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Diels-Alder Reactions of 2-Azadienes Derived From Cysteine and Serine Methyl Esters and Aldehydes

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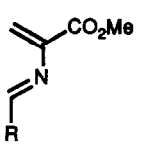
Abstract: The Diels-Alder reactions of *N*-benzylidenedehydroalanine methyl ester **1a** with but-3-en-2-one and with other electron deficient dienophiles have been found to give new dihydro- and tetrahydropyridines. The cycloaddition reactions are regioselective but not stereoselective. Cycloaddition reactions between **1a** and enamines have also been observed. The [4 + 2] cycloaddition reactions of other *N*-arylidenedehydroalanine methyl esters are also reported. Two new types of azadiene were prepared, namely *N*-(benzoylmethylene)dehydroalanine methyl ester **1e** and *N*-(ethoxycarbonylmethylene)dehydroalanine methyl ester **1f**. Their reactions with *N*-cyclohexen-1-ylpyrrolidine and with *N*-cyclopenten-1-ylpyrrolidine have led to the isolation of the dihydropyridine and pyridine esters.

Introduction The Diels-Alder reaction of acyclic 2-azadienes is a useful method for the preparation of pyridines, dihydropyridines and tetrahydropyridines. In the last decade some new methods of generating 2-azadienes have been found which have increased the scope of this approach.[1-3] The great majority of 2-azadienes studied are substituted with strongly electron donating groups and they participate in normal electron demand Diels-Alder reactions. In 1986 Wulff and Böhnke reported the first example of [4 + 2] cycloaddition of *N*-arylidenedehydroamino esters.[4] These azadienes were generated by dehydration of Schiff bases of serine methyl ester with *N,N'*-carbonyldiimidazole and triethylamine and were found to dimerise by way of a [4 + 2] cycloaddition process giving tetrahydropyridines.[5] With the exception of these dimerisations no Diels-Alder reactions were reported. *N*-Arylidenedehydroalanine methyl esters had already been prepared in 1979 by Öhler and Schmidt, by the reaction of thiazolidine esters with silver carbonate and DBU.[6] We have found that these intermediates can participate as 2-azadienes in Diels-Alder reactions with a range of dienophiles.[7] In this paper we describe the generation of the 2-azadienes **1a–1h** from the corresponding thiazolidines **2**. We have attempted to carry out cycloaddition reactions with all these azadienes and adducts have been isolated from all except **1g** and **1h**: experimental details are given for the cycloadditions. The alternative method of generation of the azadiene **1a** from the Schiff base of serine methyl ester has also been investigated.

Cycloaddition Reactions of Azadiene 1a. Initial experiments were carried out with *N*-benzylidenedehydroalanine methyl ester **1a**, which was generated by both of the methods described in the literature. The azadiene was expected to be electron deficient and therefore more likely to react with an electron rich dienophile; however, it could not be intercepted with ethyl vinyl ether even when this was used in large

excess. Attempts were then made to intercept the azadiene with an electron deficient dienophile, but-3-en-2-one, since the known dimerisation of **1a** involved cycloaddition to an electron deficient double bond.



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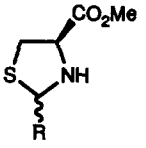

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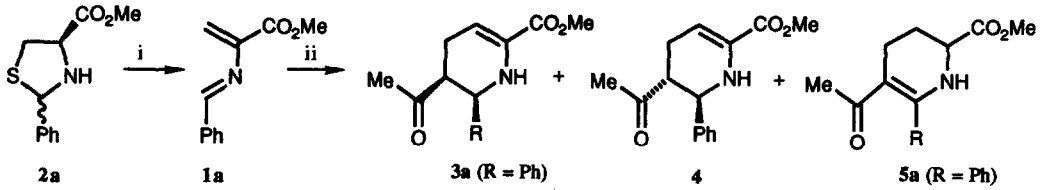
a; R = Ph
b; R = 4-$Me_2NC_6H_4$
c; R = 4-$NO_2C_6H_4$
d; R = 4-pyridyl
e; R = COPh
f; R = CO_2Et
g; R = H
h; R = Bu^t

This reaction of the azadiene **1a**, generated from the thiazolidine **2a** by the method of Öhler and Schmidt but in the presence of a large excess of but-3-en-2-one, led to the formation of three compounds in an overall yield of 76% (Scheme 1). These were separated by flash chromatography and were assigned the structures **3a** (20%), **4** (5%) and **5a** (51%). These structures were deduced on the basis of analytical and spectroscopic data. In particular, the signal for 6-H in the ^1H NMR spectra of compounds **3a** and **4** was used as a basis for assigning the stereochemistry. In the *cis* 5,6-disubstituted adduct **3a** the signal appeared at δ 4.72 as a doublet (J_{56} 3.8 Hz) whereas in the adduct **4** the signal appeared at δ 4.15 with a coupling constant (J_{56} 8.5 Hz) consistent with the *trans* configuration. Compounds **3a** and **4** are the products which would result from prototropy (*i.e.*, imine to enamine tautomerization) of *endo* and *exo* cycloadducts. In the NMR spectrum of the major product **5a** there were no signals in the region δ 5.0–7.0, indicating the absence of a vinylic CH. It also showed a carbonyl absorption at 1749 cm^{-1}.

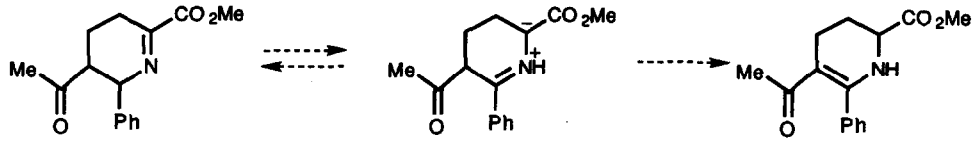


2a **1a** **3a** (R = Ph) **4** **5a** (R = Ph)

[3, 5 **b**; R = 4-$Me_2NC_6H_4$]

Scheme 1 i, Ag_2CO_3, DBU; ii, $MeCOCH{=}CH_2$.

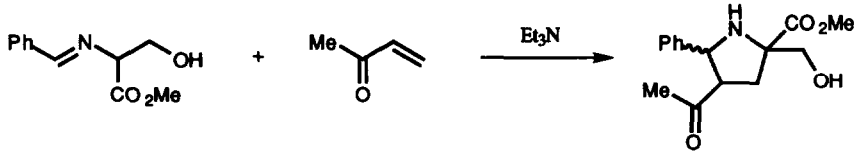
The origin of compound **5a** has not been established. We considered it likely that it was derived from one or both compounds **3a** and **4** by prototropy. However, attemps to promote this isomerization were not successful. In the presence of a base, the primary adduct **6a** might exist in equilibrium with the dipolar species **7a**; this might then isomerise to compound **5a** (Scheme 2).



6a **7a** **5a**

Scheme 2

The azadiene **1a** was also generated by the alternative route, from the Schiff base of serine methyl ester as described by Wulff and Böhnke[3], in the presence of but-3-en-2-one. This gave the tetrahydropyridine **5a** (17%) as the only isolable product. In an attempt to improve the yield we carried out the reaction under a variety of different conditions. An experiment was carried out in which triethylamine was added very slowly to a solution of the Schiff base, carbonyldiimidazole and but-3-en-2-one at room temperature but the reaction followed a quite different course: a dipolar cycloaddition occurred with the formation of compound **8**, which was isolated in 28% yield (Scheme 3). This reaction is analogous to those which Grigg and co-workers have carried out with Schiff bases of several α-amino esters, including serine derivatives.[8] The slow addition of one equivalent of triethylamine to a cooled solution containing the Schiff base, carbonyldiimidazole and but-3-en-2-one led to the formation of compound **3a** in very low yield. However, a better result was obtained when the reagents were added at –70 °C and the cooled solution then added slowly to a solution of the dienophile in dichloromethane heated at reflux: compounds **3a** and **4** were formed in an overall yield of 34% and there was no evidence for the presence of the isomer **5a**. This result lends some support to the suggestion that the isomerisation to compound **5a** might be a base catalysed process.



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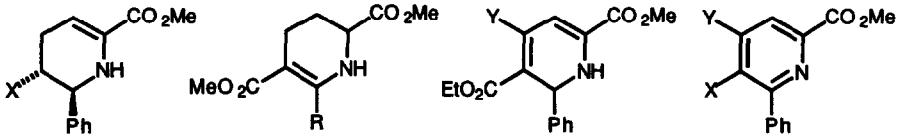
Scheme 3

Cycloaddition reactions of *N*-benzylidenedehydroalanine methyl ester **1a** (generated from the thiazolidine **2a**) were also attempted with other electron deficient dienophiles. Cycloadducts were isolated in moderate to low yield from several dienophiles (Table 1). In the cycloaddition of the azadiene **1** with acrylonitrile the *trans* isomer **9b** was the only product isolated, in 7% yield. The cycloaddition with methyl acrylate led to the formation of two tetrahydropyridine diesters: compound **9a** (15%) corresponding to the product expected from *exo* addition and the double bond isomer **10a** (4%). When this reaction was performed using three equivalents of silver carbonate (as described in the literature to generate the azadiene[6]) dimethyl 6-phenylpyridine-2,5-dicarboxylate **12a** was isolated (7%). In these reaction conditions the initially formed tetrahydropyridine was oxidised by the silver carbonate. This type of oxidation reaction was previously observed by Buchi *et al.*[9] The reaction of the intermediate **1a** with diethyl fumarate was also performed with an excess of silver carbonate and it led to the formation of the pyridine **12b** in 15% yield. In the reaction with ethyl propiolate the dihydropyridine **11a** was formed in 7% yield. With diethyl acetylenedicarboxylate a mixture of the dihydropyridine **11b** and of the pyridine **12b** was isolated. In an attempt to prevent the formation of the pyridine the reaction was carried out over a shorter reaction time at low temperature (0 °C) but again a mixture was obtained in 35% yield. We were unable to obtain a pure sample of dihydropyridine from this mixture by chromatography. However, the mixture was easily converted to the pyridine **12b** by oxidation with silver carbonate.



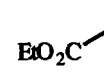
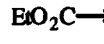
9 **a**; X = CO_2Me
b; X = CN

10 **a**; R = Ph
b; R = 4-$Me_2NC_6H_4$

11 **a**; Y = H
b; Y = CO_2Et

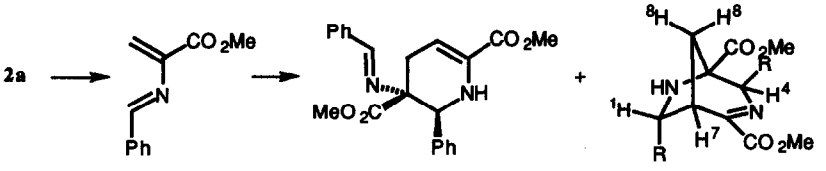
12 **a**; X = CO_2Me, Y = H
b; X = Y = CO_2Et

Table Cycloaddition reactions of azadiene **1a** with electron deficient dienophiles

Dienophile	Products (%)			
	9	**10**	**11**	**12**
	9a (15)	**10a** (4)	---	**12a**# (7)
	9b (7)	---	---	---
	---	---	---	**12b** (15)
	---	---	**11a** (7)	---
	---	---	**11b**	**12b***

Product with silver carbonate in excess. *Overall yield 35%.

No adducts could be isolated from attempted reactions of **1a** with dibenzoylacetylene, diethyl azodicarboxylate, β-nitrostyrene and *N*-phenylmaleimide. Instead, these reactions led only to products of dimerisation. The reaction of methyl 2-phenylthiazolidine-4-carboxylate **2a** with silver carbonate and DBU leads to the tetrahydropyridine **13** (8%), formed by cycloaddition reaction to itself, and to the compound **14a** (13%) formed from **13** by cyclization (Scheme 4). The synthesis of these two compounds has been described by Wulff and Böhnke[5] using the dehydration of the Schiff base of serine methyl ester method to generate the azadiene.



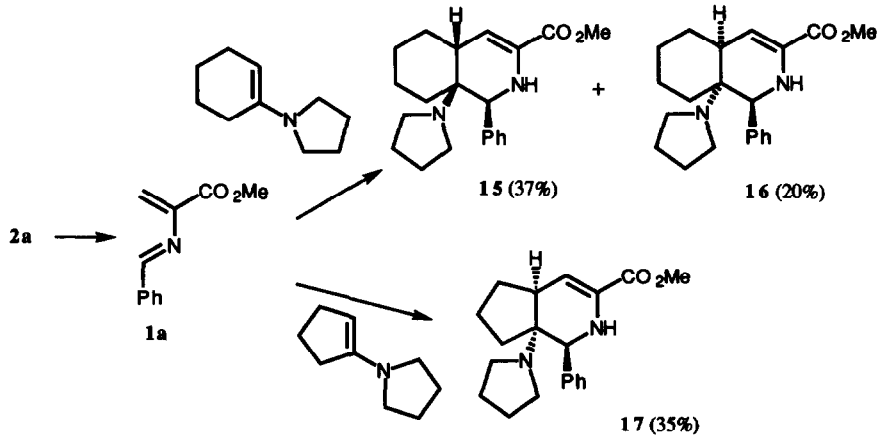
Scheme 4

Compound **13** rearranges, in solution and at room temperature, giving compound **14a** (after 6 days: 30% yield; after 18 days: 100% yield). In order to determine the complete stereochemistry of compound **14a** we obtained a NOESY spectrum (500 MHz). The protons 8-H have a cross-peak connection to 1-H, 7-H and to two aromatic protons. On the other hand, the proton 4-H has no cross-peak connection to 8-H. These results confirm the stereochemistry of **14a**.

Thus, several examples of Diels-Alder reactions with electron deficient dienophiles have been discovered and adducts have been isolated in moderate to low yield. With one dienophile, but-3-en-2-one, we were able to obtain adducts in good combined yield. The nature of the adducts formed is rather unpredictable; the cycloaddition is regioselective but the stereoselectivity, and the oxidation level of the adducts isolated, follows no clear pattern.

We then turned our attention to the possibility of carrying out cycloaddition reactions with enamines as electron rich dienophiles. The azadiene **1a** reacts with *N*-cyclohex-1-enylpyrrolidine with the formation of the cycloadducts **15** (37%) and **16** (20%) (Scheme 5). These compounds are the result of an *endo* and *exo* addition The stereochemistry was assigned on the basis of the ^{1}H NMR spectrum. The compound **15** shows a doublet assigned to 1-H with a coupling constant $J = 2.4$ Hz. The irradiation of the NH signal leads to the collapse of the doublet into a singlet. This rules out the possibility of a different regiochemistry: the other regiosisomer would be expected to show coupling between 1-H and the bridged proton 1a-H. In order to establish the full coupling relationships a homonuclear COSY spectrum was obtained. The signal for 1-H has a cross-peak connection to the signal for NH, confirming the result of the irradiation experiment. The signal for 4-H is connected to 4a-H confirming the proposed regiochemistry. The 2D NMR of the isomer **16** led to the same conclusions (correlations between 1-H and NH and between 4-H and 4a-H). The signal 1-H appears as a singlet, probably because the dihedral angle between NH and 1-H is close to 90°. A NOESY spectrum (500 MHz) of compound **16** was also obtained allowing the stereochemistry to be determined. The signal for 1-H has a crosspeak connection to 4a-H and there is also a crosspeak connection between 1-H and a methylenic group of the pyrrolidine ring. There is no crosspeak connecting 4a-H and the aromatic protons. These observations support the stereochemistry proposed for compound **16**.

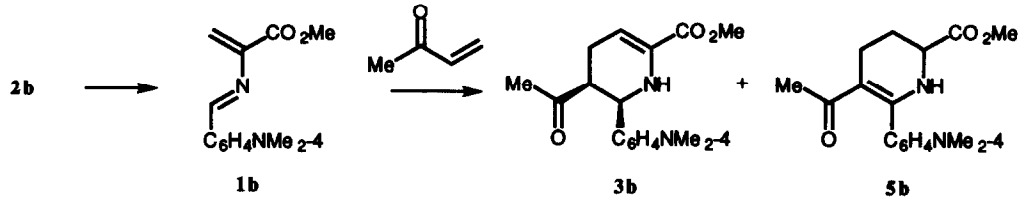
The reaction of the *N*-phenylidenedehydroalanine methyl ester **1a** with *N*-cyclopenten-1-ylpyrrolidine gave a single adduct **17** in 35% yield (Scheme 5); the structure was assigned on the basis of the close similarilty of the NMR spectrum of compound **17** to that of **16**.



Scheme 5

Cycloaddition Reactions of Other Imines of Dehydroalanine Methyl Ester. The above experiments demonstrated that the azadiene **1a** would undergo cycloaddition reactions with both electon deficient and electron rich alkenes. This led us to try to improve each type of reaction independently by using imines bearing appropriate substituents. The more electron rich azadiene **1b** formed by reaction of the thiazolidine **2b** with silver carbonate and DBU underwent a Diels-Alder reaction with but-3-en-2-one. When silver carbonate was used in excess (2.3 equivalents) a single product **3b** was isolated in 39% yield (Scheme 6). The signals for the

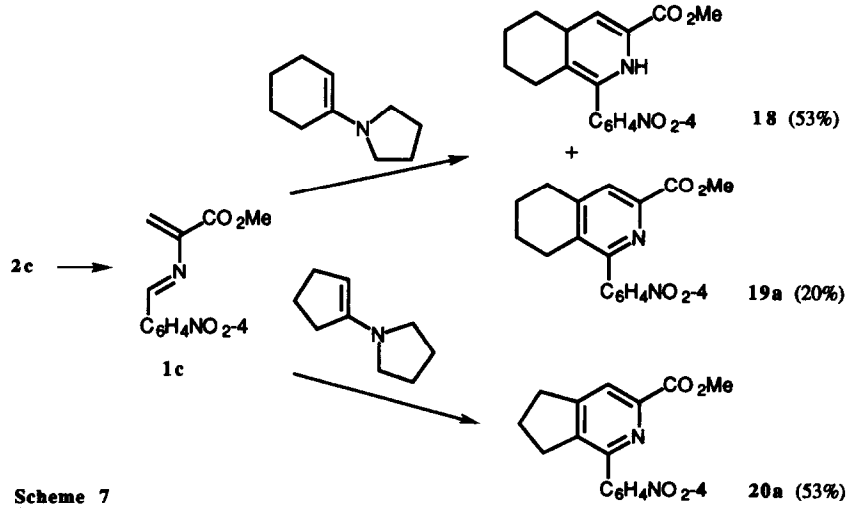
tetrahydropyridine ring hydrogens in the NMR spectrum of the product were analogous to those for compound **3a**, indicating that compound **3b** is the *cis* adduct. On the other hand, when silver carbonate was used in equimolar amount a different product, the isomer **5b**, was isolated in 37% yield; with 1.4 equivalents of silver carbonate both **3b** (9%) and **5b** (43%) were isolated.



Scheme 6

The azadiene **1b** also reacted with methyl acrylate; the cycloadduct **10b** was isolated in low yield (14%) together with a dimer **14b** of the azadiene (10%).

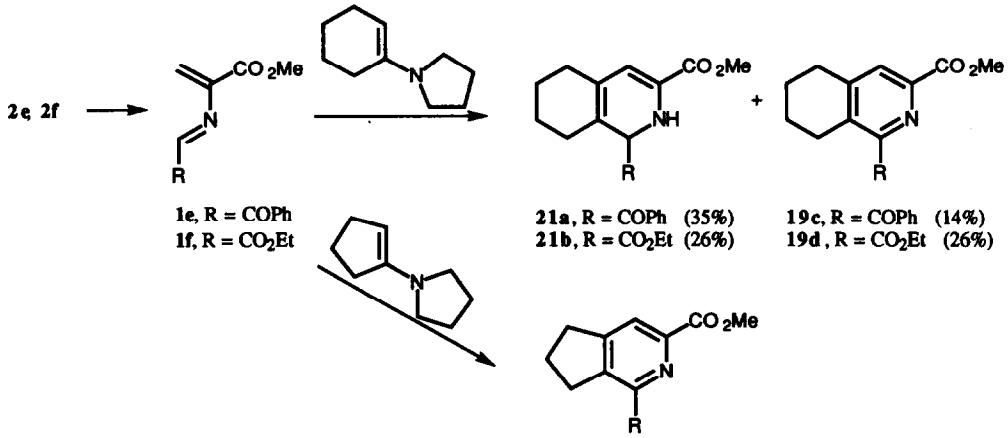
The Diels-Alder reactions of the an azadiene bearing a more electron deficient aryl substituent, *N*-(4-nitrobenzylidene)dehydroalanine methyl ester **1c**, were then investigated. The azadiene **1c** was generated from the thiazolidine **2c** in the presence of *N*-cyclohex-1-enylpyrrolidine. Two products were isolated, the hexahydroisoquinoline **18** (53%) which was presumably derived from a cycloadduct by elimination of pyrrolidine and the tetrahydroisoquinoline **19a** (20%) derived from **18** by oxidation. A reaction of azadiene **20** was also carried out with *N*-cyclopenten-1-ylpyrrolidine and this gave a single product **20a** in 52% yield (Scheme 7). No product of cycloaddition was obtained from a reaction carried out with this azadiene in the presence of ethyl vinyl ether. The azadiene **1d** bearing a 4-pyridyl substituent was also generated in the presence of *N*-cyclohex-1-enylpyrrolidine and from this reaction a single product, methyl 1-(4-pyridyl)-5,6,7,8-tetrahydroisoquinoline-3-carboxylate **19b**, was isloated (54%).



Scheme 7

In an attempt to increase the electrophilicity of the azadiene further, two new thiazolidines **2e** and **2f** were prepared from phenylglyoxal and ethyl glyoxylate, respecively, and cysteine methyl ester.¶ These compounds on reaction with silver carbonate and DBU were expected to lead to the formation of the corresponding 2-azadienes **1e** and **1f** bearing conjugative electron withdrawing groups.

The azadiene **1e** reacted with *N*-cyclohexen-1-ylpyrrolidine to give two products **21a** (35%) and **19c** (14%). From the reaction with *N*-cyclopenten-1-ylpyrrolidine a single product was obtained **20b** (27%). These relatively moderate yields may be due to the instability of this azadiene. No adducts were obtained from azadiene **1e** and ethyl vinyl ether. The azadiene **1f** reacted with *N*-cyclohexen-1-ylpyrrolidine to give two products: compounds **21b** (26%) and **19d** (26%). The reaction with *N*-cyclopenten-1-ylpyrrolidine led to a single product **20c** in 51% yield.



Scheme 8

The thiazolidines **2g** and **2h** were prepared but no adducts were isolated from their reaction with silver carbonate and DBU carried out in the presence either of but-3-en-2-one or of *N*-cyclohexen-1-ylpyrrolidine.

We explored some alternative methods of generation of 2-azadienes from cysteine methyl ester. We investigated the reaction, in the presence of a base, of methyl 4-phenylthiazolidine-2-carboxylate with electrophiles which could coordinate to sulfur; namely, *N*-chlorosuccinimide in the presence and absence of triphenylphosphine, and iodobenzene dichloride. An adduct (compound **3a**) was isolated only with iodobenzene dichloride in presence of but-3-en-2-one, and the yield was very low.

Discussion and Conclusions. *N*-Benzylidenedehydroalanine methyl ester **1a** participate in Diels-Alder reactions with both electron rich and electron deficient dienophiles. The evidence available at present does not allow us to decide whether these are true (concerted) Diels-Alder reactions or whether a stepwise mechanism (possibly involving silver ion catalysis) is operating. The fact that the same adducts can be obtained from the Schiff base of serine methyl ester, albeit in lower yields, make a catalyzed process unlikely. The cycloadditions show little consistent stereoselectivity. The compounds such as **5a** in which the double bond

¶ The reaction of phenylglyoxal with cysteine methyl ester led to the formation of two diastereoisomers (isomeric at C-2) which were separated by chromatography and which appeared to be stable in solution. This behaviour contrasts with that of the thiazolidines derived from aromatic aldehydes, which exist in solution as mixtures of diastereoisomers with a low barrier to interconversion. This interconversion occurs by reversible ring opening to the acyclic imine tautomers.[10] Presumably the electron withdrawing benzoyl group substantially increases the activation energy for ring opening.

has shifted seem to be formed independently of other cycloadducts and they may be formed a base catalysed isomerizattion of the primary Diels-Alder adducts.

It is unusual for dienes to react with both electron rich and electron deficient dienophiles. The explanation in this case may be that the HOMO and LUMO energy levels are rather close. The calculated energy levels of the HOMO and LUMO of 2-azabutadiene are slightly lower than those of butadiene.[11] The effect of the methoxycarbonyl group should be to lower both energy levels further, whereas the phenyl group should raise the HOMO and lower the LUMO. The results obtained with other 4-substituted thiazolidines are consistent with their predicted effects on the HOMO and LUMO energy levels.

The reactions provide a potentially useful route to new tetrahydropyridine esters bearing a variety of substituents and indeed, several new compounds of this type have been isolated in acceptable yield. The obvious deficiencies of the methodology at present are the relatively low yields and the unpredictability of the stereochemistry of the products. The use of an oxidant, silver carbonate, to generate the azadienes resulted in the isolation of several products which are derived by oxidation of the expected adducts. We are currently seeking a more efficient method of generation of these intermediates in order to improve the viability of the methodology.

EXPERIMENTAL

General ^{1}H NMR spectra were recorded on a Bruker ACE200 spectrometer operating at 200MHz, (where indicated) on a Bruker AMX400 instrument operating at 400 MHz or on a Varian Umity 500 instrument operating at 500 MHz. The solvent is deuteriochloroform except where indicated otherwise. Signals are singlets where no multiplicity is shown. Mass spectra were recorded under electron impact at 70 meV on a VG Micromass 7070E instrument. M.p.'s were recorded on a Reichert hot stage. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

Preparation of thiazolidines: General procedure.[6] Cysteine methyl ester hydrochloride (3.45 g, 20 mmol) was dissolved in water (15 ml) and potassium hydrogen carbonate (2.0 g, 20 mmol) was added following the addition of a solution of the aldehyde (22 mmol) in ethanol (15 ml). The reaction mixture was stirred at room temperature for 30 minutes. Water was added and the solution was extracted with dichloromethane and the solvent evaporated off.

Methyl 2-phenylthiazolidine-4-carboxylate[6] **2a** was an oil (Found: C, 59.7; H, 5.8; N, 5.6. Calç. for $C_{11}H_{13}NO_2S$: C, 59.2; H, 5.8; N, 6.3%); δ 3.07–3.24 (1 H, m, SCH_2), 3.34–3.51 (1 H, m, SCH_2), 3.58 (1 H, NH), 3.79 and 3.81 (3 H), 4.01 and 4.23 (1 H, dd, *J* 8.8 and 7.14), 5.56 and 5.81 (1 H, CHPh, ratio 66:34), 7.33-7.40 (3 H, m, Ar-H) and 7.46–7.55 (2 H, m, Ar-H); *m/z* 223 (M^+, 12%), 164 (73), 137 (100). 117 (74) 77 (24) and 59 (26).

Methyl 2-[(4-dimethylamino)phenyl]thiazolidine-4-carboxylate **2b**. This thiazolidine was prepared following the same procedure used in the syntheses of methyl 2-phenylthiazolidine-4-carboxylate, but the reaction mixture was stired overnight at room temperature, giving a solid (73%), m.p. 96–98 °C (from ether) (Found: C, 58.4; H, 6.8; N, 10.3. $C_{13}H_{18}N_2O_2S$ requires C, 58.6; H, 6.8; N, 10.5%); δ 2.97 (6 H), 3.02–3.15 (1 H, m, SCH_2), 3.40–3.49 (1 H, m, SCH_2), 3.95–4.01 and 4.25–4.32 (1 H, m, $CHCO_2$), 3.80 (3 H), 5.52 and 5.74 (1 H, CHPh), 6.70 (2 H, d, *J* 8.8, Ar-H) and 7.39 (2 H, d, *J* 8.8, Ar-H); *m/z* 266.1086 (M^+, 34%) ($C_{13}H_{18}N_2O_2S$ requires 266.1089), 220 (24), 164 (26), 160 (100), 147 (68), 77 (17) and 59 (23).

Methyl 2-(4-nitrophenyl)thiazolidine-4-carboxylate **2c**. This thiazolidine was prepared following the same procedure used for the syntheses of methyl 2-phenylthiazolidine-4-carboxylate; it was isolated (95%) as a solid,

m.p. 64–66 °C (from ether) (Found: C, 49.2; H, 4.4; N, 10.4. $C_{11}H_{12}N_2O_4S$ requires C, 49.3; H, 4.5; N, 10.4%); δ 2.90 (1 H, NH), 3.12–3.21 (1 H, m, SCH_2), 3.36–3.55 (1 H, m, SCH_2), 3.82 (3 H), 4.02–4.12 (1 H, m, $CHCO_2$), 5.63 and 5.91 (1 H, ratio 51:48), 7.71 (2 H, d, *J* 8.8, Ar-H) and 8.23 (2 H, d, *J* 8.8, Ar-H); *m/z* 268 (M^+, 5%), 209 (100), 182 (91), 162 (29), 116 (18), 89 (17) and 59 (33).

Methyl 2-(4-pyridyl)thiazolidine-4-carboxylate **2d**. A mixture of cysteine methyl ester hydrochloride (3.0 g, 17.5 mmol), triethylamine (2. 4 ml) and pyridine-4-carboxaldehyde (3.4 g, 32.0 mmol) was stirred in toluene (60 ml) and methanol (30 ml) for 15 h. The solvent was evaporated off and the residue was subjected to flash chriomatography which gave (with ethyl acetate) the *thiazolidine* **2d** (3.1 g, 79%) as an oil; δ 2.92 (1H, NH), 3.11 (1 H, d, *J* 10.5 and 6.9), 3.36 (1 H, d, *J* 10.5 and 6.9), 3.81 (3 H), 4.04 (1 H, t, *J* 6.9), 5.52 and 5.58 (1 H, 27:73), 7.36–7.45 (2 H, m, Ar-H) and 8.53–8.62 (2 H, m, Ar-H); *m/z* 224 (M^+, 1%) 223 (2), 191 (3), 165 (100), 138 (94) and 59 (76).

Methyl 2-benzoylthiazolidine-4-carboxylate **2e**. This thiazolidine was prepared following the same procedure used in the syntheses of methyl 2-phenyl-1,3-thiazolidine-4-carboxylate, but the reaction mixture was stirred for 2 h at room temperature, giving the thiazolidine as an oil (68%). The NMR spectrum showed the presence of two diastereoisomers (ratio 45:55) which were separated by flash chromatography [petroleum ether–ethyl acetate (3–1), petroleum ether–ethyl acetate (1:1) then ethyl acetate] giving (in order of elution): *the major isomer*: δ 2.80 (1 H, approx. t, *J* 10.2), 3.37 (1 H, dd, *J* 5.8 and 10.2), 3.75 and 3.84 (1 H, m), 3.84 (3 H), 5.80 (1 H), 7.47–7.63 (3 H, m, Ar-H) and 7.94–7.99 (2 H, m, Ar-H); and *the minor isomer*: δ 3.08 (1 H,dd, *J* 6.6 and 10.7), 3.40 (1 H, dd, *J* 2.75 and 10.7), 3.73–3.84 (1 H, m), 3.81 (3 H), 5.99 (1 H), 7.33–7.62 (3 H, m, Ar-H); *m/z* 251 (M^+, 2%), 250 (10), 226 (3), 220 (3), 192 (1), 174 (5) 146 (11), 105 (100), 87 (9) and 77 (90).

Ethyl (2) methyl (4) thiazolidine-2,4-dicarboxylate **2f**. This thiazolidine was prepared by reaction of cysteine methyl ester with ethyl glyoxylate[13] following the same procedure used in the synthesis of methyl 2-phenyl-1,3-thiazolidine-4-carboxylate, but the reaction mixture was stirred for 4 h at room temperature, giving the thiazolidine as an oil (88%) (Found: C, 43.3; H, 6.0; N, 6.3. $C_8H_{13}NO_4S$ requires C, 43.8; H, 5.9; N, 6.4%); δ 1.31 (3 H, t), 2.81 (1 H, approx. t, *J* 10.2), 3.30 (1 H, dd; *J* 6.0 and 10.2), 3.77 and 3.80 (3 H, 2 x s), 3.88 (1 H, dd, *J* 6.0 and 10.2), 4.27 (2 H, q), 4.92 and 5.12 (1 H, 2 x s); *m/z* 219 (M^+, 15%), 160 (19), 146 (100), 114 (74), 86 (92), 59 (70) and 45 (48).

Methyl thiazolidine-4-carboxylate hydrochloride (**2g** HCl) was prepared by a literature procedure.[12] It had m.p. 163–165 °C (from methanol–ether) (lit.,[12] m.p. 164-165 °C) (Found: C, 32.4; H, 5.5; N, 7.6. Calc. for $C_5H_9NO_2S$.HCl: C, 32.7; H, 5.4; N, 7.6%) ; δ (DMSO-d_6) 3.28 (1 H, dd, *J* 6.3 and 11.5, ABX system), 3.38 (1 H, dd, *J* 6.9 and 11.5, ABX system)), 3.92 (3H), 4.26 (1H, d, *J* 9.6, AB system), 4.32 (1 H, d, *J* 9.6, AB system) and 4.77 (1 H, approx. t, *J* 6.9 and 6.3, ABX system); *m/z* 147 (M^+– HCl, 45%), 88 (100), 61 (77). 59 (60) and 44 (55).

Methyl 2-(1,1-dimethylethyl)thiazolidine-4-carboxylate **2h**[14]. This thiazolidine was prepared following the same procedure used in the synthesis of methyl 2-phenylthiazolidine-4-carboxylate giving an oil (60%); δ 0.98 and 1.22 (2 x s, 9H), 2.33 (1 H, NH), 2.66 (1 H, t, *J* 10), 3.00–3.18 (1 H, m), 3.21–3.30 (1 H. m), 3.75 and 3.78 (3 H, 2 x s), 4.46 and 4.53 (1 H, 2 x s, 2-H, ratio 66:34); *m/z* 204 (M^++ H, 62%), 159 (100), 115 (21), 87 (34) and 42 (39).

Diels-Alder reactions of 2-azadienes derived from thiazolidines: General procedure. The thiazolidine (1 mmol) was dissolved in dry acetonitrile (10 ml) and the dienophile was added in excess (as indicated below). The solution was cooled to –20 °C and silver carbonate (1 mmol) was added, followed by the addition of a

solution of DBU (0.03 g) in dry acetonitrile (5 ml). The reaction mixture was stirred for 2 h at 0 °C then for 8 h at room temperature. Ether was added, the mixture was filtered and the solvent was evaporated from the filtrate. The products were isolated by flash chromatography.

Methyl (5S,6R)-5-acetyl-1,4,5,6-tetrahydro-6-phenyl-pyridine-2-carboxylate **3a**, *methyl (5R,6R)-5-acetyl-1,4,5,6-tetrahydro-6-phenylpyridine-2-carboxylate* **4** and *methyl 5-acetyl-1,2,3,4-tetrahydro-6-phenyl-pyridine-2-carboxylate* **5a**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure and with but-3-en-2-one (15 mmol) as the dienophile, followed by flash chromatography [petroleum ether, petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate] the following compounds in order of elution: (i) *methyl (5R,6R)-5-acetyl-1,4,5,6-tetrahydro-6-phenylpyridine-2-carboxylate* **4** (5%) as an oil (Found: C, 68.9; H, 6.9; N, 5.1. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); δ 1.71 (3 H), 2.22 (1 H, approx dt, *J* 18.8 and 5.3, 4-H), 2.48 (1 H, ddd, *J* 18.8, 9.7 and 3.6, 4-H), 2.86 (1 H, ddd, 5-H), 3.72 (3 H), 4.15 (1 H, d, *J* 8.5, 6-H), 4.25 (1 H, NH), 5.71 (1 H, dd, *J* 5.3 and 3.6, 3-H) and 7.22–7.30 (5 H, m, Ar-H); *m/z* 259 (M^+, 18%), 216 (100), 156 (95), 115 (28) and 43 (65); (ii) *methyl (5S,6R)-5-acetyl-1,4,5,6-tetrahydro-6-phenylpyridine-2-carboxylate* **3a** (20%), m.p. 78–80 °C (from petroleum ether) (Found: C, 69.4; H, 6.6; N, 5.4. $C_{17}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); δ 1.96 (3 H), 2.43 (2 H, approx. dd, 4-H), 3.05–3.15 (1 H, m, 5-H), 3.18 (3 H), 4.64 (1 H, NH), 4.72 (1 H, d, *J* 3.8, 6-H), 5.78 (1 H, t, *J* 4.4, 3-H) and 7.18–7.38 (5 H, m, Ar-H); *m/z* 259 (M^+, 21%), 216 (81), 156 (100), 115 (41) and 43 (91); (iii) *methyl 5-acetyl-1,2,3,4-tetrahydro-6-phenylpyridine-2-carboxylate* **5a** (51%), m.p. 136–137 °C (from ether–petroleum ether) (Found: C, 69.5; H, 6.6; N, 5.4. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%) ; δ (400 MHz) 1.56 (3 H), 1.65–1.85 (1 H, m, 3-H), 2.25–2.40 (2 H, m, 3-H and 4-H), 2.75–2.95 (1 H, m, 4-H), 3.80 (3 H), 3.98 (1 H, approx. dt, *J* 10.0 and 2.0, 2-H), 4.77 (1 H, NH) and 7.35–7.45 (5 H, m, Ar-H); $\upsilon_{max.}$ (KBr) 1749 (C=O of ester), 1571 and 1506 cm^{-1}; *m/z* 259 (M^+, 41%), 244 (84), 156 (69). 115 (40) and 77 (25).

Dimethyl (5R,6R)-1,4,5,6-tetrahydro-6-phenyl-pyridine-2,5-dicarboxylate **9a** and *dimethyl 1,2,3,4-tetrahydro-6-phenyl-pyridine-2,5-dicarboxylate* **10a**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure using methyl acrylate (10 mmol) as the dienophile, followed by flash chromatography [petroleum ether–ethyl acetate (4:1) then petroleum ether–ethyl acetate (3:1)] the following compounds in order of elution: (i) *dimethyl (5R,6R)-1,4,5,6-tetrahydro-6-phenylpyridine-2,5-dicarboxylate* **9a** (15%) as an oil; δ 2.25–2.40 (1 H, , approx. dt, *J* 18.4 and 5.5, 4-H), 2.49–2.55 (1 H, approx. dddd, *J*, 18.4, 9.0, 3.6 and 1.0, 4-H), 2.66–2.79 (1 H, m, 5-H), 3.31 (3 H), 3.38 (3 H), 4.22 (1 H, NH), 4.29 (1 H, d, *J* 8.5, 6-H), 5.68 (1 H, dd, *J* 5.5 and 3.6, 3-H) and 7.19–7.25 (5 H, m, Ar-H); *m/z* 275.1155 (M^+, 37%) ($C_{15}H_{17}NO_4$ requires 275.1157), 216 (41), 156 (100). 131 (30) and 77 (23); (ii) *dimethyl 1,2,3,4-tetrahydro-6-phenylpyridine-2,5-dicarboxylate* **10a** (4%), m.p. 88–90 °C (from ether–petroleum ether) (Found: C, 65.4; H, 6.2; N, 5.1. $C_{15}H_{17}NO_4$ requires C, 65.5; H, 6.2; N, 5.1%) ; δ 1.79–1.90 (1 H, m, 3-H), 2.27–2.54 (2 H, m, 3-H and 4-H), 2.62–2.77 (1 H, approx. dt, *J* 11.8 and 4.9, 4-H), 3.42 (3 H), 3.79 (3 H), 4.02 (1 H, approx. dt, *J* 9.3 and 3.0, 2-H), 4.62 (1 H, NH) and 7.29–7.38 (5 H, m, Ar-H); *m/z* 275 (M^+, 38%), 216 (100), 156 (75). 130 (19) and 77 (20).

Methyl (5R,6R)-5-cyano-1,4,5,6-tetrahydro-6-phenylpyridine-2-carboxylate **9b**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure using acrylonitrile (15 mmol) as the dienophile, followed by flash chromatography [petroleum ether, petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate], the *tetrahydropyridine* **9b** (7%) as a solid m.p. 151–153 °C (from ether–petroleum ether) (Found: C, 69.3; H, 5.8; N, 11.5. $C_{14}H_{14}N_2O_2$ requires C, 69.4; H, 5.8; N, 11.6%) ; δ 2.57–2.66 (2 H, m, 4-H), 2.91–2.99 (1 H, m, 5-H), 3.81 (3 H), 4.40 (1 H, approx, d, *J* 7.7, 6-H), 4.50 (1 H, NH), 5.66 (1 H, approx. t, *J* 4.26, 3-H) and 7.38–7.40 (5 H, m, Ar-H); *m/z* 242 (M^+, 74%), 182 (46), 126 (3). 77 (33) and 54 (48).

Dimethyl 6-phenylpyridine-2,5-dicarboxylate **12a**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure using methyl acrylate (10 mmol) as the dienophile and 3 equivalents of silver carbonate, followed by flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)], the pyridine **12a** (7%), m.p. 88–90 °C (from petroleum ether) (lit.[10] m.p. 91–92 °C); δ 4.01 (3 H), 4.70 (3 H), 7.26–7.57 (5 H, m, Ar-H), 8.13 (1 H, d, *J* 6.6) and 8.20 (1 H, d, *J* 6.6); *m/z* 271.0845 (M^+, 17%) (calc. for $C_{15}H_{13}NO_4$: 271.0845), 213 (69), 196 (96). 149 (79), 105 (100) and 77 (99).

Diethyl (4,5) methyl (2) 6-phenylpyridine-2,4,5-tricarboxylate **12b**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure using diethyl fumarate (15 mmol) as the dienophile and 3 equivalents of silver carbonate, followed by flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)], the *pyridine* **12b** (15%), m.p. 71–72 °C (from ether–petroleum ether) (Found: C, 63.9; H, 5.3; N, 3.9. $C_{19}H_{19}NO_6$ requires C, 63.9; H, 5.3; N, 3.9%) ; δ 1.10 (3 H, t, *J* 7.16), 1.41 (3 H, t, *J* 7.14), 4.03 (3 H), 4.21 (2 H, q, *J* 7.2), 4.43 (2 H, q, *J* 7.2), 7.43–7.44 (3 H, m, Ar-H), 7.60–7.63 (2 H, m, Ar-H) and 8.55 (1 H); *m/z* 357 (M^+, 30%), 328 (80), 294 (100). 268 (43), 152 (34) 105 (16) and 77 (9).

Ethyl (5) methyl (2) 1,6-dihydro-6-phenylpyridine-2,5-dicarboxylate **11a**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure using ethyl propiolate (3 mmol) as the dienophile, followed by flash chromatography [petroleum ether then]petroleum ether–ethyl acetate (4:1)], the *dihydropyridine* **11a** (7%) as an oil (Found: C, 66.1; H, 6.5; N, 3.9. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 5.9; N, 4.9%); δ 1.15 (3 H, t, *J* 7.4), 3.74 (3 H), 4.09 and 4.08 (4 H, 2 x q, *J* 7.4), 5.39 (1 H, br, NH), 5.64 (1 H, d, *J* 3.0, 6-H), 5.74 (1 H, dd, *J* 6.6 and 1.9, 3-H) and 7.19–7.35 (6 H, m); *m/z* 287.1151 (M^+, 12%) ($C_{16}H_{17}NO_4$ requires 287.1158), 210 (100), 150 (86), 105 (89) and 77 (59).

Diethyl (4,5) methyl (2) 1,6-dihydro-6-phenylpyridine-2,4,5-tricarboxylate **11b** and *diethyl (4,5) methyl (2) 6-phenylpyridine-2,4,5-tricarboxylate* **12b**. Methyl 2-phenylthiazolidine-4-carboxylate reacted with ethyl acetylenedicarboxylate (2 mmol) following the general procedure except that the reaction was performed at 0 °C and the reaction mixture was stirred for 2 h. Flash chromatography [petroleum ether, petroleum ether–ethyl acetate (4:1) then petroleum ether–ethyl acetate (3:1)] gave a mixture of the dihydropyridine **11b** and the pyridine **12** (combined yield 35%). Compound **11b** was identified by NMR: δ 1.18 (3 H, t), 1.34 (3 H, t), 3.80 (3 H), 4.12 (2 H, q), 4.31 (2 H, q), 5.56 (1 H, NH), 5.72 (1 H, d, *J* 3.2), 5.81 (1 H, d, *J* 1.8) and 7.26–7.43 (5 H, m, Ar-H); compound **12b** was identified from the NMR spectrum by comparison with that of the specimen isolated earlier. The mixture was dissolved in chloroform and silver carbonate (1 equiv.) was added. The solution was heated under reflux overnight. Flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)] gave the pyridine **12** (90%), m.p. 71–72 °C (from ether–petroleum ether).

Methyl (1S,4aR,8aS)-1,2,4a,5,6,7,8,8a-octahydro-1-phenyl-8a-(1-pyrrolidino)isoquinoline-3carboxylate **15** and *methyl (1S,4aS,8aR)-1,2,4a,5,6,7,8,8a-octahydro-1-phenyl-8a-(1-pyrrolidino)isoquinoline-3-carboxylate* **16**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure using *N*-cyclohexen-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)] the following compounds in order of elution: (i) *methyl (1S,4aS,8aR)-1,2,4a,5,6,7,8,8a-octahydro-1-phenyl-8a-(1-pyrrolidino)isoquinoline-3-carboxylate* **16** (20%), m.p. 129–131 °C (from petroleum ether) (Found: C, 73.9; H, 8.3; N, 8.2. $C_{21}H_{28}N_2O_2$ requires C, 74.1; H, 8.2; N, 8.2%); δ 1.15–1.85 (12 H, m), 1.05–2.30 (2 H, m), 2.65–2.85 (2 H, m), 2.95–3.04 (1 H, m, 4a-H), 3.68 (3 H), 3.93 (1 H, NH), 4.54 (1 H, 1-H), 5.56 (1 H, m, 4-H), 7.25–7.35 (3 H, m, Ar-H) and 7.40–7.50 (2 H, m, Ar-H).; *m/z* 340 (M^+, 31%), 249 (79), 176 (100), 162 (50) and 91 (60); (ii) *methyl (1S,4aR,8aS)-1,2,4a,5,6,7,8,8a-octahydro-1-phenyl-8a-(1-*

pyrrolidino)isoquinoline-3-carboxylate **15** (37%), m.p. 126–128 °C (from ether) (Found: C, 74.0; H, 8.3; N, 8.0. $C_{21}H_{28}N_2O_2$ requires C, 74.1; H, 8.2; N, 8.2%); δ 1.40–1.70 (14 H, m), 2.65–2.85 (2 H, m), 2.82–2.88 (1 H, m, 4a-H), 3.79 (3 H), 4.20 (1 H, d, *J* 2.4, 1-H), 4.67 (1 H, NH), 5.52–5.53 (1 H, m, 4-H) and 7.18–7.30 (5 H, m, Ar-H); *m/z* 340 (M^+, 34%), 249 (83), 176 (100), 162 (51) and 91 (57).

Methyl (1S, 4aS, 7aR)-2,4a,5,6,7,7a-hexahydro-1-phenyl-7a-(1-pyrrolidino)-1H-cyclopenta[c]pyridine)-3-carboxylate **17**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** gave, by the general procedure using *N*-cyclopenten-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether, petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)], the *pyridine* **17** (35%) as a solid, m.p. 97–99 °C (from petroleum ether) (Found: C, 73.4; H, 8.2; N, 8.2. $C_{20}H_{26}N_2O_2$ requires C, 73.6; H, 8.0; N, 8.6%); δ 1.56 (8 H, m), 2.03 (2 H, m), 2.30 (2 H, m), 2.80 (2 H, m), 2.99 (1 H, m), 3.75 (3 H), 4.09 (1 H, NH), 4.49 (1 H, 1-H), 5.64 (1 H, dd, *J* 3.7 and 1.3, 4-H), 7.25–7.31 (3 H, m, Ar-H) and 7.43–7.48 (2 H, m, Ar-H).; *m/z* 326 (M^+, 19%), 235 (100), 175 (24), 136 (59) and 77 (22).

Methyl (5S,6R)-5-acetyl-1,4,5,6-tetrahydro-6-[4-(dimethylamino)phenyl]pyridine-2-carboxylate **3b** and*methyl 5-acetyl-1,2,3,4-tetrahydro-6-(4-dimethylaminophenyl)pyridine-2-carboxylate* **5b**. Methyl 2-[4-(dimethylamino)phenyl]thiazolidine-4-carboxylate **2b** gave, by the general procedure using but-3-en-2-one (15 mmol) as the dienophile and 1.4 equiv. silver carbonate, followed by flash chromatography [petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)], (i) the *tetrahydropyridine* **3b** (10%) as a solid m.p. 90–91 °C (from ether–petroleum ether) (Found: C, 67.5; H, 7.4; N, 9.2. $C_{17}H_{22}N_2O_3$ requires C, 67.5; H, 7.3; N, 9.3%) ; δ 1.97 (3 H), 2.41 (2 H, approx. dd, 4-H), 2.91 (6 H), 3.05 (1 H, m, 5-H), 3.79 (3 H), 4.54 (1 H, NH), 4.62 (1 H, d, *J* 4.4, 6-H), 5.75 (1 H, t, *J* 4.4, 3-H), 6.64 (2 H, d, *J* 8.8, Ar-H) and 7.06 (2 H, d, *J* 8.8, Ar-H); *m/z* 302 (M^+, 50%), 259 (100), 199 (79), 174 (83) and 77 (28); (ii)*the tetrahydropyridine* **5b** (43%), m.p. 132–134 °C (from ether–petroleum ether) (Found: C, 67.2; H, 7.3; N, 8.9. $C_{17}H_{22}N_2O_3$ requires C, 67.5; H, 7.3; N, 9.3%) ; δ (300 MHz) 1.66 (3 H), 1.61–1.78 (2 H, m, 3-H and 4-H), 2.83–2.92 (1 H, m, 4-H), 3.61 (6 H), 3.80 (3 H), 3.93 (1 H, dt, *J* 9.9 and 3.0, 2-H), 4.83 (1 H, NH), 6.65 (2 H, d, *J* 8.8, Ar-H) and 7.23 (2 H, d, *J* 8.8, Ar-H); $\upsilon_{max.}$ (KBr) 3254 (NH), 1741 (C=O of ester) and 1572 cm^{-1}; *m/z* 302 (M^+, 93%), 287 (100), 259 (52), 199 (69) and 147) (45).

A reaction carried out using 1 equiv. silver carbonate gave only **5b** (37%) whereas with 2.3 equiv. silver carbonate the only product isolated was **3b** (39%).

Dimethyl 6-(4-dimethylaminophenyl)pyridine-2,5-dicarboxylate **10b** and *dimethyl (1S,4R,5S,7R)-4,7-bis(4-dimethylaminophenyl)-3,6-diazabicyclo[3.2.1]oct-2-ene-2,5-dicarboxylate* **14b**. Methyl 2-(4-dimethylaminophenyl)thiazolidine-4-carboxylate **2b** gave, by the general procedure using methyl acrylate (10 mmol) as the dienophile and 1 equivalent of silver carbonate, followed by flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)], (i) *the tetrahydropyridine* **10b** (14%), m.p. 118–120 °C (from ether) (Found: C, 64.3; H, 7.1; N, 8.6. $C_{17}H_{22}N_2O_4$ requires C, 64.1; H, 7.0; N, 8.8%); δ (300 MHz) 1.70–1.82 (1 H, m, 3-H), 2.25–2.34 (1 H, m), 2.37–2.48 (1 H, m), 2.71 (1 H, dt, *J* 15.7 and 4.8), 2.97 (6 H), 3.47 (3 H), 3.78 (3 H), 3.96 (1 H, dt, *J* 9.9 and 3.1), 4.65 (1 H, NH), 6.67 (2 H, d, *J* 8.8, Ar-H) and 7.22 (2 H, d, *J* 8.8, Ar-H); $\upsilon_{max.}$ (KBr) 3426, 1737, 1699 and 1583 cm^{-1}; *m/z* 318 (M^+, 59%), 259 (100), 199 (51), 113 (30), 105 (100) and 99 (36); (ii) *the dimer* **14b** (10%), m. p. 128–130 °C (from petroleum ether –ethyl acetate) (Found: C, 66.6; H, 7.0; N, 11.5. $C_{26}H_{32}N_4O_4$ requires C, 67.2; H, 6.9; N, 12.0%); δ (300 MHz) 2.14 (1 H), 2.16 (1 H, d, *J* 3.0), 2.89 (6 H), 3.50 (3 H), 3.54 (3 H), 3.85 (1 H, m), 4.65 (1 H, d, *J* 7.0), 5.27 (1 H), 6.62 (2 H, d, *J* 8.7, Ar-H), 6.64 (2 H, d, *J* 8.7, Ar-H), 6.88 (2 H, d, *J* 8.7, Ar-H) and 7.16 (2 H, d, *J* 8.7, Ar-H); $\upsilon_{max.}$ (KBr) 1743, 1722 and 1614 cm^{-1}; *m/z* 464 (M^+, 1%), 363 (8), 257 (56) and 149 (100).

Methyl 2,4a,5,6,7,8-hexahydro-1-(4-nitrophenyl)isoquinoline-3-carboxylate **18** and *methyl 5,6,7,8-tetrahydro-1-(4-nitrophenyl)isoquinoline-3-carboxylate* **19a.** Methyl 2-(4-nitrophenyl)thiazolidine-4-carboxylate **2c** gave, by the general procedure using *N*-cyclohexen-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether-ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)] the following compounds in order of elution: (i) *methyl 2,4a,5,6,7,8-hexahydro-1-(4-nitrophenyl)isoquinoline-3-carboxylate* **18** (53%), m.p. 98–100 °C (from ethyl acetate–petroleum ether) (Found: C, 64.8; H, 5.8; N, 8.9. $C_{17}H_{18}N_2O_4$ requires C, 65.0; H, 5.7; N, 8.9%); δ 1.25–1.80 (6 H, m), 1.83–1.88 (1 H, m), 2.20–2.32 (1 H, m), 3.30–3.45 (1 H, m, 4a-H), 3.78 (3 H), 5.18 (1 H, NH), 5.45 (1 H, d, *J* 3.6, 4-H), 7.49 (2 H, d, *J* 8.8, Ar-H) and 8.23 (2 H, d, *J* 8.8, Ar-H); *m/z* 314 (M^+, 48%), 285 (95), 225 (88), 192 (100) and 179 (48); (ii) *methyl 5,6,7,8-tetrahydro-1-(4-nitrophenyl)isoquinoline-3-carboxylate* **19a** (20%), m.p. 161–162 °C (from ethyl acetate–petroleum ether) (Found: C, 65.3; H, 5.2; N, 8.9. $C_{17}H_{16}N_2O_4$ requires C, 65.4; H, 5.1; N, 9.0%); δ 1.70–2.00 (4 H, m), 2.67 (2 H, t, *J* 6.0), 2.94 (2 H, t, *J* 6.0), 3.98 (3 H), 7.68 (2 H, d, *J* 8.8, Ar-H), 7.93 (1 H, 4-H) and 8.31 (2 H, d, *J* 8.8, Ar-H); *m/z* 312 (M^+, 4%), 254 (100), 206 (43) and 59 (11).

Methyl 6,7-dihydro-1-(4-nitrophenyl)-5H-cyclopenta[c]pyridine-3-carboxylate **20a.** Methyl 2-(4-nitrophenyl)thiazolidine-4-carboxylate **2c** gave, by the general procedure using *N*-cyclopenten-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate], the *pyridine* **20a** (53%), m.p. 138–140 °C (from ethyl acetate–petroleum ether) (Found: C, 64.3; H, 4.7; N, 9.4. $C_{16}H_{14}N_2O_4$ requires C, 64.4; H, 4.7; N, 9.4%); δ 2.19 (2 H, quintet, *J* 3.8), 3.08 (2 H, t, *J* 3.8), 3.15 (2 H, t, *J*, 3.8), 4.01 (3 H), 7.98 (2 H, d, *J* 8.8, Ar-H), 8.06 (1 H, 4-H) and 8.32 (2 H, d, *J* 8.8, Ar-H); *m/z* 298 (M^+, 9%), 268 (5), 240 (100), 192 (16) and 165 (10).

Methyl 5,6,7,8-tetrahydro-1-(4-pyridyl)isoquinoline-3-carboxylate **19b.** Methyl 2-(4-pyridyyl)thiazolidine-4-carboxylate **2d** gave, by the general procedure using *N*-cyclohexen-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether-ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)] *methyl 5,6,7,8-tetrahydro-1-(4-pyridyl)isoquinoline-3-carboxylate* **19b** (54%), m.p. 151–152 °C (from ethyl acetate–petroleum ether) (Found: C, 71.8 H, 6.0; N, 10.4. $C_{16}H_{16}N_3O_2$ requires C, 71.6; H, 6.0; N, 10.4%); δ (300 MHz) 1.74–1.88 (4 H, m), 2.68 (2 H, t, *J* 6.3), 2.92 (2 H, t, *J* 6.3), 3.97 (3 H), 7.41 (2 H, d, *J* 6.0, Ar-H), 7.91 (1 H, 4-H) and 8.69 (2 H, d, *J* 6.0, Ar-H); $\upsilon_{max.}$ (KBr) 1716 cm^{-1}; *m/z* 268 (M^+, 25%), 236 (24), 210 (100) and 182 (20).

Methyl 1-benzoyl-1,2,5,6,7,8-hexahydroisoquinoline-3-carboxylate **21a** and *methyl 1-benzoyl-5,6,7,8-tetrahydroisoquinoline-3-carboxylate* **19c.** Methyl 2-benzoylthiazolidine-4-carboxylate **2e** gave, by the general procedure using *N*-cyclohexen-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)] the following compounds in order of elution: (i) *methyl 1-benzoyl-1,2,5,6,7,8-hexahydroisoquinoline-3-carboxylate* **21a** (35%), m.p. 152–154 °C (from ether–petroleum ether) (Found: C, 72.8; H, 6.5; N, 4.6. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%) ; δ (400 MHz) 1.73–1.77 (2 H, m), 1.82–1.84 (2 H, m), 2.42 (2 H, t, *J* 6.0), 2.54 (2 H, t, *J* 6.0), 3.69 (3 H), 5.70 (2 H), 6.83 (1 H), 7.50 (2 H, approx. t, *J* 8.4, Ar-H), 7.61 (1 H, approx. t, *J* 8.4, Ar-H) and 8.02 (2 H, approx. d, *J* 8.4, Ar-H); *m/z* 297 (M^+, 25%), 238 (48), 192 (52). 178 (94), 132 (52), 105 (98) and 77 (100); (ii) *methyl 1-benzoyl-5,6,7,8-tetrahydroisoquinoline-3-carboxylate* **19c** (14%), m.p. 137–138 °C (from ether–petroleum ether) (Found: C, 73.2; H, 5.9; N, 4.7. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%); δ 1.59 (2 H, m), 1.82 (2 H, m), 2.75 (2 H, m), 2.91 (2 H, m), 3.95 (3 H), 7.41–7.49 (2 H, m, Ar-H), 7.55–7.59 (1 H, m, Ar-H) 7.83–7.88 (2 H, m, Ar-H) and 7.96 (1 H); *m/z* 295 (M^+, 17%), 266 (18), 234 (32). 206 (22), 105 (42) and 77 (100).

Methyl 1-benzoyl-6,7-dihydro-5H-cyclopenta[c]pyridine-3-carboxylate **20b**. Methyl 2-benzoylthiazolidine-4-carboxylate **2e** gave, by the general procedure using *N*-cyclopenten-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether–ethyl acetate (4:1) then petroleum ether–ethyl acetate (3–1)], the *pyridine* **20b** (27%), m.p. 83–84 °C (from ether–petroleum ether) (Found: C, 72.4; H, 5.3; N, 5.0. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.3; N, 5.0%) ; δ 2.17 (2 H, quintet, *J* 7.7), 3.05 (2 H, t, *J* 7.7), 3.21 (2 H, t, *J* 7.7), 3.98 (3 H), 7.42–7.62 (3 H, m, Ar-H), and 8.06–8.15 (2 H, m, Ar-H); *m/z* 281 (M^+, 36%), 221 (33), 192 (35), 105 (62) and 77 (100).

Ethyl (1) methyl (3) 1,2,5,6,7,8-hexahydrosoquinoline-1,3-dicarboxylate **21b** and *ethyl (1) methyl (3) \5,6,7,8-tetrahydrosoquinoline-1,3-dicarboxylate* **19d**. Ethyl (2) methyl (4) thiazolidine-2,4-dicarboxylate **2f** gave, by the general procedure using *N*-cyclohexen-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether–ethyl acetate (3:1) then petroleum ether–ethyl acetate (1:1)] the following compounds in order of elution: (i) *ethyl (1) methyl (3) 1,2,5,6,7,8-hexahydrosoquinoline-1,3-dicarboxylate* **21b** (26%), m.p. 40–42 °C (from petroleum ether) (Found: C, 63.4; H, 7.3; N, 5.1. $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2; N, 5.3%); δ 1.28 (3 H, t, *J* 7.1), 1.73–1.85 (4 H, m), 2.44–2.52 (4 H, m), 3.75 (3 H), 4.22 (2 H, q, *J* 7.1), 4.96 (2 H) and 6.77 (1 H); δ (^{13}C) 14.17, 21.88, 22.72, 23.23, 46.20, 50.89, 61.37, 116.77, 118.71, 120.35, 136.47, 161.92 and 169.06; *m/z* 265 (M^+, 33%), 233 (19), 206 (100). 176 (36), 148 (29), 132 (33), 77 (20) and 45 (21); (ii) *ethyl (1) methyl (3) 5,6,7,8-tetrahydrosoquinoline-1,3-dicarboxylate* **19d** (26%), m.p. 62–63 °C (from ether–petroleum ether) (Found: C, 63.9; H, 6.6; N, 5.2. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%) ; δ 1.42 (3 H, *J* 7.1), 1.84 (4 H, quintet, *J* 3.5), 2.88 (2 H, t, *J* 3.5), 2.98 (2 H, t, *J* 3.5), 3.98 (3 H). 4.44 (2 H, q, *J* 7.1) and 7.95 (1 H); *m/z* 263 (M^+, 54%), 203 (52), 191 (68), 159 (100), 131 (57), 103 (29) and 77 (22).

Ethyl (1) methyl (3) 6,7-dihydro-5H-cyclopenta[c]pyridine-1,3-dicarboxylate **20c**. Ethyl (2) methyl (4) thiazolidine-2,4-dicarboxylate **2f** gave, by the general procedure using *N*-cyclopenten-1-ylpyrrolidine (2 mmol) as the dienophile, followed by flash chromatography [petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate], the *pyridine* **20c** (51%), m.p. 122–123 °C (from ether–petroleum ether) (Found: C, 62.6; H, 6.1; N, 5.5. $C_{13}H_{15}NO_4$ requires C, 62.7; H, 6.0; N, 5.6%) ; δ 1.46 (3 H, t, *J* 7.1), 2.19 (2 H, quintet, *J* 7.6), 3.04 (2 H, t, *J* 7.6), 3.37 (2 H, t, *J* 7.6), 4.0 (3 H), 4.46 (2 H, q, *J* 7.1) and 8.15 (1 H); *m/z* 249 (M^+, 14%), 191 (46), 177 (93), 145 (100) 117 (31) and 59 (17).

Diels-Alder reactions of N-benzylidenedehydroalanine methyl ester derived from the Schiff base of serine methyl ester

Methyl 5-acetyl-1,2,3,4-tetrahydro-6-phenyl-pyridine-2-carboxylate **5a**. *N*-Benzylidene-L-serine methyl ester[4b] (10 mmol) and an equimolar amount of *N,N'*-carbonyldiimidazole were dissolved in dry THF (50 ml). But-3-en-2-one (10 ml) and triethylamine (5 ml) were added in excess. The mixture was stirred overnight at room temperature. The solvent was evaporated off. Workup by flash chromatography [petroleum ether, petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate] gave compound **5a** (0.47 g, 17%) which was identified by comparison with the specimen isolated earlier.

Methyl (5S,6R)-5-acetyl-1,4,5,6-tetrahydro-6-phenylpyridine-2-carboxylate **3a** and *methyl (5R,6S)-5-acetyl-1,4,5,6-tetrahydro-6-phenylpyridine-2-carboxylate* **4**. . *N*-Benzylidene-L-serine methyl ester[4b] (10 mmol) and an equimolar amount of *N,N'*-carbonyldiimidazole were dissolved in dry THF (50 ml) and the solution cooled at –70 °C. Triethylamine (0.7 ml) was added. The solution was transferred at –70 °C dropwise to a solution of but-3-en-2-one (10 ml) and dichloromethane (50 ml) heated at reflux. After the addition the solution was heated under reflux for 1 h. Water was added and the solution was extracted with dichloromethane. The organic layer was washed with water and the organic solvent was evaporated off. Flash

chromatography [petroleum ether, petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate] gave the tetrahydropyridine **4** (0.47 g, 17%) and the tetrahydropyridine **3a** (0.47 g, 17%) as solids which were identified by comparison with specimens isolated earlier.

Methyl 4-acetyl-2-hydroxymethyl-5-phenylpyrrolidine-2-carboxylate **8**. *N*-Benzylidene-L-serine methyl ester (0.54 g, 2.6 mmol) was dissolved in dry THF (15 ml) and the solution cooled in an ice bath. But-3-en-2-one (2.5 ml) and *N,N'*-carbonyldiimidazole (0.42 g, 2.6 mmol) were added. A solution of triethylamine (1.3 ml) in THF (10 ml) was added dropwise with a syringe pump (4 h). The mixture was stirred overnight at room temperature. The solution was diluted with dichloromethane and washed with water and the solvent was evaporated off. Flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate] gave the *pyrrolidine* **8** (0.2 g, 28%), m.p. 190-192 °C (from ether–petroleum ether) (Found: C, 64.4; H, 6.8; N, 4.7. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.8; N, 5.0%); $\upsilon_{max.}$ (KBr) 3490, 1739 and 1705 cm^{-1}; δ 1.50 (3 H), 1.93 (1 H, dd, *J* 7.15 and 13.75), 2.55 (1 H, dd, *J* 3.3 and 13.75), 3.43 (1 H, dt, *J* 3.3 and 7.15), 3.74 (1 H, d, *J* 10.45), 3.50 (1 H, d, *J* 10.45), 3.88 (3 H), 4.56 (1 H, d, *J* 7.15) and 7.26–7.36 (5H, m, Ar-H); *m/z* 278 (M^++ H, 1%), 277 (M^+, 1%), 246 (100), 218 (36), 174 (36), 144 (70), 106 (85) and 43 (75).

Dimerisation of the azadiene derived from methyl 2-phenylthiazolidine-4-carboxylate. Dimethyl (5S,6R)-5-benzylideneamino-1,4,5,6-tetrahydro-6-phenyl-2,5-pyridinedicarboxylate **13** and *dimethyl (1S,4R,5S,7R)-4,7-diphenyl-3,6-diazabicyclo[3.2.1]oct-2-ene-2,5-dicarboxylate* **14a**. Methyl 2-phenylthiazolidine-4-carboxylate **2a** (3.0 g, 13.45 mmol) was dissolved in dry acetonitrile (60 ml) and the solution was cooled at –20 °C. Silver carbonate (3.78 g, 13.70 mmol) was added, followed by a solution of DBU (0.36 g). After the solution had been stirred for 2 h at 0 °C and overnight at room temperature ethyl ether was added, the reaction mixture was filtered and the solvent was evaporated off from the filtrate. The products were isolated by flash chromatography [petroleum ether–ethyl acetate (4:1), petroleum ether–ethyl acetate (3:1), petroleum ether–ethyl acetate (1:1) then ethyl acetate] giving the following compounds in order of elution: (i) dimethyl (5S,6R)-5-benzylideneamino-1,4,5,6-tetrahydro-6-phenyl-2,5-pyridinedicarboxylate **13** (8%), m.p. 135–136 °C (from petroleum ether–ether) (lit.,[5] m.p. 135–136 °C) δ 2.50 (1 H, dd, J 4.3 and 18.4), 3.03 (1H, ddd, J 2.0, 4.7 and 18.4), 3.68 (3 H), 3.79 (3 H), 4.64 (1 H, NH), 4.93 (1 H), 5.78 (1 H, approx. t, *J* 4.1), 7.27–7.92 (10 H, m, Ar-H) and 8.11 (1 H); m/z 378 (M^+, 1%), 358 (5), 194 (83), 105 (91) and 77 (100); (ii) dimethyl (1*S*,4*R*,5*S*,7*R*)-4,7-diphenyl-3,6-diazabicyclo[3.2.1]oct-2-ene-2,5-dicarboxylate **14a** (13%), m.p. 127–128 °C (from petroleum ether–ether) (lit.,[5] m.p. 137 °C) (Found: C, 69.8; H, 5.9; N, 7.3. Calc. for $C_{22}H_{22}N_2O_4$: C, 69.8; H, 5.8; N, 7.4%); $\upsilon_{max.}$ (KBr) 1747 and 1719 cm^{-1}; δ 2.18 (2 H, d, *J* 2.2), 3.45 (3 H), 3.48 (3 H), 3.94 (1 H, approx. quintet), 4.77 (1 H, d, *J* 4.2), 5.35 (1 H), 7.0–7.05 (2 H, m, Ar-H) and 7.25-7.4 (8 H, m, Ar-H); δ (C_6D_6) 1.78 (1H, dd; *J* 11.8), 2.01 (1H, d, *J* 11.8), 3.08 (3 H), 3.12 (3 H), 3.78 (1 H, approx. t, *J* 3.3 and 4.2), 4.22 (1 H, d, *J* 4.2), 5.44 (1 H), 6.97–7.22 (2 H, m, Ar-H) and 7.33-7.37 (8 H, m, Ar-H); δ (^{13}C) 30.33, 44.86, 52.61, 53.38, 68.57, 69.44, 127.30, 128.49, 128.66, 128.73, 129.05, 137.95, 139.60, 164.42, 165.25 and 173.38; m/z 378 (M^+, 3%), 319 (15), 273 (54), 196 (100), 121 (32), 69 (25) and 57 (24).

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REFERENCES

1 Boger, D. L.; Weinreb, S. N. "Hetero Diels-Alder Methodology in Organic Synthesis", Academic Press, San Diego, 1987.

2 Boger, D. L. in "Comprehensive Organic Synthesis" (B. M. Trost and I. Fleming, eds.), Vol. 5, Chapter 4.3, Pergamon Press, Oxford, 1991.

3 Barluenga, J.; Tomas, M. *Adv. Heterocycl. Chem.*, **1993**, *57*, 1–80.

4 (a) Wulff, G.; Böhnke, H. *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 380–381; (b) Wulff, G.; Böhnke, H.; Klinken, H. T. *Liebigs Ann. Chem.*, **1988**, 501–505.

5 (a) Wulff, G.; Böhnke, H.; *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 90–92; (b) Wulff, G.; Lindner, H. G.; Böhnke, H.; Steigel, A.; Klinken, H. T. *Liebigs Ann. Chem.*, **1989**, 527–531; (c) Wulff, G.; Klinken, H. T. *Tetrahedron*, **1992**, *48*, 5985–5990.

6 Öhler, E.; Schmidt, U. *Chem. Ber.*, **1979**, *112*, 107–115.

7 Gilchrist, T. L.; Gonsalves, A. M. d'A. R.; Pinho e Melo, T. M. V. D. *Tetrahedron Lett.*, **1993**, *34*, 4097–4100.

8 (a) Grigg, R. *Chem. Soc. Rev.*, **1987**, *16*, 89–121; (b) Grigg, R.; Gunaratne, H. Q. N. *Tetrahedron Lett.*, **1983**, *24*, 4457–4460.

9 Büchi, G.; Wüest, H. *J. Org. Chem.*, **1971**, *36*, 609–610.

10 Szilágyi, L.; Györgydeák, Z. *J. Am. Chem. Soc.*, **1979**, *101*, 427–432.

11 González, J.; Houk, K. N. *J. Org. Chem.*, **1992**, *57*, 3031–3037.

12 Ratner, S.; Clarke, H. T. *J. Am. Chem. Soc.*, **1937**, *59*, 200–206.

13 Vargha, L.; Reményi, M. *J. Chem. Soc.*, **1951**, 1068–1069.

14 Seebach, D.; Jeanguenat, A.; Schmidt, J.; Maetzke, T. *Chimia*, **1989**, *43*, 314–317.

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