Stereoselectivity of intramolecular cyclisations of nitrones derived from 3-oxahept-6-enals

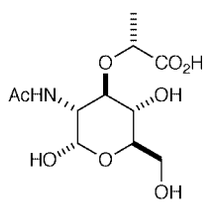
Michael B. Gravestock,[a] David W. Knight,*[b]† Jennifer S. Lovell[b] and Steven R. Thornton[b]

[a] *Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG*
[b] *Chemistry Department, University Park, Nottingham, UK NG7 2RD*

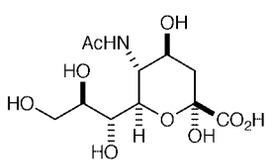
Received (in Cambridge, UK) 19th July 1999, Accepted 1st September 1999

Intramolecular [1,3]-dipolar cycloadditions of nitrones **33**, derived from 3-oxahept-6-enals **7**, substituted at either the 4- or 5-position and prepared using a variety of approaches, give good to excellent yields of the cycloadducts **34**–**37**, with good levels of stereoselectivity, especially when the substituent is adjacent to the alkene. The cyclisations appear to proceed *via* well-defined transition state conformations which should be of predictive value.

Amino sugars occupy a central position in Nature as ubiquitous components of glycoproteins. Of special interest is their association with both immune responses and infection mechanisms; especially prominent in this class are *N*-acetylmuramic acid **1**, a key component of the 'muramyl dipeptide', the minimum structural component of various bacterial cell walls[1] and neuraminic acid **2**, the parent member of the sialic acids,[2] which



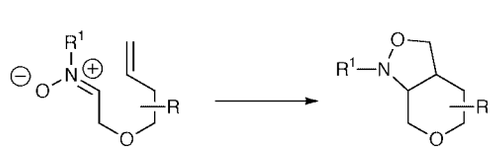
1



2

is often found at the termini of glycoproteins. Amino glycosides can also show broad-spectrum antibiotic activity, especially against Gram-negative bacteria,[3] while a number of examples of desoxyamino sugars occur as isolated residues in non-carbohydrate molecules which also exhibit useful antibiotic activities, exemplified by galantinic acid and relatives, components of galantin 1 and spicamicin.[4] Perhaps the best known of this class of compounds is (L)-daunosamine which occurs in almost all of the important anthracycline antibiotics and which is considered essential for their biological activity.[5]

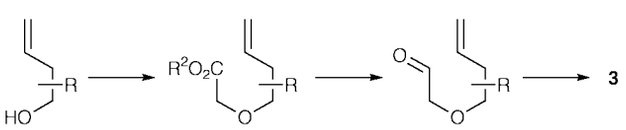
As a preliminary to synthetic studies towards these classes of amino sugars, we became interested in the prospects for employing intramolecular [1,3]-dipolar cycloadditions of nitrones **3**, derived from 3-oxahept-6-enals, to access the aza



3 **4**

dioxabicyclo[4.3.0]nonanes **4**. This approach was especially suited to our initial aim, which was the elaboration of relatives of amino sugars lacking an anomeric hydroxy function, but possessing many of the other structural and stereochemical features of the natural compounds. Such compounds might be expected to be recognized as amino sugars but then to interfere with processes such as cell wall assembly, particularly due to the absence of the anomeric group. The synthetic utility of [1,3]-dipolar cycloadditions has been amply demonstrated over the past three decades and intramolecular versions in particular have been employed as key steps in many elegant syntheses.[6] The idea of generating such bicyclic systems using intramolecular dipolar cycloadditions was first demonstrated by LeBel and co-workers who showed that such a process is well-suited to the preparation of *cis*-bicyclo[3.3.0]octanes although, in highly hindered cases, the isomeric bicyclo[3.2.1]octanes are also formed.[7] Later, this methodology was used to prepare sugar-like carbocycles.[8] The idea of incorporating ether oxygens into the chain connecting the two reacting functional groups has been extensively studied by Aurich and co-workers[9] in the elaboration of dioxabicyclo[3.3.0]octanes, from often spontaneous cycloadditions at ambient temperature. This group also found that isomeric dioxabicyclo[3.2.1]octanes were formed from some hindered substrates and that, perhaps not surprisingly, substituents exerted the greatest degree of stereocontrol when positioned adjacent to the reaction groups.[10] A brief study of the preparation of some examples of dioxabicyclo[4.3.0]nonanes, isomeric with our target compounds **4**, has also been reported by the Aurich group,[11] but only with methyl substituents and bulky *N*-*tert*-butyl or aryl groups. Again, formation of the isomeric bridged products, dioxabicyclo[4.2.1]nonanes, was observed in some cases.

It was against this background that we began our studies with a trial sequence, to test that the planned strategy leading to nitrones **3** was viable.[12] This consisted of *O*-alkylation of a homoallylic alcohol **5**, conversion of the resulting esters or acids **6** into the corresponding aldehydes **7** and condensation with an *N*-alkylhydroxylamine (Scheme 1). But-3-enol was

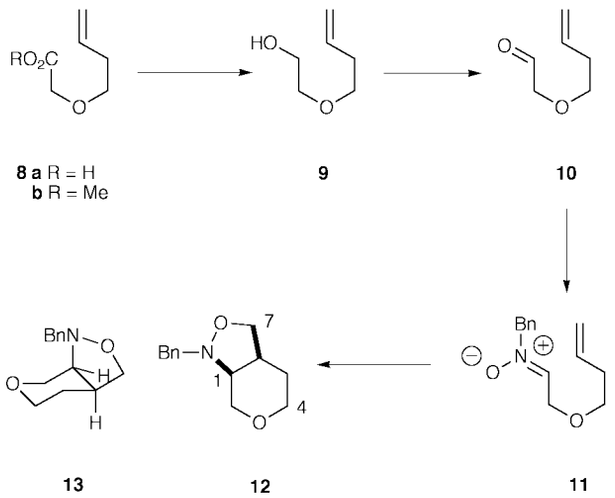


5 **6** **7**

Scheme 1

alkylated using sodium bromoacetate, formed *in situ* using sodium hydride,[13] and the resulting acid **8a** was esterified using acidic methanol (Scheme 2). Reduction of the ester **8b**

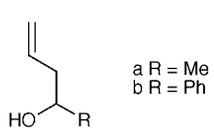
† *Present address*: Chemistry Department, Cardiff University, P.O. Box 912, Cardiff, UK CF10 3TB.



Scheme 2

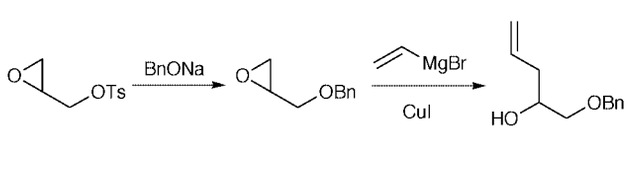
using lithium aluminium hydride gave the alcohol **9** and thence the sensitive aldehyde **10**, following oxidation with pyridinium chlorochromate.[14] This was immediately converted into the *N*-benzyl nitrone **11** which required heating in toluene to effect the dipolar cycloaddition, resulting in the isolation of only the *cis*-azadioxabicyclo[4.3.0]nonane **12** in moderate yield [traces (<5%) of other apparent products were not isolated]. Despite some signal overlap, ^{1}H NMR data showed complete disappearance of the alkene function and provided, along with the ^{13}C NMR data, excellent evidence for this structure. Double irradiation experiments allowed a full assignment of the spectral data. In particular, a dddd pattern with only one large *trans*-diaxial coupling constant at δ_H 2.89 was assigned to 6-H while an apparent dt pattern centred at δ_H 3.07 due to 1-H having relatively small coupling constants (≤6.3 Hz), suggested that this proton was equatorial to a first approximation. A coupling of 6.3 Hz ($J_{1,6}$) across the ring junction confirmed a *cis* ring fusion and suggested conformation **13** for the product.

We therefore required a representative series of homoallylic alcohols to probe the overall utility and stereochemical features of the cyclisation. These were obtained as follows: the 4-methyl derivative **14a** is commercially available and the 4-phenyl homologue **14b** was obtained by a Grignard reaction between allyl-



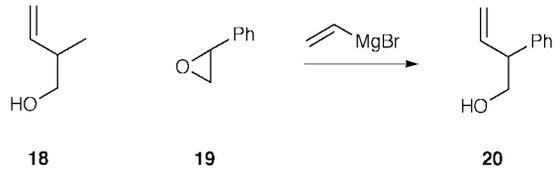
14

magnesium chloride and benzaldehyde. Displacement of tosylate from the glycidyl tosylate **15** using sodium benzyloxide gave the epoxy-ether **16** and thence the 4-*O*-benzylmethyl alcohol **17** by copper-catalysed coupling[15] with vinylmagnesium bromide (Scheme 3). In the second series, which have substitu-



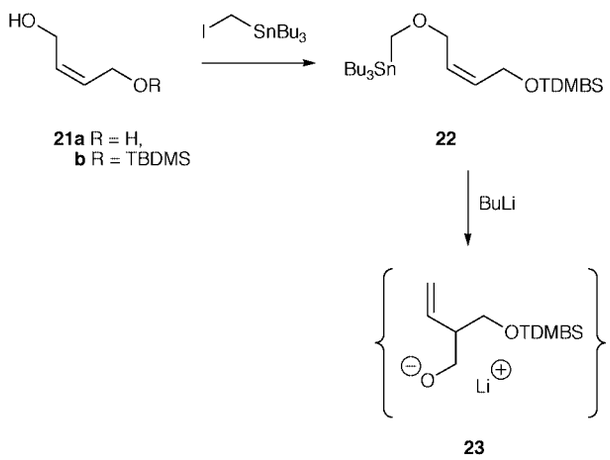
Scheme 3

ents adjacent to the alkene, the 2-methyl derivative **18** is commercially available and the 2-phenyl analogue **20** was obtained by the addition of vinylmagnesium bromide to styrene oxide **19**



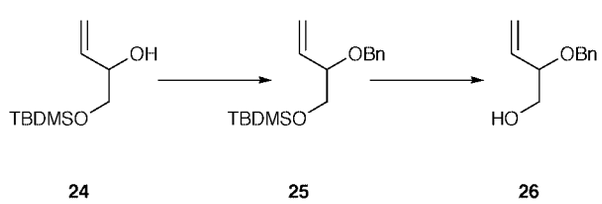
Scheme 4

(Scheme 4).[16] The 2-silyloxymethyl alcohol, as its lithium salt **23**, was obtained by [2,3]-Wittig rearrangement[17] of the alkyllithium derived from the stannane **22**, which was itself prepared by alkylation of the monoprotected butenediol **21a**[18] by iodomethyltributylstannane (Scheme 5).[19] The lower homo-



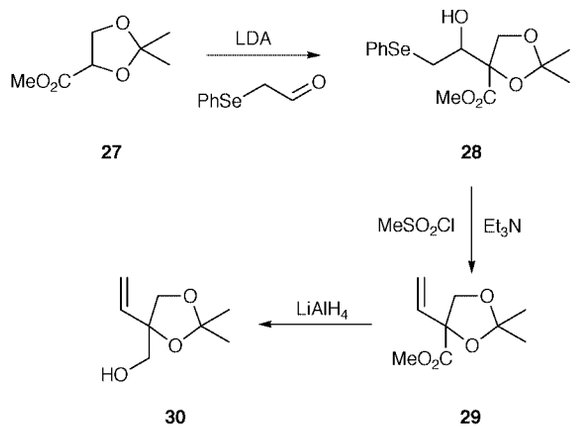
Scheme 5

logue **26** was prepared starting with butadiene monoepoxide, hydration of which using aqueous sulfuric acid[20] gave but-2-ene-1,2-diol which was selectively silylated at the primary position to give alcohol **24**; formation of the benzyl ether **25** and desilylation completed the sequence (Scheme 6). Finally,



Scheme 6

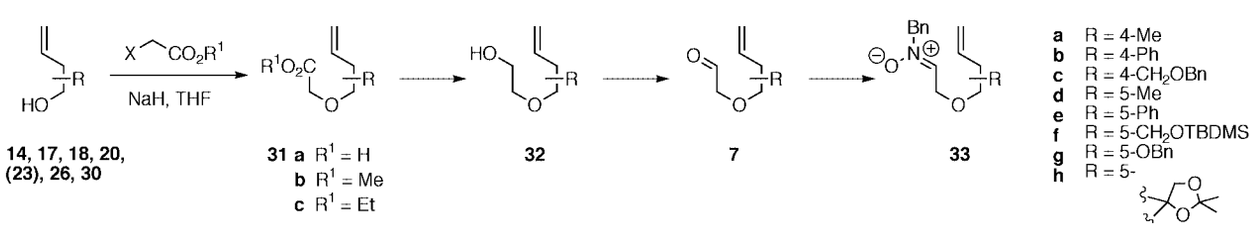
the dioxolane **30** was prepared starting from the ester **27** derived from solketal (2,2-dimethyl-1,3-dioxolane-4-methanol) by sequential oxidation with basic potassium permanganate[21] and esterification under basic conditions.[22] The ethenyl group was then constructed by condensation between the lithium enolate of ester **27** and phenylselenoacetaldehyde.[23] The resulting seleno-alcohol **28** was mesylated, resulting in elimination to the ethenyl-ester **29** which was then reduced to the target alcohol **30** (Scheme 7). Conversion of these various alcohols into the 3-oxahept-6-enoic acids or esters **31** was achieved in a number of ways. Initially, alkylation using sodium bromoacetate[13] (see above) was used, although in some examples, yields were poor and only viable in the case of acid **31ba** when DMPU was added, presumably due to lower nucleophilicity of the alkoxide because of electron withdrawal by the phenyl substituent. Similar alkylations using ethyl bromoacetate (*e.g.* for esters **31cc** and **31dc**), although quoted in the Experimental section as giving reasonable isolated yields (>60%) were, however, rather capricious. We subsequently found that sodium iodoacetate was much more suitable, routinely giving high yields of the acids **31a**. In the case of the Wittig rearrangement



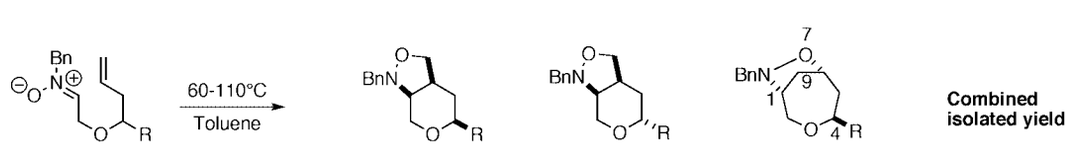
Scheme 7

approach to acid **31fa**, the intermediate lithium salt **23** was directly alkylated using sodium iodoacetate. Esterification and reduction then provided the alcohols **32** which were oxidized to the aldehydes **7a**–**d**,**h** using Swern oxidation[24] or using tetrapropylammonium perrhuthenate (TPAP)[25] in the case of aldehyde **7b**. A more rapid, if sometimes capricious method, was direct reduction of the esters **31xb** to the aldehydes **7b**,**e**–**g** using diisobutylaluminium hydride in hexanes. Finally, the nitrones **33** were formed by condensation with *N*-benzylhydroxylamine at 0–20 °C then isolated and immediately heated in toluene (Scheme 8). Some of these were characterized by ^{1}H NMR spectroscopy and found to be single geometric isomers in every case, presumably the more stable (*Z*)-isomers as depicted.[6] There is, of course, no guarantee that these isomers are the ones which react in the cycloadditions (see below).

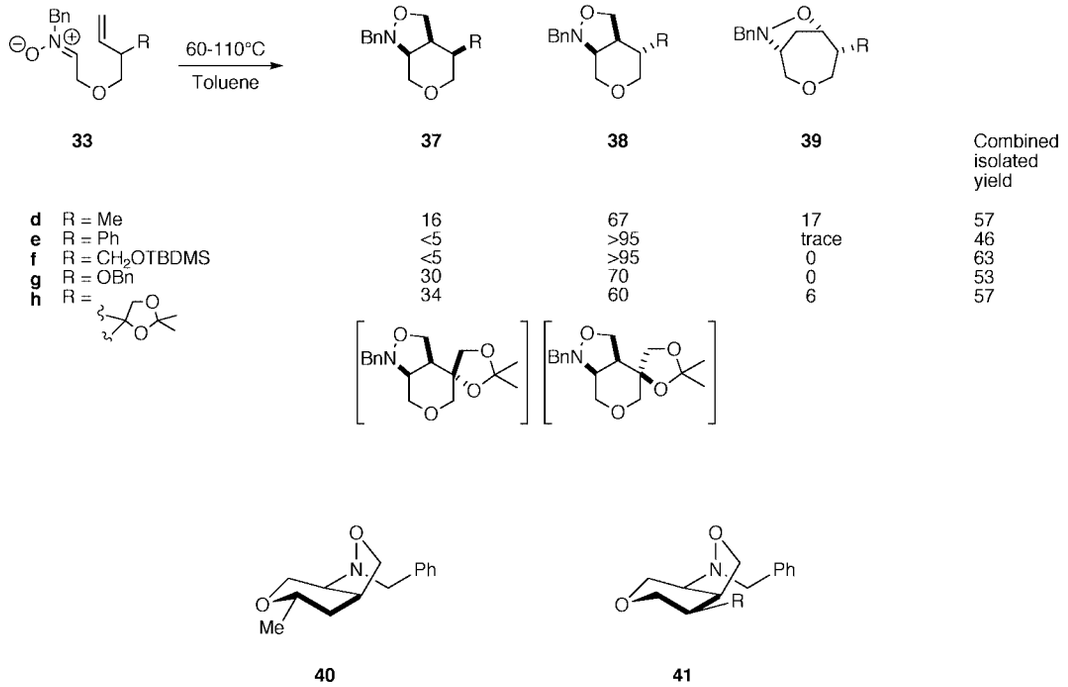
The results obtained from the [1,3]-dipolar cycloadditions are collected in Schemes 9 and 10. In general, isomer ratios were determined by careful integration of a ^{1}H NMR spectrum of the crude product, prior to separation. These, rather than isolated yields, which can vary from run to run, are quoted in Schemes 9 and 10. In all examples, all analytical data were consistent with the proposed structures; the stereochemical determinations were based largely on detailed analyses of NMR data. In the case of the 4-methyl nitrone **33a**, three separable products were isolated in a ratio 70:19:11 in 72% overall yield. The major component was identified as the all-*cis* isomer **34a** mainly on the basis of ^{1}H NMR coupling constant data. A combination of decoupling and COSY experiments allowed full assignment of the spectrum, although in deuteriochloroform, the protons at C-5 were almost coincident. Fortunately, a spectrum obtained in d_6-DMSO showed these and other obscured signals as well-resolved resonances. The presence of only one large coupling constant (J_{gem} = 12.8 Hz) for both of the C-2 protons indicated that the adjacent ring junction proton, 1-H, at δ_H 2.79, was positioned equatorially, which was confirmed by the absence of any large couplings in its ddd pattern. In contrast 4-H, at δ_H 3.39, was evidently axial ($J_{4ax,5ax}$ 12.0 Hz), confirmed by the presence of three large couplings (all *ca.* 12.0 Hz) in the resonance for 5-H_{ax} at δ_H 1.32 in DMSO, assigned to $J_{4ax,5ax}$, J_{gem} and $J_{5ax,6ax}$, showing that the other ring junction proton, 6-H, was positioned axially. Hence the overall ring system in product **34a** was *cis*-fused, which is also consistent with a coupling constant between 1-H and 6-H of 5.2 Hz. Another feature of the spectrum was the rather small couplings between one of the protons at position 7 in the five-membered ring and 6-H, a phenomenon common to many of the related derivatives obtained later. These data suggest a conformation based upon that (**13**) proposed for the model compound **12**, but having an additional equatorial 4-methyl group and doubtless some twisting of the six-membered ring from a regular cyclohexane shape. In a similar manner, the overall structure of the minor azadioxa[4.3.0]nonane was found to be the alternative *cis*-fused isomer **35a**. Following full assignment of the ^{1}H NMR data, using both decoupling and COSY experiments, 2-H_{ax} was found to have two large coupling constants (J = 10.8 Hz), showing that 1-H was also axial. Similarly, a large (10.6 Hz) coupling contained in the resonance for 4-H showed that this too was positioned axially but the adjacent axial proton, 5-H_{ax}, had only two large couplings (14.3 and 10.5 Hz), assigned to $J_{4ax,5ax}$ and J_{gem}, implying that 6-H was equatorial and certainly not axial. Further, a very small (unmeasurable) coupling between 1-H and 6-H again indicated a *cis* ring fusion and the conformation **40**. All other data were consistent with this formulation; in this and related isomers, both protons at position 7 were strongly coupling to 6-H. The final minor product was readily identified as the isomeric azadioxa[4.2.1]nonane **36a**, firstly by the occurrence in its ^{13}C NMR spectrum of two methylene resonances at 32.1 and 42.7 ppm due to C-5 and C-9; in the isomers **34a** and **35a**, only one methylene resonated below 60 ppm. Conversely, there was no methine resonance at around 40 ppm, as was the case in both **34a** and **35a** due to the 6-CH group, but an additional methine resonance above 60 ppm, due to this carbon in structure **36a**. Clearly, coupling constant data is nothing like as informative in this case and hence the stereochemical assignment to structure **36a** is based on literature precedent,[6,7,11] as well as being the most likely transition state



Scheme 8



Scheme 9



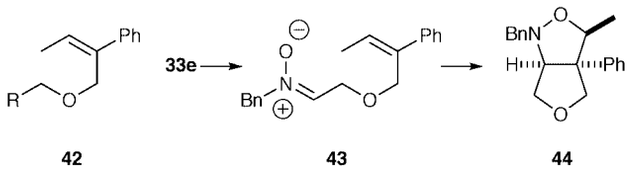
Scheme 10

conformation (see below) in which the substituent is again positioned equatorially,[7] and in which the nitrone oxygen manages to react, despite the ring constraint, in the usually preferred manner in which it becomes bonded to the more substituted carbon of the alkene.[6]

The 4-phenyl nitrone **33b** underwent a similar cyclisation to again give three products which were similarly identified as **34b**, **35b** and **36b** in the same way, in a slightly less useful ratio of 50 : 33 : 17. In the major product, coupling constant data established that 4-H was axial and coupled to a 5-H which showed three large coupling constants; hence, 6-H was also axial. The relative narrowness of 1-H, together with a ring junction coupling of 6.4 Hz between 1- and 6-H revealed a *cis*-ring fusion. Other features corresponded to those in the foregoing example. Similarly, the minor [4.3.0]nonane isomer **35b** showed features related to the minor 4-methyl isomer **35a**; in particular, a ring junction coupling of 6.6 Hz confirmed a *cis* geometry, with 1-H now in an axial position. Again, the overall structure of the least abundant product was readily identified as the [4.2.1]nonane **36b**, especially with ^{13}C NMR data, and the stereochemistry shown again based on transition state speculation and previous precedent. Cyclisation of the 4-benzyloxymethyl nitrone **33c**, somewhat to our surprise, proved more selective in favour of the usual major isomer **34c** and a slightly enhanced quantity of the bridged [4.2.1] isomer **36c**, at the expense of the minor [4.3.0] isomer **35c**. The identity of the major isomer **34c** was based on comparative data, using relatively poor ^1H NMR data, which was not improved by changes in solvent. However, characteristically very small couplings between 1-H and the protons at 2-CH_2, together with the absence of significant coupling between one of the 7-CH_2 protons and 6-H indicated that 1-H was equatorial and 6-H axial, which is also consistent with the narrow multiplet shown by the former and the broader resonance for the latter.

Not unexpectedly, a different pattern of selectivity was found in cyclisations of the related 5-substituted nitrones **33d–h** (Scheme 10). Double irradiation and COSY data again allowed assignment of the ^1H NMR spectra of the 5-methyl-substituted products **37d**–**39d**. Although overlapping signals prevented meaningful analysis of the resonances for 1-, 5- and 6-H, sufficient data was available to allow assignment of the *cis*-fused, *anti*-stereochemistry **38d** as the major product. Both protons at C-2 were clearly coupled to an equatorially positioned 1-H ($J_{1,2}$ 3.3 and 2.4 Hz); hence, the ring fusion must be *cis*. The proton at position 5 was in an axial position, indicated by the two large coupling constants associated with 4-H_{ax} ($J = 11.5$ and 10.5 Hz), showing that the substituent methyl group is positioned equatorially and hence *anti* to the five-membered ring. These conclusions are also consistent with the stereochemistry determined for the minor [4.3.0] isomer **37d**. In this case, both 2- and 4-H_{ax} showed second large couplings of 11.3 and 11.5 Hz, in addition to J_{gem} (also 11.3 and 11.5 Hz respectively), establishing that both 1- and 5-H were positioned axially. Further, analysis of the pattern displayed by 1-H showed a coupling across the ring junction of 6.2 Hz and hence *cis* fusion with the 5-methyl group *syn* to the five-membered ring, which is consistent with the minor product **37d** and its relatives discussed below adopting conformation **41**.

Cyclisation of the 5-phenyl nitrone **33e** led to essentially a single isomer, identified as **38e**, together with only traces of other components. In this example, it was clear from the coupling constant data, obtained in a mixture of $CDCl_3$–C_6H_6, which gave much better signal resolution, that the molecule was distorted from the normal chair conformation of the six-membered pyran ring. The close proximity of relevant signals precluded the use of NOE measurements. However, a $J_{1,6}$ value of 8.8 Hz indicated a typical *cis* ring fusion but the similar *J* values for the surrounding protons did not allow a definite assignment of the relative stereochemistry of the 5-phenyl substituent. Further, the data is very similar to that displayed by the related silyloxymethyl analogue **38f** and the major 5-benzyloxy isomer **38g**. It does seem highly likely, as this is almost the exclusive product, that the phenyl group is positioned *anti* to the five-membered ring as shown in Scheme 10. This is also consistent with the somewhat unexpected chemical shifts of the 4-CH_2 at δ_H 2.70 and 2.96; presumably the proximity of the 5-phenyl group is responsible for this. Great care had to be taken with intermediates **20**, **31eb**, **7e** and **33e** as each readily underwent partial or complete isomerization of the alkene into conjugation with the phenyl group to give isomers **42**. The key cyclisation was therefore carried out at 60 °C; at higher temperatures, significant quantities of the 5,5-fused compound **44**[9–11] were isolated (Scheme 11), presumably from cyclisation of nitrone **43**.

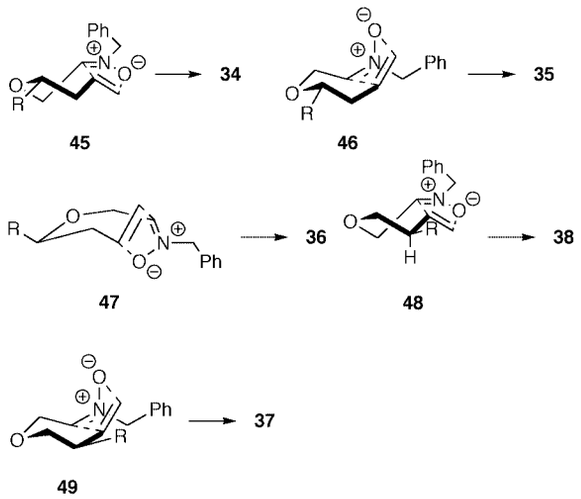


42 43 44

Scheme 11

The situation was clearer with the product from cyclisation of the silyloxymethyl nitrone **33f**. Again, virtually a single product was isolated. ^{1}H NMR data established two features: firstly, the ring fusion was again *cis* ($J_{1,6}$ = 5.5 Hz) and the 5-substituent was positioned equatorially ($J_{4ax,5ax}$ = 13.3 Hz). Similarly, the major 5-benzyloxy product **38g** was *cis*-fused ($J_{1,6}$ = 6.2 Hz) while the 1-H was evidently not in an axial position lending strong support to this structural assignment. In contrast, the minor isomer **37g** clearly had 1-H in an axial position. The final example, nitrone **33h**, was studied to show that such a dioxolane function could be taken through the overall sequence. The lack of stereoselection is not too surprising; presumably, the major isomer **38h** is that with the larger methylene group of the dioxolane *anti* to the isoxazolidine ring (see below).

Likely transition states consistent with these observations are based upon a chair-like pyran ring, leading to only *cis*-fused products.[7,11] Thus, conformation **45** with the substituent positioned equatorially would account for the formation of the major 4-substituted isomers **34a**–**c** (Scheme 12). A somewhat



Scheme 12

less favourable conformation **46**, again with an equatorial substituent, then explains the formation of the less abundant isomers **35a**–**c** (Scheme 12). Although not proven with certainty, the more likely stereochemistry[7] of the bridged isomers **36a**–**c** arises from conformation **47** (Scheme 12), in which, despite additional strain, the more normal reactivity[6] of simple monosubstituted alkenes with nitrones when the nitrone oxygen becomes bonded to the inner carbon of the alkene, is followed. Similar arguments account for the formation of the major 5-substituted isomers **38d**–**h**. In these cases, the greater proximity of the substituent to the reacting sites means that the conformation **48** is more favoured relative to the alternate **49**, especially when the substituent is relatively large, resulting in much higher stereoselections (*e.g.* **38e** and **38f**). Presumably, this proximity renders formation of the bridged isomers **39** especially unfavourable.

In conclusion, these pathways represent useful approaches to these compounds, especially when a substituent is incorporated at a site adjacent to the reacting centres, leading to high levels of stereoselection, and offer a variety of options for further homologation. The transition state conformations, deduced on the basis of these results, should be useful in planning applications of this chemistry to the synthesis of amino-sugar analogues and related species.

Experimental

General details

Melting points were determined on a Köfler hot stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity AA-10 polarimeter. Infrared spectra were recorded using a Perkin-Elmer 1600 series Fourier transform spectrometer using thin films between sodium chloride plates, unless otherwise stated. ^{1}H NMR spectra were determined using a Perkin-Elmer R32 operating at 90 MHz, a Bruker WM-250, a JEOL EX-270 or a Bruker AM-400 spectrometer, operating at the frequencies indicated (*i.e* (90) refers to 90 MHz *etc.*). ^{13}C NMR spectra were determined using any of the latter three instruments, operating at 62.5, 67.5 and 100.1 MHz respectively, as indicated after δ_C. Unless otherwise stated, all spectra were determined using dilute solutions in deuteriochloroform and tetramethylsilane as internal standard. *J* Values are expressed in Hertz. Mass spectra were measured using either an AEI MS902 or a VG 7070E instrument, both operating in the electron impact mode, unless otherwise stated; high resolution mass measurements were obtained using the latter instrument or from the EPSRC Mass Spectrometer Service, Swansea University.

Unless otherwise stated, all reactions were carried out under dry nitrogen in anhydrous solvents which were obtained by the usual methods.[26] Standard work-up involved partitioning of the reaction mixture or residue between appropriate and equal volumes of water and ether (or another named solvent). The separated aqueous layer was extracted twice with ether and the combined ether solutions washed with water (1 ×) and brine (1 ×). All organic solutions from work-ups were dried by brief exposure to dried magnesium sulfate followed by filtration. Solvents were removed by rotary evaporation. CC refers to column chromatography over Merck 9385 flash silica gel using the eluants specified. Petrol refers to light petroleum of bp 40–60 °C and ether refers to diethyl ether. THF refers to tetrahydrofuran. DMPU refers to 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one.

Methyl 3-oxahept-6-enoate 8b

A solution of but-3-enol (1.00 g, 1.2 ml, 13.87 mmol) in THF (5 ml) was added dropwise to an ice-cold, stirred suspension of sodium hydride (1.46 g of a 50% suspension in oil, 30.51 mmol) in THF (100 ml). After 0.5 h, a solution of bromoacetic acid (2.12 g, 15.26 mmol) in THF (5 ml) was added dropwise.[13] The resulting mixture was refluxed for 6 h then stirred overnight without further heating and finally diluted with ether (100 ml) and water (100 ml). Stirring was continued until all solids had dissolved then the aqueous layer was separated, washed with ether (2 × 40 ml), acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried and evaporated to leave 3-oxahept-6-enoic acid **8a** as a viscous brown oil (1.58 g, 88%) which showed ν_{max}/cm^{-1} 3700–2300, 1720 and 1640; δ_H (250) 2.41 (2H, app. qt, *J* 6.7 and *ca.* 1, 5-CH_2), 3.65 (2H, t, *J* 6.7, 4-CH_2), 4.14 (2H, s, 2-CH_2), 5.05–5.21 (2H, m, 7-CH_2), 5.83 (1H, ddt, *J* 16.7, 10.0 and 6.7, 6-H) and 8.42 (1H, br s, OH); δ_C (62.5) 33.8 (5-CH_2), 67.7 (CH_2), 71.2 (CH_2), 116.9 (7-CH_2), 134.5 (6-CH) and 175.0 (CO).

A solution of the foregoing acid **8a** (4.19 g, 32 mmol) in methanol (50 ml) was treated with acetyl chloride (0.50 ml) then refluxed for 2 h. The cooled solution was evaporated and the residue dissolved in ether (100 ml). The resulting solution was washed with water (30 ml), saturated aqueous sodium hydrogen carbonate (30 ml), water (30 ml) and brine (30 ml) then dried,

filtered through a silica gel plug and evaporated to leave the *ester* **8b** (3.31 g, 72%) as a pale oil; ν_{max}/cm^{-1} 3080, 1745 and 1640; δ_H (90) 2.25 (2H, br q, *J* 6, 5-CH_2), 3.48 (2H, t, *J* 6, 4-CH_2), 3.61 (3H, s, OMe), 3.94 (2H, s, 2-CH_2), 4.82–5.12 (2H, m, 7-CH_2) and 5.75 (1H, ddt, *J* 17, 10 and 6, 6-H); δ_C (62.5) 33.6 (5-CH_2), 51.3 (OMe), 67.8, 70.7 (both CH_2), 116.2 (7-CH_2), 134.4 (6-CH) and 170.6 (CO); *m*/*z* 103 (M^+ − allyl, 19%), 75 (20), 74 (12), 71 (13), 61 (84), 59 (20) and 55 (100) [Found: M^+ − allyl, 103.0375. $C_4H_7O_3$ requires *M*, 103.0393].

3-Oxahept-6-en-1-ol 9

A solution of the foregoing ester **8b** (1.06 g, 7.36 mmol) in ether (20 ml) was added dropwise to an ice-cold, stirred slurry of lithium aluminium hydride (0.28 g, 7.36 mmol) in ether (15 ml). The resulting mixture was stirred for 2 h at this temperature then quenched by the careful addition of 0.5 M aqueous sodium hydroxide (4 ml). The resulting grey suspension was filtered through Celite and the solid washed with ether. The combined filtrates were evaporated to leave the *alcohol* **9** (0.66 g, 77%) as a colourless oil; ν_{max}/cm^{-1} 3400, 3090 and 1640; δ_H (250) 2.22 (1H, br s, OH), 2.37 (2H, app qt, *J* 6.7 and *ca*. 1, 5-CH_2), 3.50–3.61 (4H, m, 2- and 4-CH_2), 3.74 (2H, t, *J* 7.0, 1-CH_2), 5.03–5.18 (2H, m, 7-CH_2) and 5.84 (1H, ddt, *J* 16.7, 10.0 and 6.7, 6-H); *m*/*z* 116 (M^+, 1%), 75 (52), 55 (39) and 45 (100) [Found: M^+, 116.0828. $C_6H_{12}O_2$ requires *M*, 116.0834].

(1*RS*,6*RS*)-9-Benzyl-9-aza-3,8-dioxabicyclo[4.3.0]nonane 12

A solution of the foregoing alcohol **9** (0.624 g, 5.38 mmol) in dichloromethane (20 ml) was added slowly to an ice-cold, stirred suspension of pyridinium chlorochromate (3.48 g, 16.13 mmol), 3 Å molecular sieves (6.7 g) and sodium acetate (4.41 g, 53.8 mmol) in dichloromethane (20 ml).[14] After 2 h at this temperature, the mixture was poured onto a pad of silica and eluted with a gradient solvent system of ether–petrol [1 : 1] increasing to neat ether. The major fraction was evaporated to leave the aldehyde **10** (0.58 g, 95%) as a pale yellow oil, R_f 0.26 [ether–petrol (1 : 1)]; ν_{max}/cm^{-1} 3090, 1740 and 1640; δ_H (90) 2.37 (2H, br q, *J* 6, 5-CH_2), 3.58 (2H, t, *J* 6, 4-CH_2), 4.05 (2H, s, 2-CH_2), 4.90–5.15 (2H, m, 7-CH_2), 5.82 (1H, ddt, *J* 16, 10 and 6, 6-H) and 9.22 (1H, app s, CHO).

An ice-cold, stirred solution of the foregoing aldehyde **10** (0.58 g, 5.10 mmol) in ether (20 ml) was treated with *N*-benzylhydroxylamine (0.66 g, 5.34 mmol) and the resulting yellow solution stirred for 1 h then evaporated. The residue, consisting mainly of the nitrone **11**, was dissolved in toluene (15 ml) and the resulting solution refluxed for 20 h then cooled and evaporated. CC [EtOAc–petrol (3 : 10)] of the residue separated the *bicyclo[4.3.0]nonane* **12** (0.48 g, 43%) as an oil, R_f 0.20; ν_{max}/cm^{-1} 3070, 3040, 1600, 1490 and 1450; δ_H (400) 1.82 (2H, m, 5-CH_2), 2.89 (1H, br dddd, *J* 13.4, 7.6, 6.3 and 5.5, 6-H_{ax}), 3.07 (1H, ddd, *J* 6.3, 5.0 and 5.0, 1-H_{eq}), 3.46 (1H, dd, *J* 12.2 and 6.6, 4-H_{eq}), 3.50–3.75 (4H, m, 2-CH_2, 4-H_{ax} and 7-H_a), 3.87 (1H, d, *J* 12.9, PhCH_aH$_b$), 4.03 (1H, d, *J* 12.9, PhCH$_a$$H_b$), 4.18 (1H, dd, *J* 7.6 and 7.6, 7-H_b) and 7.24–7.41 (5H, Ph); δ_C (100) 25.2 (5-CH_2), 38.0 (6-CH), 61.0 (1-CH), 61.2, 64.5, 66.7, 69.9 (all CH_2), 127.4, 128.4, 129.1 (all CH) and 137.0 (C); *m*/*z* 220 (M^+ + H, 8%), 219 (M^+, 54), 161 (20), 92 (29) and 91 (100) [Found: M^+, 219.1259. $C_{13}H_{17}NO_2$ requires *M*, 219.1255].

1-Phenylmethoxypent-4-en-2-ol 17

Vinylmagnesium bromide (2.32 mmol as a 1 M solution in THF) was added dropwise to a stirred suspension of copper(I) iodide (44 mg) in THF (15 ml), maintained at −25 °C. The resulting dark-green solution was stirred for 10 min then a solution of benzyloxymethyloxirane **16** (0.19 g, 1.16 mmol)[27] in THF (2 ml) was added dropwise, the cooling bath removed and stirring of the now black mixture continued for 2 h.[15] After quenching by the addition of saturated aqueous ammonium chloride (3 ml), a standard work-up gave the alcohol **17** (0.147 mg, 66%)[28] as a pale yellow oil; ν_{max}/cm^{-1} 3360, 3060, 3020, 1635, 1495 and 1450; δ_H (250) 2.23 (2H, br t, *J* 6.6, 3-CH_2), 2.58 (1H, br s, OH), 3.32 (1H, dd, *J* 9.5 and 6.9, 1-H_a), 3.49 (1H, dd, *J* 9.5 and 3.7, 1-H_b), 3.63–3.99 (1H, m, 2-H), 4.52 (2H, s, PhCH_2), 4.94–5.20 (2H, m, 5-CH_2), 5.83 (1H, ddt, *J* 17.0, 10.0 and 6.9, 4-CH) and 7.31 (5H, s, Ph); δ_C (100) 37.9 (3-CH_2), 69.7 (2-CH), 73.3 (1-CH_2), 73.9 (PhCH_2), 117.5 (5-CH_2), 127.8, 128.3, 128.9 (all PhCH), 134.6 (4-CH) and 138.1 (Ph); *m*/*z* 192 (M^+, 7%), 151 (9), 107 (31), 92 (68), 91 (100) and 71 (31) [Found: M^+, 192.1151. $C_{12}H_{16}O_2$ requires *M*, 192.1150].

(*Z*)-6-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-2-oxahex-4-ene 22

The monosilylated diol **21b** (2.50 g, 12.4 mmol, prepared[18] from (*Z*)-but-2-ene-1,4-diol **21a**) in THF (2 ml) was added dropwise to a suspension of sodium hydride (0.35 g, 14.2 mmol) in THF (50 ml) at ambient temperature. After 1 h, a solution of (iodomethyl)tributylstannane (5.34 g, 12.4 mmol)[19] in THF (10 ml) was slowly added. The resulting mixture was stirred for 24 h, quenched with methanol (2 ml) and poured into petrol (200 ml). The resulting solution was washed with water (150 ml) then dried and evaporated. CC [EtOAc–petrol (1 : 8)] of the residue separated the *stannane* **22** (3.08 g, 44%) as a colourless oil, R_f 0.70; δ_H (250) 0.00 (6H, s, 2 × MeSi), 0.85 (9H, s, Bu^{t}Si), 1.21–1.29 (9H, m, 3 × Me), 1.39–1.49 (18H, m, 9 × CH_2), 3.63 (2H, s, 1-CH_2), 3.87 (2H, d, *J* 8.3, 6-CH_2) and 5.48–5.56 (2H, m, 4- and 5-H); *m*/*z* 449 (M^+ − Bu, 6%), 447 (5), 291 (86), 289 (59), 235 (56), 233 (43), 184 (64), 188 (58), 120 (15), 118 (12), 97 (12) and 73 (100) [Found: 449.1894. $C_{19}H_{41}O_2SiSn$ requires *M*, 449.1898].

Methyl 5-(*tert*-butyldimethylsilyloxymethyl)-3-oxahept-6-enoate 31fb

Butyllithium (3.10 ml of a 1.5 M solution in hexanes, 4.95 mmol) was added to a stirred solution of the stannane **22** (2.25 g, 4.50 mmol) in THF (40 ml), maintained at −78 °C. After 1 h at this temperature,[17] solid sodium iodoacetate (0.94 g, 4.50 mmol) was added in one portion, the cooling bath was removed and the mixture stirred overnight then quenched by the addition of methanol (5 ml), followed by 2 M aqueous sodium hydroxide (30 ml) and ether (100 ml). Ether (50 ml) and 2 M hydrochloric acid (50 ml) were added to the separated aqueous layer. After mixing, the organic layer was separated, dried and evaporated to leave the acid **31fa** (0.48 g, 39%) as a colourless oil; ν_{max}/cm^{-1} 3600–3200, 1710 and 1640; δ_H (90) 0.00 (6H, s, 2 × MeSi), 0.81 (9H, s, Bu^{t}Si), 2.45 (1H, app tq, *J* 8 and 6, 5-H), 3.57 (2H, d, *J* 8, CH_2OSi), 3.63 (2H, d, *J* 6, 4-CH_2), 4.08 (2H, s, 2-CH_2), 5.09 (1H, br d, *J* 17, 7-H_t), 5.15 (1H, br d, *J* 10, 7-H_c), 5.70 (1H, ddd, *J* 17, 10 and 8, 6-H) and 9.11 (1H, br s, OH). The sample was pure according to this ^{1}H NMR data and was not purified further but immediately dissolved in ether (5 ml) and added to a solution diazomethane (*ca*. 10 mmol) in ether (100 ml). The resulting solution was left overnight then evaporated. CC [EtOAc–petrol (1 : 6)] of the residue gave the *ester* **31fb** (0.47 g) as a colourless oil [Found: C, 58.3; H, 9.6. $C_{14}H_{28}O_4Si$ requires C, 58.3; H, 9.8%]; ν_{max}/cm^{-1} 1741 and 1643; δ_H (250) 0.00 (6H, s, 2 × MeSi), 0.85 (9H, s, Bu^{t}Si), 2.49 (1H, tq, *J* 7.9 and 6.3, 5-H), 3.51–3.58 (2H, m, CH_2OSi), 3.60 (2H, d, *J* 6.3, 4-CH_2), 3.71 (3H, s, OMe), 4.06 (2H, s, 2-CH_2), 5.07 (1H, ddd, *J* 10.4, 1.8 and 0.9, 7-H_c), 5.11 (1H, ddd, *J* 17.4, 1.8 and 1.2, 7-H_t) and 5.76 (1H, ddd, *J* 17.4, 10.4 and 7.9, 6-H).

2-Benzyloxybut-3-en-1-ol 26

But-3-ene-1,2-diol (3.13 g, 35.5 mmol)[20] was added to a solution of *tert*-butyldimethylsilyl chloride (5.62 g, 37.3 mmol), triethylamine (5.19 ml, 37.3 mmol) and 4-(dimethylamino)-pyridine (50 mg) in dichloromethane (50 ml) and the resulting

solution stirred at ambient temperature for 24 h. 2 M Hydrochloric acid (50 ml) was then added, the phases mixed and the organic layer separated, washed successively with water (50 ml) and brine (50 ml), then dried and evaporated. CC [EtOAc–petrol (1:8)] of the residue separated 1-(*tert*-butyldimethylsilyloxy)but-3-en-2-ol **24** (3.79 g, 53%) as a colourless oil, R_f 0.38; ν_{max}/cm^{-1} 3700–3300 and 1642; δ_H (90) 0.00 (6H, s, 2 × MeSi), 0.78 (9H, s, Bu^{t}Si), 2.77 (1H, br s, OH), 3.48 (2H, m, 1-CH_2), 4.05 (1H, m, 2-H), 5.08 (1H, d, *J* 10, 4-H_c), 5.23 (1H, d, *J* 17, 4-H_t) and 5.70 (1H, ddd, *J* 17, 10 and 5, 3-H).

Butyllithium (12.2 ml of a 1.56 M solution in hexanes, 19.1 mmol) was added dropwise to a stirred solution of the foregoing alcohol **24** (3.51 g, 17.3 mmol) in hexane (50 ml) maintained at −78 °C followed, after 10 min, by benzyl bromide (2.97 g, 17.3 mmol), which was added at such a rate that the temperature remained below −70 °C. The resulting solution was allowed to warm to ambient temperature during 1 h then refluxed for 12 h. The cooled solution was quenched with water (0.5 ml), the mixture dried, filtered and the solvent evaporated to leave the doubly protected butene-1,2-diol **25** (5.01 g, >95%) as a colourless oil; ν_{max}/cm^{-1} 1642; δ_H (90) 0.02 (6H, s, 2 × MeSi), 0.85 (9H, s, Bu^{t}Si), 3.59 (1H, m, 2-H), 4.40 (2H, m, 1-CH_2), 5.08 (2H, s, $PhCH_2$), 5.16 (1H, d, *J* 10, 4-H_c), 5.27 (1H, d, *J* 17, 4-H_t), 5.68 (1H, ddd, *J* 17, 10 and 6, 3-H) and 7.10–7.35 (5H, m, Ph).

Tetrabutylammonium fluoride (17.1 ml of a 1 M solution in THF, 17.1 mmol) was added slowly to a stirred solution of the foregoing protected diol **25** (5.01 g, 17.1 mmol) in THF (20 ml) at ambient temperature. After 10 min, saturated aqueous ammonium chloride (20 ml) and ether (100 ml) were added. Standard work-up left a residue which was purified by CC [EtOAc–petrol (1:4)] to give the *alcohol* **26** (3.10 g, 95%) as a colourless oil, R_f 0.20; ν_{max}/cm^{-1} 3700–3200 and 1653; δ_H (90) 2.65 (1H, br s, OH), 3.48 (2H, d, *J* 6, 1-CH_2), 3.84 (1H, q, *J* 6, 2-H), 4.33 (1H, d, *J* 12, PhC$H_a$$H_b$), 4.57 (1H, d, *J* 12, PhCH_a-H_b), 5.23 (1H, d, *J* 10, 4-H_c), 5.33 (1H, d, *J* 17, 4-H_t), 5.68 (1H, ddd, *J* 17, 10 and 6, 3-H) and 7.20–7.35 (5H, m, Ph); *m*/*z* 147 ($M^+ - CH_2OH$, 33%), 107 (11), 91 (100) and 77 (29) [Found: $M^+ - CH_2OH$, 147.0808. $C_{10}H_{11}O$ requires *M*, 147.0810].

Methyl 2,2-dimethyl-4-ethenyl-1,3-dioxolane-4-carboxylate 29

Methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate **27** was prepared by oxidation of solketal using potassium permanganate in aqueous potassium hydroxide[21] followed by esterification of the resulting carboxylic acid using dimethyl sulfate and potassium carbonate in acetone (see preparation of ester **31ab**).[22]

The ester **27** (0.231 g, 1.44 mmol) in ether (2 ml) was added dropwise to a stirred solution of lithium diisopropylamine [from butyllithium (1 ml of 1.58 M solution in hexanes, 1.58 mmol) and diisopropylamine (0.24 ml, 1.73 mmol)] in ether (4 ml) maintained at −78 °C. After 10 min, a solution of phenylselenoacetaldehyde (0.288 g, 1.44 mmol) in ether (1 ml) was added dropwise and, after 10 min, the cooling bath was removed and the resulting colourless solution stirred for 0.5 h then quenched by the addition of saturated aqueous ammonium chloride (3 ml).[23] Standard work-up gave the crude hydroxy selenide **28** which was immediately dissolved in dichloromethane (5 ml). The resulting solution was stirred in an ice bath for 5 min before the addition of triethylamine (1 ml) followed by a solution of methanesulfonyl chloride (0.33 ml) in dichloromethane (30 ml), which was added dropwise during 1.5 h. The resulting dark solution was then warmed to ambient temperature and washed with water (3 × 10 ml). The aqueous washings were extracted with dichloromethane (10 ml) and the combined organic solutions washed with brine (10 ml) then dried and evaporated to leave a dark oil. CC [ether–petrol (3:7)] separated the *ethenyl ester* **29** (0.19 g, 70%) as a colourless oil, R_f 0.43 [Found: C, 57.8; H, 7.7. $C_9H_{14}O_4$ requires C, 58.0; H, 7.6%]; ν_{max}/cm^{-1} 3090, 1740 and 1640; δ_H (250) 1.48 (3H, s, 2-Me), 1.53 (3H, s, 2-Me), 3.84 (3H, s, OMe), 3.93 (1H, d, *J* 8.0, 5-H_a), 4.54 (1H, d, *J* 8.0, 5-H_b), 5.33 (1H, dd, *J* 10.0 and 2.2, 1′-H_c), 5.59 (1H, dd, *J* 17.0 and 2.2, 1′-H_t) and 6.15 (1H, dd, *J* 17.0 and 10.0, =CH); δ_C (67.5) 26.1 (2 × 2-Me), 52.7 (5-CH_2), 72.9 (OMe), 84.5 (4-C), 111.9 (2-C), 116.5 (=CH_2), 135.3 (=CH) and 172.5 (CO); *m*/*z* 171 ($M^+ - Me$, 16%), 129 (17), 127 (60), 97 (24), 69 (52) and 43 (100).

2,2-Dimethyl-4-ethenyl-1,3-dioxolane-4-methanol 30

A solution of the foregoing ester **29** (2.78 g, 14.9 mmol) in ether (50 ml) was added dropwise to an ice-cold, stirred suspension of lithium aluminium hydride (0.57 g, 14.9 mmol) in ether (50 ml). The resulting mixture was stirred at ambient temperature for 20 h then quenched by the careful addition of water and the resulting grey suspension filtered through silica gel. Standard work-up of the filtrate gave the *alcohol* **30** (1.77 g, 75%) as a colourless oil; ν_{max}/cm^{-1} 3440; δ_H (250) 1.41 (3H, s, 2-Me), 1.44 (3H, s, 2-Me), 2.78 (1H, br s, OH), 3.52 (2H, br s, 4-CH_2O), 3.83 (1H, d, *J* 8.0, 5-H_a), 4.07 (1H, d, *J* 8.0, 5-H_b), 5.20 (1H, dd, *J* 10.0 and 2.2, 1′-H_c), 5.36 (1H, dd, *J* 17.0 and 2.2, 1′-H_t) and 5.95 (1H, dd, *J* 17.0 and 10.0, =CH); *m*/*z* 157 ($M^+ - H$, 8%), 143 (66), 84 (31), 69 (77), 59 (38) and 57 (25) [Found: $M^+ - H$, 157.0885. $C_8H_{13}O_3$ requires *M*, 157.0865].

4-Methyl-3-oxahept-6-enoic acid 31aa

Pent-4-en-2-ol (1.60 g, 18.6 mmol; Aldrich) was alkylated with bromoacetic acid as described above for the preparation of acid **8a**, except that the final reaction mixture was refluxed for 2 h, to give the *acid* **31aa** (2.59 g, 97%) as a viscous oil; ν_{max}/cm^{-1} 3700–2300, 1720 and 1640; δ_H (90) 1.24 (3H, d, *J* 6, 4-Me), 2.35 (2H, m, 5-CH_2), 3.63–3.73 (1H, m, 4-H), 4.24 (2H, s, 2-CH_2), 5.13–5.24 (2H, m, 7-CH_2) and 5.94 (1H, ddt, *J* 17, 10 and 6, 6-H); δ_C (67.5) 19.1 (4-Me), 40.6 (5-CH_2), 65.6 (2-CH_2), 76.5 (4-CH), 117.5 (7-CH_2), 134.2 (6-CH) and 175.1 (CO); *m*/*z* 103 (M^+ − allyl, 61%), 75 (47), 69 (19), 45 (100), 43 (13) and 41 (49) [Found: M^+ − allyl, 103.0434. $C_4H_7O_3$ requires *M*, 103.0395].

Methyl 4-methyl-3-oxahept-6-enoate 31ab

A stirred solution of the acid **31aa** (2.86 g, 19.8 mmol) in acetone (230 ml) was treated with anhydrous potassium carbonate (8.22 g, 59.5 mmol) and dimethyl sulfate (2.07 ml, 21.8 mmol) and the resulting mixture was refluxed for 20 h then cooled, filtered and evaporated.[22] A standard work-up of the residue, with additional washings with aqueous 2 M ammonium hydroxide (3 ×), gave the *ester* **31ab** (2.80 g, 89%) as a colourless oil; ν_{max}/cm^{-1} 3095, 1750 and 1640; δ_H (90) 1.21 (3H, d, *J* 6, 4-Me), 2.34 (2H, m, 5-CH_2), 3.63–3.73 (1H, m, 4-H), 3.81 (3H, s, OMe), 4.18 (2H, s, 2-CH_2), 5.01–5.30 (2H, m, 7-CH_2) and 5.93 (1H, ddt, *J* 17, 10 and 6, 6-H); δ_C (67.5), 19.0 (4-Me), 40.5 (5-CH_2), 51.5 (OMe), 65.9 (2-CH_2), 76.0 (4-CH), 117.0 (7-CH_2), 134.4 (6-CH) and 171.0 (CO); *m*/*z* 117 (M^+ − allyl, 58%), 69 (19), 59 (100), 45 (17), 43 (13) and 41 (29) [Found: M^+ − allyl, 117.0546. $C_5H_9O_3$ requires *M*, 117.0549].

4-Methyl-3-oxahept-6-en-1-ol 32a

The ester **31ab** (2.50 g) was reduced using lithium aluminium hydride as described for the ester **9** to give the *alcohol* **32a** (1.71 g, 83%) as a colourless oil; ν_{max}/cm^{-1} 3420, 3080 and 1640; δ_H (90) 1.19 (3H, d, *J* 6, 4-Me), 2.29 (2H, br q, *J* 6, 5-CH_2), 2.81 (1H, br s, OH), 3.47–3.84 (5H, m, 1- and 2-CH_2 and 4-H), 4.96–5.08 (2H, m, 7-CH_2) and 5.94 (1H, ddt, *J* 17, 10 and 6, 6-H); δ_C (67.5) 19.4 (4-Me), 40.8 (5-CH_2), 61.9 (2-CH_2), 69.5 (1-CH_2), 74.4 (4-CH), 116.9 (7-CH_2) and 134.9 (6-CH); *m*/*z* 89 (M^+ − allyl, 86%), 69 (32), 55 (13), 45 (100) and 41 (56) [Found: M^+ − allyl, 89.0601. $C_4H_9O_2$ requires *M*, 89.0603].

4-Phenyl-3-oxahept-6-enoic acid 31ba

Method A. A solution of 1-phenylbut-3-en-1-ol **14b** [6.17 g,

41.65 mmol; prepared from allylmagnesium chloride and benzaldehyde] in THF (20 ml) was added dropwise to an ice-cold, stirred suspension of sodium hydride (2.19 g, 91.6 mmol) in THF (250 ml) and DMPU (20 ml). The cooling bath was removed and the darkening mixture stirred for 1 h before the dropwise addition of bromoacetic acid (5.79 g, 41.65 mmol) in THF (25 ml). The resulting pale yellow mixture was refluxed for 20 h then cooled and quenched by the addition of methanol (25 ml). The mixture was concentrated and worked up as described above to give the *acid* **31ba** (5.48 g, 64%) as a viscous oil; ν_{max}/cm^{-1} 3700–2200, 1715, 1590 and 1540; δ_H (90) 2.53–2.62 (2H, m, 5-CH_2), 3.85 (1H, d, *J* 16, 2-H_a), 4.00 (1 H, d, *J* 16, 2-H_b), 4.45 (1H, t, *J* 6, 4-H), 4.94–5.26 (2H, m, 7-CH_2), 5.54–6.12 (1H, m, 6-H) and 7.22–7.39 (5H, br s, Ph); *m*/*z* 165 (M^+ − allyl, 97%), 131 (35), 115 (13), 107 (100), 91 (39), 79 (30) and 77 (58) [Found: M^+ − allyl, 165.0567. $C_9H_9O_3$ requires *M*, 165.0552].

Method B. A solution of 1-phenylbut-3-en-1-ol **14b** (1.17 g, 7.90 mmol) in THF (10 ml) was added dropwise to an ice-cold, stirred suspension of sodium hydride (0.42 g, 17.4 mmol) in THF (60 ml). After 1 h, sodium iodoacetate (1.64 g, 7.90 mmol) was added in one portion. The resulting mixture was allowed to warm to ambient temperature then refluxed for 2 h. The cooled mixture was quenched by the addition of methanol (2 ml), then the solvents were evaporated and the residue worked up in the usual manner to leave the *acid* **31ba** (1.55 g, 95%) which exhibited spectral and analytical data identical with the foregoing example.

Methyl 4-phenyl-3-oxahept-6-enoate 31bb

Esterification of the foregoing acid **31ba** (4.13 g) using dimethyl sulfate, as described for acid **31aa**, gave the *ester* **31bb** (3.56 g, 81%) as a colourless oil [Found: C, 70.9; H, 7.5. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%]; ν_{max}/cm^{-1} 3090, 3050, 1745, 1640, 1490 and 1440; δ_H (90) 2.53–2.62 (2H, m, 5-CH_2), 3.75 (3H, s, OMe), 3.90 (1H, d, *J* 16, 2-H_a), 4.00 (1H, d, *J* 16, 2-H_b), 4.51 (1H, t, *J* 6, 4-H), 4.97–5.24 (2H, m, 7-CH_2), 5.91 (1H, ddt, *J* 17, 10 and 6, 6-H) and 7.28–7.48 (5H, br s, Ph); δ_C (100) 42.2 (5-CH_2), 51.5 (OMe), 65.6 (2-CH_2), 81.2 (4-CH), 116.9 (7-CH_2), 126.9, 127.9, 128.4 (all ArCH), 134.3 (6-CH), 140.5 (ArC) and 170.7 (CO); *m*/*z* 179 (M^+ − allyl, 100%), 131 (23), 121 (89), 105 (16), 91 (31), 77 (13) and 73 (15) [Found: M^+ − allyl, 179.0679. $C_{10}H_{11}O_3$ requires *M*, 179.0708].

Alternatively, esterification using diazomethane (see ester **31fb**) gave an identical product in 90% isolated yield.

4-Phenyl-3-oxahept-6-en-1-ol 32b

The ester **31bb** (3.30 g) was reduced using lithium aluminium hydride as described for the ester **9** to give the *alcohol* **32b** (2.35 g, 81%) as a colourless oil; ν_{max}/cm^{-1} 3420, 3080, 3020, 1640, 1490 and 1450; δ_H (90) 2.34–2.80 (2H, m, 5-CH_2), 3.42–3.91 (4H, m, 1- and 2-CH_2), 4.40 (1H, t, *J* 6, 4-H), 5.02–5.31 (2H, m, 7-CH_2), 5.93 (1H, ddt, *J* 17, 10 and 6, 6-H) and 7.46 (5H, s, Ph); δ_C (67.5) 42.5 (5-CH_2), 61.8 (2-CH_2), 70.0 (1-CH_2), 82.4 (4-CH), 117.1 (7-CH_2), 126.7, 127.7, 128.4 (all PhCH), 134.8 (6-CH) and 141.7 (PhC); *m*/*z* 151 (M^+ − allyl, 82%), 131 (16), 107 (100) and 91 (14) [Found: M^+ − allyl, 151.0766. $C_9H_{11}O_2$ requires *M*, 151.0759].

Ethyl 4-benzyloxymethyl-3-oxahept-6-enoate 31cc

A solution of the alcohol **17** (2.87 g, 14.95 mmol) in THF (20 ml) was added dropwise to a stirred suspension of sodium hydride (0.45 g, 17.9 mmol) in THF (150 ml) and DMPU (3.6 ml). The mixture was stirred at 60 °C for 1 h, then cooled to ambient temperature and ethyl bromoacetate (2.0 ml, 17.9 mmol) added dropwise. The resulting yellow suspension was refluxed for 4 h then cooled, quenched with methanol (15 ml) and concentrated. Standard work-up left an oil which was purified by CC [EtOAc–petrol (1 : 4)] to give the *ethyl ester* **31cc** (2.54 g, 61%) as a colourless oil, R_f 0.60 [Found: C, 69.2; H, 8.1. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%]; ν_{max}/cm^{-1} 3080, 3040, 3000, 1745, 1640, 1490 and 1455; δ_H (90) 1.27 (3H, t, *J* 7, OCH_2CH_3), 2.40 (2H, br t, *J* 6, 5-CH_2), 3.52–3.89 (3H, m, 4-H and CH_2OBn), 4.23 (2H, q, *J* 7, OCH_2CH_3), 4.31 (2H, s, 2-CH_2), 4.59 (2H, s, $PhCH_2$), 5.02–5.33 (2H, m, 7-CH_2), 5.97 (1H, ddt, *J* 17, 10 and 6, 6-H), and 7.42 (5H, s, Ph); δ_C (67.5) 15.9 (Me), 38.1 (5-CH_2), 62.4, 69.6, 74.4, 75.1 (all CH_2), 81.0 (4-CH), 118.9 (7-CH_2), 127.8, 129.3, 130.0 (all PhCH), 136.0 (6-CH), 139.9 (PhC) and 172.4 (CO); *m*/*z* 143 (14%), 107 (27), 91 (100), 85 (19) and 68 (34).

4-Benzyloxymethyl-3-oxahept-6-en-1-ol 32c

The ester **31cc** (0.55 g) was reduced using lithium aluminium hydride as described for the ester **8b** to give the *alcohol* **32c** (0.41 g, 87%) as a colourless oil; ν_{max}/cm^{-1} 3380, 3060, 3020, 1640, 1490 and 1450; δ_H (90) 2.23 (2H, br t, *J* 6, 5-CH_2), 3.37–3.71 (7H, m, 1- and 2-CH_2, CH_2OBn and 4-H), 4.46 (2H, s, $PhCH_2$), 4.91–5.20 (2H, m, 7-CH_2) and 5.82 (1H, ddt, *J* 17, 10 and 6, 6-H); δ_C (67.5) 35.7 (5-CH_2), 61.2, 70.9, 71.7, 72.7 (all CH_2), 78.1 (4-CH), 116.6 (7-CH_2), 127.1, 127.8, 127.9 (all PhCH), 134.0 (6-CH) and 137.6 (PhC); *m*/*z* 236 (M^+, 1%), 195 (1), 152 (5), 107 (23), 91 (100) and 71 (19) [Found: M^+, 236.1395. $C_{14}H_{20}O_3$ requires *M*, 236.1407].

Ethyl 5-methyl-3-oxahept-6-enoate 31dc

Alkylation of 2-methylbut-3-en-1-ol **18** (1.67 g) with ethyl bromoacetate as described for ester **31cc**, without DMPU but with a reflux period of 20 h, delivered, after CC [ether–petrol (1 : 9)], the *ethyl ester* **31dc** (2.10 g, 63%) as a colourless oil, R_f 0.50 [Found: C, 62.8; H, 9.6. $C_9H_{16}O_3$ requires C, 62.8; H, 9.4%]; ν_{max}/cm^{-1} 3090, 1740 and 1640; δ_H (90) 1.05 (3H, d, *J* 7, 5-Me), 1.27 (3H, t, *J* 7, OCH_2CH_3), 2.50 (1H, br sept, *J* 7, 5-H), 3.38–3.46 (2H, m, 4-CH_2), 4.06 (2H, s, 2-CH_2), 4.21 (2H, q, *J* 7, OCH_2CH_3), 4.92–5.20 (2H, m, 7-CH_2) and 5.82 (1H, ddd, *J* 17, 10 and 7, 6-H); δ_C (67.5) 14.0 (5-CH_3), 16.3 (OCH_2CH_3), 37.6 (5-CH), 60.4 (OCH_2CH_3), 68.4, 76.3 (both CH_2O), 114.1 (7-CH_2), 140.7 (6-CH) and 170.2 (CO); *m*/*z* 172 (M^+, 1%), 127 (34), 117 (100), 113 (54), 89 (30), 69 (97), 68 (66) and 55 (19) [Found: M^+, 172.1101. $C_9H_{16}O_3$ requires *M*, 172.1099].

5-Methyl-3-oxahept-6-en-1-ol 32d

The ester **31dc** (3.27 g) was reduced using lithium aluminium hydride as described for the ester **8b** to give the *alcohol* **32d** (2.32 g, 94%) as a colourless oil; ν_{max}/cm^{-1} 3400, 3080 and 1650; δ_H (90) 1.13 (3H, d, *J* 6, 5-Me), 2.49 (1H, br s, OH), 2.61 (1H, m, 5-H), 3.43–3.99 (6H, m, 1-, 2- and 4-CH_2), 5.09–5.38 (2H, m, 7-CH_2) and 5.98 (1H, ddd, *J* 17, 10 and 6, 6-H); δ_C (67.5) 16.5 (5-CH_3), 37.7 (5-CH), 61.7, 72.1, 75.9 (all CH_2O), 114.2 (7-CH_2) and 141.2 (6-CH); *m*/*z* 99 (M^+ − Me, 10%), 75 (100), 69 (37), 68 (60), 56 (18) and 55 (13) [Found: M^+ − Me, 99.0816. $C_6H_{11}O$ requires *M*, 99.0810].

Methyl 5-phenyl-3-oxahept-6-enoate 31eb

2-Phenylbut-3-en-1-ol **20**[16] (3.0 g, 20 mmol) in THF (2 ml) was added slowly to a stirred suspension of sodium hydride (1.01 g, 42 mmol) in THF (50 ml), cooled in an ice bath. After 1 h, sodium iodoacetate (4.15 g, 20 mmol) was added in one portion and the resulting mixture stirred without further cooling for 16 h. 2 M Aqueous sodium hydroxide was then added followed by ether (50 ml). The separated aqueous layer was washed with ether (100 ml) then adjusted to pH 3 using 2 M hydrochloric acid. The resulting mixture was extracted with ether (2 × 100 ml) and the combined extracts washed with brine (30 ml) then dried and evaporated to leave *5-phenyl-3-oxahept-6-enoic acid* **31ea** (2.73 g, 66%) as a colourless oil; ν_{max}/cm^{-1} 3700–3100 and 1740–1720; δ_H (250) 3.75 (1H, dd, *J* 13.7 and 6.7, 4-H_a), 3.82

(1H, d, *J* 13.7 and 6.7, 4-H_b), 4.12 (1H, d, *J* 16.3, 2-H_a), 4.17 (1H, m, 5-H), 4.20 (1H, d, *J* 16.3, 2-H_b), 5.14 (1H, dd, *J* 17.1 and 0.7, 7-H_t), 5.19 (1H, dd, *J* 10.3 and 1.0, 7-H_c), 6.10 (1H, ddd, *J* 17.1, 10.3 and 8.0, 6-H) and 7.25–7.45 (5H, m, Ph); *m/z* 206 (M^+, 12%), 147 (22), 130 (71), 117 (26), 91 (100) and 77 (24) [Found: M^+, 206.0947. $C_{12}H_{14}O_3$ requires *M*, 206.0943].

The acid **31ea** (1.0 g) was esterified using diazomethane and the resulting product purified as described for ester **31fb** to give the *methyl ester* **31eb** (1.01 g, 95%) as a colourless oil [Found: C, 70.8; H, 7.3. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%]; ν_{max}/cm^{-1} 1747 and 1638; δ_H (250) 2.85 (1H, dd, *J* 13.7 and 6.7, 4-H_a), 3.06 (1H, dd, *J* 13.7 and 6.7, 4-H_b), 3.71 (3H, s, OCH_3), 4.00 (1H, d, *J* 16.4, 2-H_a), 4.02 (1H, m, 5-H), 4.10 (1H, d, *J* 16.4, 2-H_b), 5.12 (1H, dd, *J* 17.1 and 0.7, 7-H_t), 5.19 (1H, dd, *J* 10.3 and 1.0, 7-H_c), 5.69 (1H, ddd, *J* 17.1, 10.3 and 8.0, 6-H) and 7.20–7.40 (5H, m, Ph); *m/z* 131 (100%), 117 (13), 91 (69) and 77 (11).

5-Benzyloxy-3-oxahept-6-enoic acid 31ga

Butyllithium (5.8 ml of a 1.56 M solution in hexanes, 9.0 mmol) was added dropwise to a stirred, ice-cooled solution of the alcohol **26** (1.46 g, 8.2 mmol) in THF (50 ml). After 10 min, sodium iodoacetate (1.71 g, 8.2 mmol) was added in one portion and the resulting mixture warmed to ambient temperature during 0.5 h then refluxed for 2 h. The cooled solution was quenched with methanol (2 ml) and the solvents evaporated. The residue was dissolved in 2 M aqueous sodium hydroxide (50 ml) and ether (50 ml). The separated aqueous layer was washed with ether (50 ml) then acidified to pH 4 using 2 M hydrochloric acid and extracted with ether (2 × 100 ml). The combined extracts were washed with brine (50 ml) then dried and evaporated to leave the *acid* **31ga** (1.73 g, 89%) as a colourless oil; R_f 0.42 [EtOAc–petrol (1:1)] [Found: C, 66.4; H, 7.1. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%]; ν_{max}/cm^{-1} 3600–3000 and 1740–1710; δ_H (90) 3.50 (2H, d, *J* 6, 4-CH_2), 4.05 (1H, m, 5-H), 4.14 (2H, s, 2-CH_2), 4.40 (1H, d, *J* 12, $PhCH_a$), 4.65 (1H, d, *J* 12, $PhCh_b$), 5.29 (1H, br d, *J* 10, 7-H_c), 5.34 (1H, br d, *J* 17, 7-H_t), 5.80 (1H, ddd, *J* 17, 10 and 7, 6-H), 7.25–7.35 (5H, m, Ph) and 10.20 (1H, br s, OH); *m/z* 147 (8%), 107 (14), 105 (15), 91 (100) and 77 (13).

Methyl 5-benzyloxy-3-oxahept-6-enoate 31gb

The foregoing acid **31ga** (1.72 g) was esterified using diazomethane, as described for the ester **31fb**, to give the *methyl ester* **31gb** (1.70 g, 93%) as a colourless oil [Found: C, 67.3; H, 7.1. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%]; ν_{max}/cm^{-1} 1735 and 1644; δ_H (90) 3.65 (2H, d, *J* 6, 4-CH_2), 3.70 (3H, s, OCH_3), 4.08 (1H, m, 5-H), 4.20 (2H, br s, 2-CH_2), 4.48 (1H, d, *J* 13, $PhCH_a$), 4.68 (1H, d, *J* 13, $PhCH_b$), 5.32 (1H, br d, *J* 10, 7-H_c), 5.38 (1H, br d, *J* 17, 7-H_t), 5.80 (1H, ddd, *J* 17, 10 and 7, 6-H), and 7.35–7.45 (5H, m, Ph).

2,2-Dimethyl-4-ethenyl-4-(4-hydroxy-2-oxabutyl)-1,3-dioxolane 32h

A solution of 2,2-dimethyl-4-ethenyl-1,3-dioxolane-4-methanol **30** (1.27 g, 8.01 mmol) in THF (5 ml) was added dropwise to a stirred, ice-cold suspension of sodium hydride (0.42 g, 17.6 mmol) in THF (80 ml). After 1 h, a solution of bromoacetic acid (1.11 g, 8.01 mmol) in THF (15 ml) was added dropwise and the resulting mixture refluxed for 20 h then cooled to ambient temperature, quenched by the addition of methanol (10 ml) and the solvents evaporated. The residue was partitioned between water (50 ml) and ether (50 ml). The separated aqueous layer was washed with ether (50 ml) then acidified with excess solid citric acid and extracted with ether (3 × 30 ml). The combined extracts were washed with brine (30 ml) then dried and evaporated to leave the acid **31ha** (1.40 g, 81%) as a thick, colourless oil; δ_H (90) 1.45 (3H, s, 2-Me), 1.50 (3H, s, 2-Me), 3.63 (2H, s, 4-CH_2O), 3.87 (1H, d, *J* 8.0, 5-H_a), 4.22 (1H, d, *J* 8.0, 5-H_b), 4.23 (2H, s, CH_2CO_2), 5.29 (1H, br d, *J* 10.0, =CH_cH_t), 5.51 (1H, br d, *J* 17.0, =CH_cH_t), 6.09 (1H, dd, *J* 17.0 and 10.0, =CH) and 8.30 (1H, br s, OH).

The acid **31ha** (1.40 g) was immediately dissolved in acetone and esterified using dimethyl sulfate, as described for ester **31ab**. After reflux for 5 h, standard work-up gave the methyl ester **31hb** (1.38 g) as a yellow oil; δ_H (90) 1.42 (3H, s, 2-Me), 1.48 (3H, s, 2-Me), 3.57 (2H, br s, 4-CH_2O), 3.76 (3H, s, OCH_3), 3.85 (1H, d, *J* 8.0, 5-H_a), 4.19 (2H, s, CH_2CO_2), 4.21 (1H, d, *J* 8.0, 5-H_b), 5.23 (1H, dd, *J* 10 and 2, =CH_cH_t), 5.48 (1H, dd, *J* 17 and 2, =CH_cH_t) and 6.09 (1H, dd, *J* 17 and 10, =CH).

The foregoing ester **31hb** (1.38 g) was reduced using lithium aluminium hydride as described for ester **8b**, and the crude product purified by CC using ether–petrol (1:1), to give the *alcohol* **32h** (1.13 g, 70%) as a colourless oil; ν_{max}/cm^{-1} 3440 and 1640; δ_H (90) 1.41 (3H, s, 2-Me), 1.46 (3H, s, 2-Me), 3.38–3.86 (6H, m, 3 × CH_2O), 3.81 (1H, d, *J* 8.6, 5-H_a), 4.10 (1H, d, *J* 8.6, 5-H_b), 5.20 (1H, dd, *J* 10 and 2, =CH_cH_t), 5.41 (1H, dd, *J* 17 and 2, =CH_cH_t) and 6.00 (1 H, dd, *J* 17 and 10, =CH); δ_C (67.5) 26.2 (2-CH_3), 27.0 (2-CH_3), 61.7, 70.9, 73.1, 74.9 (all CH_2O), 82.9 (4-C), 110.3 (2-C), 115.1 (=CH_2) and 138.5 (=CH); *m/z* 202 (M^+, 1%), 187 (6), 127 (100), 83 (32), 69 (97), 45 (28) and 43 (53) [Found: M^+, 202.1180. $C_{10}H_{18}O_4$ requires *M*, 202.1200].

(1*RS*,4*SR*,6*RS*)- and (1*SR*,4*SR*,6*SR*)-9-Benzyl-4-methyl-9-aza-3,8-dioxabicyclo[4.3.0]nonane 34a and 35a and (1*RS*,4*RS*,6*SR*)-8-benzyl-4-methyl-8-aza-3,7-dioxabicyclo[4.2.1]nonane 36a

Dimethyl sulfoxide (0.85 ml, 12.0 mmol) in dichloromethane (2 ml) was added dropwise to a stirred solution of freshly distilled oxalyl chloride (0.48 ml, 5.5 mmol) in dichloromethane (10 ml), maintained at −78 °C. After 6 min, a solution of the alcohol **32a** (0.325 g, 2.49 mmol) in dichloromethane (2 ml) was added dropwise. After 1 h at the same temperature, triethylamine (1.74 ml, 12.5 mmol) was added dropwise and the resulting white suspension allowed to warm spontaneously to ambient temperature.[24] Water (20 ml) was added, the layers separated and the aqueous layer extracted with dichloromethane (2 × 5 ml). The combined organic solutions were washed successively with 10 ml portions of 2 M hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, water and brine then dried and evaporated to leave the aldehyde **7a** (0.27 g, 85%); ν_{max}/cm^{-1} 3090, 1740 and 1645; δ_H (90) 1.21 (3H, d, *J* 6, 4-CH_3), 2.10–2.48 (2H, m, 5-CH_2), 3.60–3.66 (1H, m, 4-H), 4.15 (2H, s, 2-CH_2), 5.02–5.30 (2H, m, 7-CH_2), 5.93 (1H, ddt, *J* 17, 10 and 7, 6-H) and 9.87 (1H, br s, 1-H).

The crude aldehyde **7a** was immediately dissolved in ice cooled ether (15 ml) and the solution stirred with *N*-benzylhydroxylamine (0.27 g, 2.21 mmol) for 1 h then evaporated to leave the nitrone **33a**; δ_H (90) 1.11 (3H, d, *J* 6, 4-CH_3), 2.08–2.37 (2H, m, 5-CH_2), 3.46–3.54 (1H, m, 4-H), 4.44 (2H, br d, *J* 4, 2-CH_2), 4.85 (2H, br s, $PhCH_2$), 4.93–5.24 (2H, m, 7-CH_2), 5.83 (1H, ddt, *J* 17, 10 and 7, 6-H), 6.93 (1H, t, *J* 4, 1-H) and 7.25–7.56 (5H, m, Ph).

The crude nitrone was immediately dissolved in toluene (10 ml) and the resulting solution stirred at 80 °C for 20 h, then cooled and evaporated. CC [EtOAc–petrol (1:4)] separated i) the *(1RS,4SR,6RS)-bicyclo[4.3.0]nonane* **34a** (251 mg, 51%) as a colourless oil with R_f 0.25; ν_{max}/cm^{-1} 3090, 3080, 3040, 1495, 1450 and 1120; δ_H (400) 1.21 (3H, d, *J* 6.2, 4-CH_3), 1.58–1.66 (2H, m, 5-CH_2), 2.65 (1H, app dddd, *J* 12.0, 6.1, *ca*. 5.2 and 5.2, 6-H), 2.79 (1H, ddd, *J* 5.2, 2.7 and 1.0, 1-H), 3.39 (1H, br dq, *J* 12.0 and 6.2, 4-H_{ax}), 3.59 (1H, br d, *J ca*. 7.4, 7-H_a), 3.63 (1H, dd, *J* 12.8 and 2.7, 2-H_a), 3.77 (1H, br d, *J* 12.8, 2-H_b), 3.98 (1H, d, *J* 13.0, PhCH_aH_b), 4.03 (1H, partly obscured but containing d, *J* 5.2, 7-H_b), 4.04 (1H, d, *J* 13.0, $PhCH_aH_b$) and 7.23–7.42 (5H, m, Ph); δ_H (400; d_6-$(CH_3)_2SO$; selected resonances) 1.32 (1H, app q, *J* 12.0, 5-H_{ax}), 1.60 (1H, dddd, *J* 12.0, 6.2, 6.2 and 1.5, 5-H_{eq}), 3.34 (1H, dqd, *J* 12.0, 6.2 and 1.5, 4-H_{ax}) and 3.96 (1H, dd, *J* 7.4 and 5.2, 7-H_b); δ_C (100) 21.7 (4-CH_3), 34.2

(5-CH_2), 41.3 (6-CH), 62.2 ($PhCH_2$), 62.5 (1-CH), 66.0, 71.0 (both CH_2O), 72.0 (4-CH), 127.4, 128.3, 129.5 (all PhCH) and 136.9 (PhC); *m/z* 233 (M^+, 13%), 174 (24), 161 (12), 107 (12), 106 (20), 92 (13) and 91 (100) [Found: M^+, 233.1407. $C_{14}H_{19}NO_2$ requires *M*, 233.1416]; ii) the *(1SR,4SR,6SR)-bicyclo[4.3.0]nonane* **35a** (64 mg, 13%) also a colourless oil, R_f 0.29; ν_{max}/cm^{-1} 3090, 3070, 3040, 1490, 1450 and 1100; δ_H (400) 1.17 (3H, d, *J* 6.1, 4-CH_3), 1.64 (1H, ddd, *J* 14.3, 10.5 and 5.3, 5-H_{ax}), 1.76 (1H, ddd, *J* 14.3, 2.7 and 2.7, 5-H_{eq}), 3.08–3.15 (1H, m, 6-H), 3.24 (1H, app dd, *J* 10.8 and 5.5, 1-H), 3.34 (1H, dd, *J* 10.8 and 10.8, 2-H_{ax}), 3.57 (1H, dqd, *J* 10.5, 6.1 and 2.7, 4-H_{ax}), 3.76 (1H, d, *J* 12.7, PhC$H_a$$H_b$), 3.79 (1H, dd, *J* 9.3 and 7.5, 7-H_a), 3.85 (1H, dd, *J* 10.8 and 5.5, 2-H_{eq}), 4.06 (1H, d, *J* 12.7, $PhCH_a$$H_b$), 4.31 (1H, dd, *J* 9.6, and 7.5, 7-H_b) and 7.24–7.35 (5H, m, Ph); δ_C (100) 21.4 (4-CH_3), 31.3 (5-CH_2), 36.8 (6-CH), 59.0 (1-CH), 60.6, 67.1, 69.5 (all CH_2), 68.5 (4-CH), 127.4, 128.4, 128.9 (all PhCH) and 137.1 (PhC); *m/z* 233 (M^+, 26%), 174 (14), 161 (23), 92 (16) and 91 (100) [Found: M^+, 233.1404] and iii) the *(1RS,4RS,6SR)-bicyclo[4.2.1]nonane* **36a** (43 mg, 8%) as a colourless oil, R_f 0.40; ν_{max}/cm^{-1} 3090, 3060, 3030, 1490 and 1450; δ_H (400) 1.16 (3H, d, *J* 6.4, 4-CH_3), 1.30 (1H, ddd, *J* 14.2, 11.0 and 1.2, 5-H_a), 1.77 (1H, ddd, *J* 14.2, 4.8 and 2.0, 5-H_b), 2.29–2.33 (2H, m, 9-CH_2), 3.37 (1H, ddd, *J* 5.5, 5.5 and 3.1, 1-H), 3.61 (1H, app d, *J* 12.5, 2-H_a), 3.75 (1H, dd, *J* 12.5 and 5.5, 2-H_b), 3.76 (1H, d, *J* 12.8, PhC$H_a$$H_b$), 3.83 (1H, m, 4-H), 4.13 (1H, d, *J* 12.8, $PhCH_a$$H_b$), 4.64 (1H, ddd, *J* 8.7, 4.8 and *ca*. 1, 6-H) and 7.23–7.40 (5H, m, Ph); δ_C (100) 22.4 (4-CH_3), 32.1 (5-CH_2), 42.7 (9-CH_2), 64.2 (CH), 64.3 (CH_2), 72.1 (CH), 74.3 (CH_2), 76.7 (6-CH), 127.4, 128.5, 129.2 (all PhCH) and 137.5 (PhC); *m/z* 233 (M^+, 12%), 160 (20), 92 (11) and 91 (100) [Found: M^+, 233.1423].

(1*RS*,4*RS*,6*RS*)- and (1*SR*,4*RS*,6*SR*)-9-Benzyl-4-phenyl-9-aza-3,8-dioxabicyclo[4.3.0]nonane 34b and 36b and (1*RS*,4*SR*,6*SR*)-8-benzyl-4-phenyl-8-aza-3,7-dioxabicyclo[4.2.1]nonane 36b

i) Formation of 4-phenyl-3-oxahept-6-enal 7b:-

a) Swern oxidation of the 4-phenylhept-6-enol **32b** (0.601 g), as described for aldehyde **7a** above, gave crude aldehyde **7b** (0.585 g, 98%) as a colourless oil; ν_{max}/cm^{-1} 3090, 3040, 1737, 1642, 1490 and 1455; δ_H (90) 2.26–2.77 (2H, m, 5-CH_2), 3.88 (1H, d, *J* 16, 2-H_a), 3.95 (1H, d, *J* 16, 2-H_b), 4.34 (1H, dd, *J* 10 and 7, 4-H), 5.01 (1H, d, *J* 10, 7-H_c), 5.06 (1H, d, *J* 17, 7-H_t), 5.88 (1H, ddt, *J* 17, 10 and 7, 6-H), 7.27 (5H, app br s, Ph) and 9.66 (1H, t, *J ca*. 1, 1-H); *m/z* 149 (42%), 131 (14), 107 (40), 91 (100) and 77 (19). The sample was *ca*. 90% pure according to the ^{1}H NMR data.

b) Tetrapropylammonium perrhuthenate (0.16 g, 0.45 mmol) was added in one portion to a stirred mixture of the alcohol **32b** (0.94 g, 4.9 mmol), *N*-methylmorpholine *N*-oxide (0.91 g, 7.8 mmol) and powdered 4 Å molecular sieves (2.6 g) in acetonitrile (20 ml) at ambient temperature.[25] After 25 min, the solvent was evaporated and the residue stirred with dichloromethane (50 ml). The resulting mixture was filtered through a pad of Kieselruhr gel and the filtrate evaporated to leave the aldehyde **7b** (0.72 g, 78%; *ca.* 95% pure) which showed data identical to the foregoing.

c) Diisobutylaluminium hydride (4.0 ml of a 1 M solution in hexanes, 4.0 mmol) was added dropwise to a stirred solution of the ester **31bb** (0.80 g, 3.6 mmol) in hexane (40 ml), maintained at −78 °C. After 1 h at this temperature, the mixture was quenched by the addition of aqueous methanol (1:9, 1 ml) and then warmed to ambient temperature. The resulting mixture was dried, filtered through a pad of silica and the solid washed with dichloromethane (2 × 50 ml). Evaporation of the combined filtrates left the aldehyde **7b** (0.67 g, 98%) as a colourless oil of >95% purity according to the ^{1}H NMR data, which was identical to the foregoing.

N-Benzylhydroxylamine (0.37 g, 3.0 mmol) was added to a stirred mixture of freshly prepared aldehyde **7b** (0.57 g, 3.0 mmol) and dried magnesium sulfate (1.0 g) in ice-cold ether (50 ml). After 1 h at 0 °C, the mixture was allowed to warm to ambient temperature, filtered and the filtrate evaporated to leave the *nitrone* **33b** (0.87 g, 98%) as a colourless oil; ν_{max}/cm^{-1} 1641 and 1604; δ_H (90) 2.35–2.45 (2H, m, 5-CH_2), 3.63–3.67 (1H, m, 4-H), 4.25 (2H, d, *J* 4, 2-CH_2), 4.78 (2H, s, $PhCH_2$), 4.92 (1H, d, *J* 1, 7-H_c), 4.97 (1H, d, *J* 17, 7-H_t), 5.88 (1H, ddt, *J* 17, 10 and 7, 6-H), 6.73 (1H, t, *J* 4, 1-H) and 7.20–7.40 (10H, m, Ph); *m/z* 295 (M^+, 8%), 161 (18), 107 (10), 105 (13), 91 (100) and 77 (10) [Found: M^+, 295.1573. $C_{19}H_{21}NO_2$ requires *M*, 295.1572].

The nitrone **33b** (0.87 g) was heated in toluene (20 ml) at 60 °C for 10 h. The cooled solution was evaporated and the residue separated by CC [petrol–EtOAc–triethylamine (6:1:0.1)] to give i) the *(1RS,4RS,6RS)-bicyclo[4.3.0]nonane* **34b** (330 mg, 38%) as a colourless oil with R_f 0.23; ν_{max}/cm^{-1} 3090, 1954, 1883, 1813 and 914; δ_H (400) 1.88 (1H, ddd, *J* 13.3, 6.4 and 2.0, 5-H_{eq}), 2.04 (1H, app br q, *J ca*. 11.7, 5-H_{ax}), 2.86 (1H, br dq, *J* 11.7 and 6.4, 6-H), 2.87–2.96 (1H, m, $\omega_{1/2}$ 22, 1-H), 3.65 (1H, br d, *J* 7.8, 7-H_a), 3.84 (1H, dd, *J* 12.9 and 2.3, 2-H_a), 4.02 (1H, d, *J* 13.3, PhC$H_a$$H_b$), 4.06 (1H, d, *J* 13.3, $PhCH_a$$H_b$), 4.04–4.14 (2H, m, 2-$H_b$ and 7-H_b), 4.33 (1H, dd, *J* 11.6 and 2.0, 4-H_{ax}) and 7.07–7.46 (10H, m, Ph); δ_C (100) 34.7 (5-CH_2), 41.9 (6-CH), 62.2 (2-CH_2), 62.6 (1-CH), 66.6 ($PhCH_2$), 71.3 (7-CH_2), 78.3 (4-CH), 126.2, 127.7, 127.8, 128.5, 128.6, 129.6 (all PhCH), 137.0 and 142.6 (both PhC); *m/z* 295 (M^+, 19%), 161 (44), 105 (16), 91 (100) and 77 (17) [Found: M^+, 295.1563]; ii) the *(1SR,4RS,6SR)-bicyclo[4.3.0]nonane* **35b** (250 mg, 29%), R_f 0.38, as colourless crystals, mp 107–109 °C (aq. MeOH) [Found: C, 77.4; H, 7.3; N, 4.7. $C_{19}H_{21}NO_2$ requires C, 77.3; H, 7.2; N, 4.7%]; ν_{max}/cm^{-1} 3090, 1956, 1880, 1818 and 914; δ_H (400) 1.94–2.04 (2H, m, 5-CH_2), 3.18–3.27 (1H, m, $\omega_{1/2}$ 20, 6-H), 3.37 (1H, ddd, *J* 10.7, 6.6 and 6.6, 1-H), 3.52 (1H, dd, *J* 11.8 and 10.7, 2-H_{ax}), 3.81 (1H, d, *J* 12.7, PhC$H_a$$H_b$), 3.96 (1H, br t, *J* 8.3, 7-H_a), 4.02 (1H, dd, *J* 11.8 and 6.6, 2-H_{eq}), 4.11 (1H, d, *J* 12.7, $PhCH_a$$H_b$), 4.39 (1H, dd, *J* 9.3 and 7.9, 7-H_b), 4.51 (1H, dd, *J* 9.6 and 4.6, 4-H_{ax}) and 7.16–7.38 (10H, m, Ph); δ_H (400; d_6-$(CH_3)_2SO$; selected resonances) 1.86 (1H, ddd, *J* 14.0, 11.6 and 5.4, 5-H_{ax}) and 2.00 (1H, br d, *J* 14.0, 5-H_{eq}); δ_C (100) 31.8 (5-CH_2), 37.2 (6-CH), 59.0 (2-CH_2), 60.7 (1-CH), 67.5 ($PhCH_2$), 69.5 (7-CH_2), 74.7 (4-CH), 125.7, 127.6, 128.4, 128.5, 129.1 (all PhCH), 137.0 and 142.0 (both PhC); *m/z* 295 (M^+, 21%), 161 (53), 105 (12) and 91 (100) [Found: M^+, 295.1575] and iii) the *(1RS,4SR,6SR)-bicyclo[4.2.1]nonane* **36b** (138 mg, 16%) as a colourless oil; R_f 0.50; ν_{max}/cm^{-1} 2857, 1953, 1881, 1811, 1495 and 917; δ_H (400) 1.62 (1H, dd, *J* 13.9 and 11.8, 5-H_a), 2.01 (1H, dd, *J* 13.9 and 4.1, 5-H_b), 2.36 (1H, dd, *J* 11.7 and 7.7, 7-H_a), 2.42 (1H, d, *J* 7.7, 7-H_b), 3.46 (1H, ddd, *J* 11.7, 6.5 and 6.5, 1-H), 3.72 (1H, d, *J* 12.7, 2-H_a), 3.81 (1H, d, *J* 12.9, PhC$H_a$$H_b$), 3.90 (1H, dd, *J* 12.7 and 5.7, 2-H_b), 4.18 (1H, d, *J* 12.9, $PhCH_a$$H_b$), 4.72 (1H, m, 4-H), 4.97 (1H, m, 6-H) and 7.10–7.41 (10H, m, PhH); δ_C (100) 32.3 (9-CH_2), 43.0 (5-CH_2), 64.0 (1-CH), 64.3 ($PhCH_2$), 74.9 (2-CH_2), 76.6 (4-CH), 77.7 (6-CH), 127.1, 127.5, 128.3, 128.4, 128.5, 129.2 (all PhCH), 137.4 and 143.4 (PhC); *m/z* 295 (M^+, 4%), 160 (26), 106 (81), 91 (100), 77 (31) and 70 (29) [Found: M^+, 295.1562].

(1*RS*,4*RS*,6*RS*)-9-Benzyl-4-benzyloxymethyl-9-aza-3,8-dioxabicyclo[4.3.0]nonane 34c and 35c and (1*RS*,4*SR*,6*SR*)-8-benzyl-4-benzyloxymethyl-8-aza-3,7-dioxabicyclo[4.2.1]nonane 36c

The 4-benzyloxymethylhept-6-enol **32c** (0.28 g) was oxidized using the Swern method and the resulting aldehyde condensed immediately with *N*-benzylhydroxylamine to give the nitrone **33c**, exactly as described for the 4-methyl derivative **33a**. The nitrone **33c** was immediately dissolved in toluene (10 ml) and the resulting solution stirred at 80 °C for 20 h. The cooled solution was evaporated and the residue separated by CC [EtOAc–petrol (2:3)] to give i) the *(1RS,4RS,6RS)-bicyclo[4.3.0]nonane* **34c** (148 mg, 41%) as a colourless oil; ν_{max}/cm^{-1} 3090, 3060,

3030, 1490, 1450, 1115 and 1100; δ_H (400) 1.63–1.67 (2H, m, 5-CH_2), 2.62–2.71 (1H, m, 6-H), 2.80–2.85 (1H, m, 1-H), 3.37–3.44 (1H, m, 4-H), 3.50–3.56 (2H, m, CH_2OBn), 3.59 (1H, app d, *J* 7.8, 7-H_a), 3.65 (1H, dd, *J* 12.7 and 3.0, 2-H_a), 3.81 (1H, dd, *J* 12.7 and 1.0, 2-H_b), 3.98 (1H, d, *J* 13.3, PhC$H_a$$H_b$N), 4.02 (1H, d, *J* 13.3, PhC$H_a$$H_b$N), 4.03 (1H, dd, *J* 7.8 and 5.1, 7-H_b), 4.51 (1H, d, *J* 12.2, PhC$H_a$$H_b$O), 4.61 (1H, d, *J* 12.2, PhC$H_a$$H_b$O) and 7.23–7.40 (10H, m, Ph); δ_C (100) 29.0 (5-CH_2), 40.8 (6-CH), 62.1 (CH_2), 62.7 (1-CH), 65.8, 71.0, 73.3, 74.9 (all CH_2), 127.4, 127.6, 127.8, 128.3, 129.4 (all PhCH), 136.8 and 138.2 (both PhC); *m*/*z* 339 (M^+, 2%), 160 (10), 92 (18) and 91 (100) [Found: M^+, 339.1831. $C_{21}H_{25}NO_3$ requires *M*, 339.1834] and ii) the *(1RS,4SR,6SR)-bicyclo[4.2.1]nonane* **36c** (58 mg, 16%) as a colourless oil; ν_{max}/cm^{-1} 3090, 3060, 3030, 1490, 1450 and 1095; δ_H (400) 1.44 (1H, ddd, *J* 14.0, 11.6 and 1.2, 5-H_a), 1.67–1.76 (1H, m, 5-H_b), 2.28–2.34 (2H, m, 9-CH_2), 3.64 (1H, d, *J* 12.5, 2-H_a), 3.77 (1H, d, *J* 12.9, PhC$H_a$$H_b$N), 3.84 (1H, dd, *J* 12.5 and 5.7, 2-H_b), 3.91–3.98 (1H, m, 1-H), 4.13 (1H, d, *J* 12.9, PhC$H_a$$H_b$N), 4.54 (1H, d, *J* 12.5, PhC$H_a$$H_b$O), 4.58 (1H, d, *J* 12.5, PhC$H_a$$H_b$O), 4.67–4.71 (1H, m, 6-H) and 7.24–7.38 (10H, m, Ph); δ_C (100) 32.3 (5-CH_2), 37.3 (9-CH_2), 64.1 (CH), 64.3, 73.2, 73.6, 74.8 (all CH_2), 75.1 (CH), 76.4 (6-CH), 127.4, 127.5, 127.6, 128.3, 128.4, 129.2 (all PhCH), 137.5 and 138.5 (both PhC); *m*/*z* 174 (M^+, 4%), 107 (15), 91 (100) and 71 (26).

(1*SR*,5*RS*,6*SR*)- and (1*RS*,5*RS*,6*RS*)-9-Benzyl-5-methyl-9-aza-3,8-dioxabicyclo[4.3.0]nonane 37d and 38d and (1*RS*,5*RS*,6*SR*)-8-benzyl-5-methyl-8-aza-3,7-dioxabicyclo[4.2.1]nonane 39d

The 5-methylhept-6-enol **32d** (0.22 g) was oxidized using the Swern method and the resulting aldehyde condensed immediately with *N*-benzylhydroxylamine to give the nitrone **33d**, exactly as described for the 4-methyl derivative **33a**. The intermediate aldehyde **7d** showed δ_H (90) 1.08 (3H, d, *J* 7, 5-CH_3), 2.46–2.74 (1H, m, 5-H), 3.33–3.75 (2H, m, 4-CH_2), 4.15 (2H, s, 2-CH_2), 5.00–5.34 (2H, m, 7-CH_2), 5.94 (1H, ddd, *J* 17, 10 and 7, 6-H) and 9.89 (1H, br s, CHO). The nitrone **33d** was immediately dissolved in toluene (10 ml) and the resulting solution stirred at 80 °C for 20 h. The cooled solution was evaporated and the residue separated by CC [EtOAc–petrol (1 : 5)] to give i) the *(1RS,5RS,6RS)-bicyclo[4.3.0]nonane* **38d** (143 mg, 36%), R_f 0.24, as a colourless oil; ν_{max}/cm^{-1} 3090, 3060, 3030, 1450 and 1115; δ_H (400) 0.86 (3H, d, *J* 6.8, 5-CH_3), 1.91–1.99 (1H, m, 5-H), 2.19–2.24 (1H, m, 6-H), 2.85–2.92 (1H, m, 1-H), 3.02 (1H, dd, *J* 11.5 and 10.5, 4-H_{ax}), 3.56 (1H, dd, *J* 12.6 and 3.3, 2-H_a), 3.65 (1H, dd, *J* 12.6 and 2.4, 2-H_b), 3.69 (1H, dd, *J* 7.7 and 2.5, 7-H_a), 3.79 (1H, dd, *J* 11.5 and 4.1, 4-H_{eq}), 3.94 (2H, s, $PhCH_2$), 4.02 (1H, dd, *J* 7.7 and 6.0, 7-H_b) and 7.21–7.43 (5H, m, PhH); δ_C (100) 16.5 (5-CH_3), 30.3 (5-CH), 47.4 (6-CH), 61.7 (2-CH_2), 62.4 (1-CH), 66.1 ($PhCH_2$), 69.3, 71.6 (both CH_2), 127.2, 128.2, 129.1 (all PhCH) and 137.1 (PhC); *m*/*z* 233 (M^+, 36%), 188 (24), 161 (12), 92 (13) and 91 (100) [Found: M^+, 233.1423. $C_{14}H_{19}NO_2$ requires *M*, 233.1416], ii) the *(1SR,5RS,6SR)-bicyclo[4.3.0]nonane* **37d** (33 mg, 9%), R_f 0.29, as a colourless oil; ν_{max}/cm^{-1} 3090, 3070, 3040, 1490, 1455 and 1105; δ_H (400) 0.89 (3H, d, *J* 7.1, 5-CH_3), 2.17–2.25 (1H, m, 5-H), 3.07–3.21 (1H, m, 6-H), 3.15 (1H, dd, *J* 11.5 and 11.5, 4-H_{ax}), 3.19 (1H, dd, *J* 11.3 and 11.3, 2-H_{ax}), 3.31 (1H, ddd, *J* 11.3, 6.2 and 6.2, 1-H), 3.64 (1H, dd, *J* 11.5 and 5.0, 4-H_{eq}), 3.77 (1H, d, *J* 12.6, PhC$H_a$$H_b$), 3.80 (1H, dd, *J* 11.3 and 6.2, 2-H_{eq}), 3.86 (1H, dd, *J* 9.8 and 7.7, 7-H_a), 4.07 (1H, d, *J* 12.6, PhC$H_a$$H_b$), 4.17 (1H, dd, *J* 9.8 and 7.9, 7-H_b) and 7.25–7.38 (5H, m, Ph); δ_C (100) 15.4 (5-CH_3), 29.5 (5-CH), 42.6 (6-CH), 60.0 (1-CH), 60.7, 65.7, 66.8, 68.7 (all CH_2), 127.5, 128.5, 129.0 (all PhCH) and 137.2 (PhC); *m*/*z* 233 (M^+, 54%), 188 (44), 161 (15), 92 (18) and 91 (100) [Found: M^+, 233.1414] and iii) the *(1RS,5RS,6SR)-bicyclo[4.2.1]nonane* **39d** (36 mg, 10%), R_f, as a colourless oil; ν_{max}/cm^{-1} 3090, 3070, 3040, 1490 and 1455; δ_H (400) 0.87 (3H, d, *J* 7.1, 5-CH_3), 1.70–1.79 (1H, m, 5-H), 2.28–2.36 (2H, m, 9-CH_2), 3.30–3.36 (1H, m, 1-H), 3.38 (1H, dd, *J* 12.0 and 11.0, 4-H_a), 3.56 (1H, d, *J* 12.6, PhC$H_a$$H_b$), 3.69 (1H, dd, *J* 12.0 and 4.8, 4-H_b), 3.73 (1H, dd, *J* 12.8 and 6.2, 2-H_a), 3.75 (1H, d, *J* 12.8, 2-H_b), 4.41 (1H, ddd, *J* 4.5, 4.5 and 1.0, 6-H) and 7.24–7.44 (5H, m Ph); δ_C (100) 13.7 (5-CH_3), 32.2 (9-CH_2), 39.3 (5-CH), 62.9 (1-CH), 64.0, 72.0, 75.5 (all CH_2), 81.7 (6-CH), 127.4, 128.4, 129.2 (all PhCH) and 137.4 (PhC); *m*/*z* 233 (M^+, 16%), 160 (28), 91 (100) and 81 (21) [Found: M^+, 233.1411].

(1*RS*,5*SR*,6*RS*)-9-Benzyl-5-phenyl-9-aza-3,8-dioxabicyclo-[4.3.0]nonane 38e

The ester **31eb** (0.60 g) was reduced to the aldehyde **7e** directly using DIBAL-H, exactly as described for the preparation of aldehyde **7b**, method c), and was isolated as a colourless oil (0.46 g, 90%) and showed ν_{max}/cm^{-1} 1737; δ_H (90) 2.90 (1H, dd, *J* 13.7 and 6.7, 4-H_a), 2.95 (1H, dd, *J* 13.7 and 6.7, 4-H_b), 3.95 (1H, m, 5-H), 4.00 (2H, s, 2-CH_2), 5.15 (1H, dd, *J* 17.1 and 0.7, 7-H_t), 5.20 (1H, dd, *J* 10.3 and 1.0, 7-H_c), 5.72 (1H, ddd, *J* 17.1, 10.3 and 8.0, 6-H), 7.20–7.35 (5H, m, Ph) and 9.78 (1H, br s, CHO); *m*/*z* 190 (M^+, 6%), 130 (97), 130 (50), 117 (27), 91 (100) and 77 (23) and was used immediately. Both TLC and ^{1}H NMR analysis indicated *ca*. 95% purity.

The foregoing aldehyde **7e** (0.46 g) was converted into the corresponding nitrone **33e** as described for the preparation of nitrone **33b**. The crude nitrone **33e** was heated in toluene at 60 °C for 12 h and the cooled solution evaporated. CC [EtOAc–petrol (1 : 4)] of the residue gave the *(1RS,5SR,6RS)-bicyclo-[4.3.0]nonane* **38e** (350 mg, 46%), R_f 0.36, as a colourless oil; ν_{max}/cm^{-1} 3085, 3061, 3027, 1495, 1454 and 920; δ_H (400; $CDCl_3$–C_6H_6) 2.70 (1H, dd, *J* 13.8 and 7.2, 4-H_a), 2.84 (1H, dddd, *J* 8.8, 6.5, 6.5 and 2.4, 6-H), 2.96 (1H, dd, *J* 13.8 and 6.5, 4-H_b), 3.35 (1H, dd, *J* 9.1 and 2.4, 7-H_a), 3.49 (1H, dd, *J* 9.4 and 6.1, 2-H_a), 3.63 (1H, d, *J* 12.8, PhC$H_a$$H_b$), 3.68 (1H, ddd, *J* 8.8, 7.2 and 6.1, 1-H), 3.82 (1H, dd, *J* 9.1 and 6.5, 7-H_b), 3.85 (1H, ddd, *J* 7.2, 6.5 and 6.5, 5-H), 3.99 (1H, dd, *J* 9.4 and 7.2, 2-H_b) and 7.09–7.42 (10H, m, Ph); δ_C (100), 40.6 (4-CH_2), 53.9 (6-CH), 60.0 ($PhCH_2$), 69.2 (7-CH_2), 71.5 (1-CH), 72.1 (2-CH_2), 85.8 (5-CH), 128.5, 128.9, 129.0, 129.2, 129.9, 130.0 (all PhCH), 136.9 and 137.4 (both PhC); *m*/*z* 295 (M^+, 8%), 204 (14), 174 (81), 148 (32), 106 (30), 91 (100) and 77 (12) [Found: M^+, 295.1572. $C_{19}H_{21}NO_2$ requires *M*, 295.1572].

Also isolated in variable amounts (see discussion) was (1*RS*,5*SR*,6*RS*)-2-benzyl-4-methyl-5-phenyl-2-aza-3,7-dioxabicyclo[3.3.0]octane **44** as a viscous, colourless oil [Found: C, 77.2; H, 7.5; N, 4.5. $C_{19}H_{21}NO_2$ requires C, 77.3; H, 7.2; N, 4.7%]; ν_{max}/cm^{-1} 3090, 3030, 1495, 1454, 1378, 1077 and 1029; δ_H (400) 1.41 (3H, d, *J* 6.3, 4-CH_3), 3.70 (1H, m, 1-H), 3.78 (1H, d, *J* 9.5, 6-H_a), 3.90–4.10 (2H, m, 8-CH_2), 4.00 (1H, d, *J* 12.8, PhC$H_a$$H_b$), 4.19 (1H, d, *J* 12.8, PhC$H_a$$H_b$), 4.28 (1H, d, *J* 9.5, 6-H_b), 4.72 (1H, q, *J* 6.3, 4-H) and 7.02–7.41 (10H, m, Ph-H); δ_C (100) 12.6 (4-CH_3), 59.3 ($PhCH_2$), 62.0 (5-C), 65.6 (8-CH_2), 70.8 (6-CH_2), 75.8 (1-CH), 78.5 (4-CH), 125.4, 125.8, 126.3, 127.8, 128.2, 128.3 (all PhCH), 135.9 and 141.6 (both PhC); *m*/*z* 295 (M^+, 15%), 174 (3), 149 (11), 130 (6), 117 (5), 105 (6), 103 (8), 92 (9), 91 (100) and 77 (6).

(1*RS*,5*RS*,6*RS*)-9-Benzyl-5-(*tert*-butyldimethylsilyloxymethyl)-9-aza-3,8-dioxabicyclo[4.3.0]nonane 38f

The ester **31fb** was reduced to the aldehyde **7f** directly using DIBAL-H, exactly as described for the preparation of aldehyde **7b**, method c), and was isolated as a colourless oil (90–93%); ν_{max}/cm^{-1} 1740 and 1640; δ_H (250) 0.00 (6H, s, 2 × $SiCH_3$), 0.84 (9H, s, $SiC(CH_3)_3$), 2.47 (1H, m, 5-H), 3.40–3.65 (6H, m, 2- and 4-CH_2 and CH_2Si), 5.09 (1H, dd, *J* 11.6 and 1.2, 7-H_c), 5.13 (1H, dd, *J* 17.4 and 1.2, 7-H_t), 5.75 (1H, ddd, *J* 17.4, 11.6 and 7.9, 6-H) and 9.70 (1H, t, *J* 0.9, CHO) and was used immediately as it proved to be rather sensitive. Both TLC and ^{1}H NMR analysis indicated *ca*. 95% purity.

The foregoing aldehyde **7f** (55 mg, 0.21 mmol) was added to a suspension of *N*-benzylhydroxylamine hydrochloride (34 mg, 0.21 mmol) and anhydrous potassium carbonate (43 mg, 0.35 mmol) in toluene (20 ml) maintained at 0 °C. After 2 h, the mixture was filtered and evaporated to leave the crude nitrone **33f** (71 mg); ν_{max}/cm^{-1} 1642 and 1605; δ_H (250) 0.00 (6H, s, 2 × $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 2.47 (1H, m, 5-H), 3.46–3.58 (4H, m, 4-CH_2 and CH_2OSi), 4.40 (2H, d, *J* 4.7, 2-CH_2), 4.55 (2H, s, $PhCH_2$), 5.06 (1H, d, *J* 10.9, 7-H_c), 5.08 (1H, d, *J* 17.2, 7-H_t), 5.72 (1H, ddd, *J* 17.2, 10.9 and 7.8, 6-H), 6.80 (1H, t, *J* 4.7, 1-H) and 7.14–7.20 (5H, m, Ph). A sample (63 mg) was immediately heated in toluene (10 ml) at 57 °C for 18 h and the cooled solution evaporated. CC [EtOAc–petrol (1 : 4)] of the residue gave the *(1RS,5RS,6RS)-bicyclo[4.3.0]-nonane* **38f** (37 mg, 58%), R_f 0.21, as a colourless oil; ν_{max}/cm^{-1} 3090, 3030, 1495 and 920; δ_H (400) 0.00 (6H, s, 2 × $SiCH_3$), 0.84 (9H, s, $SiC(CH_3)_3$), 1.94–1.99 (1H, m, 5-H), 2.65 (1H, ddd, *J ca.* 6.5, 5.5 and 4.2, 6-H), 2.96 (1H, app br q, *J ca*. 5.5, 1-H), 3.22 (1H, app dd, *J* 13.3 and 11.7, 4-H_{ax}), 3.36 (1H, dd, *J* 11.7 and 8.3, 4-H_{eq}), 3.46 (1H, d, *J* 7.6, 7-H_a), 3.57 (1H, dd, *J* 9.8 and 5.0, C$H_a$$H_b$OSi), 3.72 (1H, dd, *J* 7.7, and 5.6, 2-H_a), 3.76 (1H, dd, *J* 9.8 and 4.9, $CH_a$$H_b$OSi), 3.81 (1H, dd, *J* 7.6 and 4.2, 7-H_b), 3.91 (1H, d, *J* 13.3, PhC$H_a$$H_b$), 3.95 (1H, d, *J* 13.3, $PhCH_a$$H_b$), 4.12 (1H, dd, *J* 7.7 and 5.6, 2-H_b) and 7.18–7.38 (5H, m, Ph); δ_C (67.5) −0.3, −0.1 (both $SiCH_3$), 18.2 (SiC), 25.8 ($SiC(CH_3)_3$), 37.7 (6-CH), 40.7 (5-CH), 61.1 (1-CH), 61.3 ($PhCH_2$), 63.6 (CH_2OSi), 66.6 (4-CH_2), 67.3 (2-CH_2), 69.7 (7-CH_2), 127.4, 128.4, 129.2 (all PhCH) and 136.9 (PhC); *m*/*z* 363 (M^+, 9%), 160 (14), 91 (100), 73 (21) and 57 (19) [Found: M^+, 363.2232. $C_{20}H_{33}NO_3Si$ requires *M*, 363.2226].

(1*RS*,5*SR*,6*RS*)- and (1*RS*,5*RS*,6*RS*)-9-Benzyl-5-benzyloxy-9-aza-3,8-dioxabicyclo[4.3.0]nonane 37g and 38g

The ester **31gb** (0.50 g) was reduced to the aldehyde **7g** directly using DIBAL-H, exactly as described for the preparation of aldehyde **7b**, method c), and was isolated, after CC [EtOAc–petrol (1 : 2)], as a colourless oil (180 mg, 41%) along with recovered ester **31gb** (235 mg, 47%). The aldehyde **7g** showed ν_{max}/cm^{-1} 1737 and 1644; δ_H (90) 3.63 (2H, d, *J* 6, 4-CH_2), 4.04–4.11 (1H, m, 5-H), 4.14 (2H, br s, 2-CH_2), 4.45 (1H, d, *J* 12, PhC$H_a$$H_b$), 4.68 (1H, d, *J* 12, $PhCH_a$$H_b$), 5.32 (1H, d, *J* 11, 7-H_c), 5.38 (1H, d, *J* 17, 7-H_t), 5.80 (1H, ddd, *J* 17, 11 and 7, 6-H) and 9.70 (1H, t, *J* 1, CHO) and was used immediately. Both TLC and ^{1}H NMR analysis indicated *ca*. 95% purity.

The foregoing aldehyde **7g** (65 mg) was converted into the nitrone **33g** (86 mg, 88%), as described in the foregoing example (**33f**); ν_{max}/cm^{-1} 1645 and 1604; δ_H (250) 3.53 (2H, d, *J* 6.2, 4-CH_2), 3.95 (2H, d, *J* 4.3, 2-CH_2), 3.93–3.99 (1H, m, 5-H), 4.40 (1H, d, *J* 12.1, PhC$H_a$$H_b$O), 4.61 (1H, d, *J* 12.1, $PhCH_a$$H_b$O), 4.81 (2H, s, $PhCH_2$), 5.29 (1H, d, *J* 10.9, 7-H_c), 5.30 (1H, d, *J* 16.9, 7-H_t), 5.75 (1H, ddd, *J* 16.9, 10.9 and 7.3, 6-H), 6.82 (1H, t, *J* 4.3, 1-H) and 7.25–7.40 (10H, m, Ph).

The crude nitrone **33g** (86 mg) was heated in toluene (10 ml) at 55 °C for 21 h. After evaporation, CC [EtOAc–petrol (1 : 2)] of the residue separated i) the *(1RS,5SR,6RS)-bicyclo-[4.3.0]nonane* **37g** (11 mg, 13%), R_f 0.29, as a viscous oil; ν_{max}/cm^{-1} 3090, 3030, 1495 and 920; δ_H (400) 3.23 (1H, br dd, *J* 10.7 and 10.7, 2-H_{ax}), 3.27 (1H, m, 6-H), 3.39–3.56 (2H, m, 1- and 5-H), 3.74 (1H, d, *J* 12.7, PhC$H_a$$H_b$N), 3.81 (1H, dd, *J* 11.7 and 6.8, 2-H_{eq}), 3.87 (1H, dd, *J* 12.0 and 5.2, 7-H_a), 3.90 (1H, dd, *J* 12.0 and 5.2, 7-H_b), 4.06 (1H, d, *J* 12.7, $PhCH_a$$H_b$N), 4.14 (1H, dd, *J* 8.7 and 8.7, 4-H_{eq}), 4.27 (1H, dd, *J* 9.2 and 8.7, 4-H_{ax}), 4.57 (2H, s, $PhCH_2O$) and 7.09–7.41 (10H, m, Ph); δ_C (100) 42.0 (6-CH), 60.0 ($PhCH_2N$), 61.1 (1-CH), 65.3 (7-CH_2), 66.1 (2-CH_2), 67.4 (4-CH_2), 71.2 ($PhCH_2O$), 71.9 (5-CH), 127.6, 127.7, 128.0, 128.6, 129.1 (PhCH), 137.1 and 138.2 (PhC); *m*/*z* 325 (M^+, 4%), 280 (3), 234 (5), 219 (15), 161 (4), 159 (4), 106 (15), 91 (100) and 77 (8) [Found: M^+, 325.1668. $C_{20}H_{23}NO_3$ requires *M*, 325.1678] and ii) the *(1RS,5RS,6RS)-bicyclo-[4.3.0]nonane* **38g** (26 mg, 30%), R_f 0.23, as a viscous oil [Found: C, 73.6; H, 6.8; N, 3.9. $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.1; N, 4.3%]; ν_{max}/cm^{-1} 3090, 3030, 1490 and 927; δ_H (400) 2.72 (1H, app br qd, *J ca.* 7 and 3.7, 6-H), 3.17 (1H, dd, *J* 6.2, 3.9 and 3.9, 1-H), 3.35 (1H, dd, *J* 11.4 and 7.9, 4-H_{ax}), 3.55 (1H, dd, *J* 12.6 and 3.9, 2-H_a), 3.65 (1H, dd, *J* 12.6 and 3.9, 2-H_b), 3.70 (1H, ddd, *J* 7.9, 7.9 and 4.0, 5-H), 3.81 (1H, dd, *J* 8.0 and 3.7, 7-H_a), 3.92 (1H, d, *J* 13.1, PhC$H_a$$H_b$N), 3.97 (1H, dd, *J* 11.4 and 4.0 4-H_{eq}), 3.98 (1H, d, *J* 13.1, $PhCH_a$$H_b$N), 4.12 (1H, dd, *J* 8.0 and 6.6, 7-H_b), 4.53 (1H, d, *J* 11.7, PhC$H_a$$H_b$O), 4.63 (1H, d, *J* 11.7, $PhCH_a$$H_b$O) and 7.11–7.42 (10H, m, Ph); δ_C (100) 46.5 (6-CH), 61.7 ($PhCH_2N$), 62.9 (1-CH), 66.5 (7-CH_2), 67.5 (2-CH_2), 68.8 (4-CH_2), 71.9 ($PhCH_2O$), 73.1 (5-CH), 127.6, 127.8, 128.0, 128.5, 128.6, 129.3 (PhCH), 136.7 and 138.1 (PhC); *m*/*z* 280 (2%), 219 (12), 106 (7), 91 (100) and 77 (8) [Found: $M^+ - 45$, 280.1340. $C_{18}H_{18}NO_2$ requires *M*, 280.1338].

Spiro-dioxolanes 37h and 38h

The dioxolane alcohol **32h** (290 mg) was oxidized using the Swern method to give the aldehyde **7h** (245 mg), exactly as described for the 4-methyl derivative **33a**, which showed δ_H (90) 1.41 (3H, s, 2-Me), 1.46 (3H, s, 2-Me), 3.64 (2H, s, 4-CH_2O), 3.92 (1H, d, *J* 9, 5-H_a), 4.25 (1H, d, *J* 9, 5-H_b), 4.26 (2H, br s, CH_2CHO), 5.23–5.66 (2H, m, =CH_2), 6.15 (12H, dd, *J* 17 and 10, =CH) and 9.89 (1H, s, CHO) and which was condensed immediately with *N*-benzylhydroxylamine to give the nitrone **33h**, also as described for the 4-methyl derivative **33a**. This was immediately dissolved in toluene (10 ml) and the resulting solution stirred at 80 °C for 20 h. The cooled solution was evaporated and the residue separated by CC [ETOAc–petrol (3 : 7)] to give i) **37h** (71 mg, 16%), R_f 0.36, as a colourless solid, mp 126–128 °C (ether–petrol) [Found: C, 66.9; H, 7.8; N, 4.7. $C_{17}H_{23}NO_4$ requires C, 66.9; H, 7.6; N, 4.6%]; ν_{max}/cm^{-1} ($CHCl_3$) 1605, 1450, 1380, 1100 and 1050; δ_H (400) 1.25 (3H, s, CCH_3), 1.41 (3H, s, CCH_3), 3.15–3.25 (2H, m, 2-H_a and 6-H), 3.32 (1H, ddd, *J* 10.8, 6.6 and 6.6, 1-H), 3.40 (1H, dd, *J* 11.4 and 1.0, 4-H_a), 3.57 (1H, d, *J* 11.4, 4-H_b), 3.75 (1H, d, *J* 12.8, PhC$H_a$$H_b$), 3.80 (1H, dd, *J* 11.5 and 6.6, 2-H_b), 3.84 (1H, dd, *J* 8.7 and 1.0, O(C)C$H_a$$H_b$O), 4.06 (1H, d, *J* 12.8, $PhCH_a$$H_b$), 4.09 (1H, dd, *J* 8.6 and 8.6, 7-H_a), 4.12 (1H, d, *J* 8.7, O(C)$CH_a$$H_b$O), 4.32 (1H, dd, *J* 9.4 and 8.6, 7-H_b) and 7.23–7.38 (5H, m, Ph); δ_C (100) 27.0, 27.2 (both CH_3), 47.3 (6-CH), 60.0 (CH_2), 61.1 (1-CH), 67.3, 67.7, 68.9, 74.9 (all CH_2), 77.9 (5-C), 109.8 (OCO), 127.7, 128.6, 128.9 (all PhCH) and 136.8 (PhC); *m*/*z* 305 (M^+, 48%), 216 (23), 161 (27), 92 (23) and 91 (100) [Found: M^+, 305.1619. $C_{17}H_{23}NO_4$ requires *M*, 305.1627] and ii) **38h** (135 mg, 31%), R_f 0.26, as a colourless oil [Found: C, 66.7; H, 8.1; N, 4.5]; δ_{max}/cm^{-1} ($CHCl_3$) 1605, 1450, 1380; δ_H (90) 1.38 (3H, s, CCH_3), 1.43 (3H, s, CCH_3), 3.28–4.44 (12H, m) and 7.24–7.39 (5H, m Ph); δ_C (100) 26.6, 27.5 (both CH_3), 47.7 (6-CH), 60.6 (CH_2), 61.3 (1-CH), 66.0, 66.5, 69.6, 70.8 (all CH_2), 78.1 (5-C), 109.6 (OCO), 127.4, 128.8, 129.3 (all PhCH) and 136.9 (PhC); *m*/*z* 305 (M^+, 15%), 126 (20), 161 (33), 92 (43) and 91 (100) [Found: M^+, 305.1622].

A small quantity (12 mg, 3%) of the bicyclo[4.2.1]nonane isomer **39h**, of unknown stereochemistry at the dioxolane centre, was also isolated, R_f 0.24, and identified by δ_C (100) 26.3, 27.4 (both CH_3), 37.8 (9-CH_2), 62.8 (1-CH), 63.9, 69.4, 73.3, 75.6 (all CH_2), 82.3 (5-C), 83.2 (6-CH), 110.3 (OCO), 127.6, 128.4, 129.2 (all PhCH) and 137.0 (PhC); *m*/*z* 305 (M^+, 10%), 161 (40), 92 (61) and 91 (100) [Found: M^+, 305.1624].

Acknowledgements

We are very grateful to the EPSRC Mass Spectrometry Service, Swansea University for the provision of some high resolution mass spectral data and to Zeneca Pharmaceuticals and the EPSRC for financial support through the CASE Scheme.

References

1 P. Lefrancier, *Forschr. Chem. Org. Naturst.*, 1981, **40**, 1; E. Ellouz, A. Adam, R. Ciorbaru and E. Lederer, *Biochem. Biophys. Res. Commun.*, 1974, **59**, 1317.

2 M. A. Sparks, K. W. Williams, C. Lukacs, A. Schrell, G. Priebe, A. Spaltenstein and G. M. Whitesides, *Tetrahedron*, 1993, **49**, 1; M. P. DeNinno, *Synthesis*, 1991, 583 and references cited therein.

3 P. M. Colman, *Pure Appl. Chem.*, 1995, **67**, 1683 and references cited therein.

4 T. Wakamiya, T. Ando, T. Teshima and T. Shiba, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 142; Y. Hayakawa, M. Nakagawa, H. Kawai, K. Tanabe, H. Nakayama, A. Shimazu, H. Seto and H. Otake, *Agric. Bio. Chem.*, 1985, **49**, 2685.

5 F. M. Hauser and S. R. Ellenberger, *Chem. Rev.*, 1986, **86**, 35 and references cited therein.

6 J. J. Tufariello, [*1,3*]-*Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley Interscience, New York, 1984, ch. 9; P. A. Wade, *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 4, p. 1113; K. B. G. Torssell, *Nitrile Oxides*, *Nitrones and Nitronates in Organic Synthesis*, VCH Publishers Inc., Weinheim, 1988, ch. 5; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1990; E. Breuer, H. G. Aurich and A. Nielsen, *Nitrones*, *Nitronates and Nitroxides*, eds. S. Patai and Z. Rappoport, John Wiley and Sons, Chichester, 1989.

7 N. A. LeBel, M. E. Post and J. J. Whang, *J. Am. Chem. Soc.*, 1964, **86**, 3759; N. A. LeBel and E. G. Banucci, *J. Org. Chem.*, 1971, **36**, 2440.

8 B. Bernat and A. Vassella, *Helv. Chim. Acta*, 1979, **62**, 2400 and 2411.

9 H. G. Aurich and K.-D. Möbus, *Tetrahedron*, 1989, **45**, 5815; H. G. Aurich and F. Biesemeier, *Synthesis*, 1995, 1171; H. G. Aurich, F. Biesemeier and M. Boutahar, *Chem. Ber.*, 1991, **124**, 2329. See also S. Baskaran and H. G. Aurich, *Synlett*, 1998, 277; H. G. Aurich, G. Frenzen and C. Gentes, *Chem. Ber.*, 1993, **126**, 787.

10 H. G. Aurich, M. Geiger and U. Sievers, *Synlett*, 1997, 1004; H. G. Aurich, F. Biesemeier, M. Geiger and K. Harms, *Liebigs Ann./Recl.*, 1997, 423.

11 H. G. Aurich, M. Boutahar, H. Köster, K.-D. Möbus and L. Ruiz, *Chem. Ber.*, 1990, **123**, 1999. See also S. Baskaran, H. G. Aurich, F. Biesemeier and K. Harms, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 3717; H. G. Aurich, M. Geiger, C. Gentes, K. Harms and H. Köster, *Tetrahedron*, 1998, **54**, 3181.

12 For a preliminary communication, see M. B. Gravestock, D. W. Knight, J. S. Lovell and S. R. Thornton, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 1661.

13 *Cf.* B. B. Snider and R. A. H. F. Hui, *J. Org. Chem.*, 1985, **50**, 5167.

14 J. Herscovici, M.-J. Egron and K. Antonakis, *J. Chem. Soc.*, *Perkin Trans. 1*, 1982, 1967.

15 C. Huynh, F. Derguini-Boumechal and G. Linstrumelle, *Tetrahedron Lett.*, 1979, 1503.

16 *Cf.* C. B. Rose and C. W. Smith, *J. Chem. Soc.*, *Chem. Commun.*, 1969, 248.

17 T. Nakai and K. Mikami, *Chem. Rev.*, 1986, **86**, 885; *Org. React.*, 1994, **46**, 105.

18 M. Sodeoka, H. Yamada and M. Shibasaki, *J. Am. Chem. Soc.*, 1990, **112**, 4906; H. M. Hull and D. W. Knight, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 857.

19 W. C. Still, *J. Am. Chem. Soc.*, 1978, **100**, 1481; D. Seyferth and S. B. Andrews, *J. Organomet. Chem.*, 1971, **30**, 151.

20 D. Carpita and A. Rossi, *Synthesis*, 1982, 469.

21 T. Reichstein, A. Pedolin and A. Grussner, *Helv. Chim. Acta*, 1935, **18**, 598.

22 J. Grundy, B. G. James and G. Pattenden, *Tetrahedron Lett.*, 1972, 757.

23 D. L. J. Clive and C. G. Russell, *J. Chem. Soc.*, *Chem. Commun.*, 1981, 434.

24 D. Swern, A. J. Mancuso and S.-L. Huang, *J. Org. Chem.*, 1978, **43**, 2480.

25 W. P. Griffith and S. V. Ley, *Aldrichimica Acta*, 1990, **23**, 13; S. V. Ley, J. Norman, W. P. Griffiths and S. P. Marsden, *Synthesis*, 1994, 639.

26 W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth Heinemann, Oxford, 1996.

27 G. Hirth and R. Barner, *Helv. Chim. Acta*, 1982, **65**, 1059; J. M. Klunder, S. Y. Ko and K. B. Sharpless, *J. Org. Chem.*, 1986, **51**, 3710.

28 *Cf.* B. H. Lipschutz, R. Moretti and R. Crow, *Org. Synth.*, 1990, **69**, 80.

Paper 9/05802H