Tetrahedron Vol. 45, No. 18, pp. 5887 to 5894, 1989
Printed in Great Britain.

0040-4020/89 \$3.00+.00

REACTIONS OF O-SILYLATED ENOLATES WITH ALLYLSILANE BIFUNCTIONAL [4+2] AND [5+2] ANNULATING REAGENTS

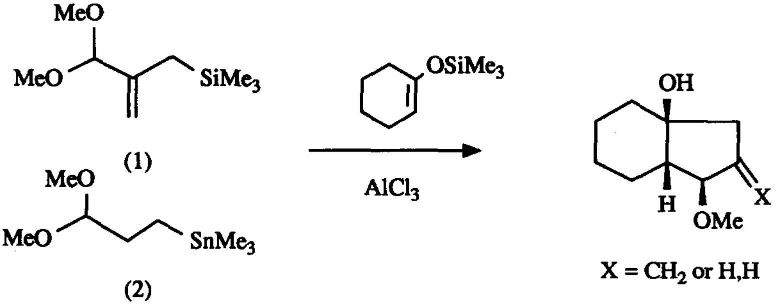
Thomas V.Lee*, Raymond J.Boucher, John R.Porter and Caroline J.M.Rockell
(School of Chemistry, The University, Bristol BS8 1TS, England)

(*Received in UK* 8 *June* 1989)

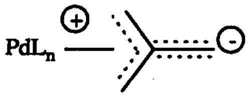
Summary: The reactions of the two allylsilane-acetals (8) and (9) with various O-silylated enolates is described. This has resulted in a new route to fused carbocyclic six and seven-membered rings in a one-pot reaction by use of a chemospecific allylsilane based bifunctional annulating reagent.

Introduction

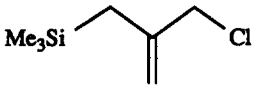
We have described the novel bifunctional annulating reagents (1) and (2) which through a sequential and chemospecific process, whereby the two reactive centres are activated by the same set of conditions, give easy access to fused cyclopentanes[1] and spirocyclopentanes[2]. The recent interest in [3+2] annulations makes these reactions of value since they present a useful alternative to other [3+2] annulating reagents. This is especially so since most of the other bifunctional [3+2] reagents described, (3) to (7), are designed to react in the opposite sense to those described by us, by initially undergoing nucleophilic conjugate addition to α,β-unsaturated ketones[3-7]. Additionally of these only (3), the palladium(0) complex of trimethylene methane, reacts in one pot to furnish a fused cyclopentane. However by definition this reagent is restricted to the preparation of five-membered rings.



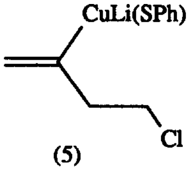
We felt that our strategy was possibly of wider synthetic utility by being applicable to the synthesis of more than one ring size and therefore we have studied the chemistry of the related allylsilane-acetals (8) and



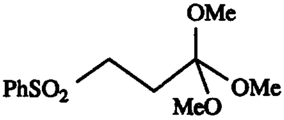
(3)



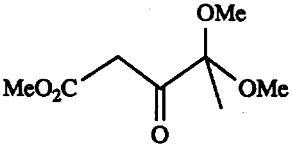
(4)



(5)

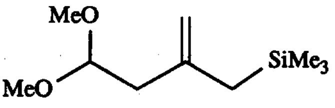


(6)

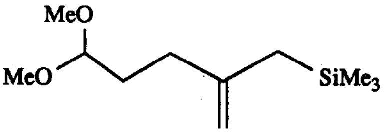


(7)

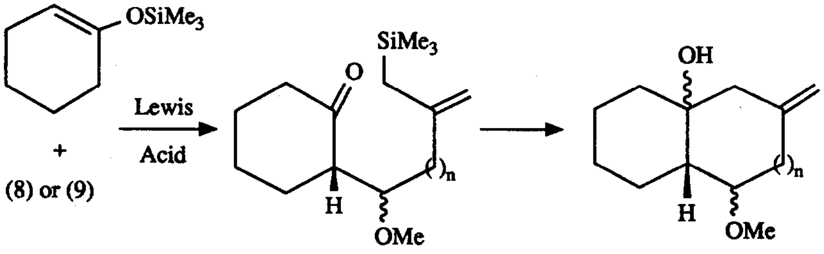
(9) to see if they give ready access to six and seven-membered rings respectively. Thus reaction of either **(8)** or **(9)** with an enol ether and Lewis acid should give, by analogy to the cyclopentane synthesis, the ketone **(10)**. Cyclization of this intermediate under the same conditions should then give a fused six or seven-membered ring, in a process corresponding to a [4+2] and a [5+2] annulation reaction[8]. These studies are the subject of this paper.



(8)



(9)

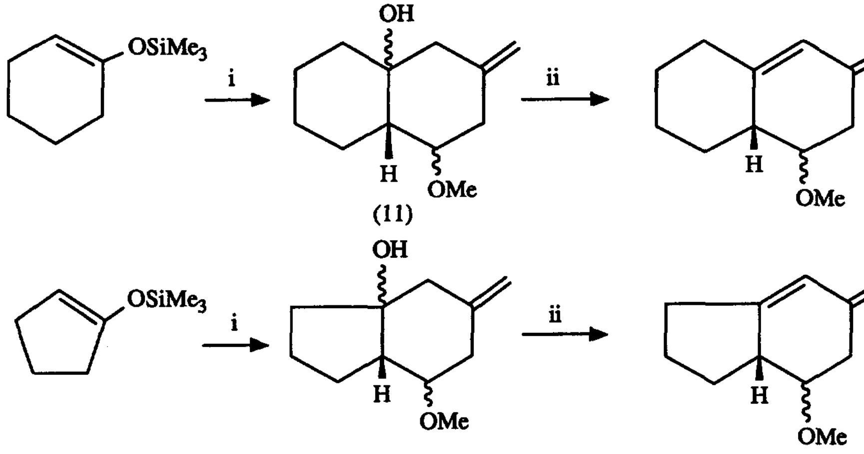


(10) n=1 or 2

Results and Discussion

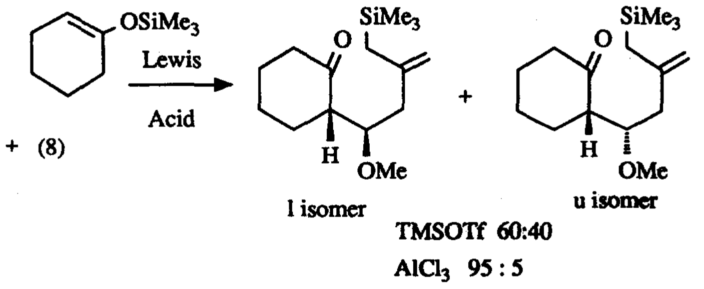
Preparation of (8) and (9). When we commenced these studies the synthesis of these two compounds was not straightforward but we have now reported a simple and efficient route to them[9].

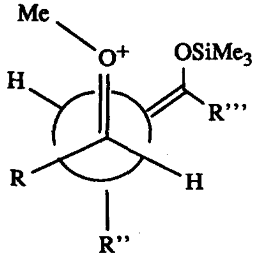
Reaction of (8) and(9). Treatment of an O-silylated enolate with the acetalsilane (8) and trimethylsilyl trifluoromethanesulphonate (TMSOTf) gave the expected ketone, corresponding to (10), which can be isolated if required. However reaction with a stronger Lewis acid (titanium tetrachloride) forms the alcohol (11) as a mixture of cis and trans isomers about the newly formed ring junction. Separation of these isomers is possible by chromatography, but normally to improve the yields of the overall process we convert this initial product to an α,β-unsaturated ketone, using osmium tetroxide or ozone, to form a β-ketol, followed by elimination of water, in an overall yield from the enol ether of 65%. Providing that care is taken in this elimination step to avoid aromatisation (by performing the reaction at low temperature in the presence of a tertiary amine) the overall sequence is very efficient with the enone products being more synthetically useful than the mixture of bridgehead alcohol isomers.



i, (8) + TMSOTf-TiCl$_4$; ii, OsO$_4$/NaIO$_4$-SOCl$_2$

Furthermore we can control the stereochemistry of the first bond forming reaction, so enhancing this process further. The use of TMSOTf gives a 3:2 mixture of the *l* to *u* isomer[10] for the intermediate ketones, whereas AlCl$_3$ gives mainly the *l* isomer. We believe that this stereochemical outcome is best explained by considering a transition state which has the topology (12) for which coordination with Lewis acid

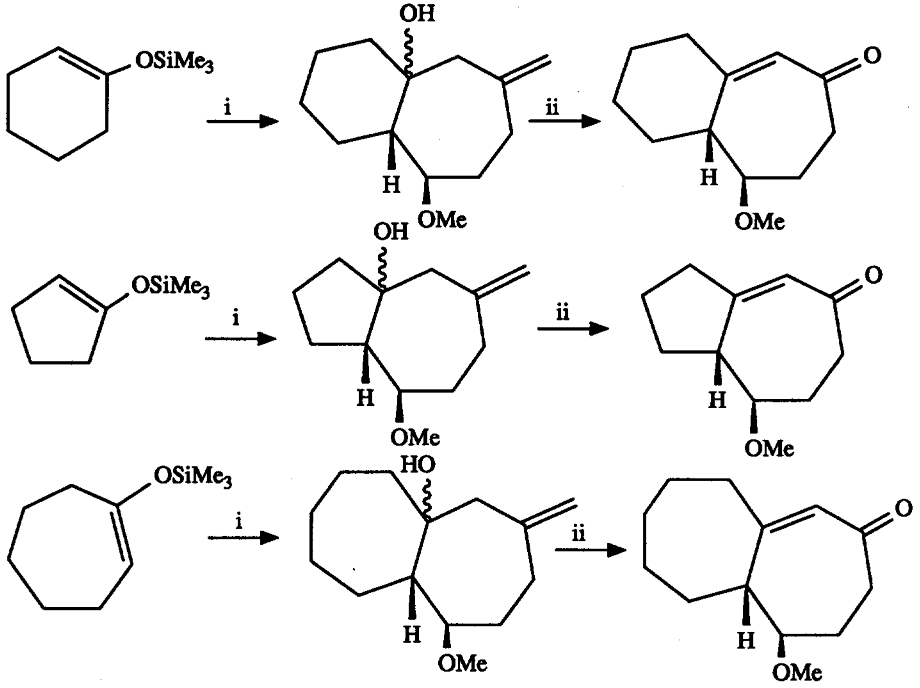




(12)

immediately prior to formation of (12) leads this gauche arrangement of the enol and the electrophile which results in formation of the *l* isomer. The greater coordinating properties of $AlCl_3$ makes it the best Lewis acid for these reactions.

A similar mode of reaction is seen for the acetal (9) leading to the fused seven-membered rings which can also be converted to the useful enones, but in higher yields (68-71 %). This acetal also displays the same dependence on Lewis acid in the stereoselectivity of the first bond forming reaction. The assignment of diastereomers in this first reaction is straightforward since they are separable and can be fully assigned by nmr analysis in which the *l* isomer shows a two way n.O.e effect between the methyl ether and the bridgehead hydrogen. After this assignment the crude products were then analysed for an accurate measurement of the isomer ratios.



i, (9) + $AlCl_3$; ii, $OsO_4/NaIO_4$-$SOCl_2$

Additionally, once separated by chromatography the bridgehead isomers can also be characterised by high-field nmr. A brief analysis of the stereochemical outcome of the cyclization step shows that there is a lack of selectivity in the ring closure which for synthetic purposes necessitates the conversion to an enone as described above.

In conclusion the bifunctional reagents (8) and (9) are extremely useful for the synthesis of six and seven-membered rings so extending considerably the concept of utilising bifunctional reagents in which the two reactive centres are activated by one set of conditions, but sequentially. The chemoselectivity displayed by these reagents is inherently interesting, offering considerable scope for multi-bond forming reactions such as those described and for the synthesis of important target molecules which we are in the process of demonstrating.

Experimental

All organic solvents were distilled prior to use as listed (tetrahydrofuran and ether, which refers to diethyl ether, from sodium/benzophenone; dichloromethane and triethylamine from calcium hydride; methanol from dimethoxymagnesium; trimethylorthoformate and carbon tetrachloride from potassium hydroxide.) Infra-red spectra were recorded on a Perkin-Elmer 1420 or 881 spectrophotometer, nmr on JEOL PMX 60, GX 270 and GX 400 spectrometers using TMS or CH_2Cl_2 as an internal standard, and mass spectra were obtained on a VG9090 mass spectrometer. Reactions involving air and/or moisture sensitive intermediates were performed under a nitrogen atmosphere and magnesium sulphate was used for drying solutions of organic compounds.

GENERAL ANNULATION PROCEDURE

Use of TMSOTf:- A solution of trimethylsilyltrifluoromethanesulphonate (1M in THF), (0.1 mmol) was added dropwise to a mixture of the O-silylated enolate (1 mmol) and the acetal-allylsilane (1.1 m mol) in anhydrous dichloromethane (20 ml) at -78°C under N_2. The reaction mixture was stirred at -78°C for 1½ hours, after which time t.l.c. analysis indicated the formation of intermediate products. Titanium tetrachloride (1M in dichloromethane; 1 mmol) was added dropwise to this mixture at -78°C and the orange/brown solution was stirred for 2 hours at -78°C and quenched with water at -78°C. The organic phase was separated and diluted with dichloromethane (20 ml), washed with saturated hydrogen carbonate solution (10 ml), brine (10 ml), dried ($MgSO_4$) and evaporated to give a brown oil. Purification by flash chromatography using petrol/ether (5:1) was achieved for each example.

Use of $AlCl_3$:- A mixture of the O-silylated enolate (1 mmol) and the acetal-allylsilane (1.1 mmol) in anhydrous dichloromethane (20 ml) was added to a stirred suspension of aluminium trichloride (4.0 mmol) in dichloromethane (20ml) at -78°C under N_2. When complete by tlc analysis the mixture was poured into saturated hydrogen carbonate solution (30 ml), washed with brine (10 ml), dried ($MgSO_4$) and evaporated to give a brown oil. Purification by flash chromatography using petrol/ether (5:1) was achieved for each example.

The examples below illustrate the use of both of these methods.

(8) + 1-TRIMETHYLSILYLOXYCYCLOHEXENE + $AlCl_3$

1-Hydroxy-3-methylene-5α-methoxy-6αH-bicyclo [4.4.0] decane was obtained as a mixture of bridgehead isomers (53%).

Found M^+ 196.1482; $C_{12}H_{20}O_2$ requires M^+, 196.1463.

$\nu_{max}(CCl_4)$ 3620, 3520 (OH), 3080 (C=CH), 1640 (C=C), 1105 cm^{-1}; δ_H $CDCl_3$, 4.89 (1H, s, vinyl H), 4.86 (1H, s, vinyl H), 3.38 (1H, m, CHOMe), 3.36 (3H, s, OCH_3), 2.71 - 1.39 (14H, m, OH and CH_2); m/z, 196 (M^+, 0.54%), 178 (6), 165 (21), 127 (100), 113 (12), 99 (34), 81 (35), 71 (20).

(8) + 1-TRIMETHYLSILYLOXYCYCLOPENTENE + $AlCl_3$

1-Hydroxy-3-methylene-5α-methoxy-6αH-bicyclo [4.3.0] nonane was obtained as a mixture of bridgehead isomers (52%).

ν_{max} (CCl_4) 3620, 3520 (OH), 1640 (C=C) cm^{-1}; δ_H $CDCl_3$, 4.8 (1H, s, vinyl H), 4.76 (1H, s, vinyl H), 3.4 (1H, m, CHOMe), 3.35 (3H, s, OCH_3), 2.6 - 1.4 (12H, m, OH and CH_2); m/z, 182 (M^+, 2%), 164, 151, 113, 71.

(9) + 1-TRIMETHYLSILYLOXYCYCLOPENTENE + TMSOTf

1-Hydroxy-3-methylene-6β-methoxy-7αH-bicyclo [5.3.0] decane, as a mixture of bridgehead isomers, was obtained as a colourless oil (24%).

Found M^+ 196.1475; $C_{12}H_{20}0_2$ requires M^+ 196.1463.

ν_{max}(CCl_4), 3620, 3520 (O-H), 3080 (C=CH), 1640 (C=C), 1105 cm^{-1}; δ_H $CDCl_3$, 4.70 (1H, s, vinyl H) 4.66 (1H, s, vinyl H), 3.51 (1H, m, CHOMe), 3.34 (3H, s, OMe), 2.60 - 1.4 (14H, m, OH and CH_2); δ_c $CDCl_3$, 145.40 (s), 110.20 (t), 80.17 (q), 77.21, 57.26, 50.79, 39.45, 34.17, 29.26, 24.59, 22.37, 20.82; m/z, 196 (M^+ 2.54), 164 (38), 140 (27), 127 (53), 121 (18), 113 (13), 112 (12), 108 (17), 97 (15), 93 (12), 86 (18), 81 (100), 80 (18), 79 (13), 67 (70), 55 (31), 41 (33).

1-Hydroxy-3-methylene-6α-methoxy-7αH-bicyclo [5.3.0] decane, as a mixture of bridgehead isomers, was obtained as a colourless oil (39%).

Found M^+ 196.1476; $C_{12}H_{20}O_2$ requires M^+ 196.1463.

ν_{max} (CCl_4), 3620, 3520 (O-H), 3080 (C=CH), 1640 (C=C), 1105 cm^{-1}; δ_H $CDCl_3$, 4.64 (1H, s, vinyl H), 4.61 (1H, s, vinyl H), 3.34 (1H, m, CHOMe), 3.29 (3H, s, CHOMe), 2.5 -1.4 (14H, s, OH and CH_2); m/z, 196 (M^+, 1), 178 (5), 164 (50), 139 (2), 127 (66), 126 (43), 121 (24), 113 (18), 112 (24), 110 (27), 108 (24), 97 (43), 93 (16), 84 (100), 81 (45), 80 (35), 55 (56), 43 (28).

(9) + 1-TRIMETHYLSILYLOXYCYCLOHEXENE + TMSOTf

1-Hydroxy-3-methylene-6β-methoxy-7αH-bicyclo [5.4.0] undecane as a colourless oil, and a mixture of bridgehead isomers (24.5%).

Found: C, 74.37, H, 10.67; requires C; 74.24, H, 10.54%

ν_{max} 3530 (OH), 3075 (C=CH), 1635 (C=C), 1105 cm^{-1}; δ_H $CDCl_3$, 4.81 (1H, s, vinyl H), 4.75 (1H, s, vinyl H), 3.33 (1H, m, CHOMe), 3.23 (3H, s, OCH_3), 2.40 - 0.78 (16H, m, OH and CH_2); δ_c $CDCl_3$, 146 (s), 113.77 (t), 113.77 (t), 85.90 (q), 71.89, 57.40, 51.10, 51.00, 40.27, 29.89, 29.70, 28.39, 28.34, 26.34, 21.62; m/z, 210 (M^+, 5%), 192 (1), 178 (54), 141 (53), 98 (64), 81 (76), 80 (100), 41 (39).

1-Hydroxy-3-methylene-6-α-methoxy-7αH-bicyclo [5.4.0] undecane as a colourless oil, and a mixture of bridgehead isomers (26.5%).

Found: C, 74.24; H, 10.73; $C_{13}H_{22}O_2$ requires C; 74.24, H; 10.54%.

ν_{max} 3460 (OH), 3075 (C=CH), 1635 (C=C), 1093 cm^{-1}; δ_H $CDCl_3$, 4.87 (1H, s, vinyl H), 4.76 (1H, s, vinyl H), 3.24 (1H, m, CHOMe), 3.22 (3H, s, OCH_3), 2.71 - 0.75 (16H, m, OH and CH_2); δ_c $CDCl_3$, 145.70 (s), 114.58 (t), 82.46, 69.45, 56.70, 52.28, 49.45, 42.04, 31.01, 30.35, 25.63, 24.81, 22.33; m/z, 210 (M^+, 4%), 192 (3), 178 (28), 141 (31), 98 (56), 97 (31), 81 (59), 80 (100), 41 (28).

(9) + 1-TRIMETHYLSILYLOXYCYCLOHEPTENE + $AlCl_3$

1-Hydroxy-3-methylene-6α-methoxy-7αH-bicyclo [5.5.0] dodecane as a mixture of bridgehead isomers (55%).

Found M^+ 224.1784; $C_{14}H_{24}O_2$ requires M^+, 224.1776.

ν_{max} (CCl_4) 3620, 3520 (OH), 3090 (C=CH), 1640 (C=C), 1105 cm^{-1}; δ_H $CDCl_3$, 4.69 (1H, s, vinyl H), 4.66 (1H, s, vinyl H), 3.46 (1H, m, CHOMe), 3.28 (3H, s, OCH_3), 2.72 - 1.2 (18H, m, OH and CH_2); m/z, 224 (M^+, 3.47%), 192 (28), 168 (13), 155 (28), 112 (25), 97 (12), 95 (24), 81 (100), 80 (11), 71 (19), 55 (23), 41 (17).

GENERAL METHOD FOR ENONE FORMATION

Osmium tetroxide (15 mg) was added to a solution of the crude alkene (0.5 mmol), ether (8 ml) and H_2O (8 ml) and the mixture was stirred for 10 minutes at room temperature when powdered sodium metaperiodate (2.2 mmol) was added over a 30 minute period and the stirring continued for a further 16 hours at room temperature. The mixture was poured into H_2O (10 ml) and extracted with ether (3 x 20 ml). The organic extract was dried, filtered and evaporated to yield the crude product which was dissolved in anhydrous benzene (10 ml) containing triethylamine (1.2 mmol) and a solution of thionyl chloride (0.6 mmol) in benzene (1 ml) was added dropwise to form a yellow suspension. This was stirred at room temperature for 12 hours when it was washed with saturated aqueous $NaHCO_3$ solution (10ml), brine (10 ml), dried ($MgSO_4$) and evaporated to yield a crude product which was purified by flash chromatography. By this method the alkenes produced above were converted to enones as illustrated by the selected examples given below for the products from both a TMSOTf and an $AlCl_3$ reaction.

(9) + 1-TRIMETHYLSILYLOXYCYCLOHEXENE + TMSOTf

3-Oxo-6-methoxybicyclo [5.4.0] undec-1-ene was obtained as a mixture of the *l* and *u* isomers which were separated by flash chromatography (petrol/ether 1:1).

***l*-Isomer:** (41%). Found M^+ 194.1296; $C_{12}H_{18}O_2$ requires 194.1307.

ν_{max} (CCl_4) 1660 (C = O), 1640 (C = C) cm^{-1}; δ_H $CDCl_3$, 5.58 (1H, s, vinyl H), 3.32 (3H, s, OCH_3), 3.10 (3H, m, CHOMe and CH_2), 2.45-1.46 (11H, m, CH_2); m/z, 194 (M^+, 47%), 162 (12), 136 (21), 120 (24), 108 (15), 107 (12), 98 (24), 95 (69), 94 (21), 93 (22), 91 (21), 79 (31), 71 (100), 41 (24).

***u*-Isomer:** (29%). Found M^+ 194.1291; $C_{12}H_{18}O_2$ requires 194.1307.

ν_{max} (CCl_4) 1660 (C = O), 1640 (C = C) cm^{-1}; δ_H $CDCl_3$, 5.85 (1H, s, vinyl H), 3.35 (3H, s, OCH_3), 3.11 (1H, m, $CHOCH_3$), 2.78 - 1.8 (11H, m, methylene); δ_c $CDCl_3$, 203.59, 158.12, 125.36, 83.29, 56.73, 51.78, 40.32, 38.79, 33.62, 28.96, 25.88, 23.93; m/z, 194 (M^+, 100%), 162 (15), 149 (24), 136 (46), 124 (11), 123 (64), 121 (26), 120 (47), 107 (30), 95 (40), 94 (26), 93 (26), 91 (33), 79 (31), 71 (61), 55 (28), 41 (36).

(8) + 1-TRIMETHYLSILYLOXYCYCLOHEXENE + $AlCl_3$

3-Oxo-5-methoxybicyclo [4.4.0] dec-1-ene was obtained as the *l* isomer (63%). Found M^+ 180.1035; $C_{11}H_{16}O_2$ requires 180.1023.

ν_{max} (CCl_4) 1660 (C = O), 1640 (C = C) cm^{-1}; δ_H $CDCl_3$, 5.86 (1H, s, vinyl H) 3.33 (3H, s, OCH_3), 3.05 (1H, m, $CHOCH_3$), 2.8-1.8 (9H, m, methylene); m/z, 180 (M^+, 100%), 148 (18), 135 (29), 122 (32), 109 (66), 106 (37).

References and Notes

1. Lee, T.V; Boucher, R.J; Porter, J.R; Taylor, D.A., *Tetrahedron* 1988, 44, 4233.; Lee,T.V; Richardson, K.A; Ellis, K.L; Visani, N., *Tetrahedron* 1989, 45, 1167.

2. Lee,T.V; Richardson, K.A; Taylor, D.A., *Tetrahedron Letters*, 1986, 27, 5021.

3. Trost, B.M. *Angew. Chem., Int. Ed. Engl.* 1986, 25, 1.

4. Knapp, S,; O'Connor, U.; Mobilio, D. *Tetrahedron Lett.* 1980, 21, 4557.

5. Piers, E.; Karunaratre, V. *J. Chem. Soc., Chem. Commun.* 1984, 959.

6. DeLombaert, S.; Nemery, I.; Roekens, B.; Carretero, J.C.; Kimmel, T.; Ghosez, L. *Tetrahedron Lett.* 1986, 27, 5099.

7. Danishefsky, S,; Etheridge, S.J. *J. Org. Chem.* 1982, 47, 4791.

8. Lee, T.V; Boucher, R.J; Rockell, C.J.M, *Tetrahedron Letters*, 1988, 29, 689.

9. Lee, T.V; Porter, J.R; Roden, F.S, *Tetrahedron Letters*, 1988, 29, 5009 and preceding paper.

10. Seebach, D; Prelog, V., *Angew.Chem.Int.Ed.Engl.*, 1982, 21, 654.

11. All chiral compounds shown are racemic mixtures but for clarity only one enantiomer is shown.