Chemodivergent Synthesis of 7-Aryl/alkyl-6-hydroxy-1,4-oxazepan-5-ones and 2-[Aryl/alkyl(hydroxy)methyl]morpholin-3-ones from a Common Epoxyamide Precursor

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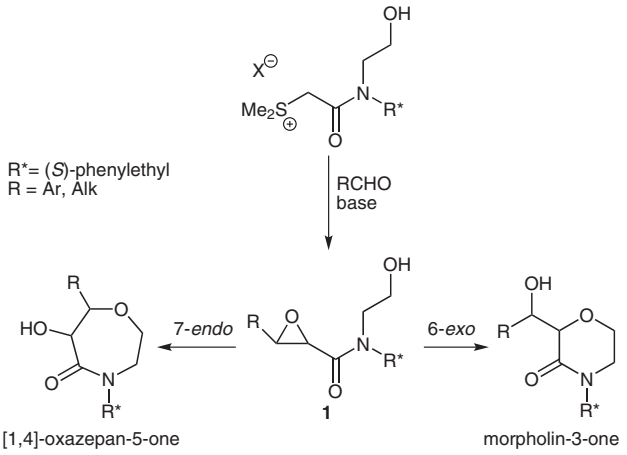
Abstract: We present here a regiospecific synthesis of 7-alkyl- or 7-aryl-6-hydroxy-1,4-oxazepan-5-ones and 2-[aryl(hydroxy)methyl]- or 2-(1-hydroxyalkyl)morpholin-3-ones from a diastereomeric mixture of *trans*-3-alkyl- or -3-aryl-*N*-(2-hydroxyethyl)-*N*-(1-phenylethyl)oxirane-2-carboxamides. This chemodivergent synthesis is easily controlled by an appropriate choice of cyclization reaction conditions.

Key words: chemoselectivity, cyclization, alkoxide, oxazepan-5-ones, morpholin-3-ones

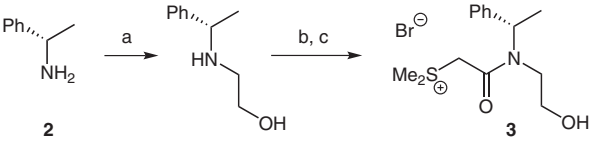
Six- and seven-membered nitrogen–oxygen-containing chiral heterocycles are general scaffolds classically associated with diverse biological activity.[1] In addition, these heterocycles frequently exhibit several stereogenic centers. As a consequence, intensive effort has been devoted towards the development of efficient strategies for their synthesis. In our ongoing work on the asymmetric synthesis of nitrogen heterocycles,[2] we have reported an expeditious access to chiral nonracemic epoxyamides.[3] Epoxyamides are known to be versatile intermediates in organic synthesis[4] offering an extensive range of synthetic possibilities.[5] Among them, the use of controlled intramolecular nucleophilic ring closure[6] could deliver, in a straightforward manner, 1,4-oxazepan-5-ones and/or morpholin-3-ones with potential biological interest. In this work, we report that epoxyamide **1** can indeed lead to both heterocyclic scaffolds using a controlled set of reaction conditions (Scheme 1).

Chiral sulfonium salt **3** was synthesized in three steps starting from (*S*)-phenylethylamine (**2**) in 77% overall yield (Scheme 2).

With the chiral sulfonium salt **3** in hand, the asymmetric epoxidation with benzaldehyde was then investigated (Table 1). Standard basic conditions (KOH, *t*-BuOK, or NaH as the base)[3,7] proved to be inappropriate with this substrate, as the NMR analysis of the crude reaction only showed traces of the corresponding epoxyamide. Best results were obtained when sulfonium salt **3** was treated with DBU, in dichloromethane, from 0 °C to room temperature (entry 5) giving the corresponding diastereomeric mixture of *trans*-epoxyamides **4a/4b** in 92% yield. The NMR spectra show the presence of an *E* vs. *Z* rotameric mixture of each diastereomer. The exclusive formation of the *trans* adducts was confirmed by the magnitude of the coupling constants of the epoxides (J = 2.1 and 1.6 Hz).



Scheme 1 Divergent synthesis of nitrogen heterocycles from epoxyamide **1**



Scheme 2 *Reagents and conditions*: (a) ethylene oxide, H_2O, sonication, 20 min, 91%; (b) bromoacetyl bromide, Et_3N, CH_2Cl_2, –10 °C; (c) Me_2S, CH_2Cl_2, r.t., 77% from (*S*)-phenylethylamine (**2**).

The detection by ^1H NMR spectroscopy of the corresponding morpholinone **4c** in the crude reaction mixture when using inorganic bases such as potassium hydroxide (entry 3), suggests that the formation of the alkoxide rath-

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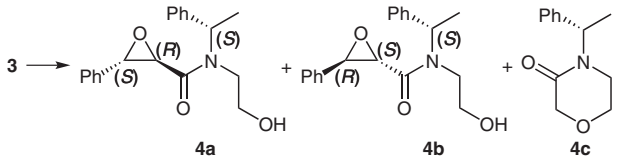
Table 1 Examination of the Conditions for the Epoxidation of **3** with Benzaldehyde[a]



Entry	Solvent	Base (equiv)	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	THF	KOH (15)	0 to r.t.	12	–	trace
2	EtOH	KOH (2)	–30 to 0	10	–	trace
3	CH_2Cl_2	KOH (15)	0 to r.t.	12	**4c**	60
4	CH_2Cl_2	DBU (2)	r.t.	8	**4c**	30
5	CH_2Cl_2	DBU (2)	0 to r.t.	12	**4a** + **4b**	92

[a] All entries were performed using 2 equiv of benzaldehyde.
[b] Isolated yield of diastereomeric mixture.

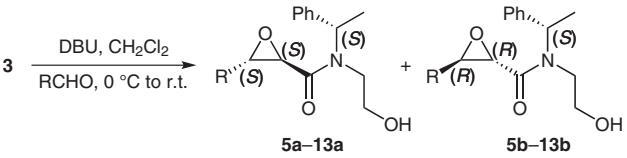
er than the sulfur ylide might be favored under these cyclization conditions, whereas DBU cleanly generated the reactive ylide when the reaction was performed from 0 °C to room temperature (Table 1).

The asymmetric epoxidation of chiral sulfonium salt **3** with several aromatic aldehydes was then investigated (Table 2). In the case of vanillin, the asymmetric epoxidation was unsuccessful; however, high yields of **11a/11b** were obtained when the hydroxy function was protected with a tosyl group (entry 7). The asymmetric epoxidation with aliphatic aldehydes was tested giving the corresponding epoxyamides **12a/12b** and **13a/13b** in good yields (entries 8 and 9).

As the separation of the diastereomers proved to be difficult at this stage, access to the oxazepanone moiety via a 7-*endo*-tet ring closure was investigated. Oxirane ring opening of epoxyamides has been reported using various Lewis acids, such as: $ZnCl_2$,[8] MgI_2,[9] $ZrCl_4$,[10] TFA or $Sc(OTf)_3$,[11] and $Zn(OTf)_2$ or $Cu(OTf)_2$.[12] Although a double substitution reaction pathway has been proposed in the presence of magnesium iodide,[9] *trans*-epoxyamides **4a/4b**, led in our hands to the diastereomeric mixture of 1,4-oxazepan-5-ones **14a/14b**, coming from the direct S_N2 opening reaction in a low yield (Table 3, entry 1), in agreement with results reported by Ohnmacht et al.[11]

The use of trifluoroacetic acid activation led to 1,4-oxazepan-5-ones **14a/14b** in better yield (Table 3, entry 2,). This reaction proved to be highly sensitive to the electron density of the aromatic moiety. Thus, only traces of 1,4-oxazepan-5-ones **15a/15b** were obtained with epoxyamides containing an electron-withdrawing group (entry 3) even using prolonged reaction times. In contrast, 1,4-oxazepan-5-ones **20a/20b** was obtained in 73% yield (entry 4). Lewis acid activation was then investigated in order to increase the reaction yields. The best results were obtained in the presence of 20 mol% copper(II) triflate, leading to the desired 1,4-oxazepan-5-ones **14a/14b–21a/21b**

Table 2 Epoxidation of **3** with Various Aromatic Aldehydes and Alkanals[a]



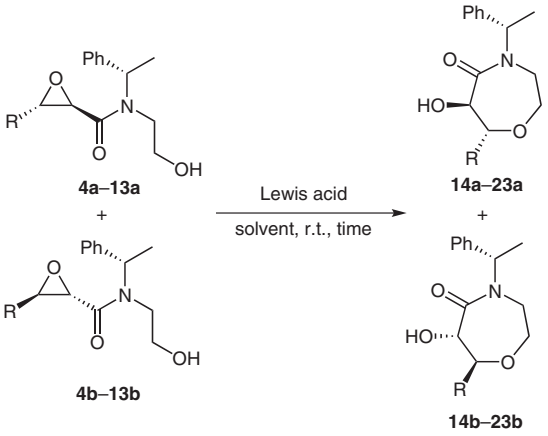
Entry	R	Product	Yield[b] (%)
1	2-$O_2NC_6H_4$	**5a/5b**	85
2	3-$O_2NC_6H_4$	**6a/6b**	85
3	4-$O_2NC_6H_4$	**7a/7b**	90
4	2,6-ClC_6H_3	**8a/8b**	90
5	3,4-ClC_6H_3	**9a/9b**	87
6	3-MeO-4-$BnOC_6H_3$	**10a/10b**	35
7	3-MeO-4-$TsOC_6H_3$	**11a/11b**	95
8	Pr	**12a/12b**	75
9	Bu	**13a/13b**	70

[a] Reaction conditions: aldehyde (2 equiv), 0 °C to r.t., 12 h.
[b] Isolated yield of diastereomeric mixture

in good to excellent yields, even in the presence of deactivating groups on the aromatic ring. This condition also was tested with epoxyamides containing an aliphatic group affording the corresponding 1,4-oxazepan-5-ones **22a/22b** and **23a/23b** in excellent yields (entries 13 and 14).

Diastereomers were easily separated at this stage by chromatographic purification (yielding for entry 7; **16a**, 50% and **16b**, 42%). Fortunately, the major diastereomer **16a** crystallized, enabling the determination of its absolute configuration and securing the presence of the 1,4-ox-

Table 3 Synthesis of 1,4-Oxazepanones via 7-*endo*-tet Ring Closure[a]



Entry	R	Lewis acid	Solvent	Time (h)	Product	Yield[b] (%)
1	Ph	MgI_2	THF	36	**14a/14b**	23
2	Ph	TFA	MeCN–H_2O	12	**14a/14b**	90
3	2-$O_2NC_6H_4$	TFA	MeCN–H_2O	360	**15a/15b**	trace
4	3-MeO-4-$BnOC_6H_3$	TFA	MeCN–H_2O	36	**20a/20b**	73
5	Ph	$Cu(OTf)_2$	MeCN	0.3	**14a/14b**	95
6	2-$O_2NC_6H_4$	$Cu(OTf)_2$	MeCN	0.5	**15a/15b**	78
7	3-$O_2NC_6H_4$	$Cu(OTf)_2$	MeCN	0.3	**16a/16b**	92
8	4-$O_2NC_6H_4$	$Cu(OTf)_2$	MeCN	0.15	**17a/17b**	95
9	2,6-$Cl_2C_6H_4$	$Cu(OTf)_2$	MeCN	0.08	**18a/18b**	91
10	3,4-$Cl_2C_6H_3$	$Cu(OTf)_2$	MeCN	0.3	**19a/19b**	87
11	3-MeO-4-$BnOC_6H_3$	$Cu(OTf)_2$	MeCN	0.6	**20a/20b**	96
12	3-MeO-4-$TsOC_6H_3$	$Cu(OTf)_2$	MeCN	0.15	**21a/21b**	98
13	Pr	$Cu(OTf)_2$	MeCN	0.08	**22a/22b**	98
14	Bu	$Cu(OTf)_2$	MeCN	0.08	**23a/23b**	98

[a] All entries except 1–4 were performed using 20 mol% of $Cu(OTf)_2$.
[b] Isolated yield of diastereomeric mixture.

azepan-5-one ring by X-ray diffraction analysis (Figure 1).

We then explored the access to the morpholinone ring based on a regiospecific 6-*exo*-tet ring closure under basic conditions.

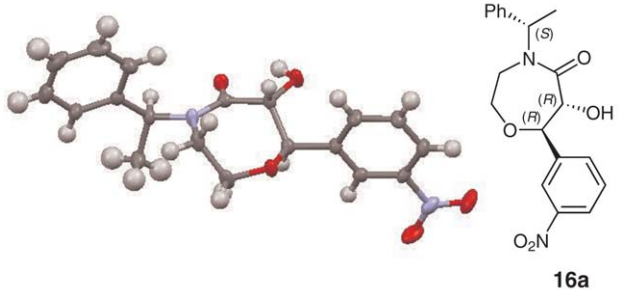


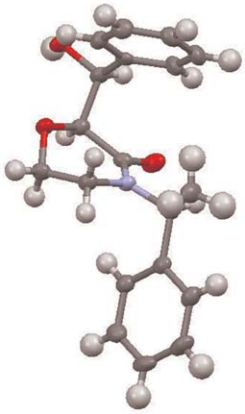
Figure 1 X-ray ORTEP diagram of compound **16a**

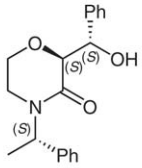
In this way, Liebscher[8] reported the intramolecular opening of oxirane carboxamide using DBU in boiling ethanol forming predominantly the corresponding morpholinone derivative, however when we applied this methodology to the corresponding diastereomeric mixture of *trans*-epoxyamides even using prolonged reaction times, we obtained the desired morpholinone in low yield.

The use of bases such as potassium hydroxide and potassium *tert*-butoxide led only to degradation of the starting material. Better results were obtained when we used a new procedure based on the in situ sodium alkoxide formation by the treated of epoxyamides **4a/4b** with sodium in anhydrous tetrahydrofuran (Table 4, entry 1).[13] The total conversion of the starting material was observed after 20 minutes. The NMR analysis of the crude reaction showed exclusively the presence of the corresponding diastereo-

meric mixture of 2-[hydroxy(phenyl)methyl]-4-(1-phenylethyl)morpholin-3-ones **24a/24b** in 95% yield.

Diastereomers were easily separated at this stage by chromatographic purification (yields of separated diastereomers: 57% for **24a** and 38% for **24b**). Fortunately, the major diastereomer **24a** crystallized, enabling the determination of its absolute configuration and the confirmation of the presence of the morpholinone ring by X-ray diffraction analysis (Figure 2).





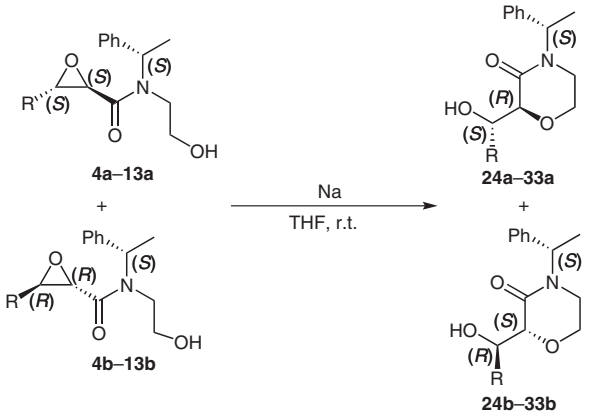
24a

Figure 2 X-ray ORTEP diagram of compound **24a**

Epoxyamides **5a/5b–13a/13b** were reacted with sodium, affording the corresponding morpholin-3-ones **25a/25b–33a/33b** in good to excellent yields, even in the presence of deactivating groups on the aromatic ring (Table 4). Even, the use of epoxyamides **8a/8b** (entry 5) gave the corresponding morpholinones **28a/28b** in good yields despite the presence of two chlorine atoms which could represent a combination of unfavorable steric and electronic effects. Also, the use of epoxyamides **9a/9b** (entry 6) led to the corresponding morpholinones **29a/29b** in 85% yield. Epoxyamides containing an aliphatic group **12a/12b** and **13a/13b** also gave the corresponding morpholinones **32a/32b** and **33a/33b** in excellent yields (entries 9 and 10).

The divergent pathways for the regiospecific ring-closure reactions can be explained as follows. Under basic conditions, the cyclization through the epoxide opening follows an *exo* mode, as a six-membered transition state is more favored than a seven-membered one, in accordance with Baldwin's rules.[14] The use of acidic activation favors a later transition state, having a positive charge developing, at the benzylic position for aromatic epoxyamides or at the more stabilized carbon by inductive effect for aliphatic

Table 4 Intramolecular 6-*exo*-tet Ring-Closure Reaction

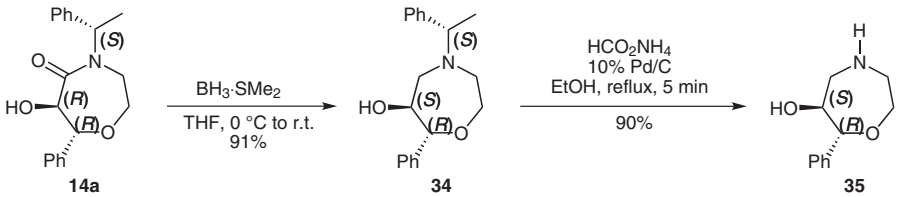


Entry	R	Substrate	Time (min)	Product	Yield (%)
1	Ph	**4a/4b**	20	**24a/24b**	95
2	2-$O_2NC_6H_4$	**5a/5b**	40	**25a/25b**	96
3	3-$O_2NC_6H_4$	**6a/6b**	70	**26a/26b**	90
4	4-$O_2NC_6H_4$	**7a/7b**	75	**27a/27b**	90
5	2,6-$Cl_2C_6H_3$	**8a/8b**	120	**28a/28b**	40
6	3,4-$Cl_2C_6H_3$	**9a/9b**	70	**29a/29b**	85
7	3-MeO-4-$BnOC_6H_3$	**10a/10b**	80	**30a/30b**	75
8	3-MeO-4-$TsOC_6H_3$	**11a/11b**	85	**31a/31b**	85
9	Pr	**12a/12b**	40	**32a/32b**	95
10	Bu	**13a/13b**	40	**33a/33b**	80

epoxyamides, and therefore favors the formation of the oxazepanone skeleton via a 7-*endo*-tet process. This mechanism also explains the influence of the aromatic substitution in the cyclization process.

Finally, we performed the removal of chiral auxiliary from 1,4-oxazepan-5-one **14a** in two steps. In the first step, compound **14a** was reduced with borane–dimethyl sulfide complex, affording the cyclic amine **34** in 91% yield. Finally, compound **34** was selectively *N*-debenzylated when it was treated under transfer hydrogenation condition to give the desired 7-phenyl-1,4-oxazepan-6-ol **35** in 90% yield (Scheme 3).

In summary, we have developed a new strategy to build in a high yielding, highly functionalized, and regiospecific manner chiral 1,4-oxazepan-5-ones and morpholin-3-ones starting from chiral *trans*-epoxyamides. This strate-



Scheme 3

gy opens a new, versatile, and scalable access to chiral six- and seven-membered *N*,*O*-heterocycles for further pharmacological investigations.

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an N_2 atmosphere and all glassware was dried in an oven at 80 °C for 2 h prior to use. Reactions at –10 °C, 0 °C were performed using ultra cold equipment (Mod. SEV CRYO1-80). Melting points were measured by a hot stage melting point apparatus (uncorrected). Optical rotations were measured with a Perkin-Elmer 341 polarimeter, using a 1-dm cell with a total volume of 1 mL and are referenced Na D-line. For flash chromatography, Silica Gel 60, 0.063–0.2 mm/70–230 mesh ASTM was employed; PE = petroleum ether. ^{1}H NMR spectra were recorded using a Varian VX400 (400 MHz) spectrometer relative to TMS (in $CDCl_3$) as internal standard. ^{13}C NMR spectra were recorded using a Varian VX400 (100 MHz) spectrometer and referenced to the residual $CHCl_3$ signal. X-ray diffraction data were obtained by using an Oxford Diffraction Gemini Atlas CCD diffractometer, with graphite-monochromatic MoKα radiation (λ = 0.71073 Å). CrysAlis RED program was used to collect and refine cell, CrysAlis RED program was used to reduce data, and SHELXL97 program was used to solve structure and refine it. Exact mass (HRMS) spectra were recorded with a Jeol JEM-AX505HA instrument at a voltage of 70 eV. Infrared spectra were obtained on a Nicolet FT-IR Magna 750 spectrophotometer.

6-Hydroxy-7-substituted-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-ones 4a/4b–13a/13b; General Procedure

To a stirred soln of the diastereomeric mixture of *trans*-*N*-(2-hydroxyethyl)-3-substituted-*N*-[(*S*)-1-phenylethyl]oxirane-2-carboxamide (0.56 mmol) in MeCN (5 mL) was added $Cu(OTf)_2$ (20% mol) at r.t. The mixture was stirred until the total disappearance of the starting material (20 min). The reaction was quenched by addition of brine (10 mL). The organic phase was separated, dried (anhyd Na_2SO_4), filtered, and the solvent was removed by evaporation. The resulting diastereomeric mixture was purified via flash column chromatography (silica gel, EtOAc–PE, 1:4).

(–)-(6*R*,7*R*)-6-Hydroxy-7-phenyl-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (14a)

Yield: 0.329 mmol (51%); R_f = 0.65 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –85.8 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3380, 1639, 1106, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 6.8 Hz, 3 H, CH_3), 3.11 (dd, *J* = 4.1, 16.3 Hz, 1 H, H3), 3.40 (dd, *J* = 9.9, 16.3 Hz, 1 H, H3), 3.53 (dd, *J* = 9.9, 12.9 Hz, 1 H, H2), 4.10 (dd, *J* = 4.1, 12.9 Hz, 1 H, H2), 4.29 (d, *J* = 9.0 Hz, 1 H, H7), 4.47 (m, 2 H, OH, H6), 6.15 (q, *J* = 6.8 Hz, 1 H, H1′), 7.24–7.39 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 45.5, 52.6, 70.6, 73.5, 82.2, 127.1–128.7, 139.1, 139.2, 174.4.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1541.

(–)-(6*S*,7*S*)-6-Hydroxy-7-phenyl-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (14b)

Yield: 0.280 mmol (44%); R_f = 0.55 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –160 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3377, 1642, 1100, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 6.9 Hz, 3 H), 2.93 (ddd, *J* = 0.8, 9.9, 13.0 Hz, 1 H, H3), 3.15 (ddd, *J* = 0.6, 4.16, 15.8 Hz, 1 H, H2), 3.60 (ddd, *J* = 0.8, 9.9, 15.8 Hz, 1 H, H2), 3.75 (ddd, *J* = 0.9, 4.16, 13.0 Hz, 1 H, H3), 4.19 (d, *J* = 8.7 Hz, 1 H, H7), 4.45 (m, 2 H, OH, H6), 6.17 (q, *J* = 6.9 Hz, 1 H, H1′), 7.29–7.41 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 44.8, 52.6, 69.8, 73.7, 82.0, 127.4–128.7, 139.2, 174.3.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1538.

(–)-(6*R*,7*R*)-6-Hydroxy-7-(2-nitrophenyl)-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (15a)

Yield: 0.188 mmol (42%); R_f = 0.88 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –223.5 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3362, 1658, 1530, 1338, 1127 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (d, *J* = 7.0 Hz, 3 H), 3.10 (dd, *J* = 4.0, 16.4 Hz, 1 H, H3), 3.38 (dd, *J* = 10.2, 16.4 Hz, 1 H, H3), 3.58 (dd, *J* = 10.2, 12.9 Hz, 1 H, H2), 4.16 (dd, *J* = 4.0, 12.9 Hz, 1 H, H2), 4.39 (m, 2 H, OH, H7), 5.28 (d, *J* = 8.3 Hz, 1 H, H6), 6.16 (q, *J* = 7.0 Hz, 1 H), 7.29–7.94 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 45.6, 52.6, 71.0, 74.0, 77.3, 124.2, 127.1–128.77, 132.9, 133.9, 139.1, 173.6.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1402.

(–)-(6*S*,7*S*)-6-Hydroxy-7-(2-nitrophenyl)-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (15b)

Yield: 0.160 mmol (36%); R_f = 0.53 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –35.4 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3375, 1654, 1552, 1347 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 7.0 Hz, 3 H), 2.95 (dd, *J* = 10.0, 13.0 Hz, 1 H, H3), 3.17 (dd, *J* = 3.9, 16.0 Hz, 1 H, H2), 3.58 (dd, *J* = 10.0, 16.0 Hz, 1 H, H2), 3.78 (dd, *J* = 3.9, 13.0 Hz, 1 H, H3), 4.32 (dd, *J* = 4.9, 8.48 Hz, 1 H, H6), 4.41 (d, *J* = 4.9 Hz, 1 H, OH), 5.24 (d, *J* = 8.48 Hz, 1 H, H7), 6.17 (q, *J* = 7.0 Hz, 1 H), 7.29–7.95 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 44.9, 52.6, 70.3, 74.2, 76.3, 124.2, 127.7–128.8, 132.9, 134.0, 139.1, 173.7.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1402.

(–)-(6*R*,7*R*)-6-Hydroxy-7-(3-nitrophenyl)-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (16a)

Yield: 0.251 mmol (50%); R_f = 0.88 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –75.6 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3377, 1640, 1536, 1330 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (d, *J* = 7.0 Hz, 3 H), 3.14 (dd, *J* = 4.2, 16.4 Hz, 1 H), 3.41 (dd, *J* = 10.0, 16.4 Hz, 1 H), 3.56 (dd, *J* = 10.0, 12.9 Hz, 1 H), 4.16 (d, *J* = 4.2, 12.9 Hz, 1 H), 4.40 (m, 2 H), 4.51 (d, *J* = 3.5 Hz, 1 H), 6.14 (q, *J* = 7.0 Hz, 1 H), 7.26–7.41 (m, 5 H), 7.53 (t, *J* = 7.9 Hz, 1 H), 7.69 (dt, *J* = 1.2, 7.7 Hz, 1 H), 8.18 (ddd, *J* = 1.2, 2.2, 8.2 Hz, 1 H), 8.3 (t, *J* = 1.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 45.5, 52.8, 70.8, 73.4, 80.0, 122.5, 123.0, 127.1, 128.0, 128.8, 134.0, 138.8, 141.2, 173.7.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1397.

(–)-(6*S*,7*S*)-6-Hydroxy-7-(3-nitrophenyl)-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (16b)

Yield: 0.213 mmol (42%); R_f = 0.55 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –134.4 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3370, 1644, 1526, 1347, 1111 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (d, *J* = 7.0 Hz, 3 H), 2.93 (dd, *J* = 9.8, 12.9 Hz, 1 H), 3.22 (dd, *J* = 3.9, 15.9 Hz, 1 H), 3.63 (dd, *J* = 9.8, 15.9 Hz, 1 H), 3.79 (dd, *J* = 3.5, 13.1 Hz, 1 H), 4.31 (d, *J* = 9.0 Hz, 1 H), 4.39 (dd, *J* = 3.2, 9.0 Hz, 1 H), 4.53 (d, *J* = 3.5 Hz, 1 H), 6.17 (q, *J* = 7.0 Hz, 1 H), 7.26–8.29 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 44.8, 52.8, 70.0, 73.6, 80.6, 122.5, 122.9, 127.1, 127.6, 128.2, 128.7, 128.8, 133.9, 141.31, 173.6.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1399.

(–)-(6*R*,7*R*)-6-Hydroxy-7-(4-nitrophenyl)-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (17a)
Yield: 0.314 mmol (52%); R_f = 0.5 (EtOAc–PE, 30:70).

$[\alpha]_D^{20}$ –69.55 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3380, 1645, 1526, 1350 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (d, *J* = 7.0 Hz, 3 H), 3.14 (dd, *J* = 4.0, 16.4 Hz, 1 H, H3), 3.39 (dd, *J* = 10.0, 16.4 Hz, 1 H, H3), 3.55 (dd, *J* = 10.0, 12.8 Hz, 1 H, H2), 4.14 (dd, *J* = 4.0, 12.8 Hz, 1 H, H2), 4.39 (m, *J* = 9.0 Hz, 2 H, H7, H6), 4.50 (d, *J* = 3.6 Hz, 1 H, OH), 6.13 (q, *J* = 7.0 Hz, 1 H), 7.26–7.56 (m, 7 H), 8.22 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 45.5, 52.8, 70.8, 73.4, 80.9, 123.2, 127.1–128.8, 138.8, 146.3, 147.5, 173.7.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1407.

(–)-(6*S*,7*S*)-6-Hydroxy-7-(4-nitrophenyl)-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (17b)
Yield: 0.269 mmol (43%); R_f = 0.4 (EtOAc–PE, 30:70).

$[\alpha]_D^{20}$ –208.3 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3277, 1654, 1555, 1264 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (d, *J* = 7.0 Hz, 3 H), 2.93 (dd, *J* = 9.5, 13.1 Hz, 1 H, H3), 3.22 (dd, *J* = 3.9, 15.8 Hz, 1 H, H2), 3.62 (dd, *J* = 9.5, 15.8 Hz, 1 H, H2), 3.79 (dd, *J* = 3.4, 13.1 Hz, 1 H, H3), 4.33 (dd, *J* = 9.0 Hz, 2 H, H6, H7), 4.50 (d, *J* = 3.9 Hz, 1 H, OH), 6.16 (q, *J* = 7.0 Hz, 1 H), 7.32–7.43 (m, 5 H), 7.54 (m, 2 H), 8.21 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 44.8, 52.8, 70.1, 73.6, 80.8, 123.2, 127.7–128.8, 139.0, 146.3, 173.6.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1395.

(–)-(6*R*,7*R*)-7-(2,6-Dichlorophenyl)-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (18a)
Yield: 0.207 mmol (49%); R_f = 0.53 (EtOAc–PE, 10:90).

$[\alpha]_D^{20}$ –65.90 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3383, 2975, 1646, 1437, 1320, 1109, 775, 735, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (d, *J* = 7.1 Hz, 3 H), 3.10 (dd, *J* = 4.2, 16.3 Hz, 1 H, H3), 3.50 (dd, *J* = 9.9, 16.3 Hz, 1 H, H3), 3.55 (dd, *J* = 9.9, 12.7 Hz, 1 H, H2), 4.15 (dd, *J* = 4.2, 12.7 Hz, 1 H, H2), 4.38 (d, *J* = 4.3 Hz, 1 H, H7), 5.19 (d, *J* = 9.3 Hz, 1 H, OH), 5.25 (dd, *J* = 4.3, 9.3 Hz, 1 H, H6), 6.14 (q, *J* = 7.1 Hz, 1 H, H1′), 7.13–7.39 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 45.4, 52.4, 70.6, 71.5, 78.6, 127.1–130.0, 134.0, 134.5, 136.4, 139.0, 174.5.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}Cl_2NO_3$: 379.0742; found: 379.0775.

(–)-(6*S*,7*S*)-7-(2,6-Dichlorophenyl)-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (18b)
Yield: 0.176 mmol (42%); R_f = 0.41 (EtOAc–PE, 10:90).

$[\alpha]_D^{20}$ –187.4 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3385, 2980, 1646, 1435, 1390, 1110, 778, 740, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.0 Hz, 3 H), 2.91 (dd, *J* = 9.8, 13.0 Hz, 1 H, H3), 3.16 (dd, *J* = 3.6, 15.9 Hz, 1 H, H2), 3.63 (dd, *J* = 9.8, 15.9 Hz, 1 H, H2), 3.76 (dd, *J* = 3.6, 13.0 Hz, 1 H, H3), 4.37 (d, *J* = 4.3 Hz, 1 H, H7), 5.13 (d, *J* = 9.2 Hz, 1 H, OH), 5.21 (dd, *J* = 4.3, 9.2 Hz, 1 H, H6), 6.16 (q, *J* = 7.0 Hz, 1 H), 7.12–7.41 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 44.8, 52.5, 70.8, 70.9, 78.5, 127.7–130.1, 134.0, 139.2, 174.5.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}Cl_2NO_3$: 379.0742; found: 379.0770.

(–)-(6*R*,7*R*)-7-(3,4-Dichlorophenyl)-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (19a)
Yield: 0.247 mmol (47%); R_f = 0.88 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –83.4 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3393, 1642, 1464, 1113, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (d, *J* = 7.1 Hz, 3 H), 3.10 (dd, *J* = 4.1, 16.4 Hz, 1 H, H3), 3.35 (dd, *J* = 9.8, 16.4 Hz, 1 H, H3), 3.50 (dd, *J* = 9.8, 12.9 Hz, 1 H, H2), 4.10 (dd, *J* = 3.9, 12.9 Hz, 1 H, H2), 4.22 (d, *J* = 9.0 Hz, 1 H, OH), 4.36 (dd, *J* = 4.1, 9.0 Hz, 1 H, H6), 4.48 (d, *J* = 4.1 Hz, 1 H, H7), 6.11 (q, *J* = 7.1 Hz, 1 H), 7.18–7.49 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 45.4, 52.7, 70.6, 73.3, 80.7, 127.0–132.2, 138.8, 139.4, 173.7.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}Cl_2NO_3$: 379.0742; found: 379.0773.

(–)-(6*S*,7*S*)-7-(3,4-Dichlorophenyl)-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (19b)
Yield: 0.211 mmol (40%); R_f = 0.79 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –143.6 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3397, 1642, 1460, 1390, 1114, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.0 Hz, 3 H), 2.89 (dd, *J* = 9.4, 13.1 Hz, 1 H, H3), 3.18 (dd, *J* = 3.8, 15.8 Hz, 1 H, H2), 3.57 (dd, *J* = 9.4, 15.8 Hz, 1 H, H2), 3.73 (dd, *J* = 3.8, 13.1 Hz, 1 H, H3), 4.15 (d, *J* = 9.0 Hz, 1 H, OH), 4.33 (dd, *J* = 4.0, 9.0 Hz, 1 H, H6), 4.49 (d, *J* = 4.0 Hz, 1 H, H7), 6.15 (q, *J* = 7.0 Hz, 1 H), 7.19 (dd, *J* = 2.0, 8.2 Hz, 1 H), 7.38–7.48 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 44.8, 52.7, 69.9, 73.6, 80.6, 127.0–129.9, 139.0, 139.4, 173.7.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}Cl_2NO_3$: 379.0742; found: 379.0778.

(–)-(6*R*,7*R*)-7-[4-(Benzyloxy)-3-methoxyphenyl]-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (20a)
Yield: 0.104 mmol (52%); R_f = 0.53 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –139.8 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3380, 2924, 1634, 1511, 1460, 1265, 1106 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.08 Hz, 3 H), 2.91 (dd, *J* = 9.8, 12.9 Hz, 1 H, H3), 3.16 (dd, *J* = 3.9, 15.7 Hz, 1 H, H2), 3.59 (dd, *J* = 9.8, 15.7 Hz, 1 H, H2), 3.73 (dd, *J* = 3.7, 12.9 Hz, 1 H, H3), 3.90 (s, 3 H, OCH_3), 4.15 (d, *J* = 8.6 Hz, 1 H, OH), 4.45 (m, 2 H, H6, H7), 5.14 (s, 2 H, CH_2Ph), 6.16 (q, *J* = 7.08 Hz, 1 H, H1′), 6.85–6.92 (m, 3 H), 7.25–7.42 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 44.8, 52.6, 55.9, 69.8, 70.9, 73.7, 81.9, 110.8, 113.4, 119.9, 127.2–128.8, 132.4, 137.2, 139.2, 148.0, 149.4, 174.3.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_5$: 447.2046; found: 447.2080.

(–)-(6*S*,7*S*)-7-[4-(Benzyloxy)-3-methoxyphenyl]-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (20b)
Yield: 0.088 mmol (44%); R_f = 0.37 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –62.8 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3390, 2929, 1634, 1509, 1455, 1270, 1110 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 7.08 Hz, 3 H), 3.09 (dd, *J* = 4.0, 16.3 Hz, 1 H, H3), 3.38 (dd, *J* = 9.8, 16.3 Hz, 1 H, H3), 3.51 (dd, *J* = 9.8, 12.7 Hz, 1 H, H2), 3.90 (s, 3 H, OCH_3), 4.09 (dd, *J* = 4.0, 12.7 Hz, 1 H, H2), 4.22 (d, *J* = 8.5 Hz, 1 H, OH), 4.48 (m, 2 H, H6, H7), 5.14 (s, 2 H, CH_2Ph), 6.13 (q, *J* = 7.08 Hz, 1 H, H1′), 6.86–6.94 (m, 3 H), 7.26–7.43 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.53, 45.55, 52.65, 55.91, 70.60, 70.90, 73.50, 82.12, 110.79, 113.45, 120.0, 127.1–132.3, 137.2, 139.1, 148.1, 149.4, 174.4.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_5$: 447.2046; found: 447.2080.

(–)-(6*R*,7*R*)-6-Hydroxy-7-[3-methoxy-4-(tosyloxy)phenyl]-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (21a)
Yield: 0.155 mmol (52%); R_f = 0.68 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –52.3 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3449, 2929, 1642, 1371, 1177, 1112, 855 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 7.1 Hz, 3 H), 2.42 (s, 3 H, CH_3-Ph), 3.10 (dd, *J* = 4.0, 16.3 Hz, 1 H, H3), 3.37 (dd, *J* = 9.8, 16.3 Hz, 1 H, H3), 3.51 (dd, *J* = 9.8, 12.7 Hz, 1 H, H2), 3.56 (s, 3 H, OCH_3), 4.10 (dd, *J* = 3.5, 12.7 Hz, 1 H, H2), 4.22 (d, *J* = 8.8 Hz, 1 H, OH), 4.41 (m, 2 H, H6, H7), 6.12 (q, *J* = 7.1 Hz, 1 H, H1′), 6.86–6.90 (m, 2 H), 7.11 (d, *J* = 8.2 Hz, 1 H), 7.26–7.36 (m, 8 H), 7.74 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 21.6, 45.4, 52.7, 55.5, 70.6, 73.4, 76.7, 81.6, 111.8, 123.5, 127.1, 127.9, 128.6, 128.8, 129.3, 139.3, 144.8, 151.4, 174.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_7S$: 511.1665; found: 511.1691.

(–)-(6*S*,7*S*)-6-Hydroxy-7-[3-methoxy-4-(tosyloxy)phenyl]-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (21b)
Yield: 0.132 mmol (46%); R_f = 0.57 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –120.3 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3421, 2929, 1638, 1365, 1112, 860 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.08 Hz, 3 H), 2.42 (s, 3 H, CH_3-Ph), 2.89 (dd, *J* = 9.4, 13.0 Hz, 1 H, H3), 3.17 (dd, *J* = 3.9, 15.7 Hz, 1 H, H2), 3.56 (s, 3 H, OCH_3), 3.58 (m, 1 H), 3.72 (m, 1 H), 4.15 (d, *J* = 8.9 Hz, 1 H, OH), 4.36 (dd, *J* = 4.0, 8.9 Hz, 1 H, H6), 4.44 (d, *J* = 4.0 Hz, 1 H, H7), 6.14 (q, *J* = 7.08 Hz, 1 H, H1′), 6.87 (m, 2 H), 7.11 (m, 1 H), 7.26–7.39 (m, 8 H), 7.73 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 21.6, 44.7, 52.7, 55.5, 69.8, 73.6, 81.4, 111.8, 119.7, 123.5, 127.6, 128.1, 128.6, 128.8, 129.3, 139.1, 139.3, 144.8, 151.4, 174.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_7S$: 511.1665; found: 511.1687.

(–)-(6*R*,7*R*)-6-Hydroxy-4-[(*S*)-1-phenylethyl]-7-propyl-1,4-oxazepan-5-one (22a)
Yield: 0.2 mmol (54%); R_f = 0.82 (EtOAc–PE, 30:70).

$[\alpha]_D^{20}$ –87.3 (*c* 1.0, CH_2Cl_2).

IR (KBr): 2957, 1639, 1111 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H), 1.37 (m, 2 H), 1.53 (d, *J* = 7.0 Hz, 3 H), 1.58 (m, 2 H), 1.89 (m, 1 H), 2.98 (dd, *J* = 4.0, 16.1 Hz, 1 H), 3.17–3.37 (m, 2 H), 3.97 (dd, *J* = 4.0, 12.7 Hz, 1 H), 4.12 (dd, *J* = 4.2, 8.9 Hz, 1 H), 4.45 (d, *J* = 4.3 Hz, 1 H), 6.08 (q, *J* = 7.0 Hz, 1 H), 7.23–7.36 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 16.3, 18.0, 34.0, 45.5, 52.2, 70.1, 73.3, 79.3, 127.0, 127.6, 128.5, 139.1, 175.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1680.

(–)-(6*S*,7*S*)-6-Hydroxy-4-[(*S*)-1-phenylethyl]-7-propyl-1,4-oxazepan-5-one (22b)
Yield: 0.165 mmol (44%); R_f = 0.71 (EtOAc–PE, 30:70).

$[\alpha]_D^{20}$ –254.4 (*c* 1.0, CH_2Cl_2).

IR (KBr): 2957, 1638, 1112 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3 H), 1.33 (m, 2 H), 1.49 (d, *J* = 7.1 Hz, 3 H), 1.54 (m, 1 H), 1.87 (m, 1 H), 2.73 (dd, *J* = 10.0, 13.0 Hz, 1 H), 3.06 (dd, *J* = 4.0, 15.7 Hz, 1 H), 3.22 (td, *J* = 2.8, 8.7 Hz, 1 H), 3.41 (dd, *J* = 10.0, 15.7 Hz, 1 H), 3.62 (dd, *J* = 4.0, 13.0 Hz, 1 H), 4.09 (dd, *J* = 3.5, 8.9 Hz, 1 H), 4.46 (d, *J* = 3.8 Hz, 1 H), 6.11 (q, *J* = 7.1 Hz, 1 H), 7.27–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 15.6, 18.37, 34.4, 45.1, 52.6, 69.7, 73.9, 79.5, 127.9, 128.2, 128.9, 139.5, 175.3.

HRMS (ESI): *m*/*z* [M] calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1680.

(–)-(6*R*,7*R*)-7-Butyl-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (23a)
Yield: 0.2 mmol (54%); R_f = 0.86 (EtOAc–PE, 30:70).

$[\alpha]_D^{20}$ –61.65 (*c* 1.0, CH_2Cl_2).

IR (KBr): 2957, 1638, 1112 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2 Hz, 3 H), 1.3 (m, 3 H), 1.53 (d, *J* = 7.0 Hz, 3 H), 1.58 (m, 2 H), 1.93 (m, 1 H), 2.97 (dd, *J* = 3.9, 16.1 Hz, 1 H), 3.17–3.37 (m, 3 H), 3.98 (dd, *J* = 3.8, 12.6 Hz, 1 H), 4.13 (dd, *J* = 4.4, 8.8 Hz, 1 H), 4.45 (d, *J* = 4.4 Hz, 1 H), 6.08 (q, *J* = 7.0 Hz, 1 H), 7.23–7.36 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 16.3, 22.6, 27.0, 31.7, 45.5, 52.2, 70.1, 73.3, 79.5, 127.0, 127.6, 128.5, 139.1, 175.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{17}H_{25}NO_3$: 291.1833; found: 291.1843.

(–)-(6*S*,7*S*)-7-Butyl-6-hydroxy-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-5-one (23b)
Yield: 0.164 mmol (44%); R_f = 0.76 (EtOAc–PE, 30:70).

$[\alpha]_D^{20}$ –197.1 (*c* 1.0, CH_2Cl_2).

IR (KBr): 2957, 1638, 1112 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H), 1.29 (m, 3 H), 1.49 (d, *J* = 7.08 Hz, 3 H), 1.54 (m, 2 H), 1.91 (m, 1 H), 2.73 (dd, *J* = 10.0, 12.9 Hz, 1 H), 3.05 (dd, *J* = 4.0, 15.7 Hz, 1 H), 3.21 (td, *J* = 2.9, 8.7 Hz, 1 H), 3.41 (dd, *J* = 10.0, 15.7 Hz, 1 H), 3.62 (dd, *J* = 4.0, 12.9 Hz, 1 H), 4.10 (dd, *J* = 3.5, 8.9 Hz, 1 H), 4.46 (d, *J* = 4.1 Hz, 1 H), 6.13 (q, *J* = 7.08 Hz, 1 H), 7.28–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 15.2, 22.6, 27.0, 31.7, 44.8, 52.2, 69.4, 73.5, 79.4, 127.5, 127.8, 128.5, 139.2, 175.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{17}H_{25}NO_3$: 291.1833; found: 291.1843.

2-[Hydroxymethyl]-4-[(*S*)-1-phenylethyl]morpholin-3-ones 24a/24b–33a/33b; General Procedure
To a stirred suspension of Na (14–18 mg) in anhyd THF (3.5 mL), was added a soln of the corresponding *trans*-diastereomeric mixture

of epoxyamide (0.64 mmol) in anhyd THF (5.0 mL) at r.t. The resulting mixture was stirred until the total conversion of the starting material. Finally, the reaction was filtered and quenched by addition of aq brine (20 mL) and the organic phase was separated, dried (anhyd Na_2SO_4), filtered, and the solvent was removed by evaporation. The resulting diastereomeric mixture was purified via flash column chromatography (silica gel, EtOAc–PE, 1:1).

(–)-(2*S*)-2-[(*S*)-Hydroxy(phenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (24a)
Yield: 0.333 mmol (57%); R_f = 0.51 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ –144 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3405, 1630, 1447, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 7.2 Hz, 3 H), 2.67 (d, *J* = 12.2 Hz, 1 H, H5), 3.17 (td, *J* = 4.1, 11.5 Hz, 1 H, H6), 3.42 (td, *J* = 2.9, 11.5 Hz, 1 H, H6), 3.80 (ddd, *J* = 1.3, 3.9, 11.8 Hz, 1 H, H5), 4.28 (d, *J* = 7.1 Hz, 1 H, H2), 4.99 (d, *J* = 7.1 Hz, 1 H, H1″), 6.02 (q, *J* = 7.2 Hz, 1 H), 7.26–7.45 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 39.9, 49.8, 63.0, 74.4, 78.8, 127.1–128.5, 138.9, 139.9, 168.4.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1539.

(+)-(2*R*)-2-[(*R*)-Hydroxy(phenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (24b)
Yield: 0.283 mmol (38%); R_f = 0.35 (EtOAc–PE, 40:60).

$[\alpha]_D^{20}$ +1.53 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3416, 1623, 1454, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.1 Hz, 3 H), 2.78 (m, 1 H, H5), 2.92 (dt, *J* = 2.7, 12.6 Hz, 1 H, H5), 3.61 (td, *J* = 3.2, 10.12, 11.9 Hz, 1 H, H6), 3.80 (ddd, *J* = 2.7, 4.15, 11.9 Hz, 1 H, H6), 4.32 (d, *J* = 7.0 Hz, 1 H, H1″), 5.03 (d, *J* = 7.0 Hz, 1 H, H2), 5.97 (q, *J* = 7.1 Hz, 1 H, H1′), 7.05–7.44 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 40.4, 49.9, 63.0, 74.4, 79.1, 127.3–128.5, 138.5, 140.0, 168.2.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1537.

(+)-(2*S*)-2-[(*S*)-Hydroxy(2-nitrophenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (25a)
Yield: 0.363 mmol (52%); R_f = 0.85 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ +113.3 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3374, 1627, 1528, 737 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.58 (d, *J* = 7.2 Hz, 3 H), 2.75 (m, 1 H), 3.39 (m, 2 H), 3.78 (m, 1 H), 3.99 (d, *J* = 8.8 Hz, 1 H, H1″), 5.53 (br, 1 H, OH), 5.86 (d, *J* = 8.8 Hz, 1 H, H2), 6.06 (q, *J* = 7.2 Hz, 1 H), 7.23–7.37 (m, 5 H), 7.26 (td, *J* = 1.6, 7.6, 8.0 Hz, 1 H), 7.64 (td, *J* = 0.8, 7.6, 8.0 Hz, 1 H), 7.81 (dd, *J* = 0.8, 1.2, 8.2 Hz, 1 H), 7.99 (dd, *J* = 1.2, 1.6, 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 40.0, 50.2, 63.1, 68.4, 78.5, 123.8, 127.2–128.7, 132.8, 134.6, 138.9, 168.9.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1390.

(–)-(2*R*)-2-[(*R*)-Hydroxy(2-nitrophenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (25b)
Yield: 0.309 mmol (44%); R_f = 0.68 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –169 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3365, 1630, 1510, 724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 7.1 Hz, 3 H), 2.98 (m, 2 H, H5, H6), 3.59 (td, *J* = 3.4, 8.8, 12.0 Hz, 1 H, H5), 3.75 (dt, *J* = 3.7, 11.8 Hz, 1 H, H6), 4.02 (d, *J* = 8.4 Hz, 1 H, H1″), 5.53 (br, 1 H, OH), 5.86 (d, *J* = 8.4 Hz, 1 H, H2), 6.04 (q, *J* = 7.1 Hz, 1 H, H1′), 7.29–7.45 (m, 6 H), 7.64 (m, 1 H), 7.82 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 40.5, 50.3, 62.9, 68.4, 78.5, 123.8, 127.3–128.8, 132.8, 134.7, 138.3, 168.8.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1385.

(–)-(2*S*)-2-[(*S*)-Hydroxy(3-nitrophenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (26a)
Yield: 0.204 mmol (49%).

$[\alpha]_D^{20}$ –134 (*c* 1.1, CH_2Cl_2); R_f = 0.79 (EtOAc–PE, 50:50).

IR (KBr): 3414, 2926, 1628, 1528, 1347 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 7.1 Hz, 3 H), 2.77 (m, 1 H), 3.32 (td, *J* = 4.2, 11.5 Hz, 1 H), 3.47 (td, *J* = 2.9, 11.5 Hz, 1 H), 3.87 (ddd, *J* = 1.4, 4.2, 11.8 Hz, 1 H), 4.19 (d, *J* = 7.7 Hz, 1 H, H1″), 5.08 (d, *J* = 7.7 Hz, 1 H, H2), 5.51 (br, OH), 6.06 (q, *J* = 7.2 Hz, 1 H, H1′), 7.28–7.37 (m, 5 H), 7.51 (t, *J* = 7.9 Hz, 1 H), 7.81 (m, 1 H), 8.16 (m, 1 H), 8.34 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 40.0, 50.1, 63.2, 73.5, 78.3, 122.6, 127.1–128.7, 133.7, 138.7, 142.3, 168.3.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1389.

(–)-(2*R*)-2-[(*R*)-Hydroxy(3-nitrophenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (26b)
Yield: 0.174 mmol (41%); R_f = 0.41 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –0.6 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3378, 2940, 1640, 1527, 1330 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.1 Hz, 3 H), 2.86 (m, 1 H), 3.00 (dt, *J* = 2.4, 12.6 Hz, 1 H), 3.67 (m, 1 H), 3.86 (ddd, *J* = 2.3, 4.1, 11.9 Hz, 1 H), 4.22 (d, *J* = 7.4 Hz, 1 H, H1″), 5.09 (d, *J* = 7.4 Hz, 1 H, H2), 6.00 (q, *J* = 7.1 Hz, 1 H, H1′), 7.15–7.35 (m, 5 H), 7.49 (t, *J* = 7.9 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 8.1 (m, 1 H), 8.33 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 40.3, 50.1, 63.0, 73.4, 78.4, 122.7, 127.2–128.7, 133.8, 138.2, 142.3, 168.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1389.

(–)-(2*S*)-2-[(*S*)-Hydroxy(4-nitrophenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (27a)
Yield: 0.341 mmol (48%); R_f = 0.8 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –75.4 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3450, 2925, 1630, 1528, 1340 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.2 Hz, 3 H), 2.75 (m, 1 H), 3.29 (td, *J* = 4.2, 11.6 Hz, 1 H), 3.47 (td, *J* = 2.9, 11.6 Hz, 1 H), 3.85 (ddd, *J* = 1.4, 4.1, 11.8 Hz, 1 H), 4.19 (d, *J* = 7.5 Hz, 1 H), 5.09 (d, *J* = 7.5 Hz, 1 H), 6.05 (q, *J* = 7.2 Hz, 1 H), 7.28–7.37 (m, 5 H), 7.64 (m, 2 H), 8.19 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 40.3, 50.4, 63.5, 73.9, 78.7, 123.3, 127.4–129.0, 139.0, 147.8, 168.4.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1387.

(+)-(2*R*)-2-[(*R*)-Hydroxy(4-nitrophenyl)methyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (27b)
Yield: 0.290 mmol (42%); R_f = 0.44 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ +12.8 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3398, 2929, 1630, 1526, 1347 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 7.1 Hz, 3 H), 2.82 (m, *J* = 4.2, 10.4, 12.5 Hz, 1 H), 3.00 (dt, *J* = 2.6, 12.6 Hz, 1 H), 3.65 (m, *J* = 3.2, 10.4, 11.9 Hz, 1 H), 3.85 (ddd, *J* = 2.3, 4.3, 11.9 Hz, 1 H), 4.24 (d, *J* = 7.1 Hz, 2 H), 5.12 (d, *J* = 7.1 Hz, 1 H), 6.98 (q, *J* = 7.1 Hz, 1 H), 7.14–7.34 (m, 5 H), 7.61 (m, 2 H), 8.16 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 40.3, 50.2, 63.1, 73.6, 78.6, 123.0, 127.3–128.6, 138.3, 147.4, 167.8.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1389.

(–)-(2*S*)-2-[(*S*)-(2,6-Dichlorophenyl)hydroxymethyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (28a)
Yield: 0.170 mmol (21%); R_f = 0.86 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –6.3 (*c* 0.9, CH_2Cl_2).

IR (KBr): 3401, 2930, 1635, 1464, 1135, 1063, 1037 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 7.1 Hz, 3 H), 2.83 (td, *J* = 3.2, 12.4 Hz, 1 H), 3.37 (ddd, *J* = 3.9, 9.2, 12.6 Hz, 1 H), 3.55 (ddd, *J* = 3.1, 9.2, 12.0 Hz, 1 H), 3.88 (td, *J* = 3.6, 11.9 Hz, 1 H), 5.01 (d, *J* = 9.6 Hz, 1 H), 5.41 (d, *J* = 1.2 Hz, 1 H), 5.76 (dd, *J* = 1.1, 9.6 Hz, 1 H), 6.11 (q, *J* = 7.1 Hz, 1 H), 7.14 (dd, *J* = 7.6, 8.4 Hz, 1 H), 7.29–7.39 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 40.3, 50.0, 63.1, 71.0, 74.7, 127.2, 127.8, 128.7, 129.3, 133.8, 138.8, 169.6.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}Cl_2NO_3$: 379.0742; found: 379.0755.

(–)-(2*R*)-2-[(*R*)-(2,6-Dichlorophenyl)hydroxymethyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (28b)
Yield: 0.145 mmol (19%); R_f = 0.77 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –5.3 (*c* 0.9, CH_2Cl_2).

IR (KBr): 3401, 2930, 1635, 1464, 1135, 1063, 1037 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 7.1 Hz, 3 H), 2.93 (ddd, *J* = 3.9, 7.5, 12.5 Hz, 1 H), 3.17 (ddd, *J* = 3.5, 5.1, 12.5 Hz, 1 H), 3.69 (ddd, *J* = 3.5, 7.5, 11.9 Hz, 1 H), 3.84 (ddd, *J* = 3.9, 5.1, 11.9 Hz, 1 H), 5.06 (d, *J* = 9.6 Hz, 1 H), 5.39 (d, *J* = 1.3 Hz, 1 H), 5.78 (dd, *J* = 1.3, 9.6 Hz, 1 H), 6.12 (q, *J* = 7.1 Hz, 1 H), 7.13–7.42 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 40.5, 50.0, 62.6, 70.8, 74.5, 122.9, 127.3, 127.8, 128.7, 129.4, 133.9, 138.6, 169.6.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}Cl_2NO_3$: 379.0742; found: 379.0759.

(–)-(2*S*)-2-[(*S*)-(3,4-Dichlorophenyl)hydroxymethyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (29a)
Yield: 0.217 mmol (45.5%); R_f = 0.47 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –129.0 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3401, 2930, 1635, 1464, 1135, 1063, 1037 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 7.2 Hz, 3 H), 2.73 (m, 1 H), 3.26 (td, *J* = 4.1, 11.5 Hz, 1 H), 3.45 (td, *J* = 2.9, 11.5 Hz, 1 H), 3.84 (ddd, *J* = 1.5, 4.1, 11.8 Hz, 1 H), 4.15 (d, *J* = 7.4 Hz, 1 H), 4.94 (d, *J* = 7.4 Hz, 1 H), 6.04 (q, *J* = 7.2 Hz, 1 H), 7.28–7.37 (m, 5 H), 7.64 (m, 2 H), 8.19 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 40.0, 50.0, 63.2, 73.3, 78.5, 127.0–131.9, 138.8, 140.5, 168.2.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}Cl_2NO_3$: 379.0742; found: 379.0766.

(+)-(2*R*)-2-[(*R*)-(3,4-Dichlorophenyl)hydroxymethyl]-4-[(*S*)-1-phenylethyl] morpholin-3-one (29b)
Yield: 0.185 mmol (39.5%); R_f = 0.17 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ +3.0 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3398, 2929, 1635, 1460, 1130, 1050, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.1 Hz, 3 H), 2.81 (m, *J* = 4.2, 10.4, 12.6 Hz, 1 H), 2.95 (dt, *J* = 2.5, 12.6 Hz, 1 H), 3.64 (ddd, *J* = 3.2, 10.4, 11.9 Hz, 1 H), 3.85 (ddd, *J* = 2.4, 4.2, 11.9 Hz, 1 H), 4.21 (d, *J* = 7.0 Hz, 1 H), 4.97 (d, *J* = 7.0 Hz, 1 H), 5.97 (q, *J* = 7.1 Hz, 1 H), 7.10 (m, 2 H), 7.26–7.39 (m, 5 H), 7.57 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 40.4, 50.1, 63.1, 73.3, 78.7, 127.2–132.0, 138.3, 140.4, 167.9.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{19}C_{l2}NO_3$: 379.0742; found: 379.0770.

(–)-(2*S*)-2-{(*S*)-[4-(Benzyloxy)-3-methoxyphenyl]hydroxymethyl}-4-[(*S*)-1-phenylethyl]morpholin-3-one (30a)
Yield: 0.072 mmol (40.5%); R_f = 0.25 (EtOAc–PE, 90:10).

$[\alpha]_D^{20}$ –87.0 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3418, 2927, 1640, 1511, 1265, 1138, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 7.2 Hz, 3 H), 2.72 (dt, *J* = 1.9, 12.2 Hz, 1 H), 3.25 (dd, *J* = 4.1, 11.5, 1 H), 3.48 (dd, *J* = 2.9, 11.4 Hz, 1 H), 3.86 (ddd, *J* = 1.6, 4.0, 11.8 Hz, 1 H), 3.91 (s, 3 H), 4.25 (d, *J* = 7.5, 1 H), 4.90 (d, *J* = 7.5 Hz, 1 H), 5.07 (br, 1 H), 5.15 (s, 2 H), 6.04 (q, *J* = 7.2 Hz, 1 H), 6.87 (m, 2 H), 7.07 (d, *J* = 1.8 Hz, 1 H), 7.25–7.44 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 40.1, 49.9, 55.9, 63.2, 70.8, 74.4, 78.8, 110.8, 113.2, 120.0, 127.2, 127.7, 127.8, 128.5, 128.7, 133.2, 137.2, 139.1, 147.9, 149.3, 168.8.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_5$: 447.2046; found: 447.2051.

(+)-(2*R*)-2-{(*R*)-[4-(Benzyloxy)-3-methoxyphenyl]hydroxymethyl}-4-[(*S*)-1-phenylethyl]morpholin-3-one (30b)
Yield: 0.061 mmol (34.5%); R_f = 0.11 (EtOAc–PE, 90:10).

$[\alpha]_D^{20}$ +7.0 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3418, 2927, 1640, 1511, 1265, 1138, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.0 Hz, 3 H), 2.82 (m, 1 H), 2.96 (dt, *J* = 2.7, 12.5 Hz, 1 H), 3.65 (td, *J* = 3.2, 11.9 Hz, 1 H), 3.84 (dd, *J* = 2.8, 7.9 Hz, 1 H), 3.87 (s, 3 H), 4.30 (d, *J* = 7.2 Hz, 1 H), 4.95 (d, *J* = 7.2 Hz, 1 H), 5.1 (s, 2 H), 5.99 (q, *J* = 7.0 Hz, 1 H), 6.86 (m, 2 H), 7.0 (m, 1 H), 7.25–7.44 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 40.4, 49.9, 55.9, 63.0, 70.8, 74.3, 79.0, 111.0, 113.1, 120.2, 127.2–128.6, 137.2, 138.5, 148.0, 149.3, 168.4.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_5$: 447.2046; found: 447.2055.

(–)-(2*S*)-2-{(*S*)-[3-Methoxy-4-(tosyloxy)phenyl]hydroxymethyl}-4-[(*S*)-1-phenylethyl]morpholin-3-one (31a)
Yield: 0.116 mmol (46%); R_f = 0.2 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –88.4 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3449, 1642, 1271, 1177, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.2 Hz, 3 H), 2.43 (s, 3 H), 2.73 (m, 1 H), 3.25 (td, *J* = 4.1, 11.5 Hz, 1 H), 3.46 (td, *J* = 2.9, 11.8 Hz, 1 H), 3.56 (s, 3 H), 3.85 (ddd, *J* = 1.5, 4.0, 11.8 Hz, 1 H), 4.17 (d, *J* = 7.4 Hz, 1 H), 4.93 (d, *J* = 7.4 Hz, 1 H), 6.03 (q, *J* = 7.2 Hz, 1 H), 6.94 (dd, *J* = 1.9, 8.3 Hz, 1 H), 7.0 (d, *J* = 1.8 Hz, 1 H),

7.10 (d, *J* = 8.2 Hz, 1 H), 7.26–7.39 (m, 6 H), 7.74 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 21.6, 40.1, 50.0, 55.5, 63.2, 74.1, 78.6, 111.6, 119.9, 123.1, 127.2–129.3, 137.9, 138.9, 140.3, 144.9, 151.4, 168.5.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_7S$: 511.1665; found: 511.1684.

(+)-(2*R*)-2-{(*R*)-[3-Methoxy-4-(tosyloxy)phenyl]hydroxymethyl}-4-[(*S*)-1-phenylethyl]morpholin-3-one (31b)

Yield: 0.098 mmol (39%); R_f = 0.06 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ +4.2 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3450, 1643, 1271, 1177, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 7.0 Hz, 3 H), 2.43 (s, 3 H), 2.8 (ddd, *J* = 4.3, 10.0, 12.6 Hz, 1 H), 2.97 (dt, *J* = 2.6, 12.6 Hz, 1 H), 3.53 (s, 3 H), 3.61 (m, 2 H), 3.82 (ddd, *J* = 2.6, 4.1, 11.8 Hz, 1 H), 4.19 (d, *J* = 7.5 Hz, 1 H), 4.94 (d, *J* = 7.3 Hz, 1 H), 5.98 (q, *J* = 7.0 Hz, 1 H), 6.93 (dd, *J* = 1.8, 8.3 Hz, 1 H), 6.90 (d, *J* = 1.8 Hz, 1 H), 7.08–7.15 (m, 3 H), 7.26–7.36 (m, 5 H), 7.74 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 21.6, 40.5, 50.1, 55.5, 63.0, 73.9, 78.7, 111.8, 120.0, 123.2, 127.2–129.3, 140.3, 144.9, 151.4, 168.3.

HRMS (ESI): *m*/*z* [M] calcd for $C_{27}H_{29}NO_7S$: 511.1665; found: 511.1687.

(–)-2*S*)-2-[(*S*)-1-Hydroxybutyl]-4-[(*S*)-1-phenylethyl)morpholin-3-one (32a)

Yield: 0.15 mmol (46%); R_f = 0.80 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –194.2 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3415, 2955, 1626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.0 Hz, 3 H), 1.44 (m, 2 H), 1.53 (d, *J* = 7.2 Hz, 3 H), 1.60 (m, 2 H), 2.78 (dt, *J* = 1.9, 11.8 Hz, 1 H), 3.41 (td, *J* = 4.2, 11.1 Hz, 1 H), 3.56 (td, *J* = 2.9, 11.1 Hz, 1 H), 3.70 (s, 1 H), 3.93–4.0 (m, 2 H), 4.35 (s, 1 H), 6.06 (q, *J* = 7.2 Hz, 1 H), 7.27–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 15.2, 18.1, 34.5, 40.1, 49.6, 63.0, 71.7, 78.8, 127.1, 127.6, 128.5, 139.1, 169.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1680.

(–)-(2*R*)-2-[(*R*)-1-Hydroxybutyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (32b)

Yield: 0.126 mmol (49%); R_f = 0.58 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –71.25 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3415, 2955, 1626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.1 Hz, 3 H), 1.39–1.51 (m, 2 H), 1.53 (d, *J* = 7.0 Hz, 3 H), 1.55–1.67 (m, 2 H), 2.94 (td, *J* = 4.3, 12.5 Hz, 1 H), 3.03 (dt, *J* = 2.9, 12.3 Hz, 1 H), 3.71 (ddd, *J* = 3.4, 10.1, 11.7 Hz, 1 H), 3.92 (ddd, *J* = 2.6, 4.2, 11.8 Hz, 1 H), 3.97 (dd, *J* = 7 Hz, 1 H), 4.32 (br, 1 H), 6.0 (q, *J* = 7.0 Hz, 1 H), 7.27–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 15.0, 18.1, 34.7, 40.4, 49.8, 62.9, 71.7, 78.7, 127.3, 127.7, 128.5, 138.7, 169.1.

HRMS (ESI): *m*/*z* [M] calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1680.

(–)-(2*S*)-2-[(*S*)-1-Hydroxypentyl)-4-[(*S*)-1-phenylethyl]morpholin-3-one (33a)

Yield: 0.153 mmol (44%); R_f = 0.76 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –162.2 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3415, 2955, 1626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3 H), 1.35 (m, 4 H), 1.53 (d, *J* = 7.2 Hz, 3 H), 1.69 (m, 1 H), 2.78 (dt, *J* = 2.0, 12.0 Hz, 1 H), 3.4 (td, *J* = 4.2, 11.4 Hz, 1 H), 3.56 (td, *J* = 2.9, 11.4 Hz, 1 H), 3.69 (s, 1 H), 3.96 (m, 3 H), 4.35 (s, 1 H), 6.06 (q, *J* = 7.2 Hz, 1 H), 7.26–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 15.2, 22.6, 27.0, 32.1, 40.21, 49.6, 63.0, 71.9, 78.8, 127.1, 127.6, 128.5, 139.1, 169.0.

HRMS (ESI): *m*/*z* [M] calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 291.1838.

(–)-(2*R*)-2-[(*R*)-1-Hydroxypentyl]-4-[(*S*)-1-phenylethyl]morpholin-3-one (33b)

Yield: 0.125 mmol (36%); R_f = 0.54 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ –98.75 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3415, 2955, 1626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H), 1.35 (m, 4 H), 1.53 (d, *J* = 7.1 Hz, 3 H), 1.67 (m, 1 H), 2.94 (td, *J* = 4.3, 10.0 Hz, 1 H), 3.03 (dt, *J* = 2.6, 12.4 Hz, 1 H), 3.71 (td, *J* = 3.4, 10.0 Hz, 1 H), 3.90–3.99 (m, 3 H), 4.31 (br, 1 H), 6.0 (q, *J* = 7.1 Hz, 1 H), 7.27–7.32 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.9, 22.7, 27.0, 32.3, 40.4, 49.7, 62.9, 71.9, 78.7, 127.3, 127.7, 128.5, 138.7, 169.1.

HRMS (ESI): *m*/*z* [M] calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 291.1838.

(+)-(6*S*,7*R*)-7-Phenyl-4-[(*S*)-1-phenylethyl]-1,4-oxazepan-6-ol (34)

To a stirred soln of 1,4-oxazepan-5-one **14a** (0.138 g, 0.443 mmol) in anhyd THF (6 mL) at 0 °C, under N_2, was added $BH_3{\cdot}SMe_2$ (0.084 g, 1.10 mmol). The mixture was stirred at r.t. for 12 h. Later, the reaction was quenched with MeOH (6 mL) and stirred for 1 h. Finally, the solvent was evaporated under reduced pressure, and the crude was purified via flash chromatography column giving the desired compound **34** (0.120 g, 0.403 mmol, 91%) as a white oil; R_f = 0.7 (EtOAc–PE, 50:50).

$[\alpha]_D^{20}$ +12.0 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3416, 2930, 1451, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.8 Hz, 3 H), 2.71 (m, 2 H), 2.86 (m, 2 H), 3.78–3.91 (m, 3 H), 4.0 (dt, *J* = 2.6, 13.0 Hz, 1 H), 4.70 (d, *J* = 2.0 Hz, 1 H), 7.17–7.35 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 50.9, 55.0, 63.4, 69.4, 74.7, 87.4, 125.8, 127.0, 127.2, 127.5, 128.1, 128.2, 141.5, 142.2.

HRMS (ESI): *m*/*z* [M] calcd for $C_{19}H_{23}NO_2$: 297.1729; found: 297.1731.

(–)-(6*S*,7*R*)-7-Phenyl-1,4-oxazepan-6-ol (35)

To a stirred suspension of 10% Pd-C (0.08 g) in abs EtOH (6 mL) at r.t. was added 1,4-oxazepan-6-ol **34** (0.08 g, 0.286 mmol). To the resulting mixture, ammonium formate (0.09 g, 1.42 mmol) was added and the mixture was refluxed for 5 min. Finally, the mixture was filtered through a path of diatomite and the solvent was eliminated in vacuo giving the desired compound **35** (0.252 mmol, 90%); R_f = 0.31 (EtOAc–MeOH, 50:50).

$[\alpha]_D^{20}$ –14.7 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3381, 2924, 1597, 1130, 1070, 1020 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.11 (m, 1 H), 3.2 (m, 2 H), 3.97–4.03 (m, 1 H), 4.13 (m, 2 H), 4.70 (d, *J* = 3.2, Hz, 1 H), 6.29 (br, 2 H), 7.23–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.9, 49.8, 68.4, 74.5, 86.9, 125.8, 127.6, 128.4, 140.7.

HRMS (ESI): *m/z* [M] calcd for $C_{11}H_{15}NO_2$: 193.1103; found: 193.1105.

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