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AN APPROACH TO THE SYNTHESIS OF GELSEMINE: THE INTRAMOLECULAR REACTION OF AN ALLYLSILANE WITH AN ACYLIMINIUM ION FOR THE SYNTHESIS OF ONE OF THE QUATERNARY CENTRES[1]

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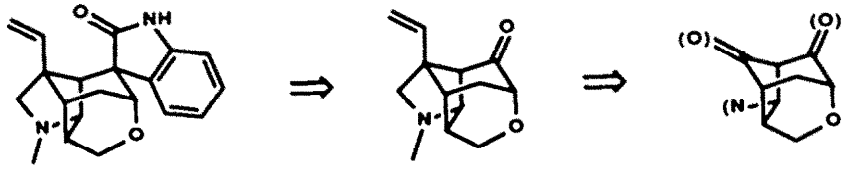
Summary—We describe an efficient synthesis (summarised in Schemes 8 and 10) of an advanced intermediate (**34**) suitable for the synthesis of gelsemine. The key steps in the synthesis are (i) the Diels-Alder reaction between 1-tetrahydropyranyloxycyclohexa-1,3-diene (**10**) and methyl β-nitroacrylate (**11**) giving an adduct (**12**), in which the chiral centre in the tetrahydropyranyl ring is produced substantially in only one sense, (ii) the rearrangement of a bicyclo[2.2.2]octane (**23**) into a bicyclo[3.2.1]octane (**24**), where control of which bridge migrates is achieved by a choice of the counterion in the Lewis acid, and (iii) the efficient formation of the quaternary centre by an intramolecular reaction between an allylsilane group and an acyliminium ion (**33** → **34**).

INTRODUCTION

We reported earlier[2,3] our plan to synthesise gelsemine (**1**)[4] by way, successively, of a diketone of the general structure (**3**), with the ketone groups differentiated in some way, and a ketone of general structure (**2**). In each of the synthetic steps (**3** → **2**) and (**2** → **1**), a ketone

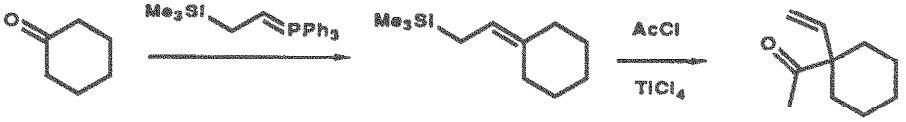


1 **2** **3**

Scheme 1

group is to serve as the precursor of a quaternary centre, and it is the challenge of these steps that has most excited our interest in the synthesis of gelsemine. We have already reported two pieces of work establishing how effective certain aspects of organosilicon chemistry can be for setting up quaternary centres, either of which might serve in the conversion (**3** → **2**): one uses

allylsilane chemistry and is illustrated by the reaction in Scheme 2;[5] the other uses a silicon-controlled carbonium ion rearrangement, and is illustrated by the reaction in Scheme 3.[6] We have also reported two new methods for making oxindoles from ketones in the sense (**2** → **1**).[7]



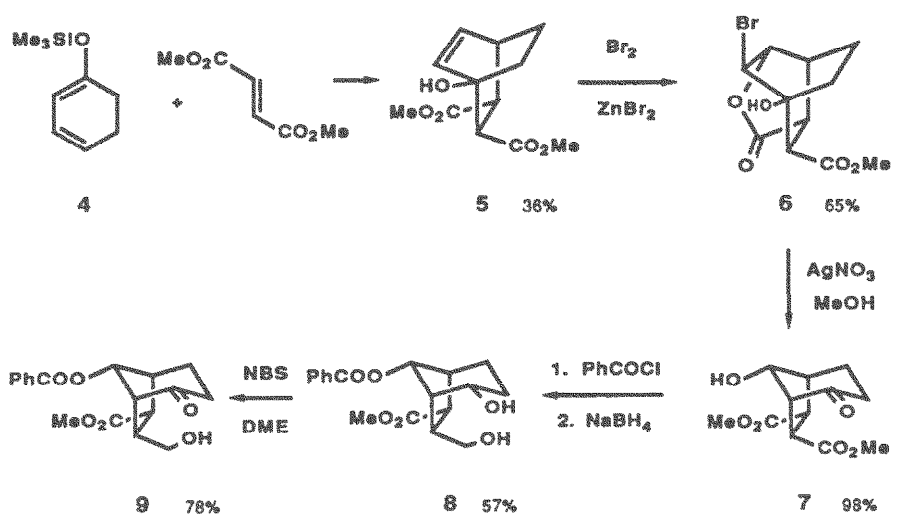
Scheme 2

Scheme 3

We now report the synthesis of the ketal (**25**), which is the real compound corresponding to the notional intermediate (**3**), and its conversion, using the intramolecular reaction of an allylsilane with an acyliminium ion, into the ketone (**34**), which is the real compound corresponding to the notional intermediate (**2**).[8]

RESULTS

All our routes begin with Diels-Alder reactions. In our earliest work,[3] we set up a bicyclo[2.2.1]heptene system, with the intention eventually of carrying out a ring expansion to get the bicyclo[3.2.1]octane skeleton embedded in the diketone (**3**). Both versions of this approach ran into obstacles, and we turned therefore to the possibility of using the Diels-Alder reaction to set up a bicyclo[2.2.2]octene, with the intention, this time, of rearranging it to a



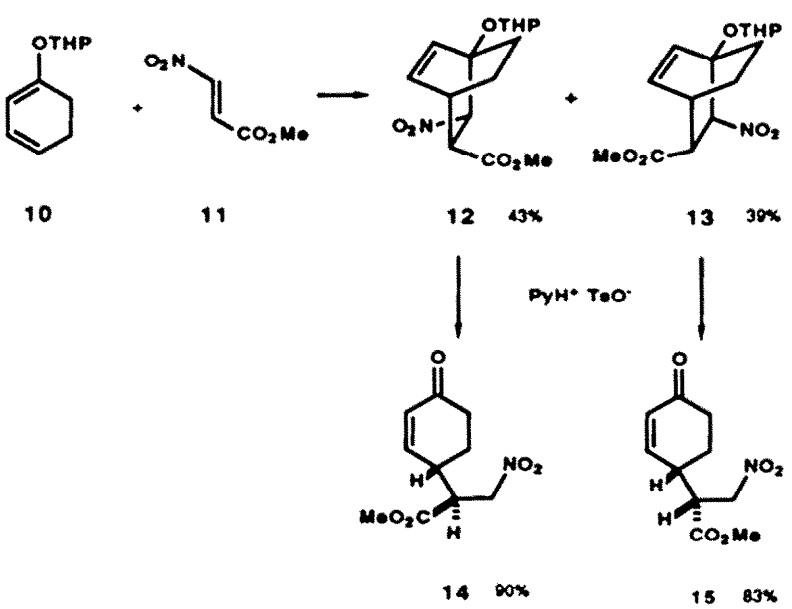
Scheme 4

bicyclo[3.2.1]octane system. The first version of this approach is illustrated in Scheme 4. The Diels-Alder reaction of the siloxycyclohexadiene (**4**) and dimethyl fumarate gave, as the major adduct, the stereoisomer (**5**), which, although it was not the one we expected from a simple frontier orbital argument,[9] was the appropriate isomer for the synthesis of geisemine. The endo

ester group allowed us to introduce the bromine substituent in the lactone (6) with the correct orientation to ensure the migration (6 → 7) of the functionalised bridge held antiperiplanar to it. This bridge, because it carries the methoxycarbonyl group is inherently slower to migrate than the unfunctionalised bridge, and it is an important feature of the design of this route that stereochemical control be used to ensure its migration. Furthermore, the ketone group in the product (7) was ideally placed to assist intramolecularly in the differentiation of the two methoxycarbonyl groups: the benzoate of the ketone (7) reacted with sodium borohydride to give the diol (8), by way of a γ-lactone intermediate, which we were able to isolate when we used a limited amount of sodium borohydride. Finally we oxidised the secondary alcohol group of 8 selectively to give the ketoalcohol (9). So far, all the substituents had cooperated in ensuring the selectivity that we needed; the problem was that the ketone group in 9 was at the wrong end of the three-carbon bridge, and this route had to be abandoned when we were unable to transpose the carbonyl group to the other side of the ring.

In the second approach along these lines we used β-nitroacrylate[10] (11) as the dienophile. This had the advantage that the two groups on the double bond were already differentiated, but it posed a number of problems. In the first place, there were now twice as many possible Diels-Alder adducts to sort out, and in the second there was no longer a methoxycarbonyl group that we could use to set up the correct regio- and stereochemistry in a bromolactonisation step like (5 → 6). Nevertheless, this approach was successful, and it illustrates how effective it is to make the first step in a synthesis create as much complexity as possible,[11] even when it means that it and subsequent steps are less easily predictable.

We tried a number of protecting groups on the diene (10), with various problems from each, but the most successful, and the only one leading to a crystalline adduct (12) was tetrahydropyranyl. With a yield of only 43% of a single compound having a sharp melting point, and seeing no sign in the NMR spectrum of any doubling of the signals, we entertained the hope

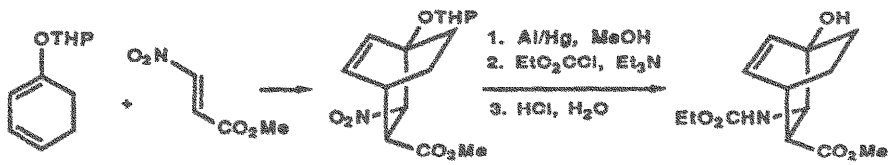


Scheme 5

that a major byproduct would turn out to be the diastereoisomer differing only in configuration at the chiral centre in the tetrahydropyranyl ring. However, the major byproduct, which accounts for a further 39% of the total product, proved to be the stereoisomer (13), in which the methoxycarbonyl group rather than the nitro group is endo, as shown by its conversion, in a retro-Henry reaction, to the ring-opened product (15), diastereoisomeric with the retro-Henry product (14) obtained from the major adduct. Only 18% of the mass balance is unaccounted for,

which implies that the chiral information in the tetrahydropyranyl ring has been transmitted into the cyclic transition state of the Diels-Alder reaction at the very least to the extent of 43:18, although in what sense, we do not yet know. Since the remaining 18% of product appears to be a mixture of several not easily separated compounds, with none obviously a major component, the selectivity must actually be much higher. This very remarkable type of transfer of chiral information is known from Stoodley's work with open-chain dienes attached anomerically to sugars,[12] and implies that if we are able to use a sugar in place of the tetrahydropyranyl ring, we should be able to convert this synthesis into one suitable for the synthesis of optically active gelsemine. The low endo selectivity of the nitro group relative to the methoxycarbonyl group, coupled with its high control of Diels-Alder regioselectivity has precedent in the work of Danishefsky.[13]

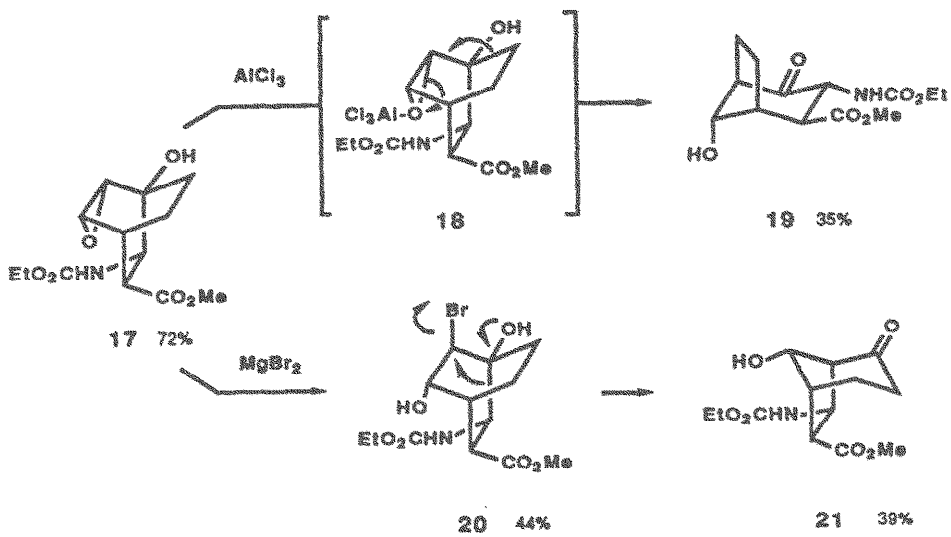
We now faced the problem of controlling a rearrangement without having the bromolactonisation step available for setting up the leaving group antiperiplanar to the functionalised bridge. After carrying out some functional group modifications (12 → 16), designed to remove any possibility of



10 11 12 49% 16 66%

Scheme 6

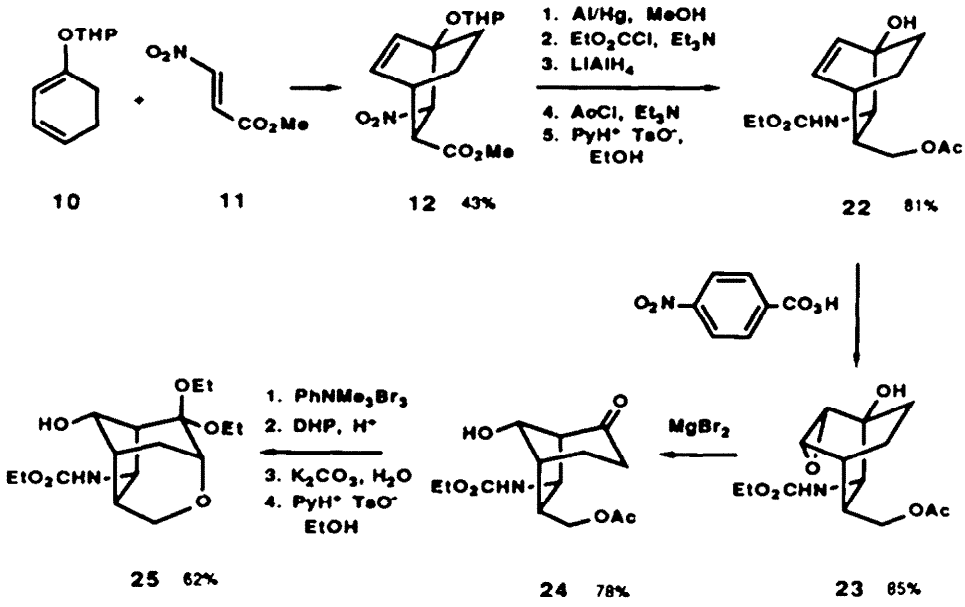
retro-Henry reaction, we found that epoxidation of the double bond took place disappointingly from the more hindered face of the double bond to give the epoxide (17), revealed by the migration (18, arrows) of the unfunctionalised bridge (17 → 19) when we treated the epoxide with aluminium chloride. The solution to this problem came when we found that migration could be subverted



Scheme 7

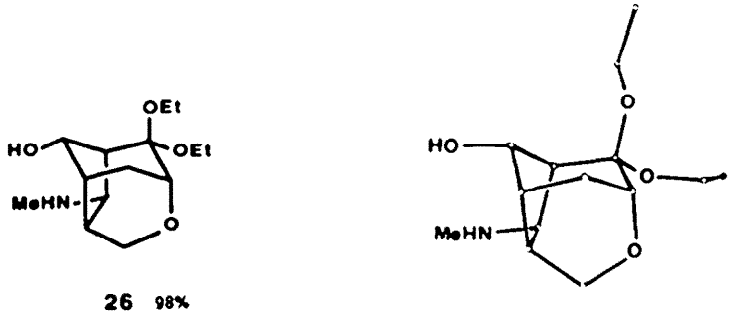
using magnesium bromide in place of aluminium chloride; now the major product was the bromohydrin (20) produced by a bromide ion opening the epoxide ring before it could set off rearrangement. Even more encouragingly, this product was accompanied by a new rearrangement product (21), which came from migration (20, arrows) of the functionalised bridge antiperiplanar to the bromine atom. Longer treatment of 20 with magnesium bromide converted it into 21, which

confirmed our analysis of the situation. Armed with this information, we optimised a slightly different sequence of events, summarised in Scheme 8, which also includes the subsequent steps establishing the ether bridge of the ketal (25). These steps are the bromination of the ketone (24), protection of the alcohol group (to avoid retro-aldol reactions), base-catalysed ether formation, and an acid-catalysed removal of the tetrahydropyranyl group in conditions that also protected the ketone group.



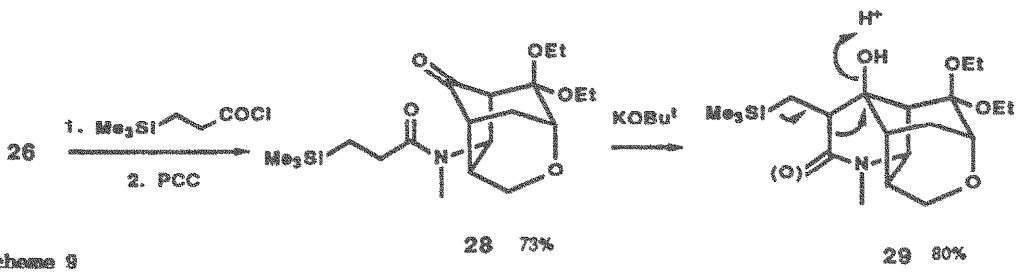
Scheme 8

We established the structure of the key intermediate (25), and hence of all the intermediates preceding it, by an X-ray crystal structure (27) of the methylamine (26) derived from it by reduction with lithium aluminium hydride. In summary, so far, we get the carbamate (25) in 15 steps from phenol, in an overall yield of 11.7%, with seven crystalline intermediates and only two serious chromatographies.



We were now ready to put in one of the quaternary centres. In our first approach, we carried out the sequence in Scheme 9 to set up a compound (29) having a silyl group γ to a tertiary alcohol—the structural subunit in which we had successfully induced silicon-controlled cationic rearrangement in our earlier work (Scheme 3).[6] In this case, however, we were unable to induce rearrangement by acid catalysis or by any other method: neither the alcohol (29) nor the amine derived from it by reduction with lithium aluminium hydride gave any recognisable product, even though the group that should have migrated, in the general sense (29, arrows), was held

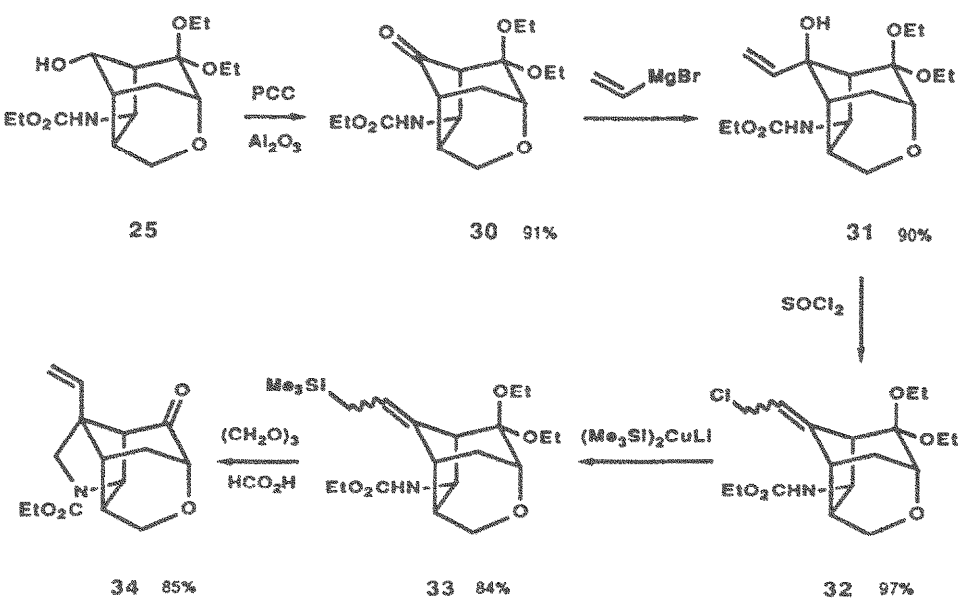
antiperiplanar to the departing hydroxy group. All our attempts to make the hydroxy group into a better leaving group failed, and we were also unsuccessful with reactions carried out on the ketone derived by hydrolysis of the diethyl acetal without success. The failure of this approach was perhaps not too surprising, in view of our earlier failure to induce ring-contractions and ring-expansions.[6] We had hoped that the rigid placing of the migrating group antiperiplanar to the leaving group in **29** would make rearrangement more favourable than it had been in the model



Scheme 9

systems, which were much less rigid, and in which hydride migration, not available in **29**, took place instead of ring contraction or expansion.

We had adopted the rearrangement route as our first choice because the second, which would follow our model work showing how powerful allylsilanes are in setting up quaternary centres (Scheme 2),[5] required a 5-endo-trig process[14] at the electrophilic end. In the meantime, Hiemstra and Speckamp and their co-workers demonstrated that allylsilanes react intramolecularly with acyliminium ions.[15] Since some of their successful reactions were 5-endo-trig in nature, we lost our inhibitions with respect to this approach, and were able quickly to set up the first of the quaternary centres in a sequence summarised in its optimised form in Scheme 10. The synthesis of



Scheme 10

the allylsilane (**33**) was not successful using a Wittig reaction[5,16] directly on the ketone (**30**), nor could we use our method involving the reaction of a silyl-cuprate reagent on a tertiary allylic acetate,[17] because the alcohol (**31**) would not form an acetate. The final step (**33** → **34**) that set up the quaternary centre, is closely modelled by a reaction reported by Hiemstra and Speckamp,[18] very shortly after we first carried out a reaction corresponding to (**33** → **34**), but having a

phenyldimethylsilyl group in place of the trimethylsilyl. In this step, the yield was significantly better with a trimethylsilyl group than with a phenyldimethylsilyl, but the yield of the allylsilane was slightly higher with the phenyldimethylsilyl group than with the trimethylsilyl group. Also, yields of the allylsilanes were slightly higher with the cuprate reagents than with the lithium reagents used by Smith in her otherwise similar allylsilane syntheses.[19]

All our attempts to put into practice our oxindole syntheses[7] on the ketone (34) (or on a ketone derived by protection of the hydroxyl and amino groups of 26 followed by hydrolysis of the ketal group), have so far met with failure: the first carbon-carbon bond-forming step works, but the subsequent steps, needing cationic intermediates, have been most discouraging. We surmise that the neighbouring oxygen function seriously interferes with the formation of cationic intermedates at the carbon atom that is to become the second quaternary centre. We also failed with a method of oxindole synthesis[20] based on a reaction of Zeeh's,[21] which similarly needs cationic intermediates, and with a Brunner synthesis,[22] which needs anionic intermediates, for which we prepared the way by improving the general conditions that this little used method needs.[23]

In summary, we have an effective route to an advanced intermediate, the ketone (34), which we call the noroxindolylgelsemine ketone. It is produced in twenty well worked upon steps with an overall yield of 6.6%, and we have, once again, demonstrated how powerful the allylsilane group is as a carbon nucleophile in organic synthesis.

EXPERIMENTAL

1-(Trimethylsilyloxy)-1,3-cyclohexadiene (4).—3-Cyclohexen-1-one[24] (23 g, 239 mmol) was added to a solution of lithium diisopropylamide (LDA)(251 mmol) in tetrahydrofuran (THF)(450 ml) at -75° and trimethylsilyl chloride (503 mmol) added. The mixture was allowed to warm to room temperature, the solvents evaporated off, and the residue taken up in pentane (300 ml). The mixture was cooled, filtered, and the solvent evaporated off, and the residue distilled to give the silyl dienol ether (31.4 g, 78%) b.p. 68-72°/12 mmHg, IR(film) 3050, 1650, 1590, and 1250 cm^{-1}, ^{1}H-NMR(CCl_4) 5.9-5.2 (2H, m), 5.02 (1H, d, J 6 Hz), 2.17 (4H, m), and 0.18 (9H, s)(Found: M$^+$, 168.0970. $C_9H_{16}OSi$ requires 168.0970).

Dimethyl 1(SR)-Hydroxybicyclo[2.2.2]oct-5-ene-2(SR),3(RS)-dicarboxylate (5).—The diene (4) (9.73 g) and dimethyl fumarate (8.34 g) were refluxed in toluene (60 ml) for 16 h. The solvent was evaporated off, the residue dissolved in MeOH (60 ml), and HCl (6 ml, 3M) added. After 2 h, the MeOH was evaporated off, and the residue worked up in $CHCl_3$, washing with sodium bicarbonate solution and water. Evaporation and chromatography (SiO_2, EtOAc-$CHCl_3$) gave first recovered fumarate (3.38 g), then the diastereoisomeric adduct followed by the adduct (5)(4.86 g, 36%) b.p. 134-135°/0.4 mmHg (Found: C, 60.2; H, 6.4. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%), IR(film) 3480 and 1725 cm^{-1}, ^{1}H-NMR($CDCl_3$) 6.28 (1H, dd, J 8 and 1.5 Hz), 6.07 (1H, dd, J 8 and 6 Hz), 3.79 (3H, s), 3.70 (3H, s), 3.5 (1H, s, OH), 3.19 (1H, dd, J 5.5 and 2.5 Hz), 3.05 (1H, dd, J 5.5 and 2 Hz), 2.9 (1H, m), and 1.8-1.35 (4H, m), m/z 240 (0.2%, M$^+$) and 153 (100).

6(RS)-Bromo-2(SR)-methoxycarbonyl-1(RS)-hydroxy-10-oxatricyclo[2.2.2.2^{1,3}]decan-9-one (6).—Bromine (10.9 g) was added to a vigorously stirred suspension of anhydrous $ZnBr_2$ (15.4 g) in a solution of 5 (16.4 g) in CH_2Cl_2 (250 ml). Aqueous workup and trituration with Et_2O gave the bromolactone (13.6 g, 65%) as prisms, m.p. 145-146° (from hexane-$CHCl_3$)(Found: C, 42.9; H, 4.2. $C_{11}H_{13}BrO_5$ requires C, 43.3; H, 4.3%), IR($CHCl_3$) 3575, 1795, and 1725 cm^{-1}, ^{1}H-NMR($CDCl_3$) 4.92 (1H, dd, J 5 and 1.5 Hz), 4.12 (1H, d, J 2 Hz), 3.85 (3H, s), 3.25 (1H, dt, J 4.5 and 1.5 Hz), 3.1 (1H, s, OH), 2.8 (1H, t, J 1.5 Hz), 2.5 (1H, m), 2.2-1.8 (4H, m), m/z 305 (2%, M$^+$) and 179 (100).

Dimethyl 8(SR)-Hydroxybicyclo[3.2.1]octan-5-one-2(RS),3(RS)-dicarboxylate (7).—Silver nitrate (5.95 g) was added to a solution of 6 (7.13 g) in MeOH (250 ml) and water (9 ml) and the mixture refluxed for 16 h. The AgBr was filtered off and the MeOH evaporated. An aqueous workup gave the ketone (5.85 g, 98%), b.p. 180-185°/0.1 mmHg, IR($CHCl_3$) 3425 and 1720 cm^{-1}, ^{1}H-NMR($CDCl_3$) 4.02 (1H, s), 3.98 (1H, t, J 6 Hz), 3.79 (2H, s), 3.70 (3H, s), 3.33 (1H, d, J 6 Hz), 3.25 (1H, s, OH), 3.20 (1H, d, J 6 Hz), 2.91 (1H, m), 2.3-2.0 (2H, m), ans 2.0-1.7 (2H, m)(Found: M$^+$, 256.0963. $C_{12}H_{16}O_5$ requires M, 256.0947), m/z 256 (31%, M$^+$) and 181 (100).

Dimethyl 8(SR)-Benzoyloxybicyclo[3.2.1]octan-5-one-2(RS),3(RS)-dicarboxylate.—Benzoyl chloride (3.32 g) and 7 (6.08 g) were kept in pyridine (54 ml) at 50° for 20 h. The pyridine was evaporated off, and the residue worked up in EtOAc washing with dilute hydrochloric acid and

sodium bicarbonate solution to give the benzoate (5.08 g, 59%) as needles, m.p. 131-132° (from hexane-$CHCl_3$)(Found: C, 63.2; H, 5.55. $C_{19}H_{22}O_7$ requires C, 63.3; H, 5.6%), IR($CHCl_3$) 1725 cm^{-1}, ^{1}H-NMR($CDCl_3$) 8.0 (2H, m), 7.5 (3H, m), 5.35 (1H, s), 4.21 (1H, t, J 6 Hz), 3.78 (3H, s), 3.69 (3H, s), 3.51 (1H,d, J 6 Hz),3.48 (1H, d, J 6 Hz), 3.28 (1H, m), 2.51-2.38 (2H, m), and 2.2-1.9 (2H, m), m/z 360 (0.3%, M$^+$) and 103 (100).

Methyl 8(SR)-Benzoyloxy-5(RS)-hydrox-3(RS)-hydroxymethylbicyclo[3.2.1]octan-2(SR)-carboxylate (8).—Sodium borohydride (1.84 g) was added over 0.75 h to a solution of the benzoate (3.51 g) in MeOH (155 ml) at 15°. After the disappearance of the starting material [Rf(EtOAc-$CHCl_3$ 1:4) 0.53] and the lactone (Rf 0.59), the solvent was evaporated and the residue worked up in $CHCl_3$ to give the diol (3.15 g, 97%) b.p. 225-230°/0.5 mmHg, Rf 0.13, IR($CHCl_3$) 3400 and 1715 cm^{-1}, ^{1}H-NMR($CDCl_3$) 8.1-7.85 (2H, m), 7.6-7.3 (3H, m), 4.83 (1H, s), 4.15 (2H, s, OH's), 4.0 (3H, m), 3.6 (3H, s), 3.12 (1H, br t, J 7 Hz), 2.92 (1H, m), 2.75 (1H, m), 2.43 (1H, d, J 7 Hz), 1.7 (4H, m). When only one equivalent of $NaBH_4$ was used we isolated the lactone, 10(SR)-benzoyloxy-2(RS)-methoxycarbonyl-9-oxatricyclo[3.2.2.^{3,5}1]decan-8-one, (43%) as needles, m.p. 100-102° (from hexane-$CHCl_3$), IR($CHCl_3$) 1760 and 1720 cm^{-1}, ^{1}H-NMR($CDCl_3$) 7.95-7.7 (2H, m), 7.5-7.2 (3H, m), 5.36 (1H, s), 5.03 (1H, br d, J 10 Hz), 3.88 (1H, dd, J 8 and 2 Hz), 3.45 (3H, s), 3.26 (1H, m), 3.1 (1H, m), 2.88 (1H, br d, J 2 Hz), 1.91 (1H, m), and 1.71 (3H, m)(Found: M$^+$, 330.1112. $C_{18}H_{22}O_6$ requires M, 330.1104).

Methyl 8(SR)-Benzoyloxy-3(RS)-hydroxymethylbicyclo[3.2.1]octan-5-one-2(SR)-carboxylate (9).—Following the method of Corey,[25] N-bromosuccinimide (1.57 g) and 8 (1.96 g) were kept in dimethoxyethane (36 ml) and water (4 ml) for 48 h, and the mixture worked up with $CHCl_3$ to give the ketone (1.525 g, 78%) as prisms m.p. 102.5-103.5° (from hexane-$CHCl_3$)(Found: C, 65.15; H, 6.05. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.05%), IR($CHCl_3$) 3575 and 1720 cm^{-1}, ^{1}H-NMR($CDCl_3$) 8.03-7.9 (2H, m), 7.65-7.25 (3H, m), 5.4 (1H, s), 4.21 (1H, dd, J 9 and 4 Hz), 3.95 (1H, d, J 9 Hz), 3.55 (3H, s), 3.47 (1H, m), 3.14 (1H, s, OH), 3.07 (1H, d, J 8 Hz), 2.90 (1H, d, J 6 Hz), 2.45 (1H, d, J 4 Hz), and 2.2-1.5 (4H, m).

Phenyl 2-Tetrahydropyranyl Ether.—p-Toluenesulphonic acid (2.8 g), phenol (106 g) and freshly distilled dihydropyran (94.8 g) were kept in CH_2Cl_2 (1000 ml) at 0° for 1 h. Solid KOH (25 g) was added and the mixture stirred for 1.5 h. Water (30 ml) was added and stirring continued for 1 h. The organic phase was separated off, dried (KOH), and the solvent evaporated to give the ether,[26] which was purified by distillation through a 15 cm Vigreux column (174.8 g, 87%) b.p. 60-66°/0.1 mmHg, ^{1}H-NMR($CDCl_3$) 7.45-6.75 (5H, m), 5.35 (1H, br s), 4.1-3.31 (2H, m), and 2.11-1.32 (6H, m).

1-(2'-Tetrahydropyranyloxy)cyclohexa-1,4-diene.—Sodium (93 g) was added in portions of 1 g to a solution of the ether (120 g) in Et_2O (1000 ml) and ammonia (3000-3500 ml) at -78°. The dark blue mixture was allowed to warm to -33°, stirred for 5 h under reflux, and then cooled to -78°. Methanol (250 ml) was added over 1 h, avoiding the deposition of solid on the side of the flask by vigorous stirring and efficient cooling. The ammonia was allowed to evaporate overnight and the residue subjected to an aqueous work up to give the ether[27] (117 g, 97%)(a sample crystallised as plates m.p. 30-32°), ^{1}H-NMR($CDCl_3$) 5.60 (2H, br s), 5.15 (1H, br s), 4.95 (1H, br s), 4.11-3.33 (2H, m), 2.82 (4H, br s), and 2.29-1.31 (6H, m), which was carried forward without further purification.

1-(2'-Tetrahydropyranyloxy)cyclohexa-1,3-diene (10).—Potassium t-butoxide (20 g) and the 1,4-diene (62.2 g) were kept in dimethyl sulphoxide (500 ml, dried over 4A molecular sieves) for 3 h. A water and ether workup gave a crude product (96%) suitable for the next step. Distillation gave a 3:1 mixture of the 1,3-[28] and 1,4-dienes (51 g, 82%), b.p. 60-64°/0.1 mmHg, IR(film) 3050, 1650, 1598, 1200, and 1040 cm^{-1}, ^{1}H-NMR($CDCl_3$) 6.01-4.85 (4H, m) 4.02-3.23 (2H, m), 2.25 (4H, br s), and 2.0-1.11 (6H, m).

5-exo-Methoxycarbonyl-6-endo-nitro-1-(2'-tetrahydropyranyloxy)bicyclo[2.2.2]oct-2-ene (12).—The mixture of dienes (46.8 g), methyl β-nitroacrylate[10] (26.2 g), and pyrogallol (300 mg) were mixed in benzene (300 ml) and stirred at 0° for 1 h, then for a further 3 h at room temperature, following the reaction by the disappearance of the vinyl signals of 11 at 8.0-7.5 ppm in the ^{1}H-NMR spectrum of the mixture. The benzene was evaporated off, the residue dissolved in a minimum of hot Et_2O (ca 300 ml), and left to crystallise, finishing at -78°. The solid was washed with cold Et_2O to give the adduct (26.7g, 43%), m.p. 85-87°, suitable for the next step. Recrystallisation gave needles, m.p. 102-103° (from Et_2O)(Found: C, 57.8; H, 6.75; N, 4.4. $C_{15}H_{21}NO_6$ requires C, 57.9; H, 6.8; N, 4.5%), IR(CCl_4) 3100, 1742, 1560, and 1360 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 6.43 (1H, dd, J 9 and 6.5 Hz), 6.35 (1H, d, J 9 Hz), 5.31 (1H, d, J, 5 Hz), 4.95 (1H, m), 3.94 (1H, m), 3.75 (3H, s), 3.49 (1H, m), 3.01 (2H, m), 1.83-1.53 (9H, m), and 1.32 (1H, m), m/z 311 (1%, M$^+$), 228 (4), 96 (15), and 85 (100). Chromatography (SiO_2, eluting first with light petroleum to remove unconjugated diene and then gradually adding Et_2O) of the mother liquors gave the isomeric adduct (13)(39%) as a yellow oil, IR(CH_2Cl_2) 2920, 2850, 1740, 1550, and 1360 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 6.66 (1H, d, J 8.8 Hz), 6.22 (1H, dd, J 8.8 and 6.2 Hz), 5.08 (1H, m), 5.04 (1H, br d, J 4.2 Hz), 4.91 (1H, m), 3.67 (3H, s), 3.50 (2H, m), 3.37 (1H, m), 2.08-1.42 (10H, m).

Hydrolysis of the Diels-Alder Adducts (12 and 13).—The adduct (12)(100 mg) and pyridinium p-toluenesulphonate[29] (8 mg) were kept in EtOH (10 ml) at 50° for 2 h. Evaporation of the solvent, an aqueous workup in CH_2Cl_2, and chromatography (SiO_2, Et_2O-light petroleum, 4:1) gave 4(SR)-[1'-(SR)-methoxycarbonyl-2-nitroethyl]cyclohex-2-enone (14)(65 mg, 90%) IR(CH_2Cl_2) 2940, 1740, 1680, and 1560 cm^{-1}, ^{1}H-NMR($CDCl_3$) 6.85 (1H, d, J 9.5 Hz), 6.17 (1H, dd, J 9.5 and 3 Hz), 4.95 (1H, dd, J 15 and 9 Hz), 4.55 (1H, dd, J 15 and 4.5 Hz), 3.80 (3H, s), 3.65-3.55 (1H, m), 3.20-2.95 (1H, m), 2.80-1.60 (4H, m). A similar reaction carried out on the

impure diastereoisomer (13) gave 4(SR)-[1'-(RS)-methoxycarbonyl-2-nitroethyl]cyclohex-2-enone (15)(83%) IR(CH_2Cl_2) 2940, 1740, 1680, and 1560 cm^{-1}, ^{1}H-NMR($CDCl_3$) 6.95 (1H, d, J 10.5 Hz), 6.17 (1H, dd, J 10.5 and 3 Hz), 4.95 (1H, dd, J 15 and 9 Hz), 4.55 (1H, dd, J 15 and 3 Hz), 3.80 (3H, s), 3.65-3.55 (1H, m), 3.20-2.95 (1H, m), 2.65-1.60 (4H, m), minutely but just detectably different from its diastereoisomer (14).

6-endo-Ethoxycarbonylamino-5-exo-methoxycarbonyl-1-(2'-tetrahydropyranyloxy)bicyclo[2.2.2]oct-2-ene.—Aqueous methanol (1750 ml, 10% H_2O) was added to a mixture of 12 (45.5 g) and aluminium amalgam[10] (48 g) in THF (800 ml) and stirred vigorously for 12-18 h. The mixture was filtered through a large fritted glass funnel and the aluminium salts washed thoroughly with ether (4 × 200 ml). Evaporation of the solvent gave the amine (38.4 g, 93%), IR(film) 3420, 3345, 3095, and 1730 cm^{-1}, ^{1}H-NMR($CDCl_3$) 6.5-5.99 (2H, m), 4.92 (1H, br s), 3.76 (3H, s), 4.2-3.4 (3H, m), 2.83 (1H, m), 2.13 (1H, m), 1.91 (2H, br s), and 2.03-1.23 (10H, m). Ethyl chloroformate (17.9 g, 15.7 ml) was added by syringe to a solution of the amine (38.4 g) and distilled triethylamine (21.8 g, 30 ml) in Et_2O (800 ml) at 0°, and the suspension stirred for 5-12 h slowly allowing it to come to room temperature. An aqueous work up using ether, and trituration in ether gave the carbamate (47.6 g, 99%), m.p. 61-69° suitable for the next step. Recrystallisation gave plates, m.p. 82-84° (from MeOH-Et_2O, 5:95)(Found: C, 61.4; H, 7.85; N, 3.95. $C_{18}H_{27}NO_6$ requires C, 61.2; H, 7.7; N, 3.95%), IR(CCl_4) 3440, 3325, 3050, and 1720 cm^{-1}, ^{1}H-NMR($CDCl_3$) 6.47-5.98 (2H, m), 4.90 (2H, m), 4.05 (2H, q, J 7 Hz), 3.71 (3H, s), 4.32-3.21 (3H, m), 2.65 (1H, m), 2.3 (1H, m), 2.0-1.35 (10H, m), and 1.18 (3H, t, J 7 Hz), m/z 353 (0.04%, M⁺), 269 (4), 174 (22), 96 (70), and 85 (100).

1-Hydroxy-6-endo-ethoxycarbonylamino-5-exo-methoxycarbonylbicyclo[2.2.2]oct-2-ene (16).—A mixture of the tetrahydropyranyl ether (3 g) in THF (70 ml) and aqueous hydrochloric acid (50 ml, 1M) was stirred for 5 h. Extraction with EtOAc and chromatography (SiO_2, Et_2O) gave the alcohol (1.9 g, 83%), IR($CHCl_3$) 3650-3050 br, 3048, 1750, and 1700 cm^{-1}, ^{1}H-NMR($CDCl_3$) 6.05-5.7 (2H, m), 4.7 (1H, br s), 3.87 (2H, q, J 7 Hz), 3.95-3.7 (1H, m), 3.57 (3H, s), 2.5 (1H, m), 2.07 (1H, m), 1.8-1.2 (4H, m), 1.2 (3H, t, J 7 Hz).

1-Hydroxy-6-endo-ethoxycarbonylamino-5-exo-methoxycarbonylbicyclo[2.2.2]octan-2,3-epoxide (17).—The alkene (16)(9.2 g), 4,4'-thiobis(2-t-butyl-6-methylphenol),[11] and p-nitroperbenzoic acid (18.7 g) were stirred in $CHCl_3$ (350 ml) for 24 h. An aqueous workup using EtOAc, followed by chromatography (SiO_2, Et_2O) gave the epoxide (7 g, 72%)(Found: C, 54.7; H, 6.5; N, 5.1. $C_{13}H_{19}NO_6$ requires C, 54.7; H, 6.7; N, 4.9%), IR($CHCl_3$) 3750-3200 and 1750-1685 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.37 (1H, br d, J 9.9 Hz), 4.24 (1H, br m), 4.1 (2H, q, J 7.1 Hz), 3.69 (3H, s), 3.48 (1H, t, J 5.1 Hz), 3.25 (1H, dd, J 5.1 and 1.7 Hz), 2.56 (2H, m), 1.76-1.56 (5H, m), and 1.22 (3H, t, J 7.1 Hz), ^{13}C-NMR($CDCl_3$) 173.23, 157.57, 74.22, 64.15, 55.8, 55.2, 53,45, 52.19, 47.95, 31.45, 29.32, 22.24, and 14.44.

syn-3-Ethoxycarbonylamino-4-anti-methoxycarbonyl-8-syn-hydroxybicyclo[3.2.1]octan-2-one (19).—The epoxide (160 mg) in CH_2Cl_2 (3 ml) was added to a suspension of $AlCl_3$ (300 mg) in CH_2Cl_2 (5 ml) at -10° and the mixture stirred at -10° for 4 h before being quenched with sodium bicarbonate solution (10 ml). An aqueous workup gave the ketone as needles m.p. 128-131° (from EtOAc-Et_2O, 1:4, at -20°)(55 mg, 35%)(Found: C, 54.7; H, 6.5; N, 5.1. $C_{13}H_{19}NO_6$ requires C, 54.7; H, 6.7; N, 4.9%), IR($CHCl_3$) 3650-3150 and 1730 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.39 (1H, br d, J 8.7 Hz), 4.5 (1H, br t, J 8.7 Hz), 4.4 (1H, t, J 5 Hz, CHOH with the H "equatorial" in the six-membered ring)(this signal was shifted to δ 5.2 on acetylation), 4.09 (2H, q, J 7.1 Hz), 3.73 (3H, s), 3.34 (1H, br d, J 8.7 Hz), 2.87 (1H, br t, J 5.5 Hz), 2.62 (1H, br m), 1.99-1.85 (3H, br m), 1.75 (1H, m), and 1.22 (3H, t, J 7.1 Hz), ^{13}C-NMR($CDCl_3$) 207.26, 173.24, 156.93, 77.61, 61.51, 55.56, 54.36, 52.19, 48.28, 41.64, 23.63, and 14.38.

Treatment of the Epoxide (17) with Magnesium Bromide.—The epoxide (1.56 g, 5.45 mmol) in THF (35 ml) was added to a stirred solution of $MgBr_2$ etherate[12] (27.25 mmol) in ether (50 ml) and benzene (70 ml). More THF (35 ml) was then added and the mixture stirred for 17 h. An aqueous workup and chromatography (SiO_2, Et_2O) gave first, Rf 0.5 (Et_2O), 2-exo-bromo-6-endo-ethoxycarbonylamino-3-hydroxy-5-exo-methoxycarbonylbicyclo[2.2.2]octan-1-ol (20)(870 mg, 44%) as prisms m.p. 163-165° (from EtOAc-Et_2O, 1:4), IR($CHCl_3$) 3600-3100 and 1740-1700 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.54 (1H, br m), 4.47 (1H, dd, J 7.1 and 5.2 Hz), 4.34 (1H, m), 4.18 (1H, br s), 4.09 (2H, q, J 7.1 Hz), 3.73 (3H, s), 3.8 (1H, br s), 3.51 (1H, br s), 3.09 (1H, br s), 2.12 (2H, m), 1.94 (1H, m), 1.71-1.5 (2H, m), 1.22 (3H, t, J 7.1 Hz)(Found: M⁺, 365.0478. $C_{13}H_{20}BrNO_6$ requires 365.0475), followed by, Rf 0.33, 7-anti-ethoxycarbonylamino-8-anti-hydroxy-6-syn-methoxycarbonylbicyclo[3.2.1]octan-2-one (21)(600 mg, 39%) as prisms m.p. 119-120° (from MeOH-Et_2O, 15:85), IR($CHCl_3$) 3550-3150 and 1740-1680 cm^{-1}, ^{1}H-NMR($CDCl_3$, 90 MHz) 5.83 (1H, br d, J 9 Hz), 4.67 (1H, dd, J 9 and 6 Hz), 4.18 (2H, q, J 7 Hz), 3.81 (3H, s), 3.5 (1H, m), 2.93 (1H, m) 2.78 (1H, br s), 2.69-2.03 (2H, m), 1.8-1.5 (2H, m), and 1.29 (3H, t, J 7 Hz)(Found: M⁺, 285.1216. $C_{13}H_{19}NO_6$ requires 285.1216).

6-endo-Ethoxycarbonylamino-5-exo-hydroxymethyl-1-(2'-tetrahydropyranyloxy)bicyclo[2.2.2]oct-2-ene.—The ester (prepared in two steps from 12 as described above) (47.6 g) in Et_2O (750 ml) was added to a suspension of $LiAlH_4$ (20.5 g) in Et_2O (400 ml) at -15° over 75 min, and the mixture stirred for a further 30 min. The excess hydride was decomposed by slow addition of EtOAc (100 ml) and the mixture stirred for 15 min. Sodium hydroxide solution (500 ml, 15%) and more ether (500 ml) were added, and the mixture filtered. Evaporation of the solvent gave the alcohol (41 g, 94%) suitable for the next step, IR(CCl_4) 3650-3150, 3055, and 1730-1695 cm^{-1}, ^{1}H-NMR($CDCl_3$, 90 MHz) 6.53 (1H, dd, J 7 and 6 Hz), 6.12 (1H, d, J 7 Hz), 5.01 (2H, br m, including NH), 4.12 (2H, q, J 7 Hz), 4.32-3.31 (6H, m, including OH), 2.52 (2H, br m), 2.0-1.2 (10H, m), and 1.23 (3H, t, J 7 Hz)(Found: M⁺ - 1 - C_3H_6O 240.1233. $C_{17}H_{27}NO_6$ - 1 - C_3H_6O requires 240.1236), m/z 240 (0.4%, M - 1 - C_3H_6O), 223 (5), 180 (5), 146 (5), 128 (51), 96 (82), and 85 (100).

5-exo-Acetoxymethyl-6-endo-ethoxycarbonylamino-1-(2'-tetrahydropyranyloxy)bicyclo[2.2.2]oct-2-ene.—Acetyl chloride (13.2 g) was added over 0.5 h to a solution of the alcohol (41 g), triethylamine (18.9 g) and 4-*N*,*N*-dimethylaminopyridine (310 mg) in THF (1500 ml) at 0° and the mixture stirred for a further 1 h, allowing it to warm to room temperature. An aqueous workup using ether (1000 ml) gave the acetate (45.7 g, 99%) as a yellow solid, m.p. 73-90°, of suitable purity for the next step. Recrystallisation gave plates, m.p. 94-97° (from Et_2O)(Found: C, 62.3; H, 8.1; N, 3.6. $C_{18}H_{29}NO_6$ requires C, 62.1; H, 7.95; N, 3.8%), IR(CCl_4) 3450, 3350, 3060, and 1745-1730 cm^{-1}, ^{1}H-NMR($CDCl_3$, 90 MHz) 6.42 (1H, dd, *J* 9 and 8 Hz), 6.15 (1H, d, *J* 9 Hz), 5.04 (1H, br s), 4.65 (1H, br d, *J* 9 Hz, NH), 4.41-3.82 (5H, m), 3.7-3.35 (2H, m), 2.50 (1H, m), 2.05 (3H, s), 2.01-1.15 (11H, m), and 1.25 (3H, t, *J* 7 Hz), *m*/*z* 368 (0.1%, *M*$^+$), 284 (3), 238 (8), 223 (25), 188 (18), 180 (43), 128 (100), 96 (85), and 85 (100).

5-exo-Acetoxymethyl-6-endo-ethoxycarbonylamino-1-hydroxybicyclo[2.2.2]oct-2-ene (**22**).—The tetrahydropyranyl ether (44.2 g) and pyridinium *p*-toluenesulphonate[29] (3.8 g) were kept in EtOH (1250 ml) at 55° for 3 h. The EtOH was evaporated off and the residue worked up using ether, to give crude product containing ethyl tetrahydropyranyl ether, which was removed at 50°/0.1 mmHg to give the alcohol (33.7 g, 95%) suitable for the next step. One crystallisation from diisopropyl ether at this stage is sometimes wise. Recrystallisation gave prisms m.p. 77-78° (from Et_2O)(Found: C, 59.6; H, 7.6; N, 4.8. $C_{14}H_{21}NO_5$ requires C, 59.4; H, 7.5; N, 4.9%), IR(CCl_4) 3600-3200, 3060, and 1750-1700 cm^{-1}, ^{1}H-NMR($CDCl_3$, 90 MHz) 6.41 (1H, dd, *J* 9 and 8 Hz), 6.15 (1H, d, *J* 8 Hz), 4.88 (1H, br d, *J* 9 Hz, NH), 4.54-3.91 (4H, m), 3.40 (1H, m), 3.03 (1H, br m, OH), 2.52 (1H, m), 2.05 (3H, s), 2.01-1.41 (5H, m), and 1.25 (3H, t, *J* 7 Hz), *m*/*z* 283 (0.1%, *M*$^+$), 223 (5), 128 (100), and 96 (44).

5-exo-Acetoxymethyl-6-endo-ethoxycarbonylamino-1-hydroxybicyclo[2.2.2]octan-2,3-endo-epoxide (**23**).—The alkene (11.25 g), 4,4'-thiobis(2-t-butyl-6-methylphenol)[31] (28.5 mg), and *p*-nitroperbenzoic acid (14.55 g) were stirred in CH_2Cl_2 (300 ml) for 16 h. An aqueous workup and chromatography (SiO_2, EtOAc-light petroleum, 85:15) separated the epoxides (10.1 g, 85%) from a less polar yellow compound, Rf (SiO_2, EtOAc) 0.75), and more polar products, Rf 0.21. Careful chromatography separated the two epoxides, but this is unnecessary. The endo-epoxide (77%) was obtained as plates, m.p. 84-87° (from CCl_4-light petroleum)(Found: C, 55.8; H, 6.9; N, 4.5. $C_{14}H_{21}NO_6$ requires C, 56.2; H, 7.05; N, 4.7%), Rf (SiO_2, EtOAc) 0.45, IR($CDCl_3$) 3700-3200 and 1750-1690 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.41 (1H, br d, *J* 10 Hz), 4.10 (2H, q, *J* 7 Hz), 4.15-3.95 (2H, m), 3.48 (1H, t, *J* 5 Hz), 3.26 (1H, dd, *J* 5 and 1.5 Hz), 3.3-3.25 (1H, m), 3.13 (1H, br m, OH), 2.23 (1H, m), 2.03 (3H, s), 2.0-1.63 (4H, m), 1.48 (1H, m), and 1.24 (3H, t, *J* 7 Hz), *m*/*z* 239 (1.8%, *M*$^+$ - AcOH), 221 (8), 166 (41), 128 (100), 122 (77), 112 (58), and 94 (44). The exo-epoxide (6%) was obtained as needles, m.p. 117-118° (from Et_2O-MeOH, 95:5)(Found: C, 56.0; H, 7.1; N, 4.7%), Rf 0.52, IR(CCl_4) 3700-3200 and 1760-1690 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 4.76 (1H, br d, *J* 10 Hz, NH), 4.28 (1H, dd, *J* 11 and 6.5 Hz), 4.18-4.07 (1H, m), 4.13 (2H, q, *J* 7 Hz), 3.5-3.37 (1H, m), 3.39 (1H, dd, *J* 5 and 1.5 Hz), 3.29 (1H, dd, *J* 5 and 1 Hz)), 3.20 (1H, br m, OH), 2.19 (1H, m), 2.04 (3H, s), 2.0-1.87 (2H, m), 1.59 (1H, m), 1.43 (1H, m), 1.28-1.15 (1H, m), and 1.25 (3H, t, *J* 7 Hz), *m*/*z* 239 (0.9%, *M*$^+$ - AcOH), 128 (100), 112 (37), 96 (39), and 56 (58).

6-endo-Acetoxymethyl-7-exo-ethoxycarbonylamino-8-exo-hydroxybicyclo[3.2.1]octan-2-one (**24**).—The mixture of epoxides (7 g, 23.4 mmol) in benzene (180 ml) and $MgBr_2$ etherate [133 mmol, prepared[32] from Mg (3.2 g) and dibromoethane (24.9 g) in Et_2O (160 ml) and solubilised by the addition of benzene (160 ml)] were mixed, enough THF (150 ml) was added to dissolve the precipitate that formed, and the mixture was refluxed (65°) for 19 h. An aqueous workup and crystallisation from diisopropyl ether gave the ketone (5.45 g, 78%), m.p. 103-106°, suitable for the next step. Recrystallisation gave needles, m.p. 110-112° (from Et_2O-MeOH, 90:10)(Found: C, 56.1; H, 7.15; N, 4.7. $C_{14}H_{21}NO_6$ requires C, 56.2; H, 7.05; N, 4.7%), IR(CCl_4) 3440, 3260, 3080, 1750-1720, and 1680 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.36 (1H, br d, *J* 9 Hz, NH), 4.42 (1H, dd, *J* 11 and 7 Hz), 4.26 (1H, dd, *J* 11 and 8.5 Hz), 4.10 (2H, q, *J* 7 Hz), 4.08 (1H, br s, CHOH "axial" in the six-membered ring, compare the chemical shift and coupling features of this signal with the corresponding signal in **19**; the difference was critical in assigning structures to the two series of rearrangement products), 3.89 (1H, m), 2.84 (1H, m), 2.73 (1H, br s), 2.73-2.6 (1H, m, OH), 2.60 (1H, m), 2.23 (2H, m), 2.07 (3H, s), 1.86 (1H, m), 1.61 (1H, m), and 1.23 (3H, t, *J* 7 Hz), *m*/*z* 299 (10%, *M*$^+$), 239 (33), 221 (61), 161 (60), 160 (67), 157 (83), 150 (42), 144 (62), 128 (87), 125 (48), 122 (100), and 94 (58). The mother liquors of the diisopropyl ether crystallisation can be evaporated and the residue treated with the same reagents as the main crop in the next step to give more of the bromoketone, which is easier to isolate and purify than the ketone (**21**). In exploratory work we isolated the unrearranged bromohydrin, 5-exo-acetoxymethyl-2-exo-bromo-6-endo-ethoxycarbonylamino-1,3-endodihydroxybicyclo[2.2.2]octane as prisms, m.p. 163-165° (from EtOAc-Et_2O)(Found: C, 43.7; H, 5.8; N, 3.6. $C_{14}H_{22}BrNO_6$ requires C, 44.2; H, 5.8; N, 3.7%), IR(CCl_4) 3600-3100, 1720, and 1700 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.10 (1H, br d, *J* 7.5 Hz, NH), 4.34 (1H, m), 4.25-4.06 (5H, m), 3.67 (1H, dd, *J* 7.5 and 6 Hz), 2.38 (1H, m), 2.06 (3H, s), 2.11-2.02 (1H, m), 1.85 (3H, m, includes OH), 1.65 (1H, m), 1.44 (1H, m), and 1.26 (3H, t, *J* 7 Hz)(Found: 300.1455. $C_{14}H_{22}BrNO_6$ - Br requires 301.1448), *m*/*z* 300 (1.8%, *M*$^+$ - Br), 282 (3), 222 (100), 194 (10), 176 (20), and 133 (51).

6-endo-Acetoxymethyl-3-exo-bromo-7-exo-ethoxycarbonylamino-8-exo-hydroxybicyclo[3.2.1]octan-2-one.—Phenyltrimethylammonium tribromide (6.47 g) was added to the ketone (**24**)(5 g) in CH_2Cl_2 (80 ml) and the solution kept for 15 min. The solvent was evaporated off, THF (40 ml) was added, the precipitate filtered off, and the solution filtered through SiO_2 (100 g), washing through with Et_2O. The solvent was again evaporated off to give the bromoketone (6.31 g, 100%), m.p. 153-155°, suitable for the next step, although a brief boil with Et_2O cleans it up a little with minimal losses, and the combined mother liquors can be concentrated and chromatographed (SiO_2, Et_2O) to recover further small amounts. Recrystallisation gave needles, m.p. 170-172° (from

$CHCl_3$)(Found: C, 44.3; H, 5.3; N, 3.8 $C_{14}H_{19}BrNO_4$ requires C, 44.5; H, 5.3; N, 3.7%), IR(CCl_4) 3500-3200, 1735, 1715, and 1690 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.23 (1H, br d, J 9.5 Hz, NH), 4.63 (1H, dd, J 12.5 and 9 Hz), 4.48 (1H, dd, J 11.5 and 6.5 Hz), 4.31 (1H, dd, J 11.5 and 8 Hz), 4.17 (1H, br s), 4.12 (2H, q, J 7 Hz), 4.02 (1H, m), 3.03 (1H, br s), 2.86 (1H, m), 2.6-2.5 (2H, m, including OH), 2.10 (3H, s), 2.08-1.91 (2H, m), and 1.25 (3H, t, J 7 Hz), m/z 298 (11%, M$^+$ - Br), 238 (51), 220 (20), 149 (37), 148 (36), 121 (40), and 94 (45).

10,10-Diethoxy-2-exo-ethoxycarbonylamino-9-exo-hydroxy-5-oxatricyclo[4.3.1.0^{3,8}]decane (25).—The alcohol (7.24 g), dihydropyran (2.61 g) and pyridinium p-toluenesulphonate (540 mg) were kept in CH_2Cl_2 (600 ml) for 2 h. The solution was concentrated to 300 ml before an aqueous work up to give the tetrahydropyranyl ether, which was dissolved in MeOH (400 ml, AR) and stirred with K_2CO_3 (8 g, finely powdered) and water (1-2 ml) for 2 h. The methanol was evaporated off, the residue taken up in EtOAc (3000 ml), washed with water (30 ml) and brine (30 ml). The aqueous layers were back extracted with EtOAc (2 × 75 ml), and the combined organic phases washed again with brine, checking that the pH of the brine was 7. The EtOAc layer was dried (Na_2SO_4), and the solvent evaporated off to give the tetracyclic ether, which was refluxed in EtOH (500 ml) with pyridinium p-toluenesulphonate (535 mg) for 2 h. The EtOH was evaporated off, the residue dissolved in CH_2Cl_2 (10-15 ml) and chromatographed (SiO_2, 500 g, Et_2O) to give the ketal (3.92 g, 62%), m.p. 129-136° suitable for the next step. Recrystallisation gave needles, m.p. 146-147° (from CH_2Cl_2-pentane)(Found: C, 58.2; H, 8.3; N, 4.3. $C_{14}H_{27}NO_6$ requires C, 58.3; H, 8.3; N, 4.3%), Rf (EtOAc) 0.4, IR(CCl_4) 3500-3200 and 1690 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 6.24 (1H, d, J 10 Hz), 4.40 (1H, d, J 8.5 Hz, NH), 4.07-4.01 (3H, m), 3.75-3.7 (3H, m), 3.52 (2H, q, J 7.1 Hz), 3.45 (2H, q, J 6.9 Hz), 3.4 (1H, br s, OH), 2.36-2.27 (3H, m), 1.97 (1H, ddd, J 14.2, 2.7, and 2.5 Hz), 1.52 (1 H, dd, J 14.1 and 2.6 Hz), 1.16 (6H, t, J 7 Hz), and 1.10 (3H, t, J 7.1 Hz), ^{13}C-NMR($CDCl_3$) 156 (s),101.3 (s), 81.1 (d), 70.0 (d), 62.9 (t), 60.5 (t), 56.7 (d), 56.2 (t), 55.9 (t), 53.6 (d), 46.3 (d), 40.2 (d), 25.4 (t), 15.5 (q), 15.3 (q), and 14.7 (q), m/z 329 (19%, M$^+$), 311 (10), 300 (5), 282 (57), 267 (100), 266 (35), 236 (33), 216 (68), 211 (87), 193 (70), 165 (57), 145 (51), 142 (71), and 114 (38).

10,10-Diethoxy-9-exo-hydroxy-2-exo-methylamino-5-oxatricyclo[4.3.1.0^{3,8}]decane (26).—The carbamate (2.43 g) was refluxed with LiAlH$_4$ (1.13 g) in THF (250 ml) for 16 h, and the excess hydride decomposed by slow addition of water (1-2 ml). The THF was decanted off, and the residue extracted with boiling THF (3 × 50 ml), filtering each time. The THF was evaporated off to give the amine (1.96 g, 98%), m.p. 118-125°, suitable for the next step. Recrystallisation gave prisms, m.p. 134-135° (from Et_2O)(Found: C, 61.5; H, 9.1; N, 5.1. $C_{13}H_{25}NO_4$ requires C, 61.9; H, 9.3; N, 5.2%), IR(CCl_4) 3400-3100 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 4.10 (2H, br s, NH and OH), 3.79-3.33 (5H, m), 3.45 (4H, q, J 7 Hz), 2.41-2.18 (3H, m), 2.30 (3H, s), 1.95 (1H, ddd, J 14.2, 2.8, and 2.6 Hz), 1.51 (1H, dd, J 14.1 and 2.5 Hz), 1.10 (3H, t, J 7 Hz), and 1.07 (3H, t, J 7 Hz), m/z 242 (3%, M$^+$ - Et), 227 (10), 226 (18), 225 (20), 224 (20), 211 (11), 208 (27), 198 (30), 196 (100), 178 (11), 145 (20), 94 (21), and 84 (53).

Crystal Data for the Amine (26).—$C_{13}H_{25}NO_4$, M = 271.35, triclinic, space group P$\bar{1}$ (No. 2), a = 7.048(1), b = 9.917(2), c = 10.519(2)Å, α = 96.68(1), β = 91.02(1), γ = 102.50(1), V = 712.2(2)Å^3, Z = 2, D_c = 1.265 g cm^{-3}, λ(Cu-Kα) = 1.5418Å, μ(Cu-Kα) = 6.84 cm^{-1}, F(000) = 296. 2547 intensities measured (5 ≤ 2θ ≤ 125°) on a Syntex P2$_1$ diffractometer, using an ω/2θ scan technique, and averaged to give 2236 unique data. Structure solved by direct methods (SHELX 86) and Fourier difference techniques, and refined by full matrix least squares to R = 0.050 and R_w = 0.063 for 1987 unique observed reflections with F > 4σ(F). The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Great Britain). Any request should be accompanied by the full literature citation.

10,10-Diethoxy-9-exo-hydroxy-2-exo-[N-methyl-N-(3'-trimethylsilylpropionyl)amino]-5-oxatricyclo-[4.3.1.0^{3,8}]decane.—The amine (26)(400 mg), 3-trimethylsilylpropionyl chloride,[33] (246 mg), and triethylamine (180 mg) were mixed in CH_2Cl_2 (25 ml) at -10° and kept at 0° for 30 min. Aqueous workup and chromatography (SiO_2, EtOAc) gave the amide (486 mg, 83%), Rf (EtOAc) 0.65, IR(CH_2Cl_2) 3300 and 1640 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 4.05 (1H, s), 3.89-3.70 (2H, m), 3.61-3.47 (6H, m, including OH), 3.03 (3H, s), 2.58-2.47 (2H, m), 2.32-2.23 (2H, m), 2.05 (1H, dd, J 13.5 and 3 Hz), 1.64 (1H, dd, J 13.5 and 3 Hz), 1.29-1.1 (8H, m), 0.88-0.71 (2H, m), and -0.13 (9H, s)(Found: 384.2199. $C_{20}H_{37}NO_4Si$ requires M - Me 384.2206), m/z 384 (15%, M - Me), 381 (10), 222 (100), and 179 (100).

10,10-Diethoxy-2-exo-[N-methyl-N-(3'-trimethylsilylpropionyl)amino]-5-oxatricyclo[4.3.1.0^{3,8}]decan-9-one (28).—The alcohol (1.17 g), propylene oxide (0.255 g), and pyridinium chlorochromate (PCC)(0.946 g) were stirred in CH_2Cl_2 (100 ml) for 3 h. The black solution was filtered through celite, evaporated, and the residue chromatographed (SiO_2, Et_2O) to give the ketone (1.01 g, 87%), Rf (EtOAc) 0.75, IR(CCl_4) 1765 and 1660 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 3.96-3.48 (7H, m), 2.97 (3H, s), 2.75-2.26 (5H, m), 2.18 (2H, t, J 8.6 Hz), 1.94 (1H, br d, J 14.7 Hz), 1.2 (3H, t, J 7 Hz), 1.11 (3H, t, J 7 Hz), 0.86-0.71 (2H, m), and -0.03 (9H, s).

9-Aza-13,13-diethoxy-1-hydroxy-9-methyl-5-oxa-11-trimethylsilylmethyltetracyclo[6.3.1.1^{4,11}.0^{2,7}]tridecan-10-one (29).—The ketone (127 mg) and potassium t-butoxide (40 mg) were kept at 60° in t-butanol (10 ml) for 2 h. An aqueous workup and chromatography (SiO_2, Et_2O-light petroleum, 4:1) gave the diastereoisomeric alcohols (102 mg, 80%). Separated, these had the following properties: more polar isomer, Rf (Et_2O) 0.28, m.p. 158-159° (from hexane)(Found: C, 60.1; H, 9.15; N, 3.6. $C_{20}H_{37}NO_4Si$ requires C, 60.4; H, 8.8; N, 3.5%), IR(CH_2Cl_2) 3450 and 1650 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 4.74 (1H, s), 3.94-3.56 (7H, m), 3.4 (1H, br s), 2.84 (3H, s), 2.55-2.45 (2H, m), 2.24-1.95 (4H, m), 1.27-1.19 (7H, m), 0.82 (1H, dd, J 15 and 7 Hz), and 0.04 (9H, s), m/z 397 (35%, M$^+$), 382 (100), and 212 (50); less polar isomer, Rf 0.38, m.p.

162-163° (from hexane)(Found: C, 60.4; H, 8.8; N, 3.5.), IR(CH_2Cl_2) 3450 and 1640 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 4.75 (1H, s), 3.83-3.56 (7H, m), 3.44 (1H, br s), 2.92 (3H, s), 2.82-2.74 (2H, m), 2.24-2.05 (4H, m), 1.25-1.18 (7H, m, including a t, J 7 Hz), 0.89 (1H, dd, J 13 and 8.5 Hz), 0.73 (1H, dd, J 13 and 6.4 Hz), and 0.07 (9H, s), m/z 397 (40%, M⁺), 382 (100), and 212 (50).

10,10-Diethoxy-2-exo-ethoxycarbonylamino-5-oxatricyclo[4.3.1.0^{3,8}]decan-9-one (30).—The alcohol (25)(2.75 g), propylene oxide (1.34 ml), and PCC on alumina[35] (16.2 g with an oxidation equivalent of 1 mmol/g) were stirred in CH_2Cl_2 (50 ml) and hexane (50 ml) for 14 h. An additional portion of PCC on alumina (2 g) was added and stirring continued for 48 h, and this was repeated once more, before the mixture was filtered through SiO_2 (15 g) eluting with Et_2O. The solid was also boiled with more Et_2O (4 × 75 ml) and filtered off each time. The combined organic solutions were thoroughly evaporated to give the ketone (2.47 g, 91%), m.p. 110-143°, suitable for the next stage. Recrystallisation gave plates (from diisopropyl ether), IR 3400, 1740, and 1710 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 4.63 (1H, br d, J 8 Hz, NH), 4.23 (1H, d, J 6 Hz), 4.09 (2H, q, J 7 Hz), 3.95-3.86 (3H, m), 3.62-3.43 (4H, m), 2.69 (1H, s), 2.54-2.41 (2H, m), 2.35 (1H, ddd, J 14.5, 5.7, and 2.7 Hz), 1.93 (1H, dd, J 14.5 and 2.7 Hz), 1.20 (6H, t, J 7 Hz), 1.10 (3H, t, J 7 Hz)(Found: M⁺, 327.1635. $C_{16}H_{25}NO_6$ requires M, 327.1689), m/z 327 (5%, M⁺) and 298 (5).

10,10-Diethoxy-2-exo-ethoxycarbonylamino-5-oxa-9-vinyltricyclo[4.3.1.0^{3,8}]decan-9-ol (31).—Vinylmagnesium bromide (14.7 ml of a 1M solution in THF) was added rapidly to the ketone (1.2 g) in THF (23 ml) at -10°, the mixture kept for 3 min at -10°, and then for 10 min at room temperature. An aqueous workup and flash chromatography (SiO_2, Et_2O) gave the alcohol (1.17 g, 90%)(Found: C, 60.8; H, 8.4; N, 3.8. $C_{18}H_{29}NO_6$ requires C, 60.8; H, 8.2; N, 3.9%), Rf (Et_2O) 0.39, IR(CH_2Cl_2) 3435, 1710, and 1630 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 6.08 (1H, dd, J 17.6 and 10.6 Hz), 5.48 (1H, br s, OH), 5.34 (1H, d, J 17.6 Hz), 5.33 (1H, d, J 10.6 Hz), 5.09 (1H, d, J 3.6 Hz, NH), 4.31 (1H, d, J 8.6 Hz), 4.09-3.44 (9H, m), and 1.26-1.07 (9H, m). The stereochemistry was assigned by assuming an "equatorial" approach of the vinyl group.

9-(2'-Chloroethylidene)-10,10-diethoxy-2-exo-ethoxycarbonylamino-5-oxatricyclo[4.3.1.0^{3,8}]decane (32).—Triethylamine (0.58 ml) and thionyl chloride (0.26 ml) were successively added to a solution of the alcohol (1.04 g) in THF (25 ml) and dimethyl formamide (0.1 ml) at 0°. After 2 h at room temperature the mixture was acidified with hydrochloric acid (0.1M). An aqueous workup using ether followed by flash chromatography (SiO_2, Et_2O) gave the chloride (1.06 g, 97%) as a mixture of stereoisomers (Found: C, 57.5; H, 7.56; N, 3.6. $C_{18}H_{28}ClNO_5$ requires C, 57.8; H, 7.55; N, 3.8%), Rf (Et_2O) 0.51, IR(CH_2Cl_2) 3400, 1700, and 1705 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.65 (0.5H, dd, J 8 and 6.2 Hz), 5.56 (0.5H, t, J 8 Hz), 4.77 (0.5H, br d, NH), 4.62 (0.5H, br d, NH), 4.34-4.27 (1H, m), 4.17-4.0 (4H, m), 3.98-3.76 (3H, m), 3.67-3.37 (4H, m), 3.05-2.96 (1H, m), 2.64 (1H, m), 2.23-2.14 (2H, m), 1.77-1.66 (1H, m), and 1.07-1.27 (9H, m), m/z 373 (5%, M⁺), 338 (30), and 118 (100).

9-(2'-Trimethylsilylethylidene)-10,10-diethoxy-2-exo-ethoxycarbonylamino-5-oxatricyclo[4.3.1.0^{3,8}]-decane (33).—Trimethylsilyl-lithium[36] (6.84 mmol) in HMPA (3.45 ml) and Et_2O (4.6 ml from the MeLi) was diluted with THF (13.7 ml) at 0°, CuCN (306 mg, 3.42 mmol) was added, and the mixture kept at 0° for 20 min.[36] The allyl chloride (294 mg) in THF (1 ml) was added to this solution at -78° and the mixture kept at that temperature for 12 min. An aqueous workup and flash chromatography (SiO_2, Et_2O-light petroleum, 4:8) gave the allylsilane (272 mg, 84%) as a mixture of stereoisomers, Rf (Et_2O-light petroleum, 4:6) 0.24, IR(CH_2Cl_2) 3410 and 1700 cm^{-1}, ^{1}H-NMR($CDCl_3$, 250 MHz) 5.34-5.21 (1H, m), 4.64 (0.5H, br d, J 6 Hz, NH), 4.55 (0.5H, br d, J 6 Hz, NH), 4.31 (0.5H, d, J 6 Hz), 4.21 (0.5H, d, J 6 Hz), 4.14-4.03 (2H, m), 3.86-3.76 (3H, m), 3.62-3.45 (4H, m), 2.90-2.78 (1H, m), 2.55-2.47 (1H, m), 2.17-2.05 (2H, m), 1.72-1.6 (2H, m), 1.21 (3H, t, J 7 Hz), 1.19 (3H, t, J 7 Hz), 1.10 (3H, t, J 7.1 Hz), and 0.04 and 0.02 (9H, 2 × s)(Found: M⁺, 411.2457. $C_{21}H_{41}NO_5Si$ requires M, 411.2432), m/z 411 (42%, M⁺), 396 (30), 366 (22), and 294 (100).

3-Aza-3-ethoxycarbonyl-12-oxa-5-vinyltetracyclo[6.2.2.0^{2,6}.0^{5,10}]dodecan-7-one (34).—1,3,5-Trioxan (19 mg) was added to the allylsilane (42 mg) in formic acid (0.5 ml, 98-100%) at 0°. The solution was stirred for 5 min at this temperature and then for 16 h at room temperature. The formic acid was evaporated off, and the residue taken up in EtOAc (5 ml), washed with sodium bicarbonate solution, water and brine, and dried ($MgSO_4$). Flash chromatography (SiO_2, Et_2O-light petroleum, 8:2) and Kugelrohr distillation (250 °/0.3 mmHg) gave the ketone (24 mg, 85%), Rf (Et_2O) 0.37, IR(CH_2Cl_2) 1710 and 1670 cm^{-1}, ^{1}H-NMR(C_5D_5N, 250 MHz, 370°K) 5.90 (1H, dd, J 17 and 11 Hz), 5.26 (1H, d, J 11 Hz)(in $CDCl_3$ at normal temperatures a further doubling of 0.6 Hz is resolved), 5.22 (1H, d, J 17 Hz)(in $CDCl_3$ at normal temperatures a further doubling of 0.6 Hz is resolved), 4.63 (1H, s, OCH or NCH), 4.28 (2H, q, J 7 Hz), 4.04 (1H, d, J 11 Hz, CH H O), 4.03 (1H, s, NCH or OCHCO), 3.85 (1H, d, J 11Hz, CH HO), 3.42 (2H, s, CH_2N), 2.93 (1H, s, bridgehead CHCO), 2.30 (2H, broadened d, which looks as though it has J 10.5 Hz; COSY connections indicate that these overlapping signals, presumably from the bridgehead CH on C-10 and one of the C-9 CH_2 H's, are coupled to the bridgehead CH on C-1, at δ 2.44, and to the other CH_2 proton, at δ 1.98), 2.44 (1H, d, J 6 Hz, CHCH$_2$O), 1.98 (1H, d, J 14.5 Hz, CH H CHCO), and 1.28 (3H, t, J 7 Hz)[COSY connections were also apparent within the olefinic set between δ 5.90 and δ 5.26, between the methylene signals at δ 4.04 and δ 3.85, and between the signals of the O-ethyl group at δ 4.28 and δ 1.28. NOE connections were apparent (i) between the signals at δ 5.90 and δ 3.42, (ii) from both of these signals to the signal at δ 2.93, (iii) from δ 5.90 to δ 1.98, which implies that the δ 1.98 signal is the "axial" hydrogen on C-10, and (iv) from δ 3.42 to δ 5.22, δ 2.30, and δ 1.28], ^{13}C-NMR(C_6D_6-$CDCl_3$) 204.69 (s), 154.2 (s), 134.25 (d), 119.08 (t), 74.61 (d), 63.43 (s), 61.50 (t)(in $CDCl_3$, this signal became two, one at 61.30 and the other at 55.06), 60.76 (d)(in $CDCl_3$, in one spectrum, this signal was resolved into

two, one at 60.53 and the other at 60.46), 55.32 (t), 44.89 (d), 38.14 (d), 25.49 (t), and 14.88 (q)(Found: M^+, 277.1309. $C_{15}H_{19}NO_4$ requires 277.1314), m/z 277 (37%, M^+), 248 (15), 233 (8), 220 (14), and 166 (100).

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