Synthetic Studies on Bicyclomycin and its Analogues. Part 1. Synthesis of Substituted 2-Oxa-8,10-diazabicyclo[4.2.2]decanes

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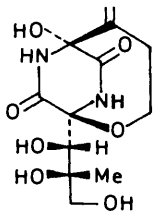
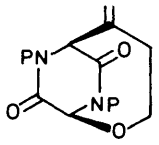
Methods have been developed for formation of the eight-membered oxygen-containing ring system (**2**) present in the antibiotic bicyclomycin. The procedure starts with *N,N'*-disubstituted piperazine-2,5-diones or the corresponding mono imino ethers. A new method is based on the oxidation of the mono imino ethers using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as oxidant: the bis imino ethers gave pyrazines under these conditions, whilst the parent piperazinedione proved to be unreactive.

The commercial antibiotic bicyclomycin (aizumycin) (**1**)[1] exhibits a broad spectrum of activity against Gram negative bacteria.[2] Its unique bicyclic [4.2.2] skeleton has made it the target of several synthetic studies,[3] culminating in its successful synthesis by Shin and colleagues[4] and Williams *et al.*[5] Herein we describe studies on the synthesis of the 2-oxa-8,10-diazabicyclo[4.2.2]decane system and, in more detail, a short route to the key intermediate (**2**), which has been used in the total synthesis of bicyclomycin.[3-6]

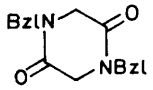
Simple bicyclo[4.2.2]decanes of the type (**8**) can be prepared by initial alkylation of *N,N'*-dibenzylpiperazine-2,5-dione (**3**) with the protected 3-iodopropanol (**4**), to give the product (**5**). Removal of the alcohol-protecting group with tetrabutylammonium fluoride (TBAF) releases the alcohol (**6**) which can be directly brominated with *N*-bromosuccinimide (NBS), according to the method of Shin,[7] to produce the cyclic ether (**8**). It is of interest to note that no formation of the isomeric five-membered ring ether occurred, *cf.* structure (**16**), indicating that bromination occurs selectively at the unsubstituted methylene group, possibly for steric reasons. However, in our hands, the eight-membered ring ether (**8**) was accompanied by considerable quantities of the bromide (**7**). Furthermore, since, in aiming at the intermediate (**2**), appropriate precursors might well possess either the double bond or functionalities used to introduce unsaturation that would render them sensitive to NBS, this route was deemed inappropriate. A search was made for milder oxidation methods for effecting cyclisation, in particular the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). In the event, DDQ did not react with the alcohol (**6**). Since the mono and bis imino ethers in the pyrazine series are known to be oxidised by DDQ,[8] an examination of these systems was made. The mono imino ether (**9**) was monoalkylated with the iodopropanol



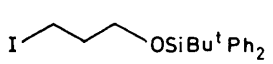
(**1**)



(**2**)
P = 4-MeOC$_6$H$_4$CH$_2$

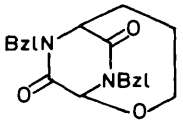


(**3**)



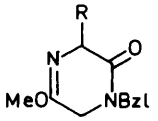
(**4**)

(**5**) R = OSiBu^{t}Ph$_2$
(**6**) R = OH
(**7**) R = Br



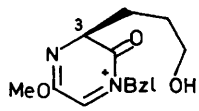
(**8**)

Bzl = CH$_2$Ph throughout



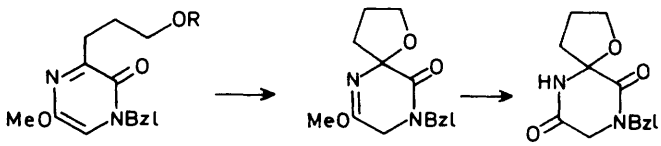
(**9**) R = H
(**10**) R = (CH$_2$)$_3$OSiBu^{t}Ph$_2$
(**11**) R = (CH$_2$)$_3$OH

(**12**)



(**13**)

derivative (**4**), alkylation occurring regioselectively adjacent to the amide carbonyl group to give the product (**10**) which could be selectively deprotected to afford the alcohol (**11**). Cyclisation of this alcohol to the corresponding eight-membered bicyclic ether (**12**) was affected by DDQ in good yield and, as before, none of the five-membered spiro ether [*cf.* Scheme 1, (**16**)] was observed.



(**14**) R = SiBu^{t}Ph$_2$
(**15**) R = H

(**16**)

Scheme 1.

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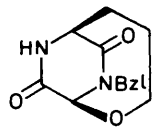
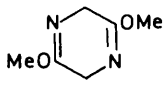
Oxidation of the alcohol (**11**) presumably occurs *via* the intermediate (**13**), trapping of the cation by intramolecular attack of the hydroxy group occurring before aromatisation by loss of the proton at position 3. Support for this proposal was gained by subjecting the protected alcohol (**10**) to oxidation with DDQ, which gave the pyrazinone (**14**). Subsequent removal of the alcohol-protecting group with TBAF, to give the alcohol (**15**), followed by brief treatment with acid gave the thermodynamically preferred five-membered ring ether (**16**), in which the imino ether function had also hydrolysed (Scheme 1). In this experiment none of the eight-membered ring ether (**12**) was formed. NBS oxidation of the mono imino ether (**11**) occurs in a fashion similar to DDQ oxidation since it also produced the ether (**12**), along with some of the corresponding amide (**17**) produced by concomitant cleavage of the imino ether function.

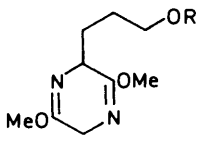
To complete these model studies the properties of the bis imino ether (**20**) were examined. This alcohol was prepared from the parent imino ether (**18**) by monoalkylation with the protected iodopropanol (**4**), as used above, and the product (**19**)



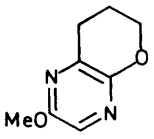
(**17**)



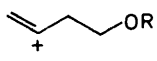
(**18**)



(**19**) R = $SiBu^tPh_2$
(**20**) R = H



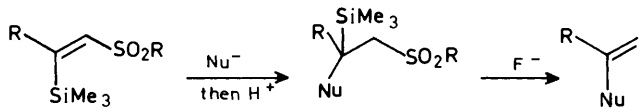
(**21**)



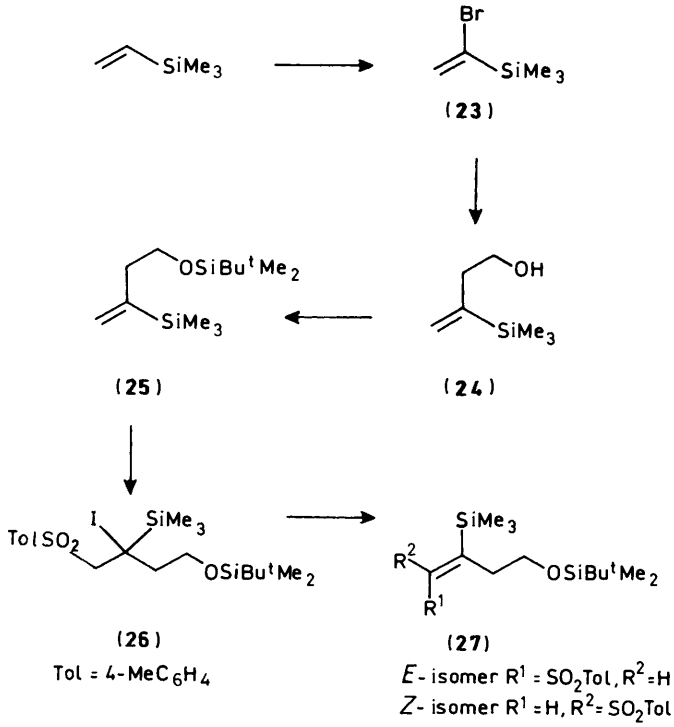
(**22**)

deprotected to give the alcohol (**20**). Oxidation of this compound with DDQ took a different course, yielding a product which contained a pyrazine chromophore and only one methoxy group, and had sustained loss of a hydroxy group. This product was assigned as the pyranopyrazine (**21**). In this case, therefore, aromatisation occurs before trapping to form a bicyclic ether, followed by intramolecular displacement of the methoxy group by the alcohol function. The reverse sequence of reactions, oxidation before alcohol deprotection, also produced the pyranopyrazine (**21**).

In order to extend these observations to a synthesis of the desired intermediate (**2**), a method for introducing the methylenic olefin unit is required. Previous studies have overcome this problem by using multiple-step sequences, often late in the synthesis.[9] We considered that a new synthon for the vinylic system (**22**) was needed, in which the double bond is masked until required. The method chosen was to make use of the known propensity of β-silylated sulphones to undergo regiospecific elimination under fluoride attack, to release the double bond.[10] Since nucleophilic addition to αβ-unsaturated sulphones is also well documented[11] the overall process is as depicted in Scheme 2, using β-silylated-αβ-unsaturated sulphones.[12] The required synthon (**27**) was initially prepared as a mixture of *E*- and *Z*-isomers by the route depicted in Scheme 3.



Scheme 2.



Scheme 3.

Vinyl bromide was converted into vinyltrimethylsilane by a Grignard reaction. Bromination gave an unstable dibromide adduct that was immediately treated with diethylamine to produce 1-bromo-1-trimethylsilylethylene (**23**). A further Grignard reaction of this halide, in the presence of copper(I) iodide, with ethylene oxide gave the alcohol (**24**) which was protected as the dimethyl-t-butylsilyl ether (**25**), in overall 32% yield. Radical-induced addition[13] of freshly prepared toluene-*p*-sulphonyl iodide in dichloromethane gave a quantitative yield of the adduct (**26**), possessing the required regiochemistry; none of the other regioisomer was detected under these reaction conditions.

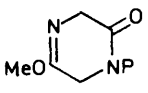
Considerable effort was expended in studying the behaviour of the iodo sulphone (**26**) with base. With triethylamine a mixture of the *E*- and *Z*-isomers of olefin (**27**) was obtained. These isomers could be separated by column chromatography and n.O.e. experiments were performed on each of them. The less polar isomer showed a signal enhancement of 8.5% for the vinylic proton when the 3-methylene group was irradiated, complemented by a reverse enhancement of 5.4% for the methylene group on irradiating the vinylic proton. In contrast, the more polar isomer showed no n.O.e. enhancements for these protons; the less polar isomer was therefore assigned as the *Z*-isomer. Chemical shifts supported these assignments (see Experimental section). No evidence for formation of the βγ-unsaturated sulphone was obtained in this reaction. The ratio of the *E*:*Z* isomers formed was dependent on the base employed (Table). Remarkably, whereas 1,4-diazabicyclo[2.2.2]octane (DABCO) gave only the *Z*-olefin, the strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced solely the *E*-isomer, the

Table. Treatment of the iodosulphone (**26**) with bases

Base	Reaction conditions	Ratio $Z:E$	Total yield (%) (**27**)
Pyridine	THF, 4 days, room temp. and 16 h reflux	1:1	40
Et_2NH	Ether, 2 days, room temp.	1:3.4	98
Et_2NH	THF, 30 min, reflux	1:2	69
Et_2NH	Benzene, 16 h, reflux	1:5	69
Et_3N	THF, 2 days, reflux	1:2	85
Et_3N	Ether, 3 days, reflux	1:2	40
$EtPr^i_2N$	THF, 3 days, reflux	1:1.9	73
DBU	THF, 16 h, room temp.	0:1	41
DBU	THF, 30 min, room temp.	0:1	77
DABCO	THF, 40 min, room temp.	1:0	83
DABCO	DMF, 40 min, room temp.	1:0	60

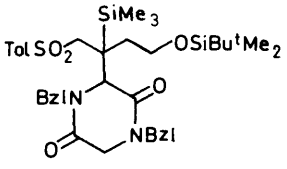
thermodynamically more stable compound. Different mechanisms must operate for these two sets of reaction conditions.[14]

Initial attempts at treating a 1:2 mixture of the $Z:E$ isomers of the sulphone (**27**) at first available to us, with the anion generated from the mono imino ether (**28**) and lithium amide bases, proved to be disappointing, variable and low yields (*ca.* 20%) of the diastereoisomeric adduct (**29**) being obtained.

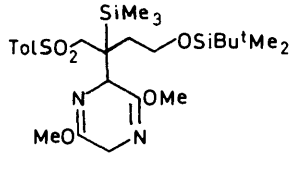


(**28**) P = 4-$MeOC_6H_4CH_2$ (Throughout)

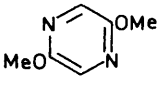
(**29**) R = $SiBu^tMe_2$
(**30**) R = H



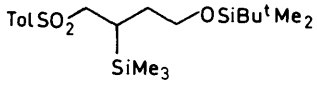
(**31**)



(**32**)



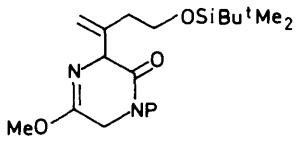
(**33**)



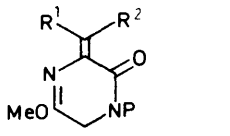
(**34**)

Considerable amounts of the starting imino ether and the *E*-olefin were recovered. Attempts to improve the yield by varying temperature, reaction times, and bases failed. However, with the availability of the separate olefin isomers it was established that whereas the *Z*-olefin was reactive, producing the Michael adduct (**29**) in >50% yield, the *E*-olefin was unreactive. Presumably the greater thermodynamic stability of the latter isomer, together with an increase of steric interactions expected during addition to this isomer, mitigate against reaction. Similar differences were obtained for reaction of the olefin isomers with the piperazinedione (**3**) and the bis imino ether (**18**). For the former the *E*-isomer proved unreactive, whilst the *Z*-isomer gave a small yield of the adduct (**31**); steric approach to the doubly substituted β-position of the vinylic sulphone is very restricted. With the bis imino ether (**18**) the *Z*-olefin gave both the adduct (**32**) (18%) and a mixture of the oxidation product, the pyrazine (**33**) and the reduction product, the sulphone (**34**), formed by a concomitant redox process. For this substrate the *E*-isomer was reactive, yielding the adduct (**32**) in 30% yield.

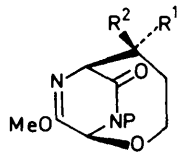
Treatment of the adduct (**29**) with an excess of TBAF in tetrahydrofuran afforded three products, the expected olefin (**35**) (9%), together with the two conjugated isomers (**36**) (14%) and (**37**) (17%). Since movement of the double bond into conjugation is essentially irreversible it was decided to leave the double bond in its masked form until after formation of the bicyclic[4.2.2] system. Thus selective removal of the alcohol protecting group, effected with TBAF–acetic acid, gave the alcohol (**30**) in high yield. Oxidation with DDQ produced a 2:1



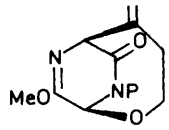
(**35**)



(**36**) R^1 = H, R^2 = CH_2CH_2OH
(**37**) R^1 = CH_2CH_2OH, R^2 = H



(**38**) R^1 = $SiMe_3$, R^2 = $TolSO_2CH_2$
(**39**) R^1 = $TolSO_2CH_2$, R^2 = $SiMe_3$



(**40**)

mixture of the desired bicyclic isomers (**38**) and (**39**) respectively, structural assignments being made on the basis of the anisotropy observed on the methylene group adjacent to the tosyl group by the amide function when these are *syn* to one another. Treatment of either isomer with fluoride anion smoothly afforded the olefin (**40**) in good yield. In order to correlate the structure of this product with the known *N,N'*-diprotected compound (**2**), the imino ether group was removed by treatment with toluene-*p*-sulphonic acid, followed by *N*-protection with 4-methoxybenzyl bromide. The olefin (**2**) thus obtained was identical in its properties with the compound previously used in the total synthesis of bicyclomycin.[5]

Experimental

M.p.s were determined on a Kofler block and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 1420 Ratio

Recording spectrophotometer either on solutions in chloroform, Nujol mulls or, for liquids, as films. ^{1}H N.m.r. spectra were recorded on a Varian 360A (60 MHz), Perkin-Elmer R32 (90 MHz), Jeol FX90Q (90 MHz) or Bruker AM400 (400 MHz) spectrometer and are quoted in p.p.m. relative to tetramethylsilane as internal reference, for solutions in deuteriochloroform. Mass spectra were obtained using a Kratos MS25 instrument and accurate mass determinations were obtained using an AEI-Kratos MS9/50 instrument. Microanalytical determinations were performed by the University of Leeds, School of Chemistry, Microanalytical Laboratory.

All chiral compounds were obtained as racemates. T.l.c. was carried out on aluminium or glass plates pre-coated with Merck Kieselgel 60 GF_{254}. Column chromatography was carried out on either MN-Kieselgel 60 (Camlab) or Kieselgel 60G (Merck); columns were generally packed and run under pressure. Solvents were dried and distilled before use using standard methods.[15] Light petroleum refers to the fraction of boiling range 40—60 °C and ether refers to diethyl ether throughout. Solutions of organic compounds from extractions were generally dried over anhydrous sodium sulphate before being filtered and evaporated under reduced pressure on a rotary evaporator. Dry nitrogen was generally employed as the atmosphere for most reactions. Ethanol was removed from chloroform by passing the solvent through an activated, basic alumina column immediately prior to use. *N*-Bromosuccinimide (NBS) was recrystallised from hot water and dried *in vacuo* over phosphorus pentaoxide. α,α′-Azoisobutyronitrile was recrystallised from ether and stored at −10 °C in the dark.

Solutions of lithium amide were prepared according to the following general prodedure. *N*-Butyl-lithium (1.05 equiv., as a 1.5M solution in hexane) was added dropwise to a stirred solution of the amine (1 equiv.) in tetrahydrofuran at −78 °C under nitrogen and stirred for a further 1 h after addition was complete. For more hindered amines, such as dicyclohexylamine, the lithium amide was prepared at −10°C.

1-(*Diphenyl*-t-*butylsilyloxy*)-3-*iodopropane* (**4**).—Diphenyl-t-butylsilyl chloride (22.1 g, 80 mmol) was added to a stirred solution of 3-chloropropan-1-ol (6.9 g, 73 mmol) and imidazole (10.9 g, 160 mmol) in dimethylformamide (100 ml) under nitrogen and the mixture stirred at room temperature overnight. The reaction mixture was diluted with hexane (100 ml) and sodium iodide (16.4 g, 109 mmol) added. The mixture was heated to reflux under nitrogen for 3 days after which the solvent was removed and the crude material taken up in light petroleum (100 ml), filtered, and the solution dried. The solvent was removed and the residue chromatographed through silica, using ethyl acetate–light petroleum (1:19) as eluant, to give the *iodo ether* (24.3 g, 79%); $\nu_{max.}$(film) 3 075, 2 960, 2 935, 2 860, 1 472, 1 428, 1 110, and 703 cm^{-1}; δ 1.07 (9 H, s, Bu^t), 2.03 (2 H, quint., *J* 7 Hz, 2-H), 3.33 (2 H, t, *J* 7 Hz, 3-H), 3.72 (2 H, t, *J* 7 Hz, 1-H), 7.3—7.5 (6 H, m, ArH), and 7.5—7.85 (4 H, m, ArH); *m/z* 424 (*M*$^+$, absent), 367 (85%), 309 (100), 239 (13), 211 (30), 181 (33), and 105 (27).

1,4-*Dibenzyl*-3-[3′-(*diphenyl*-t-*butylsilyloxy*)*propyl*]*piperazine*-2,5-*dione* (**5**).—A solution of lithium di-isopropylamide (5.3 mmol) in tetrahydrofuran (15 ml) at −78 °C was added to a stirred solution of 1,4-dibenzylpiperazine-2,5-dione (1.47 g, 5.0 mmol) in tetrahydrofuran (10 ml) cooled to −78 °C. The mixture was stirred for 1 h under nitrogen and then hexamethylphosphoramide (1.74 ml, 10 mmol) was added to it; stirring was continued for a further 10 min after which the mixture was allowed to warm to −40 °C when a solution of the iodopropane (**4**) (3.18 g, 7.5 mmol) in tetrahydrofuran (5 ml) was added. The reaction mixture was stirred at −40 °C for 1 h and then allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with saturated aqueous ammonium chloride (75 ml) and water (2 × 50 ml), the aqueous layers extracted with ether (2 × 100 ml), and the combined organic extracts dried and evaporated. Chromatography of the residue on silica, using ether as eluant, gave the substituted *piperazinedione* (1.01 g, 34%) as a viscous oil; $\nu_{max.}$($CHCl_3$) 3 070, 3 005, 2 930, 2 855, 1 662, 1 469, 1 425, 1 110, and 820 cm^{-1}; δ 1.07 (9 H, s, Bu^t), 1.2—2.2 (4 H, m, 1′-H and 2′-H), 3.62 (2 H, t, *J* 7 Hz, 3′-H), 3.75—4.1 (3 H, m, 3-H and 6-H), 3.92, 4.29, 4.81, and 5.23 (4 H, 2 × ABq, *J* 15 Hz, 2 × CH_2N), 6.9—7.5 (16 H, m, ArH), and 7.5—7.9 (4 H, m, ArH); *m/z* 590 (*M*$^+$, 1%), 533 (97), 442 (3), 386 (3), 351 (4), 199 (8), and 91 (100) (Found: *M*$^+$, 590.295 28, $C_{37}H_{42}N_2O_3{}^{28}Si$ requires *M*$^+$, 590.296 55).

1,4-*Dibenzyl*-3-(3′-*hydroxypropyl*)*piperazine*-2,5-*dione* (**6**).—TBAF (1M soln. in tetrahydrofuran; 2.3 ml, 2.3 mmol) was added to a solution of the silylated ether (**5**) (0.90 g, 1.5 mmol) in tetrahydrofuran (30 ml) and stirred at room temperature for 1.5 h. The solvent was removed and the residue chromatographed on silica, using methanol–ethyl acetate (1:19) as eluant, to yield the *title alcohol* (0.5 g, 92%), $\nu_{max.}$($CHCl_3$) 3 410, 2 995, 2 920, 1 655, 1 490, 1 465, 1 447, 1 327, and 902 cm^{-1}; δ 1.35—1.75 (2 H, m, 2′-H), 1.75—2.15 (2 H, m, 1′-H), 2.25 (1 H, br s, OH), 3.55 (2 H, t, *J* 7 Hz, 3′-H), 3.84—4.1 (3 H, m, 3-H and 6-H), 4.05 and 4.75 (2 H, ABq, *J* 14 Hz, NCH_2), 4.35 and 5.15 (2 H, ABq, *J* 15 Hz, NCH_2), and 7.27 (10 H, s, ArH); *m/z* 352 (*M*$^+$, 49%), 293 (9.5), 261 (18), 243 (9), and 91 (100) (Found: C, 71.5; H, 6.7; N, 7.9%; *M*, 352.178 30; $C_{31}H_{24}N_2O_3$ requires C, 71.6; H, 6.8; N, 7.9%; *M*, 352.178 68).

Reaction of the Alcohol (**6**) *with NBS*.—NBS (0.56 g, 3 mmol) was added to a stirred solution of the alcohol (1.10 g, 3 mmol) in chloroform (50 ml) under nitrogen and the solution heated to reflux for 2.5 h. The reaction mixture was washed with water (2 × 30 ml), dried, and evaporated. The residue was chromatographed on silica, using ether as eluant, to give, initially, 1,4-*dibenzyl*-3-(3′(*bromopropyl*)*piperazine*-2,5-*dione* (**7**) (0.16 g, 12%), $\nu_{max.}$($CHCl_3$) 3 010, 2 945, 1 670, 1 497, 1 455, 1 359, 1 175, 1 085, and 910 cm^{-1}; δ 1.6—2.3 (4 H, m, 1′-H and 2′-H), 3.34 (2 H, t, *J* 6 Hz, 3′-H), 3.8—4.2 (3 H, m, 3-H and 6-H), 4.06, 4.30, 4.84, and 5.90 (4 H, 2 × ABq, *J* 15 Hz, 2 × NCH_2), and 7.28 (10 H, m, ArH); *m/z* 416 (*M*$^+$, 4.3%), 414 (4.4), 335 (9), 293 (6), 202 (4), 174 (4), 118 (2.5), and 91 (100) (Found: *M*$^+$, 414.094 13; $C_{21}H_{23}N_2O_2{}^{79}Br$ requires *M*, 414.094 33). This fraction was followed by the bicyclic compound, 8,10-dibenzyl-2-oxa-8,10-diazabicyclo[4.2.2]decane-7,9-dione (**8**)[16] (0.53 g, 49%); $\nu_{max.}$($CHCl_3$) 2 940, 2 880, 1 675, 1 500, 1 455, 1 267, 1 167, 1 097, and 1 077 cm^{-1}; δ 1.58—1.82 (2 H, m, 4-H), 1.82—2.10 (2 H, m, 5-H), 3.27—3.60 (1 H, m, 3-H), 3.68—4.01 (1 H, m, 3-H), 4.10 (1 H, t, *J* 4 Hz, 6-H), 4.12, 4.30, 4.84, and 5.05 (4 H, 2 × ABq, 2 × NCH_2), 5.19 (1 H, s, 1-H), and 7.29 (10 H, s, ArH); *m/z* 350 (*M*$^+$, 21%), 244 (12), 174 (4), 153 (10), and 91 (100) (Found: *M*$^+$, 350.162 71. Calc. for $C_{21}H_{22}N_2O_3$: *M*, 350.163 03).

1-*Benzyl*-5-*methoxy*-3,6-*dihydropyrazin*-2(1H)-*one* (**28**).—Trimethyloxonium tetrafluoroborate (1.2 g, 8.0 mmol) was added to a suspension of 1-benzyl-2,5-dione[17] (1.14 g, 5.6 mmol) in nitromethane (30 ml) and the mixture was stirred rapidly at room temperature for 2 days when all the solids dissolved. The reaction solution was then poured slowly into vigorously stirred, saturated aqueous sodium hydrogen carbonate (100 ml) and extracted with dichloromethane (100 ml). The organic extract was washed with water, dried, and evaporated to yield a brown solid which was chromatographed through silica, using ethyl acetate as eluant, to yield the *title imino ether* (0.88 g, 72%), m.p. (from ether) 91 °C; $\nu_{max.}$(Nujol) 3 060, 1 710,

1 640, 1 500, 1 450, 1 360, 1 280, 1 100, 1 060, 1 010, 904, 780, 730, and 700 cm^{-1}; δ 3.65 (3 H, s, MeO), 3.79 (2 H, t, *J* 3 Hz, NCH_2), 4.19 (2 H, t, *J* 3 Hz, CH_2CO), 4.59 (2 H, s, $PhCH_2$), and 7.28 (5 H, s, ArH) (Found: C, 66.8; H, 6.6; N, 12.6; $C_{12}H_{14}N_2O_2$ requires C, 66.6; H, 6.5; N, 12.9%).

1-*Benzyl*-3-[3′-(*diphenyl*-t-*butylsilyloxy*)*propyl*]-5-*methoxy*-3,6-*dihydropyrazin*-2(1H)-*one* (**10**).—The imino ether (**9**) (3.00 g, 14 mmol) in tetrahydrofuran (15 ml) was added to a stirred solution of lithium dicyclohexylamide (14 mmol) in tetrahydrofuran (80 ml) at −78 °C under nitrogen and the solution stirred for 2 h. Hexamethylphosphoramide (4.8 ml, 27.5 mmol) was then added and the mixture allowed to warm to −40 °C when a solution of the silyl ether (**4**) (11.7 g, 27 mmol) in tetrahydrofuran (20 ml) was added and the solution allowed to warm to room temperature with stirring overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (100 ml) and extracted with ether (2 × 100 ml) and the latter backwashed with water (2 × 50 ml). The organic extract was dried and evaporated and the residue chromatographed through silica, using ethyl acetate–light petroleum (3:7) as eluant to give the *title ether* (4.75 g, 67%), $\nu_{max.}$(film) 3 075, 2 938, 2 860, 1 706, 1 658, 1 489, 1 430, 1 243, and 1 122 cm^{-1}; δ 1.07 (9 H, s, Bu^t), 1.5—2.2 (4 H, m, 1′-H, 2′-H), 3.63 (3 H, s, MeO), 3.65—3.85 (4 H, m, 6-H, 3′-H), 4.2 (1 H, br s, 3-H), 4.46 and 4.70 (2 H, ABq, *J* 15 Hz, NCH_2), 7.2—7.5 (1 H, m, ArH), and 7.55—7.8 (4 H, m, ArH); *m*/*z* 514 (M^+, 1%), 458 (22), 457 (62), 199 (11), 135 (5), 105 (7), and 91 (100) (Found: M^+, 514.264 71 $C_{31}H_{38}N_2O_3{}^{28}Si$ requires *M*, 514.265 16).

1-*Benzyl*-3-(3′-*hydroxypropyl*)-5-*methoxy*-3,6-*dihydropyrazin*-2(1H)-*one* (**11**).—TBAF (1M in tetrahydrofuran; 10.1 ml) was added to a stirred solution of the silyl ether (**10**) (3.5 g, 6.7 mmol) in tetrahydrofuran (80 ml). After 1.5 h at room temperature the mixture was evaporated and the residue chromatographed through silica, using methanol–ethyl acetate (1:19) as eluant, to afford the *alcohol* (1.67 g, 90%), $\nu_{max.}$(film) 3 420, 2 950, 2 870, 1 705, 1 645, 1 497, 1 447, 1 372, 1 246, and 1 010 cm^{-1}; δ 1.55—2.3 (5 H, m, 1′-H, 2′-H, and OH), 3.5—4.3 (5 H, m, 3-H, 6-H, and 3′-H), 3.66 (3 H, s, MeO), 4.49 and 4.67 (2 H, ABq, *J* 14 Hz, NCH_2), and 7.27 (5 H, s, ArH); *m*/*z* 276 (M^+, 28%), 231 (8), 218 (15), 191 (10), 167 (6), 127 (8), and 91 (100) (Found: M^+, 276.146 85. $C_{15}H_{20}N_2O_3$ requires *M*, 276.147 38).

8-*Benzyl*-9-*methoxy*-2-*oxa*-8,10-*diazabicyclo*[4.2.2]*dec*-9-*en*-7-*one*.—DDQ (1.1 g, 4.8 mmol) was added to a stirred solution of the imino ether (**11**) (1.26 g, 4.6 mmol) in deoxygenated benzene (100 ml) under nitrogen and the mixture heated to reflux for 1.5 h. The mixture was filtered, the filtrate evaporated, and the residue chromatographed through silica, using ethyl acetate as eluant, to yield the *bicyclic ether* (0.585 g, 47%), $\nu_{max.}$($CHCl_3$) 3 005, 2 945, 1 688, 1 663, 1 438, 1 241, 1 119, 1 085, 1 072, 1 049, and 1 005 cm^{-1}; δ 1.5—1.9 (2 H, m, 4-H), 2.0—2.3 (2 H, m, 5-H), 3.4—3.9 (2 H, m, 3-H), 3.70 (3 H, s, MeO), 4.02, 5.18 (2 H, ABq, *J* 15 Hz, NCH_2), 4.45 (1 H, t, *J* 4 Hz, 6-H), 4.95 (1 H, s, 1-H), and 7.26 (5 H, s, ArH); *m*/*z* 274 (M^+, 39%), 245 (7), 216 (6), 183 (7), 141 (11), 126 (13), 112 (27), and 91 (100) (Found: M^+, 274.132 01; $C_{15}H_{18}N_2O_3$ requires *M*, 274.131 73).

Oxidation of the Alcohol (**11**) *with NBS*.—NBS (83 mg, 0.5 mmol) and the imino ether (130 mg, 0.5 mmol) were heated in chloroform (20 ml) under nitrogen at reflux for 30 min. The mixture was then cooled and washed with water (2 × 15 ml) and the aqueous layer re-extracted with dichloromethane (2 × 20 ml). The combined organic extracts were dried and evaporated and the residue was chromatographed through silica, using ethyl acetate as eluant, to give, initially, the bicyclic ether (**12**) (20 mg, 16%), identical with the material described above, followed by the *bicyclic amide* (**17**) (14 mg, 12%), m.p. 199—201 °C (ethyl acetate–light petroleum); $\nu_{max.}$($CHCl_3$) 3 400, 2 940, 2 880, 1 702, 1 685, 1 455, 1 320, 1 090, 1 075, and 1 040 cm^{-1}; δ 1.65—2.0 (2 H, m, 4-H), 2.0—2.3 (2 H, m, 5-H), 3.3—3.7 (1 H, m, 3-H), 3.73—4.10 (1 H, m, 3-H), 4.10 and 5.16 (2 H, ABq, *J* 15 Hz, NCH_2), 4.2 (1 H, br s, 6-H), 5.03 (1 H, s, 1-H), 7.3 (5 H, s, ArH), and 7.62 (1 H, br s, NH); *m*/*z* 260 (M^+, 18%), 189 (4), 164 (9), 106 (25), 98 (16), and 91 (100) (Found: M^+, 260.115 51; $C_{14}H_{16}N_2O_3$ requires 260.116 08).

1-*Benzyl*-3-[3′-(*dimethyl*-t-*butylsilyloxy*)*propyl*]-5-*methoxypyrazin*-2(1H)-*one* (**14**).—DDQ (0.45 g, 2 mmol) was added to a stirred solution of the silyl ether (**10**) (1.03 g, 2 mmol) in benzene (50 ml) under nitrogen and heated to reflux for 1 h. After cooling the reaction mixture was filtered and the filtrate re-filtered through basic alumina, using dichloromethane as solvent. The solvent was removed and the residue chromatographed through silica, using ethyl acetate–light petroleum (1:1) as eluant, to give the *pyrazinone* (0.80 g, 78%), $\nu_{max.}$($CHCl_3$) 3 080, 2 940, 2 865, 1 700, 1 658, 1 600, 1 500, 1 431, 1 324, 1 112, and 925 cm^{-1}; δ 1.04 (9 H, s, Bu^t), 2.03 (2 H, quint., *J* 8 Hz, 2′-H), 2.97 (2 H, t, *J* 8 Hz, 1′-H), 3.70 (3 H, s, MeO), 3.78 (2 H, t, *J* 8 Hz, 3′-H), 5.03 (2 H, s, NCH_2), 6.51 (1 H, s, 6-H), 7.1—7.5 (11 H, m, ArH), and 7.5—7.8 (4 H, m, ArH); *m*/*z* 512 (M^+, 7%), 455 (34), 326 (13), 287 (7), 257 (10), 199 (30), and 91 (100). (Found: M^+, 512.249 73; $C_{31}H_{36}N_2O_3{}^{28}Si$ requires *M*, 512.249 51).

9-*Benzyl*-1-*oxa*-6,9-*diazaspiro*[4.5]*decane*-7,10-*dione* (**16**).—The silyl ether (**14**) (0.614 g, 1.2 mmol) in tetrahydrofuran (25 ml) was stirred at room temperature with TBAF (1M solution in tetrahydrofuran; 2.4 ml). The reaction mixture was diluted with ether (25 ml) and washed with water (2 × 25 ml), backwashing the aqueous layers with ether (2 × 25 ml). The organic extract was dried, and evaporated and the residue chromatographed through silica, using ethyl acetate as eluant, to give 1-*benzyl*-3-(3′-*hydroxypropyl*)-5-*methoxypyrazin*-2(1H)-*one* (**15**) (0.12 g, 36%), $\nu_{max.}$(film) 3 410, 3 095, 2 950, 2 885, 1 652, 1 590, 1 500, 1 445, 1 147, and 1 051 cm^{-1}; δ 2.00 (2 H, quint., *J* 7 Hz, 2′-H), 2.44 (1 H, br s, OH), 3.00 (2 H, t, *J* 7 Hz, 1′-H), 3.66 (2 H, t, *J* 7 Hz, 3′-H), 3.76 (3 H, s, MeO), 5.08 (2 H, s, NCH_2), 6.58 (1 H, s, 6-H), and 7.31 (5 H, s, ArH); *m*/*z* 274 (M^+, 10%), 183 (42), 165 (4), 153 (5), 141 (12), 111 (7), and 91 (100) (Found: M^+, 274.131 73. $C_{15}H_{18}N_2O_3$ requires *M*, 274.131 84). This material proved unstable to storage at room temperature.

The alcohol (0.34 g, 1.2 mmol) in dichloromethane (50 ml) was stirred at room temperature in the presence of Amberlyst A15 resin (H^+ form) for 10 h. The resin was filtered off, the filtrate evaporated, and the residue chromatographed through silica, using ethyl acetate–light petroleum (3:2) as eluant, to afford the title spiro-amide[18] (0.19 g, 59%); $\nu_{max.}$($CHCl_3$) 3 480, 3 000, 1 687, 1 672, 1 492, 1 449, 1 415, and 1 030 cm^{-1}; δ 1.54—2.50 (3 H, m, 3-H and 4-H), 2.80—3.10 (1 H, m, 4-H), 3.7—4.1 (2 H, ABq, *J* 17 Hz, 8-H), 3.9—4.1 (2 H, m, 2-H), 4.6 (2 H, s, NCH_2), and 7.1—7.45 (6 H, m, ArH and NH) (Found: C, 64.5; H, 6.3; N, 10.6. Calc. for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8%).

3-(3′-*Diphenyl*-t-*butylsilyloxy*)*propyl*-2,5-*dimethoxy*-3,6-*dihydropyrazine* (**19**).—The bis imino ether (**18**) (2.0 g, 14 mmol) in tetrahydrofuran (10 ml) was added to a stirred solution of lithium dicyclohexylamide (15 mmol) in tetrahydrofuran (100 ml) at −78 °C under nitrogen and the mixture stirred for 2 h. Hexamethylphosphoramide (4.9 ml, 28 mmol) was added and the mixture stirred for a further 10 min before the temperature was allowed to rise to −40 °C when a solution of the iodosilyl ether (**4**) (11.9 g, 28 mmol) in tetrahydrofuran (30 ml) was added. The reaction mixture was stirred overnight, whilst being allowed to warm to room temperature; it was then quenched

with saturated aqueous ammonium chloride (75 ml) and water (150 ml). The aqueous layer was extracted with ether (2 × 100 ml) and the combined organic layers dried and evaporated. The residue was chromatographed through silica, using ethyl acetate–light petroleum (1:4) as eluant to give the *title product* (5.83 g, 94%), $\nu_{max.}$(film) 3 075, 2 950, 2 860, 1 697, 1 462, 1 430, 1 243, 1 111, and 1 012 cm^{-1}; δ 1.05 (9 H, s, Bu^t), 1.3—2.1 (4 H, m, 1′-H and 2′-H), 3.6—3.75 (2 H, m, 3′-H), 3.65 (6 H, s, 2 × MeO), 3.95—4.25 (3 H, m, 3-H and 6-H), 7.2—7.5 (6 H, m, ArH), and 7.5—7.8 (4 H, m, ArH); *m/z* 438 (M^+, 5%), 381 (100), 213 (53), 183 (24), 141 (18), 119 (14), and 69 (52). (Found: C, 68.7; H, 7.9; N, 6.4. $C_{25}H_{34}N_2O_3Si$ requires C, 68.5; H, 7.8; N, 6.4%).

3-(3′-*Hydroxypropyl*)-2,5-*dimethoxy*-3,6-*dihydropyrazine* (**20**).—TBAF (1M in tetrahydrofuran; 2.4 ml) was added to the silyl ether (**19**) (0.70 g, 1.6 mmol) in tetrahydrofuran (125 ml) and the mixture stirred at room temperature for 1.5 h. The solvent was removed and the residue chromatographed through silica, using methanol–ethyl acetate (1:19) as eluant, to give the *title alcohol* (0.16 g, 49%), $\nu_{max.}$($CHCl_3$) 3 340, 2 995, 2 955, 1 695, 1 441, 1 252, and 910 cm^{-1}; δ 1.45—2.2 (5 H, m, 1′-H, 2′-H, and OH), 3.55—3.9 (2 H, m, 3′-H), 3.7 (6 H, s, 2 × MeO), and 4.02 (3 H, m, 3-H and 6-H); *m/z* 200 (M^+, 11%), 168 (29), 155 (17), 141 (100), 98 (19), 84 (48), 71 (34), and 55 (53) (Found: M^+, 200.116 34; $C_9H_{10}N_2O_3$ requires *M*, 200.116 08).

2-*Methoxy*-6,7-*dihydro*-8H-*pyrano*[2,3-b]*pyrazine* (**21**).—DDQ (0.18 g, 0.8 mmol) was added to a stirred solution of the bis imino ether (**20**) (0.16 g, 0.8 mmol) in benzene (10 ml) under nitrogen at room temperature for 20 min. The reaction mixture was filtered through basic alumina, using dichloromethane as solvent, and the solvent removed. The residue was recrystallised from dichloromethane–light petroleum to yield the *title pyrazine* (0.11 g, 84%), m.p. 59—61 °C; $\nu_{max.}$($CHCl_3$) 2 990, 2 955, 1 475, 1 455, 1 410, 1 368, 1 265, 1 160, and 1 007 cm^{-1}; δ 2.10 (2 H, quint., *J* 6 Hz, 7-H), 2.90 (2 H, t, *J* 6 Hz, 8-H), 3.91 (3 H, s, MeO), 4.31 (2 H, t, *J* 6 Hz, 6-H), and 7.66 (1 H, s, 3-H) (Found: C, 57.8; H, 6.0; N, 17.0. $C_8H_{10}N_2O_2$ requires C, 57.8; H, 6.1; N, 16.9%).

1-*Bromo*-1-*trimethylsilylethylene* (**23**).[19]—Bromine (14.1 ml, 0.27 mol) was added dropwise to a stirred solution of vinyltrimethylsilane (38.5 ml, 0.25 mol) in dichloromethane (100 ml) cooled to −78 °C under nitrogen. The solution was then stirred for a further 10 min and then allowed to warm to room temperature before removal of the solvent. Diethylamine (51.5 ml, 0.5 mol) was added to the yellow residue and the mixture stirred at room temperature for 7 days. It was then diluted with ether (100 ml), filtered, and the precipitate washed with more ether (50 ml). The filtrate was washed with 1M hydrochloric acid (150 ml) and water (2 × 100 ml), the latter being backwashed with ether (2 × 100 ml). The combined organic extracts were dried and evaporated and the residue distilled under reduced pressure to yield the vinyl bromide (25.1 g, 56%), b.p. 50—54 °C at 60 mmHg; $\nu_{max.}$(film) 2 970, 2 900, 1 595, 1 395, 1 252, and 913 cm^{-1}; δ 0.2 (9 H, s, Me_3Si), 6.19 (1 H, d, *J* 2 Hz, 2-H), and 6.27 (1 H, d, *J* 2 Hz, 2-H).

3-*Trimethylsilylbut*-3-*en*-1-*ol* (**24**).—The vinyl bromide (**23**) (15.0 g, 84 mmol) was added dropwise to magnesium turnings (3.02 g, 126 mmol) in tetrahydrofuran (40 ml) at 40 °C under nitrogen; simultaneously, 1,2-dibromoethane (0.3 ml) was added to initiate the reaction. On completion of the addition the mixture was stirred for 1 h at 40 °C before it was allowed to cool to room temperature and more tetrahydrofuran (160 ml) added. The mixture was then added slowly to a suspension of copper(I) iodide (1.59 g, 84 mmol) in tetrahydrofuran (100 ml) at −78 °C. After the mixture had been allowed to warm to −30 °C it was stirred for 30 min and then a solution of ethylene oxide (8.4 ml, p.16 mol) in tetrahydrofuran (30 ml), cooled to −78 °C, was added. The temperature of the reaction mixture maintained at −30 °C for 5 h, before being allowed to rise to room temperature at which temperature it was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (100 ml) and water (2 × 100 ml), the latter then being extracted with ether (3 × 100 ml). The combined organic extracts were dried and evaporated and the residue was chromatographed through silica, using ether–light petroleum (3:7) as eluant, to give the *alcohol* (7.6 g, 63%), b.p. 62—65 °C at 1.7 mmHg; $\nu_{max.}$(film) 3 360, 3 055, 2 965, 1 252, 1 050, and 960 cm^{-1}; δ 0.12 (9 H, s, Me_3Si), 1.5 (1 H, br s, OH), 2.17 (2 H, br t, *J* 8 Hz, 2-H), 3.14 (2 H, t, *J* 8 Hz, 1-H), 5.28 (1 H, d, *J* 4 Hz, 4-H), and 5.47 (1 H, m, 4-H) (Found: C, 58.3; H, 11.2; $C_7H_{16}OSi$ requires C, 58.3; H, 11.1%).

4-(*Dimethyl-t-butylsilyloxy*)-2-*trimethylsilylbut*-1-*ene* (**25**).—Imidazole (7.9 g, 0.116 mol) and dimethyl-t-butylsilyl chloride (8.75 g, 59 mmol) were added to a stirred solution of the alcohol (**24**) (7.6 g, 59 mmol) in dimethylformamide (150 ml) under nitrogen and the mixture stirred at room temperature for 24 h. The reaction mixture was diluted with hexane (300 ml) and washed with water (3 × 100 ml) and the aqueous layer was extracted with hexane (2 × 100 ml). The combined organic extracts were dried and evaporated to yield the *silyl ether* (13.7 g, 100%), b.p. 79 °C at 2 mmHg; $\nu_{max.}$(film) 3 055, 2 960, 2 860, 1 472, 1 253, 1 100, and 840 cm^{-1}; δ 0.05 (15 H, s, Me_2Si, Me_3Si), 0.90 (9 H, s, Bu^t), 2.30 (2 H, br t, *J* 8 Hz, 3-H), 3.6 (2 H, t, *J* 8 Hz, 4-H), 5.40 (1 H, d, *J* 4 Hz, 1-H), and 5.58 (1 H, m, 1-H) (Found: C, 60.6; H, 11.8; $C_{13}H_{30}OSi_2$ requires C, 60.4; H, 11.7%).

1-(*Dimethyl-t-butylsilyloxy*)-3-*iodo*-3-*trimethylsilyl*-4-(p-*tolylsulphonyl*)*butane* (**26**).—Toluene-*p*-sulphonyl iodide (19.3 g, 68 mmol) was added to a stirred solution of the butene (**25**) (13.7 g, 53 mmol) in dichloromethane (300 ml) and α,α-azoisobutyronitrile (5 mg, catalyst) added. The solution was stirred at room temperature for 5 h after which it was washed with saturated aqueous sodium thiosulphate (2 × 50 ml) and water (2 × 100 ml), the latter being back washed with dichloromethane (2 × 100 ml). The combined organic layers were dried and evaporated to yield the iodobutane (29.8 g, 100%), $\nu_{max.}$(film) 2 955, 2 855, 1 595, 1 470, 1 325, 1 252, 1 150, and 1 087 cm^{-1}; δ 0.09 (6 H, s, Me_2Si), 0.37 (9 H, s, Me_3Si), 0.90 (9 H, s, Bu^t), 2.2—2.5 (2 H, m, 2-H), 2.46 (3 H, s, Me), 3.8—4.1 (4 H, m, 1-H, 1-H), 7.39 (2 H, d, *J* 8 Hz, ArH), and 7.82 (2 H, d, *J* 8 Hz, ArH); *m/z* 483 (1.5%), 355 (2), 303 (4), 213 (12), 201 (15), and 147 (100).

(1Z)-4-(*Dimethyl-t-butylsilyloxy*)-2-*trimethylsilyl*-1-(p-*tolylsulphonyl*)*but*-1-*ene* Z-(**27**).—1,4-Diazabicyclo[2.2.2]octane (4.00 g, 36 mmol) was added to a stirred solution of the iodobutane (**26**) (9.65 g, 18 mmol) in tetrahydrofuran (125 ml) and the mixture left for 45 min at room temperature. It was then diluted with ether (125 ml) and washed with water (2 × 150 ml). The aqueous layer was extracted with ether (2 × 100 ml) and the combined organic layers were dried and evaporated. Chromatography of the residue through silica, using ethyl acetate–light petroleum (1:9) as eluant, afforded the Z-*olefin* (6.12 g, 83%), $\nu_{max.}$(film) 2 955, 2 860, 1 597, 1 323, 1 253, 1 152, 1 090, and 842 cm^{-1}; δ −0.05 (6 H, s, Me_2Si), 0.36 (9 H, s, Me_3Si), 0.79 (9 H, s, Bu^t), 2.43 (3 H, s, Me), 2.46 (2 H, dt, *J* 6.3 and 1.2 Hz, 3-H), 3.62 (2 H, t, *J* 6.3 Hz, 4-H), 6.64 (1 H, t, *J* 1.2 Hz, 1-H), 7.31 (2 H, d, *J* 8.3 Hz, ArH), and 7.75 (2 H, d, *J* 8.3 Hz, ArH) (Found: C, 58.2; H, 8.8; S, 7.5; $C_{20}H_{36}O_3SSi_2$ requires C, 58.2; H, 8.7; S, 7.8%).

(1E)-*Olefin* E-(**27**).—1,8-Diazabicyclo[5.4.0]undec-7-ene (0.055 ml, 0.4 mmol) was added to a stirred solution of the iodobutane (**26**) (0.10 g, 0.2 mmol) in tetrahydrofuran (10 ml) at room temperature. After 30 min the reaction mixture was diluted with ether (10 ml) and washed with water (2 × 10 ml). The aqueous layer was extracted with ether (2 × 10 ml) and the combined organic extracts were dried and evaporated. Chromatography of the residue through silica afforded the E-*olefin* (59 mg, 77%); δ 0.07 (6 H, s, Me_2Si), 0.13 (9 H, s, Me_3Si), 0.89 (9 H, s, Bu^t), 12.44 (3 H, s, Me), 2.95 (2 H, br t, *J* 7.2 Hz, 3-H), 3.68 (2 H, t, *J* 7.2 Hz, 4-H), 6.45 (1 H, br s, 1-H), 7.3 (2 H, d, *J* 8.1 Hz, ArH), and 7.79 (2 H, d, *J* 8.1 Hz, ArH) (Found: M^+, 412.189 76. $C_{20}H_{36}O_3S^{28}Si_2$ requires *M*, 412.192 36).

Preparation of 5-*Methoxy*-1-(4-*methoxybenzyl*)-3,6-*dihydropyrazin*-2(1H)-*one* (**28**).—A solution of chloroacetyl chloride (14.0 ml, 0.175 mol) in ether (30 ml) was added dropwise over 1.5 h to a stirred solution of *N*-(4-methoxybenzyl)glycine ethyl ester[20] (37.3 g, 0.17 mol) and ethyldi-isopropylamine (29.1 ml, 0.17 mol) in ether (150 ml) at −10 °C under nitrogen. After addition the solution was stirred for a further 1 h at −10 °C before being allowed to warm to room temperature and stirred for a further 4 h. The reaction mixture was quenched with water and the organic layer dried and evaporated. Chromatography of the residue through silica, using ethyl acetate–light petroleum (1:1) as eluant, yielded N-*chloroacetyl*-N-(4-*methoxybenzyl*)-*glycine ethyl ester* (51.2 g, 100%), b.p. 110 °C at 2 mmHg; $\nu_{max.}$(film) 2 985, 2 840, 1 743, 1 662, 1 512, 1 315, 1 250, and 1 030 cm^{-1}; δ 1.28 (3 H, t, *J* 7 Hz, Me), 3.83 (3 H, s, MeO), 4.05 (2 H, s, CH_2), 4.20 (2 H, q, *J* 7 Hz, CH_2), 4.28 (2 H, s, CH_2), 4.65 (2 H, s, CH_2), 6.90 (2 H, d, *J* 9 Hz, ArH), and 7.23 (2 H, d, *J* 9 Hz, ArH) (Found: M^+, 299.092 33. $C_{14}H_{18}{}^{35}ClNO_4$ requires M^+, 299.092 43).

A stream of ammonia was passed through a solution of the chloroacetyl derivative (51.2 g, 0.17 mol) in methanol (200 ml) at −20 °C until the latter was saturated. The reaction mixture was stirred for a further 1 h and then allowed to warm to room temperature and left for a further 24 h. The precipitate that formed was collected, washed with a little methanol, and then dried to yield 1-(4-*methoxybenzyl*)*piperazine*-2,5-*dione* (31.4 g, 79%), m.p. 230–232 °C; $\nu_{max.}$(Nujol) 3 250, 1 688, 1 657, 1 515, 1 379, 1 329, and 1 248 cm^{-1} δ($CDCl_3$–CD_3OD, 2:1) 3.81 (3 H, s, MeO), 3.84 (2 H, t, *J* 1.4 Hz, CH_2), 4.02 (2 H, t, *J* 1.4 Hz, CH_2), 4.54 (2 H, s, NCH_2), 6.90 (2 H, d, *J* 8.8 Hz, ArH), 7.2 (2 H, d, *J* 8.8 Hz, ArH), and 7.4 (1 H, s, NH) (Found: C, 61.4; H, 6.0; N, 11.8. $C_{12}H_{14}N_2O_3$ requires C, 61.5; H 6.0; N, 12.0%).

The piperazinedione (15.0 g, 64 mmol) was added to a stirred solution of trimethyloxonium tetrafluoroborate (18.9 g, 128 mmol) in nitromethane (300 ml) under nitrogen and the mixture stirred at room temperature for 7 days. It was then poured slowly into saturated aqueous sodium hydrogen carbonate (200 ml) and the aqueous layer extracted with dichloromethane (2 × 100 ml). The combined organic layers were dried and evaporated and the residue chromatographed through silica, using methanol–dichloromethane (1:19) as eluant to give the *title imino ether* (10.4 g, 65%), m.p. 109—110 °C; $\nu_{max.}$($CHCl_3$) 3 010, 2 840, 1 703, 1 650, 1 515, 1 248, and 1 037 cm^{-1}; δ 3.67 (3 H, s, MeO), 3.78 (2 H, t, *J* 2.8 Hz, CH_2), 3.80 (3 H, s, MeO), 4.21 (2 H, t, *J* 2.8 Hz, CH_2), 4.54 (2 H, s, NCH_2), 6.85 (2 H, d, *J* 8.7 Hz, ArH), and 7.20 (2 H, d, *J* 8.7 Hz, ArH) (Found: C, 63.0; H, 6.6; N, 11.3. $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.5; N, 11.3%).

Conjugate Additions of the Olefin Z-(**27**).—(a) *With the mono imino ether* (**28**). A solution of the imino ether (0.54 g, 2.2 mmol) in tetrahydrofuran (4 ml) was added dropwise to a stirred solution of lithium dicyclohexylamide (2.3 mmol) in tetrahydrofuran (50 ml) at −78 °C under nitrogen. The solution was stirred for 1.5 h at −78 °C and then allowed to warm to −40 °C when a solution of the *Z*-olefin (0.56 g, 1.4 mmol) in tetrahydrofuran (3 ml) was added: the solution was then stirred at −40 °C for 2 days. The reaction mixture was quenched with methanol (2 ml) at −40 °C before saturated aqueous ammonium chloride (50 ml) was added. The reaction mixture was allowed to warm to 0 °C, when the phases were separated, the organic phase washed with water (2 × 50 ml) and the latter back washed with ether (2 × 100 ml). The combined organic phases were dried and evaporated. Chromatography of the residue through silica, using ethyl acetate–light petroleum (1:4) as eluant gave the adduct (**29**) as a mixture of diastereoisomers (0.47 g, 53%), $\nu_{max.}$($CHCl_3$) 3 010, 2 960, 2 860, 1 710, 1 648, 1 515, 1 250, 1 150, 1 090, 1 011, and 840 cm^{-1} (Found: M^+, 660.309 42; $C_{33}H_{52}N_2O_6S^{28}Si_2$ requires *M*, 660.308 44).

(b) *With* 1,4-*dibenzylpiperazine*-2,5-*dione* (**3**). In a similar manner to the above reaction, the piperazinedione (0.50 g, 1.7 mmol) was treated with the olefin (0.35 g, 0.9 mmol), using lithium di-isopropylamide (1.8 mmol) as base, at −40 °C for 3 days. After work-up the crude material was taken up in the minimum volume of ether and the recovered piperazinedione (0.29 g, 57%) filtered off. The filtrate was dried and evaporated and the residue chromatographed through silica, using ethyl acetate–light petroleum (1:4) as eluant, to yield, initially, recovered *Z*-olefin (**27**) (0.18 g, 52%, followed by the adduct (**31**) (0.46 g, 8%); $\nu_{max.}$($CHCl_3$) 3 010, 2 960, 2 860, 1 653, 1 495, 1 452, 1 252, 1 135, 1 086, and 840 cm^{-1} (Found: M^+, 706.329 54. $C_{38}H_{54}N_2O_5S^{28}Si_2$ requires *M*, 706.329 54).

(c) *With the bis imino ether* (**18**). In a similar manner to the above reactions, the bis imino ether (0.20 g, 1.4 mmol) was treated with the olefin (0.29 g, 0.7 mmol) using lithium dicyclohexylamide as base. After work-up the residue was chromatographed through silica, using ethyl acetate–light petroleum (1:19 ⟶ 1:4) as eluant, to give, initially, 2,5-dimethoxypyrazine (**33**) (0.041 g, 21%), δ 3.90 (6 H, s, MeO) and 7.75 (2 H, s, ArH), followed by 1-(*dimethyl-t-butylsilyloxy*)-3-*trimethylsilyl*-4-(p-*tolylsulphonyl*)*butane* (**34**) (0.13 g, 44%), b.p. 173–175 °C, 0.1 mmHg; $\nu_{max.}$($CHCl_3$) 3 015, 2 955, 2 855, 1 596, 1 470, 1 315, 1 302, 1 253, 1 145, 1 087, and 840 cm^{-1}; δ 0.03 (6 H, s, Me_2Si), 0.05 (9 H, s, Me_3Si), 0.90 (9 H, s, Bu^t), 1.33 (1 H, quint., *J* 7 Hz, 3-H), 1.82 (2 H, q, *J* 7 Hz, 2-H), 2.46 (3 H, s, Me), 3.12 (2 H, m, 4-H), 3.67 (2 H, t, *J* 7 Hz, 1-H), 7.37 (2 H, d, *J* 9 Hz, ArH), and 7.81 (2 H, d, *J* 9 Hz, ArH) (Found: C, 58.1; H, 9.2; S, 7.3. $C_{20}H_{38}O_3SSi_2$ requires C, 57.9; H, 9.2; S, 7.7%).

The last fraction eluted from the column was the *conjugate* (**32**), obtained as a mixture of diastereoisomers (72 mg, 18%), $\nu_{max.}$($CHCl_3$) 2 950, 2 855, 1 692, 1 596, 1 460, 1 437, 1 318, 1 248, 1 150, 1 090, 1 008, and 840 cm^{-1} (Found: M^+, 554.264 29; $C_{26}H_{46}N_2O_5SSi_2$ requires *M*, 554.266 58).

Repetition of the reaction using the *E*-isomer of (**27**) (1 mmol scale) afforded, as the principal product the adduct (**32**) (30%) as a similar mixture of diastereoisomers.

Non-selective Deprotection of the Adduct (**29**).—TBAF (1M solution in THF; 0.81 ml) was stirred with the adduct (0.36 g, 0.54 mmol) in tetrahydrofuran (20 ml) at room temperature for 5 h. The solvent was removed and the residue chromatographed through silica, using ethyl acetate–light petroleum (3:2) as eluant, to yield, in order of elution: 3-[3′-(*dimethyl-t-butylsilyloxy*)-1′-*methylenepropyl*]-5-*methoxy*-1-(4-*methoxybenzyl*)-3,6-*dihydropyrazin*-2(1H)-*one* (**35**) (21 mg, 9%), $\nu_{max.}$($CHCl_3$) 3 010, 2 960, 2 860, 1 700, 1 653, 1 515, 1 445, 1 250, 1 179, 1 098, 1 038, 1 011, and 838 cm^{-1}; δ 0.06 (6 H, s, Me_2Si), 0.91 (9 H, s, Bu^t), 2.45 (2 H, br t, *J* 7 Hz, 2′-H), 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 3.7—4.15 (4 H, m, 6-H and 3′-H), 4.48 and 4.68 (2 H, ABq, *J* 15 Hz, NCH_2), 4.76 (1 H, s, 3-H), 5.0 (1 H, s, HC=C), 5.50 (1 H, s, HC=C), 6.91 (2 H, d, *J* 9 Hz, ArH), and 7.24 (2 H, d, *J* 9 Hz, ArH)

(Found: M^+, 432.244 15. $C_{23}H_{26}N_2O_4{}^{28}Si$ requires M, 432.244 42).

(2'E)-3-(4'-*Hydroxybut*-2-*ylidene*)-5-*methoxy*-1-(4-*methoxybenzyl*)-3,6-*dihydropyrazin*-2(1H)-*one* (**36**) (25 mg, 14%), $\nu_{max.}$($CHCl_3$) 3 350, 3 010, 2 950, 1 681, 1 641 1 611, 1 515, 1 481, 1 438, 1 251, 1 179, 1 149, 1 105, 1 035, and 893 cm^{-1}; δ 2.10 (3 H, s, Me), 2.48 (1 H, s, OH), 2.95 (2 H, t, *J* 7 Hz, 3'-H), 3.7—4.05 (4 H, m, 6-H and 4'-H) 3.69 (3 H, s, MeO), 3.82 (3 H, s, MeO), 4.60 (2 H, br s, NCH_2), 6.90 (2 H, d, *J* 7 Hz, ArH), and 7.24 (2 H, d, *J* 7 Hz, ArH) (Found: M^+, 318.158 44; $C_{17}H_{22}N_2O_4$ requires *M*, 318.157 95).

(2'Z)-3-(4'-*Hydroxybut*-2-*ylidene*)-5-*methoxy*-1-(4-*methoxybenzyl*)-3,6-*dihydropyrazin*-2(1H)-*one* (**37**) (30 mg, 17%), $\nu_{max.}$($CHCl_3$) 3 350, 3 010, 2 950, 1 681, 1 630, 1 510, 1 481, 1 250, and 1 180 cm^{-1}; δ 2.43 (3 H, s, Me), 2.78 (2 H, t, *J* 7 Hz, 3'-H), 3.0 (1 H, br s, OH), 3.7—4.0 (4 H, m, 6-H and 4'-H), 3.78 (3 H, s, MeO), 3.81 (3 H, s, MeO), 4.59 (2 H, s, NCH_2), 6.90 (2 H, d, *J* 9 Hz, ArH), and 7.25 (2 H, d, *J* 9 Hz, ArH).

3-[4'-*Hydroxy*-1'-(p-*tolylsulphonyl*)-2'-*trimethylsilylbutan*-2'-*yl*]-5-*methoxy*-1-(4-*methoxybenzyl*)-3,6-*dihydropyrazin*-2(1H)-*one* (**30**).—Acetic acid (0.75 ml, 13 mmol), TBAF (6.6 ml, 6.6 mmol), and the adduct (**29**) (0.87 g, 1.3 mmol) were stirred in tetrahydrofuran (15 ml) at room temperature for 5 h. Most of the solvent was removed and the residue filtered through silica, using ethyl acetate–light petroleum (1:1) as eluant, to give the *title alcohol* as a mixture of diastereoisomers (0.61 g, 85%); $\nu_{max.}$($CHCl_3$) 3 320, 3 010, 2 955, 1 710, 1 648, 1 513, 1 250, 1 150, 1 090, 1 037, and 845 cm^{-1}; δ 0.23, 0.28 (9 H, s, Me_3Si), 2.4—2.9 (3 H, m, 3'-H, OH), 2.48 (3 H, s, Me), 3.26 (1 H, part of ABq, *J* 16 Hz, 1'-H), 3.6—4.2 (5 H, m, 6-H, 4'-H, and 1'-H), 3.79 (3 H, s, MeO), 3.83 (3 H, s, MeO), 4.58 (2 H, br s, NCH_2), 4.93 (1 H, t, *J* 3 Hz, 3-H), 6.92 (2 H, d, *J* 9 Hz, ArH), and 7.28 (2 H, d, *J* 9 Hz, ArH); *m/z* 546 (M^+, 0.1%), 391 (1), 361 (6), 300 (4.5), 228 (6), 180 (5), 149 (12), and 121 (100) (Found: M^+, 546.221 71; $C_{27}H_{38}N_2O_6S^{28}Si$ requires *M*, 546.221 97).

9-*Methoxy*-8-(4-*methoxybenzyl*)-5-*trimethylsilyl*-5-[(p-*tolylsulphonyl*)*methyl*]-2-*oxa*-8,10-*diazabicyclo*[4.2.2]*dec*-9-*en*-7-*one* (**38**) *and* (**39**).—DDQ (0.27 g, 1.2 mmol) was added to a stirred solution of the alcohol (**30**) (0.59 g, 1.1 mmol) in benzene (40 ml) under nitrogen and the mixture heated to reflux for 40 min. The reaction mixture was cooled, filtered, and the precipitate washed with benzene. The filtrate was evaporated and the residue filtered through basic alumina, using dichloromethane as eluant. The solvent was removed and the crude product chromatographed through silica, using ethyl acetate–light petroleum (3:7) as eluant, to give the products (**38**) and (**39**) as an isomeric mixture (2:1) (0.364 g, 62%). A sample of this material was separated by preparative t.l.c. The major isomer, assigned structure (**38**), showed $\nu_{max.}$($CHCl_3$) 3 000, 2 945, 1 685, 1 655, 1 508, 1 459, 1 297, 1 245, 1 145, 1 065, and 840 cm^{-1}; δ 0.3 (9 H, s, Me_3Si), 2.23 (2 H, dt, *J* 17 and 6 Hz, 4-H), 2.50 (3 H, s, Me), 3.42 (2 H, s, 5-CH_2), 3.7—4.0 (2 H, m, 3-H), 3.80 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.18 and 4.97 (2 H, d, *J* 16 Hz, NCH_2), 4.53 (1 H, s, 6-H), 4.99 (1 H, s, 1-H), 6.93 (2 H, d, *J* 9 Hz, ArH), 7.30 (2 H, d, *J* 9 Hz, ArH), 7.46 (2 H, d, *J* 8 Hz, ArH), and 7.93 (2 H, d, *J* 8 Hz, ArH) (Found: M^+, 544.206 58; $C_{27}H_{36}N_2O_6S^{28}Si$ requires *M*, 544.221 97.

The *minor isomer* (**39**) showed $\nu_{max.}$($CHCl_3$) 3 000, 2 940, 1 688, 1 664, 1 508, 1 459, 1 299, 1 244, 1 146, 1 066, and 842 cm^{-1}; δ 0.31 (9 H, s, Me_3Si), 2.45—2.15 (2 H, m, 4-H), 2.48 (3 H, s, Me), 2.98, 3.73 (2 H, ABq, *J* 16 Hz, 5-CH_2), 3.29—3.6 (1 H, m, 3-H), 3.6—4.0 (1 H, m, 3-H), 3.70 (3 H, s, MeO), 3.84 (3 H, s, MeO), 4.09 and 5.10 (2 H, ABq, *J* 16 Hz, NCH_2), 5.03 (1 H, s, 6-H), 5.27 (1 H, s, 1-H), 6.94 (2 H, d, *J* 9 Hz, ArH), 7.33 (2 H, d, *J* 9 Hz, ArH), 7.41 (2 H, d, *J* 8 Hz, ArH), and 7.99 (2 H, d, *J* 8 Hz, ArH) (Found: M^+, 544.206 04. $C_{27}H_{36}N_2O_6S^{28}Si$ requires *M*, 544.206 32).

9-*Methoxy*-8-(4-*methoxybenzyl*)-5-*methylene*-2-*oxa*-8,10-*diazabicyclo*[4.2.2]*dec*-9-*en*-7-*one* (**40**).—TBAF (2.4 ml, 2.4 mmol) was added to a stirred solution of the 1:2 mixture of isomers (**38**) and (**39**) (0.635 g, 1.2 mmol) in tetrahydrofuran (25 ml) and the mixture stirred at room temperature for 2 h. The solvent was removed and the residue chromatographed through silica, using ethyl acetate–light petroleum (2:3) as eluant, to give the *title olefin* (0.324 g, 89%), $\nu_{max.}$($CHCl_3$) 3 010, 2 950, 1 687, 1 670, 1 515, 1 462, 1 250, 1 180, 1 072, and 921 cm^{-1}; δ 2.32—2.47 (2 H, m, 4-H), 3.45 (1 H, ddd, *J* 1.4, 9.0, and 13.0 Hz, 3-H), 3.73—3.82 (2 H, m, 4-H), 3.74 (3 H, s, MeO), 3.80 (3 H, s, MeO), 4.01 and 5.08 (2 H, ABq, *J* 14.5 Hz, NCH_2), 4.91 (1 H, s, 6-H), 5.02 (1 H, s, 1-H), 5.03 (1 H, br s, HC=C), 5.31 (1 H, br s, HC=C), 6.86 (2 H, d, *J* 8.7 Hz, ArH), and 7.22 (2 H, d, *J* 8.7 Hz, ArH) (Found: M^+, 316.142 47. $C_{17}H_{20}N_2O_4$ requires *M*, 316.142 30).

Conversion of the Imino Ether (**40**) *into the Amide* (**2**).—The imino ether (0.37 g, 1.2 mmol) was stirred with toluene-*p*-sulphonic acid hemihydrate (0.09 g, 0.5 mmol) in dichloromethane (8 ml) and water (0.5 ml) at room temperature for 5 days. The aqueous phase was separated off and the organic phase washed with water (1 ml), dried, and evaporated to provide a residue which was chromatographed through silica, using methanol–dichloromethane (1:9) as eluant, to yield 8-(4-*methoxybenzyl*)-5-*methylene*-2-*oxa*-8,10-*diazabicyclo*[4.2.2]-*decane*-7,9-*dione* (0.26 g, 73%), m.p. 149—150 °C (from ethyl acetate–light petroleum; $\nu_{max.}$($CHCl_3$) 3 395, 3 010, 2 940, 2 840, 1 692, 1 612, 1 515, 1 452, 1 298, 1 248, 1 078, and 910 cm^{-1} (Found: C, 63.5; H, 6.0; N, 9.3. $C_{16}H_{18}N_2O_4$ requires C, 63.5; H, 6.0; N, 9.3%).

The latter amide (0.10 g, 0.3 mmol) in dimethylformamide (3 ml) under nitrogen was treated with sodium hydride (60% dispersion in mineral oil; 16 mg, 0.4 mmol), with stirring at room temperature for 75 min. 4-Methoxybenzyl bromide (0.13 g, 0.7 mmol) was then added and the mixture stirred for a further 2 h before being quenched with water (10 ml) and extracted with ether (3 × 25 ml). The combined organic extracts were washed with more water, dried and evaporated. The residue was purified by chromatography through silica using ethyl acetate–light petroleum (1:1) as eluant, to give the bicyclic piperazinedione (**2**) (0.12 g, 81%), m.p. 111—113 °C (lit.,[5] 112—113 °C); $\nu_{max.}$($CHCl_3$) 3 010, 2 960, 2 840, 1 678, 1 612, 1 572, 1 452, 1 248, 1 078, and 1 036 cm^{-1} (Found: C, 68.5; H, 6.2; N, 6.6. Calc. for $C_{24}H_{26}N_2O_5$: C, 68.2; H, 6.2; N, 6.6%).

Acknowledgements

We thank the S.E.R.C. for support of this work.

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Received 19*th January* 1988; *Paper* 8/00157J