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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 19.[1] INTRAMOLECULAR CYCLOADDITIONS OF NON-STABILISED AZOMETHINE YLIDES GENERATED VIA THE DECARBOXYLATIVE ROUTE FROM α-AMINO ACIDS.

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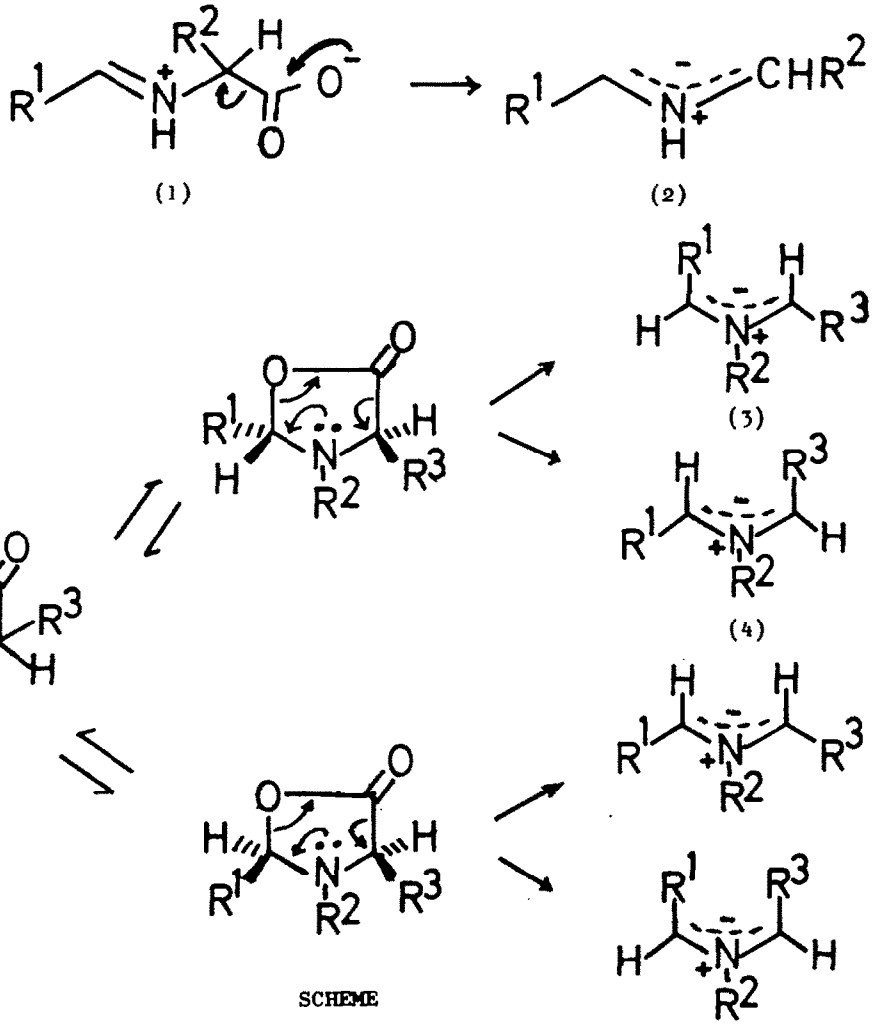
Abstract. Heating a range of acyclic and cyclic secondary α-amino acids with aryl aldehydes containing a proximate terminal alkene or alkyne results in consecutive condensation and decarboxylation, followed by intramolecular cycloaddition of the resultant non-stabilised azomethine ylides. Evidence is produced for syn-anti dipole equilibration and it is found that intramolecular cycloadditions to a terminal alkyne involve only the anti-dipole and proceed via an exo-transition state to give a single cycloadduct. In contrast, intramolecular cycloaddition to a terminal alkene involves both anti- and syn-dipoles, with trapping of the former being slightly energetically preferred, resulting in mixtures of two stereoisomeric cycloadducts. Intramolecular cycloadditions of terminal alkenes to anti-dipoles proceed via exo-transition states whilst analogous reactions of the syn-dipole involve endo-transition states.

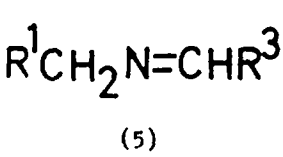
In 1984 we published evidence that the Strecker Degradation of α-amino acids involved an intermediate azomethine ylide.[2,3] Non-stabilised azomethine ylides were shown to be generated in a range of solvents [chloroform, acetonitrile, methanol, benzene, toluene, dimethylformamide (DMF), etc] at temperatures ranging from room temperature to 140°C. A wide variation in the carbonyl component was found to be tolerated and French workers subsequently showed formaldehyde functioned well in these reactions.[4] All α-amino acids (primary and secondary, cyclic and acyclic, α,α-disubstituted) except tertiary α-amino acids were shown to undergo the reaction in both inter- and intra-molecular cycloaddition processes,[2,3,5] producing a wide range of nitrogen heterocycles including bridgehead heterocycles. Our initial simple non-stereoselective mechanism for the generation of the non-stabilised azomethine ylides (1)→(2) was modified by further detailed stereochemical[6] and mechanistic[7] studies to that shown in the Scheme. Analogous processes probably occur in pyridoxal decarboxylase enzymes.[5,8] Japanese workers[9] have provided further examples of our general decarboxylative route to unstabilised azomethine ylides and concur with our mechanism (Scheme) without acknowledging our prior publications.



SCHEME

The stereochemical outcome of the cycloreversion step (Scheme) generating the azomethine ylides is dependant on the structure of both the α-amino acid and carbonyl compound. The reaction results in stereospecific or stereoselective anti-dipole formation (3) or (4).[6,7] In this paper we describe in full our studies on the intramolecular trapping of non-stabilised ylides generated by the decarboxylative route. Non-stabilised ylides generated in this way cannot usually be trapped in intermolecular cycloadditions by non-activated alkenes. When the rate of cycloaddition is slow, as in the case of non-activated olefins, prototropy e.g. (3, R^2=H)⟶(5) or (6), protonation and hydrolysis e.g. (3)⟶(7)⟶(8), or other destructive processes intervene. Thus Hashimoto et al., have recently described the use of 1% of cyclohexenone in cyclohexanol at 154°C to catalytically decarboxylate α-amino acids to the corresponding amines in good yield.[10] In certain cases where secondary α-amino acids are used to generate azomethine ylides we have shown that structural features in the α-amino acid can promote a 1,4-prototropic process in the intermediate azomethine ylide and divert the reaction to give 2-pyrrolines.[11] An earlier related observation is the formation of benzoxazines from o-hydroxyacetophenones and proline.[12] Use of ninhydrin as the carbonyl component results, in certain favourable cases, in stable azomethine ylides.[11]

We have previously reported the intramolecular cycloaddition of ester stabilised azomethine ylides, generated both by our novel 1,2-prototropy route[13] and our facile, room temperature, metallo-1,3-dipole route[14], to both



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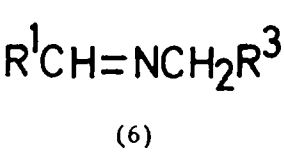

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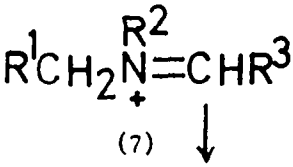

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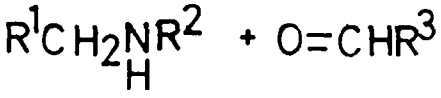

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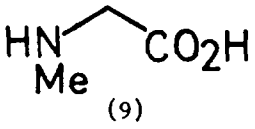

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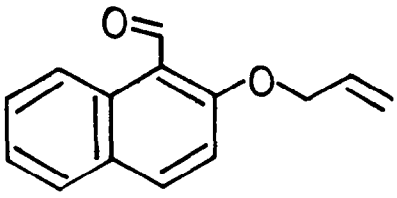

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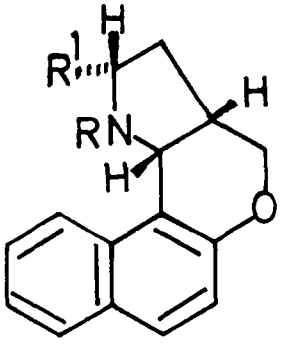
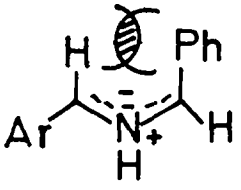


(11) a. R=H, R^1=Ph
b. R=Me, R^1=H



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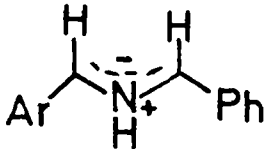

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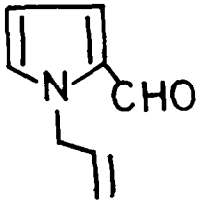

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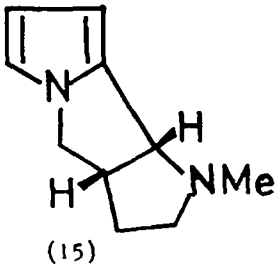

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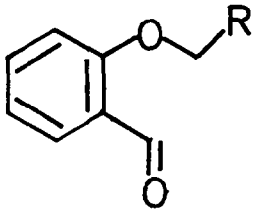
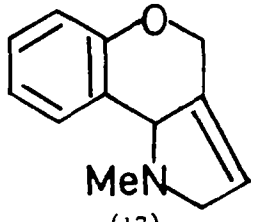


(16) a. R = CH=CH_2
b. R = C≡CH
c. R=t-CH=$CHCO_2$Me



(17)

non-activated and activated olefins. We now describe analogous studies involving a wide range of different structural types of azomethine ylides generated by the decarboxylative route. Our survey is illustrative rather than exhaustive and serves to emphasise the synthetic potential of this approach for the construction of complex molecular frameworks.

Acyclic α-Amino Acids

When phenylglycine or sarcosine (9) are heated at 100-120°C in DMF with (10) they give rise to the cycloadducts (11a) (58%) and (11b) (44%) respectively, as single isomers arising via endo-transition states. In the case of phenylglycine where syn(13)- and anti(12)-dipoles are possible, the product (11a) arises from the more stable syn-dipole (13).≠ The assignment of stereochemistry to (11a) and of

≠ There are two possible configurations of both the syn- and anti-dipoles. Only the energetically more favourable one is shown in each case.

all the stereoisomers reported herein is based on the results of n.O.e. experiments (see experimental section). Our previous detailed studies of the decarboxylative route to azomethine ylides[5-7] provided clear evidence for stereospecific or stereoselective anti-dipole formation and showed that dipole stereomutation, e.g. (12)⇌(13), does not occur in the presence of N-methylmaleimide (NMM), a reactive dipolarophile. Thus the formation of cycloadduct (11a) derived solely from the syn-dipole (13) suggests dipole stereomutation is occurring. The terminal alkene in this latter case is a non-activated dipolarophile, and the consequent slower rate of cycloaddition permits stereomutation to occur. Stereomutation is facilitated by the 1,3-diaryl substitution pattern of the intermediate azomethine ylide in which the increased conjugation lowers the energy barrier to stereomutation by reducing the bond order in the 1,3-dipole moiety. Analogous dipole stereomutation has been observed by us in the case of ester stabilised azomethine ylides.[13,15]

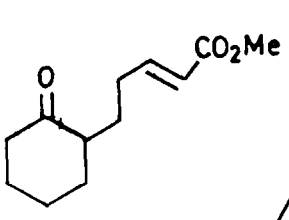
Sarcosine (9) reacts slowly with the pyrrole aldehyde (14) in boiling toluene to give, via an endo-transition state, cycloadduct (15). Even in the presence of an equimolar amount of dibutyltin dichloride[16] the reaction only goes to 65% completion after 18h. The slow reaction reflects the reduced electrophilicity of the pyrrole carbonyl group due to electron release from the π-rich pyrrole ring. Complete reaction of sarcosine (9) and (16b) occurs after 24h in boiling toluene and the product (17) is formed in good yield (72%).

5-Membered Cyclic α-Amino Acids

The cyclohexanone derivative (18) reacts with proline (toluene, 110°C, 16h) in the presence of dibutyltin dichloride to give a ca. 1:1 mixture of (19) and (20) together with a trace amount of an unidentified product in 65% yield. Isomer (19) arises from an exo-transition state (21) (with respect to the CO_2Me substituent) whilst (20) arises via an endo-transition state (22). In both transition states the side chain incorporating the dipolarophile occupies an axial orientation. This orientation avoids the $A^{1,3}$-strain[17] present in the equatorial conformer, results in a less hindered transition state (H-H non-bonded interactions), and allows the least strained approach of the four reacting carbon centres (molecular models). The relative stereochemistry of H_A–H_C, and H_F were determined by ^1H NOEDSY experiments at 400Hz (see experimental section). In particular (19) shows a positive n.O.e. between H_F and H_H whilst (20) does not exhibit an n.O.e. between these protons.

Thiazolidine-4-carboxylic acid (23) reacts with (16a) (toluene, 100°C, 24h) to give a 2:1 mixture of (24) and (25) in a combined yield of 63%. Cycloadduct (24) arises from the anti-dipole (26a) via an exo-transition state whilst the minor isomer (25) arises from the syn-dipole (26b) via an endo-transition state. Our previous work with azomethine ylides generated from (23) and benzaldehyde or pyridine-2-carboxaldehyde established that the anti-dipole (26a) is formed stereospecifically[6], and that trapping with NMM gives a mixture of endo- and exo-cycloadducts derived solely from (26a). Thus the formation of (25) again implicates dipole stereomutation (26a)⇌(26b) rather than direct formation of (26b) in the decarboxylative process (Scheme). Interestingly a substantial amount of stereomutation occurs even though the azomethine ylide has only one terminus substituted by an aryl group, whereas previous work with ester stabilised azomethine ylides indicated that substitution of both terminii by aryl groups was required to promote substantial dipole stereomutation.[13,15]

The thiazolidine carboxylic acid (23) reacts (toluene, 100°C, 17h) with (16b) to give cycloadduct (27) in 37% yield via the anti-dipole (26a). The low yield in this case probably reflects some loss of product due to aromatisation. No product arising from the syn-dipole (26b) was detected in this case.



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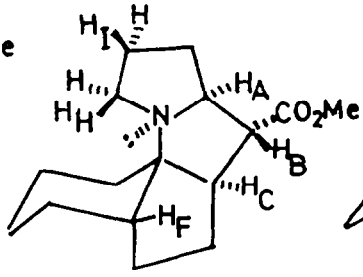

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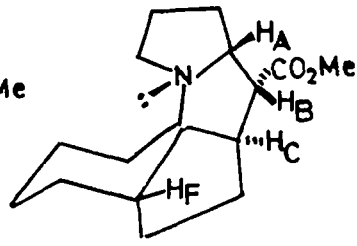

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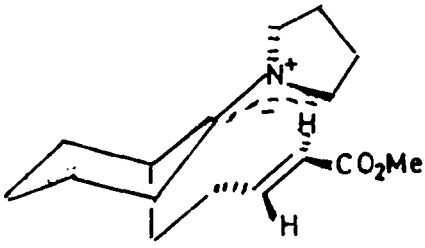

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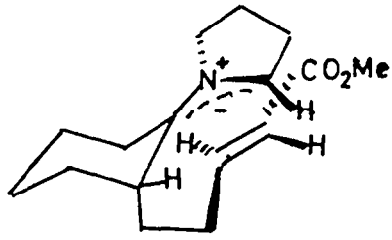

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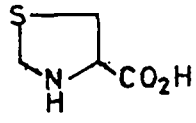

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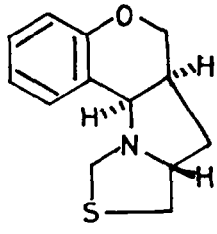

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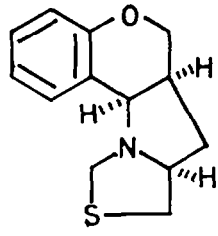

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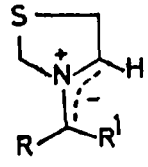
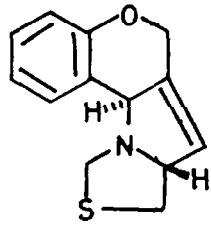


(26) a. R=H, R^1=Ar
b. R=Ar, R^1=H

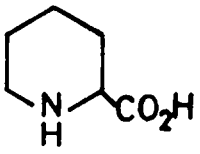


(27)

6-Membered Cyclic α-Amino Acids

Pipecolinic acid (28) reacts (DMF, 100°C, 2h) with the aldehyde (16c) to give 16.4:2:1 mixture (87%) of three isomeric cycloadducts. The major isomer (29) arises from the anti-dipole (30a) via an endo-transition state, whilst the next most abundant isomer (31) arises from the syn-dipole (30b) via an exo-transition state. There was insufficient of the third isomer for characterisation. An analogous cycloaddition involving pipecolinic acid, benzaldehyde, and NMM results in the formation of approximately equal amounts of endo- and exo-cycloadducts derived solely from the anti-dipole (30a, Ar=Ph)[6] suggesting that the minor unidentified isomer is the exo-adduct derived from (30a). The absence of adducts derived from the syn-dipole when NMM is used as the dipolarophile suggests (31) probably arises from syn-dipole produced by stereomutation of the anti-dipole

rather than directly from 1,3-cycloreversion of a cis-oxazolidin-5-one (Scheme).



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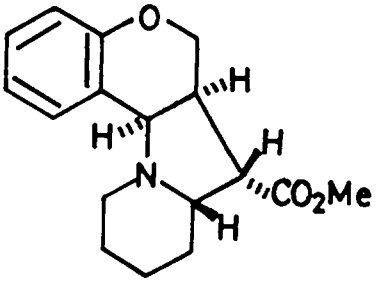

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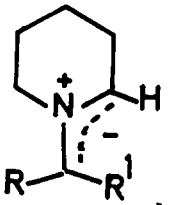
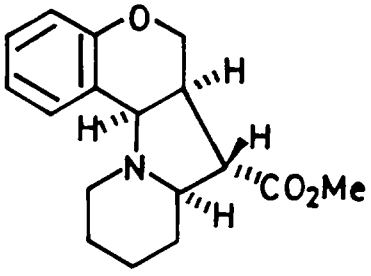


(30) a. R=H, R^1=Ar
b. R=Ar, R^1=H



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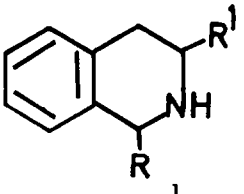
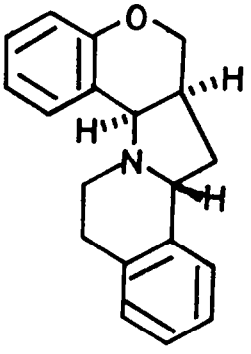


(32) a. R=CO_2H, R^1=H
b. R=H, R^1=CO_2H



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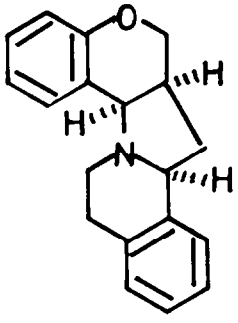

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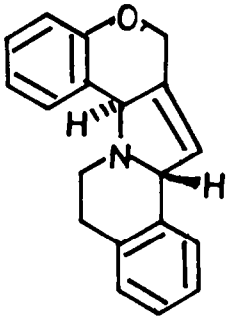

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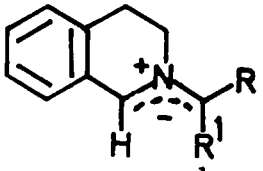
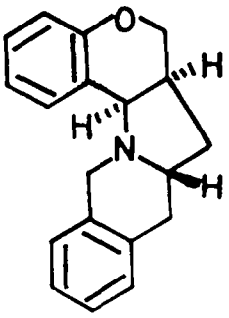


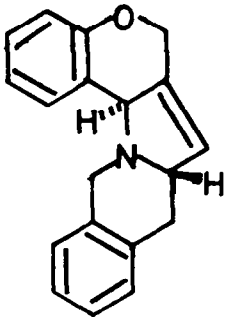
(36) a. R=H, R^1=Ar
b. R=Ar, R^1=H

The tetrahydroisoquinoline-1-carboxylic acid (32a) undergoes cycloaddition with both (16a) and (16b) on heating in DMF at 100°C for 30 min. or 120°C for 1h respectively. In the former case a 1.6:1 mixture (79%) of two cycloadducts (33) and (34) is produced while the latter reaction gives a single cycloadduct (35) (60%) derived from the anti-dipole (36a). Cycloadduct (33) is also derived from the anti-dipole (36a) via an exo-transition state whilst (34) arises from the syn-dipole (36b) via an endo-transition state. The absence of cycloadducts arising from syn-dipole in the reaction of (32a) with (16b) contrasts markedly with the corresponding reaction of (32a), benzaldehyde and NMM (DMF, 120°C, 1h) which gives a mixture of endo- and exo-cycloadducts arising from a 1:1 mixture of anti- and syn-dipole. The stereochemical outcome of the reaction of (32a) and (16a) is much closer to this latter result. The difference in stereochemical outcome of the three reactions can be rationalised if it is assumed that the anti-dipole (36a) undergoes cycloaddition at a faster rate than the syn-dipole (36b) in the intramolecular cases and that the rate differences are greater for (16b) than for (16a). These rate differences arise from the geometrical constraints imposed by the dipole geometry and, in the case of (16b), by the dipolarophile geometry.

The tetrahydroisoquinoline-3-carboxylic acid (32b) reacts (DMF, 120°C, 2h) with (16a) and (16b) to give cycloadducts (37) (37%) and (38) (31%) respectively. Both reactions involve the anti-dipole (39). In the corresponding intermolecular reaction of (32b) with benzaldehyde and NMM only cycloadducts derived from the anti-dipole (39) are obtained.[6]



(37)



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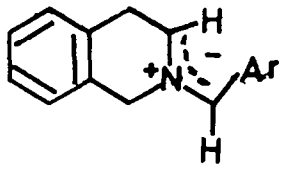

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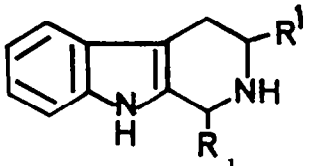
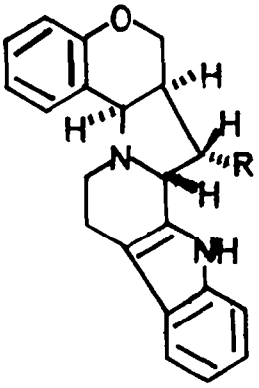
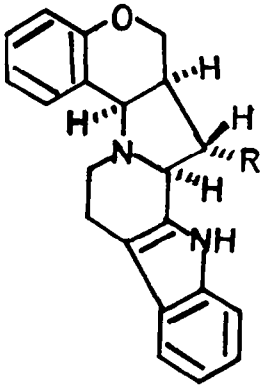


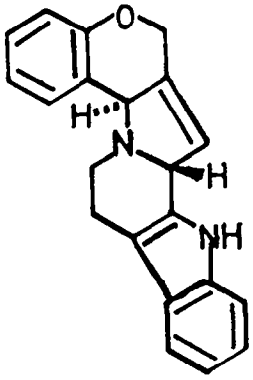
(40) a. R=CO_2H, R^1=H
b. R=H, R^1=CO_2H



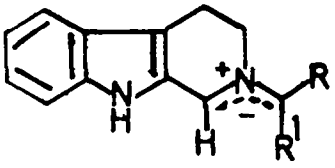
(41) a. R=H
b. R=CO_2Me



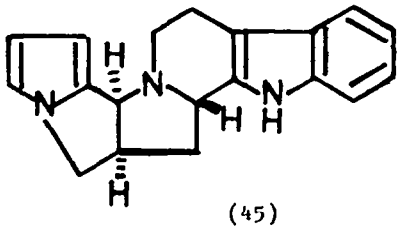
(42) a. R=H
b. R=CO_2Me



(43)



(44) a. R=H, R^1=Ar
b. R=Ar, R^1=H



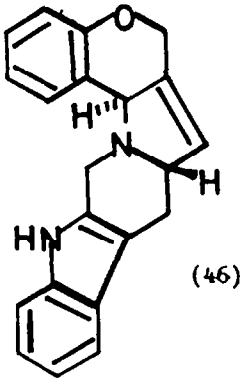
(45)

The cycloaddition of the tetrahydro-β-carboline-1-carboxylic acid (40a) to both (16a) and (16b) occurs on heating in DMF at 100°C (20 min) and 120°C (1h) respectively. In the former case a 2.8:1 mixture of (41a) and (42a) is obtained in 87% combined yield whilst the latter reaction gives a single cycloadduct (43) derived from the anti-dipole (44a). Cycloadduct (41a) is also derived from the same anti-dipole via an exo-transition state whilst (42a) arises from the syn-dipole (44b) via an endo-transition state. The corresponding intermolecular reaction between (40a), benzaldehyde, and NMM furnishes a mixture of cycloadducts arising from a ca. 2:1 mixture of anti- and syn-dipoles (44a) and (44b) respectively. A similar explanation to that advanced above for cycloadducts derived from (36a) and (36b) would account for the discrepancy between the inter- and intra-molecular cycloadditions.

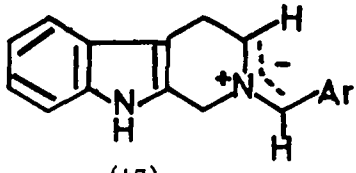
Selectivity for the anti-dipole is increased in the cycloaddition of (40a) and (16c) (DMF, 100°C, 30 min) which affords a 5:1 mixture of (41b) and (42b) in 95% yield. The reaction (DMF, 120°C, 1h) of (40a) with the pyrrole aldehyde (14) was slow and incomplete (33% conversion) and afforded a single cycloadduct (45) derived from the anti-dipole (44a).

One example of an intramolecular cycloaddition of tetrahydro-β-carboline-3-

carboxylic was studied. Thus reaction of (40b) with (16b) (DMF, 120°C, 1h) afforded a single cycloadduct (46) (37%) derived from the anti-dipole (47). In the corresponding intermolecular cycloaddition involving (40b), benzaldehyde and NMM only adducts arising from the anti-dipole (47) are obtained.[6]



(46)



(47)

Dipole Stereomutation and Endo-Exo Cycloaddition Stereospecificity.

Our stereochemical[6] and mechanistic[7] studies of the Strecker Degradation of α-amino acids employed NMM as dipolarophile to ensure that the dipole generated under kinetic control was trapped prior to stereomutation. Comparison of these earlier results with the studies presented in this paper show that dipole stereomutation occurs in the presence of less active terminal alkene and alkyne dipolarophiles. Thus the general scheme presented at the beginning of this paper needs to be modified to incorporate equilibration between the syn- and anti-dipoles. Comparison of the anti:syn dipole ratios trapped by NMM and by the intramolecular dipolarophiles reported herein shows that the acetylenic dipolarophile generated from (16b) only traps the anti-dipole from the equilibrating anti-syn mixture. Molecular models show the intramolecular cycloaddition exo-transition state involving the anti-dipole and a terminal alkyne (from 16b) can achieve good alignment of the four reacting centres with only a small twist of the salicylyl aromatic ring out-of-plane of the central dipole C-N-C moiety. The corresponding exo-transition state for the syn-dipole involves a substantial twisting of the salicylyl aromatic ring out-of-plane of the dipole segment together with less satisfactory alignment of the four reacting centres.

The situation for reactions involving a terminal alkene can be summarised as follows: (a) the newly formed ring is always cis-fused, (b) the anti-dipole always reacts via an exo-transition state (exo- with respect to the CH_2OAr moiety), (c) the syn-dipole always reacts via an endo-transition state (endo- with respect to the CH_2OAr moiety), (d) in all cases adducts derived from the anti-dipole predominate and (e) the anti:syn dipole cycloadduct ratios indicate the exo-transition state involving the anti-dipole is slightly more energetically favourable than the endo-transition state involving the syn-dipole. Both (b) and (c) involves such substantial twisting of the salicylyl aryl group out of the plane of the C-N-C dipole moiety that conjugation is lost.

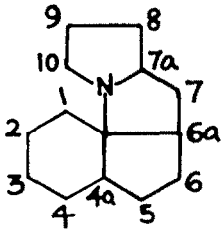
Experimental. General experimental details are as previously noted.[18] Petroleum ether refers to the fraction with b.p. 60-80°C.
General Procedure for Intramolecular Decarboxylative Cycloaddition Reactions. The carboxylic acid (1 mol) and aldehyde (1 mol) were stirred and heated in toluene at 100°C or DMF at 120°C. When carbon dioxide gas evolution had ceased (or, in the case of sparingly soluble acids, when all the solids had dissolved) the reaction mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in chloroform and the solution washed with water (3 x), dried ($MgSO_4$) and the solvent removed to yield the crude product. Integration of the p.m.r. spectrum of the crude product gave, where applicable, the isomer ratio. Mixtures of isomers were separated using flash chromatography (SiO_2).

2-Phenyl-4H-2,3,3a,11c-tetrahydropyrro[2,3-d]naphtho[2,1-b]pyran (11a). O-Allyl-2-hydroxy-1-naphthaldehyde (1.06g, 5mmol) and phenylglycine (0.76g, 5mmol) were heated in DMF (25ml) at 120° for 2h. The DMF was removed in vacuo to yield a purple gum whose nmr spectrum showed it to comprise one product together with some uncharacterised material. Trituration with EtOH/Et_2O yielded the product as a colourless solid (0.87g, 58%) which crystallised from $CHCl_3/Et_2O$ as rods, m.p. 155-157°C (Found: C, 83.85; H, 6.40; N, 4.40. $C_{21}H_{19}NO$ requires C, 83.70; H, 6.35; N, 4.65%); ν_{max} 3315, 2930, 1587, 1393, 1085, 825 and 752 cm^{-1}; m/z(%) 301 (M^+,100), 300(65), 271(29), 260(54), 195(47), 181(76), 144(25), 106(52) and 91(89); δ 8.11-7.09 (m, 11H, ArH), 4.49 (d, 1H, $11_C\beta$-H, $J_{11c,3a}$ 5.6Hz), 4.4 (t, 1H, 2-H, J 8.0Hz), 4.13 (dd, 1H, 4β-H, $J_{4\alpha,4\beta}$ 4.4Hz), 3.92 (t, 1H, 4α-H), 2.56 (m, 1H, $3_a\beta$-H), 2.54 (m, 1H, 3β-H), 2.32 (br, s, 1H, NH, exchanges with D_2O), 1.36 (m, 1H, 3α-H).

1-Methyl-4H-2,3-3a,11c-tetrahydropyrro[2,3-d]naphtho[2,1-b]pyran (11b). Prepared from (10) and sarcosine (0.45g, 5mmol) by heating in DMF at 100° for 2h. The product (0.53g, 44%) crystallised from ether-petroleum ether as pale yellow plates, 83-85°C (Found: C, 80.05; H, 7.25; N, 5.75. $C_{16}H_{17}NO$ requires C, 80.30; H, 7.15; N, 5.85%); ν_{max} 2920, 1610, 1590, 1505, 1221, 1087 and 750 cm^{-1}; m/z(%) 239 (M^+,80), 238(46), 181(66), 83(34) and 44(100); δ (C_6D_6) 7.81 (d, 1H, 11-H), 7.33-6.86 (m, 5H, ArH), 3.84 (t, 1H, 4α-H, J 10.4Hz), 3.53 (dd, 1H, 4β-H, $J_{4,3a}$ 5.3Hz), 3.31 (d, 1H, $11_C\beta$-H, $J_{11a,3a}$ 4.8Hz), 2.45 (m, 1H, 2α-H), 1.95 (s, 3H, Me), 1.89 (m, 1H, 2β-H), 1.65 (m, 1H, 3aβ-H), 1.28 (m, 1H, 3β-H), 0.78 (m, 1H, 3α-H).

2,3,3a,8b-Tetrahydro-1-methylpyrrolo[2,3-b]pyrrolizine (15) (with P. Armstrong). A mixture of N-allylpyrrole-2-carboxaldehyde (0.67g, 5g) sarcosine (0.45g, 5mmol), and dibutyltin dichloride (0.15g) was boiled under reflux in toluene (30ml) for 18h. The reaction mixture was filtered and the solvent removed in vacuo to leave a brown oil whose p.m.r. spectrum showed it to comprise a 65:35 mixture of product (15) and starting material. The mixture was separated using flash chromatography (silica gel, 9:1 Et_2O-MeOH) to yield the product (0.35g, 44%) as a pale brown oil. (Acc. Mass: 162.1151. $C_{10}H_{14}N_2$ requires 162.1157); ν_{max} (film), 2940, 2775, 1490, 1445, 1300, 1052, 765 and 700 cm^{-1}; m/z(%) 162 (M^+,100), 161(52), 119(31), 118(83), 106(12), 82(30) and 44(38); δ 6.55 (dd, 1H, 6-H), 6.23 (t, 1H, 7-H), 5.95 (m, 1H, 8-H), 4.16 (dd, 1H, 4β-H, $J_{4\alpha,4\beta}$ 10.6 and $J_{4\beta,4a\beta}$ 8.8Hz), 3.89 (d, 1H, $8_b\beta$-H, $J_{8b,3a}$ 7.6Hz) 3.80 (dd, 1H, 4α-H, $J_{4\alpha,3a\beta}$ 5.0Hz) 3.51 (m, 1H, $3_a\beta$-H), 2.83 and 2.58 (m, 2H, N(Me)CH_2), 2.48 (s, 3H, Me), 2.20 and 1.78 (m, 2H, 3α-H and 3β-H)

1,2,4,9b-Tetrahydro-1-methyl-pyrrolo[2,3-c]-chromene (17). o-Propargyl salicyl aldehyde (2.5g, 15.6mmol) and sarcosine (1.39g, 15.6mmol) were stirred and boiled in toluene (30ml) under nitrogen atmosphere for 24h. Work up in the usual way followed by molecular distillation gave the product (2.10g, 72%) as a pale yellow viscous liquid, b.p. 95-105°C (furnace temp.)/0.35 mmHg (Found: C, 77.25; H, 6.90; N, 7.60. $C_{12}H_{13}NO$ requires C, 77.00; H, 6.95; N, 7.50%); ν_{max}(film) 1680, 1595, 1570, 1480, 1450 and 755 cm^{-1}; m/z(%) 187 (M^+,68), 186(100), 172(9), 158(9), 145(5), 131(15), 115(8) and 94(7); δ 7.37, 7.12, 6.94 and 6.82 (4 x m, 4 x 1H, ArH), 5.69 (s, 1H, =CH), 4.69 (m, 2H, CH_2O), 4.38 (br s, 1H, CHN), 4.04 and 3.48 (2 x m, 2 x 1H, CH_2N), and 2.80 (s, 3H, NMe).



1,2,3,4,4a,5,6,6a,7a,8,9,10-dodecahydro-7H-10a-azapentalen[3,2-i]indene skeleton.

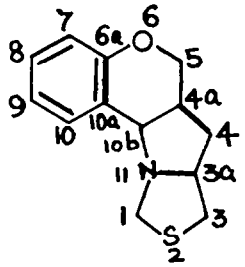
1,2,3,4,4aα,5,6,6aβ,7aβ,8,9,10-Dodecahydro-7-methoxycarbonyl-7H-10a-azapentalen[3,2-i]indene (19) and 1,2,3,4,4aα,5,6,6aβ,7aα,8,9,10-dodecahydro-7-methoxycarbonyl-7H-10a-azapentalen[3,2-i]indene (20) (with M.F. Aly). A mixture of 2-[5-(1-carbomethoxypent-2-enyl)]cyclohexanone (18) (2.10g, 10mmol), L-proline (1.15g, 10mmol) and Bu_2SnCl_2 (0.076g, 5mol%) was heated in boiling toluene (50ml) for 16h. After removal of solvent the brownish oil remaining was found (p.m.r.) to comprise ca. 85% of product as a ca. 1:1 mixture of (19) and (20), the remainder being starting material together with a trace of uncharacterised by-product. The crude oil was purified by flash chromatography [silica gel, 3:2 v/v Et_2O - CH_2Cl_2, R_f = 0.38] to give the product (1.71g, 65%), b.p. 100-102°C/0.01mmHg, as a clear colourless oil which still comprised a ca. 1:1 mixture of (19) and (20). (Found: C, 73.10; H, 9.75; N, 5.50. $C_{16}H_{25}NO_2$ requires C, 72.95; H, 9.55; N, 5.30%); ν_{max}(film) 2930, 2840, 1725, 1430, 1160 and 1010 cm^{-1}; m/z(%) 263 (M^+,33), 220(100), 204(40), 151(14) and 70(23); flash chromatography eluting with 3:2 v/v ether-ethyl acetate afforded pure samples of both isomers.

(19): δ 3.77 (m, 1H, H_A), 3.63 (s, 3H, CO_2Me), 2.96 (m, 1H, H_H), 2.88 (m, 1H, $H_{H'}$), 2.53 (m, 1H, H_C), 2.24 (t, 1H, H_B), 2.17 (m, 1H, H_F) and 1.97-1.22 (m, 16H, alicyclic residue).

(20): δ 4.00 (m, 1H, H_A), 3.63 (s, 3H, CO_2Me), 2.80 (m, 2H, H_B and H_H), 2.66 (dd, 1H, $H_{H'}$, J 16.8 and 8.6Hz), 2.47 (m, 1H, H_C) and 1.97-1.22 (m, 17H, alicyclic residue).

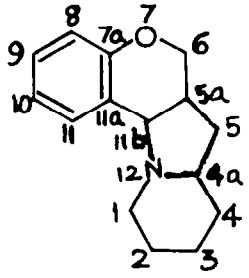
Table 1. ^{1}H NOEDSY Data for (19) and (20)

Compound	Proton Irradiated	Proton Observed, n.O.e. (%) H_A	H_B	H_C	H_H	H_I
19	H_A		1.8	2.35	8	
	H_B				3.0	
	H_F				4.6	3.7
20	H_A		6.0			
	H_B	3.3				



1,3,3a,4,4a,10b-hexahydro-5H-thiopheno[3',4'-a] chromeno[3,4-d]pyrrole

1,3,3aα,4,4aβ,10bβ-Hexahydro-5H-thiopheno[3',4'-a]chromeno[3,4-d]pyrrole (24) and 1,3,3aα,4,4aα,10bα-hexahydro-5H-thiopheno[3',4'-a]chromeno[3,4-d]pyrrole (25). Prepared from thiazolidine-4-carboxylic acid (0.82g, 6.2mmol) and 2-(2-propenyloxy)-benzaldehyde (1.0g, 6.2mmol) in toluene (50ml). Heating was continued for 24h. T.l.c., eluting with 2:3 v/v Et_2O-petroleum ether, showed two spots R_f 0.53 and 0.32 (iodoplatinate spray). The isomers were separated using flash chromatography to give (24) (0.61g, 42%) and (25) (0.30g, 21%).
(24). Colourless rods (Et_2O-petroleum ether) m.p. 61-62°C. (Found: C, 66.75; H, 6.70; N, 5.80. $C_{13}H_{15}NOS$ requires C, 66.95; H, 6.50; N, 6.00%); ν_{max} 2950, 1610, 1595, 1495, 1050 and 760 cm^{-1}; m/z(%) 233 (M^+,100), 200(20), 187(48), 186(94), 145(17), 132(85) and 131(85); δ 7.25-6.87 (m, 4H, ArH), 4.55 (d, 1H, 1β-H, J 10.65Hz), 4.20 (d, 1H, 1α-H, J 10.65Hz), 4.09 (dd, 1H, 5β-H, J 5.10 and 10.75Hz), 3.98 (t, 1H, 5α-H, J 10.60Hz), 3.65 (m, 2H, 10b-H and 3a-H), 3.15 (dd, 1H, 3α-H, J 7.70 and 10.60Hz), 2.70 (dd, 1H, 3β-H, J 6.95 and 10.60Hz), 2.60 (m, 1H, 4a-H), and 2.54 (m, 2H, 4α-H and 4β-H); ^{1} NOEDSY(%): irradiation of 1β-H caused enhancements of 1α-H (40.4), 10b-H (7.7), and Ar-H (13.3); irradiation of 2α-H caused enhancements of 3a-H (4.2) and 2β-H (9.6); irradiation of 4a-H caused enhancements of 10b-H (2.6), 5β-H (17), and 4β-H (3.4). Interpretation of the NOEDSY data was made difficult by the overlap of the signals for the 3a-H and 10b-H in the p.m.r. spectrum, and the difficulty in irradiating 2β-H and 4a-H separately.
(25). Colourless plates (Et_2O-petroleum ether) m.p. 104-105°C (Found: C, 66.75; H, 6.65; N, 5.75); ν_{max} 2960, 1610, 1580, 1490, 1225, 1050 and 760 cm^{-1}; m/z(%) 233 (M^+,77), 200(6), 187(60), 186(21), 145(18), 132(100) and 131(63); δ 7.22-6.88 (m, 4H, ArH), 4.09 (dd, 1H, 5α-H), 4.04 (d, 1H, 1β-H, J 6.55Hz), 3.87 (t, 1H, 5β-H, J 10.7Hz), 3.69 (d, 1H, 1α-H, J 6.6Hz), 3.63 (d, 1H, 10b-H, J 6.6Hz), 3.27 (m, 1H, 3a-H), 2.98 (dd, 1H, 3α-H, J 5.4 and 9.4Hz), 2.79 (m, 1H, 4a-H), 2.55 (t, 1H, 3β-H, J 9.0Hz), 2.20 (m, 1H, 4α-H) and 1.26 (m, 1H, 4β-H); ^{1}H NOEDSY(%): irradiation of 3a-H caused enhancements of 10b-H (3.2), 3α-H (2.5), and 4α-H (2.5); irradiation of 4α-H caused enhancements of 3a-H (2.7), 4a-H (4.2), and 4β-H (11.5); irradiation of 4a-H caused enhancements of 10b-H (4.3), and 4α-H (3.2); irradiation of 10b-H caused enhancements of 3a-H (3.8), 4a-H (3.8) and Ar-H (4.5).
1,3,3aα,10bβ-tetrahydro-5H-thiopheno[3',4'-a]chromeno[3,4-d]pyrrole (27). Prepared from thiazolidine-4-carboxylic acid (1.0g,7.5mmol) and 2-(2-propynloxy) benzaldehyde (1.20g, 7.5mmol) in degassed toluene (50ml). Heating was continued for 17h. Flash chromatography (SiO_2, 2:3 v/v Et_2O-petroleum ether, R_f=0.47) afforded the product (0.64g, 37%) as pale yellow prisms (Et_2O-petroleum ether), m.p. 88-90°C (Found: C, 67.20; H, 5.70; N, 6.05. $C_{13}H_{13}NOS$ requires C, 67.50; H, 5.65; N, 6.05%); ν_{max} 2863, 1603, 1576, 1506, 1221 and 760 cm^{-1}; m/z(%) 231 (M^+,9), 199(3), 198(16), 186(13), 185(100) and 157(20); δ 7.38-6.80 (m, 4H, ArH), 5.65 (m, 1H, 4-H), 4.79 (m, 2H, 5-H), 4.69 (m, 1H, 10b-H), 4.62 (m, 1H, 3a-H), 4.42 (d, 1H, 1β-H, J 10.9Hz), 4.33 (d, 1H, 1α-H, J 10.9Hz), 3.08 (dd, 1H, 3α-H, J 7.9 and 11.25Hz), and 2.86 (ddd, 1H, 3β-H, J 0.85, 2.65 and 11.25Hz); ^{1}H NOEDSY(%): irradiation of 10b-H caused enhancements of Ar-H (1.3), and 1β-H (2.7); irradiation of 3α-H caused enhancements of 3a-H (7.2), 3β-H (13), and 1α-H (1.2); irradiation of 3β-H caused enhancements of 3a-H (2.1), 3α-H (12), and 4-H (1.4).

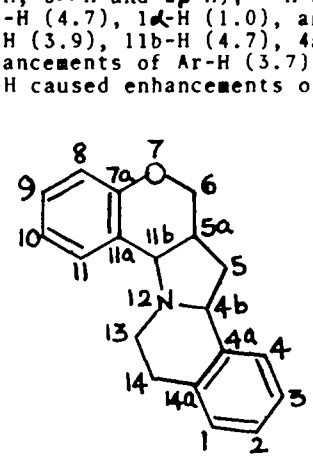


1,2,3,4,4a,5,5a,11b-octahydro-6H-chromeno[3,4-b] indolizine

1,2,3,4,4aα,5α,5aβ,11bβ-Octahydro-5-methoxycarbonyl-6H-chromeno[3,4-b]indolizine (29) and 1,2,3,4,4aα,5β,5aα,11bα-octahydro-5-methoxycarbonyl-6H-chromeno[3,4-b] indolizine (31). Prepared from pipecolinic acid (0.65g, 5mmol) and 2-[(3-carbomethoxy-2-propenyl)oxy]-benzaldehyde (1.1g, 5mmol) in DMF (50ml). Heating was continued for 2h. T.l.c., eluting with 1:1 v/v Et_2O-petroleum ether, showed three spots, R_f 0.57, 0.5 and 0.45 (iodoplatinate spray). Two isomers were separated using flash chromatography to give (31) (0.19g, 13%, R_f 0.57) and (29) (1.07g, 74%, R_f 0.45). Insufficient quantity of the third isomer precluded characterisation.

(29). Colourless prisms (Et_2O-petroleum ether), m.p. 56-57°C (Found: M, 287.15287. $C_{17}H_{21}NO_3$ requires M, 287.15213); ν_{max} 2933, 1734, 1605, 1581, 1486, 1230 and 757 cm^{-1}; m/z(%) 287 (M^+,92), 286(38), 272(22), 228(13), 205(43), 155(33), 145(26) and 131(100); δ 7.19-6.81 (m, 4H, ArH), 4.36 (d, 1H, 11b-H, J 7.9Hz), 4.01 (dd, 1H, 6-H, J 2.1 and 11.7Hz), 3.85 (dd, 1H, 6-H, J 2.5 and 11.3Hz), 3.66 (s, 3H, OMe), 3.20 (m, 2H, 5a-H and 5α-H), 3.08 (m, 1H, 1β-H), 2.63 (m, 1H, 4a-H), 2.18 (m, 1H, 1α-H), 1.66 (m, 1H, 3-H), 1.49 (m, 3H, 2 x 2-H and 4-H) and 1.05 (m, 2H, 3-H and 4-H); ^1H NOEDSY(%): irradiation of 4a-H caused enhancements of 5α-H (6.8), 1α-H (2.5), and 4α-H (3.7); irradiation of 11b-H caused enhancements of Ar-H (3.4), 5a-H (4.7), and 1β-H (2.0). Interpretation of the NOEDSY data was complicated by the overlap of the signals for the 5a-H and 5α-H in the p.m.r. spectrum.

(31). Colourless gum. (Found: C, 71.10; H, 7.40; N, 4.65. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.35; N, 4.85%); ν_{max} 2935, 1737, 1609, 1583, 1489, 1224 and 756 cm^{-1}; m/z(%) 287 (M^+,62), 286(32), 272(27), 228(12), 205(29), 155(27), 145(23), 131(100); δ 7.15-6.81 (m, 4H, ArH), 4.01 (dd, 1H, 6α-H, J 5.2 and 10.55Hz), 3.83 (t, 1H, 6β-H, J 10.45Hz), 3.67 (s, 3H, OMe), 3.23 (m, 1H, 1β-H), 3.12 (d, 1H, 11b-H, J 6.3Hz), 2.59 (m, 1H, 5a-H), 2.25 (m, 1H, 4a-H), 2.09 (m, 2H, 1α-H and 5β-H), 1.94 (m, 1H, 4α-H), 1.70 (m, 1H, 3β-H), 1.57 (m, 1H, 2α-H), and 1.25 (m, 3H, 4β-H, 3α-H and 2β-H); ^1H NOEDSY(%): irradiation of 4a-H caused enhancement of 11b-H (4.7), 1α-H (1.0), and 4α-H (2.0); irradiation of 5a-H caused enhancements of 6α-H (3.9), 11b-H (4.7), 4a-H (0.8), and 5β-H (1.6); irradiation of 11b-H caused enhancements of Ar-H (3.7), 5a-H (6.0), 4a-H (6.3), and 1α-H (3.0); irradiation of 1β-H caused enhancements of Ar-H (5.1), 1α-H (20.5), 2α-H (1.9), and 2β-H (2.8).



4b,5,5a,11b,13,14-hexahydro-6H-chromeno[3',4'-4,5] pyrrolo[2,1-a]isoquinoline

4bα,5,5aβ,11bβ,13,14-Hexahydro-6H-chromeno[3',4'-4,5]pyrrolo[2,1-a]isoquinoline (33) and 4bα,5,5aα,11bα,13,14-hexahydro-6H-chromeno[3',4'-4,5]pyrrolo[2,1-a]isoquinoline (34). Prepared from 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (0.89g, 5mmol) and 2-(2-propenyloxy)-benzaldehyde (0.81g, 5mmol) in DMF (50ml). Heating was continued for 30 min. T.l.c., eluting with 3:7 v/v Et_2O-petroleum ether, showed two spots, R_f 0.58 and 0.31 (iodoplatinate spray). The isomers were separated using flash chromatography to give (34) (0.41g, 30%) and (33) (0.67g, 49%).(33). Colourless rods (Et_2O-petroleum ether), m.p. 83-84°C (Found: C, 82.10; H, 6.85; N, 5.30. $C_{19}H_{19}NO$ requires C, 82.30; H, 6.90; N, 5.05%); ν_{max} 2930, 1605, 1580, 1485, 1225 and 764 cm^{-1}; m/z(%) 277 (M^+,100), 276(84), 236(4), 147(55), 132(16), 131(22) and 130(10); δ 7.29-6.89 (m, 8H, ArH), 4.33 (t, 1H, 4b-H, J 7.6Hz), 4.13 (m, 2H, 6-H), 4.00 (d, 1H, 11b-H, J 6.25Hz), 3.33 (m, 1H, 13β-H), 3.15 (m, 1H, 14β-H), 3.07 (m, 1H, 13α-H), 2.74 (m, 1H, 14α-H), 2.63 (m, 1H, 5a-H), 2.33 (m, 1H, 5α-H), and 2.17 (m, 1H, 5β-H).

Table 2. ^{1}H NOEDSY Data ($CDCl_3$ for (33).

Proton Irradiated	n.o.e. (%) 4b	5α	5β	5a	11b	Ar
4b		5.0				4.2
5α	8.5		14.9	2.1		1.4
5β	3.1	17.6		7.6		5.3
5a		1.0	4.8		5.2	
11b				5.4		3.9

(34) Colourless prisms (Et_2O-petroleum ether), m.p. 146-147°C (Found: C, 82.60; H, 6.90; N, 5.10. $C_{19}H_{19}NO$ requires C, 82.30; H, 6.90; N, 5.05%); ν_{max} 2960, 1610, 1580, 1490, 1220 and 760 cm^{-1}; m/z(%) 277 (M^+,71), 276(100), 236(10), 147(47), 132(23), 131(31) and 130(19); δ 7.27-6.91 (m, 8H, ArH), 4.06 (dd, 1H, 6α-H, J 5.1 and 10.8Hz), 3.88 (t, 1H, 6β-H, J 10.7Hz), 3.59 (m, 1H, 13β-H), 3.48 (t, 1H, 4b-H, J 8.8Hz), 3.23 (d, 1H, 11b-H, J 5.7Hz), 3.05 (m, 1H, 14-H), 2.86 (m, 1H, 14β-H), 2.67 (m, 1H, 5α-H), 2.57 (m, 2H, 5a-H and 13α-H) and 1.35 (m, 1H, 5β-H).

Table 3. ^{1}H NOEDSY Data ($CDCl_3$) for (34)

Proton Irradiated	n.o.e. (%) 11b	5a	5α	5β	4b
4b	6.2		6.7	1.0	
11b		5.8			7.4
5β		3.5	14.8		2.8

4bα,5,5aβ,11bβ,13,14-Tetrahydro-6H-chromeno[3',4'-4,5]pyrrolo[1,2-a]isoquinoline Prepared from 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (0.89g, 5mmol) and 2-(2-propynloxy)benzaldehyde (0.80g, 5mmol) in degassed DMF (50ml). Heating was continued for 1h. Flash chromatography (SiO_2, 1:4 v/v ether-petroleum ether afforded the pure product (840mg, 61%) as colourless prisms from ether-petroleum ether, m.p. 157-158°C (Found: C, 82.95; H, 6.25; N, 5.00. $C_{19}H_{17}NO$ requires C, 82.90; H, 6.20; N, 5.10%); ν_{max} 2820, 1600, 1580, 1480, 1210 and 760 cm^{-1}; m/z(%) 275 (M^+,66), 274(100), 272(27), 169(10) and 147(16); δ 7.48-6.84 (m, 8H, ArH), 5.92 (s, 1H, 5-H), 5.45 (d, 1H, 4b-H, J 4.5Hz), 4.90 (d, 1H, 11b-H, J 5.1Hz), 4.73 (m, 2H, 6-H), 3.59 (m, 1H, 13β-H), 3.49 (m, 1H, 13α-H), 3.13 (m, 1H, 14β-H), and 2.59 (m, 1H, 14α-H).

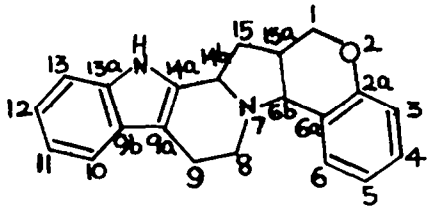
Table 4. ^{1}H NOEDSY Data ($CDCl_3$) for (35)

Proton Irradiated	n.o.e. (%) 4b	5	11b	13α	13β	14α	14β	Ar
4b		3.2		1.1				3.7
5	3.2							3.6
11b					2.6		5.2	
13α					7.8	2.7		
13β			3.1			2.7	2.3	6.3
14α				1.9	2.8		18.5	5.2
14β			7.6		1.7	16.3		

6aα,7,7aβ,8,13,14aα-Hexahydro-6H-chromeno[3',4'-4,5]pyrrolo[1,2-b]isoquinoline (37) (with D. Vipond). Prepared from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.772g, 10mmol) and o-allyl salicylaldehyde (1.62g, 10mmol) in DMF (60ml). Heating was continued for 2.5h. T.l.c., eluting with 1:2 v/v ether/hexane showed a major spot at R_f 0.19 (iodoplatinate spray). The product was purified by flash chromatography, eluting with 1:2 v/v ether/hexane to give the product (1.011g, 37%), as pale yellow prisms (ether-hexane) m.p. 72-75°C. (Found: C, 82.60; H, 7.00; N, 4.90. $C_{19}H_{19}NO$ requires C, 82.30; H, 6.90; N, 5.05%); ν_{max} 765, 755, 740, 705, and 690 cm^{-1}; m/z(%) 277 (M^+, 82), 276(100) and 104(75); δ (C_5D_5N) 7.34-7.01 (m, 8H, ArH), 4.02 (m, 4H, 6- and 13-H), 3.86 (d, 1H, 14a-H, J 6.0Hz), 3.18 (m, 1H, 7a-H), 2.71 (dd, 1H, 8α-H, J 5.0 and 15.0Hz), 2.57 (dd, 1H, 8β-H, J 9.0 and 15.0Hz), 2.47 (m, 1H, 6a-H), 1.87 (m, 1H, 7β-H), and 1.67 (m, 1H, 7α-H). ^{1}H NOEDSY(%): irradiation of 14a-H caused an enhancement of 6a-H (5.2); irradiation of 6a-H caused enhancements of 14a-H (5.5), 7β-H (0.5) and 7α-H (3.9); irradiation of 7β-H caused enhancements of 6a-H (1.6) and 7a-H (6.1); irradiation of 7α-H caused enhancements of 14a-H (0.6), 6a-H (6.4) and 7a-H (1.0); irradiation of 7a-H caused an enhancement of 7β-H (3.1) but not on 7α-H).

7aα,8,13,14aβ-Tetrahydro-6H-chromeno[3',4'-4,5]pyrrolo[1,2-b]isoquinoline (38). Prepared from tetrahydroisoquinoline-3-carboxylic acid (1.0g, 5.65mmol) and o-propargyl salicylaldehyde (0.91g) in DMF (20ml) at 120°C for 2h according to the general procedure. The crude product was purified by flash chromatography eluting with 7:3 v/v petroleum ether-ether to give the product (480mg, 31%), which crystallised from methanol as colourless rods, m.p. 111°C (Found: C, 82.80; H, 6.25; N, 5.00. $C_{19}H_{17}NO$ requires C, 82.90; H, 6.20; N, 5.10%); ν_{max}(KBr) 1620, 1580, 1500, 1460, 1240, 1000 and 750 cm^{-1}; m/z(%) 275 (M^+,100), 274(56), 171(12), 170(34), 144(7), 115(21), 105(73), 104(46) and 78(18); δ 7.48 (d, 1H, ArH), 7.26-7.11 (m, 5H, ArH), 6.98 (t, 1H, ArH), 6.79 (d, 1H, ArH), 5.64 (d, 1H, 7-H, J 1.8Hz), 4.72 (dd, 1H, 6-H, J 12.8 and 0.5Hz), 4.64 (m, 1H, 6-H), 4.60 (br d, 1H,

14aβ-H, J 5.8Hz), 4.53 (m, 1H, 7aα-H), 4.43 (d, 1H, 13β-H, J 14.2Hz), 4.10 (d, 1H, 13α-H, J 14.2Hz), 2.89 (dd, 1H, 8β-H, J 6.0 and 14.7Hz), and 2.72 (dd, 1H, 8α-H, J 5.8 and 14.7Hz). ^{1}H NOEDSY (%): irradiation of 13β-H caused enhancement of 13α-H(20) and 14aβ-H(7.5); irradiation of 13β-H caused enhancement of 13α-H(15); irradiation of 7aα-H caused enhancements of 7-H(3) and 8α-H(5).



6b,8,9,14b,15,15a-hexahydro-1H-chromeno[3',4'-2,3]indolizino[8,7-b]indole.

6bα,8,9,14bβ,15,15aα-Hexahydro-1H-chromeno[3',4'-2,3]indolizino[8,7-b]indole (41a) and 6bα,8,9,14bα,15,15aα-hexahydro-1H-chromeno[3',4'-2,3]indolizino[8,7-b]indole (42a). Prepared from 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (1.08g, 5mmol) and 2-(2-propenyloxy)-benzaldehyde (0.81g, 5mmol) in DMF (50ml). Heating was continued for 20m. T.l.c., eluting with 3:2 v/v ether-petroleum ether, showed two spots, R_f 0.42 and 0.21 (iodoplatinate spray). The isomers were separated using flash chromatography to give (42a), (360mg, 23%) and (41a) (1.01g, 64%).

(41a) Colourless prisms (ether-petroleum ether), m.p. 137-139°C). (Found: C, 79.55; H, 6.65; N, 8.55. $C_{21}H_{20}N_2O$ requires C, 79.70; H, 6.35; N, 8.85%); ν_{max} 3400, 2930, 1575, 1485, 1220 and 745 cm^{-1}; m/z(%) 316 (M^+,100), 315(89), 169(46), 156(11), 144(19) and 131(18); δ 7.79 (s, 1H, NH), 7.55-6.90 (m, 8H, ArH), 4.56 (m, 1H, 14b-H), 4.05 (m, 2H, 1-H), 3.89 (d, 1H, 6b-H, J 6.0Hz), 3.53 (m, 1H, 8-H), 3.15 (m, 2H, 8-H and 9-H), 2.69 (m, 1H, 9-H), 2.44 (m, 1H, 15a-H), and 2.10 (m, 2H, 15-H), ^{1}H NOEDSY (%): irradiation of 6b-H caused enhancements of 15a-H (9) and Ar-H (7.5),; irradiation of 15a-H caused enhancements of 6b-H (10) and 15-H (4); irradiation of NH caused an enhancement of 14b-H (3). The stereochemistry was assigned by comparison with (33).

(42a) Colourless rods (ether-petroleum ether), m.p. 211-212°C. (Found: C, 79.70; H, 6.55; N, 8.90. $C_{21}H_{20}N_2O$ requires C, 79.70, H, 6.35; N, 8.85%); ν_{max} 3393, 2919, 1581, 1489, 1223 and 739 cm^{-1}; m/z(%) 316 (M^+,97), 315(100), 287(4), 275(6), 184(8), 169(40), 144(20) and 131(16); δ 7.77 (s, 1H, NH), 7.39-6.85 (m, 8H, ArH), 3.96 (dd, 1H, 1α-H, J 4.7 and 10.4Hz), 3.76 (t, 1H, 1β-H, J 10.7Hz), 3.53 (m, 2H, 14b-H and 8β-H), 3.31 (d, 1H, 6b-H, J 5.6Hz), 2.73 (m, 2H, 9-H), 2.60-2.31 (m, 3H, 15a-, 8α- and 15α-H), and 1.24 (m, 1H, 15β-H). The stereochemistry was assigned by spectral comparisons with (34).

6bα,8,9,14bβ,15β,15aα-Hexahydro-15-methoxycarbonyl-1H-chromeno[3',4'-2,3]indolizino[8,7-b]indole (41b) and 6bα,8,9,14bα,15β,15aα-hexahydro-15-methoxycarbonyl-1H-chromeno[3',4'-2,3]indolizino[8,7]indole (42b). Prepared from 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (0.98g, 4.6mmol) and 2-[(3-carbomethoxy-2-propenyl)oxy]-benzaldehyde (1.0g, 4.6mmol) in DMF (50ml). Heating was continued for 30 min. T.l.c., eluting with 3:2 v/v ether-petroleum ether, showed two spots, R_f 0.58 and 0.47 (iodoplatinate spray). The isomers were separated using flash chromatography to give (42b) (270mg, 16%) and (41b).

(41b) Colourless rods (ether-petroleum ether), m.p. 222-223°C. (Found: C, 73.65; H, 6.05; N, 7.45. $C_{23}H_{22}N_2O_3$ requires C, 73.80; H, 5.90; N, 7.50%); ν_{max} 3376, 2939, 1709, 1584, 1439, 1214 and 764 cm^{-1}; m/z(%) 374 (M^+,75), 373(47), 343(3), 315(3), 275(26), 242(39), 169(100), 144(12) and 131(15); δ 8.28 (s, 1H, NH), 7.55-6.92 (m, 8H, ArH), 4.86 (d, 1H, 14b-H, J 7.5Hz), 4.36 (m, 2H, 1β-H and 6b-H), 3.98 (dd, 1H, 1α-H, J 3.3 and 11.5Hz), 3.72 (s, 3H, OMe), 3.67 (dd, 1H, 15-H, J 7.6 and 9.3Hz), 3.53 (m, 1H, 8-H), 3.14 (m, 2H, 8-H and 9-H), 2.95 (m, 1H, 15a-H), and 2.74 (m, 1H, 9-H); ^{1}H NOEDSY(%): irradiation of 15-H caused enhancements of 14b-H (9.7) and 15a-H (3.5); irradiation of 14b-H caused enhancements of NH (2.7) and 15-H (12.8); irradiation of 15a-H caused enhancements of 6b-H (9.8) and 15-H (2.7).

(42b) Colourless prisms (Et_2-petroleum ether), m.p. 161-162°C. (Found: C, 73.65; H, 6.10; N, 7.50); ν_{max} 3425, 2811, 1715, 1581, 1447, 1218 and 746 cm^{-1}; m/z(%) 374 (M^+,97), 373(62), 372(13), 343(6), 315(4), 242(50), 169(100), 165(34), 144(20) and 131(20); δ 8.83 (s, 1H, NH), 7.48-6.96 (m, 8H, ArH), 4.18 (dd, 1H, 1α-H, J 5.1 and 10.6Hz), 3.93 (t, 1H, 1β-H, J 10.5Hz), 3.92 (s, 3H, OMe), 3.79 (d, 1H, 14b-H, J 9.9Hz), 3.59 (d, 1H, 6b-H, J 6.4Hz), 3.55 (m, 1H, 8α-H), 2.99 (m, 1H, 15a-H), 2.80 (m, 2H, 9-H), and 2.67 (m, 2H, 8β-H and 15-H); ^{1}H NOEDSY(%): irradiation of 14b-H caused enhancements of 15a-H (12), 6b-H (8), and NH (2); irradiation of 6b-H caused enhancements of 15a-H (7.5) and 14b-H (10.5); irradiation of 15a-H caused enhancements of 6b-H (7) and 15-H (2.3).

6bα,8,9,14bβ-Tetrahydro-1H-chromeno[3',4'-2,3]indolizino[8,7-b]indole (43). Prepared from tetrahydro-β-carboline-1-carboxylic acid (2.0g, 9.26mmol) and O-propargylsalicylaldehyde (1.96g) in DMF (25ml) at 120°C for 1h. The product (1.8g, 62%), was isolated by flash chromatography eluting with 9:1 v/v ether-ethyl acetate and crystallised from methanol as colourless prisms, m.p. 199-201°C (Found: C, 79.20; H, 5.70; N, 8.65. $C_{21}H_{18}N_2O$ requires C, 80.25; H, 5.75;

N, 8.90%); ν_{max} 3440, 1630, 1610, 1580, 1490, 1300, 1230, 1000, 760 and 740 cm^{-1}; m/z(%) 314 (M^+,100), 313(84), 312(31), 285(28), 270(15), 180(7), 167(8), 156(7), 144(13) and 115(13); δ 7.87 (s, 1H, NH), 7.53 (dd, 2H, ArH), 7.33-7.08 (m, 4H, ArH), 7.00 and 6.87 (2 x m, 2 x 1H, ArH), 5.75 (s, 1H, 15-H), 5.31 (s, 1H, 14bβ-H), 4.95 (s, 1H, 6b-H), 4.64 (dd, 2H, CH_2O), 3.89 (dd, 1H, 8β-H, J 4.2 and 14.2Hz), 3.42 (m, 1H, 8α-H), 3.12 (m, 1H, 9α-H), and 2.67 (m, 1H, 9β-H, J 1.2 and 15.6Hz); ^{1}H NOEDSY(%): irradiation of 15-H caused an enhancement of 14bβ-H(5), irradiation of 14bβ-H caused enhancements of 15-H(3) and 6bβ-H(6); irradiation of 6bα-H caused enhancements of 1-H(7) and 9α-H (4.5).

1,1aα,6bα,8,9,14bβ-Hexahydro-2H-pyrrolizino[2',1'-2,3]indolizino[8,7-b]indole (45). Prepared from tetrahydro- -carboline-1-carboxylic acid (2.0g, 9.26mmol) and N-allylpyrrole-2-carboxaldehyde (1.25g, 9.26mmol) in DMF (25ml) at 120°C for 1h. The crude solid product, whose p.m.r. spectrum indicated only 33% of reaction had occurred, was purified by flash chromatography to give the product (490mg, 18%). Allowing for unreacted starting material the yield is therefore (54%). The product crystallised from methanol as colourless prisms, m.p. 211-213°C (Found: C, 78.50; H, 6.80; N, 14.50. $C_{19}H_{19}N_3$ requires C, 78.85; H, 6.60; N, 14.50%); ν_{max} 3378, 1623, 1593, 1492, 1454, 1285, 770, 754, and 701 cm^{-1}; m/z(%) 289 (M^+,91), 288(35), 210(16), 209(100), 184(10), 171(21), 169(12), 156(15), 144(13), 120(23), 119(36), 118(58) and 105(37); δ 7.51 and 7.31 (2 x d, 2 x 1H, ArH), 7.19-7.09 (m, 2H, ArH), 6.58 (dd, 1H, 4-H), 6.29 (t, 1H, 5-H), 6.02 (d, 1H, 6-H), 4.56 (d, 1H, 6bα-H, J 7.7Hz), 4.31 (t, 1H, 14bβ-H, J 6.0Hz), 4.17 (dd, 1H, 2α-H, J 8.3 and 10.6Hz), 3.89 (dd, 1H, 2β-H, J 3.9 and 10.6Hz), 3.45 and 3.16 (2 x m, 2 x H, 2 x 8-H), 3.05 and 2.75 (2 x m, 2 x 1H, 2 x 9-H), and 2.27 and 2.14 (2 x m, 2 x 1H, 2 x 1-H); ^{1}H NOEDSY(%): irradiation of 1β-H caused enhancements of 1α-H(17), 2β-H(5) and 14bβ-H(8); irradiation of 6bα-H caused enhancements of 2α-H and 8α-H (together 7), and 9α-H(5); irradiation of 1α-H caused enhancements of 1β-H(17), 14bβ-H(2), and 2α-H and 8α-H (together 9); irradiation of 2α-H caused enhancements of 2' -H(19), 4-H(2) and 1 -H(4); irradiation of 2 -H caused enhancements of 2β-H(22), and 1aα-H(7); irradiation of 14bβ-H caused enhancement of 1β-H(5); irradiation of 9β-H caused enhancements of 9α-H and 8β-H (together 25).

7aα,8,14,15aβ-Tetrahydro-6H-chromeno[3',4'-2,3]indolizino[6,7-b]indole (46). Tetrahydro-β-carboline-3-carboxylic acid (2.0g, 9.26mmol) and 0-propargylsalicylaldehyde (1.48g) were heated in DMF (25ml) at 120°C for 1h. Work up in the usual way afforded the product (1.62g, 37%) as pale yellow prisms from methanol, m.p. 203-205°C (Found: C, 80.00; H, 5.95; N, 8.90. $C_{21}H_{18}N_2O$ requires C, 80.25; H, 5.75; N, 8.90%); ν_{max} 3200, 1630, 1620, 1590, 1490, 1230, 1120, 1010, and 760 cm^{-1}; m/z(%) 314 (M^+,8), 312(6), 171(10), 144(33) and 143(100); δ 7.95 (s, 1H, NH), 7.51-6.86 (m, 8H, ArH), 5.98 (d, 1H, 7-H, J 1.1Hz), 4.92 (d, 1H, 15a -H, J 3.5Hz), 4.77 (m, 3H, CH_2O and HCHN), 4.44 (d, 1H HCHN), 4.35 (m, 1H, 7aα-H), 2.97 (dd, 1H, 8α-H, J 4.1 and 14.9Hz), and 2.62 (dd, 1H, 8β-H, J 9.6 and 14.9Hz).

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References

1. Part 18. R. Grigg, M. Dowling, J.F. Malone & V. Sridharan, Tetrahedron, in press.
2. R. Grigg, & S. Thianpatanagul, J.Chem.Soc., Chem.Commun., 1984, 180.
3. R. Grigg, M.F. Aly, V. Sridharan, & S. Thianpatanagul, J.Chem.Soc., Chem.Commun., 1984, 182.
4. M. Joucla & J. Mortier, J.Chem.Soc., Chem.Commun., 1985, 1566.
5. M.F. Aly, R. Grigg, S. Thianpatanagul & V. Sridharan, J.Chem.Soc., Perkin Trans 1, 1988, 949.
6. R. Grigg, S. Surendrakumar, S. Thianpatanagul & D. Vipond, J.Chem.Soc., Perkin Trans. 1, 1988, in press.
7. R. Grigg, J. Idle, P. McMeekin & D. Vipond, J.Chem.Soc.,Chem.Commun., 1987, 49; idem, J. Chem. Soc., Perkin Trans. 1, 1988, in press.
8. P. Armstrong, D.T. Elmore, R. Grigg & C.H. Williams, Biochem. Soc. Trans., 1986, 14, 404.
9. O. Tsuge, S. Kanemasa, M. Ohe & S. Takenaka, Bull.Chem.Soc.Jpn., 1987, 60, 4079
10. M. Hashimoto, Y. Eda, Y. Osanai, T. Iwai & S. Aoki, Chemistry Lett., 1986, 893.
11. M.F. Aly, H. Ardill, R. Grigg, S. Leong-Ling, S. Rajviroongit & S. Surendrakumar, Tetrahedron Letters, 1987, 28, 6077.
12. N. Cohen, J.F. Blount, R.J. Lapresti & D.P. Trullinger, J.Org.Chem., 1979, 44, 4005.
13. P. Armstrong, R. Grigg, M.W. Jordan & J.F. Malone, Tetrahedron, 1985, 41, 3547.
14. D.A. Barr, R. Grigg, H.Q.N. Gunaratne, J. Kemp, P. McMeekin & V. Sridharan, Tetrahedron, 1988, 44, 557.
15. R. Grigg, J. Kemp & W.J. Warnock, J.Chem.Soc.,Perkin Trans.1, 1987, 2275; K. Amornraksa, R. Grigg, H.Q.N. Gunaratne, J. Kemp & V. Sridharan, ibid, 1987, 2285.
16. C. Stetin, B. de Jeso & J.C. Pommier, Synth.Commun., 1982, 12, 495.
17. F. Johnson, Chem.Revs., 1968, 68, 375.
18. R. Grigg, H.Q.N. Gunaratne & J. Kemp, J.Chem.Soc.,Perkin Trans.1, 1984, 41.