Selectivity in the cycloadditions of carbonyl ylides with glyoxylates: an approach to the zaragozic acids—squalestatins

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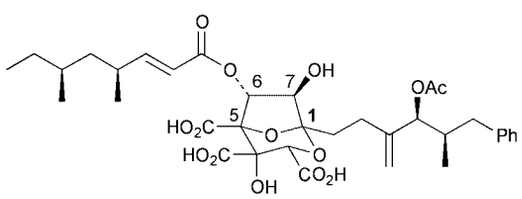
Received (in Cambridge, UK) 19th June 2000, Accepted 16th August 2000
First published as an Advance Article on the web 3rd October 2000

Reaction of diazodiketoester **8** with glyoxylates in the presence of catalytic rhodium(II) acetate generates 6,8-dioxabicyclo[3.2.1]octanes **9** and **11** in good yield. Elaboration of **9** provides a suitable alcohol **25** for acid-catalysed rearrangement to give the 2,8-dioxabicyclo[3.2.1]octane skeleton **26** of the zaragozic acids—squalestatins. More substituted diazodiketoesters **36** and **40** also undergo highly regio- and diastereoselective cycloaddition with glyoxylates to give the cycloadducts **41**, **43** and **44**.

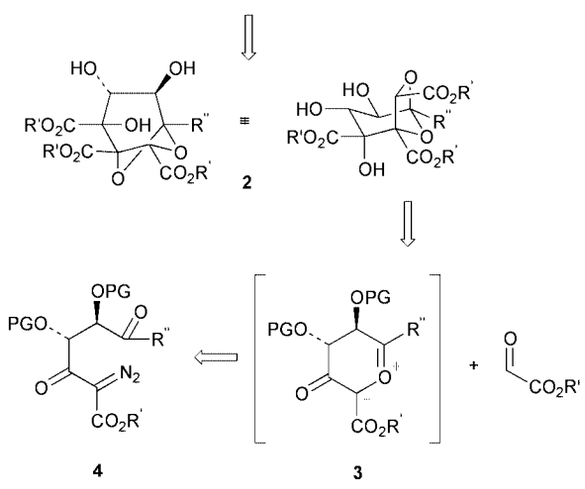
Introduction

Cardiovascular disease is one of the leading causes of death in the developed world, nearly double that of all forms of cancer combined.[1] In addition to clinical treatments presently available, the development of new leads targeting endogenous cholesterol inhibition—a major cause of coronary heart disease—is of vital importance to overcome this mortality rate. In recent years, several new classes of natural compounds have been shown to inhibit the enzyme squalene synthase, the last committed step on the biosynthetic pathway towards cholesterol production. One of the most notable of these leads are the zaragozic acids (also known as squalestatins).[2–5] This novel mode of action amongst cholesterol inhibitors is desirable over the currently favoured methods of HMG-CoA reductase inhibition and bile acid sequestration, which may interfere with other important biochemical processes. This paper details our early studies towards the synthesis of zaragozic acid A/squalestatin S1 **1**—the first isolated member of this novel class of fungal metabolites, which all contain the complex 2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core.[6]

Our strategic analysis of the anhydrofuranose core of acid **1** is detailed in Scheme 1. We reasoned that the bicyclic ketal might be formed from acid-catalysed rearrangement of the isomeric anhydropyranose core **2**. This in turn could arise from 1,3-dipolar cycloaddition reaction of carbonyl ylide **3** (PG = protecting group) with a suitable glyoxylate dipolarophile, followed by introduction of the C-5 acid (zaragozic acid numbering). The ylide precursor, diazodiketoester **4**, points to (+)-tartaric acid as a suitable starting material from the chiral pool.



Zaragozic Acid A / Squalestatin S1 **1**



Scheme 1

Results and discussion

We chose to examine the proposed chemistry first in a racemic model study towards the core of 6,7-dideoxysqualestatin H5 (C-1 alkyl chain = Me).[7] The use of ylide cycloaddition chemistry for the preparation of functionalised bicyclic heterocycles has been examined in detail by Padwa and co-workers,[8] and a simplified 6,8-dioxabicyclo[3.2.1]octane skeleton has been prepared by carbonyl ylide cycloaddition chemistry *en route* to the naturally occurring pheromone brevicomin.[9] Preparation of the known deoxy cycloaddition precursor **8** was carried out essentially using the route outlined by Padwa *et al.*[10] although 4-oxopentanal was best prepared by ozonolysis of heptenone **5**[11] (Scheme 2). Alternatively, Masamune homologation[12] of levulinic acid using the magnesium salt of ethyl hydrogen malonate gave the intermediate diketoester **6** in one step (49%). Diazoester **8** could also be obtained in a two-step procedure from commercially available γ-valerolactone. Lithiated ethyl diazoacetate was added to the lactone to give alcohol **7** in

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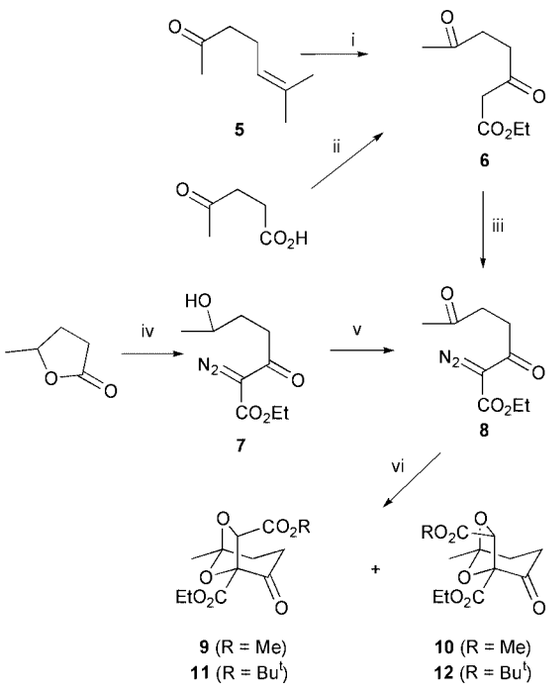
 DOI: 10.1039/b004870o

Table 1 Effect of experimental conditions on the yields and ratio of cycloadducts **9/10** and **11/12** from diazoester **8**

Entry	Glyoxylate ester	Solvent	*T*/°C	*endo*:*exo*[a]	**9/10** or **11/12** Yields (%)[b]
1	Methyl	CH_2Cl_2	25	2.4:1	50/0
2	Methyl	PhMe	110	2.5:1	60/10
3	Methyl	PhMe	25	2:1	36/13
4	Methyl	C_6H_6	70	3:1	72/15
5	Methyl	C_6H_6	25	3:1	54/20
6	Methyl	Et_2O	35	1.4:1	33/21
7	Methyl	Hexane	70	1:1	43/35
8	Methyl	Hexane	25	1.7:1	47/18
9	*tert*-Butyl	PhMe	110	3:1	61/11
10	*tert*-Butyl	Hexane	70	3:1	46/8

[a] As determined by integration of methine signals in the crude ^{1}H-NMR spectra. [b] Isolated yields of individual isomers.



Scheme 2 *Reagents and conditions*: i, O_3, CH_2Cl_2, −78 °C, then N_2CHCO_2Et, $SnCl_2$ (cat.), CH_2Cl_2, 25 °C (76% from **5**); ii, carbonyldiimidazole, THF, 25 °C, then $Mg(O_2CCH_2CO_2Et)_2$, THF, 25 °C, then H_3O^+ (49%); iii, $MeSO_2N_3$, Et_3N, MeCN, 25 °C (75%); iv, $LiC(N_2)CO_2Et$, THF, −90 to −78 °C (51%); v, PCC, NaOAc, CH_2Cl_2 (88%); vi, methyl or *tert*-butyl glyoxylate, $Rh_2(OAc)_4$ (cat.) (see Table 1).

51% yield.[13] Alcohol **7** was then oxidised using PCC[14] to the diazoester **8** in 88% yield.

Ylide formation and cyclisation were initially investigated using conditions developed previously by Padwa *et al*. for tandem decomposition–intermolecular cycloaddition reactions.[10] Reaction of diazoester **8** and freshly distilled methyl glyoxylate[15] with catalytic $Rh_2(OAc)_4$ in toluene at reflux, gave a mixture of cycloadducts (2.5:1 by ^{1}H NMR analysis of the crude reaction mixture) from which the major *endo* isomer **9** was isolated in 60% yield. Although none of the *exo* isomer **10** was observed initially, later studies have shown that small amounts of this cycloadduct (≤10%) can also be isolated from these reaction conditions. Provisional stereochemical assignments were made from NOE experiments on both isomers. X-Ray crystallographic analysis of cycloadduct **9** (Fig. 1) subsequently confirmed that it possessed *endo* stereochemistry with respect to the ylide-containing ring.

A subsequent solvent study showed that the *endo* isomer **9** was predominant under all conditions examined (Table 1); the desired *exo* isomer **10** was at best formed in a 1:1 ratio (*exo*:*endo*) using hexanes at reflux (35% isolated yield of **10**, entry 7). Using the more sterically demanding *tert*-butyl glyoxylate[16] gave no change in stereoselectivity (entries 9 and 10).

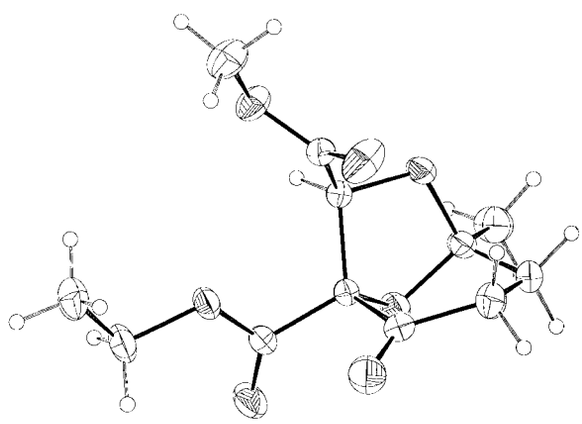
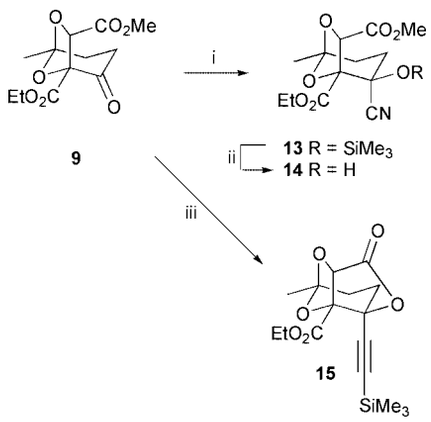


Fig. 1 Molecular structure of **9** with ellipsoids at 30% probability.

Consistently good yields for this cycloaddition contrast with a related study,[17] where the methyl ester analogue of diazoester **8** and aromatic aldehydes gave only low yields (<20%) of the desired cycloadducts. The use of a highly electron deficient aldehyde dipolarophile suggests that the favourable interaction in our case will be between the dipolarophile LUMO and dipole HOMO.[18] Houk and co-workers have shown that electron withdrawing substituents on the dipolarophile reduce both the HOMO and LUMO of the system.[19] The low lying orbitals of the aldehyde C=O π-bond further reduce the overall energy of the dipolarophile, thus bringing its LUMO into an energetically favourable interaction with the dipole HOMO. The observed *endo* selectivity in the reaction of diazoester **8** could be attributable to favourable secondary orbital overlap between the carbonyl of the glyoxylate ester (in the lower energy s-*trans* conformation)[20] and the ketone group of the ylide.

Although incorrect relative stereochemistry between C-1 and C-7 for zaragozic acid/squalestatin synthesis was present in cycloadduct **9**, the good yield and selectivity in the cycloaddition step suggested that a modified strategy would be worth pursuing with this substrate. This would first require introduction of a masked acid nucleophile to the ketone of **9** from the lower face, followed by inversion of stereochemistry at C-1 (*vide infra*). Our first effort focused on the addition of trimethylsilyl cyanide to cycloadduct **9** to generate a protected cyanohydrin which could then be hydrolysed to reveal the desired hydroxyacid moiety (Scheme 3).[21] Reaction of **9** with TMSCN and catalytic zinc(II) iodide gave TMS cyanohydrin **13** in good yield (76%) as a single isomer. The stereochemistry at C-2 was not determined at this point, but presence of the *endo* CO_2Me substituent together with the normal propensity for axial attack

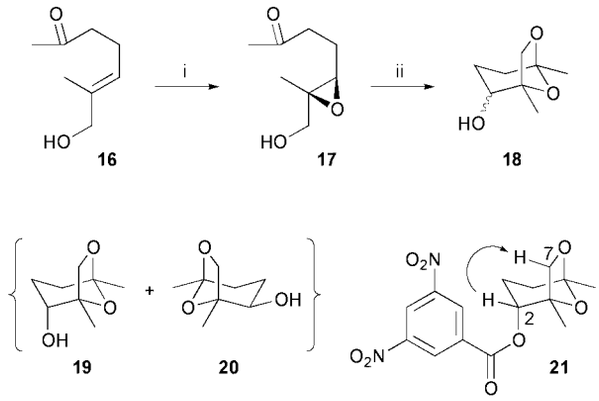


Scheme 3 *Reagents and conditions*: i, TMSCN, ZnI (cat.), CH_2Cl_2, 25 °C (76%); ii, 40% HF, MeCN, 25 °C (93%); iii, TMSC≡CH, BuLi, THF, −78 °C (80%).

by sterically small nucleophiles in conformationally biased cyclohexanones strongly suggested that **13** had the configuration as drawn. Desilylation was best achieved using 40% aqueous HF in acetonitrile to provide cyanohydrin **14** in 93% yield. The use of a plastic/polypropylene vessel for this reaction was important; glass flasks or beakers gave lower yields. A similar observation has been reported previously by Schreiber and co-workers.[22] Efforts to hydrolyse the nitrile to acid, amide or ester functionality (*e.g.* under basic peroxide or acidic conditions)[23] afforded only decomposition products. Carreira and Du Bois have also investigated cyanohydrin formation for ketone to hydroxy acid synthesis in the zaragozic acid series, although conditions for nitrile hydrolysis were not reported.[24] Attempts to add a suitable ethoxycarbonyl anion equivalent such as lithiated ethyl vinyl ether,[25] or the less basic cerium reagent generated by transmetallation with $CeCl_3$,[26] to ketone **9** were also unsuccessful. Similarly, addition of vinylmagnesium bromide or lithium acetylide to ketone **9** gave a complicated mixture of products. We were eventually successful employing lithiated trimethylsilylacetylene, addition of which to ketone **9** gave lactone **15** in 80% yield after careful quenching of the reaction mixture (1 M aq. HCl, −78 °C).

With lactone **15** in hand (which contains all the required functionality of the dideoxy core of squalestatin H-5 and the correct relative stereochemistry at C-2 and C-7), inversion of the C-1 quaternary stereocentre was now required (as well as the originally planned 6,8- to 2,8-dioxabicyclo[3.2.1]octane rearrangement). The work of Johnston and Oehlschlager towards frontalin indicated that configurational instability-inversion at such a position might be achieved under acid catalysis.[27]

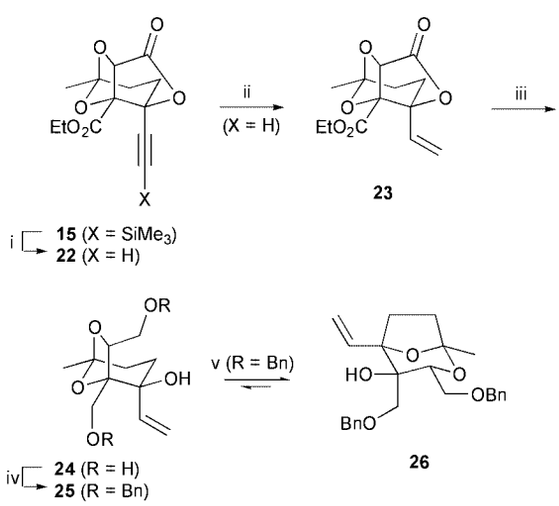
On treatment of the labile epoxide **17** with MeOH–cat. $SOCl_2$, Johnston and Oehlschlager observed two products (ratio reported after 1 h at rt, 1.5 : 1; after 18 h at rt, 15 : 1) which they assigned to an isomeric axial/equatorial alcohol mixture **18** with the major isomer not specified (Scheme 4). We interpreted this mixture **18** to consist of alcohols **19** and **20**, since configurational instability (if it occurred) would have been expected at the tertiary (rather than the secondary) centre. We repeated their work but isolated only one product, which gave ^{1}H NMR data consistent with those published for the major isomer. Attempts to prepare a crystalline derivative for X-ray analysis failed, but the dinitrobenzoate ester **21** (3,5-dinitrobenzoyl chloride, Et_3N, CH_2Cl_2, 57% yield) proved a suitable substrate for NMR NOE studies; a strong enhancement between C-2 H and one H of C-7 CH_2 confirmed the relative stereochemistry at C-2. This result provided a possible precedent in our system for equilibration to the desired axial alcohol (compare anhydropyranose **2** in Scheme 1). However, since the relative configuration between C-1 and C-2 in the 6,8-dioxabicyclo[3.2.1]octane **19** could arise from the epoxide **17**



Scheme 4 *Reagents and conditions*: i, 50% MCPBA, CH_2Cl_2, then KF, 0 °C; ii, 2% HCl–MeOH, 25 °C (51%, 2 steps).

by a simple intramolecular 'S_N2' opening of the epoxide at the tertiary position by the ketone group, our results do not prove configurational instability at the tertiary centre in this system. Finding the 6,8- rather than the 2,8-dioxygenated skeleton was favoured in this system was an additional concern to us in the context of our zaragozic acid/squalestatin synthesis. However, Nicolaou and co-workers have reported that more functionalised/oxidised systems favour the 2,8-structure.[28] The isolation of an intermediate 6,8-dioxabicyclo[3.2.1]octane skeleton from their reaction mixture before formation of the correct core also provided good precedent for our proposed transketalisation reaction (*cf.* **2** to **1**, Scheme 1).

With this information in hand, lactone **15** was required to be converted to a suitable substrate to examine the epimerisation–rearrangement chemistry. To this end lactone **15** was desilylated to give alkyne **22** in 98% yield (Scheme 5). K_2CO_3 in DMF



Scheme 5 *Reagents and conditions*: i, K_2CO_3, DMF, 25 °C (98%); ii, H_2 (1 atm), Pd/C (cat.), pyridine, 25 °C (quant.); iii, $LiAlH_4$, Et_2O, 25 °C (60%); iv, NaH (2 equiv.), NaI (cat.), BnCl (2 eq.), $MeO(CH_2)_2OMe$, 0 to 25 °C (52%); v, H^+ (see Table 2).

was found to be superior to K_2CO_3 in MeOH,[29] as it avoided capricious methanolysis of the lactone ring. $LiAlH_4$ reduction of the terminal acetylene proved difficult, affording no discernible products from the crude reaction mixture. The matter was resolved by partial hydrogenation of the alkyne using Pd on charcoal in pyridine to afford the alkene **23** quantitatively, which was subjected to further reduction using $LiAlH_4$ under carefully controlled conditions to reproducibly provide triol **24** in satisfactory yields (60%). The oily triol was not purified further but immediately benzylated to give dibenzyl ether **25** in an unoptimised 52% yield.

Although the vinyl group in ether **25** was projected to become the third carboxylic acid group of the zaragozic acid/

Table 2 Effect of experimental conditions on the yield of ketal **26**

Entry	Reagents	T/°C	Time/h	**26/25** Yields (%)[a]
1	2% HCl–MeOH	68	1	59/26
2	2% HCl–MeOH	25	0.1	64/25
3	2% HCl–MeOH	0	0.1	61/18
4	CSA (cat.)–CH_2Cl_2	0 to 40	12/6	65/34
5	CSA (cat.)–MeOH	0 to 68	12/6	67/33
6	TFA–CH_2Cl_2 (1:1)	0	12	trace[b]/89
7	TFA–CH_2Cl_2 (1:1)	40	2	0[c]
8	TFA–CH_2Cl_2– H_2O (10:20:1)	40	2	0[c]

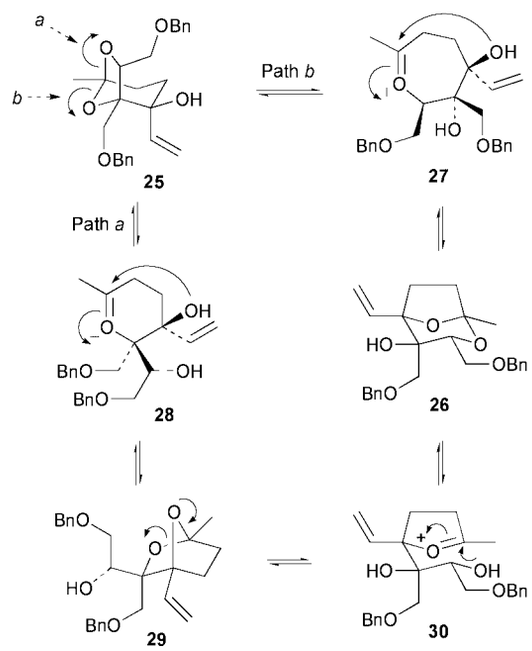
[a] Isolated, chromatographically homogeneous yields. [b] By crude ^{1}H-NMR analysis. [c] No products isolated.

squalestatin core, further manipulation of this group was postponed until after our investigation of the crucial C-1 epimerisation–skeletal rearrangement chemistry. For epimerisation to take place, a group capable of stabilising a potential carbocation at C-1 should prolong the existence of such an intermediate such that inversion might occur. The more polar, electron deficient groups destined to replace vinyl at C-2 would undoubtedly destabilise this charged intermediate more, a premise demonstrated effectively in Heathcock's studies on the acid-catalysed rearrangement of anhydrofuranoses.[26]

In the event, after treatment of ether **25** under the rearrangement conditions of Nicolaou and co-workers (2% HCl in MeOH, 25 °C)[28] no inversion of stereochemistry at C-1 was seen, but the rearranged alcohol **26** was reproducibly isolated in 60% yield, along with recovered starting material (20%). The structure of alcohol **26** was assigned on the basis of extensive ^{1}H-NMR studies. Notably, the coupling constants *trans* ^3J of 5.0 and 4.5 Hz in the dimethylene bridge are consistent with the conformation of a five- (rather than six-) membered ring.[30] A NOESY spectrum showed cross peaks between one H of both C-6 and C-7 in the dimethylene bridge and C-3 H, and between H_2C=C*H* and one H of the C-4 CH_2OBn. No cross peaks were seen between the dimethylene bridge and either of the CH_2OBn groups, confirming the structure of **26** as shown.

A range of other acidic conditions were examined for the rearrangement of ether **25** (Table 2). Trifluoroacetic acid proved to be unsuitable and only decomposition was observed at higher temperatures, no reaction occurring at lower temperatures. Entries 2 and 3 are notable in that equilibrium is reached within 5 minutes, even at reduced temperatures. CSA gave clean conversion in both CH_2Cl_2 (entry 4) or MeOH (entry 5), although elevated temperatures were required to reach equilibrium. In no case was there any indication of stereochemical lability at C-1. In a related model study by Armstrong and Barsanti, configurational instability also does not appear to have been seen where it might potentially have occurred.[31] That true equilibrium had been reached in our system was established by returning alcohol **26** to the reaction conditions (entry 2) which resulted in the same ratio of products.

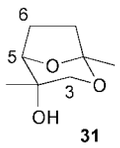
A probable mechanism for the acid-catalysed rearrangement of **25** is shown in Scheme 6, and, whilst formation of oxonium ion **28** (Path *a*) is favoured on stereoelectronic grounds,[32] **27** (Path *b*) cannot be ruled out at this time.[28b] The six-membered ring oxonium ion **28**, if formed, evidently does not undergo the desired epimerisation. Equilibration to **26** from **28** could then proceed *via* the comparatively strained 2,7-dioxabicyclo-[2.2.1]heptane **29**. Clearly the factors governing selectivity in the rearrangement of **25** to **26** are complex: Dominey and Goodman report that molecular mechanics force fields are unable to cope with the prediction of the position of equilibrium for competitive acetal formation in simple models of the zaragozic acid core, because there is competition between five- and six-membered cyclic acetals.[33] Evans[34] and Myles[35] have also reported computer modelling studies which suggest



Scheme 6 Possible mechanism of acid-catalysed rearrangement **25** to **26**. Protons omitted for clarity.

that the natural core of the squalestatins is some 2.6 kcal mol^{-1} higher in energy than the alternative 6,8-core. This effect can be seen clearly in Armstrong's preliminary studies, where his cyclisation precursor closes under thermodynamic conditions to give a 1:1 mixture of the 2,8- and the 6,8-dioxabicyclo[3.2.1]octanes.[31] Hashimoto's synthesis of zaragozic acid C however, utilises a differentially protected substrate which can first undergo kinetic cyclisation to form the furanose ring of the correct core, which ultimately results in formation of a 10:1 (2,8-:6,8-) ratio after hydrolysis of a C-3–C-4 acetonide.[36] Armstrong *et al.* were later able to utilise this same kinetic control in their total synthesis of zaragozic acid C, simply by changing the order of events from the initial model study.[37] These results further support the proposed mechanism in the present study, whereby the 2,7-dioxabicyclo[2.2.1]heptane system **29** ring opens to reveal the anhydrofuranose ring of the squalestatin core. It should be noted, however, that the presence of a functionalised C-1 side chain rather than a simple model alkyl group at C-1 can also effect the outcome of such ketalisation reactions.[38]

As communicated previously,[6] the evidence presented here strongly suggests that the minor isomer observed by Oehlschlager in his frontalin studies is in fact the rearranged 2,8-core **31**. Our initial analysis of the reported ^{1}H-NMR data is supported by the recent synthesis of frontalin by Majewski and Nowak,[39] where they prepare equatorial alcohol **20** and report data different to those of both isomers prepared by Oehlschlager and ourselves.



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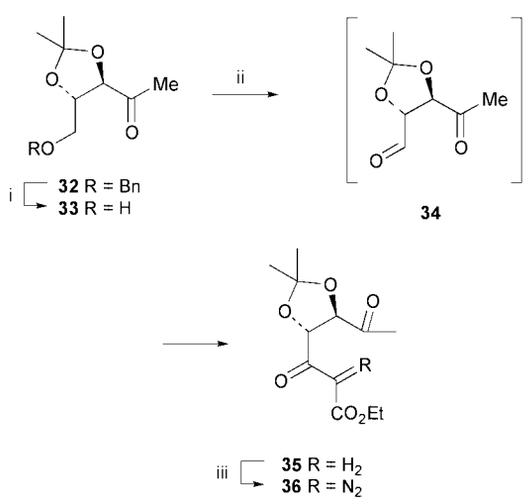
At this point it was clear that influencing the initial cycloaddition reaction by substrate manipulation would be required to solve the stereochemical problems seen in our racemic study. The use of a tartrate-derived carbonyl ylide, with the 6,7-diol unit of the natural product already in place, was considered a viable strategy to effect cycloaddition such that the *exo* cycloadduct might be preferred. It was hoped that the presence of the protected diol unit would provide suitable steric congestion over the *endo* or back-side of the ylide ring, thus forcing the dipolarophile away from the ring to give the *exo* cycloadduct. If the *exo* product was formed, but facial selectivity was not in the desired sense, then the use of a chiral Rh(II) catalyst[40] or employment of chiral auxiliaries was anticipated to provide solutions to this latter issue.

TBDMS ethers were considered as the protecting group of choice for the vicinal diol unit in cycloaddition substrate **4** (PG = TBDMS), due to their steric bulk conferring a conformational bias upon cyclohexyl (chair type) systems, by orienting themselves *trans*-diaxially thus minimising steric interactions between the two groups.[41] It was hoped that a similar conformational preference in our system would help bias the approaching dipolarophile to react *exo* with respect to these axial blocking groups. However, due to ease of synthesis, the acetonide-protected diazoketoester **36** was first prepared for examination (and eventual comparison with the di-TBDMS protected system).

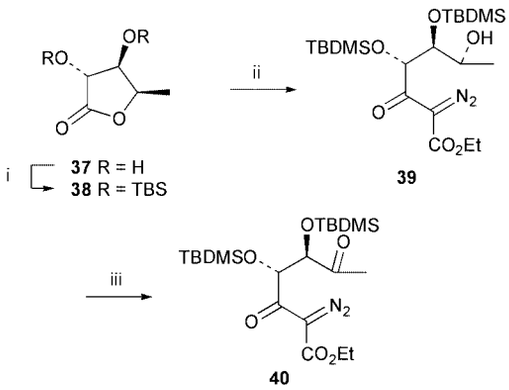
Hydrogenolysis of the known[42] benzyl ether **32** in EtOH proceeded quantitatively to give ketoalcohol **33**. (Scheme 7). A



Scheme 7 *Reagents and conditions*: i, H_2 (1 atm), $Pd(OH)_2$/C (cat.), EtOH, 25 °C (>98%); ii, (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 to 0 °C, (b) N_2CHCO_2Et, $SnCl_2$ (cat.), CH_2Cl_2, 25 °C (51%, 2 steps); iii, 4-$NO_2C_6H_4SO_2N_{32}$, Et_3N, MeCN, 0 °C (94%).

range of oxidation procedures were screened for conversion of ketoalcohol **33** to the sensitive aldehyde **34**, the Swern method proving most effective in our hands. Tin(II) chloride-catalysed homologation of the crude aldehyde **34** gave diketoester **35** in 51% yield (2 steps). Diazotransfer with 4-nitrobenzenesulfonyl azide then provided cycloaddition precursor **36** in 94% yield.

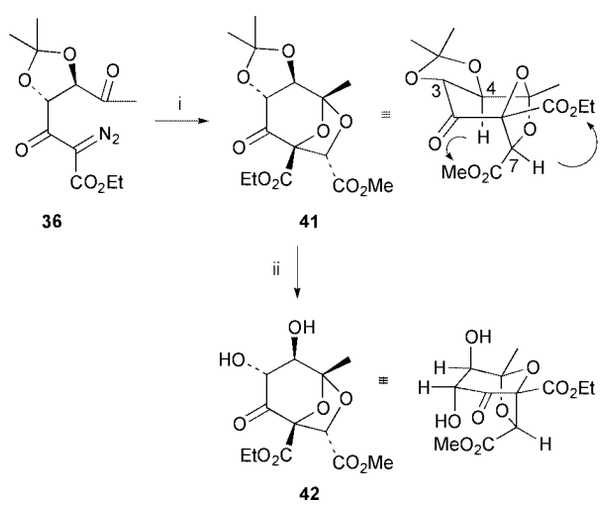
Synthesis of the di-TBDMS analogue began with the known tartrate-derived lactone diol **37** (Scheme 8).[43] Silylation with TBDMSOTf–2,6-dimethylpyridine gave bisether **38** (88%). Following Moody's protocol,[13] addition of lithiated ethyl diazoacetate furnished the desired α-diazo-β-ketoester **39** (50%, 85% based on recovered **38**). Although Padwa *et al.*[14]



Scheme 8 *Reagents and conditions*: i, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 to 25 °C (88%); ii, N_2CHCO_2Et, LDA, THF, −90 to −78 °C (50% + 42% **38**); iii, Dess–Martin periodinane, CH_2Cl_2, 25 °C (60%).

have reported that PCC oxidation of related diazoalcohols proceeds in good yield (see also **7**→**8**, Scheme 2), with the present substrate only 3% of the desired ketone **40** was obtained, along with 10% of bisether **38**. TPAP–NMO was only a slightly better oxidant,[44] giving the ketone **40** in 15% yield, and again bisether **38** was observed (16% yield). The Dess–Martin[45] reagent, however, cleanly gave ketone **40** as the sole isolated material (60%).

Diazoacetonide **36** (Scheme 9) was found to be much less

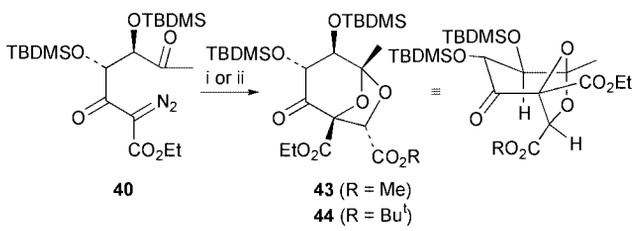


Scheme 9 *Reagents and conditions*: i, methyl glyoxylate, PhMe, reflux, then $Rh_2(OAc)_4$ (cat.) (>98%, crude); ii, $CDCl_3$, 25 °C (>98%).

reactive than diazoester **8** under similar conditions for cyclisation–cycloaddition, presumably due to steric congestion within **36**. After much experimentation, it was found that the best reaction conditions were to conduct the cyclisation at higher concentrations (1.0 to 0.5 M in toluene for both the diazoacetonide **36** and dipolarophile), with premixing of the freshly distilled aldehyde (1.5 equiv.) and substrate at 110 °C before catalyst addition. This protocol reproducibly gave quantitative yields (by ^{1}H NMR) of a single crude cycloadduct diastereomer **41**, with unreacted glyoxylate as the only other detectable material. Whilst some of the residual glyoxylate could be removed under vacuum, further purification by chromatography or distillation resulted in degradation of the cycloadduct **41**—presumably due to strain engendered by the *trans*-fused dioxolane. Nevertheless, structural identification of the cycloadduct **41** could be accomplished directly on the crude material using NMR techniques. Dissolution in $CDCl_3$ provided a complicated spectrum due to overlapping signals. Also, the slightly acidic nature of $CDCl_3$ resulted in recovery after evaporation of a more polar material lacking the isopropylidene group which was assigned as diol **42**. Using

d_6-benzene as solvent allowed irradiation of the peaks during NOE experiments on **41**,‡ indicating that the stereochemistry of **41** is as shown in Scheme 9. Specifically, C-4 H irradiation enhanced C-7 H and methyl ester protons much more than irradiating C-3 H on the top face of the 6-membered ring, thus assigning the glyoxylate bridge to the lower face of the substrate, which likely forces the six-membered ring into a boat conformation to accommodate the *trans*-fused acetonide ring. A small NOE between C-7 H and ethyl ester methylene groups suggested that C-7 H was disposed *exo* to the ylide-containing ring; this was further confirmed by the strong interaction between C-4 H and the methyl ester CH_3, compared to that between C-4 H and C-7 H. Had the H and CO_2Me groups at C-7 been reversed then a much stronger interaction between C-4 H and C-7 H would be expected, and most likely, no enhancement of the methyl ester signal upon irradiation of C-4 H. Further evidence in support of **41** having the structure shown in Scheme 9 was provided by the $CDCl_3$ decomposition product **42**. The $^3J_{H3H4}$ coupling constant was reduced from 9.5 in **41** to 7.0 Hz in **42**, reflecting a reduction of the dihedral angle between the two protons consistent with a change in conformation from boat for **41** to chair for **42**.

Repeating the cycloaddition with the di-TBDMS protected substrate **40** and methyl glyoxylate using the optimised conditions for **36** gave a single cycloadduct diastereomer **43** in 42% yield after chromatography (Scheme 10), this product proving much more stable than the acetonide analogue **41**. Using the more sterically demanding *tert*-butyl glyoxylate as the dipolarophile did not modify the selectivity of the cycloaddition reaction, from which a single diastereoisomer **44** was isolated (58%, Scheme 10). Similar NOE's were observed with



40 **43** (R = Me) **44** (R = Bu^t)

Scheme 10 *Reagents and conditions*: i, (R = Me) methyl glyoxylate, PhMe, 80 °C, then $Rh_2(OAc)_4$ (cat.) (42%); ii, (R = Bu^t) *tert*-butyl glyoxylate, PhMe, 110 °C, then $Rh(OAc)_4$ (cat.) (58%).

compounds **43** and **44** to those found for cycloadduct **41**, suggesting that they all share the same relative configuration. To provide further evidence for these stereochemical conclusions, a comparison of the $^2J_{CH}$ and $^3J_{CH}$ values for C-7 H in cycloadducts **9** and **10** (and the cycloadducts **11** and **12** obtained from reaction of **8** with *tert*-butyl glyoxylate), with cycloadducts **41**, **43** and **44** was carried out using the SIMBA method.§ Similar *J* values for the *endo* isomer **9** compared with **11**, **41**, **43** and **44**, and which are different to those seen for the *exo* isomers **10** and **12**, support the assignments of the structures as shown (Table 3 and Fig. 2).

The observed selectivity in the cycloadditions of ketones **36** and **40** is most straightforwardly explained in terms of the lower face of the intermediate dipole in each case providing a less-hindered approach to the incoming dipolarophile, when the glyoxylate ester is experiencing secondary orbital overlap with the ylide ketone group (although analysis of molecular models does not obviously indicate this to be the case). Although the cycloadditions do not provide the desired selectivity for a projected zaragozic acid/squalestatin synthesis, the present study does serve to demonstrate the ability of more highly substituted diazoketones to successfully participate in carbonyl ylide cycloadditions and that high levels of stereochemical control can be achieved.[46] Building on the study reported herein, a second generation approach involving modification of the ketone group of the ylide has recently led to the core of the zaragozic acids/squalestatins with the correct triacid stereochemistry[47] and these results will be reported in full in due course.

Table 3 Comparison of $^{2/3}J_{CH}$ values for C-7 H in the cycloadducts

		$^nJ_{CH}$/Hz				
Entry	Substrate	C-1	C-1′	C-2	C-5	C-7′
1	**9**	4.2	2.8	5.9	0.9	2.6
2	**10**	0	0.9	3.3	3.9	1.9
3	**11**	4.1	2.8	6.1	0.9	2.6
4	**12**	0	0.9	3.5	3.9	1.6
5	**41**	5.0	2.7	4.8	0.9	2.0
6	**43**	4.9	3.8	5.0	0	2.8
7	**44**	4.9	2.9	5.0	1.5	1.8

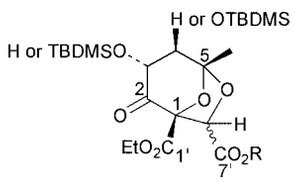


Fig. 2

Experimental

General details

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl; (chlorinated) hydrocarbons, amines, DMSO and DMF from CaH_2. Reactions were monitored by TLC using commercially available glass-backed plates, pre-coated with a 0.25 mm layer of SiO_2 containing a fluorescent indicator (Merck). Column chromatography was carried out on Kieselgel 60 (40–63 μm). Light petroleum refers to the fraction with bp 40–60 °C. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films unless stated otherwise. ^{1}H- and ^{13}C- NMR spectra were recorded in $CDCl_3$ unless stated otherwise with Varian Gemini 200, Bruker AC200, Bruker WM250, Bruker WH300, JEOL EX400, Bruker AM500 or Bruker AMX500 spectrometers. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C(central line of t) 77.0]. Coupling constants (*J*) are given in Hz.

Ethyl 3,6-dioxoheptanoate 6

A mixture of O_2 and O_3 was bubbled through a solution of 6-methylhept-5-en-2-one (7.62 g, 60.4 mmol) in CH_2Cl_2 (120 cm^3) at −78 °C for 2.5 h, until the colourless solution turned blue. The system was then flushed with oxygen and argon to remove excess ozone. The colourless solution was allowed to warm to

‡ NOE's conducted were not 1D difference experiments but 1D NOESY spectra. Therefore exact values (%) are not available for the enhancement between signals after irradiation.

§ The SIMBA experiment is, in essence, a ^{13}C-selective 1D heteronuclear multiple-bond correlation (HMBC) experiment. The experiment utilises proton observation for optimum sensitivity, and reveals the long-range coupling to the selectively excited carbon centre as an antiphase doublet splitting. The original sequence (R. Crouch and G. E. Martin, *J. Magn. Reson*., 1991, **92**, 189) was modified for the current work by the inclusion of pulsed field gradients for signal selection, as applied in the conventional gradient-selected 2D HMBC experiment. The gradients provided complete suppression of the unwanted parent ^{1}H–^{13}C resonance and revealed the required long-range coupling in the absence of artefacts.

room temperature before the solvent was evaporated to yield white crystals in a colourless oil. The crystals were filtered, and the filtrate was diluted with CH_2Cl_2 (25 cm^3) and then slowly added to a stirred solution of ethyl diazoacetate (6.89 g, 60.4 mmol) and anhydrous $SnCl_2$ (500 mg, cat.) in CH_2Cl_2 (80 cm^3) at 25 °C. After 60 h the mixture was diluted with water (30 cm^3) to yield a yellow precipitate, *heptanoate* **6**. This was filtered off, the filtrate evaporated and the resultant dark yellow oil purified by column chromatography (25% EtOAc in light petroleum) to give a second crop as a yellow oil (8.59 g in total, 76%). This material was identical in all respects to that prepared by Padwa and co-workers.[9]

Ethyl 2-diazo-3,6-dioxoheptanoate 8

To a stirred solution of heptanoate **6** (1.4 g, 7.5 mmol) and MsN_3 (0.71 cm^3, 8.3 mmol) in MeCN (20 cm^3) at 0 °C was added Et_3N (2.1 cm^3, 30 mmol) dropwise. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 cm^3) and washed with 20% aq. NaOH (3 × 20 cm^3). The aq. phase was extracted with CH_2Cl_2 (20 cm^3), and the combined organic extracts were dried and evaporated to give a yellow oil. Column chromatography (25% EtOAc in light petroleum) gave a yellow oil, *diazodione ester* **8** (1.20 g, 75%). This material was identical in all respects to that prepared by Padwa and co-workers.[9]

Ethyl (±)-*endo*-7-methoxycarbonyl-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 9 and ethyl (±)-*exo*-7-methoxycarbonyl-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 10

$Rh_2(OAc)_4$ (cat.) was added to a stirred solution of diazoester **8** (0.35 g, 1.65 mmol) and freshly distilled methyl glyoxylate[15] (0.62 g, 7.04 mmol) in toluene (5 cm^3) at 80–85 °C. Nitrogen evolution was observed, and after 1 h the reaction mixture was filtered through Celite, evaporated and the resultant oil purified by column chromatography (50% Et_2O in light petroleum). First to elute was a white crystalline solid, *dioxabicyclo[3.2.1]-octane* **9** (268 mg, 60%); mp 114–116 °C (from EtOAc–light petroleum) (Found: C, 52.85; H, 6.0. $C_{12}H_{16}O_7$ requires C, 52.95; H, 5.9%); R_f 0.48 (50% Et_2O in light petroleum); ν_{max}(paraffin)/cm^{-1} 2925, 2865, 1770 and 1745; δ_H(400 MHz) 4.73 (1 H, s, CH), 4.26–4.40 (2 H, m, OCH_2), 3.79 (3 H, s, OMe), 2.85 (1 H, ddd, *J* 18, 9 and 4, CH*H*), 2.61 (1 H, ddd, *J* 18, 9 and 7.5, C*H*H), 2.25–2.39 (2 H, m, CH_2), 1.69 (3 H, s, Me) and 1.33 (3 H, t, *J* 7, CH_2*Me*); δ_C(100 MHz) 199.3 (C, quat.), 168.1 (C, quat.), 163.9 (C, quat.), 111.0 (C, quat.), 89.1 (C, quat.), 78.5 (CH), 62.6 (OCH_2), 52.9 (OMe), 34.0 (CH_2), 33.1 (CH_2), 24.2 (Me) and 13.9 (Me); *m*/*z* (EI) 273 ($M + H^+$, 20%), 184 (30), 99 (90) and 43 (100) (Found: $M + H^+$, 273.0974. $C_{12}H_{17}O_7$ requires *M*, 273.0974).

Second to elute was a white crystalline solid, *dioxabicyclo[3.2.1]octane* **10** (45 mg, 10%); mp 62–64 °C (from EtOAc–light petroleum) (Found: C, 52.84; H, 5.97. $C_{12}H_{16}O_7$ requires C, 52.92; H, 5.93%); R_f 0.19 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 2987, 1752, 1265 and 1100; δ_H(400 MHz) 4.73 (1 H, s, CH), 4.40–4.20 (2 H, m, CH_2Me), 3.75 (3 H, s, C(O)Me), 2.65–2.55 (2 H, m, CH_2), 2.40–2.20 (2 H, m, CH_2), 1.73 (3 H, s, Me) and 1.29 (3 H, t, *J* 7, CH_2*Me*); δ_C(100 MHz) 198.2 (C, quat.), 168.4 (C, quat), 163.4 (C, quat), 111.4 (C, quat.), 89.9 (C, quat.), 77.9 (CH), 62.5 (OCH_2), 52.6 (OMe), 35.9 (CH_2), 32.9 (CH_2), 23.4 (Me) and 13.9 (Me); *m*/*z* (EI) 273 ($M + H^+$, 1%) and 99 (100) (Found: $M + H^+$, 273.0974. $C_{12}H_{17}O_7$ requires *M*, 273.0974).

X-Ray structure determination of ethyl (±)-*endo*-7-methoxycarbonyl-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 9

$C_{12}H_{16}O_7$, *M* = 272.24. Triclinic, *a* = 8.405(9), *b* = 9.044(9), *c* = 10.192(12) Å, *α* = 69.55(1), *β* = 76.80(1), *γ* = 71.60(1)°, *V* = 682.7 $Å^3$, space group $P\bar{1}$, *Z* = 2, D_c = 1.324 mg m^{-3}, μ = 0.110 mm^{-1}, *F*(000) 288. 1863 independent reflections were measured on a MAR research Image Plate using 95 frames at 2° intervals each measured for 2 min. Data analysis was carried out using the XDS program.[48] The structure was solved by direct methods using SHELX-86.[49] All non-hydrogen atoms were given anisotropic thermal parameters and hydrogen atoms included in calculated positions given isotropic thermal parameters. The structure was refined on F^2 using SHELXL-93[50] to give conventional *R* factors of 0.0645, wR_2 = 0.1822 for 1595 observed reflections [$I > 2\sigma(I)$]. The largest peak and hole in the final difference map were 0.214 and −0.252 e $Å^{-3}$. CCDC reference number 207/472. See http://www.rsc.org/suppdata/p1/b0/b004870o for crystallographic files in .cif format.

Ethyl (±)-*endo*-7-*tert*-butoxycarbonyl-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 11 and ethyl (±)-*exo*-7-*tert*-butoxycarbonyl-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 12

Rhodium(II) acetate (cat.) was added to a stirred solution of diazoester **8** (160 mg, 0.75 mmol) and freshly distilled *tert*-butyl glyoxylate[16] (147 mg, 1.13 mmol) in toluene (1.5 cm^3) at 110 °C. Nitrogen evolution was observed, and after 30 min the reaction mixture was filtered through Celite, evaporated and the resultant oil purified by column chromatography (20% Et_2O in light petroleum). First to elute was a white solid, *cycloadduct* **11** (144 mg, 61%); mp 62–64 °C (from Et_2O–light petroleum) (Found: C, 57.29; H, 7.10. $C_{15}H_{22}O_7$ requires C, 57.30; H, 7.06%); R_f 0.54 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 2984m, 1757s, 1737s, 1383m, 1313m and 1150s; δ_H(400 MHz) 4.57 (1 H, s, CH), 4.38–4.29 (2 H, m, OCH_2), 2.89–2.76 (1 H, m, CH_2), 2.57 (1 H, ddd, *J* 3.5, 9 and 18, CH_2), 2.38–2.22 (2 H, m, CH_2), 1.67 (3 H, s, Me), 1.47 (9 H, s, CMe_3) and 1.33 (3 H, t, *J* 7, CH_2*Me*); δ_C(100 MHz) 199.1 (C, quat.), 166.6 (C, quat.), 164.0 (C, quat.), 111.6 (C, quat.), 89.2 (C, quat.), 83.4 (C, quat.), 79.2 (CH), 62.4 (OCH_2), 34.1 (CH_2), 33.2 (CH_2), 27.7 (CMe_3), 24.3 (Me) and 14.0 (Me); *m*/*z* (CI, NH_3) 332 ($M + NH_4^+$, 95%), 315 (10) and 276 (100) (Found: $M + NH_4^+$, 332.1711. $C_{15}H_{26}NO_7$ requires *M*, 332.1709). Second to elute was a clear oil, *cycloadduct* **12** (27 mg, 11%); R_f 0.26 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 2982w, 1745s, 1370m, 1305m, 1156m and 1097m; δ_H(400 MHz) 4.60 (1 H, s, CH), 4.40–4.20 (2 H, m, OCH_2), 2.70–2.50 (2 H, m, CH_2), 2.40–2.20 (2 H, m, CH_2), 1.72 (3 H, s, Me), 1.45 (9 H, s, CMe_3) and 1.31 (3 H, t, *J* 7, CH_2*Me*); δ_C(100 MHz) 198.3 (C, quat.), 166.8 (C, quat.), 163.5 (C, quat.), 111.0 (C, quat.), 89.8 (C, quat.), 82.7 (C, quat.), 78.9 (CH), 62.3 (OCH_2), 36.3 (CH_2), 30.7 (CH_2), 27.7 (CMe_3), 23.5 (Me) and 13.9 (Me); *m*/*z* (APCI) 337 ($M + Na^+$, 75%), 281 (40), 250 (70), 229 (100) and 213 (55).

Ethyl (1*R**,2*R**,5*R**,7*S**)-2-cyano-7-methoxycarbonyl-5-methyl-2-(trimethylsilyl)oxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 13

TMSCN (60 μl, 0.45 mmol) in CH_2Cl_2 (2 cm^3) was added to a stirred solution of ketone **9** (100 mg, 0.37 mmol) and anhydrous ZnI_2 (*ca.* 10 mg, catalytic) in CH_2Cl_2 (3 cm^3) at 25 °C. After 3 h, a further equivalent of TMSCN (50 μl, 0.37 mmol) in CH_2Cl_2 (2 cm^3) was added. After 18 h the reaction mixture diluted with water (10 cm^3), extracted with CH_2Cl_2 (20 cm^3), and the combined organic layers dried ($MgSO_4$) and evaporated under reduced pressure. The resultant solid was triturated with EtOH and filtered to give *trimethylsilylcyanohydrin* **13**. The yellow filtrate was evaporated and purified by column chromatography (50% Et_2O in light petroleum) to yield a second crop (104 mg in total, 76%); mp 74–76 °C (from Et_2O-light petroleum); ν_{max}(KBr)/cm^{-1} 2960, 2245, 1745, 1450, 1245 and 1215; δ_H(250 MHz) 5.10 (1 H, s, CH), 4.30–4.44 (2 H, m, OCH_2), 3.75 (3 H, s, OMe), 2.85–2.91 (1 H, m, C*H*H), 2.19–2.25 (1 H, m, CH*H*), 2.03–2.14 (2 H, m, CH_2), 1.59 (3 H, s, Me),

1.37 (3 H, t, *J* 7, CH_2*Me*) and 0.25 (9 H, s, $SiMe_3$); δ_C(50 MHz) 167.6 (C, quat.), 164.3 (C, quat.), 119.5 (C≡N, quat.), 111.6 (C, quat.), 85.9 (C, quat.), 79.1 (CH), 70.2 (*C*CN, quat.), 62.8 (OCH_2), 52.3 (OMe), 33.8 (CH_2), 33.2 (CH_2), 23.3 (Me), 13.8 (Me) and 1.1 ($SiMe_3$); *m*/*z* (EI) 371 (M^+, 75%), 188 (43) and 156 (100) (Found: M^+, 371.1404. $C_{16}H_{25}NO_7Si$ requires *M*, 371.1400).

Ethyl (1*R**,2*R**,5*R**,7*S**)-2-cyano-2-hydroxy-7-methoxycarbonyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 14

HF (40% in water, 0.5 cm^3) was added to a stirred solution of trimethylsilylcyanohydrin **13** (41 mg, 0.11 mmol) in MeCN (4.5 cm^3) in a polypropylene beaker. After 24 h, another portion of HF (0.5 cm^3) was added. After a further 24 h, all the solvent had evaporated to leave a white solid. This was dissolved in CH_2Cl_2 (5 cm^3), washed with saturated aq. $NaHCO_3$ (2 × 5 cm^3) and evaporated under reduced pressure. Purification of the residue by column chromatography (60% Et_2O in light petroleum) gave *cyanohydrin* **14** (31 mg, 93%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3430, 2960, 1750, 1470, 1255 and 1205; δ_H(250 MHz) 4.72 (1 H, s, CH), 4.40–4.53 (2 H, m, OCH_2), 3.76 (3 H, s, OMe), 2.57–2.65 (1 H, m, C*H*H), 2.18–2.23 (1 H, m, CH*H*), 2.03–2.08 (2 H, m, CH_2), 1.65 (3 H, s, Me) and 1.40 (3 H, t, *J* 7, CH_2*Me*); δ_C(125 MHz) 167.8 (C, quat.), 164.5 (C, quat.), 115.0 (C≡N, quat.), 111.1 (C, quat.), 86.8 (C, quat.), 78.6 (CH), 78.8 (C, quat.), 62.7 (OCH_2), 53.0 (OMe), 34.0 (CH_2), 33.1 (CH_2), 24.5 (Me) and 14.0 (Me); *m*/*z* (CI, NH_3) 317 (M + NH_4^+, 30%) and 300 (M + H^+, 100) (Found: M + H^+, 300.1083. $C_{13}H_{18}NO_7$ requires *M*, 300.1083).

Ethyl (1*R**,4*S**,7*S**,8*R**)-1-methyl-6-oxo-4-[2-(trimethysilyl)ethynyl]-5,9,10-trioxatricyclo[5.2.1.0^{4,8}]decane-8-carboxylate 15

To a stirred solution of trimethylsilylacetylene (35 μl, 0.236 mmol) in THF (5 cm^3) at −78 °C, was added Bu^nLi (2.5 mol dm^{-3} in hexanes; 100 μl, 0.24 mmol) dropwise. After 15 min, ketone **9** (50 mg, 0.184 mmol) in THF (4 cm^3) was added. After 1 h saturated aq. NH_4Cl (5 cm^3) was added to the reaction mixture which was then warmed to room temperature and then evaporated under reduced pressure. The yellow residue was acidified with 1 M HCl (5 cm^3), until the solution turned colourless and then extracted with Et_2O (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in light petroleum) gave a white solid, *lactone* **15** (50 mg, 80%); mp 75–76 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 2960, 2175, 1795, 1770, 1255, 1245 and 850; δ_H(400 MHz) 4.50 (1 H, s, CH), 4.23–4.42 (2 H, m, OCH_2), 2.04–2.27 (3 H, m, CH_2C*H*H), 1.76–1.84 (1 H, m, CH*H*), 1.66 (3 H, s, Me), 1.35 (3 H, t, *J* 7, CH_2*Me*) and 0.17 (9 H, s, $SiMe_3$); δ_C(63 MHz) 169.8 (C, quat.), 165.0 (C, quat.), 111.0 (C, quat.), 99.0 (C, quat.), 95.1 (C≡, quat.), 88.4 (≡C-TMS, quat.), 81.2 (C-≡, quat.), 75.4 (CH), 62.4 (OCH_2), 31.1 (CH_2), 30.0 (CH_2), 24.5 (Me), 14.0 (Me) and 0.0 ($SiMe_3$); *m*/*z* (CI, NH_3) 339 (M + H^+, 5%), 310 (25), 295 (15), 249 (18) and 180 (51) (Found: M + H^+, 339.1264. $C_{16}H_{23}O_6Si$ requires *M*, 339.1264).

(1*R**,2*S**,5*R**)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-2-ol 19

To a stirred solution of enol **16**[27] (500 mg, 3.52 mmol) in CH_2Cl_2 (40 cm^3) at 0 °C, was added MCPBA (50% w/w pure; 1.23 g, 3.56 mmol) portionwise. After 1 h, anhydrous KF (5 g) was added, and the suspension was stirred for a further 1 h. The reaction mixture was then filtered, the remaining white solid washed with CH_2Cl_2 (3 × 30 cm^3) and the solvent evaporated to give a clear yellow oil, *epoxide* **17**, which was used in the next step without further purification. The crude oil was stirred at room temperature in 2% HCl in MeOH for 22 h. The solvent was evaporated to give a dark residue which was purified by column chromatography (40% EtOAc in light petroleum) to give *alcohol* **19** (284 mg, 51%). This material was identical in all respects to the major isomer prepared by the same method by Johnston and Oehlschlager.[27]

(1*R**,2*S**,5*R**)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-2-yl 3,5-dinitrobenzoate 21

3,5-Dinitrobenzoyl chloride (497 mg, 2.16 mmol) in CH_2Cl_2 (4 cm^3) was added dropwise to a stirred solution of alcohol **19** (284 mg, 1.80 mmol) and Et_3N (300 μl, 2.16 mmol) in CH_2Cl_2 (6 cm^3) at 25 °C. The reaction mixture was stirred for 6 h before water (10 cm^3) was added. The organic phase was washed with saturated aq. $NaHCO_3$ (15 cm^3), dried ($MgSO_4$) and evaporated to give a dark orange oil. Purification of the residue by column chromatography (gradient elution, 30 to 60% Et_2O in light petroleum) gave the yellow crystalline *benzoate* **21** (360 mg, 57%); mp 124–127 °C (from Et_2O–light petroleum); ν_{max}(KBr disc)/cm^{-1} 1730, 1630, 1545, 1285, 1165, 730 and 720; δ_H(500 MHz) 9.26 (1 H, m, Ar), 9.21 (2 H, m, Ar), 5.08 (1 H, app. d, *J* 4.5 and 1.5, CH), 3.98 (1 H, d, *J* 8, CH*H*), 3.60 (1 H, d, *J* 8, *CH*H), 2.18–2.39 (1 H, m, CH*H*), 1.83–1.98 (2 H, m, CH_2), 1.72 (1 H, dd, *J* 13 and 7, *CH*H), 1.56 (3 H, s, Me) and 1.37 (3 H, s, Me); δ_C(125 MHz) 162.3 (C, quat.), 148.8 (2 × Ar, quat.), 133.9 (Ar, quat.), 129.5 (2 × Ar), 122.6 (Ar), 108.5 (C, quat.), 80.8 (C, quat.), 73.0 (CH_2O), 72.9 (CH), 31.3 (CH_2), 24.3 (Me), 23.8 (CH_2) and 19.2 (Me); *m*/*z* (APCI) 375 (M + Na^+, 100%) (Found: M + H^+, 353.0985. $C_{15}H_{17}N_2O_8$ requires *M*, 353.0985).

Ethyl (1*R**,4*S**,7*S**,8*R**)-4-ethynyl-1-methyl-6-oxo-5,9,10-trioxatricyclo[5.2.1.0^{4,8}]decane-8-carboxylate 22

Lactone **15** (35 mg, 0.10 mmol) and anhydrous K_2CO_3 (*ca*. 10 mg, 70 μmol) were stirred in wet DMF (5 cm^3) at room temperature for 3 h. The solvent was evaporated, and the resultant oil dissolved in CH_2Cl_2 (10 cm^3). The solution was filtered and the filtrate purified by dry-column flash chromatography (Et_2O), to give *desilylated lactone* **22** (27 mg, 98%); mp 108–110 °C (from Et_2O); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2255, 1795, 1765, 1270 and 910; δ_H(400 MHz) 4.51 (1 H, s, CH), 4.29–4.43 (2 H, m, OCH_2), 2.79 (1 H, s, ≡CH), 2.21–2.27 (1 H, m, CH_2), 2.06–2.16 (2 H, m, CH_2), 1.78–1.86 (1 H, m, *CH*H), 1.67 (3 H, s, Me) and 1.35 (3 H, t, *J* 7.5, CH_2*Me*); δ_C(50 MHz) 165.0 (C, quat.), 169.7 (C, quat.), 111.1 (C, quat.), 88.1 (C, quat.), 80.7 (C, quat.), 78.4 (C, quat.), 77.8 (≡CH), 75.4 (OCH), 62.8 (OCH_2), 30.9 (CH_2), 29.9 (CH_2), 24.5 (Me) and 14.0 (Me); *m*/*z* (CI, NH_3) 284 (M + NH_4^+, 100%) and 267 (M + H^+, 10) (Found: M + H^+, 267.0869. $C_{13}H_{15}O_6$ requires *M*, 267.08686).

Ethyl (1*R**,4*S**,7*S**,8*R**)-4-ethenyl-1-methyl-6-oxo-5,9,10-trioxatricyclo[5.2.1.0^{4,8}]decane-8-carboxylate 23

To a solution of acetylene **22** (30 mg, 0.113 mmol) in pyridine (1 cm^3) was added 10% Pd on carbon (5 mg, cat.). The reaction mixture was stirred vigorously under 1 atmosphere of H_2 for 2 h. The mixture was then diluted with Et_2O (10 cm^3) and filtered through a pad of Celite before evaporation to give a cloudy green oil. Purification by column chromatography (Et_2O), gave *alkene* **23** (30 mg, 100%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1790, 1760, 1315 and 480; δ_H(400 MHz) 5.83 (1 H, dd, *J* 17 and 11, =CH), 5.42 (1 H, dd, *J* 17 and 0.5, CH_2=), 5.22 (1 H, dd, *J* 11 and 0.5, CH_2=), 4.46 (1 H, s, CH), 4.12–4.23 (2 H, m, OCH_2), 2.03 (1 H, m, CH*H*), 1.76–1.95 (3 H, m, CH*HC*H), 1.60 (3 H, s, Me) and 1.14 (3 H, t, *J* 7, CH_2*Me*); δ_C(50 MHz) 170.5 (C, quat.), 165.3 (C, quat.), 134.3 (CH=), 117.1 (=CH_2), 110.7 (C, quat.), 87.9 (C, quat.), 87.3 (C, quat.), 76.0 (OCH), 62.2 (OCH_2), 30.1 (CH_2), 28.9 (CH_2), 24.4 (Me) and 13.9 (Me); *m*/*z* (EI) 268 (M^+, 20%) and 184 (30) (Found: M^+, 268.0947. $C_{13}H_{16}O_6$ requires *M*, 268.0947).

(1*R,2*S**,5*R**,7*R**)-1,7-Bis(benzyloxymethyl)-2-ethenyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol 25**

$LiAlH_4$ (0.45 mol dm^{-3} in Et_2O; 3 cm^3, 1.35 mmol) was added dropwise to a stirred solution of alkene **23** (165 mg, 0.62 mmol) in THF (8 cm^3) at 25 °C. After 24 h the reaction mixture was cooled (0 °C) then water (50 μl), aq. NaOH (1.5 mol dm^{-3}; 50 μl) and finally water (150 μl) were added, and the resultant white suspension stirred vigorously at room temperature for 1 h. MeOH (15 cm^3) was then added to the mixture, and the solution was preadsorbed onto SiO_2 and purified by filtration through a pad of SiO_2 (10% MeOH in CH_2Cl_2) to give a pale yellow oil, *triol* **24** (86 mg, 60%), which was used without further purification; δ_C(50 MHz) 140.5 (CH=), 112.9 (=CH_2), 107.4 (C, quat.), 84.7 (CH), 82.5 (C, quat.), 74.3 (C, quat.), 64.1 (CH_2), 60.2 (CH_2), 34.0 (CH_2), 32.7 (CH_2) and 23.9 (Me).

NaH (19 mg, 0.785 mmol) was added to a stirred solution of triol **24** (86 mg, 0.374 mmol) in DME (7 cm^3) at 0 °C. After 20 min BnCl (91 μl, 0.785 mmol) and NaI (56 mg, 0.374 mmol) were added and the reaction mixture allowed to warm to room temperature. After 22 h water (5 cm^3) was added and the product extracted with CH_2Cl_2 (2 × 15 cm^3). The combined organic layers were washed with saturated aq. $NaHCO_3$ (15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in pentane) gave *dibenzyl ether* **25** (79 mg, 52%); ν_{max}/cm^{-1} 3500, 2925, 1455, 2365, 1205, 1075 and 700; δ_H(500 MHz) 7.26–7.40 (8 H, m, Ar), 7.12–7.17 (2 H, m, Ar), 6.40 (1 H, dd, *J* 17 and 11, CH=), 5.33 (1 H, dd, *J* 17 and 1.5, C*H*$_2$=), 5.12 (1 H, dd, *J* 11 and 1.5, C*H*$_2$=), 4.75 (1 H, d, *J* 12.5, OC*H*$_2$Ar), 4.55 (1 H, d, *J* 12.5, OC*H*$_2$Ar), 4.39 (2 H, s, OC*H*$_2$Ar), 4.23 (1 H, s, CH_2C*H*), 4.21 (1 H, app. q, *J* 9.5, CH*H*CH), 3.99 (1 H, d, *J* 9.5, C*H*HCH), 3.80 (1 H, d, *J* 9, C*H*HO), 3.47 (1 H, s, OH), 3.43 (1 H, d, *J* 9, CH*H*O), 2.28 (1 H, dt, *J* 12 and 7, C*H*HCH_2), 1.72–1.83 (2 H, m, CH_2CH_2), 1.55–1.65 (1 H, m, C*H*H) and 1.49 (3 H, s, Me); δ_C(125 MHz) 140.9 (=CH), 138.1 (Ar, quat.), 136.7 (Ar, quat.), 128.5 (2 × Ar), 128.3 (2 × Ar), 128.1 (Ar), 127.8 (4 × Ar), 127.6 (Ar), 112.6 (H_2C=), 107.7 (C, quat.), 85.4 (*C*HCH$_2$O), 81.5 (C, quat.), 74.1 (*C*H$_2$OBn), 74.0 (C, quat.), 73.3 (Ar*C*H$_2$), 72.8 (Ar*C*H$_2$), 69.1 (O*C*H$_2$CH), 33.8 (CH_2), 32.7 (CH_2) and 24.1 (Me); *m*/*z* (APCI) 433 (M + Na^+, 100%) (Found: M + H^+, 411.2172. $C_{25}H_{31}O_5$ requires *M*, 411.2172).

(1*R,3*S**,4*S**,5*R**)-3,4-Bis(benzyloxymethyl)-5-ethenyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-4-ol 26**

A solution of alcohol **25** (17.0 mg, 41.5 μmol) in 2% HCl in MeOH (1.5 cm^3) was stirred at 68 °C for 1 h. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography (gradient elution, 40 to 50% Et_2O in pentane) to give recovered alcohol **25** (4.4 mg, 26%) and the rearranged *alcohol* **26** (10.0 mg, 59%); ν_{max}/cm^{-1} 3435, 2925, 1645, 1455 and 695; δ_H(500 MHz) 7.25–7.34 (10 H, m, Ar), 6.19 (1 H, dd, *J* 17.5 and 11, CH=), 5.27 (1 H, dd, *J* 17.5 and 2, C*H*H=), 5.14 (1 H, dd, *J* 11 and 2, CH*H*=), 4.54 (1 H, d, *J* 12, OC*H*$_2$Ar), 4.50 (1 H, d, *J* 11.5, OC*H*HAr), 4.46 (1 H, d, *J* 12, OCH*H*Ar), 4.46 (1 H, d, *J* 11.5, OC*H*HAr), 3.96 (1 H, dd, *J* 7 and 4, C*H*CH$_2$O), 3.85 (1 H, d, *J* 10, C*H*$_2$O), 3.80 (1 H, dd, *J* 10 and 4, CHC*H*$_2$O), 3.61 (1 H, d, *J* 10, C*H*HO), 3.49 (1 H, dd, *J* 10 and 7, CHCH*H*O), 3.19 (1 H, s, OH), 2.52 (1 H, ddd, *J* 13, 9.5 and 5, C*H*H), 2.14 (1 H, ddd, *J* 13.5, 9.5 and 4.5, CH*H*), 1.95 (1 H, ddd, *J* 13, 13 and 5, C*H*H), 1.71 (1 H, ddd, *J* 13, 13, and 4.5, CH*H*) and 1.54 (3 H, s, Me); δ_C(125 MHz) 138.2 (Ar, quat.), 137.7 (Ar, quat.), 136.8 (=CH), 128.4 (2 × Ar), 128.3 (2 × Ar), 127.8 (5 × Ar), 127.5 (Ar), 113.5 (H_2C=), 106.6 (C, quat.), 87.2 (C, quat.), 75.6 (*C*HCH$_2$O), 73.6 (Ar*C*H$_2$), 73.4 (Ar*C*H$_2$), 69.7 (O*C*H$_2$CH), 69.5 (C, quat.), 68.7 (*C*H$_2$OBn), 34.9 (CH_2), 31.9 (CH_2) and 23.6 (Me); *m*/*z* (CI, NH_3) 428 (M + NH_4^+, 54%) and 411 (M + H^+, 100) (Found: M + H^+, 411.2171. $C_{25}H_{31}O_5$ requires *M*, 411.217145).

[(4*R*,5*S*)-5-Hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-ethanone 33

$Pd(OH)_2$ on carbon (20 mg) was added to ketone **32**[42] (510 mg, 1.93 mmol) in EtOH (5 cm^3) at 25 °C. The flask, with vigorous stirring, was evacuated, then filled with H_2. This procedure was repeated three times in total and then stirred for 14 h under H_2. The suspension was then diluted with CH_2Cl_2 (5 cm^3), then filtered through Celite and evaporated to give a colourless oil, *ketoalcohol* **33** (335 mg, 100%); $[\alpha]_D^{23}$ +42.5 (*c* 1.08 in $CHCl_3$); ν_{max}/cm^{-1} 3485, 2935, 1615, 1455, 1300, 1250 and 1170; δ_H(500 MHz) 4.22 (1 H, d, *J* 7.5, H-4), 4.07 (1 H, app. quintet, *J* 4.5, H-5), 3.87 (1 H, dd, *J* 11.5 and 4.5, C*H*$_2$), 3.70 (1 H, dd, *J* 11.5 and 4, C*H*$_2$), 2.62 (1 H, br s, OH), 2.28 (3 H, s, Me), 1.45 (3 H, s, C*Me*) and 1.39 (3 H, s, C*Me*); δ_C (125 MHz) 208.9 (C, quat.), 110.6 (*C*Me$_2$, quat.), 81.4 (CH), 78.2 (CH), 62.0 (CH_2), 27.0 (Me), 26.6 (C*Me*) and 26.0 (C*Me*); *m*/*z* (CI, NH_3) 192 (M + NH_4^+, 100%) and 175 (M + H^+, 22) (Found: M + H^+, 175.0970. $C_8H_{15}O_4$ requires *M*, 175.0970).

Ethyl 3-{(4*R*,5*R*)-2,2-dimethyl-5-[1-(oxo)ethyl]-1,3-dioxolan-4-yl}-3-oxopropanoate 35

A solution of $(COCl)_2$ (1.06 cm^3, 12.12 mmol) in CH_2Cl_2 (20 cm^3) at −78 °C was treated dropwise with DMSO (1.72 cm^3, 24.24 mmol) and stirred for 15 min after which time keto-alcohol **33** (1.92 g, 11 mmol) in CH_2Cl_2 (5 cm^3) was added. After 1 h Et_3N (3.37 cm^3, 24.24 mmol) was added and the temperature raised to 0 °C for 1 h before quenching with pH 7.0 aq. phosphate buffer (20 cm^3). The aq. phase was extracted with CH_2Cl_2 (2 × 20 cm^3) and the combined organic layers were dried ($MgSO_4$) and evaporated to give a pale yellow oil, *aldehyde* **34** that was used directly.

A stirred solution of the above aldehyde **34** in CH_2Cl_2 (30 cm^3) at 25 °C was treated with ethyl diazoacetate (1.16 cm^3, 11.05 mmol) and anhydrous $SnCl_2$ (cat.). After 24 h water (10 cm^3) was added and the organic phase washed with water (2 × 25 cm^3), brine (25 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 10 to 20% Et_2O in light petroleum) gave a colourless oil, *diketoester* **35** (1.45 g, 51%); $[\alpha]_D^{23}$ +20.8 (*c* 1.50 in $CHCl_3$); ν_{max}/cm^{-1} 2990, 1735, 1720, 1375, 1215, 1090 and 860; δ_H(300 MHz) 4.66 (1 H, d, *J* 6, H-5′), 4.55 (1 H, d, *J* 5.5, H-4′), 4.10–4.17 (2 H, m, C*H*$_2$Me), 3.61 (2 H, s, CH_2), 2.24 (3 H, s, Me), 1.34 (3 H, s, C*Me*), 1.38 (3 H, s, C*Me*) and 1.21 (3 H, t, *J* 7, CH_2*Me*); δ_C(125 MHz) 206.0 (C, quat.), 201.6 (C, quat.), 166.6 (C, quat.), 112.5 (*C*Me$_2$, quat.), 83.5 (CH), 76.1 (CH), 61.3 (CH_2), 45.5 (CH_2), 26.4 (Me), 26.2 (Me), 25.8 (Me) and 13.8 (Me); *m*/*z* (CI, NH_3) 276 (M + NH_4^+, 100%) and 259 (M + H^+, 37) (Found: M + H^+, 259.1181. $C_{12}H_{19}O_6$ requires *M*, 259.1182).

Ethyl 3-{(4*R*,5*R*)-2,2-dimethyl-5-[1-(oxo)ethyl]-1,3-dioxolan-4-yl}-2-diazo-3-oxopropanoate 36

Et_3N (0.5 cm^3) was added to a stirred solution of diketoester **35** (960 mg, 3.72 mmol) and 4-nitrobenzenesulfonyl azide (856 mg, 3.76 mmol) in MeCN (7 cm^3) at 0 °C. After 4 h the mixture was diluted with CH_2Cl_2 (10 cm^3) and washed with saturated aq. NH_4Cl (2 × 10 cm^3), brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (30% EtOAc in light petroleum) gave a yellow glassy solid, *diazoester* **36** (995 mg, 94%); mp 57–59 °C; $[\alpha]_D^{23}$ −41.7 (*c* 1.03 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2990, 2165, 1730, 1715, 1655, 1370, 1315, 1070 and 1020; δ_H(500 MHz) 5.48 (1 H, d, *J* 6, H-5′), 4.70 (1 H, d, *J* 6, H-4′), 4.26–4.31 (2 H, m, C*H*$_2$Me), 2.32 (3 H, s, Me), 1.49 (3 H, s, C*Me*), 1.48 (3 H, s, C*Me*) and 1.32 (3 H, t, *J* 7, CH_2*Me*); δ_C(125 MHz) 206.5 (C, quat.), 188.3 (C, quat.), 161.0 (C, quat.), 113.8 (*C*Me$_2$, quat.), 83.0 (CH), 78.4 (CH), 62.4 (CH_2), 27.3 (C*Me*), 26.8 (C*Me*), 26.6 (Me) and 14.7 (Me); *m*/*z* (CI, NH_3) 302

($M + NH_4^+$, 36%), 285 ($M + H^+$, 28), 276 (100), 190 (84) and 160 (91) (Found: $M + H^+$, 285.1086. $C_{12}H_{17}N_2O_6$ requires *M*, 285.1087).

(2*R*,3*S*,4*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-methylbutyrolactone 38

2,6-Dimethylpyridine (0.13 cm^3, 1.13 mmol) was added to a stirred solution of (2*R*,3*S*,4*S*)-2,3-dihydroxy-4-methylbutyrolactone[43] **37** (0.037 g, 0.28 mmol) in CH_2Cl_2 (0.5 cm^3). The solution was cooled to 0 °C and TBDMSOTf (0.195 cm^3, 0.85 mmol) was added dropwise. The reaction mixture was stirred for 3 h at 25 °C before adding water (5 cm^3). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (20% Et_2O in light petroleum) gave a white solid, *lactone* **38** (88 mg, 88%); R_f 0.54 (10% Et_2O in light petroleum); mp 39–43 °C (from Et_2O–light petroleum) (Found: C, 55.73; H, 10.06. $C_{17}H_{36}O_4Si_2$ requires C, 56.62; H, 10.06%); $[\alpha]_D^{25}$ +13.7 (*c* 1.09 in $CHCl_3$); ν_{max}/cm^{-1} 2955s, 2930s, 2886m, 1857s, 1805s, 1254s and 1073s; δ_H(400 MHz) 4.29 (1 H, d, *J* 7.5, C*H*OTBDMS), 4.15 (1 H, dq, *J* 6.5 and 6.5, C*H*Me), 3.90 (1 H, dd, *J* 7.5 and 7.5, C*H*OTBDMS), 1.42 (3 H, d, *J* 6.5, Me), 0.93 (9 H, s, $SiCMe_3$), 0.90 (9 H, s, $SiCMe_3$), 0.21 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.13 (3 H, s, SiMe) and 0.11 (3 H, s, SiMe); δ_C(100 MHz) 173.3 (C, quat.), 80.6 (OCH), 77.7 (OCH), 76.1 (OCH), 25.7 (C*Me*$_3$), 25.6 (C*Me*$_3$), 18.2 (Me), 18.1 (CSi, quat.), 17.8 (CSi, quat.), −4.0 (SiMe), −4.4 (2 × $SiMe_2$) and −4.8 (SiMe); *m*/*z* (CI, NH_3) 378 ($M + NH_4^+$, 30%), 246 (45), 132 (35) and 53 (100) (Found: $M + NH_4^+$, 378.2492. $C_{17}H_{40}Si_2NO_4$ requires *M*, 378.2496).

Ethyl (4*R*,5*S*,6*S*)-4,5-bis(*tert*-butyldimethylsilyloxy)-2-diazo-6-hydroxy-3-oxoheptanoate 39

Bu^nLi (2.3 mol dm^{-3} in hexanes; 382 μl, 0.88 mmol) was added to a solution of diisopropylamine (123 μl, 0.88 mmol) in THF at −78 °C. After 30 min the reaction mixture was cooled to −90 °C and ethyl diazoacetate (92 μl, 0.88 mmol) was added dropwise to give an orange solution. After 20 min a solution of lactone **38** (0.29 g, 0.80 mmol) in THF (3 cm^3) was added and after 1 h at −90 °C the reaction mixture was allowed to warm to −78 °C. After 5 h at −78 °C a mixture of glacial acetic acid and water was added and the reaction was then warmed to 25 °C and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and the residue purified by column chromatography (10% Et_2O in light petroleum). First to elute was recovered lactone **38** (0.122 g, 42%). Second to elute was *diazoketoester* **39** (0.164 g, 50%); R_f 0.32 (20% Et_2O in light petroleum); $[\alpha]_D^{25}$ −35.0 (*c* 1.01 in $CHCl_3$); ν_{max}/cm^{-1} 3514w, 2955s, 2931s, 2859s, 2136s, 2110s, 1715s, 1678m, 1306s, 1115s and 837s; δ_H(400 MHz) 5.48 (1 H, d, *J* 3, C*H*OTBDMS), 4.30–4.20 (3 H, m, CH_2Me and C*H*Me), 3.66 (1 H, dd, *J* 3 and 6.5, C*H*OTBDMS), 3.22 (1 H, br, OH), 1.31 (3 H, t, *J* 7, CH_2Me), 1.20 (3 H, d, *J* 6.5, Me), 0.91 (9 H, s, $SiCMe_3$), 0.85 (9 H, s, $SiCMe_3$), 0.10 (3 H, s, SiMe), 0.07 (3 H, s, SiMe), 0.05 (3 H, s, SiMe) and 0.04 (3 H, s, SiMe); δ_C(100 MHz) 191.7 (C, quat.), 161.2 (C, quat.), 76.5 (C, quat.), 76.5 (OCH), 75.7 (OCH), 69.7 (OCH), 61.5 (OCH_2), 25.7 (2 × C*Me*$_3$), 20.1 (Me), 18.0 (CSi, quat.), 17.9 (CSi, quat.), 14.3 (Me), −4.5 (SiMe), −4.9 (SiMe), −5.0 (SiMe) and −5.3 (SiMe); *m*/*z* (CI, NH_3) 457 ($[M + H - H_2O]^+$, 8%), 378 (100), 246 (100) and 132 (95) (Found: $[M + H - H_2O]^+$, 457.2555. $C_{21}H_{41}Si_2N_2O_5$ requires *M*, 457.2554).

Ethyl (4*R*,5*R*)-4,5-bis(*tert*-butyldimethylsilyloxy)-2-diazo-3,6-dioxoheptanoate 40

A mixture of the alcohol **39** (11 mg, 0.024 mmol) and Dess–Martin periodinane[45] (30 mg, 0.072 mmol) in CH_2Cl_2 (5 cm^3) was stirred at 25 °C. After 1 h a solution of sodium thiosulfate (0.12 g) in saturated aq. $NaHCO_3$ (5 cm^3) was added. The aqueous layer was separated and the organic layer was washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O in light petroleum) gave *ketone* **40** (6.5 mg, 60%); R_f 0.59 (20% Et_2O in light petroleum); $[\alpha]_D^{25}$ +47.0 (*c* 1.01 in $CHCl_3$); ν_{max}/cm^{-1} 2954m, 2930m, 2859m, 2136s, 1716s, 1674m, 1305s, 1130m and 839s; δ_H(400 MHz) 5.23 (1 H, br s, C*H*OTBDMS), 4.41 (1 H, d, *J* 3, C*H*OTBDMS), 4.37–4.29 (2 H, m, CO_2CH_2), 2.25 (3 H, s, Me), 1.34 (3 H, t, *J* 7, CH_2Me), 0.91 (9 H, s, $SiCMe_3$), 0.88 (9 H, s, $SiCMe_3$), 0.05 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.00 (3 H, s, SiMe) and −0.04 (3 H, s, SiMe); δ_C(100 MHz) 188.9 (C, quat.), 161.1 (C, quat.), 79.4 (CH), 61.7 (OCH_2), 27.8 (*Me*C=O), 25.7 (C*Me*$_3$), 25.6 (C*Me*$_3$), 18.3 (*C*Me_3), 18.0 (*C*Me_3), 14.8 (Me), −4.8 (SiMe), −4.9 (SiMe), −5.4 (SiMe) and −5.6 (SiMe); *m*/*z* (CI, NH_3) 473 ($M + H^+$, 10%), 206 (70), 132 (100), 91 (95) and 74 (93) (Found: $M + H^+$, 473.2494. $C_{21}H_{41}Si_2N_2O_6$ requires *M*, 473.2503).

Ethyl (1*R*,2*R*,6*R*,8*R*,9*R*)-9-methoxycarbonyl-1,4,4-trimethyl-7-oxo-3,5,10,11-tetraoxatricyclo[6.2.1.0^{2,6}]undecane-8-carboxylate 41

Diazoester **36** (46.0 mg, 0.162 mmol) was added to a stirred solution of freshly distilled methyl glyoxylate[15] (22.0 mg, 0.250 mmol) in toluene (0.25 cm^3) and the mixture warmed to 110 °C. $Rh_2(OAc)_4$ (cat.) was then added initiating N_2 evolution. After 1 h the mixture was cooled, diluted with Et_2O (2 cm^3) and filtered through Celite with Et_2O (5 × 10 cm^3), followed by CH_2Cl_2 (2 × 5 cm^3) washings. The filtrate was evaporated under reduced pressure to give a yellow oil, *tricyclic ester* **41** (63.5 mg, quant.); ν_{max}/cm^{-1} 1755, 1225, 1110 and 855; δ_H(500 MHz) 5.03 (1 H, d, *J* 9.5, H-3), 5.03 (1 H, s, H-10), 4.50 (1 H, d, *J* 9.5, H-7), 4.34–4.37 (2 H, m, C*H*Me), 3.84 (3 H, s, OMe), 1.82 (3 H, s, Me), 1.56 (6 H, s, 2 × Me) and 1.38 (3 H, t, *J* 7.0, CH_2Me); δ_C(125 MHz) 196.6 (C, quat.), 168.5 (C, quat.), 162.7 (C, quat.), 115.9 (*C*Me_2, quat.), 111.7 (C_2, quat.), 90.3 (C, quat.), 81.5 (CH), 79.8 (CH), 79.4 (CH), 63.5 (CH_2), 53.1 (OMe), 26.7 (C*Me*), 26.3 (C*Me*), 17.5 (Me) and 13.9 (Me); *m*/*z* (CI, NH_3) 362 ($M + NH_4^+$, 20%), 345 ($M + H^+$, 10), 322 (100) and 216 (50) (Found: $M + NH_4^+$, 362.1451. $C_{15}H_{24}NO_9$ requires *M*, 362.1451).

Ethyl (1*R*,3*R*,4*R*,5*R*,7*S*)-7-methoxycarbonyl-3,4-dihydroxy-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 42

Crude tricyclic ester **41** (25 mg, 0.073 mmol) was dissolved in $CDCl_3$ (0.5 cm^3). After standing for 1 h at 25 °C, the solvent was evaporated under reduced pressure at 40 °C to afford *diol* **42** as a pale yellow oil (22 mg, quant.); ν_{max}/cm^1 3490, 1755, 1370, 1220, 1075 and 855; δ_H(500 MHz) 4.76 (1 H, s, H-7), 4.54 (1 H, d, *J* 7, H-3), 4.31 (2 H, q, *J* 7, CH_2Me), 3.93 (1 H, d, *J* 7, H-4), 3.76 (3 H, s, OMe), 1.69 (3 H, s, Me) and 1.30 (3 H, t, *J* 7, CH_2Me); δ_C(125 MHz) 203.5 (C, quat.), 167.9 (C, quat.), 162.1 (C, quat.), 114.1 (C, quat.), 88.7 (C, quat.), 79.8 (CH), 78.0 (CH), 77.2 (CH), 63.3 (CH_2), 53.1 (OMe), 19.7 (Me) and 13.8 (Me); *m*/*z* (CI, NH_3) 322 ($M + NH_4^+$, 20%), 276 (100) and 192 (40) (Found: $M + NH_4^+$, 322.1138. $C_{12}H_{20}NO_9$ requires *M*, 322.1138).

Ethyl (1*R*,3*R*,4*R*,5*R*,7*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)-7-methoxycarbonyl-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate 43

$Rh_2(OAc)_4$ (cat.) was added to a solution of diazoketoester **40** (51 mg, 0.10 mmol) and freshly distilled methyl glyoxylate[15] (38 mg, 0.43 mmol) in toluene (1 cm^3) at 80 °C. After 4 h the reaction was cooled, diluted with Et_2O (1 cm^3), filtered through Celite and evaporated under reduced pressure. Purification of

the residue by column chromatography (10% EtOAc in light petroleum) gave a yellow oil, *cycloadduct* **43** (22 mg, 42%); R_f 0.45 (20% Et_2O in light petroleum); $[\alpha]_D^{24}$ −23.1 (*c* 1.12 in $CHCl_3$); ν_{max}/cm^{-1} 2931s, 2858s, 1763s, 1473m, 1260s, 1097s and 839s; δ_H(400 MHz) 4.81 (1 H, s, CH), 4.70 (1 H, d, *J* 7, CHC=O), 4.41–4.29 (2 H, m, CO_2CH_2Me), 3.91 (1 H, d, *J* 7, CH), 3.80 (3 H, s, CO_2Me), 1.68 (3 H, s, Me), 1.34 (3 H, t, *J* 7, Me), 0.99 (9 H, s, $SiCMe_3$), 0.98 (9 H, s, $Si CMe_3$), 0.20 (6 H, s, 2 × SiMe,), 0.10 (3 H, s, SiMe) and 0.05 (3 H, s, SiMe); ^{1}H NOE experiments: irradiation δ 4.81 saw enhancement at 3.91 (1.0%), at 1.68 (1.8%) and at 1.34 (1.0%); irradiation at δ 4.70 saw enhancement at 3.91 (3.2%); irradiation at δ 3.91 saw enhancement at 4.81 (1.0%), 4.70 (4.2%) and at 1.68 (2.5%); irradiation at δ 1.68 saw enhancement at 4.81 (4.1%), 4.70 (3.0%), at 3.91 (4.5%), at 0.99 (6.5%) and at 0.20 (9%); δ_C(100 MHz) 203.2 (C, quat.), 167.1 (CO_2Me, quat.), 162.6 (CO_2Et, quat.), 114.6 (C, quat.), 88.5 (C, quat.), 79.4 (CH), 78.9 (CH), 78.0 (CH), 63.0 (CH_2), 52.7 (CO_2Me), 26.1 (CMe_3), 25.9 (CMe_3), 21.1 (C-5 *Me*), 18.4 (CMe_3), 17.9 (CMe_3), 13.8 (Me), −3.5 (SiMe), −3.6 (SiMe), −4.1 (SiMe) and −4.9 (SiMe); *m*/*z* (CI) 550 (M + NH_4^+, 18%), 533 (M + H^+, 5%), 313 (25), 132 (65) and 91 (100) (Found: M + H^+, 533.2594. $C_{24}H_{45}Si_2O_9$ requires *M*, 533.2602).

Ethyl (1*R*,3*R*,4*R*,5*R*,7*S*)-7-*tert*-butoxycarbonyl-3,4-bis(*tert*-butyldimethylsilyloxy)-5-methyl-2-oxo-6,8-dioxabicyclo[3.2.1]-octane-1-carboxylate 44

$Rh_2(OAc)_4$ (cat.) was added to a solution of diazoester **40** (64 mg, 0.13 mmol) and freshly distilled *tert*-butyl glyoxylate[16] (26 mg, 0.20 mmol) in toluene (1 cm^3) at 110 °C. After 2.5 h the reaction was cooled, diluted with Et_2O (1 cm^3), filtered through Celite and evaporated under reduced pressure. Purification of the residue by column chromatography (10% EtOAc in light petroleum) gave a clear oil, *cycloadduct* **44** (43 mg, 58%); R_f 0.42 (10% Et_2O in light petroleum); $[\alpha]_D^{25}$ −20.2 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2931s, 2858s, 1754s, 1473m, 1257s, 1097s and 839s; δ_H(400 MHz, C_6D_6) 5.01 (1 H, s, CH), 4.88 (1 H, d, *J* 7.5, CH), 4.35 (1 H, d, *J* 7.5, CH), 3.99–3.80 (2 H, m, CO_2CH_2), 1.73 (3 H, s, Me), 1.45 (9 H, s, CMe_3), 1.17 (9 H, s, CMe_3), 1.02 (9 H, s, CMe_3), 0.99 (3 H, t, *J* 7, Me), 0.19 (3 H, s, SiMe), 0.18 (3 H, s, SiMe), 0.17 (3 H, s, SiMe) and 0.09 (3 H, s, SiMe); ^{1}H NMR NOE experiments: irradiation at δ 5.01 saw enhancements at 4.35 (1.4%), at 1.73 (1.0%) and at 1.45 (1.0%); irradiation at δ 4.88 saw enhancements at 4.35 (4.0%) and at 0.19 (6.4%); irradiation at δ 4.35 saw enhancements at 5.01 (1.0%), at 4.88 (3.0%), at 1.73 (1.8%), at 1.45 (2.2%), at 0.19 (3.2%) and at 0.09 (4.3%); δ_C(100 MHz, C_6D_6) 203.2 (C, quat.), 165.7 (C, quat.), 162.9 (C, quat.), 114.6 (C, quat.), 89.3 (C, quat.), 82.5 (C, quat.), 82.5 (CH), 80.2 (CH), 78.8 (CH), 62.3 (CH_2), 27.5 (CMe_3), 26.2 (CMe_3), 25.9 (CMe_3), 21.2 (C(5)Me), 18.4 (C, quat.), 17.8 (C, quat.), 13.4 (Me), −3.6 (SiMe), −3.7 (SiMe), −4.5 (SiMe) and −4.9 (SiMe); *m*/*z* (CI) 592 (M + NH_4^+, 18%), 443 (10) and 313 (100) (Found: M + NH_4^+, 592.3329. $C_{27}H_{54}NO_9Si_2$ requires *M*, 592.3337).

Acknowledgements

We thank the EPSRC for a Research Grant (GR/J84267) and an Earmarked Studentship and the EPSRC and Merck Sharp & Dohme for converting the Studentship into a CASE award (to J. M. B.). We also thank Dr R. Mortishire-Smith (Merck Sharp & Dohme) and Dr T. D. W. Claridge (Oxford) for expert assistance with the determination of stereochemistry using NMR, the EPSRC National Mass Spectrometry Service Centre for mass spectra and Zeneca (Strategic Research Fund) and Pfizer for additional financial support. We also thank A. W. Johans for his assistance with the crystallographic investigations and the University of Reading together with the EPSRC for funds for an Image Plate System. Professor L. Duhamel (Rouen) is thanked for additional information concerning the synthesis of lactone diol **37**.

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