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Conjugate addition of aryl nucleophiles to α,β-unsaturated cinnamic acid derivatives containing Evans type chiral auxiliaries

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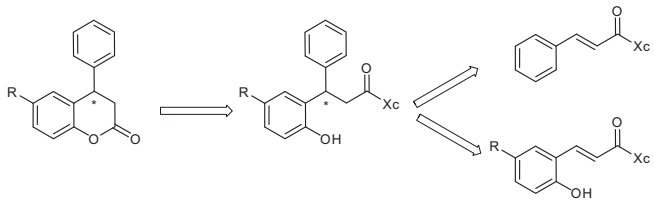
ABSTRACT

Cinnamides containing oxazolidin-2-one type auxiliaries have been prepared. A novel pathway to chiral 4-aryl-6-methyl-3,4-dihydrocoumrines via the asymmetric conjugate addition of arylmagnesium bromides to these cinnamides is described.

1. Introduction

4-Aryl-3,4-dihydrocoumarins (4-arylchroman-2-ones) are naturally occurring compounds that are a major structural type of neoflavonoids of which both enantiomers widely occur in plants.[1] Recently compounds with high antioxidant capacity have been obtained in this class.[2,3] 4-Aryl-3,4-dihydrocoumarins are also versatile synthons for the preparation of 1,3-diarylpropylamines possessing muscarinic receptor antagonist properties,[4,5] as well as intermediates for the preparation of 1,3-diaryl-2,3-dihydro-1*H*-indene-2-carboxylic acid derivatives, known as endothelin antagonists.[6]

Herein we report an approach to both enantiomerically enriched 4-aryldihydrocoumarin isomers based on the asymmetric conjugate addition of aryl magnesium species to cinnamic acid derivatives. The selection of the cinnamic substrate and the organomagnesium reagent is focused on the preparation of 6-methyl-4-aryl-3,4-dihydrocoumarins that would be suitable scaffolds for antimuscarinic drug (Tolterodine, Fesoterodine) synthesis.



The conjugate addition of aryl nucleophiles to cinnamic acid derivatives linked with a chiral auxiliary is a straightforward approach to construct an alkyl chain bearing stereogenic carbon having two different aryl groups. Oxazolidinones[5] and imidazolidinones[7] are recommended as suitable chiral auxiliaries for this purpose.

The pathway leading to (*R*)- or (*S*)-6-substituted 4-aryl-3,4-dihydrocoumarin can be switched by applying an auxiliary of opposite configuration or by altering the substituents in the cinnamoyl and arylmagnesium moieties and using the same auxiliary.

2. Results and discussion

With the above analysis in mind, we examined copper assisted addition of arylmagnesium species to 3-cinnamoyl-oxazolidin-2-ones **2a**–**i** and their phenyl ring analogues **2j**–**l** and **7a**–**c**.

N-Cinnamoyl oxazolidinones **2a**–**i** were prepared from cinnamoyl chloride **1a** and *N*-unsubstituted oxazolidinones Xc—H **3** in the presence of *n*-butyl lithium as a base (Scheme 1). Cinnamoyl oxazolidinones **2j**–**l** were prepared in the same way starting with the synthesis from corresponding acid.

Commercially unavailable (*R*)- and (*S*)-4-isobutyl-5,5-dimethyl-, (*S*)-4-secbutyl-5,5-dimethyl-, (*R*)- and (*S*)-4-phenyl-5,5-dimethyl- and (*S*)-4-benzyl-5,5-dimethyloxazolidinones necessary for the preparation of cinnamides **2c**–**g** and **7b** were obtained from methyl ester of the corresponding D- or L-amino acid in accordance with the general method.[8] Their enantiomeric purity was confirmed by comparison of the specific rotation of both enantiomers.

Other phenyl ring cinnamoyl derivatives, namely 3-(3-(2-benzyloxy-5-methylphenyl)acryloyl)oxazolidin-2-ones **7a**–**c** were prepared in three steps from the corresponding heterocycles **3** (Scheme 2). Acylation of the oxazolidinones with halogenacetyl chloride followed by the interaction of *N*-halogenacetyl derivatives **4** with triethylphosphite analogues[9] gave phosphonates **5a**–**c**.

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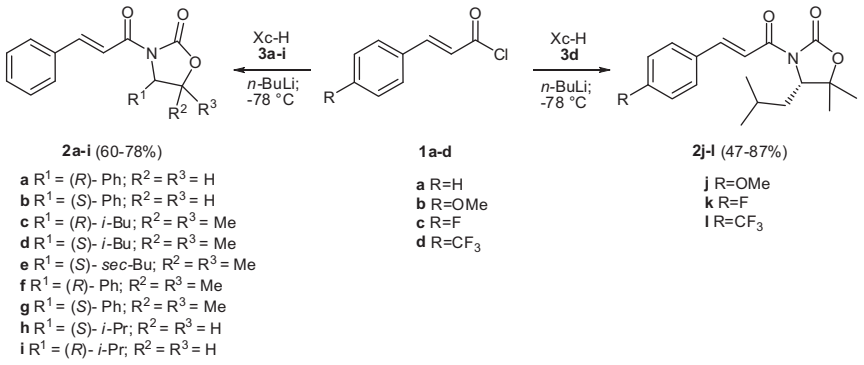
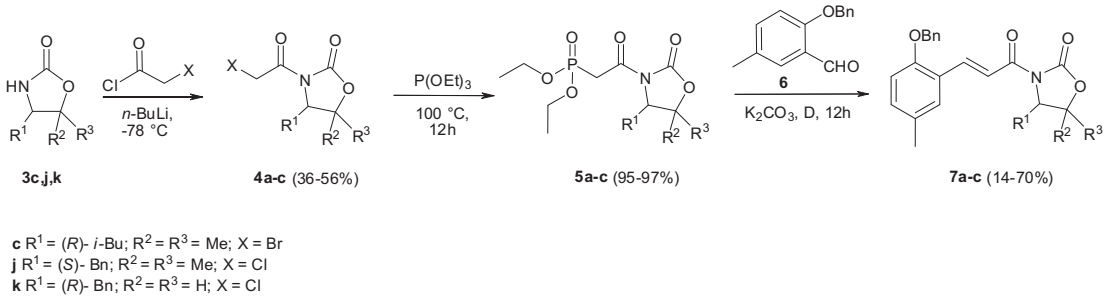
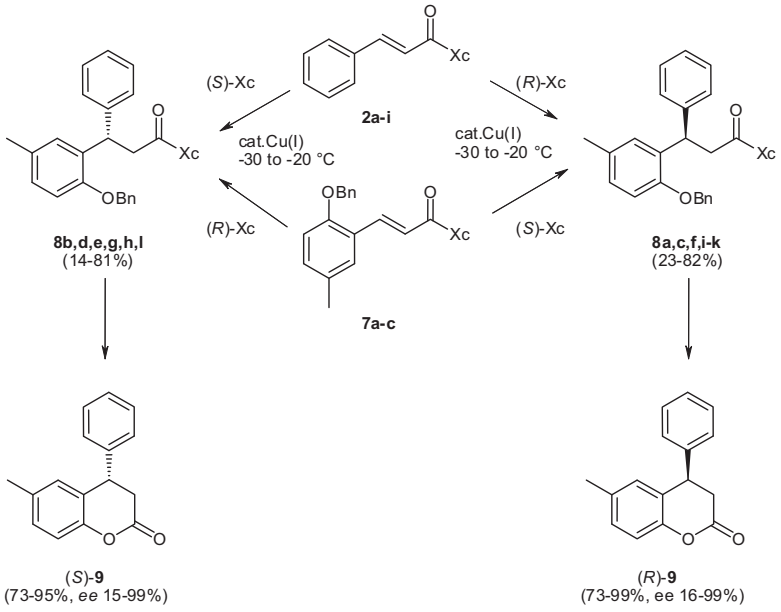


Scheme 1. Preparation of cinnamides **2a–l**.



Scheme 2. Preparation of cinnamides **7a–c**.



Scheme 3. Reaction of cinnamides **2** and **7** with arylmagnesium with subsequent cyclization of 3,3-diarylsubstrates **8** to coumarines **9**.

Condensation with 2-benzyloxy-5-methylbenzaldehyde **6**, which was obtained reaction of arylmagnesium bromide with DMF, resulted in the formation of cinnamoyl derivatives **9a–c**.[10]

N-Cinnamoyl oxazolidinones **2** and **7** underwent regioselective copper catalysed 1,4-addition of arylmagnesium in good yields (Table 1) and with moderate to high stereoselectivity (Table 2) depending on the structure of oxazolidinone **3** moiety. The products of this conjugate addition were 3,3-diarylpropionyl-oxazolidinones **8**. These products were treated with BBr_3 to remove the *O*-benzyl protection and to give phenol intermediates, which were subjected to interaction with trimethylamine, leading to chroman ring closure and affording dihydrocoumarins **9**.

A correlation between the oxazolidinone auxiliary C-4 configuration in the cinnamide and the structure of the 3-aryl-3-phenylpropanoic acid derivative is already known: the (*R*)-auxiliary initiates the formation of the (*R*)-propionyl chaine.[5] 4-Phenyloxazolidinones ensure excellent stereoselectivity whereas asymmetric induction using 4-alkyl or 4-benzyl oxazolidinone derivatives as an auxiliary is only moderate. This indicated the key role of π–π stacking in the 1,4-addition transition state. Consequently,

Table 1
Cu-catalysed conjugate aryl-/phenylmagnesium addition to cinnamoyl oxazolidinones **2a-i** and **7a–c** via Scheme 4

Entry	Substrate **2**			Copper source	3,3-Diarylpropanoyl-oxazolidinone **8**			
	Compd	R	Config.		Compd	Yield	*de*, %	Config.
1	**2a**	Ph	(*R*)	Me_2S·CuBr	**8a**	61	99	(*R*,*R*)
2	**2b**	Ph	(*S*)	Me_2S·CuBr	**8b**	62	99	(*S*,*S*)
3	**2c**	*i*-Bu	(*R*)	CuBr	**8c**	83	—	(*R*,*R*)
4	**2d**	*i*-Bu	(*S*)	Me_2S·CuBr	**8d**	81	—	(*S*,*S*)
5	**2d**	*i*-Bu	(*S*)	CuBr	**8d**	84	—	(*S*,*S*)
6	**2d**	*i*-Bu	(*S*)	2LiCl·CuCN	**8d**	82	—	(*S*,*S*)
7	**2d**	*i*-Bu	(*S*)	Li_2CuCl_4	**8d**	76	—	(*S*,*S*)
8	**2e**	*sec*-Bu	(*S*)	CuBr	**8e**	49	—	(*S*,*S*)
9	**2f**	Ph	(*R*)	Me_2S·CuBr	**8f**	55	—	(*R*,*R*)
10	**2g**	Ph	(*S*)	Me_2S·CuBr	**8g**	50	—	(*S*,*S*)
11	**2h**	*i*-Pr	(*S*)	Me_2S·CuBr	**8h**	14	—	(*S*,*S*)
12	**2i**	*i*-Pr	(*R*)	CuBr	**8i**	23	—	(*R*,*R*)
13	**7a**	*i*-Bu	(*R*)	CuBr	**8j**	51	—	(*R*,*S*)
14	**7b**	Bn	(*S*)	CuBr	**8l**	29	86	(*S*,*R*)
15	**7c**	Bn	(*R*)	CuBr	**8k**	46	—	(*R*,*S*)

In Table 1 only three examples are shown (entry 1, 2 and 14) where *de* values were measured in a 3,3-diarylpropionamides. Others (including entries 1 and 2) were converted into coumarine **9** and then the *ee* values were measured.

Table 2
Chemical yields and selectivity of coumarine **9** prepared from **8a–k** via Scheme 3

Entry	3,3-Diarylpropanoyl-oxazolidinone **8**	Coumarine **9**		
		Yield	*ee*, %	Config.
1	**8a**	90	99	(*R*)
2	**8b**	92	99	(*S*)
3	**8c**	93	65	(*R*)
4	**8d**	73	63	(*S*)
5	**8d**	90	71	(*S*)
6	**8d**	89	52	(*S*)
7	**8d**	96	65	(*S*)
8	**8e**	85	76	(*S*)
9	**8f**	99	99	(*R*)
10	**8g**	95	99	(*S*)
11	**8h**	94	15	(*S*)
12	**8i**	93	16	(*R*)
13	**8j**	91	49	(*S*)
14	**8l**	—	—	(*R*)
15	**8k**	73	60	(*S*)

π-interactions dominate over the steric bulkiness of the oxazolidinone 4-substituent.

The recognition of (3*R*)- and (3*S*)-diarylpropionamides **8a**,**b** bearing a 4-phenyloxazolidinone moiety was achieved by HPLC using a Chiralcel OD column (Table 1; entry 1, 2).

Chiral HPLC conditions suitable to distinguish the 3-diarylpropionamide diastereomers **8c–k** derived from 4-alkyl oxazolidinones were not found. Therefore the efficiency of these auxiliaries was evaluated by comparison of the *ee* values measured for the final product of this transformation, i.e. the *ee* value of 6-methyl-4-phenyl-3,4-dihydrocoumarin **9**; in this case the enantiomeric excess was measured by using a Chiralcel OD-H column (Table 2).

Usually Cu(I) salts or their complexes are used to promote conjugate addition of arylmagnesium species. All cuprous salts tested led to the formation of diarylpropionic acid derivative **8g** in similar yields (81–84%) (Table 1; entries 3–6). The highest diastereoselectivity was achieved when using Me_2S·CuBr complex. Remarkably the same reaction selectivity and product outcome were obtained when Cu(II) was applied in the Li_2CuCl_4 form (Table 1; entry 7).

The presence of the *ortho*-substituent in the starting cinnamoyloxazolidinone compounds **7a–c** decreased the yield (29–51%) of 3,3-diarylpropanoyloxazolidinones in comparison to derivatives unsubstituted in the cinnamoyl compound benzene ring (Table 1; entry 13–15). The substituent also diminishes the stereoselectivity of the addition reaction (Table 1; entry 14). However these are only a few experiments which is not enough to draw this as a general conclusion.

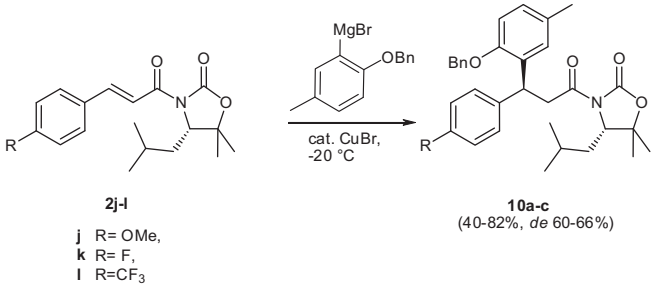
The electronic influence of the substituent in the cinnamoyl moiety was evaluated studying the addition of 2-benzyloxy-5-methylphenyl magnesium to cinnamoyloxazolidinones **2j–k** (Scheme 4).

The addition of arylmagnesium to C=C double bond proceeded with approximately the same diastereoselectivity (*de* **10a** 66%, **10b** 60% and **10c** 64%) regardless of the nature of the cinnamoyl *para*-substituent. The stereoselectivity of the conjugate addition to substrates **2** was established by HPLC, by applying a Chiralpak IA column. The yields of the diarylpropionyloxazolidinones **10** decreased in the presence of electron withdrawing groups in the cinnamoyl moiety: **10a** 82%, **10b** 62%, **10c** 40%.

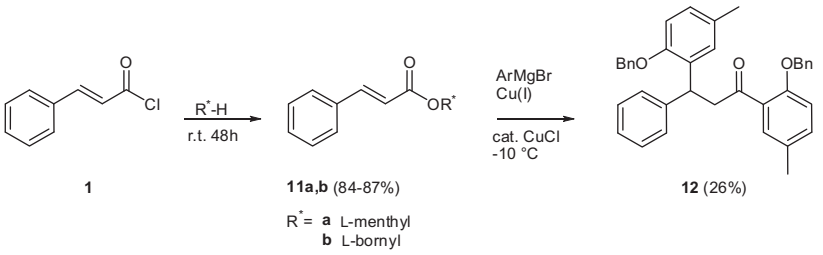
While searching for an appropriate auxiliary, besides the cinnamides discussed above, cinnamates **11** derived from inexpensive natural alcohols (L-menthol, L-borneol) were prepared. However the ester function turned out to be unsuitable to prepare 3,3-diarylpropanoic derivatives (Scheme 5).

3. Conclusion

These cinnamates do not react with 2-benzyloxy-5-methylphenylmagnesium in the presence of Me_2S·CuBr. More than 80% of unconverted esters were recovered in these trials. The same interaction of menthyl ester with arylmagnesium in the presence of Cu(I)Cl (10 mol %, THF, −10 °C) gave product of simultaneous 1,4- and 1,2-addition i.e., 1,3-bis-(2-benzyloxy-5-methyl-phenyl)-3-phenylpropan-1-one **12** in 26% yield; a remarkable amount (65%) of starting material was also recovered. The application of arylmagnesium without the addition of copper catalyst proceeded



Scheme 4. Preparation of cinnamides **2j–l** and the reaction of arylmagnesium.



Scheme 5. Preparation of cinnamoyl esters **11a**,**b** and the reactions of arylmagnesium.

in a similar manner: compound **12** was isolated in 16% yield and 63% of ester **11a** was recovered. This result is in disagreement with addition of some aryllithium reagents to *t*-butyl cinnamates.[11]

4. Experimental section

4.1. General information

NMR spectra were recorded on a Varian Mercury 200, 300, 400 and 600 MHz in $CDCl_3$ and DMSO-d_6 using signal of the solvent as internal standard. Specific rotation was measured on polarimeter Atago AP-100, the concentration *c* is given as g/100 mL in $CHCl_3$. Flush chromatography separations were carried out over Merck silica gel 60 (0.035–0.070 mm) or Silasorb 600 (0.030 mm). The eluent compositions are given as v/v ratio. The reactions were monitored on thin layer precoated silica gel plates (DC-Alufolien Kieselgel 60 F_{254}), the spots were visualized under UV light. Melting points were determined using OptiMelt MPA100 apparatus and are uncorrected. Chiral HPLC analyses were detected at 254 nm and performed on following Daicel columns: OD-H (0.46 × 25 cm); the eluent hexane/isopropanol 90:10, flow rate 0.5 mL/min —6-methyl-4-phenyl-3,4-dihydrocoumarine **9**, OD (0.46 × 25 cm); eluent hexane/isopropanol 70:30, flow rate 1.0 mL/min —3,3-diarylpropionamides **8a**,**b**,**l** and IA (0.46 × 25 cm); eluent hexane/isopropanol 90:10, flow rate 0.5 mL/min—3,3-diarylpropionamides **10a**–**c**.

4.2. General procedure for preparation of cinnamoyl chlorides 1a–d

Cinnamic acid (10.0 g, 0.067 mol) solution in thionyl chloride (100 ml, 20 equiv) was refluxed for 1.5 h, and then evaporated under reduced pressure. The crude product was used in the next step without further purification.

4.2.1. Cinnamoyl chloride 1a

Colourless oil (9.0 g, yield 80%); mp 30–35 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.65 (d, *J* = 15.3 Hz, 1H, CH═C*H*—CO), 7.35–7.52 (m, 3H, 3,4,5-aromH), 7.52–7.64 (m, 2H, 2,6-aromH), 7.85 (d, *J* = 15.3 Hz, 1H, C*H*═CH—CO).

4.2.2. 4-Methoxycinnamoyl chloride 1b

Light yellow solid (0.52 g, yield 99%); mp 45–49 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.51 (d, *J* = 15.4 Hz, 1H, CH═C*H*—CO), 6.94 (d, *J* = 8.8 Hz, 2H, 2,6-aromH), 7.53 (d, *J* = 8.8 Hz, 2H, 3,5-aromH), 7.79 (d, *J* = 15.4 Hz, 1H, C*H*═CH—CO).

4.2.3. 4-Fluorocinnamoyl chloride 1c

Green-yellow solid (0.48 g, yield 87%); mp 40–44 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.58 (d *J* = 15.5 Hz, 1H, CH═C*H*—CO), 7.07–7.21 (m, 2H, 3,5-aromH), 7.52–765 (m, 2H, 2,6-aromH), 7.80 (d *J* = 15.5 Hz, 1H, C*H*═CH—CO).

4.2.4. 4-Trifluorocinnamoyl chloride 1d

Light yellow solid (0.48 g, yield 89%); mp 60–62 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.73 (d, *J* = 15.6 Hz, 1H, CH═C*H*—CO), 7.70 (m, 4H, aromH), 7.85 (d, *J* = 15.6 Hz, 1H, C*H*═CH—CO).

4.3. General procedure of chiral cinnamic acid amides 2a–l

n-Butyllithium (1.15 mL, 1.0 equiv, 2.3 M in hexanes) was added to a cooled until −75 °C solution of the corresponding oxazolidinone (2.6 mmol) in anhydrous THF (12 mL), then the resulting solution was warmed to −30 °C and stirred for 20 min. At the same temperature, a solution of cinnamoyl chloride (1.0 equiv) in anhydrous THF (7 mL) was added dropwise and then allowed to rise to at room temperature and left overnight with continuous stirring. After work-up with 10% NH_4Cl (15 mL), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 25 ml). The combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude products were purified by chromatography or crystallized from appropriate solvents.

4.3.1. (*R*)-4-Phenyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2a

White crystals (0.28 g, 62% yield) after crystallization (Et_2O/EtOAc, 1:1); mp 169–170 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.32 (dd, *J* = 3.8, 8.8 Hz, 1H, NCHC*H*$_2$), 4.74 (t, *J* = 8.8 Hz, 1H, NC*H*CH$_2$), 5.56 (dd, *J* = 3.8, 8.8 Hz, 1H, NCHC*H*$_2$), 7.28–7.48 (m, 8H, aromH), 7.52–7.66 (m, 2H, aromH), 7.78 (d, *J* = 15.7 Hz, 1H, CH═C*H*—CO), 7.95 (d, *J* = 15.7 Hz, 1H, C*H*═CH—CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.0, 70.1, 117.0, 126.1, 128.7, 128.8, 129.0, 129.3, 130.8, 134.6, 139.2, 146.8, 153.9, 164.9.

4.3.2. (*S*)-4-Phenyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2b

White crystals (1.2 g, 69% yield). Melting point, δ_H and δ_C spectra were identical to **2a** [(*R*)-isomer].

4.3.3. (*S*)-4-Isobutyl-5,5-dimethyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2d

White crystals (7.4 g, 72% yield) after crystallization (Et_2O); mp 109–110 °C; $[\alpha]_D^{29}$ = +78 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (m, 6H, (C*H*$_3$)$_2$CH), 1.47 (s, 6H, 2 × 5-CH$_3$), 1.51–1.68 (m, 3H, C*H*CH$_2$), 4.30 (m, 1H, NC*H*CH$_2$), 7.34–7.44 (m, 3H, 3,4,5-aromH), 7.55–7.66 (m, 2H, 2,6-aromH), 7.84 (d, *J* = 15.7 Hz, 1H, CH═C*H*—CO), 7.92 (d, *J* = 15.7 Hz, 1H, C*H*═CH—CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 22.5, 23.1, 25.4, 28.5, 39.4, 61.1, 82.4, 117.6, 128.7, 129.0, 130.7, 134.8, 146.1, 153.2, 165.8. MS: *m*/*z* 301 (59, M^+), 258 (26), 172 (16), 154 (22), 130 (100), 128 (18), 111 (14). Found: C, 71.71%; H, 7.73%; N, 4.58%. $C_{18}H_{23}NO_3$ requires C, 71.73%; H, 7.69%; N, 4.65%.

4.3.4. (*R*)-4-Isobutyl-5,5-dimethyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2c

White crystals (1.3 g, 60% yield); $[\alpha]_D^{29}$ = −77 (*c* 1.0, $CHCl_3$). Melting point, δ_H and δ_C spectra are identical to **2d** [(*S*)-isomer].

4.3.5. (*S*)-4-*sec*-Butyl-5,5-dimethyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2e

White solid (1.8 g, 78% yield) after chromatography (PE/EtOAc, 10:1); mp 81–83 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H, CH_3CH_2), 1.07 (d, J = 7.3 Hz, 3H, *Me*CH), 1.11–1.34 (m, 1H, CH_3CH_2), 1.43 (s, 3H, 5-CH_3), 1.45–1.67 (m, 1H, CH_3CH_2), 1.53 (s, 3H, 5-CH_3), 1.81–2.03 (m, 1H, CH_3CH), 4.29 (d, J = 3.6 Hz, 1H, NCH), 7.33–7.44 (m, 3H, aromH), 7.56–7.66 (m, 2H, aromH), 7.83 (d, J = 15.3 Hz, 1H, CH=*CH*—CO), 7.99 (d, J = 15.3 Hz, 1H, *CH*=CH—CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 17.2, 21.9, 24.5, 29.3, 36.7, 66.8, 82.9, 117.4, 128.7, 129.0, 130.7, 134.8, 146.3, 153.7, 165.9.

4.3.6. (*R*)-4-Phenyl-5,5-dimethyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2f

White crystals (1.6 g, 66% yield) after crystallization (PE/EtOAc, 5:1); mp 153–155 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.89 (s, 3H, 5-CH_3), 1.62 (s, 3H, 5-CH_3), 5.29 (s, 1H, NCH), 7.16–7.50 (m, 8H, aromH), 7.56–7.72 (m, 2H, aromH and 1H, CH=*CH*—CO), 7.89 (d, J = 16.1 Hz, 1H, *CH*=CH—CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 29.1, 67.4, 82.6, 117.3, 126.5, 128.7, 128.8, 128.9, 129.0, 130.8, 134.7, 136.4, 146.7, 153.4, 165.2.

4.3.7. (*S*)-4-Phenyl-5,5-dimethyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2g

White crystals (0.47 g, 75% yield). Melting point, δ_H and δ_C spectra are identical to **2f** [(*R*)-isomer].

4.3.8. (*S*)-4-Isopropyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2h

White solid (1.5 g, 74% yield) after chromatography (PE/EtOAc, 3:1); mp 64–65 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.82 (d, J = 13.1 Hz, 3H, 5-CH_3), 0.85 (d, J = 13.1 Hz, 3H, 5-CH_3), 2.20–2.25 (m, 1H, $(CH_3)_2CH$), 4.29–4.39 (m, 2H, NCHCH_2), 4.39–4.53 (m, 1H, NC*H*CH_2), 7.38–7.49 (m, 3H, aromH), 7.60–7.71 (m, 2H, aromH), 7.72 (d, J = 16.1 Hz, 1H, CH=*CH*—CO), 7.84 (d, J = 16.1 Hz, 1H, *CH*=CH—CO). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 18.2, 28.7, 58.8, 63.5, 117.2, 128.7, 129.0, 130.7, 134.7, 146.3, 154.3, 165.3.

4.3.9. (*R*)-4-Isopropyl-3-[(*E*)-(3-phenylacryloyl)]-oxazolidin-2-one 2i

White solid (1.4 g, 70% yield). Melting point, δ_H and δ_C spectra are identical to **2h** [(*S*)-isomer].

4.3.10. (*S*)-4-Isobutyl-3-[(*E*)-3-(4-methoxyphenyl)-acryloyl]-5,5-dimethyl-oxazolidin-2-one 2j

Yellow oil (0.64 g, yield 75%) after chromatography (PE/EtOAc, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (m, 6H, $(CH_3)_2CH$), 1.46 (s, 6H, 2 × 5-CH_3), 1.50–1.66 (m, 3H, CH_2CH), 3.83 (s, 3H, CH_3O), 4.30 (m, 1H, NC*H*CH_2), 6.86–6.94 (m, 2H, 3,5-aromH), 7.52–7.62 (m, 2H, 2,6-aromH), 7.76 (d, J = 15.7 Hz, 1H, CH=*CH*—CO), 7.84 (d, J = 15.7 Hz, 1H, *CH*=CH—CO).

4.3.11. (*S*)-4-Isobutyl-5,5-dimethyl-3-[(*E*)-3-(4-fluorophenyl)-acryloyl]-oxazolidin-2-one 2k

Light yellow oil (0.30 g, yield 47%) after chromatography (PE/EtOAc, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (m, 6H, $(CH_3)_2CH$), 1.47 (s, 6H, 2 × 5-CH_3), 1.50–1.64 (m, 3H, $CHCH_2$), 4.29 (m, 1H, NC*H*CH_2), 7.00–7.14 (m, 2H, 3,5-aromH), 7.54–7.65 (m, 2H, 2,6-aromH), 7.78 (d, J = 17.8 Hz, 1H CH=*CH*—CO), 7.86 (d, J = 17.8 Hz, 1H, *CH*=CH—CO).

4.3.12. (*S*)-4-Isobutyl-5,5-dimethyl-3-[(*E*)-3-(4-trifluoromethyl-phenyl)-acryloyl]-oxazolidin-2-one 2l

White solid (0.69 g, yield 87%) after chromatography (PE/EtOAc, 4:1); mp 115–116 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (m, 6H, $(CH_3)_2CH$), 1.48 (s, 6H, 2 × 5-CH_3), 1.51–1.64 (m, 3H, $CHCH_2$), 4.30 (m, 1H, NC*H*CH_2), 7.63 (d, J = 8.6 Hz, 2H, 3,5-aromH), 7.70 (d, J = 8.6 Hz, 2H, 2,6-aromH), 7.82 (d, J = 15.7 Hz, 1H, CH=*CH*—CO), 7.99 (d, J = 15.7 Hz, 1H *CH*=CH—CO).

4.4. General procedure for the preparation of halogen acetyloxazolidinones 4a–c

To a cooled (−78 °C) solution of the corresponding oxazolidinone **3** (1.9 mmol) in THF (15 mL), *n*-butyllithium (1.07 mL, 2.5 M, 1.1 equiv) was added under stirring. The temperature was allowed rise to −20 °C and the mixture was stirred for 1 h, then cooled down to −78 °C, repeatedly. The halogenacetylchloride (0.23 mL, 1.5 equiv) was added dropwise at this temperature under stirring and the reaction mixture was left overnight at room temperature, after which it was quenched with 50 mL of 10% NH_4Cl. The organic layer was separated and aqueous phase was extracted by ethyl acetate (3 × 30 mL) and dried over Na_2SO_4. Concentration in vacuo gave a crude product, which was then purified by column chromatography or crystallized from appropriate solvents at −18 °C.

4.4.1. (*R*)-3-(2-Bromoacetyl)-4-isobutyl-5,5-dimethyl-oxazolidin-2-one 4a

This compound was prepared according general procedure using bromo acetylchloride. Yellow oil (2.7 g, yield 36%) after chromatography (PE/EtOAc, 50:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93–1.01 (m, 6H, $(CH_3)_2CH$), 1.47 (s, 6H, 5-CH_3), 1.48–1.64 (m, 3H, $(CH_3)_2CHCH_2$), 4.09–4.26 (m, 1H, NCH), 4.44 (d, J = 12.4 Hz, 1H, $BrCH_2$), 4.57 (d, J = 12.4 Hz, 1H, $BrCH_2$).

4.4.2. (*S*)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyl-oxazolidin-2-one 4b

White crystals (0.3 g, 56% yield) after crystallization (PE/EtOAc, 16:1); mp 68–69 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 3H, 5-CH_3), 1.39 (s, 3H, 5-CH_3), 2.88 (dd, J = 9.7, 14.4 Hz, 1H, PhCH_2), 3.20 (dd, J = 3.8, 14.4 Hz, 1H, PhCH_2), 4.50 (dd, J = 3.8, 9.7 Hz, 1H, NCH), 4.63 (d, J = 15.9 Hz, 1H, $ClCH_2$), 4.77 (d, J = 15.9 Hz, 1H, $ClCH_2$), 7.15–7.36 (m, 5H, aromH).

4.4.3. (*R*)-4-Benzyl-3-(2-chloroacetyl)-oxazolidin-2-one 4c

White crystals (0.76 g, yield 53%) after crystallization (PE/Et_2O; 4:1); mp 74–75 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.81 (dd, J = 9.5, 13.1 Hz, 1H, PhCH_2), 3.34 (dd, J = 3.6, 13.1 Hz, 1H, PhCH_2), 4.26–4.30 (m, 2H, NCHCH_2), 4.68–4.72 (m, 1H, NCH), 4.75 (s, 2H, $ClCH_2$), 7.15–7.41 (m, 5H, aromH).

4.5. General procedure for the preparation of phosphonates 5a–c

Halogenacetyl oxazolidinone **4** (1.1 mmol) dissolved in triethyl phosphite (0.73 mL, 4.0 equiv) was heated at 100 °C for 12 h. Then the solution was evaporated till dryness and then toluene (4 × 5 mL) was added with repeated evaporation before each toluene addition to obtain desired phosphonate which was used in next step without further purification.

4.5.1. [2-((*R*)-4-Isobutyl-5,5-dimethyl-2-oxo-oxazolidin-3-yl)-2-oxoethyl]phosphonic acid diethyl ester 5a

Colourless oil (3.0 g, yield 97%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, J = 5.8 Hz, 6H, $(CH_3)_2CH$), 1.25–1.38 (m, 6H, 2 × CH_3CH_2O), 1.43 (s, 3H, 5-CH_3), 1.46 (s, 3H, 5-CH_3), 1.40–1.55 (m, 3H, $(CH_3)_2$-$CHCH_2$), 3.50 (dd, J = 13.9, 22.7 Hz, 1H, $POCH_2$), 3.94–4.25 (m, 4H, 2 × CH_3CH_2O and 2H, $POCH_2$).

4.5.2. [2-((*S*)-4-Benzyl-5,5-dimethyl-2-oxo-oxazolidin-3-yl)-2-oxoethyl]phosphonic acid diethyl ester 5b

Yellow oil (0.39 g, yield 97%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28–1.37 (m, 6H, 2 × CH_3CH_2O), 1.33 (s, 3H, 5-CH_3), 1.38 (s, 3H, 5-CH_3),

2.86 (dd, J = 9.9, 14.5 Hz, 1H, PhCH_2), 3.18 (dd, J = 3.7, 14.5 Hz, 1H, PhCH_2), 3.53 (dd, J = 13.9, 22.5 Hz, POCH_2), 4.02 (dd, J = 13.9, 22.5 Hz, POCH_2), 4.07–4.25 (m, 4H, 2 × CH_3CH_2O), 4.52 (dd, J = 3.6, 9.8 Hz, 1H, NCH), 7.23–7.33 (m, 5H, aromH).

4.5.3. [2-((*R*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-oxoethyl]-phosphonic acid diethyl ester 5c

Colourless oil (0.40 g, yield 95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 6H, 2 × CH_3CH_2O), 2.75 (dd, J = 9.9, 13.4 Hz, 1H, PhCH_2), 3.35 (dd, J = 3.4, 13.4 Hz, 1H, PhCH_2), 3.75 (q, J = 14.2 Hz, 1H, POCH_2), 3.85 (q, J = 14.2 Hz, 1H, POCH_2), 4.09–4.31 (m, 4H, 2 × CH_3CH_2O and 2H, NCHCH_2), 4.61–4.79 (m, 1H, NCHCH_2), 7.17–7.40 (m, 5H, aromH).

4.6. 2-Benzyloxy-4-methylbenzaldehyde 6

This compound was prepared from appropriate arylmagnesium bromide and DMF in 39% yield.

4.7. General procedure for the preparation of chiral cinnamic acid amides 7a–c

A suspension of phosphonate **5** (0.87 mmol), arylaldehyde **6** (1.0 equiv) and K_2CO_3 (5.0 equiv) in 5 mL of dry THF was refluxed for 12 h. The mixture was dissolved in water (50 mL) and the solution was extracted with ethyl acetate (3 × 30 mL). The organic extract was dried (Na_2SO_4) and then evaporated. The crude product obtained was subjected on silica gel using a mixture of PE and dichloromethane.

4.7.1. (*R*)-4-Isobutyl-3-[(*E*)-3-(2-benzyloxy-5-methylphenyl)-acryloyl]-5,5-dimethyl-oxazolidin-2-one 7a

Light yellow oil (0.53 g, yield 14%) after chromatography (PE/DCM, 1:1.5). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95–1.05 (m, 6H, (CH_3)$_2$-CH), 1.46 (s, 6H, 2 × 5-CH_3), 2.29 (s, 3H, CH_3Ph), 4.23–4.35 (m, 1H, NCH), 5.14 (s, 2H, PhCH_2), 6.82 (d, J = 8.0 Hz, 1H, 3-aromH), 7.10 (dd, J = 1.4, 8.0 Hz, 1H, 4-aromH), 7.29–7.51 (m, 6H, aromH), 7.91 (d, J = 16.1 Hz, 1H, CH=CH—CO), 8.29 (d, J = 16.1 Hz, 1H, CH=CH—CO).

4.7.2. (*S*)-4-Benzyl-3-[(*E*)-3-(2-benzyloxy-5-methylphenyl)-acryloyl]-5,5-dimethyl-oxazolidin-2-one 7b

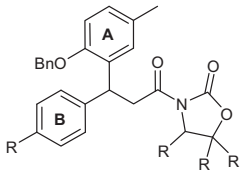
Colourless oil (0.11 g, yield 25%) after chromatography (PE/DCM, 1:2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 3H, 5-CH_3), 1.39 (s, 3H, 5-CH_3), 2.30 (s, 3H, CH_3Ph), 2.91 (dd, J = 9.8, 14.4 Hz, 1H, NCH), 3.31 (dd, J = 3.3, 14.4 Hz, 1H, PhCH_2CH), 4.62 (dd, J = 3.3, 9.8 Hz, 1H, PhCH_2CH), 5.15 (s, 2H, PhCH_2O), 6.84 (d, J = 8.4 Hz, 1H, 3-aromH), 7.12 (dd, J = 2.2, 8.4 Hz, 1H, 4-aromH), 7.17–7.53 (11H, m, aromH), 7.93 (d, J = 15.8 Hz, 1H, CH=CH—CO), 8.30 (d, J = 15.8 Hz, 1H, CH=CH—CO).

4.7.3. (*R*)-4-Benzyl-3-[(*E*)-3-(2-benzyloxy-5-methylphenyl)-acryl-oyl]-oxazolidin-2-one 7c

Yellow oil (0.83 g, yield 70%) after chromatography (PE/DCM, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3), 2.84 (dd, J = 9.5, 13.4 Hz, 1H, PhCH_2CH), 3.39 (dd, J = 3.2, 13.4 Hz, 1H, PhCH_2-CH), 4.10–4.34 (m, 2H, NCHCH_2), 4.79 (ddd, J = 3.2, 6.8, 9.5 Hz, 1H, NCH), 5.16 (s, 2H, PhCH_2O), 6.85 (d, J = 8.4 Hz, 1H, 3-aromH), 7.08–7.17 (m, 1H, 4-aromH), 7.19–7.54 (m, 11H, aromH), 7.93 (d, J = 15.8 Hz, 1H, CH=CH—CO), 8.36 (d, J = 15.8 Hz, 1H, CH=CH—CO).

4.8. General procedure for conjugate 1,4-addition of arylmagnesium bromides to cinnamic acid derivatives 2a–l in the presence of Cu(I) catalysts

Grignard reagent, prepared from 1-benzyloxy-2-bromo-4-methylbenzene (0.68 g, 2.4 mmol) and magnesium turnings (0.12 g) in dry THF (10 mL), was added to a cooled (−50 °C) suspension of CuBr (71 mg, 0.3 equiv) in dry THF (3 mL), then the temperature was allowed raise to −25 °C and solution of cinnamide **2** (1.6 mmol) in dry THF (4 mL) was added keeping the temperature below −20 °C. After the addition was completed the temperature was allowed to rise to room temperature and stirred overnight. The reaction mixture was quenched with 10% NH_4Cl (10 mL) and mixture was evaporated to remove all of the organic solvent. The aqueous layer was then extracted with ethyl acetate (3 × 25 mL), and washed with 30 ml of 17% NH_4OH and 50 ml of brine and dried over Na_2SO_4. Concentration in vacuo gave a crude product, which was purified by chromatography or crystallized.



4.8.1. (*R*)-3-[(*R*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-phenyl-oxazolidin-2-one 8a

This compound was obtained from **2a** (0.25 g, 0.85 mmol) in 0.26 g amount (yield 61%) after chromatography (PE/EtOAc, 1.2:1) and further recrystallization of ether. White crystals; mp 116–117 °C (Et_2O); $[\alpha]_D^{22}$ = −72 (*c* 1.0, $CHCl_3$); *de* 100%; Found: C, 77.50; H, 5.83; N, 2.79. $C_{32}H_{29}NO_4$ requires C, 78.19; H, 5.95; N, 2.85%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 3.62 (dd, J = 6.5, 16.8 Hz, 1H, PhCHCH_2), 3.89 (dd, J = 8.9, 16.8 Hz, 1H, PhCHCH_2), 4.16 (dd, J = 3.5, 8.8 Hz, 1H, PhCHCH$_2$), 4.50 (t, J = 8.7 Hz, 1H, NCH), 4.92 (s, 2H, PhCH_2O), 5.02 (dd, J = 6.5, 8.8 Hz, 1H, NCHCH_2), 5.28 (dd, J = 3.5, 8.6 Hz, 1H, NCHCH_2), 6.71 (d, J = 8.3 Hz, 1H, 3(A)-aromH), 6.93 (dd, J = 2.1, 8.3 Hz, 1H, 4(A)-aromH), 7.06 (d, J = 2.1 Hz, 1H, 6(A)-aromH), 7.08–7.34 (m, 15H, aromH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 40.0, 40.1, 57.7, 70.0, 70.2, 112.2, 125.7, 126.2, 127.4, 127.7, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 129.2, 130.0, 132.0, 137.4, 139.1, 143.5, 153.9, 171.1.

4.8.2. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-phenyl-oxazolidin-2-one 8b

This compound was obtained from **2b** (0.40 g, 1.36 mmol) in 0.41 g amount (yield 62%) after chromatography (PE/EtOAc, 1.2:1) and recrystallization from ether. White crystals; $[\alpha]_D^{22}$ = +75 (*c* 1.0, $CHCl_3$); *de* 100%. Melting point, δ_H and δ_C spectra are identical to **8a** ((*R*)-isomer).

4.8.3. (*R*)-3-[(*R*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-isobutyl-5,5-dimethyl-oxazolidin-2-one 8c

This compound was obtained from **2c** (0.50 g, 1.65 mmol) in 0.68 g amount (yield 82%) after chromatography (PE/EtOAc, 10:1). Light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (m, 6H, (CH_3)$_2$CH), 1.19 (s, 3H, 5-CH_3), 1.36 (s, 3H, 5-CH_3), 1.15–1.45 (m, 3H, (CH_3)$_2$CHCH_2), 2.25 (s, 3H, CH_3Ph), 3.55 (dd, J = 6.7, 16.4 Hz, 1H, PhCHCH_2), 3.92 (dd, J = 9.1, 16.4 Hz, 1H, PhCHCH_2), 4.04 (t, J = 6.7 Hz, 1H, NCH), 5.01 (s, 2H, PhCH_2O), 5.10 (dd, J = 6.7, 9.1 Hz, 1H, PhCHCH$_2$), 6.74 (d, J = 8.3 Hz, 1H, 3(A)-aromH), 6.93 (dd, J = 1.5, 8.3 Hz, 1H, 4(A)-aromH), 7.05 (d, J = 1.5 Hz, 1H, 6 (A)-aromH), 7.09–7.42 (m, 10H, aromH).

4.8.4. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-isobutyl-5,5-dimethyl-oxazolidin-2-one 8d

This compound was obtained from **2d** (0.50 g, 1.65 mmol) in 0.67 g amount (yield 81%) after chromatography (PE/EtOAc, 10:1). Light yellow oil. δ_H spectra is identical to **8c** ((*R,R*)-isomer).

4.8.5. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenyl-propionyl]-4-*sec*-butyl-5,5-dimethyl-oxazolidin-2-one 8e

This compound was obtained from **2e** (1.82 g, 6.0 mmol) in 1.48 g amount (yield 49%) after crystallization (PE/EtOAc, 1:1). White solid; mp 112–114 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79–0.83 (m, 3H, CH_3CH_2 and 3H, CH_3CH), 0.90–1.02 (m, 1H, CH_3CH_2), 1.14 (s, 3H, 5-CH_3), 1.34–1.46 (m, 1H, CH_3CH_2), 1.42 (s, 3H, 5-CH_3), 1.67–1.78 (m, 1H, CH_3CH), 2.23 (s, 3H, CH_3Ph), 3.70 (dd, J = 7.4, 16.6 Hz, 1H, PhCHCH_2), 3.80 (dd, J = 8.4, 16.6 Hz, 1H, PhCHCH_2), 4.02 (d, J = 3.3 Hz, 1H, NCH), 4.91 (d, J = 12.0 Hz, 1H, PhCH_2O), 4.96 (d, J = 12.0 Hz, 1H, PhCH_2O), 5.03–5.07 (m, 1H, PhCHCH$_2$), 6.68 (d, J = 8.2 Hz, 1H, 3(A)-aromH), 6.86 (dd, J = 1.7, 8.2 Hz, 1H, 4(A)-aromH), 7.02 (d, J = 1.7 Hz, 1H, 6(A)-aromH), 7.04–7.28 (m, 10H, aromH).

4.8.6. (*R*)-3-[(*R*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenyl-propionyl]-4-phenyl-5,5-dimethyl-oxazolidin-2-one 8f

This compound was obtained from **2f** (1.65 g, 5.1 mmol) in 1.45 g amount (yield 55%) after flush chromatography (20% EtOAc/PE 10 min → 80% EtOAc/PE 5 min → 80% EtOAc/PE 5 min; 20 mL/min; at 210 and 254 nm). White solid; mp 140–142 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 3H, 5-CH_3), 1.35 (s, 3H, 5-CH_3), 2.20 (s, 3H, CH_3Ph), 3.57 (dd, J = 6.2, 16.8 Hz, 1H, PhCHCH_2), 3.91 (dd, J = 9.0, 16.8 Hz, 1H, PhCHCH_2), 4.81–4.89 (m, 2H, PhCH_2O and 1H, NCH), 4.94 (dd, J = 6.2, 9.0 Hz, 1H, PhCHCH$_2$), 6.64 (d, J = 8.2 Hz, 1H, 3(A)-aromH), 6.85 (dd, J = 1.5, 8.2 Hz, 1H, 4(A)-aromH), 6.89–6.95 (m, 2H, aromH), 7.03 (d, J = 1.5 Hz, 1H, 6(A)-aromH), 7.10–7.24 (m, 8H, aromH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 23.8, 28.3, 47.8, 67.3, 71.0, 71.9, 83.2, 113.0, 126.7, 127.4, 127.9, 128.3, 128.4, 128.6, 128.7, 128.8, 129.0, 129.3, 130.4, 130.5, 135.9, 137.3, 140.7, 152.9, 154.5, 174.0.

4.8.7. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenyl-propionyl]-4-phenyl-5,5-dimethyl-oxazolidin-2-one 8g

This compound was obtained from **2g** (0.47 g, 1.4 mmol) in 0.38 g amount (yield 50%) after flush chromatography (20% EtOAc/PE 10 min → 80% EtOAc/PE 5 min → 80% EtOAc/PE 5 min; 20 mL/min; at 210 and 254 nm). White solid. Melting point, δ_H and δ_C spectra are identical to **8f** [(*R*,*R*)-isomer].

4.8.8. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-isopropyl-oxazolidin-2-one 8h

This compound was obtained from **2h** (1.49 g, 5.7 mmol) in 0.36 g amount (yield 14%) after flush chromatography (20% EtOAc/PE 10 min → 80% EtOAc/PE 5 min → 80% EtOAc/PE 5 min; 20 mL/min; at 210 and 254 nm). Yellow oil. δ_H and δ_C spectra are identical to **8i** [(*R*,*R*)-isomer].

4.8.9. (*R*)-3-[(*R*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-isopropyl-oxazolidin-2-one 8i

This compound was obtained from **2i** (1.42 g, 5.4 mmol) in 0.58 g amount (yield 23%) after flush chromatography (20% EtOAc/PE 10 min → 80% EtOAc/PE 5 min → 80% EtOAc/PE 5 min; 20 mL/min; at 210 and 254 nm). Yellow vitreous material. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.59 (d, J = 6.9 Hz, 3H, $(CH_3)_2$CH) diast. isomer A), 0.72 (d, J = 7.0 Hz, 3H, $(CH_3)_2$CH) diast. isomer A), 0.67 (d, J = 6.9 Hz, 3H, $(CH_3)_2$CH) diast. isomer B), 0.76 (d, J = 7.0 Hz, 3H, $(CH_3)_2$CH diast. isomer B), 1.85–2.03 (m, 2H, $(CH_3)_2CH$), 2.20 (s, 3H, CH_3Ph diast. isomer A), 2.21 (s, 3H, CH_3Ph diast. isomer B), 3.32 (dd, J = 7.4, 16.3 Hz, 1H, ArCHCH_2 diast. isomer A), 3.80 (dd, J = 8.1, 16.9 Hz, 1H, ArCHCH_2 diast. isomer A), 3.41 (dd, J = 7.6, 16.9 Hz, 1H, ArCHCH_2 diast. isomer B), 3.90 (dd, J = 8.5, 16.6 Hz, 1H, ArCHCH_2 diast. isomer B), 4.17–4.32 (m, 6H, ArCHCH$_2$ and 2H, NCHCH_2), 4.90–5.07 (m, 4H, PhCH_2O and 2H, NCH), 6.87 (d, J = 4.4 Hz, 1H, 4-aromH diast. isomer A), 6.89 (d, J = 4.4 Hz, 1H, 4-aromH diast. isomer B), 6.94 (d, J = 1.6 Hz, 1H, 3-aromH diast. isomer A), 6.96 (d, J = 1.6 Hz, 1H, 3-aromH diast. isomer B), 7.04 (d, J = 1.8 Hz, 1H, aromH diast. isomer A), 7.06 (d, J = 1.8 Hz, 1H, aromH diast. isomer B), 7.11–7.39 (m, 20H, aromH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 14.5, 17.3, 20.4, 28.2 and 28.3 (diast.), 57.9, 63.4, 69.3 and 69.4 (diast.), 112.4, 127.2, 127.3, 126.0, 127.6, 127.8, 127.9, 128.1, 128.2, 128.3, 128.3, 129.1 and 129.2 (diast.), 131.7 and 131.8 (diast.), 137.3, 143.5 and 143.6 (diast.), 153.2 and 153.3 (diast.), 154.0 and 154.1 (diast.), 170.7 and 170.8 (diast.). MS: m/z 458 (8, M^+), 440 (16), 405 (94), 287 (17), 260 (100), 130 (38).

4.8.10. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-(4-methoxy-phenyl)-propionyl]-4-isobutyl-5,5-dimethyl-oxazolidin-2-one 10a

This compound was obtained from **2j** (0.73 g, 2.2 mmol) in 0.96 g amount (yield 82%) after chromatography (PE/EtOAc, 4:1). Yellow oil; *de* 66%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (d, J = 5.7 Hz, 6H, $(CH_3)_2$CH), 1.13 (s, 3H, 5-CH_3), 1.30 (s, 3H, 5-CH_3), 1.11–1.35 (m, 3H, $(CH_3)_2CHCH_2$), 2.18 (s, 3H, CH_3Ph), 3.44 (dd, J = 6.5, 16.3 Hz, 1H, ArCHCH_2), 3.68 (s, 3H, CH_3O), 3.84 (dd, J = 9.4, 16.3 Hz, 1H, ArCHCH_2), 3.3–4.03 (m, 1H, ArCHCH$_2$), 4.95 (s, 2H, PhCH_2), 4.96–5.04 (m, 1H, NCH), 6.63–6.74 (m, 3H, aromH), 6.85 (dd, J = 2.0, 8.2 Hz, 1H, aromH), 6.98 (dd, J = 2.3, 6.6 Hz, 1H, 4(A)-aromH), 7.12 (d, J = 8.7 Hz, 2H, aromH), 7.07–7.30 (m, 5H, *Ph*CH$_2$).

4.8.11. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-(4-fluoro-phenyl)-propionyl]-4-isobutyl-5,5-dimethyl-oxazolidin-2-one 10b

This compound was obtained from **2k** (0.30 g, 0.94 mmol) in 0.30 g amount (yield 62%) after chromatography (PE/EtOAc, 4:1). Colourless oil, *de* 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80–0.91 (m, 6H, $(CH_3)_2$CH), 1.21 (s, 3H, 5-CH_3), 1.38 (s, 3H, 5-CH_3), 1.17–1.44 (m, 3H, $(CH_3)_2CHCH_2$), 2.26 (s, 3H, CH_3Ph), 3.53 (dd, J = 6.6, 16.4 Hz, 1H, ArCHCH_2), 3.89 (dd, J = 9.2, 16.4 Hz, 1H, ArCHCH_2), 4.01–4.10 (m, 1H, ArCHCH$_2$), 4.99 (d, J = 3.1 Hz, 2H, PhCH_2), 4.94–5.11 (m, 1H, NCH), 6.74 (d, J = 8.3 Hz, 1H, 3(A)-aromH), 6.83–6.98 (m, 3H, 4(A) and 3,5(B)-aromH), 7.03 (d, J = 1.7 Hz, 1H, 6(A)-aromH), 7.15–7.40 (m, 7H, 2,6(B) and *Ph*CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.7, 22.7, 22.9, 25.1, 27.9, 39.2, 39.7, 39.9, 60.8, 70.3, 82.3, 112.1, 115.0 (J = 21.1 Hz), 127.4, 127.8, 128.1, 128.5, 129.9 (J = 7.8 Hz), 130.0, 131.8, 137.4, 139.1 (J = 3.2 Hz), 153.2, 153.9, 161.5 (J = 243.9 Hz), 171.9.

4.8.12. (*S*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-(4-trifluoro-methylphenyl)-propionyl]-4-isobutyl-5,5-dimethyl-oxazolidin-2-one 10c

This compound was obtained from **2l** (0.47 g, 1.2 mmol) in 0.29 g amount (yield 40%) after chromatography (PE/EtOAc, 8:1). White solid; mp 115–116 °C; *de* 64%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (m, 6H, $(CH_3)_2$CH), 1.17 (s, 3H, 5-CH_3), 1.23–1.47 (m, 3H, $(CH_3)_2CHCH_2$), 1.37 (s, 3H, 5-CH_3), 2.27 (s, 3H, CH_3Ph), 3.54 (dd, J = 6.5, 16.5 Hz, 1H, ArCHCH_2), 3.94 (dd, J = 9.3, 16.5 Hz, 1H, ArCHCH_2), 4.04 (m, 1H, ArCHCH$_2$), 4.97 (s, 2H, PhCH_2), 5.08 (dd, J = 6.6, 9.4 Hz, 1H, NCH), 6.75 (d, J = 8.1 Hz, 1H, 3(A)-aromH), 6.96 (dd, J = 2.0, 8.1 Hz, 1H, 4(A)-aromH), 7.06 (d, J = 2.0 Hz, 1H, 6(A)-aromH), 7.17–7.39 (m, 7H, *Ph*CH$_2$ and 2,6(B)-aromH), 7.40–7.49 (m, 2H, 3,5(B)-aromH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.7, 22.6, 22.9, 25.1, 27.9, 39.2, 39.3, 40.6, 60.8, 70.2, 82.3, 112.1, 124.3 (J = 271.7 Hz), 125.0 (J = 3.9 Hz), 127.5, 127.9, 128.3 (J = 32.2 Hz), 128.5, 128.8, 130.1, 131.0, 137.2, 147.7, 153.1, 153.9, 171.7. MS: m/z 568 (12, M^+), 550 (17), 506 (14), 370 (39), 172 (100), 59 (15).

4.9. General procedure for conjugate 1,4-addition of phenylmagnesium bromide to cinnamic acid derivatives 7a–c in the presence of CuBr

To a cooled (−50 °C) $CuBr{\cdot}SMe_2$ complex (16 mg, 0.08 mmol) solution in a mixture of THF (1 mL) and dimethyl sulphide (0.5 mL), phenyl magnesium bromide (0.29 ml, 0.28 mmol, 1.0 M) was added under stirring, then the mixture was warmed to −30 °C, after which cinnamide **7** (0.26 mmol) in 10 mL of THF was added at this temperature. The reaction mixture was stirred overnight at room temperature, then quenched with 10% NH_4Cl (10 mL). The aqueous/organic emulsion was evaporated until all of dimethyl sulfide was gone then extracted by ethyl acetate (2 × 20 mL), washed with 10 mL of 17% NH_4OH and 10 mL of brine and dried over Na_2SO_4. Concentration in vacuo gave a crude product, which was purified by chromatography with mixture of PE/EtOAc.

4.9.1. (*R*)-3-[(*S*)-3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-isobutyl-5,5-dimethyl-oxazolidin-2-one 8j

This compound was obtained from **7a** (0.53 g, 1.2 mmol) in 0.31 g amount (yield 51%) after chromatography (PE/EtOAc, 5:1). Light yellow oil. δ_H spectra is identical to **8c** [(*R*,*R*)-isomer].

4.9.2. (*R*)-4-Benzyl-3-[(*S*)-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropionyl]-oxazolidin-2-one 8k

This compound was obtained from **7c** (0.83 g, 1.9 mmol) in 0.46 g amount (yield 46%) after chromatography (PE/EtOAc, 5:1). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3Ph), 2.62 (dd, J = 9.6, 13.4 Hz, 1H, PhCH_2CH), 3.13 (dd, J = 3.3, 13.4 Hz, 1H, PhCH_2CH), 3.63 (dd, J = 6.5, 16.9 Hz, 1H, ArCHCH_2), 3.89 (dd, J = 8.9, 16.9 Hz, 1H, ArCHCH_2), 3.95–4.11 (m, 1H, ArCHCH$_2$ and 1H, NCHCH_2), 4.46–4.58 (m, 1H, NCHCH_2), 5.02 (dd, J = 12.0, 13.9 Hz, 2H, PhCH_2O), 5.13 (dd, J = 6.5, 8.8 Hz, 1H, NCH), 6.78 (d, J = 8.2 Hz, 1H, 3-aromH), 6.96 (dd, J = 2.3, 8.2 Hz, 1H, 4-aromH), 7.00–7.38 (m, 16H, aromH).

4.9.3. (*S*)-4-Benzyl-5,5-dimethyl-3-[(*R*)-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropionyl]-oxazolidin-2-one 8l

This compound was obtained from **7b** (0.11 g, 0.25 mmol) in 40 mg amount (yield 30%) after chromatography (PE/EtOAc, 5:1). Light yellow oil; *de* 86%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (brs, 6H, 5-CH_3), 2.25 (s, 3H, CH_3Ph), 2.61 (dd, J = 9.9, 14.5 Hz, 1H, ArCHCH_2), 2.93 (dd, J = 3.4, 14.5 Hz, 1H, ArCHCH_2), 3.74 (d, J = 7.9 Hz, 2H, PhCH_2CH), 4.39 (dd, J = 3.4, 9.9 Hz, 1H, ArCHCH$_2$), 5.01 (s, 2H, PhCH_2O), 5.11 (t, J = 7.9 Hz, 1H, NCH), 6.75 (d, J = 8.2 Hz, 1H, 3(A)-aromH), 6.93 (dd, J = 1.9, 8.2 Hz, 1H, 4(A)-aromH), 7.07 (d, J = 1.9 Hz, 1H, 6(A)-aromH), 7.10–7.42 (m, 15H, aromH).

4.10. (*S*)-6-Methyl-4-phenyl-chroman-2-one 9

To a cooled (−75 °C) solution of (*S*)-3-[(*S*)-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropionyl]-4-isobutyl-5,5-dimethyloxazolidin-2-one **8g** (0.58 g, 1.16 mmol) in dried DCM (25 mL), BBr_3 (0.11 mL, 1.0 equiv) was added and kept overnight at −3 °C. The solution was quenched with 0.1 M NaOH (10 mL), the organic phase was separated and the aqueous solution extracted with DCM (10 mL). The combined organic solution was dried (Na_2SO_4) and evaporated. The residue oil was taken in 10 mL of 10% TEA solution in toluene and refluxed for 1 h. The crude product obtained after evaporating was subjected to chromatography on silica gel (EtOAc/PE, 3:7) to obtain compound **9** as white crystals (0.26 g, yield 95%); mp 79–81 °C; [Found: C, 80.54; H, 5.90. $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.92]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3), 3.01–3.04 (m, 2H, CHCH_2), 4.30 (t, J = 6.6 Hz, 1H, CHCH$_2$), 6.79 (d, J = 1.4 Hz, 1H, 5(Ar)-aromH), 7.03 (d, J = 8.0 Hz, 1H, 8(Ar)-aromH), 7.09–7.13 (m, 2H, aromH), 7.16 (dd, J = 1.4, 8.0 Hz, 1H, 7(Ar)-aromH), 7.23–7.43 (m, 3H, aromH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 37.3, 40.9, 117.0, 125.5, 127.6, 127.7, 128.8, 129.2, 129.4, 134.4, 140.6, 149.8, 168.0.

4.11. General procedure for preparation of chiral cinnamic acid esters 11a,b

The corresponding alcohol (0.024 mol) was added to cinnamoyl chloride **1a** (4.0 g, 0.024 mol) solution of dry benzene (10 mL) and the mixture was stirred at room temperature for 48 h, then evaporated under reduced pressure. The residue was distilled in vacuum to give title ester.

4.11.1. (*E*)-3-Phenylacrylic acid L-menthyl ester 11a

Colourless oil (6.0 g, yield 87%) after distillation; bp 215–218 °C at 9 mbar. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79 (d, J = 7.0 Hz, 3H, CH_3), 0.92 (d, J = 7.0 Hz, 6H, 2 × CH_3), 0.97–2.16 (m, 9H, menthyl-H), 4.83 (dt, J = 4.4, 10.8 Hz, 1H, CO_2CH), 6.43 (d, J = 15.8 Hz, 1H, CHCO), 7.31–7.47 (m, 3H, 3,4,5-aromH), 7.47–7.60 (m, 2H, 2,6-aromH), 7.68 (d, J = 15.8 Hz, 1H, CHPh). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.9, 22.2, 23.7, 26.5, 31.6, 34.5, 41.2, 47.4, 74.4, 118.9, 128.2, 129.0, 130.3, 134.7, 144.5, 166.7.

4.11.2. (*E*)-3-Phenylacrylic acid [(1*S*)-*endo*]-bornyl ester 11b

Colourless oil (5.7 g, yield 84%) after distillation; bp 214–218 °C at 13 mbar. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82–1.00 (m, 9H, 3 × CH_3), 1.00–2.54 (m, 7H, bornyl-H), 5.02 (ddd, J = 2.0, 3.2, 9.9 Hz, 1H, CO_2CH), 6.47 (d, J = 16.0 Hz, 1H, CHCO), 7.30–7.48 (m, 3H, 3,4,5-aromH), 7.48–7.61 (m, 2H, 2,6-aromH), 7,68 (d, J = 16.0 Hz, 1H, CHPh). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 19.0, 19.9, 27.4, 28.2, 37.0, 45.1, 48.0, 49.1, 80.1, 118.9, 128.2, 129.0, 130.3, 134.7, 144.3, 167.4.

4.12. 1,3-Bis-(2-benzyloxy-5-methylphenyl)-3-phenylpropan-1-one 12

To a cooled (−10 °C) suspension of CuCl (10 mol %) in 10 mL of dried THF 2-benzyloxy-5-methylphenylmagnesium bromide (1.0 equiv), freshly prepared from the corresponding bromide and magnesium (activated with iodine) was added. At the same temperature, a solution of 1.0 g (3.5 mmol) of ester **11a** in THF (15 mL) was then added and allowed to return to room temperature with continuous stirring overnight. The reaction mixture was quenched with 50 mL of 10% NH_4Cl; the organic phase was separated and the aqueous phase was extracted with ether (2 × 30 mL) and dried (Na_2SO_4). The extract was then evaporated and the residue subjected on silica gel (PE/$CHCl_3$, 5:2). From first fraction was isolated starting ester **11a** (0.60 g, yield 60%), the second gives compound of formula **12** (0.49 g, yield 26%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.76 (d, J = 7.7 Hz, 2H, CHCH_2), 4.91 (s, 2H, PhCH_2O), 5.05 (s, 2H, PhCH_2O), 5.13 (t, J = 7.7 Hz, 1H, CHCH$_2$), 6.68–6.72 (m, 1H, aromH), 6.83–6.94 (m, 3H, aromH), 7.08–7.40 (m, 17H, aromH).

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.07.003.

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