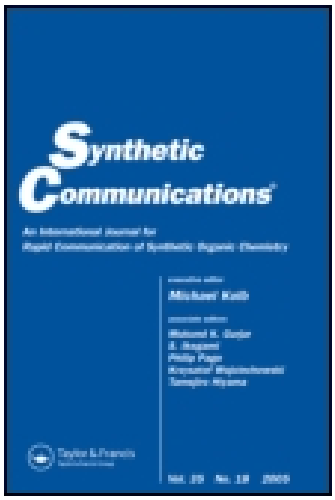

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Stereoselective Synthesis of (−)-Cytoxazone and (+)-5-Epi-cytoxazone[#]

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ABSTRACT

A novel, stereo selective synthesis of (−)-cytoxazone **1a** and stereoselective synthesis of (+)-5-epi-cytoxazone **1b** were achieved via stereoselective Grignard addition of vinylmagnesium bromide on *N*-Boc aldehyde obtained from *p*-hydroxy-D-phenylglycine **2** followed by cyclization of *N*-Boc alcohol **6**, ozonolysis and reduction to get (+)-5-epi-cytoxazone. Compound **6** underwent mitsunobu conditions, deprotection of ester followed by cyclization of *N*-Boc alcohol to get (−)-cytoxazone.

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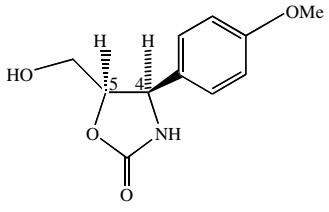
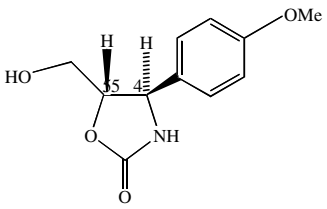
Enantiomerically pure substituted 2-oxazolidinones are important target molecules in organic synthesis. Some of them act as antibiotics against highly resistant gram positive bacteria.[1] In 1998 Osada et al., isolated[2] a novel cytokine modulator[3] from *streptomyces* species. This new 4,5-disubstituted oxazolidinone was named as (−)-cytoxazone **1a**. It interferes with cytokine IL4; IL10 and IgG production by selective inhibition of signaling pathway of Th2 cells, but not Th1 cells. Inhibition of Th2 dependent cytokine products would be potent chemotherapeutic agents in the field of immunotherapy.

Cytoxazone **1a** is different from known immunomodulators such as FK 506 and rapamycin in respect of structure and biological activity. Therefore **1a** and its analogues have been a new subject of synthetic studies for the development of a cytokine modulators. Due to its potent biological activity, several syntheses of **1a** [5b–e] and its isomers[5b–e] have been described in the literature. Very recently we reported a stereoselective synthesis[5e] of **1a** via stereoselective Grignard addition of *p*-methoxyphenylmagnesium bromide to *N*-benzylimine derived from (*S*)-2,3-*o*-isopropylidine glyceraldehyde followed by a single step conversion of *N*-Boc amine diol to oxazolidinone. Herein we report a short and stereoselective synthesis of (−)-cytoxazone **1a** and (+)-5-epi-cytoxazone **1b**, a C-5-epimer of cytoxazone.

The commercially available *p*-hydroxy-D-phenylglycine **2** was converted to *N*-Boc methyl ester **3**. Treatment of **3** with methyl iodide, potassium carbonate in DMF gave **4**.[7] The next step in the sequence is to convert the ester to aldehyde followed by stereoselective addition of vinylmagnesium bromide to get *syn N*-Boc amino alcohol based on the well established protocol.[6] Thus the ester **4** was reduced to alcohol **5** under $LiBH_4$ conditions.[7] Swern oxidation of **5** followed by in-situ reaction of the resulting aldehyde with vinylmagnesium bromide based on above said protocol[6] yielded the *syn* 1,2-amino alcohol **6**. Intramolecular cyclization[5e,8] of compound **6** in presence of NaH in THF yielded the



1a



1b

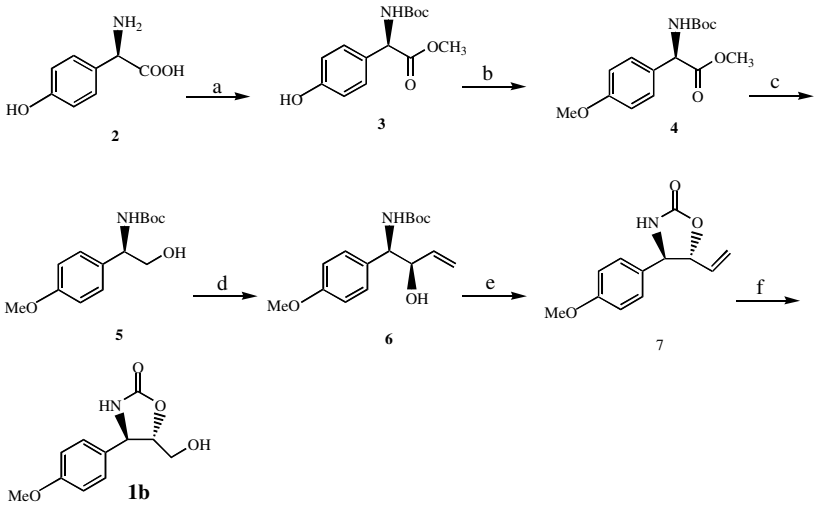
oxazolidinone **7**. Oxidative cleavage of the double bond with ozone followed by immediate reduction[5c] afford the (+)-5-epi-cytoxazone **1b** whose ^{1}H, ^{13}C NMR spectral data are in agreement with the assigned structure.

The synthesis of (−)-cytoxazone **1a** from **6** was achieved as follows: Oxidative cleavage of **6** followed by reduction gave diol **8**. Primary hydroxyl in **9** was protected as TBS ether. When compound **9** was subjected to mitsunobu condition gave **10** as *p*-nitrobenzoic ester with inverted configuration. Hydrolysis of ester and TBS ether in one pot yielded **11** whose NMR and rotational values are in agreement with the reported compound.[5e] Treatment of compound **11** with NaH in THF gave (−)-cytoxazone **1a** whose spectral data was in agreement with the reported compound.[5e]

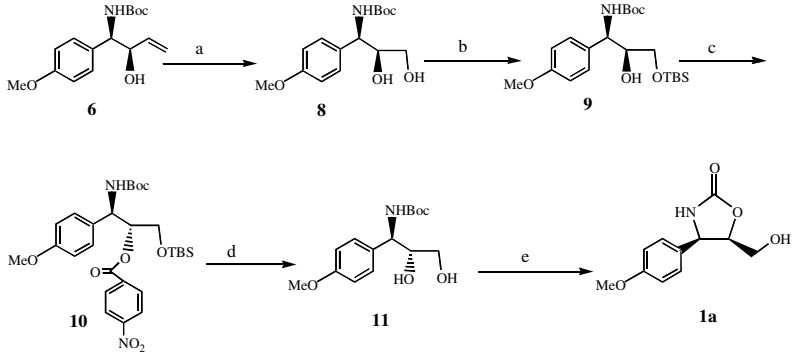
Some compounds contain oxazolidinone unit shows antibacterial activity against gram positive and gram negative bacteria. Keeping this criterion in view antibacterial testing was done for both compounds. Interestingly we observed that (+)-5-Epi-cytoxazone and (−)-cytoxazone shows some antibiotic activity against gram positive (G^{+ve}) *Bacillus subtili*s and gram negative (Gr^{-ve}) *Escherichia coli* by paper disc method.[4] The activity has been compared with standard streptomycin disc (10 Mcg). (+)-5-Epiicytoxazone shows somewhat more antibacterial activity compared to the (−)-cytoxazone against gram positive and gram negative bacteria.

S. no.	Samples	Diameter of inhibition zone	
		Basillus subtilis	*Escherichia coli*
1	(−)-Cytoxazone (100 Mcg)	12	14
2	(+)-5-Epiicytoxazone (100 Mcg)	16	20
3	Streptomycin (10 Mcg)	18	22

In conclusion we developed a short efficient and a common approach for the synthesis of 5-epi-cytoxazone **1b** and (−)-cytoxazone **1a** which involves stereoselective addition of vinylmagnesium bromide to *N*-Boc aldehyde followed by intramolecular cyclization of *N*-Boc *syn*-amino alcohol **6** to oxazolidinone **7**. Compound **6** was converted to **1a** by using mitsunobu conditions followed by deprotection and cyclization. In this approach the Boc protection was utilized to get required stereo-



Scheme 1. (a) AcCl/MeOH $(Boc)_2O$/TEA/THF, 98.2%; (b) CH_3I/K_2CO_3/DMF, 99%; (c) $LiCl/NaBH_4$/EtOH/THF, 83.9%; (d) $DMSO/(COCl)_2/CH_2CL_2$ then CH_2=CH-MgBr/THF, 60.2%; (e) NAH/THF, 97.3%; (f) O_3/CH_2Cl_2 then $NaBH_4$/MeOH, 76.1%.



Scheme 2. (a) O_3, CH_2Cl_2, $NaBH_4$, MeOH, −78°C to r.t.; 72.37%; (b) TBSCl, imidazole, CH_2Cl_2; 83%; (c) TPP, DIAD, PNBA, THF, 63.5%; (d) LiOH, THF–H_2O, TBAF, CH_2Cl_2; 88.79%; (e) NaH, THF, 94.2%.

selectivity during Grignard reaction and also it was converted to a part structure of the molecule. Our procedure is very useful to make more analogues of **1a** and **1b** for getting chemotherapeutic agents in the field of immunotherapy and antibacterial.

EXPERIMENTAL

TLC was performed on Merck Kieselgel 60, F_{254} plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer RX-1FT-IR system as KBr pellets. In the case of syrups and liquids IR spectra was recorded by adding a drop of solution of compound in chloroform on KBr pellet. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on Varian Gemini-200 MHz spectrometer. NMR (400 MHz) spectra were recorded on Varian Unity-400 MHz spectrometer. Optical rotations were measured with Jasco-Dip-360 digital polarimeter. The mass spectra were recorded on (VG MICROMASS-7070H) at 70 eV using a direct inlet system. The LSIMS (FAB) spectra were recorded on VG AUTOSPEC instrument at the structure (M + H) at m/z.

Methyl(2*R*)-2-(*tert*-butoxycarbonyl)amino-2-(4-hydroxyphenyl)acetate 3. Acetyl chloride (3.4 mL, 47.86 mmol) was added slowly to an ice-cold solution of *p*-hydroxy-D-phenylglycine **2** (4 g, 23.93 mmol) in methanol (30 mL). The mixture was slowly heated to reflux and refluxing continued for 3 h, the reaction mixture was cooled and the solvent removed in vacuo to give the crude methyl ester hydrochloride as a white solid, which was used as such for the next reaction, the methyl ester hydrochloride was suspended in THF (20 mL), to it Et_3N (8.4 mL, 60.26 mmol) was added at 0°C followed by a solution of $(Boc)_2O$ (5.4 mL, 23.50 mmol) drop wise over 10 min. The mixture was allowed to warm to room temperature and stirred for 8 h. The white solid was filtered off, solvent was removed in vacuum and the residue partitioned between ethyl acetate and water. The aqueous layer was again extracted with ethyl acetate and the combined organic phases washed with saturated NH_4Cl solution and brine. The organic layer was drying (Na_2SO_4) and removal of solvents in vacuo followed by column chromatography using 25% ethyl acetate and hexane afforded the pure compound **3** (6.6 g, 98.2%) as white solid. M.p.: 83–84°C; $[\alpha]_D^{25} = -11.54$ (c = 1.03, $CHCl_3$); IR: 3388, 1750, 1692, 1508, 1285, 1161 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.65 (s, 3H), 5.18 (d, 1H, J = 6.4 Hz), 5.52 (d, 1H, J = 6.4 Hz), 6.12 (br s, 1H), 6.7 (d, 2H, J = 9.0 Hz), 7.13 (d, 2H, J = 9.0 Hz).

Methyl(2*R*)-2-(*tert*-butoxycarbonyl)amino-2-(4-methoxyphenyl) acetate 4. To a solution of phenol **3** (6 g, 21.35 mmol) in DMF (15 mL) was added potassium carbonate (5.9 g, 42.70 mmol) and methyl iodide (1.4 mL, 22.47 mmol). The reaction was allowed to stir for 7 h at

room temperature. The reaction mixture was partitioned between water and ethyl acetate. Aqueous phase was further extracted with ethyl acetate and combined organic extracts were washed with brine. Drying (Na_2SO_4) and removal of solvent under reduced pressure followed by column chromatography using ethyl acetate:hexane (1:9) afforded the pure compound **4** (6.23 g, 99%) as a white solid. M.p.: 66–67°C; $[\alpha]_D^{25} = -95.3$ ($c = 1.2$, $CHCl_3$) (Lit.[7] $[\alpha]^{27}$D−97.4 (c 0.57, $CHCl_3$); IR: 3388, 1741, 1688, 1518, 1297, 1244, 1169 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ1.42 (s, 9H), 3.70 (s, 3H), 3.79 (s, 3H), 5.19 (br d, 1H, $J = 6.4$ Hz), 5.40 (br s,1H), 6.84 (d, 2H, $J = 9.0$ Hz), 7.24 (d, 2H, $J = 9.0$ Hz).

1,1-Dimethylethyl(*R*)-*N*-[2-hydroxy-1-(4-methoxyphenyl)-ethyl]carbamate 5. An ice-cooled solution of $NaBH_4$ (1.47 g, 38.98 mmol) and LiCl (1.65 g, 38.98 mmol) in EtOH (30 mL), stirred for 15 min, to it a solution of ester **4** (4.6 g, 15.59 mmol) in THF (35 mL) was added over 30 min. The reaction mixture was stirred at room temperature for 16 h, filtered and the filtrate treated with saturated NH_4Cl solution at 0°C, and extracted with ethylacetate. Combined organic extracts were washed with water, brine and dried (Na_2SO_4). Removal of the solvent under vacuum followed by column chromatography (ethyl acetate:hexane 1:2) gave the alcohol **5** (3.49 g, 83.9%) as a white solid. M.p.: 130–131°C (Lit.[7] m.p. 130–132°C); $[\alpha]_D^{25} = -43.59$ ($c = 1.09$, $CHCl_3$) (Lit.[7]$[\alpha]^{26}$D−38.1 (c 1.31, $CHCl_3$); IR: 3376, 1685, 1519, 1249, 1171, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.45 (br s, 1H), 3.75–3.85 (m, 2H), 3.82 (s, 3H), 4.78 (br s, 1H), 5.12 (br s, 1H), 6.86 (d, 2H, $J = 9.0$ Hz), 7.22 (d, 2H, $J = 9.0$ Hz); FABMS (m/z): 268 (M^++1).

1,1-Dimethylethyl(1*R*,2*R*)-*N*-[2-hydroxy-1-(4-methoxyphenyl)-3-butenyl]carbamate 6. To a stirred solution of oxalyl chloride (0.24 mL, 2.81 mmol) in CH_2Cl_2 (20 mL) at −78°C under nitrogen atmosphere was added DMSO (0.21 mL, 2.96 mmol) drop wise. After being stirred for 30 min at −78°C, a solution of alcohol **5** (0.5 g, 1.87 mmol) in CH_2Cl_2 (15 mL) was added over 10 min. Then the reaction mixture was stirred for 1 h at −78°C, allowed to warm to −35°C, and stirred for 1 h at this temperature followed by addition of *N*,*N*-diisopropylethyl amine (1.94 mL, 11.24 mmol) over 10 min. The reaction mixture was than warmed to 0°C in 10 min and transfer through a canula to a room temperature solution of vinylmagnesium bromide [prepared from Mg (0.59 g, 24.31 mmol) and vinylbromide (1.3 g, 12.15 mmol) in THF at 0°C] over 20 min. After being stirred for overnight, the mixture was treated with ethanol (3 mL) and saturated aq. NH_4Cl (8 mL). CH_2Cl_2 and aqueous HCl were then added and organic layer was washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure to give the crude pro-

duct. Chromatography of this material on silica gel with 20% ethyl acetate in hexane gave pure compound **6** (0.33 g, 60.2%) as a white solid. M.p.: 103–104°C; $[\alpha]_D^{25} = -13.74$ ($c = 1.035$, $CHCl_3$); IR: 3466, 3383, 1673, 1519, 1364, 1247, 1172, 1031 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$): δ 1.40 (s, 9H), 2.32 (br s, 1H), 3.80 (s, 3H), 4.30 (br s, 1H), 4.60 (br s, 1H), 5.15–5.30 (m, 2H), 5.35 (d, 1H, $J = 17.0$ Hz), 5.83 (m, 1H), 6.85 (d, 2H, $J = 9.0$ Hz), 7.2 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.03, 156.05, 137.34, 132.02, 127.98, 116.53, 114.04, 79.74, 75.78, 58.69, 55.25, 28.32.

(4*R*,5*R*)-5-(Ethenyl)-4-(4-methoxyphenyl)-2-oxazolidinone 7. To a solution of alcohol **6** (0.15 g, 0.512 mmol) in dry THF (5 mL) was added sodium hydride (0.024 g (60% w/w in wax), 0.614 mmol) at room temperature and the mixture stirred under nitrogen atmosphere for 2 h. The reaction mixture was concentrated, dichloromethane was added, washed with NH_4Cl (saturated), the organic layer separated, dried (Na_2SO_4), concentrated and purified through column chromatography using ethylacetate:hexane (6:4) to give the pure compound **7** (0.109 g, 97.3%) as a white solid. M.p.: 124–125°C; $[\alpha]_D^{25} = +23.09$ (c for 2 h at 0°C. Reaction mixture was quenched with saturated NH_4Cl solution and solvents were removed in vacuum. Crude compound was partitioned between CH_2Cl_2 and H_2O. Aqueous layer was washed with CH_2Cl_2. Combined organic layers were dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by column chromatography using ethyl acetate:hexane (6:4) afforded the pure compound **8** (0.22 g, 72.37%) as a white solid. M.p.: 108–109°C; $[\alpha]_D^{25} = -27.673$ (c = 0.17, $CHCl_3$) IR: 3376, 2925, 1688, 1511, 1367, 1247, 1169, 1035, 833 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.68 (br s, 1H), 2.84 (br s, 1H), 3.39–3.54 (m, 2H), 3.8 (s, 3H), 3.82 (m, 1H), 5.20 (br d, 1H), 6.84 (d, 2H), 7.21 (d, 2H); FABMS (m/z): $(M^+ + 1)$ 298.

3*R*-(*tert*-Butoxycarbonyl)-amino-3-(4-methoxyphenyl)-2S-propane-1-(*tert*-butyl dimethylsiloxy)-2-ol 9. To a stirred solution of compound **8** (0.2 g, 0.673 mmol) in dry CH_2Cl_2 were added imidazole (55 mg, 0.808 mmol) and TBSCl (0.102 g, 0.673 mmol). After being stirred for 2 h, CH_2Cl_2 was added to the reaction mixture, washed with water and saturated brine, dried over Na_2SO_4, and CH_2Cl_2 was concentrated in vacuo. The residue was purified by silicagel column chromatography (60–120 mesh) using hexane:EtOAc 22:3 to give compound **9** (0.229 g, 83%) as a colorless oil. $[\alpha]_D^{25} = -20.911$ ($c = 0.13$, $CHCl_3$) IR: 3422, 2926, 2855, 1696, 1511, 1366, 1249, 1170, 1115, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.92 (s, 9H), 1.38 (s, 9H), 2.42 (br s, 1H), 3.49 (dd, 1H), 3.62 (dd, 1H), 3.79 (br s, 4H), 4.56 (br, 1H), 5.36 (br d, 1H), 6.82 (d, 2H), 7.22 (d, 2H); FABMS (*m*/*z*): $(M^+ + 1)$ 412.

2*R*-Amino-1-(*tert*-butyldimethyl)-siloxymethyl-2-(4-methoxyphenyl)-(1*R*)-ethyl-3-nitrobenzoate 10. To a stirred solution of compound **9** (0.18 g, 0.438 mmol) in dry THF (10 mL) were added triphenyl phosphine (0.287 g, 1.094 mmol), *p*-nitro benzoic acid (0.183 g, 1.094 mmol) and diisopropyl aza dicarboxylate in 5 mL THF (0.22 mL, 1.094 mmol). Reaction mixture was allowed to stir at room temperature for 24 h, under nitrogen atmosphere. THF was removed under in vacuo and crude compound was added ethyl acetate and water. Organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified over silicagel column chromatography (60–120 mesh) using hexane:EtOAc 93:7 to give compound **10** as a yellow color syrup (0.16 g, 63.5%). $[\alpha]_D^{25} = 0.9$ ($c = 1$, $CHCl_3$) IR: 2933, 2360, 1723, 1610, 1529, 1348, 1273, 1171, 1104, 1035, 837, 780, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.92 (s, 9H), 1.41 (s, 9H), 3.80 (br s, 5H), 5.10–5.19 (m, 2H), 6.21 (br d, 1H), 6.84 (d, 2H), 7.24 (d, 2H), 8.18 (d, 2H), 8.24 (d, 2H).

(2*R*,3*R*)-3-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)-1,2-propanediol 11. To a compound **10** (0.093 g, 0.161 mmol) in THF (2.5 mL) and water (7.5 mL) was added LiOH (0.024 g, 0.565 mmol) at 0°C. Reaction mixture was allowed to stir at room temperature for 2 h after that THF was removed in vacuum, aqueous layer was added ethyl acetate. Aqueous layer was again washed with ethyl acetate and combined organic layer was extracted with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified over silicagel column chromatography (60–120 mesh) hexane:EtOAc 22:3 to give compound **11** as a colorless oil (0.061 g, 92%).

To an ice-cooled solution of the above hydroxy compound (0.053 g, 0.129 mmol) in dry THF (5 mL) was added 1M solution of TBAF (0.26 mL, 0.257 mmol) and stirred for 2 h at room temperature. Water was added to the reaction mixture and THF was removed under vacuum. Then aqueous layer was extracted with EtOAc and organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silicagel column chromatography (60–120 mesh) using hexane:EtOAc: 4:6 to give compound **11** as white solid (0.034 g, 88.79%). M.p.: 115–116°C (Lit.[5e] m.p. 118°C); $[\alpha]_D^{25} = -53.2$ ($c = 0.45$, $CHCl_3$) (Lit.[5e] $[\alpha]^{25}D - 51.2$ (c 1 $CHCl_3$); IR: 3333, 2976, 1688, 1511, 1247, 1169, 1035, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.32 (br s, 1H), 2.95 (br s, 1H), 3.60–3.72 (m, 2H), 3.72–3.80 (m, 1H), 3.82 (s, 3H), 4.58 (ddd, 1H), 5.02 (br s, 1H), 6.88 (d, 2H, $J = 8.8$ Hz), 7.26 (d, 2H, $J = 8.8$ Hz).

(4*R*,5*R*)-5-Hydroxymethyl-4-(4-methoxyphenyl)-2-oxazolidinone 1a. To a solution of compound **11** (0.028 g, 0.094 mmol) in dry THF

(5 mL) was added sodium hydride (0.0045 g, 0.188 mmol (60% w/w in wax) at room temperature and the mixture was stirred under a nitrogen atmosphere for 2 h. The reaction mixture was concentrated, CH_2Cl_2 was added, washed with NH_4Cl (saturated), brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the residue was purified over silicagel column chromatography (60–120 mesh) using hexane:EtOAc 7:3 to give compound **1a** (0.0198 g, 94.2%) as a white solid. M.p.: 119–121°C (Lit.[5e] m.p. 118–120°C); $[\alpha]_D^{25} = -70.46$ ($c = 0.4$, MeOH) (Lit.[5e] $[\alpha]^{25}$D−69.7 (c 0.5 in MeOH); IR: 3745, 3325, 2975, 1739, 1514, 1400, 1250, 1181, 1050 cm^{-1}; ^{1}H NMR (200 MHz, Acetone-d6): δ 3.12–3.38 (m, 2H), 3.83 (S, 3H), 3.86 (m, 1H), 4.84 (ddd, 1H, $J = 4.4$, 7.3, 8.1 Hz), 5.05 (d, 1H, $J = 8.1$), 6.94–6.99 (m, 3H), 7.26 (d, 3H); ^{13}C NMR (Acetone-d6, 75 MHz): δ 159.83, 158.61, 129.44, 128.15, 113.77, 80.59, 61.70, 57.05, 54.71. FABMS (m/z): ($M^+ + 1$) 224.

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REFERENCES

1. (a) Schierle-Arndt, K.; Kolter, D.; Danielmeier, K.; Steckhan, E. Eur. J. Org. Chem. **2001**, 2425 and references cited therein; (b) Glaeve, D.M.; Brickner, S.J. J. Org. Chem. **1996**, *61*, 6470 and references cited therein.
2. Kakeya, H.; Morishita, M.; Kobinata. K.; Osono, M.; Osada, H. J. Antibiot. **1998**, *51*, 1126.
3. Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. J. Org. Chem. **1999**, *64*, 1052.
4. Jones, R.N.; Barry, A.L. Gaven Th, Washington, J.A. *Manual of Clinical Microbial*; 1984; 972–977.
5. (a) Park, J.N.; Ko, S.Y.; Koh, H.Y. Tetrahedron Lett. **2000**, *41*, 5553; (b) Sakamoto, Y.; Shiraishi, A.; Seonhee, J.; Nakata, T. Tetrahedron Letters **1999**, *40*, 4203; (c) Miyata, O.; Asai, H.; Naito, T. Synlett **1999**, 1915; (d) Seki, M.; Mori, K. Eur. J. Org. Chem. **1999**, 2965; (e) Madhan, A.; Ravi Kumar, A.; Venkateswara Rao, B. Tetrahedron: Asymmetry **2001**, *12*, 2009–2011; (f) Zdenko Hamersak; Edina

Ljubovic; Mladen Mercep; Milan Mesic; Vitomer Sunjic. Synthesis **2001**, (13), 1989–1992; (g) Enders, D.; Kallfass, U.; Nolte, B. Synlett. **2002**, (1), 33–36.

6. (a) Denis, J.-N.; Correa, A.; Greene, A.E. J. Org. Chem. **1991**, *56*, 1639; (b) Veeresa, G.; Datta. Tetrahedron Lett. **1998**, *39*, 119.
7. Matsuura, F.; Hamada, Y.; Shioiri. Tetrahedron **1994**, *50*, 9457.
8. Kim, B.M.; Guare, J.P.; Hanifin, C.M.; Arford-Bickerstaff, D.J.; Vacca, J.P.; Ball, R.G. Tetrahedron Lett. **1994**, 153.

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