Tetrahedron Vol 47, No 35, pp 7271-7278, 1991
Printed in Great Britain

0040-4020/91 $3 00+00

Chiral Spirocyclic (Z)-5-Arylmethylene-1,3-oxazine-4,6-diones, New Chiral Heterodienes[1,2]

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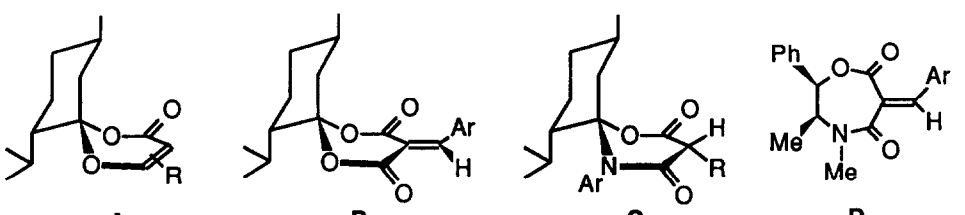
(*Received in Japan* 24 *June* 1991)

Summary A series of (Z)-5-arylmethylene-1,3-oxazine-4,6-diones was synthesized in enantiomerically pure form and found to serve as the attractive alternatives of 6-arylmethylene-1,4-oxazepane-5,7-diones

Previously, we examined the reactions of chiral spirocyclic dioxinones (e g **A** R as an electron-withdrawing group)[3] and cyclopentadiene and found a remarkable diastereofacial selectivity (isopropyl side preference) and thus, have offered a new methodology for asymmetric Diels-Alder reactions[4] The same isopropyl side preference to the C-C double bond has also been observed when these dioxinones are used as the enone components in the 2+2 photocycloadditions[5-8] We reasoned that the selectivity of **A** was due to a sofa conformation of the dioxinone ring with five of the six atoms approximately in a plane and the acetal carbon out of the plane Quite recently, two important developments on the use of spirocyclic compounds in asymmetric synthesis have been made 1) the same diastereofacial selectivity still holds for the corresponding 5-arylmethylenedioxanediones (**B**)[9] in which the prochiral center is extended out of the dioxane ring, and 2) base-catalyzed alkylation of the 5-mono-substituted derivatives of spirocyclic 1,3-oxazine-4,6-diones (**C**) also proceeds by the same diastereofacial selectivity[10]

In this line of works, we have been interested in synthesizing the title compounds (**1**), which would serve as the attractive alternatives of 6-arylmethylene-1,4-oxaze-

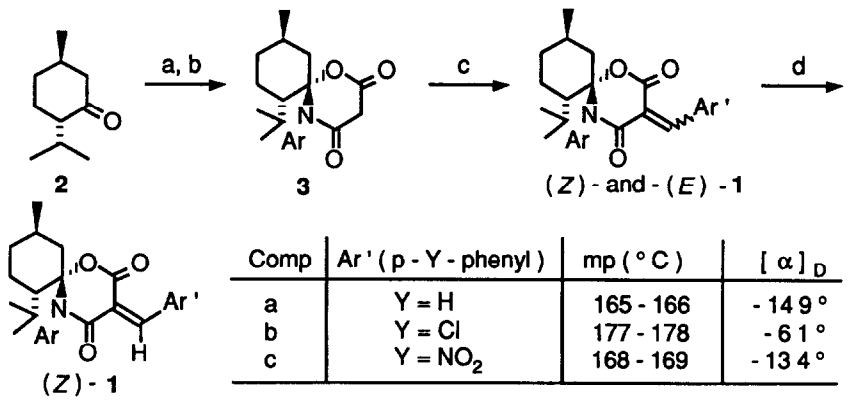


Scheme 1

pane-5,7-diones (**D**) The latter compounds have originally been synthesized by Mukaiyama[11] and used successfully in a variety of asymmetric reactions (as chiral Michael acceptors,[11-13] heterodienes,[13-15] and dipolarophiles[16]).

When chiral oxazinedione (*S*)-**3** previously synthesized from *l*-menthone[10] was subjected to the reaction with benzaldehyde and its para-substituted derivatives, the corresponding arylmethylene derivatives (**1a-c**) were obtained all in satisfactory yields. Though mixtures of (*E*)- and (*Z*)-isomers were formed in the reactions, their recrystallization from ethyl acetate was accompanied by *E*/*Z*-isomerization and afforded a single stereoisomer in each case. This kind of recrystallization-induced isomerizartion has previously been observed in the 5-arylmethylenedioxanedione series (**B**) and the induction occurs to give either (*E*)- or (*Z*)-isomers depending upon the kind of the aryl groups.[9] It should be noted in the present case, however, that only (*Z*)-isomers were crystallized preferentially irrespective of the kind of the aryl groups. The structure of (*Z*)-**1a** was determined by X-ray crystallographic analysis (*vide infra*). The assignment of (*Z*)-**1b** and **1c** was made by comparison of the chemical shift of the vinyl protons with those of (*Z*)- and (*E*)-**1a** (see experimental section).

Scheme 2[a,b]



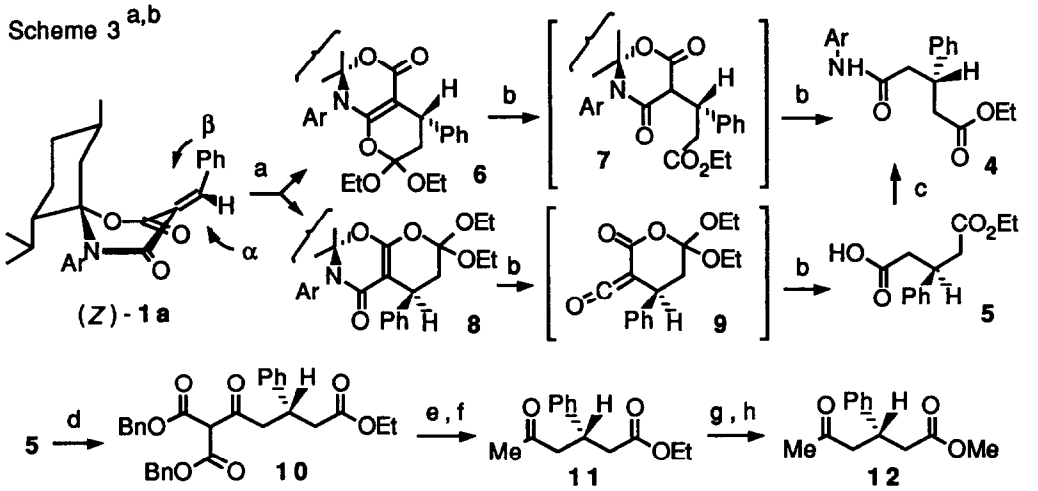
Comp	Ar' (p - Y - phenyl)	mp (°C)	$[\alpha]_D$
a	Y = H	165 - 166	- 149°
b	Y = Cl	177 - 178	- 61°
c	Y = NO_2	168 - 169	- 134°

a (a) p - anisidine, p - TsOH, benzene, reflux, (b) $CH_2(CO_2H)_2$, Ac_2O (26%, two steps), (c) Ar'CHO, piperidine, AcOH, (d) recrystallization from AcOEt
b Ar = p - methoxyphenyl

In order to see whether or not oxazinediones **1** could serve as heterodienes, Diels-Alder reactions with ketene diethylacetal were carried out Taking (*Z*)-**1a** as the typical example, the following successful result was obtained When (*Z*)-**1a** was allowed to react with the acetal and the adducts thus formed were refluxed in aq dioxane, two products (**4** and **5**) were obtained in 24% (84% ee) and 70% (77% ee)

yields, respectively. E.e of each products was determined by high-pressure liquid chromatomatography (hplc) over Chiralcel OJ. The absolute structure of each product was identical as determined by transformation of the acid (**5**) to the amide (**4**) and finally determined as (2*S*)-structure by the conversion of **5** to the known

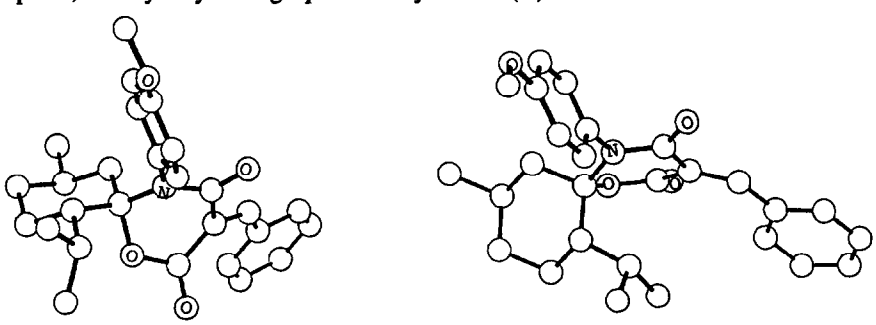
Scheme 3 [a,b]



[a] (a) $CH_2C(OEt)_2$, AcOEt, -15 °C, (b) H_2O-dioxane(1.5), reflux(4 24%, 5 70%), (c) p-anisidine, DCC, CH_2Cl_2, 0 °C(67%), (d) $NaCH(CO_2Bn)_2$, 1,1'-carbonyldiimidazole, THF, (e) H_2, 10% Pd-C, AcOEt, (f) bezene, reflux, (g) KOH, H_2O, (h) CH_2N_2, ether
[b] Ar = p-methoxyphenyl

methyl (*S*)-3-phenyl-5-oxohexanoate (**12**) [17] The overall yield of **12** from **5** was 43% Though exact mechanism for the formation of **4** and **5** is uncertain as yet, we assume that, while **6** gives **4** via the normal acetal hydrolyzed product (**7**), **5** is formed from the ketene (**9**) formed by six-electron electrocyclic ring opening of **8**.[18]

To our surprise, X-ray crystallographic analysis of (Z)-**1a** has revealed that two



(Z)-**1a**-E (Z)-**1a**-F

Figure 1. Molecular structures of (Z)-**1a**

conformations (**E** and **F**) exist in 1 1 ratio (Fig. 1), in which both oxazinedione rings take a boat-conformation.

Since both products (**4** and **5**) have (*S*)-structure, it is reasonable to assume that (*Z*)-**1a** exists as **E** conformation in solution phase whose α-side (isopropyl side) is more exposed than β-side (see, schematic conformational structure of (*Z*)-**1a**-**E** in Scheme 3) and not as (*Z*)-**1a**-**F** conformation whose β-side is more exposed.

In summary, the following could be said: 1) The chiral spirocyclic oxazinediones could serve as new alternatives for **D**[19] and 2) the prediction of diastereofacial selectivity based on X-ray crystallographic analysis, which is currently employed for determining the conformation of the reacting molecules, is not applicable to the present case due to coexistence of two conformations (**E** and **F**) whose more exposed faces are reversed each other. This fact indicates that one should aware the possible differences between conformations in crystalline and solution phase and it is essential to know the conformation of the reacting molecules in solution by other means

Experimental Section

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected Optical rotations were measured on a JASCO DIP-340 polarimeter Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer ^{1}H-NMR spectra were recorded with a JEOL JNM PMX 60SI or a JEOL JNM-GX 500 spectrometer, with tetramethylsilane as an internal standard Mass spectra (MS) were taken with a JEOL-JMS-01SG-2 spectrometer Silica gel used for column chromatography was Wakogel C-200 and the ratio of solvent mixtures is shown as volume/volume.

(6*S*,7*S*,10*R*)-7-Isopropyl-5-(4-methoxyphenyl)-10-methyl-2,4-dioxo-5-aza-1-oxaspiro[5.5]undecane (3)

The synthesis of compound **3** was carried out through two steps (1· the imine formation from *l*-(-)-menthone and *p*-anisidine and 2 the condensation of the imine with malonic acid)

Step 1. A solution of *l*-(-)-menthone (50.8 g, 0 33 mol), *p*-anisidine (36 9 g, 0 3 mol) and *p*-toluenesulfonic acid (0.5 g) in benzene (300 ml) was refluxed for 2 days with azeotropic removal of water The solvent was evaporated off *in vacuo* The residue was heated at 100 °C under 0.1 mmHg to remove excess *l*-menthone to give the oily imine in a quantitative yield This oil was crystallized in a refrigerator and used directly for the next reaction.

Step 2. A mixture of malonic acid (3.06 g, 30 mmol), imine (7.77 g, 30 mmol) and acetic anhydride (21 4 g, 0 21 mol) was stirred under ice-cooling for 30 min The clear solution was kept standing at room temperature for 1 day Most of acetic anhydride was evaporated off at below 30 °C. The residue was chromatographed

over silica gel (300 g) using hexane-ethyl acetate (3:1) to give pale yellow solid which was recrystallized from a mixture of hexane and dichloromethane to give **3** (3.60 g, 35%).

3. colorless needles, mp 153-155 °C. $[\alpha]_D^{25}$ -1.24° (*c* 1.5, $CHCl_3$). Anal Calcd for $C_{20}H_{27}NO_4$· C, 69.54; H, 7 88; N, 4.06 Found· C, 69.69; H, 8 00; N, 4.04. IR ($CHCl_3$) 1760, 1670 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.65 (3H, d, *J*=6 Hz, $CH(C\underline{H}_3)_2$), 0 80 (1H, dq, *J*=12, 4 Hz, 9-H(axial)), 0.92 (3H, d, *J*=6 Hz, 10-CH_3), 0 93 (3H, d, *J*=6 Hz, $CH(C\underline{H}_3)_2$), 1 57 (1H, m, 8-H(equatorial)), 1.64 (1H, t, *J*=14 Hz, 11-H(axial)), 1 68 (1H, m, 8-H(axial)), 1 78 (1H, m, 9-H(equatorial)), 1.89 (1H, m, 10-H(axial)), 2.11 (1H, ddd, *J*=14, 4, 2 Hz, 11-H(equatorial)), 2 19 (1H, m, $C\underline{H}(CH_3)_2$), 3.60 and 3.66 (each 1H, d, *J*=21 Hz, 3-H_2), 3 83 (3H, s, $OC\underline{H}_3$), 6.90-7 25 (4H, m, ArH)

Synthesis of (*Z*)-(6*S*,7*S*,10*R*)-3-Arylmethylene-7-isopropyl-5-(4-methoxyphenyl)-10-methyl-2,4-dioxo-5-aza-1-oxaspiro[5.5]undecanes [(*Z*)-1a-1c]: General Procedure is Described Taking the Benzylidene Derivative (1a) as an Example

A mixture of **3** (1 380 g, 4 mmol), benzaldehyde (0 508 g, 4 8 mmol), piperidine (15 drops), acetic acid (15 drops) and Molecular Sieve 4A (2 0 g) in benzene (40 ml) was stirred at room temperature for 6 h The mixture was filtered and the filtrate was evaporated *in vacuo* Purification of the residue by silica gel column chromatography using a mixture of hexane-ethyl acetate (3·1) afforded a mixture of (*E*)- and (*Z*)-**1a** (*ca* 1 1) (1 492 g, 86%) as a solid Slow recrystallization of the mixture from ethyl acetate gave (*Z*)-**1a** (1 260 g, 73%).

(*Z*)-**1a** colorless prisms, mp 165-166 °C Anal Calcd for $C_{27}H_{31}NO_4$· C, 74 80, H, 7 21, N, 3 23 Found C, 74.94, H, 7 37; N, 3 21. IR ($CHCl_3$) 1730, 1660, 1610 cm^{-1} ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (*inter alia*) 0 59 (3H, d, *J*=7 Hz, $CH(C\underline{H}_3)_2$), 0.89 (3H, d, *J*=6 Hz, 10-$C\underline{H}_3$), 0 93 (3H, d, *J*=7 Hz, $CH(C\underline{H}_3)_2$), 1.63 (1H, dd, *J*=13, 12 Hz, 11-H(axial)), 2.25 (1H, m, $C\underline{H}(CH_3)_2$), 3 85 (3H, s, $OC\underline{H}_3$), 6 95-7.97 (9H, m, ArH), 8 33 (1H, s, PhC<u>H</u>=). δ of the same signal of (*E*)-**1a**: 8.26 $[\alpha]_D^{24}$ -14.88° (*c* 1.29, $CHCl_3$). Using corresponding aldehydes, the following compounds were prepared.

(*Z*)-**1b** pale yellow needles (CH_2Cl_2-hexane), mp 177-178 °C $[\alpha]_D^{20}$ -6 13° (*c* 1.0, $CHCl_3$) Anal Calcd for $C_{27}H_{30}ClNO_4$ C, 69.29; H, 6.46, N, 2.99, Cl, 7 58 Found C, 69 28, H, 6 48, N, 2 99, Cl, 7 73 IR ($CHCl_3$) 1740, 1660, 1610, 1590 cm^{-1} ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 8.27 (8 23 for (*E*)-**1b**)

(*Z*)-**1c** pale yellow frakes (CH_2Cl_2-hexane), mp 168-169 °C $[\alpha]_D^{24}$ -13 44° (*c* 1 2, $CHCl_3$) Anal Calcd for $C_{27}H_{30}N_2O_6$. C, 67.76, H, 6 32, N, 5 85 Found C, 68.04, H, 6 28, N, 5 58 IR ($CHCl_3$) 1740, 1670, 1600 cm^{-1} ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 8 37 (8 27 for (*E*)-**1c**)

Diels-Alder Reaction of (*Z*)-1a with Ketene Diethylacetal followed by Hydrolysis Giving 4 and 5

Ketene diethylacetal (290 mg, 0 5 mmol) was added to a solution of (**Z**)-**1a** in dry ethyl acetate (6 ml) and the solution was stirred for 1 h at *ca* -15 °C. The solvent was evaporated off *in vacuo*, and the residue was heated under reflux in a mixture of water (1 ml) and dioxane (5 ml) for 8 h The mixture was evaporated, dissolved in ether and washed with 1% hydrochloric acid and then with brine. The organic layer was dried over magnesium sulfate, evaporated, and purified by silica gel column chromatography using hexane-ethyl acetate (3 1) to give **4** (41 mg, 24%). Further elution with the same solvent gave **5** (82 mg, 70%,). The ee of **4** was 84% on hplc analysis with Chiralcel OJ column (Daicel Chemical Industries, Ltd)

4: colorless needles (ether-CH_2Cl_2), mp 108-110 °C. $[\alpha]_D^{23}$ -20 73° (*c* 1.1, $CHCl_3$) Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4 10 Found: C, 70.44; H, 6.89, N, 4.43. IR ($CHCl_3$) 3450, 3350, 1720, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 1.1 (3H, t, *J*=7 Hz, CH_3), 2.5-2.9 (4H, m, $COCH_2$ x 2), 3.4-3 8 (1H, m, CHPh), 3.9 (3H, s, OCH_3), 4.3 (2H, q, *J*=7 Hz, OCH_2), 6.7-7.4 (10H, m, ArH).

5 colorless oil. $[\alpha]_D^{24}$ -6.19° (*c* 1.55, benzene). High-resolution MS *m/z* Calcd for $C_{13}H_{16}O_4$ (M^+) 236 1048. Found. 236 1055. IR ($CHCl_3$) 3350-2500, 1720 (br) cm^{-1} ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 1.1 (3H, t, *J*=7 Hz, CH_3), 2 6-2.9 (4H, m, $COCH_2$ x 2), 3 4-3.9 (1H, m, CHPh), 4 0 (2H, q, *J*=7 Hz, OCH_2), 7.2 (5H, br s, Ph), 9.7 (1H, br s, OH)

Conversion of 5 to 4

1,3-Dicyclohexylcarbodiimide (80 mg, 0.39 mmol) and *p*-anisidine (48 mg, 0 39 mmol) were added to a solution of **5** (82 mg, 0.35 mmol) in dichloromethane (4 ml) and the mixture was stirred under ice-cooling for 1 h The mixture was filtered and the filtrate was washed with 1% hydrochloric acid and then with brine The organic layer was dried over magnesium sulfate and evaporated. Purification of the residue by silica gel column chromatography using hexane-ethyl acetate (2 1) gave colorless oil **4** (80 mg, 67%). $[\alpha]_D^{22}$ -19 94° (*c* 1 32, $CHCl_3$). The ee of **4** obtained was 77% based on hplc analysis with Chiralcel OJ column

Dibenzyl (*S*)-(4-Ethoxycarbonyl-1-oxo-3-phenylbutyl)malonate (10)

A solution of **5** (79 mg, 0 33 mmol) and 1,1'-carbonyldiimidazole (59 mg, 0 36 mmol) in dry tetrahydrofuran was stirred for 6 h at room temperature. This solution was added to an ice-cooled solution of metalated malonate prepared from sodium hydride (16 mg, 0.39 mmol) and dibenzyl malonate (102 mg, 0 36 mmol) in tetrahydrofuran (1 ml). The whole was stirred for 5 h at room temperature and diluted with ether. The mixture was washed with 5% hydrochloric acid and then with saturated sodium bicarbonate solution, and dried over magnesium sulfate The organic layer was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (5.1) to give **10** (151 mg, 91%)

10: colorless oil High-resolution MS *m/z* Calcd for $C_{30}H_{30}O_7$ (M^+) 502.1990 Found 502 2019 IR ($CHCl_3$) 1730 cm^{-1} ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 1 1 (3H, t, *J*=7 Hz, CH_3),

2.4-3.0 (4H, m, $COCH_2$ x 2), 3.4 (1H, s, COCH), 3.5-3.8 (1H, m, CHPh), 3.9 (2H, q, J=7 Hz, OCH_2), 5.1 (4H, s, CH_2Ph x 2), 7.0-7.4 (15H, m, ArH).

Ethyl (*S*)-3-Phenyl-5-oxohexanoate (11)

A mixture of compound **10** (151 mg, 0.30 mmol) and 10% Pd-C (40 mg) in MeOH (10 ml) was shaken in hydrogen under atmospheric pressure for 1 h at room temperature After filtration to remove the catalyst, the filtrate was concentrated. The residue was purified by silica gel column chromatography. The dicarboxylic acid thus obtained was heated in benzene (4 ml) under reflux for 8 h. After evaporation of the solvent, the residue was chromatographed on silica gel using hexane-ethyl acetate (5:1) to give **11** (37 mg, 48%)

11. colorless oil. High-resolution MS *m/z* Calcd for $C_{14}H_{18}O$ (M^+) 234.1256 Found 234 1262. IR ($CHCl_3$) 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 1.1 (3H, t, J=8 Hz, CH_3), 2.0 (3H, s, $COCH_3$), 2.7 (4H, dd, J=8, 12 Hz, CH_2 x 2), 3.7 (1H, quint, C_3-H), 4.0 (2H, q, J=8 Hz, CH_2CH_3), 7 2 (5H, br s, Ph)

Methyl (*S*)-3-Phenyl-5-oxohexanoate (12)

Compound **11** (37 mg, 0 16 mmol) was stirred with 10% potassium hydroxide solution for 4 h at room temperature After addition of conc HCl, the product was extracted with ether and the organic layer was washed with brine and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was dissolved in ether and methylated by the addition of an excess of diazomethane. Purification of the product by silica gel column chromatography gave colorless oil **12** (31 mg, 89%) $[\alpha]_D^{24}$ -15 67° (*c* 2.36, benzene) [lit.[17] $[\alpha]_D^{20}$ -22 35° (*c* 2.0, benzene)]. IR and ^{1}H-NMR spectra are identical with those of an authentic sample

Crystallographic Measurement

Crystal data for (**Z**)-**1a**, $C_{27}H_{31}NO_4$ monoclinic, $P2_1$, a=15 349(2) Å, b=10 8560(8) Å, c=14.60(1) Å, β=94.27(3)°, V=2426(2) $Å^3$, Z=4; Rigaku AFC-5R automated four-circle diffractometer, T=298K, Cu Kα radiation, data was collected to 2θ=120° There are two independent molecules in the asymmetric unit. The structure was solved by direct methods using SHELXS86, and successive analysis of difference maps with 2447 observed unique reflections ($|Fo| > 3\sigma|Fo|$) Anisotropic block-diagonal least-squares refinement of all non-hydrogen atoms gave R=0 046, R_w=0 045

Further details have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambrige CB2 1EW, UK.

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18 We have found that when 1,3-oxazine-4,6-diones are treated with diazomethane in ether, only 4-methoxy-1,3-oxazin-4-ones which are isoelectronic with **6**, are obtained as the sole isolable products in *ca* 45% yield The fact that none of the isomeric methylated oxazinones, which are isoelectronic with **8**, was isolated in the above reactions suggests strongly a facile six-electron ring opening of **8**.

19 One serious drawback of these oxazepanediones (**D**) is an inevitable use of ephedrine The latter is the direct synthetic precursor of methamphetamine (notorious for tolerance and physical dependence). Hence, its use is severely restricted in most countries