Regio- and diastereo-selectivity in 1,3-dipolar cycloadditions of nitrile oxides to 4-substituted cyclopent-2-enones

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The behaviour of 4-hydroxy-4-methylcyclopent-2-enone and related 4-substituted cyclopent-2-enones towards 1,3-dipolar cycloaddition with nitrile oxides is studied. The reactions are always completely regioselective while the diastereofacial selectivity depends on the nature of the substituents. Remarkably, the reaction of 4-acetoxycyclopent-2-enone shows complete regio- and diastereo-facial selectivity.

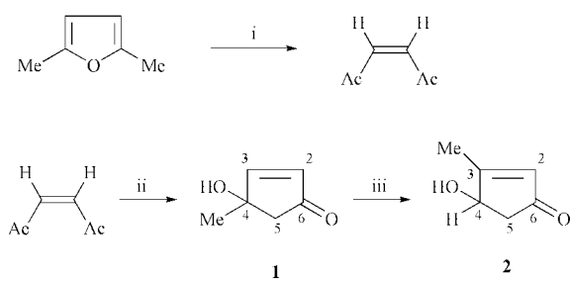
Introduction

Isoxazolines are valuable intermediates for obtaining β-hydroxy ketones or γ-amino alcohols[1] but they are also important in their being possibly endowed with biological activity or lending themselves to further transformations leading to natural products or pharmacologically active compounds.[2–8]

The 1,3-dipolar cycloaddition of nitrile oxides to alkenes has been one of the most general methods used for the preparation of isoxazoline derivatives.[9–12] This reaction is both regio- and stereo-selective and the selectivity is enhanced in alkenes bearing an allylic chiral centre. Several important studies have been performed to determine the influence on selectivity of the nature of the substituents at the allylic centre.[13–20]

Considering our interest in obtaining cyclopentanes which are polyfunctionalized in a stereocontrolled way (these molecules are present in many classes of natural and synthetic compounds), we decided to study regio- and stereo-selectivity in the 1,3-dipolar cycloaddition of nitrile oxides to several 4-substituted cyclopent-2-enones. In these molecules, regio-selectivity is expected to be mainly determined by the α,β unsaturated ketone moiety, and diastereoselectivity by the nature of the substituents at the 4 position. The allylic substituents in cyclopent-2-enones are part of a quite rigid structure and this will possibly enhance facial selectivity. 4-Hydroxy-4-methylcyclopent-2-enone, **1**, is a particularly promising starting molecule, having at its allylic centre two groups that should exert a strong diastereofacial selectivity through hydrogen bonding, involving the 4-OH and the oxygen of the nitrile oxide, and through steric hindrance mainly due to the methyl.[19]

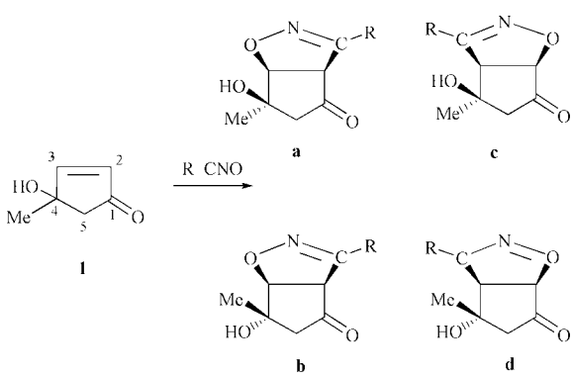
For the synthesis of compound **1** we followed the pathway outlined in ref. 21, where, however, the reaction conditions and the yield are not indicated. In Scheme 1 we report the reaction conditions that gave the best yield according to our attempts. Compound **1** was obtained in a good yield (80%) which was considerably better than that given by another procedure found in the literature.[22] These conditions must be strictly followed in order to avoid the formation of 4-hydroxy-3-methylcyclopent-2-enone,[23] **2**, derived from rearrangement of **1**. Compound **1** is completely transformed into compound **2** when warming is carried out for longer times or when operating in stronger alkaline conditions (see Scheme 1).



Scheme 1 *Reagents and conditions*: i, MCPBA, CH_2Cl_2, −10 °C; ii, 1% Na_2CO_3, 30 °C, 5 min; iii, reflux, 2 h.

Results and discussion

The reaction of **1** with nitrile oxides could give a mixture of four possible stereoisomers as shown in Scheme 2.



Scheme 2

On the basis of frontier orbital theory a preference for stereoisomers **a** and **b** over stereoisomers **c** and **d** is expected.[13,24,25] Furthermore the discrimination exerted between the two faces of **1** by the allylic substituents should favour the approach of the nitrile oxide leading to **a** over that leading to **b**. In fact, for this approach the substituents at the allylic centre are oriented in the most favourable way: the OH group on the same side as the oxygen of the incoming nitrile oxide and the methyl

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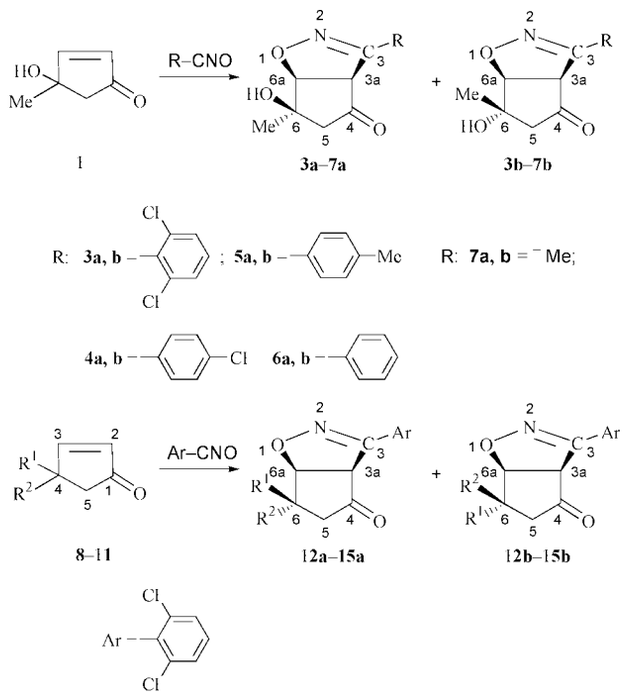
group antiperiplanar to it.[19] The rigidity of the cyclopentenone moiety should magnify the effect, since the two allylic substituents are held in fixed positions during the nitrile oxide attack.

The reactions of **1** with several nitrile oxides gave only two adducts in all cases (Scheme 3).



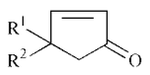
Scheme 3

From the chemical shifts of the protons bonded to the bridgehead carbons (3a-H and 6a-H) we can deduce, according to the literature,[13,25,26] that the two products are type **a** and **b** stereoisomers; in fact the difference in chemical shift between protons 6a-H and 3a-H, $\Delta\delta_{6a-3a}$, is obtained for all the stereoisomers within the following ranges: $\Delta\delta_{6a-3a} = 0.58–1.09$ ppm for **3a**–**7a** and $\Delta\delta_{6a-3a} = 0.58–1.22$ ppm for **3b**–**7b**, while $\Delta\delta_{6a-3a}$ is expected to be considerably lower for the other regioisomers (**c** and **d**).

The reactions are thus, somewhat surprisingly, completely regioselective. Reactions of nitrile oxides with cyclopent-2-enone itself in fact give both regioisomers.[13] The reaction of 2,6-dichlorobenzonitrile oxide with cyclopent-2-enone run in our laboratories under the same conditions as the corresponding reaction of **1** gave the two regioisomers in the ratio **a** : **c** = 85 : 15. Reactions of nitrile oxides with molecules that have a certain resemblance to ours, such as 3- or 3,5-substituted cyclopentenes and 5-substituted furan-2(5*H*)-ones, also give both regioisomers.[14,15,27,28] We found very few exceptions to this behaviour; the reactions of benzonitrile oxide with (−)-5-menthyloxyfuran-2(5*H*)-one[29] and of acetonitrile oxide with 5-(ethylthio)furan-2(5*H*)-one are completely regioselective.[28]

On the other hand the ratios between the two diastereoisomers (**3a**–**7a** to the corresponding **3b**–**7b**; see Table 1), determined by integration of the methyl-group's signals in the ^{1}H NMR spectrum of the crude reaction mixtures, are in agreement with the orienting effects of the hydroxy and methyl groups: **3a**–**7a** are always the major isomers even if the ratio also depends on the nature of the nitrile oxide.

The assignment of the structure of diastereoisomers **3a**–**7a** and **3b**–**7b** was made on the basis of a nuclear Overhauser effect (NOE) study. Irradiation of the protons of the methyl group at the allylic centre gave, in all cases, an NOE on 6a-H (5-8%) for one stereoisomer and no NOE for the other stereoisomer (it thus follows that the structures are **3a**–**7a** for the former and **3b**–**7b** for the latter). Moreover, on presaturation of the aromatic protons or the protons of the methyl group (3-CH_3) we always found a small NOE on 3a-H (2–3%) for all stereoisomers **3a**–**7a** and **3b**–**7b** (this is also a confirmation of the previous regiochemical assignment).



1	R^1 – OH	R^2 – CH_3
8	R^1 – OAc	R^2 – CH_3
9	R^1 – OH	R^2 – H
10	R^1 – CH_3	R^2 – H
11	R^1 – OAc	R^2 – H

Table 1 Yields and stereoisomers ratios[a] of compounds **3a**–**7a**, **12a**–**14a** and **3b**–**7b**, **12b**–**15b** obtained according to Scheme 3

Compound	**a**	**b**	Yield (**a** + **b**) (%)
3	85	15	87
4	75	25	75
5	65	35	82
6	80	20	85
7	70	30	68
12	57	43	74
13	55	45	81
14	32	68	75
15	0	100	71

[a] Ratios were estimated by ^{1}H NMR spectroscopy.

In order to investigate the relative importance of steric hindrance and hydrogen bonding in determining the ratio of the diastereoisomers, we changed the substituents at the allylic centre according to Fig. 1. The reactions were performed using the same nitrile oxide (2,6-dichlorobenzonitrile oxide). This strategy should allow at least partial separation of the two effects, leading to the evaluation of their respective weights on the reaction course. At the same time we can see if and to what extent the nature of the substituents affects the regioselectivity.

Compound **7**, 4-acetoxy-4-methylcyclopent-2-enone, was prepared by acetylation of **1** with acetic anhydride, while the other 4-substituted cyclopent-2-enones, **9**–**11**, were prepared according to refs. 30, 31 and 32 respectively. From the results of the reactions shown in Scheme 3 it is immediately evident that complete regioselectivity is retained regardless of the nature of these substituents. This result is perhaps even more surprising for compounds **9**–**11**. In fact, in these compounds one of the faces of the cyclopentenone ring presents a hydrogen atom, as does cyclopent-2-enone itself (which gives both regioisomers). It seems that one substituent (*i.e.*, one of the above substituents) at the allylic position is sufficient to induce complete regioselectivity.

The ratio of diastereoisomers is strongly affected by the substituents at the allylic centre (see Table 1). For compounds **8** and **9** the proportions of the corresponding diastereoisomers, **12a** : **12b** = 57 : 43 and **13a** : **13b** = 55 : 45 are almost equal. The difference in steric hindrance between methyl and hydrogen in compounds **1** and **9** should favour diastereoisomer **13b** with respect to **13a** more than **3b** with respect to **3a** and indeed this is what we found. However the fact that **13a** is still formed in comparable quantity (**13a** : **13b** = **55** : **45**) underlines the importance of the hydrogen bonding effect. The importance of hydrogen bonding is also evident in comparing **1** with **8**; acetylation of the hydroxy group causes a drop in the ratio of the diastereoisomers from **3a** : **3b** = 85 : 15 to **12a** : **12b** = 57 : 43. Moreover if we consider compounds **9** and **11**, the acetylation of the hydroxy group produces a far more pronounced effect: the attack of the nitrile oxide is only *syn* with the hydrogen atom at the allylic centre. So for compound **11** the reaction is not only completely regioselective but also completely

Table 2 Selected NOE effects for compounds **12a**–**14a** and **12b**–**15b** in 0.05 M solutions in $CDCl_3$

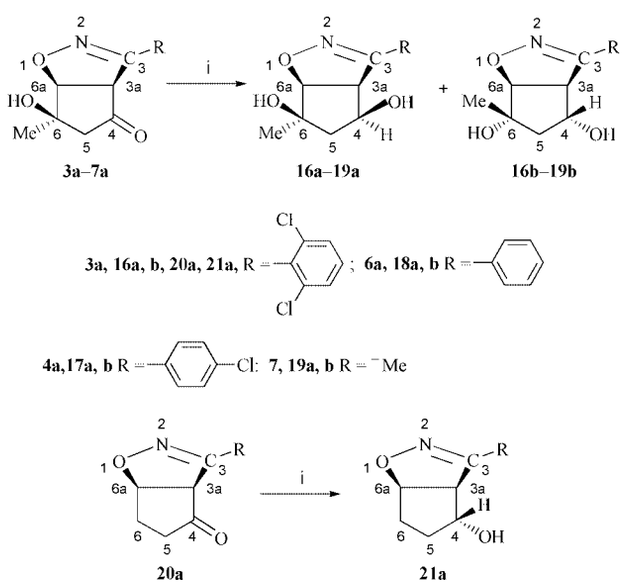
Compound	Irradiated	Observed	NOE %
12a	6-CH_3	6a-H	6.7
12b	6-CH_3	6a-H	0
13a	3a-H	6a-H	4.0
	6-H	6a-H	7.5
	6a-H	3a-H	11.7
	6a-H	6-H	4.4
13b	3a-H	6a-H	5.0
	6-H	6a-H	1.5
	6a-H	3a-H	9.7
14a	6-CH_3	6a-H	0
14b	6-CH_3	6a-H	5.8
15b	6-H	6a-H	1.2

diastereoselective. In compound **10** only steric effects can play a role in addressing the approach of nitrile oxide and, as expected, isomer **14b** predominates over **14a**.

The relative stereochemistry of the cycloadducts was determined through NOE analysis (see Table 2).

The complete regioselectivity diminishes the number of the isomers from four to two and, in the case of compound **11**, to only one (**15b**). In these isomers the relative stereochemistry of the three chiral centres is defined. We should then expect that these centres would exert a good degree of chiral induction in the formation of any new chiral centre. This possibility is of particular importance given our general purpose of obtaining cyclopentanes which are polyfunctionalized in a stereocontrolled way. In order to have a first glimpse at the effectiveness of this strategy we made a preliminary attempt involving the reduction of the carbonyl group in compound **3a**, which should give cyclopentane derivatives with two hydroxy groups in 1,3 relative positions.

The reduction was performed using $NaBH_4$, which gives higher (almost quantitative) yields than $LiAlH_4$. Results are reported in Scheme 4.



Scheme 4 *Reagents and conditions*: i, $NaBH_4$, MeOH, −10 °C.

The attack of the reagent is always predominantly from the less hindered face opposite the isoxazoline ring and stereoisomers **16a**–**19a** prevail (Table 3). This behaviour is particularly significant for compound **3a**: the diastereoisomeric ratio **16a**:**16b** is considerably greater than the ratios of **17a**, **18a** and **19a** to the corresponding isomers **17b**, **18b** and **19b**. Probably the chlorine atoms on the benzene ring of **3a** are strategically

Table 3 Yields and stereoisomers ratios[a] of compounds **16a**–**19a**, **16b**–**19b** and **21a** obtained according to Scheme 4

Compound	**a**	**b**	Yield (**a** + **b**) (%)
16	90	10	92
17	68	32	96
18	75	25	94
19	75	25	92
21	100	0	90

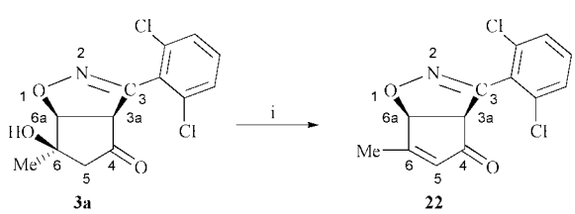
[a] Ratios were estimated by ^1H NMR spectroscopy.

located to maximize the difference between the two faces of the cyclopentane ring and to give the highest diastereoisomeric ratio. However, the methyl group bonded to C-6 could also have an influence on the pathway chosen by the reagent. In order to test this possibility we performed the same reaction under identical conditions on the adduct of 2,6-dichlorobenzonitrile oxide with cyclopent-2-enone (adduct **20a**).

When this methyl group was absent, the approach of the reagent was only from the face opposite the isoxazoline ring, leading to compound **21a** with no evidence of its diastereoisomer (see Table 3).

The relative stereochemistry of compounds **16a**–**19a**, **16b**–**19b** and **21a** was established from qualitative NOE experiments. Presaturation of the methyl protons, 6-Me, gave an NOE on the proton of the hydroxy group, 4-OH, for the minor isomers (4–6%) and no NOE on 4-OH for the major isomers, while presaturation of 3a-H gave an NOE on 4-H for the major isomers (6–11%) and no NOE or far smaller NOE for the minor isomers (0–2.5%). Thus major isomers have structures **16a**–**19a** and minor isomers have structures **16b**–**19b**.

The synthesis of polyfunctionalized substrates is based on a carefully planned protection/deprotection strategy. In our case it may be very important to protect the hydroxy group in key compound **1**. However, attempts to acetylate **1** under various conditions gave the corresponding 4-acetoxy-4-methylcyclopent-2-enone **8** in 45–50% yield. This quite low yield is due to the low reactivity of the tertiary hydroxy group but also to the competing reaction leading to the rearranged product **2**. If acetylation is tried in the next stage on the adduct of **1** with 2,6-dichlorobenzonitrile oxide, **3a**, the result is even worse since the dehydrated compound, **22**, is practically the only product (see Scheme 5). The structure of this compound is immediately



Scheme 5 *Reagents and conditions*: AcCl, 40 °C.

recognizable by its ^1H NMR spectrum: disappearance of the AB system of the methylene protons and appearance of a new signal (br s) at δ 6.04 (H-5), while the signal of the methyl protons shifts from δ 1.44 to δ 2.31.

The reduction of the carbonyl moiety in **3a** leads to the introduction of a secondary hydroxy group (compound **16a**). This group should react to give the monoacetylated derivative. In fact, reaction of **16a** with acetyl chloride gave only one product in very good yield (92%). However, the NMR analysis showed that this product was not the expected monoacetylated derivative, but the diacetylated product **23a** (see Scheme 6), as was confirmed by X-ray crystal diffraction. The ORTEP plot is shown in Fig. 1, where it can be seen that the two acetoxy groups retained the same relative stereochemistry as the corresponding hydroxy groups in the parent compound **16a**.

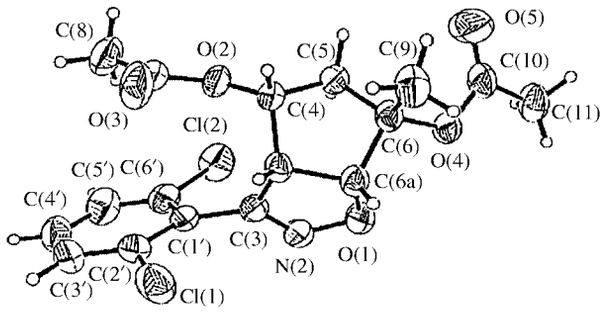
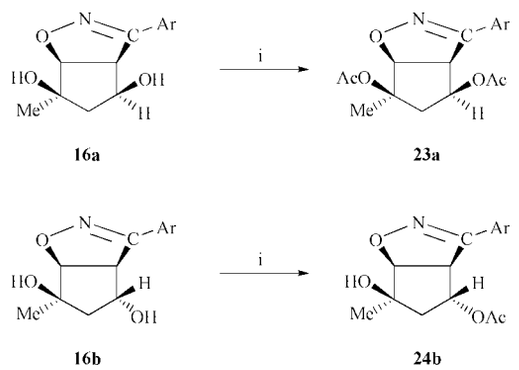


Fig. 1 X-Ray molecular structure of diacetate **23a** with crystallographic numbering scheme.



Scheme 6 *Reagents and conditions*: AcCl, 40 °C.

This finding could be explained by a mechanism of intramolecular transesterification. Similar examples can be found in the literature; see, for instance, the rapid conversion of *N*-benzoylnor-ψ-tropine into *O*-benzoylnor-ψ-tropine in acid solution.[33]

In order to test this probable mechanism we tried the same reaction on the other diastereoisomer produced in the reduction of cycloadduct **3a** in which the two hydroxy groups are in a relative *trans* relationship, **16b**. In this case we obtained only the monoacetylated product **24b** (see Scheme 6), derived, as expected, from the reaction of the secondary OH group.

The structure of compound **24b** follows from the disappearance of the broad doublet in the proton NMR spectrum due to the proton of the secondary hydroxy group (this proton is coupled with 4-H), while the broad singlet of the proton of the tertiary hydroxy group is still present.

The remarkably complete regioselectivity that we found in these reactions could thus be an interesting basis for the stereocontrolled functionalization of 4-substituted cyclopent-2-enones. The behaviour of 4-acetoxycyclopent-2-enone that reacts with 2,6-dichlorobenzonitrile oxide giving only one adduct (**15b**) (complete regio- and stereo-selectivity) is of special significance. This adduct has three chiral centres with assigned relative stereochemistry and a fourth chiral centre can be introduced with good stereoselectivity, for instance by reduction of the carbonyl group, as we have shown.

Further studies for the development of these promising results are therefore underway.

Experimental

Mps were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyser. NMR spectra were recorded for $CDCl_3$ solutions (unless otherwise stated) on a Bruker AC 200 spectrometer (200 MHz). Chemical shifts (δ) were measured in ppm, relative to TMS as internal standard, and coupling constants (J) are in hertz. When necessary, NMR data were assigned using HH- and CH-correlated spectra. Proton–proton NOEs were measured with gated decoupling techniques using NOE difference-pulse sequences.

Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 70–230 mesh) were used for analytical TLC and for column chromatography, respectively. Extracts were dried over sodium sulfate. Concentrations were performed on a rotary evaporator. Petroleum spirit refers to the fraction of distillation range 30–50 °C.

4-Hydroxy-4-methylcyclopent-2-enone 1

1% aq. Na_2CO_3 (10 ml) was added to (*Z*)-diacetylethylene (1.5 g, 13.4 mmol). The mixture was stirred at 30 °C for 5 min, and then left at room temperature without stirring. The reaction was followed by TLC (diethyl ether–petroleum spirit 2:1). The solution was extracted with CH_2Cl_2, then the extract was dried (Na_2SO_4), filtered and concentrated to give **1** as a colourless oil (1.2 g, 80%) (Found: C, 64.13; H, 7.05. Calc. for $C_6H_8O_2$: C, 64.28; H, 7.14%); δ_H 1.39 (3 H, s, CH_3), 2.32 (1 H, d, $J_{5,5'}$ 18.5, 5-H), 2.42 (1 H, d, $J_{5,5'}$ 18.5, 5′-H), 3.70 (1 H, br s, OH), 5.91 (1 H, d, $J_{2,3}$ 5.4, 2-H), 7.34 (1 H, d, $J_{2,3}$ 5.4, 3-H); δ_C 27.1 (CH_3), 50.2 (C-5), 76.0 (C-4), 132.0 (C-2), 167.5 (C-3), 207.8 (C-1).

4-Hydroxy-3-methylcyclopent-2-enone 2

1% aq. Na_2CO_3 (10 ml) was added to (*Z*)-diacetylethylene (1.5 g, 13.4 mmol). The mixture was refluxed for 2 h. The solution was extracted with CH_2Cl_2, then the extract was dried, filtered and the filtrate concentrated to give **2** as a yellow oil (1 g, 70%) (Found: C, 64.08; H, 7.21. Calc. for $C_6H_8O_2$: C, 64.28; H, 7.14%); δ_H 2.10 (3 H, br s, CH_3), 2.24 (1 H, dd, $J_{5,5'}$ 18.4, $J_{4,5}$ 2.1, 5-H), 2.70 (1 H, dd, $J_{5,5'}$ 18.4, $J_{4,5'}$ 6.1, 5′-H), 3.55 (1 H, br s, OH), 4.69 (1 H, dd, $J_{4,5}$ 2.1, $J_{4,5'}$ 6.1, 4-H), 5.86 (1 H, br s, 2-H); δ_C 15.7 (CH_3), 45.1 (C-5), 72.3 (C-4), 131.0 (C-2), 178.1 (C-3), 206.4 (C-1).

4-Acetoxy-4-methylcyclopent-2-enone 8

A catalytic amount of 4-(dimethylamino)pyridine and then, dropwise, triethylamine (2.49 ml) were added to a solution of cyclopentenone **1** (2 g, 17.8 mmol) in stirred acetic anhydride. The resulting mixture was stirred at rt for 72 h. The solution was concentrated and the residue purified by column chromatography (diethyl ether–petroleum spirit 1:1, then 2:1 and only diethyl ether at the end) to give compound **8** (1.12 g, 45%) as an oil (Found: C, 62.23; H, 6.15. Calc. for $C_8H_{10}O_3$: C, 62.34; H, 6.49%); δ_H 1.69 (3 H, s, 6-CH_3), 2.02 (3 H, s, $COCH_3$), 2.53 (1 H, d, $J_{5,5'}$ 18.0, 5-H), 2.83 (1 H, d, $J_{5,5'}$ 18.0, 5′-H), 6.18 (1 H, d, $J_{2,3}$ 5.6, 2-H), 7.73 (1 H, d, $J_{2,3}$ 5.6, 3-H); δ_C 21.7 ($COCH_3$), 24.7 (CH_3), 48.5 (C-5), 83.6 (C-4), 134.1 (C-2), 163.1 (C-3), 205.0 (C-1).

The other 4-substituted cyclopent-2-enones, 4-hydroxycyclopent-2-enone **9**, 4-methylcyclopent-2-enone **10** and 4-acetoxycyclopent-2-enone **11** were prepared according to the procedures cited in refs. 30, 31 and 32, respectively.

The arylnitrile oxides were prepared by dehydrohalogenation of the corresponding hydroxamoyl chlorides with triethylamine.[34–36] For 2,6-dichlorobenzonitrile oxide the dehydrohalogenation of the corresponding hydroxamoyl chloride was performed by treatment with sodium hypochlorite.[37–39] Acetonitrile oxide was prepared from nitroethane according to the Mukaiyama–Hoshino method.[40] In order to minimize their dimerization [formation of furazan *N*-oxides (furoxans)],[10,11] all nitrile oxides were generated just before use and their solutions were added dropwise in a few minutes to a solution of the respective cyclopentenone. The furoxans were easily separated by column chromatography.

General method for the preparation of compounds 3a, 3b, 12a–14a and 12b–15b

A solution of 2,6-dichlorobenzonitrile oxide (1.68 g, 9.1 mmol) in CH_2Cl_2 (15 ml) was added dropwise under stirring to a

solution of the appropriate 4-substituted cyclopent-2-enone (6.0 mmol) in CH_2Cl_2 (10 ml) at room temperature. The solution was stirred at room temperature for 8 h and then concentrated and the residue was purified by flash chromatography (diethyl ether–petroleum spirit, 1:1) to give the corresponding cycloadduct.

(3a*RS*,6*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-hydroxy-6-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 3a and (3a*RS*,6*SR*,6a*SR*)-3-(2,6-dichlorophenyl)-6-hydroxy-6-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 3b. Compound **3a** (1.3 g, 85%) (white solid), mp 174–176 °C (from cyclohexane) (Found: C, 52.31; H, 3.80; N, 4.66. Calc. for $C_{13}H_{11}Cl_2NO_3$: C, 52.00; H, 3.66; N, 4.66%); δ_H 1.44 (3 H, s, CH_3), 2.45 (1 H, d, $J_{5,5'}$ 17.0, 5-H), 2.67 (1 H, d, $J_{5,5'}$ 17.0, 5′-H), 2.86 (1 H, s, OH), 4.42 (1 H, d, $J_{3a,6a}$ 9.8, 3a-H), 5.21 (1 H, d, $J_{3a,6a}$ 9.8, 6a-H), 7.36 (3 H, m, ArH); δ_C 25.9 (Me), 50.0 (C-5), 63.9 (C-3a), 75.1 (C-6), 89.6 (C-6a), 125.9 (C), 128.1 (2 × CH), 131.4 (CH), 135.0 (2 × CCl), 150.7 (C-3), 204.5 (C-4).

Compound **3b** (0.23 g, 15%) (pale yellow oil) (Found: C, 52.40; H, 3.62; N, 4.55%); δ_H 1.68 (3 H, s, CH_3), 2.44 (1 H, d, $J_{5,5'}$ 17.2, 5-H), 2.77 (1 H, d, $J_{5,5'}$ 17.2, 5′-H), 4.36 (1 H, d, $J_{3a,6a}$ 9.8, 3a-H), 5.18 (1 H, d, $J_{3a,6a}$ 9.8, 6a-H), 7.34 (3 H, m, ArH); δ_C 22.7 (Me), 48.8 (C-5), 63.4 (C-3a), 77.0 (C-6), 92.0 (C-6a), 126.2 (C), 128.1 (2 × CH), 131.3 (CH), 135.0 (2 × CCl), 150.3 (C-3), 206.3 (C-4).

(3a*RS*,6*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-methyl-4-oxo-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazol-6-yl acetate 12a and (3a*RS*,6*SR*,6a*SR*)-3-(2,6-dichlorophenyl)-6-methyl-4-oxo-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazol-6-yl acetate 12b. Compound **12a** (0.56 g, 57%) (white solid), mp 161–163 °C (from cyclohexane) (Found: C, 52.35; H, 3.67; N, 4.15. Calc. for $C_{15}H_{13}Cl_2NO_4$: C, 52.63; H, 3.80; N, 4.09%); δ_H 1.61 (3 H, s, CH_3), 2.16 (3 H, s, $COCH_3$), 2.75 (1 H, dt, $J_{5,5'}$ 16.9, $J_{5',6a} = J_{3a,5'} = 1.2$, 5′-H), 3.15 (1 H, br d, $J_{5,5'}$ 16.9, 5-H), 4.30 (1 H, br d, $J_{3a,6a}$ 8.7, 3a-H), 5.75 (1 H, br d, $J_{3a,6a}$ 8.7, 6a-H), 7.26–7.42 (3 H, m, ArH); δ_C 21.5 (CH_3), 23.7 ($CO\mathit{C}H_3$), 48.3 (C-5), 64.0 (C-3a), 81.8 (C-6), 89.0 (C-6a), 126.4 (C), 128.3 (2 × CH), 131.6 (CH), 135.4 (2 × CCl), 149.6 (C-3), 170.1 (OCO), 203.5 (C-4).

Compound **12b** (0.42 g, 43%) (white solid), mp 192–194 °C (from cyclohexane) (Found: C, 52.85; H, 3.60; N, 4.18%); δ_H 1.78 (3 H, s, CH_3), 2.04 (3 H, s, $COCH_3$), 2.70 (1 H, d, $J_{5,5'}$ 18.6, 5-H), 2.91 (1 H, dt, $J_{5,5'}$ 18.6, $J_{5',6a} = J_{3a,5'} = 1.0$, 5-H), 4.62 (1 H, dd, $J_{3a,6a}$ 9.5, $J_{3a,5'}$ 1.0, 3a-H), 5.44 (1 H, dd, $J_{3a,6a}$ 9.5, $J_{5',6a}$ 1.0, 6a-H), 7.40–7.52 (3 H, m, ArH); δ_C 21.2 (CH_3), 21.3 ($CO\mathit{C}H_3$), 47.9 (C-5), 64.8 (C-3a), 84.6 (C-6), 90.1 (C-6a), 126.0 (C), 128.0 (2 × CH), 131.4 (CH), 135.6 (2 × CCl), 150.0 (C-3), 170.6 (OCO), 204.2 (C-4).

(3a*RS*,6*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-hydroxy-3a,5,6,-6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 13a and (3a*RS*,6*SR*,6a*SR*)-3-(2,6-dichlorophenyl)-6-hydroxy-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 13b. Compound **13a** (0.78 g, 55%) (white solid), mp 110–112 °C (from cyclohexane) (Found: C, 50.55; H, 3.30; N, 4.98. Calc. for $C_{12}H_9Cl_2NO_3$: C, 50.35; H, 3.15; N, 4.8%); δ_H 2.63 (2 H, m, 5-H_2), 4.40 (1 H, d, $J_{3a,6a}$ 10.0, 3a-H), 4.62 (1H, dd, $J_{6,6a}$ 5.4, $J_{5,6}$ 5.9, 6-H), 5.53 (1 H, dd, $J_{6,6a}$ 5.4, $J_{3a,6a}$ 10.0, 6a-H), 7.28–7.45 (3 H, m, ArH); δ_C 44.5 (C-5), 63.1 (C-3a), 69.5 (C-6), 84.9 (C-6a), 126.0 (C), 128.2 (2 × CH), 131.5 (CH), 135.2 (2 × CCl), 150.7 (C-3), 205.5 (C-4).

Compound **13b** (0.63 g, 45%) (white solid), mp 142 °C (from cyclohexane) (Found: C, 50.22; H, 3.04; N, 4.78%); δ_H 2.47 (1 H, br d, $J_{5,5'}$ 17.8, 5′-H), 2.91 (1 H, dd, $J_{5,5'}$ 17.8, $J_{5,6}$ 5.5, 5-H), 4.34 (1 H, br d, $J_{3a,6a}$ 8.9, 3a-H), 4.76 (1 H, br d, $J_{5,6}$ 5.5, 6-H), 5.41 (1 H, d, $J_{3a,6a}$ 8.9, 6a-H), 7.30–7.50 (3 H, m, ArH); δ_C 44.5 (C-5), 61.9 (C-3a), 71.9 (C-6), 90.6 (C-6a), 128.3 (2 × CH), 128.6 (C), 131.6 (CH), 135.3 (2 × CCl), 150.1 (C-3), 206.6 (C-4).

(3a*RS*,6*RS*,6a*RS*)-3-(2,6-Dichlorophenyl)-6-methyl-3a,5,6,-6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 14a and (3a*RS*,6*SR*,6a*RS*)-3-(2,6-dichlorophenyl)-6-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 14b. Compound **14a** (0.42 g, 32%) (white solid), mp 115 °C (from cyclohexane) (Found: C, 54.72; H, 3.74; N, 4.76. Calc. for $C_{13}H_{11}Cl_2NO_2$: C, 54.90; H, 3.87; N, 4.93%); δ_H 1.18 (3 H, d, $J_{Me,6}$ 6.6, Me), 2.14 (1 H, m, 5′-H), 2.78 (1 H, m, 6-H), 2.81 (1 H, m, 5-H), 4.24 (1 H, d, $J_{3a,6a}$ 9.1, 3a-H), 5.21 (1 H, dd, $J_{3a,6a}$ 9.1, $J_{6,6a}$ 2.5, 6a-H), 7.25–7.50 (3 H, m, ArH); δ_C 19.2 (CH_3), 36.2 (C-6), 43.7 (C-5), 62.3 (C-3a), 91.2 (C-6a), 126.7 (C), 128.2 (2 × CH), 131.5 (CH), 135.3 (2 × CCl), 149.7 (C-3), 208.6 (C-4).

Compound **14b** (0.90 g, 68%) (white solid), mp 133–135 °C (from diethyl ether) (Found: C, 55.08; H, 3.94; N, 5.06%); δ_H 1.39 (3 H, d, $J_{Me,6}$ 6.6, Me), 2.51 (2 H, m, 5-H_2), 2.65 (1 H, m, 6-H), 4.20 (1 H, d, $J_{3a,6a}$ 8.7, 3a-H), 5.44 (1 H, dd, $J_{3a,6a}$ 8.7, $J_{6,6a}$ 4.5, 6a-H), 7.25–7.50 (3 H, m, ArH); δ_C 14.5 (Me), 35.9 (C-6), 42.8 (C-5), 64.3 (C-3a), 88.1 (C-6a), 126.7 (C), 128.0 (2 × CH), 131.7 (CH), 135.3 (2 × CCl), 150.1 (C-3), 208.9 (C-4).

(3a*RS*,6*SR*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-oxo-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazol-6-yl acetate 15b. Compound **15b** (1.0 g, 100%) (white solid), mp 127–129 °C (from cyclohexane) (Found: C, 53.98; H, 3.64; N, 4.71. Calc. for $C_{14}H_{11}Cl_2NO_3$: C, 53.84; H, 3.52; N, 4.48%); δ_H 2.18 (3 H, s, CH_3), 2.43 (1 H, dd, $J_{5,5'}$ 18.4, $J_{3a,5'}$ 1.4, 5′-H), 2.95 (1 H, dd, $J_{5,5'}$ 18.4, $J_{5,6}$ 5.2, 5-H), 4.30 (1 H, dd, $J_{3a,6a}$ 6.5, $J_{3a,5'}$ 1.4, 3a-H), 5.34 (1 H, br d, $J_{5,6}$ 5.2, 6-H), 5.60 (1 H, br d, $J_{3a,6a}$ 6.5, 6a-H), 7.22–7.44 (3 H, m, ArH); δ_C 20.8 (Me), 42.1 (C-5), 62.3 (C-3a), 73.9 (C-6a), 88.2 (C-6), 126.1 (C), 128.3 (2 × CH), 131.7 (CH), 135.3 (2 × CCl), 150.0 (C-3), 169.7 (OCO), 205.5 (C-4).

(3a*RS*,6*RS*,6a*SR*)-3-(4-Chlorophenyl)-6-hydroxy-6-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 4a and (3a*RS*,6*SR*,6a*SR*)-3-(4-chlorophenyl)-6-hydroxy-6-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 4b. A solution of 4-chlorobenzonitrile oxide (1.2 g, 7.8 mmol) in diethyl ether (25 ml) was added dropwise under stirring at −5 °C to a solution of the cyclopentenone **1** (0.6 g, 5.3 mmol) in diethyl ether (10 ml). The solution was stirred at room temperature for 8 h. It was then concentrated to give a residue, which was resolved by column chromatography (diethyl ether–petroleum spirit 2:1) to provide cycloadducts **4a** and **4b** (1.1 g, 75%).

Compound **4a** (0.8 g, 75%) (white needles), mp 126–129 °C (from diethyl ether) (Found: C, 58.42; H, 4.51; N, 5.13. Calc. for $C_{13}H_{12}ClNO_3$: C, 58.76; H, 4.52; N, 5.27%); δ_H 1.44 (3 H, s, CH_3), 2.46 (1 H, d, $J_{5,5'}$ 16.9, 5-H), 2.66 (1 H, d, $J_{5,5'}$ 16.9, 5′-H), 2.87 (1 H, s, OH), 4.36 (1 H, d, $J_{3a,6a}$ 9.7, 3a-H), 5.13 (1 H, d, $J_{3a,6a}$ 9.7, 6a-H), 7.38 (2 H, d, *J* 8.4, ArH), 7.82 (2 H, d, *J* 8.4, ArH); δ_C 25.8 (CH_3), 50.0 (C-5), 61.7 (C-3a), 74.8 (C-6), 90.4 (C-6a), 125.9 (C), 128.9 (2 × CH), 129.2 (2 × CH), 136.8 (CCl), 153.1 (C-3), 205.2 (C-4).

Compound **4b** (0.27 g, 25%) (white needles), mp 149–151 °C (from diethyl ether) (Found: C, 58.52; H, 4.41; N, 5.38%); δ_H 1.65 (3 H, s, CH_3), 2.43 (1 H, dt, $J_{5,5'}$ 16.9, $J_{5,6a} = J_{5,3a} = 1.2$, 5-H), 2.60 (1 H, d, $J_{5,5'}$ 16.9, 5′-H), 3.01 (1 H, s, OH), 4.34 (1 H, dd, $J_{3a,6a}$ 8.3, $J_{5,3a}$ 1.2, 3a-H), 5.09 (1 H, dd, $J_{3a,6a}$ 8.3, $J_{5,6a}$ 1.2, 6a-H), 7.38 (2 H, d, *J* 8.7, ArH), 7.82 (2 H, d, *J* 8.7, ArH); δ_C 23.1 (Me), 49.0 (C-5), 60.8 (C-3a), 76.5 (C-6), 92.8 (C-6a), 126.2 (C), 128.9 (2 × CH), 129.0 (2 × CH), 136.7 (CCl), 152.9 (C-3), 207.1 (C-4).

(3a*RS*,6*RS*,6a*SR*)-6-Hydroxy-6-methyl-3-(4-methylphenyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 5a and (3a*RS*,6*SR*,6a*SR*)-6-hydroxy-6-methyl-3-(4-methylphenyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 5b. A solution of 4-methylbenzonitrile oxide (2 g, 15 mmol) in CH_2Cl_2 (60 ml) at −5 °C was added dropwise to a solution of the cyclopentenone **1** (1 g, 8.9 mmol) in CH_2Cl_2 (30 ml), cooled to −5 °C. The mixture was stirred at room temperature for 24 h.

The solution was concentrated, treated with benzene, and filtered. The benzene solution was concentrated and the residue was resolved by column chromatography (diethyl ether–petroleum spirit 2:1) to yield the cycloadducts **5a** and **5b** (1.8 g, 82%).

Compound **5a** (1.16 g, 65%) (white solid), mp 144–146 °C (from diethyl ether) (Found: C, 68.38; H, 6.12; N, 5.71. Calc. for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71%); δ_H 1.42 (3 H, s, 6-CH_3), 2.36 (3 H, s, CH_3), 2.49 (1 H, d, $J_{5,5'}$ 16.1, 5′-H), 2.69 (1 H, d, $J_{5,5'}$ 16.1, 5-H), 4.44 (1 H, d, $J_{3a,6a}$ 9.0, 3a-H), 5.02 (1 H, d, $J_{3a,6a}$ 9.0, 6a-H), 7.24 (2 H, d, *J* 8.1, ArH), 7.77 (2 H, d, *J* 8.1, ArH); δ_C 21.3 (Me), 25.8 (6-*C*H_3), 49.9 (C-5), 62.0 (C-3a), 74.7 (C-6), 90.0 (C-6a), 124.3 (C), 127.8 (2 × CH), 129.3 (2 × CH), 141.0 (C), 153.8 (C-3), 205.1 (C-4).

Compound **5b** (0.62 g, 35%) (colourless oil) (Found: C, 68.78; H, 6.32; N, 5.84%); δ_H 1.64 (3 H, s, 6-Me), 2.38 (3 H, s, Me), 2.46 (1 H, d, $J_{5,5'}$ 16.1, 5′-H), 2.66 (1 H, d, $J_{5,5'}$ 16.1, 5-H), 3.90 (1 H, d, $J_{3a,6a}$ 9.0, 3a-H), 5.12 (1 H, d, $J_{3a,6a}$ 9.0, 6a-H), 7.22 (2 H, d, *J* 8.1, ArH), 7.71 (2 H, d, *J* 8.1, ArH); δ_C 21.3 (Me), 23.3 (6-*C*H_3), 48.5 (C-5), 60.4 (C-3a), 76.7 (C-6), 92.1 (C-6a), 124.2 (C), 127.6 (2 × CH), 129.4 (2 × CH), 141.0 (C), 153.6 (C-3), 206.1 (C-4).

(3a*RS*,6*RS*,6a*SR*)-6-Hydroxy-6-methyl-3-phenyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 6a and (3a*RS*,6*SR*,6a*SR*)-6-hydroxy-6-methyl-3-phenyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 6b. A solution of benzonitrile oxide (3 g, 25 mmol) in CH_2Cl_2 (90 ml) at −5 °C was added dropwise to a solution of the cyclopentenone **1** (2 g, 17.8 mmol) in CH_2Cl_2 (50 ml) cooled to −5 °C. The mixture was stirred at room temperature for 8 h. The solution was concentrated, treated with benzene, filtered, and resolved by column chromatography (diethyl ether–petroleum spirit 2:1) to yield the cycloadducts **6a** and **6b** (3.5 g, 85%).

Compound **6a** (2.8 g, 80%) (white solid), mp 137–138 °C (from cyclohexane) (Found: C, 67.21; H, 5.62; N, 5.85. Calc. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06%); δ_H 1.44 (3 H, s, Me), 2.46 (1 H, dd, $J_{5,5'}$ 16.8, $J_{3a,5}$ 1.0, 5-H), 2.68 (1 H, d, $J_{5,5'}$ 16.8, 5′-H), 2.82 (1 H, br s, OH), 4.40 (1 H, dd, $J_{3a,6a}$ 9.2, $J_{3a,5}$ 1.0, 3a-H), 5.12 (1 H, d, $J_{3a,6a}$ 9.2, 6a-H), 7.40–7.46 (3 H, m, ArH), 7.85–7.91 (2 H, m, ArH); δ_C 25.9 (Me), 50.0 (C-5), 62.0 (C-3a), 74.8 (C-6), 90.3 (C-6a), 127.4 (C), 127.9 (2 × CH), 128.7 (2 × CH), 130.7 (CH), 153.9 (C-3), 205.1 (C-4).

Compound **6b** (0.7 g, 20%) (colourless oil) (Found: C, 67.81; H, 5.82; N, 5.95%); δ_H 1.65 (3 H, s, Me), 2.53 (1 H, d, $J_{5,5'}$ 16.8, 5-H), 2.79 (1 H, br d, $J_{5,5'}$ 16.8, 5′-H), 4.43 (1 H, d, $J_{3a,6a}$ 9.2, 3a-H), 5.01 (1 H, d, $J_{3a,6a}$ 9.2, 6a-H), 7.40–7.46 (3 H, m, ArH), 7.85–7.91 (2 H, m, ArH); δ_C 22.6 (Me), 49.4 (C-5), 60.8 (C-3a), 75.4 (C-6), 91.6 (C-6a), 127.5 (C), 127.9 (2 × CH), 128.8 (2 × CH), 130.9 (CH), 152.7 (C-3), 206.3 (C-4).

(3a*RS*,6*RS*,6a*SR*)-6-Hydroxy-3,6-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 7a and (3a*RS*,6*SR*,6a*SR*)-6-hydroxy-3,6-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 7b. An acetonitrile oxide solution (27.2 mmol in benzene) was added dropwise to a solution of the cyclopentenone **1** (3 g, 26.8 mmol) in benzene (90 ml). The reaction mixture was stirred overnight at room temperature, filtered, and the resulting solution was concentrated to give a residue. This was resolved by flash chromatography (ethyl acetate–*n*-hexane 1:1) to yield compounds **7a** and **7b** (3.1 g, 68%).

Compound **7a** (2.1 g, 70%) (white solid), mp 77 °C (from cyclohexane) (Found: C, 56.46; H, 6.38; N, 8.17. Calc. for $C_8H_{11}NO_3$: C, 56.80; H, 6.51; N, 8.28%); δ_H 1.43 (3 H, s, 6-Me), 2.05 (3 H, d, $J_{3a,3Me}$ 1.0, 3-Me), 2.36 (1 H, d, $J_{5,5'}$ 17.2, 5′-H), 2.56 (1 H, d, $J_{5,5'}$ 17.2, 5-H), 2.68 (1 H, s, OH), 3.87 (1 H, br d, $J_{3a,6a}$ 9.9, 3a-H), 4.96 (1 H, d, $J_{6a,3a}$ 9.9, 6a-H); δ_C 11.4 (6-*C*H_3), 25.9 (3-*C*H_3), 50.1 (C-5), 64.6 (C-3a), 75.1 (C-6), 87.9 (C-6a), 152.6 (C-3), 206.2 (C-4).

Compound **7b** (0.92 g, 30%) (pale yellow oil) (Found: C, 56.56; H, 6.48; N, 8.20%); δ_H 1.54 (3 H, s, 6-Me), 2.00 (3 H, s, 3-Me), 2.10 (1 H, dd, $J_{5,6a}$ 1.0, $J_{5,5'}$ 19.4, 5-H), 2.35 (1 H, d, $J_{5,5'}$ 19.4, 5′-H), 2.44 (1 H, s, OH), 3.83 (1 H, br d, $J_{3a,6a}$ 8.3, 3a-H), 4.90 (1 H, dd, $J_{5,6a}$ 1.0, $J_{3a,6a}$ 8.3, 6a-H); δ_C 11.4 (6-*C*H_3), 22.5 (3-*C*H_3), 48.5 (C-5), 64.5 (C-3a), 76.5 (C-6), 90.9 (C-6a), 152.1 (C-3), 209.3 (C-4).

General method for the reduction of compounds 3a–7a and 20a with $NaBH_4$

$NaBH_4$ (3 mmol for 1 mmol of cycloadduct) was slowly added under stirring to a cooled solution (−5 °C) of the appropriate cycloadduct (0.5 g) in CH_3OH (26 ml). The reaction mixture was stirred at −5 °C for 1 h. The solution was concentrated, treated with dil. HCl, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate; hence it was filtered and concentrated to give the reduced cycloadducts.

(3a*RS*,4*RS*,6*SR*,6a*RS*)-3-(2,6-Dichlorophenyl)-6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diol 16a and (3a*RS*,4*SR*,6*SR*,6a*RS*)-3-(2,6-dichlorophenyl)-6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diol 16b. The cycloadduct mixture was resolved by column chromatography (diethyl ether–petroleum spirit 3:1) to provide reduced cycloadducts **16a** and **16b** (0.46 g, 92%).

Compound **16a** (0.41 g, 90%) (white solid), mp 197–199 °C (from cyclohexane) (Found: C, 51.26; H, 4.58; N, 4.56. Calc. for $C_{13}H_{13}Cl_2NO_3$: C, 51.55; H, 4.30; N, 4.64%); δ_H (DMSO-d_6) 1.12 (3 H, s, Me), 1.71 (1 H, dd, $J_{4,5'}$ 5.8, $J_{5,5'}$ 11.5, 5′-H), 1.84 (1 H, t, $J_{5,5'}$ 11.5, $J_{4,5}$ 11.5, 5-H), 4.15 (1 H, m, $J_{4,5}$ 11.5, $J_{4,5'}$ 5.8, $J_{OH,4}$ 4.4, 4-H), 4.42 (1 H, dd, $J_{3a,6a}$ 9.2, $J_{3a,4}$ 7.4, 3a-H), 4.51 (1 H, d, $J_{3a,6a}$ 9.2, 6a-H), 4.74 (1 H, d, $J_{OH,4}$ 4.4, 4-OH), 4.83 (1 H, s, 6-OH), 7.32–7.50 (3 H, m, ArH); δ_C (DMSO-d_6) 24.6 (Me), 44.8 (C-5), 58.1 (C-3a), 71.8 (C-6a), 77.6 (C-6), 90.4 (C-4), 128.0 (2 × CH), 130.2 (C), 130.4 (CH), 134.1 (2 × CCl), 153.8 (C-3).

Compound **16b** (0.05 g, 10%) (white solid), mp 96–98 °C (from cyclohexane) (Found: C, 51.20; H, 4.25; N, 4.40%); δ_H (DMSO-d_6) 1.25 (3 H, s, 6-Me), 1.58 (1 H, dd, $J_{5,5'}$ 12.1, $J_{4,5'}$ 10.7, 5′-H), 1.81 (1 H, dd, $J_{5,5'}$ 12.1, $J_{4,5}$ 5.5, 5-H), 4.39–4.60 (3 H, m, 4-, 3a-, 6a-H), 4.76 (1 H, d, $J_{OH,4}$ 3.8, 4-OH), 4.86 (1 H, s, 6-OH), 7.32–7.50 (3 H, m, ArH); δ_C (DMSO-d_6): 24.2 (Me), 43.5 (C-5), 56.3 (C-3a), 70.0 (C-6a), 78.1 (C-6), 92.4 (C-4), 128.2 (2 × CH), 130.4 (C), 131.0 (CH), 135.1 (2 × CCl), 152.3 (C-3).

(3a*RS*,4*RS*,6*SR*,6a*RS*)-3-(4-Chlorophenyl)-6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diol 17a and (3a*RS*,4*SR*,6*SR*,6a*RS*)-3-(4-chlorophenyl)-6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-46-diol 17b. The cycloadduct mixture was resolved by column chromatography (chloroform–methanol 95:5) to afford the reduced cycloadducts **17a** and **17b** (0.48 g, 96%).

Compound **17a** (0.32 g, 68%) (white solid), mp 158–160 °C (Found: C, 58.49; H, 5.5; N, 5.3. Calc. for $C_{13}H_{14}ClNO_3$: C, 58.32; H, 5.2; N, 5.2%); δ_H (CD_3COCD_3) 1.36 (3 H, s, Me), 1.89 (1 H, dd, $J_{5,5'}$ 13.2, $J_{5,4}$ 4.6, 5-H), 1.98 (1 H, dd, $J_{5,5'}$ 13.2, $J_{4,5'}$ 5.6, 5′-H), 3.98 (2 H, br s, 4-OH, 6-OH), 4.04 (1 H, dd, $J_{3a,4}$ 7.1, $J_{3a,6a}$ 10.3, 3a-H), 4.24 (1 H, m, 4-H), 4.68 (1 H, d, $J_{3a,6a}$ 10.3, 6a-H), 7.39 (2 H, d, *J* 8.4, ArH), 7.75 (2 H, d, *J* 8.4, ArH); δ_C (CD_3COCD_3) 26.5 (Me), 47.6 (C-5), 61.7 (C-3a), 75.1 (C-4), 78.8 (C-6), 91.7 (C-6a), 127.9 (C), 129.4 (2 × CH), 129.6 (2 × CH), 135.9 (CCl), 156.6 (C-3).

Compound **17b** (0.15 g, 32%) (white solid), mp 169–170 °C (Found: C, 58.42; H, 5.3; N, 5.4%); δ_H (CD_3COCD_3) 1.42 (3 H, s, Me), 1.73 (1 H, dd, $J_{5,5'}$ 13.1, $J_{5,4}$ 6, 5-H), 2.03 (1 H, dd, $J_{5,5'}$ 13.1, $J_{4,5'}$ 6.2, 5′-H), 3.63 (2 H, br s, 4-OH, 6-OH), 4.03 (1 H, dd, $J_{3a,4}$ 3.5, $J_{3a,6a}$ 10.5, 3a-H), 4.34 (1 H, m, 4-H), 4.88 (1 H, d, $J_{3a,6a}$ 10.5, 6a-H), 7.46 (2 H, d, *J* 8.4, ArH), 7.87 (2 H, d, *J* 8.4, ArH); δ_C (CD_3COCD_3) 25.9 (Me), 47.1 (C-5), 58.3 (C-3a), 73.7 (C-4), 79.6 (C-6), 93.3 (C-6a), 128.2 (C), 129.1 (2 × CH), 129.5 (2 × CH), 135.2 (CCl), 157.1 (C-3).

(3a*RS*,4*RS*,6*SR*,6a*RS*)-6-Methyl-3-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diol 18a and (3a*RS*,4*SR*,6*SR*,6a*RS*)-6-methyl-3-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diol 18b. The cycloadduct mixture was resolved by column chromatography (chloroform–methanol 95 : 5), to afford **18a** and **18b** (0.47 g, 94%).

Compound **18a** (0.35 g, 75%) (white solid), mp 135–137 °C (Found: C, 67.1; H, 6.7; N, 6.2. Calc. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.4; N, 6.0%); δ_H (CD_3COCD_3) 1.36 (3 H, s, Me), 1.90 (1 H, dd, $J_{5,5'}$ 13.2, $J_{5,4}$ 4.4, 5-H), 1.98 (1 H, dd, $J_{5,5'}$ 13.2, $J_{4,5'}$ 4.6, 5′-H), 3.90 (1 H, d, $J_{OH,4}$ 9.2, 4-OH), 3.94 (1 H, s, 6-OH), 4.40 (1 H, dd, $J_{3a,4}$ 7.2, $J_{3a,6}$ 10.5, 3a-H), 4.59 (1 H, m, 4-H), 4.77 (1H, d, $J_{3a,6a}$ 10.5, 6a-H), 7.37 (3 H, m, ArH), 7.75 (2 H, m, ArH); δ_C (CD_3COCD_3) 25.9 (Me), 47.3 (C-5), 58.7 (C-3a), 73.9 (C-4), 79.8 (C-6), 93.0 (C-6a), 127.9 (2 × CH), 128.9 (2 × CH), 129.9 (CH), 131.7 (C), 157.9 (C-3).

Compound **18b** (0.12 g, 25%) (white solid), mp 146–149 °C (Found: C, 66.5; H, 6.0; N, 6.3%); δ_H (CD_3COCD_3) 1.43 (3 H, s, Me), 1.74 (1 H, dd, $J_{5,5'}$ 13.2, $J_{5,4}$ 5.6, 5-H), 2.02 (1 H, dd, $J_{5,5'}$ 13.2, $J_{4,5'}$ 6.0, 5′-H), 3.35 (1 H, s, 6-OH), 4.04 (1 H, dd, $J_{3a,4}$ 3.2, $J_{3a,6a}$ 10.3, 3a-H), 4.36 (1 H, m, 4-H), 4.52 (1 H, d, $J_{OH,4}$ 5.3, 4-OH), 4.84 (1 H, d, $J_{3a,6a}$ 10.3, 6a-H), 7.43 (3 H, m, ArH), 7.86 (2 H, m, ArH); δ_C (CD_3COCD_3) 26.6 (Me), 47.6 (C-5), 61.9 (C-3a), 75.0 (C-4), 83.6 (C-6), 91.4 (C-6a), 127.8 (2 × CH), 129.4 (2 × CH), 129.9 (C), 130.4 (CH), 158.4 (C-3).

(3a*RS*,4*RS*,6*SR*,6a*RS*)-3,6-Dimethyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diol 19a and (3a*RS*,4*SR*,6*SR*,6a*RS*)-3,6-dimethyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diol 19b. The cycloadduct mixture was resolved by column chromatography (*n*-hexane–ethyl acetate 2 : 1) to afford **19a** and **19b** (0.47 g, 92%).

Compound **19a** (0.35 g, 75%) (white solid), mp 118–120 °C (Found: C, 56.40; H, 7.7; N, 8.4. Calc. for $C_8H_{13}NO_3$: C, 56.14; H, 7.6; N, 8.2%); δ_H 1.36 (3 H, s, 6-Me), 1.75 (1 H, dd, $J_{5,5'}$ 14, $J_{5',4}$ 4.8, 5′-H), 2.05 (1 H, d, $J_{5,5'}$ 14, 5-H), 2.07 (3 H, s, 3-Me), 2.95 (1 H, br d, J 1.7, 6-OH), 3.61 (1 H, br d, $J_{4,OH}$ 11.2, 4-OH), 3.86 (1 H, dd, $J_{3a,6a}$ 11.3, 3a-H), 4.39 (1 H, m, 4-H), 4.63 (1 H, d, $J_{3a,6a}$ 11.3, 6a-H); δ_C 13.1 (3-*C*H_3), 25.6 (6-*C*H_3), 46.3 (C-5), 62.6 (C-3a), 73.6 (C-4), 80.3 (C-6), 90.2 (C-6a), 153.4 (C-3).

Compound **19b** (0.12 g, 25%) (white solid), mp 114–116 °C (Found: C, 56.20; H, 7.5; N, 8.7%); δ_H 1.41 (3 H, s, 6-Me), 1.71 (1 H, dd, $J_{5,5'}$ 15.8, $J_{5,4}$ 5.8, 5-H), 2.03 (3 H, s, 3-Me), 2.07 (1 H, dd, $J_{5,5'}$ 15.8, $J_{5',4}$ 6.2, 5′-H), 2.52 (1 H, br s, 6-OH), 2.68 (1 H, br s, 4-OH), 3.53 (1 H, dd, $J_{3a,4}$ 9.3, 3a-H), 4.39 (1 H, m, 4-H), 4.68 (1 H, d, $J_{3a,6a}$ 10.6, 6a-H); δ_C 11.2 (3-CH_3), 26.4 (6-CH_3), 46.9 (C-5), 64.6 (C-3a), 73.9 (C-4), 79.1 (C-6), 88.7 (C-6a), 156.7 (C-3).

(3a*RS*,6a*RS*)-3-(2,6-Dichlorophenyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazol-4-one 20a and (3a*RS*,6a*SR*)-3-(2,6-dichlorophenyl)-3a,4,5,6a-tetrahydro-6*H*-cyclopent[*d*]isoxazol-6-one 20c. A solution of 2,6-dichlorobenzonitrile oxide (1.5 g, 8.1 mmol) in CH_2Cl_2 (20 ml) was slowly added to a solution of cyclopent-2-enone (0.6 g, 7.3 mmol) in CH_2Cl_2 (15 ml) at room temperature. The solution was stirred at room temperature for 8 h. It was then concentrated and the residue, resolved by column chromatography (diethyl ether–petroleum spirit 2 : 1), gave **20a** and **20c** (1.44 g, 73%).

Compound **20a** (1.2 g, 85%) (white solid), mp 126 °C (from cyclohexane) (Found: C, 53.1; H, 3.15; N, 5.00. Calc. for $C_{12}H_9Cl_2NO_2$: C, 53.33; H, 3.33; N, 5.20%); δ_H 2.40–2.85 (4 H, m, 5- and 6-H_2), 4.27 (1 H, d, $J_{3a,6a}$ 9.2, 3a-H), 5.72 (1 H, m, $J_{3a,6a}$ 9.2, 6a-H), 7.33–7.50 (3 H, m, ArH); δ_C 28.6 (C-6), 35.2 (C-5), 62.6 (C-3a), 85.0 (C-6a), 126.4 (C), 127.9 (2 × CH), 131.2 (CH), 134.9 (2 × CCl), 149.3 (C-3), 209.1 (C-4).

Compound **20c** (0.22 g, 15%) (white solid), mp 119 °C (from cyclohexane) (Found: C, 53.13; H, 3.20; N, 5.10%); δ_H 2.05–2.20 (2 H, m, 4-H_2), 2.38–2.65 (2 H, m, 5-H_2), 4.59 (1 H, m, 3a-H), 4.88 (1 H, d, $J_{3a,6a}$ 9.7, 6a-H), 7.29–7.51 (3 H, m, ArH); δ_C 22.3 (C-4), 34.5 (C-5), 51.9 (C-3a), 83.1 (C-6a), 126.9 (C), 128.4 (2 × CH), 131.4 (CH), 135.3 (2 × CCl), 155.1 (C-3), 211.3 (C-6).

(3a*RS*,4*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4-ol 21a. $NaBH_4$ was slowly added to a cooled solution (−5 °C) of the cycloadduct **20a** (0.5 g, 1.85 mmol) in CH_3OH (15 ml). The reaction mixture was stirred at 0 °C for 1 h. The solution was concentrated to give a white solid, which was treated with dil. HCl. The solution was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give **21a** as a white solid (0.45 g, 90%), mp 196–198 °C (from cyclohexane) (Found: C, 52.86; H, 3.95; N, 4.99. Calc. for $C_{12}H_{11}Cl_2NO_2$: C, 52.94; H, 4.04; N, 5.15%); δ_H 1.55–2.03 (5 H, m, 3a-H, 5- and 6-H_2), 4.35 (1 H, m, 4-H), 5.25 (1 H, m, 6a-H), 7.2–7.4 (3 H, m, ArH); δ_C 31.0 (C-6), 31.6 (C-5), 57.3 (C-3a), 77.1 (C-6a), 86.8 (C-4), 126.1 (C), 128.5 (2 × CH), 129.8 (CH), 134.8 (2 × CCl), 152.9 (C-3).

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-methyl-3a,6a-dihydro-4*H*-cyclopent[*d*]isoxazol-4-one 22

Acetyl chloride was added in excess to the cycloadduct **3a** (0.5 g, 1.7 mmol). The mixture was stirred and heated at 40 °C until the solid dissolved. The reaction was stirred for 12 h at room temperature and the solution was then concentrated; the resulting oily residue was treated with diethyl ether to provide **22** as a white solid (0.36 g, 77%), mp 175–177 °C (from cyclohexane) (Found: C, 52.99; H, 3.24; N, 4.97. Calc. for $C_{12}H_9Cl_2NO_2$: C, 53.33; H, 3.33; N, 5.20%); δ_H 2.31 (3 H, s, Me), 4.33 (1 H, d, $J_{3a,6a}$ 7.5, 3a-H), 5.67 (1 H, br d, $J_{3a,6a}$ 7.5, 6a-H), 6.04 (1 H, br s, 5-H), 7.26–7.40 (3 H, m, ArH); δ_C 16.6 (Me), 61.1 (C-3a), 86.3 (C-6a), 128.2 (C), 130.4 (2 × CH), 131.5 (CH), 132.8 (C-5), 135.3 (2 × CCl), 151.2 (C-3), 173.1 (C-6), 199.4 (C-4).

(3a*RS*,4*RS*,6*SR*,6a*RS*)-3-(2,6-Dichlorophenyl)-6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole-4,6-diyl diacetate 23a

Acetyl chloride was added in excess to the cycloadduct **16a** (0.5 g, 1.65 mmol). The mixture was stirred and heated at 40 °C until the solid dissolved. The reaction was refluxed for 4 h and then concentrated. The residue, treated with methylene dichloride and concentrated, gave **23a** as white needles (0.59 g, 92%), mp 154–155 °C (from cyclohexane) (Found: C, 53.04; H, 4.25; N, 4.05. Calc. for $C_{17}H_{17}Cl_2NO_5$: C, 52.9; H, 4.4; N, 3.6%); δ_H 1.46 (3 H, s, Me), 1.57 (3 H, s, Me), 2.13 (3 H, s, Me), 2.27 (1 H, d, $J_{5,5'}$ 11.2, 5′-H), 2.42 (1 H, d, $J_{5,5'}$ 11.2, 5-H), 4.82 (1 H, t, $J_{3a,6a} = J_{3a,4} = 9.3$, 3a-H), 5.07 (1 H, m, 4-H), 5.33 (1 H, d, $J_{3a,6a}$ 9.3, 6a-H), 7.25 (1 H, m, ArH), 7.38 (2 H, m, Ar H); δ_C 19.6 (6-CH_3), 21.5 (Me), 23.2 (Me), 39.6 (C-5), 53.7 (C-3a), 72.2 (C-4), 82.9 (C-6), 88.5 (C-6a), 128.5 (2 × CH), 128.9 (C), 130.5 (CH), 135.4 (2 × CCl), 151.9 (C-3), 169.9 (OCO), 170.1 (OCO).

(3a*RS*,4*SR*,6*SR*,6a*RS*)-3-(2,6-Dichlorophenyl)-6-hydroxy-6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazol-4-yl acetate 24b

Acetyl chloride was added in excess to the cycloadduct **16b** (0.5 g, 1.65 mmol). The mixture was stirred and heated at 40 °C until the solid dissolved. The reaction mixture was refluxed for 24 h and then concentrated. The resulting residue was treated with methylene dichloride and concentrated to give **24b** as white needles (0.51 g, 90%), mp 260 °C (decomp.) (from cyclohexane) (Found: C, 52.0; H, 4.2; N, 3.98. Calc. for $C_{15}H_{15}Cl_2NO_4$: C, 52.3; H, 4.4; N, 4.1%); δ_H 1.56 (3 H, s, Me), 2.11 (3 H, s, OCOMe), 2.25 (2 H, dd, 5-H_2), 4.78 (1 H, m, 3a-H), 4.88 (1 H, s, 6-OH), 5.05 (1 H, m, 6a-H), 5.25 (1 H, d, 4-H), 7.20–7.40 (3 H, m, ArH); δ_C 19.6 (OCO*C*H_3), 23.3 (6-CH_3), 39.6 (C-5), 53.7 (C-3a), 72.2 (C-4), 82.0 (C-6), 88.5 (C-6a), 127.1 (C), 128.5 (2 × CH), 130.5 (CH), 135.5 (2 × CCl), 151.9 (C-3), 170.0 (OCO).

Crystal structure determination of compound 23a †

Crystal data. $C_{17}H_{17}Cl_2NO_5$, $M = 386.22$, monoclinic, $a = 17.410(3)$, $b = 8.739(2)$, $c = 12.188(2)$ Å, $\beta = 107.29(1)°$, $V = 1770.7(5)$ Å^3, $T = 295$ K, space group $P2(1)/c$ (no. 14), $Z = 4$, μ(Mo-Kα) = 0.04 cm^{-1}, 3126 independent reflections ($R_{int} = 0.024$), 1974 observed reflections [$I > 2\sigma(I)$], R_1 [$I > 2\sigma(I)$] = 0.049, wR_2 [$I > 2\sigma(I)$] = 0.093.

Structure analysis and refinement. Direct methods implemented in the SHELXS-97.[41] Full-matrix anisotropic least-squares on F^2 for all reflections for all non-H-atoms. The hydrogen atoms were located on Fourier difference maps and were included in the structure-factor calculations as riding atoms on the appropriate atoms. Minimized function $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/[\Sigma w(F_o^4)]^{1/2}$ with weighting scheme $w = 1/[\sigma^2(F_o)^2 + 0.0356P^2 + 0.5238P]$, where $P = (F_o^2 + 2F_c^2)/3$. Min. max. height in last $\Delta\rho$ map of -0.24 and 0.22 e Å^{-3}. Atomic scattering factors were taken from ref. 42. Structure refinement and molecular graphics were performed by using SHELXL-97,[43] and SHELXTL-Plus[44] package. Bond angles and bond distances have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

† CCDC reference number 207/450. See http://www.rsc.org/suppdata/p1/b0/b003549l/ for crystallographic files in .cif format.

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