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3-BENZOYL-2-ISOPROPYL-4-ALKYLOXAZOLIDIN-5-ONES AS EFFICIENT AND INEXPENSIVE SOURCES OF ENANTIOPURE α,α-DIALKYL α-AMINO ACIDS AND α,β-DIALKYL α,β-DIAMINOPROPIONIC ACIDS

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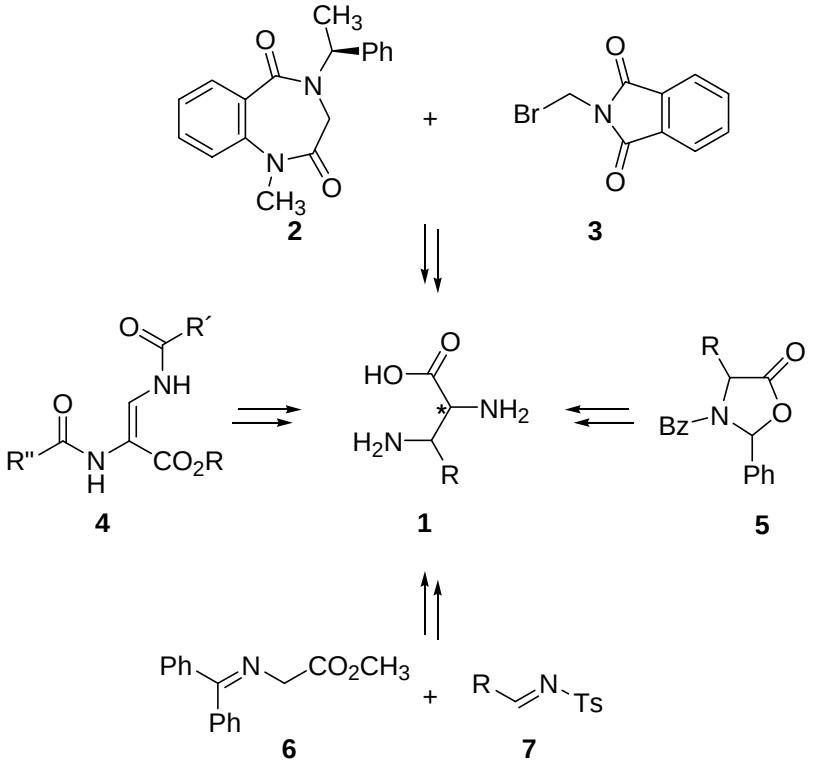
Abstract - It is shown that the 3-benzoyl-2-isopropyl-4-alkyloxazolidin-5-ones (**12**), derived from isobutyraldehyde and α-amino acids are as efficient as, but more economical than, the corresponding *tert*-butyl compounds (**9**), as sources of enantiopure α,α-dialkylated α-amino acids (e.g., **21-23**). In the absence of alkylating agents, the anions of (2*R*,4*S*)-**12** and its enantiomer undergo a fragmentation-recombination process to generate (*1S,2'R,4'S*)-*N*-[1-(3-benzoyl-2-isopropyl-4-methyl-5-oxo-oxazolidin-4-yl)-2-methylpropyl]benzamide ((1*S*, 2'*R*,4'*S*)-**20**), and its enantiomer. Acidic methanolysis of these condensation products provides access to α,β-dialkylated α,β-diaminopropionic acids [e.g., (2*S*,3*S*)-2,3-bisbenzoylamino-2,4-dimethylpentanoic acid methyl ester ((2*S*,3*S*)-**24**)).

1. INTRODUCTION

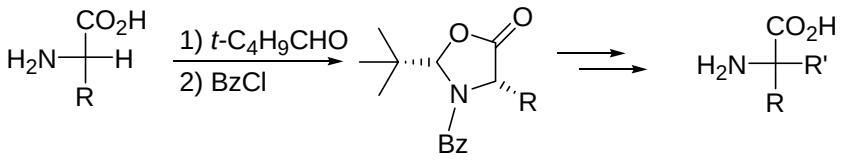
In recent years the preparation of enantiopure α,α-dialkylated α-amino acids has received substantial attention owing to the interesting chemical and biological properties exhibited by these compounds.[1-5] It can be anticipated that α,β-diaminopropionic acids will also possess interesting properties.[6] Furthermore, peptides incorporating such geminally-branched amino acids will likely show unusual conformations.[7,8]

Because of their potential roles in physiological processes, α,β-diaminopropionic acids (**1**) are especially interesting objects for study and several enantioselective synthetic routes thereto have recently been reported. For example, they have been prepared by the alkylation of the chiral benzodiazepinone (**2**) by Juaristi and coworkers[9] and the catalytic asymmetric hydrogenation of the enamines (**4**) by Robinson *et al.*[10] In addition, Jones[11] prepared such compounds through the alkylation of the phenyl substituted oxazolidinones (**5**) and Jorgensen[12] prepared α,β-diaminopropionic acids by a Mannich type reaction of the glycine derivatives (**6**) with imines (**7**) (Scheme 1).



Scheme 1

In addition to **5**, other oxazolidinones such as 2-*tert*-butyloxazolidinones (**9**), which are derived form α-amino acids, have been used to prepare α,α-disubstituted α-amino acids[13] (**10a-d**) (Scheme 2). Due to the steric interaction with the incoming electrophile, the *tert*-butyl group in the oxazolidinone (**9**) directs alkylation of the enolates to the opposite side of the ring. The required pivalaldehyde, however, is



8a R = -CH_3 **9** **10**
8b R = -$CH_2CH(CH_3)_2$
8c R = -$CH_2C_6H_5$
8d R = -$CH(CH_3)_2$
8e R = -$CH(CH_3)CH_2CH_3$

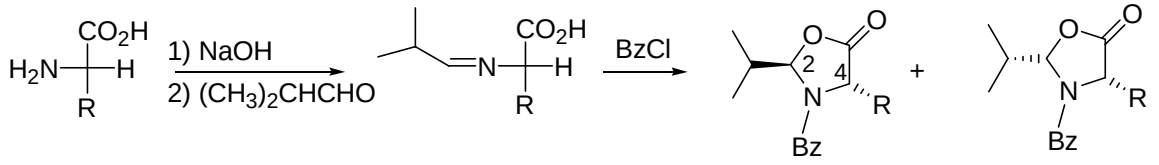
Scheme 2

expensive and we reasoned that incorporation of the inexpensive isobutyraldehyde into this heterocyclic system would probably afford equally high levels of diastereoselection upon alkylation of the enolates. In the present paper we describe a convenient preparation of enantiopure α,α-dialkylated α-amino acids and α,β-diaminopropionic acid derivatives starting from the readily available and inexpensive 2-isopropyloxazolidinone derivatives (**12**) derived from isobutyraldehyde and α-amino acids.

2. RESULTS AND DISCUSSION

2.1. Preparation of the chiral oxazolidinones(12-a-e) and configurational assignments.

The sodium salts of the amino acids (*S*)-alanine, (*S*)-leucine, (*S*)-phenylalanine, (*S*)-valine and (*S*)-isoleucine (**8a-e**) were condensed with isobutyraldehyde[14] to give the corresponding Schiff bases (**11a-e**) wich were treated with benzoyl chloride to provide a *trans*/*cis* mixture of the α-alkylated 2-isopropyloxazolidinones (**12a-e**) (Scheme 3). After chromatographic separation of the isomers, their structures were assigned by comparison of the chemical shifts of H-2 and H-4 with those of the corresponding *cis*- and *trans*- 2-*tert*-butyloxazolidinones (**9**). The absolute configuration of all these compounds was further confirmed by X-Ray analysis of several of the oxazolidinones.[15] (See Figure 1).



11a-e

***trans*-12** ***cis*-12**

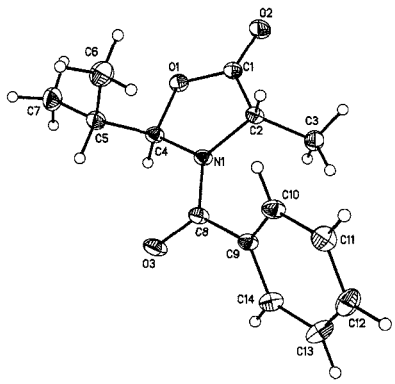
8a R = -CH_3
8b R = -$CH_2CH(CH_3)_2$
8c R = -$CH_2C_6H_5$
8d R = -$CH(CH_3)_2$
8e R = -$CH(CH_3)CH_2CH_3$

12a R = -CH_3 (3:1)
12b R = -$CH_2CH(CH_3)_2$ (2:1)
12c R = -$CH_2C_6H_5$ (3:1)
12d R = -$CH(CH_3)_2$ (5:1)
12e R = -$CH(CH_3)CH_2CH_3$ (5:1)

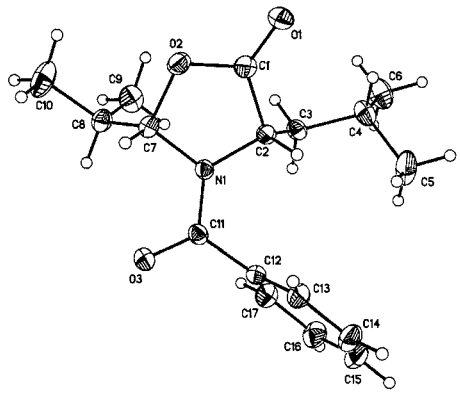
Scheme 3

2.2. Stereoselectivity of alkylation of (2*R*,4*S*)-12a and (2*R*,4*S*)-12c

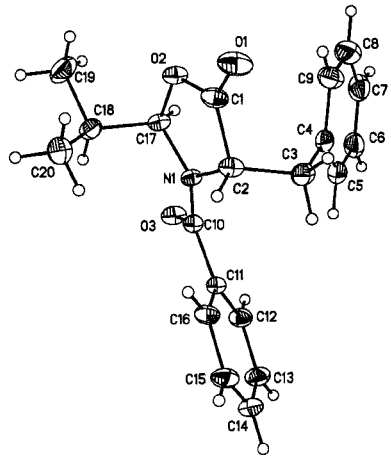
The lithium enolates of oxazolidinones ((2*R*,4*S*)-**12a)** and ((2*R*,4*S*)-**12c**), generated with lithium bis(trimethylsilyl)amide (LiHMDS) in THF, were alkylated with benzyl bromide, allyl bromide and ethyl bromoacetate at –78°C to afford the *trans* disubstituted oxazolidinones (**13-17**) exclusively (the minor diastereomer could not be detected by ^{1}H NMR spectroscopy [16]) and in good yields. (Table 1). The X-Ray data for (2*R*,4*S*)-**13,** (2*R*,4*R*)-**16** and (2*R*,4*S*)-**17** (Figure 2) show that alkylation took place from the side of the ring opposite to the isopropyl group.[15]



(2*R*,4*S*)-**12a**



(2*S*,4*S*)-**12b**

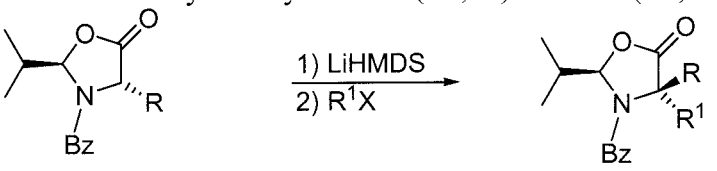


(2*R*,4*S*)-**12c**

Figure 1. X-Ray structure of solid-state conformation of (2*R*,4*S*)-**12a,** (2*S*,4*S*)-**12b** and (2*R*,4*S*)-**12c** (numbers in structures refer to X-Ray coodinates as deposited CCDC).

The high stereoselectivity observed in the alkylation of lithium enolates of oxazolidinones ((2*R*,4*S*)-**12a**) and ((2*R*,4*S*)-**12c**) is undoubtedly due to the steric hindrance generated on one face of the enolate at C-2 by the remote isopropyl group, which directs the alkylation to the opposite face.[14,17] Indeed, allylic $A^{1,3}$ strain in the lithium enolates of (2*R*)-**12a** and (2*R*)-**12c** is responsible for the *pseudo* axial orientation of the isopropyl group which effectively hinders *syn* alkylations. Consequently, in this system the inexpensive isobutyraldehyde can efficiently replace the much costlier pivalaldehyde in the alkylation of the chiral oxazolidinones.

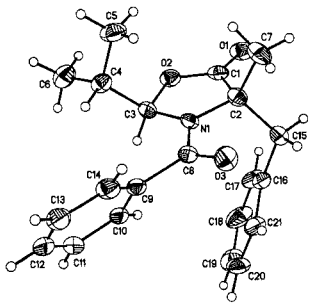
Table 1. Diastereoselectivity of alkylation of (2*R*,4*S*)-**12a** and (2*R*,4*S*)-**12c**



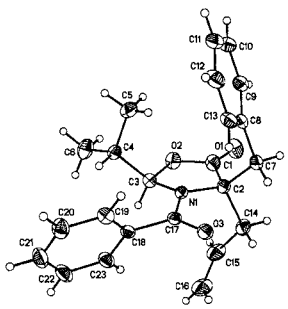
R	R^1X	Product	ds (%)†	mp (°C)	$[\alpha]_D^{20}$	Yield (%)
CH_3	$PhCH_2Br$	(2*R*,4*S*)-**13**	>98	117-118	+ 174.4°	91
CH_3	CH_2=$CHCH_2Br$	(2*R*,4*S*)-**14**	>98	64-65	+ 15.5°	79
CH_3	$C_2H_5O_2CCH_2Br$	(2*R*,4*S*)-**15**	>98	a	+ 75.9°	85
CH_2Ph	CH_2=$CHCH_2Br$	(2*R*,4*R*)-**16**	>98	115-116	- 86.4°	53
CH_2Ph	$C_2H_5O_2CCH_2Br$	(2*R*,4*S*)-**17**	>98	107-108	+ 6.67°	79

a – viscous oil.

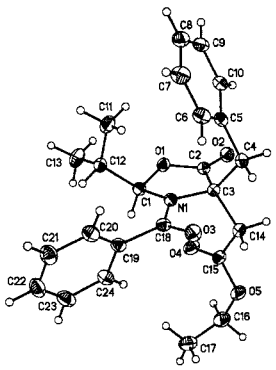
† ds ratio was determined by both ^1H and ^{13}C NMR spectroscopy of the crude reaction mixture



(2*R*,4*S*)-**13**



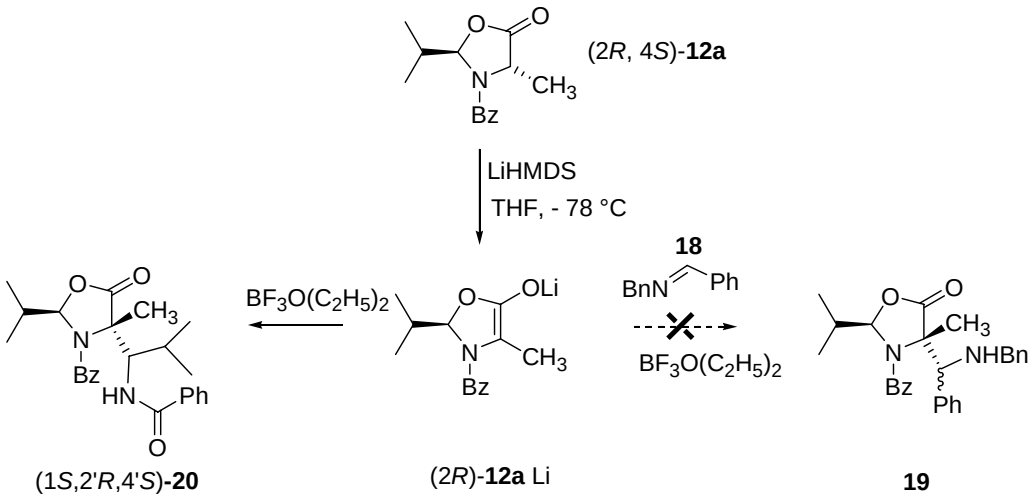
(2*R*,4*R*)-**16**



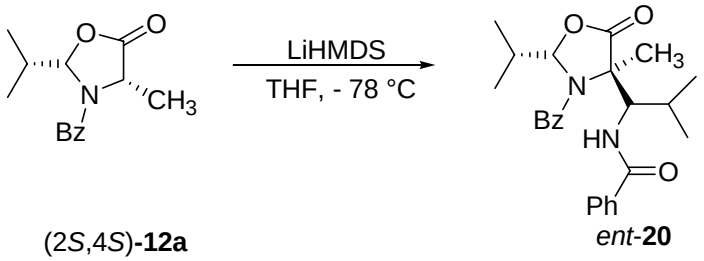
(2*R*,4*S*)-**17**

Figure 2. X-Ray structure and solid-state conformation of (2*R*,4*S*)-**13,** (2*R*,4*R*)-**16** and (2*R*,4*S*)-**17** (numbers in structures refer to X-Ray coodinates as deposited CCDC).

Interestingly, addition of the lithium salt of oxazolidinone ((2*R*,4*S*)-**12a**) to benzylbenzylideneamine (**18**) catalyzed by $BF_3{\cdot}O(C_2H_5)_2$ lead to the formation of the amide ((1*S*,2'*R*,4'*S*)-**20**) instead of the expected amine (**19**) (Scheme 4). Compound ((1*S*,2'*R*,4'*S*)-**20**) was fully characterized by spectroscopic means, including an X-Ray crystal structure determination (Figure 3).[15] The formation of compound ((1*S*,2'*R*,4'*S*)-**20**) is explained, in part, as self addition of the enolate of (2*R*)-**12a-Li**. Repetition of the experiment in the absence of benzylbenzylideneamine (**18**) gave (1*S*,2'*R*,4'*S*)-**20** in considerably better yield (Scheme 4) . Similarly, (2*S*,4*S*)-**12a** gave the enantiomeric product *ent*-**20** (Scheme 5).

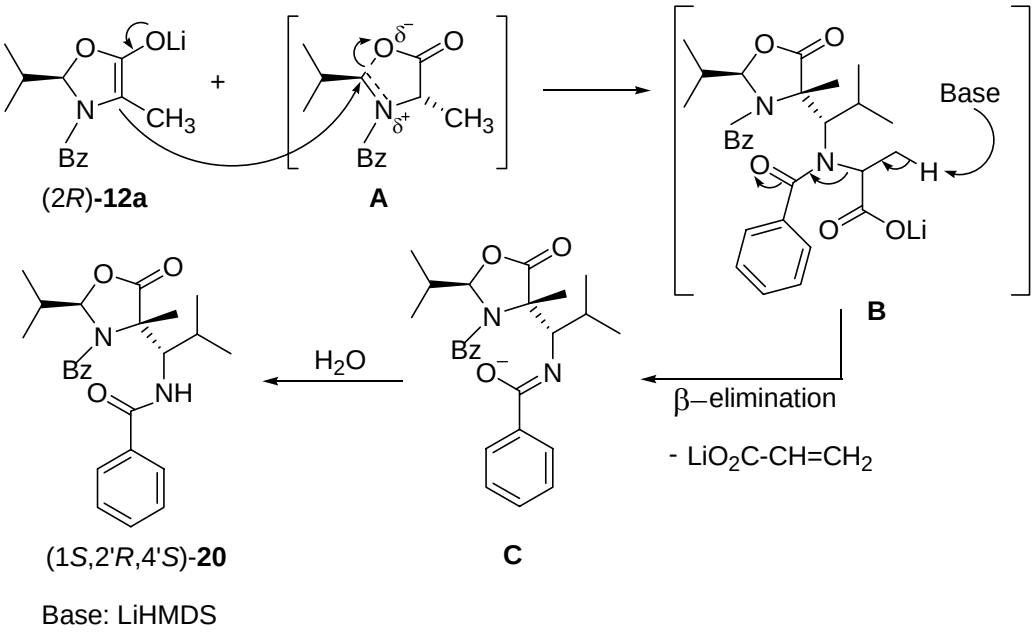


Scheme 4

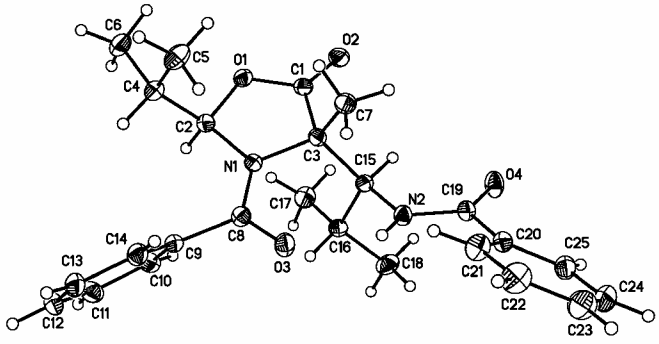


Scheme 5

We propose a fragmentation-recombination process as a rationale for the formation of the unexpected product (1*S*,2'*R*,4'*S*)-**20**. The steric repulsion between the phenyl ring of benzamide and the substituent at C-2 on unreacted (2*R*,4*S*)-**12a** drives the opening of the oxazolidinone ring to form a pseudo iminium ion **A** which alkylates enolate (2*R*)-**12a**-Li to form intermediate **B**. Then **B** undergoes a LiHMDS-promoted fragmentation to lithium acrylate and the anion **C**, from which the observed product (1*S*,2'*R*,4'*S*)-**20** is obtained upon quenching of the reaction mixture. (Scheme 6). The steric repulsion in the oxazolidinone ring that drives its fragmentation to pseudo-iminium ion **A** is evident in the crystal structure of (2*R*,4*S*)-**12a** (Figure 1). This structure shows that the crowding between the benzoyl group and the substituent at C-2 is partially aleviated by distortion of the dihedral angles N-CO-Ph (N_1-C_8-C_9-C_{10} =46.3^o and N_1-C_8-C_9-C_{14} = -136.4^o) which avoids the planarity and the stabilization of this benzamide moeity.



Scheme 6



(1*S*,2'*R*,4'*S*)-**20**

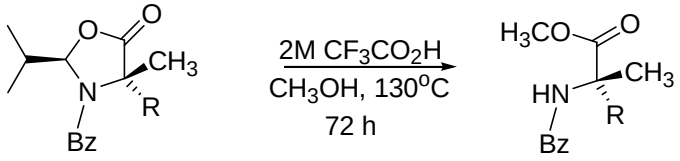
Figure 3. X-Ray structure and solid-state conformation of (1*S*,2'*R*,4'*S*)-**20** (numbers in structur refer to X-Ray coodinates as deposited CCDC).

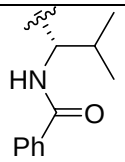
2.3. Methanolysis of oxazolidinones (13-15 and 20). Production of enantiopure α,α-dialkylated α-amino acids and α,β-dialkylated α,β-diamino acids.

Methanolysis of the alkylated heterocycles ((2*R*,4*S*)-**13-15**) was achieved by treatment with 2M CF_3CO_2H in CH_3OH (130°C, 72 h). The *N*-benzoylated amino esters ((*S*)-**21-23**) thus obtained were

purified by flash chromatography. Oxazolidinone ((1*S*,2'*R*,4'*S*)-**20**) was converted into the di-*N*-benzoyl-α,β-diamino acid methyl ester ((2*S*,3*S*)-**24**) in the same manner (Table 2).

Table 2. Methanolysis of the products ((2*R*,4*S*)-**13-15**) to give *N*-benzoylated amino acid esters ((2*S*)-**21-23**) and ((1*S*,2'*R*,4'*S*)-**20**) to give di-*N*-benzoyl-α,β-diamino acid methyl ester ((2*S*,3*S*)-**24**)



R	Product	$[\alpha]_D^{20}$	Yield (%)
-$CH_2C_6H_5$	(2*S*)-**21**	+ 77.5°	97
-$CH_2CH{=}CH_2$	(2*S*)-**22**	+ 9.74°	87
-CH_2COOCH_3	(2*S*)-**23**	+4.84°	85
	(2*S*,3*S*)-**24**	-55.4°	95

In summary, inexpensive isobutyraldehyde and (*S*)-amino acids, were converted to enantiopure oxazolidinones ((2*R*,4*S*)-**12a-e**) which were then alkylated with high stereoselectivity with various alkyl halides to give the products (**13-17**) of *trans* addition. Methanolysis of the alkylated derivatives was accomplished under acidic conditions to afford enantiopure α,α-dialkyl α-amino acids methyl esters (**21-23**). Methanolysis of oxazolidinone (**20**) afforded α,β-dialkylated α,β-diaminopropionic acid methyl esters derivatives ((2*S*,3*S*)-**24**). The present synthetic protocol constitutes a useful application of the so called "self-regeneration of stereogenic centers" concept.[18]

3. EXPERIMENTAL

Flasks, stirring bars, and glass syringes used for the generation and reactions of organolithium reagents were dried for *ca.* 12 h at 120°C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[19] TLC was performed on Merck-DC-F_{254} plates, detection was made by shining UV light. Flash column chromatography[20] was performed using Merck silica gel (230-240 mesh). All melting points are uncorrected. ^{1}H NMR spectra were recorded on a JEOL Eclipse+400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL Eclipse+400 (100 MHz) spectrometer. Chemical shifts (δ) are indicated in ppm downfield from internal TMS reference; the coupling constants (*J*) are given in Hz. Optical rotation were measured in a Perkin-Elmer Model 341

Polarimeter, using the sodium D-line (586 nm). Elemental analyses were performed on a Perkin-Elmer Serie II CHNS/O Analyzer 2400.

3.1. General procedure for the preparation of oxazolidinones (12a-e)

In a 500 mL round-bottom flask was placed (1.0 equiv) of amino acid in 200 mL of dry C_2H_5OH. NaOH (1.2 equiv.) was added, and the resulting solution was stirred at rt until complete dissolution of the amino acid (*ca*. 30 min.). After evaporation, the sodium salt of the amino acid was dried under high vacuum and then suspended in 150 mL of CH_2Cl_2. This suspension was treated with (1.1 equiv.) of isobutyraldehyde and heated to reflux for 8 h with simultaneous removal of the generated H_2O (*Dean-Stark trap*). The reaction flask was cooled in an ice-water bath before addition of benzoyl chloride (1.0 equiv.). The reaction mixture was stirred at rt overnight, washed once with 2 x 200 mL of aq. 5% $NaHCO_3$ and once with water. The organic phase was dried (Na_2SO_4), filtered and concentrated at reduced pressure.

3.1.2. (2*R*,4*S*) and (2*S*,4*S*)-3-Benzoyl-2-isopropyl-4-methyloxazolidin-5-one (12a)

The general procedure was followed using 3.0 g (33.7 mmol) of (*S*)-alanine (**8a**), 1.62 g (40.4 mmol) of NaOH, 3.3 mL (37.1 mmol) of isobutyraldehyde and 3.8 mL (33.7 mmol) of benzoyl chloride to give 6.9 g (83 %) of the crude product as a 3:1 (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 2.7 g (37 %) of (2*R*,4*S*)-**12a** as white crystals (recrystallization solvent CH_2Cl_2-hexane), mp 112-114°C, $[\alpha]_D^{20}$ = + 170° (*c* = 2.0, $CHCl_3$) and 1.0 g (14 %) of (2*S*,4*S*)-**12a** as a colorless oil, $[\alpha]_D^{20}$ = + 8.72° (*c* = 1.0, $CHCl_3$).

3.1.2.1. (2*R*,4*S*)-12a, ^{1}H NMR ($CDCl_3$) δ 7.6-7.4 (m, 5H), 5.98 (s, 1H), 4.46 (q, *J* = 6.6 Hz, 1H), 2.94 (br, 1H), 1.25 (br, 3H), 1.02 (d, *J* = 7.0 Hz, 1H), 0.89 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 172.6, 169.1, 135.7, 131.5, 129.0, 127.0, 93.5, 53.5, 31.4, 18.1, 17.5, 13.3. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93, N, 5.66. Found: C, 68.37; H, 6.84, N, 5.34.

3.1.2.2. (2*S*,4*S*)-12a ^{1}H NMR ($CDCl_3$; 60°C) δ 7.55-7.38 (m, 5H) 5.88 (d, *J* = 5.9 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 1H), 2.05 (m, 1H), 1.41 (d, *J* = 7.0Hz, 3H), 0.98 (d, *J* = 6.76 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$; 60°C) δ 172.6, 171.0, 135.5, 130.5, 128.8, 126.4, 93.8, 53.1, 34.0, 19.1, 17.7, 16.1. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93, N,5.66. Found: C, 68.04; H, 6.66, N, 5.39.

3.1.3. (2*R*,4*S*) and (2*S*,4*S*)-3-Benzoyl-4-isobutyl-2-isopropyloxazolidin-5-one (12b)

The general procedure was followed using 3.0 g (22.9 mmol) of (*S*)-leucine (**8b**), 1.1 g (27.5 mmol) of

NaOH, 2.3 mL (25.2 mmol) of isobutyraldehyde and 3.4 mL (33.7 mmol) of benzoyl chloride to give 6.5 g (98%) of the crude product as a 5:1 (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 3.0 g (45%) of (2*R*,4*S*)-**12b** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 124-126°C, $[\alpha]_D^{20}$ + 155.3° (*c* = 1.0, $CHCl_3$) and 1.0 g (14 %) of (2*S*,4*S*)-**12b** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 91-93°C, $[\alpha]_D^{20}$ = + 49.4° (*c* = 1.0, $CHCl_3$).

3.1.3.1. (2*R*,4*S*)-12b, ^{1}H NMR ($CDCl_3$; 60°C) δ 7.48 (m, 5H), 5.92 (s, 1H), 4.47 (dd, *J* = 8.0 Hz, *J* = 7.7 Hz, 1H), 2.35 (br, 1H), 1.73 (br, 1H), 1.51 (br, 2H), 1.02 (d, *J*= 6.6 Hz, 3H), 0.86 (d, *J*= 7.0 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$; 60°C) δ 172.2, 169.1, 135.7, 131.5, 129.0, 127.1, 93.7, 56.3, 40.0, 30.9, 23.9, 23.4, 21.4,17.6,13.0. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01, N, 4.84. Found: C, 70.30; H, 8.18, N, 4.63.

3.1.3.2. (2*S*,4*S*)-12b, ^{1}H NMR ($CDCl_3$) δ 7. 36-7. 48 (m, 5-H), 5.86 (d, *J*= 7.0 Hz, 1H), 4.20 (d, *J*= 6.6 Hz, 1H), 2.03 (m, 1H), 1.84 (m, 1H), 1.76 (m,1H), 1.52 (m, 1H), 1.02 (d, *J*= 6.6 Hz, 3H), 1.00 (d, 7.0 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.61 (d, *J*= 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 172.3, 171.2, 135.3, 130.6, 128.9, 126.4, 93.8, 55.1, 43.5, 34.7, 24.5, 23.2, 21.0, 17.9, 16.9. $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01, N, 4.84. Found: C, 70.44; H, 8.00, N, 4.86.

3.1.4. (2*R*,4*S*) and (2*S*,4*S*)-3-Benzoyl-4-benzyl-2-isopropyloxazolidin-5-one (12c)

The general procedure was followed using 3.0 g (18.2 mmol) of (*S*)-phenylalanine (**8c**), 0.87 g (21.8 mmol) of NaOH, 1.8 mL (20.0 mmol) of isobutyraldehyde and 2.1 mL (18.2 mmol) of benzoyl chloride to give 5.23 g (89 %) of the crude product as a 3:1 (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 2.5 g (42.5 %) of (2*R*,4*S*)-**12c** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 161-163°C, $[\alpha]_D^{20}$ = + 230.4° (*c* = 1.0, $CHCl_3$) and 1.5 g (26 %) of (2*S*,4*S*)-**12c** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 126-128°C, $[\alpha]_D^{20}$ = + 75.9° (*c* = 1.0, $CHCl_3$).

3.1.4.1. (2*R*,4*S*)-12c, ^{1}H NMR ($CDCl_3$) δ7.50-7.00 (m, 10H), 5.18 (s, 1H), 4.83 (dd, *J*= 4.0 Hz, *J*= 3.3 Hz, 1H), 3.14 (br, 2H), 1.63 (br, 6H), 0.76 (br, 6H). ^{13}C NMR ($CDCl_3$) δ 171.5, 168.6, 135.5, 134.8, 131.5, 129.8, 129.1, 128.7, 127.6, 127.0, 94.1, 58.8, 36.0, 31.0, 17.4, 12.7. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55, N, 4.33. Found: C, 73.98; H, 6.47, N 4.51

3.1.4.2. (2*S*,4*S*)-12c, ^{1}H NMR ($CDCl_3$; 60°C) δ 7.00-7.50 (m, 10H), 5.79 (d, *J* = 7.3 Hz, 1H), 4.51 (dd, *J*= 7.0 Hz, *J* = 5.0 Hz 1H), 3.13 (dd, *J* = 14.0 Hz, *J* = 5.0 Hz, 1H), 3.07 (dd, *J*= 14.0 Hz, *J*= 7.0 Hz, 1H), 1.28 (m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60°C) δ 171.4, 171.3, 135.5,

135.4, 130.3, 129.7, 128.9, 128.7, 127.4, 126.3 94.1, 59.0, 39.1, 34.4, 18.0, 16.7. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55, N, 4.33. Found: C, 74.19; H, 6.61, N 4.45

3.1.5. (2*R*,4*S*) and (2*S*,4*S*)-3-Benzoyl-2,4-diisopropyloxazolidin-5-one (12d)

The general procedure was followed using 3.0 g (25.6 mmol) of (*S*)-valine (**8d**), 1.23 g (30.7 mmol) of NaOH, 2.5 mL (28.2 mmol) of isobutyraldehyde and 3.0 mL (25.6 mmol) of benzoyl chloride to give 6.33 g (90 %) of the crude product as a 5:1 (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 5.0 g (71 %) of (2*R*,4*S*)-**12d** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 129-131°C, $[\alpha]_D^{20}$ = + 108.2° (*c* = 1.0, $CHCl_3$) and 1.0 g (14 %) of (2*S*,4*S*)-**12d** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 69-71°C, $[\alpha]_D^{20}$ = + 46.1° (*c* = 1.0, $CHCl_3$).

3.1.5.1. (2*R*,4*S*)-12d, ^{1}H NMR (DMSO-d_6; 120°C) δ7. 46-7. 71 (m, 5-H), 5.98 (s, 1H), 4.65 (d, *J* = 3.3 Hz, 1H), 2.17 (br, 1H), 1.99 (br, 1H), 0.96 (d, *J*=7.0 Hz, 3H), 0.95 (d, *J*= 7.0 Hz, 3H), 0.85 (d, *J*= 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6; 120°C) δ 170.7, 168.7, 136.1, 131.9, 129.4, 127.5, 94.0, 62.5, 61.7, 31.1, 30.9, 18.0, 17.9, 16.4, 13.3. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69, N, 5.09 Found: C, 69.77; H, 7.59, N, 4.96.

3.1.5.2. (2*S*,4*S*)-12d ^{1}H NMR ($CDCl_3$; 60°C) δ 7. 30-7. 47 (m, 5H), 5.62 (d, *J* = 7.7 Hz, 1H), 4.24 (d, *J* = 8.1 Hz, 1H), 1.98 (m, 1H), 1.91 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J*= 7.0 Hz, 3H), 0.96 (d, *J*= 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$; 60°C) δ 172.0, 171.2, 135.6, 130.2, 128.7, 126.6, 94.3, 61.6, 35.3, 32.6, 19.9, 18.6, 18.2, 17.5. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69, N, 5.09 Found: C, 69.74; H, 7.69, N, 5.06.

3.1.6. (2*R*,4*S*) and (2*S*,4*S*)-3-Benzoyl-4-*sec*-butyl-2-isopropyloxazolidin-5-one (12e)

The general procedure was followed using 3.0 g (22.9 mmol) of (*S*)-isoleucine (**8e**), 1.1 g (27.5 mmol) of NaOH, 2.3 mL (25.2 mmol) of isobutyraldehyde and 2.7 mL (22.9 mmol) of benzoyl chloride to give 6.5 g (98 %) of the crude product as a 5:1 (*trans*/*cis*) mixture, which was purified by flash column chromatography (hexane-ethyl acetate; 98:2) to afford 5.0 g (76 %) of (2*R*,4*S*)-**12e** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 131-133°C, $[\alpha]_D^{20}$ = + 202.3° (*c* = 1.0, $CHCl_3$) and 1.0 g (15 %) of (2*S*,4*S*)-**12e** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 88-90°C, $[\alpha]_D^{20}$ = + 65.2° (*c* = 1.0, $CHCl_3$).

3.1.6.1. (2*R*,4*S*)-12e, ^{1}H NMR (DMSO-d_6; 120^{o}C) δ7.10-7.50 (m, 5H), 5.97 (d, *J*= 2.0 Hz, 1H), 4.72 (d, *J* = 3.3 Hz, 1H), 2.24 (br, 1H), 1.68 (br, 1H), 1.49 (m, 1H), 1.26 (m, 1H), 0.96 (d, *J*= 7.0 Hz, 3H), 0.93 (d, *J* = 7.3 Hz, 3H), 0.82 (d, *J* = 7.3 Hz, 3H, H-13), 0.68 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6; 120^{o}C) δ 170.8, 168.6, 132.0, 129.5, 127.6, 127.4, 94.0, 61.1, 38.0, 31.0, 25.2 18.0, 17.9, 14.2, 13.5, 11.9, 11.8. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01, N, 4.84 Found: C, 70.40; H, 8.03, N, 4.94.

3.1.6.2. (2*S*,4*S*)-12e ^{1}H NMR ($CDCl_3$) δ 7.30-7.50 (m, 5H), 5.66 (d, *J* = 8.0 Hz, 1H), 4.27 (d, *J* = 7.4 Hz, 1H), 1.92 (m, 1H), 1.68 (m, 1H), 1.53 (m, 1H), 1.14 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.69 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 172.4, 171.2, 135.5, 130.3, 128.8, 126.4, 94.2, 60.8, 38.9, 35.4, 26.1 18.1, 17.7, 15.2, 11.4. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01, N, 4.84.Found: C, 70.64; H, 8.19, N, 4.62.

3.2. General procedure for the reaction of oxazolidinones enolates ((2*R*,4*S*)-Li-12a) and ((2*R*,4*S*)-Li-12c) with electrophiles

In a 25 mL round-bottom flask fitted with a magnetic bar was placed 500 mg (2.02 mmol) of ((2*R*,4*S*)-**12a** or (2*R*,4*S*)-**12c** in 15 mL of dry THF under nitrogen. The flask was cooled in a dry ice-acetone bath (-78 ^{o}C) and 1.2 equiv. of 1.0 M LiHMDS was added *via* syringe. The resulting solution was allowed to react for 30 min before the addition of electrophile (dropwise addition). The reaction mixture was then stirred at -78 ^{o}C for 2 h then it was allowed to warm up to rt and stirring was continued overnight. The reaction was quenched with 5 mL of saturated aq. NH_4Cl, and the product was extracted with CH_2Cl_2 (3 X50 mL). The combined extracts were dried over anhydrous Na_2SO_4, and concentrated. Final purification was accomplished by flash chromatography

3.2.1. (2*R*,4*S*)-3-Benzoyl-4-benzyl-2-isopropyl-4-methyloxazolidin-5-one ((2*R*,4*S*)-13)

The general procedure was followed using 0.5 g (2.02 mmol) of (2*R*,4*S*)-**12a** in 15 mL of THF, 2.5 mL (2.5 mmol) of LiHMDS and 0.5 mL (4.20 mmol) of benzyl bromide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 8:2) afforded 0.62 g (91% yield) of (2*R*,4*S*)-**13** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp. 117.2-117.4 °C. $[\alpha]_D^{20}$ = +174.40^o (*c* = 1.0, $CHCl_3$).

(2*R*,4*S*)-**13** ^{1}H NMR ($CDCl_3$) δ 7.40-6.95 (m, 10H), 4.87 (s, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.22 (d, *J* = 13.5 Hz, 1H), 1.96 (s, 3H), 1.07 (m, 1H), 0.68 (d, *J* = 6.6 Hz, 3H), 0.58 (d, *J*= 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.2, 168.1, 136.4, 130.6, 129.9, 128.9, 127.7, 125.8, 93.3, 65.6, 41.0, 31.0, 23.8, 17.6, 13.1. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87, N, 4.15. Found: C 74.65, H, 6.88, N,.4.28.

3.2.2. (2*R*,4*S*)-4-Allyl-3-benzoyl-2-isopropyl-4-methyloxazolidin-5-one ((2*R*,4*S*)-14)

The general procedure was followed using 0.5 g (2.02 mmol) of (2*R*,4*S*)-**12a** in 15 mL of THF, 2.5 mL (2.5 mmol) of LiHMDS and 0.35 mL (4.16 mmol) of allyl bromide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 8:2) afforded 0.46 g (79 % yield) of (2*R*,4*S*)-**13** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 63.8-65.9 °C. $[\alpha]_D^{20}$ = + 15.45 ^{o} (*c* = 1.0, $CHCl_3$).

(2*R*,4*S*)-**13** ^{1}H NMR ($CDCl_3$) δ 7.55-7.46 (m, 5H), 5.82 (d, *J* = 2.6 Hz, 1H), 5.75 (m, 1H), 5.27 (d, *J*= 10.2 Hz, 1H), 5.15 (d, *J*= 17.2 Hz, 1H), 3.0 (br, 1H), 2.47 (dd, *J* = 14.3 Hz, *J* = 6.6 Hz 1H), 1.69 (s, 3H), 1.60 (m, 1H), 0.79 (d, *J* = 7.0 Hz), 0.78 (d, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 174.6, 168.9, 136.6, 131.3, 130.5, 128.7, 126.4, 131.3, 121.1, 93.4, 63.7, 40.2, 31.5, 24.1, 17.7, 13.6. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37, N, 4.87. Found: C 71.01, H, 7.60, N, 4.73.

3.2.3. [(2*R*,4*S*)-3-Benzoyl-2-isopropyl-4-methyl-5-oxo-oxazolidin-4-yl]acetic acid ethyl ester ((2*R*,4*S*)-15)

The general procedure was followed using 0.5 g (2.02 mmol) of (2*R*,4*S*)-**12a** in 15 mL of THF, 2.5 mL (2.43 mmol) of LiHMDS and 0.5 mL (4.04 mmol) of ethyl bromoacetate. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 8:2) afforded 0.53 g (85% yield) of (2*R*,4*S*)-**13** as a viscous oil. $[\alpha]_D^{20}$ = + 75.91^o (*c* = 1.0, $CHCl_3$).

(2*R*,4*S*)-**13** ^{1}H NMR ($CDCl_3$) δ 7.33-7.26 (m, 5H), 5.79 (d, *J* = 2.2 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.5 (br, 1H), 2.77 (d, *J*= 17.9 Hz, 1H), 1.63 (s, 3H), 1.09 (t, *J*= 7.1 Hz, 3H), 0.69 (d, *J*= 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 174.0, 170.3, 168.3, 136.5, 130.5, 128.8, 126.1, 93.9, 60.9, 60.5, 39.3, 30.8, 24.0, 17.7, 13.9, 13.6. anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95, N, 4.20. Found: C 64.52, H, 7.16 N, 4.13.

3.2.4. (2*R*,4*R*)-4-Allyl-3-benzoyl-4-benzyl-2-isopropyloxazolidin-5-one ((2*R*,4*R*)-16)

The general procedure was followed using 0.2 g (0.62 mmol) of (2*R*,4*S*)-**12c** in 15 mL of THF, 0.7 mL (0.74 mmol) of LiHMDS and 0.11 mL (1.27 mmol) of allyl bromide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 8:2) afforded 0.12 g (53 % yield) of (2*R*,4*R*)-**16** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 104.7-105.8 °C. $[\alpha]_D^{20}$ = - 86.39 ^{o} (*c* = 1.0, $CHCl_3$).

(2*R*,4*R*)-**16** ^{1}H NMR ($CDCl_3$) δ 7.53-7.18 (m, 10H), 5.84 (m, 1H), 5.41 (d, *J* = 3.7 Hz, 1H), 5.35 (d, *J*= 16.5 Hz, 1H), 5.34 (d, *J*= 11.4 Hz, 1H), 3.88 (d, *J* = 13.2 Hz, 1H), 3.47 (t, *J* = 11.4 Hz, 1H), 3.36 (d, *J* = 13.5 Hz, 1H), 2.67 (dd, *J*= 5.9 Hz, *J*= 13.9 Hz, 1H), 0.58 (m, 1H), 0.40 (d, *J* = 7.0 Hz, 3H), -0.18 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.4, 169.2, 137.0, 136.1, 131.3, 130.7, 130.3, 128.8, 128.5, 127.4, 126.1, 121.7, 93.7, 69.7, 42.0, 39.7, 31.6, 18.5, 12.4. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93, N,

3.85. Found: C 75.99, H, 7.23, N, 3.65.

3.2.5. [(2*R*,4*S*)-3-Benzoyl-4-benzyl-2-isopropyl-5-oxo-oxazolidin-4-yl]acetic acid ethyl ester ((2*R*,4*S*)-17)

The general procedure was followed using 0.51 g (1.58 mmol) of (2*R*,4*S*)-**12c** in 15 mL of THF, 1.9 mL (1.9 mmol) of LiHMDS and 0.35 mL (3.15 mmol) of ethyl bromoacetate. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 8:2) afforded 0.51 g (79% yield) of (2*R*,4*R*)-**16** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 107.2-108.1 °C. $[\alpha]_D^{20}$ = + 6.67 ^{o} (*c*= 1.0, $CHCl_3$). (2*R*,4*R*)-**16** ^{1}H NMR ($CDCl_3$) δ 7.59-7.39 (m, 10H), 5.78 (d, *J*= 3.7 Hz, 1H), 4.16 (q, *J*= 5.1 Hz, 2H), 3.87 (d, *J* = 16.8 Hz, 1H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.37 (d, *J* = 13.6 Hz, 1H) 2.95 (d, *J* = 17.6 Hz, 1H) 1.24 (t, *J* = 7.1 Hz, 3H), 0.70 (m, 1H), 0.48 (d, *J* = 7.0 Hz, 3H) 0.03 (d, *J*= 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.2, 170.8, 169.2, 136.6, 135.0, 130.9, 130.6, 128.9, 128.7, 127.8, 126.2, 94.4, 66.0, 61.3, 42.6, 38.7, 31.2, 18.8, 14.1, 13.0. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65. N, 3.42 Found: C 70.26, H, 6.75, N, 3.57.

3.2.6. (*1S,2'R,4'S*)-*N*-[1-(3-Benzoyl-2-isopropyl-4-methyl-5-oxo-oxazolidin-4-yl)-2-methylpropyl]benzamide ((*1S,2'R,4'S*)-20)

The general procedure was followed using 0.2 g (0.81 mmol) of (2*R*,4*S*)-**12c** in 15 mL of THF, 0.89 mL (0.89 mmol) of LiHMDS without electrofile. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 8:2) afforded 0.08 g (47% yield) of **(*1S,2'R,4'S*)-20** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 200-202 °C. $[\alpha]_D^{20}$ = + 31.15 ^{o} (*c* = 0.5, $CHCl_3$).

(*1S,2'R,4'S*)-20 ^{1}H NMR ($CDCl_3$) δ 7.50-7.44 (m, 10H) 5.83 (d, *J* = 2.9 Hz, 1H), 4.76 (d, *J* = 8.0 Hz, 1H), 1.88 (m, 1H,), 1.74 (s, 1H), 1.37 (m, 1H), 1.10 (d, *J*= 7.0 Hz, 1H), 1.05 (d, *J*= 7.0 Hz, 1H), 0.80 (d, *J*= 7.0 Hz, 1H), 0.78 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 173.5, 170.4, 166.9, 135.8, 134.09, 131.6, 131.3, 129.5, 128.7, 127.2, 125.6, 93.3, 66.2, 60.4, 31.4, 21.5, 20.9, 20.0, 18.0, 14.1. Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.07; H, 7.16, N, 6.63. Found: C, 71.25, H, 7.32, N, 6.40.

3.3. General procedure for the methanolysis of (2*R*,4*S*)-13-15 and (*1S,2'R,4'S*)-20

A solution of 1 mmol of adduct in 10 mL of methanolic 2M CF_3CO_2H was heated in a sealed ampule at 130^{o}C for 72 h. The solution was then allowed to cool to rt, and was concentrated in a rotary evaporator. The residue was dissolved in 200 mL of CH_2Cl_2, washed three times with H_2O, dried over anh. Na_2SO_4 and concentrated in the rotary evaporator to afford the crude product that was purified by flash chromatography (hexane: ethyl acetate, 8:2).

3.3.1. (2*S*)-2-Benzylamino-2-methyl-3-phenylpropionic acid methyl ester ((2*S*)-21)

Derivative ((2*R*,4*S*)-**13**) (100 mg, 0.30 mmol) was hydrolyzed according to the general procedure to afford 85 mg (95 % yield) of (2*S*)-**21** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 112-114 °C. $[\alpha]_D^{20}$ = + 78.53 ^{o} (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.67-7.06 (m, 10H), 6.82 (s, 1H), 3.81 (s, 3H), 3.71 (d, *J* = 13.6 Hz, 1H), 3.29 (d, *J* = 13.6 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 174.6, 167.0, 136.5, 135.0, 131.6, 129.9, 128.6, 128.4, 127.0, 126.9, 61.7, 52.8, 41.2, 23.5. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44, N, 4.71. Found: C, 72.49, H, 6.57, N, 4.63.

3.3.2. (2*S*)-2-Benzylamino-2-methylpent-4-enoic acid methyl ester ((2*S*)-22)

Derivative ((2*R*,4*S*)-**14**) (77 mg, 0.27 mmol) was hydrolyzed according to the general procedure to afford 58 mg (87 % yield) of (2*S*)-**22** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 67-68 °C. $[\alpha]_D^{20}$ = + 9.74 ^{o} (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.76-7.39 (m, 5H), 6.94 (s, 1H), 5.68 (m, 1H), 5.12 (d, *J* = 19.0 Hz, 1H), 5.10 (d, *J* = 9.2 Hz, 1H), 3.80 (s, 3H) 3.08 (dd, *J* = 13.18 Hz, *J* = 7.32 Hz, 1H), 2.66 (dd, *J* = 13.55 Hz, *J* = 7.32 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 174.7, 166.5, 134.8, 132.5, 131.6, 128.6, 126.9, 119.6, 60.3, 52.9, 40.8, 22.9. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93, N, 5.66. Found: C, 67.90, H, 7.16, N, 5.49.

3.3.3. (2*S*)-2-Benzylamino-2-methyl-succinic acid dimethyl ester ((2*S*)-23)

Derivative ((2*R*,4*S*)-**15**) (112 mg, 0.34 mmol) was hydrolyzed according to the general procedure to afford 70 mg (79 % yield) of (2*S*)-**24** as a viscous oil. $[\alpha]_D^{20}$ = + 4.84 ^{o} (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.78-7.35 (m, 5H), 3.81 (s, 3H), 3.61 (d, *J* = 16.5 Hz, 1H), 3.61 (s, 3H), 3.04 (d, *J* = 16.5 Hz, 1H), 1.74 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 174.2, 171.3, 166.6, 134.5, 131.7, 128.6, 127.1, 58.1, 53.2, 51.9, 40.0, 23.30. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51, N, 5.32. Found: C, 63.78, H, 6.76, N, 5.53.

3.3.4. (2*S*,3*S*)-2,3-Bisbenzoylamino-2,4-dimethylpentanoic acid methyl ester ((2*S*,3*S*)-24)

Derivative ((1*S*,2'*R*,4'*S*)-**20)** (100 mg, 0.24 mmol) was hydrolyzed according to the general procedure to afford 79 mg (88 % yield) of (2*S*,3*S*)-**23** as white crystals, (recrystallization solvent CH_2Cl_2-hexane), mp 188-190 °C. $[\alpha]_D^{20}$ = -55.4 ^{o} (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.06-7.46 (m, 10H) 4.81 (dd, *J* = 9.7 Hz, *J* = 8.0 Hz, 1H), 3.90 (s, 1H), 1.75 (m, 1H), 1.62 (s, 1H), 0.94 (d, *J* = 7.0 Hz, 1H), 0.90 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 175.8, 167.9, 167.3, 134.3, 134.4, 132.1, 131.5, 128.9, 128.7, 127.3, 127.1, 64.0, 58.9, 53.7, 31.3, 22.0, 20.5, 19.6. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85, N, 7.32. Found: C 68.99, H 6.61, N, 7.16

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