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Graphical Abstract

DDQ Mediated Stereoselective Intermolecular Benzylic C–N Bond Formation: Synthesis of (-)-Cytoxazone, (-)-4-*epi*-Cytoxazone and their Analogues and Immunological Evaluation of their Cytokine Modulating Activity

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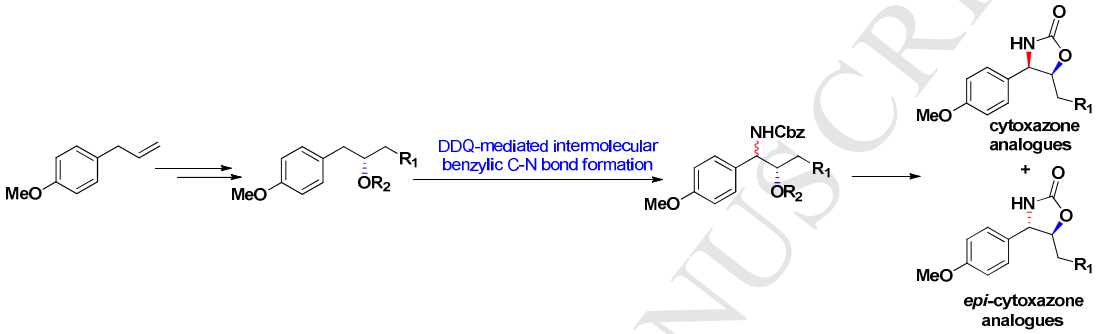

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ABSTRACT

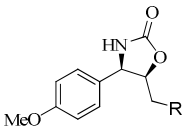
A short and efficient strategy for the synthesis of (-)-cytoxazone, (-)-4-*epi*-cyoxazone and their analogues by using DDQ mediated diastereoselective intermolecular benzylic amination has been described. Immunological evaluation of their cytokine modulating activity revealed that the change of hydroxy methyl to methyl group increased the cellular immunity in *in-vitro* cultures. Changes in the stereochemistry of oxazolidine haven't influenced the biological activity.

1. Introduction

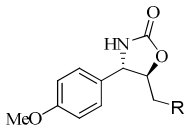
Direct conversion of sp^3 C–H bonds into C–N bonds is an important strategy for the synthesis of different nitrogen containing compounds.[1,2] In general the C–N bond is constructed by interconversion of various functional groups.[3,4] Direct amidation on unfunctionalized substrates is an important strategy to get C–N bond, which makes the synthetic sequence, shorter, simpler and also economical.[5] In this context, we have recently developed the DDQ-mediated activation of benzylic/allylic sp^3 C–H bond and its coupling with amide to get C–N bond intramolecularly and applied this strategy for the synthesis of pyrrolidine alkaloids.[6] The high stereoselective in the above intramolecular reaction is due to the neighboring group participation of the adjacent acetate group followed by cyclization with nitrogen nucleophile (Scheme 1).

As a part of the ongoing programme for immune therapeutics here in, we present the application of this strategy for the intermolecular C–N bond formation[5] and for the synthesis of (-)-cytoxazone **1** and their analogues (**2**-**8**) (Figure 1). The cytokine modulating activities of the above synthesised compounds are also evaluated.

Y.V.lu *et al*.,[5] has studied the intermolecular DDQ-mediated amidation of benzylic systems on different substrates, but so far these are no reports on the stereoselective aspects of this intermolecular reaction. Herein, we are presenting the study on the stereoselectivity of this reaction on chiral homo bezylic alcohols to give chiral 1,2-amino alcohols.[7]



cytoxazone **1,** R= OH
deoxy cytoxazone **3,** R= H
cytoxazone derivative **5,** R= CH_3
cytoxazone derivative **7**, R=$C_{14}H_{29}$



epi-cytoxazone **2,** R= OH
epi-ceoxy cytoxazone **4,** R= H
epi-cytoxazone derivative **6**, R= CH_3
epi-cytoxazone derivative **8**,R=$C_{14}H_{29}$

Figure 1: Cytoxazone and their analogues

(-)-Cytoxazone **1** which contains 4,5-disubstituted- 2-oxazolidinone moiety was isolated from *Streptomyces sp*.[8] It is a novel cytokine-modulator and interferes with cytokine IL4, IL10 and IgG production *via* the selective inhibition of the signaling

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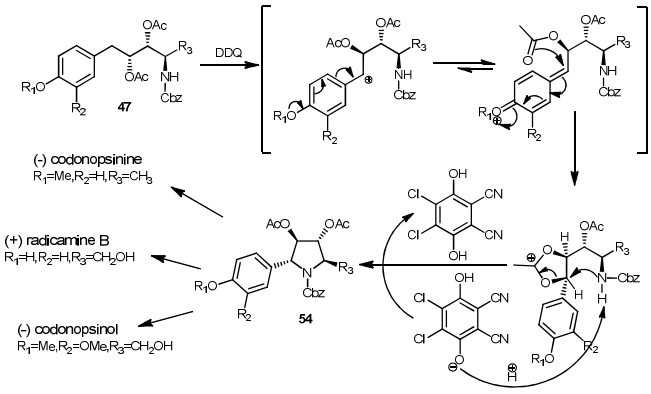
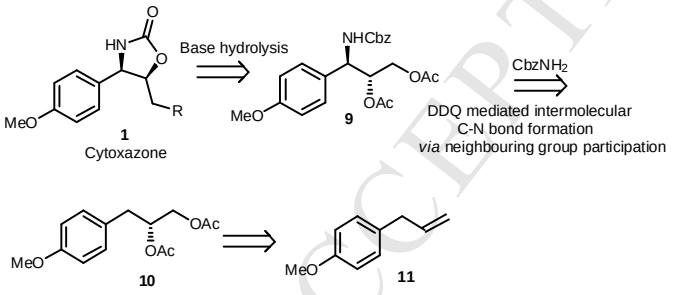
pathway in Th2 cells. Inhibitors of Th2-dependent cytokine production could lead to potent chemotherapeutic agents in the field of immunotherapy and immune response to allergens.[9] Due to its potent bioactivity and structural features, several methods for synthesizing (-)-cytoxazone **1** and its *trans*-diastereomer (4-*epi*-cytoxazone) have been accomplished.[9] More over the synthetic precursors of (-)-cytoxazone **1** and (-)-4-*epi*-cytoxazone **2** are 1,2-aminoalcohols, which are also part structures of many biologically active compounds and have been the subject of interest to many synthetic organic chemists over the years.[7]



The retrosynthetic analysis was envisaged based on our earlier strategy as shown in scheme 2.[6] (-)-Cytoxazone **1** and their derivatives can be obtained from key amino alcohol intermediate **9**. The synthesis of key compound **9** was envisaged from compound **10** using DDQ mediated intermolecular C–N bond formation at benzylic position. Compound **10** can be prepared by using literature procedure from **11** (Scheme 2).[9d]



Scheme 2: Retrosynthetic pathway

2. Results and discussion

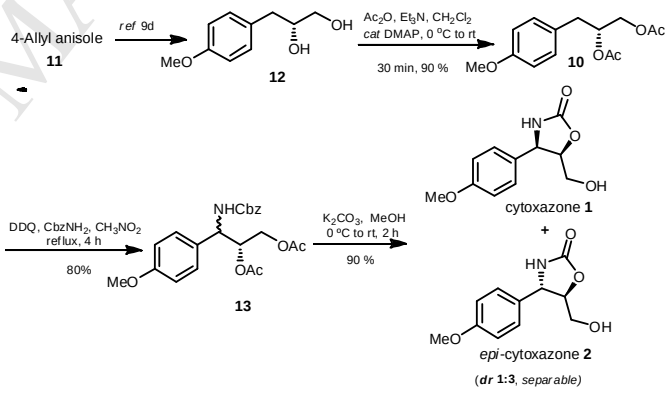
For the synthesis of (-)-cytoxazone **1**, treatment of diol compound **12** (obtained from 4-methoxy allylbenzene **11**)[9d] with Ac_2O and Et_3N in DCM gave diacetate compound **10** in 92% yield. The next step is to study the stereoselective installation of the amino group at the benzylic position of diacetate compound **10**, to get compound **13.** The reaction was carried out under different conditions as shown in the table 1.

Table 1: Optimization of reaction conditions[a]

Entry	Oxidant	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	DDQ	$CHCl_3$	refux	12 h	40
2	DDQ	CH_2Cl_2	reflux	12 h	35
3	DDQ	$ClCH_2CH_2Cl$	reflux	12 h	60
4	DDQ	THF	reflux	12 h	35
5	DDQ	Dioxane	reflux	6 h	30
6	DDQ	CH_3CN	reflux	12 h	no reaction[c]
7	DDQ	CH_3NO_2	rt	12 h	10
8	**DDQ**	**CH_3NO_2**	**85**	**4 h**	**85**

[a]**10** (1.0 mmol), DDQ (1.1 mmol) and indicated solvent temperature and time. [b] Isolated yield. [c] based on TLC analysis.

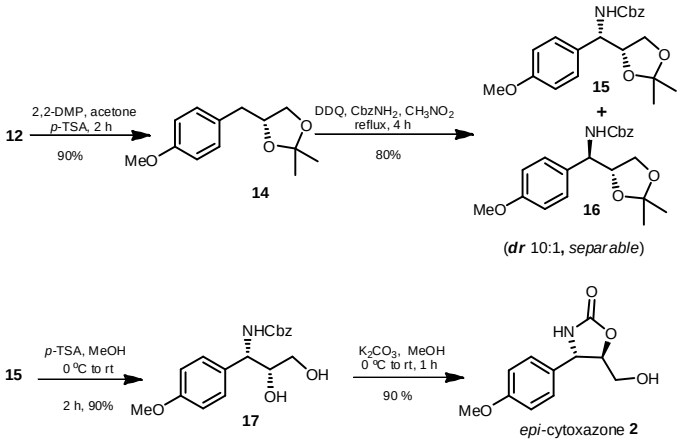
Finally when the compound **10** was treated with benzyl carbamate and DDQ in CH_3NO_2 at 85℃ for 4 h, the conditions developed by Y.V.lu *et al.*,[5] gave inseparable diastereomeric mixtures of compound **13** in 85% yield. Surprisingly the reaction could not yield the product in acetonitrile which is a better choice for intramolecular reaction. When the compound **13** was treated with K_2CO_3 in MeOH afforded cytoxazone **1**[9k] and *epi*-cytoxazone **2**[9e] in 90% yield (*dr* 1:3) (Scheme 3). Their spectral and physical data were in good agreement with the reported values.[9e,k]



Scheme 3: Synthesis of (-)-cytoxazone **1** and (-) 4-*epi*-cytoxazone **2**

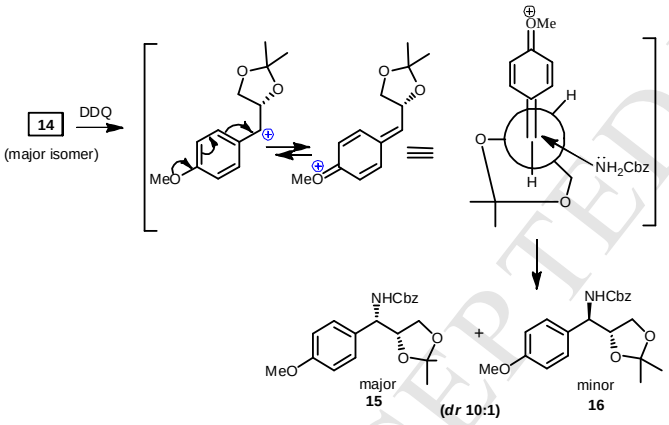
Formation of (-)-4-*epi*-cytoxazone **2** as a major product, indicated that the nucleophile attack has taken place before neighbouring group participation unlike in intramolecular version. In order, to see the stereochemical outcome in the absence of acetate group, the diol compound **12** was protected with 2,2-DMP and $BF_3.OEt_2$ to give the acetonide **14**. Stereoselective installation of the amino group at the benzylic position of the compound **14** was carried by treating with $CbzNH_2$ and DDQ in CH_3NO_2 at 85℃ for 4 h to afford separable diastereomeric mixtures of compounds **15** and **16** in 85% yield (*dr* 10:1). Deprotection of major compound **15** with *p*-TSA gave

the amino diol **17**. Treatment of amino diol **17** with K_2CO_3 in MeOH furnished the *epi*-cytoxazone **2** (Scheme 4).



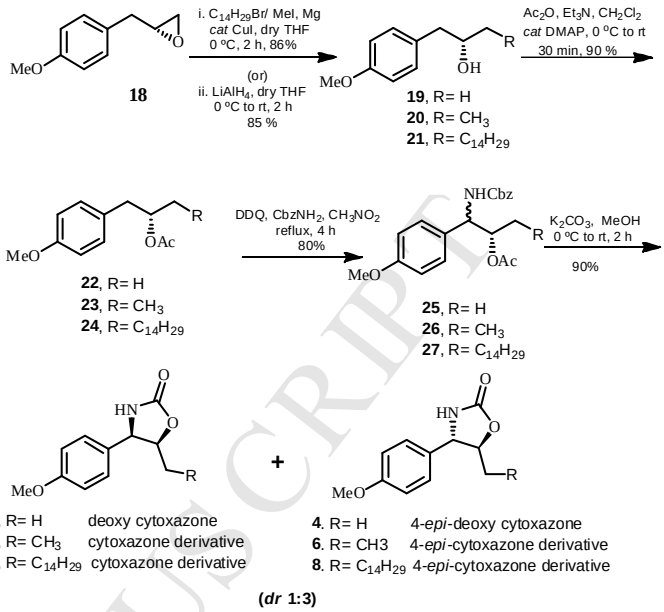
Scheme 4. Synthesis of (-)-4-*epi*-cytoxazone **2**

The high stereoselectivity in this reaction can be explained by intermolecular *N*-nucleophilic attack on the sp^2 carbon of the stabilised benzylic carbocation formed during the oxidation of **14** leading to diastereomeric compounds **15** and **16** (*dr* 10:1), Here the incoming $CbzNH_2$ nucleophile approached from the opposite face of the acetonide group to give major isomer *i.e* from the less hindered side as shown in Felkin-Anh model (Scheme 5).



Scheme 5: A plausible reaction pathway

For the synthesis of other derivatives of cytoxazone the following strategy was adopted. Regioselective epoxide opening of compound **18** obtained from 4-allylanisole **11** using reported procedure,[9d] with $LiAlH_4$ afforded compound **19** in 85% yield. Whereas with alkyl magnesium halides (MeI and $C_{14}H_{29}Br$) in dry Et_2O or dry THF gave compounds **20** and **21**. Protection of the hydroxyl groups in **19, 20** & **21** with Ac_2O and Et_3N in DCM afforded the mono acetate derivatives **22**, **23** & **24** in 92% yield respectively. Stereoselective installation of the amino group at the benzylic position of the acetate compounds **22, 23** & **24** was carried by treating with benzyl carbamate and DDQ in CH_3NO_2 at 85℃ for 4 h to give compounds **25, 26** & **27** in 85% yield respectively. The compound **25, 26** & **27** was treated with K_2CO_3 in MeOH to afford the oxazolidinone derivatives **3, 5** & **7** and **4**, **6** & **8** respectively (*dr* 1:3) (Scheme 6).



Scheme 6: Synthesis of Oxazolidinone derivatives

3. Cytoxazone modulate activity

All the synthesized compounds (**3**-**8**) were subjected to biological evaluation to see the influence of stereochemistry and chain length on the cellular response. Standard protocols related to animal use which was approved by the Institutional Animal Ethics Committee (IAEC) of the Council of Scientific & Industrial Research-Indian Institute of Chemical Technology (CSIR-IICT) (IICT/BIO/TOX/PG/26/08/2013/11). Male BALB/c mice weighing 25-28g, 7-8 weeks old were obtained from Centre for Cellular & Molecular Biology (CCMB), Hyderabad, India and maintained under standard laboratory conditions (temperature 22±2℃, relative humidity 50±15%, 12:12 light:dark cycle). All animals were given free access to water and food *ad libitum*. Animals were sacrificed under light ether anesthesia. The lymphocytes from spleen were isolated aseptically in RPMI 1640 medium. Briefly, single cell suspensions were prepared by homogenisation of spleen between the ends of frosted slides and homogenized cells were passed through 100 µM cell strainer. Cells were centrifuged at 2000 rpm for 10 min at 4℃. RBC was lysed with RBC lysis buffer (0.5 M ammonium chloride, 10 mM potassium bicarbonate and 0.1 mM disodium ethylene diamine tetraacetic acid, pH 7.2) for 5 min at 4℃ or 90 seconds at room temperature. Lymphocytes obtained were then washed twice with PBS and cell density was counted by the trypan blue dye exclusion method. Finally spleen cell suspension (10^5 cell/well)

was prepared in complete medium (RPMI 1640 media supplemented with 0.05 mM 2-mercaptoethanol, 100 IU/ml penicillin, 100 µg/ml streptomycin, and 10 % FBS) and seeded into a 96 well plates containing cytoxazone and its analogues and incubated with or without LPS and Con-A for 48 h at 37℃. The plates were centrifuged at 2000 rpm; 5 min at 4 ℃ and supernatant was collected for the estimation of cytokines. The cytoxazone and its analogues were dissolved in DMSO only. Cell control indicates vehicle control.

(a) Estimation of cytokines by ELISA[10]

Cytokines, such as IL-2, IL-4, IL-10 & IFN-γ levels in the cell supernatant were determined by sandwich ELISA (Enzyme-linked immunosorbent assay) kits according to the manufacturer's instructions (Biolegend, San Diego, USA) using ELISA plate reader (Tecan-infinite pro200).

(b) Splenocyte proliferation assay[11]

Spleen cell suspension (10^5 cell/well) was prepared in complete medium (RPMI 1640 media supplemented with 0.05 mM 2-mercaptoethanol, 100 IU/ml penicillin, 100 µg/ml streptomycin, and 10 % FBS) and seeded into a 96 well plates containing cytoxazone and its analogues and incubated for 48 h at 37℃. After 48 h of incubation, 20 µl of MTT (5 mg/ml in PBS) solution was added to each well and incubated for 4 h. The plates were centrifuged at 2000 rpm for 5 min and the supernatant was removed. To each well, 100 µl of DMSO solution was added and kept for 15 min aside and the absorbance was taken at 630 nm in TECAN multimode reader.

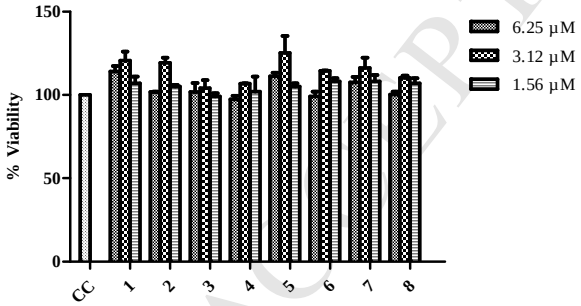
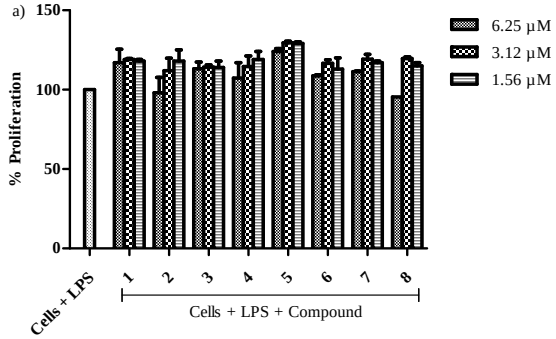


Figure 1: Effect of cytoxazone derivatives on splenocytes viability. The splenocytes were cultured with or without cytoxazone derivatives for 48 h and % viability of the cells were assessed by MTT assay. Results were represented in the mean±SD.



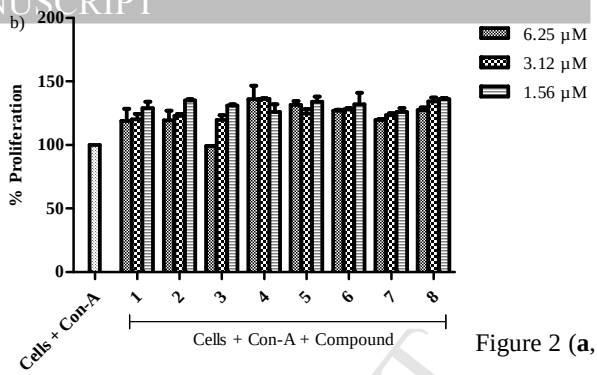
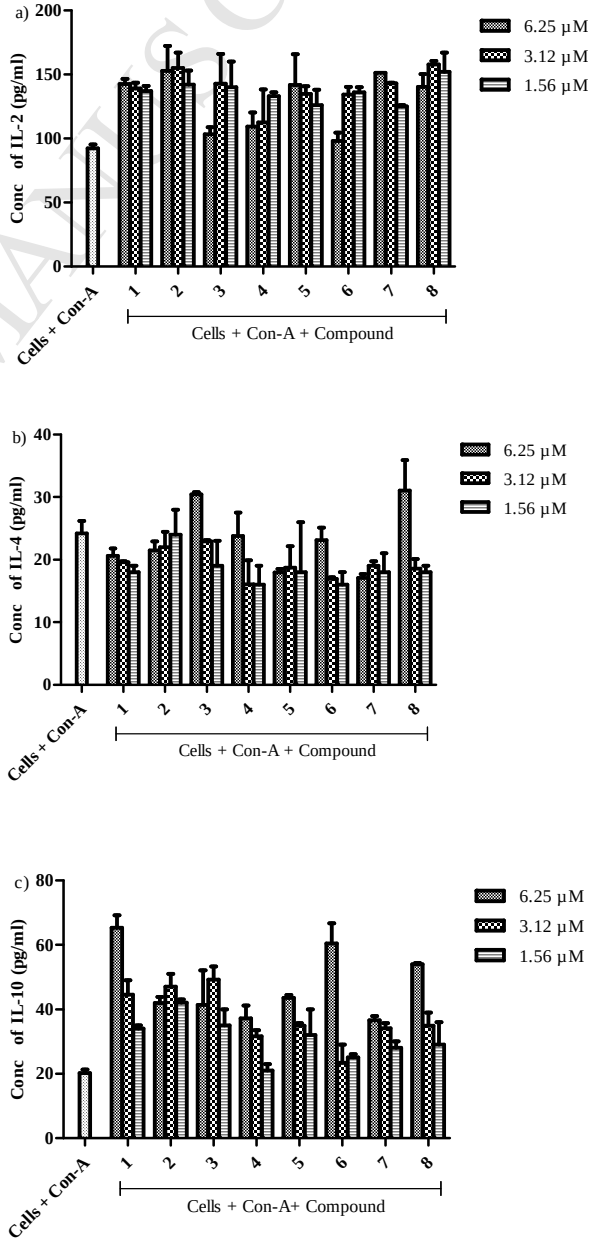


Figure 2 (**a**, **b**): Effect of compounds on LPS & Con-A induced splenocyte proliferation. Splenocytes were cultured in presence of LPS (10 µg/ml) and Con-A (2 µg/ml) with or without cytoxazone derivatives for 48 h. Splenocyte proliferation was assessed by MTT assay and results were represented in the mean±SD.



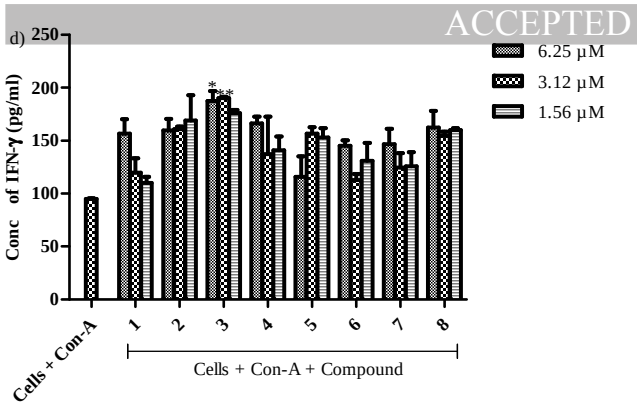


Figure 3 (**a**, **b**, **c** & **d**): Cytokine production from Con-A activated mouse splenocytes. Mouse splenocytes were stimulated with Con-A (2 µg/ml) and simultaneously treated with cytoxazone derivatives for 48 h. Production of cytokines (IL-2, IL-4, IL-10 & IFN-γ) in the culture supernatant was estimated by ELISA. Values were represented in the mean±SD.

The data were analyzed with the Prism software (GraphPad, San Diego, CA, USA). Data were expressed as mean±SD and statistical analysis was carried out using one-way ANOVA (Bonferroni correction multiple comparison tests). Error bars represent standard deviations (SD). **P*>0.05, ** *P*>0.01 verses cytoxazone.

Discussion

Compounds **1**–**6** were shown significant toxicity at 50 µg/ml on spleen cells (Refer supplementary material) indicates the potency of the compounds, whereas at 6.25 µg/ml and lower doses were shown 100% viability (Figure 1). The further studies were carried with the nontoxic doses. Compounds were treated with spleen cells with or without LPS and Con-A to confirm T and B cell mediation. All compounds exhibited a significant proliferation of T and B cells as compared to cell control (Figure 2). Effect of compounds on splenocyte proliferation in the presence of LPS and Con-A, revealed that the derivatives are activating T cells (Con-A-induced splenocytes). Increased concentration of IL-2 in cell culture supernatant treated with compounds indicated T- helper cells activity (Th0)[12] (Figure 3a), increased IFN-γ levels (Figure 3d) indicated that all compounds are biased towards Th1 cells activation and suppression of IL-4 levels indicted that Th2 inhibitory activity (Figure 3b). Even though all the derivatives induced higher levels of IL-10 (Figure 3c) indicating enhanced anti-inflammatory activity compared to cells with Con-A treated control, the overall activity was not very significant when compared to *epi*-cytoxazone and cytoxazone. Moreover, studies by Percy H. Carter *et al*., have shown that their analogues with less Th1 cytokines inhibitory response at 30 µM but whereas our analogues were shown potent Th1 cytokine (IFN-γ) increasing activity even at lower concentrations (6.25, 3.12 and 1.56 µg/ml).[8c] Furthermore, compound **3** (deoxy cytoxazone) strongly increased the Th1 response-mediated cytokine IFN-γ and decreased Th2 response-mediated cytokines IL-4 and IL-10 expression at 6.5 µg/mL on Con-A activated splenocytes (Figure 3). Whereas other analogues are showing more or less same activity as cytoxazone, which represents the modification of stereochemistry and lipid chain variability is not affecting biological activity. All the results obtained in these studies are correlating to the observation by Hideaki Kakeya *et al*., in which they found inhibition of Th2 type cytokines (IL-4, IL-10 but not GM-CSF) by cytoxazone.[8c] The present study reveals that the compound **3** induced better cellular immunity, indicating the possible application of these new chemical entities as promising compounds for the treatment of cellular immunity related diseases.

4. Conclusion

In conclusion, we have developed a common strategy for the diastereoselective synthesis of (-)-cytoxazone **1** and their derivatives by using DDQ-mediated intermolecular C-N bond formation. Cytokine modulate activity of the synthesised compounds has been established. The biological study revealed that the compound **3** induced better cellular immunity. The above strategy also helps in making the oxazolidinone derivatives in larger quantities for further evaluation of their activity. Application of this strategy for the synthesis of molecules containing 1, 2-amino alcohols, which includes some aryl/alkyl/amino hydroxy acids is in progress. Further, this study will help in designing superior active compounds.

5. Experimental section

All solvents were dried according to standard literature procedures. The reactions were performed in oven-dried round-bottom flasks, the flasks were fitted with rubber septa, and the reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvents. Crude products were purified by column chromatography on silica gel of 60−120 or 100−200 mesh. Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to a methanolic acidic solution of *p*-anisaldehyde, followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 35−40 °C. IR spectra were recorded on an FT-IR

spectrometer.[1]H spectra were recorded in $CDCl_3$ solvent on 300, 400, 500 MHz NMR spectrometers and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on 75, 100, 125 MHz NMR spectrometers. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer by electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) technique. Optical rotations were measured in digital polarimeter.

*5.1. (R)-3-(4-Methoxyphenyl)propane-1,2-diyl diacetate **(10)***:

To an ice cooled, stirred solution of **12** (1.5 g, 8.2 mmol) in dry DCM (10 mL), were added Et_3N (3.44 mL, 24.7 mmol), Ac_2O (1.33 mL, 18.1 mmol) and DMAP (5 mg), the reaction was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with DCM (30 mL) and the organic layer was washed with saturated *aq*.NH_4Cl solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (ethyl acetate/hexane 1:8) to afford acetate derivative **10** (2.0 g, 90%) as an oil. $[\alpha]_D^{25}$ = -22.3 (*c* 1.2, $CHCl_3$); IR (neat): 2955, 2838, 1734, 1612, 1512, 1369, 1217, 1178, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.22 (m, 1H), 4.22 (dd, J = 2.9, 11.9 Hz, 1H), 4.01 (dd, J = 5.9, 11.9 Hz, 1H), 3.79 (s, 3H), 2.90-2.79 (m, 2H), 2.07 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.2, 158.3, 130.1, 128.0, 113.8, 72.1, 64.0, 55.0, 35.9, 20.8, 20.6; ESIMS (*m/z)*: 289 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{14}H_{18}O_5Na$ 289.1046 Found 289.1045.

*5.2.(R)-3-(Benzyloxycarbonylamino)-3-(4-methoxyphenyl) propane-1,2-diyl diacetate **(13)***:

To a stirred solution of diacetate compound **10** (1.8 g, 6.7 mmol) in CH_3NO_2 (0.6 mL) was added DDQ (1.68 g, 7.4 mmol). The resulting mixture was heated at 85 ^oC for 4 h under nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to rt and quenched with Et_3N, concentrated under reduced pressure to give crude residue, which was purified by column chromatography (ethyl acetate/hexane 1:7) to give amido compound **13** (2.24 g, 80%) as mixture of diastereomers and as a colourless oil. IR (neat): 3335, 2932, 2840, 1719, 1610, 1512, 1455, 1370, 1218, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 7.20 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.42-5.30 (m, 2H), 5.14-4.95 (m, 3H), 4.21 (dd, J = 3.9, 11.8 Hz, 1H), 3.98 (m, 1H), 3.80 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.4, 170.3, 170.1, 159.36, 159.31, 155.7, 155.5, 136.1, 136.0, 130.9, 130.3, 128.5, 128.3, 128.1, 127.7, 114.3, 114.0, 73.1, 67.0, 62.8, 55.2, 20.7, 20.6; ESIMS (*m/z)*: 438 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{22}H_{25}O_7NNa$ 438.1523 Found 438.1517.

*5.3. (4R,5R)-5-(Hydroxymethyl)-4-(4-methoxyphenyl) oxazolidin-2-one {(-)-cytoxazone **1**} and (4S,5R)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one {(-)-4-epi-cytoxazone **2**}*:

To a stirred solution of acetyl derivative **13** (1.0 g, 2.4 mmol) in dry MeOH (10 mL) was added K_2CO_3 (0.83 g, 6.0 mmol) under nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was filtered through a celite pad and washed with ethyl acetate. Then MeOH was evaporated under reduced pressure. The residue was extracted with $CHCl_3$ (3X15 mL), dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (ethyl acetate/hexane 1:3) to give **1**[9k] (0.12 g) and **2**[9e] (0.36 g) with 90% yield (*dr* = 1:3) as solids.

Data of compound **1**: mp 117-120 °C, $[\alpha]_D^{25}$ = -70.5 (*c* 0.8, MeOH) {lit.[11p] mp 118-120 °C, $[\alpha]_D^{25}$ = -69.7 (*c* 0.5, MeOH)}; IR (neat): 3317, 2943, 2831, 1659, 1449, 1416, 1219, 1113, 1029 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.15 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 4.90 (d, J = 8.2 Hz, 1H), 4.81 (t, J = 5.1 Hz, 1H), 4.69 (m, 1H), 3.75 (s, 3H), 2.99-2.94 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 160.2, 159.1, 129.8, 128.6, 114.2, 81.0, 62.1, 57.4, 55.1; ESIMS (*m/z)*: 224 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{11}H_{14}O_4N$ 224.0917 found 224.0915.

Data of compound **2**: mp 110-115 °C, $[\alpha]_D^{25}$ = -23.6 (*c* 0.8, MeOH); {lit.[11b] mp 110-112 °C, $[\alpha]_D^{28}$ = -22.8 (*c* 0.5, MeOH)} IR (neat): 3291, 2932, 2838, 1733, 1611, 1512, 1391, 1245, 1177, 1029 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6): δ 7.34 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 4.79 (d, J = 6.4 Hz, 1H), 4.38 (m, 1H), 4.26 (dt, J = 4.1, 6.4 Hz, 1H), 3.84 (m, 1H), 3.81 (s, 3H), 3.71 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6): δ 160.0, 158.3, 133.3, 127.7, 114.4, 84.9, 61.8, 57.0, 54.9; ESIMS (*m/z)*: 246 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{11}H_{13}O_4NNa$ 246.0736 Found 246.0735.

*5.4. (R)-4-(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxolane **(14)***:

To a stirred solution of diol **12** (1.5 g, 8.24 mmol) in acetone (10 mL) were added 2,2-dimethoxy propane (0.65 mL, 82.4 mmol) and *cat*. *p*-TSA. The reaction mixture was stirred for 3 h at room temperature and neutralized with Et_3N (1 mL) at 0 °C. The volatiles were removed on a rotary evaporator and the residue was purified by column chromatography (ethyl acetate/hexane 1:8) to give the pure compound **14** (1.64 g, 90%) as a colourless oil. $[\alpha]_D^{25}$ = +38.9 (*c* 1.0, $CHCl_3$); IR (neat): 2985, 2934, 1612, 1511, 1459, 1371, 1243, 1178, 1154, 1057, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.28 (m, 1H), 3.95 (dd, *J* = 5.9, 8.0 Hz, 1H) 3.78 (s, 3H), 3.62 (dd, *J* = 7.0, 8.0 Hz, 1H), 2.95 (dd, *J* = 5.9, 13.7 Hz, 1H) 2.71 (dd, *J* = 7.0, 13.7 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 130.0, 129.5, 113.8, 109.0, 76.8, 68.8, 55.1, 39.1, 26.9, 25.6; ESIMS (*m/z)*: 245 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{13}H_{18}O_3Na$ 245.1148 found 245.1138.

*5.5.Benzyl(S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(4-methoxyphenyl) methylcarbamate **(15)***:

To a stirred solution of acetonoid compound **14** (1.5 g, 6.7 mmol) in CH_3NO_2 (0.6 mL) was added DDQ (1.68 g, 7.4 mmol). The resulting mixture was heated at 85 ^oC for 4 h under nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to rt and quenched with Et_3N, concentrated under reduced pressure to give crude residue, which was purified by column chromatography (ethyl acetate/hexane 1:7) to give amido compounds **15** (1.8 g) and **16** (0.18 g) in 80% yield (*dr* = 10:1) as syrups. $[\alpha]_D^{25}$ = +38.6 (*c* 0.8, $CHCl_3$); IR (neat): 3331, 2984, 2924, 1703, 1611, 1510, 1456, 1373, 1239, 1178, 1065, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.52 (d, *J* = 7.7 Hz, 1H) 5.13-5.02 (m, 2H), 4.68 (m, 1H), 4.33 (m, 1H), 3.96 (t, *J* = 7.0 Hz, 1H), 3.78 (s, 3H), 3.77-3.71 (m, 1H), 1.46 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 156.0, 136.2, 132.1, 128.6, 128.4, 128.09, 128.02, 113.9, 109.8, 78.1, 66.8, 55.6, 55.1, 26.4, 25.0; ESIMS (*m/z)*: 394 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{21}H_{25}O_5NNa$ 394.1624 found 394.1623.

*5.6. Benzyl (R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(4-methoxyphenyl)methylcarbamate **(16)***:

$[\alpha]_D^{25}$ = +15.3 (*c* 0.9, $CHCl_3$); IR (neat): 3331, 2984, 2924, 1703, 1611, 1510, 1456, 1373, 1239, 1178, 1065, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.06 (m, 7H), 6.89-6.78 (m, 2H), 6.70 (m, 1H), 4.94 (d, *J* = 11.2 Hz, 1H), 4.82-4.65 (m, 2H), 3.98 (m, 1H), 3.84-3.77 (m, 2H), 3.81 (s, 3H), 3.60 (dd, *J* = 2.5, 12.5 Hz, 1H), 1.78-1.60 (bs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 152.6, 135.9, 131.9, 128.0, 127.4, 114.1, 95.2, 82.9, 66.5, 60.5, 55.2, 26.4, 25.6; ESIMS (*m/z)*: 372 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{21}H_{26}O_5N$ 372.1805 found 372.1807.

*5.7. Benzyl (1S,2R)-2,3-dihydroxy-1-(4-methoxyphenyl)propyl carbamate **(17)***:

To a solution of major compound **15** (0.45 g, 1.21 mmol) in methanol (10 mL) was added *p*-toluenesulphonic acid (0.016 g, 0.08 mmol) and the mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated and purified through column chromatography (ethyl acetate/hexane 1:5) to give **17** (0.34 g, 85%) as a colourless oil. $[\alpha]_D^{25}$ = +20.6 (*c* 1.0, $CHCl_3$); IR (neat): 3392, 3367, 2922, 2852, 1698, 1611, 1511, 1459, 1293, 1244, 1178, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.65 (m, 1H), 5.12-5.02 (m, 2H), 4.77 (m, 1H), 3.89 (m, 1H), 3.78 (s, 3H), 3.55 (dd, *J* = 4.7, 11.2 Hz, 1H), 3.49 (dd, *J* = 6.5, 11.2 Hz, 1H), 3.06-2.67 (m, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 156.9, 136.0, 131.4, 128.4, 128.1, 127.8, 114.1, 74.9, 67.1, 63.6, 55.2; ESIMS (*m/z)*: 354 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{18}H_{21}O_5NNa$ 354.1311 found 354.1317.

*5.8. (R)-1-(4-Methoxyphenyl)propan-2-ol **(19)***:

To a well stirred suspension of $LiAlH_4$ (930 mg, 26.57 mmol) in dry THF (15 mL), a solution of epoxide **18** (2.0 g, 12.1 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at this temperature for 30 min and quenched with *aq*. 20% solution of sodium hydroxide (2 mL) at 0 ^oC. The reaction mixture was concentrated and purified through column chromatography (ethyl acetate/hexane 1:8) to give compound **19** (1.7 g, 85%) as a colourless oil. $[\alpha]_D^{25}$ = -8.8 (*c* 1.0, $CHCl_3$); IR (neat): 3406, 2923, 1627, 1429, 1384, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.98 (m, 1H), 3.80 (s, 3H), 2.74 (dd, *J* = 13.7 Hz, 4.7Hz, 1H), 2.62 (dd, *J* = 13.7 Hz, 8.0 Hz, 1H), 1.58 (bs, 1H), 1.24 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 130.4,

130.2, 113.9, 68.9, 55.2, 44.8, 22.6; ESIMS (*m/z*): 167 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{10}H_{14}O_2$ 167.1067 Found 167.1080.

*5.9. (S)-1-(4-Methoxyphenyl)butan-2-ol **(20)***:

To a pre cooled (-20° C) solution of epoxide **18** (1.0 g, 6.0 mmol) and CuCN (0.5 mg) in dry THF (10 mL) was added dropwise methyl magnesium bromide (1.5 mL, 12.1 mmol, 3 M solution) in diethyl ether for approximately 1 h under nitrogen atmosphere. After stirring for 4 h, the reaction mixture was quenched with saturated NH_4Cl at 0 °C. The residue was extracted with ethyl acetate (3X50 mL), dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (ethyl acetate/hexane 1:9) to give **20** (0.9 g, 85%) as a colorless oil; $[\alpha]_D^{25}$ = -12.5 (*c* 1.4, $CHCl_3$); IR (neat): 3446, 2963, 2929, 2838, 1708, 1611, 1511, 1461, 1378, 1298, 1246, 1177, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.70 (m, 1H), 2.78 (dd, *J* = 13.7 Hz, 4.4 Hz, 1H), 2.58 (dd, *J* = 13.7 Hz, 8.3 Hz, 1H), 1.60-1.46 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.1, 130.5, 130.3, 113.9, 74.0, 55.2, 42.5, 29.4, 10.0; ESIMS (*m/z*): 181 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{11}H_{15}O_2$ 181.04921 Found 181.04925.

*5.10. (S)-1-(4-Methoxyphenyl)heptadecan-2-ol **(21)***:

To the solution of tetradecyl magnesium bromide prepared from Mg (0.3 g, 12.1 mmol) and tetradecyl bromide (2.7 mL, 9.1 mmol) in THF (20 mL), was added CuCN (5 mg) at -20 °C, stirred for 30 min and added chiral epoxide **18** (1.0 g, 6.0 mmol) in dry THF (10 mL) dropwise at -20 °C under nitrogen atmosphere. After stirring for 2 h, the reaction mixture was quenched with saturated NH_4Cl at 0 °C. The residue was extracted with ethyl acetate (3X50 mL), dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (ethyl acetate/hexane 1:9) to give **21** (1.87 g, 85%) as a colorless oil; $[\alpha]_D^{25}$ = -11.4 (*c* 1.0, $CHCl_3$); IR (neat): 3415, 2919, 2849, 1615, 1517, 1467, 1350, 1302, 1255, 1178, 1104, 1076, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.76 (m, 1H), 2.78 (dd, *J* = 13.7 Hz, 4.1 Hz, 2H), 2.57 (dd, *J* = 13.7 Hz, 8.3 Hz, 2H), 1.55-1.53 (m, 2H), 1.37-1.21 (m, 26H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.1, 130.5, 130.2, 113.8, 72.6, 55.1, 43.0, 36.7, 31.8, 29.6, 2 X 29.3, 25.7, 22.6, 14.0; ESIMS (*m/z*): 380 $[M+Na]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{24}H_{46}O_2N$ 380.3517 Found 380.3518.

5.11. (*R)-1-(4-Methoxyphenyl)propan-2-yl acetate **(22)***:

To an ice cooled, stirred solution of **19** (1.0 g, 6.0 mmol) in dry DCM (10 mL), were added Et_3N (1.67 mL, 12.0 mmol), Ac_2O (0.68 mL, 7.2 mmol) and DMAP (5 mg), the reaction was allowed to stir at room temperature for 3h. The reaction mixture was diluted with DCM (20 mL) and the organic layer was washed with saturated *aq*.NH_4Cl solution, water, brine and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated and purified through column chromatography (ethyl acetate/hexane 1:8) to give acetate derivative **22** (1.1 g, 90%) as a syrup. $[\alpha]_D^{25}$ = -16.6 (*c* 1.0, $CHCl_3$); IR (neat): 2934, 2836, 1727, 1612, 1512, 1460, 1372, 1241, 1178, 1133, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.06 (m, 1H), 3.79 (s, 3H), 2.86 (dd, *J* = 13.7 Hz, 6.7Hz, 1H), 2.69 (dd, *J* = 13.7 Hz, 6.5 Hz, 1H), 2.0 (s, 3H), 1.20 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 158.1, 130.2, 129.5, 113.6, 71.5, 55.1, 41.2, 21.2, 19.2; ESIMS (*m/z*): 231 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{12}H_{16}O_3Na$ 231.0987 Found 231.0986.

5.12. (*S)-1-(4-Methoxyphenyl)butan-2-yl acetate **(23)***:

Experimental procedure is similar to compound **22** preparation to give compound **23** as a syrup (1.1 g , 90%); $[\alpha]_D^{25}$ = -14.6 (*c* 1.0, $CHCl_3$); IR (neat): 2934, 2836, 1727, 1612, 1512, 1460, 1372, 1241, 1178, 1133, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.96 (m, 1H), 3.79 (s, 3H), 2.69-2.85 (m, 2H), 2.0 (s, 3H), 1.46-1.63 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 158.1, 130.3, 129.6, 113.6, 76.1, 55.1, 39.1, 26.2, 21.1, 9.6; ESIMS (*m/z*): 245 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{13}H_{18}O_3Na$ 245.1076 Found 245.1142.

*5.13. (S)-1-(4-Methoxyphenyl)heptadecan-2-yl acetate **(24)***:

Experimental procedure is similar to preparation of the compound **22** to give compound **24** (0.6 g , 90%) as a syrup; $[\alpha]_D^{25}$ = -10.6 (*c* 1.3, $CHCl_3$); IR (neat): 2918, 2848, 1735, 1610, 1512, 1467, 1369, 1296, 1243, 1118, 1083, 1027 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.01 (m, 1H), 3.78 (s, 3H), 2.79 (dd, *J* = 6.8, 13.8 Hz, 1H), 2.74 (dd, *J* = 6.1,13.8 Hz, 1H), 1.99 (s, 3H), 1.48-1.54 (m,

2H), 1.21-1.33 (m, 26H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 158.1, 130.2, 129.6, 113.6, 74.9, 55.0, 39.6, 33.4, 31.8, 29.65, 29.62, 29.59, 29.51, 29.47, 29.41, 29.36, 25.3, 22.6, 21.1, 14.0; ESIMS (*m/z)*: 427 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{26}H_{44}O_3Na$ 427.3182 Found 427.3159.

*5.14. (S)-1-(Benzyloxycarbonylamino)-1-(4-methoxyphenyl) propan-2-yl acetate **(25)***:

To a stirred solution of acetate compound **22** (0.8 g, 3.8 mmol) in CH_3NO_2 (0.6 mL) was added DDQ (0.96 g, 4.2 mmol). The resulting mixture was heated at 85 ^oC for 4 h under nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to rt and quenched with Et_3N, concentrated under reduced pressure to give crude residue, which was purified by column chromatography (ethyl acetate/hexane 1:8) to give amido compounds **25 (**1.0 g, 80%) as a mixture of diastereomers and as a syrup. IR (neat): 2927, 1719, 1611, 1513, 1453, 1373, 1335, 1298, 1243, 1219, 1180, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.38 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.41 (m, 1H), 5.02-5.20 (m, 3H), 4.73 (m,1H), 3.79 (s, 3H), 1.96 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H) (3:1 ratio and values for major isomer has been given); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.4, 159.0, 156.7, 155.9, 136.2, 136.17, 136.14, 131.5, 128.5, 128.4, 128.19, 128.14, 128.1, 127.7, 114.0, 113.8, 72.5, 72.3, 66.99, 66.90, 58.7, 55.2, 21.1, 20.9, 17.7; ESIMS (*m/z)*: 380 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{20}H_{23}O_5NNa$ 380.1466 Found 380.1465.

*5.15. (S)-1-(Benzyloxycarbonylamino)-1-(4-methoxyphenyl) butan-2-yl acetate **(26)***:

Experimental procedure is similar to preparation of the compound **25** to give compound **26** as mixture of diastereomers and as a syrup (0.8 g , 80%); IR (neat): 3338, 2967, 2935, 1719, 1612, 1512, 1457, 1373, 1293, 1220, 1180, 1147, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.38 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.41 (bs, 1H), 5.02-5.15 (m, 3H), 4.89 (m,1H), 3.79 (s, 3H), 1.96 (s, 3H), 1.53-1.58 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H) (values for major isomer has given); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 170.3, 159.0, 155.8, 136.3, 136.2, 131.6, 128.5, 128.1, 127.1, 114.0, 113.8, 76.7, 66.8, 57.0, 55.2, 24.6, 20.8, 9.7; ESIMS (*m/z)*: 394 $[M+Na]^+$; HRMS (esi) $[M+Na]^+$: Anal. Calcd for $C_{21}H_{25}O_5NNa$ 394.1618 Found 394.1620.

*5.16. (S)-1-(Benzyloxycarbonylamino)-1-(4-methoxyphenyl) heptadecan-2-yl acetate **(27)***:

Experimental procedure is similar to preparation of the compound **25** to give compound **27** (0.5 g , 80%) as mixture of diastereomers and as a syrup. IR (neat): 3337, 2922, 2852, 1724, 1612, 1512, 1463, 1372, 1239, 1179, 1031 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.25 (m, 5H), 7.22-7.14 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.43 (bs, 1H), 5.17-4.99 (m, 3H), 4.82 (m, 1H), 3.79 (s, 3H), 1.95 (s, 3H), 1.46 (m, 1H), 1.36-1.16 (m, 27H), 0.88 (t, *J* = 6.9 Hz, 3H) (values for major isomer has given); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.89, 170.82, 159.0, 155.8, 155.6, 136.3, 136.2, 131.6, 130.1, 128.4, 128.1, 127.7, 114.0, 113.8, 75.99, 75.92, 66.9, 66.8, 57.3, 57.1, 55.2, 31.9, 31.5, 30.6, 29.67, 29.64, 29.5, 29.4, 29.39, 29.34, 29.2, 25.4, 25.3, 22.6, 21.0, 20.8, 14.1; ESIMS (*m/z)*: 554 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{34}H_{52}O_5N$ 554.3829 Found 554.3831.

*5.17. (4R,5S)-4-(4-Methoxyphenyl)-5-methyloxazolidin-2-one **(3)** and (4S,5S)-4-(4-Methoxyphenyl)-5-methyloxazolidin-2-one **(4)***:

To a stirred solution of acetyl derivative **25** (0.6 g, 2.2 mmol) in dry MeOH (5 mL) was added K_2CO_3 (0.77 g, 5.6 mmol) under nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was filtered through a celite pad and washed with ethyl acetate. Then MeOH was evaporated under reduced pressure. The residue was extracted with $CHCl_3$ (3X15 mL), dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (ethyl acetate/hexane 1:3) to give **3** (0.08 g) and **4** (0.23 g) with 90% yield (*dr* = 1:3) as syrups.

Data of compound **3**: $[\alpha]_D^{25}$ = -85.5 (*c* 1.1, $CHCl_3$); IR (neat): 3289, 2926, 2851, 1746, 1611, 1513, 1460, 1383, 1249, 1219, 1178, 1080, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.14 (bs, 1H), 4.99 (m, 1H), 4.85 (d, *J* = 7.9 Hz, 1H), 3.82 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 159.9, 128.4, 128.0, 114.2, 76.1, 59.4, 55.3, 16.5; ESIMS (*m/z)*: 208 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{11}H_{14}O_3N$ 208.0964 Found 208.0963.

Data of compound **4**: $[\alpha]_D^{25}$ = -45.5 (*c* 1.2, $CHCl_3$); IR (neat): 3289, 2926, 2851, 1746, 1611, 1513, 1460, 1383, 1249, 1219, 1178, 1080, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.51 (bs, 1H), 4.39-4.43 (m, 2H), 3.82 (s, 3H), 1.48 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 158.8, 130.3, 127.5, 114.4, 81.8, 63.6, 55.3, 19.0; ESIMS (*m/z*): 208 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{11}H_{14}O_3N$ 208.0964 Found 208.0964.

5.18. (4R,5S)-5-Ethyl-4-(4-methoxyphenyl)oxazolidin-2-one ***(5)*** *and (4S,5S)-5-ethyl-4-(4-methoxyphenyl)oxazolidin-2-one* ***(6)***:

Experimental procedure is similar to compound **3** and **4** preparation to give **5** (0.08 g) and **6** (0.24 g) with 90% yield (*dr* = 1:3) as syrups.

Data of compound **5**: $[\alpha]_D^{25}$ = -57.5 (*c* 1.3, $CHCl_3$); IR (neat): 3288, 2964, 2925, 2852, 1748, 1612, 1513, 1461, 1383, 1248, 1219, 1177, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.14 (bs, 1H), 4.84 (d, *J* = 7.9 Hz, 1H), 4.72 (m, 1H), 3.82 (s, 3H), 1.20-1.37 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 128.6, 128.2, 114.1, 82.7, 59.1, 55.3, 24.3, 10.1; ESIMS (*m/z*): 222 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{12}H_{16}O_3N$ 222.1124 Found 222.1122.

Data of compound ***6***: $[\alpha]_D^{25}$ = -12.8 (*c* 1.0, $CHCl_3$); IR (neat): 3288, 2964, 2925, 2852, 1748, 1612, 1513, 1461, 1383, 1248, 1219, 1177, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.21 (bs, 1H), 4.45 (d, *J* = 7.0 Hz, 1H), 4.26 (m, 1H), 3.82 (s, 3H), 1.77-1.84 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 159.9, 128.6, 128.2, 114.5, 86.6, 61.4, 55.3, 26.9, 10.1; ESIMS (*m/z*): 222 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{12}H_{16}O_3N$ 222.1124 Found 222.1119.

5.19.(4R,5S)-4-(4-Methoxyphenyl)-5-pentadecyloxazolidin-2-one ***(7)*** *and (4S,5S)-4-(4-Methoxyphenyl)-5-pentadecyloxazolidin-2-one* ***(8)***:

Experimental procedure is similar to compounds **3** and **4** preparation to give **7** (0.06 g) and **8** (0.19 g) with 90% yield (*dr* = 1:3) as syrups.

Data of compound ***7***: $[\alpha]_D^{25}$ = -46.5. (*c* 1.2, $CHCl_3$); IR (neat): 2924, 2853, 1752, 1611, 1513, 1464, 1383, 1250, 1219, 1177, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.09 (bs, 1H), 4.82-4.76 (m, 2H), 3.82 (s, 3H), 1.40 (m, 1H), 1.31-1.13 (m, 26H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 159.3, 128.7, 128.3, 114.1, 81.4, 59.2, 55.3, 31.9, 30.9, 29.6, 29.5, 29.4, 29.1, 25.6, 22.6, 14.1; ESIMS (*m/z*): 404 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{25}H_{42}O_3N$ 404.3152 Found 404.3151.

Data of compound ***8***: $[\alpha]_D^{25}$ = -12.8 (*c* 0.8, $CHCl_3$); IR (neat): 2924, 2853, 1752, 1611, 1513, 1464, 1383, 1250, 1219, 1177, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.92(d, *J* = 8.6 Hz, 2H), 5.29 (bs, 1H), 4.44 (d, *J* = 7.1 Hz, 1H), 4.30 (m, 1H), 3.82 (s, 3H), 1.75 (m, 1H), 1.54-1.19 (m, 27H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 158.6, 131.0, 127.6, 114.5, 85.5, 77.2, 61.9, 55.3, 33.9, 31.9, 29.6, 29.5, 29.4, 29.37, 29.35, 29.2, 24.9, 22.6, 14.1; ESIMS (*m/z*): 404 $[M+H]^+$; HRMS (esi) $[M+H]^+$: Anal. Calcd for $C_{25}H_{42}O_3N$ 404.3152 Found 404.3151.

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