Synthesis of 6-alkyl analogues of the 1-azabicyclo[4.3.0]nonan-2-one system by a strategy of geminal acylation and Beckmann rearrangement

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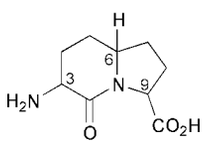
Compounds with the 1-azabicyclo[4.3.0]nonan-2-one nucleus have been prepared with methyl and isobutyl groups at C-6. The synthetic sequence was: geminal acylation to produce a but-2-enylcyclopentane-1,3-dione derivative, treatment with *O*-mesitylenesulfonylhydroxylamine and then Beckmann rearrangement with $BF_3{\cdot}Et_2O$ and cyclization of the amidic nitrogen onto the terminal double bond. In addition, the results of exploratory reactions are presented.

Introduction

The 1-azabicyclo[4.3.0]nonane (indolizidine) system is the annular portion of a rapidly growing group of biologically important molecules.[1] These are usually lactams that carry a substituent (often an amino group) at C-3 and a carboxylate at C-9. Compound **1** is a prototypical structure. Some naturally occurring compounds possessing this ring system, such as the powerful ACE-inhibitor (−)-A58365A (**2**), have been isolated,[2] but at present most research activity involving **1** centres on the use of synthetic analogues of **1** as templates for the design of conformationally restricted ("β-turn") dipeptide mimics. The synthetic variants of **1** include compounds of different ring sizes, with replacement of annular carbons by heteroatoms, with substitution at almost every position, and with many stereochemical alternatives.[1,3] In spite of this, substitution at C-6 of the 1-azabicyclo[4.3.0]nonane system has not been reported, even though Meyers[4] has exploited enantiomerically enriched 6-alkyl-1-aza-6-oxabicyclo[4.3.0]nonan-2-ones in the asymmetric synthesis of very diverse types of molecules. The effect of substitution at C-6 in molecules such as **1** would be of considerable pharmacological interest, and the biological activities of such molecules might provide insight into the modes of activity of pharmacological agents of this general structure.



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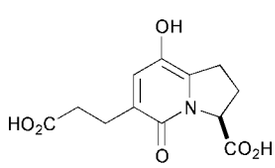

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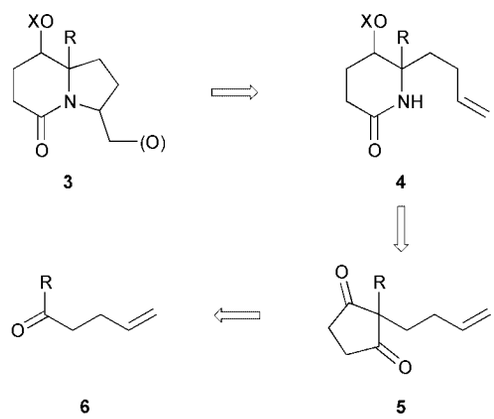
A common synthetic approach to molecules containing the 1-azabicyclo[4.3.0]nonan-2-one nucleus is to derive key carbons and the absolute stereochemistry from proline, glutamic acid, pyroglutamic acid or, for sulfur-containing analogues, cysteine. Beginning a synthesis with an amino acid might be a stereochemically assured process, but this approach does not readily allow substitution at C-6. In this paper we disclose for the first time access to 6-alkyl-substituted analogues of the 1-azabicyclo[4.3.0]nonane system. The approach differs very markedly from previous syntheses of these molecules.

Results and discussion

Retrosynthetic analysis

The approach to the 1-azabicyclo[4.3.0]nonan-2-one nucleus that is outlined retrosynthetically in Scheme 1 was designed to



Scheme 1 Retrosynthetic analysis.

introduce an alkyl substituent at C-6. This approach has three key steps. The five-membered ring of **3** could arise by closure onto the terminal double bond of **4**. Beckmann rearrangement would expand the cyclopentanedione moiety of **5** to the keto-lactam **4** and the cyclopentanedione ring of **5** would be produced by geminal acylation of ketone **6** or an acetal derived from **6**. A host of ketones such as **6** could be produced by the addition of an organometallic onto commonly available aldehydes, followed by oxidation. Although both geminal acylation and Beckmann rearrangements have been studied quite thoroughly, the reactions shown in Scheme 1 present particular difficulties that were explored in preliminary studies.

Geminal acylation

The Lewis acid catalyzed geminal acylation using 1,2-bis-[(trimethylsilyl)oxy]cyclobutene (**7**)[5–11] or methylated analogues such as **8**[11–13] is now a well-established process for the formation of a 2,2-disubstituted cyclopentane-1,3-dione. Geminal acylation using **7** has been exploited in the syntheses of a number

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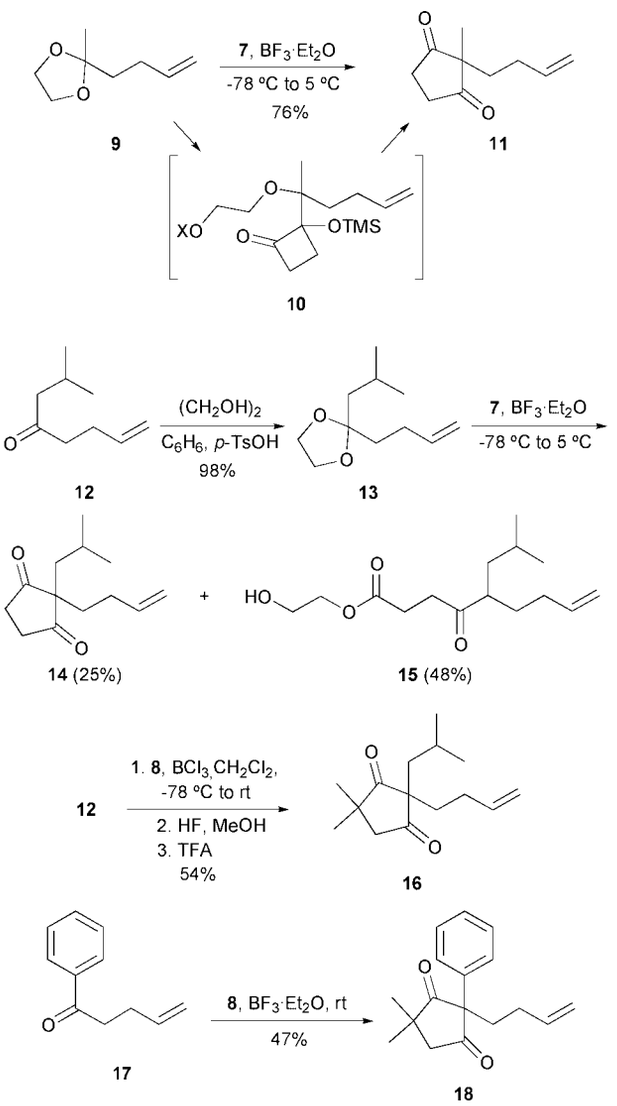
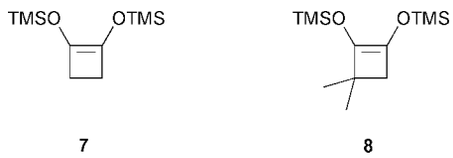
of natural products and other structurally interesting molecules.[6,14] In the present study, simple compounds resembling **5** were envisaged with R being methyl, isobutyl, phenyl and terminally substituted alkyl. It seemed that this last type might be prepared by cleavage of a substituted ring after geminal acylation, to give a spirocyclic diketone, and Beckmann rearrangement. Spirocyclic diketones can generally be prepared in high yield with **7**.[6–8] Geminal acylation with γ,δ-unsaturated acyclic ketones or acetals is a very poor process, which has been recognized for some time with ketones.[8] Curran and coworkers[9] showed that this is the result of acid-promoted cyclization onto the double bond that can occur at temperatures not much above 0 °C. By following Curran's example of quenching the reaction at 5 °C,[9] the acetal **9** with **7** in the presence of $BF_3{\cdot}Et_2O$ provided the desired diketone **11** (*i.e.*, **5** with R = Me) in 76% yield (*via* the cyclobutanone **10**). It was disappointing that when the same procedure was applied to the reaction of acetal **13** (prepared from the ketone **12**) with **7**, the diketone **14** (**5** with R = isobutyl) was obtained in only 25% yield (Scheme 2).



Scheme 2 Geminal acylation reactions.

The problem was not the cyclization onto the double bond, but acid-mediated rupture of the cyclopentanedione of **14** to give, in 48% yield, the γ-keto-ester **15**. This sort of fragmentation can be promoted by using tin(IV) chloride as the Lewis acid,[15] and it had been problematic in geminal acylation reactions that furnished some encumbered acyclic diketones[7] and strained bicyclic diketones.[10] The use of different acetals[7] and variations to the reaction conditions failed to improve the yield of **14**. The reactions of **8** are usually slower and lower in yield than those with **7**, but it was found that by using the ketone as the substrate, not the acetal, and by using BCl_3 in the place of $BF_3{\cdot}Et_2O$ one can obtain good yields of geminal acylation products with **8**.[13] When the ketone **12** was reacted with **8** using BCl_3 to mediate the initial carbon–carbon bond formation, diketone **16** was obtained in 54% yield. (This procedure did not improve yields with **7**.) The geminal acylation of aromatic ketones is known to be quite different from the reactions of other ketones.[11] In this instance, the aromatic ketone **17** with **8** in the presence of $BF_3{\cdot}Et_2O$ provided a modest amount of **18**.



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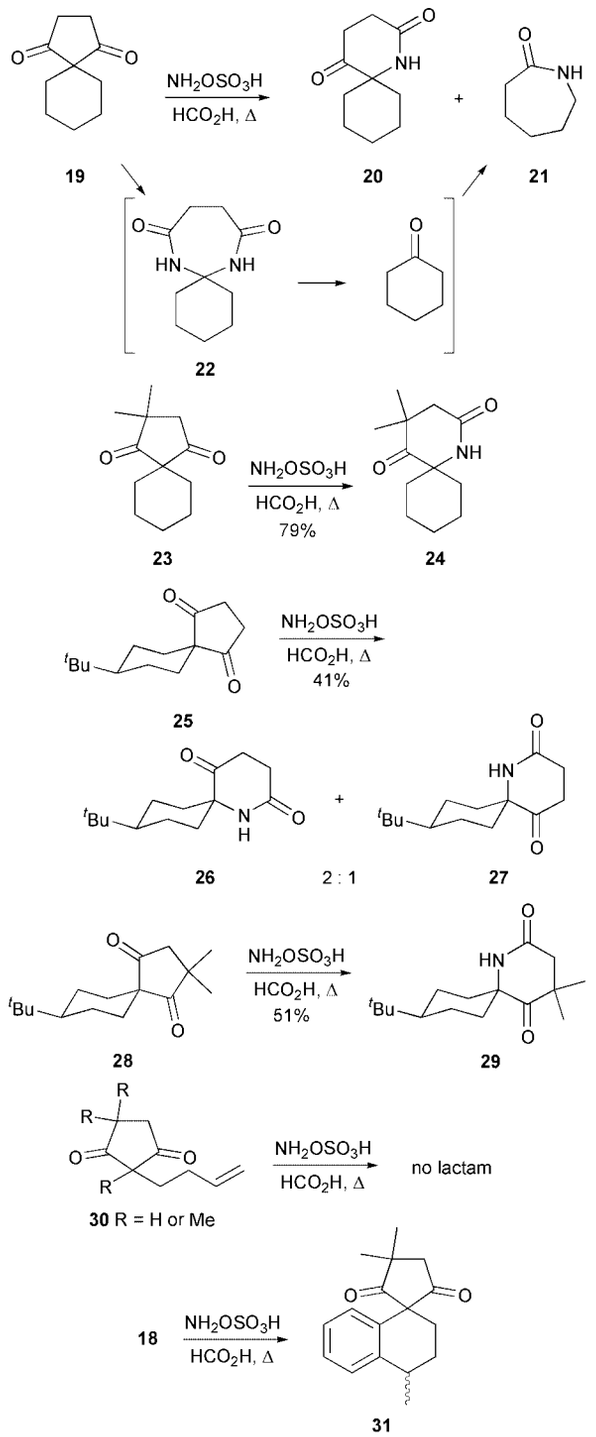
Beckmann rearrangement

A perusal of the literature did not reveal examples of Beckmann rearrangements involving 1,3-diketones. Therefore, the 1,3-diketones shown in Scheme 2 and others that had also been produced by geminal acylation with **7** and **8**,[7,8,13] were subjected to standard Beckmann conditions. In an initial experiment, following the procedure of Ganboa and Palomo,[16] the oxime of the spirocyclic diketone **19** was rearranged under catalysis with triflic acid.† This gave the desired keto-lactam **20** in only 17% yield, and none of the starting diketone or the oxime was recovered. The use of hydroxylamine *O*-sulfonic acid, as described by Olah,[17] was studied in more detail (Scheme 3). Yields of **20** were sensitive to both the number of equivalents of hydroxylamine *O*-sulfonic acid and the concentration of the diketone in the solution. At a concentration of less than 0.4 mmol ml^{-1}, **19** with 1.5 equivalents of hydroxylamine *O*-sulfonic acid gave only small amounts of lactam **20**, and much **19** was returned. At a concentration of 0.4 mmol ml^{-1}, under conditions that were otherwise the same (reflux *ca.* 20 hours), the yield of **20** rose to 46%, but a second product was evident in 9% yield. This proved to be ε-caprolactam **21**. Its presence could be rationalized by Beckmann rearrangement of cyclohexanone generated by hydrolysis of a bis-lactam **22**. Maintaining the concentration of **19** at 0.4 mmol ml^{-1} while increasing the amount of hydroxylamine *O*-sulfonic acid to 3 equivalents led to the major product being **21** (78%). On the other hand, when the formation of a bis-lactam was discouraged sterically in the *gem*-dimethyl diketone **23** the Beckmann product **24** was obtained in 79% yield. The conformationally restrained spirocyclic diketone **25** provided the equatorial (**26**) and axial (**27**) lactams in a 2 : 1 ratio. NOE measurements with **26** showed that the hydrogen on C-9 and the N–H were on the same side of the cyclohexane ring. The structure of **26** was confirmed by X-ray crystallography. When the dimethyl diketone **28** was the substrate, the only lactam was axial (**29**). Its structure was also corroborated by X-ray crystallography. Although the yields of the lactams produced from the spirocyclic diketones were usually modest, it is important to note that in every instance the Beckmann rearrangement did take place exclusively by insertion of the nitrogen toward the C-2 of the cyclopentane-1,3-dione moiety.

Unfortunately, the 2-alkyl diketones **30** gave intractable mixtures under these Beckmann conditions. The NMR spectra of the crude reaction products showed no evidence for the presence of lactams, and there was considerable reduction in the size of the olefinic signals. Shorter reaction times and lower temperatures just returned more **30**, not the desired products. The 2-phenyl diketone **18** gave one identifiable component in its product mixture, a small amount of the Friedel–Crafts product

† The IUPAC name for triflic acid is trifluoromethanesulfonic acid.



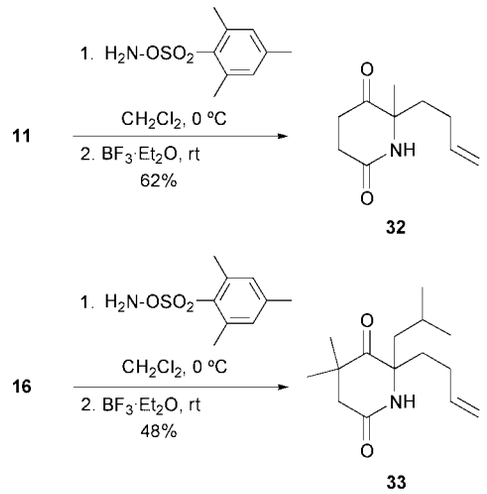
Scheme 3 Beckmann rearrangements with hydroxylamine *O*-sulfonic acid in formic acid.

31 (as a 1 : 1 epimeric mixture). It appeared that either the diketones or the lactams were unstable in the acidic medium.

Attention turned to a two-step procedure using first *O*-mesitylenesulfonylhydroxylamine to produce a sulfonylated oxime.[18,19] Whereas with basic alumina[20] there was no reaction at all, heating with $BF_3{\cdot}Et_2O$[21] did effect the Beckmann rearrangement. A two-step, but one-pot, procedure delivered **32** as the only lactam product from diketone **11**, and the more heavily substituted lactam **33** was produced from **16** (Scheme 4). However, these conditions once again failed to give any lactam with **18**, so only lactams **32** and **33** were used in the final cyclizations.

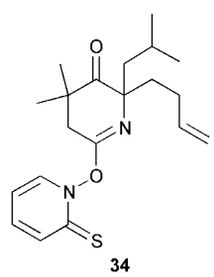
Cyclization onto the alkene

Formation of the second ring was attempted first by a radical

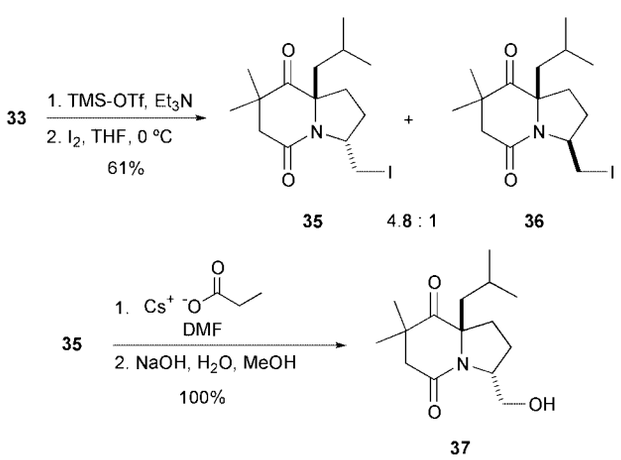


Scheme 4 Beckmann rearrangements with *O*-mesitylenesulfonylhydroxylamine and $BF_3{\cdot}Et_2O$.

method. The lactam **33** was converted to the imidate **34**.[22] Irradiation of solutions of **34** with various wavelengths of light led always to destruction of the material rather than cyclization.



An ionic process that was successful consisted of formation of the silyl imidate with trimethylsilyl triflate[23] and then, in the same pot, attack of the nitrogen onto the iodonium generated by addition of iodine to the terminal alkene. The result from **33** was the formation of two, epimeric 1-azabicyclo[4.3.0]nonan-2-one derivatives (4.8 : 1) (Scheme 5). A number of NOE



Scheme 5 Cyclization of the lactam **33**.

measurements were made with both the major and the minor isomers, but the stereochemistry on neither could be assigned with confidence. Therefore, the structure of the major product was determined by X-ray crystallography (Fig. 1) to be the *trans*-isomer **35**. Obviously, the minor product was the *cis*-isomer **36**.

It was expected that **35** would be the major isomer because it was thought that the stereochemistry at C-6 would control

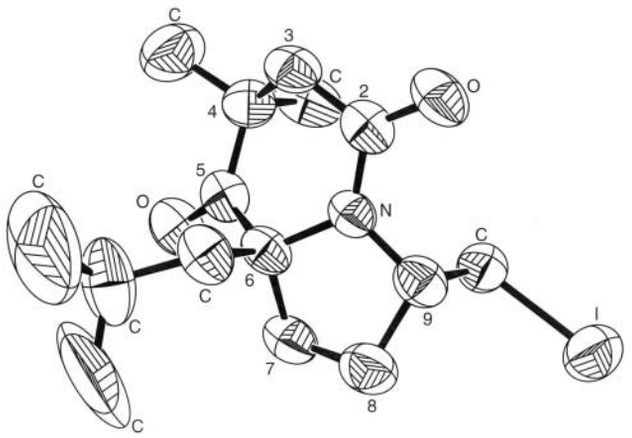
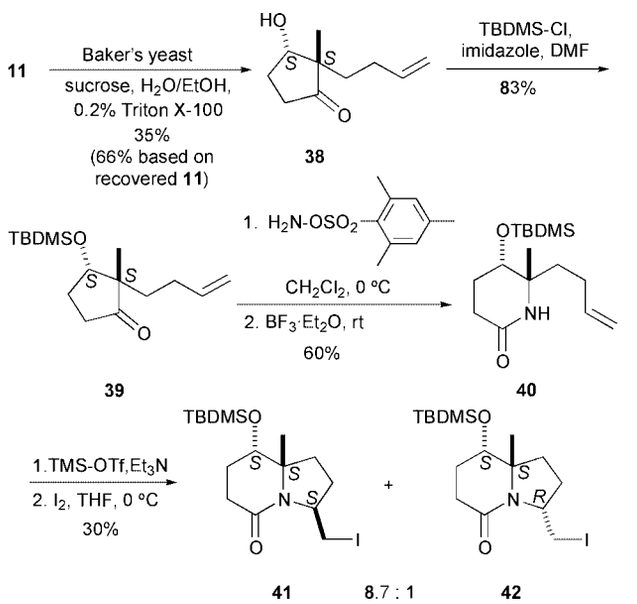


Fig. 1 Thermal ellipsoid plot (50% probability) for **35**.

sterically the developing stereochemistry at C-9. It was a straightforward and high-yield operation to replace the iodine of **35** with an hydroxy (**37**) *via* the propionate.[24]

It can be presumed that the enolizable ketone at C-5 was the reason for the complete failure of this cyclization procedure with lactam **32**. Instead of modifying racemic **32**, the prochiral diketone **11** was reductively desymmetricized by Baker's yeast[25,26] to a 9 : 1 diastereomeric mixture of monoalcohols (Scheme 6) that were difficult to separate. The yield was low, as



Scheme 6 Cyclization to enantiomerically enriched 1-azabicyclo-[4.3.0]nonan-2-ones derived from diketone **11**.

is often the case with reductions with yeast, but much of the unreduced diketone was recovered. (The same diastereomeric ratio was obtained by monoreduction of **11** with catechol-borane.) At a later stage, the major product proved to be the (1*S*,2*S*)-compound **38**. Precedence, especially from the careful work of Brooks,[25] was consistent with the formation of this enantiomer. The alcohol was protected as the *tert*-butyl-dimethylsilyl ether **39**. (The epimeric TBDMS ethers could be separated more easily by flash chromatography.) Treatment of **39** with *O*-mesitylenesulfonylhydroxylamine and then with $BF_3{\cdot}Et_2O$ gave **40** as the only Beckmann rearrangement product. Cyclization of the amidic nitrogen onto the double bond of **40** led to the formation of two, epimeric iodolactams in an 8.7 : 1 ratio. Saturation of the ^1H NMR signal for the C-6 methyl for the major product led to nuclear Overhauser effect enhancements for the hydrogen on C-5 and one of the hydrogens of the iodomethyl group. This would be reasonable if these were on the same side of the ring system, *i.e.* with the relative stereochemistry of **41**. X-Ray crystallography with **41** not only confirmed this relative stereochemistry, it also established the absolute stereochemistry as (5*S*,6*S*,9*S*) (Fig. 2). This was not

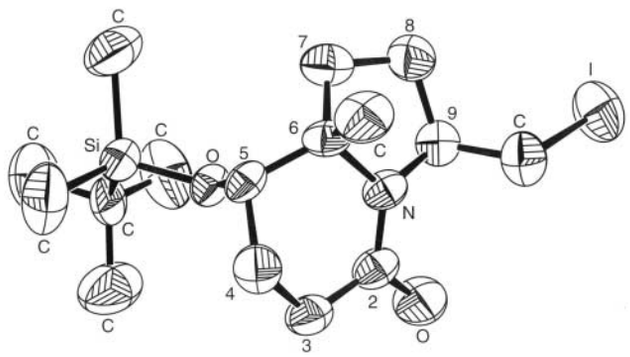


Fig. 2 Thermal ellipsoid plot (50% probability) for **41**.

the expected relative stereochemistry since in **41**, unlike in **35**, the C-6 alkyl and the iodomethyl groups are *cis*. It may thus be inferred that the (*anti*)-silyloxy group at C-5 played a more important steric role than did the (*syn*)-methyl group at C-6 in determining the developing stereochemistry at C-9 in **41**. The structure of the minor product was very likely to be **42** (5*S*,6*S*,9*R*), but this compound was not isolated.

Conclusions

The sequence of geminal acylation, Beckmann rearrangement and cyclization presented synthetic challenges at every step. Nevertheless, this synthetic sequence provided the first examples of 6-substituted 1-azabicyclo[4.3.0]nonan-2-one (indolizidinone) derivatives. The geminal acylation of an unencumbered γ,δ-unsaturated acyclic acetal was successful with **7** only by careful control of the temperature. Geminal acylation with **8**, mediated by BCl_3, gave a diketone product with a more encumbered γ,δ-unsaturated acyclic ketone. Subjecting unsaturated diketone substrates to hydroxylamine *O*-sulfonic acid in formic acid led to destruction of the material. Beckmann rearrangement products were obtained with these unsaturated diketone substrates using *O*-mesitylenesulfonyl-hydroxylamine and then $BF_3{\cdot}Et_2O$. Finally, cyclization by the attack of a silyl imidate onto the iodonium ion generated from the alkene gave the 1-azabicyclo[4.3.0]nonan-2-one derivatives. The diastereoselectivity of the cyclization was sensitive to the configuration at both C-6 and C-5.

Experimental

General

Uncorrected melting points were determined on a Fisher–Johns apparatus. Infrared spectra were measured on a Mattson Polaris FT instrument. Unless otherwise indicated, a General Electric GE 300-NB spectrometer provided the ^1H and ^{13}C NMR spectra (300 MHz for ^1H, 75 MHz for ^{13}C). Some ^1H NMR spectra were obtained at 500 MHz with a Bruker Avance spectrometer. NMR spectra were run in $CDCl_3$ solution, except where noted, and shifts are relative to internal tetramethyl-silane. Nuclear Overhauser effect (NOE) measurements were made using difference spectra. The NOE data have this form: saturated signal (enhanced signal, enhancement). Most ^{13}C NMR signals are followed in parentheses by the number of attached hydrogens (*e.g.* 2 = CH_2). Assignments, were aided by APT spectra and heterocorrelated spectra. Low resolution mass spectra (EI) were obtained on a V. G. Micromass 7070HS instrument. High resolution mass spectra were obtained from the University of Ottawa mass spectral facility. The X-ray

diffractometer was a Rigaku AFC6S instrument. Flash column chromatography employed 230–400 mesh silica gel. Dichloromethane, dimethylformamide and pentane were distilled from calcium hydride. THF was distilled from sodium metal.

Hex-5-en-2-one ethylene acetal 9

To a solution of ethane-1,2-diol (6.35 g, 102 mmol) in dry benzene (75 ml) were added hex-5-en-2-one (1.96 g, 20.0 mmol) and *p*-TsOH (20 mg). The mixture was heated under reflux for 2 days with azeotropic removal of H_2O. The solution was washed with saturated aqueous $NaHCO_3$ (2 × 50 ml). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 50 ml), and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to provide **9** (2.52 g, 89%) as a colourless liquid: ν_{max}(film)/cm^{-1} 2962; δ_H 5.84 (1 H, m, C*H*=CH$_2$), 4.98 (2 H, m, CH=C*H*$_2$), 3.95 (4 H, m), 2.16 (2 H, m), 1.74 (2 H, m) and 1.33 (3 H, s, Me); δ_C 138.7, 114.4, 110.0, 64.9, 38.5, 28.5 and 24.1; *m*/*z* no M$^+$, 127 (15%, M$^+$ − Me), 87 (100), 55 (22), 43 (93), 41 (14) and 28 (40).

2-(But-3-enyl)-2-methylcyclopentane-1,3-dione 11

A solution of acetal **9** (758 mg, 5.33 mmol) in CH_2Cl_2 (53 ml) was cooled to −78 °C before freshly distilled $BF_3{\cdot}Et_2O$ (6.76 ml, 53.4 mmol) was added. After 10 min, **7**[27] (1.61 g, 7.00 mmol) was introduced dropwise. The mixture was stirred at −78 °C for 3 h before it was warmed to 5 °C. After stirring at this temperature for 10 min, the mixture was diluted with diethyl ether (35 ml) and H_2O (35 ml) was added. The aqueous layer was extracted with diethyl ether (3 × 50 ml). The combined organic solutions were washed with brine (75 ml) and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography (33% ethyl acetate–hexanes) of the residue gave **11** (677 mg, 76%) as a colourless liquid: ν_{max}(film)/cm^{-1} 2927, 1765 and 1722; δ_H 5.64 (1 H, m, C*H*=CH$_2$), 4.94 (2 H, m, CH=C*H*$_2$), 2.77 (4 H, m), 1.96 (2 H, m), 1.77 (2 H, m) and 1.12 (3 H, s, Me); δ_C 216.8, 137.5, 116.0, 56.4, 35.3, 34.3, 29.3 and 20.3; *m*/*z* 166 (3%, M$^+$), 125 (28), 112 (100), 97 (15), 69 (37) and 41 (55).

2-Methyloct-7-en-4-one 12

Magnesium turnings (1.46 g, 59.9 mmol) were activated by stirring them vigorously under an atmosphere of dry nitrogen for 24 h.[28] THF (40 ml) was added followed by a solution of 4-bromobut-1-ene (4.23 g, 31.3 mmol) in THF (10 ml). This was heated under reflux for 2.5 h before it was cooled in an ice–salt bath. A solution of 4-methylbutanal (3.30 g, 38.3 mmol) in THF (10 ml) was added dropwise, and the mixture was stirred at rt for 16 h. The mixture was poured into saturated aqueous NH_4Cl (100 ml). The aqueous layer was extracted with diethyl ether (4 × 100 ml). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum to yield the crude alcohol. A solution of this alcohol (4.45 g, 38.3 mmol) in CH_2Cl_2 (10.5 ml) was added to a solution of PCC (10.7 g, 49.8 mmol) in CH_2Cl_2 (52.5 ml). The mixture was stirred at rt for 4.5 h. The solution was decanted from a black precipitate, and the precipitate was extracted with Et_2O (4 × 50 ml). The volume of the organic solution was reduced to 50 ml under vacuum, and this more concentrated solution was passed through a Florisil column containing activated charcoal. The eluant was concentrated under vacuum to yield **12** (3.84 g, 88%) as a yellow liquid: ν_{max}(film)/cm^{-1} 2957 and 1712; δ_H 6.00 (1 H, m, C*H*=CH$_2$), 5.81 (2 H, m, CH=C*H*$_2$), 2.49 (2 H, m), 2.31 (4 H, m), 2.17 (1 H, septet, *J* 6.4, *C*HMe$_2$) and 0.91 (6 H, d, *J* 6.4, CH*Me*$_2$); δ_C 210.0, 137.1, 115.0, 51.8, 42.2, 27.6, 24.5 and 22.5.

2-Methyloct-7-en-4-one ethylene acetal 13

To a solution of ethane-1,2-diol (3.20 g, 51.5 mmol) and **12** (1.43 g, 10.2 mmol) in benzene (75 ml) was added *p*-TsOH (20 mg), and the mixture was heated under reflux for 2 days with azeotropic removal of H_2O. The solution was washed with saturated aqueous $NaHCO_3$ (2 × 50 ml). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 50 ml), and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to yield **13** (1.87 g, 98%) as a colourless liquid: ν_{max}(film)/cm^{-1} 2952; δ_H 5.84 (1 H, m, C*H*=CH$_2$), 4.97 (2 H, m, CH=C*H*$_2$), 3.93 (4 H, s, OCH$_2$CH$_2$O), 2.12 (2 H, m, 6-H), 1.74 (3 H, m, 2-H and 5-H) and 1.52 (6 H, d, *J* 6.3, CH*Me*$_2$); δ_C 138.9 (1, *C*H=CH$_2$), 114.3 (2, CH=*C*H$_2$), 111.9 (0, C-4), 64.8 (2C, 2, OCH$_2$CH$_2$O), 45.5 (2, C-3), 36.7 (2, C-5), 28.3 (2, C-6), 24.3 (1, C-2) and 24.2 (2C, 3, CH*Me*$_2$); *m*/*z* no M$^+$, 129.0889 (77%, M$^+$ − C$_4$H$_7$, C$_{11}$H$_{20}$O$_2$ requires 129.0915), 127 (73), 85 (35), 57 (35), 55 (38), 45 (11), 43 (18), 41 (28), 39 (14), 32 (21), 29 (17) and 28 (100).

2-(But-3-enyl)-2-isobutylcyclopentane-1,3-dione 14 and 2-hydroxyethyl 5-isobutyl-4-oxonon-8-enoate 15

A solution of **13** (188 mg, 1.02 mmol) in CH_2Cl_2 (10.2 ml) was cooled to −78 °C. Freshly distilled $BF_3{\cdot}Et_2O$ (1.45 ml, 11.4 mmol) was added before **7** (304 mg, 1.32 mmol) was introduced over 2 h. The mixture was stirred at −78 °C for 3 h and then warmed gradually to 5 °C. The mixture was diluted with Et_2O (20 ml), followed immediately by H_2O (20 ml). The aqueous layer was extracted with Et_2O (3 × 25 ml). The combined organic solutions were washed with brine (50 ml) and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography (20% ethyl acetate–hexanes) of the residue yielded **14** (54.1 mg, 25%) as well as **15** (133 mg, 48%).

For **14**: pale yellow liquid; ν_{max}(film)/cm^{-1} 2958 (broad), 1764 and 1722; δ_H 5.63 (1 H, m, C*H*=CH$_2$), 4.95 (2 H, m, CH=C*H*$_2$), 2.76 (4 H, s, 4-H and 5-H), 1.92 (2 H, m), 1.62 (5 H, m) and 0.77 (6 H, d, *J* 6.7, CH*Me*$_2$); δ_C 217.4 (2C, 0, C-3 and C-1), 137.3 (1, *C*H=CH$_2$), 115.9 (2, CH=*C*H$_2$), 60.4 (0, C-2), 44.5 (2), 36.3 (2), 36.2 (2, C-4 and C-5), 28.8 (2, C-2′), 25.2 (3, CH*Me*$_2$) and 24.0 (2C, 1 and 3, *C*HMe$_2$ and CH*Me*$_2$); *m*/*z* 208 (1%, M$^+$), 154 (60, M$^+$ − C$_4$H$_6$), 152 (12), 125 (14), 112 (100), 111 (37), 107 (15), 81 (13), 55 (31), 43 (22) and 41 (47).

For **15**: pale yellow liquid; ν_{max}(film)/cm^{-1} 3459 (broad), 2956 and 1737; δ_H 5.76 (1 H, m, C*H*=CH$_2$), 4.99 (2 H, m, CH=C*H*$_2$), 4.24 (2 H, m, CH$_2$OCO), 3.82 (2 H, m, C*H*$_2$OH), 2.79 (2 H, t, *J* 6.0, 3-H), 2.60 (3 H, m, 2-H and 5-H), 2.02 (2 H, m, 7-H), 1.72 (2 H, m), 1.50 (2 H, m), 1.23 (1 H, m), 0.90 (3 H, d, *J* 6.3, CH*Me*$_2$) and 0.88 (3 H, d, *J* 6.3, CH*Me*$_2$); δ_C 213.3 (0, C-4), 173.3 (0, C-1), 138.3 (1, *C*H=CH$_2$), 115.4 (2, CH=*C*H$_2$), 66.4 (2, *C*H$_2$OCO), 61.2 (2, CH$_2$OH), 49.3 (2, C-2), 41.1 (2, isobutyl), 37.1 (2, C-3), 31.6 (2, C-7), 31.2 (2, C-6), 27.9 (1, C-5), 26.1 (1, *C*HMe$_2$), 23.1 (3, CH*Me*$_2$) and 22.6 (3, CH*Me*$_2$); *m*/*z* 270.1803 (1%, M$^+$, C$_{15}$H$_{26}$O$_4$ requires 270.1829), 198 (11), 173 (24), 155 (57), 154 (13), 153 (12), 145 (16), 111 (97), 101 (100), 83 (22), 69 (52), 57 (19), 55 (45), 45 (26), 43 (33) and 41 (36).

2-(But-3-enyl)-2-isobutyl-4,4-dimethylcyclopentane-1,3-dione 16

BCl_3 (28.0 ml, 28.0 mmol) and then **8** (11.0 g, 42.5 mmol) in CH_2Cl_2 (18.5 ml) were added to a solution of **12** (3.84 g, 27.4 mmol) in CH_2Cl_2 (50 ml) at −78 °C. The solution was allowed to warm to rt over 10 h. The solution was recooled to −78 °C before a solution of 50% HF (22.6 ml) in methanol (48.5 ml) was added, and this mixture was stirred for 15 min. The mixture was warmed to rt and stirred for 1 h. Much of the solvent was evaporated under vacuum before trifluoroacetic acid (77 ml) was added. The mixture was stirred at rt for 24 h. Water (200 ml) was added followed by solid $NaHCO_3$ until pH 7. This was extracted with CH_2Cl_2 (100 ml). The organic layer was

washed with H_2O (100 ml), and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 150 ml). The combined organic layers were washed with brine (150 ml) and dried over anhydrous $MgSO_4$. The solution was evaporated under vacuum. Flash chromatography (10% ethyl acetate–hexanes) yielded **16** (3.46 g, 54%) as a colourless liquid: ν_{max}(film)/cm^{-1} 2960 (broad), 1761 and 1720; δ_H 5.69 (1 H, m, C*H*=CH$_2$), 4.96 (2 H, m, CH=C*H*$_2$), 2.69 (1 H, d, *J* 18.8, 5-H), 2.60 (1 H, d, *J* 18.8, 5-H), 1.89 (2 H, m, 2′-H), 1.68 (5 H, m), 1.30 (3 H, s, 4-Me), 1.25 (3 H, s, 4-Me), 0.84 (3 H, d, *J* 7, CH*Me*$_2$) and 0.82 (3 H, d, *J* 7, CH*Me*$_2$); δ_C 220.7 (0, C=O), 215.9 (0, C=O), 137.3 (1, *C*H=CH$_2$), 115.5 (2, CH=*C*H$_2$), 61.0 (0, C-2), 51.2 (2, C-5), 45.8 (0, C-4), 43.8 (2), 34.8 (2), 28.7 (2, C-2′), 26.6 (3, 4-Me), 26.3 (3, 4-Me), 24.9 (1, *C*HMe$_2$), 24.3 (3, CH*Me*$_2$) and 24.2 (3, CH*Me*$_2$); *m*/*z* no M$^+$, 182 (37%, M$^+$ − C$_4$H$_6$), 140 (42), 111 (85), 109 (25), 93 (20), 81 (30), 55 (59), 43 (31), 41 (100), 39 (32), 29 (32) and 27 (32).

1-Phenylpent-4-en-1-one 17

Magnesium turnings (1.06 g, 43.6 mmol) were stirred vigorously under an atmosphere of dry nitrogen for 24 h.[28] THF (30 ml) was added followed by a solution of 4-bromobut-1-ene (4.90 g, 36.3 mmol) in THF (10 ml). The mixture was heated under reflux for 2.5 h, before it was cooled first to rt and then in an ice–salt bath. A solution of benzaldehyde (3.93 g, 37.0 mmol) in THF (10 ml) was added, and the mixture was stirred at rt for 13 h. The mixture was poured into saturated aqueous NH_4Cl (100 ml). The aqueous layer was extracted with Et_2O (4 × 80 ml). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum to leave the crude alcohol (5.50 g, 93%). A solution of this alcohol (5.25 g, 32.4 mmol) in CH_2Cl_2 (14 ml) was added to a solution of PCC (10.5 g, 48.6 mmol) in CH_2Cl_2 (65 ml). The mixture was stirred at rt for 4 h, and then the solution was decanted from the black precipitate. The precipitate was extracted with Et_2O (4 × 100 ml). The volume of the combined organic solutions was reduced under vacuum to 50 ml, and this was passed through a Florisil column containing activated charcoal to furnish **17** (4.70 g, 91%) as a yellow liquid: ν_{max}(film)/cm^{-1} 2919 and 1667; δ_H 7.96 (2 H, m), 7.58–7.42 (3 H, m), 5.89 (1 H, m, C*H*=CH$_2$), 5.03 (2 H, m, CH=C*H*$_2$), 3.01 (2 H, m) and 2.50 (2 H, m); δ_C 199.3, 137.3, 136.9, 133.0, 128.6, 128.0, 115.3, 37.7 and 28.1.

2-(But-3-enyl)-4,4-dimethyl-2-phenylcyclopentane-1,3-dione 18

A solution of **17** (328 mg, 2.35 mmol), **8** (833 mg, 3.22 mmol), and BF_3·Et_2O (0.41 ml, 3.2 mmol) in CH_2Cl_2 (10 ml) was stirred at rt for 25 hours. H_2O (30 ml) and CH_2Cl_2 (30 ml) were added. The organic layer was washed with H_2O (2 × 30 ml), and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 30 ml). The combined organic solutions were concentrated under vacuum. Flash chromatography (40% ethyl acetate–hexanes) provided **18** (248 mg, 47%) as a yellow liquid: ν_{max}(film)/cm^{-1} 3064, 1751 and 1721; δ_H 7.29 (5 H, m), 5.68 (1 H, m, C*H* × CH$_2$), 4.93 (2 H, m, CH=C*H*$_2$), 2.71 (1 H, d, *J* 18.1, 5-H), 2.50 (1 H, d, *J* 18.1, 5-H), 1.91 (4 H, m), 1.22 (3 H, s, 4-Me) and 1.16 (3 H, s, 4-Me); δ_C 218.2 (0, C-3), 213.2 (0, C-1), 137.6 (1, *C*H=CH$_2$), 136.4 (0, C-1′), 129.4 (2C, 1, C-6′ and C-2′), 128.0 (1, C-4′), 126.7 (2C, 1, C-3′ and C-5′), 115.5 (2, CH=*C*H$_2$), 65.4 (0, C-2), 51.5 (2, C-5), 46.8 (0, C-4), 36.6 (2, C-1″), 30.0 (2, C-2″), 26.9 (3, 4-Me) and 25.7 (3, 4-Me); *m*/*z* 256.1460 (1%, M$^+$, $C_{17}H_{20}O_2$ requires 256.1462), 215 (19), 202 (30), 131 (71) and 103 (100).

5-Azaspiro[5.5]undecane-1,4-dione 20

A solution of NH_2OSO_3H (106 mg, 1.00 mmol) and **19** (103.6 mg, 0.6233 mmol) in 98% formic acid (1.56 ml) was heated under reflux for 2 h. The solution was cooled in an ice bath before H_2O (10 ml) was added. The mixture was adjusted to pH 9–10 with 20% aqueous NaOH. The mixture was extracted with $CHCl_3$ (5 × 30 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. Flash chromatography (75% acetone–hexanes) gave **20** (51.1 mg, 45%) and **21** (6.2 mg, 9%).

For **20**: white solid; mp 187–189 °C; ν_{max}(Nujol)/cm^{-1} 3425, 1713 and 1657; δ_H 6.94 (1 H, broad s, NH), 2.69 (4 H, s, 2-H and 3-H) and 1.80–1.52 (10 H, m); δ_C 208.9 (0, C-1), 171.6 (0, C-4), 63.3 (0, C-6), 32.0 (2, C-2), 31.6 (2C, 2, C-7 and C-11), 26.2 (2, C-3), 21.8 (2C, 2, C-8 and C-10) and 17.7 (2, C-9); *m*/*z* 181.1080 (0.1%, M$^+$, $C_{10}H_{15}NO_2$ requires 181.1102), 153 (62), 110 (18), 98 (59), 97 (100), 96 (16), 82 (18), 81 (11), 69 (34), 57 (22), 56 (12), 55 (17), 54 (41), 41 (34), 28 (39) and 27 (35).

For **21**: white solid; mp 66–69 °C (lit.[29] 70–72 °C); δ_H 7.16 (1 H, broad s), 3.20 (2 H, m), 2.45 (2 H, m,) and 1.69 (6 H, m); δ_C 197.6, 42.8, 36.8, 30.7, 29.8 and 23.3.

5-Aza-2,2-dimethylspiro[5.5]undecane-1,4-dione 24

A solution of NH_2OSO_3H (77.9 mg, 0.689 mmol) and **23** (86.3 mg, 0.444 mmol) in 98% formic acid (1.1 ml) was heated under reflux for 3 h. The solution was cooled in an ice bath before H_2O (15 ml) was added. The mixture was adjusted to pH 9–10 with 20% aqueous NaOH. The mixture was extracted with $CHCl_3$ (4 × 30 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum to leave **24** (73.3 mg, 79%) as a white solid: mp 186–189 °C; ν_{max}(CCl_4)/cm^{-1} 2928, 1721 and 1672; δ_H 6.45 (1 H, broad s, NH), 2.51 (2 H, s, 3-H), 1.79 (4 H, m), 1.37 (5 H, m) and 1.20 (6 H, s, 2 × 2-Me); δ_C 212.4 (0, C-1), 170.2 (0, C-4), 62.8 (0, C-6), 42.6 (2, C-3), 42.2 (0, C-2), 34.6 (2C, 2, C-7 and C-11), 24.5 (2C, 3, 2 × 2-Me), 24.3 (2, C-9) and 20.3 (2C, 2, C-8 and C-10); *m*/*z* 209 (3%, M$^+$), 181 (54), 138 (22), 110 (13), 98 (100), 97 (99), 69 (20), 56 (29), 55 (23), 54 (39) and 41 (57).

(*trans*)-5-Aza-9-*tert*-butylspiro[5.5]undecane-1,4-dione 26 and (*cis*)-5-aza-9-*tert*-butylspiro[5.5]undecane-1,4-dione 27

Following the procedure for **20**, NH_2OSO_3H (23.4 mg, 0.207 mmol) and **25** (25.5 mg, 0.145 mmol) in 98% formic acid (1.6 ml) provided a mixture of **26** and **27** (11.7 mg, 41%; 56% taking into account recovered **20**). Repeated chromatography (50% acetone–hexanes) gave small homogeneous samples of **26** and **27**.

For **26**: mp 160–162 °C; ν_{max}(CCl_4)/cm^{-1} 3196, 3088, 2967, 1712 and 1659; δ_H (500 MHz) 5.91 (1 H, broad s, NH), 2.68 (4 H, s, 3-H and 4-H), 2.16 (2 H, d of narrow multiplets, *J* 13.2), 1.62–1.49 (4 H, m), 1.32 (2 H, dt, *J* 4.3 and 13.2, 7-H and 11-H, *syn* to NH), 1.02 (1 H, m, 9-H) and 0.87 (9 H, s, ^{t}Bu); NOE data 5.91 (1.32, 4%), 2.16 (1.62–1.49, 2%; 14%) and 1.32 (5.91, 9%; 2.16, 17%; 1.02, 11%); δ_C 208.0 (0, C-1), 171.8 (0, C-4), 61.7 (0, C-6), 46.9 (1, C-9), 37.5 (2C, 2, C-7 and C-11), 35.1 (2), 32.6 (0, ^{t}Bu), 29.3 (2), 27.7 (3C, 3, ^{t}Bu) and 23.4 (2C, 2, C-8 and C-10); *m*/*z* 237.1722 (<1%, M$^+$, $C_{14}H_{23}NO_2$ requires 237.1728), 209 (25), 194 (15), 154 (11), 152 (12), 125 (28), 124 (65), 110 (30), 97 (23), 96 (31), 86 (22), 84 (60), 71 (42), 69 (54), 57 (100), 55 (38), 43 (69), 41 (62) and 28 (60).

For **27**: white solid: mp 230–233 °C; ν_{max}(CCl_4)/cm^{-1} 3193, 2933, 1722 and 1660; δ_H (500 MHz) 6.12 (1 H, broad s, NH), 2.69 (4 H, narrow m, 3-H and 4-H, becomes two well-resolved but second-order signals in C_6D_6 solution), 1.87–1.75 (6 H, m), 1.11 (3 H, m) and 0.87 (9 H, s, ^{t}Bu); δ_C 208.6 (0, C-1), 171.1 (0, C-4), 63.5 (0, C-6), 47.0 (1, C-9), 35.1 (2), 35.0 (2C, 2), 32.7 (0, ^{t}Bu), 29.2 (2), 27.6 (3C, 3, ^{t}Bu) and 21.7 (2C, 2); *m*/*z* 237.1698 (<1%, M$^+$, $C_{14}H_{23}NO_2$ requires 237.1728), 209 (63), 194 (41), 154 (30), 153 (20), 152 (28), 138 (25), 125 (57), 110 (59), 100 (14), 97 (33), 96 (61), 69 (100), 55 (31) and 41 (54).

X-Ray crystal structure determination for 26‡

A colourless plate crystal of dimensions 0.20 × 0.10 × 0.42 mm was mounted on a glass fibre: $C_{14}H_{23}NO_2$, M = 237.34, orthorhombic, a = 20.714(1), b = 6.033(1), c = 21.606(1) Å, V = 2699.9(4) Å^3, T = 299 K, space group $Pca2_1$ (no. 29), Z = 8, μ(Cu-Kα) 6.10 cm^{-1}, 2372 reflections collected, 1540 observed ($I > 2.00\sigma(I)$); R = 0.094, R_w = 0.108, goodness of fit = 4.03. The *ORTEP* plot is shown in Fig. 3.

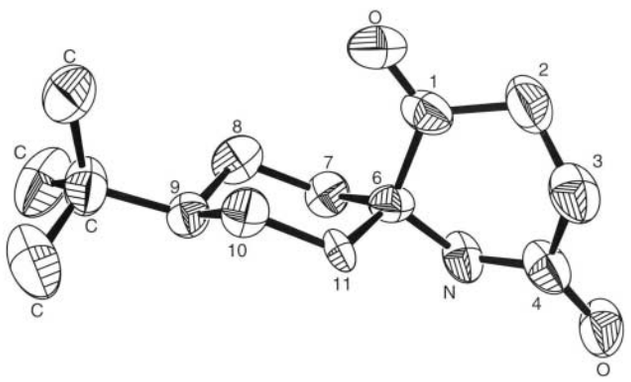


Fig. 3 Thermal ellipsoid plot (50% probability) for **26**.

5-Aza-9-*tert*-butyl-2,2-dimethylspiro[5.5]undecane-1,4-dione 29

Following the procedure for **20**, NH_2OSO_3H (370 mg, 3.27 mmol) and **28** (542 mg, 2.16 mmol) in 98% formic acid (5.4 ml) provided **29** (306 mg, 54%) as a beige solid: mp: 251–253 °C; ν_{max}(Nujol)/cm^{-1} 3213, 3091, 1712 and 1666; δ_H 6.35 (1 H, broad s, NH), 2.53 (2 H, s, 3-H), 1.84–1.70 (8 H, m), 1.20 (6 H, s, 2 × 2-Me), 1.12 (1 H, m, 9-H) and 0.87 (9 H, s, ^{t}Bu); δ_C 212.8 (0, C-1), 170.3 (0, C-4), 63.1 (0, C-6), 46.7 (1, C-9), 43.0 (2, C-3), 42.6 (0, C-2), 35.6 (2C, 2, C-7 and C-11), 32.7 (0, ^{t}Bu), 27.6 (3C, 3, ^{t}Bu), 24.9 (2C, 3, 2 × 2-Me) and 21.7 (2C, 2, C-8 and C-10); *m*/*z* no M$^+$, 250.1825 (7%, M$^+$ − Me, $C_{16}H_{27}NO_2$ requires 250.1806), 237 (58), 222 (17), 180 (12), 154 (77), 153 (35), 138 (73), 97 (43), 96 (49), 69 (57), 57 (98), 56 (46), 55 (48) and 41 (100).

X-Ray crystal structure determination for 29

A colourless prism crystal of dimensions 0.25 × 0.15 × 0.42 mm was mounted on a glass fibre: $C_{16}H_{27}NO_2$, M = 265.39, triclinic, a = 10.807(1), b = 12.290(2), c = 6.044(1) Å, α = 102.16(1), β = 90.42(1), γ = 99.49(1)°, V = 773.3(2) Å^3, T = 299 K, space group $P\bar{1}$ (no. 2), Z = 2, μ(Cu-Kα) 5.80 cm^{-1}, 2433 reflections collected, 1871 observed ($I > 2.00\sigma(I)$); R = 0.038, R_w = 0.040, goodness of fit = 3.22. The *ORTEP* plot is shown in Fig. 4.

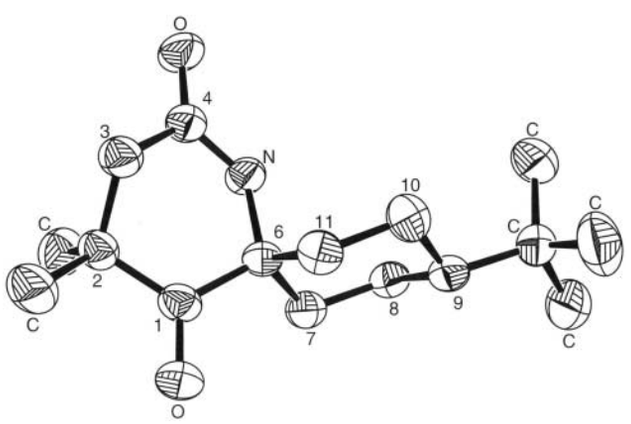


Fig. 4 Thermal ellipsoid plot (50% probability) for **29**.

‡ CCDC reference number(s) 171040–171042 and 174417. See http://www.rsc.org/suppdata/p1/b1/b108164k for crystallographic files in .cif or other electronic format.

1′,2′,3′,4′-Tetrahydro-4,4,4′-trimethylspiro[cyclopentane-1,1′-naphthalene]-2,5-dione 31

Following the procedure for **20**, NH_2OSO_3H (180 mg, 1.60 mmol) and **18** (258 mg, 1.00 mmol) in 98% formic acid (2.5 ml) gave a very complex mixture from which a small amount of an almost 1 : 1 epimeric mixture **29** (15.3 mg, 6%) was obtained as a tan-coloured resin: ν_{max}(film)/cm^{-1} 2962, 1765 and 1721; δ_H (C_6D_6; unless noted, signals were coincident in both isomers) 7.17–6.92 (3 H, m), 6.62 (1 H, d, *J* 7.3), 2.39 (1 H, two almost coincident d, *J* 18.9, one 3-H of both isomers), 2.23 (1 H, two d, *J* 18.9, one 3-H of both isomers), 2.0–1.4 (m), 1.15 (3 H, d, *J* 7.0, one isomer), 1.11 (3 H, d, *J* 7.0, other isomer), 1.02 (3 H, s, one isomer), 1.01 (3 H, s, one isomer), 0.95 (3 H, s, one isomer) and 0.94 (3 H, s, one isomer); *m*/*z* 256.1443 (61%, M$^+$, $C_{17}H_{20}O_2$ requires 256.1462), 228 (8), 213 (6), 172 (100), 144 (16), 129 (48) and 104 (1).

3-Aza-2-(but-3-enyl)-2-methylcyclohexane-1,4-dione 32

A solution of *O*-mesitylenesulfonylhydroxylamine (316 mg, 1.45 mmol) in CH_2Cl_2 (1.2 ml) was added to a solution of **11** (188 mg, 1.13 mmol) in CH_2Cl_2 (2.3 ml) at 0 °C. The mixture was stirred at rt for 15 h. $BF_3{\cdot}Et_2O$ (0.42 ml) was added, and the mixture was stirred at rt for 3.5 h, and then it was heated under reflux for 3.5 h. The mixture was washed with saturated aqueous $NaHCO_3$ (2 × 10 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (3 × 20 ml). The combined organic solutions were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. Flash chromatography (50% acetone–hexanes) gave **32** (128 mg, 62%) as a white solid: mp 115–117 °C; ν_{max}(CCl_4)/cm^{-1} 3195 (broad), 1729 and 1674; δ_H XX signal missing here (1 H, broad s, NH), 5.75 (1 H, m, C*H*=CH$_2$), 5.06 (2 H, m, CH=C*H*$_2$), 2.68 (4 H, m, 5-H and 6-H), 2.62 (1 H, m), 2.13 (2 H, m), 1.59 (1 H, m) and 1.38 (3 H, s, 2-Me); δ_C 208.6 (0, C-1), 172.0 (0, C-4), 137.1 (1, *C*H=CH$_2$), 115.8 (2, CH=*C*H$_2$), 64.2 (0, C-2), 39.7 (2, C-1′), 35.4 (2), 29.1 (2), 28.5 (2, C-2′) and 27.2 (3, 2-Me); *m*/*z* (%): 181 (<1%, M$^+$), 153 (34), 138 (12), 126 (31), 112 (25), 98 (100), 97 (48), 96 (30), 82 (37), 57 (24), 56 (22), 55 (20), 42 (58) and 41 (25).

3-Aza-2-(but-3-enyl)-2-isobutyl-6,6-dimethylcyclohexane-1,4-dione 33

A solution of *O*-mesitylenesulfonylhydroxylamine (318 mg, 1.49 mmol) in CH_2Cl_2 (1.0 ml) was added to solution of **16** (188 mg, 0.798 mmol) in CH_2Cl_2 (1.6 ml) at 0 °C. The solution was stirred at this temperature for 20 min before it was warmed to rt. It was maintained at rt for 14 h and then heated under reflux for 6 h. $BF_3{\cdot}Et_2O$ (0.30 ml) was added, and the mixture was heated under reflux for 30 min. The mixture was washed with saturated aqueous $NaHCO_3$ (2 × 10 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. The ^{1}H NMR spectrum of the crude product showed signals for **33** and **16** in a ratio of 2 : 1. Flash chromatography (25% acetone–hexanes) of the crude product provided homogeneous **33** (97.9 mg, 49%) as a white solid: mp 69.5–71 °C; ν_{max}(CCl_4)/cm^{-1} 3198, 3083, 2961, 1718 and 1673; δ_H 6.64 (1 H, m, NH), 5.73 (1 H, m, C*H*=CH$_2$), 4.99 (2 H, m, CH=C*H*$_2$), 2.54 (1 H, d, *J* 17.5, 5-H), 2.49 (1 H, d, *J* 17.5, 5-H), 2.08 (1 H, m), 1.98–1.75 (2 H, m), 1.71–1.43 (3 H, m), 1.29 (1 H, m), 1.22 (3 H, s, 6-Me), 1.19 (3 H, s, 6-Me), 0.97 (3 H, d, *J* 6.6, CH*Me*$_2$) and 0.89 (3 H, d, *J* 6.7, CH*Me*$_2$); δ_C 212.5 (C-1), 171.5 (C-4), 137.3 (*C*H=CH$_2$), 115.7 (CH=*C*H$_2$), 67.5 (C-2), 47.9, 43.3, 42.2 (C-6), 39.0, 28.5, 25.5, 25.3, 24.9, 24.7, 24.4; *m*/*z* no M$^+$, 225 (15%), 223 (11), 196 (20), 182 (47), 142 (44), 140 (54), 112 (19), 97 (22), 96 (25), 84 (21), 83 (27), 82 (21), 57 (100), 56 (39), 55 (45), 43 (34), 42 (29) and 41 (81).

(6*R,9*R**)-1-Aza-9-(iodomethyl)-6-isobutyl-4,4-dimethylbicyclo[4.3.0]nonane-2,5-dione 35 and (6*R**,9*S**)-1-aza-9-(iodomethyl)-6-isobutyl-4,4-dimethylbicyclo[4.3.0]nonane-2,5-dione 36**

Triethylamine (0.21 ml, 2.9 mmol) and TMS-OTf (0.50 ml, 2.9 mmol) were added to a stirred solution of **33** (238 mg, 0.948 mmol) in dry pentane (1.4 ml) at 0 °C. The solution was stirred for 20 min at rt, after which time the two layers were allowed to separate. The pentane layer was removed, and the remaining, oily material was extracted with more pentane (2 × 2 ml). The combined pentane extracts were concentrated under vacuum. The residue was cooled in an ice bath and iodine (0.53 g, 2.1 mmol) in THF (2.1 ml) was added. The mixture was stirred for 10 min. Saturated aqueous solutions of sodium sulfite (3.5 ml), and sodium bicarbonate (3.5 ml) were added. This was extracted with ethyl acetate (3 × 15 ml). The combined organic solutions were washed with saturated aqueous sodium bicarbonate (25 ml) and then dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum. Flash chromatography (30% ethyl acetate–hexanes) yielded a mixture of **35** and **36**, in a 4.8 : 1 ratio, (218 mg, 61%) as a beige solid. Small homogeneous samples were obtained by repeated chromatography.

For **35**: white solid; mp 83–85 °C; ν_{max} (CCl_4)/cm^{-1} 1712 and 1654; δ_H 4.25 (1 H, m, 9-H), 3.67 (1 H, dd, *J* 2.7 and 9.7, CH_2I), 3.43 (1 H, dd, *J* 8.4 and 9.7, CH_2I), 2.84 (1 H, d, *J* 16.6, 3-H), 2.49 (1 H, d, *J* 16.6, 3-H), 2.16–2.05 (3 H, m), 1.98 (1 H, m, 7-H), 1.78–1.64 (3 H, m CH_2CHMe_2), 1.25 (3 H, s, 4-Me), 1.22 (3 H, s, 4-Me), 0.95 (3 H, d, *J* 6.3, $CHMe_2$) and 0.87 (3 H, d, *J* 6.2, $CHMe_2$); NOE data 4.25 (3.67, 4%; 3.43, 1%; 2.16–2.05, 1%; 1.98, 2%), 3.67 (4.25, 7%; 3.43, 28%; 1.98, 2%) and 3.43 (4.25, 4%; 3.67, 24%); δ_C 213.0 (0, C-5), 167.0 (0, C-2), 73.8 (0, C-6), 57.6 (1, C-9), 45.3 (2), 44.9 (2, C-3), 42.5 (0, C-4), 31.2 (2, C-8), 28.0 (2, C-7), 27.8 (3, Me), 26.0 (3, Me), 24.8 (3, $CHMe_2$), 24.6 (3, $CHMe_2$), 24.1 (1, $CHMe_2$) and 8.6 (2, CH_2I); *m*/*z* no M^+, 349.0906 (68%, $M^+ - CO$, $C_{15}H_{24}INO_2$ requires 349.0904), 320 (41), 306 (11), 292 (12), 266 (65), 265 (29), 250 (24), 223 (63), 138 (40), 96 (26), 83 (43), 82 (88), 56 (66), 55 (77), 43 (56), 41 (100), 39 (37), 29 (49), 28 (49) and 27 (36).

For **36**: beige solid: mp 75–77 °C; ν_{max}(CCl_4)/cm^{-1} 1718 and 1639; δ_H 4.36 (1 H, m, 9-H), 3.85 (1 H, dd, *J* 3.6 and 9.1, CH_2I), 3.06 (1 H, dd, *J* 9.1 and 10.1, CH_2I), 2.79 (1 H, d, *J* 15.7, 3-H), 2.39 (1 H, d, *J* 15.7, 3-H), 2.23 (1 H, m, 8-H), 2.08 (1 H, m, 7-H), 1.97–1.75 (3 H, m), 1.69–1.52 (2 H, m, CH_2CHMe_2 and $CHMe_2$), 1.19 (3 H, s, 4-Me), 1.12 (3 H, s, 4-Me), 0.92 (3 H, d, *J* 6.3, $CHMe_2$) and 0.89 (3 H, d, *J* 6.3, $CHMe_2$); NOE data 4.36 (3.85, 4%; 3.06, 3%; 2.23, 4%), 3.85 (4.36, 6%; 3.06, 25%), 3.06 (4.36, 2%; 3.85, 23%; 1.69–1.52, 1%) and 1.12 (2.39, 4%); δ_C 213.5 (0, C-5), 167.0 (0, C-2), 74.3 (0, C-6), 60.1 (1, C-9), 47.8 (2), 43.9 (2, C-3), 42.4 (0, C-4), 36.7 (2, C-7), 29.6 (2, C-8), 26.2 (3, 4-Me), 24.9 (1, $CHMe_2$), 24.6 (3, $CHMe_2$), 24.6 (3, $CHMe_2$), 24.3 (3, 4-Me) and 9.9 (2, CH_2I); *m*/*z* no M^+, 349.0915 (52%, $M^+ - CO$, $C_{15}H_{24}INO_2$ requires 349.0904), 320 (11), 266 (55), 265 (24), 250 (21), 223 (55), 138 (34), 96 (22), 83 (30), 82 (81), 56 (62), 55 (72), 53 (19), 43 (31), 41 (100), 39 (34), 29 (46), 28 (30) and 27 (33).

X-Ray crystal structure determination for 35. A colourless prism crystal of dimensions 0.35 × 0.25 × 0.40 mm was mounted on a glass fibre: $C_{15}H_{24}INO_2$, M = 377.26, monoclinic, a = 10.999(1), b = 5.926(6), c = 26.445(2) Å, β = 99.11(1)°, V = 1702(1) $Å^3$, T = 299 K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo-Kα) 18.81 cm^{-1}, 4544 reflections collected, 2598 observed ($I > 2.00\sigma(I)$); R = 0.041, R_w = 0.040, goodness of fit = 3.05.

(6*R,9*R**)-1-Aza-9-(hydroxymethyl)-6-isobutyl-4,4-dimethylbicyclo[4.3.0]nonane-2,5-dione 37**

Caesium propionate (28.0 mg, 0.136 mmol) in DMF (1.4 ml) was added to a solution of **35** (48.0 mg, 0.127 mmol) in DMF (1.3 ml). The mixture was stirred at rt for 2 h, heated under reflux for 4 h, and then stirred at rt for 14 h. Brine (25 ml) was added and this was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography with 30% ethyl acetate–hexanes and then with 50% acetone–hexanes gave homogeneous **37** (20.6 mg, 60%) and some of the corresponding propionate (16.4 mg, 40%). Heating a methanol solution of the propionate, to which was added an aqueous solution of NaOH, for 2 h transformed the propionate to **37** quantitatively.

For **37**: beige solid: mp 80–82 °C; ν_{max}(CCl_4)/cm^{-1} 3426 (broad), 2962, 1721 and 1644; δ_H 4.67 (1 H, m, OH), 4.16 (1 H, m, 9-H), 3.74 (2 H, m, CH_2OH), 2.87 (1 H, d, *J* 16.5, 3-H), 2.49 (1 H, d, *J* 16.5, 3-H), 2.09 (2 H, m, 8-H), 1.64 (5 H, m), 1.23 (3 H, s, 4-Me), 1.19 (3 H, s, 4-Me), 0.95 (3 H, d, *J* 6.2, $CHMe_2$) and 0.88 (3 H, d, *J* 6.2, $CHMe_2$); δ_C 213.0 (0, C-5), 170.8 (0, C-2), 74.3 (0, C-6), 66.5 (2, CH_2OH), 62.2 (1, C-9), 45.7 (2), 44.8 (2, C-3), 42.0 (0, C-4), 32.7 (2, C-8), 26.9 (3, 4-Me), 26.3 (2), 25.6 (3, 4-Me), 24.9 (1, $CHMe_2$), 24.7 (3, $CHMe_2$) and 24.3 (3, $CHMe_2$); *m*/*z* no M^+, 249 (4%, $M^+ - H_2O$), 239.1855 (24, $M^+ - CO$, $C_{15}H_{25}NO_3$ requires 239.1833), 210 (27), 196 (13), 182 (14), 180 (30), 178 (32), 156 (62), 155 (24), 140 (22), 124 (23), 113 (39), 95 (27), 83 (77), 82 (97), 57 (31), 56 (49), 55 (77), 44 (41), 43 (64), 41 (100) and 39 (34).

For the propionate of **37**: ν_{max}(CCl_4)/cm^{-1} 2960, 1740, 1719 and 1662; δ_H 4.53 (1 H, dd, *J* 4.5 and 11.2, CH_2O), 4.32 (2 H, m, CH_2O and 9-H), 2.86 (1 H, d, *J* 16.5, 3-H), 2.43 (1 H, d, *J* 16.5, 3-H), 2.27 (2 H, q, *J* 7.5, $COCH_2CH_3$), 2.13 (3 H, m, 8-H and 7-H), 1.84 (1 H, m, 7-H), 1.68 (3 H, m), 1.23 (3 H, s, 4-Me), 1.17 (3 H, s, 4-Me), 1.09 (3 H, t, *J* 7.5, $COCH_2CH_3$), 0.95 (3 H, d, *J* 6.2, $CHMe_2$) and 0.88 (3 H, d, *J* 6.1, $CHMe_2$); δ_C 213.6 (0, C-5), 174.2 (0, $COCH_2CH_3$), 168.9 (0, C-2), 73.4 (0, C-6), 63.3 (2, CH_2O), 56.0 (1, C-9), 45.7 (2, isobutyl), 45.0 (2, C-3), 42.6 (0, C-4), 32.6 (2, C-8), 27.7 (2, $COCH_2CH_3$), 26.9 (3, 4-Me), 25.8 (3, 4-Me), 25.7 (2, C-7), 24.9 (1, $CHMe_2$), 24.7 (3, $CHMe_2$), 24.2 (3, $CHMe_2$) and 9.2 (3, $COCH_2CH_3$); *m*/*z* 295 (15%, $M^+ - CO$), 252 (13), 212 (65), 211 (26), 210 (48), 196 (23), 169 (21), 97 (29), 83 (30), 82 (75), 57 (66), 56 (37), 55 (44), 41 (64), 29 (100) and 27 (31).

(2*S*,3*S*)-2-(But-3-enyl)-3-hydroxy-2-methylcyclopentanone 38

Fleischman's "Traditional" dry yeast (8.0 g) and sucrose (18.0 g) were added to de-ionized H_2O (100 ml). The mixture was agitated in a 32 °C bath. After 10 minutes, a solution of **11** (167 mg, 1.00 mmol) in 95% EtOH (3.0 ml) and 0.2% Triton X-100 (12 ml) was added. This suspension was agitated for 2 days. Diethyl ether (100 ml) was added, and the suspension was allowed to stand for 20 h. The ether layer was decanted, and the process was repeated three times with 100 ml of diethyl ether. The combined organic layers were washed with brine (150 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum. Flash chromatography (50% ethyl acetate–hexanes) to furnish **38** (58.7 mg, 35%) a yellow liquid and 80.1 mg of **11** was recovered. (The yield based on recovered starting material was 66%.) For **38**: ν_{max}(film)/cm^{-1} 3456 (broad), 2967 and 1729; $[\alpha]_D$ +62 (c = 0.00095, MeOH); δ_H 5.85 (1 H, m, $CH{=}CH_2$), 5.01 (2 H, m, $CH{=}CH_2$), 4.13 (1 H, t, *J* 4.5, 3-H), 2.47 (1 H, m, 5-H), 2.30 (1 H, m, 5-H), 2.24–2.13 (2 H, m, 4-H and 2′-H), 2.06 (1 H, m, 2′-H), 1.96 (1 H, m, 4-H), 1.63 (2 H, t, *J* 8.1, 1′-H) and 1.01 (3 H, s, 2-Me); δ_C 220.6 (0, C-1), 138.8 (1, $CH{=}CH_2$), 115.1 (2, $CH{=}CH_2$), 77.6 (1, C-3), 53.2 (0, C-2), 34.1 (2, C-5), 29.5 (2, C-4), 28.3 (2, C-1′), 28.1 (2, C-2′), 19.4 (3, 2-Me); *m*/*z* 168.1149 (1%, M^+, $C_{10}H_{16}O_2$ requires 168.1149), 114 (100), 113 (54), 99 (31), 97 (27), 85 (30), 84 (30), 81 (37), 49 (48), 43 (39) and 41 (36).

(2*S*,3*S*)-2-(But-3-enyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylcyclopentanone 39

Imidazole (170 mg, 2.50 mmol), and then TBDMS-Cl (200 mg, 1.30 mmol) were added to a solution of **38** (189 mg, 1.12 mmol) in DMF (5.0 ml). The solution was stirred for 24 h at rt. H_2O (10 ml) was added, and this was extracted with petroleum ether (3 × 15 ml). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum. Flash chromatography (20% ethyl acetate–hexanes) yielded **39** (262 mg, 83%) as a yellow liquid: ν_{max}(film)/cm^{-1} 2956 and 1741; δ_H 5.79 (1 H, m, C*H*=CH$_2$), 4.99 (2 H, m, CH=C*H*$_2$), 4.03 (1 H, t, *J* 6.3, 3-H), 2.40 (1 H, m, 5-H), 2.23 (1 H, m, 5-H), 2.14–1.87 (4 H, m, 4-H and 2′-H), 1.66 (1 H, m, 1′-H), 1.51 (1 H, m, 1′-H), 0.98 (3 H, s, 2-Me), 0.89 (9 H, s, Si^{t}Bu), 0.10 (3 H, s, SiMe) and 0.08 (3 H, s, SiMe); δ_C 220.8 (0, C-1), 139.0 (1, *C*H=CH$_2$), 114.5 (2, CH=*C*H$_2$), 78.4 (1, C-3), 53.4 (0, C-2), 34.4 (2, C-5), 29.8 (2, C-1′), 28.6 (2), 28.3 (2), 25.8 (3C, 3, Si^{t}Bu), 19.5 (3, 2-Me), 18.2 (0, Si^{t}Bu), −4.1 (3, SiMe) and −4.6 (3, SiMe); *m*/*z* no M$^+$, 241 (15%), 225.1310 (17, M$^+$ − ^{t}Bu, $C_{16}H_{30}O_2Si$ requires 225.1310), 133 (24), 129 (28), 107 (25), 101 (33), 75 (100), 73 (80), 59 (18) and 41 (21).

(3*S*,4*S*)-2-Aza-3-(but-3-enyl)-4-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclohexanone 40

A solution of *O*-mesitylenesulfonylhydroxylamine (760 mg, 3.53 mmol) in CH_2Cl_2 (1.70 ml) was added to a solution of **39** (436 mg, 1.54 mmol) in CH_2Cl_2 (3.1 ml) at 0 °C. After 20 min the temperature was raised to rt. The solution was stirred for 14 h. BF_3·Et_2O (0.60 ml) was added, and the mixture was stirred at rt for 1 h. CH_2Cl_2 (20 ml) was added, and the organic solution was washed with saturated aqueous $NaHCO_3$ (2 × 25 ml). The aqueous layers were re-extracted with diethyl ether (3 × 25 ml). The combined organic layers were dried over anhydrous $MgSO_4$. The volume was reduced to approximately 10 ml under vacuum. The resultant solution was passed through a pad (1.5 cm × 2.0 cm) of Dowex 1X 8–400 ion exchange resin, and the resin was flushed with 75 ml of diethyl ether. The combined ether solutions were concentrated under vacuum. Flash chromatography (50% ethyl acetate–hexanes) furnished **40** (279 mg, 60%) as a white solid: mp 67–69 °C; ν_{max}(film)/cm^{-1} 3136, 2956 and 1662; δ_H 6.49 (1 H, broad s, NH), 5.81 (1 H, m, C*H*=CH$_2$), 5.02 (2 H, m, CH=C*H*$_2$), 3.72 (1 H, t, *J* 5.6, 4-H), 2.54 (1 H, m, 6-H), 2.35 (1 H, m, 6-H), 1.93 (2 H, m, 2′-H), 1.77 (2 H, m, 5-H), 1.73 (1 H, m, 1′-H), 1.57 (1 H, m, 1′-H), 1.20 (3 H, s, 3-Me), 0.90 (9 H, s, Si^{t}Bu) and 0.10 (6 H, s, SiMe$_2$); δ_C 171.4 (0, C-1), 138.4 (1, *C*H=CH$_2$), 115.0 (2, CH=*C*H$_2$), 72.3 (1, C-4), 58.4 (0, C-3), 36.2 (2, C-1′), 27.8 (2C, 2, C-6 and C-2′), 26.3 (3, 3-Me), 25.9 (3C, 3, Si^{t}Bu), 25.4 (2, C-5), 18.2 (0, Si^{t}Bu), −3.9 (3, SiMe) and −4.9 (3, SiMe); *m*/*z* 297.2115 (2%, M$^+$, $C_{16}H_{31}NO_2Si$ requires 297.2122), 256 (28), 242 (44), 240 (40), 198 (37), 115 (33), 101 (25), 98 (24), 75 (100), 74 (35), 73 (98), 59 (34), 58 (46) and 41 (37).

(6*S*,5*S*,9*S*)-1-Aza-5-[(*tert*-butyldimethylsilyl)oxy]-9-(iodomethyl)-6-methylbicyclo[4.3.0]nonan-2-one 41

Triethylamine (0.18 ml, 1.3 mmol) and TMS-OTf (0.23 ml, 1.3 mmol) were added to a solution of **40** (174 mg, 0.584 mmol) in dry pentane (0.9 ml) at 0 °C. The mixture was stirred at rt for 30 min after which the two layers were allowed to separate. The pentane was removed, and the remainder was extracted with dry pentane (2 × 2 ml). The pentane extracts were combined and concentrated under vacuum. The residue was cooled in an ice bath, and a solution of iodine (0.33 g, 1.3 mmol) in THF (1.3 ml) was added. The mixture was stirred at this temperature for 10 min. Saturated aqueous solutions of sodium sulfite (2.2 ml), and sodium bicarbonate (2.2 ml) were added. This was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried over anhydrous $MgSO_4$. Flash chromatography (30% ethyl acetate–hexanes) of the difficult to separate diastereomeric mixture provided some homogeneous **41** (34.6 mg, 14%) and a fraction containing **41** and putative **42** (39.8 mg, 16%) in a ratio of 4.2 : 1. The remainder was a much more polar material.

For **41**: beige solid; mp 128–129 °C; ν_{max}(CCl_4)/cm^{-1} 2956 and 1648; $[\alpha]_D^{24}$ −6.5 (*c* = 0.0035, MeOH); δ_H (500 MHz) 4.04 (1 H, m, 9-H), 3.82 (2 H, dd, *J* 9.0 and 3.2, CH$_2$I), 3.79 (1 H, dd, *J* 3.8 and 1.7, 5-H), 3.23 (1 H, t, *J* 9.0, CH$_2$I), 2.44 (1 H, ddd, *J* 18.0, 10.2 and 8.1, 3-H), 2.32 (1 H, dd, *J* 18.0 and 7.6, 3-H), 2.25–2.14 (2 H, m, 7-Hβ and 8-Hβ), 2.10 (1 H, m, 4-Hα), 1.81 (1 H, m, 4-Hβ), 1.73 (1 H, m, 8-Hα), 1.45 (1 H, m, 7-Hα), 1.26 (3 H, s, 6-Me), 0.87 (9 H, s, Si^{t}Bu), 0.08 (3 H, s, SiMe) and 0.06 (3 H, s, SiMe); NOE data 4.04 (3.82, 1%; 2.25–2.14, 2%); 3.23 (4.04, 1%; 3.82, 20%; 1.73, 1%) and 1.26 (3.79, 7%; 3.23, 2%; 2.10, 7%; 1.73, 5%; 1.45, 13%); δ_C 170.5 (0, C-2), 70.4 (1, C-5), 67.6 (0, C-6), 59.7 (1, C-9), 32.9 (2, C-7), 29.5 (2, C-8), 27.2 (3, 6-Me), 26.8 (2, C-3), 26.2 (3C, 3, Si^{t}Bu), 25.5 (2, C-4), 18.5 (0, Si^{t}Bu), 12.5 (2, CH$_2$I), −4.1 (3, SiMe) and −4.6 (3, SiMe); *m*/*z* 423.1091 (6%, M$^+$, $C_{16}H_{31}O_2INSi$ requires 423.1091), 366 (19), 366 (100), 296 (21), 292 (33), 265 (24), 224 (31), 223 (16), 115 (44), 101 (32), 98 (33), 96 (30), 75 (45), 73 (58), 59 (27), 57 (21), 55 (24) and 41 (36).

For **42**: δ_H (clearly discerned signals only) 4.16 (1 H, m), 3.87 (1 H, dd, *J* 9.2 and 3.4), 3.53 (1 H, dd, *J* 11.3 and 4.9), 3.10 (1 H, dd, *J* 9.5 and 9.2) and 1.25 (3 H, s).

X-Ray crystal structure determination for 41. A colourless prism crystal of dimensions 0.20 × 0.10 × 0.40 mm was mounted on a glass fibre: $C_{16}H_{30}INO_2Si$, *M* = 423.41, orthorhombic, *a* = 13.151(3), *b* = 21.506(3), *c* = 7.204(3) Å, *V* = 2037.5(7) Å^3, *T* = 299 K, space group $P2_12_12_1$ (no. 19), *Z* = 4, μ(Mo-Kα) 16.35 cm^{-1}, 5259 reflections collected, 1381 observed ($I > 2.00\sigma(I)$); *R* = 0.044, R_w = 0.045, goodness of fit = 1.67.

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