Synthetic and computational studies on the tricarboxylate core of 6,7-dideoxysqualestatin H5 involving a carbonyl ylide cycloaddition–rearrangement†

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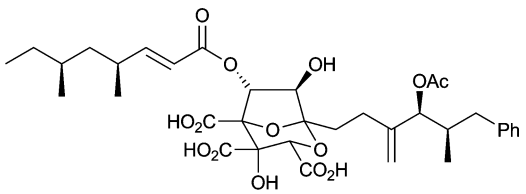
Received 19th March 2010, Accepted 8th June 2010
First published as an Advance Article on the web 2nd July 2010
DOI: 10.1039/c004496b

Reaction of diazodiketoesters **17** and **28** with methyl glyoxylate in the presence of catalytic rhodium(II) acetate generates predominantly the 6,8-dioxabicyclo[3.2.1]octanes **29** and **30**, respectively. Acid-catalysed rearrangement of the corresponding alcohol **31** favours, at equilibrium, the 2,8-dioxabicyclo[3.2.1]octane skeleton **33** of the squalestatins–zaragozic acids. Force field calculations on the position of the equilibrium gave misleading results. DFT calculations were correct in suggesting that the energy difference between **31** and **33** should be small, but did not always suggest the right major product. Calculation of the NMR spectra of the similar structures could be used to assign the isomers with a high level of confidence.

Introduction

More people die annually from cardiovascular diseases (CVDs), a group of disorders of the heart and blood vessels, than from any other cause.[1] High levels of cholesterol are strongly associated with CVDs and statins are effective in preventing heart diseases by inhibiting HMG-CoA reductase, the rate-controlling enzyme of the cholesterol biosynthetic pathway. Squalene synthase inhibitors have shown promise as an alternative to statins in reducing levels of cholesterol.[2] As part of the search for more effective medicines, fungal extracts were screened for inhibition of squalene synthase, which lead to the isolation of the zaragozic acids (squalestatins) in the early 1990s [*e.g.* zaragozic acid A (squalestatin S1) (**1**) (Fig. 1)].[3–5] Squalene synthase catalyses the first committed step of cholesterol biosynthesis, and zaragozic acids are picomolar inhibitors of this enzyme. The structurally novel and synthetically challenging 2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core, together with the biological activity of the zaragozic acids, has resulted in this family of molecules becoming irresistible targets for synthetic chemists. Total syntheses of several zaragozic acids and many synthetic studies towards the highly oxygenated core have been reported.[6]



Zaragozic acid A (**1**)

Fig. 1

As part of a research programme exploring the scope of diazocarbonyl-derived carbonyl ylide [3+2] dipolar cycloadditions as a powerful complexity-generating strategy in target and asymmetric synthesis,[7] we detail here our successful synthetic approach (together with associated computational studies) to the triester of an anhydrofuranose core **3**[8] (Scheme 1) of 6,7-dideoxysqualestatin H5 (**2**),[9] the least oxygenated member of the squalestatin family. Our approach to this core **3** envisages as keys steps an acid-catalysed intramolecular transketalisation of a 6,8-dioxabicyclo[3.2.1]octane system **4** forged by a carbonyl ylide cycloaddition (**6**→**4**). The latter involves a glyoxylate as dipolarophile to directly produce the triacid functionality at the correct oxidation level, and requires preferential generation of 1 out of 8 possible cycloadducts.

In earlier cycloaddition studies, we demonstrated the viability of glyoxylates as dipolarophiles with more commonly used 2-diazo-3,6-diketoesters substrates.[10,11] While these cycloadditions occurred with the regioselectivity desired in Scheme 1 unfortunately, and under all conditions examined, the glyoxylate ester group was preferentially incorporated *endo* with respect to the ylide-containing ring (*e.g.*, **7**→**8** in Scheme 2).

By incorporating the α-hydroxy ester functionality at C-3 shown in the cycloaddition substrate **6** (Scheme 1), we aimed to reverse the earlier *endo* preference exemplified in Scheme 2—which was ascribed to secondary orbital overlap between ketone(dipole) and ester(dipolarophile) functionality. Also, by appropriate choice of hydroxyl protection, it was hoped to provide a strong

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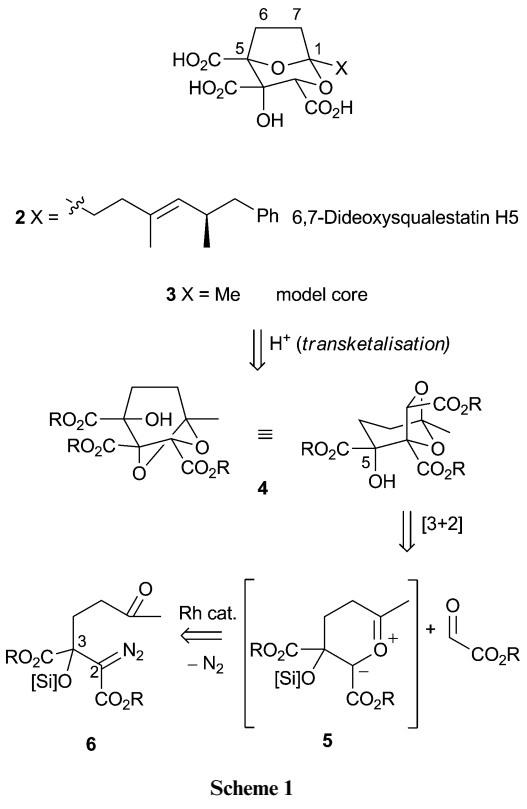
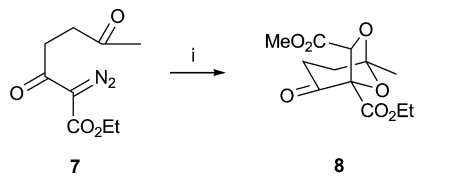
† Electronic supplementary information available: Experimental details for compounds **11**–**19**, **20** (*via* **19**), **21** (*via* **24**), **22**–**24** and **29**, assignment of spirolactones **34**, structures arising from opposite facial selectivity in cycloaddition, comparison of NMR spectra of alcohols **31** and **33** with natural product **2**, ^{1}H and ^{13}C NMR spectra of new compounds, Cartesian coordinates and energies of the DFT structures, and CP3 calculations. See DOI: 10.1039/c004496b

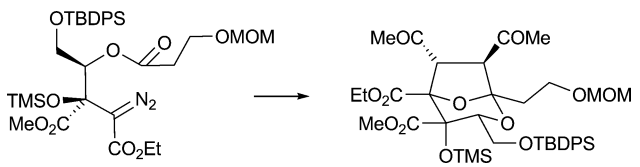


Scheme 1



Scheme 2 *Reagents and conditions*: methyl glyoxylate, $Rh_2(OAc)_4$ (cat.), PhMe, 110 °C (60%).[10,11]

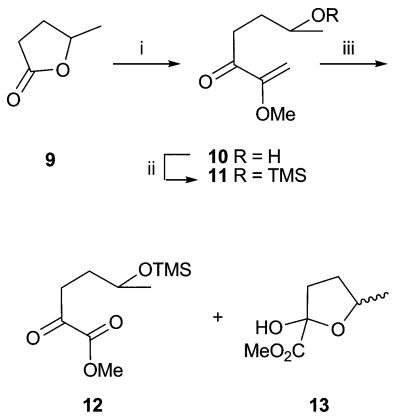
diastereofacial bias in the ylide **5** to the incoming dipolarophile. In this regard, we were encouraged by a related carbonyl ylide formation–cycloaddition from a triester in Hashimoto and co-workers' approach to zaragozic acid C (Scheme 3, note however, that the diastereomeric triester failed to undergo cycloaddition).[6h,12]



Scheme 3 *Reagents and conditions*: (*E*)-3-hexene-2,5-dione, $Rh_2(OAc)_4$ (cat.), benzene, 80 °C (47%).[12]

Results and discussion

So as to examine the chemistry outlined in Scheme 1, a synthesis of cycloaddition substrate **6** (R = Me, [Si] = $SiMe_3$ was developed. The synthesis of TMS-protected α-diazoester **17** commenced with γ-valerolactone (**9**) and proceeded as shown in Scheme 4 and Scheme 5. Ring-opening of lactone **9** by an amine followed by suitable protection of the free alcohol and nucleophilic attack on

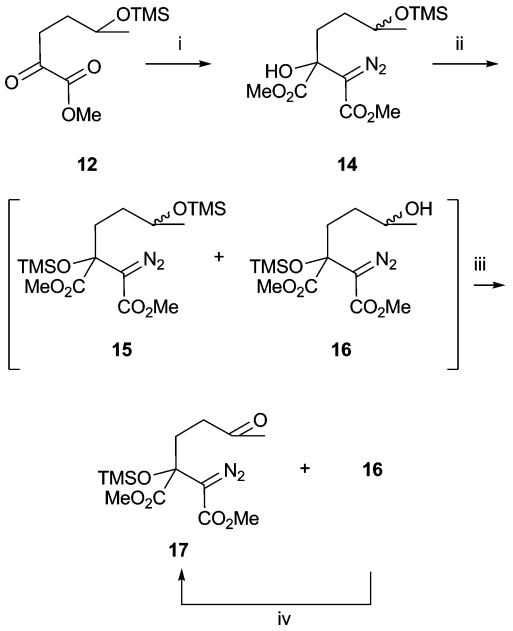


Scheme 4 *Reagents and conditions*: i, methyl vinyl ether, *t*-BuLi, THF, –78 °C (92%); ii, TMSCl, pyridine, THF, 0 °C, (92%); iii, O_3, CH_2Cl_2, –78 °C, then Ph_3P (**12** : 33% and **13**: 30%).

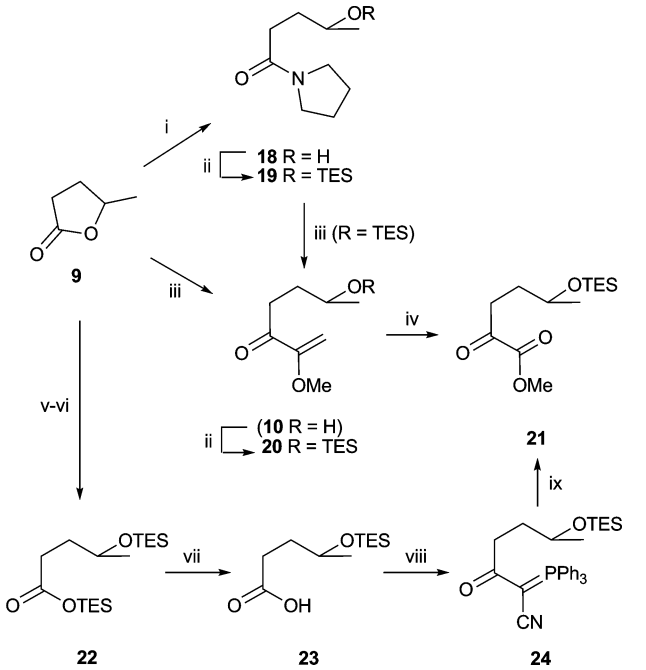
the generated amide by a masked carboxylate nucleophile was not considered necessary in this unsubstituted lactone. Indeed, addition of 1-methoxyvinyllithium was found to be straightforward, generating the unstable ring-opened hydroxyketone **10**, in 92% yield. However, if the reaction was allowed to warm to room temperature before being quenched, a mixture of hydroxyketone **10** and the corresponding lactol was obtained; only for highly substituted lactones is the lactol generated quantitatively on addition of a 1-alkoxyvinyllithium[13] and therefore requires an initial transformation into an amide, as seen in Carreira and Dubois' total synthesis of zaragozic acid C.[14] Moreover, in the current studies, a strategy proceeding through an intermediate amide did not provide significant improvement (*vide infra*).

Protection of the free hydroxyl group of hydroxyketone **10** using TMSCl-pyridine provided the TMS ether **11**, in 92% yield [this silyl group was found to be quite labile (*vide infra*) and would later be (preferably) replaced by the less labile triethylsilyl group]. Ozonolysis of TMS ether **11** provided α-ketoester **12** in low yield. Cleavage of the TMS ether was found to occur in solution, and ozonolysis of a solution of TMS ether **11** which had been standing at room temperature for a couple of hours gave lactol **13** as the major product. Repetition of the reaction using freshly prepared **11** gave the same components, indicating that desilylation was also occurring to some extent at low temperatures, though now favouring the desired α-ketoester **12** in the crude mixture (1.6 : 1) albeit isolated in only 33% yield (lactol **13** was also isolated, in 30% yield).

Addition of lithiated methyl diazoacetate[15] to α-ketoester **12** gave α-diazoester **14** in 44% yield (53% based on recovered **12**, Scheme 5). TMS protection of the free tertiary hydroxyl group was achieved using TMS-imidazole in THF; however, deprotection (or, possibly, silyl migration to the tertiary alcohol) occurred at the labile secondary TMS ether to some extent during this step and the crude reaction mixture contained disilyl and monosilyl ethers **15** and **16** in 1 : 0.4 ratio, respectively. The latter was not inconvenient since selective cleavage of the secondary TMS ether was next required, although the lability of the secondary TMS ether may account for some of the low yields throughout this synthetic sequence. Reaction of the crude mixture of silyl ethers **15** and **16** with PCC effected concomitant deprotection of the secondary TMS ether in **15** and oxidation, giving the desired cycloaddition



Scheme 5 *Reagents and conditions*: i, LDA, N_2CHCO_2Me, THF, −78 °C (44%); ii, TMS-Im, THF, 25 °C, **15** : **16** 1 : 0.4; iii, PCC, CH_2Cl_2, 25 °C (**17** : 58% and **16**: 7%); iv, PCC, NaOAc, CH_2Cl_2, 25 °C (62%).



Scheme 6 *Reagents and conditions*: i, pyrrolidine, PhMe, 25 °C (86%); ii, TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (65% from **10** and 92% from **18**); iii, methyl vinyl ether, *t*-BuLi, THF, −78 °C (92%); iv, O_3, pyridine, CH_2Cl_2, −78 °C, then Ph_3P (57%); v, NaOH, MeOH (88%); vi, TESCl, Imidazole, DMF, 100 °C (42%); vii, K_2CO_3, MeOH, THF, H_2O, 25 °C (71%); viii, Ph_3P=CHCN, EDCI, DMAP, CH_2Cl_2, 0 °C to 25 °C (50%); ix, O_3, pyridine, CH_2Cl_2, MeOH, −78 °C, then Ph_3P (34%).

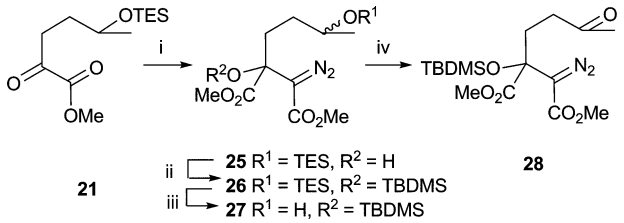
substrate α-diazoester **17** in 58% yield from α-diazoester **14**. A small amount of alcohol **16** (7%) was also isolated from this last reaction, which could be oxidised with PCC to provide further α-diazoester **17** (62%).

A cycloaddition substrate possessing an alternative silyl ether to that in TMS-protected α-diazoester **17** (such as TBDMS protection) was also sought, to enable comparison of the effect of a more sterically demanding ether in the subsequent cycloaddition chemistry. This also provided an opportunity to improve on the above synthetic sequence by moving away from the rather labile secondary TMS ether. However, the protecting group for the secondary alcohol would need to be sufficiently stable to survive the previously developed chemistry (Scheme 4 and Scheme 5), and at the same time be labile enough to be cleaved in the presence of a TBDMS-protected tertiary alcohol under conditions which would not destroy the diazo group, whose stability is lowered due to the presence of the α-hydroxy group. Triethylsilyl ethers are typically 10–100 times more stable than TMS ethers, but are labile to mild acidic conditions.[16] With the above considerations in mind, TES-protected ketone **20** was obtained in 65% yield by silylation of hydroxyketone **10** with TESOTf–2,6-lutidine (Scheme 6). An alternative route to triethylsilyl ether **20** was also achieved, *via* amide **18**.[17] Addition of excess α-lithio methyl vinyl ether to TES-protected amide **19** gave ketone **20** (92% yield), without any signs of overaddition according to ^{1}H NMR analysis of the crude reaction mixture. Optimal yields of α-ketoester **21** (57%) were obtained by submitting freshly prepared ketone **20** to ozonolysis in the presence of pyridine[18] [to minimise (acid-catalysed) hydrolysis of the vinyl ether]; no lactol was observed, which is indicative of the robustness of the TES protecting group.

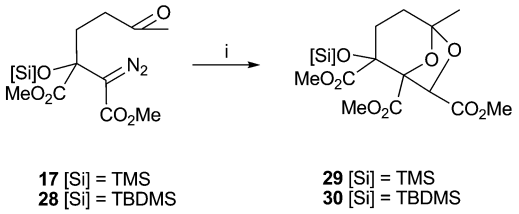
An alternative strategy to α-ketoester **21** utilised chemistry of Wasserman and Ho, wherein a β-ketocyanophosphorane is ozonolysed to yield the corresponding α-keto ester.[19] The required β-ketocyanophosphorane **22** was synthesised from γ-valerolactone (**9**) by hydroxide-induced ring-opening (88%),[20] TES-capping of both acid and hydroxyl groups (42%), then selective cleavage of the resulting silyl ester **2** using K_2CO_3 to reveal acid **23** (71%), which was finally coupled with (cyanomethylene)triphenylphosphorane in moderate yield (50%). Ozonolysis of β-ketocyanophosphorane **24** was first attempted in a solution of MeOH and CH_2Cl_2;[21] however, these reaction conditions led to the formation of lactol **13**, presumably due to the *in situ* formation of HCN which cleaved the silyl protecting group and promoted ring-closure. Addition of pyridine to the reaction mixture circumvented this problem and α-ketoester **21** was obtained in 34% yield. The moderate yields from the ozonolyses reactions are attributed to hydration of the α-ketoesters on silica;[6g] however, in the present case addition of Me_2S instead of Ph_3P following ozonolysis (in order to avoid chromatographic purification), did not lead to improvement.

Addition of lithiated methyl diazoacetate[15] to α-ketoester **21** gave α-diazoester **25**, in 62% yield (Scheme 7). Pleasingly, the derived TBDMS ether **26** (72% from **25** using TBDMSOTf and 2,6-lutidine) underwent selective deprotection (76%) of the secondary TES ether using AcOH in THF–water after 1 h, without affecting either the tertiary silyl ether or the diazo group. Oxidation of the resulting secondary alcohol **27** using PCC generated the desired cycloaddition substrate **28**, in 90% yield.

α-Diazoesters **17** and **28** underwent $Rh_2(OAc)_4$-catalysed tandem carbonyl ylide formation–cycloaddition with methyl glyoxylate to each give a mixture of three cycloadducts in ratios 8 : 1 : 1 and 12 : 2 : 1, respectively (Scheme 8). The isomer proportions were assigned from the clear singlets of the bridge methines in the crude ^{1}H NMR spectra. The isomers could not be totally



Scheme 7 *Reagents and conditions*: i, LDA, N_2CHCO_2Me, THF, −78 °C (62%); ii, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to 25 °C (72%); iii, AcOH–THF–H_2O, 25 °C (76%); iv, PCC, NaOAc, CH_2Cl_2, 25 °C (90%).



Scheme 8 *Reagents and conditions*: i, methyl glyoxylate, PhMe, 110 °C, then $Rh_2(OAc)_4$ (cat.) (**29** : 54%; **30** : 63.5%).

separated after column chromatography. From α-diazoester **17** a 54% combined yield of cycloadducts was obtained, with a major fraction (47%) predominantly consisting of cycloadduct **29** (Fig. 2) along with traces (10 : 0 : 1) of a minor cycloadduct. Cycloadducts **30** (63.5%) was similarly isolated along with traces (10 : 0 : 1) of a minor cycloadduct.

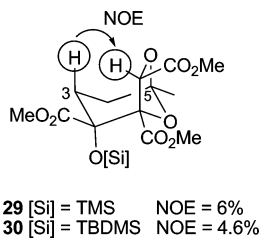
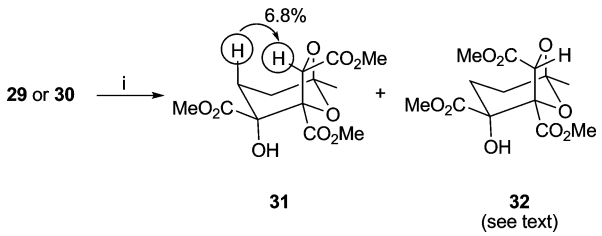


Fig. 2

The stereochemistry of the major cycloadduct isomer in both cases was assigned as that required for 6,7-dideoxysqualestatin H5 synthesis. Configurational assignments were made following NOE studies on the major isomers (Fig. 2). An NOE betweeen C7–H and one H of C3–H_2 of 6% for cycloadduct **29** and 4.6% for cycloadduct **30** suggest the major isomers to be *exo*- with respect to the six-membered ring. Facial selectivity was assigned on the basis of Hashimoto's precedent,[12] together with the fact that the cycloaddition on the more sterically demanding α-diazo ester **28** provided a higher proportion of the major cycloadduct. Data supporting the cycloaddition regioselectivity in cycloadducts **29** and **30** are ketal carbon C5 [δ_C 110.2 for both cycloadducts, and δ_C 111.0 for C5 in cycloadduct **8** (Scheme 2), where the structure was previously established by X-ray crystallographic analysis[11]] and HMBC conectivities with C4–H_2 and C5–Me. It is apparent that modification of the α-keto group of the ylide to bulkier α-silyloxy ester functionality led to 1,3-dipolar cycloaddition occurring preferentially on the less-hindered face (the one opposite to the silyloxy group) to avoid steric interactions, and with the methyl glyoxylate orienting itself *exo* to the ylide-containing ring.

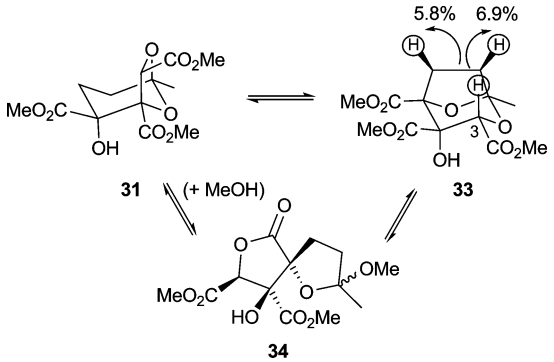
With the major cycloadducts possesing the desired stereochemistry, their propensity to undergo the transketalisation process was next examined. Firstly, desilylation of the cycloadducts **29** and **30** was performed using TBAF in THF. From the reaction of cycloadduct **29** the resulting isomeric alcohols were now separable, however, the desired alcohol **31** was isolated in only 15% yield. More promising results were obtained from the desilylation of cycloadduct **30** using TBAF, with alcohol **31** being isolated in 72% yield as a single isomer (Scheme 9). From a larger scale desilylation using cycloadduct **30**, containing some of a minor isomer, a fraction consisting of mainly the corresponding desilylated minor isomer (tentatively assigned as alcohol **32**), could be isolated (5.5% yield) and differences between the NOE spectra of the two different alcohol isomers could then be compared in order to further strengthen the assigned structure of the major cycloadduct. An NOE for the major desilylated cycloadduct **31** of 6.8% betweeen C7–H and one H of C3–H_2 and the absence of a corresponding NOE for the minor cycloadduct **32**, together with the NOE data on the rearranged material (*vide infra*) further suggests the major isomer **31** to have the glyoxylate-derived ester group *exo*-disposed relative to the six-membered ring.



Scheme 9 *Reagents and conditions*: i, TBAF, THF, 25 °C (**31** : 15% from **29**; 72% from **30**).

Treatment of cycloadduct alcohol **31** under the rearrangement conditions previously described by Nicolaou and co-workers (2% HCl in MeOH at reflux)[22] gave, after 15 h, a mixture of four bicyclic compounds in a ratio of 69 : 21 : 5 : 5, as suggested by integration of the methine singlets in the δ 5.60 to 4.80 region of the ^{1}H NMR spectrum of the crude mixture; the major component of the mixture being starting material. Separation of the two major components could be achieved after column chromatography in 40% and 13% yield respectively, while the two minor less polar compounds were isolated as a 1 : 1.5 mixture in 5% combined yield. The latter mixture was tentatively assigned as a mixture of diastereomeric spirolactones **34** (Scheme 10, further information is given in the ESI†).

Assignment of the most polar component as the desired 2,8-dioxabicyclic core **33** was made on the basis of ^{1}H NMR and NOE studies. Small vicinal coupling constants around the ring suggested that the dimethylene group was confined to a five-membered ring,[23] while NOE enhancements were obtained on two protons, one of each methylene, when H-3 was irradiated. The observed NOE enhancements further corroborate the assigned facial selectivity in the cycloaddition step; opposite facial selectivity would have resulted in a rearranged bicyclic compound where NOE enhancements between the H-3 and the 5-membered ring



Scheme 10 *Reagents and conditions*: H^+ (see Table 1).

Table 1 Effect of experimental conditions on the transketalisation process

Entry	Conditions	Crude ratio **31** : **33** : **34**	Substrate
1	2% HCl, MeOH, Δ, 15 h	69 : 21 : 10	**31**
2	CSA, MeOH, Δ, 24 h	83 : 13 : 14	**31**
3	2% HCl, $CHCl_3$, Δ, 15 h	100 : 0 : 0	**31**
4	Triflic acid, DMSO-d_6, 25 °C, 4 d	100 : 0 : 0	**31**
5	Triflic acid, $CDCl_3$, 25 °C, 4 d	75 : 25 : 0	**31**
6	CH_2Cl_2/TFA/H_2O 20 : 10 : 1, Δ, 15 h	40 : 60 : 0	**31**
7	CH_2Cl_2/TFA/H_2O 20 : 10 : 1, Δ, 15 h	28 : 78 : 0	**33**
8	CH_2Cl_2/TFA/H_2O 20 : 10 : 1, Δ, 68 h	34 : 66 : 0	**31**
9	CH_2Cl_2/TFA/H_2O 20 : 10 : 1, Δ, 68 h	34 : 66 : 0	**33**

protons would have been absent (see ESI†). Moreover, the ^1H and ^{13}C NMR spectra of 2,8-dioxabicyclo[3.2.1]octanetrioate **33** were very similar with regard to the corresponding signals reported for the natural product **2**[9] (particularly ring methine chemical shifts, for a detailed comparison see the ESI†).

A range of other acidic conditions were then screened for the rearrangement of alcohol **31** (Table 1). CSA in MeOH gave some signs of isomerisation to the core **33**, although a 1 : 1 mixture of spirolactones **34** was again observed and starting **31** was still the major component present (Table 1, entry 2). To avoid the formation of spirolactones **34** other solvents were examined. No reaction occurred with 2% HCl in $CHCl_3$ at reflux after 15 h (entry 3) or with triflic acid in DMSO-d_6 after 4 days at 25 °C (entry 4).[24] Triflic acid in $CDCl_3$ generated **33** but only in a poor ratio with respect to starting **31** (entry 5). Encouraging results were found under Evans' conditions (CH_2Cl_2/TFA/H_2O 20 : 10 : 1)[25] (40 : 60 **31** : **33**, entry 6). However, submitting the isolated rearranged material **33** to the same conditions did not provide the same ratio (entry 7), suggesting that true equilibrium had not been reached. Prolonged exposure to Evans' conditions (68 h) slightly increased the proportion of **33** (entry 8), so that it dominated the reaction mixture (**31**:**33**, 34 : 66), thus validating our rearrangement strategy to the 2,8-dioxabicyclo[3.2.1]octane core of the zaragozic acids/squalestatins. The desired core **33** was then isolated in 54% yield (83% based on recovered **31**). That true equilibrium had been reached was established by subjecting core **33** to these latter reaction conditions, which resulted in the same ratio of alcohols **31** : **33** (entry 9).

Molecular mechanics calculations for cycloadduct alcohol **31** and rearranged alcohol **33** using the MM2* force field[26] and the OPLSAA force field[27] as implemented in MacroModel[28] lead to the prediction that rearranged alcohol **33** should not be observed at equilibrium, as the energy difference between the two isomers is greater than 25 kJ mol^{-1} in both cases (Table 2, entries 1–3). However, such force fields underestimate the energies of 1,3-dioxolanes compared to 1,3-dioxanes, because key atoms are now in a 1,4 relationship instead of a 1,3 relationship, and so the intra-ring electrostatic interactions are treated inconsistently.[24] This anomaly can be treated by scaling the electrostatic interactions, or, in the case of reasonably small molecules like **31** and **33**, using a higher level of theory. The DFT methods, using Jaguar,[29] all suggest that the energy differences between **31** and **33** should

Table 2 Calculated equilibrium ratios **31** : **33**[a]

Entry	Theory	E(**33**) – E(**31**)/kJ mol^{-1}	Calcd. **31** : **33**
1	MM2*	26.6	100 : 0
2	OPLSAA	25.9	100 : 0
3	OPLSAA with continuum water	25.1	100 : 0
4	B3LYP/6-31G**	0.0	50 : 50
5	B3LYP/6-31G** with CH_2Cl_2 model[bc]	–1.3	38 : 62
6	B3LYP/6-31G** with CH_2Cl_2 model[bd]	–2.0	31 : 69
7	B3LYP/6-31++G**	–0.4	46 : 54
8	LMP2/6-31G** [ce]	3.5	80 : 20
9	LMP2/6-31G** [de]	4.0	83 : 17

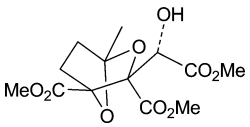
	E(**33**) – E(**31**)/kJ mol^{-1}			Calcd. **31** : **33**		
	6-31G**	6-311+G**	cc-pVTZ	6-31G**	6-311+G**	cc-pVTZ
B3LYP	0.0	2.2	–4.0	50 : 50	71 : 29	17 : 83
BHandHLYP	3.3	3.5	1.2	79 : 21	80 : 20	62 : 38
M05	2.8	1.5	–1.4	76 : 24	64 : 36	36 : 64
M06	4.6	6.0	2.1	86 : 14	92 : 8	70 : 30
MPW1PW91	–2.5	–0.2	–2.2	27 : 73	48 : 52	29 : 71

[a] Conformation searches were carried out with MM2* and OPLSAA. The lowest energy OPLSAA geometries were reminimised using the DFT methods. [b] Continuum model using Jaguar's Poisson–Boltzmann continuum solvation model and default parameters for dichloromethane.[36a] [c] Single point. [d] Optimisation. [e] Local MP2, all pairs.[36b]

be small (entries 4–7), and LMP2 calculations reinforce this (entries 8–9). Only B3LYP[30,31] used with a solvent model and MPW1PW91[32] suggested that rearranged alcohol **33** should be thermodynamically preferred to cycloadduct alcohol **31** by a small amount, as is experimentally observed. BHandHLYP,[33] M05[34] and M06[35] all show, correctly, that the energy differences between the structures are small, but suggest a favoured structure opposite to that found from experiment. Increasing the size of the basis set (Table 2, section 2) did not give consistent results. 6-311+G** give similar results to 6-31G**, slightly increasing the preference for **31** in most cases. The largest basis set investigated, cc-pVTZ, slightly overestimates the preference for **33**.

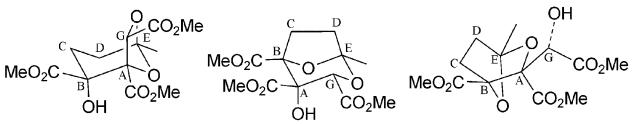
We conclude that calculations on equilibria with these structures must be treated with caution, even when quite a high level of theory is being used. The force fields give very misleading estimates of the energy differences, as expected. The DFT methods, however, do not give a reliable guide to the major isomer in most cases, and in the seven where they do (B3LYP/6-31G** with a solvent model, MPW1PW91/6- 31G**, B3LYP/6-31++G**, MPW1PW91/6-311+G**, B3LYP/cc-pVTZ, M05/cc-pVTZ, and MPW1PW91/cc-pVTZ) it may be that the agreement is fortuitous. LMP2 (entries 8 and 9) gives similar results to the DFT methods, intermediate between M05 and M06 with the same basis set. This is a particularly difficult comparison, because the experimental results suggest that the energy difference should be small, and so a high degree of precision is required to ensure that the right sense of selectivity is obtained. The calculations could have been improved by performing DFT calculations on all fifty of the OPLSAA calculated conformations, and further improved by doing a further conformation search on the DFT potential energy surface. Both of these procedures would take a prohibitive amount of computer power. Calculations on these systems appear to be useful at the DFT level, provided that they are not expected to be accurate to more than a few kJ mol^{-1} in comparing the isomers.

5,7-Dioxabicyclo[2.2.1]heptanetrioate **35** could not be unambiguously ruled out as the major product from the acid-catalysed rearrangement of cycloadduct alcohol **31**, as alcohols **33** and **35** would be anticipated to have very similar NMR spectra (see Table 3). In order to check that bicyclo[2.2.1]heptane **35** is higher in energy, we carried out an OPLSAA conformation search on **35** and re-calculated the energy using B3LYP/6-31G** in the same way as we had done for alcohols **31** and **33** in Table 2, entry 4. These calculations show that **35** is much higher in energy (about 20 kJ mol^{-1}) than alcohol **33**. The comparison of **31** and **33** suggested that these calculations were probably accurate to within a few kJ mol^{-1}. This level of precision makes a large difference when comparing two structures with similar energies, such as **31** and **33**. For the comparison of **33** and **35** this uncertainty is less than 10% of the difference, and so we can be confident that under equilibrium conditions the ratio between bicyclic alcohols **31**, **33** and **35** would contain almost no **35**.



35

As a further check, we calculated the ^{13}C NMR spectra for bicyclic alcohols **31**, **33**, and **35**, at the B3LYP/6-31G** level of theory, using the same structures reported above and the GIAO method.[37] Our earlier studies suggest that this is an appropriate level of theory for structures of this type.[38] The results are given in Table 3. We have developed a comparison parameter, CP3, to help to pair computational and experimental NMR data and to give a measure of the confidence that we can have in the results.[39] CP3 is positive for the assignment of alcohols **31** and **33** illustrated in Scheme 10, suggesting that this is the correct assignment. Swapping the assignments of alcohols **31** and **33** gives a negative CP3 value, suggesting this is the incorrect assignment. A Bayesian analysis of these values indicates that we can be confident (>99.9%) that the spectra have been assigned the correct way around, consistent with the result expected from the cycloaddition reaction. If we assume that one of the two compounds is bicyclo[2.2.1]heptane **35**, then the CP3 value is negative for all pairings, indicating that the experimental data do not fit the calculated values, further reaffirming the assignment of **31** and **33**.



31 **33** **35**

Table 3 Experimental and calculated ^{13}C data for bicyclic alcohols **31**, **33** and **35**

C atom[a]	**31** *expt*	**31** *calc*	**33** *expt*	**33** *calc*	**35** *calc*
B-CO_2	173.8	170.4	168.7	163.9	160.9
A-CO_2	169.2	165.1	169.9	163.8	165.8
G-CO_2	166.7	163.2	167.4	162.3	167.8
E	111.0	111.7	107.6	107.6	112.3
A	89.4	94.6	74.9	79.5	92.0
G	77.6	80.3	74.9	78.7	71.4
B	73.7	76.1	88.3	92.8	94.7
A-CO_2*Me*	53.7	52.0	53.3	52.1	52.0
B-CO_2*Me*	53.0	52.6	52.9	51.7	51.6
G-CO_2*Me*	52.6	51.7	52.7	51.6	52.4
D	30.8	32.7	32.8	34.0	38.0
C	29.6	32.8	29.4	31.3	33.2
E-Me	23.6	24.5	23.6	24.0	19.3

[a] The assignments of the ester and methoxy C atoms are based on matching their peaks as closely as possible to the calculated values.

Conclusions

The carbonyl ylide cycloaddition precursors α-diazoesters **17** and **28** [each 7 steps from γ-valerolactone (**9**)] were designed to remove the potential secondary orbital effect between previously studied carbonyl ylides and a glyoxylate dipolarophile. This effect was considered a significant influence on the cycloadduct stereochemistry, which was undesired for projected squalestatin synthesis. In the current work, the putative carbonyl ylides generated *in situ* from the rhodium-catalysed decomposition of α-diazoesters **17** and **28** underwent highly diastereoselective cycloadditions using methyl glyoxylate as the dipolarophile, with the major cycloadduct diastereomers **29** and **30** now possessing the required stereochemistry for 6,7-dideoxysqualestatin H5 (**2**) synthesis. Use of α-diazoesters **29** and **30** not only reversed the *endo*-selectivity previously observed simple α-diazo-β-ketoesters,

but also delivered strongly biased face selectivity arising from the α-silyloxyester stereocentre. Transketalisation of cycloadduct **31** under thermodynamic conditions resulted in favourable isomerisation to the bicyclic core **33** contained in 6,7-dideoxysqualestatin H5 (**2**). All of the DFT calculations calculated, correctly, that the energy difference between the isomers should be small. However, the methods disagreed about the degree and sense of the preference. Application of the above chemistry to the synthesis of 6,7-dideoxysqualestatin H5 is currently under investigation, and the results will be reported in due course.

Experimental

General details

All reactions requiring dry or inert conditions were conducted in flame-dried equipment under an atmosphere of argon. Syringes and needles were oven-dried and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium-benzophenone; (chlorinated) hydrocarbons, amines, MeOH and DMF from CaH_2 and TMSCl from quinoline; acetone was dried over 4 Å molecular sieves for 30 min. Reactions were monitored by TLC using commercially available Merck silica gel 60 F_{254} glass-backed plates. Visualisation of reaction components was achieved with a UV lamp (254 nm) and with vanillin or $KMnO_4$ stains. Column chromatography was carried out on silica gel 60 (particle size 40–63 μm) as supplied by Merck. Preparative TLC was performed using 2 mm pre-coated glass-backed plates (Merck). Light petroleum refers to the fraction with bp 40–60 °C. IR spectra were recorded as thin films unless stated otherwise using a Perkin-Elmer 1733 instrument. Peak intensities are specified as strong (s), medium (m) or weak (w). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless stated otherwise on Varian Gemini 200, Brüker DPX400, Brüker DPX330 or Brüker AMX330 instruments. Chemical shifts are reported relative to the internal solvent [*e.g.* δ_H 7.27, δ_C (central line of t) 77.0 for $CDCl_3$]. Coupling constants (J) are given in Hz to the nearest 0.5 Hz. Mass spectra were obtained from the EPSRC National Mass Spectrometry Service Centre, Swansea with a VG Micromass Zab-E instrument under EI or CI (NH_3) conditions, or at Oxford with a Micromass Platform APCI spectrometer. Organolithiums were titrated before use.[40]

6-Hydroxy-2-methoxyhept-1-en-3-one 10. *t*-BuLi (1.7 mol dm^{-3} in pentane; 100 cm^3, 170 mmol) was added to a stirred solution of methyl vinyl ether (22.0 g, 380 mmol) in THF (100 cm^3) at −78 °C. The resulting yellow solution was allowed to warm to 0 °C and stirred at this temperature for 10 min. The solution was then cooled to −78 °C and a solution of γ-valerolactone (**9**) (13 cm^3, 137 mmol) in THF (20 cm^3) was added. After 16 h at −78 °C, saturated aq. NH_4Cl (10 cm^3) was added and the reaction mixture was allowed to warm to 25 °C, then diluted with EtOAc (15 cm^3) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 15 cm^3) and the combined organic layers were washed with brine (10 cm^3), water (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, crude *alcohol* **10** (20.0 g, 92%) which was used directly in the next step; R_f 0.23 (60% Et_2O in light petroleum); ν_{max}/cm^{-1} 3400 s, 2968 s, 1698 s, 1613 s, 1454 m, 1377 m, 1299 m, 1058 s and 852 m; δ_H(200 MHz) 5.23 (1 H, d, J 3, H of =CH_2), 4.48 (1 H, d, J 3, H of =CH_2), 3.90–3.70 (1 H, m, CH), 3.64 (3 H, s, OMe), 2.82 (2 H, t, J 7.5, CH_2), 1.90–1.60 (2 H, m, CH_2) and 1.21 (3 H, d, J 6, Me); δ_C(100 MHz) 197.9 (C(3), quat.), 158.4 (C(2), quat.), 90.7 (CH_2=), 67.3 (CH), 55.2 (OMe), 34.2 (CH_2), 32.6 (CH_2) and 23.5 (Me).

6-(Triethylsilyloxy)-2-methoxyhept-1-en-3-one 20. From **10**: TESOTf (1.0 cm^3, 4.7 mmol) was added to a stirred solution of 2,6-lutidine (1.0 cm^3, 4.7 mmol) in CH_2Cl_2 (8 cm^3) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, then cooled to −78 °C. A solution of crude alcohol **10** (500 mg, 3.16 mmol) in CH_2Cl_2 (5 cm^3) was then added, and the reaction mixture was stirred at −78 °C for 5 min. Water (10 cm^3) was then added, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic layers were washed with brine (10 cm^3), water (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a colourless oil, *silyl ether* **20** (0.56 g, 65%) which was used directly in the next step; R_f 0.56 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 2956 m, 2913 s, 2877 s, 1709 m, 1613 s, 1458 m, 1376 m, 1139 m, 1055 s, 1005 s, 848 w and 743 s; δ_H(400 MHz) 5.20 (1 H, d, J 3, =CH_2), 4.46 (1 H, d, J 3, =CH_2), 3.87–3.81 (1 H, m, CH), 3.63 (3 H, s, Me), 2.81–2.67 (2 H, m, CH_2), 1.80–1.63 (2 H, m, CH_2), 1.15 (3 H, d, J 6, Me), 0.95 (9 H, t, J 8, Si(CH_2*Me*)$_3$) and 0.58 (6 H, q, J 8, Si(*CH*$_2$Me)$_3$); δ_C(100 MHz) 197.7 (C(3), quat.), 158.5 (C(2), quat.), 90.6 (CH_2=), 67.4 (CH), 55.2 (OMe), 34.0 (CH_2), 33.2 (CH_2), 23.7 (Me), 6.8 (Si(CH_2*Me*)$_3$) and 4.9 (Si(*C*H$_2$Me)$_3$); m/z (APCI) 141 (M–OTES, 100%).

Methyl-5-(triethylsilyloxy)-2-oxohexanoate 21. From **20**: A mixture of O_3/O_2 was bubbled through a stirred solution of silyl ether **20** (138 mg, 0.51 mmol) and pyridine (0.5 cm^3) in CH_2Cl_2 (50 cm^3) at −78 °C. After 40 min, the stream of O_3/O_2 was stopped and argon was bubbled through for 10 min. Ph_3P (146 mg, 0.56 mmol) was then added, the reaction mixture allowed to warm to 25 °C and then evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution: 5% Et_2O in light petroleum to 10% Et_2O in light petroleum) gave a colourless oil, *α-ketoester* **21** (80 mg, 57%); R_f 0.44 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 2956 s, 2913 m, 2878 s, 1732 s, 1458 w, 1378 m, 1062 m, 1005 s and 743s; δ_H(400 MHz) 3.95–3.80 (1 H, m, CH), 3.85 (3 H, s, OMe), 2.98–2.71 (2 H, m, CH_2), 1.88–1.65 (2 H, m, CH_2), 1.14 (3 H, d, J 6, Me), 0.93 (9 H, t, J 8, Si(CH_2*Me*)$_3$) and 0.56 (6 H, q, J 8, Si(*CH*$_2$Me)$_3$); δ_C(100 MHz) 194.1 (C(2), quat.), 161.4 (C(1), quat.), 67.0 (CH), 52.8 (OMe), 35.3 (CH_2), 32.6 (CH_2), 23.5 (Me), 6.8 (Si(CH_2*Me*)$_3$) and 4.8 (Si(*C*H$_2$Me)$_3$); m/z (CI, NH_3) 292 (M + NH_4^+, 20%), 275 (100), 245 (10), 217 (15), 160 (20) and 143 (30) (Found M + H$^+$: 275.1678. $C_{13}H_{27}O_5Si$ requires M, 275.1681).

Methyl 2-diazo-3-hydroxy-3-(methoxycarbonyl)-6-triethylsilyloxy heptanoate 25. A solution of LDA (3.88 mmol) [prepared from the addition of *n*-BuLi (1.9 mol dm^{-3} in hexanes; 2.0 cm^3, 3.88 mmol) to a solution of diisopropylamine (0.55 cm^3, 3.88 mmol) in THF (30 cm^3) at −78 °C] was slowly added to a stirred solution of α-ketoester **21** (626 mg, 2.28 mmol) and methyl diazoacetate[15] (92% w/w in CH_2Cl_2, 421 mg, 3.88 mmol) in THF (10 cm^3) at −78 °C. After 30 min at −78 °C, saturated aq. NH_4Cl (10 cm^3) was added, the mixture allowed to warm to 25 °C and then diluted with Et_2O (5 cm^3). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 cm^3). The combined organic layers

were washed with brine (15 cm^3), water (15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (20% Et_2O in light petroleum). First to elute was recovered ketone **21** (40 mg, 6%). Second to elute was a yellow oil, *α-diazoester* **25** [530 mg, 62% (69% based on recovered **21**); 1 : 1 mixture of diastereomers, by ^1H NMR analysis of the hydroxyl signals)]; R_f 0.50 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 3490 m, 2956 s, 2913 m, 2877 s, 2098 s, 1752 s, 1703 s, 1439 m, 1321 s, 1244 m, 1141 m, 1058 m and 744 s; δ_H(400 MHz) 4.31 (1 H, br, OH), 4.27 (1 H, br, OH), 3.90–3.70 (2 H, m, 2 × CH), 3.80 (6 H, s, 2 × OMe), 3.76 (6 H, s, 2 × OMe), 2.10–1.60 (6 H, m, 6 × H of CH_2), 1.40–1.20 (2 H, m, H of CH_2), 1.14 (6 H, d, *J* 6, 2 × Me), 0.95 (9 H, t, *J* 8, $Si(CH_2Me)_3$), 0.94 (9 H, t, *J* 8 $Si(CH_2Me)_3$), 0.59 (6 H, q, *J* 8, $Si(CH_2Me)_3$) and 0.57 (6 H, q, *J* 8, $Si(CH_2Me)_3$); δ_C(100 MHz) 173.5 (C, quat.), 173.4 (C, quat.), 166.1 (C, quat.), 166.1 (C, quat.), 73.8 (C, quat.), 73.7 (C, quat.), 68.1 (CH), 67.5 (CH), 53.4 (OMe), 53.4 (OMe), 52.0 (2 × OMe), 32.8 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.8 (CH_2), 23.9 (Me), 23.5 (Me), 6.8 (2 × $Si(CH_2Me)_3$), 4.9 ($Si(CH_2Me)_3$), and 4.8 ($Si(CH_2Me)_3$); *m/z* (APCI) 397 (M + Na^+, 10%), 315 (5), 287 (5), 215 (55), 183 (100) and 155 (50).

Methyl 3-*tert*-butyldimethylsilyloxy-2-diazo-6-(triethylsilyloxy)-3-(methoxycarbonyl)heptanoate 26. TBSOTf (5.2 cm^3, 22.6 mmol) was added to a stirred solution of 2,6-lutidine (3.7 cm^3, 33.5 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C. After 30 min, a solution of α-diazoester **25** (4.22 g, 11.3 mmol) in CH_2Cl_2 (5 cm^3) was added and the reaction mixture stirred at 25 °C. After 54 h, water was added (10 cm^3), the layers separated and the aqueous solution extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic layers were washed with brine (10 cm^3), water (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O in light petroleum) gave a yellow oil, bis(*silyl ether*) **26** [4.0 g, 72% (77% based on recovered **25**); 1 : 1 mixture of diastereomers, by ^1H NMR analysis of the SiMe group)]; R_f 0.64 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 2955 s, 2878 s, 2859 s, 2096 s, 1765, 1711 s, 1437 m, 1317 m, 1250 m, 1141 s, 1059 m and 839 m; δ_H(400 MHz) 3.80–3.70 (2 H, m, 2 × CH), 3.74 (3 H, s, OMe), 3.74 (3 H, s, OMe), 3.73 (6 H, s, 2 × OMe), 2.09 (1 H, ddd, *J* 12.5, 12.5 and 4, H of CH_2), 1.99 (1 H, ddd, *J* 12.5, 12.5 and 4.5, H of CH_2), 1.90 (1 H, ddd, *J* 12.5, 12.5 and 4.5, H of CH_2), 1.85 (1 H, ddd, *J* 12.5, 12.5 and 4.0, H of CH_2), 1.63–1.49 (2 H, m, CH_2), 1.43–1.29 (2 H, m, CH_2), 1.13 (6 H, d, *J* 6, 2 × Me), 0.95 (9 H, t, *J* 8, $Si(CH_2Me)_3$), 0.94 (9 H, t, *J* 8, $Si(CH_2Me)_3$), 0.88 (9 H, s, $SiCMe_3$), 0.88 (9 H, s, $SiCMe_3$), 0.58 (6 H, q, *J* 8, $Si(CH_2Me)_3$), 0.57 (6 H, q, *J* 8, $Si(CH_2Me)_3$), 0.13 (3 H, s, SiMe), 0.11 (3 H, s, SiMe), 0.06 (3 H, s, SiMe) and 0.05 (3 H, s, SiMe); δ_C(100 MHz) 171.6 (C, quat.), 171.5 (C, quat.), 76.2 (C, quat.), 76.0 (C, quat.), 68.1 (CH), 67.9 (CH), 52.6 (OMe), 52.6 (OMe), 51.8 (OMe), 51.8 (OMe), 34.8 (CH_2), 34.7 (CH_2), 33.3 (2 × CH_2), 25.7 (2 × $SiCMe_3$), 23.9 (Me), 23.8 (Me), 18.4 (C, quat.), 18.4 (C, quat.), 6.8 (2 × $Si(CH_2Me)_3$), 4.9 ($Si(CH_2Me)_3$), 4.9 ($Si(CH_2Me)_3$), –3.6 (SiMe), –3.6 (SiMe), –4.0 (SiMe) and –4.0 (SiMe); *m/z* (APCI) 511 (M + Na^+, 20%), 461 (20), 429 (100), 329 (90) and 183 (50). Second to elute was recovered alcohol **25** (250 mg, 6%); data as above.

Methyl 3-*tert*-butyldimethylsilyloxy-2-diazo-6-hydroxy-3-(methoxycarbonyl) heptanoate 27. A solution of silyl ether **26** (361 mg, 0.74 mmol) in acetic acid (2 cm^3), water (1 cm^3) and THF (1 cm^3) was stirred at 25 °C for 1 h. The reaction mixture was then evaporated, the residue redissolved in CH_2Cl_2 (5 cm^3) and the solution washed with saturated aq. $NaHCO_3$ (2 cm^3), water (2 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution: 40% Et_2O in light petroleum to 50% Et_2O in light petroleum) gave a yellow oil, *alcohol* **27** (210 mg, 76%; 1 : 1 mixture of diastereomers, by ^1H NMR of the SiMe groups); R_f 0.31 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 3417 w, 2956 m, 2931 m, 2858 m, 2098 s, 1747 m, 1704 s, 1438 m, 1317 s, 1142 s and 838 m; δ_H(400 MHz) 3.86–3.76 (2 H, m, 2 × CH), 3.75 (6 H, s, 2 × OMe), 3.73 (6 H, s, 2 × OMe), 2.18–2.06 (2 H, m, CH_2), 2.01–1.88 (2 H, m, CH_2), 1.75 (1 H, br, OH), 1.63–1.35 (5 H, m, 2 × CH_2 and OH), 1.19 (6 H, d, *J* 6, 2 × Me), 0.87 (18 H, s, 2 × $SiCMe_3$), 0.12 (3 H, s, SiMe), 0.11 (3 H, s, SiMe), 0.06 (3 H, s, SiMe) and 0.05 (3 H, s, SiMe); δ_C(100 MHz) 171.6 (C, quat.), 171.5 (C, quat.), 165.1 (2 × C, quat.), 76.0 (C, quat.), 76.0 (C, quat.), 67.8 (CH), 67.7 (CH), 52.7 (2 × OMe), 51.8 (2 × OMe), 34.5 (CH_2), 34.4 (CH_2), 32.9 (2 × CH_2), 25.7 (2 × $SiCMe_3$), 23.6 (2 × Me), 18.4 (2 × C, quat.), –3.6 (2 × SiMe) and –4.1 (2 × SiMe); *m/z* (ES) 397 (M + Na^+, 10%), 369 (15), 347 (5), 287 (10) and 215 (55) (Found M + Na^+: 397.1770. $C_{16}H_{30}N_2NaO_6Si$ requires *M*, 397.1771).

Methyl 3-*tert*-butyldimethylsilyloxy-2-diazo-3-methoxycarbonyl-6-oxoheptanoate 28. PCC (136 mg, 0.63 mmol) was added to a stirred solution of alcohol **27** (215 mg, 0.57 mmol) and NaOAc (24 mg, 0.28 mmol) in CH_2Cl_2 (10 cm^3). After 16 h at 25 °C, a slurry of silica gel in Et_2O (5 cm^3) was added, the mixture was filtered, evaporated under reduced pressure and purified by column chromatography (40% Et_2O in light petroleum) to give a yellow oil, *ketone* **28** (191 mg, 90%); R_f 0.50 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 2955 w, 2858 m, 2099 s, 1749 m, 1713 s, 1438 m, 1317 s, 1253 s, 1137 s, 1032 m and 838 s; δ_H(400 MHz) 3.74 (3 H, s, OMe), 3.73 (3 H, s, OMe), 2.64–2.56 (1 H, m, H of CH_2), 2.49–2.40 (1 H, m, H of CH_2), 2.25–2.21 (2 H, m, 2 × H of CH_2), 2.14 (3 H, s, Me) 0.87 (9 H, s, $SiCMe_3$), 0.10 (3 H, s, SiMe) and 0.05 (3 H, s, SiMe); δ_C(100 MHz) 207.0 (C(6), quat.), 171.1 (C, quat.), 165.0 (C, quat.), 75.4 (C, quat.), 52.8 (OMe), 51.9 (OMe), 37.8 (CH_2), 32.0 (CH_2), 30.0 (Me), 25.7 ($SiCMe_3$), 18.4 (C, quat.), –3.7 (SiMe) and –4.1 (SiMe); *m/z* (ES) 395 (M + Na^+, 100%), 367 (30), 313 (20), 285 (10) and 213 (20) (Found: M + Na^+, 395.1614. $C_{16}H_{28}NaO_6Si$ requires *M*, 395.1614).

Trimethyl (1*R,2*S**,5*R**,7*R**) 2-*tert*-butyldimethylsilyloxy-5-methyl-6,8-dioxabicyclo[3.2.1]octane-1,2,7-tricarboxylate 30.** $Rh_2(OAc)_4$ (cat.) was added to a stirred solution of diazoester **28** (189 mg, 0.50 mmol) in toluene (1 cm^3) and freshly distilled methyl glyoxylate[41] (187 mg, 2.13 mmol) at 110 °C. After 1 h, the reaction mixture was cooled, diluted with Et_2O (3 cm^3), filtered through Celite® and evaporated under reduced pressure. ^1H NMR analysis of the residue suggested 3 cycloadduct isomers in a ratio 12 : 2 : 1, as indicated by singlets assigned to the bridge methines at δ 5.57, 4.84 and 4.60, respectively. Purification of the residue by column chromatography (20% Et_2O in light petroleum) gave a colourless oil, *cycloadduct* **30** (140 mg, 63.5%, 10 : 0 : 1 with a minor isomeric cycloadduct); R_f 0.38 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 2954 s, 2894 m, 2857 s, 1753 s, 1437 s, 1387 m, 1261 s, 1164 s, 1117 s, 1097 s 1004 m and 830 s; δ_H(400 MHz)

5.57 (1 H, s, CH), 3.80 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.67 (3 H, s, OMe), 2.38 (1 H, ddd, *J* 14, 13 and 6, H*endo* of C(3)H_2), 1.93 (1 H, ddd, *J* 13, 13 and 5.5, H of C(4)H_2), 1.77–1.69 (2 H, m, H*exo* of C(3)H_2 and H of C(4)H_2), 1.67 (3 H, s, Me), 0.86 (9 H, s, SiCMe_3), 0.12 (3 H, s, SiMe) and 0.10 (3 H, s, SiMe) [discernible data for minor isomer, 4.60 (1 H, s, CH) and 3.79 (3 H, s, OMe)]; ^{1}H NMR NOE experiment: irradiation at δ 5.57 saw enhancement at 2.38 (4.6%); δ_C(100 MHz) 173.1 (C(2)*C*O, quat.), 169.5 (C, quat.), 166.6 (C, quat.), 110.2 (C(5), quat.), 90.4 (C(1), quat.), 77.4 (CH), 77.1 (C(2), quat.), 52.6 (OMe), 52.4 (OMe), 52.4 (OMe), 30.7 (C(4)H_2), 29.9 (C(3)H_2), 25.7 (SiCMe_3), 23.9 (Me), 18.9 (C, quat.), −2.8 (SiMe) and −3.1 (SiMe) [discernible data for minor isomer, 79.6 (CH), 31.3 (CH_2) and 29.5 (CH_2)]; *m*/*z* (CI, NH_3) 450 (M + NH_4^+, 100%) and 433 (70) (Found: M + H^+, 433.1892. $C_{19}H_{33}O_9Si$ requires *M*, 433.1894).

Trimethyl (1*R,2*S**,5*R**,7*R**) 2-hydroxy-5-methyl-6,8-dioxabicyclo[3.2.1]octane-1,2,7-tricarboxylate 31 and trimethyl (1*R**,2*S**,5*R**,7*S**) 2-hydroxy-5-methyl-6,8-dioxabicyclo[3.2.1]octane-1,2,7-tricarboxylate 32.** From **29**: TBAF (1.0 mol dm^{-3} in THF; 1.3 cm^3, 1.3 mmol) was added to a solution of cycloadduct **29** (170 mg, 0.43 mmol) in THF (5 cm^3). After 1 h at 25 °C, the mixture was diluted with Et_2O (3 cm^3), water (2 cm^3) added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 5 cm^3) and the combined organic layers were washed with brine (2 cm^3), water (2 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution: 50% Et_2O in petroleum ether to 100% Et_2O) gave a colourless oil, *alcohol* **31** (20 mg, 15%); R_f 0.24 (100% Et_2O); ν_{max}/cm^{-1} 3436 br, 2957 w, 1747 s, 1640 m, 1298 m, 1207 m and 1059 m; δ_H(500 MHz) 5.47 (1 H, s, CH), 3.92 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.73 (1 H, s, OH), 3.71 (3 H, s, OMe), 2.32 (1 H, ddd, *J* 14, 12.5 and 6, H*endo* of C(3)H_2), 1.99 (1 H, ddd, *J* 14, 13 and 5.5, H of C(4)CH_2), 1.80–1.74 (2 H, m, H*exo* of C(3)H_2 and H of C(4)CH_2) and 1.70 (3 H, s, Me); ^{1}H NMR NOE experiment: irradiation at δ 5.47 saw enhancement at 2.32 (6.8%); δ_C(125 MHz) 173.8 (C(2)*C*O, quat.), 169.2 (C, quat.), 166.7 (C, quat.), 111.0 (C(5), quat.), 89.4 (C(1), quat.), 77.6 (CH), 73.7 (C(2), quat.), 53.7 (OMe), 53.0 (OMe), 52.6 (OMe), 30.8 (C(4)H_2), 29.6 (C(3)H_2) and 23.6 (Me); *m*/*z* (CI, NH_3) 336 (M + NH_4^+, 35%), 319 (5), 176 (100), 164 (5), 147 (30), 132 (55) and 77 (40) (Found M + H^+: 319.1019. $C_{13}H_{19}O_9$ requires *M*, 319.1029).

From **30**: TBAF (1.0 mol dm^{-3} in THF; 110 µl, 0.11 mmol) was added to a solution of cycloadduct **30** (45 mg, 0.10 mmol, 10 : 1 with a minor isomeric cycloadduct) in THF (1 cm^3). After 15 min at 25 °C, the mixture was diluted with Et_2O (1 cm^3), water (1 cm^3) added and the layers separated. The aqueous solution was extracted with Et_2O (3 × 1 cm^3) and the combined organic layers were washed with brine (1 cm^3), water (1 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution: 50% Et_2O in petroleum ether to 100% Et_2O) gave a colourless oil, *alcohol* **31** (23 mg, 72%); data as above. From a larger scale desilylation [using cycloadduct **30** (638 mg, 1.47 mmol) in THF (10 cm^3) and TBAF (1.0 mol dm^{-3} in THF; 1.95 cm^3, 1.95 mmol)], was obtained *alcohol* **31** (304 mg, 65%) and *endo-ester-alcohol* **32** (26 mg, 5.5%); R_f 0.32 (100% Et_2O); δ_H(400 MHz) 4.83 (1 H, s, CH), 4.15 (1 H, br, OH), 3.88 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.78 (3 H, s, OMe), 2.63 (1 H, ddd, *J* 14, 13 and 6, H of CH_2), 2.04 (1 H, ddd, *J* 14, 13 and 5.5, H of CH_2), 1.90 (1 H, ddd, *J* 14, 6 and 1, H of CH_2), 1.78 (1 H, ddd, *J* 14, 5.5 and 1, H of CH_2), and 1.61 (3 H, s, Me); ^{1}H NMR NOE experiment: irradiation at δ 4.83 saw no enhancements in 2.7–1.7 region; δ_C(100 MHz) 172.3 (C, quat.), 167.4 (C, quat.), 167.2 (C, quat.), 110.7 (C(5), quat.), 86.8 (C(1), quat.), 79.2 (CH), 73.9 (C(2), quat.), 53.4 (OMe), 53.1 (OMe), 52.4 (OMe), 31.4 (CH_2), 28.0 (CH_2) and 23.8 (Me); *m*/*z* (CI, NH_3) 319 (M + H^+, 100%).

Trimethyl (1*R,3*R**,4*R**,5*S**) 4-hydroxy-1-methyl-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate 33 and (5*R**,8*R**,9*S**) 9-Hydroxy-2-methoxy-2-methyl-8,9-bis(methoxycarbonyl)-1,7-dioxaspiro[4,4]nonan-6-one 34. Method A**: 6,8-Dioxabicyclo[3.2.1]octan-2-ol **31** (20 mg, 0.06 mmol) was stirred in 2% HCl in MeOH (1 cm^3) at reflux. After 15 h, the reaction mixture was concentrated in vacuum and the residue redissolved in CH_2Cl_2 (5 cm^3). $NaHCO_3$ was then added, the mixture was filtered and evaporated under reduced pressure. The residue was purified by column chromatography (50% Et_2O in light petroleum). First to elute was *spirolactones* **34** (1 mg, 5%, 1 : 1.5 mixture of diastereomers, by ^{1}H NMR analysis of the methoxy signals); R_f 0.50 (100% Et_2O in light petroleum); δ_H(500 MHz) major isomer: 5.08 (1 H, s, CH), 3.92 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.82 (1 H, s, OH), 3.16 (3 H, s, OMe), 2.66 (1 H, ddd, *J* 13, 11 and 8, H of CH_2), 2.52–2.05 (3 H, m, 3 × H of CH_2 and 1.38 (3 H, s, Me); δ_H(500 MHz) minor isomer: 5.13 (1 H, s, CH), 3.91 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.84 (1 H, s, OH), 3.32 (3 H, s, OMe), 2.28–1.76 (4 H, m, 4 × H of CH_2) and 1.44 (3 H, s, Me); δ_C(125 MHz) 170.5 (C, quat.), 170.1 (C, quat.), 166.2 (C, quat.), 166.0 (C, quat.), 163.5 (2 × C, quat.), 110.9 (C(7), quat.) 110.6 (C(7), quat.), 53.9 (2 × OMe), 52.7 (2 × OMe), 49.7 (2 × OMe), 37.7 (CH_2), 37.5 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 21.6 (Me) and 21.4 (Me); *m*/*z* (CI, NH_3) 336 (M + NH_4^+, 15%), 304 (100) and 287 (85) (Found: M + NH_4^+, 336.1289. $C_{13}H_{22}NO_9$ requires *M*, 336.1295). Second to elute was recovered alcohol, *6,8-dioxabicyclo[3.2.1]octan-2-ol* **31** (8 mg, 40%); data as above. Third to elute was a white solid, *2,8-dioxabicyclo[3.2.1]octan-4-ol* **33** (2.6 mg, 13%); (Found: C, 49.00; H, 5.78. $C_{13}H_{18}O_9$ requires C, 49.00; H, 5.70%); R_f 0.14 (100% Et_2O in light petroleum); mp 118–123 °C; ν_{max}/cm^{-1} 3425w, 2958w, 1732 s, 1436 m, 1221 s, 1123 m, 1063 m and 867m; δ_H(500 MHz) 4.92 (1 H, s, CH), 3.90 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.74 (1 H, s, OH), 3.15 (1 H, ddd, *J* 9.5, 9.5 and 1.5, H*endo* of C(6)H_2), 2.25 (1 H, ddd, *J* 9.5, 9.5 and 2, H*endo* of C(7)H_2), 2.18–2.05 (2 H, m, H*exo* of C(6)H_2 and H*exo* of C(7)H_2) and 1.75 (3 H, s, Me); ^{1}H NMR NOE experiment: irradiation at δ 4.92 saw enhancements at 3.15 (5.8%) and at 2.25 (6.9%); δ_C(125 MHz) 169.9 (C(4)*C*O, quat.), 168.7 (C(5)*C*O, quat.), 167.4 (C(3)*C*O, quat.), 107.6 (C(1), quat.), 88.3 (C(5), quat.), 74.9 (CH), 74.9 (C(4), quat), 53.3 (OMe), 52.9 (OMe), 52.7 (OMe), 32.8 (C(7)H_2), 29.4 (C(6)H_2) and 23.6 (Me); *m*/*z* (CI, NH_3) 336 (M + NH_4^+, 100%) and 319 (10) (Found: M + H^+, 319.1032. $C_{13}H_{19}O_8$ requires *M*, 319.1029).

Method B: A solution 6,8-dioxabicyclo[3.2.1]octan-2-ol **31** (22 mg, 0.07 mmol) in a mixture of CH_2Cl_2 (500 µl), TFA (250 µl) and H_2O (25 µl) was stirred at 40 °C for 68 h. The reaction mixture was then evaporated under reduced pressure and the residue purified by preparative TLC (100% Et_2O). First to elute was recovered alcohol **31** (7.5 mg, 34%); data as above. Second to

elute was a white solid, *2,8-dioxabicyclo[3.2.1]octane* **33** (12 mg, 54%; 83% based on recovered **31**); data as above.

Acknowledgements

We thank the EPSRC National Mass Spectrometry Service Centre for mass spectra.

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