Synthesis of enantiopure 1,3-oxazolidin-2-ones from α-dibenzylamino esters

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Abstract
A new method to obtain enantiopure 5-substituted 1,3-oxazolidin-2-ones **1** from α-dibenzylamino esters **2** is reported. This methodology is based on the Lewis acid catalyzed stereoselective addition of trimethylsilyl cyanide to chiral α-dibenzylamino aldehydes **3**. Magnesium chloride and zinc iodide were tested to catalyze the addition, obtaining higher stereoselectivity with zinc iodide than with magnesium chloride.

Keywords: Enantiopure, 1,3-oxazolidin-2-ones, stereoselective addition

Introduction

In 1981, 4-substituted 1,3-oxazolidin-2-ones were introduced into organic synthesis as chiral auxiliaries by Evans.[1] Since then they have been used in many reactions. These compounds are mainly prepared from the cyclization of chiral amino alcohols derived from nonracemic amino acids. Usually, *N*-acyloxazolidinones participate in stereoselective processes as alkylations, α-substitution reactions, aldol reactions, conjugate additions and pericyclic reactions. The majority of these reactions are performed in the presence of a metal ion.[2]

Meanwhile, a group of 5-substituted 1,3-oxazolidin-2-ones, typified by linezolid (**4**) and eperozolid (**5**), represent a new class of synthetic antibacterial agents with potent activity against clinically important susceptible and resistant *Gram*-positive and anaerobic pathogens.[3] This class of compounds has a novel mechanism of action that shows selective and unique binding to 50S ribosomal subunit, inhibiting bacterial translation at the initiation phase of protein synthesis.[4] Due to its protein synthesis inhibitory activity these compounds are used against methicilline or vancomicin-resistant staphylococci, streptococci and enterococci bacteria that causes skin and soft tissue infections and pneumonia.[5] Moreover, there are many reports for the synthesis of new

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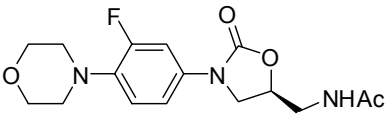
compounds structurally related to linezolid that avoid bacterial resistance against these new antibiotics.[6]



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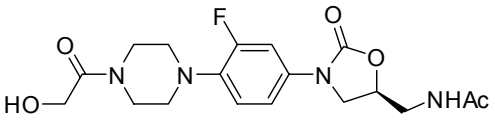

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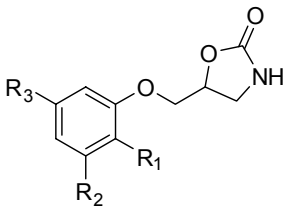
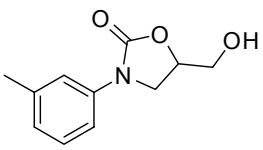


6: R_1 = OMe R_2 = R_3 = H
7: R_1 = H R_2 = R_3 = Me



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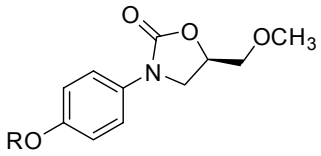


9: R= (3-cyano)benzyl
10: R= (3*S*)-4,4,4-trifluoro-3-hydroxybutyl

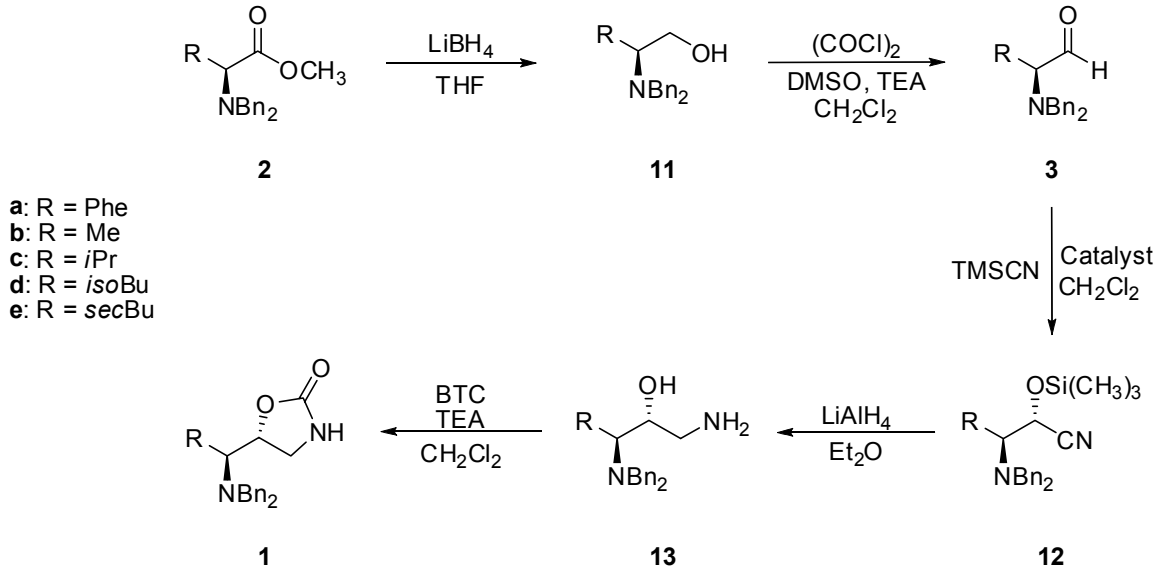
Mephenoxalone (**6**) and metaxalone (**7**) are 5-aryloxymethyl-1,3-oxazolidin-2-one type compounds, which have shown activity as interneuron blocking agents or depressants of central synaptic transmission. They are generally antagonists of strychnine convulsions and have been used as skeletal muscle relaxants, anticonvulsants, and tranquilizers.[7] These products are prescribed to rest, physical therapy, and for the relief of discomfort associated with acute, painful musculoskeletal conditions.[8] Also, there are 5-substituted 1,3-oxazolidin-2-ones, which are a new class of reversible and selective third-generation of potent and selective monoamine oxidase type A (MAO) inhibitors as toloxatone (**8**; Humoryl ®), cimoxatone (**9**) and befloxatone (**10**) which are indicated in the treatment of several neurological diseases.[9] Therefore, the synthesis of chiral 1,3-oxazoldin-2-ones is an important field of research due to the potential as chiral inductors or biological active substances.[10]

Reetz and coworkers reported the stereoselective cyanosilylation of non-racemic α-dibenzylamino aldehydes **3** by the addition of trimethylsilyl cyanide with different inorganic salts as Lewis acid catalysts.[11] The application of some organometallic compounds have also been reported.[12] These silylated intermediates are important building blocks in the synthesis of pharmacologically active compounds,[13] but to the best of our knowledge, the synthesis of 1,3-oxazolidin-2-ones from these silylated intermediates has yet to be reported. Only the *N*-benzoyl-1,3-oxazolidin-2-one derivative from L-phenylalanine has been synthesized from a ring-closure reaction of β-hydroxyalkyl phenyl selenides through intramolecular displacement of the phenylselenoyl group with nitrogen nucleophiles.[14] Previously, we have explored the construction of 1,3-oxazolidin-2-one ring from a silylated intermediate,[15] as well as the stereoselective synthesis of new compounds with potential biological activity by transformation of chiral α-amino esters.[16] In this work, we have developed a new methodology for the synthesis

of enantiopure 5-substituted 1,3-oxazolidin-2-ones from chiral silylated intermediates prepared from enantiopure α-dibenzylamino esters.

Results and Discussion

N,*N*-Dibenzylamino esters **2** were prepared from L-phenylalanine, L-alanine, L-valine, L-leucine and L-isoleucine under standard procedures to generate **2a-e,** respectively,[17] and then reduced with lithium borohydride at reflux temperature in THF, to obtain amino alcohols **11a-e** in 44% to 99% yield (Scheme 1). α-Dibenzylamino aldehydes **3a-e** were obtained in very good yields (83% to 98%) by oxidation of compounds **11a-e**, respectively, in Swern oxidation conditions. The stereoselective *anti* addition of trimethylsilyl cyanide to the α-dibenzylamino aldehydes **3** was achieved using zinc iodide (ZnI_2) or magnesium chloride ($MgCl_2$) in dichloromethane at 0 °C to give the corresponding trimethylsilylcyanohydrins **12a-e** in 72% to 99% yield. When $MgCl_2$ was used, two molar equivalents of TMSCN were required to complete the reaction.



Scheme 1. Synthesis of 5-substituted 1,3-oxazolidin-2-ones **1**.

Silylated cyanohydrins **12a-e** were reduced with lithium aluminum hydride in diethyl ether at 0 °C to obtain the corresponding α-dibenzylamino alcohols **13a-e** in 77% to 94% yield. Triphosgene (BTC) was used for the cyclization of amino alcohols **13a-e** in dichloromethane at room temperature with yields of 35% to 73%. 1,3-Oxazolidin-2-ones **1a-e** were obtained in moderate overall yields (15% to 64%, Table 1). Two reaction steps were critical in this synthesis; for the reduction of amino esters **2a-e** different reaction times and yields were observed for each amino ester. Those with bulkier R substituent required longer reaction times and were obtained

in lower yield in the order *sec*butyl< *iso*propyl< *iso*butyl. A similar effect was observed in the cyclization of amino alcohols **13a-e** with BTC to form 1,3-oxazolidin-2-ones **1a-e**.

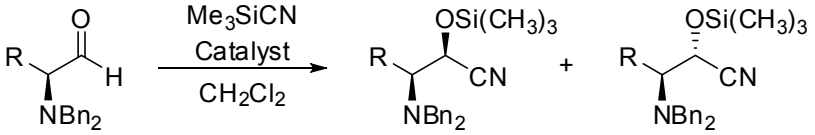
Table 1. Yields in the synthesis of 5-substituted 1,3-oxazolidin-2-ones

Compound	Bn	Me	*iso*Pr	*iso*Bu	*sec*Bu
11	99	94	60	76	44
3	95	83	97	98	96
12	99	97	82	94	72
13	94	81	92	89	77
1	73	67	35	62	66
Overall yield	64	41	15	39	16

The stereoselectivity in the synthesis of silylated cyanohydrins **12a-e** was established by proton NMR chemical shifts and coupling constants. For the trimethylsilylcyanohydrin **12a** synthesized using ZnI_2 as catalyst, a doublet signal at 4.46 ppm with J = 6.0 Hz was assigned to the hydrogen on the new chiral center. When the trimethylsilyl group was removed under mild acid conditions to afford the corresponding cyanohydrins compound,[11d] the proton NMR signal for the same hydrogen was observed at 4.00 ppm with a J = 5.4 Hz. Comparing these values with those reported in literature, this compound was found to be the *anti* stereoisomer.[12a] When trimethylsilylcyanohydrin **12a** was prepared using $MgCl_2$ as catalyst, in the proton NMR spectra was observed, in a minor proportion, a doublet signal at 4.34 ppm with J = 4.0 Hz, which was assigned to the hydrogen on the new chiral center for the *syn* stereoisomer. The addition was completely stereoselective with ZnI_2, but with $MgCl_2$ a mixture of stereoisomers was obtained (Table 2, entries 1 and 2). For compounds **12b-e** only the *anti* stereoisomer was obtained when the addition was catalyzed with ZnI_2.

The stereoselectivity observed in the addition of trimethylsilyl cyanide to α-dibenzylamino aldehydes **3** was explained in terms of a non-chelating control mechanism proposed by Reetz,[11a,11d] where the metal ion coordinates with the carbonyl group, but not with the the α-dibenzylamino. Also, the addtion resulted to be in line with the Felkin-Ahn model (Figure 1), where the nucleophile approaches in an orthogonal position to the less hindered face of the carbonyl group and opposite to the dibenzylamino group resulting in an *anti* addition selectivity.

Table 2. Addition of trimethylsilyl cyanide to α-dibenzylamino aldehydes **3**



3 ***syn*-12** ***anti*-12**

Entry	Compound	R	Catalyst	Yield (%)	*syn*:*anti*
1	**12a**	Bn	ZnI_2	99	1 : >99
2	**12a**	Bn	$MgCl_2$	98	34 : 66
3	**12b**	Me	ZnI_2	97	1 : >99
4	**12c**	*i*Pr	ZnI_2	82	1 : >99
5	**12d**	*i*Bu	ZnI_2	94	1 : >99
6	**12e**	*s*Bu	ZnI_2	72	1 : >99

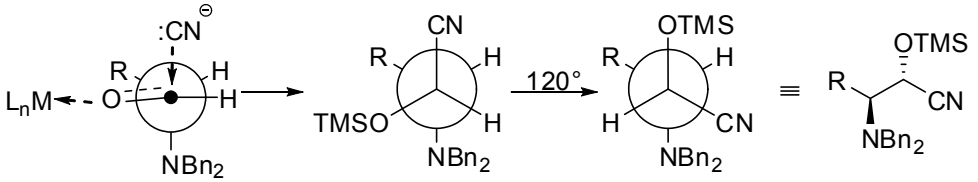


Figure 1. Felkin-Ahn model for the addition of TMSCN to aldehydes **3**.

Finally, the configuration of 1,3-oxazolidin-2-ones **1a-e** was confirmed by the correlations of ^{1}H NMR coupling constants, COSY and NOESY experiments. In COSY experiments, the H-5 hydrogen (4.83 ppm, J = 8.6 Hz for **1c**) showed coupling with C4$_\alpha$-H (3.62 ppm, J = 8.6 Hz for **1c**), C4$_\beta$-H (3.23 ppm, J = 8.6 Hz for **1c**) and with C1'-H (2.58 ppm, J = 8.6, 3.2 Hz for **1c**). However, in NOESY experiments C5-H hydrogen showed only one correlation with C4$_\alpha$-H, which demonstrates the stereochemical *anti* relation between C5-H with C1'-H and with H C4$_\beta$-H. Similar correlations were observed for the rest of the 1,3-oxazolidin-2-ones **1**. Therefore, since the original asymmetric center in α-dibenzylamino ester **2** had an *S* absolute configuration and had not been involved in any epimerization-promoting processes, the absolute configuration of compounds **1a-e** was established as 1′*S*, 5*R*.

Conclusions

In this work a new methodology has been developed for the synthesis of enantiopure 5-substituted 1,3-oxazolidin-2-ones with potential biological activity from non-racemic α-dibenzylamino esters in moderate yields and high stereoselectivity. Magnesium chloride and zinc iodide were tested as catalysts in the addition of trimethylsilyl cyanide to α-dibenzylamino

aldehydes showing higher stereo selectivity with zinc iodide in comparison with magnesium chloride or other catalysts reported previously.[11]

Experimental Section

General Procedures. All reagents were purchased in the higher quality available and were used without further purification. The solvents used in column chromatography were obtained from commercial suppliers and used without further distillation. Infrared spectra (FTIR) were recorded on a Perkin Elmer FT-IR 1600 spectrophotometer. Nuclear magnetic resonance ^{1}H (at 200 MHz) and ^{13}C (at 50 MHz) spectra were recorded on a Varian Mercury 200 MHz Spectrometer in $CDCl_3$ with TMS as internal standard. Liquid chromatograms were obtained on an Agilent 1100 Series LC with a reverse phase ZORBAX sβ-C18 column (5 mm, 3 x 150 mm) and MSD Trap. Electrospray ionization mass spectra (ESI-MS) were obtained with an ion trap, and the intensities are reported as a percentage relative to the base peak after the corresponding *m*/*z* value. HR-MS were obtained in an Agilent LCTOF (2006), a high resolution TOF analyzer with Windows XP based OS and APCI/ESI ionization. Melting points were obtained on an Electrothermal 88629 apparatus and are uncorrected. Optical rotations were determined using an Autopol III polarimeter.

General procedure for the synthesis of α-dibenzylamino alcohols 11

To a solution of the α-dibenzylamino ester **2** in dry THF was added $LiBH_4$ (2.0 equiv.) at 25ºC under argon atmosphere. Then, the reaction mixture was refluxed for 8 h. A saturated NH_4Cl solution was added and the mixture stirred for 30 min and then filtered. The liquid phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated and dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to give a crude product that was purified by flash chromatography when was necessary.

(S)-2-Dibenzylamino-3-phenylpropan-1-ol (11a). White solid. 99% yield. FTIR (KBr): 3426, 3026, 2958, 1601, 1029 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.28 (m, 15H), 4.64 (br s, 1H), 3.91 (d, *J* = 13.2 Hz, 2H), 3.47 (d, *J* = 13.2 Hz, 2H), 3.32 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.10 (m, 3H), 2.42 (dd, *J* = 14.0, 10.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.8 (C), 138.7 (2 × C), 128.7 (6 × CH), 128.2 (6 × CH), 127.0 (2 × CH), 125.9 (CH), 60.7 (CH), 60.1 (CH_2), 53.2 (2 × CH_2), 31.7 (CH_2). ESI-MS *m/z*: 332 $[M+H]^+$; MS/MS *m/z* (rel. int.): 240(75), 224(96), 181(100), 117(30). ESI-MS *m/z*: 354 $[M+Na]^+$

(*S*)-2-Dibenzylaminopropan-1-ol (11b). Colorless oil. 94% yield. FTIR (neat): 3421, 3060, 2929, 1601, 1365, 1035 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30 (m, 10H), 4.63 (br s, 1H), 3.81 (d, *J* = 13.4 Hz, 2H), 3.45 (t, *J* = 10.6 Hz, 1H), 3.35 (d, *J* = 13.4 Hz, 2H), 3.34 (dt, *J* = 10.6, 5.6 Hz, 1H), 2.98 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.8 (2 × C), 128.7 (4 × CH), 128.2 (4 × CH), 126.9 (2 × CH), 62.5 (CH), 56.0 (CH_2), 52.7 (2 × CH_2), 8.6

(CH_3). ESI-MS *m/z*: 256 $[M+H]^+$; MS/MS *m/z* (rel. int.): 181(96), 164(35), 148(60), 91(100). ESI-MS *m/z*: 278 $[M+Na]^+$.

(*S*)-2-Dibenzylamino-4-methylpentan-1-ol (11c). Colorless oil. 76% yield. FTIR (neat): 3430, 3027, 2955, 1601, 1364 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.27 (m, 10H), 3.88 (d, *J* = 13.2 Hz, 2H), 3.67 (d, *J* = 13.2 Hz, 2H), 3.62 (br s, 1H), 3.57 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.43 (dd, *J* = 10.6, 9.6 Hz, 1H), 2.51 (ddd, *J* = 9.6, 8.6, 4.8 Hz, 1H), 2.04 (m, 1H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.7 (2 × C), 128.8 (4 × CH), 128.4 (4 × CH), 127.2 (2 × CH), 64.7 (CH), 59.2 (CH_2), 54.2 (2 × CH_2), 27.6 (CH), 22.7 (CH_3), 22.1 (CH_3). ESI-MS *m/z*: 284 $[M+H]^+$; MS/MS *m/z* (rel. int.): 192(35), 181(90), 120(90), 91(100). ESI-MS *m/z*: 306 $[M+Na]^+$.

(*S*)-2-Dibenzylamino-3-methylbutan-1-ol (11d). Colorless oil. 60% yield. FTIR (neat): 3440, 3060, 2952, 1600, 1151, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.27 (m, 10H), 3.80 (d, *J* = 13.2 Hz, 2H), 3.44 (m, 2H), 3.36 (d, *J* = 13.2 Hz, 2H), 3.25 (br s, 1H), 2.84 (m, 1H), 1.51 (m, 2H), 1.15 (m, 1H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.0 (2 × C), 128.7 (4 × CH), 128.1 (4 × CH), 126.9 (2 × CH), 67.7 (CH), 56.7 (CH_2), 52.9 (2 × CH_2), 33.9 (CH_2), 25.4 (CH), 23.9 (CH_3), 22.0 (CH_3). ESI-MS *m/z*: 298 $[M+H]^+$; MS/MS *m/z* (rel. int.): 206(50), 190(96), 181(90), 91(100). ESI-MS *m/z*: 320 $[M+Na]^+$.

(2*S*,3*S*)-2-Dibenzylamino-3-methylpentan-1-ol (11e). Colorless oil. 44% yield. FTIR (neat): 3376, 3060, 2962, 1601, 1377, 1070, 1027 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.26 (m, 10H), 4.67 (br s, 1H), 3.88 (d, *J* = 13.2 Hz, 2H), 3.59 (d, *J* = 13.2 Hz, 2H), 3.53 (d, *J* = 7.2 Hz, 2H), 2.64 (q, *J* = 7.0 Hz, 1H), 1.87 (m, 1H), 1.60 (m, 1H), 1.25 (m, 1H), 0.90 (d, *J* = 4.4 Hz, 3H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.4 (2 × C), 128.8 (4 × CH), 128.1 (4 × CH), 126.8 (2 × CH), 62.7 (CH), 58.6 (CH_2), 53.9 (2 × CH_2), 32.7 (CH), 28.3 (CH_2), 15.9 (CH_3), 11.5 (CH_3). ESI-MS *m/z*: 298 $[M+H]^+$; MS/MS m/z (rel. int.): 206(35), 181(95), 120(85), 91(100). ESI-MS *m/z*: 320 $[M+Na]^+$.

General procedure for the synthesis of α-dibenzylamino aldehydes 3

To a solution of oxalyl chloride (1.1 equiv.) in dry CH_2Cl_2 was added dropwise a solution of DMSO (2.2 equiv.) in dry CH_2Cl_2 at -78 ºC under argon atmosphere and the mixture was stirred for 10 min. Then, a solution of the dibenzylamino alcohol **11** in dry CH_2Cl_2 was added dropwise and the reaction mixture was stirred for 30 min at the same temperature. After this time, a solution of triethylamine (5 equiv.) in CH_2Cl_2 was added dropwise and the mixture was stirred for 1 h and allowed to reach room temperature. The organic layer was washed with brine, separated, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to give a crude product that was used in the next reaction without further purification.

(*S*)-2-Dibenzylamino-3-phenylpropanal (3a). Yellow oil. 95% yield. FTIR (neat): 3026, 2922, 2709, 1727, 1122 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 9.70 (s, 1H), 7.27 (m, 15H), 3.82 (d, *J* = 13.6 Hz, 2H), 3.66 (d, *J* = 13.6 Hz, 2H), 3.55 (t, *J* = 6.8 Hz, 1H), 3.14 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.92 (dd, *J* = 13.6, 6.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 201.7 (CH), 138.8 (C), 138.5 (2 ×

C), 129.1 (2 × CH), 128.4 (4 × C), 128.1 (6 × CH), 127.0 (2 × CH), 125.9 (CH), 68.3 (CH), 54.7 (2 × CH_2), 30.0 (CH_2). ESI-MS *m*/*z*: 362 $[M+MeOH+H]^+$; MS/MS *m*/*z* (rel. int.): 344(100), 330(35).

(*S*)-2-Dibenzylaminopropanal (3b). Yellow oil. 83% yield. FTIR (neat): 3060, 2807, 2706, 1725, 1372, 1149, 1028 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 9.71 (s, 1H), 7.28 (m, 10H), 3.73 (d, *J* = 13.6 Hz, 2H), 3.55 (d, *J* = 13.6 Hz, 2H), 2.77 (q, *J* = 6.6 Hz, 1H), 1.17 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 204.0 (CH), 138.7 (2 × C), 128.5 (4 × CH), 128.1 (4 × CH), 127.0 (2 × CH), 62.7 (CH), 54.8 (2 × CH_2), 6.7 (CH_3). ESI-MS *m*/*z*: 254 $[M+H]^+$.

(*S*)-2-Dibenzylamino-3-methylbutanal (3c). Yellow oil. 97% yield. FTIR (neat): 3060, 2961, 2723, 1728, 1198 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 9.83 (d, *J* = 3.4 Hz, 1H), 7.32 (m, 10H), 4.01 (d, *J* = 13.6 Hz, 2H), 3.70 (d, *J* = 13.6 Hz, 2H), 2.71 (dd, *J* = 10.0, 3.4 Hz, 1H), 2.25 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 204.6 (CH), 138.8 (2 × C), 128.4 (4 × CH), 128.0 (4 × CH), 126.8 (2 × CH), 71.3 (CH), 54.4 (2 × CH_2), 25.9 (CH), 20.1 (CH_3), 19.7 (CH_3). ESI-MS *m*/*z*: 282 $[M+H]^+$. ESI-MS *m*/*z*: 314 $[M+MeOH+H]^+$.

(*S*)-2-Dibenzylamino-4-methylpentanal (3d). Yellow oil. 98% yield. FTIR (neat): 3061, 2954, 2706, 1727, 1370, 1145 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 9.74 (s, 1H), 7.31 (m, 10H), 3.78 (d, *J* = 13.8 Hz, 2H), 3.69 (d, *J* = 13.8 Hz, 2H), 3.21 (t, *J* = 6.4 Hz, 1H), 1.56 (m, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 203.5 (CH), 138.9 (2 × C), 128.5 (4 × CH), 128.0 (4 × CH), 126.9 (2 × CH), 64.6 (CH), 54.6 (2 × CH_2), 32.9 (CH_2), 25.1 (CH), 22.6 (CH_3), 22.4 (CH_3). ESI-MS *m*/*z*: 296 $[M+H]^+$. ESI-MS *m*/*z*: 328 $[M+MeOH+H]^+$.

(2*S*,3*S*)-2-Dibenzylamino-3-methylpentanal (3e). Yellow oil. 96% yield. FTIR (neat): 3030, 2964, 2730, 1723, 1207, 1028 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 9.84 (d, *J* = 4.0 Hz, 1H), 7.31 (m, 10H), 4.00 (d, *J* = 13.7 Hz, 2H), 3.68 (d, *J* = 13.7 Hz, 2H), 2.81 (dd, *J* = 9.6, 4.0 Hz, 1H), 2.07 (m, 1H), 1.87 (m, 1H), 1.19 (m, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 205.0 (CH), 138.8 (2 × C), 128.5 (4 × CH), 128.0 (4 × CH), 126.8 (2 × CH), 69.8 (CH), 54.4 (2 × CH_2), 31.9 (CH), 25.4 (CH_2), 15.8 (CH_3), 10.4 (CH_3). ESI-MS *m*/*z*: 296 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 206(35), 181(95), 120(85), 91(100). ESI-MS *m*/*z*: 328 $[M+MeOH+H]^+$.

General procedure for the synthesis of trimethylsilylcyanohydrins 12

To a solution of aldehyde **3** (1 .0 equiv.) in dry CH_2Cl_2 was added ZnI_2 (1.0 equiv.) at 0 ºC under argon atmosphere and the mixture was stirred for 10 min. Then, trimethylsilyl cyanide (1.0 equiv.) was added dropwise and the reaction mixture was stirred for 2 h at the same temperature. After this time, water was added and the mixture was stirred for 5 min and allowed to reach room temperature. The organic layer was washed with brine, separated, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to give a pure crude product that was used in the next reaction without further purification.

(2*S*,3*S*)-3-Dibenzylamino-4-phenyl-2-(trimethylsilyloxy)butanenitrile (12a). Colorless oil. 99% yield. FTIR (neat): 3028, 2950, 2368, 1254, 1114, 850 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.22 (m, 15H), 4.46 (d, *J* = 6.2 Hz, 1H), 3.72 (br s, 4H), 3.38 (dt, *J* = 8.0, 6.2 Hz, 1H), 2.99 (m, 2H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.9 (C), 138.6 (2 × C), 129.1 (2 × CH), 128.5 (4 × CH), 128.0 (2 × CH), 127.9 (4 × CH), 126.8 (2 × CH), 126.0 (CH), 119.5 (C), 63.0 (CH), 62.7 (CH), 54.7 (2 × CH_2), 33.1 (CH_2), -0.4 (3 × CH_3). ESI-MS *m*/*z*: 429 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 311(100), 210(20). ESI-MS *m*/*z*: 451 $[M+Na]^+$.

(2S,3S)-3-Dibenzylamino-2-(trimethylsilyloxy)butanenitrile (12b). Colorless oil. 97% yield. FTIR (neat): 3061, 2959, 2212, 1253, 1092, 845 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.43 (m, 10H), 4.47 (d, *J* = 8.8 Hz, 1H), 3.87 (d, *J* = 13.6 Hz, 2H), 3.64 (d, *J* = 13.6 Hz, 2H), 3.24 (m, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.0 (2 × C), 128.8 (4 × CH), 128.4 (4 × CH), 127.2 (2 × CH), 120.0 (C), 65.2 (CH), 57.6 (CH), 55.1 (2 × CH_2), 9.5 (CH_3), 0.08 (3 × CH_3). ESI-MS *m*/*z*: 353 $[M+H]^+$. ESI-MS *m*/*z*: 375 $[M+Na]^+$.

(2*S*,3*S*)-3-Dibenzylamino-4-methyl-2-(trimethylsilyloxy)pentanenitrile (12c). Colorless oil. 82% yield. FTIR (neat): 3062, 2957, 2218, 1250, 1085, 840 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.32 (m, 10H), 4.77 (d, *J* = 4.4 Hz, 1H) 4.19 (d, *J* = 13.2 Hz, 2H), 3.73 (d, *J* = 13.2 Hz, 2H), 2.66 (dd, *J* = 10.6, 5.8 Hz, 1H), 2.15 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.27 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.9 (2 × C), 129.2 (4 × CH), 128.5 (4 × CH), 127.4 (2 × CH), 119.9 (C), 64.6 (CH), 59.3 (CH), 54.6 (2 × CH_2), 28.9 (CH), 22.4 (CH_3), 20.1 (CH_3), -0.2 (3 × CH_3). ESI-MS *m*/*z*: 367 $[M-Me+2H]^+$; MS/MS *m*/*z* (rel. int.): 325(95), 275(100), 199(10).

(2*S*,3*S*)-3-Dibenzylamino-5-methyl-2-(trimethylsilyloxy)hexanenitrile (12d). Colorless oil. 94% yield. FTIR (neat): 3061, 2955, 2228, 1255, 1106, 848 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.34 (m, 10H), 4.45 (d, *J* = 5.8 Hz, 1H), 3.81 (d, *J* = 13.8 Hz, 2H), 3.63 (d, *J* = 13.8 Hz, 2H), 3.00 (m, 1H), 1.75 (m, 2H), 1.25 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.0 (2 × C), 128.6 (4 × CH), 128.0 (4 × CH), 126.8 (2 × CH), 119.8 (C), 63.2 (CH), 58.8 (CH), 54.6 (2 × CH_2), 36.4 (CH_2), 25.0 (CH), 23.3 (CH_3), 22.0 (CH_3), -0.4 (3 × CH_3). ESI-MS *m*/*z*: 395 $[M+H]^+$. ESI-MS *m*/*z*: 417 $[M+Na]^+$. ESI-MS *m*/*z*: 381 $[M-Me+2H]^+$; MS/MS *m*/*z* (rel. int.): 290(100), 248(10), 213(12), 157(10).

(2*S*,3*S*,4*S*)-3-Dibenzylamino-4-methyl-2-(trimethylsilyloxy)hexanenitrile (12e). Colorless oil. 72% yield. FTIR (neat): 3060, 2958, 2232, 1245, 1102, 845 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.33 (m, 10H), 4.78 (d, *J* = 4.8 Hz, 1H), 3.87 (d, *J* = 13.6 Hz, 2H), 3.65 (d, *J* = 13.6 Hz, 2H), 2.79 (dd, *J* = 7.8, 4.8 Hz, 1H), 1.94 (m, 2H), 1.17 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 3H), 0.24 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.1 (2 × C), 129.0 (4 × CH), 128.2 (4 × CH), 126.9 (2 × CH), 120.3 (C), 64.0 (CH), 61.0 (CH), 54.9 (2 × CH_2), 33.0 (CH), 27.1 (CH_2), 16.0 (CH_3), 11.2 (CH_3), -0.2 (3 × CH_3). ESI-MS *m*/*z*: 395 $[M+H]^+$. ESI-MS *m*/*z*: 417 $[M+Na]^+$.

General procedure for the synthesis of α-dibenzylamino amino alcohols 13

To a solution of trimethylsilylcyanohydrins **12** (1.0 equiv.) in dry THF was added drop wise a solution of $LiAlH_4$ (2.0 equiv.) in dry diethyl ether at 0 ºC under argon atmosphere and stirred for 5 h at same temperature . Then, a 5% KOH solution was added drop wise until a white solid was

form and the reaction mixture was filtered. The organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give a crude product that was used in the next reaction without further purification.

(2*R*,3*S*)-1-Amino-3-dibenzylamino-4-phenylbutan-2-ol (13a). Colorless oil. 94% yield. FTIR (neat): 3365, 3299, 2926, 1600, 1251, 1110 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.21 (m, 15H), 4.63 (s, 1H), 3.93 (dd, *J* = 13.4, 9.4 Hz, 1H), 3.70 (d, *J* = 13.6 Hz, 2H), 3.57 (d, *J* = 13.6 Hz, 2H), 3.43 (dd, *J* = 15.0, 13.4 Hz, 1H), 2.82 (m, 4H), 1.96 (br s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 141.1 (C), 139.5 (2 × C), 129.1 (2 × CH), 128.5 (4 × CH), 128.2 (2 × CH), 127.9 (4 × CH), 126.6 (2 × CH), 125.5 (CH), 72.0 (CH), 61.4 (CH), 54.4 (2 × CH_2), 44.6 (CH_2), 32.5 (CH_2). ESI-MS *m*/*z*: 361 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 344(98), 300(20), 210 (100).

(2*R*,3*S*)-1-Amino-3-dibenzylaminobutan-2-ol (13b). Colorless oil. 81% yield. FTIR (neat): 3363, 3284, 3027, 2958, 1578, 1076 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.25 (m, 10H), 4.59 (s, 1H), 3.65 (d, *J* = 13.6 Hz, 2H), 3.62 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.43 (m, 1H), 3.31 (d, *J* = 13.6 Hz, 2H), 2.76 (dd, *J* = 11.0, 6.4 Hz, 1H), 2.55 (q, *J* = 6.6 Hz, 1H), 1.76 (br s, 2H), 1.10 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 140.3 (2 × C), 129.1 (4 × CH), 128.5 (4 × CH), 127.2 (2 × CH), 73.5 (CH), 65.6 (CH), 54.7 (2 × CH_2), 44.6 (CH_2), 12.1 (CH_3). ESI-MS *m*/*z*: 286 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 268(100), 199(5), 91(10).

(2*R*,3*S*)-1-Amino-3-dibenzylamino-5-methylhexan-2-ol (13c). Colorless oil. 92% yield. FTIR (neat): 3342, 3283, 3061, 2955, 1601, 1361, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.24 (m, 10H), 3.87 (d, *J* = 13.2 Hz, 2H), 3.76 (s, 1H), 3.66 (d, *J* = 13.2 Hz, 2H), 3.56 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.42 (t, *J* = 10.6 Hz, 1H), 3.19 (br s, 2H), 2.52 (m, 1H), 2.06 (m, 1H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.5 (2 × C), 128.9 (4 × CH), 128.0 (4 × CH), 126.8 (2 × CH), 70.5 (CH), 64.0 (CH), 55.1 (2 × CH_2), 44.7 (CH_2), 26.3 (CH), 23.6 (CH_3), 20.1 (CH_3). ESI-MS *m*/*z*: 313 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 296(100), 278(5), 199(10), 91(7).

(2*R*,3*S*)-1-Amino-3-dibenzylamino-5-methylhexan-2-ol (13d). Colorless oil. 89% yield. FTIR (neat): 3300, 3061, 2952, 1601, 1366, 1072 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.30 (m, 10H), 3.76 (m, 1H), 3.63 (s, 1H), 3.62 (br s, 4H), 3.38 (dd, *J* = 13.2, 11.8 Hz, 1H), 2.76 (dd, *J* = 12.6, 3.8 Hz, 1H) 2.66 (m, 3H), 1.60 (m, 1H), 1.83 (br s, 2H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.9 (2 × C), 128.7 (4 × CH), 127.9 (4 × CH), 126.6 (2 × CH), 71.4 (CH), 56.8 (CH), 54.6 (2 × CH_2), 44.9 (CH_2), 35.5 (CH_2), 25.2 (CH), 23.2 (CH_3), 22.7 (CH_3). ESI-MS *m*/*z*: 327 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 310(100), 233(45), 198(30).

(2*R*,3*S*,4*S*)-1-Amino-3-dibenzylamino-4-methylhexan-2-ol (13e). Colorless oil. 77% yield. FTIR (neat): 3345, 3289, 3060, 2955, 1601, 1376, 1061, 1027 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.24 (m, 10H), 3.75 (d, *J* = 13.2 Hz, 2H), 3.73 (m 2H), 3.63 (s, 1H), 3.54 (d, *J* = 13.2 Hz, 2H), 2.65 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.44 (dd, *J* = 7.6, 4.6 Hz, 1H), 2.24 (m, 1H), 2.03 (br s, 2H), 1.90 (m, 1H), 1.65 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.7 (2 × C), 128.8 (4 × CH), 128.0 (4 × CH), 126.8 (2 × CH), 70.1 (CH), 62.5 (CH), 54.8 (2 × CH_2), 44.6 (CH_2), 32.4 (CH), 29.8 (CH_2), 16.1 (CH_3), 12.2 (CH_3). ESI-MS *m*/*z*: 327 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 309(100), 292(10), 198(35), 91(5).

General procedure for the synthesis of 1,3-oxazolidin-2-ones 1

To a solution of amino alcohol **13** in dry CH_2Cl_2 was added dropwise a solution of triphosgene (1.0 equivalent) in dry CH_2Cl_2 at 0 ºC. Then, the reaction mixture was stirred at room temperature for 8 h. A saturated $NaHCO_3$ solution was added and the mixture was stirred for 30 min and then was extracted with dichloromethane (3 × 20 mL). The organic layer was separated, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to give a crude product that was purified by flash chromatography.

(*R*)-5-((*S*)-1-Dibenzylamino-2-phenylethyl)-1,3-oxazolidin-2-one (1a). White solid. 73% yield. Mp 102 ºC. R_f 0.50 (ethyl acetate/petroleum ether 1/1); $[\alpha]_D^{20}$ =+8.0° (*c* 1.00, $CHCl_3$). FTIR (KBr): 3283, 3026, 2931, 1754, 1368, 1240 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.21 (m, 15H), 5.91 (br s, 1H), 4.80 (m, 1H), 3.62 (br s, 4H), 3.52 (t, *J* = 8.8 Hz, 1H), 3.08 (t, *J* = 8.8 Hz, 1H), 3.06 (br s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.6 (C), 139.5 (C), 138.8 (2 × C), 129.3 (2 × CH), 128.4 (4 × CH), 128.1 (2 × CH), 127.9 (4 × CH), 126.8 (2 × CH), 126.0 (CH), 76.8 (CH), 62.4 (CH), 54.4 (2 × CH_2), 44.8 (CH_2), 32.4 (CH_2). ESI-MS *m*/*z*: 387 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 326(75), 295(100), 181(40). HPLC: 0.8 mL/min; 70:30 MeOH/H_2O; t_R: 6.3 min. HRMS calculated for $[C_{25}H_{26}N_2O_2 + H]^+$ 387.2073. Found 387.2075.

(*R*)-5-((*S*)-1-Dibenzylaminoethyl)oxazolidin-2-one (1b). White solid. 67% yield. Mp 95 ºC. R_f 0.48 (ethyl acetate/petroleum ether 1/1); $[\alpha]_D^{20}$ =+21.2° (*c* 1.00, $CHCl_3$). FTIR (KBr): 3254, 2826, 1748, 1239 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.25 (m, 10H), 5.84 (br s, 1H), 4.46 (q, *J* = 8.6 Hz, 1H), 3.70 (d, *J* = 13.6 Hz, 2H), 3.54 (t, *J* = 8.6 Hz, 1H), 3.43 (d, *J* = 13.6 Hz, 2H), 3.23 (t, *J* = 8.6 Hz, 1H), 2.82 (dd, *J* = 8.6, 6.6 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.7 (C), 138.8 (2 × C), 128.7 (4 × CH), 128.1 (4 × CH), 127.0 (2 × CH), 78.3 (CH), 56.5 (CH), 54.4 (2 × CH_2), 44.7 (CH_2), 8.6 (CH_3). ESI-MS *m*/*z*: 311 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 250(50), 219(100), 181(93), 91(60). HPLC: 0.8 mL/min; 70:30 MeOH/H_2O; t_R: 5.8 min. HRMS calculated for $[C_{19}H_{22}N_2O_2 + H]^+$ 311.1760. Found 311.1758.

(*R*)-5-((*S*)-1-Dibenzylamino-2-methylpropyl)oxazolidin-2-one (1c). White solid. 35% yield. Mp 45 ºC. R_f 0.55 (ethyl acetate/petroleum ether 1/1); $[\alpha]_D^{20}$ =-9.0° (*c* 1.00, $CHCl_3$). FTIR (KBr): 3284, 2958, 1752, 1239, 1078 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.25 (m, 10H), 5.73 (br s, 1H), 4.83 (q, *J* = 8.6 Hz, 1H), 3.67 (d, *J* = 13.4 Hz, 2H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.55 (d, *J* = 13.4Hz, 2H), 3.23 (t, *J* = 8.6 Hz, 1H), 2.58 (dd, *J* = 8.6, 3.2 Hz, 1H), 2.33 (m, 1H), 1.13 (d, *J* = 7.4 Hz, 3H), 1.09 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.7 (C), 138.8 (2 × C), 128.7 (4 × CH), 128.1 (4 × CH), 127.0 (2 × CH), 75.4 (CH), 64.1 (CH), 54.6 (2 × CH_2), 45.5 (CH_2), 25.1 (CH_2), 23.3 (CH_3), 19.0 (CH_3). ESI-MS *m*/*z*: 339 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 283(100), 247(40), 188(45). HPLC: 0.8 mL/min; 70:30 MeOH/H_2O; t_R: 5.8 min. HRMS calculated for $[C_{21}H_{26}N_2O_2 + H]^+$ 339.2073. Found 339.2071.

(*R*)-5-((*S*)-1-Dibenzylamino-3-methylbutyl)-1,3-oxazolidin-2-one (1d). White solid. 62% yield. Mp 43 ºC. R_f 0.52 (ethyl acetate/petroleum ether 1/1); $[\alpha]_D^{20}$ =-30.9° (*c* 1.00, $CHCl_3$). FTIR (KBr): 3277, 3028, 1753, 1240, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.27 (m, 10H), 6.09

(br s, 1H), 4.75 (m, 1H), 3.72 (d, *J* = 13.8 Hz, 2H), 3.58 (t, *J* = 8.4 Hz, 1H), 3.55 (d, *J* = 13.8 Hz, 2H), 3.12 (t, *J* = 8.4 Hz, 1H), 2.67 (q, *J* = 7.0 Hz, 1H), 1.96 (hpt, *J* = 6.6 Hz, 1H), 1.73 (q, *J* = 7.0 Hz, 1H), 1.27 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.9 (C), 139.2 (2 × C), 128.6 (4 × CH), 128.0 (4 × CH), 126.9 (2 × CH), 76.8 (CH), 58.2 (CH), 54.4 (2 × CH_2), 44.9 (CH_2), 35.1 (CH_2), 24.7 (CH), 23.3 (CH_3), 22.4 (CH_3). ESI-MS *m*/*z*: 353 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 261(100), 202(75), 181(80). HPLC: 0.8 mL/min; 70:30 MeOH/H_2O; t_R: 6.8 min. HRMS calculated for $[C_{22}H_{28}N_2O_2 + H]^+$ 353.2229. Found 353.2226.

(*R*)-5-((1*S*,2*S*)-1-Dibenzylamino-2-methylbutyl)oxazolidin-2-one (1e). White solid. 66% yield. Mp 42 ºC. R_f 0.62 (ethyl acetate/petroleum ether 1/1); $[\alpha]_D^{20}$ =+11.5° (*c* 1.00, $CHCl_3$). FTIR (KBr): 3277, 2961, 1752, 1237, 1077 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.27 (m, 10H), 5.49 (br s, 1H), 4.86 (q, *J*=8.4 Hz, 1H), 3.73 (d, *J* = 13.6 Hz, 2H), 3.66 (t, *J* = 8.4 Hz, 1H), 3.48 (d, *J* = 13.6 Hz, 2H), 3.26 (t, *J* = 8.4 Hz, 1H), 2.66 (dd, *J* = 9.0, 1.6 Hz, 1H), 2.03 (m, 1H), 1.44 (m, 2H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.9 (C), 139.2 (2 × C), 129.0 (4 × CH), 128.4 (4 × CH), 127.3 (2 × CH), 75.4 (CH), 63.6 (CH), 54.7 (2 × CH_2), 45.7 (CH_2), 31.7 (CH), 30.0 (CH), 15.6 (CH_3), 12.4 (CH_3). ESI-MS *m*/*z*: 353 $[M+H]^+$; MS/MS *m*/*z* (rel. int.): 283(100), 202(45). HPLC: 0.8 mL/min; 70:30 MeOH/H_2O; t_R: 8.4 min. HRMS calculated for $[C_{22}H_{28}N_2O_2 + H]^+$ 353.2229. Found 353.2225.

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