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## Graphical Abstract

**Dramatic influence of ester steric hindrance on the diastereoselectivity of a Michael addition towards the synthesis of the ABC tricycle of hexacyclinic acid**

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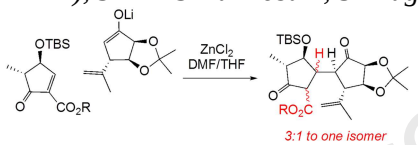

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# Dramatic influence of ester steric hindrance on the diastereoselectivity of a Michael addition towards the synthesis of the ABC tricycle of hexacyclinic acid

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ABSTRACT

During our studies toward the synthesis of the ABC ring system of hexacyclinic acid, we observed an unexpected influence of the steric bulk of the ester group of the Michael acceptor in a key conjugate addition. We propose an eight-membered ring transition state to explain the formation of the undesired diastereomer in the case of unhindered esters.





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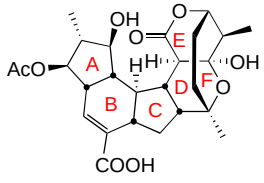
## 1. Introduction

Hexacyclinic acid (Fig. 1) is a polyketide isolated for the first time by Zeeck *et al.* in 2000 from a bacterium, *Streptomyces cellulosae* (strain S1013).[1] The general structure and relative configuration were elucidated with the aid of several NMR experiments and X-ray analysis; the absolute configuration was successfully determined by Mosher's ester methodology. Hexacyclinic acid is composed of six cycles, a 5/6/5 fused ring system (A, B and C) connected to a bridged tricycle (D, E and F) with a cyclic hemiketal and a *δ*-lactone. Hexacyclinic acid possesses cytotoxic activity against three cancerous cell lines: HM02 (gastric carcinoma), HEPG2 (hepatocellular carcinoma) and MCF7 (breast carcinoma) with $GI_{50}$ values up to 14.0 $\mu molmL^{-1}$, and the truncated DEF ring system was shown to induce mitotic arrest by interfering with microtubule dynamics.[2]

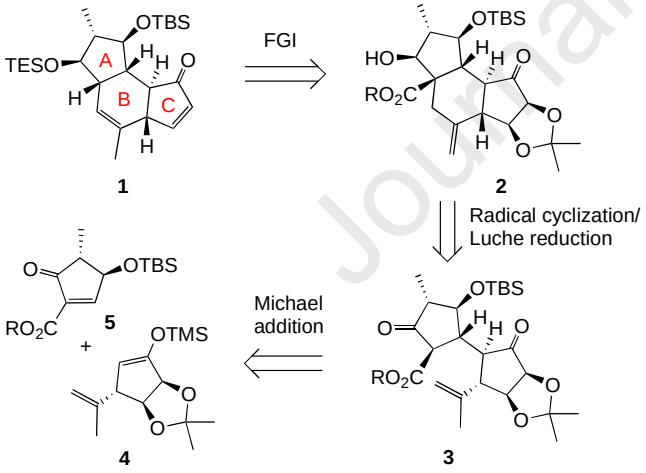



**Hexacyclinic acid**

**Fig. 1.** Structure of hexacyclinic acid.

The biological activity of hexacyclinic acid coupled to its complex structure has made it a target of choice for organic chemists, but although syntheses of DEF[2,3] and ABC[4,5] fragments of this compound have been published, no total synthesis has been reported yet.

The retrosynthesis we envisaged for the ABC tricycle **1** of the target molecule is shown in Scheme 1.



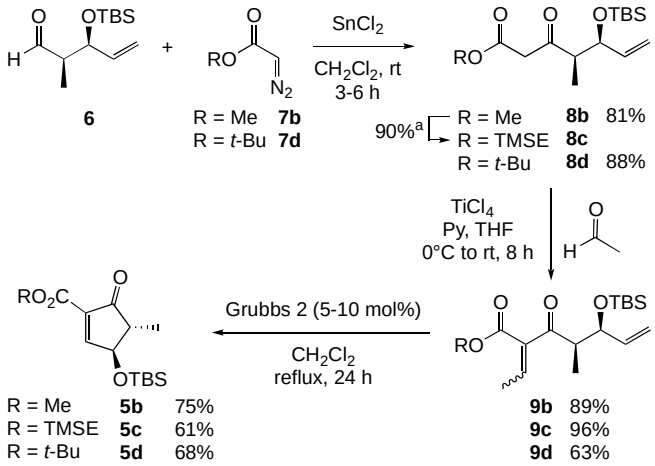

**Scheme 1.** Retrosynthesis of the ABC tricycle of hexacyclinic acid.

Compound **1** would be obtained from ester **2** by functional group interconversions (FGI) - decarboxylation, alkene migration, alcohol protection and acetonide deoxygenation. Tricycle **2** would be formed by intramolecular addition of the radical of the β-keto ester of **3** onto the isopropenyl group, followed by Luche reduction of the A ring ketone. Compound **3** would be assembled by Michael addition of the enolate derived from silyl enol ether **4** to enone **5**.

In a preliminary communication, we reported the synthesis of the two partners **4** and **5a** (R = Et) and the optimization of the Michael addition.[5] Treatment of silyl enol ether **4** with *n*-BuLi generates *in situ* the lithium enolate and subsequent addition of this enolate to the double Michael acceptor **5a** in the presence of $ZnCl_2$ as a Lewis acid, afforded the Michael adduct **3a** (R = Et). The best yield of 60% was obtained using an excess of 3.3 equiv of silyl enol ether with 3 equiv of *n*-BuLi. Also, the use of polar coordinating solvents was essential to obtain the desired diastereomer as the major product, and a diastereoselectivity of 7:1 was obtained in a 4:1 mixture of DMF/THF (see Table 1).[5] Unfortunately, any attempt to hydrolyze derivatives of tricyclic ester **2a** (R = Et) under basic conditions only led to decomposition.[6] Direct decarboxylation was also not possible. To address this problem, other esters **5** were envisaged. We report here their synthesis and their behavior in the Michael addition with silyl enol ether **4**, which led us to propose a revised model for the diastereoselectivity observed in this reaction.

## 2. Results and discussion

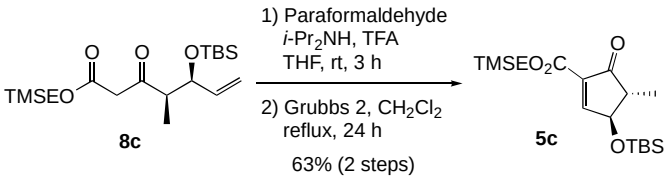
We selected three different esters **5**, methyl ester **5b**, trimethylsilylethyl (TMSE) ester **5c** and *tert*-butyl ester **5d**. The methyl ester should be hydrolyzed under milder basic conditions than the corresponding ethyl ester.[7] The TMSE ester requires fluorides, and the *tert*-butyl ester acidic conditions. Another factor in the choice of these esters was their relative size. We had observed that the selectivity of the Michael addition onto ester **5b** depended on the size of the nucleophile,[6] and we wanted to probe if the steric bulk of the ester had an influence on this selectivity as well. The synthesis of the three Michael acceptors **5b-d** is shown in Scheme 2. It follows the route that was used for the preparation of ester **5a**.[5] Known aldehyde **6** was subjected to a Roskamp homologation with methyl diazoacetate **7b** and *tert*-butyl diazoacetate **7d** to furnish β-keto esters **8b** and **8d** in 81% and 88% yield, respectively. Since only ethyl diazoacetate is commercially available, diazoacetates **7b** and **7d** had to be synthesized. Rather than preparing the TMSE diazoacetate as well, TMSE ester **8c** was obtained in 90% yield by transesterification (see Scheme 4 for conditions) of methyl ester **8b**, which we had made on large scale. Knoevenagel condensation with acetaldehyde proceeded in good yield, giving unsaturated β-keto esters **9b-d** in moderate to excellent yields. Ring-closing metathesis reaction with Grubbs 2 catalyst led to the desired esters **5b-d**, but an important amount of expensive catalyst was required (10 mol%) for the reaction of the *tert*-butyl ester.




**Scheme 2.** Synthesis of diverse esters **5**. [a]See Scheme 4 for conditions.

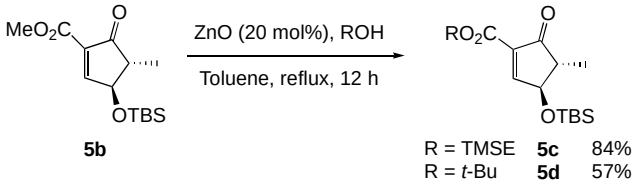
Since steric hindrance is deleterious to metathesis reactions, we performed the Knoevenagel reaction on **8c** with paraformaldehyde instead of acetaldehyde.[8] Indeed, the methyl group of acetaldehyde is not present in the structure of esters **5**, but is eliminated within propene after the RCM reaction. Attempts to purify the intermediate methylenated product only led to complete decomposition, so the crude product was used

directly for the RCM step, affording ester **5c** in 63% yield for the two steps, only a marginal improvement on the previous route.




**Scheme 3.** Alternative synthesis of esters **5c** and **5d**.

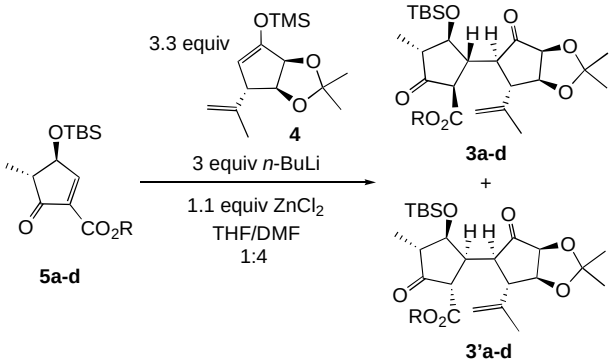
Finally, for a gram-scale synthesis of compounds **5c** and **5d**, it was found more convenient to prepare them by direct transesterification of ester **5b**, using 20 mol% of zinc oxide as catalyst (Scheme 4).




**Scheme 4.** Alternative synthesis of esters **5c** and **5d**.

We then studied the key Michael addition, as shown in Table 1. The conjugate addition with methyl ester **5b** proved disappointing, giving compounds **3b** and **3b'** in 30-40% yield in a 2 to 3:1 ratio. The undesired diastereomer results from attack of the enolate derived from **4** onto the other diastereotopic face of the alkene in **5b**; both diastereomers feature *trans* relationships on the A and C rings between the stereogenic centers formed during the Michael addition. The stereochemistry of both isomers was inferred from our previous work,[5] where extensive NOE studies had been performed on **3a** and **3a'**. The diastereoselectivity and the yield observed for the Michael addition to TMSE compound **5c** were also lower than those obtained with the ethyl ester. However, this reaction was not optimized, as *tert*-butyl ester **5d** proved to be the optimum substrate for this reaction, giving the bicyclic product as the single diastereomer **3d** in 55% yield. As we suspected, there is a marked correlation between the size of the ester substituent and the selectivity of the Michael addition. We observed that the selectivity was higher when the enolate derived from **4** was added to enones **5** and $ZnCl_2$ rather than when the inverse addition was performed, but we have not rational explanation for this.

**Table 1.** Michael additions on esters **5a-d**.




| | R | T | Yield | Ratio **3**/**3'** |
|---|---|---|---|---|
| **3a** | Et | -78 °C to 0 °C | 60% | 5:1[a] to 7:1[b] |
| **3b** | Me | -78 °C | 30-40% | 2:1[a] to 3:1[b] |
| **3c** | TMSE | -78 to -20°C | 35% | 3:1[a] |
| **3d** | *t*-Bu | -78 to -20°C | 55% | **3d** only[b] |

[a]Addition of enone and $ZnCl_2$ to enolate. [b]Addition of enolate to enone and $ZnCl_2$.

To explain the influence of the steric bulk of the ester group on the diastereoselectivity of this conjugate addition, two different transition states were proposed to rationalize the formation of both the desired product **3** and the undesired diastereomer **3'** (Fig. 2). We hypothesized that the stereoselectivity of this reaction under kinetic conditions would be entirely controlled by steric factors. The required diastereomer **3** would be formed *via* an open transition state **I** while the undesired diastereomer **3'** formation could be explained by an 8-membered cyclic transition state **I'**.

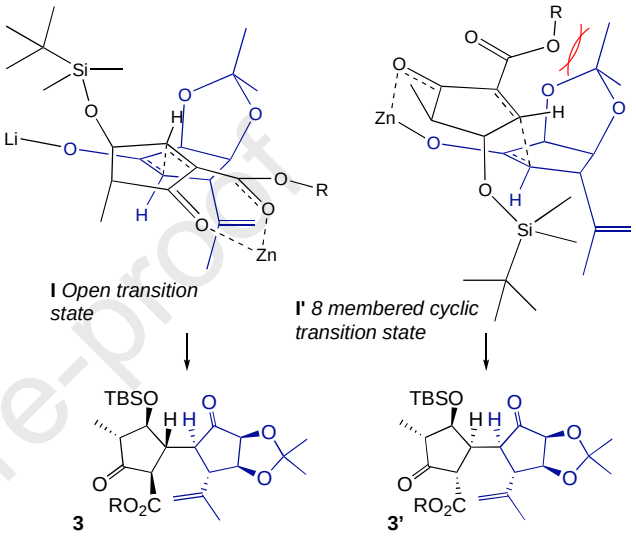



**Fig. 2.** Open transition and 8-membered cyclic transition states.

Such type of eight-membered cyclic transition state **I'** formed between an enolate and a Michael acceptor has already been described in the literature by Heathcock and co-workers,[9] and some computational investigations were reported by Kwan and Evans.[10] According to this model, the transition state **I'** would be disfavored by a steric clash between the R group of the ester and the acetonide methyl groups, interaction which is not present in the open transition state **I**. This explains why the reaction of the bulky *tert*-butyl ester is very diastereoselective. In addition, it provides a rationale for the difference in selectivity that we previously observed for the reaction with the ethyl ester **5a** in different solvents – 1:7 in diethyl ether *vs* 7:1 in 4:1 DMF/THF.[5] The more polar solvents disrupt the chelation of the zinc dichloride in cyclic transition state **I**, while this transition state is favored in less polar solvents.

## 3. Conclusion

In this study, we uncovered the influence of the steric bulk if the ester group on the diastereoselectivity of the key Michael addition to form a precursor of the ABC tricycle of hexacyclinic acid. The unhindered esters led to low selectivity, while reaction with the *tert*-butyl ester substrate only gave one diastereomer. We propose that the desired diastereomer results from a classical open transition state, while the undesired product stems from an eight-membered transition state. This cyclic transition state is destabilized by bulky ester group substituents. We are currently pursuing the synthesis of the ABC fragment of hexacyclinic acid using this route.

## 4. Experimental section

Air or moisture sensitive reactions were carried out in pre-dried glassware; either overnight in an oven (125 °C) or by flame drying under vacuum. Argon was used to create an inert atmosphere. Degassing solvent was done using freeze and thaw method. Reactions were collected from an in-house solvent purification system (THF, $CH_2Cl_2$, $Et_2O$, $CH_3CN$, and toluene). Chromatography solvents were HPLC grade solvents, stored in Winchester bottles. All reagents were used directly from supplier, unless prior purification is explicitly stated. Flash chromatography was executed under forced flow conditions, using the indicated solvent system and the EMD Geduran silica gel 60 as solid support. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 covered aluminium sheets, and monitored by UV-light or by staining with a solution of anisaldehyde or $KMnO_4$ mixture. NMR spectra were recorded using a Bruker DPX-400 spectrometer ($^1$H NMR: 400 MHz, $^{13}$C NMR: 101 MHz) and a Bruker DPX-500 spectrometer ($^1$H NMR: 500 MHz, $^{13}$C NMR: 126 MHz). Deuterated chloroform ($CDCl_3$) was used as the solvent for both $^1$H and $^{13}$C NMR, with residual solvent peak δ 7.26 being used for calibration of $^1$H NMR and $CDCl_3$ peak at δ 77.16 for $^{13}$C. Signal splitting patterns are described as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), octet (oct), nonet (non), multiplet (m), broad singlet, or any combination of the above. Two dimensional experiments (COSY, HSQC, HMBC, and HMQC) were recorded, where necessary, for assignment. Sn-H and Sn-C couplings were averaged over 117/119Sn. IR spectra were recorded using a Golden Gate™ attachment, utilizing a type IIa diamond as a single reflection element, allowing for the direct reading of powder and oil samples. High resolution mass spectra were recorded under FAB, ESI and CI conditions by the University of Glasgow analytical service.

### *4.1. Methyl diazoacetate (**7b**)*

To a vigorously stirred solution of methyl 3-oxobutanoate (11.0 g, 94.0 mmol), *p*-acetamidobenzenesulfonyl azide (24.8 g, 103 mmol, 1.10 equiv) and tetrabutylammonium bromide (12.1 g, 37.6 mmol, 0.40 equiv) in pentane (720 mL) was slowly added a 3N aqueous solution of NaOH (125 mL, 376 mmol, 4.0 equiv) at 20 °C. After 1 h of vigorous stirring, the mixture was partitioned between $Et_2O$ and $H_2O$ and the layers were separated. The aqueous layer was extracted 3 times with $Et_2O$. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was used for the next step without further purifications; $R_f$ (95:5 PE/$Et_2O$) 0.2; $\delta_H$ (400 MHz $CDCl_3$) 4.75 (1H, brs, 1H, $N_2C\underline{H}$), 3.74 (3H, s, $OC\underline{H}_3$).

### *4.2. tert-Butyl diazoacetate (**7d**)*

To a vigorously stirred solution of *tert*-butyl 3-oxobutanoate (2.50 mL, 15.6 mmol), *p*-acetamidobenzenesulfonyl azide (4.20 g, 17.2 mmol, 1.10 equiv) and tetrabutylammonium bromide (2.0 g, 6.2 mmol, 0.40 equiv) in pentane (120 mL) was slowly added a 3N aqueous NaOH solution (21 mL, 62 mmol, 4.0 equiv) at 20 °C. After 1 h of vigorous stirring, the mixture was partitioned between $Et_2O$ and $H_2O$. The aqueous layer was extracted 3 times with $Et_2O$. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (75:25 PE/$Et_2O$) to afford pure *tert*-butyl 2-diazoacetate **7d** as a bright yellow oil (1.80 g, 81%); $R_f$ (50:50 PE/$Et_2O$) 0.5; $\delta_H$ (400 MHz $CDCl_3$) 4.62 (1H, brs, $N_2C\underline{H}$), 1.48 (9H, s, $OC(C\underline{H}_3)_3$).

### *4.3. Methyl (4R,5S)-5-((tert-butyldimethylsilyl)oxy)-4-methyl-3-oxohept-6-enoate (**8b**)*

To a solution of methyl 2-diazoacetate (1.40 g, 14 mmol, 2.0 equiv) in $CH_2Cl_2$ (45 mL) was added tin (II) chloride (0.65 g, 3.5 mmol, 0.50 equiv). The reaction was stirred at RT for 5 min then a solution of aldehyde **6** (1.60 g, 7.0 mmol) in $CH_2Cl_2$ (15 mL) was added dropwise and the mixture was left to stir at RT for 3 h. The crude mixture was concentrated under vacuum and purified by flash column chromatography (95:5 PE/$Et_2O$) to yield a 3:1 mixture of β-keto ester **8b** and enol form as a colorless oil (1.70 g, 81%); (β-keto ester form) $R_f$ (95:5 PE/$Et_2O$) 0.43; $[a]_D^{25}$ -45.5 (*c* 1.02, $CHCl_3$); $n_{max}$ (liquid film) 2957, 2931, 2858, 1749, 1716, 1648, 1625, 1472, 1422, 1366, 1307, 1258, 1225, 1154, 1073, 1029 cm$^{-1}$; $\delta_H$ (400 MHz $CDC1_3$) 5.74 (1H, ddd, *J* 17.0, 10.4, 6.5 Hz, $CH_2C\underline{H}CH$), 5.19 (1H, dt, *J* 17.1, 1.4 Hz, $C\underline{H}_{2trans}CHCH$), 5.13 (1H, dt, *J* 10.4, 1.4 Hz, $C\underline{H}_{2cis}CHCH$), 4.26 (1H, ddt, *J* 6.6, 5.3, 1.2 Hz, $CH_2CHC\underline{H}OSi$), 3.72 (3H, s, $C\underline{H}_3O$), 3.60 (1H, d, *J* 15.9 Hz, $OCC\underline{H}_2CO$), 3.54 (1H, d, *J* 15.9 Hz, $OCC\underline{H}_2CO$), 2.87 (1H, qd, *J* 7.0, 5.3 Hz, $CH_3C\underline{H}(COCHOSi)$), 1.09 (3H, d, *J* 7.0 Hz, $C\underline{H}_3CH(COCHOSi)$), 0.90 (9H, s, $SiC(C\underline{H}_3)_3$), 0.07 (3H, s, $SiC\underline{H}_3$), 0.03 (3H, s, $SiC\underline{H}_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 204.4, 167.6, 138.2, 116.4, 75.5, 52.2 , 52.1, 49.8, 25.8, 17.8, 12.1, -4.4, -4.6; HRMS (EI): $M^+$, found 300.4665. $C_{15}H_{28}O_4Si$ requires 300.4659.

### *4.4. 2-(Trimethylsilyl)ethyl (4R,5S)-5-((tert-butyldimethylsilyl)oxy)-4-methyl-3-oxohept-6-enoate (**8c**)*

To a solution of **8b** (1.73 g, 5.75 mmol) and 2-(trimethylsilyl)ethanol (8.24 mL, 57.5 mmol, 10 equiv) in toluene (35 mL) was added ZnO (94 mg, 1.2 mmol, 0.20 equiv). The mixture was heated under reflux for 12 h, then the solvent was concentrated under vacuum and the crude material was purified by column chromatography (95:5 PE/EtOAc) to furnish the transesterification product **8c** (2.0 g, 90%); (β-keto ester form) $R_f$ (95:5 PE/EtOAc) 0.30; $[a]_D^{25}$ -77.0 (*c* 1.0, $CHCl_3$); $n_{max}$ (liquid film) 2956, 2930, 2858, 1745, 1714, 1645, 1463, 1250, 1224, 1028 cm$^{-1}$; $\delta_H$ (400 MHz $CDC1_3$) 5.74 (1H, ddd, *J* 17.1, 10.4, 6.5 Hz, $CH_2C\underline{H}(CHOSi)$), 5.18 (1H, dt, *J* 17.1, 1.4 Hz, $C\underline{H}_2CH(CHOSi)$), 5.13 (1H, dt, *J* 10.4, 1.4 Hz, $C\underline{H}_2CH(CHOSi)$), 4.28–4.24 (1H, m, $CH_2CHC\underline{H}OSi$), 4.23–4.18 (2H, m, $CH_2C\underline{H}_2O$), 3.57 (1H, d, *J* 15.8 Hz, $COC\underline{H}_2CO$), 3.49 (1H, d, *J* 15.8 Hz, $COC\underline{H}_2CO$), 2.87 (1H, qd, *J* 7.0, 5.4 Hz, $CH_3C\underline{H}$), 1.09 (3H, d, *J* 7.0 Hz, $C\underline{H}_3CH$), 1.03–0.97 (2H, m, $C\underline{H}_2Si$), 0.90 (9H, s, $SiC(C\underline{H}_3)_3$), 0.07 (3H, s, $SiC\underline{H}_3$), 0.05 (3H, s, $SiC\underline{H}_3$), 0.03 (9H, s, $Si(C\underline{H}_3)_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 205.1, 167.7, 138.1, 116.4, 75.8, 63.6, 53.0, 50.5, 26.0, 18.3, 17.5, 12.4, -1.4, -4.2, -4.9; HRMS (ESI): $M+Na^+$, found 409.2210. $C_{19}H_{38}O_4Si_2Na$ requires 409.2207.

### *4.5. tert-Butyl (4R,5S)-5-((tert-butyldimethylsilyl)oxy)-4-methyl-3-oxohept-6-enoate (**8d**)*

To a suspension of $SnCl_2$ (415 mg, 2.20 mmol, 0.50 equiv) in anhydrous $CH_2Cl_2$ (13 mL) was added *tert*-butyl diazoacetate **7d** (1.3 g, 8.8 mmol, 2.0 equiv) at 20 °C under argon atmosphere. A solution of aldehyde **6** (1.0 g, 4.4 mmol) in anhydrous $CH_2Cl_2$ (4.4 mL) was then added dropwise *via cannula*. After 4 h of stirring, the reaction was not over and a further of $SnCl_2$ (208 mg, 1.10 mmol, 0.25 equiv) followed by *tert*-butyl diazoacetate **7d** (1.3 g, 8.8 mmol, 2.0 equiv) were added. After another 2 h, no significant evolution of the reaction was observed by TLC. The solvent was then removed *in vacuo* and the crude material was purified by flash chromatography on silica gel (98:2 PE/$Et_2O$) to yield pure product **8d** as a yellow oil (1.35 g, 88%); (β-keto ester form) $R_f$ (95:5 PE/$Et_2O$) 0.5; $[a]_D^{25}$ -67.0 (*c* 1.00, $CHCl_3$); $n_{max}$ (liquid film) 2932, 1728, 1680, 1255, 1151, 1084, 1002 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 5.74 (1H, ddd, *J* 17.2, 10.4, 6.4 Hz, $CH_2CHCH$), 5.18 (1H, dt, *J* 17.2, 1.6 Hz, $CH_{2trans}CHCH$), 5.12 (1H, dt, *J* 10.0, 1.2 Hz, $CH_{2cis}CHCH$), 4.27-4.24 (1H, m, $CH_2CHCHOSi$), 3.50 (1H, d, *J* 16.0 Hz, $OCCH_2CO$), 3.41 (1H, d, *J* 16.0 Hz, $OCCH_2CO$), 2.86 (1H, dq, *J* 6.8, 5.6 Hz, $CH_3CH(COCHOSi)$, 1.46 (9H, s, $(CH_3)_3)C$), 1.09 (3H, d, *J* 6.8 Hz, $CH_3CH(COCHOSi)$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 205.5, 166.6, 138.0, 116.1, 81.6, 75.6, 52.6, 51.4, 27.9, 25.8, 18.1, 12.2, -4.4, -5.0; HRMS (CI): $M+H^+$, found 343.5555. $C_{18}H_{35}O_4Si$ requires 343.5554.

*4.6. Methyl (4R,5S)-5-((tert-butyldimethylsilyl)oxy)-2-ethylidene-4-methyl-3-oxohept-6-enoate (**9b**)*

To a vigorously stirred solution of titanium (IV) chloride (1.39 mL, 12.7 mmol, 1.80 equiv) in THF (25 mL) under nitrogen atmosphere at 0 °C were successively added freshly distilled acetaldehyde (1.80 mL, 31.7 mmol, 4.50 equiv), a solution of β-keto ester **8b** (2.12 g, 7.05 mmol) in THF (10 mL), and pyridine (1.98 mL, 24.6 mmol, 3.50 equiv). The reaction mixture was allowed to reach 20 °C and stirred for 2 h. It was then quenched with a slow addition of water, extracted with $Et_2O$, dried under $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was then purified by flash chromatography on silica gel (95:5 PE/$Et_2O$) to yield the product **9b** (2.13 g, 92%) as an inseparable 1:1 mixture of diastereomers; $R_f$ (95:5 PE/ $Et_2O$) 0.25; $n_{max}$ (liquid film) 2966, 2935, 2858, 1725, 1702, 1464, 1381, 1252, 1193, 1134, 1068, 1029 $cm^{-1}$; diastereomer A: $\delta_H$ (400 MHz $CDC1_3$) 7.05 (1H, q, *J* 7.6 Hz, $CH_3CHC$), 5.82 (1H, ddd, *J* 17.3, 10.4, 6.8 Hz, $CH_2CHCH$), 5.19 (1H, dd, *J* 17.2, 1.2 Hz, $CH_{2trans}CHCH$), 5.08 (1H, dd, *J* 10.4, 1.6 Hz, $CH_{2cis}CHCH$), 4.34-4.31 (1H, m, $CH_2CHCHOSi$), 3.82 (3H, s, $OCH_3$), 3.14-3.06 (1H, m, $CH_3CHCO$), 1.97 (3H, d, *J* 7.6 Hz, $CH_3CHCO$), 1.14 (3H, d, *J* 7.2 Hz, $CH_3CHC$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.05 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), diastereomer B: $\delta_H$ (400 MHz $CDC1_3$) 6.89 (1H, q, *J* 7.2 Hz, $CH_3CHC$), 5.84-5.69 (1H, m, $CH_2CHCH$), 5.15 (1H, dd, *J* 17.6, 1.2 Hz, $CH_{2trans}CHCH$), 5.10 (1H, m, $CH_{2cis}CHCH$), 4.27-4.24 (1H, m, $CH_2CHCHOSi$), 3.76 (3H, s, $OCH_3$), 3.14-3.06 (1H, m, $CH_3CHCO$), 1.88 (3H, d, *J* 7.6 Hz, $CH_3CHCO$), 1.14 (3H, d, *J* 6.8 Hz, $CH_3CHC$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.01 (3H, s, $SiCH_3$), -0.00 (3H, s, $SiCH_3$); mixture of diasteromers $\delta_C$ (100.6 MHz, $CDCl_3$) 205.2, 200.2, 166.5, 164.9, 145.5, 143.9, 139.4, 139.2, 138.5, 136.8, 115.8, 115.8, 75.6, 75.5, 53.0, 52.9, 52.5, 49.2, 26.0, 18.4, 18.3, 16.0, 15.8, 13.7, 13.2, -4.1, - 5.0; HRMS (EI): $M^+$, found 326.1920. $C_{17}H_{30}O_4Si$ requires 326.1913.

*4.7. 2-(Trimethylsilyl)ethyl (4R,5S)-5-((tert-butyldimethylsilyl)oxy)-2-ethylidene-4-methyl-3-oxohept-6-enoate (**9c**)*

To a stirred solution of titanium (IV) chloride (1.02 mL, 9.30 mmol, 1.80 equiv) in THF (25 mL) at 0 °C was added freshly distilled acetaldehyde (1.30 mL, 23.3 mmol, 4.50 equiv), a solution of **8c** (2.00 g, 5.20 mmol) in THF (25 mL), and pyridine (1.46 mL, 18.1 mmol, 3.50 equiv). The reaction was allowed to warm up to RT and stirred for 3 h. The mixture was then quenched by a slow addition of water and extracted with $Et_2O$ (3 x 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was then purified by flash chromatography (95:5 PE/EtOAc) to furnish the product **9c** as a colorless oil (2.05 g, 96%) as an inseparable 1:1 mixture of diastereomers; $R_f$ (95:5 PE/EtOAc) 0.43; $n_{max}$ (liquid film) 2955 2857, 1764 1726, 1697, 1449, 1387, 1274, 1248, 1131, 1057 $cm^{-1}$; diastereomer A: $\delta_H$ (400 MHz $CDC1_3$) 7.02 (1H, q, *J* 7.3 Hz, $CH_3CHC$), 5.82 (1H, ddd, *J* 17.2, 10.4, 6.8 Hz, $CH_2CH(CHOSi)$), 5.21–5.04 (2H, m, $CH_2CH(CHOSi)$), 4.36–4.22 (3H, m, $CH_2CH(CHOSi)$ and $CH_2O$), 3.11 (1H, quint, *J* 7.0 Hz, $CH_3CHCHO$), 1.87 (3H, d, *J* 7.3 Hz, $CH_3$), 1.15 (3H, d, *J* 7.0 Hz, $CH_3$), 1.10–1.00 (2H, m, $CH_2Si$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (9H, s, $Si(CH_3)_3$), 0.04 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), diastereomer B: $\delta_H$ (400 MHz $CDC1_3$) 6.86 (1H, q, *J* 7.3 Hz, $CH_3CHC$), 5.75 (1H, ddd, *J* 17.2, 10.4, 6.8 Hz, $CH_2CH(CHOSi)$), 5.21–5.04 (2H, m, $CH_2CH(CHOSi)$), 4.36–4.22 (3H, m, $CH_2CH(CHOSi)$ and $CH_2O$), 3.11 (1H, quint, *J* 7.0 Hz, $CH_3CHCHO$), 1.98 (3H, d, *J* 7.3 Hz, $CH_3$), 1.14 (3H, d, *J* 7.0 Hz, $CH_3$), 1.10–1.00 (2H, m, $CH_2Si$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.05 (9H, s, $Si(CH_3)_3$), 0.04 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$); diasteromer A: $\delta_C$ (100.6 MHz, $CDCl_3$) 206.2, 166.6, 146.6, 140.7, 140.0, 117.1, 76.9, 65.0, 53.8, 27.4, 19.8, 19.0, 17.2, 15.2, 0.00, -2.7, -3.4 , diasteromer B: $\delta_C$ (100.6 MHz, $CDCl_3$) 201., 168.1 145.0, 140.8, 138.3, 117.2, 76.9, 64.9, 50.5, 27.4 , 19.7, 19.0, 17.3, 14.5, 0.00, -2.7, -3.4; HRMS (ESI): $M+Na^+$, found 435.2373. $C_{21}H_{40}O_4Si_2Na$ requires 435.2365.

*4.8. tert-Butyl (4R,5S)-5-((tert-butyldimethylsilyl)oxy)-2-ethylidene-4-methyl-3-oxohept-6-enoate (**9d**)*

To a vigorously stirred solution of titanium (IV) chloride (0.75 mL, 6.8 mmol, 1.80 equiv) in THF (25 mL) under nitrogen atmosphere at 0 °C were successively added freshly distilled acetaldehyde (0.98 mL, 17.2 mmol, 4.50), a solution of β-keto ester **8d** (1.3 g, 3.8 mmol) in THF (5.8 mL), and pyridine (1.1 mL, 13 mmol, 3.4 equiv). The reaction mixture was allowed to reach 20 °C and stirred for 2 h. It was then quenched with a slow addition of water and extracted with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The crude material was then purified by flash chromatography on silica gel (98:2 PE/$Et_2O$) to yield the product **9d** (900 mg, 63%) as an inseparable 1.6:1 mixture of diastereomers, only one diastereomer is described; $R_f$ (95:5 PE/$Et_2O$) 0.30; $[a]_D^{25}$ -44 (*c* 1.00, $CHCl_3$); $n_{max}$ (liquid film) 2955, 2930, 2858, 1722, 1697, 1643, 1462, 1392, 1367, 1249, 1151, 1070, 1026, 1005 $cm^{-1}$; $\delta_H$ (400 MHz $CDCl_3$) 6.94 (1H, q, *J* 7.6 Hz, $CH_3CHC$), 5.86-5.69 (1H, m, $CH_2CHCH$), 5.16 (1H, d, *J* 17.2 Hz, $CH_{2trans}CHCH$), 5.09 (1H, d, *J* 9.2 Hz, $CH_{2cis}CHCH$), 4.35-4.31 (1H, m, $(CH_2CH)CHOSi$), 3.14-3.07 (1H, m, $CH_3CHCO$), 1.85 (3H, d, *J* 7.2 Hz, $CH_3CHCO$), 1.46 (9H, s, $OC(CH_3)_3$), 1.14 (3H, d, *J* 6.8 Hz, $CH_3CHC$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); $\delta_C$ (100.6 MHz $CDCl_3$) δ 205.4, 164.1, 144.3, 138.8, 138.1, 115.7, 81.7, 75.5, 52.1, 28.0, 25.2, 18.2, 15.6, 12.9, −4.3, −4.9; HRMS (ESI): $M+Na^+$, found 391.2271. $C_{20}H_{36}O_4SiNa$ requires 391.2275.

*4.9. Methyl (3S,4R)-3-(tert-butyldimethylsilyloxy)-4-methyl-5-oxocyclopent-1-enecarboxylate (**5b**)*

Compound **9b** (2.10 g, 6.40 mmol) was dissolved in dry and degassed $CH_2Cl_2$ (128 mL), then Grubbs 2 catalyst was added (272 mg, 0.05 equiv). The solution was refluxed for 24 h. The mixture was then concentrated *in vacuo*. Purification by flash

chromatography on silica gel (90:10 PE/$Et_2O$) affording **5b** as a dark yellow oil (1.36 g, 75%); $R_f$ (80:20 PE/EtOAc) 0.7; $[a]_D^{25}$ + 79.0 (*c* 1.22, $CHCl_3$); $n_{max}$ (liquid film) 2958, 2890, 2857, 1760, 1733, 1628, 1475, 1463, 1393, 1370, 1330, 1307, 1258, 1217, 1160, 1110, 1074, 1054, 1023, 1003 $cm^{-1}$; $\delta_H$ (400 MHz $CDCl_3$) 7.94 (1H, d, *J* 2.0 Hz, (CHOSi)C<u>H</u>(C)), 4.49 (1H, dd, *J* Hz, ($CHCH_3$)C<u>H</u>OSi(CH)), 3.82 (3H, s, OC<u>H</u>$_3$), 2.43 (1H, qd, *J* 7.2, 2.8 Hz, (C<u>H</u>OSi)C<u>H</u>$CH_3$), 1.23 (3H, d, *J* 7.2 Hz, CHC<u>H</u>$_3$), 0.90 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.14 (3H, s, SiC<u>H</u>$_3$), 0.13 (3H, s, SiC<u>H</u>$_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 201.5, 167. 7, 162.2, 136.4, 67.3, 61.7, 53.7, 25.8, 18.2, 12.6, -4.5; HRMS (EI): $M^+$, found 284.1450. $C_{14}H_{24}O_4Si$ requires 284.1444.

*4.10. 2-(Trimethylsilyl)ethyl (3S,4R)-3-(tert-butyldimethylsilyloxy)-4-methyl-5-oxocyclopent-1-enecarboxylate (**5c**)*

Compound **9c** (2.0 g, 4.8 mmol) was dissolved in dry degassed $CH_2Cl_2$ (110 mL). Grubbs 2 catalyst (0.20 g, 0.24 mmol, 0.05 equiv) was added in one portion and the solution was heated under reflux for 24 h. An additional portion of Grubbs 2 catalyst was added (82 mg, 0.096 mmol, 0.02 equiv) and the mixture heated under reflux for a further 12 h. The solvent was removed under vacuum and the product purified by column chromatography (95:5 PE/$Et_2O$) furnishing the product **5c** as a pale brown oil (1.1 g, 61%).

To a solution of **9c** (90 mg, 0.35 mmol) and 2-(trimethylsilyl)ethanol (500 µL, 3.5 mmol, 10 equiv) in 500 µL of toluene, was added 7 mg of zinc oxide (0.07 mmol, 0.20 equiv). After 12 h of reflux, the mixture was concentrated *in vacuo*. Purification by flash chromatography (Petroleum ether/diethyl ether 8:2) gave 110 mg of pure compound **5c** (84%) as a viscous yellow oil; $R_f$ (80:20 PE/$Et_2O$) 0.60; $[a]_D^{25}$ +70.3 (*c* 1.22, $CHCl_3$); $n_{max}$ (liquid film) 2955, 2930, 2858, 1749, 1724, 1621, 1460, 1342, 1251, 1155, 1139, 1055, 1012 $cm^{-1}$; $\delta_H$ (400 MHz $CDC1_3$) 7.91 (1H, d, *J* 2.1 Hz, CC<u>H</u>(CHOSi)), 4.50 (1H, dd, *J* 3.0, 2.1 Hz, CHC<u>H</u>OSi), 4.34 (2H, td, *J* 8.3, 1.5 Hz, C<u>H</u>$_2$O), 2.44 (1H, qd, *J* 7.4, 3.0 Hz, C<u>H</u>$CH_3$), 1.25 (3H, d, *J* 7.4 Hz, CHC<u>H</u>$_3$), 1.13–1.04 (2H, m, C<u>H</u>$_2$Si), 0.92 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.16 (3H, s, SiC<u>H</u>$_3$), 0.15 (3H, s, SiC<u>H</u>$_3$), 0.06 (9H, s, Si(C<u>H</u>$_3$)$_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 201.0, 166.9, 162.0, 136.5, 76.4, 63.8, 52.8, 25.8, 18.2, 17.6, 12.6, -1.4, -4.5; HRMS (ESI): M+$Na^+$, found 393.1899. $C_{18}H_{34}O_4Si_2Na$ requires 393.1893.

*4.11. tert-Butyl (3S,4R)-3-(tert-butyldimethylsilyloxy)-4-methyl-5-oxocyclopent-1-enecarboxylate (**5d**)*

Compound **9d** (2.0 g, 5.4 mmol) was dissolved in dry degassed $CH_2Cl_2$ (110 mL). Grubbs 2 catalyst (0.23 g, 0.27 mmol, 0.05 equiv) was added in one portion and the solution was heated under reflux for 24 h. An additional portion of Grubbs 2 catalyst was added (0.23 g, 0.27 mmol, 0.05 equiv) and the mixture heated under reflux for a further 12 h. The solvent was removed under vacuum and the product purified by column chromatography (70:30 PE/$Et_2O$) furnishing the product **5d** as a pale brown oil (1.2 g, 68%).

To a solution of **5b** (500 mg, 1.76 mmol) and *tert*-butanol (775 µL, 17.6 mmol, 10 equiv) in 1.7 mL of toluene was added 29 mg of zinc oxide (0.35 mmol, 0.20 equiv). After 12 h of reflux, the mixture was concentrated *in vacuo*. Purification by flash chromatography (80:20 PE/$Et_2O$) gave pure compound **5d** (326 mg, 57%) as a viscous yellow oil; $R_f$ (80:20 PE/$Et_2O$) 0.50; $[a]_D^{25}$ +65.0 (*c* 1.22, $CHCl_3$); $n_{max}$ (liquid film) 2955, 2930, 2858, 1751, 1736, 1716, 1626, 1460, 1342, 1251, 1155, 1109, 1072, 1055, 1006 $cm^{-1}$; $\delta_H$ (400 MHz $CDC1_3$) 7.82 (1H, d, *J* 2.1 Hz, CC<u>H</u>(CHOSi)), 4.48 (1H, dd, *J* 3.1, 2.1 Hz, CHC<u>H</u>OSi), 2.42 (1H, qd, *J* 7.4, 3.1 Hz, C<u>H</u>$CH_3$), 1.54 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.25 (3H, d, *J* 7.4 Hz, CHC<u>H</u>$_3$), 0.93 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.17 (3H, s, SiC<u>H</u>$_3$), 0.15 (3H, s, SiC<u>H</u>$_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 201.0, 165.9, 160.9, 137.3, 82.2, 76.1, 52.6, 28.0, 25.6, 18.0, 12.4, -4.7, -4.7; HRMS (ESI): M+$Na^+$, found 349.1806. $C_{15}H_{28}O_4Si$ requires 349.1811.

*4.12. Methyl (1R,2R,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-2-((3aS,5R,6S,6aS)-2,2-dimethyl-4-oxo-6-(prop-1-en-2-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-5-yl)-4-methyl-5-oxocyclopentane-1-carboxylate (**3b**) and (**3b'**)*

To a solution of silyl enol ether **4** (563 mg, 2.1 mmol) in THF (1.4 mL) at 0 °C under nitrogen atmosphere was added a 1.4 M hexane solution of *n*-BuLi (4.7 mL, 6.6 mmol). The solution was then stirred at 0 °C for 1.5 h. This reaction solution was cooled down to -78 °C and was then cannulated dropwise to a solution of **5b** (200 mg, 0.70 mmol) and dried $ZnCl_2$ (105.3 mg, 0.77 mmol) in distilled DMF (5.6 mL) at -60 °C. The reaction was followed by TLC and after 45 min at -78 °C, all the starting material was consummed. It was quenched by addition of a mixture of THF/saturated aqueous $NH_4Cl$ 5:1 at -78 °C and was then allowed to warm until RT. The aqueous layers was extracted with $Et_2O$ three times. The combined organic layers extracted were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (80:20 PE/$Et_2O$) gave an inseparable 3:1 mixture of diastereomers **3b**/**3b'** as a viscous brown oil (101 mg, 30%); $R_f$ (1:1 PE/$Et_2O$) 0.4; $n_{max}$ (liquid film) 2935, 2934, 2859, 1756, 1727, 1657, 1463, 1378, 1325, 1254, 1220, 1150, 1115, 1060, 1025 $cm^{-1}$; $\delta_H$ (400 MHz $CDC1_3$) 4.99 (1H, s, C<u>H</u>$_2$C($CH_3$)CH, 4.95 (1H, s, C<u>H</u>$_2$C($CH_3$)CH), 4.55 (1H, dd, *J* 6.0, 0.8 Hz, (OCO)C<u>H</u>(CO)), 4.44 (1H, dd, *J* 6.2, 3.2 Hz, (OCO)C<u>H</u>(CH)), 3.86 (1H, t, *J* 8.4 Hz, (CH)C<u>H</u>(OSi)), 3.72 (3H, s, OC<u>H</u>$_3$), 3.27 (1H, d, *J* 10.4 Hz, ($O_2$C)C<u>H</u>(CO)(CH)), 3.16 (1H, ddd, *J* 11.6, 8.4, 3.2 Hz, (CH)$_2$C<u>H</u>(CHOSi)), 2.96 (1H, m, (CO)C<u>H</u>(CH)$_2$), 2.85 (1H, dd, *J* 12.8, 3.2 Hz, (CH)C<u>H</u>(C)), 2.42 (1H, dq, *J* 8.8, 7.2 Hz, (CHOSi)C<u>H</u>($CH_3$)), 1.86 (3H, s, $CH_2$C(C<u>H</u>$_3$)CH)), 1.47 (3H, s, OCC<u>H</u>$_3$), 1.34 (3H, s, OCC<u>H</u>$_3$), 1.17 (3H, d, *J* 6.8 Hz, CHC<u>H</u>$_3$), 0.87 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.09 (3H, s, SiC<u>H</u>$_3$), 0.07 (3H, s, SiC<u>H</u>$_3$); mixture of diastereomers, $\delta_C$ (100.6 MHz $CDC1_3$) 215.3, 212.4, 211.7, 208.5, 169.0, 168.7, 144.4, 143.8, 114.1, 113.3, 113.2, 112.9, 80.5, 79.5, 79.3, 78.9, 77.5, 75.5, 57.5, 57.2, 57.0, 56.5, 52.7, 52.6, 49.6, 49.4, 49.3, 47.6, 46.1, 45.5, 26.8, 26.0, 25.9, 25.3, 24.7, 22.4, 20.4, 18.2, 18.0, 13.3, 12.6, -3.4, -3.7, -3.9, -4.7; HRMS (EI): found 480.2554. $C_{25}H_{40}O_7Si$ requires 480.2543.

*4.13. 2-(Trimethylsilyl)ethyl (1R,2R,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-2-((3aS,5R,6S,6aS)-2,2-dimethyl-4-oxo-6-(prop-1-en-2-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-5-yl)-4-methyl-5-oxocyclopentane-1-carboxylate (**3c**) and (**3c'**)*

Silyl enol ether **4** (0.64 g, 2.4 mmol, 3.0 equiv) was dissolved in THF (3.5 mL) then cooled to 0 °C and a 2.1 M solution of *n*-BuLi in hexane (1.3 mL, 2.7 mmol, 3.3 equiv) was added dropwise. The reaction was stirred at 0 °C for 1 h then cooled to -78 °C and a mixture of $ZnCl_2$ (122 mg, 0.89 mmol, 1.10 equiv) and enone **5c** (300 mg, 0.81 mmol) in DMF (10 mL) was added over 30 min to the reaction mixture. The mixture was stirred at -78 °C for 1 h, -40 °C for 1 h, -20 °C for 1 h and 0 °C for 1h. The crude was then quenched with a saturated aqueous solution of ammonium chloride (10 mL) and diluted with THF (10 mL). The aqueous phase was extracted with $Et_2O$ (3 × 10 mL), the organic phases combined and dried over magnesium sulfate, filtered then concentrated under vacuum. The crude material was purified by column chromatography (95:5 PE/$Et_2O$) to furnish a 3:1 mixture of inseparable diastereomers of **3c**/**3c'** as a yellow oil (161 mg, 35%); $n_{max}$ (liquid film) 2954, 2932, 2862, 1754, 1725, 1697,

1641, 1462, 1375, 1147, 1041 $cm^{-1}$; $\delta_H$ (400 MHz $CDC1_3$) 4.99 (1H, t, *J* 1.4 Hz, C<u>H</u>$_2$C(CH$_3$)CH), 4.94 (1H, s, C<u>H</u>$_2$C(CH$_3$)CH), 4.60–4.52 (1H, m, (OCO)C<u>H</u>(CO)), 4.43 (1H, dd, *J* 6.4, 3.0 Hz, (OCO)C<u>H</u>(CH)), 4.28–4.13 (2H, m, $CH_2O$), 3.87 (1H, t, *J* 8.4 Hz, (CH)C<u>H</u>(OSi)), 3.25 (1H, d, *J* 10.4 Hz, ($O_2$C)C<u>H</u>(CO)(CH)), 3.16 (1H, ddd, *J* 10.4, 8.4, 3.2 Hz, (CH)$_2$C<u>H</u>(CHOSi)), 2.95 (1H, ddd, *J* 10.0, 3.2, 1.6 Hz, (CO)C<u>H</u>(CH)$_2$), 2.84 (1H, dd, *J* 10.0, 3.0 Hz, (CH)C<u>H</u>(C)), 2.42 (1H, dq, *J* 8.6, 7.0 Hz, (CHOSi)C<u>H</u>(CH$_3$)), 1.86 (3H, s, CH$_2$C(C<u>H</u>$_3$)CH)), 1.48 (3H, s, OCC<u>H</u>$_3$), 1.33 (3H, s, OCC<u>H</u>$_3$), 1.17 (3H, d, *J* 7.0 Hz, CHC<u>H</u>$_3$), 1.06–0.97 (2H, m, $CH_2Si$), 0.87 (9H, s, SiC(CH$_3$)$_3$), 0.09 (3H,s, SiCH$_3$), 0.08 (3H, s, SiCH$_3$), 0.02 (9H, s, Si(CH$_3$)$_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 211.6, 208.5, 168.7, 143.8, 114.0, 113.2, 80.4, 79.5, 77.3, 64.3, 56.7, 52.7, 49.7, 49.4, 45.5, 26.8, 26.0, 25.3, 20.5, 18.2, 17.4, 12.6, -1.4, -3.4, -3.7; HRMS (ESI): M+Na$^+$, found 589.2966. $C_{29}H_{50}NaO_7Si_2$ requires 589.2987.

*4.14. tert-Butyl (1R,2R,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-2-((3aS,5R,6S,6aS)-2,2-dimethyl-4-oxo-6-(prop-1-en-2-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-5-yl)-4-methyl-5-oxocyclopentane-1-carboxylate (**3d**)*

To a solution of silyl enol ether **4** (113 mg, 0.42 mmol, 3.0 equiv) in THF (280 mL) at 0 °C under nitrogen atmosphere was added dropwise a 1.6 M hexane solution of *n*-BuLi (275 µL, 0.44 mmol, 3.15 euiv). The resulting solution was then stirred at 0 °C for 1.5 h and then cooled to -78 °C for 30 min. In another flask, $ZnCl_2$ (21 mg, 0.15 mmol, 1.1 equiv) was melted with a heat gun under high vacuum. The flask was then allowed to cool back to RT, then a solution of **5d** (47 mg, 0.14 mmol) in distilled DMF (1.12 mL) was cannulated onto $ZnCl_2$. The solution obtained, after vigorous stirring, was cooled to -78 °C. The lithium enolate cooled down to -78 °C for 30 min was cannulated the solution containing $ZnCl_2$ and **5d** in DMF/THF. The reaction was monitored by TLC and after 2h at -78 °C, the temperature was slowly increased to -40 °C for 30 min then increased to -20 °C and kept at this temperature until all the starting material was consumed. The reaction was quenched by addition of a mixture of THF/saturated aqueous $NH_4Cl$ 5:1 at -20 °C and was then allowed to warm to RT. The aqueous layer was extracted with $Et_2O$ three times. The combined organic layers were washed with water to remove DMF and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (80:20 PE/$Et_2O$) gave only one diastereomer of product **3d** as a viscous colourless oil (47 mg, 55%); $R_f$ (50:50 PE/$Et_2O$) 0.6; $[a]_D^{25}$ -25.0 (*c* 1.0, $CHCl_3$); $n_{max}$ (liquid film) 2945, 2934, 2860, 1755, 1724, 1699, 1641, 1462, 1375, 1311, 1210, 1220, 1147, 1041 $cm^{-1}$; $\delta_H$ (400 MHz $CDCl_3$) 4.99 (1H, t, *J* 1.2 Hz, C<u>H</u>$_2$C(CH$_3$)), 4.95 (1H, m, C<u>H</u>$_2$C(CH$_3$)), 4.57 (1H, dd, *J* 6.0, 1.2 Hz, (OCO)C<u>H</u> (CH)), 4.43 (1H, dd, *J* 6.0, 2.8 Hz, (OCO)C<u>H</u> (CH)), 3.83 (1H, t, *J* 8.6 Hz, (CH)C<u>H</u>(OSi)), 3.16 (1H, ddd, *J* 18.0, 10.0, 3.2 Hz, (CH)$_2$C<u>H</u>(CHOSi)), 3.11 (1H, d, *J* 10.0 Hz, (CH)$_2$C<u>H</u>(CHOSi)), 2.96 (1H, ddd, *J* 10.0, 2.8, 1.6 Hz, (CO)C<u>H</u>(CH)$_2$), 2.80 (1H, dd, *J* 10.0, 2.8 Hz, (CH)C<u>H</u>(C)(CHO)), 2.43 (1H, dq, *J* 8.8, 7.0 Hz, (CHOSi)C<u>H</u>(CH$_3$)), 1.86 (3H, s, CH$_2$C(C<u>H</u>$_3$)CH), 1.46 (9H, s, OCH(C<u>H</u>$_3$)$_3$), 1.43 (3H, s, OCC<u>H</u>$_3$), 1.34 (3H, s, OCC<u>H</u>$_3$), 1.16 (3H, d, *J* 7.2 Hz, CHC<u>H</u>$_3$), 0.87 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.09 (3H, s, SiC<u>H</u>$_3$), 0.07 (3H, s, SiC<u>H</u>$_3$); $\delta_C$ (100.6 MHz $CDCl_3$) 212.2, 209.5, 168.2, 145.4, 139.6, 118.8, 82.8, 80.1, 79.8, 74.5, 55.5, 53.3, 50.2, 46.8, 44.8, 27.2, 26.0, 25.8, 23.4, 17.7, 13.3, 10.6, −3.9, –4.3; HRMS (EI): M$^+$, found 522.7336. $C_{28}H_{46}O_7Si$ requires 522.7330.

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**References and notes**

1. Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3258.
2. Kobayakawa, Y.; Mori, Y.; Okajima, H.; Terada, Y.; Nakada, M. *Org. Lett.* **2012**, *14*, 2086.
3. (a) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560; (b) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, 61,353; (c) Iqbal, M.; Black, R. J. G.; Winn, J.; Reeder, A. T.; Blake, A. J.; Clarke, P. A. *Org. Biomol. Chem.* **2011**, *9*, 5062.
4. (a) Stellfeld, T.; Bhatt, U.; Kalesse, M. *Org. Lett.* **2004**, *6*, 3889; (b) Stelmakh, A.; Stellfeld, T.; Kalesse, M. *Org. Lett.* **2006**, *8*, 3485; (c) Clarke, P. A.; Cridland, A. P. *Org. Lett.* **2005**, *7*, 4221; (d) Clarke, P. A.; Cridland, A. P.; Rolla, G. A.; Iqbal, M.; Bainbridge, N. P.; Whitwood, A. C.; Wilson, C. *J. Org. Chem.* **2009**, *74*, 7812; (e) James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K. *J. Org. Chem.* **2005**, *70*, 7985.
5. Toueg, J.; Prunet, J. *Org. Lett.* **2008**, *10*, 45.
6. Toueg, J. Ph.D. Dissertation, Ecole Polytechnique (Palaiseau), 2007.
7. Nicolaou, K. C.; Estrada, A.A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1378.
8. Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715.
9. Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.
10. Kwan, E. E.; Evans, D. A. *Org. Lett.* **2010**, *12*, 5124.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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