Developing Molecular Diversity in the Construction of a Family of Bicyclic Isoxazolines Scaffolds: Control of Regio-and Diastereoselectivities

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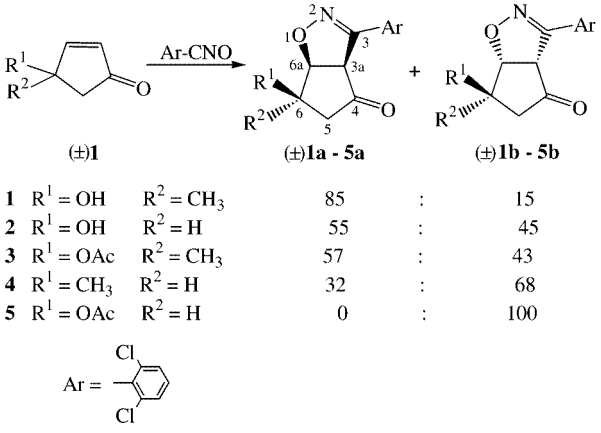
A completely regioselective approach to bicyclic isoxazolines has been found starting from 4-cyclopentene-1,3-dione or 2-cyclopentenones. 1,3-Dipolar cycloaddition with nitrile oxides gave different semirigid bicyclic scaffolds with at least four points of elaboration for molecular diversity. From these intermediates, two families of regioisomer isoxazolines can be prepared with complete control of their relative stereochemistry. Further elaboration of functional groups was demonstrated in order to exploit a successive parallel preparation of arrays of compounds.

Introduction

Isoxazolines are very important heterocycles, lending themselves to a series of interesting chemical transformations. Key functionalities such as β-hydroxy ketones or β-amino alcohols can be disclosed by their ring opening.[1] As isoxazolines are prepared by cycloaddition of nitrile oxides on double bonds, the relative stereochemistry of the introduced functional groups can be controlled precisely.[2] Moreover, isoxazolines are valuable in themselves, since pharmacological activity has been found in molecules containing these moieties.[3−11]

Recently, we synthesised a series of bicyclic isoxazoline scaffolds by 1,3-dipolar cycloadditions of nitrile oxides on 4-substituted 2-cyclopentenones (Scheme 1).[12]

The facial diastereoselectivity of the reaction depended on the nature of the groups at the allylic positions and, in some cases, on the nature of the solvent.[13] On the other hand, the regioselectivity of the reactions was independent of the nature of the substituents, nitrile oxides, and solvent employed. On the basis of these results, we decided to further explore the molecular diversity that can be created within these bicyclic scaffolds, in view of its exploitation for the parallel synthesis of molecule arrays . Structures such as **1a** are potentially interesting, rigid scaffolds with at least four possibilities for the development of molecular diversity. At the same time, exploiting the diversity is possible, if we find a way of controlling the regio- and stereochemistry of the substituent introduction around the eight atoms of the bicyclic rings.



Scheme 1

Moreover, we wanted to find a way to invert the functional groups in positions 4 and 6, again with a high degree of regioselectivity control. Indeed, regioselectivity is important, since it reduces (by half) the number of possible isomers and the use of chromatographic separations, albeit it denies access to all the possible regioisomers.

Results and Discussion

As the cycloaddition of cyclopentenone **1** with 2,6-dichlorobenzonitrile oxide gave compound **1a**, the latter com-

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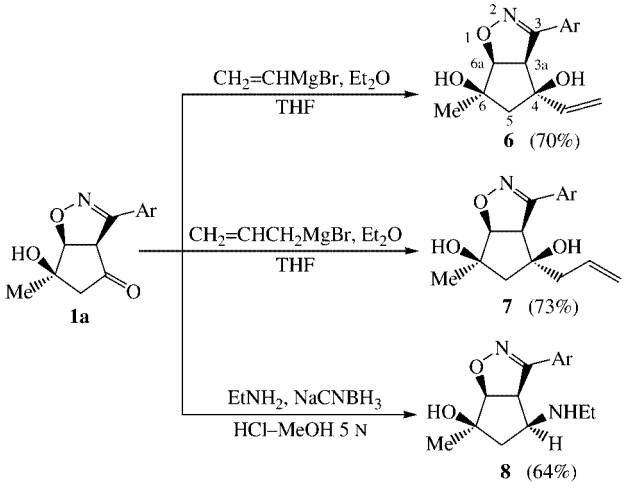
pound was used as the starting point for the study of functional group modifications. Reactions of **1a** with vinylmagnesium bromide and allylmagnesium bromide were completely stereoselective giving compounds **6** and **7** in good yields (70 and 73 %, respectively; Scheme 2). Their relative configurations were determined by ^{1}H NMR and NOE experiments. Saturation of vinyl CH proton in **6** and of allylic CH_2 protons in **7** gave NOE enhancements on corresponding 3a-H protons (4.4 and 3.6 %, respectively). Reductive amination of the same carbonyl group ($CH_3CH_2NH_2$, $NaBH_3CN$) was again completely stereoselective, giving amine **8** in good yield (64 %). The relative stereochemistry resulted from NOE analysis. Irradiation of 4-H in **8** gave a NOE enhancement on 3a-H (11.5 %).

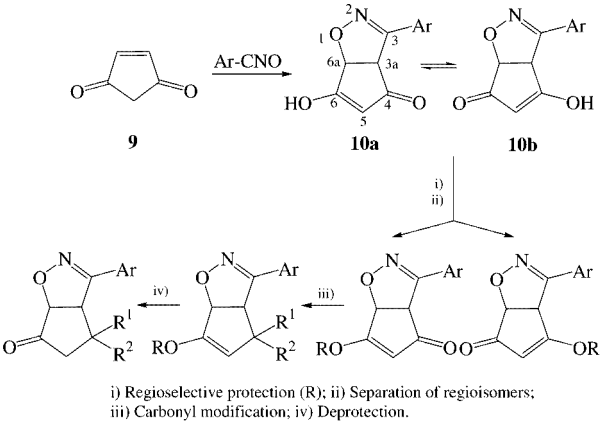


Scheme 2

As the functionalisation of the right side of the molecule was possible with good control of the stereochemistry, as may be expected looking at the structure of the starting material, we turned our attention to the functionalisation of the other side. The best solution could be to prepare isoxazolines with opposite regiochemistry in 1,3-dipolar cycloaddition. Coming back to the cycloaddition step, several attempts were made to find conditions that could revert the regiochemistry of the addition, however without appreciable success. Consequently, we needed to develop a new strategy. We envisaged in 4-cyclopentene-1,3-dione (**9**) a possibly appropriate molecule to realise our purpose.

Compound **9** has been used in several cycloadditions, mainly Diels–Alder reactions,[14–26] and, in one case, in 1,3-dipolar cycloadditions.[27] While **9** is present in solution exclusively as the keto tautomer, after cycloaddition it exists as an equilibrium of the two possible tautomers as shown in Scheme 3.[28] Thus, regioselective protection of the hydroxy group (6-OH) of **10a**, followed by separation of regioisomers, chemical elaboration of carbonyl group (C-4) and deprotection, should afford the desired inverted regioisomers (Scheme 3).

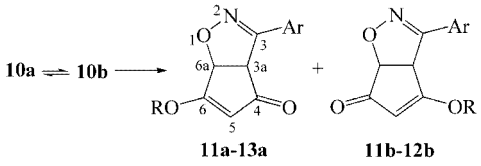
Compound **9** reacted smoothly with 2,6-dichlorobenzonitrile oxide to give, in very good yield, the cycloadduct **10**. The ^{1}H and ^{13}C NMR spectra confirmed that **10** is present



Scheme 3

in solution as a mixture of its enol tautomers in rapid equilibrium on the NMR time scale (absence of signals due to protons and carbon atoms belonging to a methylene group, and presence of a singlet due to 5-H, δ = 5.23 ppm and of the resonances due to C-5, δ = 104.2 ppm, and C-6, δ = 185.6 ppm). Protection of the hydroxy group (6-OH) as ether or ester derivative was then attempted. Methyl, benzyl and MEM (methoxyethoxymethyl) ethers were obtained according to Table 1 with good to poor regioselectivity dependent on the nature of the protection employed.

Table 1. Transformation of **10a**,**b** into ether derivatives



Reagents	Products	R	Yield (%)	**a**:**b**
CH_2N_2, MeOH	**11a**, **11b**	Me	86	2:1
$TiCl_4$, MeOH	**11a**, **11b**	Me	96	18:1
BnBr, Na_2CO_3, DMF	**12a**, **12b**	Bn	87	3:1
MEMCl, DIPEA	**13a**	$CH_2O(CH_2)_2OCH_3$	30	

The low selectivity obtained in the formation of the methyl ether using CH_2N_2 was increased using $TiCl_4$ in methanol.[29] Structure determination of compounds **11**–**13** was performed by X-ray and ^{1}H NMR analyses. An X-ray of the single crystal of the most abundant methyl ether derivative was obtained and the structure was reported (as ORTEP plot) in Figure 1, corresponding to **11a**.

The ^{1}H NMR spectra of these ether derivatives showed an important feature related to the chemical shifts of the protons bonded to the bridgehead carbons, 3a-H and 6a-H together with 5-H. In the more abundant regioisomers, these chemical shifts are (from low field to high field) singlet (5-H); doublet (6a-H) and doublet (3a-H), while in the less abundant regioisomer the order is doublet (6a-H); singlet (5-H) and doublet (3a-H). Combining this information

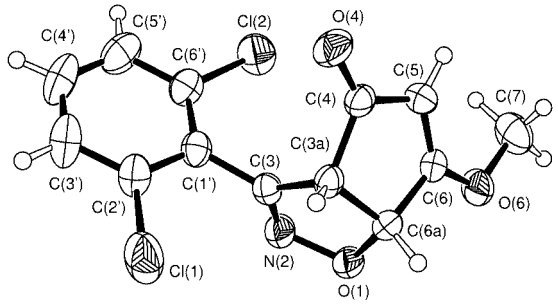
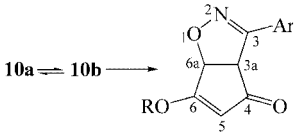


Figure 1. Crystal structure of compound **11a**; ellipsoids enclose 50 % probability

with X-ray analysis we could exploit the difference in chemical shifts to assign the correct structure to all the ethers obtained (**12a**, **12b**, **13a**). These results also show that steric hindrance plays an important role, as should be expected, in determining the ratio of the regioisomers.

Transformation of **10a**,**b** into the enol esters **14**−**18** gave exclusively one derivative in all the cases: acetylation, benzoylation, carbobenzoxylation, mesylation and tosylation (Table 2).

Table 2. Transformation of **10a,b** into enol esters



14-18

Reagents	Products	R	Yield (%)
AcCl, reflux	**14**	Ac	100
BzCl, TEA, CH_2Cl_2	**15**	Bz	90
CbzCl, $NaHCO_3$	**16**	Cbz	55
MsCl, TEA, THF	**17**	Ms	88
TsCl, NaH, THF	**18**	Ts	65

As ^1H NMR and NOE analyses were not helpful in assigning the regiochemistry, we turned to X-ray structure determination of the mesyl derivative **17**. The ORTEP plot of this derivative clearly shows that it has the required regiochemistry (Figure 2).

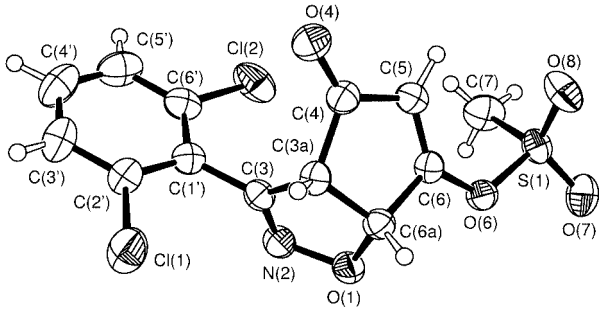
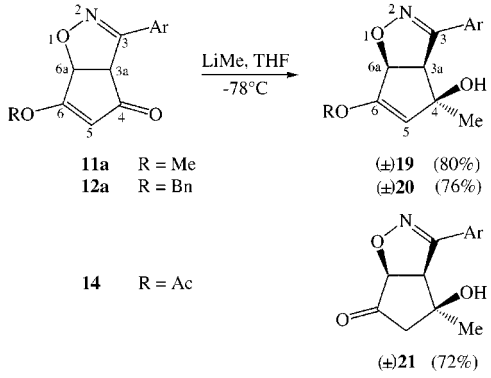


Figure 2. Crystal structure of compound **17**; ellipsoids enclose 50 % probability

Since all ester derivatives displayed the same chemical shift trend for 3a-H, 6a-H and 5-H, we assigned to them the same regiochemistry as that found for **17**.

As selective functionalisation of the left side of the molecule can be easily achieved using different protective groups, the reactivity of the carbonyl could be expected to be more versatile.

Transformation of the carbonyl group (C-4) into 4-hydroxy-4-alkyl group was carried out by direct treatment with alkyllithium. Derivatives **11a** and **12a** reacted with methyllithium to give the corresponding 4-hydroxy-4-methyl compounds **19** and **20**, respectively (Scheme 4). Acetyl derivative **14** reacted with methyllithium by contemporary deacetylation to give compound **21** (Scheme 4), as was immediately evident from its ^1H and ^{13}C NMR spectra (see Exp. Sect.).



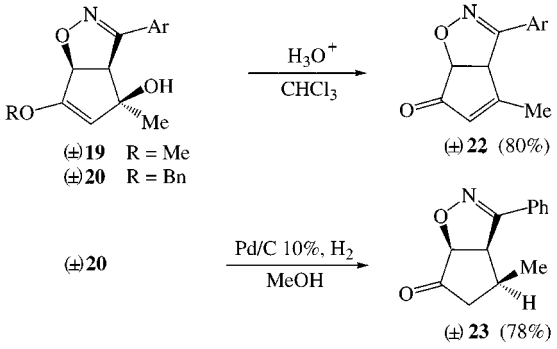
Scheme 4

These reactions were completely diastereoselective as only one (**19**, **20** or **21**) of the possible diastereoisomers was formed. The relative stereochemistry at C-4 was determined by NOE experiments. Irradiation of methyl protons gave NOE enhancements on 3a-H (3.9−4.2 %) and 6a-H (1.1−1.4 %) and thus the methyl group, 3a-H and 6a-H are on the same side of the cyclopentenone ring. The NOE experiments were also an indirect proof of the correct regiochemistry assigned to the corresponding ester derivatives.

The methyl and benzyl ether derivatives **19** and **20** were converted in the presence of catalytic amounts of acids into compound **22** through elimination of the intermediate β-hydroxy ketone (Scheme 5). Reduction of compound **20** by catalytic hydrogenation (Pd/C 10 %, H_2) gave direct access to 4-methyl derivative **23**, probably passing through an intermediate like **22**. In this case, the hydrogenation also affected the aromatic ring, transforming the 2,6-dichlorophenyl moiety into the phenyl moiety (Scheme 5).

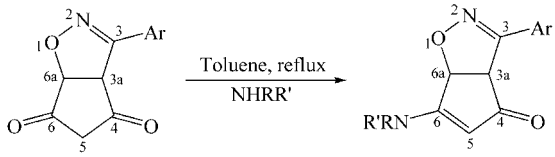
Products **22** and **23** were obtained as single stereoisomers. The relative stereochemistry at C-4 was assigned by NOE experiments. Enhancements at 3a-H (9.6 %) and 6a-H (1.9 %) followed the irradiation of 4-H signal.

Reduction of **11a**, **15**, **17** and **18** to the corresponding 4-hydroxy derivatives was accomplished using $NaBH_4/CeCl_3$. In these conditions the reduced and still-protected bicyclic



Scheme 5

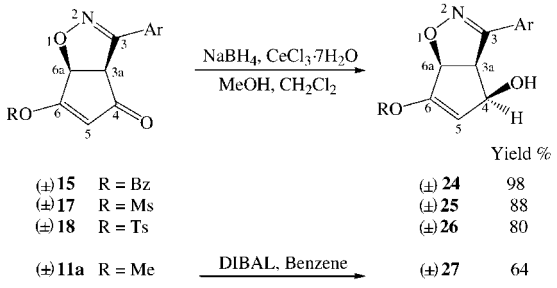
Table 3. Transformation of **10a**,**b** into enamines



10a,b (±)**28 - 31a,b**

NHRR′	Product	Yield (%)
Benzylamine	**28**	97
Pyrrolidine	**29**	97
L-Proline	**30a**,**b**	90
L-Proline methyl ester	**31a**,**b**	90

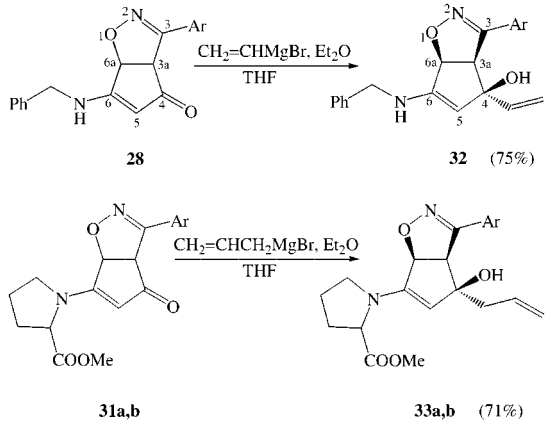
isoxazolines **24**, **25** and **26** were obtained in good yields (98, 88 and 80 % respectively; Scheme 6). NOE experiments confirmed the relative stereochemistry. Irradiation of 4-H gave NOE enhancements on 3a-H (8.2−10.4 %) and 6a-H (1.6−1.8 %) and again this result also confirmed the regiochemistry attributed to the tosyl and benzoyloxy derivatives. Compound **11a** could be reduced by treatment with DIBAL to the corresponding protected 4-hydroxy derivative **27**. The relative stereochemistry at C-4 was determined by NOE experiments and it is the same as that of compounds **24**−**26**.



Scheme 6

These results led us to probe further the molecular diversity that can be expressed through simple and stereoselective pathways by **10**. We tried direct amination through treatment of **10** with different amines in refluxing toluene (Table 3).[26] The reactions with benzylamine and pyrrolidine were completely regioselective giving **28** and **29** as single isomers, the stereochemistry of which was established by NOE analysis: irradiation of N−CH_2 protons gave NOE effects on 6a-H (2.2 and 2.8 % for **28** and **29,** respectively). Using L-proline, we obtained the expected diastereoisomer mixture, **30a,b**, in very good yield (Table 3), albeit we were not able to separate them by chromatography. A second attempt made employing the L-proline methyl ester gave the corresponding diastereoisomer mixture, **31a,b**, but once again the chromatographic separation failed.

Since the creation of a new stereogenic center at C-4 in ether or ester derivatives was completely diastereoselective, we wanted to see if this behaviour was also presented by the amine derivatives. The reaction of benzylamine derivative **28** with vinylmagnesium bromide gave only one diastereoisomer, **32** (Scheme 7), whose relative configuration was determined by NOE experiments. Irradiation of vinyl CH proton gave a NOE on 3a-H (3.4 %). Thus, the reaction of **31a,b** with allylmagnesium bromide was completely diastereoselective giving a mixture of only two stereoisomers, **33a,b** (Scheme 7). Their relative stereochemistry followed from NOE analysis: saturation of allylic methylene protons gave a NOE on corresponding 3a-H protons, 4.0 and 4.3 % respectively. Unfortunely the separation of these diastereoisomers was not possible.



Scheme 7

Thus, we have demonstrated that, starting from compounds **1** and **9**, it is possible to synthesise families of bicyclic isoxazoline scaffolds with complete regio- and stereocontrol, introducing up to four chiral centers with known relative stereochemistry. Moreover, we have developed a series of reliable chemical transformations around the eight-membered bicyclic scaffold for the parallel preparation of arrays

of isoxazoline derivatives. This methodology proved to be very general and may be extended to other α,β-unsaturated cyclic ketones and to different nitrile oxides.[12]

Experimental Section

General: Melting points were determined using a Kofler apparatus and are uncorrected. Elemental analysis was performed with a Perkin−Elmer 240C elemental analyser. NMR spectra were recorded with a Bruker AC 200 spectrometer (200 MHz). Chemical shifts are in ppm (δ) from TMS as an internal standard, and coupling constants (*J*) are in Hertz. Proton−proton NOE was measured with gated decoupling techniques by using NOE difference-pulse sequences. Silica-gel plates (Merck F_{254}) and silica gel 60 (Merck 40−230 mesh) were used for analytical TLC and for column chromatography, respectively. Extracts were dried with anhydrous sodium sulfate. Solvents were removed under reduced pressure in a rotary evaporator. Petroleum ether refers to the fraction of boiling range 40-60 °C. 4-Cyclopentene-1,3-dione (**9**), was purchased from Aldrich and always sublimed before use.

General Method for Obtaining (3a*SR*,4*SR*,6*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-methyl-4-vinyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazol-4,6-diol (6), and (3a*SR*,4*SR*,6*RS*,6a*SR*)-4-Allyl-3-(2,6-dichlorophenyl)6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazol-4,6-diol (7): Under dry nitrogen, the selected Grignard reagent in diethyl ether (1 M solution, 2 mL) was added to a solution of **1a** (200 mg, 0.67 mmol) in anhydrous THF (20 mL) under stirring at room temperature. The reaction was monitored by TLC (diethyl ether/petroleum ether, 3:1) until the disappearance of **1a**. The reaction was then treated with a saturated solution of NH_4Cl and extracted with diethyl ether (at least three times). The ethereal extracts were dried on anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (diethyl ether/petroleum ether, 3:1). The products (**6** or **7**) were obtained as solids.

6: Yield 0.160 g (73 %); m.p. 165−167 °C. ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 2.02 (m, 2 H, 5-H), 4.61 (d, *J* = 8.2 Hz, 1 H, 3a-H), 5.02 (br. d, *J* = 10.4 Hz, 1 H, CH_2=), 5.13 (br. d, *J* = 17.1 Hz, 1 H, CH_2=), 5.43 (br. s, 1 H, 6-OH), 5.45 (d, *J* = 8.2 Hz, 1 H, 6a-H), 5.47 (br. s, 1 H, 4-OH), 5.85 (dd, *J* = 10.4, *J* = 17.1 Hz, 1 H, CH=), 7.20−7.37 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7 (CH_3), 29.7 (C-5), 69.9 (C-3a), 86.2 (C-6), 90.8 (C-6a), 91.2 (C-4), 112.9 (CH_2), 125.0 (CH), 128.5 (CH), 130.3 (Cq), 132.7 (Cl−C), 142.1 (CH), 153.5 (C-3) ppm. $C_{15}H_{15}Cl_2NO_3$ (328.2): calcd. C 54.90, H 4.61, N 4.27; found C 54.68, H 4.46, N 4.15.

7: Yield 0.170 g (73 %); m.p. 174−176 °C. ^{1}H NMR ($CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 1.67 (d, $J_{5,5'}$ = 14.3 Hz, 1 H, 5-H), 1.93 (d, *J* = 14.3 Hz, 1 H, 5′-H), 2.18 (m, 2 H, CH_2), 4.70 (d, *J* = 8.2 Hz, 1 H, 3a-H), 4.88 (d, *J* = 8.2 Hz, 1 H, 6a-H), 4.90 (br. d, *J* = 11.0 Hz, 1 H, CH_2=), 5.04 (br. d, *J* = 17.6 Hz, 1 H, CH_2=), 5.43 (br. s, 1 H, 6-OH), 5.58 (m, 1 H, CH=), 7.20−7.40 (m, 3 H, ArH) ppm. $C_{16}H_{17}Cl_2NO_3$ (342.2): calcd. C 56.15, H 5.01, N 4.09; found C 55.94, H 4.87, N 4.15.

(3a*SR*,4*SR*,6*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-ethylamino-6-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazol-6-ol (8): To a solution of ethylamine (5 mL, 5.2 mmol) were added a solution (0.20 mL, 5 N) of HCl/MeOH, **1a** (120 mg, 0.4 mmol) and $NaCNBH_3$ (330 mg, 0.4 mmol) under stirring at room temperature. The reaction was monitored by TLC (diethyl ether/petroleum ether, 3:1) until the **1a** disappeared. The reaction was then treated with HCl to pH ≤ 2 and methanol was evaporated under reduced pressure. The residue was treated with 5 mL of water and extracted with diethyl ether. The aqueous solution was treated with solid KOH to pH = 10, saturated with NaCl and extracted with diethyl ether. The ethereal extracts were dried on anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (diethyl ether/petroleum ether, 3:1). The product **8** was obtained as a pale yellow solid. **8:** Yield 0.084 g (64 %); m.p. 156−158 °C. ^{1}H NMR ($CDCl_3$): δ =0.52 [t, *J* = 7.3 Hz, 3 H, CH_3(Et)], 1.86 (s, 3 H, CH_3), 2.00−2.20 (m, 2 H, 5′-H, N−CH_2), 2.35−2.55 (m, 2 H, 5-H, N−CH_2), 3.97 (m, 1 H, 4-H), 4.74 (dd, *J* = 6.9, *J* = 8.2 Hz, 1 H, 3a-H), 5.43 (d, *J* = 8.2 Hz, 1 H, 6a-H), 5.58 (br. s, 1 H, OH), 7.20−7.40 (m, 3 H, ArH) ppm. $C_{15}H_{18}Cl_2N_2O_2$ (329.2): calcd. C 54.72, H 5.51, N 8.51; found C 54.54, H 5.33, N 8.67.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6(4)-hydroxy-3a,6a-dihydrocyclopenta[*d*]isoxazol-4(6)-one (10): To a stirred solution of freshly sublimed 4-cyclopentene-1,3-dione (**9,** 340 mg, 3.54 mmol) in dichloromethane (10 mL) was added dropwise a solution of 2,6-dichlorobenzonitrile oxide (660 mg, 5.51 mmol) in dichloromethane (5 mL) at room temperature. The solution immediately became opalescent and a white solid precipitated during the reaction. When **9** had disappeared (TLC; diethyl ether/petroleum ether, 2:1), the white precipitate of **10** was filtered. **10:** Yield 855 mg (85 %); m.p. 267−268 °C. ^{1}H NMR ([D_6]DMSO): δ = 3.40 (br. s, 1 H, OH), 4.32 (d, *J* = 7.8 Hz, 1 H, 3a-H), 5.23 (s, 1 H, 5-H), 5.74 (d, *J* = 7.8 Hz, 1 H, 6a-H), 7.51−7.62 (m, 3 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 60.7 (C-3a), 82.6 (C-6a), 104.2 (C-5), 126.8 (Cq), 127.9 (CH), 128.5 (CH), 132.3 (C−Cl), 152.0 (C-3), 185.6 (C-6), 195.6 (C-4) ppm. $C_{12}H_7Cl_2NO_3$ (284.1): calcd. C 50.73, H 2.48, N 4.93; found C 50.61, H 2.37, N 4.82.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-methoxy-3a,6a-dihydrocyclopenta[*d*]isoxazol-4-one (11a), and (3a*SR*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-methoxy-3a,6a-dihydrocyclopenta[*d*]isoxazol-6-one (11b). Method A: To a stirred suspension of **10** (300 mg, 1.06 mmol) in methanol (10 mL) was added dropwise a solution of diazomethane in diethyl ether. During the addition, the cycloadduct **10** was solubilized and the solution became clear. At the end of the reaction (TLC, diethyl ether/petroleum ether, 2:1), the two regioisomers **11a** and **11b** (2:1 ratio) were separated by column chromatography (diethyl ether/petroleum ether, 3:1) (271 mg, 86 %).

Method B: To a stirred solution of **10** (400 mg, 1.41 mmol) in methanol (60 mL) was added a 1 M solution of $TiCl_4$ in dichloromethane (0.5 mL, 0.5 mmol) at room temperature. When the reaction was completed (TLC; diethyl ether/petroleum ether 3:1), water (10 mL) was added to the solution. The solution was then concentrated under reduced pressure and the residue was extracted with diethyl ether. The organic extracts were combined, dried on Mg_2SO_4, concentrated under vacuum and, after column chromatography (ethyl ether/petroleum ether 3:1), gave the separated regioisomers **11a** and **11b** (403 mg, 96 %) in 18:1 ratio.

11a: White solid, m.p. 190−192 °C (crystallized from ether). ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3 H, CH_3), 4.41 (d, *J* = 8.1 Hz, 1 H, 3a-H), 5.37 (s, 1 H, 5-H), 5.68 (d, *J* = 8.1 Hz, 1 H, 6a-H), 7.27−7.39 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 59.7 (CH_3), 61.4 (C-3a), 82.2 (C-6a), 104.0 (C-5), 126.2 (Cq), 128.3 (CH), 128.5 (CH), 131.5 (C−Cl), 151.8 (C-3), 185.4 (C-6), 195.8 (C-4) ppm. $C_{13}H_9Cl_2NO_3$ (298.1): calcd. C 52.37, H 3.04, N 4.70; found C 52.23, H 2.96, N 4.62.

11b: White solid, m.p. 153−155 °C. ^{1}H NMR ($CDCl_3$): δ = 3.81 (s, 3 H, CH_3), 4.68 (dd, *J* = 8.1, *J* = 1.0 Hz, 1 H, 3a-H), 5.24 (d,

J = 8.1 Hz, 1 H, 6a-H), 5.40 (d, J = 1.0 Hz, 1 H, 5-H), 7.33−7.43 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.8 (CH_3), 59.8 (C-3a), 83.7 (C-6a), 103.6 (C-5), 127.4 (Cq), 128.1 (CH), 128.3 (CH), 131.4 (C−Cl), 151.5 (C-3), 186.9 (C-4), 192.0 (C-6) ppm. $C_{13}H_9Cl_2NO_3$ (298.1): calcd. C 52.37, H 3.04, N 4.70; found C 52.27, H 2.94, N 4.64.

(3a*SR*,6a*SR*)-6-Benzyloxy-3-(2,6-dichlorophenyl)-3a,6a-dihydrocyclopenta[*d*]isoxazol-4-one (12a), and (3a*RS*,6a*SR*)-4-benzyloxy-3-(2,6-dichlorophenyl)-3a,6a-dihydrocyclopenta[*d*]isoxazol-6-one (12b): To a solution of **10** (700 mg, 2.46 mmol) in anhydrous DMF (4 mL) were added anhydrous Na_2CO_3 (522 mg, 4.93 mmol) and benzyl bromide (0.2 mL, 2.46 mmol). When the starting compound disappeared (TLC; petroleum ether/diethyl ether, 1:3), the solution was diluted with water (20 mL) and extracted with dichloromethane. The organic extracts were dried with Na_2SO_4 and the solvent evaporated under vacuum. Compounds **12a** and **12b** were obtained as a mixture in a 3:1 ratio. Separation by column chromatography (ethyl ether/petroleum ether, 3:1) gave **12a** (600 mg) and **12b** (200 mg) (total yield 87 %).

12a: White solid, m.p. 185−186 °C. ^{1}H NMR ($CDCl_3$): δ = 4.40 (d, J = 8.0 Hz, 1 H, 3a-H), 5.12 (d, J = 11.9 Hz, 1 H, CH_2), 5.19 (d, J = 11.9 Hz, 1 H, CH_2), 5.41 (s, 1 H, 5-H), 5.73 (d, J = 8.0 Hz, 1 H, 6a-H), 7.22−7.44 (m, 8 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 61.2 (C-3a), 74.6 (C-7), 82.5 (C-6a), 105.3 (C-5), 126.8 (Cq), 127.8 (CH), 128.9 (CH), 129 (CH), 131.4 (CH), 133.8 (C−Cl), 151.7 (C-3), 184.0 (C-6), 195.9 (C-4) ppm. $C_{19}H_{13}Cl_2NO_3$ (374.2): calcd. C 60.98, H 3.50, N 3.74; found C 60.84, H 3.40, N 3.67.

12b: White solid, m.p. 171−173 °C. ^{1}H NMR ($CDCl_3$): δ = 4.73 (dd, J = 8.7, J = 1.4 Hz, 1 H, 3a-H), 4.91 (d, J = 11.2 Hz, 1 H, CH_2), 4.99 (d, J = 11.2 Hz, 1 H, CH_2), 5.24 (d, J = 8.7 Hz, 1 H, 6a-H), 5.48 (d, J = 1.4 Hz, 1 H, 5-H) 7.03−7.11 (m, 2 H, ArH), 7.21−7.37 (m, 6 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.9 (C-3a), 74.9 (CH_2), 83.5 (C-6a), 104.4 (C-5), 127.8 (CH), 128.1 (CH), 128.6 (CH), 129.0 (CH), 131.2 (CH), 133.3 (C−Cl), 151.4 (C-3), 198.1 (C-6) ppm. $C_{19}H_{13}Cl_2NO_3$ (374.2): calcd. C 60.98, H 3.50, N 3.74; found C 60.86, H 3.37, N 3.62.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-(2-methoxyethoxymethoxy)-3a,6a-dihydrocyclopenta[*d*]isoxazol-4-one (13a): To a stirred solution of **10** (300 mg, 1.06 mmol) in dichloromethane (20 mL) were added MEMCl (198 mg, 1.58 mmol) and DIPEA (205 mg, 1.30 mmol). The reaction was monitored by TLC (ethyl ether/petroleum ether, 3:1) until compound **10** disappeared. The solvent was evaporated under reduced pressure. The residue was treated with water and extracted with dichloromethane. The organic extracts were dried, the solvent evaporated and the residue purified by column chromatography (chloroform/methanol, 9:1). Compound **13a** was obtained as an oil. **13a:** Yield 118 mg (30 %). ^{1}H NMR ($CDCl_3$): δ = 3.35 (s, 3 H, OCH_3), 3.50 (m, 2 H, OCH_2), 3.65 (m, 2 H, OCH_2), 4.34 (d, J = 7.8 Hz, 1 H, 3a-H), 5.25 (d, J = 17.8 Hz, 1 H, OCH_2O), 5.33 (d, J = 17.8 Hz, 1 H, OCH_2O), 5.51 (s, 1 H, 5-H), 5.67 (d, J = 7.8 Hz, 1 H, 6a-H), 7.25−7.35 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 58.8 (OCH_3), 60.8 (C-3a), 66.7 (OCH_2), 71.6 (OCH_2), 82.4 (C-6a), 95.5 (OCH_2O), 106.6 (C-5), 126.7 (Cq), 128.1 (CH), 131.3 (CH), 134.9 (C−Cl), 151.6 (C-3), 181.7 (C-6), 196.1 (C-4) ppm. $C_{16}H_{15}Cl_2NO_5$ (372.2): calcd. C 51.63, H 4.06, N 3.76; found C 51.49, H 3.95, N 3.61.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-oxo-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Acetate (14): A suspension of compound **10** (430 mg, 1.5 mmol) in acetyl chloride (5 mL) was heated under reflux (after a few hours, compound **10** was completely dissolved and the solution became clear). The reaction was followed by TLC (chloroform/methanol, 2:1) until the starting compound disappeared. The solution was concentrated under vacuum. The residue was treated with petroleum ether and the solvent was eliminated by distillation under reduced pressure. The steps in this last passage were repeated three times and, at the end, compound **14** was obtained as a white solid. Yield 493 mg (quantitative yield); m.p. 157−158 °C. ^{1}H NMR ($CDCl_3$): δ = 2.54 (s, 3 H, CH_3), 4.57 (d, J = 7.8 Hz, 1 H, 3a-H), 6.05 (d, J = 7.8 Hz, 1 H, 6a-H), 6.58 (s, 1 H, 5-H), 7.43−7.58 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.2 (CH_3), 56.8 (C-3a), 80.2 (C-6a), 120.0 (C-5), 126.4 (Cq), 128.6 (CH), 129.3 (CH), 130.0 (C−Cl), 148.3 (C-3), 168.3 (COO), 172.0 (C-6), 196.4 (C-4) ppm. $C_{14}H_9Cl_2NO_4$ (326.1): calcd. C 51.56, H 2.78, N 4.29; found C 51.44, H 2.69, N 4.17.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-oxo-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Benzoate (15): To a suspension of **10** (390 mg, 1.37 mmol) in chloroform (10 mL) were added benzoyl chloride (0.16 mL, 1.38 mmol) and triethylamine (0.57 mL, 4.1 mmol). After these additions, the suspension became a clean solution. The solution was kept at 50 °C for 2 h (TLC; diethyl ether/petroleum ether, 3:1). The solution was then concentrated under vacuum, treated with water (10 mL) and extracted with chloroform. After the usual workup, the extracts gave compound **15** as a solid. Yield 480 mg (90 %); m.p. 181−182 °C. ^{1}H NMR ($CDCl_3$): δ = 4.46 (d, J = 7.7 Hz, 1 H, 3a-H), 6.02 (d, J = 7.7 Hz, 1 H, 6a-H), 6.59 (s, 1 H, 5-H), 7.30−7.70 (m, 6 H, ArH), 8.20 (d, J = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 60.1 (C-3a), 82.9 (C-6a), 115.8 (C-5), 126.5 (Cq), 128.3 (CH), 128.9 (CH), 130.5 (Cq), 130.7 (CH), 131.6 (CH), 134.9 (C−Cl), 151.4 (C-3), 174.1 (C-6), 196.9 (C-4) ppm. $C_{19}H_{11}Cl_2NO_4$ (388.2): calcd. C 58.78, H 2.86, N 3.61; found C 58.63, H 2.74, N 3.53.

Benzyl (3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-oxo-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Carbonate (16): To a stirred suspension of **10** (200 mg, 0.70 mmol) in water (2 mL) were added acetone (5 mL) and sodium hydrogen carbonate (700 mg, 0.84 mmol). The stirring was continued until complete dissolution. Then benzyl chloroformate (290 mg, 1.70 mmol) was added dropwise. The reaction was followed by TLC (dichloromethane) until the disappearance of **10**. The solvent was evaporated under reduced pressure and the residue was treated with water and extracted with dichloromethane. The organic extracts were combined, dried with anhydrous sodium sulfate, filtered and the solvents evaporated to dryness. The residue was purified by chromatography (dichloromethane/*n*-hexane, 4:1) to give compound **16**. Yield 162 mg (55 %); m.p. 169−171 °C. ^{1}H NMR ($CDCl_3$): δ = 4.40 (d, J = 7.8 Hz, 1 H, 3a-H), 5.30 (s, 2 H, CH_2), 5.86 (d, J = 7.8 Hz, 1 H, 6a-H), 6.38 (s, 1 H, 5-H), 7.26−7.45 (m, 8 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 60.4 (C-3a), 71.6 (CH_2), 82.2 (C-6a), 114.8 (C-5), 126.3 (Cq), 126.8 (Cq), 128.2 (CH), 128.7 (CH), 128.7 (CH), 128.9 (CH), 131.6 (CH), 133.4 (C−Cl), 150.0 (O−C(O)−O), 151.2 (C-3), 174.2 (C-6), 196.1 (C-4) ppm. $C_{20}H_{13}Cl_2NO_5$ (418.2): calcd. C 57.44, H 3.13, N 3.35; found C 57.33, H 3.04, N 3.26.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-oxo-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Methanesulfonate (17): To a stirred solution of **10** (200 mg, 0.70 mmol) in anhydrous THF (15 mL) kept at 0 °C were added triethylamine (0.4 mL, 1.85 mmol) and then mesyl chloride (168 mL, 2.15 mmol) . After the addition, the solution turned opalescent. The temperature was increased to 40 °C and the reaction was followed by TLC (ethyl ether/petroleum ether, 3:1) to the disappearance of **10**. The solid was filtered off and the solution was concentrated under reduced pressure. The residue was treated with water and extracted with dichloromethane. The organic extracts were dried on Na_2SO_4 and concentrated under vacuum.

Compound **17** was obtained as a white solid. Yield 205 mg (88 %); m.p. 162−163 °C; (crystallized from *n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.36 (s, 3 H, CH_3), 4.49 (d, *J* = 8.0 Hz, 1 H, 3a-H), 5.68 (d, *J* = 8.0 Hz, 1 H, 6a-H), 6.21 (s, 1 H, 5-H), 7.34−7.41 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.0 (CH_3), 61.2 (C-3a), 82.2 (C-6a), 115.2 (C-5), 126.0 (Cq), 128.3 (CH), 131.8 (CH), 151.4 (C-3), 172.9 (C-6), 194.8 (C-6) ppm. $C_{13}H_9Cl_2NO_5S$ (362.2): calcd. C 43.11, H 2.50, N 3.87; found C 42.95, H 2.40, N 3.78.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-oxo-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Toluene-4-sulfonate (18): To a suspension of NaH (450 mg, 19 mmol) in anhydrous THF (15 mL) kept at 0 °C was added dropwise a solution of **10** (500 mg, 1.76 mmol) in anhydrous THF (25 mL). The mixture was stirred at room temperature for 4 h and then tosyl chloride (0.67 mL, 3.52 mmol) was added dropwise. The suspension was treated with a 1 % solution of Na_2CO_3, giving a clear solution. The THF was evaporated under vacuum and the remaining solution was extracted with dichloromethane. The organic extract was dried with anhydrous Na_2SO_4, filtered and the solvents evaporated to dryness. The residue was purified by column chromatography (dichloromethane/*n*-hexane, 4:1). Compound **18** was obtained as a white solid. Yield 501 mg (65 %); m.p. 187−189 °C. ^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 4.37 (d, *J* = 8.0 Hz, 1 H, 3a-H), 5.71 (d, *J* = 8.0 Hz, 1 H, 6a-H), 6.13 (s, 1 H, 5-H), 7.21−7.45 (m, 5 H, ArH), 7.89 (d, *J* = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.7 (CH_3), 60.9 (C-3a), 82.3 (C-6a), 114.4 (C-5), 125.1 (Cq), 128.2 (CH), 128.6 (CH), 130.2 (CH), 131.7 (CH), 147.1 (C-3), 173.4 (C-6), 195.2 (C-4) ppm. $C_{19}H_{13}Cl_2NO_5S$ (438.3): calcd. C 52.07, H 2.99, N 3.20; found C 51.92, H 2.86, N 3.11.

General Method for the Synthesis of (3a*RS*,6a*SR*,4*SR*)-3-(2,6-Dichlorophenyl)-6-methoxy-4-methyl-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-4-ol (19), and (3a*RS*,6a*SR*,4S*R*)-6-Benzyloxy-3-(2,6-dichlorophenyl)-4-methyl-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-4-ol (20): To a solution of **11a** or **12a** (1 mmol) in anhydrous THF (6 mL) was added a solution 1.4 M of CH_3Li in diethyl ether (0.82 mL, 1.15 mmol) at −78 °C. The reaction was kept at −78 °C for 30 min, then for at 0 °C for 30 min and finally it was allowed to reach room temperature. The reaction was followed by TLC (dichloromethane) until the starting compound disappeared. The solvent was evaporated under reduced pressure and the residue was treated with a 2M solution of glacial acetic acid in diethyl ether (0.5 mL) and then water (6 mL). The solution was extracted with diethyl ether. The extracts were washed with a saturated $NaHCO_3$ solution and then with brine. After the usual workup, the residue was purified by column chromatography (ethyl ether/*n*-hexane, 2:1) to give the product as a white solid.

19: Yield 251 mg (80 %); m.p. 175−177 °C. ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 3.72 (s, 3 H, OCH_3), 4.59 (dd, *J* = 9.5 Hz, 1 H, 3a-H), 4.78 (s, 1 H, 5-H), 5.49 (d, *J* = 9.5 Hz, 1 H, 6a-H), 7.19−7.38 (m, 3 H, Ar) ppm. $C_{14}H_{13}Cl_2NO_3$ (314.2): calcd. C 53.52, H 4.17, N 4.46; found C 53.38, H 4.08, N 4.39.

20: Yield 296 mg (76 %); m.p. 182−184 °C. ^{1}H NMR ($CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 4.59 (d, *J* = 9.5 Hz, 1 H, 3a-H), 4.83 (s, 1 H, 5-H), 4.92 (s, 2 H, CH_2), 5.61 (d, *J* = 9.5 Hz, 1 H, 6a-H), 7.19−7.42 (m, 8 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.5 (CH_3), 61.7 (C-3a), 81.6 (C-4), 86.6 (C-6a), 107.2 (C-5), 126.9 (Cq), 127.4 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 129.6 (Cq), 132.4 (CH), 135.7 (C−Cl), 153.9 (C-3), 156.3 (C-6) ppm. $C_{20}H_{17}Cl_2NO_3$ (390.3): calcd. C 61.55, H 4.39, N 3.59; found C 61.41, H 4.23, N 3.45.

(3a*RS*,6a*SR*,4*RS*)-3-(2,6-Dichlorophenyl)-4-hydroxy-4-methyl-3a,4,5,6a-tetrahydrocyclopenta[*d*]isoxazol-6-one (21): To a solution of **14** (480 mg, 1.47 mmol) in anhydrous THF (7.5 mL) was added a solution (1.2 mL, 1.4 M in ether) of $LiCH_3$ (1.71 mmol) at −78 °C. The reaction was kept at −78 °C for 30 min, then at 0 °C for 30 min and finally at room temperature. The reaction was followed by TLC (dichloromethane) until the starting compound disappeared. The solvent was evaporated under reduced pressure and the residue was treated with a 2 M solution of acetic acid in diethyl ether (0.9 mL) and then with water (8 mL). The solution was extracted with diethyl ether and the organic extracts were washed with a saturated $NaHCO_3$ solution and then with brine. After workup the solid obtained was purified by column chromatography (dichloromethane) affording **21**. Yield 334 mg (72 %); m.p. 187−188 °C. ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 2.52 (dd, *J* = 16.9, *J* = 1.3 Hz, 1 H, 5′-H), 2.89 (br. d, *J* = 16.9 Hz, 1 H, 5-H), 3.63 (br. s, 1 H, OH), 4.64 (dd, *J* = 9.1, *J* = 1.2 Hz, 1 H, 3a-H), 4.98 (dd, *J* = 9.1, *J* = 1.3 Hz, 1 H, 6a-H), 7.27−7.41 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.6 (CH_3), 50.8 (C-5), 63.5 (C-3a), 76.3 (C-4), 85.9 (C-6a), 128.1 (Cq), 128.6 (CH), 130.8 (CH), 132.9 (C−Cl), 153.6 (C-3), 206.2 (C-6) ppm. $C_{13}H_{11}Cl_2NO_3$ (300.1): calcd. C 52.02, H 3.69, N 4.67; found C 51.89, H 3.56, N 4.58.

(3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-3a,6a-dihydro-4-methylcyclopenta[*d*]isoxazol-6-one (22): A solution of **19** or **20** (1 mmol) in chloroform (15 mL) was kept under stirring at room temperature. The reaction was monitored by TLC (dichloromethane) until the disappearance of the starting compound (24 h). The solvent was evaporated under reduced pressure to give a white solid. Yield 226 mg (80 %); m.p. 181−183 °C. ^{1}H NMR ($CDCl_3$): δ = 1.88 (s, 3 H, CH_3), 4.75 (d, *J* = 8.2 Hz, 1 H, 3a-H), 5.15 (d, *J* = 8.2 Hz, 1 H, 6a-H), 6.05 (s, 1 H, 5-H), 7.25−7.49 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.2 (CH_3), 60.0 (C-3a), 83.4 (C-6a), 127.5 (Cq), 128.5 (C-5), 130.8 (CH), 131.6 (CH), 135.2 (C−Cl), 152.2 (C-3), 174.6 (C-4), 201.9 (C-6) ppm. $C_{13}H_9Cl_2NO_2$ (282.1): calcd. C 55.34, H 3.22, N 4.96; found C 55.24, H 3.10, N 4.83.

(3a*RS*,6a*SR*,4*SR*)-4-Methyl-3-phenyl-3a,4,5,6a-tetrahydrocyclopenta[*d*]isoxazol-6-one (23): To a solution of **20** (348 mg, 0.9 mmol) in methanol (20 mL) was added Pd/C (10 %, 10 mg). The suspension was subjected to hydrogenation at atmospheric pressure. The reaction was monitored by TLC (diethyl ether/petroleum ether, 3:1) until the starting compound disappeared. The suspension was filtered through celite and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (diethyl ether/petroleum ether, 1:1) giving compound **23** as a solid. Yield 206 mg (78 %); m.p. 132−133 °C. ^{1}H NMR ($CDCl_3$): δ = 0.84 (d, *J* = 7.5 Hz, 3 H, CH_3), 2.26 (dd, *J* = 17.6, *J* = 2.2 Hz, 1 H, 5-H), 2.55 (dd, *J* = 17.6, *J* = 2.2 Hz, 1 H, 5′−H), 2.77 (m, *J* = 17.6, *J* = 2.2, *J* = 7.5, *J* = 8.1 Hz, 1 H, 4-H), 4.39 (dd, *J* = 10.2, *J* = 8.1, 1 H, 3a-H), 4.85 (d, *J* = 10.2 Hz, 1 H, 6a-H), 7.40−7.49 (m, 3 H, ArH), 7.62−7.70 (m, 2 H, ArH) ppm. ^{13}C NMR: δ = 17.9 (CH_3), 31.9 (C-4), 45.3 (C-5), 53.5 (C-3a), 85.7 (C-6a), 126.9 (CH), 128.5 (CH), 129.6 (Cq), 130.3 (CH), 158.0 (C-3), 208.9 (C-6) ppm. $C_{13}H_{11}Cl_2NO_2$ (284.1): calcd. C 54.95, H 3.90, N 4.93; found C 54.81, H 3.78, N 4.82.

General Method for the Synthesis of (3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-hydroxy-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Benzoate (24), (3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-4-hydroxy-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Methanesulfonate (25), and (3a*RS*,6a*SR*)-3-(2,6-Dichloro-phenyl)-4-hydroxy-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl Toluene-4-sulfonate (26): To a solution of the ester derivative (1 mmol) in 10 mL of dichloromethane were added a solution of $CeCl_3 \cdot 7H_2O$ (373 mg, 1 mmol) in methanol (4 mL) and then $NaBH_4$ (380 mg, 1 mmol). The reaction was moni-

tored by TLC (dichloromethane) until the disappearance of the starting compound. After evaporation of the solvents under vacuum, the residue was treated with 6 N HCl (6 mL) and extracted with dichloromethane. The organic extracts were dried with Na_2SO_4, filtered and the solvents evaporated under reduced pressure. The reaction products were obtained as white solids.

24: Yield 382 mg (98 %); m.p. 173−174 °C. ^{1}H NMR ($CDCl_3$): δ = 4.70 (br. s, 1 H, OH), 4.89 (dd, *J* = 9.1, *J* = 7.3 Hz, 1 H, 3a-H), 5.11 (dd, *J* = 7.3, *J* = 1.9 Hz, 1 H, 4-H), 5.83 (d, *J* = 9.1 Hz, 1 H, 6a-H), 6.14 (d, *J* = 1.9 Hz, 1 H, 5-H), 7.25−7.65 (m, 6 H, ArH), 8.16 (d, *J* = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 54.9 (C-3a), 75.0 (C-6a), 86.2 (C-4), 118.3 (C-5), 128.6 (CH), 128.7 (CH), 129.5 (Cq), 130.3 (CH), 130.7 (CH), 133.8 (CH), 134.5 (C−Cl), 148.6 (C-6), 153.2 (C-3), 163.5 (COO) ppm. $C_{19}H_{13}Cl_2NO_4$ (390.2): calcd. C 58.48, H 3.36, N 3.59; found C 58.37, H 3.24, N 3.48.

25: Yield 319 mg (88 %); m.p. 158−160 °C. ^{1}H NMR ($CDCl_3$): δ = 3.33 (s, 3 H, CH_3), 4.45 (br. s, 1 H, OH), 4.89 (dd, *J* = 8.5, *J* = 7.1 Hz, 1 H, 3a-H), 5.18 (dd, *J* = 7.1, *J* = 1.1 Hz, 1 H, 4-H), 5.64 (d, *J* = 8.5 Hz, 1 H, 6a-H), 5.95 (d, *J* = 1.1 Hz, 1 H, 5-H), 7.35−7.46 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 37.6 (CH_3), 56.6 (C-3a), 73.2 (C-6a), 85.6 (C-4), 121.9 (C-5), 126.4 (Cq), 129.0 (CH), 131.4 (CH), 135.6 (C−Cl), 147.2 (C-3), 155.9 (C-6) ppm. $C_{13}H_{11}Cl_2NO_5S$ (364.2): calcd. C 42.87, H 3.04, N 3.85; found C 42.79, H 2.95, N 3.77.

26: Yield 350 mg (80 %); m.p. 150−152 °C. ^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 4.75 (dd, *J* = 9.0, *J* = 7.3 Hz, 1 H, 3a-H), 4.95 (dt, *J* = 7.3, *J* = 1.6, *J* = 7.3 Hz, 1 H, 4-H), 5.43 (d, *J* = 9.0 Hz, 1 H, 6a-H), 5.85 (d, *J* = 1.6 Hz, 1 H, 5-H), 7.20−7.29 (m, 5 H, ArH), 7.35 (d, *J* = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.7 (CH_3), 54.9 (C-3a), 74.3 (C-6a), 85.2 (C-4), 118.3 (C-5), 128.5 (CH), 128.6 (CH), 129.2 (Cq), 130.0 (CH), 130.7 (CH), 132.0 (Cq), 134.5 (C−Cl), 145.9 (C-6), 147.6 (Cq), 153.2 (C-3) ppm. $C_{19}H_{15}Cl_2NO_5S$ (440.3): calcd. C 51.83, H 3.43, N 3.18; found C 51.71, H 3.34, N 3.11.

(3a*SR*,6a*SR*,4*SR*)-3-(2,6-Dichlorophenyl)-6-methoxy-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-4-ol (27): To a solution of **11a** (200 mg, 0.66 mmol) in benzene (8 mL) were added dropwise under stirring, 46 μL (0.80 mmol) of DIBAL at 10 °C. The reaction was monitored by TLC (diethyl ether/petroleum ether, 3:1). The reaction was treated with 10 mL of water and 1 mL of 1 M HCl. The aqueous phase was extracted with 10 mL of diethyl ether. To the ethereal extract were added 5 mL of THF and 5 mL of 1 M HCl. The solution was kept under stirring for 30 min at 20 °C. The organic phase was separated and washed with a saturated $NaHCO_3$ solution. The organic phase was then dried on anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography giving **27** as an oil (64 % yield). Yield 192 mg (64 %); oil. ^{1}H NMR ($CDCl_3$): δ = 3.73 (s, 3 H, CH_3), 4.75−4.88 (m, 2 H, 3a-H, 4-H), 4.92 (br. s, 1 H, 5-H), 5.45 (d, *J* = 9.4 Hz, 1 H, 6a-H), 7.20−7.40 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.3 (CH_3), 57.8 (C-3a), 75.1 (C-4), 86.3 (C-6a), 101.3 (C-5), 128.5 (Cq), 128.6 (CH), 130.5 (CH), 134.3 (C−Cl), 150.3 (C-3), 159.5 (C-6) ppm. $C_{13}H_{11}Cl_2NO_3$ (300.1): calcd. C 52.02, H 3.69, N 4.67; found C 51.89, H 3.55, N 4.77.

General Method for the Synthesis of (3a*RS*,6a*SR*)- 6-Benzylamino-3-(2,6-dichlorophenyl)-3a,6a-dihydrocyclopenta[*d*]isoxazol-4-one (28), (3a*RS*,6a*SR*)-3-(2,6-Dichlorophenyl)-6-pyrrolidin-1-yl-3a,6a-dihydrocyclopenta[*d*]isoxazol-4-one (29), (3a*RS*,6a*SR*)-1-[3-(2,6-Dichlorophenyl)-4-oxo-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl]-(2*S*)-pyrrolidine-2-carboxylic Acid (30a,b), and Methyl (3a*RS*,6a*SR*)-1-[3-(2,6-Dichlorophenyl)-4-oxo-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl]-(2*S*)-pyrrolidine-2-carboxylate (31a,b): To a suspension of **10** (1 mmol) in toluene (20 mL) was added the amine (1.2 mmol) and the reaction mixture was kept at reflux for 24 h. During this period compound **10** dissolved. The solution was cooled and the solvent was evaporated under reduced pressure. The residue was washed with diethyl ether and filtered. The remaining reaction products were solids (**28** and **29**) or oils (**30a,b** and **31a,b**).

28: Yield 359 mg (97 %); m.p. 172−174 °C. ^{1}H NMR ($CDCl_3$): δ = 4.45 (br. d, 3 H, 3a-H, N−CH_2), 5.03 (s, 1 H, 5-H), 5.71 (d, *J* = 8.0 Hz, 1 H, 6a-H), 5.95 (br. s, 1 H, NH), 7.23−7.40 (m, 8 H, ArH) ppm. ^{13}C NMR: δ = 49.5 (N−CH_2), 61.4 (C-3a), 82.4 (C-6a), 99.0 (C-5), 127.1 (Cq), 127.5 (CH), 127.9 (CH), 128.2 (CH), 129.0 (CH), 131.2 (CH), 135.7 (C−Cl), 153.6 (C-3), 171.6 (C-6-), 194.0 (C-4) ppm. $C_{19}H_{14}Cl_2N_2O_2$ (373.2): calcd. C 61.14, H 3.78, N 7.51; found C 60.98, H 3.68, N 7.39.

29: Yield 327 mg (97 %); m.p. 157−158 °C. ^{1}H NMR ($CDCl_3$): δ = 2.03 (br. d, 4 H, CH_2−CH_2), 3.37 (m, 2 H, 2 × N−CH), 3.63 (m, 1 H, N−CH), 3.91 (m, 1 H, N−CH), 4.33 (d, *J* = 8.2 Hz, 1 H, 3a-H), 4.84 (s, 1 H, 5-H), 5.75 (d, *J* = 8.2 Hz, 1 H, 6a-H), 7.20−7.35 (m, 3 H, ArH) ppm. ^{13}C NMR: δ = 24.8 (CH_2), 25.6 (CH_2), 48.4 (N−CH_2), 49.8 (N−CH_2), 61.3 (C-3a), 81.8 (C-6a), 98.5 (C-5), 127.1 (Cq), 128.8 (CH), 131.2 (CH), 134.0 (C−Cl), 153.8 (C-3), 169.2 (C-6), 193.3 (C-4) ppm. $C_{16}H_{14}Cl_2N_2O_2$ (337.2): calcd. C 56.99, H 4.18, N 8.31; found C 56.85, H 4.06, N 8.22.

30a,b: Yield 343 mg (90 %); oil. ^{1}H NMR ([D$_6$]DMSO): δ = 2.00−2.45 (m, 8 H, 2 × CH_2−CH_2), 3.93 (m, 4 H, 2 × N−CH_2), 4.06 (m, 2 H, 2 × N−CH), 4.42 (d, *J* = 8.2 Hz, 2 H, 2 × 3a-H), 4.94 (s, 2 H, 2 × 5-H), 5.98 (d, *J* = 8.2 Hz, 1 H, 6a-H), 6.06 (d, *J* = 8.2 Hz, 1 H, 6a-H), 7.40−7.55 (m, 6 H, ArH) ppm. $C_{17}H_{14}Cl_2N_2O_4$ (381.2): calcd. C 53.56, H 3.70, N 7.35; found C 53.42, H 3.61, N 7.22.

31a,b: Yield 356 mg (90 %); oil. ^{1}H NMR ([D$_6$]DMSO): δ = 1.95−2.45 (m, 8 H, 2 × CH_2−CH_2), 3.25−3.55 (m, 4 H, 2 × N−CH_2), 3.69 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.06 (m, 2 H, 2 × N−CH), 4.42 (d, *J* = 8.2 Hz, 2 H, 2 × 3a-H), 4.94 (s, 2 H, 2 × 5-H), 5.98 (d, *J* = 8.2 Hz, 1 H, 6a-H), 6.06 (d, *J* = 8.2 Hz, 1 H, 6a-H), 7.40−7.55 (m, 6 H, ArH) ppm. $C_{18}H_{16}Cl_2N_2O_4$ (395.2): calcd. C 54.70, H 4.08, N 7.09; found C 54.57, H 3.98, N 6.95.

(3a*SR*,6a*SR*,4*SR*)-6-Benzylamino-3-(2,6-dichlorophenyl)-4-vinyl-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-4-ol (32), and Methyl (3a*SR*,6a*SR*,4*SR*)-1-[4-Allyl-3-(2,6-dichlorophenyl)-4-hydroxy-4,6a-dihydro-3a*H*-cyclopenta[*d*]isoxazol-6-yl]pyrrolidine-2-carboxylate (33a,b): To a solution of vinylmagnesium bromide (or allylmagnesium bromide) (4 mmol) in diethyl ether (1 M, 4 mL) were added under nitrogen with stirring 0.70 mmol of **28** (or, **31a,b**) in anhydrous THF at room temperature. The reaction was monitored by TLC (diethyl ether/petroleum ether, 3:1). The reaction was treated with a saturated ammonium chloride solution and extracted with diethyl ether. The diethyl ether of the extracts was evaporated under reduced pressure and the residue purified by flash chromatography. Compound **32** was obtained as a solid (**33a,b** as an oil).

32: Yield 210 mg (75 %); m.p. 167−169 °C. ^{1}H NMR ($CDCl_3$): δ = 4.35 (br. d, 3 H, 3a-H, N−CH_2), 5.01 (s, 1 H, 5-H), 5.10 (m, 2 H, CH_2), 5.67 (d, *J* = 7.9 Hz, 1 H, 6a-H), 5.83 (m, 1 H, CH), 6.04 (br. t, 1 H, NH), 7.25−7.40 (m, 8 H, ArH) ppm. $C_{21}H_{18}Cl_2N_2O_2$ (401.3): calcd. C 62.85, H 4.52, N 6.98; found C 62.70, H 4.40, N 6.85.

33a,b: Yield 217 mg (71 %); oil. ^{1}H NMR ($CDCl_3$): δ = 1.90−2.25 (m, 8 H, 4 × CH_2), 2.30−2.50 (m, 4 H, 2 × CH_2), 3.28−3.58 (m,

4 H, 2 × N−CH_2), 4.13 (m, 2 H, 2 × N−CH), 4.36 (d, J = 8.2 Hz, 1 H, 3a-H), 4.61 (d, J = 8.2 Hz, 1 H, 3a-H), 4.96 (s, 2 H, 2 × 5-H), 5.34 (m, 4 H, 2 × CH_2), 5.67 (d, J = 8.2 Hz, 2 H, 2 × 6a-H), 5.70−6.05 (m, 2 H, 2 × CH), 7.23−7.42 (m, 6 H, 2 × ArH) ppm. $C_{21}H_{22}Cl_2N_2O_4$ (437.3): calcd. C 57.68, H 5.07, N 6.41; found C 57.55, H 4.96, N 6.49.

X-ray Crystal Structure Determination: Single crystals of **11a** and **17** suitable for X-ray data collection were obtained by dissolving 100 mg of powder in 50 mL of ethyl acetate and allowing it to concentrate at room temperature. Crystal data for **11a** and **17** are summarized in Table 4. Data were collected using a Siemens P4 four-circle diffractometer with graphite-monochromated Mo-K_α radiation. The structures were solved by the direct methods implemented in the SHELX-97.[30] Structure refinements were carried out by full-matrix anisotropic least-squares on F^2 for all reflections for all non-H atoms by using SHELX-97.[30] The hydrogen atoms were located on Fourier difference maps and were included in the structure-factor calculations without any constraint for both the structures. Min./max. height in last Δρ map of −0.20 and 0.11 e·Å^{-3} for **11a** and −0.44 and 0.29 e·Å^{-3} for **17**. Atomic scattering factors were taken from ref.[30]. Molecular graphics were performed by using WinGX package.[31] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 213919 (**11a**) 213918 (**17**). 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].

Table 4. Crystal data for **11a** and **17**

	11a	**17**
Formula	$C_{13}H_9Cl_2NO_3$	$C_{13}H_9Cl_2NO_5S$
M	298.11	362.17
Crystal size (mm)	0.20 × 0.10 × 0.15	0.20 × 0.10 × 0.15
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$ (no.19)	$P2_1/c$ (no. 14)
a (Å)	8.064(2)	7.841(1)
b (Å)	11.174(2)	16.199(1)
c (Å)	14.403(6)	11.871(1)
β (°)		105.68(1)
U (Å^3)	1297.8(7)	1451.7(2)
Z	4	4
F(000)	608	736
$D_{calcd.}$ (g cm^{-3})	1.526	1.657
μ (Mo-K_α) (cm^{-1})	0.502	0.613
Radiation graphite-monochromated	Mo-K_α (λ = 0.71073)	Mo-K_α (λ = 0.71073)
Scan mode	ω/2Θ	ω/2Θ
Scan range (°)	1 ≤ Θ ≤ 25	1 ≤ Θ ≤ 27
Scan width (°)	1.2	0.9
Scan speed (° min^{-1})	3	3
Temperature (°C)	22	22
Unique reflections	2280 (R_{int} = 0.017)	3329 (R_{int} = 0.021)
Number of parameters refined	208	235
$R_1[I > 2\sigma(I)]$	0.030	0.036
$wR_2[I > 2\sigma(I)]$	0.065	0.089

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