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# Towards the Synthesis of the $C_{37}$-$C_{42}$ Fragment of Rapamycin: Intramolecular Reactions of Allyl Silanes with Oxonium Ions Generated from α-Alkoxy Sulfones.

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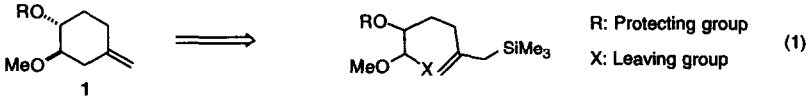
***Abstract:*** A new method for the formation of methylene cyclohexane derivatives has been developed, using intramolecular trapping by allyl silanes of oxonium ions generated from α-alkoxysulfones. These acyclic precursors were prepared by quenching the anion of methoxymethyl phenyl sulfone **2** with various electrophiles containing the allyl silane moiety. When a β-substituent is present, the stereochemical outcome of the cyclisation reaction has proved to be dependant on the stereochemistry of the starting material. This methodology has been applied to the synthesis of **1**, a synthetic precursor to the $C_{37}$-$C_{42}$ fragment of rapamycin.

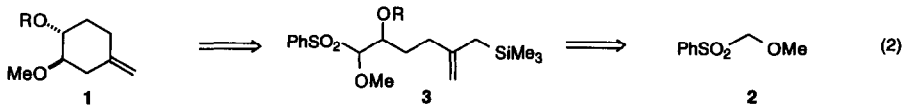
## Introduction

The nucleophilic reactions of allyl silanes have been recognised as one of the most powerful tools for carbon-carbon bond formation.[1] In particular, the intramolecular trapping of various electrophiles by an allyl silane is a very convenient method for stereoselective ring formation, and has found many applications in synthesis.[2] In our efforts towards the synthesis of rapamycin,[3] we wished to prepare **1** as a synthetic precursor to the cyclohexyl fragment ($C_{37}$-$C_{42}$ fragment), using an intramolecular reaction of an allyl silane with an oxonium ion[4] (equation 1).




**1** (1)

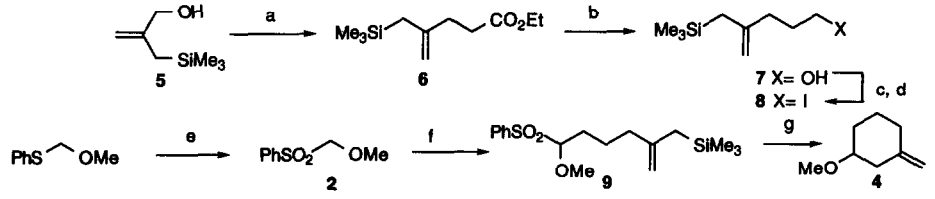
An example of ring closure of an allyl silane onto a dimethyl acetal, leading to a related ring system, has been reported.[5] We anticipated that the synthesis of **1** could be achieved using the chemistry of α-alkoxy sulfones, both as formyl carbanion equivalents[6] and as potential oxonium ion precursors.[7] Thus, starting from the readily available methoxymethyl phenyl sulfone **2**, we would rapidly be able to prepare the acyclic precursor **3**, which could in turn be cyclised to **1**, bearing the required *trans* arrangement of substituents on the ring system. The *exo* methylene double bond would allow further side-chain elaboration (equation 2).




In this paper, we wish to present our efforts and observations on the development of suitable methodology towards the synthesis of **1**.

## Results and discussion

In order to investigate the viability of this methodology, we first focussed on a simpler model, lacking the protected hydroxyl group. Thus, the known[5] 3-methoxy-1-methylene cyclohexane **4** was prepared as shown below (Scheme 1). According to a described procedure,[8] 2-trimethylsilylmethyl-2-propen-1-ol[9] **5** was subjected to a Claisen-Johnson rearrangement with triethyl orthoacetate, giving the ester **6** which was reduced to the alcohol **7**, which was then converted to the iodide **8** in a two-step sequence. Methoxymethyl phenyl sulfone **2**, prepared by oxidation of the corresponding sulfide[10] (available from Aldrich) was deprotonated with an excess of *tert*-butyllithium (DME, -78°C) and the yellow anion solution was treated with the iodide **8** to give **9** in 83% isolated yield. This particular method of deprotonation avoids the use of cosolvents such as HMPA.[11] Upon treatment of **9** with magnesium bromide etherate at 0°C, a rapid and clean reaction occurred, leading to **4** as single product in 90% yield, as judged by $^1$H NMR analysis of the crude product.



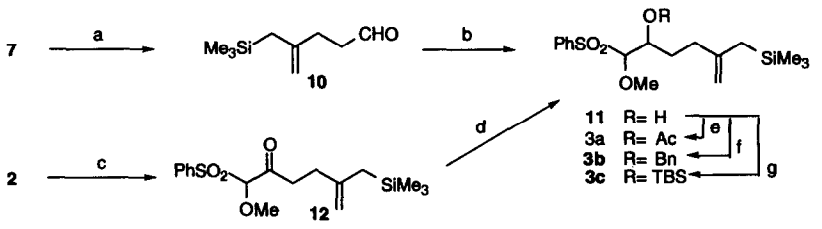

a: $MeC(OEt)_3$, $EtCO_2H$, 140°C; b: $LiAlH_4$, $Et_2O$, 25°C, 78% (two steps); c: MsCl, $Et_3N$, $CH_2Cl_2$, 0°C; d: NaI, $NaHCO_3$, acetone, 25°C, 80% (two steps); e: Oxone®, pH 4 buffer, MeOH, 25°C, 75%; f: *t*BuLi (1.1 eq.), DME, -78°C, then **8**, 83%; g: $MgBr_2.OEt_2$, $CH_2Cl_2$, 0°C, 90% (yield estimated by $^1$H NMR)

**Scheme 1**

In contrast to Fleming's original report,[5] this milder method, using a sulfone as the leaving group, allows the cyclisation to proceed without further isomerisation of the double bond. Unfortunately, **4** proved to be unstable and volatile, and could not be fully characterised. Nevertheless, this short and high yielding synthesis of **4** demonstrates the efficiency of this methodology and shows that α-alkoxy sulfones can be used as oxonium ion precursors in carbon-carbon bond formation.

Following this encouraging result, we decided to investigate the stereochemical outcome of the cyclisation of **3**. Aware that this may be influenced by the nature of the protecting group as well as the Lewis acid, we wished to prepare acyclic precursors bearing different protecting groups. Thus, alcohol **7** was oxidised (Swern[12]) to the known aldehyde **10**.[13] This was condensed with the anion of **2** to give the β-hydroxy sulfone **11** as a 1:1 mixture of *syn* and *anti* isomers. **11** could also be prepared by condensation of the anion of **1** with the ester **6** to give the β-keto sulfone **12** which was reduced ($NaBH_4$) to give **11**. This reduction was not stereoselective and gave rise to a 1:1 ratio of isomers. The *syn* and *anti* isomers could be separated by chromatography on Florisil[14] and assigned on the basis of their $^1$H NMR spectra.[15] Protection of the

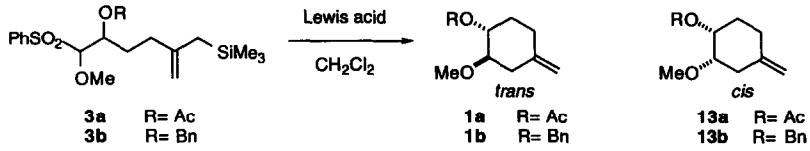
hydroxyl group proved to be troublesome due to low reactivity, sensitivity of the α-alkoxy sulfone moiety towards electrophilic reagents, and the possibility of elimination under strongly basic conditions. Control experiments showed that only small groups could be introduced in appreciable yields. Indeed, acetylation of **11** (as a mixture of isomers) proceeded in excellent yield to give **3a**, while benzylation afforded **3b** in lower yield and purity. After considerable experimentation, it was possible to realise silylation using *tert*-butyldimethylsilyl triflate, by lowering its electrophilic nature with strong nucleophilic bases (pyridine, DMAP). The use of this reagent with 2,6-lutidine led to complete decomposition while the silyl chloride reacted too sluggishly (Scheme 2).




a: $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 to 25°C, 70%; b: **2**, *t*BuLi (1.1 eq), DME, -78°C, then **10**, -78 to 25°C, 97%; c: *t*BuLi (1.1 eq), DME, -78°C, then **6** (0.5 eq.), -78 to 25°C, 86% (based on **6**); d: $NaBH_4$, EtOH, 25°C, 99%; e: $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$, 0°C, 92%; f: BnBr, $Ag_2O$, DMF, 60%; g: TBSOTf, pyridine, DMAP, $CH_2Cl_2$, 0°C, 70%.

**Scheme 2**

With the acyclic precursors **3a**, **3b** and **3c** in hand, their cyclisations were investigated. When **3a** or **3b** (as a 1:1 mixture of isomers) were treated with various Lewis acids, a clean reaction occured to give the cyclised products in good to excellent yields (Scheme 3). In both cases, the exocyclic double bond was stable, allowing chromatographic purification. The stereoisomers were separable and were fully characterised by $^1H$ NMR. The results are summarised in Table 1.




**3a** R= Ac
**3b** R= Bn

**1a** R= Ac
**1b** R= Bn

**13a** R= Ac
**13b** R= Bn

**Scheme 3**

| Entry | Precursor | Lewis acid (eq.) | Temp. | Time | Yield % | ratio **1**/ **13**[a] |
|---|---|---|---|---|---|---|
| 1 | **3b** | $BF_3.OEt_2$ (2) | -78°C | 10 min | 0[b] | / |
| 2 | **3b** | $AlCl_3$ (2) | -78°C | 1h | 66 | 1/1 |
| 3 | **3b** | $Me_2AlCl$ (2) | -78°C | 15 min | 65 | 1/1 |
| 4 | **3b** | $MgBr_2.OEt_2$ (3) | 0°C | 15 min | 67 | 1.2/1 |

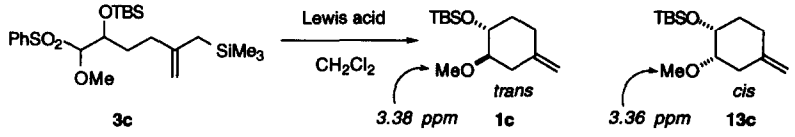
**Table 1**

| Entry | Precursor | Lewis acid (eq.) | Temp. | Time | Yield % | ratio 1/ 13[a] |
|---|---|---|---|---|---|---|
| 5 | **3b** | $SnCl_4$ (2) | -78°C | 15 min | 60 | 1.5/1 |
| 6 | **3b** | $TiCl_4$ (2) | -78°C | 15 min | 60 | 1/1 |
| 7 | **3a** | $TiCl_4$/ $Ti(OiPr)_4$ (6/5) | -78°C | 2 h[c] | 92 | 1/1 |
| 8 | **3a** | $MgBr_2$. $OEt_2$ | 0°C | 15 min | 90 | 1/1 |

a: ratio determined by $^1H$ NMR analysis of the crude product
b: protodesilylation was observed; c: Lewis acid added over 2 h by syringe pump

**Table 1 (continued)**

The results were rather disappointing in that the reaction showed little or no stereoselectivity. Reaction of the benzyl-protected precursor **3b** gave varying results depending on the reagent used, while the acetate **3a** gave a 1:1 ratio, regardless of the Lewis acid used. We then turned to the silylated precursor **3c**, where we expected to achieve more selectivity, because of the steric bulk of the TBS group. Once again, the reaction proceeded very cleanly, to give the cyclised products **1c** and **13c** in excellent yields (Scheme 4). In contrast to the acetyl- or benzyl-protected products, these could not be separated by chromatography. Correlation was achieved by conversion of the pure *trans* acetyl isomer **1a** into **1c**. The results of the cyclisation reactions of **3c** are summarised in Table 2.




**Scheme 4**

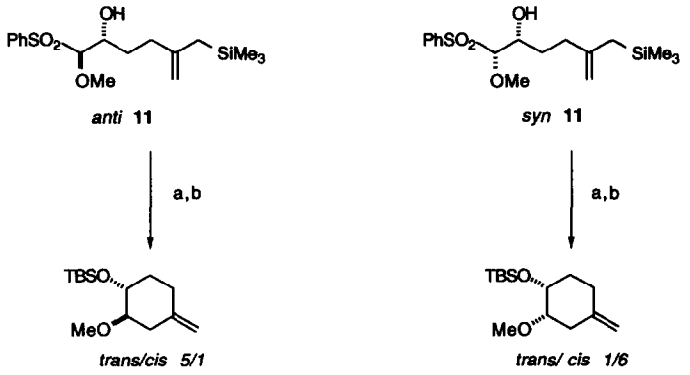
| Entry | Lewis acid (eq.) | Temp. | Time | Yield % | ratio 1c/ 13c[a] |
|---|---|---|---|---|---|
| 1 | TMSOTf (0.1) | -78°C | 30 min | 0[b] | / |
| 2 | $BF_3$. $OEt_2$ (2) | -78°C | 30 min | 0[b] | / |
| 3 | $ZnBr_2$ (2.5) | 0°C | 1h | 60[c] | 1/1 |
| 4 | $Et_2AlCl$ (2) | -78°C | 15 min | 80 | 1/3 |
| 5 | $SnCl_4$ (2) | -78°C | 15 min | 90 | 1/1 |
| 6 | $TiCl_4$/ $Ti(OiPr)_4$ (6/ 5) | -78°C | 2h[d] | 90 | 1/2 |
| 7 | $MgBr_2$. $OEt_2$ (3) | -40°C | 15 min | 90 | 1/2 |
| 8 | $MgBr_2$. $OEt_2$ (3) | 0°C | 15 min | 92 | 1/1.5 |
| 9 | $MgBr_2$. $OEt_2$ (3) | 25°C | 10 min | 90 | 1/1 |

a: ratio determined by $^1H$ NMR analysis of the crude product; b: protodesilylation was observed; c: partial protodesilylation was observed; d: Lewis acid added over 2h by syringe pump.

**Table 2**

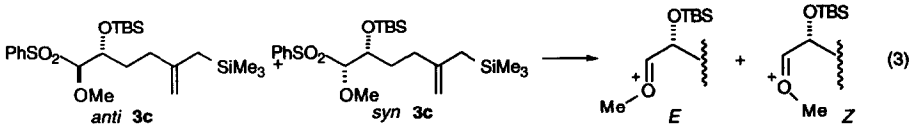
This series of experiments shows again a general lack of stereoselectivity in the cyclisation of **3c**. An interesting observation is the effect of temperature on the reaction (entries 7, 8 and 9), suggesting a possible conformational equilibrium in the intermediate cation. The influence of parameters like solvent and substituents on silicon were also studied but showed little effect on the stereochemical outcome. For instance, switching from a trimethyl to a dimethylphenyl silane did not affect the stereoselectivity.[16]

We then decided to carry out the cyclisations on stereochemically pure acyclic precursors. Our initial hypothesis was that upon treatment with Lewis acids, both *syn* and *anti* isomers would give rise to a single oxonium intermediate. With regard to the general lack of stereoselectivity in the reaction, we decided to verify this hypothesis. Thus, *syn* **11** and *anti* **11** were separated, both silylated and rapidly purified to avoid epimerisation. When exposed to the same conditions ($SnCl_4$, $CH_2Cl_2$, -78°C, 15 min), the two substrates showed *completely opposite stereoselectivity*, the *anti* isomer leading to the *trans* product **1c** and the *syn* isomer leading to the *cis* product **13c**[17](Scheme 5).




**Scheme 5**

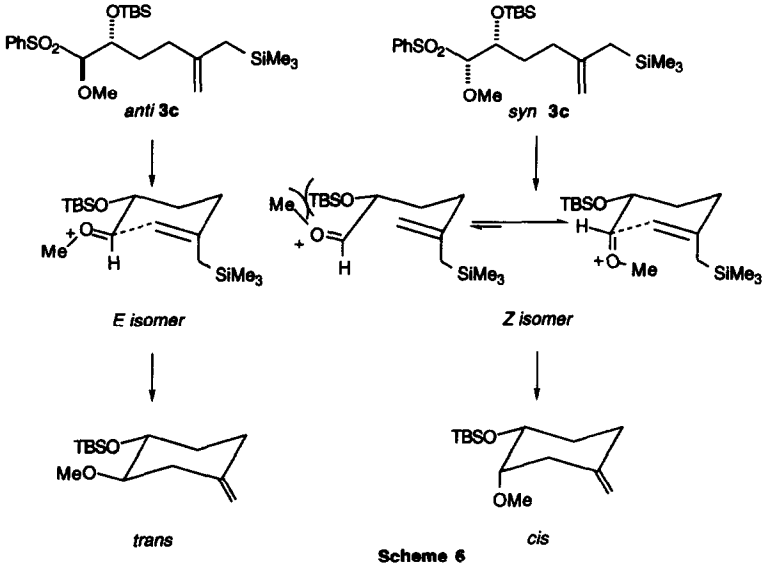
These results forced us to rethink our hypothesis and prompted us to undertake some more investigation. Although the possibility of competition between $SN_1$ and $SN_2$ reactions cannot completely be ruled out, we were more interested in the possibility of isomerism in the intermediate oxonium ions, the hypothesis now being that *syn* and *anti* **3c** give rise to two distinct *Z* and *E* oxonium ions (equation 3).




*Z/E* isomerism in oxonium ions is a known phenomenon, but the low energetic barrier usually allows easy equilibration.[18] However, because of the fast intramolecular trapping of intermediates with the allyl silane moiety, it is believed that the oxonium ions would not have time to equilibrate before reacting.

The hypothesis that each stereoisomer of **3c** gives rise to distinct isomers in the transition state has been supported by theoretical calculations. Molecular mechanics conformational searches (MM2) on both starting materials showed that the ground states had the methyl group of the methoxyl *anti* to the leaving group, a

conformation which is probably unable to react. Further conformational searches were performed, for which the methoxyl lone pairs were constrained to be *anti* to the leaving group. This should be a ground state analogous to the transition state for the reaction. Alignment of the "*pro-R*" lone pair should give the Z intermediate, while alignment of the "*pro-S*" lone pair should give the *E* intermediate. The lowest energy structures were reminimised using the PM3 semi-empirical molecular orbital Hamiltonian. These results show that *anti* **3c** has a preference of 12.5 kJ $mol^{-1}$ for the *E* oxonium ion, while *syn* **3c** has a preference of 17.2 kJ $mol^{-1}$ for the *Z* oxonium ion. These correspond to ratios of about 1:1000. Thus, PM3/MM2 calculations predict the *syn* and *anti* starting materials are likely to form opposite geometrical isomers of the oxonium ions. The difference in the stereochemical behaviour of *Z* and *E* intermediates can be explained in terms of steric repulsions (Scheme 6). It is likely that in the transition state, the oxonium ion adopts the favoured pseudo-equatorial position, thus giving the *trans* diequatorial disubstituted ring. In the *Z* oxonium intermediate, the steric repulsion between the TBS group and the methyl group of the methoxyl forces the oxonium ion to adopt a pseudo-axial position, giving rise to a *cis* disubstituted ring:




**Scheme 6**

All attempts to obtain predominantly the *trans* isomer from a mixture of starting materials failed, while controlled epimerisation of **11** or **3c** under both acidic and basic conditions disappointingly gave the unwanted *syn* isomer. Fortunately, *syn* and *anti* isomers of the β-hydroxysulfone **11** could be separated (see above) and the undesired *syn* isomer could be recycled by oxidation to the β-ketosulfone **10** (PCC, $CH_2Cl_2$, 50%, unoptimized) and reduction, thus improving the overall yield of the synthesis.

## Conclusion

A concise and high yielding synthesis of the *trans* disubstituted methylene cyclohexane **1c** has been achieved using original methodology. This exploits the ability of α-alkoxysulfones such as **2** to be used both as formyl

anion equivalents and as oxonium ion precursors. Unfortunately, both isomers of α,β-dialkoxysulfones cannot be used in the stereoselective synthesis of **1**. Nevertheless, the possibility of recycling unwanted stereoisomers and the low number of steps makes this methodology attractive for the synthesis of cyclohexane rings such as **1**. We are currently investigating the possibility of an asymmetric synthesis of **1c** as well as its application to the total synthesis of rapamycin.

**Acknowledgements**

Financial support for this work has been provided by SERC, Pfizer Central Research and the BP endowment (to SVL at Cambridge). We thank M.C. Sleep and C. Sporikou for assistance in the preparation of some starting materials, and Dr J.M. Goodman for performing the calculations.

## Experimental section

$^1H$ and $^{13}C$ NMR spectra were recorded on AC-200, AM-250 and AM-500 Bruker apparatus, using residual solvent as a reference ($CDCl_3$: $\delta_H$: 7.26 ppm; $\delta_C$: 77.14 ppm). IR spectra were recorded on a Perkin-Elmer FT-IR 1600 apparatus. Mass spectra were recorded in the University Chemical Laboratory service and at the SERC mass spectrometry service at Swansea. Microanalyses were performed in the University Chemical Laboratory microanalytical service. Flash chromatography was performed using Merck Kieselgel 60 (230-400 mesh) or BDH Florisil (finer than 200 mesh) using the indicated solvent system. Petroleum ether refers to 40-60°C petrol and was distilled before use. Diethyl ether, tetrahydrofuran and 1,2-dimethoxyethane were distilled from sodium benzophenone ketyl. Dichloromethane, dimethylformamide, pyridine and triethylamine were distilled from calcium hydride. The ester **6** and alcohol **7** were prepared according to literature procedures.[8] **6** was distilled before use (bp: 100°C/1 mmHg). All commercial reagents were used as received. Unless otherwise stated, all non-aqueous reactions were performed under an argon atmosphere using oven/flame-dried glassware.

### Methoxymethyl Phenyl Sulfone (2)

A solution of Oxone® (138 g, 0.225 mol, 1.5 eq.) in aqueous pH4 buffer solution (750 ml) was added dropwise to a stirred solution of commercial (Aldrich) methoxymethyl phenyl sulfide (22.5 ml, 0.15 mol) in methanol (750 ml). The white slurry was stirred overnight at room temperature, then diluted with water (500 ml) and extracted with dichloromethane (3 x 750 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a white solid. Recrystallisation from diethyl ether (550 ml) gave the title sulfone as white needles (18g, 70% yield); mp: 68-70°C (lit.[10]: 69-70°C); TLC: Rf: 0.35 (30% ethyl acetate/petroleum ether); IR (nujol): $\nu_{max}$ ($cm^{-1}$): 1443, 1328, 1238, 1199, 1142, 1118, 1078, 908, 748, 686; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm); 7.98-7.91 (2H, m, Ar-H), 7.72-7.65 (1H, m, Ar-H), 7.63-7.55 (2H, m, Ar-H), 4.52 (2H, s, $CH_2$), 3.68 (3H, s, $CH_3$).

### 4-Trimethylsilylmethyl-1-iodo-4-pentene (8)

A solution of 4-trimethylsilylmethyl-4-penten-1-ol **7** (2.58 g, 15 mmol) and triethylamine (3.13 ml, 22.5 mmol, 1.5 eq.) in dichloromethane (25 ml) was cooled to 0°C with stirring and methanesulfonyl chloride (1.45 ml,

18.17 mmol, 1.25 eq.) was added dropwise. The yellow-orange slurry was stirred at 0°C for 1.5 h. Water (25 ml) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (100 ml) and the combined organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude mesylate as a yellow oil (3.8 g, 101% material balance) which was used in the next reaction without purification.
The crude mesylate was dissolved in dry acetone (10 ml) and added *via* cannula to a solution of sodium iodide (10g, 66 mmol, 4.5 eq) in acetone (10ml) containing solid sodium hydrogen carbonate (200 mg). The mixture was stirred in the dark overnight at room temperature, then filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the residue taken up in diethyl ether (25 ml), affording a white precipitate. This was refiltered through celite, and the filtrate concentrated *in vacuo* to a yellow oil. Purification by silica gel chromatography (5% ethyl acetate/ petroleum ether) gave the iodide as a colourlesss oil (3.51 g, 83% yield); TLC: Rf: 0.75 (10% ethyl acetate/ petroleum ether); IR (film): $\nu_{max}$ ($cm^{-1}$): 2957, 1628, 1243, 1165, 858; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm): 4.73 (2H, 2s, $C_5$-H x 2), 3.19 (2H, t, J= 8Hz, $C_1$-H x 2), 2.12 (2H, t, J= 8Hz, $C_3$-H x 2), 1.98 (2H, m, $C_2$-H x 2), 1.71 (2H, s, $C_{1'}$ x 2), 0.00 (9H, s, $Me_3Si$); Mass (EI): m/z: 282 ($M^{+\cdot}$), 199, 185, 82, 74, 73, 67.

**1-Methoxy-5-trimethylsilylmethyl-5-hexen-1-yl-phenyl sulfone (9)**

A stirred solution of methoxymethyl phenyl sulfone **2** (338 mg, 1.82 mmol) in dry 1,2-dimethoxyethane (8 ml) was cooled to-78°C and a solution of *tert*-butyllithium (1.7 M in pentane, 1.18 ml, 2 mmol, 1.1 eq.) was added dropwise. The yellow solution was stirred for 10 min at -78°C and a solution of the iodide (566 mg, 2 mmol, 1.1 eq.) in 1,2-dimethoxyethane (3ml plus 1ml rinse) was added dropwise. The resulting reddish solution was stirred at -78°C for 1.5 h during which time the colour slowly faded. The reaction was quenched by careful addition of water (1 ml) and the cooling bath was removed. The mixture was diluted with diethyl ether (50 ml) and the solution was washed with water, brine (40 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by silica gel chromatography (20% ethyl acetate/ petroleum ether) gave the alkylated compound as a pale yellow oil (512 mg, 83% yield).TLC: Rf: 0.38 (20% ethyl acetate/ petroleum ether); IR (film): $\nu_{max}$ ($cm^{-1}$): 2954, 1346, 1151, 1050, 852; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm): 7.92-7.87 (2H, m, Ar-H), 7.70-7.51 (3H, m, Ar-H), 4.53 and 4.51 (2H, 2s, J=1Hz, $C_6$-H x 2), 4.17 (1H, dd, $J_1$=10 Hz $J_2$=3Hz, $C_1$-H), 3.64 (3H, s, OMe), 2.04-1.88 (3H, m, $C_2$-H x 2 and one of $C_4$-H), 1.65-1.27 (3H, m, $C_3$-H x 2 and one of $C_4$-H), 1.46 (2H, d, J=1Hz, $C_{1'}$-H x 2), 0.0 (9H, s, $Me_3Si$); Mass (EI): m/z: 340, 214, 200, 166, 141, 135, 95; elemental analysis, calculated for $C_{17}H_{28}O_3SSi$, MW: 340.15283; Calc.: C: 59.96%; H: 8.29%; Found: C: 59.75%; H: 8.53%.

**3-Methylene-1-cyclohexyl methyl ether (4)**

A solution of the sulfone **9** (340 mg, 1 mmol) in dichloromethane/diethyl ether (5/3, 8ml) was cooled to 0°C with stirring and magnesium bromide etherate (775 mg, 3 mmol, 3 eq) was added in one portion. The pale yellow solution was stirred at 0°C for 10 min then poured into 1N HCl solution (25 ml) and extracted with petroleum ether (25 ml). The organic layer was washed with water, saturated sodium bicarbonate solution, water, brine (25 ml each), dried ($MgSO_4$), filtered and carefully concentrated *in vacuo* to give pale yellow volatile liquid (150 mg; 105% mass balance). $^1H$ NMR analysis of the crude product showed the yield to be >90%.$^1H$

NMR (200 MHz, $CDCl_3$): δ (ppm): 4.82 (2H, broad s, C=C$H_2$), 3.67 (1H, m, $C_1$-H), 3.20 (3H, s, OMe), 2.52 (1H, m, one of $C_2$-H), 2.03 (1H, m, one of $C_2$-H), 1.85 (2H, m, $C_4$-H x 2), 1.48 (2H, m, $C_6$-H x 2), 0.99 (2H, m, $C_5$-H x 2). The olefinic signals corresponding to isomerised product[5] (ca 5.1 ppm) are almost undetectable.

**1-Methoxy-1-phenylsulfonyl-5-trimethylsilylmethyl-5-hexen-2-one (12)**

A stirred solution of the sulfone **2** (41 g, 0.22 mol) in dry 1,2-dimethoxyethane (600 ml) was cooled to -78°C and a solution of *tert*-butyllithium (1.7 M in pentane, 142 ml, 0.242 mol, 1.1 eq.) was added dropwise over 1 h. The yellow-orange solution was stirred for 10 min at -78°C, then a solution of the ester **6** (24.5 g, 0.115 mol, 0.5 eq.) in 1,2-dimethoxyethane (50 ml) was added dropwise. The reddish solution was stirred for 45 min at -78°C, warmed to room temperature over 2 h, then stirred for 30 min. The reaction was quenched by careful addition of saturated ammonium chloride solution (5 ml). The bulk of the solvent was removed *in vacuo*, and the residue was taken up with ether (1 L). The solution was washed with water, brine (500 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual solid (57 g) was purified by silica gel chromatography in two batches (15% ethyl acetate/ petroleum ether) to give, in order of elution, the β-keto sulfone **12** (35.4 g, 87% yield based on ester), followed by the recovered sulfone **2** (13.2 g, 68% recovery). The β-keto sulfone was collected as a pale yellow oil which solidified on standing: TLC: Rf: 0.29 (15% ethyl acetate/ petroleum ether); IR ($CHCl_3$): $\nu_{max}$ ($cm^{-1}$): 2952, 2900, 1633, 1477, 1447, 1323, 1309, 1247, 854; $^1H$ NMR (250 MHz, $CDCl_3$): δ (ppm): 7.85, 7.69 and 7.56 (5H, Ar-H), 4.70 (1H, s, $C_1$-H), 4.49 (2H, d, J= 1 Hz, $C_6$-H x 2), 3.71 (3H, s, OMe), 2.84 (1H, m, $C_3$-H), 2.51 (1H, m, $C_3$-H), 2.10 (2H, m, $C_4$-H x 2), 1.47 (2H, s, $C_{1'}$-H x 2), 0 (9H, s, $SiMe_3$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$); δ (ppm): 200.7 ($C_2$), 145.6 ($C_5$), 136.0, 134.5, 129.6, 129.2 (Ar), 107.4 ($C_6$), 100.3 ($C_1$), 61.7 (MeO), 38.7 ($C_3$), 31.0 ($C_4$), 27.0 ($C_{1'}$), -1.4 ($Me_3Si$); Mass (EI); m/z: 354, 339, 258, 215, 199, 181, 168, 147, 89, 69, 49; elemental analysis, calculated for $C_{17}H_{26}O_4SSi$, MW: 354.132098; Calc.: C: 57.59%; H: 7.39%; Found: C: 57.62%; H: 7.50%.

**1-Methoxy-1-phenylsulfonyl-5-trimethylsilyl-5-hexen-2-ol (11)**

Sodium borohydride (8.43 g, 0.22 mol, 2.2 eq.) was added portionwise to a stirred solution of the β-keto sulfone **12** (35.4 g, 0.1 mol) in absolute ethanol (500 ml). The cloudy solution was stirred for 1.5 h at room temperature then the excess hydride was consumed by careful addition of acetone (10 ml). After stirring for 10 min the solution was concentrated in vacuo. The residual solid was partitioned between diethyl ether (1.5 L) and water (0.5 L). The layers were separated, the organic layer was washed with water, brine (500 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **11** as a colourless oil, consisting as a 1:1 mixture of isomers (35.5 g, 100% yield). This oil was homogeneous by TLC and $^1H$ NMR and could be carried through to the next reaction without purification. Separation could be achieved by careful chromatography on florisil (> 200 mesh, 13% ethyl acetate/ petroleum ether) to give, in order of elution the *anti* isomer, followed by the *syn* isomer.

Data for *anti* isomer (clear oil): TLC: Rf: 0.44 (20% ethyl acetate/ petroleum ether); IR (film): $\nu_{max}$ ($cm^{-1}$): 3341, 2929, 1558, 1539, 1457, 1006. $^1H$ NMR (250 MHz, $CDCl_3$): δ (ppm): 7.93-7.91 (2H, m, Ar-H), 7.72-7.68 (1H, m, Ar-H), 7.61-7.57 (2H, m, Ar-H), 4.54 and 4.49 (2H, 2s, $C_6$-H x 2), 4.09 (1H, d, J= 8 Hz, $C_1$-H),

3.73 (1H, ddd, with $J_{H1H2}$= 8 Hz, $C_2$-H), 3.61 (3H, s, OMe), 3.31 (1H, s, exchangeable with $D_2O$, OH), 2.17-2.11 (1H, m, one of $C_3$-H), 2.04-1.96 (1H, m, one of $C_3$-H), 1.84-1.77 (1H, m, one of $C_4$-H), 1.59-1.52 (1H, m, one of $C_4$-H), 1.48 (2H, s, $C_{1'}$-H), 0.0 (9H, s, $Me_3Si$). $^{13}C$ NMR (50 MHz, $CDCl_3$): δ (ppm): 137.6 ($C_5$), 137.4, 134.1, 129.3, 129.2 (Ar), 110.2 ($C_6$), 98.5 ($C_1$), 69.4 ($C_2$), 62.5 (MeO), 32.7 ($C_3$), 31.1 ($C_4$), 26.6 ($C_{1'}$), -1.6 ($Me_3Si$). Mass (CI, $NH_3$): m/z: 374 ($MNH_4^+$), 357 ($MH^+$), 287, 232, 215, 199, 183, 160, 125. Elemental analysis, calculated for $C_{17}H_{28}O_4SSi$, MW: 356.14774; Calc.: C: 57.20%; H: 7.92%; Found: C: 57.35%; H: 7.83%.

Selected data for *syn* isomer (clear oil): TLC: Rf: 0.38 (20% ethyl acetate/ petroleum ether); $^1H$ NMR (250 MHz, $CDCl_3$): δ (ppm): 7.93-7.91 (2H, m, Ar-H), 7.70-7.65 (1H, m, Ar-H), 7.60-7.55 (2H, m, Ar-H), 4.58 and 4.53 (2H, 2s, $C_6$-H x 2), 4.11 (1H, ddd, with $J_{H1H2}$= 2 Hz, $C_2$-H), 4.10 (1H, d, J= 2 Hz, $C_1$-H), 3.61 (3H, s, OMe), 2.13 (1H, s, exchangeable with $D_2O$, OH), 2.16-2.12 (1H, m, $C_3$-H), 2.03-1.97 (1H, m, $C_3$-H), 1.73 (2H, m, $C_4$-H x 2), 1.51 (2H, s, $C_{1'}$-H x 2), 0.0 (9H, s, $Me_3Si$). $^{13}C$ NMR (50 MHz, $CDCl_3$): δ (ppm): 146.5 ($C_5$), 137.4, 134.1, 129.7, 129.0 (Ar), 107.7 ($C_6$), 99.4 ($C_1$), 69.2 ($C_2$), 62.5 (MeO), 34.0 ($C_3$), 32.4 ($C_4$), 26.8 ($C_{1'}$), -1.3 ($Me_3Si$).

**Direct synthesis of the hydroxy sulfone 11**

A solution of methoxymethyl phenyl sulfone **2** (997 mg, 5.36 mmol) in dry 1,2-dimethoxyethane (30 ml) was cooled to -78°C with stirring. A solution of *tert*-Butyllithium (1.7 M in pentane, 3.4 ml, 5.9 mmol, 1.1 eq.) was added dropwise and the yellow-orange solution was stirred for 15 min at -78°C. A solution of the aldehyde **10** (1 g, 5.9 mmol, 1.1 eq.) in 1,2-dimethoxyethane (10 ml) was added dropwise by cannula, resulting in a discharge of the colour. The solution was stirred for 30 min at -78°C, warmed to room temperature over 2 h, then stirred for 30 min. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (0.5 ml). The solution was taken up with ether (200 ml), washed with water, brine (100 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification and separation were carried out as before, giving the two β-hydroxysulfone diastereoisomers **11** as a 1:1 ratio (1.85 g, 97% combined yield).

**2-Acetoxy-1-methoxy-1-phenylsulfonyl-5-trimethylsilyl-5-hexene (3a)**

A solution of the β-hydroxy sulfone **11** (2.87 g, 8mmol), pyridine (0.84 ml, 10.4 mmol, 1.3 eq.) and 4-dimethylamino pyridine (147 mg, 1.2 mmol, 0.15 eq.) in dichloromethane (25 ml) was cooled to 0°C with stirring and acetic anhydride (0.84 ml, 8.8 mmol, 1.1 eq.) was added dropwise. The clear solution was allowed to warm to room temperature and stirred for 3h. The reaction mixture was diluted with diethyl ether (100 ml), washed with 1N HCl, water, saturated sodium bicarbonate solution, brine (50 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid purification by silical gel chromatography (15% ethyl acetate/petroleum ether) gave the acetate as a clear and colourless oil (2.95g, 92% yield).

*Note*: when this reaction was carried out on the mixture of isomers, the diastereoisomeric acetates could not be separated by chromatography.

data for *anti* isomer: TLC: Rf: 0.45 (20% ethyl acetate/petroleum ether); IR (film): $\nu_{max}$ ($cm^{-1}$): 2957, 2253, 1741,1548, 1249, 1143; $^1H$ NMR (250 MHz, $CDCl_3$): δ (ppm): 7.93-7.88 (2H, m, Ar-H), 7.70-7.52 (3H, m, Ar-H), 5.13 (1H, m, $C_2$-H), 4.49 (2H, 2s, $C_6$-H x 2), 4.29 (1H, d, J= 6Hz, $C_1$-H), 3.59 (3H, s, OMe), 2.0

(3H, s, AcO), 1.98-1.54 (4H, m, $C_3$-H x 2 and $C_4$-H x 2), 1.45 (2H, s, $C_{1'}$-H x 2), 0.0 (9H, s, $Me_3Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ (ppm): 170.0 (C=O), 146.1 ($C_5$), 138.6, 134.1, 129.7, 129.0 (Ar), 107.6 ($C_1$), 97.5 ($C_6$), 70.8 (MeO), 62.4 ($C_2$), 33.3 ($C_4$), 28.1 ($CH_3$-CO), 26.7 ($C_3$), 20.9 ($C_{1'}$), -1.4 ($Me_3Si$); Mass (EI): m/z: 399 ($MH^+$), 344, 257, 215, 197, 185, 160, 125, 90; High resolution mass, calculated for $C_{19}H_{31}O_5SSi$, ($MH^+$): 399.1661; Found: 399.1661.

Selected data for *syn* isomer: $^1H$ NMR (250 MHz, $CDCl_3$): δ (ppm): 7.93-7.87 (2H, m, Ar-H), 7.70-7.53 (3H, m, Ar-H), 5.33 (1H, m, $C_2$-H), 4.58 and 4.50 (2H, 2s, $C_6$-H x 2), 4.28 (1H, d, J= 3Hz, $C_1$-H), 3.76 (3H, s, OMe), 2.0-1.73 (4H, m, $C_3$-H x 2 and $C_4$-H x 2), 1.64 (3H, s, AcO), 1.46 (2H, s, $C_{1'}$-H x 2), 0.0 (9H, s, $Me_3Si$); $^{13}C$ NMR (62,5 MHz, $CDCl_3$): δ (ppm): 169.8 (C=O), 145.8 ($C_5$), 137.8, 134.1, 129.5, 129.2 (Ar), 108.2 ($C_1$), 97.9 ($C_6$), 70.6 (MeO), 63.2 ($C_2$), 33.8 ($C_4$), 29.6 ($CH_3$-CO), 26.7 ($C_3$), 20.7 ($C_{1'}$), -1.2 ($Me_3Si$).

**2-*tert*-Butyldimethylsilyloxy-1-methoxy-1-phenylsulfonyl-5-trimethylsilyl-5-hexene (3c)**

A solution of the β-hydroxy sulfone **11** (1.95 g, 5.5 mol), pyridine (0.666 ml, 8.25 mmol, 1.5 eq.) and 4-dimethylaminopyridine (100 mg, 0.825 mmol, 0.15 eq.) in dichloromethane (25 ml) was cooled to 0°C with stirring and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.5 ml, 6.5 mmol, 1.2 eq.) was added dropwise. The solution was stirred at 0°C for 1.5h then quenched by addition of methanol (1.5 ml). After stirring for 10 min at 0°C, the solution was diluted with diethyl ether (300 ml) and successively washed with 3N HCl, saturated sodium bicarbonate solution, water, brine (150 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude silyl ether as a pale yellow oil (2.56 g, 99% material balance) which could be used in the next reaction without purification. An analytical sample was prepared by rapid chromatography on silica gel (5% ethyl acetate/petroleum ether, 70% yield).

*Note*: when this reaction was carried out on the mixture of isomers, the diastereoisomeric silyl ethers could not be separated by chromatography.

data for the *anti* isomer: TLC: Rf: 0.8 (20% ethyl acetate/petroleum ether); IR (film moistened with $CHCl_3$): $\nu_{max}$ ($cm^{-1}$): 2954, 1190, 1150, 1077, 909; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm): 7.94-7.92 (2H, m, Ar-H), 7.68-7.65 (1H, m, Ar-H), 7.58-7.55 (2H, m, Ar-H), 4.47 (2H, 2s, $C_6$-H x 2), 4.26 (1H, m, $C_2$-H), 4.23 (1H, d, J= 2Hz, $C_1$-H) 3.44 (3H, s, OMe), 2.05 (1H, m, one of $C_4$-H), 1.85 (1H, m, one of $C_4$-H), 1.68 (1H, m, one of $C_3$-H), 1.53 (1H, m, one of $C_3$-H), 1.46 (2H, s, $C_{1'}$-H x 2), 0.88 (9H, s, *t*BuSi), 0.09 and 0.08 (6H, 2s, $Me_2Si$), 0.00 (9H, s, $Me_3Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ (ppm): 147.1 ($C_5$), 138.0, 133.9, 129.4, 129.1 (Ar), 107.1 ($C_1$), 101.3 ($C_6$), 70.9 (MeO), 62.5 ($C_2$), 34.3 ($C_4$), 30.3 ($C_3$), 27.0 ($C_{1'}$), 25.8 (($CH_3$)$_3$-*C*-Si), 17.9 (($CH_3$)$_3$-C-Si), -1.3 ($Me_3Si$), -4.5 and -4.7 ($Me_2Si$); Mass (EI); m/z: 471 ($MH^+$), 413, 391, 329, 297, 215, 90; High resolution mass, calculated for $C_{23}H_{43}O_4SSi_2$, ($MH^+$): 470.2420; Found: 471.2421.

selected data for the *syn* isomer: $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm): 7.94-7.92 (2H, m, Ar-H), 7.68-7.65 (1H, m, Ar-H), 7.58-7.55 (2H, m, Ar-H), 4.57 (2H, 2s, $C_6$-H), 4.02 (1H, d, J=8Hz, $C_1$-H), 3.90 (1H, m, $C_2$-H), 3.33 (3H, s, OMe), 2.16-2.10 (1H, m, one of $C_4$-H), 2.05-1.97 (1H, m, one of $C_4$-H), 1.95-1.89 (2H, m, $C_3$-H x 2), 1.55 (2H, s, $C_{1'}$-H x 2), 0.86 (9H, s, *t*BuSi), 0.34 (9H, s, $Me_3Si$), -0.31 and -0.58 (6H, 2s, $Me_2Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ (ppm): 146.5 ($C_5$), 138.4, 133.8, 129.5, 129.0 (Ar), 110.2 ($C_1$), 99.1 ($C_6$), 71.3 (MeO), 61.9 ($C_2$), 33.4 ($C_4$), 30.4 ($C_3$), 26.6 ($C_{1'}$), 26.0 (($CH_3$)$_3$-*C*-Si), 19.3 (($CH_3$)$_3$-C-Si), -0.9 ($Me_3Si$), -4.2 and -4.7 ($Me_2Si$).

**Cyclisation of the acetoxy protected hydroxy sulfone 3a: *cis* and *trans* 1-acetoxy-2-methoxy-4-methylene cyclohexane (1a) and (13a)**

Titanium tetraisopropoxide (2.98 ml, 10 mmol, 5 eq.) was added dropwise at room temperature to a stirred solution of titanium tetrachloride (1.38 ml, 12 mmol, 6 eq.) in dichloromethane (20 ml). The solution was stirred for 15 min then taken up in a 20 ml gas-tight syringe and added over 2h (syringe pump) to a stirred and cooled (-78°C) solution of the acetate (809 mg, 2 mmol, 1 eq.) in dichloromethane (60 ml). After completion of the addition, the solution was stirred for further 15 min, then poured into 1N HCl solution (250 ml) and extracted with petroleum ether (250 ml). The organic layer was washed with water, saturated sodium bicarbonate solution, water, brine (200 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil. $^1H$ NMR analysis of the crude product showed a 1:1 ratio of diastereoisomers. The crude product was purified by silica gel chromatography (5% ethyl acetate/petroleum ether), to give, in order of elution, the *trans* product **1a** (170 mg; 46% yield), followed by the *cis* product **13a** (170 mg; 46% yield).

*Trans* product **1a**: TLC: Rf: 0.44 (10% ethyl acetate/petroleum ether); IR (film moistened with $CHCl_3$): $\nu_{max}$ ($cm^{-1}$): 2954, 1735, 1248, 912, 735; $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm): 4.91 (1H, m, 2 ax-ax and 1 ax-eq couplings, $C_1$-H), 4.74 (2H, d, J= 6Hz, $CH_2$), 3.65 (1H, m, 2 ax-ax and 1 ax-eq couplings, $C_2$-H), 3.40 (3H, s, OMe), 2.51 (1H, m, one of $C_3$-H), 2.30-2.15 (3H, m, one of $C_3$-H and $C_5$-H x 2), 2.09 (3H, s, Ac), 1.67 (2H, m, $C_6$-H x 2); $^{13}C$ NMR (50 MHz, $CDCl_3$): δ (ppm): 170.8 (C=O), 144.3 ($C_4$), 110.5 (=$CH_2$), 79.1 ($C_1$), 73.4 (OMe), 56.8 ($C_2$), 37.2 ($C_3$), 31.0 ($C_5$), 29.0 ($C_6$), 21.4 (AcO); Mass (EI); m/z: 168 (M-$CH_4$), 149, 125 (M-OAc), 109, 91; High resolution mass, calculated for $C_8H_{13}O$ (M-OAc): 125.096; Found: 125.096.

*cis* product **13a**: TLC: Rf: 0.40 (10% ethyl acetate/petroleum ether); $^1H$ NMR (200 MHz, $CDCl_3$): δ (ppm): 5.20 (1H, m, 2 ax-ax and 1 ax-eq couplings, $C_1$-H), 4.74 (2H, d, J= 6Hz, $CH_2$), 3.39 (1H, m, 2 ax-ax and 1 ax-eq couplings, $C_2$-H), 3.37 (3H, s, OMe), 2.45 (1H, m, one of $C_3$-H), 2.20-2.0 (3H, m, one of $C_3$-H and $C_5$-H x 2), 2.10 (3H, s, Ac), 1.65 (2H, m, $C_6$-H x 2); $^{13}C$ NMR (50 MHz, $CDCl_3$): δ (ppm): 170.8 (C=O), 144.3 ($C_4$), 110.6 (=$CH_2$), 79.1 ($C_1$), 70.3 (OMe), 56.8 ($C_2$), 36.4 ($C_3$), 30.0 ($C_5$), 28.1 ($C_6$), 21.4 (AcO).

***trans*-1-*tert*-butyldimethylsilyloxy-2-methoxy-4-methylene cyclohexane (1c)**

A solution of crude *anti* **3c** (2.54. g, prepared by silylation of pure *anti* **11**) in dichloromethane (60 ml) was cooled to -78°C with stirring and tin tetrachloride (1M solution in dichloromethane, 8.1 ml) was added over 15 min. The yellow solution was stirred for 10 min at -78°C then poured into 1N HCl solution (250 ml) and extracted with petroleum ether (300 ml). The organic layer was washed with water, saturated sodium bicarbonate solution, water, brine (200 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo*. $^1H$ NMR analysis of the crude product showed a 5:1 ratio of diastereoisomers in favour of the *trans* product **1c.** The crude product was purified by silica gel chromatography (2% ethyl acetate/petroleum ether) to give the cyclised product as a colourless oil (mixture of diastereoisomers, 795 mg, 60% yield based on **11**). A 90% yield could be achieved using this protocol starting from purified *anti* **3c**.

data for *trans* isomer: TLC Rf: 0.45 (5% ethyl acetate/petroleum ether); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm): 4.68 (2H, d, C=C*H*$_2$ x 2), 3.73 (1H, m, 2 ax-ax and 1 ax-eq couplings, $C_2$-H), 3.38 ppm (3H,s, MeO), 3.11 (1H, m, 2 ax-ax and 1 ax-eq couplings, $C_1$-H), 2.58-2.30 (2H, m, $C_3$-H x 2), 2.18-1.90 (2H, m, $C_6$-H x 2), 1.72 (1H, m, one of $C_5$-H), 1.45 (1H, m, one of $C_5$-H), 0.88 (6H, s, *t*BuSi), 0.09 (9H,s, $Me_3Si$); $^{13}$C NMR (62,5 MHz, $CDCl_3$): δ (ppm): 145.6 ($C_4$), 109.1 (=*C*$H_2$), 82.8 ($C_2$), 71.0 (MeO), 57.2 ($C_1$), 36.0 ($C_3$), 32.0 ($C_6$), 30.5 ($C_5$), 25.9 ((*C*$H_3$)$_3$-C-Si), 18.2 ((CH$_3$)$_3$-*C*-Si), -4.5 and -4.7 ($Me_2Si$); Mass (EI): m/z: 257 ($MH^+$), 241, 225, 199, 93; High resolution mass, calculated for $C_{14}H_{29}O_2Si$, ($MH^+$): 257.1936; Found: 257.1954.

The *cis* product **13c** can be prepared as the major product by cyclisation (same protocol) of *syn* **3c**
data for *cis* isomer: $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm): 4.05 (1H, m, 2 ax-eq and 1 eq-eq couplings, $C_2$-H), 3.36 (3H, s, MeO), 3.35 (1H, m, obscured by peak at 3.36 ppm, $C_1$-H). Others signals are identical to those in the *trans* isomer; $^{13}$C NMR (62,5 MHz, $CDCl_3$): δ (ppm): 146.4 ($C_4$), 109.0 (=*C*$H_2$), 82.0 ($C_2$), 68.4 (MeO), 56.6 ($C_1$), 35.8 ($C_3$), 32.0 ($C_6$), 29.3 ($C_5$), 25.8 ((*C*$H_3$)$_3$-C-Si), 18.1 ((CH$_3$)$_3$-*C*-Si), -4.7 and -4.8 ($Me_2Si$).

**Conversion of (1a) to (1c)**

Potassium carbonate (1.27 g, 9 mmol, 2 eq.) was added in one portion to a stirred and cooled (0°C) solution of the *trans* acetate **1a** (846 mg, 4.5 mmol) in methanol (15 ml). After 3h, the slurry was diluted with water (10 ml) and extracted with ethyl acetate (50 ml). The organic layer was washed with brine (25 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to the crude alcohol which was used in the next reaction without purification.
A solution of the crude alcohol and 2,6-lutidine (0.785 ml, 6.75 mmol, 1.5 eq) in dichloromethane (20 ml) was cooled to 0°C and treated dropwise with *tert*-butyldimethylsilyl trifluoromethanesulfonate. The solution was stirred at 0°C for 45 min then partitionned between diethyl ether and saturated sodium carbonate solution (50 ml each). The organic layer was washed with water, brine (40 ml each), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (5% ethyl acetate/petroleum ether) to give the silyl ether **1c** as a colourless oil (1.03 g, 90% overall yield), identical to the major product obtained by cyclisation of *anti* **13c**.

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