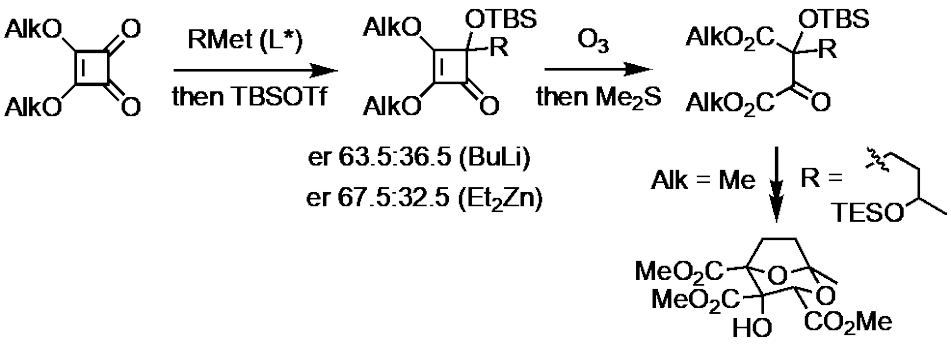
AlkO
O
AlkO
O
RMet (L*)
then TBSOTf
AlkO
OTBS
R
AlkO
O
$O_3$
then $Me_2S$
$AlkO_2C$
OTBS
R
$AlkO_2C$
O
er 63.5:36.5 (BuLi)
er 67.5:32.5 ($Et_2Zn$)
Alk = Me
R =
TESO
$MeO_2C$
$MeO_2C$
O
O
HO
$CO_2Me$

# Squarate desymmetrisation–ozonolysis as an approach to β-substituted-α-ketosuccinates and squalestatin synthesis

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A contribution to the Steve Davies honor issue; recognising his many achievements and long service to the Tetrahedron journals, especially Tetrahedron: Asymmetry.

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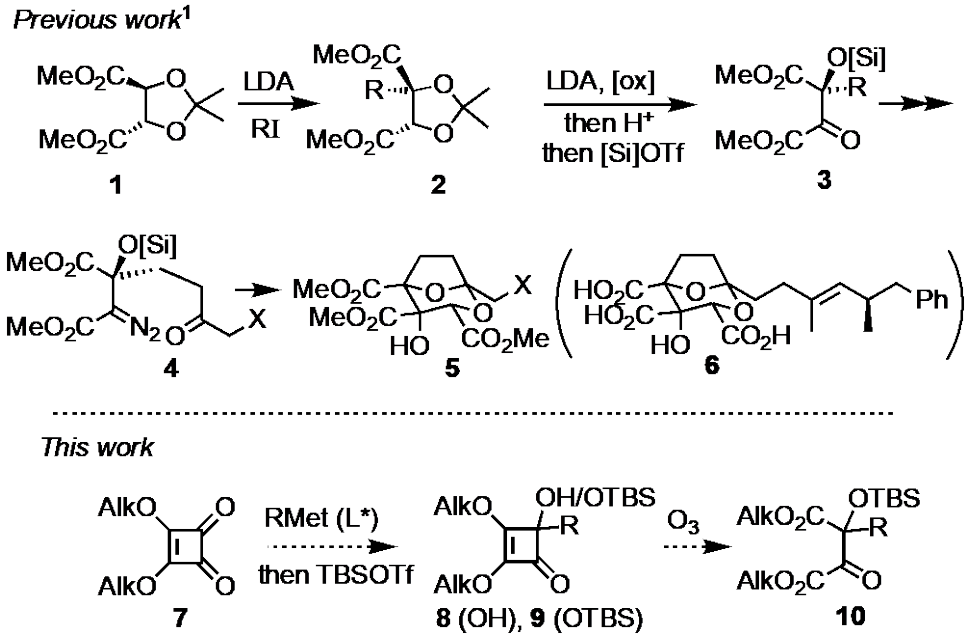
Abstract
Silylated tertiary alcohols from 1,2-addition of alkyllithiums to dialkyl squarates undergo alkene ozonolysis to give β-substituted-α-keto-β-(silyloxy)succinates. With 3-(triethylsilyloxy)butyllithium the methodology was applied to the 2,8-dioxabicyclo[3.2.1]octane core of the squalestatins. Enantioselective 1,2-addition to di-*tert*-butyl squarate using butyllithium or diethylzinc / Ti(*i*PrO)$_4$ in the presence of chiral ligands (such as bisoxazolines or camphorsulfonamides, respectively) gave the corresponding tertiary alcohols in up to 67.5:32.5 er.

Keywords: Squarate, Ozonolysis, Succinate, Organolithium, Organozinc, Squalestatin

## 1. Introduction

In our studies towards the squalestatins (eg, 6,7-dideoxysqualestatin H5 (**6**), Scheme 1), we have shown that β-substituted-α-keto-β-(silyloxy)succinates **3** can be precursors to diazoketones **4** for subsequent carbonyl ylide formation–cycloaddition and rearrangement chemistry to give the 2,8-dioxabicyclo[3.2.1]octane core **5** of the natural products.[1-3] Our approach to substituted succinates **3** involved stereoselective alkylation of tartrate acetonide **1**, then hydroxylation and hydrolysis of the alkylated tartrate **2**. Here, we report a squarate desymmetrisation strategy to α-

keto-β-(silyloxy)succinates **10**, by nucleophilic addition to a dialkyl squarate **7** to give a tertiary alcohol **8**, followed by ozonolysis of the corresponding silyl ether **9**.



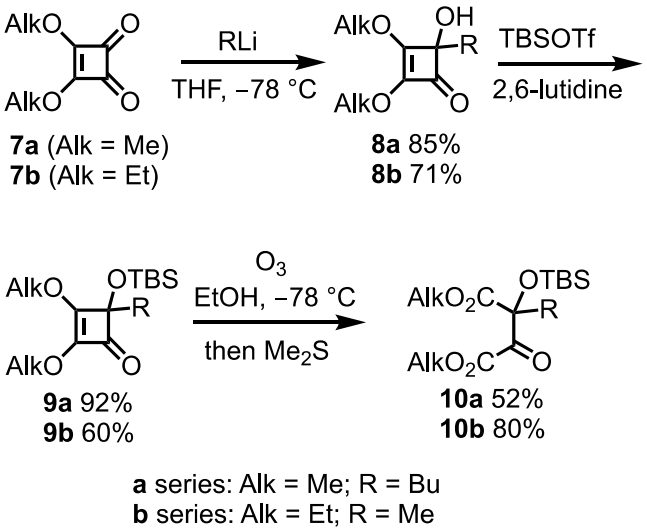

Scheme 1

## 2. Results and Discussion

Squarates and their simple derivatives possess a rich history of applications in synthesis,[4-7] but to our knowledge there are no examples of their oxidative cleavage to (α-keto) succinates. However, encouragement for this transformation is found in several reports on the conversion of substituted cyclobutenes to succinic acids and esters, typically using $KMnO_4$[8,9] or ozone,[10-13] following the first example (1,2-dibromocyclobutene to succinic acid) by Willstätter and Bruce from more than a century ago.[8]

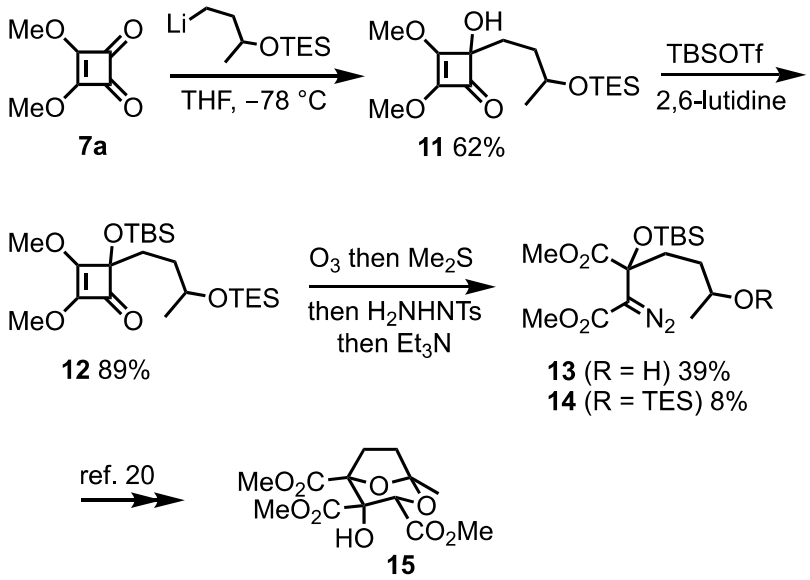
The dialkyl squarates **7** used in this work (Alk = Me, Et, *t*-Bu) are all commercially available, but were conveniently prepared from considerably less expensive squaric acid, following the esterification procedure of Moore and co-workers.[14,15] Regioselectivity in the addition of organometallics to dialkyl squarates is known to strongly depend on the metal,[4] with Grignard reagents typically reacting in a "conjugate" (1,4-)sense,[4,16] whereas alkyllithiums generally proceed by the currently desired 1,2-addition pathway.[4,7,17] Simple substrates **9a,b** (Scheme 2) to

examine the viability of the ozonolysis approach to α-ketosuccinates were obtained from dimethyl and diethyl squarate using BuLi and MeLi respectively, followed by silylation of the known alcohols **8a,b**.[18,19]



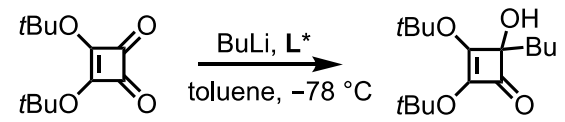

Scheme 2

In the event, squarate silyl ethers **9a,b** underwent ozonolysis to deliver, following addition of $Me_2S$ and purification on florisil®,[2] α-ketosuccinates **10a,b** in 52% and 80% yields, respectively (Scheme 2). Progress of the ozonolysis could be followed by IR (bands at 1770 $cm^{-1}$ and 1640 $cm^{-1}$ replaced by one at 1740 $cm^{-1}$). To demonstrate that the methodology could be applied to the 2,8-dioxabicyclo[3.2.1]octane core of the squalestatins, a triethylsilyloxy-substituted butyl side-chain was introduced onto the squarate system (**7a**→ **11**, Scheme 3). Following ozonolysis of silyl ether **12**, the resulting sensitive α-ketosuccinate was best taken directly via the hydrazone to the corresponding diazodiketoester **13** (39% over 3 steps).[3] A small amount of the diazodiketoester **14** still retaining the TES group was also isolated (8%). Both diazodiketoesters **13** and **14** have previously been transformed into the 2,8-dioxabicyclo[3.2.1]octane **15**, by oxidation to the 1,5-diazoketone, Rh(II)-induced tandem carbonyl ylide formation–cycloaddition with methyl glyoxylate and acid-catalysed rearrangement.[20]

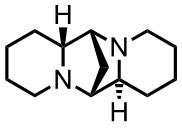



Scheme 3

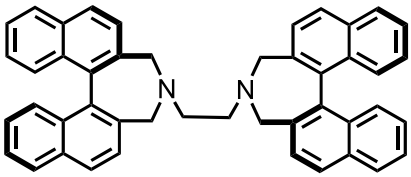
Having shown that dialkyl squarates could be transformed into α-ketosuccinates (**7**→**10**, Scheme 1), we considered squarate addition by an organolithium in the presence of a chiral ligand (L*) as a potential asymmetric variation towards these systems. As mentioned above, the racemic 1,2-monoaddition of organolithiums to squarates is well known[4] and examples of (weakly) diastereoselective addition of chiral alkenyllithiums have also been noted by Paquette.[7] However, while enantioselective addition of organolithiums to carbonyl compounds (aldehydes in particular, but also ketones) have been reported with a variety of chiral ligands,[21,22] to our knowledge no enantioselective additions to squarates by organolithiums (or any organometallics) exist. The racemic tertiary alcohol **16** from butyllithium addition to di-*tert*-butyl squarate **7c** (Scheme 4) could be resolved (by chiral HPLC) and this process was studied in the presence of representative chiral ligands (40-94% yields, in toluene unless otherwise indicated).



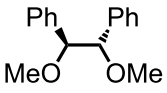

**7c** **16**



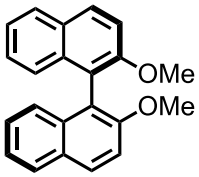
**L1**
(**16** er 54:46)



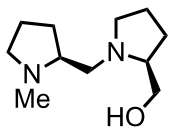
**L2**
(**16** er 50:50, in $Et_2O$)



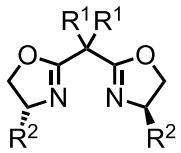
**L3**
(**16** er 55:45)



**L4**
(**16** er 50:50)



**L5**
(**16** er 56:44)



**L6** ($R^1$ = *i*Bu, $R^2$ = *i*Pr)
(**16** er 55:45; 63.5:36.5 with 3 equiv **L6**)

**L7** ($R^1$ = Et, $R^2$ = *i*Pr)
(**16** er 55:45)

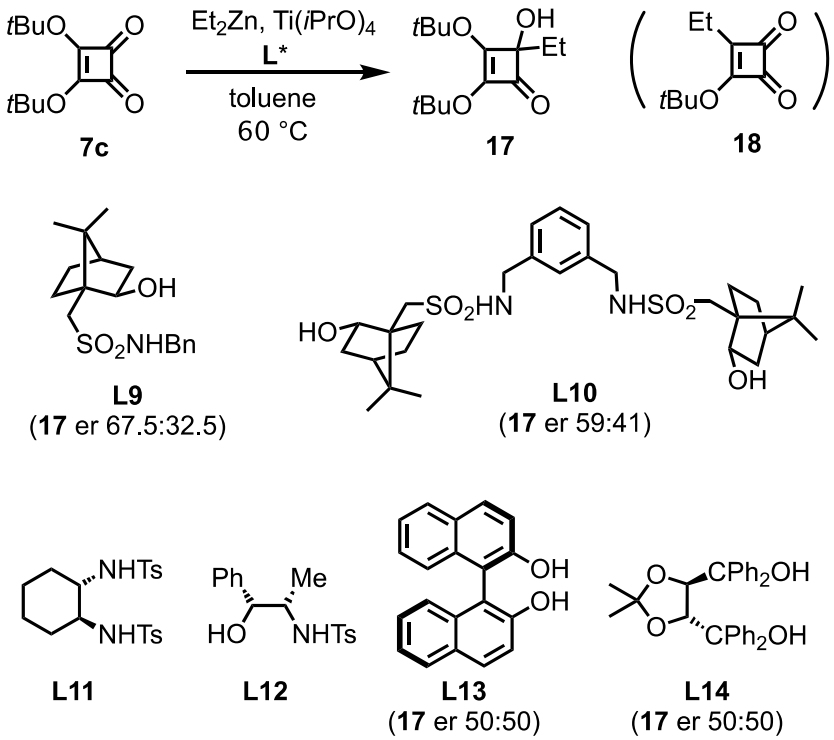
**L8** ($R^1$ = Me, $R^2$ = *t*Bu)
(**16** er 54:46)

Scheme 4

No or low enantioselectivities in the formation of alcohol **16** were observed with the diamines sparteine **L1** (er 54:46; same er in ether) or **L2**[23] (racemic, in ether), diethers **L3** (er 55:45) or **L4** (racemic), and diaminoalcohol **L5** (er 56:44). Of the ligands screened, bisoxazoline **L6** displayed the highest (although still modest) enantioselectivity (er 63.5:36.5), however in low conversion (25% yield). Also, the latter result was observed with 3 equiv of **L6** relative to BuLi; equimolar quantities gave a lower er (55:45), similar to other bisoxazolines **L7**-**8**.

The ligands were used stoichiometrically or in excess,[24] since the ligand-free reaction was complete within 10 min, whereas there was no significant conversion after this time in the presence of **L2** or **L6**.

Given the low asymmetric induction observed using BuLi with chiral ligands, we considered alternative alkyl metals and focused on organozincs. Although the latter have previously been unexplored with squarates, dialkylzincs have shown good results in enantioselective additions to ketones,[25-27] following the first report by Ramón and Yus[28,29] using titanium alkoxide species as promoter[30] and camphorsulfonamides as chiral ligands.[31] Reaction between di-*tert*-butyl squarate **7c** and $Et_2Zn$ (3 equiv) in the presence of Ti(*i*PrO)$_4$ (1.7 equiv) and ligands **L9** or **L10** (50 mol %) in toluene at rt for 3 days (Scheme 5) mainly returned unreacted **7c** (~80%); however, the desired 1,2-mono-addition product, ethylated squarate **17** (ers 65.5:34.5, 53.5:46.5, respectively) dominated the converted material with only traces (<2%) of known[32,33] 1,4-addition product **18** being detected. At 60 °C with ligands **L9** or **L10** (20 mol %), significantly greater conversion (~60%) was observed, with the er for **17** using **L9** being unchanged from that at rt, and slightly higher for **L10** (59:41). As other ligands known to induce enantioselective addition of $Et_2Zn$ to aldehydes either gave no (**L11**-**12**) or racemic (**L13**-**14**) ethylated squarate **17**, then attention focused on variation of the reaction conditions with camphorsulfonamide **L9** at 60 °C. Higher (60 mol %) or lower (5 mol %) chiral catalyst loadings gave ers for **17** of 67.5:32.5 and 59.5:40.5. Equimolar quantities of $Et_2Zn$ and Ti(*i*PrO)$_4$ (1, 2 or 3 equivs) led to poorer conversions and ers for **17** below 55:45. Switching the Lewis acid to Cu(OTf)$_3$ was ineffective and no asymmetric induction was observed in the absence of Ti(*i*PrO)$_4$. Finally, with **L9** at 60 °C for 20 h the reaction was shown to be scale dependent: at 0.2 mmol scale, ethylated squarate **17** was isolated in only 5% yield (er 65.5:34.5), whereas at 3 mmol scale a 51% yield of **17** (er 58:42) was obtained. Instability of the ethylated squarate **17** on silica (67% was recovered on exposure to $SiO_2$ for 1.5 h) could be contributing to the variation in isolated yields.




Scheme 5

## 3. Conclusion

In summary, a new route to β-substituted-α-keto-β-(silyloxy)succinates has been developed, from alkene ozonolysis of silyl ethers of tertiary alcohols obtained by 1,2-addition of alkyllithiums to (commercially available) dialkyl squarates **7**. The utility of the methodology towards squalestatin synthesis was demonstrated using 3-(triethylsilyloxy)butyllithium and dimethyl squarate, followed after ozonolysis by α-keto to α-diazo functional group interconversion. Using di-*tert*-butyl squarate with BuLi or $Et_2Zn$ / Ti(*i*PrO)$_4$ in the presence of chiral ligands (such as bisoxazolines or camphorsulfonamides, respectively) gives the corresponding tertiary alcohols in up to 67.5:32.5 er. While the asymmetric induction is currently modest, these results constitute the first enantioselective desymmetrising 1,2-additions to squarates and it is also noteworthy that the asymmetric addition of $Et_2Zn$ displays good selectivity for 1,2-addition.

## 4. Experimental Section

### 4.1. General

All reactions requiring anhydrous conditions were carried out in flame–dried glassware under an atmosphere of nitrogen (or argon), the later having been passed through a column of calcium chloride and silica gel. $Et_3N$ and 2,6-lutidine were distilled under nitrogen from $CaH_2$. BuLi in hexanes was titrated by adding a solution of 2-propanol (1.0 M in toluene with 0.2% of 1,10–phenanthroline) slowly to a solution of BuLi in toluene until the end-point: a change of colour from clear to red then yellow. Commercial starting materials were used without further purification, unless otherwise stated. Light petroleum 40–60 °C was used in column chromatography, which was carried out using silica gel (VWR chemicals, BDH), and monitored by TLC (Merck 60 F254) plates. TLC plates were viewed using ultraviolet light (λmax = 254/365 nm) and by immersion in $KMnO_4$ or anisaldehyde stains, followed by heating. Infrared spectra were obtained using a PerkinElmer FT–IR spectrometer (Universal ATR Sampling Accessory) with absorption maxima quoted in wavenumbers ($cm^{-1}$). Peaks are described as broad (br), weak (w), medium (m) and strong (s). Nuclear magnetic resonance ($^1H$ NMR, $^{13}C$ NMR) spectra were recorded in $CDCl_3$. Chemical shifts are quoted in parts per million (ppm). The splittings are quoted as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Proton coupling constants (*J*) are reported to the nearest 0.5 Hz. Specific rotation values are given in $10^{-1}$ deg $cm^2$ $g^{-1}$. Concentrations (*c*) are given in $g/cm^3$. Low resolution mass spectra were obtained using electrospray ionisation (ESI). High resolution mass spectra were obtained by ESI using tetraoctylammonium bromide or sodium dodecyl sulfate as the lock mass; values are quoted as ratio of mass to charge (*m*/*z*) in Daltons. Chiral stationary phase HPLC was performed using a Daicel Chiralcel OD column (4.6 mm × 250 mm) on a Gilson system with 712 Controller Software and a 118 UV/VIS detector set at 254 nm. Retention times for major ($t_R$mj) and minor ($t_R$mn) enantiomers are given in min.

4.2. Experimental procedures and data for synthetic compounds

**4.2.1. 4-Butyl-4-(*tert*-butyldimethylsilyloxy)-2,3-dimethoxycyclobut-2-enone 9a**

TBSOTf (230 µL, 1.0 mmol) was added to 2,6-lutidine (0.17 mL, 1.46 mmol) in $CH_2Cl_2$ (770 µL) at 0 °C. After 30 min, a solution of tertiary alcohol **8a**[18] (100 mg, 0.50 mmol) in $CH_2Cl_2$ (770 µL) was added at 0 °C *via* cannula. After 30 min, water was added (1 mL) and the reaction mixture extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic

layers were washed with brine (10 mL), dried ($MgSO_4$), evaporated under reduced pressure and the residue purified by column chromatography (2% ether in light petroleum) to give silyl ether **9a** (146 mg, 92%) as a yellow oil. $R_f$ 0.30 (5% ether in light petroleum); $\nu_{max}/cm^{-1}$ 2956 s, 2932 s, 2858 s, 1774 s (C=O), 1643 s (C=C), 1466 s, 1341 m; $\delta_H$(400 MHz) 4.09 (3H, s, $OCH_3$), 3.93 (3H, s, $OCH_3$), 1.84-1.67 (2H, m, $CCH_2$), 1.37-1.25 (4H, m, 2 x $CH_2$), 0.91 (3H, t, *J* 7, $CH_3$), 0.86 (9H, s, $SiCMe_3$), 0.04 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$); $\delta_C$(100 MHz) 187.4 (C=O), 169.0 (*C*=C), 133.5 (C=*C*), 88.2 (quat. C), 59.9 ($OCH_3$), 58.4 ($OCH_3$), 34.5 (C*C*$H_2$), 27.3 ($CH_2$), 25.8 (SiC(*C*$H_3$)$_3$), 23.0 ($CH_2$), 18.1 (Si*C*($CH_3$)$_3$), 14.1 ($CH_3$), −3.5 (2 x $SiCH_3$); ***m/z*** ($Cl^+$) 315 (M + $H^+$, 2), 314 (M, 4), 183 (M − OTBS, 100); HRMS [M + $H^+$] found: 315.1996, $C_{16}H_{31}O_4Si$ requires 315.1992.

### 4.2.2. 2,3-Diethoxy-4-methyl-4-(*tert*-butyldimethylsilyloxy)cyclobut-2-enone 9b

Following the above silylation procedure for **9a**, but using TBSOTf (2.6 g, 9.8 mmol), 2,6-lutidine (1.58 g, 14.7 mmol) in $CH_2Cl_2$ (7.5 mL) and addition of tertiary alcohol **8b**[19] (4.9 mmol) in $CH_2Cl_2$ (7.5 mL), gave after purification by column chromatography (5% $Et_2O$ in light petroleum) silyl ether **9b** (0.882 g, 60%). $R_f$ 0.65 (50% $Et_2O$ in light petroleum); $\nu_{max}/cm^{-1}$ 2929 m, 1772 m, 1638 s, 1473 w; $\delta_H$(200 MHz) 4.40-4.25 (2H, m, OC*H*$_2$Me), 4.15 (2H, q, *J* 7, OC*H*$_2$Me), 1.42-1.31 (6H, m, $OCH_2$*Me* and C(OTBS)*Me* ), 1.21 (3H, t, *J* 7, $OCH_2$*Me*), 0.82 (9H, s, $SiCMe_3$), 0.05 (3H, s, SiMe), 0.01 (3H, s, SiMe); $\delta_C$(50 MHz) 187.4 (C=O), 169.2 (C=C), 131.5 (C=C), 84.6 (quat. C), 68.5 ($OCH_2$), 66.2 ($OCH_2$), 25.3 (SiC*Me*$_3$), 20.6 (Me), 17.6 (SiC), 15.3 (Me), 14.9 (Me), –3.9 ($SiMe_2$); ***m/z*** (EI) 300 ($M^+$, 10%), 243 (10), 83 (85), 75 (50), 73 (80); HRMS [$M^+$] found: 300.1759, $C_{15}H_{28}O_4Si$ requires 300.1757.

### 4.2.3. Dimethyl 2-butyl-2-(*tert*-butyldimethylsilyloxy)-3-oxosuccinate 10a

A solution of silyl ether **9a** (168 mg, 0.54 mmol) in EtOH (8.20 mL) was ozonised at −78 °C. After 30 min the reaction mixture was flushed with argon and then $Me_2S$ (78 μL, 1.07 mmol) added. After 1 h at −78 °C, the mixture was warmed to room temperature and stirred overnight. Water (8 mL) was then added and the reaction mixture extracted with $CH_2Cl_2$ (3 x 7 mL). The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and the residue purified by column chromatography (10% ether in light petroleum on florisil) to give α-ketosuccinate **10a**

(98 mg, 52%) as a pale yellow oil. $R_f$ 0.50 (10% ether in light petroleum); $\nu_{max}/cm^{-1}$ 2958 s, 2859 s, 1742 s (C=O), 1464 m, 1437 m, 1362 w, 1258 s, 1174 s, 1091 s, 840 s, 782 s, 700 w; $\delta_H$(400 MHz) 3.85 (3H, s, $OCH_3$), 3.77 (3H, s, $OCH_3$), 2.11-1.92 (2H, m, $CCH_2$), 1.38-1.18 (4H, m, 2 x $CH_2$), 0.90 (3H, t, *J* 7, $CH_3$), 0.87 (9H, s, $SiCMe_3$), 0.16 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$); $\delta_C$(100 MHz) 190.3 (C=O), 169.8 ($CO_2Me$), 162.7 ($CO_2Me$), 84.0 (quat. C), 52.7 (2 x $OCH_3$), 36.0 ($CCH_2$), 25.7 ($SiC(CH_3)_3$), 25.1 ($CH_2$), 22.7 ($CH_2$), 18.7 ($SiC(CH_3)_3$), 13.8 ($CH_2CH_3$), −3.2 ($SiCH_3$), −3.4 ($SiCH_3$); *m/z* ($CI^+$) 364 ($M + NH_4^+$, 100), 347 ($M + H^+$, 100), 289 (10); HRMS [$M + NH_4^+$] found: 364.2141, $C_{16}H_{34}NO_6Si$ requires 364.2155.

**4.2.4. Diethyl 2-methyl-3-oxo-2-(*tert*-butyldimethylsilyloxy)succinate 10b**

Following the above ozonolysis procedure for **10a**, but using silyl ether **9b** (100 mg, 0.33 mmol) in EtOH (5 mL) then $Me_2S$ (40.2 mg, 0.66 mmol) gave after column chromatography (20% $Et_2O$ in light petroleum on florisil) α-ketosuccinate **10b** (88.5 mg 80%). $R_f$ 0.50 (10% ether in light petroleum); $\nu_{max}/cm^{-1}$ 2956 m, 2930 m, 1742 s; $\delta_H$(200 MHz) 4.11-4.30 (4H, m, $OCH_2Me$), 1.55 (3H, s, CMe), 1.31-1.11 (6H, m, 2 x $CH_2Me$), 0.79 (9H, s, $SiCMe_3$), 0.15 (3H, s, SiMe), 0.10 (3H, s, SiMe); $\delta_C$(50 MHz) 189.4 (CO), 170.0 ($CO_2Et$), 162.3 ($CO_2Et$), 80.4 (quat. C), 62.1 ($OCH_2$), 61.8 ($OCH_2$), 25.2 ($SiC(Me)_3$), 22.1 (Me), 18.0 (SiC), 13.6 (2 x Me), –3.3 (SiMe), –3.5 (SiMe); *m/z* (EI); 333 ($M + H^+$, 40%), 318 (15), 317 (100), 307 (15), 289 (55); HRMS [$M + H^+$] found: 333.1738, $C_{15}H_{29}O_6Si$ requires 333.1733).

**4.2.5. 2,3-Dimethoxy-4-hydroxy-4-(3-(triethylsilyloxy)butyl)cyclobut-2-enone 11**

A solution of triethyl((4-iodobutan-2-yl)oxy)silane[34] (486 mg, 1.60 mmol) in $Et_2O$ (3.20 mL) was cooled to −78 °C and *t*-BuLi (1.70 M in pentane, 1.90 mL, 3.20 mmol) was added dropwise. After 1 h at −78 °C, the reaction mixture was warmed to room temperature for 1 h then transferred *via* cannula to a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (**7a**) (200 mg, 1.41 mmol) in THF (14 mL) at −78 °C. After 4 h at −78 °C, water (5 mL) was added and the reaction mixture extracted with $Et_2O$ (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (30% ether in light petroleum with ~1% $Et_3N$) gave alkylated squarate **11** (288 mg, 62%; 1:1 dr) as a straw-coloured oil. $R_f$ 0.25 (50% ether in light petroleum); $\nu_{max}/cm^{-1}$ 3316 br (OH),

2956 s, 2878 s, 2251 w, 1771 s (C=O), 1627 s, 1469 s; $\delta_H$(400 MHz) 4.12 (6H, s, 2 x $OCH_3$), 4.08 (2H, bs, OH), 3.95 (6H, s, 2 x $OCH_3$), 3.92-3.88 (2H, m, 2 x CH), 2.04-1.86 (4H, m, 2 x $CCH_2$), 1.73-1.68 (4H, m, 2 x $CH_2$), 1.18 (6H, d, *J* 8, 2 x $CH_3$), 0.96 (18H, t, *J* 8, 2 x $SiCH_2CH_3$), 0.65-0.59 (12H, q, 2 x $SiCH_2CH_3$); $\delta_C$(100 MHz) 187.5 (2 x C=O), 168.8 (2 x *C*=C), 133.3 (2 x C=*C*), 85.6 (2 x quat. C), 68.6 (2 x CH), 60.2 (2 x $OCH_3$), 58.6 (2 x $OCH_3$), 34.0 (2 x $CH_2$), 29.3 (2 x $CCH_2$), 23.1 (2 x $CH_3$), 6.9 (6 x $SiCH_2CH_3$), 4.9 (6 x $SiCH_2CH_3$); *m/z* ($EI^+$) 331 (M + $H^+$, 20), 330 (M, 100), 301 (25); HRMS [$M^+$] found: 330.1875, $C_{16}H_{30}O_5Si$ requires 330.1863.

### 4.2.6. 4-(*tert*-Butyldimethylsilyloxy)-2,3-dimethoxy-4-(3-(triethylsilyloxy)butyl)cyclobut-2-enone 12

Following the above silylation procedure for silyl ether **9a**, but using TBSOTf (1.64 mL, 7.10 mmol), 2,6-lutidine (1.25 mL, 11.0 mmol) in $CH_2Cl_2$ (5.5 mL) and addition of alkylated squarate **11** (1.18 g, 3.60 mmol) in $CH_2Cl_2$ (5.5 mL), gave after purification by column chromatography (1% ether in light petroleum) silyl ether **12** (1.41 g, 89%, 1:1 dr) as a colourless oil. $R_f$ 0.41 (2% ether in light petroleum); $\nu_{max}/cm^{-1}$ 2956 s, 2878 s, 1774 m (C=O), 1644 s, 1466 s, 1342 s; $\delta_H$(400 MHz) 4.06 (6H, s, 2 x $OCH_3$), 3.90 (6H, s, 2 x $OCH_3$), 3.80-3.70 (2H, m, 2 x CH), 1.86-1.66 (4H, m, 2 x $CCH_2$), 1.54-1.35 (4H, m, 2 x $CH_2$), 1.10 (6H, d, *J* 6, 2 x $CH_3$), 0.92 (18H, t, *J* 8, 2 x $SiCH_2CH_3$), 0.84 (18H, s, $SiCMe_3$), 0.56 (12H, q, *J* 8, 2 x $SiCH_2CH_3$), 0.09 (6H, s, 2 x $SiCH_3$), 0.06 (6H, s, 2 x $SiCH_3$); $\delta_C$(100 MHz) 187.2, 187.1 (2 x C=O), 170.0, 168.8 (2 x *C*=C), 133.5, 133.4 (2 x C=*C*), 88.1, 87.9 (2 x quat. C), 68.4, 68.3 (2 x CH), 59.8, 59.7 (2 x $OCH_3$), 58.3 (2 x $OCH_3$), 35.0, 34.8 ($CH_2$), 31.1, 31.0 (2 x $CCH_2$), 25.7, 25.7 (2 x $SiC(CH_3)_3$), 23.9, 23.7 (2 x $CH_3$), 18.1, 18.1 (2 x $SiC(CH_3)_3$), 6.9, 6.9 (6 x $SiCH_2CH_3$), 5.0 (6 x $SiCH_2CH_3$), –3.5 (4 x $SiCH_2CH_3$); *m/z* ($EI^+$) 445 (M + $H^+$, 15), 313 (M – OTBS, 100), 181 (20), 132 (20), 52 (18); HRMS [M + $H^+$] found: 445.2799, $C_{16}H_{34}N_3O_5Si$ requires 445.2800.

### 4.2.7. Dimethyl 2-(*tert*-butyldimethylsilyloxy)-3-diazo-2-(3-hydroxybutyl) succinate 13 and dimethyl 2-(*tert*-butyldimethylsilyloxy)-3-diazo-2-(3-(triethylsilyloxy)butyl) succinate 14

Following the above ozonolysis procedure for α-ketosuccinate **10a**, but using silyl ether **12** (140 mg, 0.30 mmol) in $CH_2Cl_2$ (4 mL) then $Me_2S$ (46 μL, 0.63 mmol) gave the crude α-ketosuccinate (133 mg) as a colourless oil. The crude α-ketosuccinate and *p*-$TsNHNH_2$ (78 mg, 0.42 mmol) in THF (2 mL) were heated to reflux After 24 h, the reaction mixture was evaporated under reduced pressure to give the crude hydrazone (221 mg). A mixture of $CH_2Cl_2$:$Et_3N$ (5 mL, 2:1 (v/v)) was added to the crude hydrazone. After 4 h at rt, the reaction mixture was evaporated under reduced pressure, then passed through a short column of silica (5% ether in light petroleum). First eluted diazodiketoester **14**[20] (12 mg, 8% from silyl ether **12**). $R_f$ 0.28 (5% ether in light petroleum); $\nu_{max}/cm^{-1}$ 2958 s, 2097 s (C=$N_2$), 1711 s (C=O), 1438 m, 1260 s, 1017 s; $\delta_H$(400 MHz) 3.81-3.73 (2H, m, 2 x CH), 3.75 (6H, s, 2 x $OCH_3$), 3.74 (6H, s, 2 x $OCH_3$), 2.14-1.80 (4H, m, 2 x CC*H*$_2$) 1.66-1.30 (2 x $CH_2$), 1.14, 1.13 (6H, d, *J* 6, 2 x $CH_3$), 0.95, 0.94 (18H, t, *J* 8, 2 x $SiCH_2CH_3$), 0.88, 0.87 (18H, s, 2 x $SiCMe_3$), 0.58, 0.57 (12H, q, *J* 8, 2 x $SiCH_2CH_3$), 0.13, 0.12 (6H, s, 2 x $SiCH_3$), 0.06, 0.05 (6H, s, 2 x $SiCH_3$); $\delta_C$(100 MHz) 171.8, 171.7 (2 x *C*$O_2$Me), 165.1 (2 x *C*$O_2$Me), 76.3, 76.2 (2 x quat. C), 68.3, 68.1 (2 x CH), 52.8 (2 x $CO_2$*Me*), 52.1 (2 x $CO_2$*Me*), 35.0 (2 x $CH_2$), 33.5 (2 x $CH_2$), 25.9, 25.9 (2 x $SiC(CH_3)_3$), 24.0, 24.0 (2 x $CH_3$), 18.6 (2 x $SiC(CH_3)_3$), 7.0 (6 x $SiCH_2CH_3$), 5.1 (6 x $SiCH_2CH_3$), –3.4 (2 x $SiCH_3$), –3.9 (2 x $SiCH_3$). Diazo carbon not observed due to slow relaxation time.

Second eluted diazodiketoester **13**[20] (46 mg, 39% from silyl ether **12**) as a yellow oil. $R_f$ 0.28 (50% ether in light petroleum); $\nu_{max}/cm^{-1}$ 3515 br, 2955 s, 2858 s, 2099 s, 1746 s, 1706 s, 1438 m, 1319 s, 1143 s; $\delta_H$(400 MHz) 3.83-3.70 (2H, m, 2 x C*H*), 3.75 (6H, s, 2 x $OCH_3$), 3.73 (6H, s, 2 x $OCH_3$), 2.18-1.22 (10H, m, 4 x $CH_2$, 2 x OH), 1.20 (6H, d, *J* 7, 2 x $CH_3$), 0.88 (18H, s, 2 x $SiCMe_3$), 0.12, 0.11 (6H, s, 2 x $SiCH_3$), 0.07, 0.05 (6H, s, 2 x $SiCH_3$); $\delta_C$(100 MHz) 171.8, 171.7 (2 x *C*$O_2$Me), 165.3 (2 x *C*$O_2$Me), 76.2, 76.2 (2 x quat. C), 68.0, 67.9 (2 x CH), 52.8 (2 x $CO_2$*Me*), 52.0 (2 x $CO_2$*Me*), 34.7, 34.6 (2 x $CH_2$), 33.1 (2 x $CH_2$), 25.9 (2 x $SiC(CH_3)_3$), 23.8 (2 x $CH_3$), 18.6 (2 x $SiC(CH_3)_3$), –3.4 (2 x $SiCH_3$) and –3.9 (2 x $SiCH_3$). Diazo carbon not observed due to slow relaxation time.

### 4.2.8. 2,3- Di-*tert*-butoxy-4-butyl-4-hydroxy-cyclobut-2-enone 16

BuLi (140 μL, 1.6 M in hexanes, 0.220 mmol) was added dropwise to di-*tert*-butyl squarate **7c** (50 mg, 0.22 mmol) in THF (2 mL) at –78 °C. After 30 min, water (1 mL)

was added and the reaction mixture extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (50% $Et_2O$ in light petroleum) gave butylated squarate **16** (40 mg, 65%) as a colourless oil. $R_f$ 0.41 (50% $Et_2O$ in light petroleum); $\nu_{max}/cm^{-1}$ 3400 w, 3019 s, 2979 m, 1757 m, 1600 s; $\delta_H$(200 MHz) 2.45 (1H, bs, OH), 1.78-1.70 (2H, m, C(OH)*CH*$_2$CH$_2$), 1.53 (9H, s, CMe$_3$), 1.47 (9H, s, CMe$_3$), 1.30-1.20 (4H, m, CH$_2$(*CH*$_2$)$_2$Me), 0.88 (3H, t, *J* 7, CH$_2$*Me*); $\delta_C$(100 MHz) 188.8 (*C*O), 167.1 (*C*=C), 129.9 (C=*C*), 85.2 (quat. C), 83.6 (quat. C), 80.2 (quat. C), 32.1 (C(OH)*CH*$_2$), 28.9 (C*Me*$_3$), 28.5 (C*Me*$_3$), 27.1, 22.9 (CH$_2$-(*C*H$_2$)$_2$-CH$_3$), 14.1 (Me); ***m/z*** (EI) 302.3 (M + $NH_4^+$, 10%), 267.3 (10), 228.3 (100), 189.2, 172.2; HRMS [M + $NH_4^+$] found: 302.2333, $C_{16}H_{32}NO_4$ requires 302.2331.

*4.2.8.1. Representative reaction in presence of a chiral ligand.*

BuLi (0.28 mL, 2.3 M in hexane, 0.5 mmol) was added dropwise to (–)-sparteine (117 mg, 0.5 mmol) in toluene (3 mL) at –85 °C. After 1 h, di-*tert*-butyl squarate **7c** (50 mg, 0.25 mmol) in toluene (1 mL) was added dropwise. After 12 h at –85 °C, water (0.5 mL) was added and the reaction mixture was diluted with $Et_2O$ (5 mL) and water (2 mL). The organic layer was washed with phosphoric acid (0.5 M , 2 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (25% $Et_2O$ in light petroleum) gave butylated squarate **16** [66.7 mg, 94%, er 54:46 by HPLC (OD column, 2% *i*-PrOH in hexane, flow rate 0.25 mL min$^{-1}$, **16** 10 μg/ml, $t_R$mj (20.56), $t_R$mn (24.04))]. $[\alpha]_D^{22}$ = –1.1 (*c* = 1.0, $CHCl_3$); other data as above.

### 4.2.9. 2,3-Di-*tert*-butoxy-4-ethyl-4-hydroxy-cyclobut-2-enone 17

Ti(*i*PrO)$_4$ (45 μL, 0.1 mmol) was added to a solution of $Et_2Zn$ (265 μL, 1 M in hexanes, 0.3 mmol) in toluene (850 μL). After 10 min, di-*tert*-butyl squarate **7c** (20 mg, 0.09 mmol) in toluene (1.5 mL) was added to the yellow solution. The reaction mixture was heated to 60 °C for 15 h, then MeOH (1 mL) was added, followed by sat aq $NH_4Cl$ (1 mL). The reaction mixture was extracted with $CH_2Cl_2$ (3 x 10 mL), then the organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (25% $Et_2O$ in light petroleum) gave ethylated squarate **17** (5.0 mg, 22%) as a colourless oil. ***Rf*** 0.59 (50% $Et_2O$ in

light petroleum); $\nu_{max}/cm^{-1}$ 3474 m, 2973 w, 1758 m and 1598 s; $\delta_H$(500 MHz) 2.05 (bs, 1H, OH), 1.90-1.76 (1H, m, C*H*$_2$-CH$_3$), 1.53 (9H, s, CMe$_3$), 1.47 (9H, s, CMe$_3$), 0.87 (3H, t, *J* 7.5, CH$_2$*Me*); $\delta_C$(125 MHz) 186.3 (*C*O), 166.7 (*C*=C), 130.2 (C=*C*), 86.0 (quat. C), 83.7 (quat. C), 80.2 (quat. C), 29.0 (C*Me$_3$*), 28.5 (C*Me$_3$*), 25.3 (*C*H$_2$-CH$_3$), 9.4 (CH$_2$-*C*H$_3$); *m/z* (TOF Cl$^+$) 274 (M + NH$_4^+$, 5), 257 (M + H$^+$, 11), 239 (45), 200 (M - *t*Bu, 100), 183 (69), 144 (M – 2*t*Bu, 100), 127 (10); HRMS [M + H$^+$] found: 257.1757, $C_{14}H_{25}O_4$ requires 257.1753.

*4.2.9.1. General Reaction protocol in presence of a chiral ligand.*

Et$_2$Zn (1 M in hexanes, 2.5-3.8 equiv) was added to a solution of ligand **L9-14** (20-65 mol %) in toluene (850 μL) at room temperature. Then Ti(*i*PrO)$_4$ (1.1-3.0 equiv) was added. After 10 min, di-*tert*-butyl squarate **7c** (20 mg, 0.09 mmol) in toluene (1.5 mL) was added to the yellow solution. The reaction mixture was stirred at 60 °C for 15-20 h (or at rt for 3 days), then MeOH (1 mL) was added, followed by sat aq NH$_4$Cl (1 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. GC analysis (Et$_3$N added to sample before injection), Cydex-B column (0.22 mm × 30 m, thickness 0.25 μm) on a Trace GC (carrier gas: He, inlet temperature: 240 °C, detector: F.I.D., 280 °C. 0.5 °C/min from 100 °C to 130°C, then 130 °C for 30 min, flow 1.0 mL/min), $t_R$mn (81.64), $t_R$mj (84.33); other data as above.

*4.2.9.2. Reaction using **L9** (3 mmol scale)*

Following the general reaction protocol above, using Et$_2$Zn (9 mL, 1 M in hexanes, 9 mmol), **L9** (200 mg, 0.62 mmol, 20 mol%) in toluene (10 mL), Ti(*i*PrO)$_4$ (1.15 mL, 3.3 mmol) and di-*tert*-butyl squarate **7c** (678 mg, 3.0 mmol) in toluene (10 mL) added by cannula, gave after purification by column chromatography (25% Et$_2$O in light petroleum) ethylated squarate **17** (395 mg, 51%, er 58:42) as a colourless oil. $[\alpha]_D^{23}$ = +13.0 (*c* =1.0, $CHCl_3$) ; other data as above.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at xx.

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