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Synthesis of Optically Active 1,4-Benzoxazinones and 1,5-Benzoxazepinones by Regiocontrolled Ring Transformations of Oxirane Carboxylic Acids and Esters with Aromatic *o*-Hydroxyarylamines

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Abstract. Enantiopure diethyl oxirane dicarboxylate **1** reacts with *o*-aminophenols **2** either to 1,4-benzoxazin-2-ones **5** or to the 1,5-benzoxazepin-2-one **4** while a condensed 1,4-oxazin-3-one **6** was obtained with 2-amino-3-hydroxypyridine. On the other hand optical active oxirane carboxylic acids **7** react with *o*-aminophenols **8** in the presence of DCC (dicyclohexylcarbodiimide) or isobutyl chloroformiate affording oxirane carboxamides **9** that can be ring transformed to either 2,3-dihydro-*4H*-1,4-benzoxazin-3-ones **10** or 3-hydroxy-2,3-dihydro-*5H*-1,5-benzoxazepin-4-ones **11** depending on the reaction conditions.

INTRODUCTION

Glycidates are versatile bielectrophilic systems forming heterocycles in reaction with several binucleophiles, such as *o*-aminothiophenols [1, 2,3] or *o*-phenylenediamines[4,5] by reaction at the carbonyl group and nucleophilic opening of the oxirane ring. They can either act as C_3-building block or as C_2-synthon (attack of the nucleophile at the carbonyl group and the ß-position or α-position, respectively). Our results in the application of chiral glycidates lacking aryl substituents in the synthesis of optically active heterocycles demonstrated a strong dependence of the mode of reaction on the kind of binucleophile, the reaction conditions and the substitutents attached to the oxirane ring. Thus glycidates react with *o*-phenylenediamines affording either benzodiazepinones[5] or hydroxyalkylquinoxalinones[4] depending on whether a solvent is used or the reactants are

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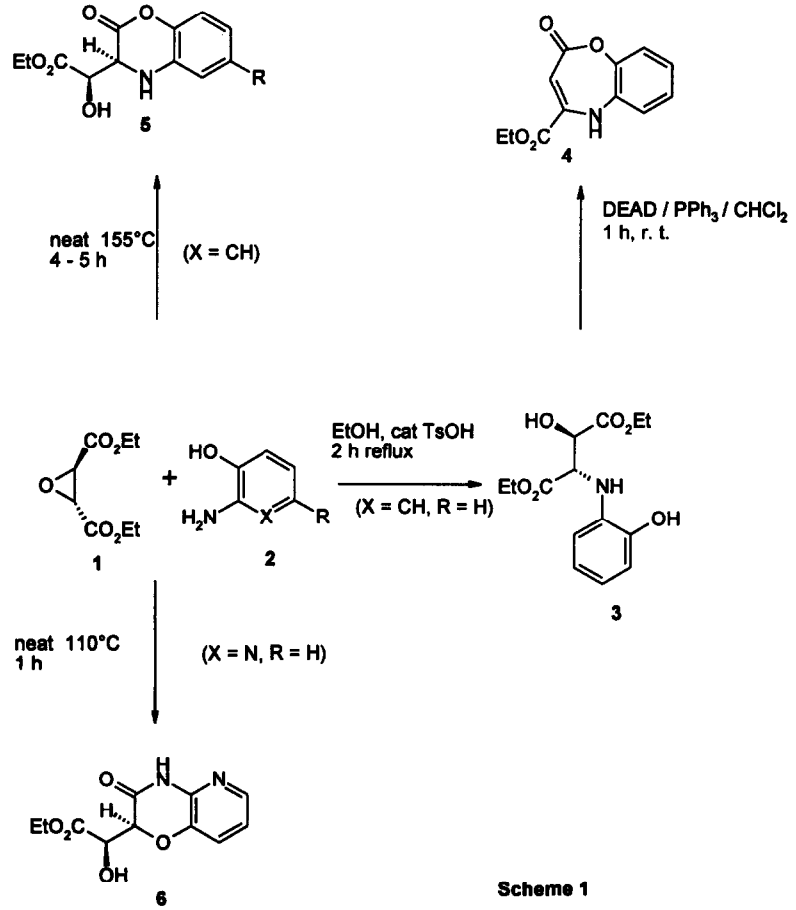
heated as neat mixtures. Reactions of aliphatic glycidates with *o*-aminothiophenols result in the formation of hydroxyalkylbenzothiazinones[1] while aryl glycidates gave benzothiazepinones[3]. The well-known Ca-channel blocking drug Diltiazem® is synthesised by application of the latter reaction. Ring forming reactions of *o*-aminophenols with glycidates were not reported in the literature yet.

RESULTS AND DISCUSSION

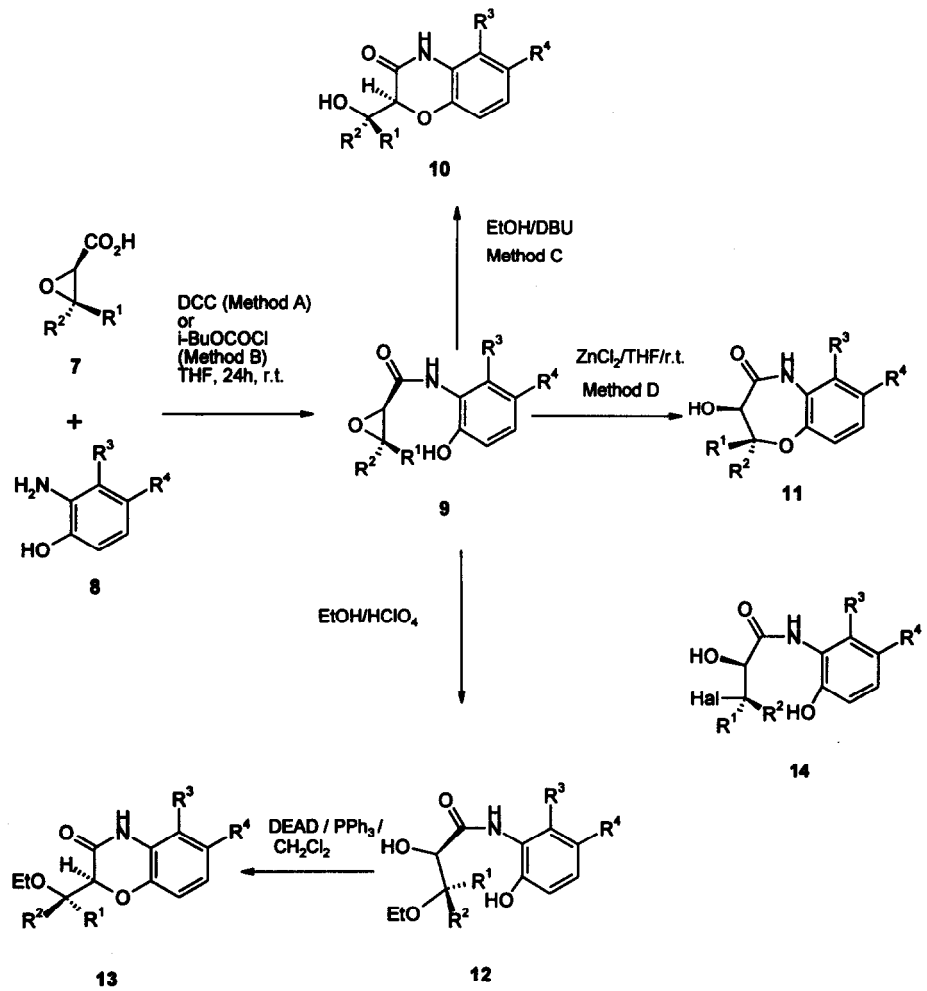
Our investigations with optically active *cis* and *trans* alkyl glycidates derived from corresponding acids **7** revealed that these systems were reluctant to reactions with *o*-aminophenol even if the favorable neat procedure was applied. *trans*-Diethyl oxirane dicarboxylate **1**, however, reacted with *o*-aminophenols **2** (X = CH) and 2-amino-3-hydroxypyridine **2** (X = N). Refluxing reactants **1** and **2** (X=CH) in ethanolic solution gave the α-arylamino-ß-hydroxy ester **3** by nucleophilic opening of the oxirane ring by the amino



Scheme 1

group. Further cyclisation by nucleophilic attack of the phenolic hydroxy group at an ester group was possible under Mitsunobu conditions (diethyl azodicarboxylate DEAD/PPh_3). But these strong dehydrating conditions caused additional elimination of the alcoholic hydroxy group thus resulting in the formation of the achiral 1,5-benzoxazepinone **4**. If the oxirane dicarboxylate was heated with *o*-aminophenols **2** (X = H) without a solvent to 155°C six-membered 1,4-benzothiazin-2-ones **5** were obtained by nucleophilic attack at one ester function and at the adjacent position of the oxirane ring. Obviously, the course of the reaction of **1** with **2** to either products **3** or **5** can be controlled by the reaction conditions. Remarkably, 2-aminopyridine **2** reacted in the opposite way with diethyl oxirane dicarboxylate **1**, i. e. the phenolic OH group opened the oxirane ring while the amino group attacked one carboxylate thus affording the pyridoxazin-3-one **6**. Presumably the 2-amino-3-hydroxypyridine **2** (X = N, R = H) exists as a zwitterionic pyridiniumolate structure and thus primarily attacks the oxirane dicarboxylate ring via the stronger nucleophilic phenolate oxygen rather than via the amino group.

Since alkyl-substituted oxirane monocarboxylates were reluctant to reactions with *o*-aminophenols we further investigated reactions of corresponding enantiopure carboxylic acids **7**. Reactions with *o*-aminophenols **8** in the presence of DCC or via activation with i-BuOCOCl resulted in primary attack of the amino group at the carboxyl moiety. Interestingly, the oxirane carboxamides **9** formed can selectively be ring transformed either to 1,4-benzoxazin-3-ones **10** (function of **7** as C_2-building block) or to 3-hydroxy-2,3-dihydro-*5H*-1,5-benzoxazepin-4-ones **11** (function of **7** as C_3-building block) depending on the reaction conditions. Treatment of **9** with DBU in ethanol (Method C) afforded predominantly **10** while cyclisation in THF in the presence of $ZnCl_2$ (Method D) gave **11** in excellent yields in the *trans*-series **9**. Both cyclisations occurred with inversion of configuration. The effect of $ZnCl_2$ in the formation of **11** might be similar to that exerted by $Ti(OR)_4$ in intermolecular reactions of glycidic amides with nucleophiles,[6] i. e. coordination of the zinc ion at NH and the oxirane O atom activating the oxirane ring and directing the attack of the phenolic OH to the ß-position. The application of $Ti(Oi\text{-}Pr)_4$ to the glycidic amides **9**, however, left the reactant unchanged. The *cis* glycidic amides gave no benzoxazepinones **11** when exposed to Method D, but chlorohydrines **14** by nucleophilic cleavage of the oxirane ring by chloride. Obviously an intramolecular ß-attack at the oxirane ring is sterically hindered in the *cis*-series. The ring opening of glycidic amides to chlorohydrines is a well-known reaction.[7,8] Considerable amounts of chlorohydrines **14** together with corresponding benzoxazepinones **11j** and **11k** were also formed if 3-unsubstituted glycidic amides **9** (R^1=R^2=H) were used (see Experimental part, Method D). The application of other Lewis acids in the reaction of glycidic amides **9** was not successful (see Table 1) since chlorohydrines **14** were predominantly or entirely formed (see also Experimental Part), decomposition occurred or no reaction took place. It should also be stressed that dichloromethane was not suitable as solvent even when $ZnCl_2$ was used.



9	10	11	12	13	R^1	R^2	R^3	R^4
a	a	a	a	a	Me	H	H	H
b	b	b			Me	H	H	Me
c	c	c			Me	H	CH=CH-CH=CH	
d	d				Me	H	H	NO_2
e	e	e			H	n-Pr	H	H
f	f	f			H	n-Pr	H	Me
g	g	g			H	n-Pr	CH=CH-CH=CH	
h	h	h			H	n-Pr	H	Cl
i		i			H	n-Pr	H	NO_2
j	j	j			H	H	H	H
k		k			H	H	H	Me

Scheme 2

Table 1: Effect of different Lewis acids on the formation of **11a**

Lewis acid	equivalents / reaction time	solvent	ratio **14 : 11e**
Et_3Al	1.2 / 2 h	CH_2Cl_2	(decomp.)
Et_3B	2.5 / 3 d	CH_2Cl_2	(no reaction)
Et_2Zn	1.2 / 2 d	CH_2Cl_2	(decomp.)
Me_3SnCl	2.5 / 5 h	CH_2Cl_2	(no reaction)
$AlCl_3$; $AlBr_3$	1.2 / 2 h	CH_2Cl_2	100 : 0
$SnCl_2$ x 2 H_2O	1.7 / 3 d	CH_2Cl_2	70 : 30
ZnF_2	1.7 / 2 d	CH_2Cl_2	(no reaction)
$ZnCl_2$	2.5 / 2 h	CH_2Cl_2	50 : 50
$ZnCl_2$	1.2 / 2 h	CH_2Cl_2	46 : 54
$ZnBr_2$	1.2 / 2 h	CH_2Cl_2	60 : 40
ZnI_2	1.2 / 2 h	CH_2Cl_2	79 : 21
$ZnCl_2$	2.5 (2 portions) / 30 h	THF	11 : 89

Small quantities of 3-hydroxy-2,3-dihydro—*5H*-1,5-benzoxazepin-4-ones **11** were obtained as by-products of the major 1,4-benzoxazin-3-ones **10** applying Method C, i. e. basic conditions to some *cis*-substituted oxirane carboxamides **9**. If solutions of oxirane carboxamides **9** in ethanol were heated in the presence of an acid such as perchloric acid primary ring opening of the oxirane moiety occurred by the solvent affording ß-ethoxyalcohols **12**. Further cyclisation under Mitsunobu conditions gave 2-(α-ethoxyalkyl)-1,4-benzoxazin-3-ones **13**. As compared with the 2-(α-hydroxyalkyl)-1,4-benzoxazin-3-ones **10** the configuration at the α-position of the side chain is reversed.

The structural elucidation of the different regioisomeric final products was possible by NMR techniques and X-ray crystal analysis. HMBC allowed to assign each structure **6, 10** and **11** unambiguously. Thus an HMBC shows a coupling between the OH hydrogen atom and the carbon atom in α-position of the alkyl substituent R^1 or R^2 for benzoxazines **10** proving the sequence HO-C(R^1/R^2). Furthermore an X-ray crystal analysis could be obtained from the benzodiazepinone **11e** (see Fig. 1).

All products **4, 5, 6, 10, 12,** and **13** are new. So far no optically active 1,4-benzoxazin-3-ones or 1,5-benzoxazepin-4-ones have been reported in the literature. Racemic 1,4-benzoxazin-2-ones were synthesised from *o*-aminophenols and α-halocarboxylic acids[9], corresponding acid derivatives[10-13] or α-keto esters[14] by ring closure or by hydrogenation of 1,4-benzoxazin-2-ones[15,16] . Dihydropyrido[3.2-b]oxazin-3- ones were

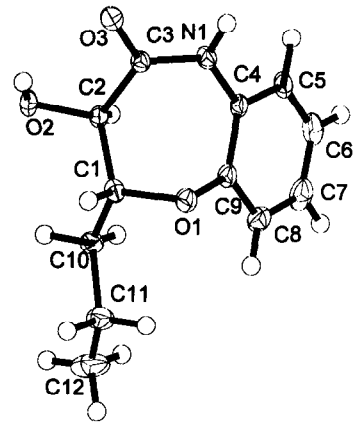


Figure 1: X-ray crystal analysis of the 3-hydroxy-benzoxazepin-4-one **11e**

prepared by similar cyclisations[17,18] and found interest as pharmacologically active compounds[19]. In the 1,5-benzoxazepin-4-one series[20-24] only a few compounds with a 3-hydroxy substituent were reported. [21] Interestingly, racemic *cis* and *trans* 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-*5H*-1,5-benzoxazepin-4-one related to Diltiazem® and to **11** could not be obtained by reaction of the corresponding 3-(4-methoxyphenyl)-glycidate and *o*-aminophenol, but had to be synthesised with *o*-nitrophenol.[21] After nucleophilic opening of the oxirane ring by the phenolic hydroxy group the nitro group was hydrogenated allowing intramolecular amide formation to the benzoxazepinone.

The results presented here demonstrate a further important application of ring transformation of glycidic acids and esters with binucleophiles in the synthesis of new optically active heterocycles. The regioselectivity could be controlled by the reaction conditions.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively on a BRUKER AC-300 with tetramethyl silane as internal standard (solvent $CDCl_3$ if not otherwise mentioned). Optical rotation was determined with a PERKIN ELMER polarimeter 241. Silicagel (0.04 - 0.063 mm, MERCK) was used for preparative column chromatography. If not otherwise mentioned, chemicals were purchased from MERCK or ALDRICH. Starting materials **1** and **7** were prepared according to reported procedures. [25-28]

2-Hydroxy-3-(o-hydroxyanilino)-succinate (3). A mixture of (*R,R*)-diethyl oxirane-2,3-dicarboxylate **1** (1 g, 5.3 mmol), 2-aminophenol **2** (0.64 g, 5.85 mmol), and a catalytic amount of p-TsOH (20 mg) was dissolved in ethanol and heated under argon for 4 h. After cooling to room temperature the mixture was evaporated and the remainder was purified by column chromatography with $CHCl_3$/MeOH (9/1) (R_f = 0.49) to give **3** as a light brown oil in 78 % yield. - ^{1}H NMR: 1.13-1.28 (m, 2 CH_3), 4.06-4.52 (m, 2 CH_2), 4.33 (d, *J*=2.9, CH-N), 4.59 (d, *J*=2.8, CH-O), 6.64-6.75 (m, 4 CH_{Ar}). The product was converted to **4** without further characterisation.

Ethyl-1,5-benzoxazepin-2-one-4-carboxylate (4). Triphenylphosphine (524 mg, 2 mmol) was added to a solution of **3** (500 mg, 1.7 mmol) in CH_2Cl_2 (13 ml). A solution of diethyl azodicarboxylate (453 mg, 2.6 mmol) in CH_2Cl_2 (20 ml) was added dropwise at 0°C. After 1 h stirring at room temperature the solvent was evaporated and the remainder was purified by column chromatography with hexane/Et_2O (1:1). Additional recrystallisation is possible. Yield: 31 %, yellow crystals, m.p. = 94-95°C (hexane), R_f = 0.70. - ^{1}H NMR: 1.23 (t, *J* = 7.10, CH_3), 4.13 (q, *J* = 7.10, CH_2), 5.81 (s, CH), 6.85-7.19 (m, 4 CH_{Ar}), 10.57 (s, NH). - ^{13}C NMR: 14.6 (CH_3), 60.7 (CH_2), 91.5 (CH), 115.2, 117.3, 123.1, 126.0 (CH_{Ar}), 124.6, 138.4, 140.4 (C_{Ar}), 156.3, 170.2 (COO). – $C_{12}H_{11}NO_4$ (233.24): calcd. C 61.79, H 4.76, N 6.06; found C 61.73, H 4.79, N 6.00.

General Procedure for the Synthesis of 1,4-Benzoxazin-2-ones 5 and the Pyrido[3.2-b]-1,4-oxazin-3-one 6.
A mixture of (*R,R*)-diethyl oxirane-2,3-dicarboxylate **1** (188 mg, 1 mmol) and 2-aminophenol or 2-amino-3-hydroxypyridine **2** (1.05 mmol) was heated under stirring in an argon atmosphere to 155°C for 4-5h or to 110°C for 1h (for **5** or **6**, respectively). After cooling to room temperature the mixture was dissolved in a small amount of the solvent mixture which was later on used for purification by column chromatography (**5**: CH_2Cl_2/acetone (95:5); **6** $CHCl_3$/MeOH (9:1) if X=N). Additional recrystallisation is possible.

Ethyl (1'R, 3S)-Hydroxy-(2-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-3-yl)-acetate (5a). Yield: 60%, colourless crystals, m.p. = 125 -127°C (hexane:AcOEt 1:1), R_f = 0.43, $[\alpha]^D_{20}$ = -66.8 ° (c = 1, $CHCl_3$). - ^{1}H NMR: 1,07(t, *J* = 7.15, CH_3), 3.43(d, *J* = 3.37, OH), 3.92-4.08 (m, CH_2), 4.31 (s, NH), 4.48 (m, CH-N), 4.71 (m, CH-O), 6.63 - 6.92 (m, 4 CH_{Ar}). - ^{13}C NMR: 14.1 (CH_3), 63.3 (CH_2), 58.1 (CH-N), 72.3 (CH-O), 115.3, 117.0, 120.2, 125.6 (CH_{Ar}), 131.0, 140.4 (C_{Ar}), 164.2, 172.0 (COO). – $C_{12}H_{13}NO_5$ (251.26). calcd. C 57.36, H 5.23, N 5.58; found C 57.28, H 5.15, N 5.74.

Ethyl (1'R, 3S)-Hydroxy-(6-methyl-2-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-3-yl)-acetate (5b): (R=Me) yield: 50 %, colourless crystals, m.p. = 143-44 °C (hexane:AcOEt 1:1), R_f = 0.45, $[\alpha]^D_{20}$ = -43.6 ° (c = 1, $CHCl_3$). - ^{1}H NMR: 1.08 (t, *J*=7.2, CH_3), 2.16 (s, CH_3), 3.92-4.08 (m, CH_2), 4.31 (s, NH), 4.45 (m, CH-N), 4.70 (d, *J*=2.9, CH-O), 6.45 and 6.79 (m, 3 CH_{Ar}). - ^{13}C NMR: 14.1, 21.3 (CH_3), 58.0 (CH-N), 72.2 (CH-O), 115.7, 116.7,

120.8 (CH_{Ar}), 130.6, 135.6, 138.4 (C_{Ar}), 164.3, 172.1 (COO). – $C_{13}H_{15}NO_5$ (265.29): calcd. C 58.85, H 5.71, N 5.28; found C 58.81, H 5.83, N 5.22.

Ethyl (1'R, 2S)-Hydroxy-(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-2-yl)-acetate (6): Yield: 33 %, light brown crystals, m.p. = 147 -148°C (hexane:AcOEt 1:9), R_f = 0.33, $[\alpha]^D_{20}$ = +20.5 °C (c = 1, MeOH). - ^{1}H NMR: 1.10 (t, *J* = 7.1, CH_3), 4.30 (q, *J* = 7.1, CH_2), 4.61 (m, CH-OH), 5.11 (d, *J* = 2.3, CH-OPh), 6.04 (s, OH), 6.91-7.84 (m, 3 CH_{Ar}), 11.26 (s, NH). - ^{13}C NMR: 14.2 (CH_3), 60.9 (CH_2), 72.2 (CH-OH), 79.2 (CH-OPh), 119.3, 122.5, 140.4 (CH_{Ar}), 139.0, 141.0 (C_{Ar}), 164.7 (CON), 171.1 (COO). – $C_{11}H_{12}N_2O_5$ (216.23): calcd. C 52.37, H 4.80, N 11.11; found C 52.30, H 4.96, N 10.88.

General Procedures for the Synthesis of Oxirane-carboxanilides 9:

Method A: DCC (4.07 g, 20 mmol) was added to a solution of oxirane carboxylic acid **7** (20 mmol) and *o*-aminophenol **8** (20 mmol) in THF (150 ml). The mixture was kept at room temperature for 24 h. After dilution with Et_2O the appearing precipitate was filtered off and the filtrate was evaporated. The remaining material was purified by column chromatography with CH_2Cl_2/acetone (95:5). Yield: 78-98 %; colourless crystals.

Method B: *i*-Butyl chloroformiate (2.59 ml, 21 mmol) was added to a suspension of the K salt of the oxirane carboxylic acid **7** (20 mmol) in THF (150 ml) at 0 °C under argon. After adding a catalytic amount of N-methylmorpholine (0.5 ml) the mixture was stirred for about 1 h. A solution of 2-aminophenol **8** (20 mmol) in THF (20 ml) was added at 0 °C and the mixture was stirred at room temperature for 20 h. After dilution with Et_2O the appearing precipitated was filtered off and the filtrate was evaporated. The remaining material was purified by column chromatography with CH_2Cl_2/acetone (95:5). The resulting **9** (colourless crystals, yield: 45-73 %) were characterised by ^{1}H NMR spectroscopy and converted to **10** and **11** without further analytical investigations.

9a: (Method B) R_f = 0.53, yield: 48 %, ^{1}H NMR: 1.45 (d, *J*=5.5, CH_3), 3.45 (m, CH), 3.71 (d, *J*=4.7, CH), 6.92-7.44 (m, 4 CH_{Ar}), 8.30 (s, NH), 8.55 (s, OH).

9b: (Method B) R_f = 0.63, yield: 48 %, ^{1}H NMR: 1.35 (d, *J*=5.5, CH_3), 2.19 (s, CH_3), 3.35 (m, CH), 3.60 (d, *J*=4.7, CH), 6.81-6.88 (m, 3 CH_{Ar}), 8.01 (s, NH), 8.13 (s, OH).

9c: (Method B) R_f = 0.58, yield: 45 %, ^{1}H NMR: 1.45 (d, *J*=5.5, CH_3), 3.45 (m, CH), 3.76 (d, *J*=4.8, CH), 7.18-7.77 (m, 6 CH_{Ar}), 8.47 (s, NH), 8.50 (s, OH).

9d: (Method B) R_f = 0.35 ($CHCl_3$/MeOH 9:1), yield: 58 %, ^{1}H NMR (DMSO-d_6): 1.31 (d, *J*=4.5, CH_3), 3.39 (m, CH), 3.81 (d, *J*=4.1, CH), 7.04 (m, CH_{Ar}), 7.95 (m, 2 CH_{Ar}), 8.94 (s, NH), 9.13 (s, OH).

9e: (Method A) R_f = 0.70, yield: 98 %, ^{1}H NMR: 0.94 (t, *J*=7.1, CH_3), 1.44-1.70 (m, 2 CH_2), 3.08 (m, CH), 3.53 (d, *J*=2.1, CH), 6.77-7.19 (m, 4 CH_{Ar}), 7.99 (s, NH), 9.13 (s, OH).

9f: (Method A) R_f = 0.73, yield: 97 %, ^{1}H NMR: 0.93 (t, *J*=7.2, CH_3), 1.40-1-68 (m, 2 CH_2), 2.17 (s, CH_3), 3.06 (m, CH), 3.33 (d, *J*=2.1, CH), 6.82-7.19 (m, 3 CH_{Ar}), 8.00 (s, NH), 8.27 (s, OH).

9g: (Method B) R_f = 0.67, yield: 73 %, ^{1}H NMR: 0.95 (t, *J*=7.2, CH_3), 1.46-1.73 (m, 2 CH_2), 3.20 (m, CH), 3.46 (d, *J*=2.0, CH), 7.15-7.73 (m, 6 CH_{Ar}), 8.44 (s, NH), 8.55 (s, OH).

9h: (Method A) R_f = 0.59, yield: 78 %, ^{1}H NMR: 1.02 (t, *J*=7.2, CH_3), 1.51-1.78 (m, 2 CH_2), 3.16 (m, CH), 3.42 (d, *J*=2.1, CH), 6.91-7.28 (m, 3 CH_{Ar}), 8.15 (s, NH), 8.35 (s, OH).

9i: (Method B) R_f = 0.59, yield: 78 %, ^{1}H NMR (DMSO-d_6): 0.99 t, *J*=7.2, CH_3), 1.46-1.70 (m, 2 CH_2), 3.27 (m, CH), 3.70 (d, *J*=2.8, CH), 7.10 (d, *J*=9.0, CH_{Ar}), 7.98 (m, CH_{Ar}), 9.01 (d, *J*=2.8, CH_{Ar}), 9.30 (s, OH), 11.90 (s, NH).

9j: (Method B) R_f = 0.49 ($CHCl_3$/MeOH 9:1), yield: 49 %, ^{1}H NMR: 2.91 (m, 1 H (CH_2)), 3.09 (m, 1 H (CH_2)), 3.58 (m, CH), 6.78-7.10 (m, 4 CH_{Ar}), 8.00 (s, NH), 8.26 (s, OH).

9k: (Method B) R_f = 0.56 ($CHCl_3$/MeOH 9:1), yield: 60 %, ^{1}H NMR δ 2.21 (s, CH_3), 2.93 and 3.03 (m, CH_2), 3.73 (m, CH), 6.78 (m, 2 CH_{Ar}), 7.77 (s, CH_{Ar}), 9.08 (s, NH), 9.77 (s, OH)

*General Procedure for the Synthesis of 2-Substituted 3,4-Dihydro-2H-1,4-benzoxazin-3-ones **10** (Method C):*
Oxirane-carboxanilide **9** (1 mmol) was dissolved in ethanol (2 ml) and heated under reflux with a catalytic amount of DBU (20 µl, for R^4 = NO_2 40 µl) for 1.2 h (for *cis*-epoxides) or 1.5 h (for *trans*-epoxides) After cooling to room temperature the mixture was evaporated and the remainder was purified by column chromatography (**10e – 10i**: CH_2Cl_2/acetone = 95:5); **10a – 10c,10j** and **10k**: $CHCl_3$/MeOH = 9:1).

*(2S, 1'R)-2-(1-Hydroxy-ethyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one (**10a**):* Yield: 86 %, colourless crystals, m.p. = 103°C (hexane:AcOEt = 1:1), R_f = 0.29, $[\alpha]^D_{20}$ = +18.4° (c=1, $CHCl_3$). - ^{1}H NMR: 1.43 (d, *J* = 6.5,

CH_3), 3.14 (d, J = 7.2, OH), 4.43 (m, CH-OH), 4.51 (d, J = 3.6, CH-OAr), 6.82 - 6.99 (m, 4 CH_{Ar}), 9.59 (s, NH). - ^{13}C NMR: 18.4 (CH_3), 67.1, 79.2 (CH), 115.9, 116.4, 122.4, 124.3 (CH_{Ar}), 125.6, 143.2 (C_{Ar}), 166.9 (CO). – $C_{10}H_{11}NO_3$ (193.22): calcd. C 62.16, H 5.75, N 7.25; found C 62.11, H 5.83, N 7.19.

*(2S, 1'R)-2-(1-Hydroxy-ethyl)-6-methyl-3,4-dihydro-2H-1,4-benzoxazin-3-one (**10b**):* Yield: 88 %, colourless crystals, m.p. = 143 °C (hexane:AcOEt = 1:1), R_f = 0.27, $[\alpha]^D_{20}$ = +14.5° (c=1, $CHCl_3$). - ^1H NMR: 1.34 (d, J =6.5, CH_3), 2.18 (s, CH_3), 2.93 (d, J = 7.2, OH), 4.33 (m, CH-OH), 4.38 (d, J = 3.8, CH-OAr), 6.54-6.80 (m, 3 CH_{Ar}), 9.37 (NH). - ^{13}C NMR: 18.8, 21.0 (CH_3), 67.5, 79.7 (CH), 116.6, 116.8, 125.2 (CH_{Ar}), 125.6, 132.7, 141.5 (C_{Ar}), 167.6 (CO). – $C_{11}H_{13}NO_3$ (207.25): calcd. C 63.74, H 6.34, N 6.76; found C 63.58, H 6.32, N 6.78.

*(3S, 1'R)-2-(1-Hydroxy-ethyl)-3,4-dihydro-2H-naphth[2,1-b]-1,4-oxazin-2-one (**10c**):* Yield: 80 %, colourless crystals, m.p. = 144.5-145°C (hexane:AcOEt = 3:7), R_f = 0.23, $[\alpha]^D_{20}$ = -57.7° (c=1, MeOH). - ^1H NMR (DMSO-d_6): 1.25 (d, J = 6.5, CH_3), 4.17 (m, CH-OH), 4.54 (d, J = 3.3, CH-OAr), 4.92 (d, J = 5.5, OH), 7.23-8.25 (m, 6 CH_{Ar}),10.90 (s, NH). – ^{13}C NMR: 19.7 (CH_3), 66.2, 85.6 (CH), 118.0, 120.5, 123.3, 124.3, 126.3, 128.5 (CH_{Ar}), 119.5, 123.0, 129.4, 140.1 (C_{Ar}), 166.2 (CO). - $C_{14}H_{13}NO_3$ (243.28): calcd. C 69.11, H 5.40, N 5.76; found C 69.12, H 5.42, N 5.72.

*(2S, 1'R)-2-(1-Hydroxy-ethyl)-6-nitro-3,4-dihydro-2H-1,4-benzoxazin-3-one (**10d**):* Yield: 93 %, light yellow crystals, m.p. = 218-220°C (hexane:AcOEt), R_f = 0.21, $[\alpha]^D_{20}$ = +11.2°C (c=1, MeOH). - ^1H NMR (DMSO-d_6): 1.22 (d, J = 6.5, CH_3), 4.16 (m, CH-OH), 4.70 (d, J = 1.9 CH-OPh), 5.08 (d, J = 5.1, OH), 7.08-7.82 (m, 3 CH_{Ar}), 11.0 (s, NH). - ^{13}C NMR: 19.5 (CH_3), 67.7, 81.2 (CH), 110.4, 116.2, 119.4 (CH_{Ar}), 127.4, 141.4, 149.9 (C_{Ar}), 165.0 (CO). – $C_{10}H_{10}N_2O_5$ (238.22): calcd. C 50.42, H 4.24, N 11.76; found C 50.14, H 4.27, N 11.56.

*(2S, 1'S)-2-(1-Hydroxy-butyl)-3,4-dihydro-2H-1.4-benzoxazin-3-one (**10e**):* Yield: 98 %, colourless crystals, m.p. = 87°C (hexane:AcOEt = 9:1), R_f = 0.27, $[\alpha]^D_{20}$ = +43.5° (c=1, $CHCl_3$). - ^1H NMR: 0.90 (t, J = 7.2, CH_3), 1.35-1.82 (m, 2 CH_2), 3.45 (d, J = 4.3, OH), 4.11 (m, CH-OH), 4.30 (d, J = 6.8, CH-OAr), 6.75-6.95 (4 CH_{Ar}), 9.17 (s, NH). - ^{13}C NMR: 14.4 (CH_3), 18.7, 35.0 (CH_2), 71.6, 78.4 (CH), 116.3, 117.1, 123.2, 124.9 (CH_{Ar}), 126.1, 144.0 (C_{Ar}), 168.4 (CO). – $C_{12}H_{15}NO_3$ (221.28): calcd. C 65.13, H 6.85, N 6.33; found C 65.15, H 6.79, N 6.31.

*(2S, 1'S)-2-(1 Hydroxy-ethyl)-6-methyl-3,4-dihydro-2H-1,4-benzoxazin-3-one (**10f**):* Yield: 93 %, colourless crystals, m.p. = 127-128°C (hexane:AcOEt = 8:2), R_f = 0.26, $[\alpha]^D_{20}$ = +62.9° (c=1, $CHCl_3$). - ^1H NMR: 0.90 (t, J = 7.2, CH_3), 1.40-1.77 (m, 2 CH_2), 2.20 (s, CH_3), 3.50 (d, J = 4.2, OH), 4.09 (m, CH-OH), 4.25 (d, J = 7.0, CH-OAr), 6.56-6.81 (m, 3 CH_{Ar}), 9.21 (s, NH). - ^{13}C NMR: 12.8, 19.5 (CH_3), 17.1, 33.4 (CH_2), 69.9, 76.8

(CH), 115.1, 115.2, 123.8 (CH_{Ar}), 124.2, 131.4, 140.2 (C_{Ar}), 167.2 (CO). – $C_{13}H_{17}NO_3$ (235.31): calcd. C 66.35, H 7.30, N 5.95; found C 66.27, H 7.13, N 5.89.

*(2S, 1'S) -2-(1-Hydroxy-butyl)-3,4-dihydro-2H-naphth[2,1-b]-1,4-oxazin-3-one (**10g**):* Yield: 97 %, colourless crystals, m.p. = 180-181°C (hexane:AcOEt = 2:8), R_f = 0.35, $[\alpha]^D_{20}$ = -50.3° (c=1, MeOH). - ^{1}H NMR (DMSO-d_6): 0.93 (t, *J* = 7.1, CH_3), 1.31-1.66 (m, 2 CH_2), 4.03 (m, CH-OH), 4.69 (d, *J* = 4.0, CH-OAr), 5.11 (d, *J* = 6.2, OH), 7.30-8.33 (m, 6 CH_{Ar}), 11.03 (s, NH). - ^{13}C NMR: 14.2 (CH_3), 18.8, 34.8 (CH_2), 70.7, 80.2 (CH), 117.8, 120.6, 123.5, 124.4, 125.4, 128.5 (CH_{Ar}), 119.8, 123.0, 129.5, 140.1 (C_{Ar}), 165.6 (CO). – $C_{16}H_{17}NO_3$ (271.34): calcd. C 70.82, H 6.33, N 5.16; found C 70.53, H 6.36, N 5.21.

*(2S, 1'S)-6-Chloro-2-(1-hydroxy-butyl)-3,4-dihydro -2H-1,4-benzoxazin-3-one (**10h**):* Yield: 95 %, colourless crystals, m.p. = 138 °C (hexane:AcOEt = 8:2), R_f = 0.31, $[\alpha]^D_{20}$ = +40.9 (c=1, $CHCl_3$). - ^{1}H NMR: 0.90 (t, *J*=7.7, CH_3), 1.36-1.82 (m, 2 CH_2), 3.31 (d, *J*=4.9, OH), 4.08 (m, CH-OH), 4.32 (d, *J*=6.3, CH-OAr), 6.76-6-89 (m, 3 CH_{Ar}), 9.36 (s, NH). - ^{13}C NMR: 13.9 (CH_3), 18.3, 34.6 (CH_2), 71.4, 78.2 (CH), 115.8, 117.6, 124.1 (CH_{Ar}), 126.6, 127.5, 142.1 (C_{Ar}), 167.6 (CO). – $C_{12}H_{14}NO_3Cl$ (255.72): calcd. C 56.36, H 5.53, N 5.48; found C 56.22, H 5.53, N 5.36.

*(2S)-2-Hydroxymethyl-3,4-dihydro-2H-1,4-benzoxazin-3-one (**10i**)*: Yield: 90 %, colourless crystals, m.p. = 136-137°C (hexane:AcOEt = 2:8), R_f = 0.16, $[\alpha]^D_{20}$ = +15.6° (c=1, MeOH). - ^{1}H NMR (DMSO-d_6): 3.72-3.86 (m, CH_2), 4.63 (dd, *J* = 2.9, 4.6, OH), 5.08 (t, *J* = 5.7, CH), 6.82-6.94 (m, 4 CH_{Ar}), 10.67 (s, NH). - ^{13}C NMR: 63.3 (CH_2), 80.3 (CH), 117.7, 118.3, 124.0, 125.2 (CH_{Ar}), 129.1, 145.3 (C_{Ar}), 167.3 (CO). – $C_9H_9NO_3$ (179.19): calcd. C 60.32, H 5.07, N 7.82; found C 60.25, H 5.18, N 7.81.

*General Procedure for the Synthesis of 2,3-Dihydro-3-hydroxy-1,5-benzoxazepin-4(5H)-ones **11** (Method D):*
The carboxamide **9** (1 mmol) was dissolved in dry THF (3 ml) under an argon atmosphere. In case of the synthesis of **11e – i** water-free $ZnCl_2$ (205 mg, 1.5 mmol) was added and the mixture was stirred for 8 h. Another portion of $ZnCl_2$ (136 mg, 1.0 mmol) was added and the mixture was stirred for additional 22 h. In case of the 3-unsubstituted **9** ($R^1 = R^2 = H$, synthesis of **11j - k**) three portions of water-free $ZnCl_2$ (3 x 48 mg, 3 x 0.35 mmol) were added over a period of 8 h and the mixture was stirred for additional 15 h. The solvent was evaporated and the remainder was dissolved in CH_2Cl_2 (7 ml) (**11e – h**) or $CHCl_3$ (**11i – k**) and washed with diluted NH_4Cl/HCl-solution (7 ml) and dried with $MgSO_4$. After evaporation the crude product was purified by column chromatography (**11e – h**: CH_2Cl_2/acetone = 95:5; **11i – k**: $CHCl_3$/MeOH = 9:1).

(2S, 3R)- 3-Hydroxy-2-methyl-2,3-dihydro-(5H)-1,5-benzoxazepin-4-one (11a): Yield: 10 % (Method C), colourless crystals, m.p. = 139-40 °C (hexane:AcOEt 7:3), R_f = 0.52, $[\alpha]^D_{20}$ = +119.8° (c=1, $CHCl_3$). - ^1H NMR: 1.32 (d, *J* = 6.4, CH_3), 3.65 (d, *J* = 4.2, OH), 4.43 (m, CH-OAr), 4.74 (m, CH-OH), 6.92 - 7.08 (m, 4 CH_{Ar}), 8.65 (NH). - ^{13}C NMR: 15.5 (CH_3), 70.1, 81.6 (CH),122.6, 123.1, 124.5, 127.2 (CH_{Ar}), 128.7, 148.7 (C_{Ar}), 173.4 (CO). - $C_{10}H_{11}NO_3$ (193.22): calcd. C 62.16, H 5.75, N 7.25; found C 62.22, H 5.59, N 7.16.

(2S, 3R) -3-Hydroxy-2,7-dimethyl-2,3-dihydro-5H-1,5-benzoxazepin-4-one (11b): Yield: 10 % (Method C), colourless crystals, m.p. = 124 -125°C (hexane:AcOEt 7:3), R_f = 0.49, $[\alpha]^D_{20}$ = +179.4° (c=1, $CHCl_3$). - ^1H NMR: 1.31 (d, *J* = 6.4, CH_3), 2.23 (s, CH_3), 3.63 (d, *J* = 4.8, OH), 4.42 (m, CH-OAr), 4.71 (m, CH-OH), 6.73-6.96 (m, 3 CH_{Ar}), 8,61 (s, NH). - ^{13}C NMR: 15.6, 21.0 (CH_3), 70.0, 82.0 (CH), 122.8, 122.9, 127.8 (CH_{Ar}), 128.6, 134.5, 146.6, (C_{Ar}), 173.4 (CO). - $C_{11}H_{13}NO_3$ (207.25): calcd. C 63.74, H 6.34, N 6.76; found C 63.50, H 6.32, N 6.75.

(8S, 9R)-3-Hydroxy-2-methyl-2,3-dihydro-5H-1,5-naphthoxazepin-4-one (11c): Yield: 16 % (Method C), colourless crystals, m.p. = 206-209°C (hexane:AcOEt 1:1), R_f = 0.39, $[\alpha]^D_{20}$ = +410.8° (c=1, MeOH). - ^1H NMR: 1.36 (d, *J* = 6.3 CH_3), 4.33 (m, CH-OAr), (m, CH-OH), 5.21 (d, *J* = 8.1, OH), 7.32-8.05 (m, 6CH_{Ar}), 10.24 (s, NH). - ^{13}C NMR: 16.2 (CH_3), 69.2, 85.6 (CH), 122.5, 122.7, 125.6, 126.2, 126.6, 128.3, (CH_{Ar}), 126.4, 127.5, 131.1, 146.8 (C_{Ar}), 173.0 (CO). - $C_{14}H_{13}NO_3$ (243.28): calcd. C 69.11, H 5.40, N 5.76; found C 68.90, H 5.43, N 5.76.

(2R, 3R) -3-Hydroxy-2-n-propyl-2,3-dihydro-5H-1,5-benzoxazepin-4-one (11e): Yield: 85% (Method D), R_f = 0.36, colourless crystals, m.p. = 137-138 °C (hexane/AcOEt 7/3), $[\alpha]^D_{20}$ = +267.5 ° (c=1, $CHCl_3$). - ^1H NMR δ 0.95 (t, *J*=7.1, CH_3), 1.47-1.78 (m, 2 CH_2), 3.68 (d, *J*=5.3, OH), 3.91 (m, CH-OH), 4.22 (m, CH-OAr), 6.96-7.19 (m, 4 CH_{Ar}), 8.70 (s, NH). ^{13}C NMR δ 14.3 (CH_3), 19.2, 34.4 (CH_2), 71.7 (CH-OH), 88.3 (CH-OAr), 122.8, 124.4, 125.1, 127.0 (CH_{Ar}), 130.1, 148.0 (C_{Ar}), 174.3 (CON). - $C_{12}H_{15}NO_3$ (221.28): calcd. C, 65.13; H, 6.85; N, 6.33, found C, 65.21; H, 6.78; N, 6.28.

Crystal Structure Analysis of 11e:[29] A colourless crystal of **11e** with the dimensions 0.84 x 0.48 x 0.32 mm^3 was measured on a STOE IPDS diffractometer using MoK_α radiation (λ = 0.71073 Å). Crystal data: $C_{12}H_{15}NO_3$, M = 221.25, monoclinic space group P 21, a = 5.1056(11) Å, b = 15.759(4) Å, c = 13.849(3) Å, β = 90.25(3)°, V = 1114.3(5) $Å^3$, Z = 4, D_c = 1.319 g/cm^3, F(000) = 472, μ (MoK_α) = 0.095 mm^{-1}. At 200(2) K in the range of 2.97° < Θ < 25.25° 7361 reflections were measured ($R_{(sig)}$ = 0.0640) of which 3939 were unique ($R_{(int)}$ = 0.0614) and 3524, flagged as observed, had intensities larger than 2σ(I). The structure was solved by direct methods and refined by least squares procedure within the SHELX program system. The final residuals were $wR_{2\ (all)}$ =

0.1073, $R_{1(all)}$ = 0.0476 and $R_{1(obs)}$ = 0.0431. The maximum and minimum peaks in the final difmap were 0.223 and -0.218 e/Å^3, respectively.

(2R, 3R)-3-Hydroxy-7-methyl-2-n-propyl-2,3-dihydro-5H-1,5-benzoxazepin-4-one (11f): Yield: 87% (Method D), R_f = 0.38, colourless crystals, m.p. = 119-120 °C (hexane/AcOEt 7/3), $[\alpha]^D_{20}$ = +365.4 ° (c=1, $CHCl_3$). - ^{1}H NMR δ 0.94 (t, *J*=7.0, CH_3), 1.50-1.74 (m, 2 CH_2), 2.24 (s, CH_3), 3.65 (d, *J*=5.4, OH), 3.88 (m, CH-OH), 4.19 (m, CH-OAr), 6.77 (s, CH_{Ar}), 6.87 (m, 2 CH_{Ar}), 8.53 (s, NH). - ^{13}C NMR δ 14.3, 21.1 (CH_3), 19.2, 34.4 (CH_2), 71.8 (CH-OH), 88.6 (CH-OAr), 123.2, 124.2, 127.6 (CH_{Ar}), 129.7, 135.1, 145.6 (C_{Ar}), 174.3 (CON). – MS m/z(%): 235 (M^+, 30), 163 (100), 150 (64), 123 (77). - $C_{13}H_{17}NO_3$ (235.31): calcd. C, 66.35; H, 7.30; N, 5.95, found C, 66.43; H, 7.27; N, 5.94.

(2R, 3R)-3-Hydroxy-2-n-propyl-2,3-dihydro-5H-1,5-naphthoxazepin-4-one (11g): Yield: 93% (Method D), R_f = 0.40, colourless crystals, m.p. = 125-127 °C (hexane/AcOEt 7/3), $[\alpha]^D_{20}$ = +449.5 ° (c=1, $CHCl_3$). - ^{1}H NMR δ 0.96 (t, *J*=7.1, CH_3), 1.51-1.79 (m, 2 CH_2), 3.65 (d, *J*=6.2, OH), 3.93 (m, CH-OH), 4.41 (m, CH-OAr), 7.16-7.91 (m, 6 CH_{Ar}), 8.99 (s, NH). - ^{13}C NMR δ 13.9 (CH_3), 18.9, 34.4 (CH_2), 71.2 (CH-OH), 91.3 (CH-OAr), 121.0, 123.4, 125.7, 127.2, 127.3, 128.4 (CH_{Ar}), 123.8, 127.7, 131.2, 145.6 (C_{Ar}), 174.6 (CON). - $C_{16}H_{17}NO_3$ (271.34): calcd. C, 70.82; H, 6.33; N, 5.16, found C, 70.79; H, 6.32; N, 5.05.

(2R, 3R)-7-Chloro-3-hydroxy-2-n-propyl-2,3-dihydro-5H-1,5-benzoxazepin-4-one (11h): Yield: 95% (Method D), R_f = 0.34, colourless crystals, m.p. = 111 °C (hexane/AcOEt 7/3), $[\alpha]^D_{20}$ = +289.5 ° (c=1, $CHCl_3$). - ^{1}H NMR δ 0.94 (t, *J*=7.0, CH_3), 1.45-1.79 (m, 2 CH_2), 3.64 (d, *J*=5.3, OH), 3.91 (m, CH-OH), 4.22 (m, CH-OAr), 6.92-7.06 (m, 3 CH_{Ar}), 8.83 (s, NH). - ^{13}C NMR δ 13.3 (CH_3), 18.7, 33.9 (CH_2), 73.1 (CH-OH), 88.1 (CH-OAr), 122.3, 125.1, 126.5 (CH_{Ar}), 129.6, 130.7, 146.2 (C_{Ar}), 174.1 (CON). - $C_{12}H_{14}NO_3Cl$ (255.72): calcd. C, 56.36; H, 5.53; N, 5.42, found C, 56.59; H, 5.51; N, 5.40.

(2R, 3R)-3-Hydroxy-7-nitro-2-n-propyl-2,3-dihydro-5H-1,5-benzoxazepin-4-one (11i): Yield: 90% (Method D), R_f = 0.33, light yellow crystals, m.p. = 151-153 °C (hexane/AcOEt 7/3), $[\alpha]^D_{20}$ = +219.9 ° (c=1, MeOH). - ^{1}H NMR (DMSO-d_6) δ 0.94 (t, *J*=7.0, CH_3), 1.44-1.76 (m, 2 CH_2), 3.98 (m, CH-OH), 4.37 (m, CH-OAr), 5.56 (d, *J*=5.9, OH), 7.22 (d, *J*=9.1, CH_{Ar}), 7.89-7.93 (m, 2 CH_{Ar}), 10.32 (s, NH). - ^{13}C NMR δ 14.1 (CH_3), 18.5, 33.9 (CH_2), 72.4 (CH-OH), 87.3 (CH-OAr), 117.0, 120.3, 123.9 (CH_{Ar}), 132.2, 143.4, 153.2 (C_{Ar}), 172.8 (CON). - $C_{12}H_{14}N_2O_5$ (266.28): calcd. C, 54.12; H, 5.31; N, 10.52, found C, 53.92; H, 5.45; N, 10.25.

(3R)-3-Hydroxy-2,3-dihydro-5H-1,5-benzoxazepin-4-one (11j): Yield: 35% (Method D, together with 60% of **14j-Cl** v.i.), R_f = 0.19, colourless crystals, m.p. = 174-175 °C (hexane/AcOEt 1:1), $[\alpha]^D_{20}$ = +279.8 ° (c=1, MeOH). - ^{1}H NMR (DMSO-d_6) δ 4.15-4.48 (m, 3 H; CH and CH_2), 5.42 (D, *J*=5.7, OH), 7.11 (m, 4 CH_{Ar}), 10.03 (s, NH). - ^{13}C NMR δ 68.5 (CH), 75.8 (CH_2), 121.9, 122.4, 124.3, 125.3 (CH_{Ar}), 130.5, 149.2 (C_{Ar}), 173.2 (CON). - $C_9H_9NO_3$ (179.19): calcd. C, 60.32; H, 5.07; N, 7.82, found C, 60.42; H, 5.11; N, 7.68.

(3R)-2,3-Dihydro-3-hydroxy-7-methyl-1,5-benzoxazepin-4(5H)-one (11k): Yield: 38% (Method D, together with 59% **14k-Cl** v. i.), R_f = 0.37, colourless crystals, m.p. = 147-148 °C (hexane/AcOEt 1/1), $[\alpha]^D_{20}$ = +288.5 ° (c=1, MeOH). - ^{1}H NMR (DMSO-d_6) δ 2.23 (s, CH_3), 4.21 (m, CH), 4.08 and 4.36 (m, CH_2), 5.31 (d, *J*=5.9, OH), 6.84-6.96 (m, 3 CH_{Ar}), 9.89 (s, NH). - ^{13}C NMR δ 20.6 (CH_3), 68.4 (CH), 76.3 (CH_2), 121.6, 122.6, 125.9 (CH_{Ar}), 130.4, 133.5, 147.1 (C_{Ar}), 173.2 (CON). - $C_{10}H_{11}NO_3$ (193.22): calcd. C, 62.16; H, 5.75; N, 7.25, found: C, 62.01; H, 5.80; N, 7.17.

(2S, 1'S)-3,4-Dihydro-2-(1-ethoxy-ethyl)-2H-1,4-benzoxazin-3-one (13a): Oxirane-carboxyanilide **9a** (150 mg 0.77 mmol) was dissolved in ethanol (2 ml) and treated with $HClO_4$ (70 %, 33 µl, 0.33 mmol). The mixture was refluxed for 1 h and, after cooling to room temperature, diluted with CH_2Cl_2 (15 ml) and washed with water. The organic layer was dried with $MgSO_4$, evaporated and purified by column chromatography with CH_2Cl_2/acetone (95:5) (R_f = 0.41) affording **12a** (145 mg, 83 %) as colourless crystals (characterisation only by ^{1}H NMR). **12a** ^{1}H NMR: 1.02 (t, *J*=7.0, CH_3); 1.10 (d, *J*=6.4, CH_3), 3.32 (m, CH), 3.48 (m, CH_2), 3.81 (m, CH), 3.97 (m, OH), 6.67-7.08 (m, 4 CH_{Ar}), 8.57 (s, NH), 8.77 (s, OH).

140 mg (0.59 mmol) of **12a** was converted to **13a** using 162 mg (0.62 mmol) Ph_3P and 98 µl (0.62 mmol) DEAD by a procedure similar to **4** (*v. s.*). **13a:** Yield: 31 %, colourless crystals, m.p. = 113°C (hexane:AcOEt 8:2), R_f = 0.50, $[\alpha]^D_{20}$ = -12.5° (c=1, $CHCl_3$). - ^{1}H NMR: 0.99 (t, *J* = 7.0, $\underline{CH_3}$-CH_2), 1.24 (d, *J* = 6.5, $\underline{CH_3}$-CH), 3.34-3.56 (m, CH_2), 3.98 (m, $\underline{CH}$-OEt), 4.67 (d, *J* = 3.0, $\underline{CH}$-OAr), 6.72-6.95 (m, 4 CH_{Ar}), 9.25 (s, NH). - ^{13}C NMR: 15.6, 15.8 (CH_3), 65.5 (CH_2), 76.5, 79.2 (CH), 115.9, 116.8, 122.4, 124.5 (CH_{Ar}), 126.1, 144.0 (C_{Ar}), 166.4 (CO). – $C_{10}H_{15}NO_3$ (197.26): calcd. C 65.13, H 6.85, N 6.33; found C 65.13, H 6.86, N 6.34.

(2R, 3R)-3-Bromo-2-hydroxyhexane-anilide (14e-Br) (R^1 = R^3 = R^4 = H; R^2 = n-Pr; Hal = Br): Obtained from **9e** by Method D using $AlBr_3$ rather than $ZnCl_2$ (see also Table 1); R_f = 0.52 (CH_2Cl_2/acetone 95:5), colourless crystals. - ^{1}H NMR δ 1.04 (t, *J*=7.2, CH_3), 1.74-2.07 (m, 2 CH_2), 3.84 (s, br, OH), 4.70-4.78 (m, 2 CH), 7.02-7.39 (m, 4 CH_{Ar}), 8.75 (s, NH), 9.01 (s, OH). - ^{13}C NMR δ 13.6 (CH_3), 21.5, 34.4 (CH_2), 58.8, 76.4 (CH), 119.7, 121.1, 122.6, 127.8 (CH_{Ar}), 124.9, 148.7 (C_{Ar}), 169.3 (CON).

(2R, 3R)-3-Chloro-2-hydroxyhexane-anilide (14e-Cl) ($R^1 = R^3 = R^4 = H$; R^2 = n-Pr; Hal = Cl): Obtained from **9e** by Method D using $AlCl_3$ rather than $ZnCl_2$ (see also Table 1);R_f = 0.47 (CH_2Cl_2/acetone 95:5), colourless crystals. - ^{1}H NMR δ 0.93 (t, *J*=7.2, CH_3), 1.62-1.87 (m, 2 CH_2), 3.70 (s, br, OH), 4.51 (m, CH), 4.62 (d, *J*=2.7, CH), 6.88-7.28 (m, 4 CH_{Ar}), 8.60 (s, br, NH), 8.89 (s, OH). - ^{13}C NMR δ 13.7 (CH_3), 20.2, 33.7 (CH_2), 64.9, 76.1 (CH), 119.7, 121.1, 122.6, 127.8 (CH_{Ar}), 125.0, 148.7 (C_{Ar}), 169.5 (CON).

(R)-3-Chloro-2-hydroxypropaneanilide (14j-Cl) ($R^1 = R^2 = R^3 = R^4 = H$, *Hal = Cl*): The compound was formed in 60% yield as by-product in the synthesis of the benzoxazepinone **11j**. R_f = 0.19, colourless crystals. - ^{1}H NMR (DMSO-d_6) δ 3.79 (m, CH_2), 4.38 (m, CH), 6.79-7.11 (m, 4 CH_{Ar}), 9.21 (s, NH), 9.80 (s, OH). - ^{13}C NMR δ 49.1 (CH_2), 73.1 (CH), 115.2, 119.9, 123.1, 124.9 (CH_{Ar}), 127.8, 145.2 (C_{Ar}), 169.2 (CON).

(R)-3-Chloro-2-hydroxypropane-(3-toluidide) (14k-Cl) ($R^1 = R^2 = R^3 = H$, $R^4 = Me$, *Hal = Cl*)*:* The compound was formed in 59% yield as by-product in the synthesis of the benzoxazepinone **11k**. R_f = 0.31, colourless crystals. - ^{1}H NMR (DMSO-d_6) δ 2.10 (CH_3), 3.78 (m, CH_2), 4.34 (m, CH), 6.61-6.69 (m, 3 CH_{Ar}), 9.14 (s, NH), 9.7 (s, OH). - ^{13}C NMR δ 21.0 (CH_3), 48.2 (CH_2), 71.5 (CH), 114.8, 119.7, 124.5 (CH_{Ar}), 126.0, 128.0, 144.1 (C_{Ar}), 168.9 (CON).

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29. Full details have been deposited at: Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, whence this material can be obtained on quoting a full literature citation and the deposition number CSD 410682.