si^+, 29). *m/z* (APCI) 308 (M^+, 1), 285 (88), 215 (100).

δ_H : 0.01 (9H, s, OTMS), 0.30(5) (3H, s, $SiMe_2$), 0.31(2) (3H, s, $SiMe_2$), 0.80 (9H, s, Bu^t), 0.98 (1H, dd, *J* 15.4 and 7.0, $SiCH^A$), 1.17 (1H, dd, *J* 15.4 and 4.7, $SiCH^B$), 3.57 (1H, dd, *J* 7.0 and 4.7,CH), 7.33 (3H, m, Ph), 7.50 (2H, m, Ph)

δ_C : -1.9, -1.2, 1.1, 20.8, 26.2, 36.4, 76.6, 78.3, 127.7, 128.7, 133.7, 140.0.

When the same reaction was repeated, using perfluorohexane-1-sulphenyl chloride as a catalyst instead of *tert*-dodecanethiol, the ^1H NMR spectrum of crude mixture indicated both the adduct **23** and the β-hydroxyalkylsilane **35** were formed in equal amounts.

2-Acetoxy-1-triethylsilylpropane 25



25

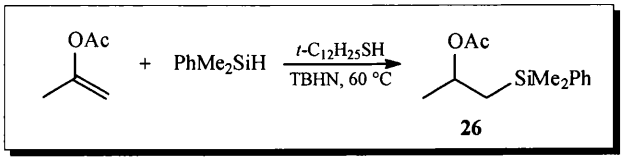
The product was obtained as a colourless oil (2.13 g, 98 %).

Found: C, 60.67; H, 11.51. $C_{11}H_{24}O_2Si$ requires C, 61.06; H, 11.18 %.

δ_H : 0.51 (2H, q, *J* 7.8, $SiEt_3$), 0.85 (1H, dd, *J* 14.5 and 7.4, $SiCH^A$), 0.91 (3H, t, *J* 7.8, $SiEt_3$), 1.03 (1H, dd, *J* 14.5 and 7.3, $SiCH^B$), 1.23 (3H, d, *J* 6.14, CH_3), 1.98 (3H, s, $COCH_3$), 5.02 (1H, sextet, <*J*> 7.4, CH).

δ_C : 3.7, 7.3, 20.0, 21.6, 23.3, 70.0, 170.6

2-Acetoxy-1-dimethylphenylsilylpropane 26



26

The product was obtained as a colourless oil (2.02 g, 85 %).

Found: C, 65.52; H, 8.51. $C_{13}H_{20}O_2Si$ requires C, 66.05; H, 8.53 %.

m/z (APCI) 259 (M^++ Na, 41), 237 (M^++1, 34), 177 (M^+-OAc, 6), 149 ($PhMe_2SiCH_2^+$, 89), 135 ($PhMe_2Si^+$, 57), 123 (98), 121 (100), 117 (80), 101 (M^+-$SiMe_2Ph$, 15), 89 (44).

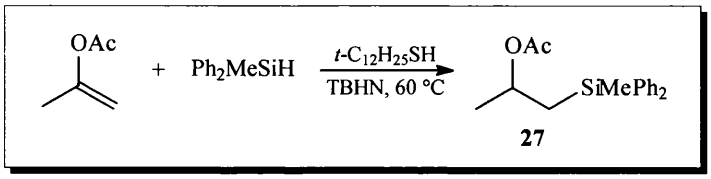
δ_H : 0.31 (3H, s, $SiMe_2$), 0.32 (3H, s, $SiMe_2$), 1.12 (1H, dd, *J* 14.6 and 7.2, $SiCH^A$), 1.19 (3H, d, *J* 6.1, CH_3), 1.30 (1H, dd, *J* 14.6 and 7.0, $SiCH^B$),

1.88 (3H, s, $COCH_3$), 5.03 (1H, sextet, <*J*> 6.2, CH), 7.35 (3H, m, Ph), 7.50 (2H, m, Ph).

δ_C : 2.4, 23.7, 25.5, 26.7, 72.0, 130.2, 131.4, 135.8, 141.0, 172.8.

When methyl thioglycolate was used as the catalyst, the product was obtained in 75 % yield. When pentafluorothiophenol was used as the thiol catalyst, the ^1H NMR spectrum of the crude mixture indicated only a trace (<1 %) of product had been formed. In the absence of a thiol catayst, <1 % product was formed.

2-Acetoxy-1-diphenylmethylsilylpropane 27



The product was obtained as a colourless oil (1.48 g, 99 %).

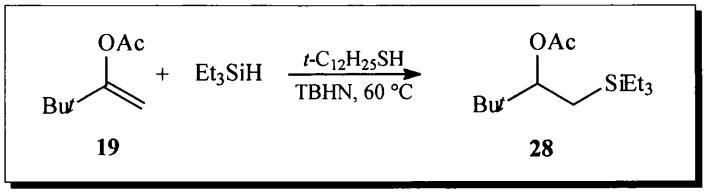
Found : C, 72.25; H, 7.57. $C_{18}H_{22}O_2Si$ requires C, 72.44; H, 7.43 %.

m/z (APCI) 321 (M^+ + Na, 22), 298 (M^+, 2), 297 (M^+-1, 4), 296 (M^+-2, 14), 229 (24), 197 (Ph_2MeSi^+, 30), 179 (43), 165 (77), 151 (47), 137 (100), 133 (51), 105 (37).

δ_H : 0.62 (3H, s, SiMe), 1.19 (3H, d, *J* 6.2, CH_3), 1.42 (1H, dd, *J* 14.6 and 7.0, $SiCH^A$), 1.64 (1H, dd, *J* 14.9 and 7.3, $SiCH^B$), 1.76 (3H, s, $COCH_3$), 5.09 (1H, sextet, <*J*> 6.2, CH), 7.35 (6H, m, Ph), 7.50 (4H, m, Ph).

δ_C : 21.2, 22.9, 23.3, 69.4, 127.9, 129.3, 134.3(5), 134.4(3), 136.5, 136.7, 170.4.

2-Acetoxy-3,3-dimethyl-1-triethylsilylbutane 28



The product was also distilled under reduced pressure to afford a colourless oil (1.09 g, 84 %), b.p. 65 °C/0.04 Torr.

Found : C, 65.07; H, 11.92. $C_{14}H_{30}O_2Si$ requires C, 65.06; H, 11.70 %.

m/z (APCI) 281 (M^+ + Na, 4), 258 (M^+, <1), 228 (M^+-2 Me, 100), 214 (M^+-CO_2, 31), 145 (60), 115 (Et_3Si^+, 30).

δ_H : 0.48 (2H, complex m, *J* 8.2, $SiEt_3$), 0.73 (1H, dd, *J* 15.1 and 2.2, $SiCH^A$),

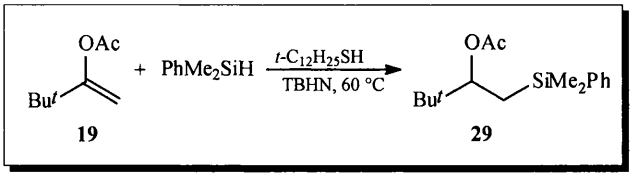
(other H from $SiCH^B$, overlapping with $SiEt_3$ triplet),

0.84 (9H, s, Bu^t), 0.89 (3H, t, *J* 8.2, $SiEt_3$), 1.99 (3H, s, $COCH_3$),

4.90 (1H, dd, *J* 11.6 and 2.1, CH).

δ_C : 3.4, 7.4, 11.4, 21.4, 25.6, 36.1, 78.0, 170.6.

2-Acetoxy-3,3-dimethyl-1-dimethylphenylsilylbutane 29



19 29

Product was also distilled under reduced pressure to afford a colourless oil (1.25 g, 90 %), b.p. 86 °C/0.3 Torr. The yield was high, but the adduct was difficult to purify by flash-column chromatography.

Found : C, 68.69; H, 9.46. $C_{16}H_{26}O_2Si$ requires C, 69.01; H, 9.41 %.

m/z (APCI) 301 (M^++ Na, 97), 279 (M^++1, 7), 270 (100), 248 (M^+-2 Me, 22), 149 ($PhMe_2SiCH_2^+$, 70), 135 ($PhMe_2Si^+$, 33), 117 (92), 100 (63).

δ_H : 0.26 (3H, s, $SiMe_2$), 0.32 (3H, s, $SiMe_2$), 0.85 (9H, s, Bu^t),

0.97 (1H, dd, *J* 14.9 and 2.1, $SiCH^A$), 1.15 (1H, dd, *J* 14.9 and 11.8, $SiCH^B$),

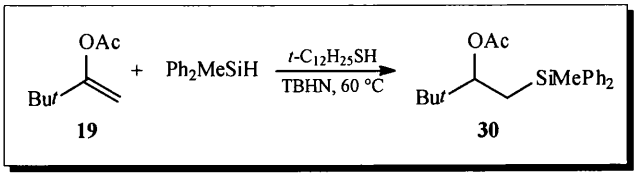
1.67 (3H, s, $COCH_3$), 4.95 (1H,dd, *J* 11.7 and 1.8, CH), 7.34 (3H, m, Ph),

7.49 (2H, m, Ph).

δ_C : -2.3, 16.6, 20.9, 25.6, 35.9, 77.7, 128.8, 133.6, 139.1, 170.6.

A reaction was also attempted using pentafluorothiophenol as catalyst, but the ^1H NMR spectrum of the crude product indicated a trace (<1 %) amount of adduct **29**.

2-Acetoxy-3,3-dimethyl-1-diphenylmethylsilylbutane 30



19 30

The product was obtained as a colourless oil (1.67g, 98 %).

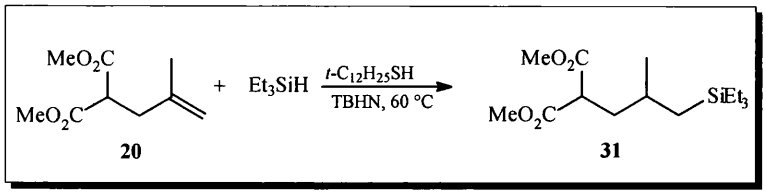
Found : C, 74.04; H, 8.31. $C_{21}H_{28}O_2Si$ requires C, 74.07; H, 8.29 %.

m/z (APCI) 363 (M^++ Na, 52), 340 (M^+, <1), 310 (M^+-2 Me, 18), 270 (27), 197 (Ph_2MeSi^+, 48), 151 (55), 137 (100).

δ_H : 0.62 (3H, s, SiMe), 0.88 (9H, s, Bu^t), 1.28 (1H, dd, J 15.1 and 2.2, SiCH^A),
1.39 (3H, s, $COCH_3$), 1.50 (1H, dd, J 15.1 and 11.9, SiCH^B),
5.01 (1H, dd, J 11.9 and 2.1, CH), 7.35 (6H, m, Ph), 7.45 (2H, m, Ph),
7.54 (2H, m, Ph).

δ_C : 16.6, 35.9, 77.7, 127.7, 128.8, 133.6, 139.1, 170.6.

Dimethyl (2-methyl-3-triethylsilyl)malonate 31



The product was obtained as a colourless oil (1.47 g, 97 %).

Found : C, 59.50; H, 10.08. $C_{15}H_{30}O_4Si$ requires C, 59.56; H, 10.00 %.

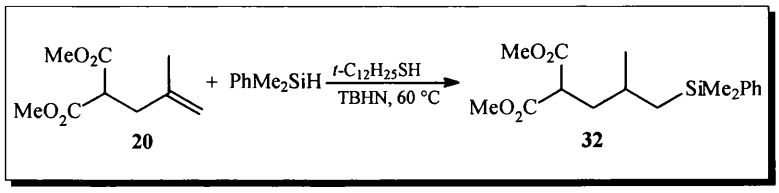
m/z (EI) 301 (M^+-1, <1), 273 (M^+-Et, 100), 87 ($^+SiEt_2$+1, 50), 59 (MeO_2C^+, 49).

m/z (APCI) 325 (M^++ Na, 20), 303 (M^++1, 12), 157 ($MeC^+HCH_2SiEt_3$, 52), 147 (100),
115 (Et_3Si^+, 47).

δ_H : 0.40 (1H, dd, J, 14.7 and 9.1, SiCH^A), 0.50 (2H, q, J 7.9, $SiEt_3$),
0.61 (1H, dd, J 14.8 and 4.6, SiCH^B), 0.90 (3H, t, J 7.9, $SiEt_3$),
0.91 (3H, d, J 5.3, CH_3), 3.46 (1H, dd, J 8.2 and 7.1, CH),
3.70(8) (3H, s, CO_2Me), 3.71(3) (3H, s, CO_2Me).

δ_C : 3.9, 7.4, 19.4, 22.5, 27.5, 39.6, 49.9, 52.3(8), 52.4(1), 170.0, 170.1.

Dimethyl (3-dimethylphenylsilyl-2-methyl)malonate 32



The product was obtained as a colourless oil (1.47 g, 90 %).

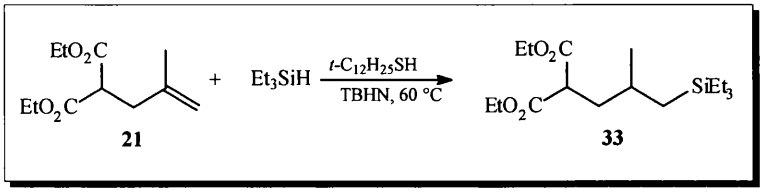
Found : C, 62.98; H, 8.19. $C_{17}H_{26}O_4Si$ requires C, 63.32; H, 8.13 %.

δ_H : 0.28 (3H, s, $SiMe_2$), 0.29 (3H, s, $SiMe_2$),
0.66 (1H, dd, J 14.8 and 8.9, SiCH^A), 0.87 (3H, d, J 6.6, CH_3),
0.88 (1H, dd, J 14.7 and 4.8, SiCH^B), 1.56 (1H, m, CH), 1.76 (1H, m, CH_2),
1.89 (1H, m, CH_2), 3.43 (1H, dd, J 7.9 and 7.5, CH), 3.68(2) (3H, s, CO_2Me),

3.68(4) (3H, s, CO_2Me), 7.33 (3H, m, Ph), 7.48 (2H, m, Ph).

δ_C : 22.5, 23.9, 27.7, 39.3, 49.8, 52.4, 52.4, 127.7, 128.8, 133.5, 139.5, 169.9, 170.1.

Diethyl (2-methyl-3-triethylsilyl)malonate 33



The product was obtained as a colourless oil (1.52 g, 92 %).

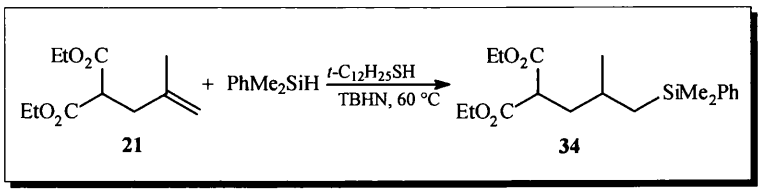
Found : C, 61.68; H, 10.45. $C_{17}H_{34}O_4Si$ requires C, 61.77; H, 10.37 %.

m/z (EI) 330 (M^+, 6), 329 (M^+-1, 22), 301 (M^+-Et, 64), 115 (Et_3Si^+, 67), 87 (Et_2Si^++1, 100). *m/z* (APCI) 353 (M^++Na, 21), 331 (M^++1, 47), 161 [$(EtO_2C)_2CH^+$+2, 100).

δ_H : 0.41 (1H, dd, *J* 14.8 and 9.1, $SiCH^A$), 0.51 (2H, q, *J* 7.9, $SiEt_3$),
0.63 (1H, dd, *J* 14.8 and 4.6, $SiCH^B$), 0.91 (3H, t, *J* 7.9, $SiEt_3$),
0.93 (3H, d, *J* 6.5, CH_3), 1.25 (3H, m, CO_2Et), 1.56 (1H, m, CH),
1.75 (1H, m, CH_2), 1.87 (1H, m, CH_2), 3.42 (1H, dd, *J* 8.2 and 7.1, CH),
4.18 (2H, m, CO_2Et).

δ_C : 4.0, 7.5, 14.1, 19.5, 22.6, 27.5, 39.5, 50.3, 61.3, 169.7, 169.8.

Diethyl (3-dimethylphenylsilyl-2-methyl)malonate 34



The product was obtained as a colourless oil (1.44 g, 82 %).

Found : C, 65.36; H, 8.79. $C_{19}H_{30}O_4Si$ requires C, 65.10; H, 8.63 %.

m/z (APCI) 373 (M^++ Na, 6), 351 (M^++1, <1), 274 (44), 273 (M^+-Ph, 100), 245 (20), 227 (24), 155 (19), 141 (13).

δ_H : 0.27(1) (3H, s, $SiMe_2$), 0.27(4) (3H, s, $SiMe_2$),
0.66 (1H, dd, *J* 14.6 and 8.9, $SiCH^A$), 0.86 (3H, d, *J* 6.4, CH_3),
0.88 [1H, dd, (upfield d overlaps with CH_3 d), *J* 14.6, 4.5, $SiCH^B$],
0.22 (3H, m, CO_2Et), 1.58 (1H, m, CH), 1.74 (1H, m, CH_2),
1.86 (1H, m, CH_2), 3.37 (1H, t, *J* 8.1, CH), 4.14 (2H, m, CO_2Et),

7.31 (3H, m, Ph), 7.47 (2H, m, Ph).

δ_C : -2.1, 14.0, 22.4, 23.9, 27.7, 39.2, 50.2, 61.2, 127.7, 128.8, 133.4, 139.6, 169.6, 169.7.

Chiral-stationary-phase HPLC analysis was also carried out on this racemate using a Chiralcel-OJ column (Daicel Chemical Industries) at 240 nm using 0.2 % isopropanol in hexane eluent [retention time (RT): 9 and 12 min at a flow rate of 1.0 cm^3min^{-1}].

Hydrosilylation of prochiral cyclic alkenes

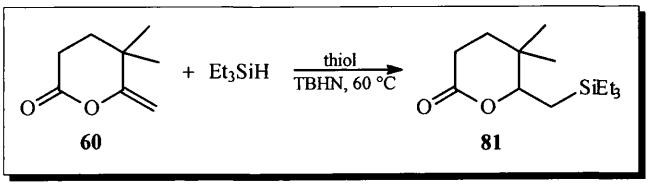
These hydrosilylation reactions followed the same basic procedure and were carried out on a 2.5 mmol scale (unless otherwise stated) of alkene. The achiral thiol (5 mol %) and the solvent were varied.

General procedure

A solution of the alkene (2.5 mmol), silane (3.25 mmol), thiol (0.125 mmol) and TBHN (22 mg, 0.125 mmol) were dissolved in the appropriate solvent (stated below). A short condenser was attached to the reaction flask, the apparatus was flushed with nitrogen and the solution was stirred and heated for 2.5 h at 60 °C. After cooling to room temperature, the solvent was removed by evaporation under reduced pressure and the crude product was purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the product.
The thiol in these experiments was added all at the beginning of the reaction and no reduction of yield was observed.

The column, conditions (% IPA, isopropyl alcohol in hexane) with retention times for chiral-stationary-phase HPLC analyses for the silane adducts (except **81** and **85**) are also given.

5,5-Dimethyl-6-triethylsilylmethyltetrahydropyran-2-one 81



This reaction was carried out on a 5 mmol scale of lactone and *tert*-dodecanethiol was

used as the thiol catalyst. In this reaction, Et_3SiH (3.49 g, 30 mmol) was used as solvent. The crude material was purified by flash-column chromatography [eluent: petroleum-ether (9:1), followed by petroleum-ether (6:1), followed by petroleum-ether (4:1)] to afford the product as a colourless oil (0.39 g, 30 %).

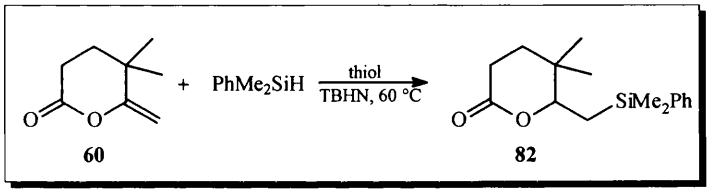
Found : C, 65.33; H, 11.26. $C_{14}H_{28}O_2Si$ requires C, 65.57; H, 11.00 %.

δ_H : 0.60 (6H, m, $SiC\underline{H}_2CH_3$), 0.73 (1H, dd, *J* 14.8 and 2.5, $SiCH^A$), 0.84 (1H, dd, *J* 14.8 and 12.0, $SiCH^B$), 0.91 (3H, s, CMe^A), 0.92 (9H, t, *J* 7.9, $SiCH_2C\underline{H}_3$), 0.94 (3H, s, CMe^B) 1.64 (2H, m, CH_2), 2.52 (2H, m, CH_2CO_2), 4.11 (1H, dd, *J* 12.0 and 2.5, CHO).

δ_C : 3.6, 7.4, 12.4, 19.0, 26.5, 27.4, 32.9, 33.8, 85.9, 171.5.

The ^1H NMR spectrum of the crude product indicated a 60 % yield.

5,5-Dimethyl-6-dimethylphenylsilylmethyltetrahydropyran-2-one 82



This reaction was carried out on a 5 mmol scale of lactone and methyl thioglycolate was used as the catalyst; hexane (4.0 cm^3) was used as the solvent. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (9:1), followed by petroleum-ether (6:1), followed by petroleum-ether (4:1)] to afford the adduct as a colourless oil (1.04 g, 93 %).

Found : C, 69.35; H, 8.79. $C_{16}H_{24}O_2Si$ requires C, 69.52; H, 8.75 %.

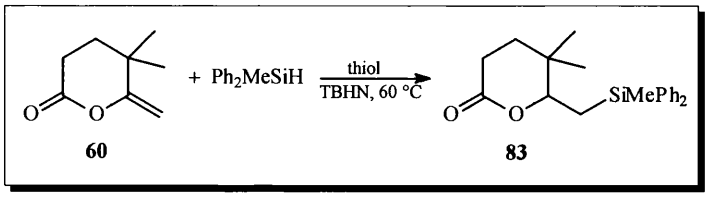
m/z (EI) 276 (M^+, 2), 261 (M^+-Me, 40), 199 (M^+-Ph, 28), 135 ($PhMe_2Si^+$, 100), 42 (47).

δ_H : 0.37 (3H, s, $SiMe^A$), 0.41 (3H, s, $SiMe^B$), 0.89 (3H, s, CMe^A), 0.91 (3H, s, CMe^B), 0.96 (1H, dd, *J* 14.7 and 2.6, $SiCH^A$), 1.07 (1H, dd, *J* 14.7 and 11.9, $SiCH^B$), 1.61 (2H, t, *J* 7.3, CH_2), 2.49 (2H, m, CH_2CO_2), 4.06 (1H, dd, *J* 11.9 and 2.6, CHO), 7.34 (3H, m, Ph), 7.52 (2H, m, Ph).

δ_C : -2.9, -1.6, 17.2, 19.2, 26.4, 27.4, 32.9, 33.8, 85.9, 127.8, 129.0, 133.6, 138.6, 171.4.

When *t*-$C_{12}H_{25}SH$ was used as the thiol catalyst, a 75 % yield of the product was obtained. For chiral-phase HPLC: Chiralcel-OJ column at 254 nm {eluent: 20 % IPA, flow rate: 1.0 cm^3min^{-1}, RT: 5 and 8 min} or {eluent: 5 % IPA, RT: 9 and 20 min}.

5,5-Dimethyl-6-diphenylmethylsilylmethyltetrahydropyran-2-one 83



This reaction was carried out on a 5 mmol scale of alkene and *tert*-dodecanethiol was used as the catalyst; hexane (4.0 cm^3) was used as the solvent. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (9:1), followed by petroleum-ether (6:1), followed by petroleum-ether (4:1)] to afford the adduct as a colourless oil (1.44 g, 85 %).

Found : C, 74.46; H, 7.84. $C_{21}H_{26}O_2Si$ requires C, 74.51; H, 7.74 %.

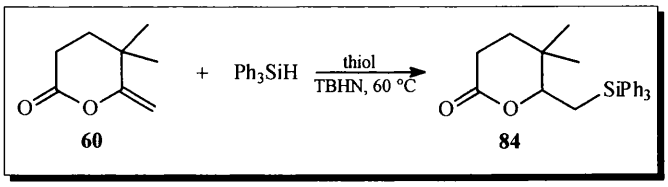
m/z (EI) 338 (M^+, 3), 323 (M^+-Me, 45), 261 (M^+-Ph, 74), 197 (Ph_2MeSi^+, 100), 137 (83).

δ_H: 0.74 (3H, s, SiMe), 0.90 (3H, s, CMe^A), 0.96 (3H, s, CMe^B),
1.35 (2H, apparent d, *J* 6.6, $SiCH_2$), 1.59 (2H, m, CH_2), 2.46 (2H, m, CH_2CO_2),
4.05 (1H, apparent t, *J* 7.1, CHO), 7.35 (6H, m, Ph), 7.52 (4H, m, Ph).

δ_C: -3.2, 15.6, 19.1, 26.4, 27.4, 32.9, 33.8, 85.3, 127.8, 127.9, 129.2, 129.3, 134.3, 134.7, 135.8, 137.1, 171.2.

For chiral-stationary-phase HPLC: Chiralcel-OJ column at 254 nm {eluent: 7 % IPA, flow rate: 1.0 cm^3min^{-1}, RT: 7 and 15 min} or {eluent: 10 % IPA, RT: 6 and 11 min}.

5,5-Dimethyl-6-triphenylsilylmethyltetrahydropyran-2-one 84



tert-Dodecanethiol was used as the catalyst and hexane (4.0 cm^3) was used as the solvent. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (9:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the adduct as a white solid (0.31 g, 54 %), m.p. 114-116 °C. ^1H NMR analysis indicated a 63 % yield before purification.

Found : C, 77.90; H, 7.11. $C_{26}H_{28}O_2Si$ requires C, 77.96; H, 7.05 %.

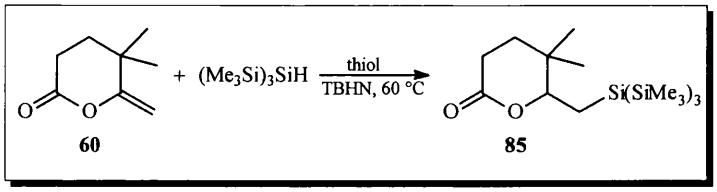
m/z (EI) 400 (M^+, 1), 323 (M^+-Ph, 96), 259 (Ph_3Si^+, 100), 199 (96), 181 (27), 105 (24), 77 (Ph, 10), 41 (24).

δ_H: 0.92 (3H, s, CMe^A), 1.00 (3H, s, CMe^B), 1.58 (3H, m, CH_2 and $SiCH^A$),
1.79 (1H, dd, *J* 15.0 and 11.5, $SiCH^B$), 2.40 (2H, m, CH_2CO_2),
4.11 (1H, dd, *J* 11.5 and 2.4, CHO), 7.38 (9H, m, Ph), 7.59 (6H, m, Ph).

δ_C: 15.0, 19.3, 26.6, 27.4, 33.1, 34.0, 84.6, 127.8, 129.5, 134.5, 135.9, 170.9.

This reaction was repeated using Ph_3SiSH as the catalyst in hexane (4.0 cm^3) or dioxane (4.0 cm^3). The ^1H NMR spectrum of the crude material after the evaporation of solvent indicated >90 % yield of the product for both solvents. For chiral-stationary-phase HPLC: Chiralcel-OD column at 254 nm {eluent: 1 % IPA, flow rate: 1.0cm^3min^{-1}, RT: 12 and 13 min}.

5,5-Dimethyl-6-tris(trimethylsilyl)silylmethyltetrahydropyran-2-one 85



60 **85**

tert-Dodecanethiol was used as the catalyst and hexane (4.0 cm^3) was used as the solvent. The crude material was purified by flash-column chromatography [eluent: neat petroleum, followed by petroleum-ether (10:1), followed by petroleum-ether (6:1)] to afford the product as a colourless oil (0.58 g, 60 %).

Found : C, 51.03; H, 10.50. $C_{17}H_{40}O_2Si_4$ requires C, 52.51; H, 10.37 %.

m/z (EI) 315 (M^+-Me_3Si), 73 (Me_3Si^+). *m/z* (CI) 389 (M^++H), 406 (M^++ NH_4).

m/z (EI with NH_3) 373 (M^+- Me), 315 [M^+- Me-Si$(Me)_2$].

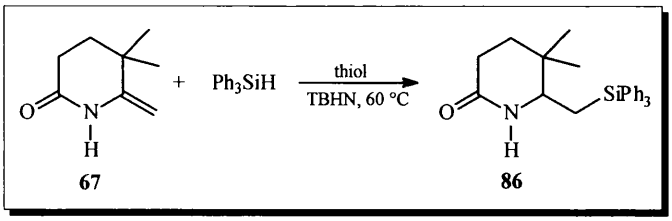
Exact mass : Found (CI) : (M^++H), 389.2207. $C_{17}H_{40}O_2Si_4$ requires, 389.2184.

δ_H: 0.18 [27H, s, $Si(SiMe_3)_3$], 0.91 (3H, s, CMe^A), 0.96 (3H, s, CMe^B),
0.99 (1H, dd, *J* 14.5 and 11.5, $SiCH^A$), 1.06 (1H, dd, *J* 14.5 and 2.5, $SiCH^B$),
1.63 (2H, m, CH_2CMe_2), 2.50 (2H, m, CH_2CO_2),
4.01 (1H, dd, *J* 11.5 and 2.5, CHO).

δ_C: 1.1, 8.8, 18.6, 26.9, 27.7, 33.6, 34.5, 87.4, 171.3.

When 10 mol % *tert*-dodecanethiol was used as catalyst, the ^1H NMR spectrum of the crude material indicated a 74 % yield of product. In the absence of the thiol catalyst, the ^1H NMR spectrum indicated 44 % yield. The racemate adduct was analysed using homochiral shift reagent [Eu(hfc)$_3$].

5,5-Dimethyl-6-triphenylsilylmethylpiperidin-2-one 86



Triphenylsilanethiol was used as catalyst and a mixture of hexane and dioxane (2.0 cm^3 and 2.0 cm^3, respectively) was used as the solvent. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (9:1), followed by petroleum-ether (1:1), followed by neat ether] to afford the product as a white solid (0.64 g, 65 %), m.p. 129-130 °C.

Found: C, 77.92; H, 7.37; N, 3.35. $C_{26}H_{29}ONSi$ requires C, 78.15; H, 7.31; N, 3.51 %.

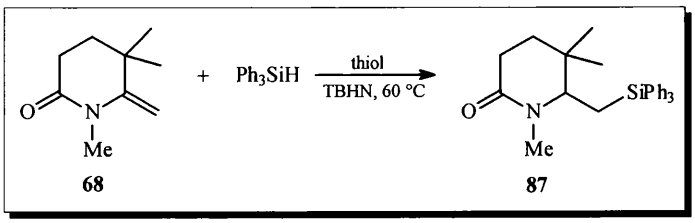
m/z (EI) 399 (M^+, 20), 343 (M^+-CH_2CMe_2, 20), 259 (Ph_3Si^+, 100), 181 (Ph_2Si^+-1, 20), 140 (M^+-$SiPh_3$, 63), 126 (M^+-CH_2SiPh_3, 14), 105 ($PhSi^+$, 20).

δ_H: 0.97 (3H, s, CMe^A), 0.98 (3H, s, CMe^B), 1.34 (1H, dd, *J* 15.0 and 11.7, $SiCH^A$), 1.57 (2H, m, CH_2CMe_2), 1.75 (1H, dd, *J* 15.0 and 1.1, $SiCH^B$), 2.27 (2H, m, CH_2CO), 3.40 (1H, apparent d, *J* 11.5, CHNH), 5.17 (1H, brs, NH), 7.37-7.60 (15H, m, Ph).

δ_C: 15.3, 18.6, 27.1, 28.4, 33.2, 34.8, 58.2, 128.4, 130.2, 133.5, 135.6, 171.2.

The ^1H NMR spectrum of the crude product indicated a 74 % yield of product had been formed. When *tert*-dodecanethiol was used as the catalyst, the ^1H NMR spectrum of the crude material indicated a 40 % yield of the product. For chiral-stationary-phase HPLC: Chiralpak-AD column at 254 nm {eluent: 10 % IPA, flow rate: 1.0 cm^3min^{-1}, RT: 7 and 11 min}.

1,5,5-Trimethyl-6-triphenylsilylmethylpiperidin-2-one 87



tert-Dodecanethiol was used as the catalyst and hexane (4.0 cm^3) was used as the solvent. The crude material was purified by flash-column chromatography [eluent: petroleum-ether (9:1), followed by petroleum-ether (3:1), followed by petroleum-ether (1:1)] to

afford the product as a white solid (0.33 g, 33 %). The product was recrystallized from CH_2Cl_2/hexane, m.p.131-132 °C.

Found: C, 78.06; H, 7.54; N, 3.55. $C_{27}H_{31}ONSi$ requires C, 78.40; H, 7.55; N, 3.39 %.

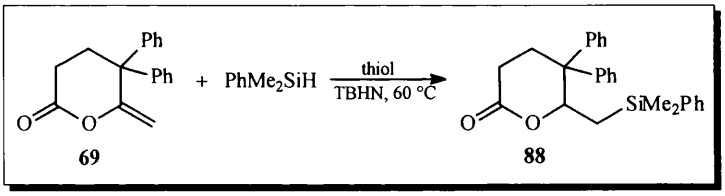
m/z (EI) 413 (M^+, 20), 259 (Ph_3Si^+, 85), 154 (M^+-$SiPh_3$, 100), 140 (M^+-CH_2SiPh_3, 55).

δ_H: 0.81 (3H, s, CMe^A), 0.89 (3H, s, CMe^B), 1.41 (1H, dddd, *J* 13.8, 7.9, 3.5 and 1.6, CH^ACMe_2), 1.58 (1H, dd, *J* 15.5 and 8.2, $SiCH^A$), 1.89 (1H, dd, *J* 15.5 and 3.7, $SiCH^B$), 2.02 (1H, dt, *J* 13.8 and 9.0, CH^BCMe_2), 2.36 (2H, m, CH_2CO), 2.43 (3H, s, NMe), 3.01 (1H, ddd, *J* 8.2, 3.7 and 1.6, CHN), 7.29-7.55 (15H, m, Ph).

δ_C: 16.5, 25.7, 27.5, 28.3, 29.2, 34.8, 36.4, 65.8, 128.1, 129.7, 134.3, 135.5, 169.8.

The ^{1}H NMR spectrum of the crude product before chromatography indicated a 50 % yield of adduct. For chiral-stationary-phase HPLC: Chiralpak-AD column at 254 nm {eluent: 5 % IPA, flow rate: 1.0 cm^3min^{-1}, RT: 7 and 9 min}.

6-Dimethylphenylsilylmethyl-5,5-diphenyltetrahydropyran-2-one 88



69 88

Triphenylsilanethiol was used as catalyst and a mixture of hexane and dioxane (5.0 cm^3 and 1.0 cm^3, respectively) as the solvent. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (6:1)] to afford the product as a colourless oil (0.65 g, 65 %). The ^{1}H NMR spectrum of the crude product indicated an 80 % yield of adduct The product and starting alkene have similar R_f values.

Found : C, 77.62; H,7.03. $C_{26}H_{28}O_2Si$ requires C, 77.96; H, 7.05 %.

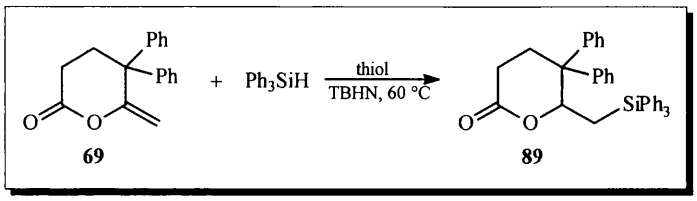
m/z (APCI) 423 (M^++ Na, 10), 401 (M^++1, 4), 323 (M^+-Ph, 50), 249 (67), 207 (100).

δ_H: 0.35 (3H, s, $SiMe^A$), 0.46 (3H, s, $SiMe^B$), 0.65 (1H, dd, *J* 14.9 and 2.1, $SiCH^A$), 1.15 (1H, dd, *J* 14.9 and 12.0, $SiCH^B$), 2.13 (1H, m, CH^APh_2), 2.46 (1H, m, CH^BPh_2), 2.56 (1H, ddd, J 18.6, 6.1 and 2.2, CH^ACO_2), 2.89 (1H, m, CH^BCO_2), 5.34 (1H, dd, *J* 12.0 and 2.1, CHO), 7.06-7.45 (15H, m, CPh_2 and SiPh).

δ_C: -3.0, -2.0, 19.9, 26.2, 27.4, 48.7, 82.7, 126.5, 126.6, 127.1, 127.5, 127.7, 128.5(0), 128.5(3), 130.0, 133.5, 137.9, 143.8, 144.4, 169.5.

For chiral-stationary-phase HPLC: Chiralcel-OD column at 254 nm {eluent: 4 % IPA, flow rate: 0.5 cm^3min^{-1}, RT: 16 and 17 min}.

5,5-Diphenyl-6-triphenylsilylmethyltetrahydropyran-2-one 89



Triphenylsilanethiol was used as catalyst and a mixture of hexane and dioxane (5.0 cm^3 and 1.0 cm^3, respectively) was used as the solvent. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (9:1), followed by petroleum-ether (6:1), followed by petroleum-ether (2:1)] to afford the product as a white solid (0.13 g, 33 %), m.p. 161-162 °C.

Found : C, 82.11; H, 6.02. $C_{36}H_{32}O_2Si$ requires C, 82.40; H, 6.15 %.

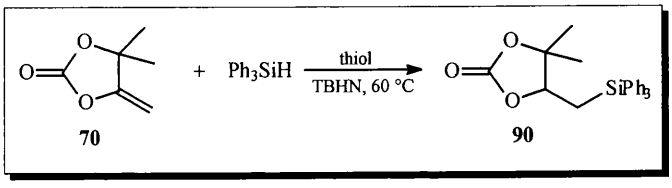
m/z (EI) 524 (M^+, <1), 259 (Ph_3Si^+, 65), 222 (M^+-Ph_3SiCH_2CHO, 100), 180 (97), 57 (30), 44 (CO_2^+, 33).

δ_H: 1.28 (1H, dd, *J* 15.1 and 1.8, $SiCH^A$), 1.78 (1H, dd, *J* 15.1 and 11.5, $SiCH^B$), 2.09 (1H, m, CH^ACPh_2), 2.50 (2H, m, CH^ACO_2 and CH^BCPh_2), 2.92 (1H, m, CH^BCO_2), 5.41 (1H, br. d, *J ca.* 11.5, CHO), 7.02-7.47 (25H, m, $SiPh_3$ and CPh_2).

δ_C: 17.9, 26.5, 27.5, 49.1, 81.8, 126.6, 126.8, 127.3, 127.6, 127.9, 128.7, 129.6, 134.0, 135.8, 143.8, 144.4, 169.0 (overlap of two aryl C).

This reaction was also carried out using *tert*-dodecanethiol and *n*-dodecanethiol as catalysts. The yields obtained were 10-20 % and 20-30 % respectively, as determined by ^1H NMR analysis. For chiral-stationary-phase HPLC: Chiralcel-OD column at 254 nm {eluent: 10 % IPA, flow rate: 1.0 cm^3min^{-1}, RT: 8 and 11 min}.

4,4-Dimethyl-5-triphenylsilylmethyl-1,3-dioxolan-2-one 90



tert-Dodecanethiol was used as the catalyst and hexane (4.0 cm^3) was used as the solvent.

The crude material was purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the adduct as a white solid (0.29 g, 30 %), m.p. 150-151 °C.

Found : C, 74.06; H, 6.15. $C_{24}H_{24}O_3Si$ requires C, 74.19; H, 6.23 %.

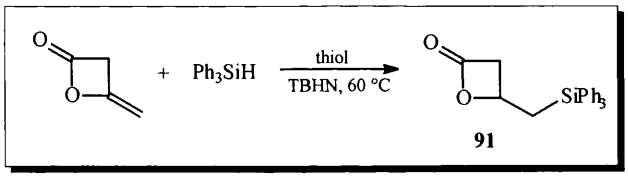
m/z (EI) 388 (M^+, 4), 259 (Ph_3Si^+, 100), 243 (50), 199 (95).

δ_H : 1.32 (3H, s, CMe^A), 1.39 (3H, s, CMe^B), 1.49 (1H, dd, *J* 15.0 and 3.0, $SiCH^A$), 1.90 (1H, dd, *J* 15.0 and 11.4, $SiCH^B$), 4.40 (1H, dd, *J* 11.4 and 3.0, CHO), 7.33-7.55 (15H, m, Ph).

δ_C : 14.3, 21.4, 25.2, 83.2, 84.9, 128.1, 130.0, 133.2, 135.7, 153.7.

The ^1H NMR spectrum of the crude product indicated a 50 % yield of adduct. For chiral-stationary-phase HPLC: Chiralcel-OD column at 254 nm {eluent: 10 % IPA, flow rate: 1.0 cm^3min^{-1}, RT: 7 and 8 min}.

4-Triphenylsilylmethyloxetan-2-one 91



91

tert-Dodecanethiol was used as the catalyst and either dioxane or hexane (4.0 cm^3) could be used as the solvent. The crude material could not be purified by flash-column chromatography because the product decomposes on standard silica. After the removal of the solvent (hexane or dioxane) under reduced pressure, the crude material was recrystallized from CH_2Cl_2 / hexane to afford the product as a white crystalline solid (0.32 g, 37 %). Recrystallization from benzene / hexane proved preferable and improved the yield to 57 %. m.p. 91-92 °C.

Found : C, 77.00; H, 5.71. $C_{22}H_{20}O_2Si$ requires C, 76.71; H, 5.85 %.

m/z (APCI) 367 (M^++ Na, 10), 344 (M^++, 1), 291 (42), 267 (M^+-Ph, 56), 259 (Ph_3Si^+, 98), 213 (65), 153 (100).

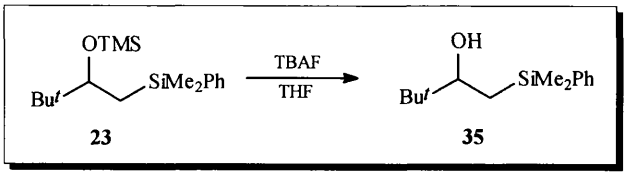
δ_H : 1.86 (1H, dd, *J* 14.1 and 10.8, $SiCH^A$), 2.36 (1H, dd, *J* 14.1 and 4.4, $SiCH^B$), 2.65 (1H, dd, *J* 16.5 and 4.4, H^A-3), 3.10 (1H, dd, *J* 16.5 and 5.7, H^B-3), 4.77 (1H, m, CHO), 7.33-7.53 (15H, m, Ph).

δ_C : 21.2, 44.5, 70.4, 128.3, 130.2, 132.9, 135.4, 168.2.

The ^1H NMR spectrum of the crude product indicated a yield of >90 %. In the absence of

the thiol catalyst, the ^{1}H NMR spectrum of the crude material indicated < 5 % yield of product. For chiral-stationary-phase HPLC: Chiralcel-OD column at 254 nm {eluent: 20 % IPA, flow rate: 1.0 cm^3min^{-1}, RT: 10 and 13 min}.

3,3-Dimethyl-1-dimethylphenylsilyl-2-hydroxybutane 18



23 **35**

The adduct **23** (106 mg, 0.34 mmol) in THF (0.2 cm^3) was cooled to 0 °C. TBAF, (1M soln. in THF) (0.38 cm^3, 0.38 mmol) was added dropwise by syringe. The reaction mixture was warmed to room temperature and left to stir for 3 h. The reaction mixture was then diluted with ether (10 cm^3) and washed with sat. brine (10 cm^3). The ether layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash-column chromatography to afford the product as a colourless oil (74.1 mg, 93 %). IR (liq. film): 3410, 1440, 1135, 860 cm^{-1}.

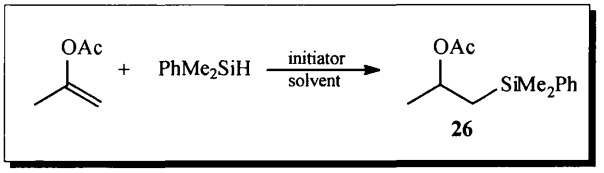
Found : C, 68.9; H, 10.1. $C_{14}H_{24}OSi$ requires C, 71.1; H, 10.2 %.

m/z (APCI) 259 (M^++ Na, 19), 237 (M^++1, 9), 219 (M^+-OH, 22), 167 (38), 149 ($PhMe_2SiCH_2^+$, 46), 135 ($PhMe_2Si^+$, 35), 121 (100), 89 (53).

δ_H : 0.33 (3H, s, $SiMe_2$), 0.34 (3H, s, $SiMe_2$), 0.84 (9H, s, Bu^t), 0.87 (1H, dd, *J* 14.9 and 11.4, $SiCH^A$), 0.99 (1H, dd, *J* 14.9 and 2.3, $SiCH^B$), 1.16 (1H, brs, OH), 3.41 (1H, dd, *J* 11.5 and 2.2, CH), 7.34 (3H, m, Ph), 7.54 (2H, m, Ph).

δ_C : 18.7, 25.4, 29.7, 35.9, 77.6, 127.8, 128.9, 133.6(0), 139.6(3).

Effects of changing solvent and initiator on the standard hydrosilylation reaction



26

All these reactions follow the same basic procedure. The general procedure when using AIBN (5 mol %) as initiator is shown below.

General procedure

Isopropenyl acetate (0.50 g, 5.0 mmol), dimethylphenylsilane (0.89 g, 6.5 mmol) and AIBN (41mg, 0.25 mmol) in dry solvent (3.0 cm^3) were placed in a 10 cm^3 flask round-bottomed equipped with a stirrer bar, fitted with a short condenser and flushed with nitrogen. The flask was placed in an oil bath preheated to 80 °C and stirred. *tert*-Dodecanethiol (50 mg, 0.25 mmol) in dry solvent (1.0 cm^3) was added over a period of 2 h to the mixture (using a syringe pump *via* a Teflon tube which passed down the condensor). After the addition, the reaction mixture was heated and stirred for a further 30 min. The mixture was then cooled and solvent was removed under reduced pressure. The crude product was then purified by flash-column chromatography [eluent: petroleum followed by petroleum-ether (19:1)] to afford the silane adduct as a colourless oil.
All the results have been summarised in Table 2 (p. 30) which is reproduced below.

Table 2: Hydrosilylation of isopropenyl acetate **18** with $PhMe_2SiH$ using *t*-$C_{12}H_{25}SH$ as catalyst

Entry	Initiator[a]	Solvent	Yield (%)
1	TBHN	hexane	93
2	TBHN	DMF	40
3	AIBN	benzene	42
4	AIBN	dioxane	35
5	AIBN	cyclohexane	39
6	ACHN	cyclohexane	<1

a. Reactions using AIBN and ACHN (entries 3-6) as initiators were carried out at 80 °C (bath temperature) and those using TBHN at 60 °C.

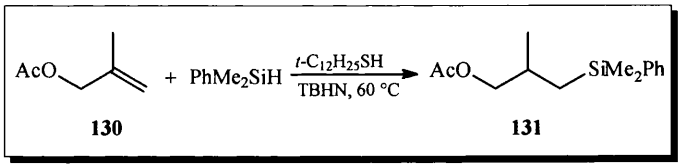
Hydrosilylation of miscellaneous alkenes

Hydrosilylations of these alkenes all follow the same basic procedure.

General procedure

A solution of alkene (5.0 mmol), TBHN (44 mg, 0.25 mmol) and dimethylphenylsilane (0.89 g, 6.5 mmol) in hexane (3.0 cm^3) [or triethylsilane (3.49 g, 30 mmol) and no hexane] was placed in a flask containing a magnetic stirrer bar and fitted with a short reflux condenser, equipped with a septum inlet and a nitrogen by-pass bubbler. The reaction mixture was heated in an oil bath and stirred at 60 °C. *tert*-Dodecanethiol (50 mg, 0.25 mmol) in hexane (1.0 cm^3) was added *via* a syringe pump over 2 h to the stirred reaction mixture. After the addition, the reaction mixture was heated for a further 30 min and then allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was purified either by flash-column chromatography or by distillation.

1-Acetoxy-3-dimethylphenylsilyl-2-methylpropane 131



After removal of the solvent at the rotary evaporator, unreacted alkene was removed by pumping the crude product at 0.02 Torr. The residue was purified by flash-column chromatography [eluent: petroleum-ether (9:1)] to afford the product as a colourless oil (0.88 g, 70 %).

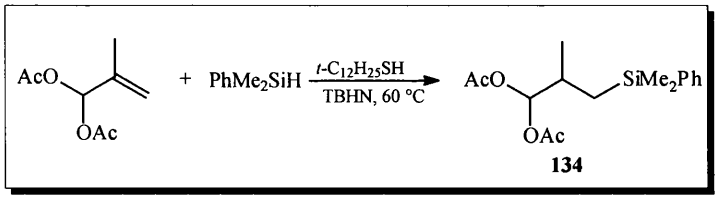
Found : C, 66.98; H, 8.95. $C_{14}H_{22}O_2Si$ requires C, 67.15; H, 8.86 %.

m/z (APCI) 273 (M^++ Na, 2), 251 (M^++1, 1), 173 (M^+-Ph, 33), 149 (M^+-CH_2SiMe_2Ph, 62), 117 (100).

δ_H: 0.31 (6H, s, $SiMe_2$), 0.64 (1H, dd, *J* 14.9 and 9.05, $SiCH^A$),
0.90 (3H, d, *J* 6.7, CH_3), 0.91 (1H, dd, *J* 14.9 and 4.6, $SiCH^B$),
1.92 (1H, m, $CH_3C\underline{H}$), 2.02 (3H, s, Ac), 3.77 (1H, dd, *J* 10.7 and 7.1, $C\underline{H}^AOAc$),
3.85 (1H, dd, *J* 10.7 and 5.9, $C\underline{H}^BOAc$), 7.33 (3H, m, Ph), 7.48 (2H, m, Ph).

δ_C: -2.3, -2.1, 19.8, 20.2, 20.9, 29.1, 71.4, 127.7, 128.8, 133.4, 139.3, 171.0.

1,1-Diacetoxy-3-dimethylphenylsilyl-2-methylpropane 134



Because the product and starting alkene have similar R_f values, the product was purified by distillation (to remove unreacted alkene b.p. 70° C/10 Torr). The residue was purified by flash-column chromatography [eluent: petroleum-ether (9:1)] to afford the product as a colourless oil (0.45 g, 30 %).

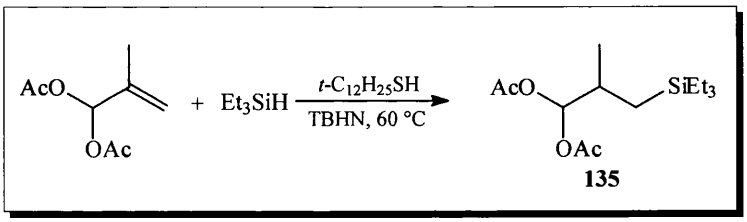
Found : C, 62.22; H, 7.68. $C_{16}H_{24}O_4Si$ requires C, 62.30; H, 7.84 %.

m/z (APCI) 331 (M^++ Na, 27), 221 (21), 189 (30), 121 (60), 89 (100).

δ_H: 0.31 (3H, s, $SiMe^A$), 0.32 (3H, s, $SiMe^B$), 0.65 (1H, dd, *J* 14.8 and 10.5, $SiCH^A$), 0.90 (3H, d, *J* 6.8, CH_3), 1.00 (1H, dd, *J* 14.8 and 3.6, $SiCH^B$), 1.98 (1H, m, $CH_3C\underline{H}$), 2.03 (3H, s, Ac^A), 2.05 (3H, s, Ac^B), 6.58 (1H, d, *J* 4.3, CH), 7.33 (3H, m, Ph), 7.48 (2H, m, Ph).

δ_C: -2.4, -2.1, 16.3, 17.2, 20.7, 20.8, 32.9, 93.3, 127.8, 128.9, 133.5, 138.9, 169.0(8), 169.1(2).

1,1-Diacetoxy-2-methyl-3-triethylsilylpropane 135



Because the product and starting alkene have similar R_f values, the product was purified by distillation (to remove unreacted alkene b.p. 70 ° C/10 Torr). The residue was purified by flash-column chromatography [eluent: petroleum-ether (9:1)] to afford the product as a colourless oil (0.45 g, 31 %).

Found : C, 58.39; H, 9.61. $C_{14}H_{28}O_4Si$ requires C, 58.29; H, 9.78 %.

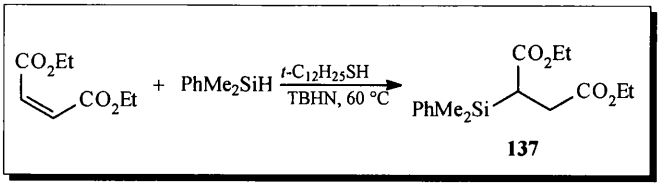
m/z (APCI) 311 (M^++ Na, 71), 288 (M^+, 2), 239 (84), 125 (72), 107 (100), 85 (83).

δ_H: 0.38 (1H, dd, *J* 14.8 and 10.7, $SiCH^A$), 0.52 (2H, q, *J* 7.9, $SiC\underline{H}_2CH_3$), 0.72 (1H, dd, *J* 14.8 and 3.3, $SiCH^B$), 0.91 (3H, t, 7.9, $SiCH_2C\underline{H}_3$), 0.95 (3H, d, *J* 6.7, CH_3), 1.96 (1H, m, $C\underline{H}CH_3$), 2.06 (6H, s, 2x Ac),

6.57 (1H, d, *J* 4.5, CH).

δ_C: 3.7, 7.3, 12.5, 16.4, 20.8, 32.7, 93.5, 169.2

Diethyl (2-dimethylphenylsilyl)succinate 137



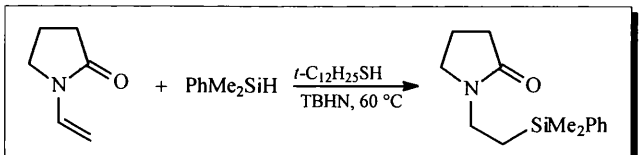
137

The product was not isolated but was identified in the crude mixture by its ^{1}H NMR spectrum; this indicated a yield of *ca.* 37 %.

200 MHz ^{1}H NMR

δ_H: 0.34 (3H, s, $SiMe^A$), 0.36 (3H, s, $SiMe^B$), 1.14 (3H, t, *J* 7.1, $C^AO_2CH_2C\underline{H}_3$), 1.17 (3H, t, *J* 7.1, $C^BO_2CH_2C\underline{H}_3$), 2.21 (1H, dd, *J* 14.0 and 1.2, SiCH), 2.62-2.74 (2H, m, CH_2), 4.04 (4H, q, *J* 7.1, 2x $CO_2C\underline{H}_2CH_3$), 7.31-7.56 (5H, m, Ph).

***N*-Dimethylphenylsilylethylpyrrolidin-2-one 139**



139

The product was purified by flash-column chromatography [eluent: neat petroleum, followed by neat ether] to afford the product as a colourless oil (0.66 g, 53 %).

Found: C, 66.98; H, 8.63; N, 5.42. $C_{14}H_{21}ONSi$ requires C, 67.97; H, 8.56; N, 5.66 %.

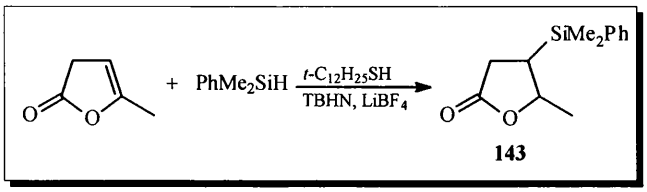
m/z (APCI) 495 (2 M^++1, 3), 270 (M^++ Na, 5), 248 (M^++1, 5), 172 (11), 171 (36), 170 (M^+-Ph, 100), 142 (3). Not many peaks were observed.

δ_H: 0.31 (6H, s, $SiMe_2$), 1.03 (2H, m, $SiCH_2$), 1.84 (2H, m, H-4), 2.26 (2H, t, *J* 8.1, H-3), 3.25 (2H, t, *J* 7.1, H-5), 3.34 (2H, m, NCH_2), 7.34 (3H, m, Ph), 7.49 (2H, m, Ph).

δ_C: -3.3, 14.3, 17.4, 31.1, 38.2, 46.0, 127.7, 129.0, 133.3, 138.2, 174.2.

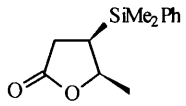
In the absence of thiol catalyst, the ^{1}H NMR spectrum of the crude mixture after solvent removal indicated < 1 % product had been found along with a large amount of an uncharacterised polymer.

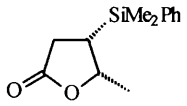
4-Dimethylphenylsilyl-5-methyltetrahydrofuran-2-one 143



In this reaction, $LiBF_4$ (0.47 g, 5 mmol) and DMF or sulpholan as solvent were used in addition to all other reagents (as stated in the general procedure). At the end of the reaction, the mixture was diluted with ether (10 cm^3) and washed successively with water (10 cm^3) and sat. brine (10 cm^3) then dried over $MgSO_4$. After evaporation of ether under reduced pressure, the product was purified by flash-column chromatography [eluent: neat petroleum, followed by petroleum-ether (8:1)] to afford the product as a colourless oil (0.23 g, 20 %). The *cis*- and *trans*-products were not separately isolated, but could be identified from the ^1H NMR spectra of two fractions collected. One of the fractions contained 90 % *cis*-isomer and 10 % *trans*-isomer. The other fraction contained equal amounts of the *cis*- and *trans*-isomers. In the absence of the Lewis acid, under otherwise identical conditions, the ^1H NMR analysis of the reaction mixture indicated a 4-5 % yield of product.

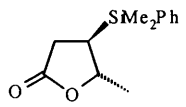
***Cis*-isomer**

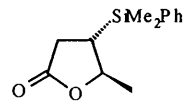




δ_H: 0.36 (3H, s, $SiMe^A$), 0.40 (3H, s, $SiMe^B$), 1.21 (3H, d, *J* 6.7, Me), 2.16 (1H, ddd, *J* 12.4, 9.3 and 7.6, CHSi), 2.45-2.49 (2H, m, CH_2CO_2), 4.80 (1H, dq, *J* 7.5 and 6.7, CHO), 7.34-7.48 (5H, m, Ph).

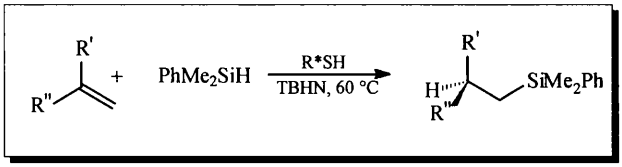
***Trans*-isomer**





δ_H: 0.36 (3H, s, $SiMe^A$), 0.40 (3H, s, $SiMe^B$), 1.27 (3H, d, *J* 6.1, Me), 1.58 (1H, ddd, *J* 12.5, 10.3 and 8.9, CHSi), 2.37 (1H, dd, *J* 18.0 and 12.9, CH^ACO_2), 2.53 (1H, dd, *J* 18.6 and 9.4, CH^BCO_2), 4.43 (1H, dq, *J* 10.0 and 6.1, CHO), 7.34-7.48 (5H, m, Ph).

Enantioselective hydrosilylation of prochiral acyclic alkenes using homochiral thiols



All these hydrosilylation reactions follow the same basic procedure using a homochiral thiol (5 mol %) as the catalyst.

General procedure

A solution of alkene (5 mmol), TBHN (44 mg, 0.25 mmol) and dimethylphenylsilane (0.89 g, 6.5 mmol) in hexane or dioxane (3.0 cm^3) was placed in a flask containing a stirrer bar and fitted with a short reflux condenser, equipped with a septum inlet and a nitrogen by-pass bubbler. The mixture was stirred and heated at 60 °C. The homochiral thiol (0.25 mmol) in hexane or dioxane (1.0 cm^3) was added *via* a syringe pump over 2 h to the stirred reaction mixture. After the addition, the mixture was heated for a further 30 min, then allowed to cool to room temperature, concentrated *in vacuo* and purified by flash-column chromatography [eluent: neat petroleum, followed by petroleum-ether (19:1)].

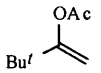
All the results for these reactions have been summarised in Table 3 (p. 35) which is reproduced below.

Table 3: Enantioselective hydrosilylation of acyclic prochiral alkenes with $PhMe_2SiH$ using homochiral thiol catalysts

Entry	Alkene	Product	Thiol catalyst[a]	Isolated yield (%)	Product ee (%)[b]
1	**18**	**26**	**49**	33	3
2	**18**	**26**	**50**	72	1
3	**18**	**26**	**56**	94	3
4	**18**	**26**	**57**	94	3
5	**19**	**29**	**49**	55	3
6	**19**	**29**	**50**	74	7
7	**19**	**29**	**56**	62	5
8	**19**	**29**	**57**	87	3
9	**21**	**34**	**49**	60	4
10	**21**	**34**	**49**[c]	50	12
11	**21**	**34**	**50**	54	13
12	**21**	**34**	**56**	82	10
13	**21**	**34**	**57**	41	4

a. Hexane was used as solvent with the thiols **49** and **50**; dioxane was used as solvent with the thiols **56** and **57**. *b* The enantiomeric excesses of the products **26** and **29** were determined by using the homochiral NMR shift reagent, $Eu(hfc)_3$. The ee of the adduct **34** was determined by chiral-stationary-phase HPLC analysis using a Chiralcel-OJ column (Daicel Chemical Industries) at 240 nm (0.2 % IPA in hexane; flow rate: 1.0 cm^3min^{-1}, RT: 9 and 12 min). The second running enantiomer (12 min) was produced in excess with all the homochiral thiols used. *c*. All the thiol was added at the beginning of the experiment.

18



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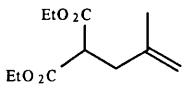

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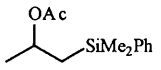

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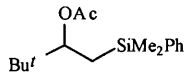

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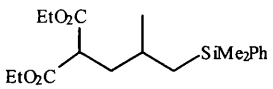

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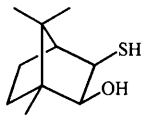

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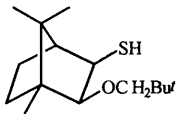

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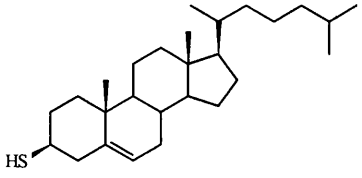

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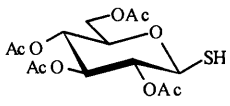
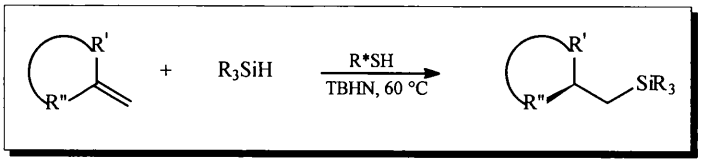


57

Enantioselective hydrosilylation of lactone 60 using homochiral thiol as catalysts



These experiments follow the same basic procedure, but using a homochiral thiol (5 mol %) as the catalyst. The lactone **60** was used for these initial enantioselective hydrosilylation experiments.

General procedure

A solution of the lactone **60** (0.70 g, 5.0 mmol), arylsilane (6.5 mmol), homochiral thiol (0.25 mmol) and TBHN (44 mg, 0.25 mmol) in dry dioxane [or hexane] (4.0 cm^3) was placed in a flask containing a stirrer bar and fitted with a short condenser and flushed with nitrogen. The mixture was stirred and heated for 2.5 h at 60 °C. The solvent was evaporated under reduced pressure and the crude product was purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the product.

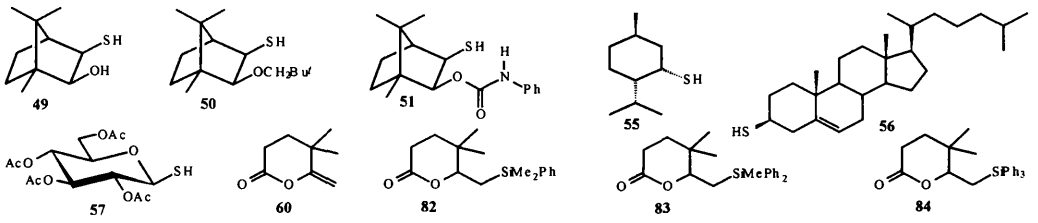
Addition of the thiol over 2 h, instead of adding it all in one portion at the start of the reaction, had no significant effect on either the overall yield or enantiomeric excess of the product. More solvent (increased from 2.0 cm^3 to 4.0 cm^3) was used in these experiments than in earlier experiments using acyclic alkenes. This resulted in increased yields (*e.g.* for lactone **60** with Ph_3SiH the yield increased from 60 % to 77 %). This increase in yield may be a consequence of more efficient stirring of the turbid reaction mixture. During some of these experiments when using hexane as solvent, the homogenous reaction mixture became turbid because the reaction product was insoluble.

All the results for these reactions have been summarised in Table 5 (p. 27) which is reproduced below.

Table 5: Enantioselective hydrosilylation of lactone **60** at 60 °C initiated by TBHN and using homochiral thiols as catalysts

Entry	Silane	Solvent	Thiol catalyst	Product	Yield (%)[a]	Product ee (%)[b]
1	$PhMe_2SiH$	hexane	**50**	**82**	26 (48)	2
2	$PhMe_2SiH$	dioxane	**51**	**82**	40	6
3	$PhMe_2SiH$	hexane	**55**	**82**	39	3
4	$PhMe_2SiH$	dioxane	**56**	**82**	47	7
5	$PhMe_2SiH$	dioxane	**57**	**82**	74	16
6	$PhMe_2SiH$	hexane	**57**	**82**	52	23
7	$PhMe_2SiH$	DMF	**57**	**82**	20	8
8	Ph_2MeSiH	hexane	**49**	**83**	<1	-
9	Ph_2MeSiH	hexane	**50**	**83**	<1	-
10	Ph_2MeSiH	dioxane	**51**	**83**	76	10
11	Ph_2MeSiH	hexane	**55**	**83**	69	1
12	Ph_2MeSiH	dioxane	**56**	**83**	40	4
13	Ph_2MeSiH	dioxane	**57**	**83**	78	26
14	Ph_2MeSiH	hexane	**57**	**83**	65 (80)	32
15	Ph_3SiH	hexane	**49**	**84**	6	6
16	Ph_3SiH	dioxane	**51**	**84**	60 (78)	10
17	Ph_3SiH	hexane	**55**	**84**	36	3
18	Ph_3SiH	dioxane	**56**	**84**	33	3
19	Ph_3SiH	dioxane	**57**	**84**	63	40[c]
20	Ph_3SiH	hexane	**57**	**84**	72 (80)	50[d]

a. The isolated yields are shown and the yields determined by ^1H NMR analysis before purification are shown in the parentheses. *b*. Determined by chiral-stationary-phase HPLC analysis using a Daicel Chemical Industries Chiralcel-OJ column for **82** and **83** and a Chiralcel-OD column for **84**. With the thiols **55** and **56** as catalysts, the enantiomer present in excess was eluted second; for the remaining thiol catalysts, the predominant enantiomer was eluted first. *c*. For 40 % ee material, $[\alpha]_D^{20} = -31.3°$ (c = 1.48, $CHCl_3$). *d*. For 50 % ee material, $[\alpha]_D^{20} = -38.8°$ (c = 1.82, $CHCl_3$).



Enantioselective hydrosilylation of prochiral cyclic alkenes using homochiral carbohydrate thiols

These experiments follow the same basic procedure. The solvent and homochiral carbohydrate thiol (5 mol %) were varied.

General procedure

A solution of the alkene (2.50 mmol), silane (3.25 mmol), thiol (0.125 mmol) and TBHN (22 mg, 0.125 mmol) was made up in the appropriate solvent and was placed in a flask containing a stirrer bar. The flask was fitted with a short condenser and flushed with nitrogen. The mixture was stirred and heated for 2.5 h at 60 °C. The solvent was evaporated under reduced pressure and the crude product was purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the product.

The results of these experiments have been summarised in Table 7 (p. 70) which is reproduced below. The enantiomeric excesses for the adducts were carefully determined by chiral-stationary-phase HPLC analysis, except for adduct **85** which was determined using homochiral shift reagent [$Eu(hfc)_3$]. All the facts regarding the HPLC analysis are summarised in Table 8 and are also given with the racemic adduct details.

In these experiments, for adduct **84**, the enantiomer present in excess was eluted first except when using the thiols **96**, **97** and **99** as catalysts. For adducts **86-88**, enantiomer present in excess was eluted second. For adduct **89**, the predominant enantiomer was eluted first except when using **99** as catalyst. For adducts **90** and **91**, the predominant enantiomer was eluted first.

Recrystallization [benzene-hexane (1:2)] of adduct **84** (50 % ee) produces enantiopure (*R*)-adduct. When adduct **89** (95 % ee) was recrystallized (CH_2Cl_2-hexane), the crystals obtained were lower in ee (68 %) and the mother liquor after evaporation was upgraded in ee (98 %).

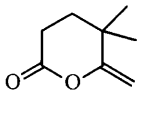
Table 7: Enantioselective hydrosilylation of cyclic prochiral alkenes using homochiral carbohydrate thiols at 60 °C

Entry	Alkene	Silane	Solvent[a]	Thiol	Product	Yield (%)[b]	Product ee (%)[c]
1	**60**	Ph_3SiH	dioxane	**57**	**84**	63	40
2	**60**	Ph_3SiH	hexane	**57**	**84**	72 (80)	50
3	**60**	Ph_3SiH	benzene	**57**	**84**	84	43
4	**60**	Ph_3SiH	hex-diox	**94**	**84**	68	15
5	**60**	Ph_3SiH	hex-diox	**94**[d]	**84**	67	30
6	**60**	Ph_3SiH	hexane	**95**	**84**	79	40
7	**60**	Ph_3SiH	hexane	**96**	**84**	81	6
8	**60**	Ph_3SiH	hexane	**97**	**84**	88	9
9	**60**	Ph_3SiH	hexane	**98**	**84**	77	44
10	**60**	Ph_3SiH	hexane	**99**	**84**	79	3
11	**60**	Ph_3SiH	hexane	**100**	**84**	84	76
12	**60**	Ph_3SiH	benzene	**100**	**84**	82	60
13	**60**	Ph_3SiH	benzene	**100**[e]	**84**	80	54
14	**60**	$(Me_3Si)_3SiH$	hexane	**57**[f]	**85**	92	47
15	**60**	$(Me_3Si)_3SiH$	hexane	**100**	**85**	91	55
16	**67**	Ph_3SiH	hex-diox	**57**	**86**	31 (45)	29
17	**67**	Ph_3SiH	hex-diox	**94**	**86**	25 (35)	9
18	**67**	Ph_3SiH	hex-diox	**100**	**86**	33 (40)	41
19	**67**	Ph_3SiH	hex-diox	**51**[g]	**86**	68	5
20	**68**	Ph_3SiH	hexane	**57**	**87**	43	5
21	**68**	Ph_3SiH	hexane	**100**	**87**	48	5
22	**69**	$PhMe_2SiH$	hex-diox	**100**	**88**	60 (80)	73
23	**69**	Ph_3SiH	dioxane	**57**	**89**	88	80
24	**69**	Ph_3SiH	hexane	**57**	**89**	58	88
25	**69**	Ph_3SiH	benzene	**57**	**89**	92	86
26	**69**	Ph_3SiH	hex-diox	**57**	**89**	93	87
27	**69**	Ph_3SiH	hex-diox	**95**	**89**	96	84

Table 7 - Continued

Entry	Alkene	Silane	Solvent[a]	Thiol	Product	Yield (%)[b]	Product ee (%)[c]
28	**69**	Ph_3SiH	hex-diox	**98**	**89**	97	87
29	**69**	Ph_3SiH	hex-diox	**99**	**89**	92	5
30	**69**	Ph_3SiH	hex-diox	**100**	**89**	90	95
31	**69**	Ph_3SiH	benzene	**100**	**89**	95	93
32	**70**	Ph_3SiH	hexane	**57**	**90**	96	31
33	**70**	Ph_3SiH	hexane	**100**	**90**	76	55
34	**71**	Ph_3SiH	hex-diox	**57**	**91**	35 (57)	5

a. Between 4.0 and 6.0 cm^3 of solvent used. For entries 4 and 5, hexane (3.5 cm^3) and dioxane (0.5 cm^3) used as solvent. For alkene **67**, hexane (4.0 cm^3) and dioxane (0.5 cm^3) used as solvent. For alkene **69**, hexane (5.0 cm^3) and dioxane (1.0 cm^3) was used as solvent. For alkene **71**, hexane (3.0 cm^3) and dioxane (1.0 cm^3) used as solvent. *b*. Isolated yields are given with yields determined by ^1H NMR analysis before purification shown in the parentheses. *c*. The methods for ee determination are shown in Table 8. *d*. The thiol in hexane and dioxane (0.5 cm^3 and 0.5 cm^3) was added over a 2 h period. *e*. 1 mol% thiol catalyst was used. *f*. Identical results were obtained when using 5 or 10 mol % thiol **57** as catalyst. *g*. This thiol is not carbohydrate-derived.



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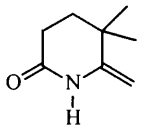

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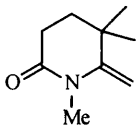

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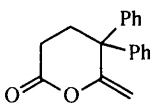

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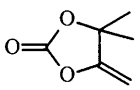

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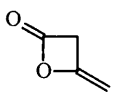

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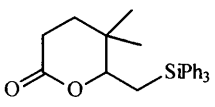

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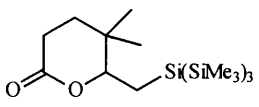

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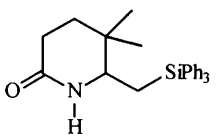

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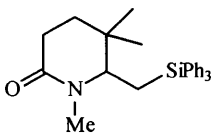

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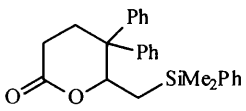

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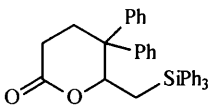

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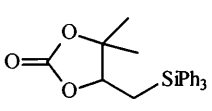

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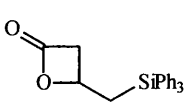

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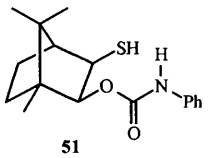

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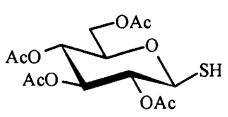

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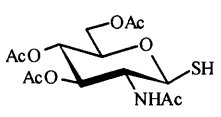

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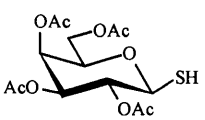

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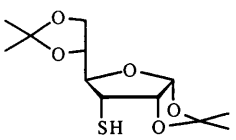

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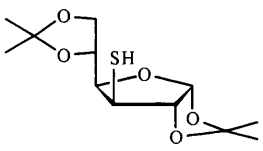

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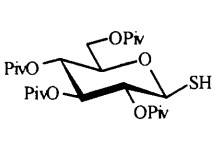

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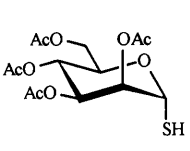

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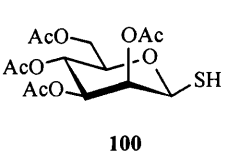
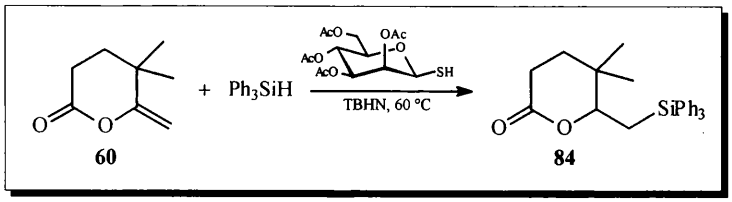


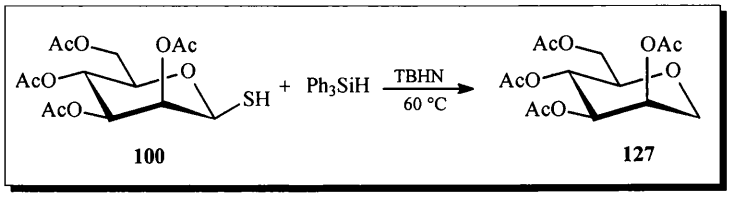
100

Large-scale hydrosilylation



A solution of the lactone **60** (10.50 g, 75.00 mmol), Ph_3SiH (25.35g, 97.40 mmol), TBHN (0.66 g, 3.75 mmol) and the β-mannose thiol **100** (1.37 g, 3.75 mmol) in hexane (120 cm^3) was stirred and heated at 60 °C for 2.5 h under an atmosphere of nitrogen. During the reaction, the enantiomerically pure adduct **84** crystallized out of solution. It was then cooled to room temperature. (If desired, the enantiomerically pure adduct **84** could isolated from the mixture by filtration and washed with hexane). The reaction mixture was diluted with CH_2Cl_2 to obtain a homogenous solution and a small aliquot was taken to determine the ee. The solvent was evaporated under reduced pressure to give a solid. This solid was triturated with hexane (120 cm^3), the slurry was filtered and the solid was washed on the sinter with more hexane (2 x 120 cm^3). The white solid obtained was dried [19.10 g, 64 % yield, >99% ee in favour of first running enantiomer (*R*)]. The filtrate was evaporated under reduced pressure and the residue was purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the remaining product as a white solid [4.15 g, 14 % yield, 17.5 % ee in favour of the second enantiomer (*S*)]. The product (total yield : 23.25 g, 78 %) had overall 74 % ee in favour of the 1st running enantiomer-(*R*). If the enantiomerically pure adduct was not isolated initially, the 73 % ee material could be recrystallized from benzene-hexane (1:2) to afford the enantiopure (*R*)-adduct. For enantiopure (*R*)-adduct: $[\alpha]_D^{22}$ = -77.5 ° (c = 1.78, $CHCl_3$), m.p. 135-136 °C.

2,3,4,6-Tetra-*O*-acetyl-1,5 anhydro-D-mannitol 127



This compound was isolated by flash-column chromatography during the purification of the product from the large-scale hydrosilylation reaction using the β-mannose thiol **100** as catalyst. It was formed by the radical-chain desulphurization of the thiol **100** by

triphenylsilane, m.p. 154-156 °C (lit.[80] m.p. 154-155 °C).

m/z (APCI) 355 (M^++ Na, 15), 333 (M^++1, 5), 273 (M^+-OAc, 84), 231 (13), 153 (100), 111 (23).

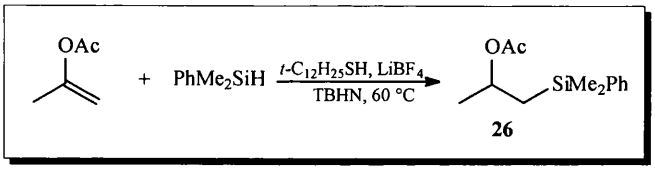
δ_H: 2.00 (3H, s, Ac), 2.04 (3H, s, Ac), 2.10 (3H, s, Ac), 2.16 (3H, s, Ac), 3.59 (1H, ddd, *J* 9.9, 5.4 and 2.3, H-5), 3.67 (1H, dd, *J* 13.2 and 1.1, H^A-1), 4.06 (1H, dd, *J* 13.2 and 2.1, H^B-1), 4.13 (1H, dd, *J* 12.4 and 2.3, H^A-6), 4.24 (1H, dd, *J* 12.4 and 5.4, H^B-6), 5.05 (1H, dd, *J* 10.0 and 3.6, H-3), 5.26 (1H, t, *J* 10.0, H-4), 5.31 (1H, br. m, H-2). This analysis was confirmed by ^1H-^1H decoupling experiments.

δ_C: 20.6, 20.7, 20.8, 21.0, 62.7, 66.1, 68.1, 68.6, 71.6, 76.7, 169.6, 170.1, 170.3, 170.7.

The NMR data obtained were in agreement with data available in the literature.[80]

Lewis acid-mediated hydrosilylation reactions

Using lithium tetrafluoroborate

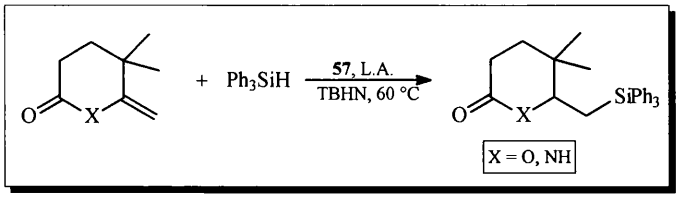


26

A solution of isopropenyl acetate (0.50 g, 5.0 mmol), TBHN (44 mg, 0.25 mmol), dimethylphenylsilane (0.89 g, 6.5 mmol) and $LiBF_4$ (0.47 g, 5 mmol) in DMF (3.0 cm^3) was placed in a flask containing a stirrrer bar and fitted with a short reflux condenser, equipped with a septum inlet and a nitrogen by-pass bubbler. The mixture was heated at 60 °C. *tert*-Dodecanethiol (50 mg, 0.25 mmol) in DMF (1.0 cm^3) was added *via* a syringe pump over 2 h to the stirred reaction mixture. After the addition, the mixture was heated for a further 30 min, then allowed to cool to room temperature and diluted with ether (5.0 cm^3) and finally washed with water (5.0 cm^3). The ether solution was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (19:1)] to afford the product as a colourless oil (1.02 g, 86 %). In the absence of the Lewis acid, the ^1H NMR spectrum of the crude product indicated a 40 % yield of adduct. In the absence of initiator, the ^1H NMR spectrum of the crude product indicated <1 % product had been formed.

General procedure when using 10 mol % Lewis acid

For the prochiral cyclic alkenes, the Lewis acid (10 mol %) was used in conjunction with the glucose thiol **57** (5 mol %) in an attempt to increase the ee.



A solution of the lactone **60** or the lactam **67** (0.35 g, 2.50 mmol), triphenylsilane (0.85 g, 3.25 mmol), the glucose thiol **57** (45.5 mg, 0.125 mmol), the Lewis acid (0.25 mmol) and TBHN (22.0 mg, 0.125 mmol) was made up in dry dioxane (4.0 cm^3). A short condenser was attached to the reaction flask, flushed with nitrogen and the solution was stirred and heated for 2.5 h at 60 °C. The solvent was evaporated under reduced pressure and the crude product was purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the product. In the experiment with the lactam, the eluent was petroleum-ether (10:1), followed by petroleum-ether (1:1), followed by neat ether.

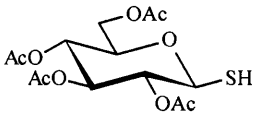
The results from these experiments have been summarised in Table 6 (p. 56) which is reproduced below.

Table 6: Lewis acid mediated enantioselective hydrosilylation of prochiral cyclic alkenes **60** and **67** with Ph_3SiH using the homochiral thiol **57** as catalyst

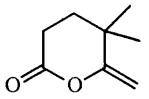
Entry	Product	Lewis acid [a]	Isolated yield (%)	Product ee (%) [b]
1	**84**	-	63	40
2	**84**	$Eu(fod)_3$	82	42
3	**84**	$Yb(OTf)_3$	71	39
4	**84**	$La(OTf)_3$	79	41
5	**84**	$Zn(OTf)_2$	71	39
6	**84**	$Mg(OTf)_2$	80	43
7	**84**	$Y(OTf)_3$	63	39

8	**84**	$Er(OTf)_3$	68	38
9	**84**	$Sc(OTf)_3$	60	37
10	**84**	$ZnCl_2$	77	35
11	**86**	-	42	29
12	**86**	$Yb(OTf)_3$	61	33

a. All the Lewis acids (10 mol %) were > 90 % soluble in the reaction mixture, except $Eu(fod)_3$ [europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)] (entry 2) which was essentially insoluble. *b*. The product enantiomeric excesses were determined by chiral-stationary-phase HPLC analysis using Daicel Chemical Industries columns (Chiralcel-OD column for **84** and Chiralpak-AD column for **86**).



57



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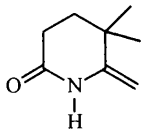

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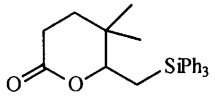

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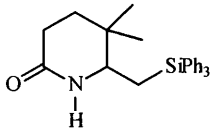
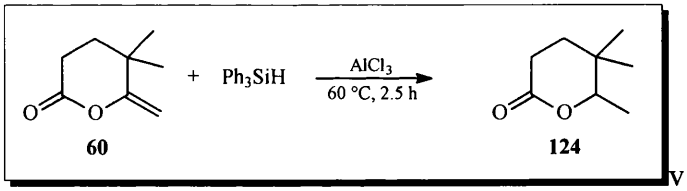


86

Control experiments

5,5-Dimethyl-6-methyltetrahydropyran-2-one 124



60 **124**

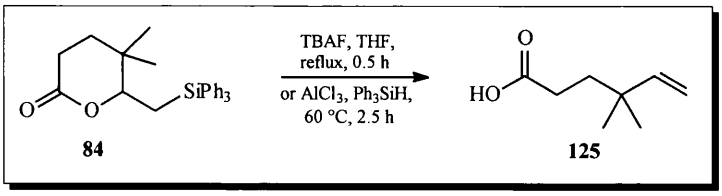
V

A solution of the lactone **60** (0.35 g, 2.50 mmol), triphenylsilane (0.85 g, 3.25 mmol) and anhydrous aluminium trichloride (0.33 g, 2.50 mmol) in dry dioxane was stirred and heated at 60 °C for 2.5 h. The mixture was cooled, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (15 cm^3). The CH_2Cl_2 solution was washed with water (20 cm^3) and then dried over $MgSO_4$. After solvent removal under reduced pressure, the crude material was purified by flash-column chromatography [eluent: petroleum-ether (10:1)] to afford the product as a colourless oil (0.11 g, 30 %). The ^1H NMR spectrum of the crude material indicated a 38 % yield of product and a large amount of unreacted lactone **60**.

200 MHz ^1H NMR

δ_H: 0.98 (3H, s, Me), 1.01 (3H, s, Me), 1.26 (3H, d, *J* 11.0, Me),
1.68 (2H, m, CH_2CMe_2), 2.56 (2H, m, CH_2CO_2), 4.19 (1H, q, *J* 11.0, CHO).

4,4-Dimethylhex-5-enoic acid 125



A stirred solution of the silane adduct **84** (1.0 g, 2.5 mmol), TBAF (1.0 M solution in THF) (5.0 cm^3, 5.0 mmol) in THF (10 cm^3) was heated under reflux for 30 min. The mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The crude material was then dissolved in CH_2Cl_2 (10 cm^3), washed with water (10 cm^3) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash-column chromatography [eluent: petroleum-ether (9:1)] to afford the product as a colourless oil (0.2 g, 55 %).

IR (neat): 2964, 1709, 1414, 1294, 1223, 1001 cm^{-1}.

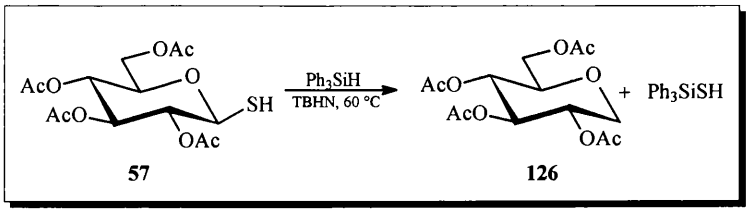
Found : C, 68.53; H, 9.62. $C_8H_{14}O_2$ requires C, 67.57; H, 9.92 %.

δ_H : 0.98 (6H, s, CMe_2), 1.62 (2H, m, CH_2CMe_2), 2.25 (2H, m, CH_2CO), 4.92 (2H, m, vinyl CH_2), 5.69 (1H, dd, *J* 17.4 and 10.8, vinyl CH), 10.21 (1H, brs, OH).

δ_C : 26.4, 29.9, 36.2, 36.7, 111.6, 146.9, 180.9.

This product was also formed in a similar yield when the silane adduct **84** (0.35 g, 2.50 mmol), triphenylsilane (0.85 g, 3.25 mmol) and aluminium trichloride (0.33 g, 2.50 mmol) were heated in dioxane (4.0 cm^3) at 60 °C for 2.5 h.

2,3,4,6-Tetra-*O*-acetyl-1-deoxy-D-glucose 126



A solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose **57** (364 mg, 1.0 mmol), triphenylsilane (313 mg, 1.2 mmol) and TBHN (8.70 mg, 0.05 mmol) in dry dioxane (2.0 cm^3) was stirred at 60 °C for 2.5 h under an atmosphere of nitrogen and then allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the crude material was purified by flash-column chromatography [eluent: petroleum-ether (6:1)] to afford the product as a white solid (304 mg, 91 %), m.p. 73-75 °C

(lit.[79] m.p. 73-75 °C). In the absence of initiator, no reaction takes place.

δ_H: 2.00 (9H, brs, 3 x Ac), 2.06 (3H, s, Ac), 3.27 (1H, t, *J* 10.5, H-4), 3.56 (1H, ddd, *J* 10.5, 4.9 and 2.3, H-5), 4.07-4.19 (3H, m, H^A-1 and H-6), 4.94-5.02 (2H, m, H-2 and H-3), 5.17 (1H, t, *J* 9.5, H^B-1).

δ_C: 20.6, 20.7 (0) (2C), 20.7 (2), 62.2, 66.8, 68.4, 68.9, 73.7, 76.4, 169.5, 169.7, 170.3, 170.6.

The NMR data obtained were consistent with data available in the literature.[79]

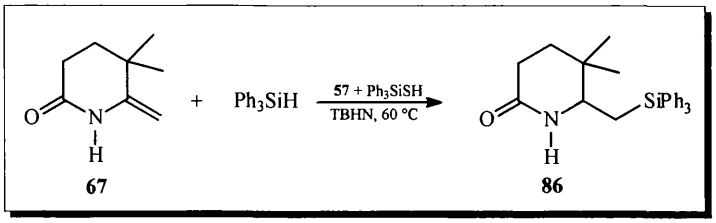
Mixed thiol catalysis

These experiments follow the same basic procedure. A mixture of triphenylsilanethiol (2.5 mol %) and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **57** (2.5 mol %) was used. The experiments were designed to show which of the two thiols had the greater influence on the reaction.

General procedure

A solution of the alkene (2.50 mmol), triphenylsilane (0.85 g, 3.25 mmol), 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **57** (23 mg, 0.063 mmol), triphenylsilanethiol (18 mg, 0.063 mmol) and TBHN (22 mg, 0.125 mmol) was made up in the appropriate solvent and the solution was stirred and heated for 2.5 h at 60 °C under an atmosphere of nitrogen. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (6:1), followed by petroleum-ether (3:1)] to afford the adduct. The eluent used for the purification of the lactam-adduct **86** was petroleum-ether (10:1), followed by petroleum-ether (1:1), followed by neat ether. The enantiomeric excesses of the two lactone-adducts **84** and **89** were determined by chiral-stationary-phase HPLC analysis using a Chiralcel-OD column and a Chiralpak-AD column for the lactam-adduct **86**.

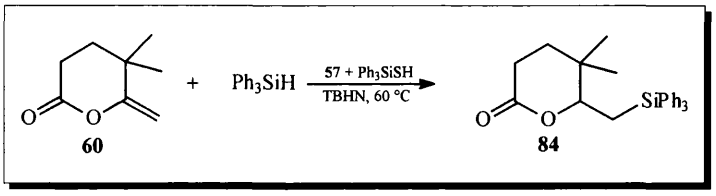
Hydrosilylation of the lactam 67



67 86

This reaction was carried out in a mixture of hexane and dioxane (4.0 cm^3 and 0.5 cm^3) solvent. The product (6 % ee) was obtained as a white solid (0.51 g, 52 %). The ^1H NMR spectrum of the crude material indicated a 71 % yield of product. The triphenylsilanethiol evidently takes the dominant role, because the yield obtained with the glucose thiol **57** was 40 % and the ee was 30 %.

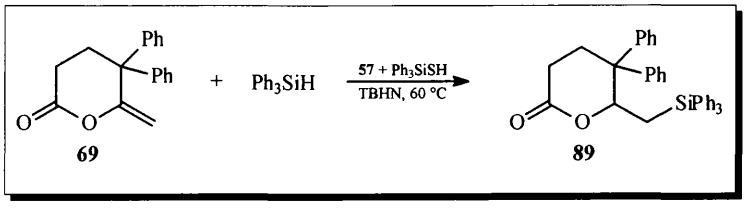
Hydrosilylation on the lactone 60



60 84

This reaction was carried out both in hexane (4.0 cm^3) and in dioxane (4.0 cm^3) as solvent. In hexane, the product was obtained as a white solid (0.80 g, 80 %) with a 30 % ee. In dioxane, the product was obtained as a white solid (0.79 g, 79 %) with a 30 % ee. Both the thiols give quantitative yields of the adduct when used separately as catalysts. With **57** alone as catalyst, the product showed an ee of 50 % with hexane solvent and an ee of 40 % with dioxane.

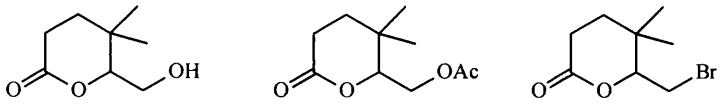
Hydrosilylation of the diphenyl lactone 69



69 89

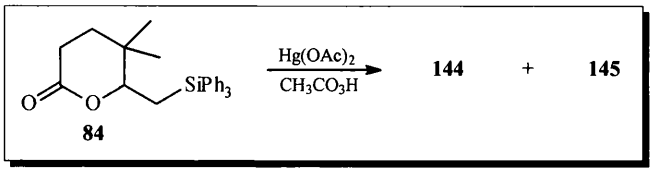
This reaction was carried out in dioxane (4.0 cm^3). The product was obtained as a white solid (1.03 g, 79 %) with an ee of 69 %. The glucose thiol **57** has the greater influence on the course of this reaction, because only a low yield was obtained when using triphenylsilanethiol alone as catalyst. When using the glucose thiol **57** alone as catalyst, the adduct **89** was obtained with an 88 % yield and 80 % ee.

Desilylation of the silane adduct 84. Formation of alcohol 144, acetate 145 and bromide 146



144 145 146

Desilylation using mercury acetate and peracetic acid



84

A flask containing the enantiopure (*R*)-silane adduct **84** (0.50 g, 1.25 mmol) and mercury acetate (0.42 g, 1.31 mmol) was cooled in an ice-bath and peracetic acid (40 % in AcOH, 10.0 cm^3, 65 mmol) was added. The heterogenous mixture was warmed to room temperature and stirred for 2 days. Another equal portion of mercury acetate (0.42 g, 1.31 mmol) was added to the mixture at room temperature and was stirred for another 2 days (at room temperature). More mercury acetate (0.42 g, 1.31 mmol) was added again and the heterogenous mixture was stirred for a further 2 days [a total 6 days stirring and total amount of mercury acetate: 1.26 g, 3.95 mmol]. The mixture was filtered (to remove all insoluble materials) and the sinter was thoroughly washed with CH_2Cl_2 (3 x 20 cm^3). The CH_2Cl_2 washing was co-evaporated with toluene (3 x 50 cm^3) carefully (to remove the excess acetic and peracetic acid) under reduced pressure. The crude product was then purified by flash-column chromatography [eluent: petroleum-ether (10:1), followed by petroleum-ether (1:1)] to afford the acetate **145** as a colourless oil (0.092 g, 37 %). The alcohol **144** which was also formed in this reaction, was difficult to isolate (pure) from the same flash-column (due to the alcohol 'sticking' throughout the length of the column). Therefore, this same flash-column was eluted with neat MeOH after the isolation of the acetate **145** and the crude alcohol **144** obtained (after the evaporation of MeOH under reduced pressure), was re-purified by flash-column chromatography [eluent: petroleum-EtOAc (2:1)] to afford the alcohol as a white solid (0.051 g, 26 %). Both the alcohol **144** and acetate **145** [combined yield: 63 %] were obtained with retention of configuration at the chiral centre, which was confirmed by chiral-stationary-phase HPLC using a Chiralcel-OD column at 233 nm {eluent: 10 % IPA

in hexane; flow rate: 1.0 cm^3min^{-1}; RT: 10 min for **144**; RT: 13 min for **145**}.

Enantiopure alcohol:

(*R*)-(-)-5,5-Dimethyl-6-hydroxymethyltetrahydropyran-2-one 144

IR (liq. film): 3420, 1740, 1451, 1060, 740 cm^{-1}, m.p. 73-76 °C,

$[\alpha]_D^{19}$ = -66.2 ° (c = 2.55, $CHCl_3$).

Found : C, 60.48; H, 9.18. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92 %.

m/z (APCI) 181 (M^++ Na, 8), 159 (M^++1, 89), 141 (M^+-OH, 64), 129 (100), 123 (42).

δ_H: 0.92 (3H, s, CMe^A), 1.02 (3H, s, CMe^B), 1.59 (1H, m, CH^ACMe_2),
1.70 (1H, m, CH^BCMe_2), 2.52 (2H, m, CH_2CO_2), 2.93 (1H, brs, OH),
3.71 (2H, m, CH_2O), 4.09 (1H, dd, *J* 7.1 and 3.4, CHO).

δ_C: 20.2, 26.3, 27.3, 30.8, 34.4, 61.7, 88.2, 171.4.

Enantiopure acetate:

(R)-(-)-5,5-Dimethyl-6-acetoxymethyltetrahydropyran-2-one 145

IR (neat): 1741, 1371, 1235, 1040 cm^{-1},

$[\alpha]_D^{19}$ = -96.0 ° (c = 1.06, $CHCl_3$).

Found : C, 59.97; H, 8.27. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05 %.

m/z (EI) 200 (M^+, 3), 126 (53), 70 (45), 56 (60), 43 (Ac^+, 100).

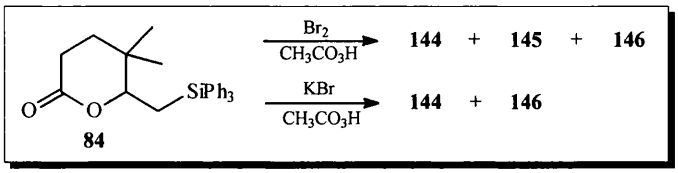
δ_H: 0.98 (3H, s, CMe^A), 1.07 (3H, s, CMe^B), 1.61 (1H, m, CH^ACMe_2),
1.73 (1H, m, CH^BCMe_2), 2.05 (3H, s, Ac), 2.54 (2H, m, CH_2CO_2),
4.05 (1H, dd, *J* 12.0 and 8.1, CH^AOAc), 4.20 (1H, dd, *J* 8.1 and 2.3, CH^BOAc),
4.31 (1H, dd, *J* 12.0 and 2.3, CHO).

δ_C: 19.8, 20.6, 26.2, 27.0, 30.9, 34.3, 63.4, 84.4, 170.5, 170.7.

When the above reaction is carried out starting with racemic silane adduct **84**, the reaction mixture becomes homogenous after the first portion of mercury acetate but again becomes heterogenous after the second portion of mercury acetate. In this experiment, the alcohol **144** was not isolated, as it was not identified at the time, but the racemic acetate **145** was obtained with a (0.12 g) 48 % yield. It is very likely that the alcohol **144** was also produced with a similar yield. This procedure is a modification to the Fleming method as described in the literature.[47b] In these experiments, no aqueous work-up was

carried out as stated in the Fleming method because the products would decompose. For example, when an aqueous work-up was carried out, no alcohol **144** was ever produced and the acetate **145** was obtained in 5-10 % yields.

Using Br_2 or KBr instead of $Hg(OAc)_2$



The above oxidative desilylation using peracetic acid was carried out in the presence of bromine instead of mercury acetate. Bromine (1.5 equiv.) was added at the beginning and further equal amounts were added every 15 min to the reaction mixture, which was monitered by tlc (like in the Fleming method). The alcohol **144** and acetate **145** were obtained in low yields (10-15 %) with retention of configuration at the chiral centre. Additionally, the bromide **146** was also obtained in low yields but was always racemic. For example, when the silane adduct **84** (38 % ee) was oxidized by the above procedure using bromine, the bromide (racemic) was isolated first then the acetate **145** (38 % ee) was isolated during flash-column chromatography. The alcohol **144** was not isolated in this experiment because an aqueous work-up was carried out (which decomposed **144**).

Racemic bromide: 5,5-Dimethyl-6-bromomethyltetrahydopyran-2-one 146

The racemic bromide **146** was confirmed by chiral-stationary-phase HPLC using a Chiralcel-OD column at 233 nm {eluent: 15 % IPA in hexane; flow rate: 1.0 cm^3min^{-1}; RT: 9 and 10 min}.

IR (film): 1730, 1462, 1378, 1270, 1044 cm^{-1}, m.p. 128-129 °C,

Found : C, 43.40; H, 5.92. $C_8H_{13}O_2Br$ requires C, 43.46; H, 5.93 %.

m/z (EI) 221 (M^+, <1), 141 (M^+-Br, 5), 127 (M^+-CH_2Br, 17), 98 (80), 70 (70), 56 ($^+CH_2CMe_2$, 100), 43 (50).

δ_H: 0.96 (3H, s, CMe^A), 1.08 (3H, s, CMe^B), 1.63 (1H, m, CH^ACMe_2), 1.75 (1H, m, CH^BCMe_2), 2.57 (2H, m, CH_2CO_2), 3.35 (1H, dd, *J* 11.2 and 9.3, CH^ABr), 3.55 (1H, dd, *J* 11.2 and 2.2, CH^BBr), 4.25 (1H, dd, *J* 9.3 and 2.2, CHO).

δ_C: 19.3, 26.6, 27.3, 30.5, 33.1, 34.5, 87.1, 170.3.

Racemic alcohol 144

RT: 10 min (*R*-enantiomer) and 11 min (*S*-enantiomer) for the same previously described chiral-stationary-phase HPLC conditions.

Racemic acetate 145

RT: 13 min (*R*-enantiomer) and 14 min (*S*-enantiomer) for the same previously described chiral-stationary-phase HPLC conditions. When potassium bromide is used instead of bromine, no acetate **145** is formed but the yields still remain lower than the mercury acetate procedure.

The optical rotation of the acetate **145** (38 % ee) is $[\alpha]_D^{19} = -31.9\ ^\circ$ (c = 1.47, $CHCl_3$).

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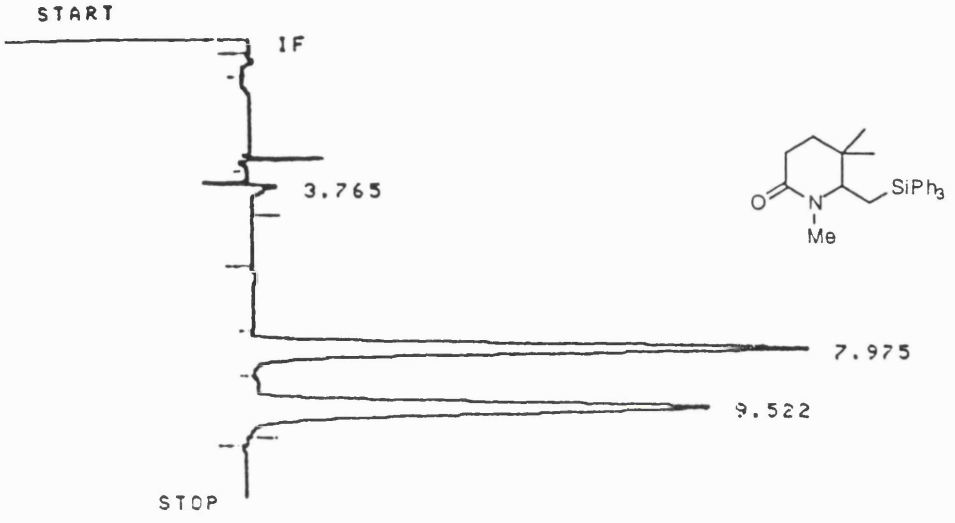
Appendix

Representative HPLC traces



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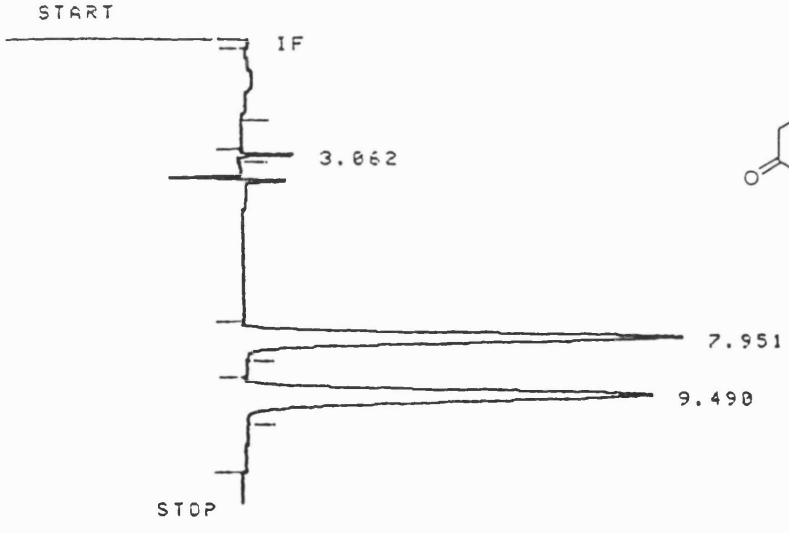
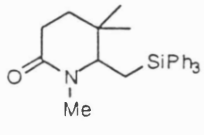
column	Chiralpak-AD
eluent	5 % IPA
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm





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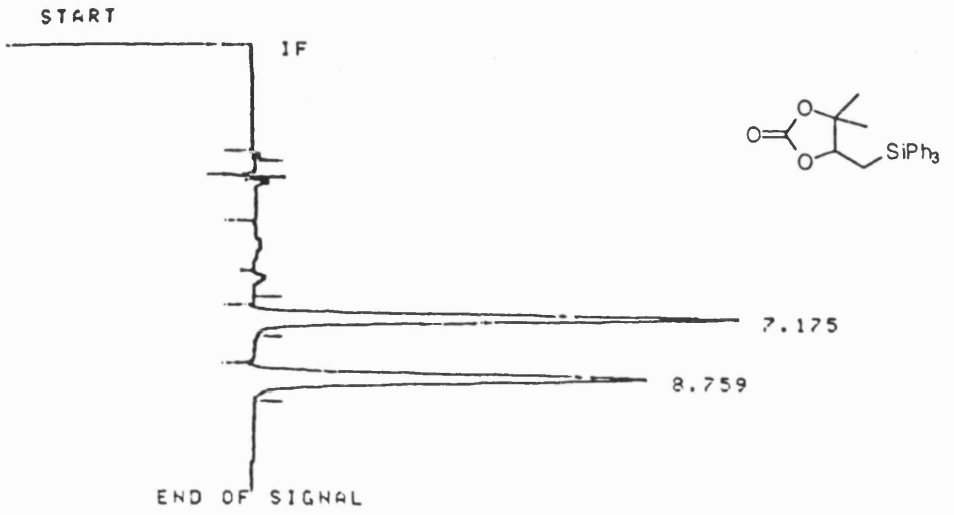
column	Chiralpak-AD
eluent	5 % IPA
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



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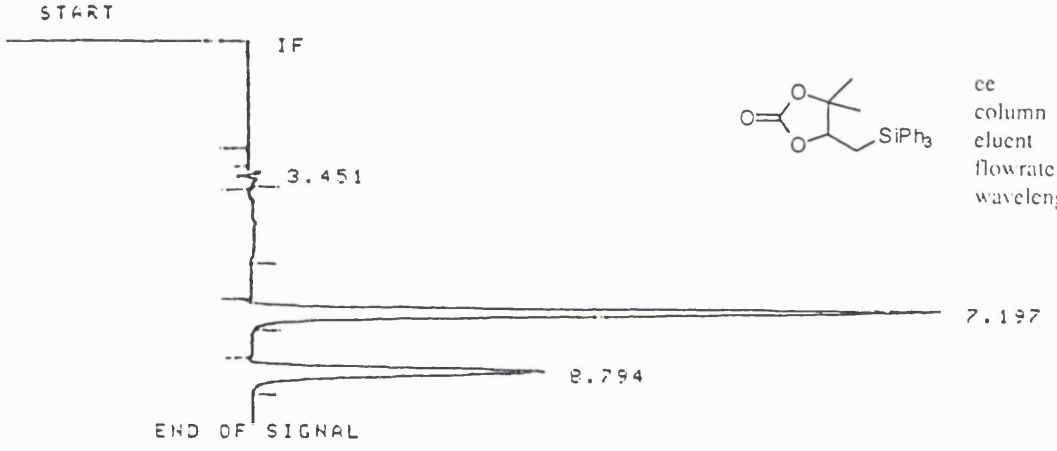
column	Chiralcel-OD
eluent	10 % IPA
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



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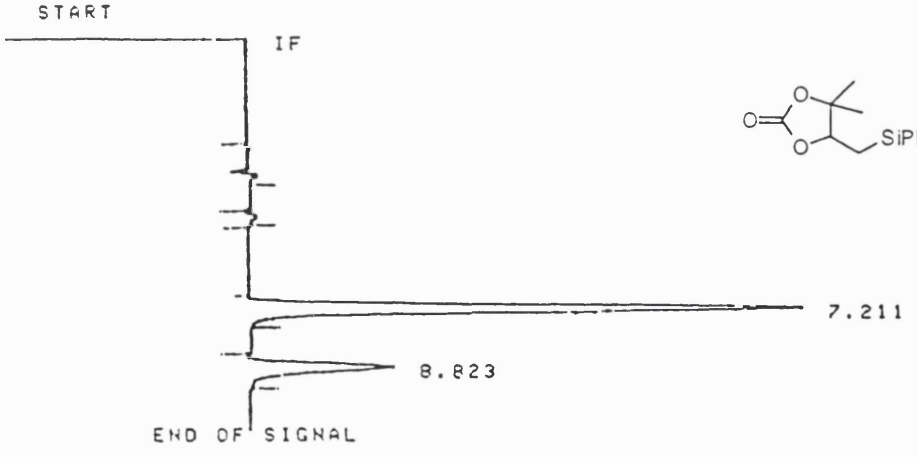
column	Chiralcel-OD
eluent	10 % IPA
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



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column	Chiralcel-OD
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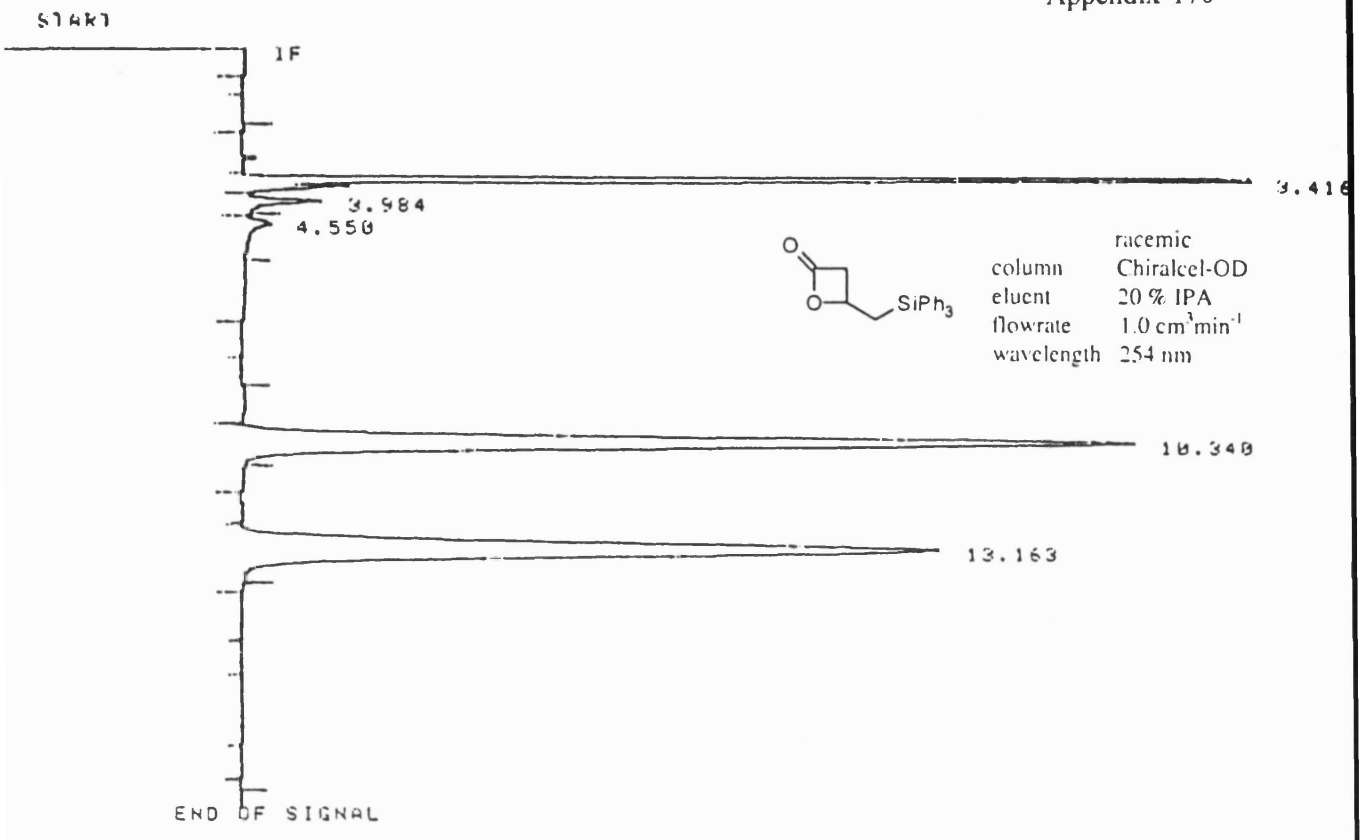
wavelength	254 nm


START
IF
3.984
4.550
9.416
10.340
13.163
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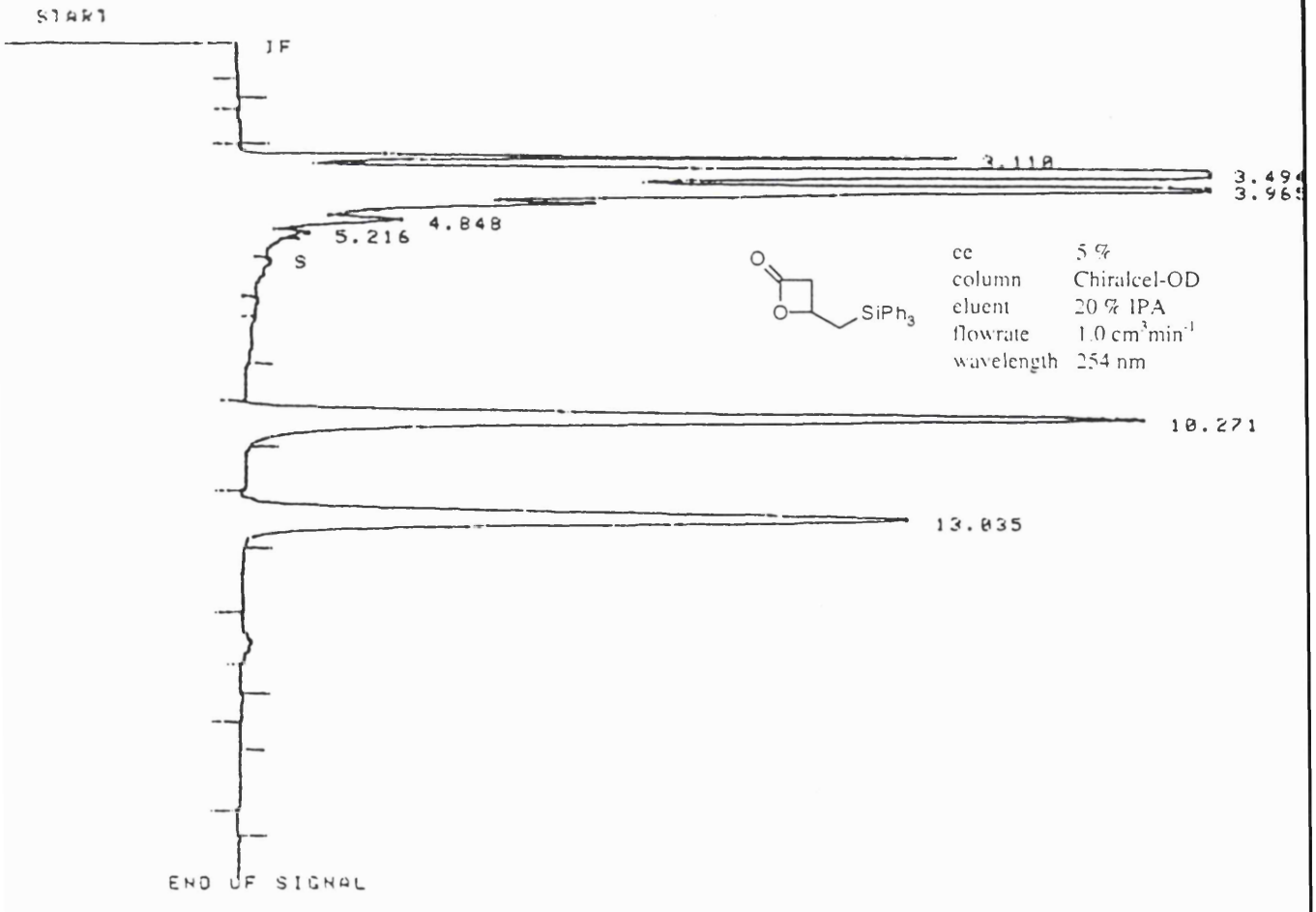
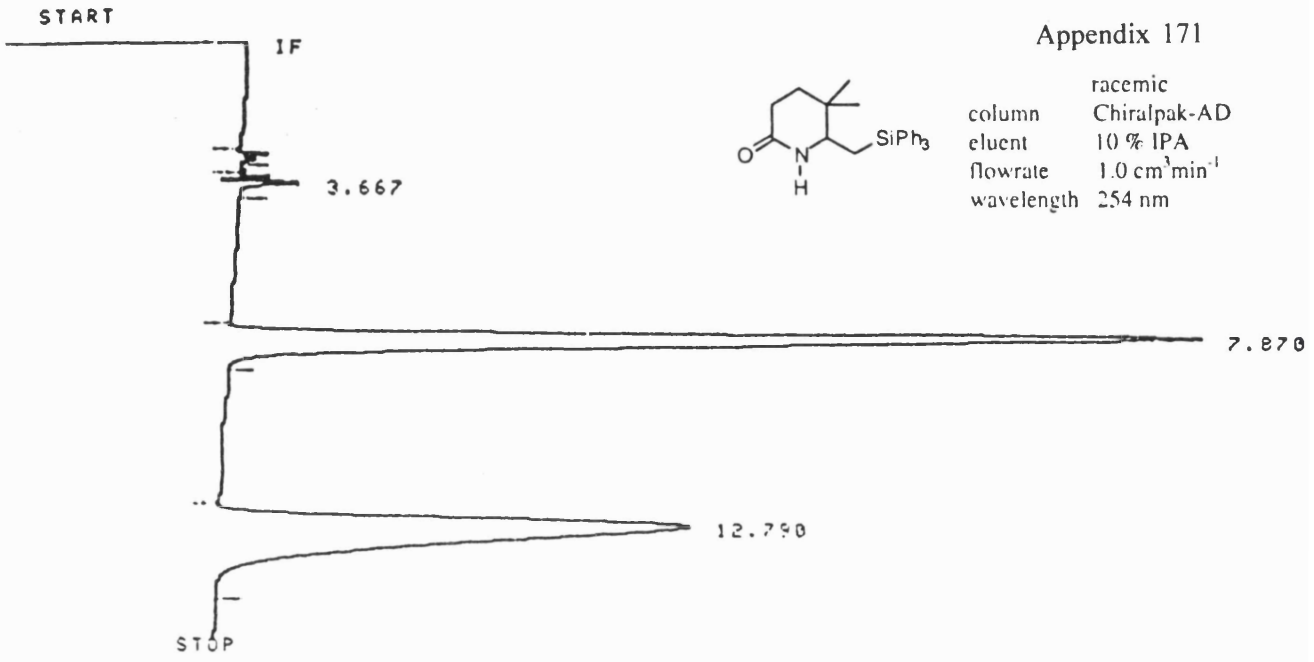
SiPh3
racemic
column Chiralcel-OD
eluent 20 % IPA
flowrate 1.0 cm3min-1
wavelength 254 nm


START
IF
3.110
3.494
3.965
4.848
5.216
S
10.271
13.035
END OF SIGNAL
SiPh3
ee 5 %
column Chiralcel-OD
eluent 20 % IPA
flowrate 1.0 cm3min-1
wavelength 254 nm



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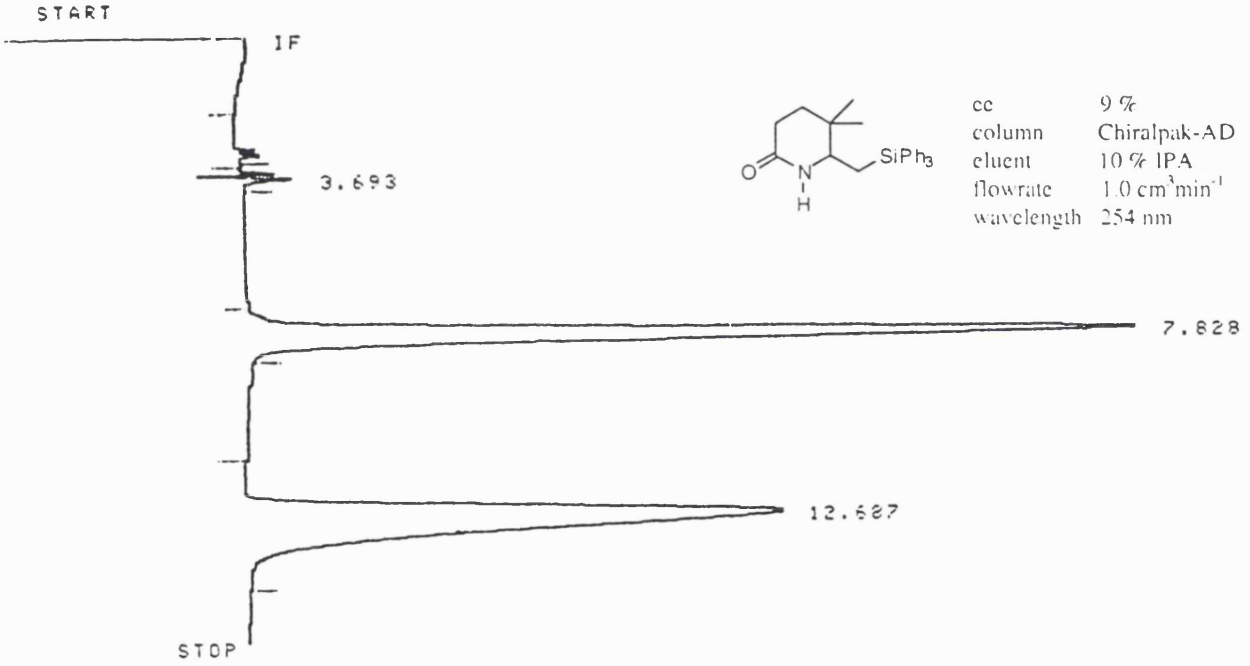
column	Chiralpak-AD
eluent	10 % IPA
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



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column	Chiralpak-AD
eluent	10 % IPA
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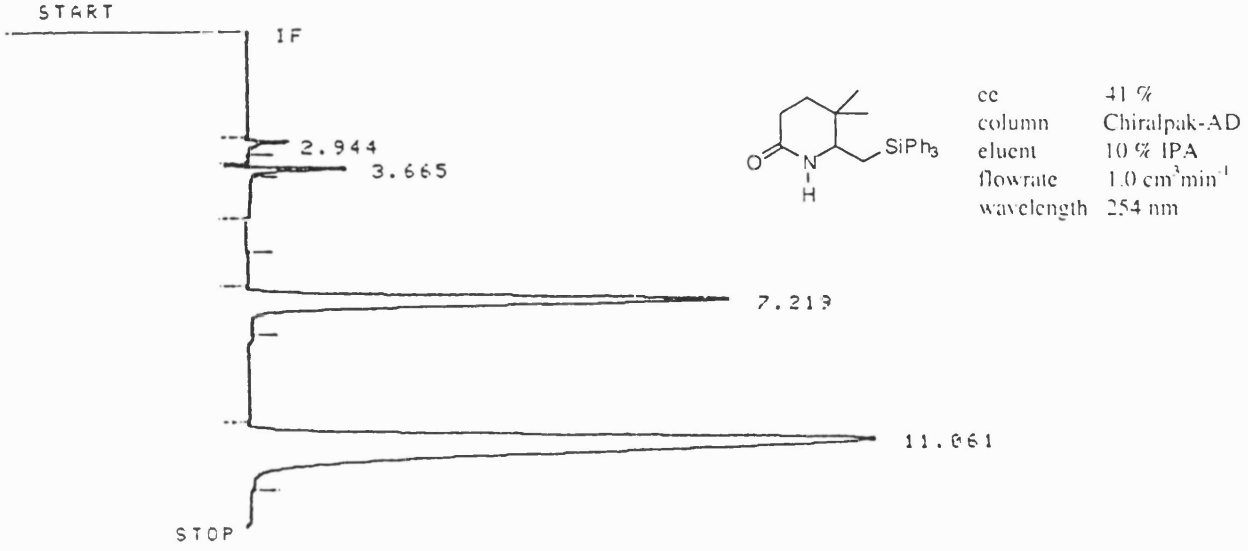
wavelength	254 nm



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column	Chiralpak-AD
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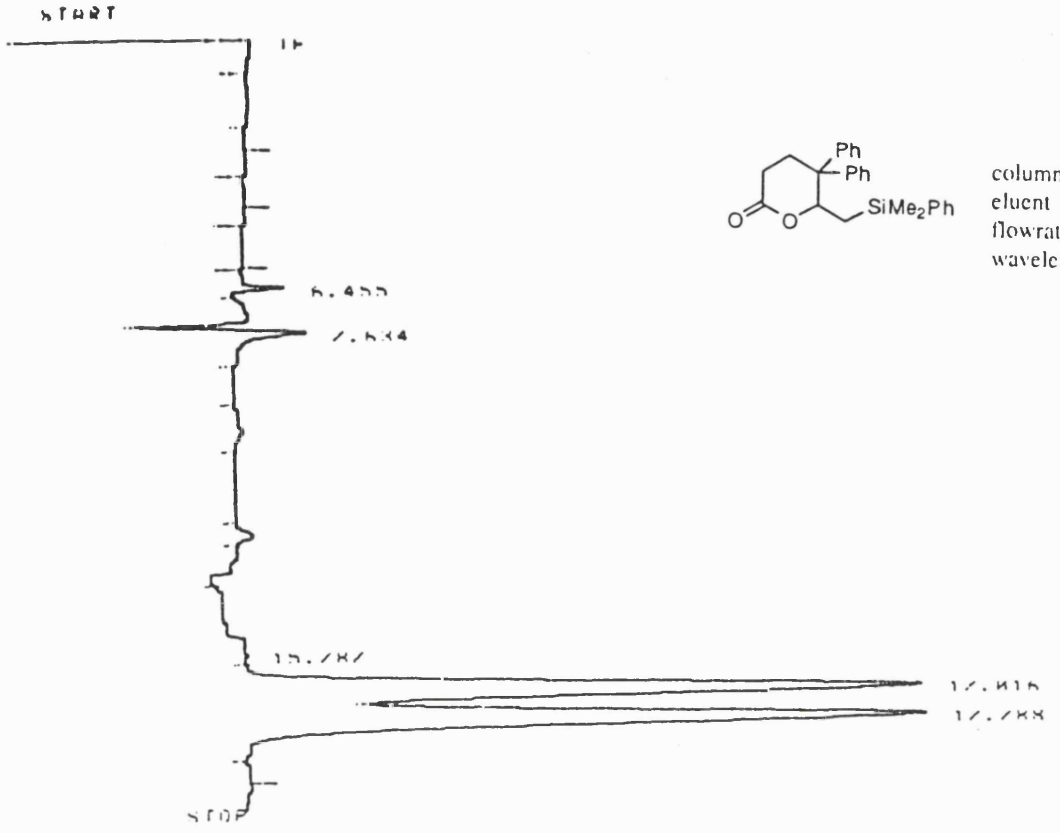
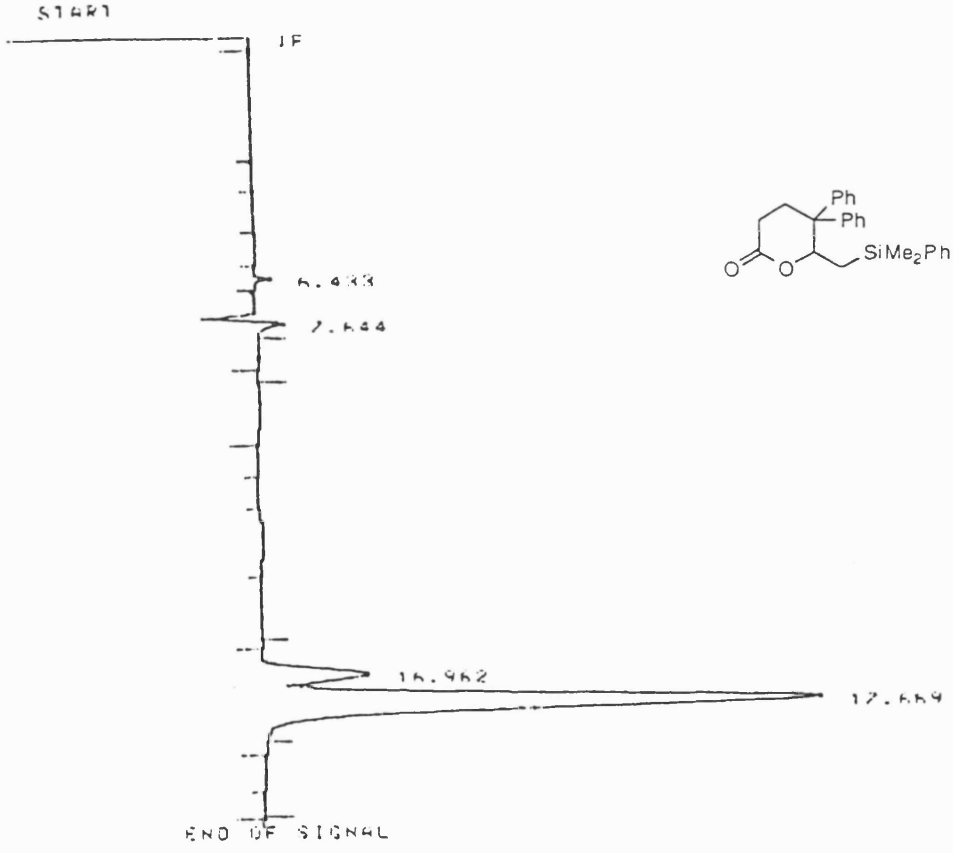
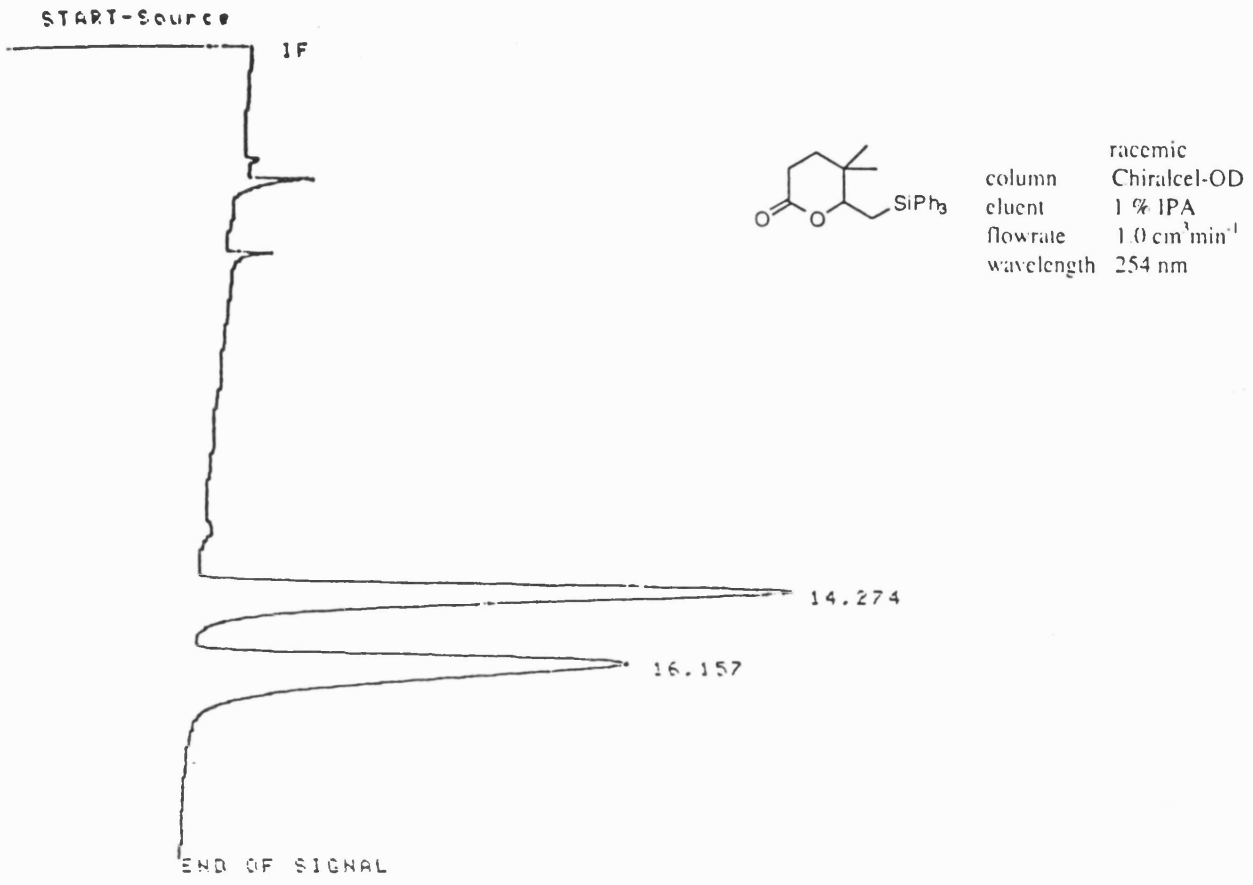
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



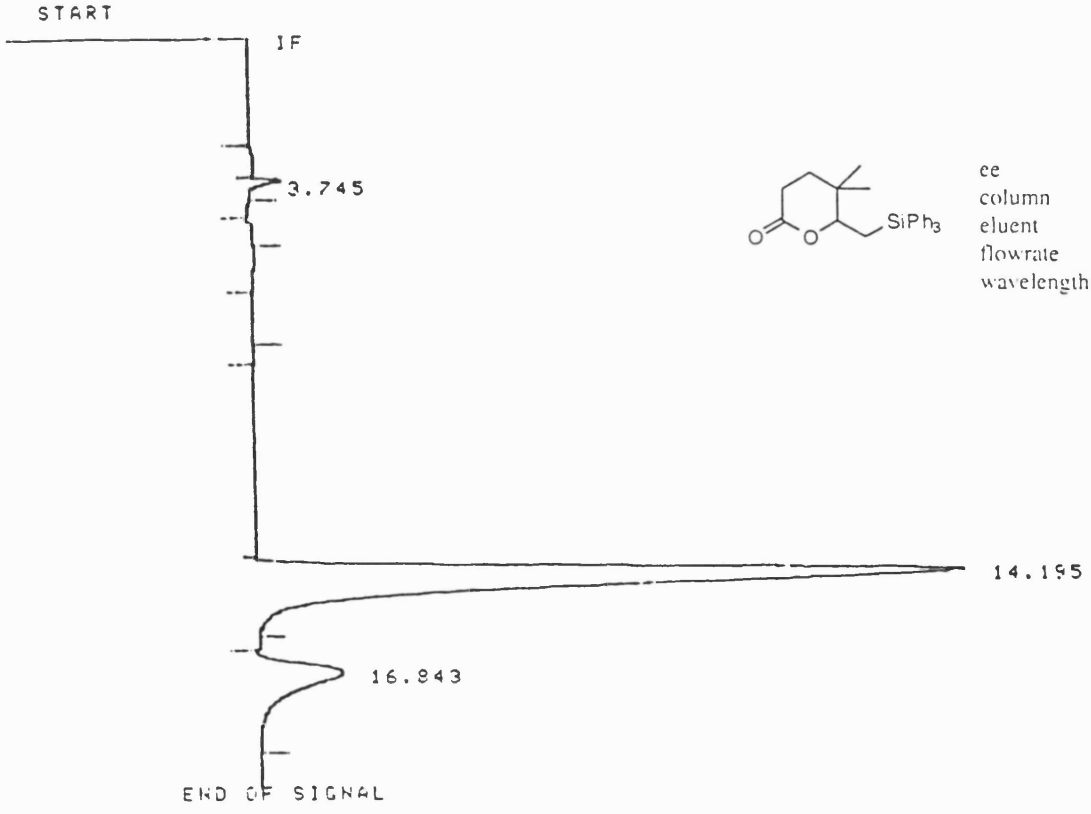
	racemic
column	Chiralcel-OD
eluent	4 % IPA
flowrate	0.5 cm^3min^{-1}
wavelength	254 nm



ee	73 %
column	Chiralcel-OD
eluent	4 % IPA
flowrate	0.5 cm^3min^{-1}
wavelength	254 nm



	racemic
column	Chiralcel-OD
eluent	1 % IPA
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



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column	Chiralcel-OD
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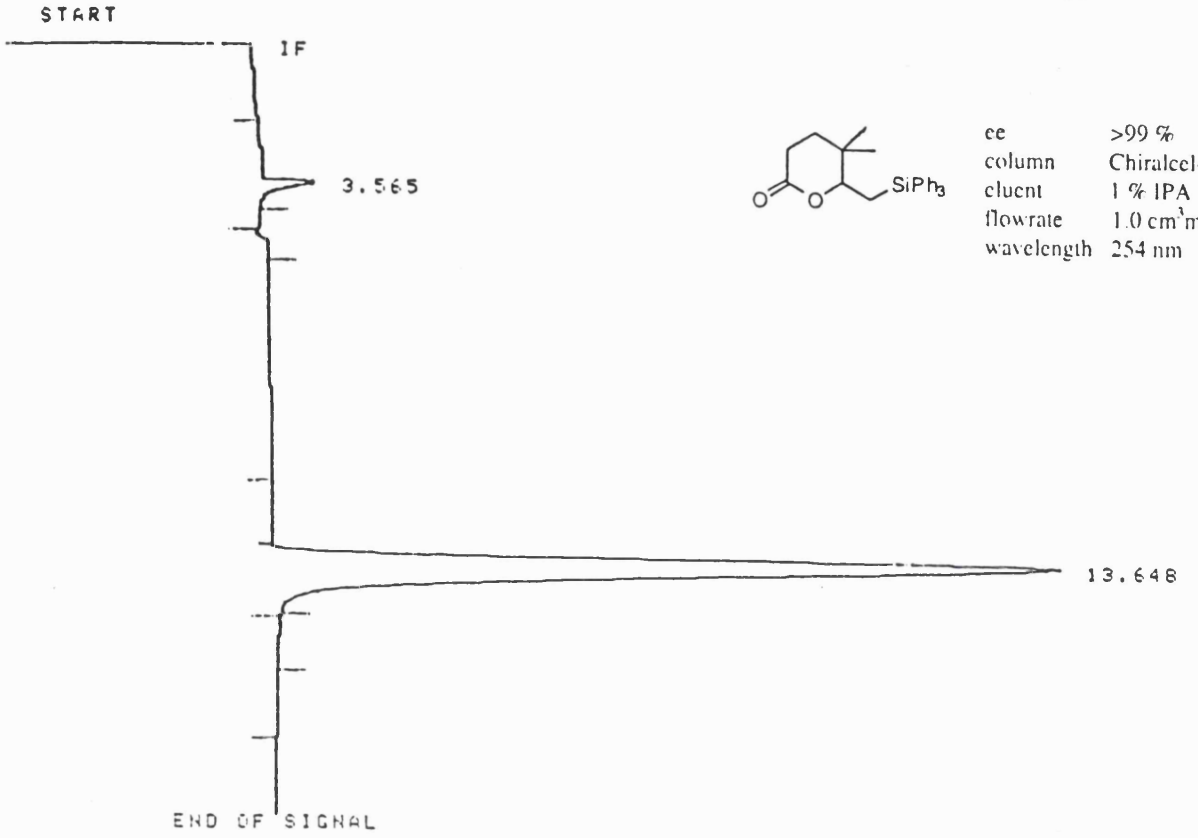
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



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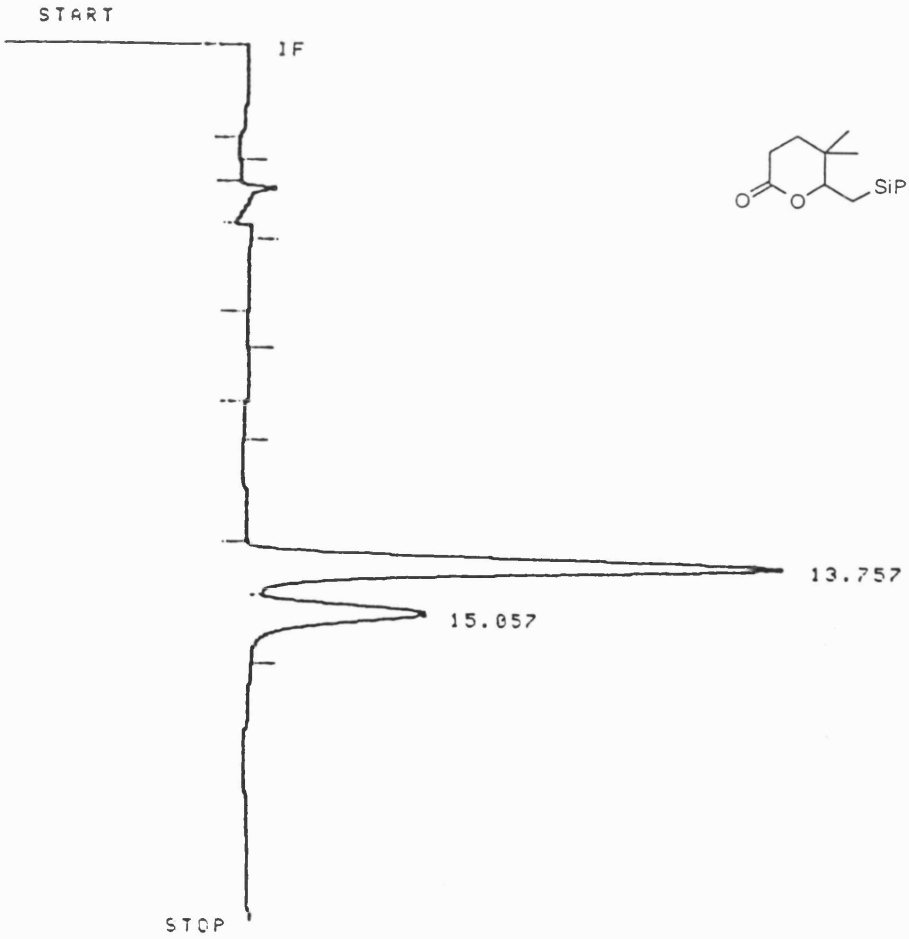

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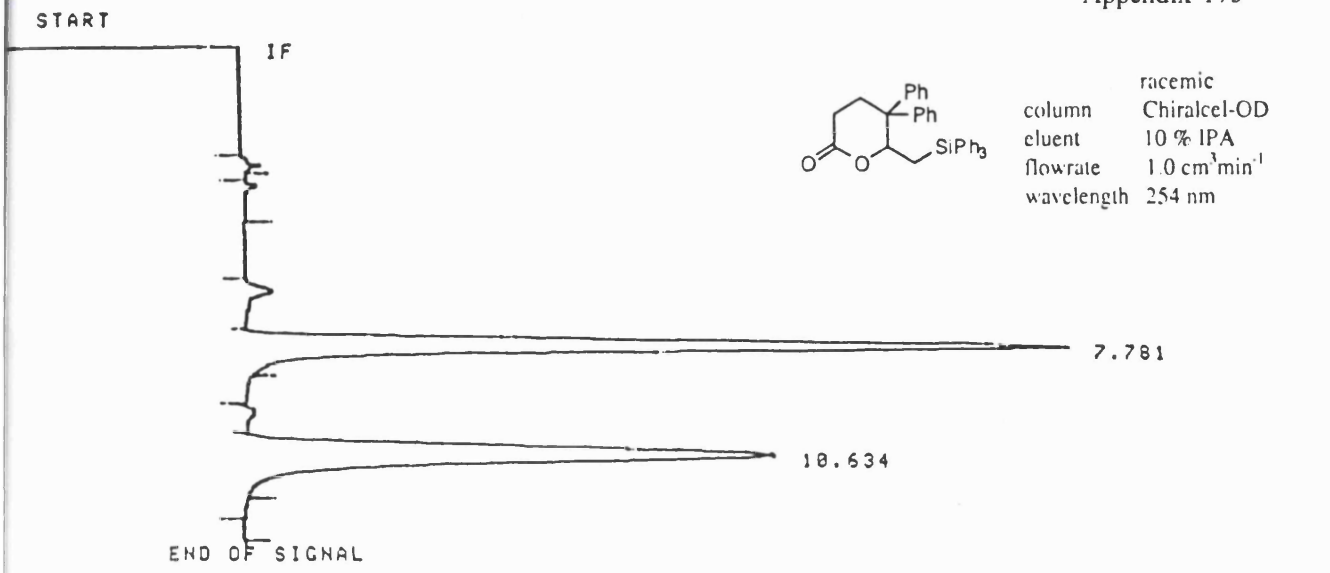

	racemic
column	Chiralcel-OD
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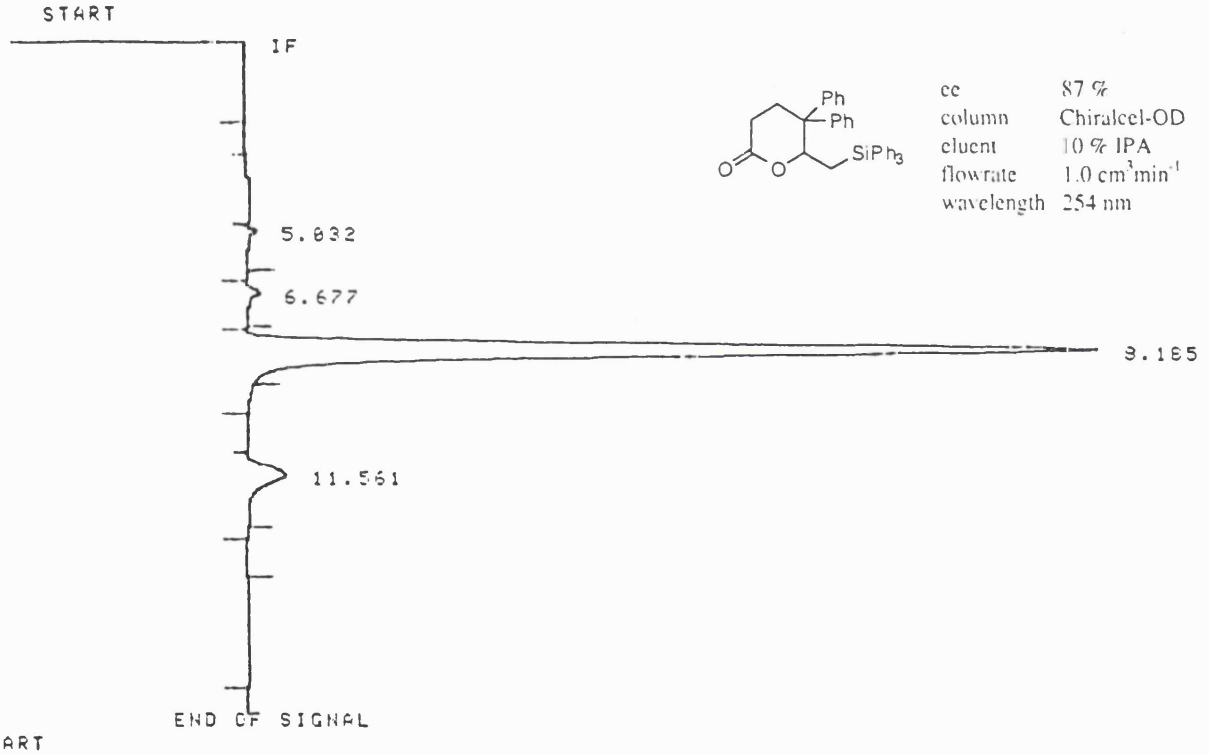
flowrate	1.0 cm^3min^{-1}
wavelength	254 nm



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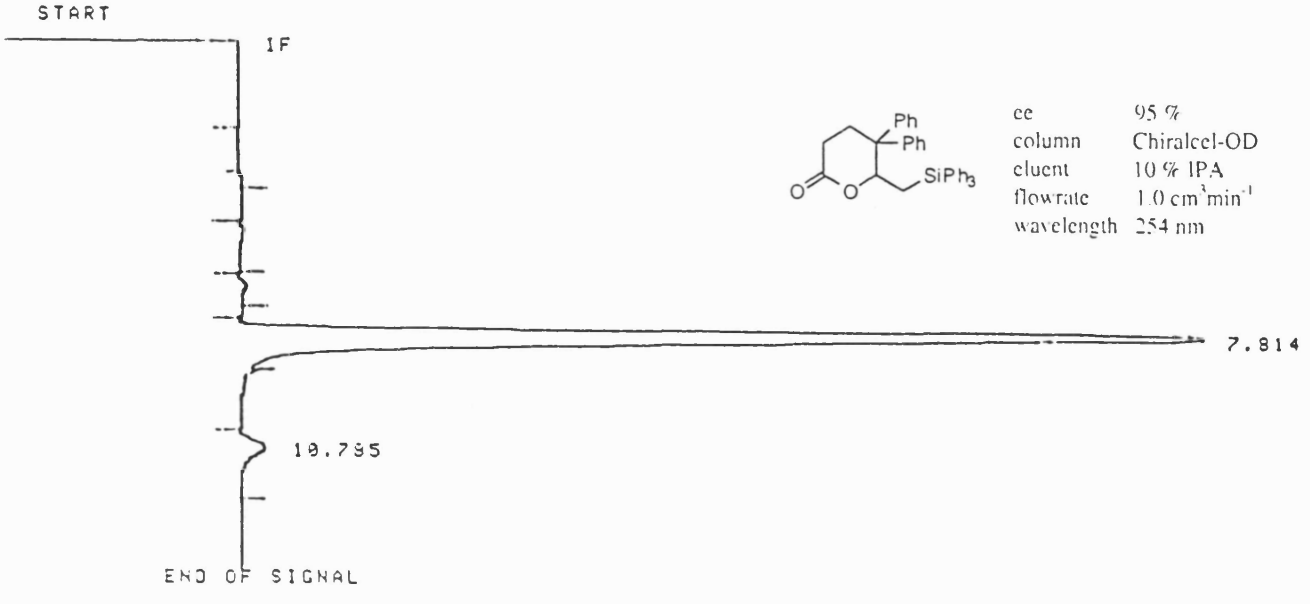

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column	Chiralcel-OD
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flowrate	1.0 cm^3min^{-1}
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