

Asymmetric Synthesis of Substituted Prolines by 1,3-Dipolar Cycloadditions of Azomethine Ylides from Chiral 6-Isopropyl-5-phenylmorpholin-2-ones

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Chiral saturated alanine- and glycine-derived 6-isopropyl-5-phenylmorpholin-2-ones **11** and **12** have been prepared and employed for the generation of carboxy-stabilized ylides in asymmetric 1,3-dipolar cycloaddition reactions under thermal conditions, with electron-deficient dipolarophiles bear-

ing double and triple bonds. The cycloadducts are obtained with high stereocontrol and mainly with *endo* selectivity, and can be used for the synthesis of highly substituted enantiomerically pure prolines.

Introduction

The proline structure is present in many compounds with interesting biological features. Examples are drugs such as captopril and enalapril, which are employed clinically due to their anti-hypertensive properties.^[1] In addition, the *trans*-4-hydroxy-L-proline (L-Hyp) is present in plants bonded to small lateral chains of polysaccharides to form glycoproteins.^[2] In animals, proline residues of procollagen are hydroxylated to hydroxyproline, thus stabilizing the triple helix of procollagen.^[2] L-Hyp is also formed in a number of secondary metabolites, which act as antibiotics such as the echinocandins.^[3] Moreover, the kainoids form an important family of proline derivatives that exhibit potent neuroexcitatory activity in the mammalian central nervous system.^[4] Proline and derivatives have also been used as chiral ligand or synthetic precursors.^[5]

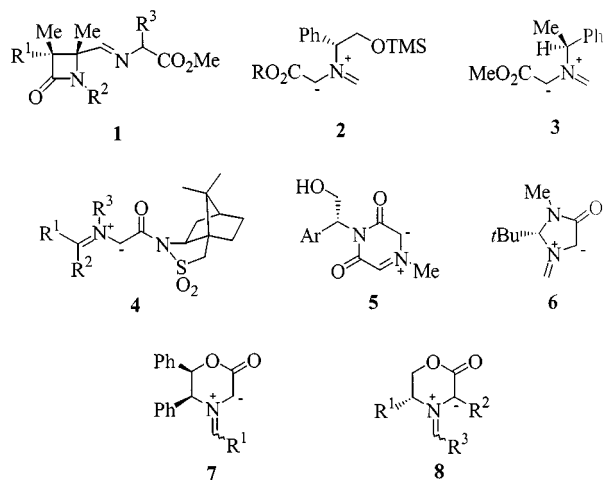
The most direct strategy for the synthesis of functionalized proline derivatives is the 1,3-dipolar cycloaddition reaction between an in situ generated carboxy-stabilized azomethine ylide and a dipolarophile.^[6] The asymmetric version of this reaction allows the synthesis of enantiomerically enriched prolines with the simultaneous creation of up to four stereochemically defined centers.^[7] Different strategies have been developed for achieving this asymmetric 1,3-dipolar cycloaddition reaction with α -imino ester derived dipoles, the use of chiral azomethine ylides being one of the most successfully employed.^[7] Examples of these chiral azomethine ylides have been reported from β -lactam imines **1**, which afforded the corresponding metalodipoles by reaction with DBU as base and AgOAc.^[8] Ylides **2** have

been used in the cycloaddition with *N*-methylmaleimide, but achieving almost no facial selectivity when R = Me.^[9] However, total stereoselectivity was obtained with ylides **2** by double asymmetric induction when R = (+)- or (-)-menthyl or (-)-8-phenylmenthyl.^[10] Related ylide **3** has been used in a cycloaddition reaction with vinylene carbonate for the chiral synthesis of both enantiomers of 1,4-dideoxy-1,4-iminolyxitol and 1,4-dideoxy-1,4-iminoribitol.^[11] Oppolzer's camphor sultam derived azomethine ylides **4**^[12] have also been employed as dipoles, whereas the cyclic species **5** reacted with Oppolzer's chiral acryloyl sultam as part of an asymmetric synthesis of the antitumor antibiotic (-)-quinocarcin.^[13] Seebach's imidazolidinone-derived ylide **6**^[14] and Williams' oxazin-2-one-derived ylides **7**^[15] have been used in 1,3-dipolar cycloaddition reactions with high stereocontrol. Ylides **7** are generated as mixtures of the corresponding (*E*)- and (*Z*)-azomethine ylides, affording the corresponding mixtures of diastereomers after 1,3-dipolar cycloaddition reactions, although with high *endo* selectivity.^[15a] Ylides **7** can be obtained mainly as the (*E*) isomer when sterically demanding R¹ groups are present,^[15a] a fact which has been used in the asymmetric synthesis of the antimitotic arrest agent (+)-spirotryprostatin B, the natural (-) enantiomer being obtained by using *ent*-**7** [R¹ = CH₂C(Me)₂OMe].^[15b]

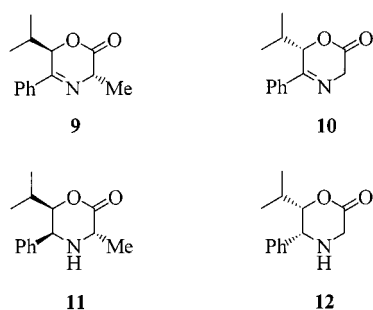
However, the most widely used chiral carboxy-stabilizing azomethine ylides have been Harwood's saturated oxazin-2-one derivatives **8** or *ent*-**8**,^[16] specially those prepared from (*R*)-phenylglycinol (R¹ = Ph). These species reacted with dipolarophiles bearing two electron-withdrawing groups at C-3 with high *de* and *endo* selectivity. The addition of MgBr₂·Et₂O improved the cycloaddition yields, and other dipolarophiles with a single electron-withdrawing group could be used affording mainly the *endo* adducts.^[16] The reaction has also been performed with aldehydes^[16d,16e] and imines^[16m] as dipolarophiles affording, after hydrolysis, *syn*- β -hydroxy α -amino acids and *syn*- β -amino α -amino acids, respectively. Moreover, intramolecular dipolar cycloaddition reactions to double^[16e] and triple^[16g] bonds have also been carried out using these derivatives.

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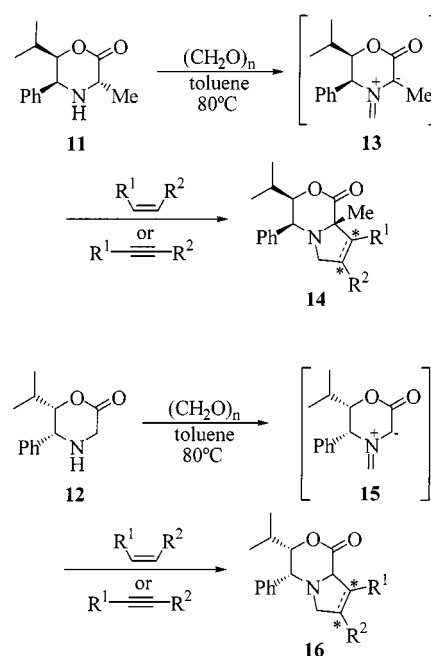
Recently, we have prepared chiral alanine and glycine imine derivatives with 3,5-dihydro-2H-1,4-oxazin-2-one structure **9** and **10**, which have been used as templates for the asymmetric synthesis of α -methyl α -amino acids after alkylation,^[17] and for the preparation of useful chiral dihydro amino acid derivatives after condensation reaction with aldehydes.^[18] In this context, we were interested to investigate the possible use of the corresponding reduced tetrahydro-1,4-oxazin-2-ones as starting materials for the preparation of chiral carboxy-stabilized ylides with oxazin-2-one structure. Moreover, the presence of a bulky isopropyl group at C-6 could influence the enantioselective bias of the cycloaddition reaction. We report therefore the use of the saturated oxazin-2-ones **11** and **12**, prepared by catalytic hydrogenation of **9** and **10**, respectively, for the generation of chiral azomethine ylides and reactivity of these as 1,3-dipoles suitable for the asymmetric synthesis of highly substituted prolines.^[19]



Results and Discussion

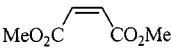
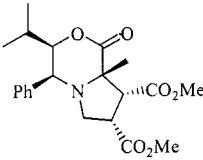
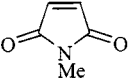
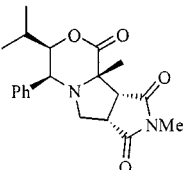
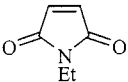
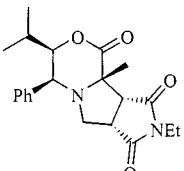
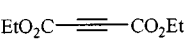
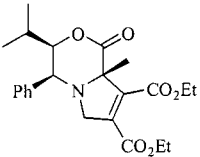
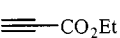
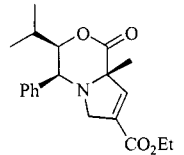
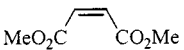
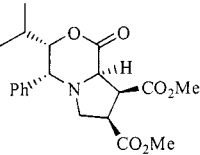
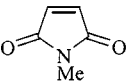
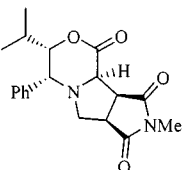
Starting 3,5-dihydro-2H-1,4-oxazin-2-ones **9**^[17c] and **10**^[18c] were prepared as previously described. Catalytic hydrogenation^[20] of these derivatives under normal pressure in the presence of palladium on carbon allowed the isolation of the corresponding saturated *cis*-oxazinones **11** and **12** in 99 and 70% yield, respectively. No other diastereomers were detected (¹H NMR) and the relative stereochemistry was determined by NOE experiments, confirming that the

hydrogenation of the imine moiety took place opposite to the bulky isopropyl group. Reaction of these derivatives with different electron-deficient olefins or acetylenes in the presence of an excess of paraformaldehyde in toluene at 80 °C, afforded the corresponding cycloadducts produced by a 1,3-dipolar cycloaddition reaction between the in situ generated azomethine ylides **13** or **15** and the dipolarophiles (Scheme 1 and Table 1). When alanine-derived dipole **13** was allowed to react with symmetrically substituted electron-poor olefins such as dimethyl maleate, a high 91:9 *endo*:*exo* diastereoselectivity was detected in the crude product by ¹H NMR (Table 1, Entry 1). The major isomer **14a** was isolated by column chromatography, and its configuration determined by NOESY experiments, which showed correlations between the isopropyl and methyl groups of the oxazin-2-one skeleton and between the former methyl group and the hydrogen atoms at the α -position relative to the carbonyl group. When *N*-methylmaleimide was used as dipolarophile a lower *endo*:*exo* ratio was observed (Table 1, Entry 2), the configuration of the *endo* major isomer **14b** being unequivocally determined by X-ray analysis^[21] (Figure 1). This observed *endo*:*exo* ratio is higher than for the reported examples when using a related dipole **8** ($R^1 = 2$ -Naph, $R^2 = \text{Me}$, $R^3 = \text{H}$), which afforded a low value (36% *endo* and 26% *exo*).^[16i] In addition, the use of *N*-ethylmaleimide as dipolarophile lowered even more the *endo*:*exo* ratio (Table 1, Entry 3). From the results in Table 1 we could deduce that the degree of asymmetric induction using these ylides is fairly high. This can also be observed in the reaction of acetylenes such as diethyl acetylenedicarboxylate with alanine-derived 1,3-dipole **13**, which gave almost exclusively cycloadduct **14d** in 75% isolated yield after attack of the dipolarophile to the less hindered side of the 1,3-dipole (Table 1, Entry 4). The reported reaction of a comparable alanine-derived dipole such as **8** ($R^1 = 2$ -naphthyl,



Scheme 1

Table 1. 1,3-Dipolar cycloaddition reaction of dipoles **13** and **15** and different dipolarophiles

Entry	Dipole	Dipolarophile	<i>t</i> [h]	<i>endo/exo</i> ratio ^[a]	Major adduct		
					Structure	No.	Yield (%) ^[b]
1	13		24	91:9		14a	33
2	13		6	75:16:others		14b	32
3	13		6	58:31:others		14c	22
4	13		3	— ^[c]		14d	75
5	13		3	— ^[d]		14e	44
6	15		3	85:8:others		16a	34
7	15		6	55:25:others		16b	58

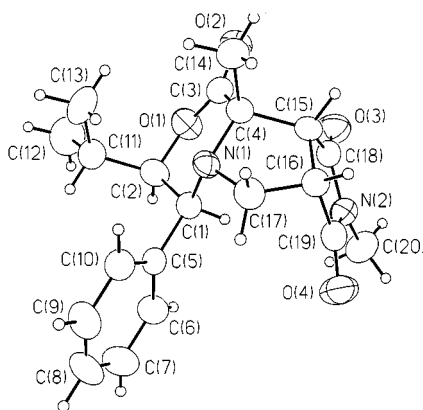
^[a] From the crude reaction mixture (GC and ¹H NMR 300 MHz). — ^[b] Isolated pure isomer after column chromatography and crystallization. — ^[c] 99:1 *dr*. — ^[d] 96:4 *dr*.

R² = Me, R³ = H) with dimethyl acetylenedicarboxylate, even in the presence of a Lewis acid such as MgBr₂·OEt₂ and under sonication, afforded only 4% of the corresponding cycloadduct.^[16i]

When the reaction was performed with unsymmetrically substituted dipolarophiles such as ethyl acetylenecarboxylate, only the regioisomer **14e** was detected (Table 1, Entry 5). This regioselectivity agrees with the expected values of the coefficients of the frontier orbitals in stabilized azomethine ylides and dipolarophiles,^[7b,7f] however being opposite to a reported result employing methyl acetylenecarboxylate and dipole **8** (R¹ = Ph, R² = R³ = H).^[16c] The

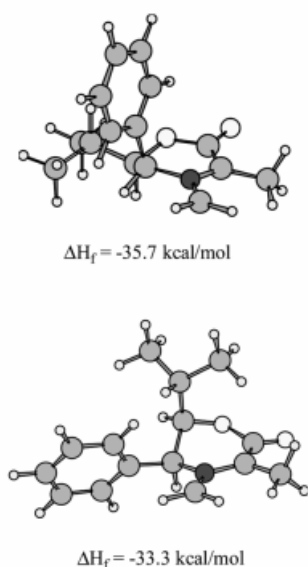
methyl substituent on dipole **13** might also play a role in driving the regioselectivity. Moreover, the previous reaction of an alanine-derived dipole **8** (R¹ = 2-Naph, R² = Me, R³ = H) with methyl acetylenecarboxylate under thermal conditions afforded only a Michael adduct of the tetrahydro-1,4-oxazin-2-one to the triple bond, the cycloadduct being obtained under Lewis acid catalysis but also with opposite regiochemistry compared to **14e**.^[16i]

The use of the in situ generated glycine-derived dipole **15** afforded a similar *endo/exo* ratio in the reaction with dimethyl maleate than when using dipole **13** in shorter reaction times (Table 1, Entry 6). This obtained *endo/exo* ratio

Figure 1. X-ray structure of *endo* adduct **14b**

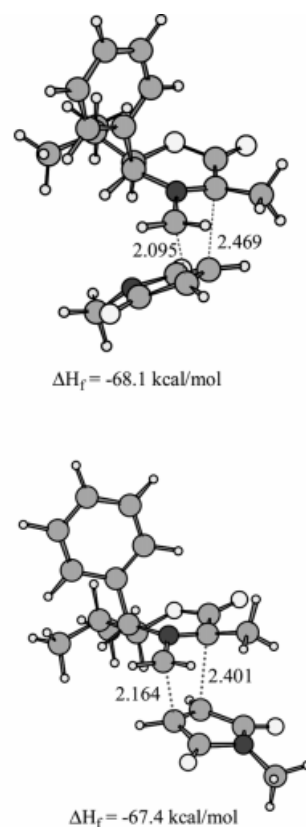
is higher than the reported when using a similar glycine-derived dipole **8** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$), which afforded a 77:23 *endo/exo* ratio,^[16c] although lower than the reported using dipole **7** ($R^1 = \text{H}$), which afforded only the *endo* diastereomer.^[15a] However, when *N*-methylmaleimide was employed, a lower *endo/exo* ratio was achieved (Entry 7) compared to the result obtained using dipole **13** (Entry 2), a similar value than the reported when related dipole **8** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) was used (68:32 *endo/exo* isolated ratio).^[16c]

A theoretical study was carried out in order to obtain insight into the observed preferred *endo* selectivity of this dipolar cycloaddition reaction. Computational studies on the asymmetric induction in 1,3-dipolar cycloadditions of related oxazin-2-ones **8** have been reported recently employing semi-empirical (PM3 and AM1) and *ab initio* methods (HF/3-21G), but only for the intramolecular version.^[22] In our case, semi-empirical calculations were performed on the dipole **13** using the PM3 Hamiltonian^[23] as implemented in MOPAC in CS Chem3D,^[24] showing a conformation 2.4 kcal more stable with the phenyl and isopro-

Figure 2. The two possible low energy conformations (PM3 Hamiltonian) of the dipole **13**

pyl groups in *pseudo*-axial and *pseudo*-equatorial positions, respectively, than occupying *pseudo*-equatorial and *pseudo*-axial positions (Figure 2). Although these two conformations would exist as an equilibrium, any of them shows an axial substituent to the approaching dipolarophile thus blocking one of the faces of the dipole. The most stable conformation was employed for further calculations. As a comparison, a PM3 calculation was performed on dipole **7** ($R^1 = \text{H}$), which also bears two substituents at C-5 and C-6, also giving a higher stability for the conformer showing a *pseudo*-axial phenyl group at C-5, although in this case the difference of energies between both conformers was lower than 1 kcal/mol.

The next step consisted in searching transition structures from the reaction between the dipole **13** and *N*-methylmaleimide using the PM3 semi-empirical method;^[24] *endo* and *exo* transition structures were located showing that the process is concerted but asynchronous (Figure 3), and a heat of formation favoring the *endo* approach by 0.7 kcal/mol. We also performed calculations using the hybrid Hartree–Fock (HF)/DFT methods implemented in the GAUSSIAN 98 suite of programs^[25] searching *endo* and *exo* transition structures from a similar reaction but using a dipole deprived of the phenyl and isopropyl groups due to computational limitations. Thus, the combination of the three-parameter Becke exchange functional with the Lee–Yang–Parr nonlocal correlation functional known as

Figure 3. The *endo* and *exo* transition structures of the reaction between dipole **13** and *N*-methylmaleimide (PM3 Hamiltonian, distances are expressed in Å)

B3LYP^[26] was applied with the basis set 6-31G(d); *endo* and *exo* transition structures were located showing a degree of asynchronicity similar than the calculated at the semi-empirical level, and a difference in energies of 1.2 kcal/mol favoring the *endo* transition state (Figure 4). All transition structures were characterized by frequency calculations as first-order saddle points showing only one imaginary frequency corresponding to the new created C–C bonds. The obtained electronic energies at B3LYP/6-31G(d) were corrected for zero-point energies, which were scaled by a factor of 0.96.^[27]

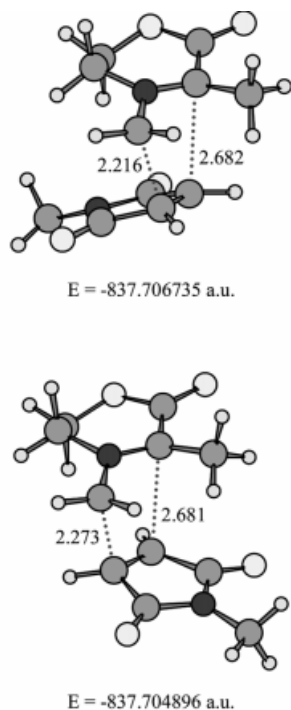
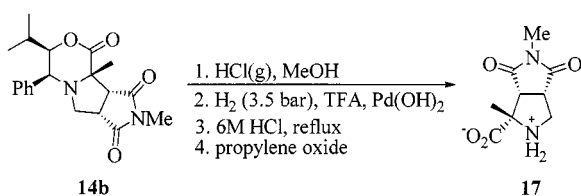


Figure 4. The *endo* and *exo* transition structures of the reaction between the model dipole and *N*-methylmaleimide (B3LYP/6-31G(d), distances are expressed in Å)

The isolated cycloadducts **14** and **16** can be used for the preparation of highly functionalized prolines. Thus, transesterification reaction of adduct **14b** with methanol followed by hydrogenolysis at 3.5 bar in the presence of a catalytic amount of Pearlman's catalyst and trifluoroacetic acid in a mixture of methanol and water, afforded the corresponding α -amino acid methyl ester. Hydrolysis and further treatment with propylene oxide in methanol allowed the isolation of proline derivative **17** in 60% overall yield (Scheme 2).



Scheme 2

Conclusions

We conclude that chiral 2,3,5,6-tetrahydro-6-isopropyl-5-phenyl-1,4-oxazin-2-ones derived from glycine and alanine, which have been prepared by catalytic hydrogenation of the corresponding 3,5-dihydro-2*H*-1,4-oxazin-2-ones, are useful systems for the generation of chiral carboxy-stabilized ylides after reaction with formaldehyde. These ylides can be used for the thermally-induced 1,3-dipolar cycloaddition reaction to electron-deficient olefins and acetylenes giving the corresponding cycloadducts mainly with *endo* selectivity, as has been observed with other oxazin-2-one-derived systems. The diastereoselectivity of the reaction proves high, and a superior reactivity towards acetylenic compounds compared to related oxazin-2-one-derived ylides has been observed. The isolated cycloadducts can be employed for the preparation of highly substituted enantiomerically pure proline derivatives.

Experimental Section

General: Melting points were determined with a Reichert Thermo-var hot plate apparatus and are uncorrected. – IR spectra were recorded with a Nicolet 510 P-FT and only the structurally important peaks are listed. – NMR spectra were measured with a Bruker AC-300 and DRX-500 using CDCl₃ as solvent and TMS as internal standard, unless otherwise stated. – Optical rotations were measured with a Jasco DIP-1000 polarimeter. – Low-resolution electron-impact (EI) mass spectra were obtained at 70 eV with a Shimadzu QP-5000. – HRMS (EI) were recorded with a Finnigan MAT 95S. Microanalyses were performed by the Microanalysis Service of the University of Alicante. – X-ray data were collected using Mo- K_{α} radiation (graphite crystal monochromator; λ = 0.71073 Å). – Analytical TLC was performed with Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized with UV light at 254 nm. – Flash chromatography was carried out with Merck silica gel 60 (0.040–0.063 nm).

Synthesis of Saturated Oxazinones **11 and **12**:** A solution of oxazinone **9** or **10** (1 mmol) and Pd/C (80 mg) in EtOAc (6 mL) was stirred under hydrogen (1 atm) for 1.5 and 4 h, respectively. The suspension was filtered through Celite and the solvent removed in vacuo (15 Torr) to afford **11** in 99% yield and, after column chromatography (silica gel), **12** in 70% yield.

(3*S*,5*S*,6*R*)-6-Isopropyl-3-methyl-5-phenylmorpholin-2-one (11**):** White solid. – M.p. 135–136 °C from *n*-hexane/ethyl acetate. – $[\alpha]_D^{25}$ = +76.7 (c = 1.0, CH₂Cl₂). – TLC: R_f = 0.35 (*n*-hexane/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu}$ = 3311, 1728 cm⁻¹. – ¹H NMR (300 MHz): δ = 0.75, 1.11, 1.42 (3 d, J = 6.7 Hz, 9 H, 3 $\times$ CH₃), 1.87 [m, 2 H, CH(CH₃)₂, NH], 3.66 (q, J = 6.7 Hz, 1 H, CHC=O), 4.23 (d, J = 3.4 Hz, 1 H, CHPh), 4.41 (dd, J = 9.8, 3.4 Hz, 1 H, CHO), 7.36 (m, 5 H, ArH). – ¹³C NMR (75 MHz): δ = 18.3, 19.0, 19.2 (3 $\times$ CH₃), 29.9 [CH(CH₃)₂], 49.0, 56.5 (CHPh, CHC=O), 88.7 (CHO), 128.0, 128.6, 128.9, 137.2 (ArC), 171.7 (C=O). – MS (EI): m/z (%) = 233 (2) [M⁺], 146 (15), 133 (81), 132 (100), 131 (41), 91 (40), 65 (16), 44 (30), 43 (15), 41 (19). – HRMS calcd. for C₁₄H₁₉NO₂: 233.1416; found 233.1418.

(5*R*,6*S*)-6-Isopropyl-5-phenylmorpholin-2-one (12**):** White solid. – M.p. 104–105 °C from *n*-hexane/ethyl acetate. – $[\alpha]_D^{25}$ = –102.0 (c = 1.0, CH₂Cl₂). – TLC: R_f = 0.41 (*n*-hexane/ethyl acetate, 1:2).

– IR (KBr): $\tilde{\nu}$ = 3312, 1723 cm^{-1} . – ^1H NMR (300 MHz): δ = 0.80, 1.08 (2 d, J = 6.7 Hz, 6 H, $2 \times \text{CH}_3$), 1.75 [m, 1 H, $\text{CH}(\text{CH}_3)_2$], 3.67, 3.76 (2 d, J = 17.7 Hz, 2 H, CH_2), 4.31 (m, 2 H, CHPh , CHO), 7.34 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 19.0, 19.1 ($2 \times \text{CH}_3$), 29.4 [$\text{CH}(\text{CH}_3)_2$], 45.4 (CH_2), 57.3 (CHPh), 86.8 (CHO), 128.1, 128.9, 138.1 (ArC), 169.9 (C=O). – MS (EI): m/z (%) = 219 (2) [M^+], 119 (63), 118 (100), 91 (29), 41 (15). – HRMS calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: 219.1259; found 219.1256.

Thermal Cycloadditions. – General Procedure: A suspension of paraformaldehyde (10 mmol, 300 mg) and the corresponding dipolarophile (5 mmol) in sodium-dried toluene (30 mL) was heated at 80 °C and a solution of oxazinone **11** or **12** (1 mmol) in toluene (10 mL) was added dropwise. The reaction mixture was stirred at 80 °C until completion (GC), cooled at room temperature and filtered through a plug of silica gel (EtOAc). The solvents were removed in vacuo (15 Torr). Column chromatography eluting with mixtures of *n*-hexane and ethyl acetate gave cycloadducts in yields and diastereoselectivities shown in Table 1. Physical and analytical data follow.

Dimethyl (3*S*,4*S*,7*S*,8*R*,8*aS*)-3-Isopropyl-8*a*-methyl-1-oxo-4-phenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7,8-dicarboxylate (14a**):** Colourless oil. – $[\alpha]_{\text{D}}^{25}$ = +111.7 (c = 2.0; CH_2Cl_2). – TLC: R_f = 0.64 (*n*-hexane/ethyl acetate, 1:1). – IR (film): $\tilde{\nu}$ = 1736 cm^{-1} . – ^1H NMR (300 MHz): δ = 0.41, 1.05 [2 d, J = 6.4 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.41 (s, 3 H, CH_3CN), 2.20 [m, 1 H, $(\text{CH}_3)_2\text{CH}$], 3.34 (m, 1 H, CHHN), 3.37 (d, J = 6.3 Hz, 1 H, CHCN), 3.44 (dd, J = 11.3, 6.3 Hz, 1 H, CHCH_2), 3.52 (dd, J = 14.0, 6.7 Hz, 1 H, CHHN), 3.67, 3.70 (2 s, 6 H, $2 \times \text{OCH}_3$), 4.34 (d, J = 3.7 Hz, 1 H, CHPh), 4.44 (dd, J = 9.8, 3.7 Hz, 1 H, CHO), 7.30, 7.43 (2m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 19.4, 20.4, 28.4 [CH_3CN , $(\text{CH}_3)_2\text{CH}$], 30.9 [$(\text{CH}_3)_2\text{CH}$], 43.5 (CHCH_2), 52.2, 52.4 (CHCN , OCH_3), 56.1 (CH_2N), 57.6 (OCH_3), 62.4 (CHPh), 67.2 (CN), 85.8 (CHO), 127.8, 128.6, 128.8, 137.8 (ArC), 170.6, 172.7, 173.5 ($3 \times \text{C}=\text{O}$). – MS (EI): m/z (%) = 389 (5) [M^+], 344 (45), 230 (54), 200 (70), 146 (100), 131 (91), 91 (61), 59 (27), 55 (29), 43 (26), 41 (37). – HRMS calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_6$: 389.1838; found 389.1836.

(4*S*,6*aS*,9*bS*,3*R*,9*aR*)-3-Isopropyl-8,9*b*-dimethyl-4-phenylhexahydropyrrolo[3',4':3,4]pyrrolo[2,1-*c*][1,4]oxazine-1,7,9(8*H*)-trione (14b**):** White solid. – M.p. 210–211 °C from *n*-hexane/ethyl acetate. – $[\alpha]_{\text{D}}^{25}$ = +44.0 (c = 1.0, CH_2Cl_2). – TLC: R_f = 0.37 (*n*-hexane/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu}$ = 1732, 1704 cm^{-1} . – ^1H NMR (300 MHz): δ = 0.76, 1.09 [2 d, J = 6.8 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.58 (s, 3 H, CH_3CN), 1.75 [m, 1 H, $(\text{CH}_3)_2\text{CH}$], 2.99 (s, 3 H, NCH_3), 3.28 (m, 1 H, CHCH_2), 3.35 (dd, J = 13.6, 1.8 Hz, 1 H, CHHN), 3.47 (d, J = 7.9, 1 H, CHCN), 3.54 (dd, J = 13.6, 9.4 Hz, 1 H, CHHN), 3.89 (d, J = 4.2 Hz, 1 H, CHPh), 4.16 (t, J = 4.2 Hz, 1 H, CHO), 7.21, 7.35 (2 m, 5 H, ArC). – ^{13}C NMR (75 MHz): δ = 17.8, 21.1, 25.2, 25.5 ($4 \times \text{CH}_3$), 28.3 [$\text{CH}(\text{CH}_3)_2$], 43.5 (CHCH_2), 53.4 (CH_2N), 56.3 (CHCN), 63.2 (CHPh), 68.8 (CN), 86.7 (CHO), 128.1, 128.5, 129.0, 136.3 (ArC), 169.1, 175.8, 178.3 ($3 \times \text{C}=\text{O}$). – MS (EI): m/z (%) = 341 (0.43) [$\text{M}^+ - \text{Me}$], 146 (100), 131 (76), 104 (20), 91 (45), 55 (27), 43 (23), 41 (29). – $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_4$ (356.4): calcd. C 67.4, H 6.8, N 7.9; found C 67.0, H 6.8, N 7.6.

(3*R*,4*S*,6*aS*,9*aR*,9*bS*)-8-Ethyl-3-isopropyl-9*b*-methyl-4-phenylhexahydropyrrolo[3',4':3,4]pyrrolo[2,1-*c*][1,4]oxazine-1,7,9(8*H*)-trione (14c**):** White solid. – M.p. 161–162 °C from *n*-hexane/ethyl acetate. – $[\alpha]_{\text{D}}^{25}$ = +46.9 (c = 1.0, CH_2Cl_2). – TLC: R_f = 0.37 (*n*-hexane/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu}$ = 1748, 1702 cm^{-1} . – ^1H NMR (300 MHz): δ = 0.76, 1.08 [2 d, J = 6.7 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.21, (t, J = 7.3 Hz, 3 H, CH_3CH_2), 1.60 (s, 3 H, CH_3CN), 1.71 [m, 1 H, $(\text{CH}_3)_2\text{CH}$], 3.25 (t, J = 7.9 Hz, 1 H,

CHCH_2), 3.36 (d, J = 13.4 Hz, CHCHH), 3.44 (d, J = 7.9 Hz, 1 H, CHCN), 3.56 (m, 3 H, CHCHH , CH_3CH_2), 3.98 (d, J = 4.3 Hz, 1 H, CHPh), 4.16 (m, 1 H, CHO), 7.21, 7.34 (2 m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 12.2, 17.8, 21.3, 25.4 ($4 \times \text{CH}_3$), 28.3 [$\text{CH}(\text{CH}_3)_2$], 34.1 (CH_2CH_3), 43.6 (CHCH_2), 53.6 (CHCH_2), 56.5 (CHCN), 63.2 (CHPh), 68.8 (CN), 86.6 (CHO), 127.9, 128.4, 29.0, 136.6 (ArC), 169.2, 175.5, 178.0 ($3 \times \text{C}=\text{O}$). – MS (EI): m/z (%) = 355 (11) [$\text{M}^+ - \text{Me}$], 181 (20), 147 (12), 146 (100), 104 (18), 91 (42), 66 (11), 55 (21), 44 (10), 43 (17), 41 (20), 40 (14). – HRMS calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4$: 355.1658; found 355.1660.

Diethyl (3*R*,4*S*,8*aS*)-3-Isopropyl-8*a*-methyl-1-oxo-4-phenyl-3,4,6,8*a*-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7,8-dicarboxylate (14d**):** White solid. – M.p. 117–118 °C from *n*-hexane/ethyl acetate. – $[\alpha]_{\text{D}}^{25}$ = +106.6 (c = 1.45, CH_2Cl_2). – TLC: R_f = 0.71 (*n*-hexane/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu}$ = 1737 cm^{-1} . – ^1H NMR (300 MHz): δ = 0.63, 1.10 [2 d, J = 6.7 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.25, 1.36 (2 t, J = 7.3 Hz, 6 H, $2 \times \text{CH}_3\text{CH}_2$), 1.70 (s, 3 H, CH_3CN), 2.03 [m, 1 H, $(\text{CH}_3)_2\text{CH}$], 3.72 (d, J = 16.5 Hz, 1 H, CHHN), 4.17, 4.32 (2 m, 7 H, $2 \times \text{CH}_2\text{O}$, CHHN , CHPh , CHO), 7.35 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 13.9, 14.0, 18.6, 21.0, 26.2 ($5 \times \text{CH}_3$), 28.2 [$\text{CH}(\text{CH}_3)_2$], 58.9 (CH_2N), 61.4, 61.8 ($2 \times \text{CH}_2\text{O}$), 63.4 (CHPh), 75.4 (CN), 85.9 (CHO), 128.2, 128.3, 128.9, 130.3, 137.3, 146.5 (C=C, ArC), 162.1, 164.4, 168.7 ($3 \times \text{C}=\text{O}$). – MS (EI): m/z (%) = 370 (5) [$\text{M}^+ - \text{OEt}$], 226 (19), 147 (11), 146 (100), 131 (89), 91 (32), 43 (15), 41 (11). – $\text{C}_{23}\text{H}_{29}\text{NO}_6$ (415.5): calcd. C 66.5, H 7.0, N 3.4; found C 66.3, H 7.0, N 3.4.

Ethyl (3*R*,4*S*,8*aS*)-3-Isopropyl-8*a*-methyl-1-oxo-4-phenyl-3,4,6,8*a*-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7-carboxylate (14e**):** White solid. – M.p. 92–93 °C from *n*-hexane/ethyl acetate. – $[\alpha]_{\text{D}}^{25}$ = +31.9 (c = 1.2, CH_2Cl_2). – TLC: R_f = 0.67 (*n*-hexane/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu}$ = 1738 cm^{-1} . – ^1H NMR (300 MHz): δ = 0.69, 1.08 [2 d, J = 6.4 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.31 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.52 (s, 3 H, CH_3CN), 3.74 (dd, J = 18.3, 1.8 Hz, 1 H, CHHN), 3.99 (d, J = 2.4 Hz, 1 H, CHPh), 4.21–4.36 (m, 4 H, CH_2O , CHO, CHHN), 6.84 (s, 1 H, $\text{CH}=\text{C}$), 7.27–7.42 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 14.0, 19.1, 19.2, 27.5 ($4 \times \text{CH}_3$), 29.2 [$\text{CH}(\text{CH}_3)_2$], 60.9, 61.1 ($2 \times \text{CH}_2$), 64.5 (CHPh), 71.1 (CN), 84.4 (CHO), 127.9, 128.7, 129.0, 137.3, 137.4, 140.0 (C=C, ArC), 162.8 ($\text{CH}_2\text{OC}=\text{O}$), 170.1 ($\text{CHOC}=\text{O}$). – MS (EI): m/z (%) = 298 (3) [$\text{M}^+ - \text{OEt}$], 170 (24), 154 (29), 146 (76), 132 (11), 131 (100), 91 (38), 43 (14), 41 (16). – HRMS calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_3$: 298.1443; found 298.1427.

Dimethyl (3*S*,4*R*,7*R*,8*S*,8*aR*)-3-Isopropyl-1-oxo-4-phenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-7,8-dicarboxylate (16a**):** White solid. – M.p. 188–190 °C from *n*-hexane/ethyl acetate. – $[\alpha]_{\text{D}}^{25}$ = +44.4 (c = 1.0, CH_2Cl_2). – TLC: R_f = 0.58 (*n*-hexane/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu}$ = 1737, 1729 cm^{-1} . – ^1H NMR (300 MHz): δ = 0.75, 1.10 [2 d, J = 6.9 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.87 [m, 1 H, $\text{CH}(\text{CH}_3)_2$], 3.09 (t, J = 9.3 Hz, 1 H, CHCH_2), 3.29 (m, 2 H, CH_2), 3.67, 3.71 (2 s, 6 H, $2 \times \text{CH}_3\text{O}$), 3.73 (m, 1 H, CHCHCH_2), 4.17 (d, J = 6.4 Hz, 1 H, NCHCO), 4.41 (d, J = 3.7 Hz, 1 H, CHPh), 4.44 (t, J = 4.4 Hz, 1 H, CHO), 7.33 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 17.9, 20.7 [$(\text{CH}_3)_2\text{CH}$], 28.4 [$\text{CH}(\text{CH}_3)_2$], 44.7, 49.5 ($2 \times \text{CHCO}_2\text{CH}_3$), 52.2, 52.4 ($2 \times \text{CH}_3\text{O}$), 54.6 (CH_2), 61.9, 63.6 (CHPh , NCHCOO), 87.6 (CHO), 127.9, 128.4, 128.6, 136.7 (ArC), 170.2, 170.5, 172.2 ($3 \times \text{C}=\text{O}$). – MS (EI): m/z (%) = 375 (5) [M^+], 330 (12), 316 (19), 275 (21), 217 (15), 216 (100), 186 (20), 154 (14), 146 (66), 131 (77), 91 (40), 59 (17), 43 (16), 41 (23). – HRMS calcd. for $\text{C}_{14}\text{H}_{25}\text{NO}_6$: 375.1682; found 375.1674.

(3*R*,4*R*,6*aR*,9*aS*,9*bR*)-3-Isopropyl-8-methyl-4-phenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,7,9(8*H*)-trione (16b**):** White solid. –

M.p. 242–243 °C from *n*-hexane/dichloromethane. – $[\alpha]_D^{25} = +1.60$ ($c = 1.0$, CH_2Cl_2). – TLC: $R_f = 0.37$ (*n*-hexane/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu} = 1741, 1693 \text{ cm}^{-1}$. – ^1H NMR (300 MHz): $\delta = 0.70, 1.20$ [2 d, $J = 6.4 \text{ Hz}$, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.85 [m, 1 H, $\text{CH}(\text{CH}_3)_2$], 2.22 (t, $J = 9.0 \text{ Hz}$, 1 H, CHHN), 3.02 (s, 4 H, CH_3N , CHCH_2), 3.16 (d, $J = 6.7 \text{ Hz}$, 1 H, CHCOO), 3.25 (d, $J = 9.0 \text{ Hz}$, 1 H, CHHN), 3.54 (t, $J = 6.7 \text{ Hz}$, 1 H, NCHCHCON), 4.08 (d, $J = 3.7 \text{ Hz}$, 1 H, CHPh), 4.37 (dd, $J = 10.4, 3.7 \text{ Hz}$, 1 H, CHO), 7.19, 7.39 (2 m, 5 H, ArH). – ^{13}C NMR (75 MHz): $\delta = 17.7, 19.6$ [$(\text{CH}_3)_2\text{CH}$], 25.9 (CH_3N), 29.6 [$\text{CH}(\text{CH}_3)_2$], 41.7, 44.3 ($2 \times \text{CHCON}$), 51.4 (CH_2), 59.7 (CHPh , NCHCOO), 89.6 (CHO), 128.7, 128.8, 129.3, 129.8 (ArC), 165.3 (OC=O), 175.5, 178.0 ($2 \times \text{NC=O}$). – MS (EI): m/z (%) = 342 (3) [M^+], 242 (58), 241 (29), 146 (100), 131 (99), 91 (46), 65 (20), 41 (27). – $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4$ (375.4): calcd. C 66.6, H 6.5, N 8.2; found C 66.0, H 6.5, N 7.8.

Synthesis of (1*S*,3*aS*,6*aR*)-1,5-Dimethyl-4,6-dioxohexahydro-1*H*-pyrrolo[3,4-*c*]pyrrole-1-carboxylic Acid (17): A solution of **14b** (0.6 mmol) in HCl (g)/MeOH (10 mL) was stirred overnight and the solvent removed in vacuo (15 Torr). The residue was dissolved in MeOH (8 mL), H_2O (0.8 mL), and TFA (160 μL), and $\text{Pd}(\text{OH})_2$ on carbon (160 mg) was added. The reaction vessel was charged with H_2 , and the mixture was hydrogenated at 3.5 bar for 36 h. The mixture was then purged with nitrogen and filtered (Celite) to remove the catalyst. The filtrate was concentrated (15 Torr), and the resulting residue was dissolved in 6 *N* HCl (5 mL) and heated under reflux for 4 h. Water was added, and the mixture was extracted with EtOAc. The aqueous layer was concentrated (15 Torr), and the solid residue was dissolved in MeOH (3 mL). Propylene oxide (1 mL) was added, and the mixture was again heated under reflux for 30 min. The solvent was evaporated and the residue was washed with a mixture of Et_2O /MeOH and filtered, affording **17** in 60% yield as a white solid. – M.p. 202–206 °C. – $[\alpha]_D^{25} = +67.1$ ($c = 1.0$, 2 *M* HCl). – ^1H NMR (500 MHz, D_2O): $\delta = 1.66$ (s, 3 H, CH_3CN), 2.95 (s, 3 H, CH_3N), 3.56 (d, $J = 8.9 \text{ Hz}$, 1 H, CHCN), 3.74 (dd, $J = 12.7, 8.9 \text{ Hz}$, 1 H, CHHN), 3.80 (m, 1 H, CHHN), 3.89 (dt, $J = 8.9, 2.4 \text{ Hz}$, 1 H, CHCH_2).

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- [1] A. Katritzky, A. F. Pozharskii, A. T. Soldatenkov, *Heterocycles in Life and Society*, Wiley, New York, **1997**, p. 158.
- [2] P. Remuzon, *Tetrahedron* **1996**, *52*, 13803–13835.
- [3] C. F. Wichmann, J. M. Liesch, R. E. Schwartz, *J. Antibiotics* **1989**, *42*, 168–173.
- [4] [4a] A. F. Parsons, *Tetrahedron* **1996**, *52*, 4149–4174. – [4b] J. E. Baldwin, A. M. Fryer, G. J. Pritchard, M. R. Spyvee, R. C. Whitehead, M. E. Wood, *Tetrahedron* **1998**, *54*, 7465–7484.
- [5] [5a] J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**. – [5b] F. J. Sordina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825–1872. – [5c] G. R. Stephenson, *Advanced Asymmetric Synthesis*, Chapman and Hall, London, **1996**.
- [6] [6a] J. W. Lown in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley-Interscience, New York, **1984**, vol. 1, p. 653. – [6b] O. Tsuge, S. Kanemasa, *Adv. Heterocycl. Chem.* **1989**, *45*, 231.

- [7] [7a] R. Grigg, *Chem. Soc. Rev.* **1987**, *16*, 89–121. – [7b] R. Grigg, V. Sridharan, *Advances in Cycloaddition*, JAI Press, Inc., Greenwich, **1993**, vol. 3, p. 161–204. – [7c] H. Waldmann, *Synlett* **1995**, 133–141. – [7d] R. Grigg, *Tetrahedron: Asymmetry* **1995**, *6*, 2475–2486. – [7e] B. Frigaderè, M. Pichon, *Tetrahedron: Asymmetry* **1996**, *7*, 927–964. – [7f] K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863–909. – [7g] C. P. Dell, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873–3905. – [7h] G. Brogini, G. Zecchi, *Synthesis* **1999**, 905–917. – [7i] T. Abellán, R. Chinchilla, N. Galindo, G. Guillena, C. Nájera, J. M. Sansano, *Targets in Heterocyclic Systems*, vol. 4 (Eds.: O. A. Attanasi, D. Spinelli), Italian Society of Chemistry, Camerino, **2001**.
- [8] R. Grigg, M. Thornton-Pett, J. Xu, L.-H. Xu, *Tetrahedron* **1999**, *55*, 13841–13866.
- [9] P. Deprez, J. Rouden, A. Chiaroni, C. Riche, J. Royer, H.-P. Husson, *Tetrahedron Lett.* **1991**, *32*, 7531–7534.
- [10] P. Deprez, J. Royer, H.-P. Husson, *Tetrahedron: Asymmetry* **1991**, *2*, 1189–1192.
- [11] S. Takano, M. Moriya, K. Ogasawara, *Tetrahedron: Asymmetry* **1992**, *3*, 681–684.
- [12] P. Garner, O. Dogen, *J. Org. Chem.* **1994**, *59*, 4–6.
- [13] P. Garner, W. B. Ho, H. Shin, *J. Am. Chem. Soc.* **1993**, *115*, 10742–10753.
- [14] J.-F. Peyronel, S. Grisoni, B. Carboni, T. Courgeon, R. Carrié, *Tetrahedron* **1994**, *50*, 189–198.
- [15] [15a] R. M. Williams, W. Zhai, D. J. Aldons, S. C. Aldons, *J. Org. Chem.* **1992**, *57*, 6527–6532. [15b] P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.
- [16] [16a] A. S. Anslow, L. M. Harwood, H. Phillips, D. Watkin, *Tetrahedron: Asymmetry* **1991**, *2*, 169–172. – [16b] A. S. Anslow, L. M. Harwood, H. Phillips, D. Watkin, *Tetrahedron: Asymmetry* **1991**, *2*, 997–1000. – [16c] A. S. Anslow, L. M. Harwood, H. Phillips, D. Watkin, L. F. Wong, *Tetrahedron: Asymmetry* **1991**, *2*, 1343–1358. – [16d] L. M. Harwood, J. Macro, D. Watkin, C. E. Williams, L. F. Wong, *Tetrahedron: Asymmetry* **1992**, *3*, 1127–1130. – [16e] L. M. Harwood, I. A. Lilley, *Tetrahedron Lett.* **1993**, *34*, 537–540. – [16f] L. M. Harwood, A. C. Manage, S. Robin, S. F. G. Hopes, D. Watkin, C. E. Williams, *Synlett* **1993**, 777–780. – [16g] L. M. Harwood, L. C. Kitchen, *Tetrahedron Lett.* **1993**, *34*, 6603–6606. [16h] J. E. Baldwin, T. McKenzie, M. G. Moloney, *Synlett* **1994**, 925–928. – [16i] A. S. Anslow, G. G. Cox, L. M. Harwood, *Chem. Heterocycl. Comp.* **1995**, *31*, 1222–1230. – [16j] A. S. Anslow, L. M. Harwood, I. A. Lilley, *Tetrahedron: Asymmetry* **1995**, *6*, 2465–2468. – [16k] L. M. Harwood, I. A. Lilley, *Tetrahedron: Asymmetry* **1995**, *6*, 1557–1560. – [16l] D. Alker, L. M. Harwood, C. E. Williams, *Tetrahedron* **1997**, *53*, 12671–12678. – [16m] D. Alker, L. M. Harwood, C. E. Williams, *Tetrahedron Lett.* **1998**, *39*, 475–478. – [16n] L. M. Harwood, S. M. Robertson, *Chem. Commun.* **1998**, 2641–2642. – [16o] D. Alker, G. Hamblet, L. M. Harwood, S. M. Robertson, D. Watkin, C. E. Williams, *Tetrahedron* **1998**, *54*, 6089–6098.
- [17] [17a] R. Chinchilla, L. R. Falvello, N. Galindo, C. Nájera, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 995–997. [17b] R. Chinchilla, N. Galindo, C. Nájera, *Tetrahedron: Asymmetry* **1998**, *9*, 2769–2772. [17c] R. Chinchilla, N. Galindo, C. Nájera, *Synthesis* **1999**, 704–717.
- [18] [18a] R. Chinchilla, L. R. Falvello, N. Galindo, C. Nájera, *Tetrahedron: Asymmetry* **1998**, *9*, 2223–2227. [18b] R. Chinchilla, L. R. Falvello, N. Galindo, C. Nájera, *Tetrahedron: Asymmetry* **1999**, *10*, 821–825. [18c] R. Chinchilla, L. R. Falvello, N. Galindo, C. Nájera, *J. Org. Chem.* **2000**, *65*, 3034–3041.
- [19] Preliminary communication at the 4th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4) (<http://reprints.net/ecsoc-4/a0022/a0022.htm>); uploaded July 30, **2000**.
- [20] V. Caplar, A. Lisini, F. Kajfez, D. Kolbah, V. Sunjic, *J. Org. Chem.* **1978**, *43*, 1355–1360.

- [21] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-156248. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
- [22] M. G. B. Drew, L. M. Harwood, D. W. Price, M.-S. Choi, G. Park, *Tetrahedron Lett.* **2000**, *41*, 5077–5081.
- [23] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209–220.
- [24] *CS Chem3D 4*, CambridgeSoft Corporation, Cambridge, USA, **1997**.
- [25] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian 98, Revision A.9*, Gaussian, Inc., Pittsburgh, PA, **1998**.
- [26] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- [27] A. P. Scott, L. Radom, *Phys. Chem.* **1996**, *100*, 16502–16513.

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