# Studies on the Origin of 1,5-*anti* Induction in Boron-Mediated Aldol Reactions

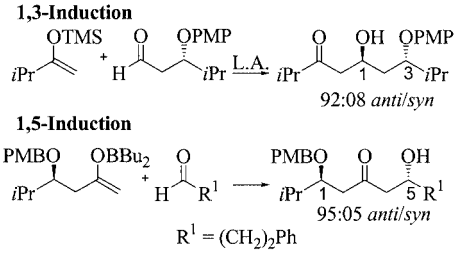
**Bridget L. Stocker,[a] Paul Teesdale-Spittle,[b] and John O. Hoberg*[a][‡]**

**Keywords:** Boron / Aldol reactions / 1,5-*anti* induction / Peloruside A

A model for the origin of selectivity in boron-mediated 1,5-*anti*-aldols is presented. This model involves π-stacking between the boron enolate and a remote aromatic ring. A short, facile method for the synthesis of the C-12 to C-22 segment of peloruside A and its 1,5-*anti*-aldol coupling using the proposed model is also presented.


## Introduction

The aldol reaction is one of the fundamental methods for carbon−carbon bond formation and is an extremely powerful method for the assembly of 1,3-polyols.[1] A controlling element that influences the stereochemical outcome of this process is the β-heteroatom substituent (Scheme 1). For example, in the addition of enol silanes to β-alkoxy aldehydes excellent levels of 1,3-*anti* induction are observed.[2] Alternatively, Evans[3] and Paterson[4] pioneered the area of remote 1,5-induction, in which a β-alkoxy substituent on the enolate nucleophile provides for the aldehyde π-facial selectivity. In this latter system, high selectivities are almost always obtained when the β-hydroxy protecting group is benzylic or a benzylidene acetal,[3a,4] and as a result these protecting groups are used almost exclusively. The selectivities with *tert*-butylsilyl protecting groups depends on the conditions used. For example, Evans has reported high 1,5-*syn* selectivities when using the *syn*-selective chloro(phenyl)-boryl enolates,[5] and Paterson has reported two examples of *anti* induction when using (−)-$Ipc_2BCl$ derived enolates.[4a] In this latter situation however, stereochemical control was only achieved by using the chiral Ipc ligand as the stereocontrolling moiety, as use of the achiral dibutyl ligands gave almost no selectivity.




Scheme 1. Stereochemical outcomes for 1,3- and 1,5-aldols

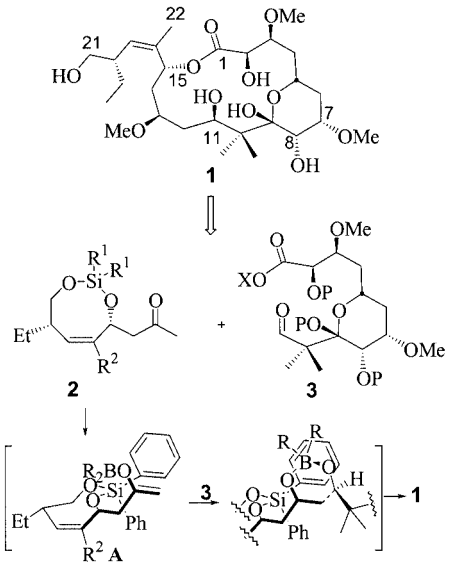
The selectivity in these reactions has long been speculated to be an electrostatic effect exerted by the β-alkoxy substituent,[3a,6] and that the nature of the β-oxygen protecting group is critical in determining the level of induction.[4] However to date, no studies or models have been reported for this surprising process. In view of this, we have designed and conducted experiments that provide insight into the nature of this reaction.

## Results and Discussion

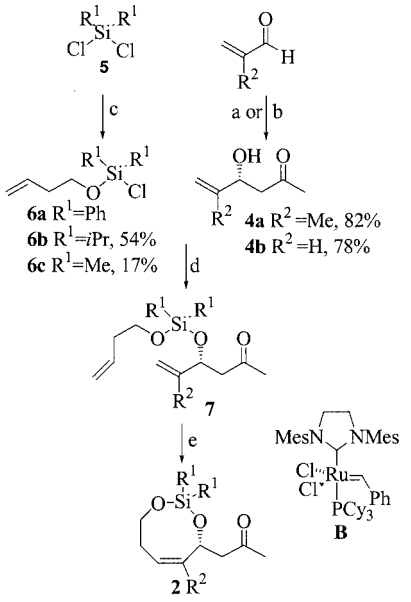
This investigation started as a result of our efforts towards a synthesis of peloruside A (**1**),[7] in which we sought to take advantage of a boron-mediated 1,5-*anti*-aldol reaction for the coupling of fragments **2** and **3**, Scheme 2. Coupling of these two would require efficient *anti* induction between C-11 and C-15 in which the stereochemical controlling element is the silyl-protected β-alkoxy substituent in **2**. Our working model for this coupling was based on enolate **A**, in which orbital interaction between the enolate and a phenyl group on the silyl produces aldehyde π-facial discrimination through a twist-boat transition state.[8] In this transition state, the large alkyl group on the aldehyde adopts a geometry away from the phenyl ring and the aldehyde proton is orientated towards the phenyl ring, thus producing minimum steric interactions and leading to the desired 1,5-*anti* product. Potentially, this model also explains the previously reported results in which β-methoxybenzyl ethers interact with the boron enolate. We have

[a] School of Chemical and Physical Sciences, Victoria University of Wellington,
Wellington, New Zealand
[b] School of Biological Sciences, Victoria University of Wellington,
Wellington, New Zealand
E-mail: john.hoberg@vuw.ac.nz
[‡] Current address: Department of Chemistry, University of Wyoming,
Laramie, WY 82071, USA
E-mail: Hoberg@uwyo.edu
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

  DOI: 10.1002/ejoc.200300592 



Scheme 2. Aldol coupling reaction towards the synthesis of peloruside A, see Table 1 for $R^1$ and $R^2$

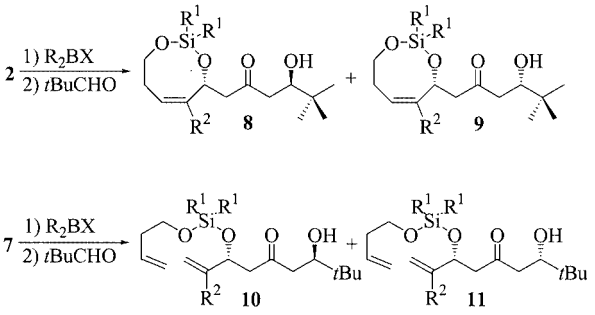


Scheme 3. Synthesis of fragment **2**; reagents: (a) acetone/LDA, THF; (b) acetone, DMSO, 20 % L-proline, 38 % for **4a**; (c) 3-butenol, $Et_3N$, $CH_2Cl_2$, (d) $Et_3N$, $CH_2Cl_2$; (e) 9−12 mol % **B**, $CH_2Cl_2$

therefore constructed a series of derivatives to test this model's validity.

Synthesis of fragment **2** began with an initial formation of racemic **4a** and **4b**[9] using the enolate of acetone, but we subsequently adopted List's direct aldol procedure[10] for the enantioselective formation of **4a**, obtaining **4a** in 74 % *ee*, Scheme 3.[11] Although low yielding, this is an extremely facile and inexpensive step, which is easily performed on a gram scale. For simplicity, we coupled 3-butenol to silanes **5** using standard procedures[12] to give **6** in modest to good yields. It should be noted that both (*R*)- and (*S*)-2-ethyl-3-butenol are available in one step using a Zr-catalyzed ethylmagnesation of 2,5-dihydrofuran, thus making this strategy adaptable to peloruside A.[13] Subsequent coupling of **4** and **6** occurs without difficulty providing derivatives of **7** in high yields, Table 1, Entries 1−5. For Entries 1 and 2, crude **6a** is used without purification, thus the overall yield in Table 1 is from **5**. In attempts to improve the yields, we reversed this sequence by silylation of the larger **4** with **5**, however decomposition of **4** resulted. Cyclization of **7** was carried out using Grubbs catalyst **B**,[14] which gave derivatives of **2** in good yields, Entries 6−10.[15,16] The cyclizations did require the use of 9−12 mol % of the catalyst at room temperature, as heating the reaction mixture resulted in decomposition of the diene.[17] We also investigated the use of a Schock/Hovedya molybdenum catalyst,[18] but this gave only unmodified starting material.[19]

With the required substrates in hand, we turned our attention towards the aldol reaction of **2** and the comparison of an aromatic vs. nonaromatic participating group. Given that the dimethylsilane derivatives gave consistently low yields, we abandoned the use of these and focused on the higher yielding diphenyl and diisopropyl derivatives. We initially tested both **2c** and **7c** using a variety of boron-mediated aldol reactions to ascertain the inherent selectivity of the diisopropyl silyl group (Scheme 4). Although excellent



Scheme 4. Aldol reaction of silyl-protected enolates

Table 1. Synthesis of ketone **2**

| Entry | **7** (isolated yield) | Entry | **2** (isolated yield) |
|---|---|---|---|
| 1 | **7a** $R^1$ = Ph, $R^2$ = Me (61 %)[a][b] | 6 | **2a** $R^1$ = Ph, $R^2$ = Me (54 %)[a] |
| 2 | **7b** $R^1$ = Ph, $R^2$ = H (65 %)[b][c] | 7 | **2b** $R^1$ = Ph, $R^2$ = H (81 %)[c] |
| 3 | **7c** $R^1$ = *i*Pr, $R^2$ = Me (86 %)[a][d] | 8 | **2c** $R^1$ = *i*Pr, $R^2$ = Me (60 %)[a] |
| 4 | **7d** $R^1$ = *i*Pr, $R^2$ = H (82 %)[b] [d] | 9 | **2d** $R^1$ = *i*Pr, $R^2$ = H (74 %)[b] |
| 5 | **7e** $R^1$ = Me, $R^2$ = H (77 %)[b] | 10 | **2e** $R^1$ = Me, $R^2$ = H (42 %)[b] |

[a] Formed using nonracemic **4a**. [b] Overall yield from $Ph_2SiCl_2$. [c] Formed using racemic **4b**. [d] Catalytic DMAP used.

Table 2. Comparison of aldol reactions

| Entry | Substrate/$R_2BX$[a] | Yield | Ratio |
|---|---|---|---|
| 1 | **2c** $R^1$ = *i*Pr/(−)-$Ipc_2BCl$ | 88 % | **8/9** (1.5:1) |
| 2 | **2c** $R^1$ = *i*Pr/$Cy_2BOTf$ | 95 % | **8/9** (1.2:1) |
| 3 | **7c** $R^1$ = *i*Pr/(−)-$Ipc_2BCl$ | 93 % | **10/11** (2.2:1) |
| 4 | **7c** $R^1$ = *i*Pr/$Cy_2BOTf$ | 97 % | **10/11** (1.2:1) |
| 5 | **2a** $R^1$ = Ph/(−)-$Ipc_2BCl$ | 94 % | **8/9** (> 99:1) |
| 6 | **2a** $R^1$ = Ph/$Cy_2BOTf$ | 68 %[b] | **8/9** (> 99:1) |
| 7 | **2b** $R^1$ = Ph/(−)-$Ipc_2BCl$ | 60 %[b] | **8/9** (> 99:1) |

[a] Performed in $Et_2O$ with $Et_3N$ at −78 °C. [b] Unoptimised.

yields were obtained for the aldol reaction, as expected poor selectivities were obtained (Table 2 Entries 1−4). To our delight, however, the aldol with the diphenylsilyl group reacted with excellent diastereoselectivity (Entries 5−7), illustrating that a phenylsilyl protecting group does provide excellent *anti* induction. It is also apparent that the use of the chiral Ipc ligand is not responsible for the high selectivity by comparison of Entries 5 and 6. Given that the size of the silyl substituents are comparable, we maintain that an orbital interaction between the phenyl group and the enolate is responsible for the observed induction. Modelling studies on fragment **2** of peloruside A using a methyl enol ether in replace of the boron enolate further support this proposal (Figure 1). As seen, excellent overlap between the enol ether and a phenyl ring is occurring (**II**), while with the isopropylsilane **I** no interaction is available and the enol ether adopts an open geometry.

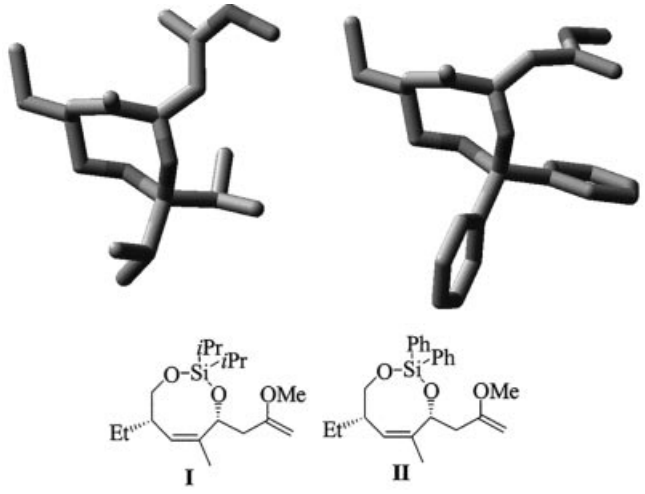
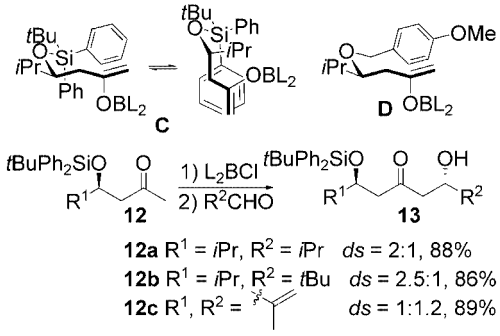



Figure 1. Molecular modelling of $iPr_2Si$ and $Ph_2Si$ enol ethers

We next investigated acyclic, *tert*-butyldiphenylsilyl ethers. Theoretically, these also could involve aromatic−enolate interactions; however, as there are two phenyl moieties incorporated in a flexible system, two different conformations could arise as depicted in **C** (Scheme 5). To test this, aldol reactions of the model ketones **12a−c** were performed and as expected resulted in a relatively nonselective process. Analogously, the attempted aldol reaction using **7b** with $Cy_2BOTf$ and *t*BuCHO gave a 2:1 ratio. Molecular mechanics calculations of **12a−c** confirm the ease of rotation in conformation **C**. Importantly though, this does indicate that the selectivities observed with **2a−b** are not due to an electrostatic effect exerted by the β-alkoxy moiety but are likely a result of the enolate fixed into a conformation conducive to interaction with a single phenyl ring. However, in the previously reported *p*-methoxybenzyl-protected β-hydroxy ketones (Scheme 1), these enolates are able to adopt a geometry as depicted in **D**.




Scheme 5. Aldol reactions of acyclic *tert*-butydiphenylsilyl-protected enolates

## Conclusion

In conclusion, experimental evidence points to a model in which orbital interaction between the enolate and a remote phenyl substituent is a plausible component in controlling the stereochemistry in 1,5-*anti*-aldols. Furthermore, we have developed a short, facile method for the synthesis of the C-12 to C-22 segment of peloruside, and have established a protocol for its desired coupling.

## Experimental Section

**General:** All reagents were of commercial quality and solvents were dried using standard procedures. Standard syringe techniques were used and all reactions were carried out under argon unless otherwise noted. Reaction progress was monitored using aluminium-backed TLC plates pre-coated with silica UV254 and visualised by either UV radiation (254 nm) or ceric ammonium molybdate dip. Flash chromatography was performed using silica gel 60 (220−240 mesh) with the solvent systems as indicated. $^1H$ and $^{13}C$ NMR spectra were recorded with a Varian Inova at 300 and 75 MHz, respectively; and referenced to solvent peaks ($^1H$: residual $CHCl_3$; $^{13}C$: $CDCl_3$). Accurate masses were recorded with a Mariner time of flight spectrometer. For the modelling studies, energy-minimized low-energy conformations were obtained using the MM3 forcefield and a Monte Carlo Molecular Mechanics conformational search routine as implemented in Macromodel v7.2 using the Maestro v4.1 interface, and the lowest energy structures retained. The global minimum energy structure obtained was additionally validated by minimization in Mopac with the AM1 Hamiltonian. AM1- and MM3-minimized structures showed no significant differences.

**4-Hydroxy-5-methyl-5-hexen-2-one (4a):** To a solution of diisopropylamine (1.37 mL, 9.81 mmol) in dry THF (40 mL), cooled to

−78 °C, was added a solution of 2 M butyllithium in hexanes (4.90 mL, 9.81 mmol). After stirring at −78 °C for 10 min, a solution of acetone (600 μL, 8.17 mmol) in THF (4 mL) was slowly added over 5 min. Stirring was continued at −78 °C for 50 min and then a solution of methacrolein (811 μL, 9.81 mmol) in THF (4 mL) was added. The mixture was stirred at −78 °C for a further 10 min, followed by addition of saturated ammonium chloride solution. The mixture was then extracted twice with diethyl ether and the organic extracts washed with brine, dried with $MgSO_4$ and the solvent removed under reduced pressure. The residual product was purified by bulb-to-bulb distillation (58−60 °C, 0.4 Torr) to give **4a** as a colourless oil (882 mg, 84 %). Spectral data match that previously reported.[11]

**(*R*)-4-Hydroxy-5-methyl-5-hexen-2-one (4a):** L-proline (438 mg, 3.76 mmol) was added to 125 mL of DMSO/acetone (4:1) and the resulting suspension stirred at room temperature for 15 min. Freshly distilled methacrolein (1.04 mL, 12.5 mmol) was then added. After being stirred at room temperature overnight, the resulting yellow solution was quenched with saturated ammonium chloride, extracted twice with diethyl ether and the organic extracts washed with brine, dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residual oil purified by flash chromatography on a neutralised silica gel column (hexanes/EtOAc, 3:1). The resulting oil (611 mg, 38 %) was then used immediately. The *ee* was determined by silylation followed by chiral GC analysis as follows: To a solution of the β-hydroxy ketone (200 mg, 1.56 mmol) in DMF (3 mL) was added *tert*-butyldimethylsilyl chloride (259 mg, 1.72 mmol) and imidazole (212 mg, 3.12 mmol). After stirring at room temparture for 24 h, the solution was quenched with saturated ammonium chloride, extracted twice with diethyl ether, and the organic extracts were washed with brine, dried with $MgSO_4$, filtered and the solvents removed under reduced pressure. The residual oil was then purified by flash chromatography (hexanes/EtOAc, 50:1) to give 202 mg of pure hydroxy ether; 74 % *ee*; determined using a 60 m × 0.25 mm Cyclodex-B column. $^1$H NMR (300 MHz, $CDCl_3$): δ = 4.95 (s, 1 H), 4.78 (s, 1 H), 4.54 (dd, *J* = 3.9, 8.4 Hz, 1 H), 2.74 (dd, *J* = 8.7, 14.7 Hz, 1 H), 2.39 (dd, *J* = 3.9, 18.3 Hz, 1 H), 2.16 (s, 3 H), 1.69 (s, 3 H), 0.85 (s, 9 H), 0.02 (s, 3 H), 0.00, (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 207.8, 147.0, 111.5, 73.7, 50.6, 32.0, 26.0, 18.3, 17.46, −4.6, −5.1 ppm. IR (neat): $\tilde{\nu}$ = 2930 $cm^{-1}$, 2857, 1360, 1718, 1251, 1074, 835, 776. HRMS (ESI) calcd. for $C_{13}H_{26}O_2Si$ [M + $H^+$] 243.1774, found 243.1780.

**(3-Butenoxy)diisopropylsilyl Chloride (6b):** To a stirred mixture of diisopropylsilyl dichloride (4 mL, 22.2 mmol) and triethylamine (3.4 mL, 24.4 mmol) in $CH_2Cl_2$ (85 mL) at 0 °C was added a solution of 3-buten-1-ol (1.91 mL, 22.2 mmol) in $CH_2Cl_2$ (20 mL) over 30 min. The reaction mixture was then stirred at room temperature before being heated at reflux for 48 h. After cooling to room temperature and concentrating under reduced pressure, the resultant oil was dissolved in diethyl ether/pentane (1:1, 100 mL), suction-filtered and reconcentrated to afford an oil. Fractional distillation of the crude material gave **6b** as a colourless oil (58−60 °C, 1 Torr, 2.64 g, 54 %). $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 5.06 (m, 2 H), 3.83 (t, *J* = 6.6 Hz, 2 H), 2.32 (dt, *J* = 6.9, 13.5 Hz, 2 H) 1.07 (m, 14 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 135.1, 117.0, 63.6, 37.0, 17.0, 16.9, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 2954 $cm^{-1}$, 2876, 1109, 994, 922, 886.

**(3-Butenoxy)diphenylsilyl Chloride (6a):** To a stirred mixture of diphenylylsilyl dichloride (330 μL, 1.57 mmol) and triethylamine (241 μL, 1.73 mmol) in $CH_2Cl_2$ (6 mL) at 0 °C was added a solution of 3-buten-1-ol (135 μL, 1.57 mmol) in $CH_2Cl_2$ (1 mL) dropwise. The reaction mixture was stirred at room temperature before being heated at reflux for 36 h. The solution was then cooled to room temperature and concentrated under reduced pressure. The resultant oil was dissolved in diethyl ether/pentane (1:1, 10 mL), suction-filtered, and reconcentrated to afford an oil, which was used without further purification.

**General Procedure for the Formation of Diphenylsilyl Ethers 7a and 7b:** To a cold (0 °C), stirred solution of the crude of (3-butenoxy)diphenylsilyl chloride (2.0 mmol) and β-hydroxy ketone (1.73 mmol) in $CH_2Cl_2$ (5 mL) was added triethylamine (241 μL, 1.73 mmol) dropwise. The ice bath was then removed and the solution stirred at room temparature for 2.5 h before being quenched with saturated sodium hydrogencarbonate, extracted twice with diethyl ether, and the organic extracts washed with water, brine, and dried with $MgSO_4$. Filtration and concentration gave a residue oil, which was purified by flash chromatography on silica gel (hexanes/EtOAc, 20:1) to give the diphenylsilyl ether as a clear oil. Yields are reported for the total conversion from dichlorodiphenylsilyl chloride (**5**).

**4-[(3-Butenoxy)diphenylsilyloxy]-5-methyl-5-hexen-2-one (7a):** Dichlorodiphenylsilane (330 μL, 1.57 mmol) produced **7a** (335 mg, 0.95 mmol) in an overall yield of 61 %. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.41 (m, 6 H), 5.84 (m, 1 H), 5.07 (m, 2 H), 4.93 (s, 1 H), 4.80 (m, 2 H), 3.80 (t, *J* = 6.9 Hz, 2 H), 2.82 (dd, *J* = 7.5, 15 Hz, 1 H), 2.58 (dd, *J* = 5.4, 15 Hz, 1 H), 2.35 (dt, *J* = 6.6, 13.2 Hz, 2 H), 2.10 (s, 3 H), 1.73 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 206.9, 145.7, 135.4, 135.3, 132.9, 130.6, 130.5, 128.0, 116.8, 112.5, 73.5, 62.9, 50.5, 37.1, 31.2, 17.6, ppm. IR (neat): $\tilde{\nu}$ = 3079 $cm^{-1}$, 2924, 2878, 1714, 1087, 719. HRMS (ESI) calcd. for $C_{23}H_{28}O_3Si$ [M + $Na^+$] 403.1680, found 403.1699.

**4-[(3-Butenoxy)diphenylsilyloxy]-5-hexen-2-one (7b):** Dichlorodiphenylsilane (330 μL, 1.57 mmol) produced **7b** (374 mg, 1.02 mmol) in an overall yield of 65 %. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.41 (m, 6 H), 5.50 (m, 2 H), 5.09 (m, 4 H), 4.84 (dt, *J* = 6.0, 12.9 Hz, 1 H), 3.81 (t, *J* = 6.9 Hz, 2 H), 2.79 (dd, *J* = 6.6, 15 Hz, 1 H), 2.61 (dd, *J* = 5.7, 15.4 Hz, 1 H), 2.35, (dt, *J* = 6.9, 13.8 Hz, 2 H), 2.11 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 206.7, 139.5, 135.4, 135.3, 130.6, 128.1, 128.0, 116.8, 115.5, 70.8, 63.0, 51.8, 37.1, 31.3 ppm. IR (neat): $\tilde{\nu}$ = 3071 $cm^{-1}$, 3003, 2874, 1715, 1115, 1079, 914, 717. HRMS (ESI) calcd. for $C_{22}H_{26}O_3Si$ [M + $Na^+$] 389.1542, found 389.1543.

**General Procedure for the Formation of Diisopropylsilyl Ethers 7c and 7d:** To a stirred solution of (3-butenoxy)diisopropylsilyl chloride (1.2 mmol), β-hydroxy ketone (1 mmol), and DMAP (0.05 mmol) in $CH_2Cl_2$ (5 mL) was added triethylamine (1.2 mmol) dropwise The resulting solution was stirred at reflux for 18 h, cooled to room temperature, quenched with saturated sodium hydrogencarbonate, and extracted twice with diethyl ether. The organic extracts were washed with water, brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography (hexanes/EtOAc, 20:1).

**4-[(3-Butenoxy)diisopropylsilyloxy]-5-methyl-5-hexen-2-one (7c):** β-Hydroxy ketone (**4a**) (329 mg, 2.57 mmol) gave **7c** as a colourless oil in 86 % (687 mg). $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.84 (m, 1 H), 5.04 (m, 2 H), 4.81 (s, 1 H), 4.76 (t, *J* = 6.3 Hz, 1 H), 3.74 (t, *J* = 6.9 Hz, 2 H), 2.74 (dd, *J* = 7.2, 15 Hz, 1 H), 2.57 (dd, *J* = 5.4, 14 Hz, 1 H), 2.30, (dt, *J* = 6.6, 13.8 Hz, 2 H), 2.17 (s, 3 H), 1.73 (s, 3 H), 1.02 (m, 14 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 207.4, 146.5, 135.6, 116.6, 111.8, 73.0, 62.8, 50.9, 37.5, 31.7, 17.6, 17.5, 12.5, 12.4 ppm. IR (neat): $\tilde{\nu}$ = 2945 $cm^{-1}$, 2867, 1716,

1085, 1060, 999, 883, 688. HRMS (ESI) calcd. for $C_{17}H_{32}O_3Si$ [M + $Na^+$] 335.2012, found 335.2013.

**4-[(3-Butenoxy)diisopropylsilyloxy]-5-hexen-2-one (7d):** β-Hydroxy ketone (**4b**) (243 mg, 2.13 mmol) gave **7d** as a colourless oil in 82 % (521 mg). $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.84 (m, 2 H), 5.20 (m, 4 H), 4.78 (dt, *J* = 6.3, 12.3 Hz, 1 H), 3.75 (t, *J* = 6.9 Hz, 2 H), 2.74 (dd, *J* = 6.6, 15.3 Hz, 1 H), 2.57 (dd, *J* = 6.3, 15.3 Hz, 1 H), 2.29 (dt, *J* = 6.6, 13.5 Hz, 2 H), 2.16 (s, 3 H), 1.01 (m, 14 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 207.2, 140.3, 135.6, 116.6, 114.8, 70.2, 62.8, 52.2, 37.5, 31.7, 17.6, 17.5, 12.5, 12.4 ppm. IR (neat): ṽ = 2944 $cm^{-1}$, 2867, 1717, 1087, 990, 883, 689. HRMS (ESI) calcd. for $C_{16}H_{30}O_3Si$ [M + $Na^+$] 321.1847, found 321.1856.

**General Procedure for RCM:** To a solution of the diene (1 mmol) in $CH_2Cl_2$ (100 mL) was added (benzylidene)[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene](tricyclohexylphosphane)-ruthenium(IV) dichloride (0.09 mmol for $R^2$ = H, 0.12 mmol for $R^2$ = Me). The reaction mixture was stirred at room temperature for 8−12 h, the solvent was removed under reduced pressure and the dark residue filtered through a short pad of silica gel (hexanes/EtOAc, 10:1). The filtered solution was then stirred with activated charcoal (8.5 g) for 24 h. The mixture was filtered, concentrated in vacuo and purified by careful gradient flash chromatography (hexanes/EtOAc, 50:1 to 20:1) to provide the cyclic olefin as a colourless oil.

**(4*R*)-4,8-*O*-Diphenylsilanediyl-4,8-dihydroxy-5-methyl-5-octen-2-one *((AUthor: Nomenclature affords inclusion of "4,8-dihydroxy"!))*** **(2a):** Diene **7a** (270 mg, 0.71 mmol) gave **2a** in 54 % (135 mg). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.64 (m, 4 H), 7.39 (m, 6 H), 5.44 (t, *J* = 8.1 Hz, 1 H), 4.90 (dd, *J* = 3.9, 9.6 Hz, 1 H), 4.05 (m, 2 H), 2.94 (dd, *J* = 9.9, 15.3 Hz, 1 H), 2.93 (m, 1 H), 2.62 (dd, *J* = 3.6, 15.3 Hz, 1 H), 2.26 (m, 1 H), 2.25 (s, 3 H), 1.60 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 207.6, 140.8, 134.8, 133.8, 133.5, 130.5, 130.4, 128.1, 125.1, 71.7, 64.4, 49.6, 31.2, 30.9, 21.5 ppm. IR (neat): ṽ = 3070 $cm^{-1}$, 2919, 2876, 1713, 1115, 1083, 716, 699. HRMS (ESI) calcd. for $C_{21}H_{24}O_3Si$ [M + $H^+$] 353.1568, found 353.1565.

**4,8-*O*-Diphenylsilanediyl-4,8-dihydroxy-5-octen-2-one (2b):** Diene **7b** (80 mg, 0.22 mmol) gave **2b** in 81 % (60 mg). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.39 (m, 6 H), 5.73 (m, 2 H), 5.13 (m, 1 H), 4.09 (m, 1 H), 3.94 (m, 1 H), 2.96 (dd, *J* = 8.1, 15 Hz, 1 H), 2.64 (dd, *J* = 4.5, 15 Hz, 1 H), 2.63 (m, 1 H), 2.42 (m, 1 H), 2.22 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 207.3, 135.2, 135.0, 134.8, 133.7, 130.5, 130.4, 129.3, 128.2, 128.1, 67.4, 63.7, 51.5, 31.3, 31.1 ppm. IR (neat): ṽ = 3067 $cm^{-1}$, 3013, 2955, 2926, 2878, 1715, 1128, 1082, 720, 700. HRMS (ESI) calcd. for $C_{20}H_{22}O_3Si$ [M + $H^+$] 339.1408, found 339.1411.

**(4*R*)-4,8-*O*-Diisopropylsilanediyl-4,8-dihydroxy-5-methyl-5-octen-2-one (2c):** Diene **7c** (110 mg, 0.35 mmol) gave **2c** in 60 % (60 mg). $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.42 (m, 1 H), 4.89 (dd, *J* = 3.6, 9.6 Hz, 1 H), 3.9 (m, 2 H), 2.82 (dd, *J* = 9.6, 14.4 Hz, 1 H), 2.72 (m, 1 H), 2.50 (dd, *J* = 3.6, 14.7 Hz, 1 H), 2.25 (s, 3 H), 2.24 (m. 1 H), 1.74 (s, 3 H), 1.00 (m, 14 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 208.1, 140.6, 125.0, 71.0, 64.3, 49.6, 31.6, 30.8, 21.1, 17.6, 17.5, 12.8, 12.5 ppm. IR (neat): ṽ = 2943, 2866, 1715, 1112, 1036, 883, 693 $cm^{-1}$. HRMS (ESI). Calcd. for $C_{15}H_{28}O_3Si$ [M + $H^+$] 285.1891, found 285.1881.

**4,8-*O*-Diisopropylsilanediyl-4,8-dihydroxy-5-octen-2-one (2d):** Diene **7d** (340 mg, 1.14 mmol) gave **2d** in 74 % (229 mg). $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.72 (m, 2 H), 4.93 (m, 1 H), 3.91 (m, 2 H), 2.80 (dd, *J* = 8.4, 14.7 Hz, 1 H), 2.56 (m, 1 H), 2.54 (dd, *J* = 4.8, 14.7 Hz, 1 H), 2.40 (m, 1 H), 2.23 (s, 3 H), 1.02 (m, 14 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 207.9, 135.3, 129.4, 66.9, 63.8, 51.5, 31.7, 31.1, 17.7, 17.6, 17.5, 12.8, 12.5 ppm. IR (neat): ṽ = 2944, 2867, 1715, 1120, 1011, 732 $cm^{-1}$. HRMS (ESI) calcd. for $C_{14}H_{27}O_3Si$ [M + $H^+$] 271.1717, found 271.1724.

**Representative Procedure for Aldol Reactions:** To a stirred solution of $Cy_2OBTf$ or (−)-$Ipc_2BCl$ (1.5 mmol) in anhydrous diethyl ether (4 mL) at −78 °C (for $Cy_2OBTf$) or 0 °C (for (−)-$Ipc_2BCl$) was slowly added triethylamine (1.7 mmol). A solution of the ketone (1 mmol) in $CH_2Cl_2$ (4 mL) was then added through a cannula. The reaction mixture was stirred at −78 °C for 30 min or 0 °C, respectively, before being cooled to −78 °C, at which point pivaldehyde (2 mmol) was added dropwise. The solution was stirred at −78 °C for 3 h then at −20 °C for 10 h, then quenched at −20 °C by addition of a pH = 7 buffer solution (30 % methanol, hydrogen peroxide solution). The solution was then stirred at room temperature for 3 h and extracted twice with diethyl ether. The organic extracts were washed with water, brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by flash chromatography (hexanes/EtOAc, gradient 50:1 to 10:1) gave the aldol adducts as colorless oils.

**7,11-*O*-Diisopropylsilanediyl-7,11-dihydroxy-2,2,8-trimethyl-8-undecen-5-one:** Reaction of **2c** (106 mg, 0.37 mmol) with (−)-$Ipc_2BCl$ gave a mixture of **8** and **9** in 88 % yield (120 mg), *ds* = 1.5:1. Spectral data reported for one diastereomer, separated by flash chromatography. $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.43 (t, *J* = 8.7 Hz, 1 H), 4.89 (dd, *J* = 3.3, 9.6 Hz, 1 H), 3.85 (m, 2 H), 3.00−2.48 (m, 5 H), 2.22 (m, 1 H), 1.75 (s, 3 H), 1.02 (m, 14 H), 0.93 (s, 9 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 211.9, 140.5, 125.0, 74.7, 71.2, 64.3, 49.5, 46.4, 34.3, 30.8, 25.9, 21.2, 17.7, 17.6, 17.5, 17.4, 12.8, 12.5 ppm. IR (neat): ṽ = 3479 $cm^{-1}$, 2954, 2868, 1709, 1114, 1006, 940, 733, 696. HRMS (ESI) calcd. for $C_{20}H_{38}O_4Si$ [M + $H^+$] 371.2602, found 371.2612.

**Aldol Reaction with 2c Using $Cy_2BOTf$:** Reaction of **2c** (30 mg, 0.11 mmol) with $Cy_2BOTf$ gave a mixture of **8** and **9** in 95 % (37 mg), *ds* = 1.2:1.

**3-[(3-Butenoxy)diisopropylsilyloxy]-7-hydroxy-2,8,8-trimethyl-1-nonen-5-one (10 and 11):** Reaction of **7c** (50 mg, 0.16 mmol) with (−)-$Ipc_2BCl$ gave **10** and **11** in 93 % yield (59 mg), *ds* = 2.2:1. Spectral data is reported for the combined diastereomers. $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.86 (m, 1 H), 5.06 (m, 2 H), 5.00 (s, 1 H), 4.84 (s, 1 H), 4.78 (t, *J* = 6.3 Hz, 1 H), 3.74 (m, 2 H), 2.79−2.44 (m, 4 H), 2.31 (dt, *J* = 6.9, 13.5 Hz, 2 H), 1.75 (s, 3 H), 1.03 (m, 14 H), 0.92 (s, 9 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 211.2, 211.1, 146.4, 135.5, 116.6, 112.0, 111.9, 74.9, 74.8, 72.9, 62.9, 50.8, 50.7, 46.2, 46.1, 37.5, 34.3, 26.0, 25.9, 17.6, 17.5, 17.3, 12.5, 12.4 ppm. IR (neat): ṽ = 3530 $cm^{-1}$, 2948, 2868, 1709, 1101, 909. HRMS (ESI) calcd. for $C_{22}H_{42}O_4Si$ [M + $Na^+$] 421.2734, found 421.2744.

**Aldol Reaction with 7c Using $Cy_2BOTf$:** Ketone **7c** (50 mg, 0.16 mmol) gave **10** and **11** in 97 % yield (61 mg), *ds* = 1.2:1.

**(3*R*,7*R*)-7,11-*O*-Diphenylsilanediyl-7,11-dihydroxy-2,2,8-trimethyl-8-undecen-5-one:** Reaction of **2a** (100 mg, 0.28 mmol) with (−)-$Ipc_2BCl$ gave **8a** in 94 % yield (115 mg), *ds* > 99:1. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.61 (m, 4 H), 7.38 (m, 6 H), 5.44 (t, *J* = 9.6 Hz, 1 H), 4.90 (dd, *J* = 3.3, 9.6 Hz, 1 H), 4.06 (m, 2 H), 3.76 (dd, *J* = 1.8, 10.5 Hz, 1 H), 2.99 (dd, *J* = 9.8, 14.9 Hz, 1 H), 2.91 (m, 1 H), 2.76 (dd, *J* = 1.8, 17.8 Hz, 1 H), 2.62 (dd, *J* = 3.6, 14.7 Hz, 1 H), 2.58 (dd, *J* = 10.2, 17.7 Hz, 1 H), 2.28 (m, 1 H), 1.61 (s, 3 H), 0.89 (s, 9 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ =

211.5, 140.7, 134.8, 134.7, 133.6, 133.3, 130.5, 130.4, 128.1, 74.8, 71.9, 64.3, 49.5, 46.1, 34.3, 30.9, 25.9, 21.5 ppm. IR (neat): $\tilde{\nu}$ = 3480 $cm^{-1}$, 3070, 2955, 2873, 2247, 1706, 1116, 1073, 909, 730, 716, 699. HRMS (ESI) calcd. for $C_{26}H_{34}O_4Si$ [M + $Na^+$] 461.2120, found 461.2119.

**(3*R*,7*R*)-7,11-*O*-Diphenylsilanediyl-7,11-dihydroxy-2,2-dimethyl-8-undecen-5-one:** Reaction of **2b** (114 mg, 0.34 mmol) with (−)-$Ipc_2BCl$ gave **8b** in 60 % (86 mg, not optimised) *ds* > 99:1. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.64 (m, 4 H), 7.40 (m, 6 H), 5.74 (m, 2 H), 5.14 (m, 1 H), 4.09 (m, 1 H), 3.94 (m, 1 H), 3.74 (d, *J* = 10.2 Hz, 1 H), 3.03−2.39 (m, 6 H), 0.88 (s, 9 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 211.2, 135.0, 134.7, 133.5, 133.4, 130.6, 130.4, 129.4, 128.2, 128.1, 74.8, 67.6, 63.7, 51.3, 46.1, 34.3, 31.0, 25.9 ppm. IR (neat): $\tilde{\nu}$ = 3509 $cm^{-1}$, 3019, 2959, 2873, 1709, 1125, 1070, 723. HRMS (ESI) calcd. for $C_{25}H_{32}O_4Si$ [M + $Na^+$] 447.1961, found 447.1962.

**Representative Procedure for the Synthesis of *tert*-Butyldiphenylsilyl Ethers 12a−c:** To a solution of the β-hydroxy ketone (1 mmol) in DMF (1.5 mL) was added dimethyl(phenyl)silyl chloride (1.1 mmol) and imidazole (2 mmol). After stirring at room temperature for 24 h, the solution was quenched with saturated ammonium chloride, extracted twice with diethyl ether. The organic extracts were washed with brine, dried with $MgSO_4$, filtered and the solvents removed under reduced pressure. The residual oil was purified by flash chromatography.

**(*R*)-4-(*tert*-Butyldiphenylsiloxy)-5-methylhexan-2-one (12a):** 4-Hydroxy-5-methylhexane-2-one (646 mg, 5.0 mmol) produced **12a** (1.27 g, 3.44 mmol) in an overall yield of 69 % after purification by flash chromatography (hexanes/ethyl acetate, 50:1). $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.70 (m, 4 H), 7.42 (m, 6 H), 4.18 (m,1 H), 2.56 (dd, *J* = 6.6, 15.9 Hz, 1 H), 2.42 (dd, *J* = 5.4, 15.9 Hz, 1 H), 1.88 (s, 3 H), 1.72 (m, 1 H), 1.06 (s, 9 H), 0.94 (d, *J* = 6.6 Hz), 0.81 (d, *J* = 6.9 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 207.6, 136.3, 1362, 134.5, 134.3, 129.9, 127.8, 127.7, 73.9, 47.8, 33.7, 30.8, 27.3, 19.8, 18.0, 17.5 ppm. IR (neat): $\tilde{\nu}$ = 3072 $cm^{-1}$, 2960, 2932, 2857, 1715, 1660, 1110, 1068, 740, 703. HRMS (ESI) calcd. for $C_{23}H_{32}O_2Si$ [M + $H^+$] 369.2305, found 369.2245.

**(*R*)-4-(*tert*-Butyldiphenylsiloxy)-5-methyl-5-hexen-2-one (12c):** 4-Hydroxy-5-methyl-5-hexen-2-one[20] (546 mg, 4.2 mmol) produced **12b** (1.15 g, 3.14 mmol) in an overall yield of 75 % after purification by flash chromatography (hexanes/ethyl acetate, 50:1). $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.38 (m, 6 H), 4.78 (s, 1 H), 4.72 (s, 1 H), 4.59 (t, *J* = 6 Hz, 1 H), 2.61 (dd, *J* = 6.0, 14.7 Hz,1 H), 2.52 (dd, *J* = 6.6, 14.7 Hz, 1 H), 2.10 (s, 3 H), 1.68 (s, 3 H), 1.06 (s, 9 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 206.8, 145.8, 136.2, 134.1, 133.7, 130.0, 128.0, 127.8, 127.7, 112.6, 74.1, 50.8, 31.1, 27.2, 19.6, 17.4 ppm. IR (neat): $\tilde{\nu}$ = 3072 $cm^{-1}$, 2931, 2857, 1713, 1427, 1360, 1162, 1106, 1063, 739, 700. HRMS (ESI) calcd. for $C_{23}H_{30}O_2Si$ [M + $Na^+$] 389.1922, found 389.1907.

**Aldol Reactions with Ketones 12a−c**

**7-(*tert*-Butyldiphenylsiloxy)-3-hydroxy-2,2,8-trimethylnonan-5-one (13a):** Aldol reaction of **12a** (201 mg, 0.52 mmol) with pivaldehyde gave **13a** in 88 % yield (201 mg), *ds* = 2:1. Spectral data reported for one diastereomer. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 1.2, 7.2 Hz, 2 H), 7.68 (dd, *J* = 1.2, 7.5 Hz, 2 H), 7.42 (m, 6 H), 4.20 (m, 1 H), 3.52 (dd, *J* = 2.1, 9 Hz, 1 H), 2.61 (dd, *J* = 6.6, 16.2 Hz, 1 H), 2.43 (dd, *J* = 4.8, 16.2 Hz, 1 H), 2.28 (m, 2 H), 1.73 (m, 1 H), 1.06 (s, 9 H), 0.95 (d, *J* = 6.3 Hz, 3 H), 0.86 (br. s, 6 H), 0.81 (d, *J* = 6.6 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 211.3, 136.3, 136.2, 134.6, 134.1, 129.9, 127.8, 74.7, 73.6, 47.7, 45.2, 34.2, 33.7, 27.3, 25.9, 19.7, 17.9, 17.6 ppm. IR (neat): $\tilde{\nu}$ = 3502 $cm^{-1}$, 3072, 2957, 2858, 1709, 1110, 1057, 823, 702. HRMS (ESI) calcd. for $C_{28}H_{42}O_3Si$ [M + $Na^+$] 477.2854, found 477.2796.

**7-(*tert*-Butyldiphenylsiloxy)-3-hydroxy-2,8-dimethylnonan-5-one (13b):** Aldol reaction of **12b** (119 mg, 0.32 mmol) and isobutylaldehyde gave **13b** in 86 % yield (125 mg), *ds* = 2.5:1. Spectral data reported for one diastereomer. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 1.5, 7.8 Hz, 2 H), 7.63 (dd, *J* = 1.5, 7.8 Hz, 2 H), 7.37 (m, 6 H), 4.16 (m, 1 H), 3.55 (dt, *J* = 6.0, 11.7 Hz, 1 H), 2.79 (br. s, 1 H), 2.55−2.24 (m, 4 H), 1.68 (m, 1 H), 1.54 (m, 1 H), 1.02 (s, 9 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H), 0.81 (d, *J* = 6.9 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 211.2, 136.3, 136.2, 134.6, 134.1, 130.0, 129.8, 127.8, 127.7, 73.6, 72.0, 47.6, 47.1, 33.7, 33.0, 27.3, 19.7, 18.6, 18.0, 17.9, 17.6 ppm. IR (neat): $\tilde{\nu}$ = 3478 $cm^{-1}$, 3072, 2929, 2932, 2859, 1707, 1109, 1006, 760, 701. HRMS (ESI) calcd. for $C_{27}H_{40}O_3Si$ [M + $Na^+$] 463.2653, found 463.2638.

**7-(*tert*-Butyldiphenylsiloxy)-3-hydroxy-2,8-dimethyl-2,8-nonadien-5-one (13c):** Aldol reaction of **12c** (453 mg, 1.23 mmol) with methacrolein gave **13c** in 89 % yield (505 mg), *ds* = 1.2:1. Spectral data reported for the combined diastereomers. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.67 (m, 4 H), 7.40 (m, 6 H), 4.95 (s, 1 H), 4.83 (br. s, 2 H), 4.77 (s, 1 H), 4.61 (m, 1 H), 4.32 (m, 1 H), 3.90 (br. s, 1 H), 2.73−2.2.40 (m, 4 H), 1.70 (s, 3 H), 1.68 (s, 3 H), 1.07 (s, 9 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 209.5, 145.7, 136.2, 136.1, 134.1, 133.5, 130.1, 130.0, 127.9, 127.8, 112.7, 111.4, 73.8, 73.7, 70.9, 50.5, 49.0, 48.8, 27.2, 19.6, 18.6, 18.5, 17.5 ppm. IR (neat): $\tilde{\nu}$ = 3450 $cm^{-1}$, 3073, 2932, 2858, 1709, 1111, 1072, 822, 702, 612. HRMS (ESI) calcd. for $C_{27}H_{36}O_3Si$ [M + $H^+$] 437.2528, found 437.2507.

## Acknowledgments

Financial support was provided by the New Zealand Cancer Society, the Public Good Science Fund and the Foundation for Research Science and Tecnology (fellowship to B. S.). Dr. Peter Northcote's assistance in determination of relative stereochemistry is also greatly acknowledged.

[1] For approaches to C−C bond formations with formation of 1,3-diols see: [1a] Y. Mora, M. Asai, A. Okumura, *Tetrahedron* **1995**, *51*, 5299−5314. [1b] S. D. Rychnovsky, R. C. Hoye, *J. Am. Chem. Soc.* **1994**, *116*, 1753−1765. [1c] P. Knochel, W. Brieden, M. J. Rozema, C. Eisenberg, *Tetrahedron Lett.* **1993**, *34*, 5881−5884.

[2] Notably, enol borinate additions to the same system result in poor selectivity: [2a] D. A. Evans, J. L. Duffy, M. J. Dart, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343. [2b] D. A. Evans, J. L. Duffy, M. J. Dart, *Tetrahedron Lett.* **1994**, *35*, 8537−8540.

[3] [3a] D. A. Evans, P. J. Coleman, B. Cote, *J. Org. Chem.* **1997**, *62*, 788−789. [3b] D. A. Evans, D. M. Fitch, T. E. Smith, V. J. Cee, *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. [3c] D. A. Evans, B. W. Trotter, P. J. Coleman, B. Cote, L. C. Dias, H. A. Rajapakse, A. N. Tyler, *Tetrahedron* **1999**, *55*, 8671−8726.

[4] [4a] I. Paterson, K. R. Gibson, R. M. Oballa, *Tetrahedron Lett.* **1996**, *37*, 8585−8588. [4b] I. Paterson, L. A. Collett, *Tetrahedron Lett.* **2001**, *42*, 1187−1191. [4c] I. Paterson, M. Emilia Di Francesco, T. Kuhn, *Org. Lett.* **2003**, *5*, 509−602. [4d] I. Paterson, R. M. Oballa, R. D. Norcross, *Tetrahedron Lett.* **1996**, *37*, 8581−8584.

[5] [5a] D. A. Evans, M. A. Calter, *Tetrahedron Lett.* **1993**, *34*, 6871−6874. [5b] D. A. Evans, D. M. Fitch, *J. Org. Chem.* **1997**, *62*, 454−455.

[6] S. A. Kozmin, *Org. Lett.* **2001**, *3*, 755−758.
[7] [7a] L. M. West, P. T. Northcote, C. N. Battershill, *J. Org. Chem.* **2000**, *65*, 445−449. [7b] K. A. Hood, L. M. West, B. Rouwé, P. T. Northcote, M. V. Berridge, St. J. Wakefield, J. H. Miller, *Cancer Res.* **2002**, *62*, 3356−3360. [7c] K. A. Hood, B. T. Bäckström, L. M. West, P. T. Northcote, M. V. Berridge, J. H. Miller, *Anti-Cancer Drug Des.* **2001**, *16*, 155−166. [7d] De Brabander and co-workers have recently published the first total synthtesis of peloruside A subsequent to this study, in which the absolute stereochemistry was shown to be opposite of that shown: X. Liao, Y. Wu, J. K. De Brabander, *Angew. Chem. Int. Ed.* **2003**, *42*, 1648−1652.
[8] The twist-boat transition state is based on Houk's and Evan's calculations. See ref.[5b] and: Y. Li, M. N. Padden-Row, K. N. Houk, *J. Org. Chem.* **1990**, *55*, 481−493.
[9] A. B. Smith, P. A. Levenberg, *Synthesis* **1981**, 567−569.
[10] [10a] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. [10b] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573−575. [10c] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas, *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267.
[11] *ee* determined by chiral GC using the *tert*-butyldimethylsilyl derivative. Alternatively, this can be synthesized in 60 % yield and 73 % *ee* using the Ipc boron enolate of acetone: I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, R. D. Norcross, *Tetrahedron* **1990**, *46*, 4663−3684.
[12] [12a] J. W. Gillard, R. Fortin, H. E. Morton, C. Yoakim, C. A. Quesnelle, S. Daignault, Y. Guindon, *J. Org. Chem.* **1988**, *53*, 2602−2608. [12b] S. Rover, P. Wipf, *Tetrahedron Lett.* **1999**, *40*, 5667−5670. [12c] C. Colombier, T. Skrydstrup, J.-M. Beau, *Tetrahedron Lett.* **1994**, *35*, 8167−8170.
[13] Z. Xu, C. W. Johannes, A. F. Houri, D. S. La, D. A. Cogan, G. E. Hofilena, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 10302−10316.
[14] For stereoselective RCM including silyl-tethered olefins see: [14a] P. A. Evans, J. Cui, G. P. Buffone, *Angew. Chem. Int. Ed.* **2003**, *42*, 1734−1737. [14b] J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954−4955.
[15] For reports on RCM of silyl-tethered olefins see: [15a] J.-G. Boiteau, P. J. Van de Weghe, J. Eustache, *Tetrahedron Lett.* **2001**, *42*, 239−242. [15b] B. A. Harrison, G. L. Verdine, *Org. Lett.* **2001**, *3*, 2157−2159. [15c] P. Van de Weghe, D. Aoun, J.-G. Boiteau, J. Eustache, *Org. Lett.* **2002**, *4*, 4105−4108. [15d] T. R. Hoye, M. A. Promo, *Tetrahedron Lett.* **1999**, *40*, 1429−1432. [15e] A. Briot, M. Bujard, V. Gouverneur, S. P. Nolan, C. Mioskowski, *Org. Lett.* **2000**, *2*, 1517−1519. [15f] M. Lobbel, P. Koll, *Tetrahedron: Asymmetry* **2000**, *11*, 393−396.
[16] Residual traces of ruthenium were found to hinder subsequent aldol reaction but are removed using a literature procedure: J. H. Cho, B. M. Kim, *Org. Lett.* **2003**, *5*, 531−533.
[17] A potential advantage of this overall strategy is the selective mono-deprotection of the disilyl group: M. Yu, B. L. Pagenkopf, *J. Org. Chem.* **2002**, *67*, 4553−4558.
[18] A. F. Kiely, J. A. Jernelius, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 2868−2869.
[19] Blechert has reported a modified ruthenium catalyst that greatly improves the yields of problematic closures: H. Wakamatsu, S. Blechert, *Angew. Chem. Int. Ed.* **2002**, *41*, 2403−2404.
[20] Synthesized by adaptation of ref.[9]

Received September 23, 2003