Diastereoselectivity in 1,3-Dipolar Cycloaddition Reactions between Indolic Nitrones and Electron-Deficient Alkenes

Lucedio Greci,*[a] Giampaolo Tommasi,[a] Paolo Bruni,[a] Paolo Sgarabotto,[b] and Lara Righi[b]

Keywords: Alkenes / Cycloadditions / Diastereoselectivity / Nitrogen heterocycles

2-Phenyl-3*H*-indol-3-one *N*-oxide (2-phenylisatogen), 2-phenyl-3-phenylimino-3*H*-indole *N*-oxide and 2-phenyl-3*H*-indole *N*-oxide (the tautomeric form of 1-hydroxy-2-phenylindole) reacted in refluxing toluene with maleimides with different substituents at the nitrogen, yielding 1,3-cycloaddition products. The cycloaddition was diastereoselective for the first two nitrones, whereas in the case of 2-phenyl-3*H*-indole *N*-oxide only the formation of the *endo* cycloadduct was observed. This different behaviour is attributed to the substituent at C-3 of the five-membered ring in the indole nucleus. In 95% ethanol at room temperature, metal cations such as Co^{II}, Cu^{II}, Ca^{II}, Mn^{II}, Zn^{II}, and Ni^{II} catalyse the reaction between 2-phenylisatogen and *N*-phenylmaleimide without substantially affecting the diastereoselectivity. The crystal structures of *endo*-3a,10,10a,10b-tetrahydro-10a-phenyl-1*H*-pyrrolo[3′,4′:4,5]isoxazolo[2,3-*a*]indole-1,3,10-trione (**5a**), *endo*-2-methyl-10a-phenyl-3a,10,10a,10b-tetrahydropyrrolo[3′,4′:4,5]isoxazolo[2,3-*a*]indole-1,3-dione (**8a**), and *endo*-2,10a-diphenyl-3a,10,10a,10b-tetrahydropyrrolo-[3′,4′:4,5]isoxazolo[2,3-*a*]indole-1,3-dione (**8b**) are reported.

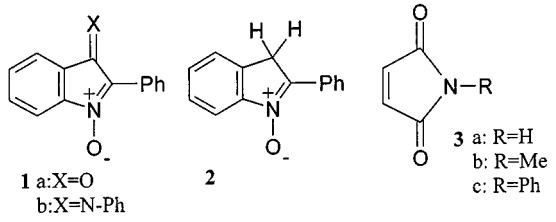
Introduction

The 1,3-dipolar cycloaddition reaction has been extensively utilised for the synthesis of five-membered heterocyclic rings.[1] The isoxazolidine adducts obtained can be converted into γ-amino alcohols, which are precursors of biologically important compounds such as β-lactam antibiotics.[2] During the past two decades, great effort has been dedicated to asymmetric 1,3-dipolar cycloaddition reactions, performed variously with chiral nitrones,[3] chiral olefins[4] or under catalytic conditions in the presence of optically active Lewis acids complexes.[5] A less common use of 1,3-dipolar cycloaddition, described in 1963, is for the trapping of unstable nitrones.[6] The coexistence of the cycloadduct and a free radical has been observed in a particular cycloaddition reaction.[7] To the best of our knowledge, however, relatively few studies have been performed on cyclic nitrones,[8] and − in particular − very few of them on indolic nitrones.[9] Here we report the achiral reactivity of 2-phenyl-3*H*-indol-3-one 1-oxide (**1a**), 2-phenyl-3*H*-indol-3-phenylimino 1-oxide (**1b**) and 2-phenyl-3,3-dihydro-3*H*-indole 1-oxide (**2**) with three *N*-substituted maleimides **3**. The catalytic effect of different metal ions is described, while the crystal structures of three cycloadducts are also reported.

[a] Dipartimento di Scienze dei Materiali e della Terra, Università, via Brecce Bianche, 60131 Ancona, Italy
Fax: (internat.) +39 071/2204714
E-mail: greci@popcsi.unian.it
[b] Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica, Università, Viale delle Scienze, I-43100 Parma, Italy

Results and Discussion

Treatment of nitrones **1** and **2** with maleimides **3** (Scheme 1) was performed in refluxing toluene using a 1:4 molar ratio; the cycloadducts produced were isolated by column chromatography. With 2-phenylisatogen **1a** and **3c**, no reaction was observed after 8 days in toluene at room temperature, but the same treatment in the presence of metal ions [(Ca^{II}, Mg^{II}, Zn^{II}, Ni^{II}, Cu^{II}, Co^{II}] produced mixtures of the *exo* (**4c**) and *endo* (**5c**) cycloadducts (Table 1). The products of the reactions between **1a/1b** and **3** are reported in Scheme 2. The structure of compound **5a** was confirmed by X-ray analysis (Figure 1). Treatment of nitrone **1b** with maleimides **3** also produced pairs of diastereomeric cycloadducts. In particular, nitrone **1b** and maleimides **3a−c** afforded cycloadducts **6a−c** and **7a−c**. Nitrone **2**, which is one of the two tautomeric forms of 1-hydroxy-2-phenylindole,[10] gave the cycloadducts **8a** and **8b**, together with compound **9**. In this last case, only the *endo* cycloadducts were obtained and the structures were established by X-ray analysis (Figure 2); the presence of the *exo* form was ruled out by direct analysis of the crude reaction mixture by ^{1}H NMR (see Exp. Section). The conditions for all the above reactions are summarised in Table 1. All prod-



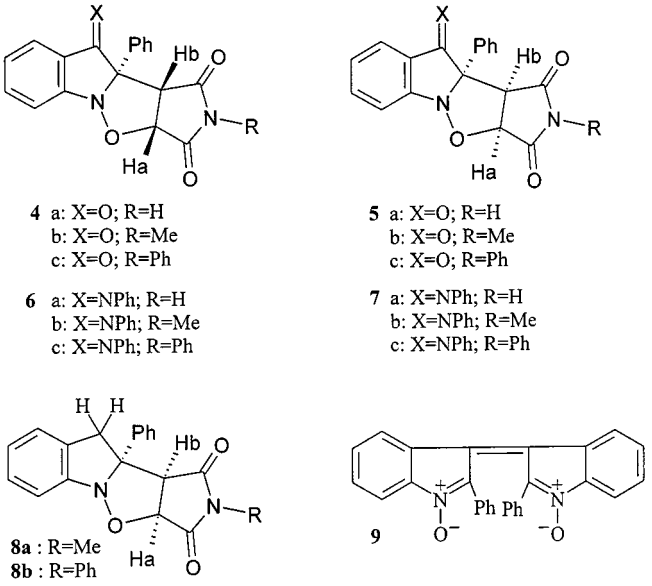
Scheme 1

  1434−193X/01/0816−3147 $ 17.50+.50/0

Table 1. Experimental data for all the reactions performed

Entry	Reagents	Solvent	*T* [°C]	*t* [h]	Conversion [%][a]	*exo*/*endo* [%]	Metal ion[II]
1	**1a**+**3c**	toluene	room temp.	8 days	≈0 (0)	–	–
2	**1a**+**3c**	EtOH[b]	reflux	70	91 (84)	56/44	–
3	**1a**+**3a**	toluene	reflux	20	90 (79)	52/48	–
4	**1a**+**3b**	toluene	reflux	20	96 (92)	74/26	–
5	**1a**+**3c**	toluene	reflux	20	95 (85)	58/42	–
6	**1b**+**3a**	toluene	reflux	6	73 (71)	91/9	–
7	**1b**+**3b**	toluene	reflux	6	94 (86)	90/10	–
8	**1b**+**3c**	toluene	reflux	6	89 (75)	100/0	–
9	**2**+**3a**	toluene	reflux	72	18 (0)	–	–
10	**2**+**3b**	toluene	reflux	72	30 (18)	0/100	–
11	**2**+**3c**	toluene	reflux	72	32 (21)	0/100	–
12	**1a**+**3c**	EtOH[b]	room temp.	48	30 (100)	47/53	Co[c]
13	**1a**+**3c**	EtOH[b]	room temp.	48	27 (100)	51/49	Cu[d]
14	**1a**+**3c**	EtOH[b]	room temp.	48	25(100)	52/48	Cu[c]
15	**1a**+**3c**	EtOH[b]	room temp.	48	19 (100)	49/51	Ca[e]
16	**1a**+**3c**	EtOH[b]	room temp.	48	29 (100)	50/50	Mn[e]
17	**1a**+**3c**	EtOH[b]	room temp.	48	22 (100)	47/53	Mn[c]
18	**1a**+**3c**	EtOH[b]	room temp.	48	12 (100)	49/51	Zn[e]
19	**1a**+**3c**	EtOH[b]	room temp.	48	23 (100)	59/41	Ni[c]
20	**1a**+**3c**	EtOH[b]	room temp.	48	≈0 (0)	–	–

[a] The sum of the yields for the two cycloadducts is reported in parenthesis; the remaining percentage is accounted for by the starting materials and unanalysed by-products. – [b] 95% EtOH. – [c] Acetate. – [d] Nitrate. – [e] Chloride.



Scheme 2

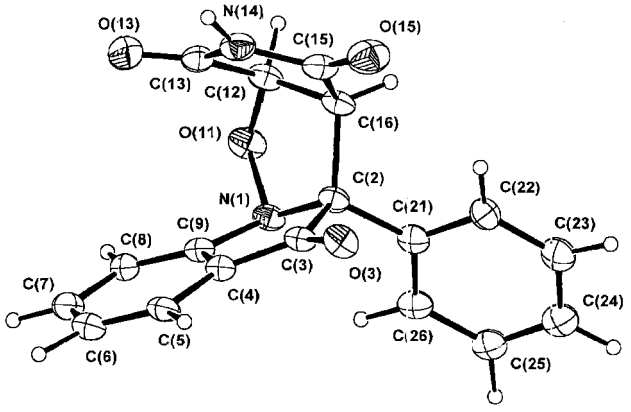


Figure 1. ORTEP view of compound **5a**, the thermal ellipsoids are given at 50% probability

ucts were identified by comparison of their spectroscopic data (^{1}H NMR, IR, MS) with those of the compounds examined by X-ray analysis.

No reaction took place between 2-phenylisatogen **1a** and maleimide **3c** at room temperature, but the isoxazolidines **4c** and **5c** were obtained on refluxing. It has been reported[11] that nitrones may show two different reactivities, originating from the dominant form of polarisation [the direct (**10**) and the back one (**11**)], working under thermodynamic or kinetic conditions, respectively (Scheme 3). It has also been postulated that other canonical forms are irrelevant for these reactions.[12] The lack of reactivity at room temperature is probably due to the low contribution from structure **11**. The *exo*/*endo* ratio of the diastereomeric mixture of **4** and **5** (Table 1) was determined by chromatographic isolation of both compounds, but it can also be calculated from the relative integrals of the ^{1}H NMR spectra signals (Figure 3). The pattern shown in Figure 3 is followed by all cycloadducts **4** and **5**. To explain this trend, the structures of **4a** and **5a** were simulated with a molecular modelling program, optimising the geometry by the PM3 semiempirical method (Figure 4).[13] The calculated structure **5a** was sufficiently close to that obtained by X-ray analysis (Figure 1) to allow us to calculate the interatomic distances in compound **4a** directly with the molecular modelling program. The approximated distances between H_A (and H_B) and the centre of the nearest aromatic ring were calculated for both structures (Table 2) and their values appear very close to those measured in the structures deter-

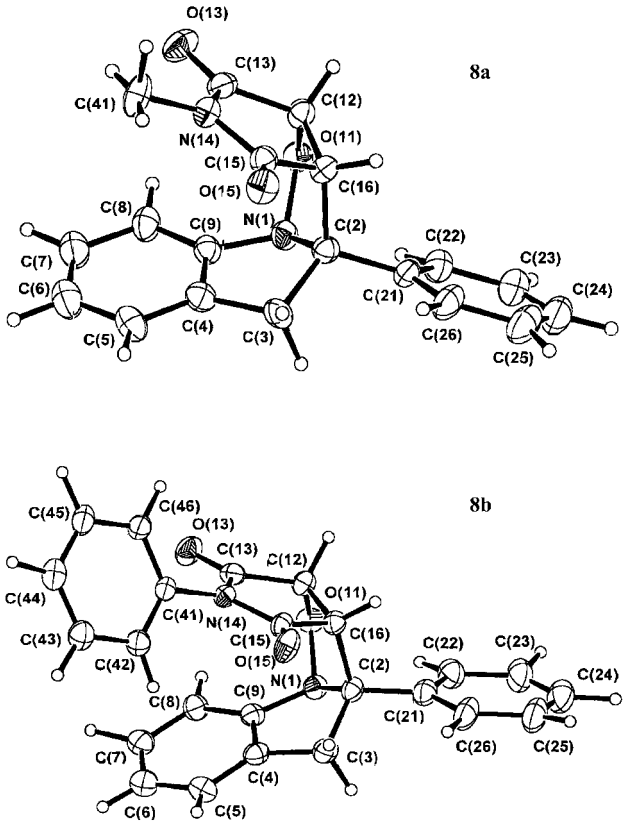
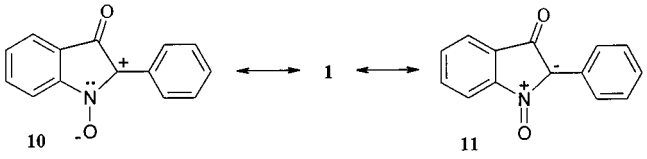


Figure 2. ORTEP views of compounds **8a** and **8b**, the thermal ellipsoids are given at 50% probability

mined by X-ray analysis. H_A in the *exo* structure is nearer to the aromatic shielding cone than its counterpart in the *endo* structure, so the signal of the former falls at a much higher field; the opposite is the case for H_B, fully explaining the NMR pattern described above. Similar calculations gave the same results for the pairs **4b−5b** and **4c−5c**.



Scheme 3

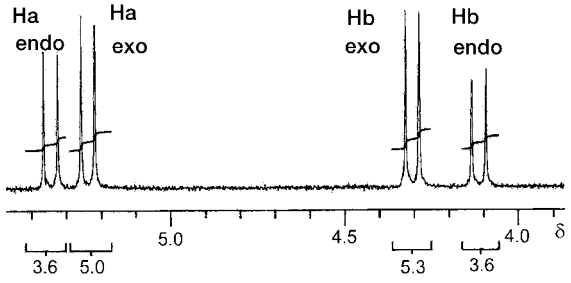


Figure 3. Portion of the ^1H NMR spectrum of a mixture of **4a** and **5a** (from the reaction **1a**+**3a**)

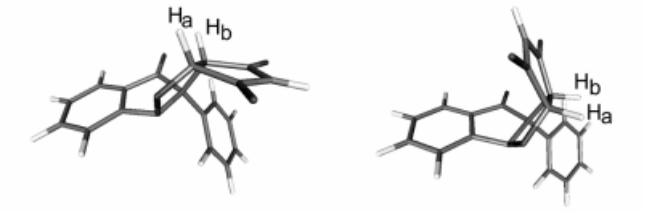


Figure 4. PM3-optimised structures of compounds **4a** (left) and **5a** (right)

Table 2. Distances [Å] between H_A (and H_B) and the centre of the nearest aromatic ring, calculated for compounds **4a** (*exo*) and **5a** (*endo*)

Proton diastereomer	Distance H···aromatic ring [Å]
H_A-*exo*	5.01 [5.42(4)][a]
H_B-*exo*	4.92 [3.52(3)][a]
H_A-*endo*	5.15
H_B-*endo*	3.50

[a] Values measured in the X-ray structure **5a**.

The reaction between nitrone **1a** and **3c**, carried out at room temperature in 95% EtOH and in the presence of stoichiometric amounts of several bivalent metal ions (Table 1, entries 12−20), also afforded the diastereomers **4c** and **5c**, although at lower degrees of conversion than under thermal reaction conditions. The metal ions and their counterions did not affect the diastereoselectivity observed in the thermal reactions (see Table 1); lower concentrations of metal ion only decreased the degree of conversion. It is noteworthy that the reaction did not occur at all in absolute ethanol; this could well be due to better solvation of the anions by water, leaving the cations more free. However, on the basis of these findings it appears impossible to explain the mechanism of the last reactions, because either or both reactants may act as ligand on the metal complex.[14]

Treatment of nitrone **1b** with maleimides **3** also gave pairs of cycloadducts (isoxazolidines **6** and **7**), with a higher diastereoselectivity than observed in the reaction between **1a** and **3c**. The reasons for this behaviour may probably be attributed to the different groups at C-3 in compounds **1a** and **1b**: the more hindered phenylimino group in compound **1b** might favour the formation of the *endo* form.

As previously reported,[10] nitrone **2** is the tautomeric form of 1-hydroxy-2-phenylindole; the ratio of the two forms is solvent-dependent. In toluene − the choice of solvent being dictated by kinetic demands − the nitronic form is less than 20%; the reaction, which was very slow, was performed under argon to minimise the oxidation side reaction, producing compound **9**.[15]

Molecular Geometry of Compounds 5a, 8a, and 8b

Selected bond lengths and angles for the three derivatives are listed in Table 3. The arbitrary numbering scheme used in the crystal analysis is shown in Figure 1 and Figure 2, which represent perspective views of compounds **5a** and **8a**, **8b**, respectively.

Table 3. Selected bond lengths [Å] and angles [°] with esd values in parentheses

	5a	8a	8b
O(3)−C(3)	1.214(3)		
O(11)−N(1)	1.449(4)	1.446(4)	1.449(4)
O(11)−C(12)	1.431(5)	1.444(5)	1.434(4)
O(13)−C(13)	1.195(4)	1.217(5)	1.203(4)
O(15)−C(15)	1.201(4)	1.205(5)	1.209(4)
N(1)−C(2)	1.489(4)	1.486(5)	1.484(4)
N(1)−C(9)	1.427(4)	1.423(5)	1.428(4)
N(14)−C(13)	1.389(5)	1.371(5)	1.386(4)
N(14)−C(15)	1.376(4)	1.389(5)	1.400(4)
C(2)−C(3)	1.569(4)	1.552(6)	1.543(5)
C(2)−C(16)	1.575(6)	1.574(6)	1.581(4)
C(3)−C(4)	1.451(3)	1.501(6)	1.511(5)
C(4)−C(9)	1.387(4)	1.379(6)	1.382(5)
C(12)−C(13)	1.536(5)	1.506(5)	1.529(5)
C(12)−C(16)	1.502(5)	1.522(5)	1.520(5)
C(15)−C(16)	1.517(5)	1.505(5)	1.515(5)
N(1)−O(11)−C(12)	105.7(2)	106.3(2)	106.7(2)
O(11)−N(1)−C(2)	108.5(2)	106.7(2)	106.6(2)
C(2)−N(1)−C(9)	107.9(2)	113.0(3)	105.6(2)
C(13)−N(14)−C(15)	114.3(3)	112.7(3)	112.6(3)
N(1)−C(2)−C(3)	103.4(2)	102.4(3)	103.1(3)
N(1)−C(2)−C(16)	104.7(3)	102.8(3)	102.9(2)
C(2)−C(3)−C(4)	106.6(2)	102.5(3)	102.1(3)
C(3)−C(4)−C(9)	109.0(2)	108.7(4)	108.7(3)
N(1)−C(9)−C(4)	112.0(2)	110.8(3)	110.6(3)
O(11)−C(12)−C(16)	108.1(3)	107.4(3)	107.9(2)
C(13)−C(12)−C(16)	104.6(3)	105.6(3)	105.5(3)
N(14)−C(13)−C(12)	105.3(3)	108.2(3)	107.8(3)
N(14)−C(15)−C(16)	107.1(3)	108.9(3)	108.9(3)
C(2)−C(16)−C(12)	102.9(3)	104.3(4)	104.0(2)
C(12)−C(16)−C(15)	104.0(3)	103.9(3)	104.5(3)

The intramolecular bond lengths and angles are in agreement with the expected hybridization for the atoms involved and in reasonable agreement with those reported in the literature for analogous compounds in which the isoxazole and pyrrole rings are adjacent,[16,17] in particular with 3-(2-acetoxy-1-hydroxyethyl)-3,6-dimethyl-dipyrrolidino-[1,2-*b*][3′,4′-*d*]isoxazole-5,7-dione of ref.[18], in which the same system of three condensed rings is present, although in the *exo* conformation.

The main differences between the three derivatives lie in the bond length and angles in the five-membered ring of the indole nucleus, as a consequence of the different hybridizations of the carbon atom in position 3, this being sp^2 in **5a** and sp^3 in **8a** and **8b**. This fact is also responsible for the minor deviation from coplanarity observed in the pyrrole ring of **5a**. For the three compounds, the system of the three condensed five-membered rings adopts the *endo* conformation, giving rise to considerable overlapping; this, as far we are aware, is the first example reported in the literature. The dihedral angles formed by the mean planes of the indolic pyrrole and the succinimide moieties with respect to the isoxazole rings are 65.8(1), 72.6(1), 69.6(1) and 69.1(1), 68.2(2), 69.4(1)° in **5a**, **8a**, **8b**, respectively.

In the three compounds, the five-membered rings are all non-planar and their deviation from planarity is considerable (χ^2 is 1221, 6104, 9997 for the indolic pyrrole rings; 9560, 12305, 13697 for the isoxazole rings and 3617, 387, 1000 for the succinimide rings for **5a**, **8a**, **8b** respectively); the Cremer and Pople parameters[18] show that the conformations adopted by these rings are *envelope* for the indolic pyrrole systems in **8a** and **8b** and for the succinimide in **8b**; *twist* for the succinimide systems in **5a** and **8a** and for the isoxazole in **5a**; and intermediate *envelope-twist* for the others.

In **5a**, molecular packing is determined by a long intermolecular hydrogen bond of the N−H···O type, bridging the imine N(14) and the carbonyl O(3) in the $1 - x$, $1 - y$, $-z$ position: N(14)···O(3) 3.048(4), H(14)···O(3) 2.23(4) Å; N(14)−H(14)···O(3) 161(4)°. Other contacts in the three derivatives are consistent with van der Waals interactions.

Conclusion

The results of treatment of nitrones **1a** and **1b** with maleimides **3** show that the formation of the *exo* adduct is favoured with respect to the *endo* one, while the same treatment with the nitrone **2** gives only the *endo* form. A likely explanation for this behaviour might be found in a different molecular approach of the reagents: in fact, when the two molecules come close to each other to form the *endo* adduct and the atoms involved in the cycloaddition are at bond length, the carbonyl oxygen of the dipolarophile is also at bond length with the atom of C-3 of the dipole. Thus, in the case of nitrone **1b**, in which a phenylimino group is present at C-3, the *endo* form is disfavoured, due to steric hindrance. The fact that nitrone **2** only affords the *endo* cycloadduct could be due to the presence of two hydrogens at C-3, which might in some way favour the transition state leading to the *endo* product.

It has been reported that some alkoxyamines may be effective as initiators and regulators in free radical polymerisation, through thermal cleavage of the oxygen-carbon bond.[19] The possible use of all the synthesised cycloadducts **4−8** bearing alkoxyaminic bonds in this field is currently under investigation.

Experimental Section

Melting points are uncorrected and were measured with an electrothermal apparatus. − IR solid-state spectra were measured on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer equipped with a Spectra Tech. "Collector" for DRIFT measurements. − ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ or C_6D_6 solution on a Varian Gemini 200 spectrometer (TMS was taken as reference peak). − Mass spectra were recorded on a Carlo Erba QMD 1000 mass spectrometer, equipped with a Fisons GC 8060 gas chromatograph.

Compounds **1a**,[20] **1b**,[21] and **3**[22] were synthesised and purified according to literature methods. Maleimides **3**, $Co(OCOCH_3)_2{\cdot}4H_2O$, $Cu(OCOCH_3)_2{\cdot}H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$, $CaCl_2{\cdot}2H_2O$, $Mn(OCOCH_3){\cdot}4H_2O$, $MnCl_2$, $ZnCl_2$, $Ni(OCOCH_3)_2{\cdot}4H_2O$, toluene, and absolute ethanol were pur-

chased from Aldrich and used without further purification; 95% and 90% ethanol was prepared from absolute ethanol by addition of water.

Treatment of 2-Phenyl-3*H*-indol-3-one 1-Oxide (1a) and 2-Phenyl-3*H*-indol-3-phenylimino 1-Oxide (1b) with Maleimides. − General Procedure: Table 1 reports the different experimental conditions and appropriate parameters. Compounds **1a** or **1b** (0.45 mmol) and **3** (1.8 mmol) were dissolved in the appropriate solvent (30 mL) and allowed to react under the conditions given. The reaction mixtures were evaporated to dryness: the crude residue was analysed by ^{1}H NMR in $CDCl_3$ in order to measure the degree of conversion and the ratio of the two diastereomers (see Figure 3) and then washed with ethyl ether (3 × 10 mL) and filtered. The resulting solids were chromatographed on a silica column, using cyclohexane/ethyl acetate in 7:3 ratio, and the *exo* and the *endo* products were obtained in that order of elution. The products were crystallised from ethanol: yields are shown in Table 1, while specific analytical data are reported below.

Compound 4a: M.p. 202 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.18 (d, *J* = 8.0 Hz, 1 H), 5.10 (d, *J* = 8.0 Hz, 1 H), 7.48 (m, 5 H,), 7.66 (m, 3 H,), 7.83 (d, *J* = 7.6 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3220 (N−H), 3075, 2996, 1787, 1733, 1461, 1383. − MS (EI^+): *m*/*z* = 320 (4) [M^+], 292 (5), 223 (44), 179 (70), 97 (34), 77 (86). − $C_{18}H_{12}N_2O_4$ (320.296): calcd. C 67.49, H 3.78, N 8.75; found C 67.56, H 3.85, N 8.61.

Compound 5a: M.p. 197 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.04 (d, *J* = 7.8 Hz, 1 H), 5.09 (d, *J* = 7.8 Hz, 1 H), 7.40 (m, 5 H,), 7.70 (m, 3 H,), 7.88 (d, *J* = 7.7 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3222 (N−H), 3070, 2981, 1790, 1730, 1473, 1380. − MS (EI^+): *m*/*z* = 320 (5) [M^+], 292 (15), 223 (90), 179 (100), 97 (50), 77 (80). − $C_{18}H_{12}N_2O_4$ (320.296): calcd. C 67.49, H 3.78, N 8.75; found C 67.45, H 3.60, N 8.58.

Compound 4b: M.p. 212 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.45 (s, 3 H, CH_3), 4.13 (d, *J* = 7.7 Hz, 1 H), 5.06 (d, *J* = 7.7 Hz, 1 H), 7.21 (d, *J* = 7.7 Hz, 1 H), 7.48 (m, 5 H,), 7.84 (d, *J* = 7.5 Hz, 1 H), 7.95 (d, *J* = 7.1 Hz, 1 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3071, 2996, 1758, 1724, 1454, 1375. − MS (EI^+): *m*/*z* = 334 (3) [M^+], 318 (4), 248 (4), 223 (6), 207 (38), 179 (100), 111 (18). − $C_{19}H_{14}N_2O_4$ (334.322): calcd. C 68.25, H 4.22, N 8.38; found C 68.15, H 4.38, N 8.12.

Compound 5b: M.p. 207 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.68 (s, 3 H, CH_3), 3.99 (d, *J* = 8.1 Hz, 1 H), 6.00 (d, *J* = 8.1 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.50 (m, 5 H,), 7.90 (d, *J* = 7.7 Hz, 1 H), 8.02 (d, *J* = 7.2 Hz, 1 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3033, 2960, 1784, 1720, 1450, 1381. − MS (EI^+): *m*/*z* = 334 (15) [M^+], 318 (10), 248 (17), 223 (90), 207 (92), 179 (80), 111 (23). − $C_{19}H_{14}N_2O_4$ (334.322): calcd. C 68.25, H 4.22, N 8.38; found C 68.35, H 4.12, N 8.47.

Compound 4c: M.p. 210 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.29 (d, *J* = 7.8 Hz, 1 H), 5.22 (d, *J* = 7.8 Hz, 1 H), 6.51 (m, 1 H,), 7.32 (m, 5 H,), 7.47 (m, 5 H,), 7.68 (q, *J* = 9.0 Hz, 2 H), 7.89 (1 H, td, *J* = 6.6, 1.8 Hz). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3060, 1783, 1729, 1457, 1384. − MS (EI^+): *m*/*z* = 396 (6) [M^+], 380 (2), 367 (16), 248 (21), 223 (18), 208 (57), 179 (100), 173 (26), 119 (50). − $C_{24}H_{16}N_2O_4$ (396.388): calcd. C 72.72, H 4.07, N 7.07; found C 72.61, H 3.94, N 7.24.

Compound 5c: M.p. 203 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.10 (d, *J* = 8.2 Hz, 1 H), 5.32 (d, *J* = 8.2 Hz, 1 H), 6.60 (m, 1 H,), 7.28 (m, 5 H,), 7.40 (m, 5 H,), 7.73 (m, 2 H,), 8.06 (m, 1 H,). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3065, 1740, 1728, 1462, 1387. − MS (EI^+): *m*/*z* = 396 (100) [M^+], 380 (4), 367 (91), 248 (50), 223 (65), 208 (41), 179 (32), 173 (31), 119 (18). − $C_{24}H_{16}N_2O_4$ (396.388): calcd. C 72.72, H 4.07, N 7.07; found C 72.81, H 4.24, N 7.23.

Compound 6a: M.p. 230 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.32 (d, *J* = 7.9 Hz, 1 H), 5.05 (d, *J* = 7.9 Hz, 1 H), 6.30 (d, *J* = 7.9 Hz, 1 H), 6.86 (d, *J* = 7.2 Hz, 2 H), 7.11 (t, *J* = 7.9 Hz, 1 H), 7.36 (m, 8 H,), 7.72 (1 H), 7.89 (d, *J* = 7.9 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3218 (N−H), 3101, 2970, 1712, 1450, 1380. − MS (EI^+): *m*/*z* = 395 (2) [M^+], 298 (72), 282 (76), 267 (100), 205 (26), 97 (48). − $C_{24}H_{17}N_3O_3$ (395.406): calcd. C 72.90, H 4.33, N 10.63; found C 72.80, H 4.44, N 10.82.

Compound 7a: M.p. 221 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.52 (d, *J* = 7.6 Hz, 1 H), 5.18 (d, *J* = 7.6 Hz, 1 H), 6.34 (d, *J* = 8.1 Hz, 1 H), 6.84 (d, *J* = 7.3 Hz, 2 H), 7.20 (m, 8 H,), 7.60 (1 H), 7.90 (d, *J* = 8.1 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3199 (N−H), 3066, 2940, 1718, 1457, 1385. − MS (EI^+): *m*/*z* = 395 (18) [M^+], 298 (90), 282 (83), 267 (95), 205 (50), 97 (53). − $C_{24}H_{17}N_3O_3$ (395.406): calcd. C 72.90, H 4.33, N 10.63; found C 72.80, H 4.56, N 10.54.

Compound 6b: M.p. 242 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.40 (s, 3 H, CH_3), 4.27 (d, *J* = 7.6 Hz, 1 H), 5.01 (d, *J* = 7.6 Hz, 1 H), 6.34 (d, *J* = 8.0 Hz, 1 H), 6.77 (t, *J* = 7.4 Hz, 1 H), 6.90 (d, *J* = 8.1 Hz, 2 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.38 (m, 7 H,), 7.91 (d, *J* = 8.1 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3062, 2962, 1710, 1444, 1380. − MS (EI^+): *m*/*z* = 409 (4) [M^+], 381 (32), 324 (5), 298 (60), 282 (68), 111 (50). − $C_{25}H_{19}N_3O_3$ (409.432): calcd. C 73.33, H 4.68, N 10.26; found C 73.39, H 4.82, N 10.12.

Compound 7b: M.p. 238 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.79 (s, 3 H, CH_3), 4.46 (d, *J* = 7.8 Hz, 1 H), 5.16 (d, *J* = 7.8 Hz, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 6.80 (t, *J* = 7.5 Hz, 1 H), 6.95 (d, *J* = 8.2 Hz, 2 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 7.43 (m, 7 H,), 8.01 (d, *J* = 8.2 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3070, 2950, 1778, 1448, 1382. − MS (EI^+): *m*/*z* = 409 (3) [M^+], 381 (8), 324 (6), 298 (27), 282 (100), 205 (47), 111 (33). − $C_{25}H_{19}N_3O_3$ (409.432): calcd. C 73.33, H 4.68, N 10.26; found C 73.21, H 4.55, N 10.34.

Compound 6c: M.p. 244 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.46 (d, *J* = 8.0 Hz, 1 H), 5.19 (d, *J* = 8.0 Hz, 1 H), 6.40 (d, *J* = 8.2 Hz, 1 H), 6.49 (m, 2 H,), 6.85 (d, *J* = 7.5 Hz, 2 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 7.30 (m, 4 H,), 7.44 (m, 5 H,), 7.52 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 7.5 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3062, 2960, 1718, 1672 (C=N), 1454, 1394. − MS (EI^+): *m*/*z* = 471 (3) [M^+], 443 (20), 323 (33), 298 (30), 282 (57), 205 (41), 173 (64). − $C_{30}H_{21}N_3O_3$ (471.498): calcd. C 76.42, H 4.49, N 8.91; found C 76.54, H 4.33, N 9.12.

Treatment of 2-Phenyl-3*H*-indole-3-one 1-Oxide (1a) with Maleimide (3c) in the Presence of Bivalent Metal Ions: Compounds **1a** (0.1 mmol) and **3c** (0.1 mmol) and the bivalent metal ion (0.1 mmol) were stirred at room temperature in 5 mL of 95% EtOH for 48 h. The solvent was evaporated and the residue, dried under vacuum, was analysed by ^{1}H NMR in $CDCl_3$. The ratio of the *endo* and the *exo* forms and the degree of conversion of the reagents were evaluated by signal integration.

The reactions carried out with lower concentrations of metal ion showed a proportional decrease in the degree of conversion of the reagents.

Treatment of 2-Phenyl-3*H*-indol 1-Oxide (2) with Maleimides 3b and 3c: Compounds **2** (9.6 mmol) and **3** (10.4 mmol) were dissolved in

toluene (40 mL) and the reaction mixtures were refluxed under Ar for 72 h. The solutions were evaporated to dryness and the crude residues washed with ethyl ether (5 × 10 mL). The resulting white solids **8a** and **8b** were crystallised from ethanol. The filtrates were evaporated to dryness and the residues were first analysed by ^{1}H NMR in $CDCl_3$ and then chromatographed on a silica column, using cyclohexane/ethyl acetate in 7:3 ratio; *bis*-nitrone **9** was eluted first, followed by small amounts of the cycloadducts **8a** and **8b**.

Compound 8a: M.p. 157 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.34 (s, 3 H, CH_3), 3.11 (d, 1 H, H−C-3, J = 15.7 Hz), 3.79 (d, 1 H, Hb, J = 7.9 Hz), 4.27 (d, 1 H, H−C-3, J = 15.7 Hz), 4.91 (d, 1 H, Ha, J = 7.9 Hz), 6.98 (t, 1 H, arom, J = 7.5 Hz), 7.22 (m, 3 H, arom), 7.42 (m, 3 H, arom), 7.66 (d, 2 H, arom, J = 8.2 Hz). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3070, 2987, 1705, 1465, 1377. − MS (EI^+): m/z = 320 (41) [M^+], 209 (100), 193 (64), 111 (7). − $C_{19}H_{16}N_2O_3$ (320.338): calcd. C 71.23, H 5.03, N 8.75; found C 71.30, H 5.14, N 8.94.

Compound 8b: M.p. 168 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 3.16 (d, 1 H, H−C-3, J = 16.0 Hz), 3.98 (d, 1 H, Hb, J = 8.2 Hz), 4.38 (d, 1 H, H−C-3, J = 16.0 Hz), 5.07 (d, 1 H, Ha, J = 8.2 Hz), 6.50 (dd, 2 H, J = 7.5, 1.1 Hz), 7.11 (m, 2 H, arom), 7.30 (m, 5 H, arom), 7.45 (t, 3 H, arom, J = 7.5 Hz) 7.70 (d, 2 H, arom, J = 7.8 Hz). − IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3072, 2971, 1706, 1465, 1386. − MS (EI^+): m/z = 382 (8) [M^+], 209 (80), 191 (92), 173 (100). − $C_{19}H_{16}N_2O_3$ (382.404): calcd. C 75.37, H 4.74, N 7.33; found C 75.28, H 4.91, N 7.21.

Crystal Structures of *endo*-3a,10,10a,10b-Tetrahydro-10a-phenyl-1*H*-pyrrolo[3′,4′:4,5]isoxazolo[2,3-*a*]indole-1,3,10-trione (5a), *endo*-3a,10,10a,10b-Tetrahydro-2-methyl-10a-phenylpyrrolo-[3′,4′:4,5]isoxazolo[2,3-*a*]indole-1,3-dione (8a), and *endo*-3a,10,10a,10b-Tetrahydro-2,10a-diphenylpyrrolo[3′,4′:4,5]isoxazolo[2,3-*a*]-indole-1,3-dione (8b): Table 4 shows the experimental and crystallographic data for **5a**, **8a**, and **8b**. The intensities I_{hkl} were determined at room temperature on a Siemens AED single-crystal diffractometer by analysing the reflection profiles with the Lehmann and Larsen procedure.[26] One standard reflection was measured every 100 collected reflections to monitor crystal decomposition and instrumental linearity, and showed no significant variations. Corrections for Lorentz and polarization effects were performed; there were no corrections for absorption effects. The structures were solved by direct methods and refined by cycles of full-matrix anisotropic least-squares; the hydrogen atoms were located in the difference map and isotropically refined.

Atomic scattering factors were from the International Tables for X-ray Crystallography.[27] Bibliographic searches were carried out using the Cambridge Structural Database Files through the Servizio Italiano di Diffusione Dati Cristallografici, Parma, Italy.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-162155−162157. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44(1223) 336-033; E-mail: teched@chemcrys.cam.ac.uk].

Acknowledgments

We thank the Italian MURST and the University of Ancona for financial support.

Table 4. Experimental data for the X-ray diffraction studies on crystalline compounds **5a**, **8a**, and **8b**

Compound	6a	8a	8b
empirical formula	$C_{18}H_{12}N_2O_4$	$C_{19}H_{16}N_2O_3$	$C_{24}H_{18}N_2O_3$
formula mass	320.3	320.3	382.4
cryst. syst.	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$
cell parameters at 295 K			
a [Å]	8.477(3)	21.882(16)	11.113(5)
b [Å]	11.882(7)	11.010(7)	6.957(2)
c [A]	7.297(3)	6.623(5)	24.717(14)
α [deg]	106.00(6)	90	90
β [deg]	99.00(5)	93.90(8)	99.01(6)
γ [deg]	85.89(5)	90	90
V [Å^3]	697.5(6)	1591.9(19)	1887.4(16)
Z	2	4	4
d_{calc} [g·cm^{-3}]	1.53	1.34	1.35
crystal dimensions [mm]	0.17 × 0.24 × 0.58	0.31 × 0.32 × 0.62	0.23 × 0.27 × 0.49
linear abs. coeff [cm^{-1}]	9.14	7.48	7.26
unique total data	2615	3446	3985
criterion of observation	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
unique observed data (NO)	1843	1598	1948
no. of refined parameters (NV)	265	281	334
overdetermination ratio (NO/NV)	7.0	5.7	5.8
R	0.052	0.050	0.044
R_w	0.059	0.061	0.051
GOF	4.603	0.684	1.024
largest shift/esd	0.656	0.683	0.756
largest peak [e·Å^{-3}]	0.231	0.255	0.219
programs	[a]	[a]	[a]

[a] SIR97,[23] SHELX76,[24] PARST[25]; $R = \Sigma|\Delta F|/\Sigma|F_o|$, $R_w = [\Sigma w(\Delta F^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, GOF = $[\Sigma w|\Delta F|^2/(NO-NV)]^{1/2}$.

[1] [1a] K. B. Jensen, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **1999**, *64*, 2353. – [1b] K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863.
[2] [2a] *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2 (Ed.: A. Padwa), John Wiley & Sons, New York, **1984**. – [2b] K. B. G. Torsell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH Publisher, New York, **1988**.
[3] [3a] C. Mukai, I. J. Kim, W. J. Cho, M. Kido, M. J. Hanaoka, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2495. – [3b] S. Saito, T. Ishikawa, K. Kishimoto, T. Kohara, T. Moriwake, *Synlett* **1994**, 282. – [3c] A. Brandi, S. Cicchi, A. Goti, *J. Org. Chem.* **1994**, *59*, 1315. – [3d] L. A. G. M. van den Broek, *Tetrahedron* **1995**, *52*, 4467. – [3e] G. Broggini, F. Folcio, N. Sardone, M. Sonzogni, G. Zecchi, *Tetrahedron: Asymmetry* **1996**, *7*, 797.
[4] [4a] A. Brandi, S. Cicchi, A. Goti, K. M. Pietrusiewicz, M. Zablocka, W. Wieniewski, *J. Org. Chem.* **1991**, *56*, 4383. – [4b] T. Takahashi, A. Fujii, J. Sugita, T. Hagi, K. Kitano, Y. Arai, T. Koizumi, *Tetrahedron: Asymmetry* **1991**, *2*, 1379. – [4c] M. Iyo, M. Maeda, C. Kibayashi, *Tetrahedron Lett.* **1992**, *33*, 3765. – [4d] P. Bravo, L. Bruchè, A. Farina, G. Fronza, S. V. Meille, A. Merli, *Tetrahedron: Asymmetry* **1993**, *4*, 2131. – [4e] H. Ina, M. Ito, C. Kibayashi, *J. Org. Chem.* **1996**, *61*, 1023.
[5] [5a] K. V. Gothelf, K. A. Jorgensen, *J. Chem. Soc. Chem. Comm.* **2000**, *16*, 1449. – [5b] K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863. – [5c] K. V. Gothelf, K. A. Jorgensen, *Acta Chem. Scand.* **1996**, *50*, 652. – [5d] K. Hori, H. Kodama, T. Ohata, I. Furukawa, *J. Org. Chem.* **1999**, *64*, 5017.
[6] H. E. De La Mare, G. M. Coppinger, *J. Org. Chem.* **1963**, *28*, 1068.
[7] H. Sang, E. G. Janzen, J. L. Poyer, *J. Chem. Soc., Perkin Trans. 2* **1996**, 1183.
[8] [8a] A. Ali, M. I. M. Wazeer, *Tetrahedron* **1993**, *49*, 4339. – [8b] P. de March, M. Figueredo, J. Font, S. Milán, A. Alvarez-Larena, J. F. Piniella, E. Molins, *Tetrahedron* **1997**, *53*, 2979. – [8c] F. Busquè, P. de March, M. Figueredo, J. Font, M. Monsalvatje, A. Virgili, A. Alvarez-Larena, J. F. Piniella, *J. Org. Chem.* **1996**, *61*, 8578. – [8d] J. F. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, A. Ali, *J. Am. Chem. Soc.* **1979**, 2435.
[9] [9a] D. Döpp, M. Nour-el-Din, *Tetrahedron Lett.* **1978**, *17*, 1463. – [9b] D. Döpp, C. Krüger, G. Makedakis, M. Nour-el-Din, *Chem. Ber.* **1985**, *118*, 510.
[10] P. Bruni, E. Giorgini, G. Tommasi, L. Greci, *Tetrahedron* **1998**, *54*, 5305.
[11] G. R. Delpierre, M. Lamchen, *J. Chem. Soc.* **1963**, 4693.
[12] D. B. Adams, M. Hooper, C. J. Swain, E. S. Raper, B. Stoddart, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1005.
[13] J. J. P. Stewart, *J. Comp. Chem.* **1989**, *10*, 209.
[14] [14a] S. Kanemasa, T. Tsuruota, *Chem. Letters* **1995**, 49. – [14b] S. Kanemasa, T. Uemura, E. Wada, *Tetrahedron Lett.* **1992**, *33*, 7889. – [14c] K. V. Gothelf, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **1996**, *61*, 346.
[15] M. Colonna, L. Greci, *Gazz. Chim. Ital.* **1969**, *99*, 351.
[16] [16a] D. Döpp, C. Kruger, G. Makedakis, A. M. Nour-el-Din, *Chem. Ber.* **1985**, *118*, 510. – [16b] R. Grigg, M. Hadjiisoteriou, P. Kennewell, J. Markandu, M. Thornton-Pett, *J. Chem. Soc. Chem. Comm.* **1993**, 1340. – [16c] M. Frederickson, R. Grigg, J. Markandu, M. Thornton-Pett, J. Redpath, *Tetrahedron* **1997**, *53*, 15051. – [16d] M. Frederickson, R. Grigg, M. Thornton-Pett, J. Redpath, *Tetrahedron Lett.* **1997**, *38*, 7777.
[17] H. Ali Dondas, M. Frederickson, R. Grigg, J. Markandu, M. Thornton-Pett, *Tetrahedron* **1997**, *53*, 14339. –
[18] D. Cremer, A. Pople, *J. Am. Chem. Soc.* **1975**, *97*, 1354.
[19] [19a] E. Malmström, R. D. Miller, C. J. Hawker, *Tetrahedron* **1997**, *53*, 15225. – [19b] C. J. Hawker, *Acc. Chem. Res.* **1997**, *30*, 373.
[20] C. C. Bond, *Synthesis* **1974**, 443.
[21] L. Marchetti, L. Greci, G. Tosi, *Gazz. Chim. Ital.* **1970**, *100*, 770
[22] E. Fisher, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 2062.
[23] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, M. C. Burla, G. Polidori, M. Camalli, R. Spagna, *SIR97*, A Package for Crystal Structure Solution by Direct Methods, Refinement, **1997**, private communication.
[24] G. M. Sheldrick, *SHELX76*, System of Computer Programs for Crystal Structure Determination, University of Cambridge, **1976**.
[25] M. Nardelli, *Comput. Chem.* **1983**, *7*, 95.
[26] M. S. Lehmann, F. K. Larsen, *Acta Crystallogr., Sect. A* **1974**, *30*, 580.
[27] International Tables for X-ray Crystallography, Kynoch Press, Birmingam, **1974**, vol. IV.

Received February 6, 2001
[O01059]