# Synthesis, Structure and Reactions of Chiral Oxazinones Derived from L-Ephedrine

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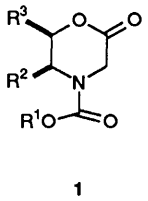
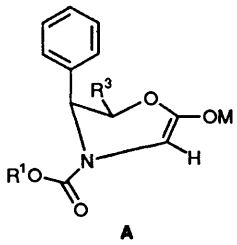
Optically pure 4,5-dimethyl-3,6-diphenylperhydro-1,4-oxazin-2-one **4** and 4,5-dimethyl-6-phenyl-3-(2-phenylvinyl)perhydro-1,4-oxazin-2-one **5** have been prepared by condensation of ephedrine, potassium cyanide and benzaldehyde or cinnamaldehyde. The lithium enolates of compounds **4** and **5** reacted with halogenoalkanes in a stereospecific manner (*si*-attack) to give the 3-substituted derivatives **10–15**. The structures of **10** and **12** were established by X-ray diffraction, while the stereochemistry of the other compounds was determined by correlation of their $^1$H NMR and CD spectra. The allylic enolate of **5** was selectively hydroxylated with oxygen or *m*-CPBA at the α-site to give **16**. Palladium-catalysed substitution of **16** acetate with malonate or phenoxide ions occurred also at the α-site. Acid-catalysed rearrangement of **16** in ethanol gave an 2-ethoxyperhydro-1,4-oxazin-3-one **20**, which reacted with trimethylsilyl cyanide to give a 2-cyano derivative **22**.

Asymmetric synthesis of enantiomerically pure α-amino acids [1] has been realized by the electrophilic substitution of chiral glycine enolate equivalents [2] or by nucleophilic alkylation of chiral glycine cation equivalents.[3] Optically active 1,4-oxazinones such as **1** have been prepared and used as the glycine templates for the synthesis of non-proteinogenic α-amino acids.[3] According to the studies of Williams,[2a,b] Dellaria [2c,d] and co-workers, the diastereofacial selectivity in alkylation of the enolate ion of **1** is the result of it adopting preferential conformation **A** in which the 5-phenyl group is in an axial



**1**

$R^1$ = Bu$^t$ or $PhCH_2$
$R^2$ = Ph or $PhCH_2$
$R^3$ = H or Ph



**A**

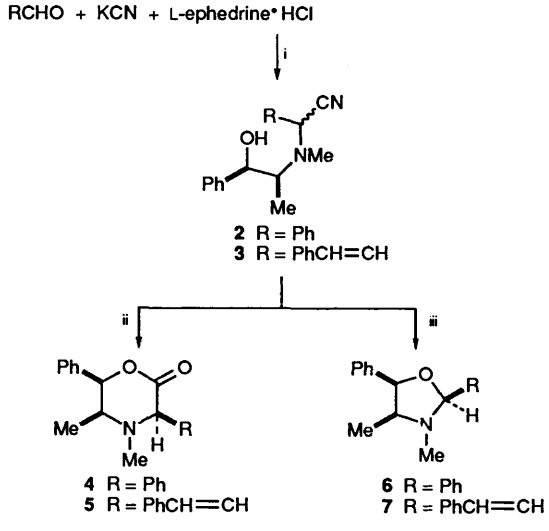
$R^1$ = Bu$^t$ or $PhCH_2$
$R^3$ = H or Ph
M = Na or K

orientation in order to avoid the $A^{1,3}$-strain exerted by the *N*-acyl group. The *N*-acyl group, generally in the form of carbamate, appears to be essential in directing the expected stereoselectivity at the C-3 position; with an *N*-benzyl group different selectivity may be shown.[2d]

Thus, Baker and his co-workers have reported that an oxazinone having a 5-benzyl group instead of a phenyl group also undergoes alkylation exclusively from the opposite face of the benzyl group.[2f] The stereoselectivity so induced decreases, however, when the oxazinone has an isopropyl group or other substituent. In these studies, deprotonation of the oxazinones is effected by using sodium (or potassium) hexamethyldisilazide, and the enolate ion formed in this way may result in mono- or di-alkylation. Baldwin has also demonstrated [2e] that the successful dialkylation is assisted by using 15-crown-5 as an additive. Other bases, such as lithium diisopropylamide (LDA), BuLi, Bu'Li or NaH, are less effective in the alkylations.[2b] The glycine template methods were, however, not used to introduce an alkenyl group at the C-3 by either electrophilic or nucleophilic alkylations. To circumvent this problem, we report herein an alternative method for the preparation of oxazinones **4** and **5** having a 3-phenyl or 3-phenylvinyl group, respectively, from the readily available auxiliary L-1-methylaminoethyl(phenyl)methanol [L-(−)-ephedrine]. The base LDA was used to generate the enolates, and their subsequent electrophilic reactions proved to be highly regio- and stereoselective to give varied 3,3-disubstituted oxazinones.

## Results and Discussion

According to Strecker's method, the α-aminoalkenenitrile **2** was obtained by condensation of benzaldehyde, KCN and the hydrochloric salt of L-ephedrine at room temperature (Scheme 1).[4] Treatment of **2** with concentrated HCl gave the chiral oxazinone **4** as a single isomer, the 3*R*-configuration of which was assigned by comparison of its optical rotation and $^1$H NMR data with literature results.[5] Condensation of cinnamaldehyde, KCN and L-ephedrine by a similar procedure afforded the amino nitrile **3**, which was subjected to acid-catalysed cyclization to give the 3*R*-oxazinone **5** in 88% yield. It was noted




**Scheme 1** *Reagents and conditions:* i, $Et_2O$, $H_2O$; ii, conc. HCl, PhH, room temp., 48 h; iii, 100 °C/5 mmHg

**Table 1** Alkylation of the lithium enolates of the oxazinones **4** and **5** (LDA, THF, HMPA, −78 °C)

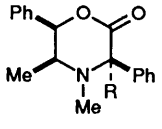
| Substrate | Electrophile | Product | Yield (%) | Chemical shifts (δ) 5-H | 6-H | Cotton effect |
|---|---|---|---|---|---|---|
| **4** | $CH_2$=$CHCH_2Br$ | **8** | 78 | 3.58 | 5.68 | + |
| **4** | MeI | **9** | 75 | 3.61 | 5.37 | + |
| **4** | $PhCH_2Br$ | **10** | 93 | 3.12 | 4.22 | + |
| **4** | *o*-$BrC_6H_4CH_2Br$ | **11** | 82 | 3.15 | 4.32 | + |
| **5** | $CH_2$=$CHCH_2Br$ | **12** | 68 | 3.33 | 5.68 | + |
| **5** | MeI | **13** | 86 | 3.40 | 5.45 | + |
| **5** | $PhCH_2Br$ | **14** | 84 | 3.09 | 4.48 | + |
| **5** | *o*-$BrC_6H_4CH_2Br$ | **15** | 65 | 3.11 | 4.59 | + |

**Table 2** Crystal data for (3*R*,5*S*,6*R*)-3-Benzyl-4,5-dimethyl-3,6-diphenylperhydro-1,4-oxazin-2-one **10**, (3*R*,5*S*,6*R*)-3-allyl-4,5-dimethyl-6-phenyl-3-(2-phenylvinyl)perhydro-1,4-oxazin-2-one **12** and (2*S*,5*S*,6*R*)-2-ethoxy-4,5-dimethyl-6-phenyl-2-(2-phenylvinyl)perhydro-1,4-oxazin-3-one **20***

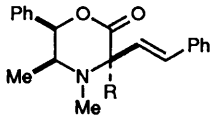
| | **10** | **12** | **20** |
|---|---|---|---|
| Formula | $C_{24}H_{25}NO_2$ | $C_{23}H_{25}NO_2$ | $C_{22}H_{25}NO_3$ |
| Space group | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ |
| *Z* | 4 | 4 | 4 |
| *a*/Å | 20.280 (2) | 9.772 (2) | 6.574 (1) |
| *b*/Å | 14.838 (1) | 10.337 (2) | 16.889 (3) |
| *c*/Å | 6.970 (1) | 19.364 (2) | 17.779 (2) |
| α/° | 90 | 90 | 90 |
| β/° | 90 | 90 | 90 |
| γ/° | 90 | 90 | 90 |
| Radiation | Mo-Kα (=0.7107 Å) | Mo-Kα (=0.7107 Å) | Mo-Kα (=0.7107 Å) |
| *T*/K | 298 | 298 | 298 |
| $2\theta_{max}$/° | 2–50 | 2–50 | 2–45 |
| Scan parameters | 2 (0.70 + 0.35 tan θ) | 2 (0.70 + 0.35 tan θ) | 2 (0.70 + 0.35 tan θ) |
| Scan speed (°/min$^{-1}$) | 16.48/7 ~ 16.48/2 | 16.48/7 ~ 16.48/2 | 16.48/7 ~ 16.48/2 |
| No. of measurements | 2138 | 1926 | 1508 |
| No. of observed reflections | 1179 (> 2σ) | 993 (> 2σ) | 1098 (> 2σ) |
| *R* | 0.043 | 0.041 | 0.041 |
| $R_w$ | 0.042 | 0.041 | 0.039 |
| *S* | 1.66 | 1.81 | 1.60 |

* Bond distances, bond angles, atomic coordinates and thermal parameters for structures **10**, **12** and **20** have been deposited with the Cambridge Crystallographic Data Centre.†

that the amino nitriles **2** and **3** eliminated HCN to give the corresponding oxazolidines **6** and **7**, respectively, when heated under reduced pressure (100 °C/5 mmHg).[5a]



**8** R = $CH_2$=$CHCH_2$
**9** R = Me
**10** R = $PhCH_2$
**11** R = *o*-$BrC_6H_4CH_2$



**12**
**13**
**14**
**15**

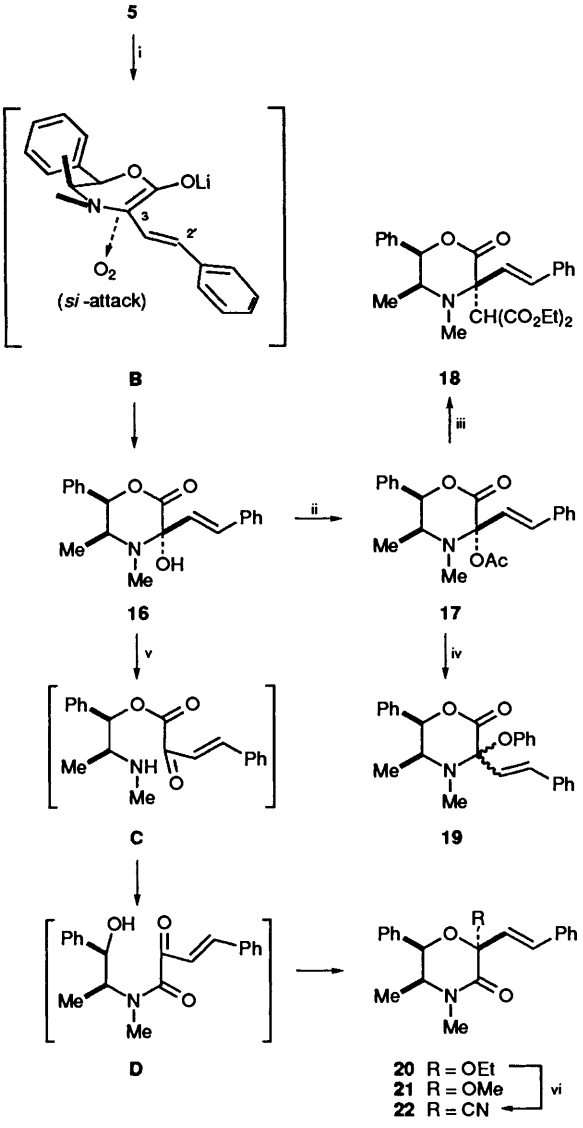
Metallation of **4** was effected by treating it with LDA in the presence of hexamethylphosphoramide (HMPA) (3 equiv.) at −78 °C. The subsequent alkylations occurred exclusively on the *si*-face to give **8**–**11** in high yields (Table 1). The anion of oxazinone **5**, generated by treatment with LDA, underwent stereospecific α-protonation with $NH_4Cl$ at −78 °C, regenerating **5**. No 3*S*-epimer of **5** or γ-protonation product was observed. Treatment of **5** with Bu$^t$OK in Bu$^t$OH under thermodynamically controlled conditions had no effect on the stereochemistry of **5**.

† See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.

Alkylation of the presumed lithium dienolate intermediate **B** formed from **5** may, in principle, occur at C-3 (α-site) or C-2′ (γ-site) to give eight possible products (*E*/*Z* and diastereoisomers). Alkylation of **5** occurred, however, exclusively at the α-site to give α,α-disubstituted oxazinones **12**–**15** in a stereospecific manner. In contrast, the amino nitrile **3** underwent protonation and alkylation with exclusively γ-regioselectivity.[4]

It was established that the alkylated products **10** and **12** had a 3*R*-configuration by X-ray crystallographic analysis (Table 2). Inspection of molecular models and computer calculation of the enolates of **4** and **5** (where Li was replaced with $BH_2$) conformed to the stereochemical outcome. The study indicated that the anions of **4** and **5** had half-chair conformations, such as structure **B**, with the three substituents (*N*-Me, 5-Ph and 6-Me) orientated on the same face and causing electrophiles approaching on the less hindered *si*-face to furnish products of 3*R*-configuration. The oxazinones **8**–**15** were consistent in showing positive Cotton effects with maxima close to 260 or 270 nm in their CD spectra (Table 1). The exciton couplings exerted by the 6-phenyl group and the C-3 group (phenyl or styryl group) of the assigned chiralities account for the observed Cotton effects.[6] Because the benzyl and *o*-bromobenzyl groups exhibited shielding effects, the NMR spectra of **10**, **11**, **14** and **15** showed 5-H and 6-H resonances at relatively higher fields than the corresponding signals in **8**, **9**, **12** and **13**.

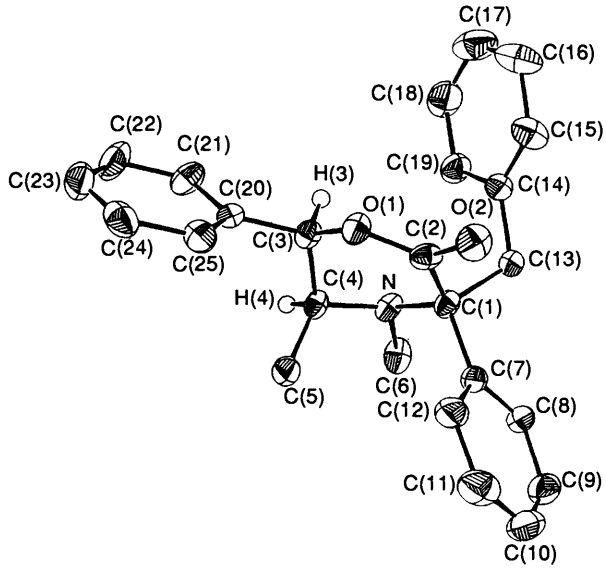
The enolate of **5** was trapped with molecular oxygen, followed by reduction with KI, to give the α-hydroxylated product **16** (Scheme 2). Treatment of **5** with *m*-chloroperoxybenzoic acid ($CH_2Cl_2$/aq. $NaHCO_3$, 27 °C, 25 h) gave **16** (34%) along with



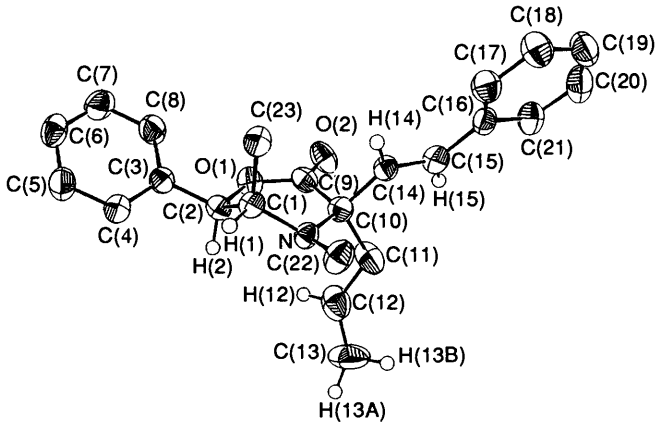

**Scheme 2** *Reagents and conditions:* i, LDA, THF, $O_2$, −78 °C, 15 min; aq. KI; 86%; ii, $Ac_2O$, $Et_3N$, DMAP cat., $CH_2Cl_2$, room temp., 2 h; 86%; iii, $NaCH(CO_2Et)_2$, $[PdCl_2(PPh_3)_2]$ cat., THF, reflux, 2 h; 86%; iv, PhONa, $[PdCl_2(PPh_3)_2]$ cat., THF, reflux, 2 h; 73%; v, EtOH (or MeOH), CSA cat., $CH_2Cl_2$, reflux, 6 h; **20**, 86%; **21**, 87%; vi, $Me_3SiCN$, $TiCl_4$, $CH_2Cl_2$, −78 °C, 10 min; 83%

recovery of **5** (66%). Acetylation of **16** afforded **17**, which underwent $[Pd(PPh_3)_2Cl_2]$-catalysed substitution with diethyl sodiomalonate to give **18**.[7] The 3*S*-chirality in compounds **16**–**18** was inferred from mechanistic considerations and supported by positive Cotton effects in their CD spectra. The reaction of **17** and PhONa/$[Pd(PPh_3)_2Cl_2]$ gave **19**, which showed a negative Cotton effect with $\theta_{min}$ at 261.5 nm in its CD spectrum. Since **19** contains a chromophore (PhO) additional to the phenyl and styryl groups, its observed CD spectrum does not, therefore, provide unambiguous evidence for the assignment of the C-3 chirality.

An alcoholic solution of **16** when heated in the presence of camphorsulfonic acid gave the rearrangement product **20** in 86% yield (Scheme 2), whilst the acid-catalysed rearrangement of **16** in MeOH gave **21** in 87% yield. The reaction presumably proceeded with reversal of the amino hemiacetal **16** to an amino ketone **C**. Intramolecular aminolysis of **C** gave **D**, which subsequently formed acetals **20** or **21** in EtOH or MeOH. The structure of **20** was confirmed by an X-ray analysis. The reaction of **20** and cyanotrimethylsilane was promoted by $TiCl_4$ to give **22**.[8] Both **20** and **22** showed positive Cotton effects in their CD spectra. Compound **22** was probably obtained by an addition of cyano group to the oxonium intermediate on the less hindered *re*-face.




ORTEP drawing of compound **10**

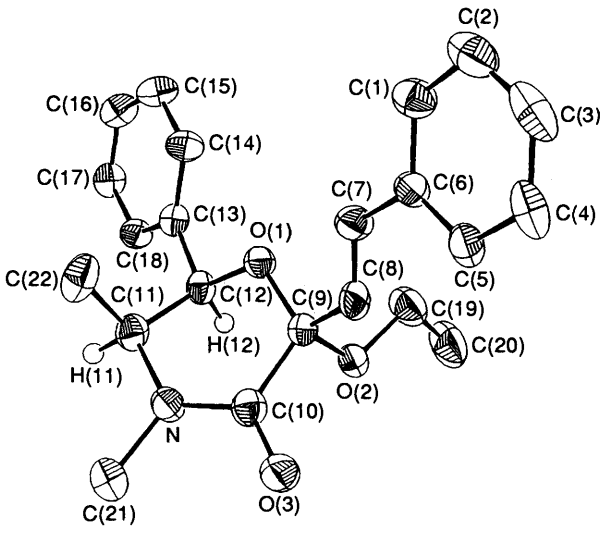



ORTEP drawing of compound **12**

In summary, we have demonstrated an efficient and stereospecific method of preparing α-phenyl- and α-phenylvinyloxazinones **4** and **5** as well as their α,α-disubstituted derivatives **8**–**15**. This method is complementary to the previously reported glycine template methods.[1–3] Hydroxylation of **5** also occurred in a stereospecific manner to give **16**, which was elaborated to other substituted oxazinones **17**–**22**. Since the oxazinone **4** has been saponified and treated with $Pb(OAc)_4$ to give optically pure 2-methylamino-2-phenylacetic acid (α-phenylsarcosine),[5] similar treatment of oxazinones **5** and **8**–**15** may also lead to formation of varied α-methylamino acids.

## Experimental

M.p.s are uncorrected. $^1H$ NMR spectra were recorded at 200 or 300 MHz and $^{13}C$ NMR at 50 or 74 MHz using chlorotrimethylsilane as internal standard (*J* values in Hz). Mass spectra (using a Finnigan TSQ 46c spectrometer) were recorded at an ionizing voltage of 70 eV. Merck silica gel 60F sheets were used for analytical thin-layer chromatography (TLC). Column chromatography was performed on $SiO_2$ (70–230 mesh) with




ORTEP drawing of compound **20**

elution by gradients of EtOAc in hexane and carried out on a liquid chromatograph, equipped with a refractive index detector. The samples were analysed and/or separated on a Hibar Lichrosorb Si 60 (7 μm) column (25 cm × 1 cm) by the indicated eluent with 5 $cm^3$ $min^{-1}$ flow rate. $[\alpha]_D$ Values are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. THF was distilled from sodium benzophenone ketyl under $N_2$. The X-ray diffraction data were collected on a CAD-4 diffractometer. The analyses were carried out on a microVAX III computer using NRC SDP software. Sybyl molecular modelling software version 5.5 (Tripos Associate Inc.) was used for calculation of the favourable conformations of the enolates of **4** and **5** where Li was replaced with $BH_2$. The closest local minima of the potential energy surface of molecules were searched with the Sybyl fitting function.

2-[*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylamino]-4-phenylbut-3-enenitrile **3**,[4b] and (2*S*,4*S*,5*R*)-3,4-dimethyl-2,5-diphenyl-1,3-oxazolidine **6**[5b] are known compounds.

2-[N-(2-*Hydroxy*-1-*methyl*-2-*phenylethyl*)-N-*methylamino*]-2-*phenylethanenitrile* **2**.—To an acetonitrile solution (3 $cm^3$) of L-ephedrine hydrochloride (179 mg, 1 mmol) was added benzaldehyde (0.1 $cm^3$, 1 mmol), followed by a solution of KCN (65 mg, 1 mmol) in water (1 $cm^3$). The solution was stirred at room temperature (26 °C) for 5 h and then concentrated and partitioned between EtOAc (10 $cm^3$) and brine (5 $cm^3$); the aqueous phase was then extracted with EtOAc (10 $cm^3$ × 2). The combined organic phase and extracts were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was chromatographed on a silica-gel column with EtOAc–hexane (15:85) as eluent to give the amino nitrile **2** (204 mg, 73%) as a mixture of two C-2 epimers (1:1); oil; TLC (EtOAc–hexane, 15:85) $R_f$ 0.25; HPLC (EtOAc–hexane, 15:85) $t_R$ = 3.6 min and 4.8 min; $\nu_{max}$(neat)/$cm^{-1}$ 3445br (OH) and 2247 (CN); $\delta_H$($CDCl_3$) 1.12, 1.20 (3 H, d, *J* 6.8), 2.21, 2.39 (3 H, s), 2.85–2.98, 3.07–3.15 (1 H, m, 1'-H), 4.92 (1 H, d, *J* 4.6), 5.06, 5.17 (1 H, s) and 7.23–7.44 (10 H, m); $\delta_C$($CDCl_3$) 9.5, 10.85 (q, C-3'), 32.7, 36.0 (q, $NCH_3$), 58.0, 59.3 (d, C-1'), 62.6, 64.9 (d, C-1) 73.7, 74.7 (d, C-2'), 116.8, 117.2 (s, CN), 125.9, 126.1, 127.3, 127.4, 127.7, 128.3, 128.5, 128.6, 128.7, 128.8, 134.2, 134.5 (s), 141.70 and 142.8 (s); *m*/*z* 280 (2%, $M^+$) and 173 (100) (Found: $M^+$, 280.1578. $C_{18}H_{20}N_2O$ requires *M*, 280.1576).

(3R,5S,6R)-4,5-*Dimethyl*-3,6-*diphenylperhydro*-1,4-*oxazin*-2-*one* **4**.—Treatment of the amino nitrile **2** by a procedure similar to that for **5** gave the oxazinone **4** in 94% yield. TLC (EtOAc–hexane, 8:92) $R_f$ 0.20; white crystals, m.p. 87–90 °C; $[\alpha]_D^{25}$ + 140 (*c* 5, EtOH); $\nu_{max}$(neat)/$cm^{-1}$ 1733 (C=O); $\delta_H$($CDCl_3$) 0.86 (3 H, d, *J* 6.8), 2.25 (3 H, s), 3.37 (1 H, dq, *J* 6.8, 2.8), 4.21 (1 H, s), 5.99 (1 H, d, *J* 2.8), 7.27–7.42 (8 H, m) and 7.50–7.62 (2 H, m); $\delta_C$($CDCl_3$) 3.14 (C-7), 39.71 ($NCH_3$), 57.78 (C-5), 66.58 (C-3), 83.50 (C-6), 125.35 (d), 127.96 (d), 128.31 (d), 128.45 (d), 128.61 (d), 136.73 (s), 137.98 (s) and 169.07 (s, C=O) (Found: C, 76.1; H, 6.6; N, 4.8; $C_{18}H_{19}NO_2$ requires C, 76.84; H, 6.81; N, 4.98%); *m*/*z* 281 (10%, $M^+$) and 146 (100) (Found: $M^+$, 281.1411. $C_{18}H_{19}NO_2$ requires *M*, 281.1415).

(3R,5S,6R)-4,5-*Dimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)*perhydro*-1,4-*oxazin*-2-*one* **5**.—To a cold (0 °C) benzene solution (4.5 $cm^3$) of the amino nitrile **3** (918 mg, 3 mmol) was added dropwise concentrated HCl (12 mol $dm^{-3}$; 5.1 $cm^3$). The mixture was warmed to room temperature (27 °C) and stirred for 48 h. The resulting yellowish brown solid was collected and dissolved in saturated aqueous $NaHCO_3$ (*ca.* 10 $cm^3$) until the solution was pH 7. The mixture was extracted with EtOAc (10 $cm^3$ × 3) and the combined extracts were dried ($Na_2SO_4$) and concentrated to give the oxazinone **5** (826 mg, 90%), m.p. 108–109 °C; TLC (EtOAc–hexane, 30:70) $R_f$ 0.62 $[\alpha]_D^{25}$ +92 (*c* 1, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$) 248 (13 538) and 220 (15 384); CD (MeOH) $[\theta]_{216}$ 5135, $[\theta]_{226}$ 3401, $[\theta]_{248}$ 10 570, $[\theta]_{270}$ 2244 and $[\theta]_{280}$ 4.9; $\nu_{max}$(KBr)/$cm^{-1}$ 1740 (C=O); $\delta_H$($CDCl_3$) 0.81 (3 H, d, *J* 6.9), 2.42 (3 H, s), 3.31 (1 H, dq, *J* 6.9, 2.5, 5-H), 3.90 (1 H, d, *J* 7.4, 3-H), 5.83 (1 H, d, *J* 2.5, 6-H), 6.23 (1 H, dd, *J* 15.7, 7.4), 6.84 (1 H, d, *J* 15.7) and 7.21–7.56 (10 H, m); $\delta_C$($CDCl_3$, DEPT) 3.31 (q), 39.75 (q), 57.52 (d, C-5), 64.32 (d, C-3), 83.29 (d, C-6), 125.09 (d), 125.37 (d), 126.65 (d), 127.96 (d), 128.42 (d), 128.50 (d), 128.51 (d), 134.82 (d), 136.06 (s), 136.65 (s) and 168.98 (s, C=O); *m*/*z* 307 (15%, $M^+$ + 1), 263 (52), 144 (100) and 118 (83) (Found: $M^+$ + 1, 307.1560. $C_{20}H_{21}NO_2$ requires *M* + 1, 307.1513).

(2S,4S,5R)-3,4-*Dimethyl*-5-*phenyl*-2-(2-*phenylvinyl*)-1,3-*oxazolidine* **7**.[9]—To an acetonitrile solution (3 $cm^3$) of L-ephedrine hydrochloride (179 mg, 1 mmol) was added cinnamaldehyde (0.13 $cm^3$, 1 mmol), followed by a solution of KCN (65 mg, 1 mmol) in water (1 $cm^3$). The solution was stirred at room temperature for 8 h, concentrated and heated (100 °C bath) under reduced pressure (5 mmHg) for 2 h. The residue was chromatographed on a silica-gel column by elution with EtOAc–hexane (15:85) to give the oxazolidine **7** (256 mg, 92%). Pale yellow solid, m.p. 61–62 °C; $[\alpha]_D^{25}$ −41.94 (*c* 3.5, $CHCl_3$); $\nu_{max}$(KBr)/$cm^{-1}$ 1653 and 1602; $\delta_H$($CDCl_3$) 0.71 (3 H, d, *J* 6.4), 2.24 (3 H, s), 2.65 (1 H, dq, *J* 7.9, 6.4), 4.29 (1 H, d, *J* 7.5), 5.08 (1 H, d, *J* 7.9), 6.35 (1 H, dd, *J* 15.9, 7.5), 6.78 (1 H, d, *J* 15.9), 7.21–7.43 (8 H, m) and 7.45–7.49 (2 H, m); $\delta_C$($CDCl_3$) 14.61 (q), 35.69 (q), 63.73 (d, C-4), 82.50 (d, C-5), 98.61 (d, C-2), 126.86 (d), 127.17 (d), 127.52 (d), 127.59 (d), 127.63 (d), 128.14 (s), 128.49 (d), 139.87 (s), 135.86 (d) and 135.97 (d); *m*/*z* 279 (8%, $M^+$) and 173 (100) (Found: $M^+$, 279.1597. $C_{19}H_{21}NO$ requires *M*, 279.1623).

*General Procedure for Alkylation of Compounds* **4** *and* **5**.—Under a nitrogen atmosphere, a cold (−78 °C) THF solution (5 $cm^3$) of the oxazinone **4** or **5** (1 mmol) was treated with HMPA (3 mmol) and LDA (1.1 mmol) [prepared by addition of BuLi (1.6 mol $dm^{-3}$ hexane solution; 1.1 mmol) to a THF solution (2 $cm^3$) of diisopropylamine (1.2 mmol)]. The mixture became reddish brown after being stirred for 20 min at −78 °C. An electrophile (allyl bromide, iodomethane, benzyl bromide or *o*-bromobenzyl bromide; 1.25 mmol) was added to the mixture which was then warmed to 26 °C and stirred for 3 h. After this it was quenched by the addition of saturated aqueous $NH_4Cl$, concentrated, diluted with brine (10 $cm^3$) and extracted with EtOAc (10 $cm^3$ × 3). The combined extracts were dried

($Na_2SO_4$), filtered, concentrated and chromatographed on a silica-gel column by elution with gradients of EtOAc–hexane to give the alkylation products **8**–**15**.

(3R,5S,6R)-3-*Allyl*-4,5-*dimethyl*-3,6-*diphenylperhydro*-1,4-*oxazin*-2-*one* **8**. Oil; TLC (EtOAc–hexane, 8:92) $R_f$ 0.22; $[\alpha]_D^{25}$ +5.76 (*c* 1.7, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 260 (12 820); CD (MeOH) $[\theta]_{220}$ 338.2, $[\theta]_{226}$ −2051, $[\theta]_{240}$ −4.4, $[\theta]_{249}$ 747.4, $[\theta]_{260}$ 940 and $[\theta]_{282}$ 425.8; $\nu_{max}$(neat)/cm$^{-1}$ 1732; $\delta_H$($CDCl_3$) 0.82 (3 H, d, *J* 6.9), 2.34 (3 H, s), 3.11 (2 H, d, *J* 7.2), 3.58 (1 H, dq, *J* 6.9, 3.5), 5.23 (2 H, dd, *J* 15.4, 7.4), 5.68 (1 H, d, *J* 3.5), 6.07 (1 H, ddt, *J* 15.3, 7.4, 7.2), 7.25–7.39 (8 H, m) and 7.53 (2 H, dd, *J* 8.4, 1.4); $\delta_C$($CDCl_3$) 11.62 (q), 35.49 (q), 41.90 (t), 55.62 (d), 83.15 (d), 71.25 (s), 119.42 (t), 126.41 (d), 127.43 (d), 127.83 (d), 127.95 (d), 128.15 (d), 128.68 (d), 134.03 (d), 136.52 (s), 140.31 (s) and 172.14 (s); *m*/*z* 321 (0.5%, $M^+$) and 280 (100) (Found: $M^+$, 321.1719. $C_{21}H_{23}NO_2$ requires *M*, 321.1729).

(3R,5S,6R)-3,4,5-*Trimethyl*-3,6-*diphenylperhydro*-1,4-*oxazin*-2-*one* **9**. White solid, m.p. 112–115 °C; TLC (EtOAc–hexane, 40:60) $R_f$ 0.35; $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 216 (4136); CD (MeOH) $[\theta]_{214}$ −660.5, $[\theta]_{223}$ −16 930 $[\theta]_{239}$ −6143, $[\theta]_{254}$ −144.6, $[\theta]_{246}$ 1621 and $[\theta]_{270}$ 1397; $\nu_{max}$(KBr)/cm$^{-1}$ 1706; $\delta_H$($CDCl_3$) 0.99 (3 H, d, *J* 6.8), 1.84 (3 H, s), 2.07 (3 H, s), 3.61 (1 H, dq, *J* 6.7, 3.9), 5.37 (1 H, d, *J* 3.9), 7.23–7.43 (8 H, m) and 7.75 (2 H, dd, *J* 8.0, 1.3); $\delta_C$($CDCl_3$) 15.68 (q), 17.89 (q), 34.11 (q), 52.10 (d), 68.12 (s), 84.17 (d), 127.52 (d), 127.81 (d), 128.05 (d), 128.14 (d), 128.22 (d), 136.12 (s), 141.91 (s) and 172.58 (s); *m*/*z* 295 (1%, $M^+$) and 132 (100) ($M^+$, 295.1582. $C_{19}H_{21}NO_2$ requires *M*, 295.1572).

(3R,5S,6R)-3-*Benzyl*-4,5-*dimethyl*-3,6-*diphenylperhydro*-1,4-*oxazin*-2-*one* **10**. White needle-like crystals, m.p. 133–134 °C (from hexane); TLC (EtOAc–hexane, 10:90) $R_f$ 0.38; $[\alpha]_D^{25}$ +38.5 (*c* 0.2, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 226 (2222), 240 (2296) and 260 (1185); CD (MeOH) $[\theta]_{220}$ 5.2, $[\theta]_{223}$ −541.3, $[\theta]_{228}$ −5.2, $[\theta]_{245}$ 2351, $[\theta]_{254}$ 1950, $[\theta]_{258}$ 1885, $[\theta]_{274}$ 1259 and $[\theta]_{287}$ 667.6; $\nu_{max}$(KBr)/cm$^{-1}$ 1729; *m*/*z* 372 (0.1%, $M^+$ + 1) and 280 (100); $\delta_H$($CDCl_3$) 0.73 (3 H, d, *J* 6.8), 2.40 (3 H, s), 3.17 (1 H, dq, *J* 6.8, 3.2), 3.46 (1 H, d, *J* 12.8), 3.68 (1 H, d, *J* 12.8), 4.22 (1 H, d, *J* 3.2), 7.09 (2 H, dd, *J* 7.8, 2.4), 7.22–7.41 (11 H, m) and 7.49 (2 H, dd, *J* 7.8, 1.6); $\delta_C$($CDCl_3$) 9.81 (q), 36.01 (q), 42.58 (t), 56.27 (d), 71.66 (s), 81.14 (d), 125.46 (d), 127.15 (d), 127.37 (d), 127.63 (d), 127.96 (d), 128.08 (d), 128.14 (d), 128.44 (d), 131.22 (d), 136.85 (s), 136.90 (s), 141.06 (s) and 173.1 (s) (Found: C, 80.4; H, 6.8; N, 3.8. $C_{25}H_{25}NO_2$ requires C, 80.83; H, 6.78; N, 3.77%).

(3R,5S,6R)-3-(2-*Bromobenzyl*)-4,5-*dimethyl*-3,6-*diphenylperhydro*-1,4-*oxazin*-2-*one* **11**. White solid; m.p. 155–157 °C; TLC (EtOAc–hexane, 10:90) $R_f$ 0.33; $[\alpha]_D^{25}$ +31.8 (*c* 1, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 228 (14 250), 240 (8400) and 248 (5850); CD (MeOH) $[\theta]_{214}$ −310.9, $[\theta]_{228}$ −14 850, $[\theta]_{235}$ −12 720, $[\theta]_{239}$ 12 000, $[\theta]_{257}$ −226.3, $[\theta]_{272}$ 7647, $[\theta]_{290}$ 1912 and $[\theta]_{295}$ 1199; $\nu_{max}$(KBr)/cm$^{-1}$ 1734; *m*/*z* 450 (3%, $M^+$ for $^{81}$Br), 448 (3) and 280 (100); $\delta_H$($CDCl_3$) 0.80 (3 H, d, *J* 6.7), 2.30 (3 H, s), 3.17 (1 H, dq, *J* 6.7, 3.0), 3.55 (1 H, d, *J* 12.9), 4.20 (1 H, d, *J* 12.9), 4.32 (1 H, d, *J* 3.0) and 7.14–7.68 (14 H, m); $\delta_C$($CDCl_3$) 9.08 (C-1′), 37.79 ($NCH_3$), 42.03 (C-2), 56.38 (C-2′), 71.85 (C-1), 81.26 (C-3′), 125.38 (d), 127.42 (d), 127.56 (d), 127.71 (d), 128.01 (d), 128.23 (d), 128.30 (d), 128.76 (d), 132.76 (d), 136.60 (s), 141.11 (s) and 173.9 (s) (Found: C, 66.1; H, 4.5; N, 3.1. $C_{25}H_{24}BrNO_2$ requires C, 66.67; H, 5.37; N, 3.11%).

(3R,5S,6R)-3-*Allyl*-4,5-*dimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)-*perhydro*-1,4-*oxazin*-2-*one* **12**. Oil; TLC (EtOAc–hexane, 15:85) $R_f$ 0.43; $[\alpha]_D^{25}$ +7.8 (*c* 0.5, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 220 (13 889), 240 (13 194) and 268 (13 194); CD (MeOH) $[\theta]_{214}$ −3870, $[\theta]_{222}$ −13 880, $[\theta]_{231}$ −3876, $[\theta]_{240}$ −10 570, $[\theta]_{249}$ −7170, $[\theta]_{256}$ −160.3, $[\theta]_{274}$ 10 690 and $[\theta]_{286}$ 5212; $\nu_{max}$(neat)/cm$^{-1}$ 1733; $\delta_H$($CDCl_3$) 0.86 (3 H, d, *J* 6.8), 2.49 (3 H, s), 2.81 (2 H, dd, *J* 10.1, 8.2), 3.32 (1 H, dq, *J* 6.8, 3.1), 5.68 (1 H, d, *J* 3.1), 6.00 (1 H, m), 6.34 (1 H, d, *J* 16.2), 6.70 (1 H, d, *J* 16.2) and 7.20–7.40 (10 H, m); $\delta_C$($CDCl_3$) 9.04 (q), 34.90 (q), 40.85 (t), 56.65 (d), 67.94 (s), 83.08 (d), 119.06 (t), 125.65 (d), 126.49 (d), 127.87 (d), 128.32 (d), 128.57 (d), 129.63 (d), 131.41 (d), 133.42 (d), 136.54 (s), 136.87 (s) and 171.49 (s); *m*/*z* 348 (1.5%, $M^+$ + 1) and 306 (100) (Found: $M^+$, 347.1878. $C_{23}H_{25}NO_2$ requires *M*, 347.1885).

(3R,5S,6R)-3,4,5-*Trimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)*perhydro*-1,4-*oxazin*-2-*one* **13**. Oil; TLC (EtOAc–hexane, 15:85) $R_f$ 0.25; $[\alpha]_D^{25}$ −4.1 (*c* 0.3, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 220 (60 995) and 254 (26 966); CD (MeOH) $[\theta]_{222}$ −542.1, $[\theta]_{244}$ −37 000 and $[\theta]_{267}$ −584.1; $\nu_{max}$(neat)/cm$^{-1}$ 1725; $\delta_H$($CDCl_3$) 0.92 (3 H, d, *J* 6.7), 1.67 (3 H, s), 2.30 (3 H, s), 3.40 (1 H, dq, *J* 6.7, 3.5), 5.45 (1 H, d, *J* 3.5), 6.36 (1 H, d, *J* 16.1), 6.78 (1 H, d, *J* 16.1) and 7.22–7.45 (10 H, m); $\delta_C$($CDCl_3$) 13.01 (q), 19.73 (q), 34.41 (q), 53.81 (d), 65.37 (s), 84.18 (d), 126.62 (d), 127.35 (d), 127.79 (d), 128.01 (d), 128.15 (d), 128.56 (d), 130.95 (d), 131.46 (d), 136.31 (s), 136.52 (s) and 172.37 (s); *m*/*z* 321 (2%, $M^+$) and 158 (100) (Found: $M^+$, 321.1719. $C_{21}H_{23}NO_2$ requires *M*, 321.1729).

(3R,5S,6R)-3-*Benzyl*-4,5-*dimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)-*perhydro*-1,4-*oxazin*-2-*one* **14**. Oil; TLC (EtOAc–hexane, 15:85) $R_f$ 0.45; $[\alpha]_D^{25}$ +7.2 (*c* 1.3, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 252 (20 000) and 272 (11 111); CD (MeOH) $[\theta]_{214}$ 1868, $[\theta]_{225}$ −15 640, $[\theta]_{230}$ −15 330, $[\theta]_{239}$ 23 060, $[\theta]_{254}$ −10 490, $[\theta]_{259}$ −638.8, $[\theta]_{278}$ 17 010 and $[\theta]_{290}$ 7650; $\nu_{max}$(neat)/cm$^{-1}$ 1729; $\delta_H$($CDCl_3$) 0.81 (3 H, d, *J* 6.8), 2.6 (3 H, s), 3.09 (1 H, dq, *J* 6.8, 2.2), 3.35 (2 H, s), 4.48 (1 H, d, *J* 2.2), 6.38 (1 H, d, *J* 16.3), 6.78 (1 H, d, *J* 16.3), 7.12 (2 H, dd, *J* 7.8, 1.9) and 7.17–7.45 (13 H, m); $\delta_C$($CDCl_3$) 8.13 (q), 35.27 (q), 41.55 (t), 56.68 (d), 68.60 (s), 82.11 (d), 125.31 (d), 126.54 (d), 126.96 (d), 127.70 (d), 127.94 (d), 128.25 (d), 128.61 (d), 130.39 (d), 130.88 (d), 131.47 (d), 136.46 (s), 136.53 (s), 136.86 (s) and 171.96 (s); *m*/*z* 397 (0.1%, $M^+$) and 306 (100) (Found: $M^+$, 397.2029. $C_{27}H_{27}NO_2$ requires *M*, 397.2042).

(3R,5S,6R)-3-(2-*Bromobenzyl*)-4,5-*dimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)*perhydro*-1,4-*oxazin*-2-*one* **15**. Oil; TLC (EtOAc–hexane, 15:85), $R_f$ 0.42; $[\alpha]_D^{25}$ −6.2 (*c* 0.1, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 228 (45 238), 245 (30 476) and 264 (20 000); CD (MeOH) $[\theta]_{212}$ −1509, $[\theta]_{222}$ −47 960, $[\theta]_{231}$ −2483, $[\theta]_{238}$ −24 060, $[\theta]_{256}$ −5701, $[\theta]_{271}$ 20 720 and $[\theta]_{293}$ 7186; $\nu_{max}$(neat)/cm$^{-1}$ 1733; $\delta_H$($CDCl_3$) 0.83 (3 H, d, *J* 6.7), 2.59 (3 H, s), 3.11 (1 H, dq, *J* 6.7, 1.9), 3.46 (2 H, d, *J* 13.4), 3.75 (1 H, d, *J* 13.4), 4.59 (1 H, d, *J* 1.9), 6.36 (1 H, d, *J* 16.4), 6.81 (1 H, d, *J* 16.4), 7.10 (1 H, d, *J* 7.9), 7.59 (2 H, d, *J* 7.9) and 7.18–7.42 (1 H, m); $\delta_C$($CDCl_3$) 7.72 (q), 37.01 (q), 40.90 (t), 56.75 (d), 68.79 (s), 82.35 (d), 125.41 (d), 126.61 (d), 127.36 (d), 127.80 (d), 127.94 (d), 128.32 (d), 128.53 (d), 128.63 (d), 130.47 (d), 131.32 (d), 132.11 (d), 132.87 (d), 136.46 (s), 136.54 (s), 136.72 (s), 137.21 (s) and 172.83 (s); *m*/*z* 477 (1%, $M^+$ for $^{81}$Br), 475 (1, $M^+$ for $^{79}$Br) and 306 (100) (Found: $M^+$, 475.1127. $C_{27}H_{26}NO_2{}^{79}Br$ requires *M*, 475.1147).

(3S,5S,6R)-3-*Hydroxy*-4,5-*dimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)*perhydro*-1,4-*oxazin*-2-*one* **16**.—A cold (−78 °C) THF solution (3 cm$^3$) of the oxazinone **5** (306 mg, 1 mmol) was treated with an LDA solution (1.1 mmol) for 20 min. (The following hydroxylation was carried out regardless of whether in the presence of HMPA or not.) A slow stream of oxygen was bubbled into the solution for 15 min, followed by addition of aqueous KI (10%, 1 cm$^3$). The mixture was extracted with EtOAc and the combined extracts were washed with aq. $Na_2S_2O_3$ (5%), dried ($Na_2SO_4$), filtered, concentrated and chromatographed on a silica-gel column to give **16** (278 mg, 86%); oil; TLC (EtOAc) $R_f$ 0.18; $[\alpha]_D^{25}$ +11.5 (*c* 4, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 244 (7758) and 268 (6545); CD (MeOH) $[\theta]_{215}$ 563.4, $[\theta]_{219}$ −4457, $[\theta]_{230}$ −8.8, $[\theta]_{241}$ 9842 and $[\theta]_{254}$ 661.1; $\nu_{max}$(neat)/cm$^{-1}$ 3347br (OH) and

1641 (s, C=O); $\delta_H(CDCl_3)$ 1.03 (3 H, d, *J* 6.4), 3.04 (3 H, s), 3.51 (1 H, dq, *J* 6.4, 2.6), 3.67 (1 H, br s, OH), 5.60 (1 H, d, *J* 2.6), 6.55 (1 H, d, *J* 16.0), 7.09 (1 H, d, *J* 16.0) and 7.25–7.48 (10 H, m); $\delta_C(CDCl_3)$ 12.39 (q), 33.73 (q), 59.43 (d), 72.17 (d), 95.31 (s), 125.58, 127.13, 128.35, 128.49 (d), 125.70, 127.74, 128.09, 131.97 (d), 128.22, 135.82 (s) and 167.34 (s, C=O); *m/z* 324 (1%, $M^+$ + 1), 131 (61), 118 (80) and 58 (100) (Found: $M^+$, 323.1527. $C_{20}H_{21}NO_3$ requires *M*, 323.1521).

(3S,5S,6R)-3-*Acetyl*-4,5-*dimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)-*perhydro*-1,4-*oxazin*-2-*one* **17**.—A cold (−35 °C) $CH_2Cl_2$ solution (6 $cm^3$) of **16** (323 mg, 1 mmol) was treated with acetic anhydride (0.2 $cm^3$, 1.2 mmol), $Et_3N$ (0.4 $cm^3$, 3 mmol) and 4-dimethylaminopyridine (small amount). The mixture was gradually warmed to room temperature (27 °C) over a period of 2 h after which the volatiles were removed by rotary evaporation and the residue was partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc. The organic phase and extracts were combined, dried ($Na_2SO_4$), filtered, concentrated and chromatographed on a silica-gel column by elution with EtOAc–hexane (1:1) to give the acetate **17** (315 mg, 86%); oil; TLC (EtOAc–hexane, 50:50) $R_f$ 0.43; $[\alpha]_D^{25}$ −18.2 (*c* 0.4, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$) 240 (13 014) and 266 (12 671); CD (MeOH) $[\theta]_{218}$ 6132, $[\theta]_{223}$ 2840, $[\theta]_{231}$ 6991, $[\theta]_{239}$ 3637 and $[\theta]_{284}$ 8982; $\nu_{max}$(neat)/$cm^{-1}$ 1743 and 1670; $\delta_H(CDCl_3)$ 1.00 (3 H, t, *J* 6.6), 2.12 (3 H, s), 3.08 (3 H, s), 3.63 (1 H, dq, *J* 6.6, 2.8), 6.08 (1 H, d, *J* 2.8), 6.46 (1 H, d, *J* 16.1), 7.16 (1 H, d, *J* 16.1) and 7.25–7.52 (10 H, m); $\delta_C(CDCl_3)$ 12.58 (q), 21.37 (q), 33.76 (q), 59.42 (d), 74.97 (d), 97.10 (s), 125.56 (d), 125.98 (d), 126.60 (d), 127.19 (d), 127.81 (d), 128.47 (d), 128.52 (d), 132.88 (d), 135.48 (s), 137.15 (s), 163.83 (s) and 170.10 (s); *m/z* 365 (10%, $M^+$) and 118 (100) (Found: $M^+$, 365.1618. $C_{22}H_{23}NO_4$ requires *M*, 365.1627).

(3S,5S,6R)-3-*Bis*(*ethoxycarbonyl*)-4,5-*dimethyl*-6-*phenyl*-3-(2-*phenylvinyl*)*perhydro*-1,4-*oxazin*-2-*one* **18**.—Under a nitrogen atmosphere, a THF solution (3 $cm^3$) of $NaCH(CO_2Et)_2$, prepared from diethyl malonate (0.03 $cm^3$, 0.15 mmol) and NaH (13 mg, 0.15 mmol), was added dropwise to a THF solution (3 $cm^3$) of the acetate **17** (55 mg, 0.15 mmol) and $[PdCl_2(PPh_3)_2]$ (10 mg, 0.015 mmol). The mixture was heated (80 °C bath) at reflux for 2 h, cooled, and quenched by addition of saturated aqueous $NH_4Cl$. The mixture was concentrated and partitioned between brine and $Et_2O$. The aqueous layer was extracted with $Et_2O$ (10 $cm^3$ × 3) and the combined organic phase and extracts were dried ($Na_2SO_4$), filtered, concentrated and chromatographed on a silica-gel column by elution with EtOAc–hexane (35:65) to give **18** (60 mg, 86%); oil; TLC (EtOAc–hexane, 35:65) $R_f$ 0.32; $[\alpha]_D^{25}$ −20.1 (*c* 2.1, $CHCl_3$); $\lambda_{max}$/nm ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$) 248 (7364) and 282 (4360); CD (MeOH) $[\theta]_{213}$ 510.1, $[\theta]_{220}$ −3240, $[\theta]_{234}$ 1374, $[\theta]_{244}$ −1127, $[\theta]_{253}$ 2242, $[\theta]_{263}$ −4002, $[\theta]_{274}$ 3948 and $[\theta]_{284}$ 404.5; $\nu_{max}$(neat)/$cm^{-1}$ 1775 and 1700; $\delta_H(CDCl_3)$ 0.97 (3 H, d, *J* 6.6), 1.03 (3 H, t, *J* 7.2), 1.22 (3 H, t, *J* 5.5), 3.06 (3 H, s), 3.60 (1 H, dq, *J* 6.6, 2.7), 4.12 (2 H, q, *J* 5.5), 4.18 (2 H, q, *J* 7.2), 4.35 (1 H, s), 6.06 (1 H, d, *J* 2.7), 6.49 (1 H, d, *J* 15.8), 6.99 (1 H, d, *J* 15.8) and 7.18–7.48 (10 H, m); $\delta_C(CDCl_3)$ 12.71 (q), 13.90 (q), 34.06 (q), 59.35 (d), 60.95 (d), 61.27, 61.56 (t), 73.89 (d), 80.24 (s), 125.45 (d), 126.83 (d), 126.92 (d), 127.27 (d), 127.41 (d), 127.84 (d), 128.29 (d), 128.43 (d), 128.53 (d), 128.59 (d), 128.71 (d), 136.40 (s), 138.30 (s), 166.09 (s), 167.50 (s) and 168.10 (s); *m/z* 465 (12%, $M^+$) and 306 (100) (Found: $M^+$, 465.2166. $C_{27}H_{31}NO_6$ requires *M*, 465.2151).

(3S,5S,6R)-4,5-*Dimethyl*-3-*phenoxy*-6-*phenyl*-3-(2-*phenylvinyl*)*perhydro*-1,4-*oxazin*-2-*one* **19**.—Treatment of the acetate **17** with PhONa (prepared from PhOH and NaH), by a procedure similar to that for **18**, gave **19** (44 mg, 73%); oil; TLC (EtOAc–hexane, 35:65) $R_f$ 0.30; $[\alpha]_D^{25}$ −27.5 (*c* 0.4, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$) 221 (8000) and 256 (4160); CD (MeOH) $[\theta]_{214}$ −3019, $[\theta]_{220}$ 25 120, $[\theta]_{232}$ −11 530, $[\theta]_{240}$ −6249, $[\theta]_{252}$ −3327, $[\theta]_{262}$ −11 360 and $[\theta]_{278}$ −1339; $\nu_{max}$(neat)/$cm^{-1}$ 1742; $\delta_H(CDCl_3)$ 1.05 (3 H, d, *J* 6.5), 3.09 (3 H, s), 3.63 (1 H, dq, *J* 6.5, 2.7), 5.83 (1 H, d, *J* 2.7), 6.56 (1 H, d, *J* 16.0), 7.04 (1 H, d, *J* 16.0) and 7.23–7.45 (15 H, m); $\delta_C(CDCl_3)$ 12.80 (q), 33.96 (q), 59.10 (d), 71.72 (d), 99.99 (s), 121.84 (d), 123.35 (d), 125.55 (d), 125.75 (d), 126.20 (d), 127.17 (d), 127.92 (d), 128.33 (d), 128.49 (d), 128.63 (d), 128.85 (d), 134.14 (s), 135.77 (s), 136.96 (s) and 162.73 (s); *m/z* 399 (36%, $M^+$) and 118 (100) ($M^+$, 399.1835. $C_{26}H_{25}NO_3$ requires *M*, 399.1834).

(3S,5S,6R)-2-*Ethoxy*-4,5-*dimethyl*-6-*phenyl*-2-(2-*phenylvinyl*)-*perhydro*-1,4-*oxazin*-3-*one* **20**.—A $CH_2Cl_2$ solution (6 $cm^3$) of the alcohol **16** (323 mg, 1 mmol), ethanol (0.2 $cm^3$, 5 mmol) and camphorsulfonic acid (small amount) was heated (80 °C bath) at reflux for 6 h. The mixture was concentrated and chromatographed on a silica-gel column by elution with EtOAc–hexane (1:1) to give the oxazinone acetal **20** (301 mg, 86%); white crystals, m.p. 153–153.5 °C (hexane); TLC (EtOAc–hexane, 50:50) $R_f$ 0.51; $[\alpha]_D^{25}$ +19.3 (*c* 0.3, $CHCl_3$); $\lambda_{max}$-(MeOH)/nm ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$) 215 (35 100) and 256 (42 120); CD (MeOH) $[\theta]_{206}$ −51 120, $[\theta]_{212}$ −12 320, $[\theta]_{224}$ −233 300, $[\theta]_{251}$ 32 210, $[\theta]_{261}$ −18 620, $[\theta]_{271}$ 88 410 and $[\theta]_{282}$ 3174; $\nu_{max}$(KBr)/$cm^{-1}$ 1660; *m/z* 351 (9%, $M^+$ + 1) and 118 (100); $\delta_H(CDCl_3)$ 1.00 (3 H, d, *J* 6.5), 1.14 (3 H, t, *J* 7.1), 3.02 (3 H, s), 3.54 (2 H, q, *J* 6.5), 3.53 (1 H, dq, *J* 6.5, 2.9), 6.58 (1 H, d, *J* 16.1), 7.12 (1 H, d, *J* 16.1) and 7.26–7.53 (10 H, m); $\delta_C(CDCl_3)$ 12.58 (q), 15.45 (q), 33.74 (q), 57.60 (t), 59.11 (d), 70.85 (d), 98.26 (s), 125.51 (d), 126.36 (d), 127.10 (d), 127.76 (d), 128.24 (d), 133.53 (d), 135.89 (s), 137.48 (s) and 165.91 (s).

(3S,5S,6R)-2-*Methoxy*-4,5-*dimethyl*-6-*phenyl*-2-(2-*phenylvinyl*)*perhydro*-1,4-*oxazin*-3-*one* **21**.—The acid-catalysed reaction of **16** and MeOH, by a procedure similar to that for **20** gave the acetal **21** (292 mg, 87%); TLC (EtOAc–hexane, 50:50), $R_f$ 0.38; white crystals, m.p. 109–111 °C; $[\alpha]_D^{25}$ +46.15 (*c* 0.6, $CHCl_3$); $\nu_{max}$(KBr)/$cm^{-1}$ 1727 and 1661; $\delta_H(CDCl_3)$ 1.01 (3 H, d, *J* 6.5, 1′-H), 3.03 (3 H, s), 3.24 (3 H, s), 3.53 (1 H, dq, *J* 6.5, 2.9), 5.53 (1 H, d, *J* 2.9), 6.54 (1 H, d, *J* 16.1), 7.13 (1 H, d, *J* 16.1) and 7.24–7.54 (10 H, m); $\delta_C(CDCl_3)$ 12.55 (q), 33.73 (q), 49.30 (q), 59.13 (d), 71.02 (d), 98.27 (s), 125.52 (d), 127.12 (d), 127.81 (d), 128.33 (d), 128.53 (d), 128.59 (d), 134.23 (d), 135.84 (s), 137.38 (s) and 165.9 (s); *m/z* 337 (0.2%, $M^+$) and 118 (100) (Found: $M^+$, 337.1674. $C_{21}H_{23}NO_3$ requires *M*, 337.1678).

(2S,5S,6R)-2-*Cyano*-4,5-*dimethyl*-6-*phenyl*-2-(2-*phenylvinyl*)-*perhydro*-1,4-*oxazin*-3-*one* **22**.—To a cold (−78 °C) $CH_2Cl_2$ solution (3 $cm^3$) of the acetal **20** (88 mg, 0.25 mmol) and $TiCl_4$ (0.34 mol $dm^{-3}$ cyclohexane solution; 1 $cm^3$) was added dropwise $Me_3SiCN$ (0.05 $cm^3$, 0.28 mmol). The mixture was stirred at −78 °C for 10 min after which aqueous KOH (0.5 $cm^3$, 10%) was added to it. The mixture was then suction filtered through a pad of Celite and the filtrate was partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic phase and extracts were dried ($Na_2SO_4$), concentrated and chromatographed on a silica-gel column by elution with EtOAc–hexane (3:2) to give **22** (69 mg, 83%); oil; TLC (EtOAc–hexane, 60:40) $R_f$ 0.43; $[\alpha]_D^{25}$ +49.5 (*c* 0.33, $CHCl_3$); $\lambda_{max}$(MeOH)/nm ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$) 220 (58 101) and 256 (38 180); CD (MeOH) $[\theta]_{205}$ 77 130, $[\theta]_{211}$ −139 700, $[\theta]_{221}$ −53 360, $[\theta]_{229}$ −315.1, $[\theta]_{238}$ 42 280, $[\theta]_{249}$ 105 400, $[\theta]_{262}$ 74 230 and $[\theta]_{286}$ −4248; $\nu_{max}$(neat)/$cm^{-1}$ 1670 $cm^{-1}$; $\delta_H(CDCl_3)$ 1.05 (3 H, d, *J* 6.5), 3.10

(3 H, s), 3.61 (1 H, dq, *J* 6.5, 2.6), 5.49 (1 H, d, *J* 2.6), 6.45 (1 H, d, *J* 15.8), 7.20 (1 H, d, *J* 15.8) and 7.26–7.52 (10 H, m); $\delta_C(CDCl_3)$ 13.11 (q), 34.59 (q), 58.79 (d), 75.93 (d), 70.10 (s), 112.3 (s), 122.53 (d), 125.47 (d), 127.30 (d), 128.37 (d), 128.72 (d), 128.98 (d), 134.48 (d), 134.21 (s), 135.81 (s) and 162.40 (s); *m/z* 332 (10%, $M^+$) and 118 (100) (Found: $M^+$, 332.1532. $C_{21}H_{20}N_2O_2$ requires *M*, 332.1525).

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