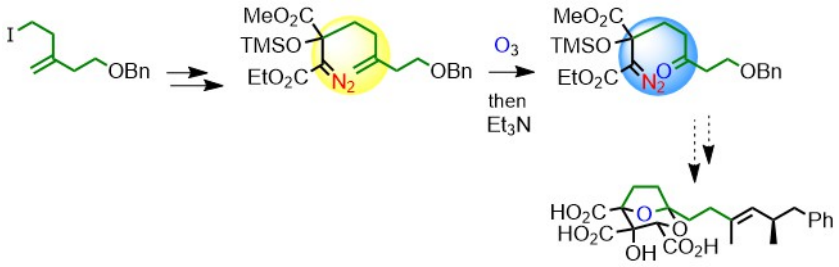
Alkene ozonolysis in the presence of diazo functionality: accessing an intermediate for squalestatin synthesis

Hasanain A. A. Almohseni[a,1]
Younes Fegheh-Hassanpour
Tanzeel Arif
David M. Hodgson*[a]

[a] Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, United Kingdom.

david.hodgson@chem.ox.ac.uk



Received:
Accepted:
Published online:
DOI:

Abstract Studies on both the propensity for intramolecular cycloaddition between diazo and alkene functionality, and the tolerance of α-substituted α-diazoesters towards ozone in the presence of an alkene, led to chemoselective alkene ozonolysis of an ε-unsaturated-α-diazoester to give a key racemic diazoketone for the synthesis of 6,7-dideoxysqualestatin H5.

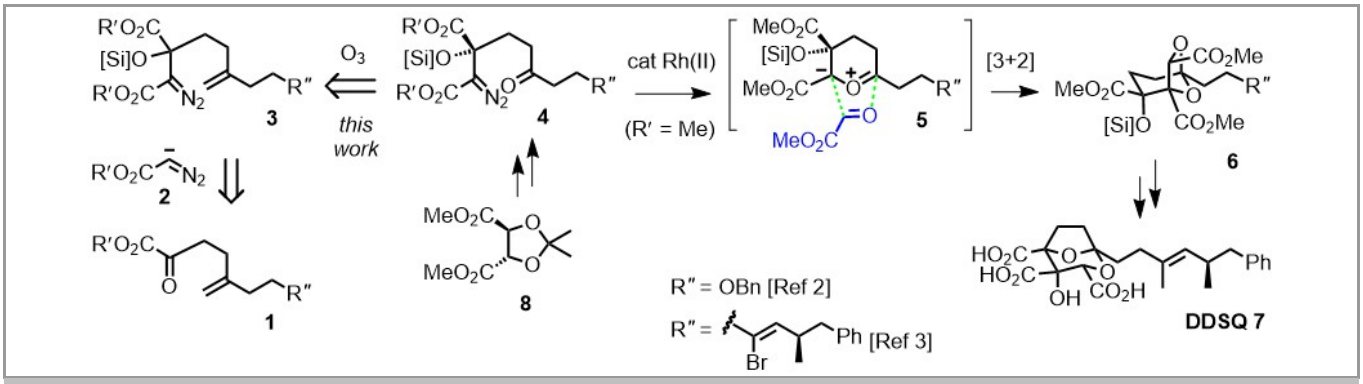
Key words 6,7-dideoxysqualestatin H5, squalestatin synthesis, alkene ozonolysis, intramolecular cycloaddition, diazo stability, pyrazoline.

Introduction

We recently reported two syntheses of 6,7-dideoxysqualestatin H5 (DDSQ) **7** (Scheme 1).[2,3] Both syntheses proceeded through diazoketones **4**, which underwent rhodium(II)-catalysed tandem carbonyl ylide formation–intermolecular dipolar cycloadditions (**4**→**5**→**6**),[4] followed by acid-catalysed rearrangement to generate the characteristic 2,8-dioxabicyclo [3.2.1]octane core of the squalestatins / zaragozic acids at the correct tricarboxylic acid oxidation level. Also in both cases, the silyloxyester stereocentre was created by stereoselective alkylation of dimethyl tartrate acetonide (**8**), with 5–6 steps being subsequently required to produce the diazoketones **4**. In principle, a more concise approach to such cycloaddition precursors **4** could proceed by aldol reaction between a diazoacetate anion **2** and an unsaturated α-ketoester **1**, followed by chemoselective alkene ozonolysis of the resulting unsaturated diazodiester **3** (Scheme 1). Here we report the realisation of this latter strategy, despite concerns over both intrinsic instability of the aldol product to spontaneous intramolecular cycloaddition between the diazo and alkene functionality, and of undesired conversion of diazo into keto functionality by ozone.

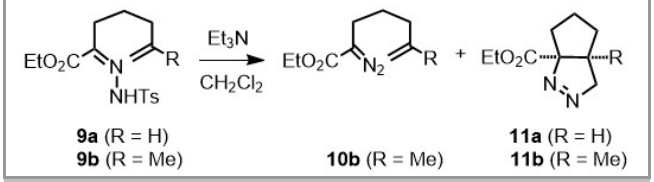
Results and discussion

Before embarking on the above route (**1**→**3**→**4**), it was considered prudent to first establish on simpler substrates the proclivity of α-diazoester functionality to engage in intramolecular cycloaddition with an electron-rich alkene to form bicyclic pyrazolines.[5]



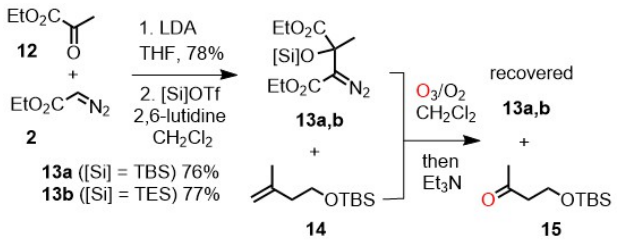
Scheme 1 Approaches to 6,7-dideoxysqualestatin H5 (**7**).

Unsaturated hydrazones **9a**,**b**[6] underwent Et_3N-induced diazo formation[7] in CH_2Cl_2 at rt (Scheme 2). As anticipated from Dauben's studies,[5b] this led hydrazone **9a** to form 1-pyrazoline **11a**, in 92% yield (Scheme 2). However, intramolecular cycloaddition was minimised with the 2,2-dialkyl-substituted terminal alkene **9b**, to give a mixture (52%) mainly consisting of unsaturated diazoester **10b** together with only small amounts of bicycle **11b** (**10b**:**11b**, 91:9).



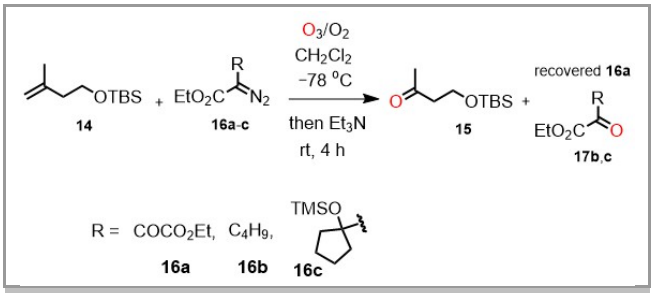
Scheme 2 Propensity for diazoalkenes to undergo intramolecular cycloaddition.

The stability of the α-diazoester motif towards ozone was next examined. The diazo moiety could be oxidised to a carbonyl group by ozone.[6,8] Model compounds **13a**,**b** (Scheme 3), that contain the diazo moiety in a similar environment to diazodiester **3** (Scheme 1), were prepared by aldol reaction between ethyl pyruvate (**12**) and the anion of ethyl diazoacetate (**2**),[9] followed by silylation. Equimolar solutions of α-diazoesters **13a,b** and alkene **14**, the latter mimicking the alkene portion of **3**, were exposed to ozone at –78 °C in CH_2Cl_2, followed by addition of Et_3N.[10] Pleasingly, these conditions gave ketone **15**, with diazoesters **13a,b** being recovered intact (Scheme 3, see also SI: Figure S1).



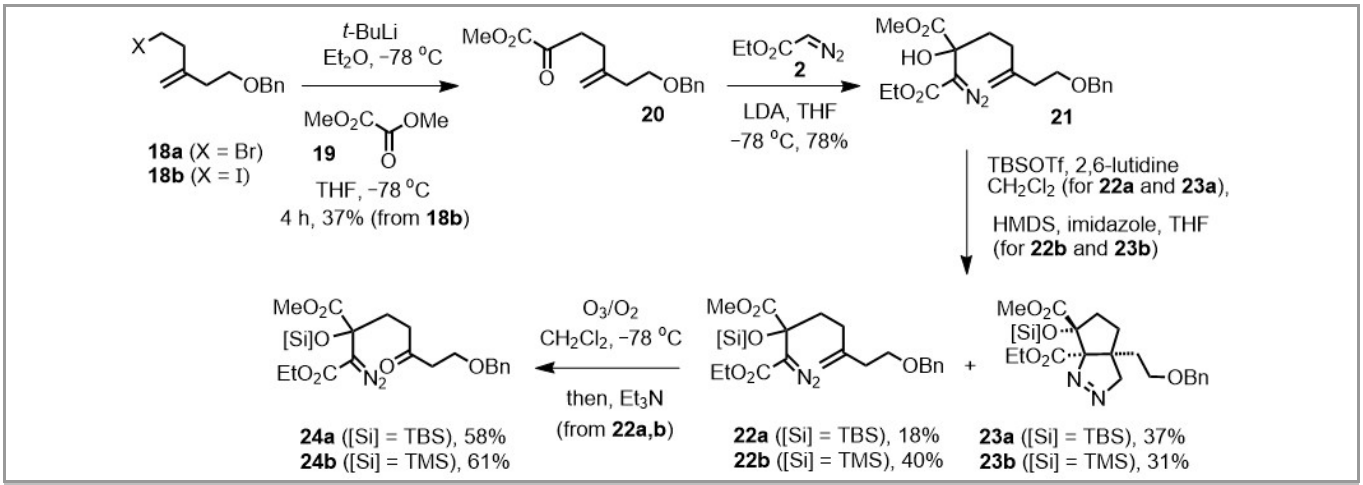
Scheme 3 Preparation and stability of α-diazoesters **13a,b** towards ozone.

The presence of further electron–withdrawing functionality on the diazocarbonyl likely reduces the reactivity of the diazo group towards ozone.[11] For example, α-diazo-β-ketoester **16a**[12] (Scheme 4) was stable to ozone even at –15 °C for 1 h (alkene **14** converted to ketone **15** within 5 min at –78 °C), whereas, the diazo moiety in **13a** (Scheme 3, CO_2Me instead of CO_2Et) is converted to the corresponding ketone on ozonolysis at –15 °C.[6] α-Substituted α-diazoesters **16b**,**c** (Scheme 4) were also examined, to study the effect of different substitution on the stability of the diazo moiety to ozonolysis; however, they were both reactive to ozonolysis at –78 °C, being converted to the corresponding ketones **17b**,**c** after addition of Et_3N.



Scheme 4 Examining the tolerance of α-substituted α-diazoesters **16** towards ozone.

Following the above observations, we focused on a synthesis of the racemic DDSQ intermediate **4** (Scheme 1, R′′ = OBn), through diazoacetate anion addition to homoallylic α-ketoester **20** (Scheme 5). Although many methods are known for synthesis of α-ketoesters,[13] only a limited number of organometallic additions to oxalates are suitable for the synthesis of homoallylic α-ketoesters.[14] When the freshly prepared Grignard reagent from bromide **18a** (available from the corresponding alcohol,[2] see experimental) was added to a solution of dimethyl oxalate (**19**) in THF at –65 °C, only a low yield of α-ketoester **20** was obtained (11%). Halogen–lithium exchange of iodide **18b**[2] using *t*-BuLi (2 equiv) at – 78 °C[15] and dropwise addition of the resulting organolithium to a solution of oxalate **19** in Et_2O (at –78 °C) gave a similar yield (~15%). The low yield could be due to the limited solubility of dimethyl oxalate in Et_2O at –78 °C, as switching from Et_2O to THF led to an improved yield of α-ketoester **20** (37%). Next, diazo-alcohol **21** was prepared through the addition of lithiated ethyl diazoacetate **2** to α-ketoester **20** (78%).



Scheme 5 Synthesis of α-diazo-ε-ketoesters **24a,b**.

Pleasingly, and following the trend seen with the model studies (Scheme 2), no undesired intramolecular cycloaddition was observed for diazo-alcohol **21**. At this stage we proceeded to protect the OH group, since otherwise it would be highly likely to undergo problematic γ-lactolisation with the ketone subsequently generated on ozonolysis.[16] A silyl group was the protecting group of choice for this purpose. Interestingly, when diazo-alcohol **21** was treated with TBSOTf in the presence of 2,6-lutidine (CH_2Cl_2, 48 h), a mixture of desired TBS ether **22a** along with cycloadduct **23a** (as a single diastereomer)[17] was obtained (**22a**:**23a**, 1:2). Using DMAP or pyridine as the base was not successful in preventing the 1,3-dipolar cycloaddition, whereas using Et_3N led to retro-aldolisation. The partial formation of cycloadduct **23a** on silylation could be rationalised by a Thorpe–Ingold effect, from the bulky silyl group. With this in mind, it was considered that minimising the steric effect by using a less-hindered silyl group might reduce the bicyclic product formation; indeed on trimethylsilylation, the ratio of silyl-ether **22b** to cycloadduct **23b** was 4:3 in favour of the desired non–cyclic product. Finally, ozonolysis of silyl ethers **22a** and **22b** led to diazoketones **24a** and **24b** (58% and 61%, respectively). The silyl ethers **22a**,**b** should be directly subjected to ozonolysis following their isolation, as they undergo intramolecular cyclisation to cycloadducts **23a**,**b** with the rate being slower for **22b** (see SI: Figure S2).

In summary, we have developed a strategy for the synthesis of α-diazo-ε-ketoesters, for application in squalestatin synthesis, based on chemoselective ozonolysis of unsaturated α-diazoesters. To survive ozonolysis, α-diazoester functionality requires to be either further substituted with a β-carbonyl group, or be sterically shielded by substituents at the β-position. Further studies will focus on construction of the enantiomerically enriched intermediate for the natural product (DDSQ).

The experimental section has no title; please leave this line here.

All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen in flame-dried glassware. Tetrahydrofuran (THF), dichloromethane and dimethylformamide (DMF) were obtained from Grubbs' drying stills.[18] Flash column chromatography was carried out using silica gel (VWR chemicals, BDH), monitored by thin-layer chromatography (TLC) (Merck 60 F_{254}) plates. TLC plates were viewed using ultraviolet light (λ_{max} = 254/365 nm) and immersion in $KMnO_4$, followed by heating. Except where stated otherwise, commercially available reagents were used as received. Infrared spectra were obtained using a PerkinElmer FT–IR spectrometer (Universal ATR Sampling Accessory), with absorption maxima quoted in wavenumbers (cm^{-1}). Peak intensities are described as broad (br), weak (w), medium (m) or strong (s). Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded on Bruker Avance AVIIIHD 400, NEO 400, and AVIIIHD 500 spectrometers in $CDCl_3$ (referenced to residual $CHCl_3$ singlet at δ 7.27 for ^1H NMR spectra, and to the central line of $CDCl_3$ triplet at δ 77.16 for ^{13}C NMR spectra). Chemical shifts are quoted in parts per million (ppm). Coupling constants (*J*) are measured to the nearest 0.5 Hertz (Hz). The splittings are quoted as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of triplets (tt), doublet of doublet of doublets (ddd), doublet of quartets (dq), or multiplet (m). The ^{13}C signal of CN_2 was often not observed due to quadrupolar relaxation. High-resolution mass spectra were obtained by electrospray ionization, using a Thermo Fisher Orbitrap Exactive mass spectrometer.

Procedures

(a) Propensity of diazoalkenes to undergo intramolecular cycloaddition

Ethyl 3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6a(3*H*)-carboxylate (11a)

To a solution of hydrazone **9a**[6] (500 mg, 1.42 mmol) in CH_2Cl_2 (2 ml) was added Et_3N (0.62 ml, 4.4 mmol) and stirred at rt. After 3 h, the mixture was passed through a short pad of silica (~2 cm), and washed through with CH_2Cl_2 (20 ml). The eluent was evaporated under reduced pressure and the mixture purified by column chromatography (30% Et_2O in petrol) to give 1-pyrazoline **11a** (240 mg, 92%), as a yellow oil; R_f = 0.52 (30% EtOAc in petrol).

ν_{max}/cm^{-1}(film) 296 w, 2871 w, 1730 s, 1556 w, 1267 s, 1222 s, 1094 s.

^1H NMR (500 MHz; $CDCl_3$) δ 4.67 (1H, dd, *J* 18.5 and 9, CHCH*H*N=N), 4.40 (1H, dd, *J* 18.5 and 3, CHC*H*HN=N), 4.23–4.15 (2H, m, CH_2CH$_3$), 2.64 (1H, tt, *J* 9 and 3, C*H*CH$_2$N=N), 2.40–2.34 (1H, m, CH*H*CCO$_2$Et), 2.32–2.24 (1H, m, C*H*HCCO$_2$Et), 1.85–1.76 (1H, m, CHCH*H*CH$_2$), 1.69–1.61 (1H, m, CHCH$_2$CH*H*), 1.40–1.34 (1H, m, CHC*H*HCH$_2$), 1.25 (3H, t, *J* 8, COCH$_2$C*H*$_3$), 1.12–1.02 (1H, m, CHCH$_2$C*H*H).

^{13}C NMR (125 MHz; $CDCl_3$) δ 170.5 (*C*O$_2$Et), 106.8 (quat. *C*CO$_2$Et), 86.1 (CH$_2$N=N), 61.8 (CO*C*H$_2$CH$_3$), 39.3 (*C*HCH$_2$N=N), 34.3 (*C*H$_2$CCO$_2$Et), 34.2 (CH*C*H$_2$CH$_2$), 24.0 (CHCH$_2$*C*H$_2$), 14.2 (COCH$_2$*C*H$_3$).

HRMS *m/z* (M+Na$^+$) found 205.0949, $C_9H_{14}N_2{}^{23}NaO_2$ requires 205.0948.

Ethyl 2-diazo-6-methylhept-6-enoate (10b) and **Ethyl 3a-methyl-3a,4,5,6-tetrahydrocyclo penta[*c*]pyrazole-6a(3*H*)-carboxylate (11b)**

To a solution of hydrazone **9b**[6] (45 mg, 0.13 mmol) in CH_2Cl_2 (3 ml) was added Et_3N (53.0 µl, 0.38 mmol) and stirred at rt. After 3 h, the mixture was passed through a short pad of silica (~2 cm), and washed through with CH_2Cl_2 (20 ml). The eluent was evaporated under reduced pressure and the mixture purified by column chromatography (30% Et_2O in petrol) to give an inseparable mixture of diazoalkene **10b** and cycloadduct **11b** (13 mg, 52%, 91:9 respectively, by integration at **10b** [δ C=CH$_2$] and **11b** [δ CH$_2$N=N] peaks), as a yellow oil; R_f = 0.54 (30% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2934 w, 2361 w, 2078 s, 1688 s, 1447 m, 1371 m, 1304 m, 1157 s, 1110 s.

HRMS [M+Na$^+$] found 219.1106, $C_{10}H_{16}N_2{}^{23}NaO_2$ requires 219.1109.

Data for diazoalkene **10b**:

^1H NMR (500 MHz; $CDCl_3$) δ 4.73 (1H, s, C=C*H*H), 4.68 (1H, s, C=CH*H*), 4.22 (2H, q, *J* 7, CO*C*H_2CH$_3$), 2.30 (2H, t, *J* 7.5, CH_2C=CH$_2$), 2.07 (2H, t, *J* 7.5, CH$_2$CN=N), 1.71 (3H, s, CH_3C=CH$_2$), 1.66 (2H, m, , CH_2CH$_2$CN=N), 1.27 (3H, t, *J* 7, COCH$_2$CH_3).

^{13}C NMR (125 MHz; $CDCl_3$) δ 169.7 (*C*O$_2$Et), 144.9 (*C*=CH$_2$), 110.7 (C=*C*H$_2$), 60.9 (CO*C*H$_2$CH$_3$), 36.9 (*C*H$_2$CN=N), 25.7 (*C*H$_2$CH$_2$CN=N), 22.9 (*C*H$_2$C=CH$_2$), 22.4 (*C*H$_3$C=CH$_2$), 14.7 (COCH$_2$*C*H$_3$).

Data for cycloadduct **11b**:

^1H NMR (500 MHz; $CDCl_3$) δ 4.53 (0.1H, d, *J* 18, CH*H*N=N), 4.34 (0.1H, d, *J* 18, C*H*HN=N), 2.52–2.41 (C*H*H), 1.11 (0.3H, s, quat. CCH$_3$).

^{13}C NMR (125 MHz; $CDCl_3$) δ 167.8 (*C*O$_2$Et), 105.7 (quat. *C*CO$_2$Et), 91.7 (CH$_2$N=N), 61.7 (CO*C*H$_2$CH$_3$), 47.2 (quat. *C*CH$_3$), 42.5 (*C*H$_2$CCO$_2$Et), 34.0 (*C*H$_2$CH$_2$CCO$_2$Et), 23.3 (*C*H$_2$CCH$_3$), 22.2 (quat. C*C*H$_3$).

(b) Preparation and stability of α-substituted α-diazoesters towards ozone

α-Diazo-β-ketoester **16a** was prepared according to a literature procedure[12] and α-diazoester **16b** was prepared following a procedure reported by Wang and co-workers.[19]

Diethyl 3-diazo-2-hydroxy-2-methylsuccinate (25)

The procedure of Padwa and co-workers[5h] was followed with slight modifications. A solution of LDA [prepared from *n*-BuLi (3.1 ml, 1,4 M in hexanes, 4.6 mmol) and *i*-Pr$_2$NH (600 µl, 4.6 mmol) in THF (5 ml) at –78 °C] was added dropwise to a stirred solution of ethyl diazoacetate (**2**) (525 mg, 4.60 mmol) and ethyl pyruvate (**12**) (534 mg, 4.60 mmol) in THF (20 ml) at –78 °C. The solution was warmed to rt and stirred for 3 h, and then AcOH (0.26 ml, 4.6 mmol) added dropwise. The mixture was extracted with Et$_2$O (2 x 15 ml), the combined organic layers washed with brine (10 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (10% Et$_2$O in petrol) to give diethyl 3-diazo-2-hydroxy-2-methylsuccinate (**25**) (825 mg, 78%), as a yellow liquid; R_f = 0.27 (30% Et$_2$O in petrol).

ν_{max}/cm^{-1}(film) 3380 br, 2956 m, 2096 s, 1745 s and 1698 s.

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.29–4.16 (4H, m, 2 x OC*H*$_2$Me), 4.13 (1H, s, OH), 1.56 (3H, s, Me), 1.30–1.22 (6H, m, 2 x OCH$_2$*Me*).

^{13}C NMR (100 MHz; $CDCl_3$) δ 173.8 (*C*O$_2$Et), 165.7 (*C*O$_2$Et), 71.6 (quat. C), 62.9 (OCH$_2$), 61.3 (OCH$_2$), 23.8 (Me), 14.5 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$).

HRMS *m/z* (M+Na$^+$) found: 253.0795, $C_9H_{14}O_5N_2{}^{23}Na$ requires 253.0794.

Diethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-diazo-2-methylsuccinate (13a)

TBSOTf (0.4 ml, 1.7 mmol) was added to 2,6-lutidine (0.3 ml, 2.6 mmol) in CH_2Cl_2 (1 ml) and stirred for 10 min at 0 °C. A solution of diethyl 3-diazo-2-hydroxy-2-methylsuccinate (**25**) (200 mg, 0.87 mmol) in CH_2Cl_2 (2 ml) at 0 °C was then added. The mixture was warmed to rt and stirred for 48 h. The mixture was quenched with water (4 ml), extracted with CH_2Cl_2 (3 x 10 ml), washed with brine (10 ml) and dried ($MgSO_4$). After evaporation under reduced pressure, the residue was purified by column chromatography (10% Et$_2$O in petrol) to give TBS ether **13a** (227 mg 76%); R_f = 0.3 (20% Et$_2$O in petrol).

ν_{max}/cm^{-1}(film) 2956 m, 2931 m, 2858 m, 2096 s, 1745 s, 1698 s, 1464 m, 1309 s, 1255 s, 1144 s, 1069 s, 839 w.

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.25–4.14 (4H, m, 2 x OC*H*$_2$CH$_3$), 1.66 (3H, s, Me), 1.30–1.22 (6H, m, 2 x OCH$_2$C*H*$_3$), 0.86 (9H, s, OSiC(CH$_3$)$_3$), 0.11 and 0.08 (6H, 2 x s, OSi(CH$_3$)$_2$).

^{13}C NMR (100 MHz; $CDCl_3$) δ 172.0 (*C*O$_2$Et), 165.0 (*C*O$_2$Et), 73.7 (quat. C), 61.9 (OCH$_2$), 60.9 (OCH$_2$), 25.9 (Me), 25.7 (SiC(*C*H$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 14.6 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$) –3.0 (OSi(CH$_3$)$_2$), –3.5 (OSi(CH$_3$)$_2$).

HRMS [M+Na$^+$] found: 367.1656. $C_{15}H_{28}O_5N_2{}^{28}Si^{23}Na$ requires 367.1659.

Diethyl 3-diazo-2-methyl-2-((triethylsilyl)oxy)succinate (13b)

Following the procedure for silyl ether **13a** above, but using TESOTf, diethyl 3-diazo-2-hydroxy-2-methylsuccinate (**25**) (200 mg, 0.87 mmol) gave after column chromatography (10% Et$_2$O in petrol) TES ether **13b** (230 mg, 77%), as a yellow oil; R_f = 0.3 (20% Et$_2$O in petrol).

ν_{max}/cm^{-1}(film) 2956 m, 2931 m, 2858 m, 2096 s, 1745 s, 1698 s, 1464 m, 1309 s, 1255 s, 1144 s, 1069 s, 839 w.

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.25–4.13 (4H, m, 2 x OC*H*$_2$CH$_3$), 1.67 (3H, s, Me), 1.27 (3H, t, *J* 7, OCH$_2$C*H*$_3$), 1.24 (3H, t, *J* 7, OCH$_2$C*H*$_3$), 0.93 (9H, t, *J* 8, OSi(CH$_2$C*H*$_3$)$_3$), 0.62 (6H, q, *J* = 8, OSi(C*H*$_2$CH$_3$)$_3$).

^{13}C NMR (100 MHz; $CDCl_3$) δ 172.0 (*C*O$_2$Et), 165.1 (*C*O$_2$Et), 73.6 (quat. C), 61.9 (OCH$_2$), 60.9 (OCH$_2$), 25.9 (Me), 14.6 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$) 6.9 (OSi(CH$_2$*C*H$_3$)$_3$), 6.1 (OSi(*C*H$_2$CH$_3$)$_3$).

HRMS [M+Na$^+$] found: 367.1656. $C_{15}H_{28}O_5N_2{}^{23}Na^{28}Si$ requires 367.1659.

Ethyl 2-diazo-2-(1-((trimethylsilyl)oxy)cyclopentyl)acetate (16c)

TMSCl (127 µl, 1.0 mmol) was added slowly to a solution of ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate[5h] (100 mg, 0.50 mmol) and imidazole (170 mg, 2.50 mmol) in DMF (1.4 ml) at 0 °C. After 4 h at rt, Et$_2$O (5 ml) was added, the organic layer was washed with water (2 x 2 ml), brine (2 ml) and dried (Na_2SO_4). After evaporation under reduced pressure, the residue was purified by column chromatography (0–10% Et$_2$O in petrol) to give silyl ether **16c** (118 mg, 87%), as a yellow liquid; R_f = 0.59 (10% Et$_2$O in petrol).

ν_{max}/cm^{-1}(film) 2960 m, 1714 s, 1370 w, 1204 m, 1040 m.

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.22 (2H, q, *J* 7, OC*H*$_2$CH$_3$), 2.05–1.99 (2H, m, CH$_2$), 1.94–1.86 (2H, m, CH$_2$), 1.84–1.78 (2H, m, CH$_2$), 1.70–1.63 (2H, m, CH$_2$), 1.28 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$), 1.10 (OTMS).

^{13}C NMR (100 MHz; $CDCl_3$) δ 165.7 (*C*O$_2$Et), 81.0 (*C*OTMS), 60.6 (O*C*H$_2$CH$_3$), 40.1 (2 x CH$_2$), 22.8 (2 x CH$_2$), 14.7 (OCH$_2$*C*H$_3$), 1.5 (OSi(CH$_3$)$_3$).

HRMS *m/z* (M+Na$^+$) found: 293.1292. $C_{12}H_{22}O_3N_2{}^{23}Na^{28}Si$ requires 293.1291.

General procedure for ozonolysis

A stream of O_3/O_2 was bubbled through a mixture of α-diazoester (1 mmol) and alkene **14**[20] (1 mmol) in CH_2Cl_2 at −78 °C until the colour of the reaction mixture changed from yellow to blue (~5 min). Then the excess of O_3 was removed by bubbling N_2 through the reaction mixture, followed by addition of Et$_3$N (3 mmol). After 4 h at rt, the reaction mixture was evaporated under reduced pressure and the residue analysed by ^{1}H NMR (see SI: Figure S1).

Ethyl 2-oxohexanoate (17b)

Following the general ozonolysis procedure above, α-diazoester **16b** (100 mg, 0.58 mmol) was oxidised to give after column chromatography (5% EtOAc in petrol) an inseparable mixture of α-ketoester **17b** and the corresponding trioxane trimer **26** (66 mg, 73%, ~60:40 respectively, by integration at **17b** [δ CH$_2$C*H*$_2$CO] and **26** [δ CH$_2$C*H*$_2$CO] peaks), as a colourless liquid; R_f = 0.56 (5% EtOAc in petrol).

ν_{max}/cm^{-1}(film) 2961 m, 2935 m, 1750 s, 1727 s, 1466 s, 1275 m, 1246 m, 1142 m, 1120 m, 1048 s, 856 m.

Data for α-ketoester **17b**:

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.30 (2H, q, *J* 7, OC*H*$_2$CH$_3$), 2.81 (2H, t, *J* 7, CH$_2$C*H*$_2$CO), 1.68–1.55 (2H, m, C*H*$_2$CH$_2$CO), 1.42–1.27 (5H, m, CH$_2$ and CO$_2$CH$_2$C*H*$_3$), 0.91 (3H, t, *J* 7, OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz; $CDCl_3$) δ 194.9 (C=O), 161.5 (*C*O$_2$Et), 62.5 (CO$_2$*C*H$_2$CH$_3$), 39.1 (*C*H$_2$CO), 25.2 (*C*H$_2$CH$_2$CO), 22.2 (CH$_3$*C*H$_2$CH$_2$), 14.1 (OCH$_2$*C*H$_3$), 13.9 (CH$_2$*C*H$_3$).

HRMS *m/z* (M+Na$^+$) found: 181.0836. $C_8H_{14}O_3{}^{23}Na$ requires 181.0835.

Data for triethyl 2,4,6-tributyl-1,3,5-trioxane-2,4,6-tricarboxylate **26**:

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.27–4.21 (1H, m, OC*H*$_2$CH$_3$), 2.10–1.91 (1H, m, CH$_2$C*H*$_2$CO), 1.42–1.27 (5H, m, 2 x CH$_2$ and CO$_2$CH$_2$C*H*$_3$), 0.88 (2H, t, OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz; $CDCl_3$) δ 168.2 (*C*O$_2$Et), 107.6 (quat. C), 62.1 (CO$_2$*C*H$_2$CH$_3$), 31.6 (*C*H$_2$CO), 25.0 (*C*H$_2$CH$_2$CO), 22.6 (CH$_3$*C*H$_2$CH$_2$), 14.2 (OCH$_2$*C*H$_3$), 13.8 (CH$_2$*C*H$_3$).

Ethyl 2-oxo-2-(1-((trimethylsilyl)oxy)cyclopentyl)acetate (17c)

Following the general ozonolysis procedure above, TMS ether **16c** (47 mg, 0.17 mmol) was oxidised to give after column chromatography (10% Et$_2$O in petrol) α-ketoester **17c** (17 mg, 39%), as a colourless liquid; R_f = 0.5 (10% Et$_2$O in petrol).

ν_{max}/cm^{-1}(film) 2958 m, 1727 s, 1251 s, 1216 m, 1066 s, 1028 m, 917 m, 839 s.

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.31 (2H, q, *J* 7, OC*H*$_2$CH$_3$), 2.26–2.15 (2H, m, CH$_2$), 1.93–1.87 (2H, m, CH$_2$), 1.85–1.78 (2H, m, CH$_2$), 1.77–1.69 (2H, m, CH$_2$), 1.36 (3H, t, *J* 7, OCH$_2$C*H*$_3$), 0.13 (OTMS).

^{13}C NMR (100 MHz; $CDCl_3$) δ 200.0 (C=O), 165.2 (*C*O$_2$Et), 88.8 (*C*OTMS), 61.9 (O*C*H$_2$CH$_3$), 39.0 (2 x CH$_2$), 24.7 (2 x CH$_2$), 14.2 (OCH$_2$*C*H$_3$), 1.8 (OSi(CH$_3$)$_3$).

HRMS *m/z* (M+Na$^+$) found: 281.1180. $C_{12}H_{22}O_4{}^{23}Na^{28}Si$ requires 281.1179.

(c) Synthesis of α-diazo-ε-ketoesters **24a,b**.

(((5-Bromo-3-methylenepentyl)oxy)methyl)benzene (18a)

Ph_3P (365 mg, 1.39 mmol) and CBr_4 (577 mg, 1.74 mmol) was added to a solution of 5-(benzyloxy)-3-methylenepentan-1-ol[2] (240 mg, 1.16 mmol) in CH_2Cl_2 (8 ml) at rt. After 10 min, the reaction mixture was poured into sat. aq. $NaHCO_3$ (5 ml) and the aq. layer was extracted with CH_2Cl_2 (2 x 5 ml). The combined organic layers were washed with brine (5 ml), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (5% Et_2O in petrol) to give bromide **19a** (225 mg, 72%), as a colourless oil; R_f = 0.41 (5% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2858 w, 1646 m, 1453 m, 1208 m, 1098 s, 901 s, 736 s, 697 s.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.25 (5H, m, Ar*H*), 4.94 (1H, s, C=CH*H*), 4.89 (1H, s, C=C*H*H), 4.53 (2H, s, C*H*$_2$Ph), 3.59 (2H, t, *J* 7, C*H*$_2$OBn), 3.47 (2H, t, *J* 7, CH$_2$Br), 2.62 (2H, t, *J* 7, C*H*$_2$CH$_2$Br), 2.36 (2H, t, *J* 7.0, C*H*$_2$CH$_2$OBn).

^{13}C NMR (100 MHz; $CDCl_3$) δ 143.7 (*C*=CH$_2$), 138.4 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 113.4 (C=*C*H$_2$), 73.1 (*C*H$_2$Ph), 68.9 (*C*H$_2$OBn), 39.7 (*C*H$_2$CH$_2$Br), 35.9 (*C*H$_2$CH$_2$OBn), 31.0 (CH$_2$Br).

HRMS *m/z* (M+Na$^+$) found: 291.0354. $C_{13}H_{17}O^{79}Br^{23}Na$ requires 291.0355.

Methyl 7-(benzyloxy)-5-methylene-2-oxoheptanoate (20)

To a solution of (((5-iodo-3-methylenepentyl)oxy)methyl)benzene (**18b**)[2] (100 mg, 0.31 mmol) in Et_2O (3 ml) at −78 °C was added *t*-BuLi (0.44 ml, 1.7 M in pentane, 0.75 mmol) dropwise. After 1 h, the reaction mixture was transferred slowly by cannula to a solution of dimethyl oxalate (**19**) (186 mg, 1.58 mmol) in THF (0.5 ml) at −78 °C and stirred for 4 h. Then, sat. aq. NH_4Cl (2 ml) was added and the mixture allowed to warm to rt. The aq. layer was extracted with Et_2O (2 x 5 ml) and the combined organic layers were washed with water (5 ml), brine (5 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography (20% Et_2O in petrol) gave α-ketoester **20** (32 mg, 37%), as a colourless liquid; R_f = 0.15 (20% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2931 m, 1743 s, 1452 w, 1276 m, 1099 m, 716 w.

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40–7.26 (5H, m, Ar*H*), 4.84 (1H, s, C=CH*H*), 4.80 (1H, s, C=C*H*H), 4.51 (2H, s, C*H*$_2$Ph), 3.86 (3H, s, CO$_2$Me), 3.58 (2H, t, *J* 7, C*H*$_2$OBn), 3.00 (2H, t, *J* 7, CH$_2$C=O), 2.42–2.33 (4H, m, C*H*$_2$C(=CH$_2$)C*H*$_2$).

^{13}C NMR (125 MHz; $CDCl_3$) δ 193.6 (C=O), 161.5 (*C*O$_2$Me), 144.7 (*C*=CH$_2$), 138.4 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.5 (C=*C*H$_2$), 73.1 (*C*H$_2$Ph), 68.9 (*C*H$_2$OBn), 53.1 (CO$_2$*Me*), 37.7 (*C*H$_2$CH$_2$OBn), 36.5 (*C*H$_2$CH$_2$C=O), 29.3 (CH$_2$*C*H$_2$C=O).

HRMS *m/z* (M+Na$^+$) found: 299.1254. $C_{16}H_{20}O_4{}^{23}Na$ requires 299.1264.

4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-methylenepentyl)-3-diazo-2-hydroxysuccinate (21)

A solution of LDA [prepared from *n*-BuLi (90 µl, 2.5 M in hexanes, 0.22 mmol) and *i*-Pr$_2$NH (30 µl, 0.22 mmol) in THF (1 ml) at −78 °C] was added dropwise to a solution of ethyl diazoacetate (**2**) (23 µl, 0.22 mmol) and α-ketoester **20** (36 mg, 0.13 mmol) in THF (350 µl) at – 78 °C. After 2 h, the reaction mixture was quenched with NH_4Cl (2 ml), extracted with Et_2O (2 x 5 ml), and dried ($MgSO_4$). After evaporation under reduced pressure, the residue was purified by a short column chromatography (10% EtOAc in petrol) to give diazo-alcohol **21** (40 mg, 78%), as a yellow oil; R_f = 0.25 (50% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 3390 br, 3027 w, 2920 m, 1732 s, 1453 m, 1261 s, 1097 s, 739 m, 699 m.

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.39–7.26 (5H, m, Ar*H*), 4.81 (2H, d, *J* 11.5, C=CH$_2$), 4.50 (2H, s, C*H*$_2$Ph), 4.28 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.78 (3H, s, CO$_2$Me), 3.56 (2H, t, *J* 7, C*H*$_2$OBn), 2.34 (2H, t, *J* 7, C*H*$_2$CH$_2$OBn), 2.32–2.26 (1H, m, CH*H*C(OH)), 2.02–1.97 (1H, m, C*H*HC(OH)), 1.96–1.90 (2H, m, C*H*$_2$CH$_2$C(OH)), 1.27 (3H, t, *J* 7, CO$_2$CH$_2$C*H*$_3$).

^{13}C NMR (125 MHz; $CDCl_3$) δ 173.6 (*C*O$_2$Me), 165.9 (*C*O$_2$Et), 145.2 (*C*=CH$_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.5 (C=*C*H$_2$), 73.8 (quat. *C*(OH)CO$_2$Me), 73.1 (*C*H$_2$Ph), 68.9 (*C*H$_2$OBn), 61.4 (CO$_2$*C*H$_2$CH$_3$), 53.6 (CO$_2$*Me*), 36.4 and 34.6 (*C*H$_2$C(=CH$_2$)*C*H$_2$), 29.7 (*C*H$_2$C(OH)), 14.5 (CO$_2$CH$_2$*C*H$_3$).

HRMS *m/z* (M+H$^+$) found: 391.1882. $C_{20}H_{27}O_6N_2$ requires 391.1863.

4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-methylenepentyl)-2-((*tert*-butyldimethylsilyl)oxy)-3-diazosuccinate (22a) and **6a-Ethyl 6-methyl (3a*R*, 6*S*, 6a*R*)-3a-(2-(benzyloxy)ethyl)-6-((*tert*-butyl dimethylsilyl)oxy)-3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6,6a (3*H*)-dicarboxylate (23a)**

TBSOTf (35 µl, 0.15 mmol) was added to a solution of 2,6-lutidine (26 µL, 0.22 mmol) in CH_2Cl_2 (200 µl) at 0 °C and stirred for 15 min. A solution of diazo-alcohol **21** (30 mg, 0.076 mmol) in CH_2Cl_2 (200 µl) was added. The reaction mixture was stirred for 48 h at rt, then water (1 ml) was added, extracted with CH_2Cl_2 (2 × 5 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude mixture was purified by column chromatography (0–20% Et_2O in petrol).

First eluted TBS ether **22a** (7 mg, 18%), as a yellow oil; R_f = 0.23 (20% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2953 m, 2857 m, 2096 s, 1745 s, 1701 s, 1454 w, 1369 m, 1304 s, 1254 m, 1135 s, 838 s, 780 m.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.37–7.26 (5H, m, Ar*H*), 4.80 (2H, s, C=CH$_2$), 4.50 (2H, s, C*H*$_2$Ph), 4.26–4.11 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.72 (3H, s, CO$_2$Me), 3.55 (2H, t, *J* 7, C*H*$_2$OBn), 2.33 (2H, t, *J* 7, C*H*$_2$CH$_2$OBn), 2.24–1.94 (4H, m, C*H*$_2$C*H*$_2$C(OTBS)), 1.24 (3H, t, *J* 7, CO$_2$CH$_2$C*H*$_3$), 0.88 (9H, s, OSiCMe$_3$), 0.11 and 0.05 (6H, 2 x s, OSi(CH$_3$)$_2$).

^{13}C NMR (100 MHz; $CDCl_3$) δ 173.6 (*C*O$_2$Me), 145.6 (*C*=CH$_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.2 (C=*C*H$_2$), 76.0 (quat. *C*(OTBS)CO$_2$Me), 73.1 (*C*H$_2$Ph), 68.9 (*C*H$_2$OBn), 61.1 (CO$_2$*C*H$_2$CH$_3$), 52.8 (CO$_2$*Me*), 36.9 and 36.4 (*C*H$_2$C(=CH$_2$)*C*H$_2$), 30.2 (*C*H$_2$C(OH)), 25.9 (SiC(*C*H$_3$)$_3$), 18.6 (Si*C*(CH$_3$)$_3$), 14.6 (CO$_2$CH$_2$*C*H$_3$), −3.4 and −3.08 (2 x SiCH$_3$).

HRMS *m/z* (M+H$^+$) found: 505.2729. $C_{26}H_{41}O_6N_2{}^{28}Si$ requires 505.2728.

Second eluted cycloadduct **23a** (14 mg, 37%), as a pale yellow oil; R_f = 0.34 (20 % Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2928 m, 2855 m, 1741 s, 1454 m, 1365 w, 1313 m, 1253 s, 1100 m, 1056 m, 838 s, 779 m.

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.38–7.27 (5H, m, Ar*H*), 4.73 (1H, d, *J* 4.5, CH*H*N=N), 4.52–4.43 (3H, m, C*H*$_2$Ph and CH*H*N=N), 4.17 (2H, qd, *J* 7 and 2, CO$_2$C*H*$_2$CH$_3$), 3.79 (3H, s, CO$_2$Me), 3.57–3.48 (2H, m, C*H*$_2$OBn), 2.41–2.32 (1H, m, CH*H*C(OTBS)), 2.09–2.02 (1H, m, CH*H*CH$_2$C(OTBS)), 1.88–1.78 (2H, m, C*H*HC(OTBS) and CH*H*CH$_2$OBn), 1.65–1.60 (1H, m, C*H*HCH$_2$OBn), 1.57–1.50 (1H, m, C*H*HCH$_2$C(OTBS)), 1.25 (3H, t, *J* 7, CO$_2$CH$_2$C*H*$_3$), 0.82 (9H, s, OSiCMe$_3$), 0.05 (6H, 2 x s, OSi(CH$_3$)$_2$).

^{13}C NMR (125 MHz; $CDCl_3$) δ 172.0 (*C*O$_2$Me), 168.2 (*C*O$_2$Et), 138.1 (Ar*C*), 128.6 (Ar*C*H), 127.9 (Ar*C*H), 127.7 (Ar*C*H), 110.5 (quat. *C*CO$_2$Et), 90.9 (CH$_2$N=N), 87.1 (quat. *C*(OTBS)CO$_2$Me), 73.4 (*C*H$_2$Ph), 67.8 (*C*H$_2$OBn), 61.9 (CO$_2$*C*H$_2$CH$_3$), 52.3 (CO$_2$*Me*), 49.6 (quat. *C*CH$_2$N=N), 37.4 (*C*H$_2$C(OTBS)), 35.3 (*C*H$_2$CH$_2$OBn), 34.5 (*C*H$_2$CH$_2$C(OTBS)), 25.7 (SiC(*C*H$_3$)$_3$), 18.5 (Si*C*(CH$_3$)$_3$), 14.2 (CO$_2$CH$_2$*C*H$_3$), −3.1 and −4.0 (2 x SiCH$_3$).

HRMS *m/z* (M+H$^+$) found: 505.2732. $C_{26}H_{41}O_6N_2{}^{28}Si$ requires 505.2728.

4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-methylenepentyl)-3-diazo-2-((trimethylsilyl)oxy) succinate (22b) and **6a-Ethyl 6-methyl (3a*R*, 6*S*, 6a*R*)-3a-(2-(benzyloxy)ethyl)-6-((trimethylsilyl)oxy)-3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6,6a(3*H*)-dicarboxylate (23b)**

Hexamethyldisilazane (66 µl, 0.32 mmol) was added to a solution of diazo-alcohol **21** (30 mg, 0.076 mmol) and imidazole (11 mg, 0.16 mmol) in THF (0.8 ml) at rt. After 48 h, the reaction mixture was concentrated by blowing nitrogen, followed by purification of the residue by column chromatography (0–10% Et_2O in petrol).

First eluted TMS ether **22b** (14 mg, 40%), as a yelow oil; R_f = 0.26 (20% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2954 m, 2096 s, 1744 s, 1701 s, 1454 m, 1369 m, 1304 s, 1251 s, 1135 m, 844 s.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.37–7.27 (5H, m, Ar*H*), 4.80 (2H, s, C=CH_2), 4.51 (2H, s, CH_2Ph), 4.26–4.11 (2H, m, $CO_2CH_2CH_3$), 3.73 (3H, s, CO_2Me), 3.56 (2H, t, *J* 7, CH_2OBn), 2.34 (2H, t, *J* 7, CH_2CH_2OBn), 2.22–1.92 (4H, m, CH_2CH_2C(OTBS)), 1.25 (3H, t, *J* 7, $CO_2CH_2CH_3$), 0.13 (9H, s, OTMS).

^{13}C NMR (100 MHz; $CDCl_3$) δ 171.8 (*C*O_2Me), 164.9 (*C*O_2Et), 145.6 (*C*=CH_2), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.1 (C=*C*H_2), 76.2 (quat. *C*(OTMS)CO_2Me), 73.1 (*C*H_2Ph), 68.9 (*C*H_2OBn), 61.0 ($CO_2CH_2CH_3$), 52.8 (CO_2*Me*), 36.7 and 36.5 ($CH_2C(=CH_2)CH_2$), 30.2 (CH_2C(OTMS)), 14.6 ($CO_2CH_2CH_3$), 1.4 (OTMS).

HRMS *m/z* (M+H$^+$) found: 463.2258. $C_{23}H_{35}O_6N_2{}^{28}Si$ requires 463.2258.

Second eluted cycloadduct **23b** (11 mg, 31%), as a pale yellow oil; R_f = 0.34 (20% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2951 m, 2928 m, 1741 s, 1455 m, 1254 s, 1101 m, 1056 m, 839 s, 779 m.

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.38–7.27 (5H, m, Ar*H*), 4.72 (1H, d, *J* 18.5, CH*H*N=N), 4.53–4.42 (3H, m, CH_2Ph and CH*H*N=N), 4.17 (2H, qd, *J* 7 and 4, $CO_2CH_2CH_3$), 3.80 (3H, s, CO_2*Me*), 3.56–3.47 (2H, m, CH_2OBn), 2.33 (1H, dt, *J* 13.5 and 7.5, CH*H*C(OTBS)), 2.12–2.04 (1H, m, CH*H*CH_2C(OTBS)), 1.85 (1H, dt, *J* 13.5 and 5.5, CH*H*CH_2OBn), 1.75 (1H, ddd, *J* 13.5, 7.5 and 6.5, C*H*HC(OTBS)), 1.64–1.52 (1H, m, C*H*HCH_2OBn and C*H*HCH_2C(OTBS)), 1.24 (3H, t, *J* 7, $CO_2CH_2CH_3$), 0.10 (9H, s, OSi$(CH_3)_3$).

^{13}C NMR (125 MHz; $CDCl_3$) δ 172.4 (*C*O_2Me), 167.8 (*C*O_2Et), 138.2 (Ar*C*), 128.6 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 110.1 (quat. *C*CO_2Et), 91.9 (CH_2N=N), 87.0 (quat. *C*(OTBS)CO_2Me), 73.4 (*C*H_2Ph), 67.7 (*C*H_2OBn), 61.8 ($CO_2CH_2CH_3$), 52.3 (CO_2*Me*), 49.6 (quat. *C*CH_2N=N), 37.5 (CH_2C(OTBS)), 35.5 (*C*H_2CH_2OBn), 34.8 (*C*H_2CH_2C(OTBS)), 14.2 ($CO_2CH_2CH_3$), 1.6 (Si$(CH_3)_3$).

HRMS *m/z* (M+H$^+$) found: 463.2251. $C_{23}H_{35}O_6N_2{}^{28}Si$ requires 463.2258.

4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-oxopentyl)-2-((tert-butyl dimethylsilyl)oxy)-3-diazosuccinate (24a)

Following the general procedure for ozonolysis above, using TBS ether **22a** (4 mg, 0.008 mmol), gave after column chromatography (0–40% Et_2O in petrol) diazoketone **24a** (2.3 mg, 58%), as a yellow oil; R_f = 0.53 (50% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2931 m, 2856 m, 2095 s, 1747 s, 1700 s, 1456 w, 1305 m, 1256 m, 1132 m, 838 m.

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.37–7.27 (5H, m, Ar*H*), 4.50 (2H, s, CH_2Ph), 4.24–4.12 (2H, m, $CO_2CH_2CH_3$), 3.75–3.68 (5H, m, CO_2Me and CH_2OBn), 2.69 (2H, t, *J* 6, CH_2CH_2OBn), 2.67–2.61 (1H, m, CH*H*C(OTBS)), 2.51–2.44 (1H, m, C*H*HC(OTBS)), 2.27–2.21 (2H, m, CH_2CH_2C(OTBS)), 1.24 (3H, t, *J* 7, OCH_2CH_3), 0.86 (9H, s, OSiCMe_3), 0.09 and 0.04 (6H, 2 x s, OSi$(CH_3)_2$).

^{13}C NMR (125 MHz; $CDCl_3$) δ 207.7 (C=O), 171.4 (*C*O_2Me), 164.8 (*C*O_2Et), 138.2 (ArC), 128.5 (ArCH), 127.8 (ArCH), 127.8 (ArCH), 75.6 (quat. *C*(OTBS)CO_2Me), 73.4 (*C*H_2Ph), 65.4 (*C*H_2OBn), 61.2 ($CO_2CH_2CH_3$), 52.9 (CO_2*Me*), 43.2 (O=C–CH_2), 37.8 (O=C–*C*H_2), 32.2 (*C*H_2C(OTBS)), 25.9 (SiC(*C*$H_3)_3$), 18.6 (Si*C*$(CH_3)_3$), 14.6 ($CO_2CH_2CH_3$), –3.5 and –3.9 (2 x SiCH_3).

HRMS *m/z* (M+Na$^+$) found: 529.2341. $C_{25}H_{38}O_7N_2{}^{23}Na^{28}Si$ requires 529.2340.

4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-oxopentyl)-3-diazo-2-((tri methylsilyl)oxy)succinate (24b)

Following the procedure for ozonolysis above, using TMS ether **22b** (6 mg, 0.013 mmol), gave after column chromatography (0–40% Et_2O in petrol) diazoketone **24b** (3.7 mg, 61%), as a yellow oil; R_f = 0.51 (50% Et_2O in petrol).

ν_{max}/cm^{-1}(film) 2953 w, 2871 w, 2096 s, 1747 s, 1702 s, 1455 w, 1369 m, 1305 s, 1251 s, 1135 m, 845 s.

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.37–7.27 (5H, m, Ar*H*), 4.50 (2H, s, CH_2Ph), 4.27–4.11 (2H, m, $CO_2CH_2CH_3$), 3.75–3.71 (5H, m, CO_2Me and CH_2OBn), 2.70 (2H, t, *J* 6.5, CH_2CH_2OBn), 2.66–2.58 (1H, m, CH*H*C(OTMS)), 2.48–2.41 (1H, m, C*H*HC(OTMS)), 2.26–2.20 (2H, m, CH_2CH_2C(OTMS)), 1.25 (3H, t, *J* 7, OCH_2CH_3), 0.11 (3H, s, OTMS).

^{13}C NMR (125 MHz; $CDCl_3$) δ 207.8 (C=O), 171.5 (*C*O_2Me), 164.8 (*C*O_2Et), 138.2 (ArC), 128.6 (ArCH), 127.8 (ArCH), 127.8 (ArCH), 75.8 (quat. *C*(OTMS)CO_2Me), 73.4 (*C*H_2Ph), 65.4 (*C*H_2OBn), 61.2 ($CO_2CH_2CH_3$), 53.0 (CO_2*Me*), 43.2 (O=C–*C*H_2), 37.7 (O=C–*C*H_2), 32.2 (*C*H_2C(OTMS)), 14.6 ($CO_2CH_2CH_3$), 1.3 (OTMS).

HRMS *m/z* (M+Na$^+$) found: 487.1867. $C_{22}H_{32}O_7N_2{}^{23}Na^{28}Si$ requires 487.1871.

Funding Information

We thank the Higher Committee for Education Development in Iraq, the EPSRC and the Higher Education Commission of Pakistan for studentship support (to H. A. A. A., Y.F.H. and T.A., respectively).

Supporting Information

YES (this text will be updated with links prior to publication)

References and Notes

(1) Permanent address: University of Kufa, Najaf Governorate, Iraq.
(2) Fegheh-Hassanpour, Y.; Arif, T.; Sintim, H. O.; Al-Mamari, H. A.; Hodgson, D. M. *Org. Lett*., **2017**, *19*, 3540; *corrigendum*, **2018**, *20*, 5528.
(3) Almohseni, H. A. A.; Al-Mamari, H. A.; Valade, A.; Sintim, H. O.; Hodgson, D. M. *Chem. Commun*., **2018**, *52*, 5354.
(4) Hodgson, D. M.; Labande, A. H.; Muthusamy, S. *Org. React.*, **2013**, *80*, 133.
(5) For intramolecular cycloadditions between diazo and alkene functionality, see: (a) Padwa, A.; Ku, H. *J. Org. Chem*., **1980**, *45*, 3756; (b) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.*, **1990**, *31*, 6969; (c) Jung, M. E.; Huang, A. *Org. Lett.*, **2000**, *2*, 2659; (d) Taber, D. F.; Guo, P. *J. Org. Chem*., **2008**, *73*, 9479; (e) Liu, H.; O'Connor, M. J.; Sun, C.; Wink, D. J.; Lee, D. *Org. Lett*., **2013**, *15*, 2974; (f) Barroso, R.; Escribano, M.; Cabal, M.-P.; Valdés, C. *Eur. J. Org. Chem*., **2014**, 1672; (g) Xia, Y.; Wang, J. *Chem. Soc. Rev.*, **2017**, *46*, 2306. See also: (h) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.*, **1990**, *55*, 4144.
(6) Fegheh-Hassanpour, Y.; Ebrahim, F.; Arif, T.; Sintim, H. O.; Claridge, T. D. W.; Amin, N. T.; Hodgson, D. M. *Org. Biomol. Chem*., **2018**, *16*, 2876.
(7) (a) House, H. O.; Blankley, C. J. *J. Org. Chem*., **1968**, *33*, 53; (b) Blankley, C. J.; Sauter, F. J.; House, H. O. *Org. Synth. Coll. Vol. V*; John Wiley & Sons: London, **1973**, 258.
(8) For examples of ozonolysis of diazo compounds to give ketones, see: (a) Erickson, R. E.; Andrulis Jr., P. J.; Collins, J. C.; Lungle, M. L.; Mercer, G. D. *J. Org. Chem.*, **1969**, *34*, 2961; (b) Sekiguchi, A.; Ando, W. *J. Chem. Soc., Chem. Commun*., **1979**, 575; (c) Ursini, A.; Pellicciari, R.; Tamburini, B.; Carlesso, R.; Gaviraghi, G. *Synthesis*, **1992**, 363.
(9) (a) Schöllkopf, U.; Frasnelli, H. *Angew. Chem., Int. Ed. Engl.*, **1970**, *9*, 301; (b) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc*., **1972**, *94*, 8084.

(10) Hon and co-workers (Hon, Y.-S.; Lin, S.-W.; Lu, L.; Chen, Y.-J. *Tetrahedron*, **1995**, *51*, 5019) report that, for ozonolysis of alkenes (eg, 2,2-disubstituted-1-alkenes), Et_3N typically gives better yields and proceeds faster compared to Me_2S. Me_2S also proved viable in the current transformation, but the crude reaction mixture was not as clean as with Et_3N.

(11) (a) Poschenrieder, H.; Stachel, H.-D. *Arch. Pharm. (Weinheim, Ger.)*, **1989**, *322*, 301; (b) Hodgson, D. M.; Man, S. *Chem. Eur. J*., **2011**, *17*, 9731; (c) Hodgson, D. M.; Moreno-Clavijo, E.; Day, S. E.; Man, S. *Org. Biomol. Chem*., **2013**, *11*, 5362.

(12) Jiang, Y.; Khong, V. Z. Y.; Lourdusamy, E.; Park, C.-M. *Chem. Commun*., **2012**, *48*, 3133.

(13) (a) Eftekhari-Sis, B.; Zirak, M. *Chem. Rev.*, **2015**, *115*, 151; (b) de las Heras, M. A.; Vaquero, J. J.; García-Navio, J. L.; Alvarez-Builla, J. *J. Org. Chem*., **1996**, *61*, 9009; (c) Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Synth. Commun.*, **1981**, *11*, 943.

(14) For examples, see: (a) Macritchie, J. A.; Silcock, A.; Willis, C. L. *Tetrahedron: Asymmetry*, **1997**, *8*, 3895; (b) Vickers, T. D.; Keay, B. A. *Synlett*, **2003**, 1349.

(15) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.*, **1990**, *55*, 5404.

(16) On a similar motif, γ-lactolisation of a β-hydroxy-ε-oxo-α-diazoester was observed: Villalonga–Barber, C. *D Phil Thesis*, University of Oxford, **2002**.

(17) The stereochemistry of pyrazolines **23a,b** were supported by NOESY experiments.

(18) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

(19) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.*, **2008**, *130*, 1566.

(20) Siu, J. C.; Parry, J. B.; Lin, S. *J. Am. Chem. Soc.*, **2019**, *141*, 2825.