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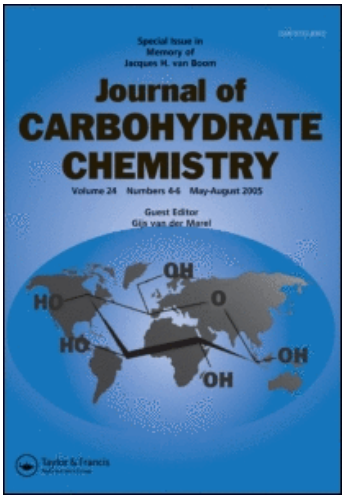


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# A Novel Stereoselective Total Synthesis of (+)-5-*epi*-Cytoxazone[#]

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## ABSTRACT

Stereoselective synthesis of a potent cytokine modulator cytoxazone isomer has been achieved from 2,3-*O*-isopropylidene D-glyceraldehyde involving Grignard reaction, subsequent formation of an azide followed by reduction to the aminodiol, and finally cyclization of the *N*-Boc diol.


*Key Words:* 2,3-*O*-Isopropylidene D-glyceraldehyde; Grignard reaction; (+)-5-*epi*-Cytoxazone.

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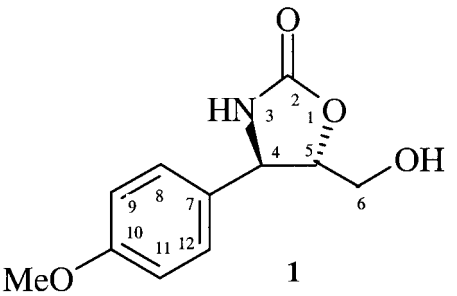
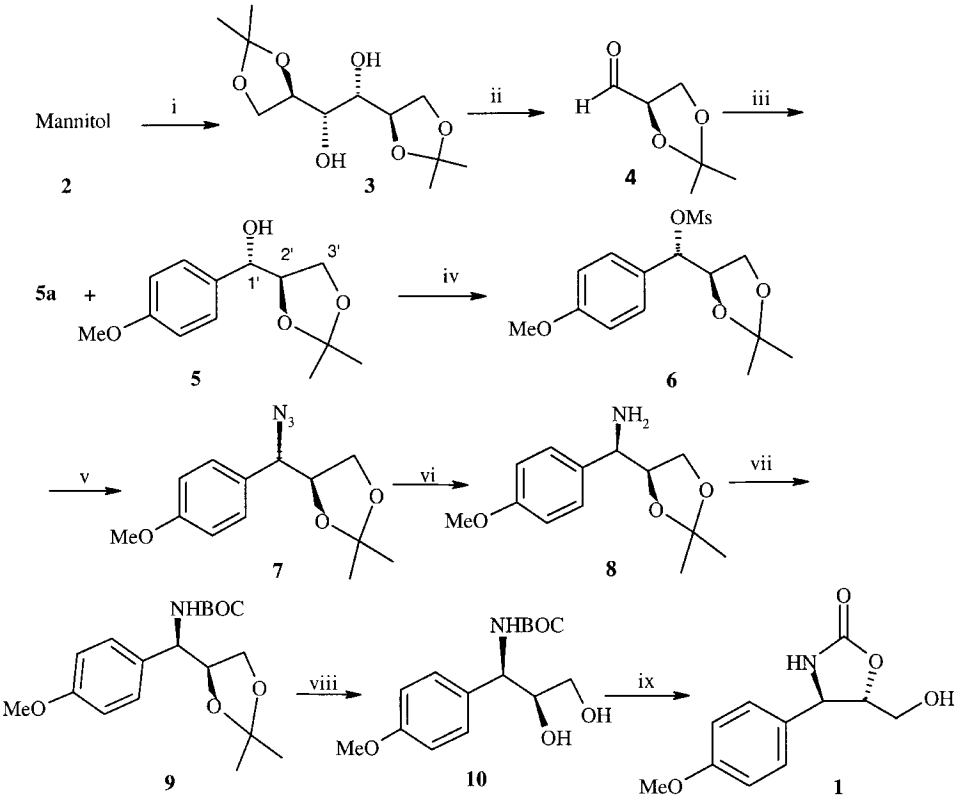
## INTRODUCTION

The synthesis of biologically active natural products from carbohydrate substrates is an important tool for rapid accesses to the desired constitution and stereochemistry. This certainly correlated with the discovery of highly chemo- and stereoselective methods of modern organic synthesis. The subject of total synthesis of biologically active natural products has been covered in several surveys.[1–3] Cytoxazone (**1**) containing a 4,5-disubstituted 2-oxazolidinone ring[4,5] was recently isolated from the fermentation broth of *Streptomyces* sp. in low yield[4] and its absolute configuration has been determined by x-ray crystallographic analysis and CD-spectroscopy.




**1**

Cytoxazone exhibits cytokine-modulating activity by inhibiting the signaling pathway of $TH_2$ cells.[6,7] Inhibitors of $TH_2$-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Therefore, the cytoxazone and its analogs have been a contemporary subject of synthetic studies for the development of new cytokine modulators. Several stereoselective syntheses have been reported during the last 2 years.[8–10] The first total asymmetric synthesis was reported by Nakata et al.[8] employing sharpless asymmetric dihydroxylation of a *p*-methoxycinnamic derivative, and later Sunjic et al.[9] obtained the compound from readily available glycidic ester derivative. Here, we describe the stereoselective synthesis of 5-*epi*-cytoxazone, Grignard reaction of (*R*)-2,3-*O*-isoproplideneglyceraldehyde (**4**) with *p*-methoxyphenyl magnesium bromide to give the corresponding alcohol (**5**) in 60% enantiomeric excess, and this compound was further elaborated to give (+)-5-*epi*-cytoxazone (Sch. 1).




***Scheme 1.*** Reagents and conditions: (i) acetone, $ZnCl_2$, r.t.; (ii) $NaIO_4$/DCM, aqueous $NaHCO_3$; (iii) *p*-methoxyphenyl magnesium bromide/dry THF; (iv) MsCl/$Et_3N$, DCM; (v) acetone, $NaN_3$, reflux; (vi) LAH/dry THF; (vii) $Boc_2O$/$Et_3N$, DCM; (viii) *p*-toluenesulfonic acid/MeOH, r.t.; (ix) NaH/DMF.

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## RESULTS AND DISCUSSION

Our approach for the synthesis of 5-*epi*-cytoxazone employs inexpensive and readily available starting material, mannitol diacetonide (**3**), which on chopping with $NaIO_4$ in dichloromethane at room temperature afforded (*R*)-2,3-*O*-isoproplidene glyceradehyde (**4**). This on reaction with *p*-methoxyphenyl magnesium bromide in dry THF gave a diastereomeric mixture of alcohols **5** (80%) and **5a** (20%). The diastereomers **5** and **5a** were separated by silica gel column chromatography. Compound **5** was converted to corresponding mesylate (**6**), which on further treatment with sodium azide in acetone gave azide (**7**) in excellent yield. Reduction of azide **7** with lithium aluminum hydride gave the amine (**8**), which was protected with di-*tert*-butyldicarbonate in dichloromethane in presence of triethylamine to give the *N*-Boc derivative **9** in 82% yield. Compound **9** was hydrolyzed in the presence of PTSA in MeOH to afford the Boc protected aminodiol (**10**) in 78% yield. In the final step, the *N*-Boc protective group was advantageously utilized for

the regioselective formation of the oxazolidinone ring using NaH in THF, which avoided the protection and deprotection of primary hydroxyl group.

## CONCLUSION

We have accomplished the stereoselective total synthesis of (+)-5-*epi*-cytoxazone (**1**) starting from easily available D-mannitol. This method is a valuable alternative route for the synthesis of this class of compounds.

## EXPERIMENTAL

**(2*R*,3*S*)-3-Hydroxy-1,2-*O*-isopropylidene-3-*p*-methoxyphenyl-1,2-propanediol (5).** To a solution of compound **3** (5 g, 21 mmol) in $CH_2Cl_2$ (15 mL) were added $NaIO_4$ (8.94 g, 42.01 mmol), saturated aqueous $NaHCO_3$ (0.5 mL), and stirred for 3 hr. After completion of the reaction, the reaction mixture was extracted into dichloromethane ($3 \times 15$ mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give (*R*)-2,3-*O*-isoproplidene glyceradehyde (**4**) in 81% yield (1.59 g, 19.91 mmol). This was immediately reacted with *p*-methoxyphenyl magnesium bromide (3.90 g, 18.57 mmol) in dry THF (20 mL) under nitrogen atmosphere for 3 hr at room temperature. After completion of the reaction, the reaction was quenched with saturated ammonium chloride solution (15 mL) and extracted with ethyl acetate ($3 \times 15$ mL). The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give a crude diastereomeric mixture of **5** (80%) and **5a** (20%). This diastereomeric mixture was separated by silica gel chromatography eluting with ethyl acetate : hexane (1 : 9) to give **5** (3.09 g, 14.43 mmol) in 80% yield. $[\alpha]_D^{25}$ 9.27 (*c* 1, $CHCl_3$), $^1$H NMR ($CDCl_3$, 200 MHz), $\delta$ 1.37 (s, 3H), 1.48 (s, 3H), 3.64 (dd, $J = 5.5$, 8.5 Hz, 1H, $H_a$-3$^1$), 3.74 (dd, $J = 5.5$, 8.5 Hz, 1H, $H_b$-3$^1$), 3.80 (s, 3H, OMe), 4.18 (dd, $J = 5.5$, 8.0 Hz, 1H, H-2$^1$), 4.48 (d, $J = 6$ Hz, 1H, H-1$^1$), 6.84 (d, $J = 7$ Hz, 2H, Ar), 7.3 (d, $J = 7$ Hz, 2H, Ar).

**(2*R*,3*S*)-1,2-*O*-Isopropylidene-3-*O*-mesyl-3-*p*-methoxyphenyl-1,2-propanediol (6).** To an ice-cooled solution of compound **5** (2.80 g, 13.08 mmol) in dry dichloromethane (15 mL) were added triethyl amine (5.46 mL, 39.25 mmol) and methanesulfonyl chloride (0.9 mL, 14.39 mmol) and stirred at room temperature for 3 hr. After completion of the reaction, water was added to the reaction, mixture and extraction done with dichloromethane ($3 \times 20$ mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give mesylate (**6**) (3.05 g) in 80% yield, which was used for the next reaction without further purification.

**(2*S*,3*R*)-3-Azido-1,2-*O*-isopropylidene-3-*p*-methoxyphenyl-1,2-propanediol (7).** To a solution of compound **6** (2.7 g, 9.24 mmol) in dry acetone (15 mL) was added sodium azide (0.66 g, 10.17 mmol) and refluxed for 3 hr. After completion of the reaction, acetone was removed under reduced pressure, water was added, and the contents extracted with EtOAc, dried over anhydrous $Na_2SO_4$, and concentrated to give a crude product, which was purified by silica gel column chromatography to afford the pure compound **7** (1.85 g, 7.03 mmol) in 84% yield. $^1$H NMR ($CDCl_3$, 200 MHz), $\delta$ 1.39 (s, 3H), 1.5 (s, 3H), 3.58 (dd, $J = 5.6$, 10.0 Hz, 1H, $H_a$-3$^1$), 3.68 (dd, $J = 5.6$, 10.0 Hz, 1H, $H_b$-3$^1$),

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3.8 (s, 3H, OMe), 3.92 (dd, $J = 5.6$, 8.5 Hz, 1H, H-$2^1$), 4.3 (d, $J = 6$ Hz, 1H, H-$1^1$), 6.88 (d, $J = 8$ Hz, 2H, Ar), 7.22 (d, $J = 8$ Hz, 2H, Ar).

**(2*S*,3*R*)-3-Amino-1,2-*O*-isopropylidene-3-*p*-methoxyphenyl-1,2-propanediol (8).** To an ice-cooled solution of compound **7** (1.50 g, 5.70 mmol) in dry THF (15 mL) was added LAH (0.211 g, 5.7 mmol) and stirred at room temperature. After 3 hr, the reaction was quenched with ethyl acetate, water was added, extraction done with ethyl acetate, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give the crude amino compound, which was purified by silica gel column chromatography eluting with ethyl acetate : hexane (6 : 4) to give title compound **8** (0.94 g 3.96 mmol) in 70% yield. $^1$H NMR ($CDCl_3$, 200 MHz), $\delta$ 1.38 (s, 3H), 1.43 (s, 3H), 3.59 (dd, $J = 6$, 8 Hz, 1H, $H_a$-$3^1$), 3.68 (dd, $J = 6$, 8 Hz, 1H, $H_b$-$3^1$), 3.8 (s, 3H, OMe), 3.84 (d, $J = 6$ Hz, 1H, H-$2^1$), 4.1 (dd, $J = 6$, 8 Hz, IH, H-$1^1$), 6.81 (d, $J = 7$ Hz, 2H, Ar), 7.24 (d, $J = 7$ Hz, 2H, Ar).

**(2*S*,3*R*-3-*tert*-Butoxycarbonylamino-1,2-*O*-isopropylidene-3-*p*-methoxyphenyl-1,2-propanediol (9).** To an ice-cooled solution of compound **8** (0.8 g, 3.37 mmol) in dry dichloromethane (15 mL) were added triethylamine (1.4 mL, 10.12 mmol) and di-*tert*-butyl dicarbonate (0.8 g, 3.71 mmol) under nitrogen atmosphere and stirred at room temperature. After 3 hr, water was added, extracted into dichloromethane (3 × 15 mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography eluting with ethyl acetate : hexane (2 : 8) to give the title compound **9** (0.93 g) in 82% yield. $[\alpha]_D^{25}$ − 7.76 (*c* 1, $CHCl_3$), $^1$H NMR ($CDCl_3$, 200 MHz), $\delta$ 1.31 (s, 3H), 1.39 (s, 9H),1.48 (s, 3H), 3.7 (dd, $J = 5$, 8 Hz, 1H, $H_a$-$3^1$),3.78 (s, 3H, OMe), 3.91 (dd, $J = 5$, 8 Hz, 1H, $H_b$-$3^1$), 4.28 (m, 1H, H-$2^1$), 5.17 (d, $J = 8$ Hz, 1H, H-$1^1$), 6.81 (d, $J = 8$ Hz, 2H, Ar), 7.21 (d, $J = 8$ Hz, 2H, Ar).

**(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-3-*p*-methoxyphenyl-1,2-propanediol (10).** To a solution of compound **9** (0.7 g, 2.07 mmol) in methanol (10 mL) was added *p*-TSA (0.39 g, 2.07 mmol) and stirred at room temperature for 2 hr. After completion of the reaction, the reaction mixture was neutralized with saturated $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give the crude product **10**, which was purified by silica gel column chromatography to give pure diol **10** (0.46 g) in 76% yield. M.p. 125–128°C, $[\alpha]_D^{25}$ 1.09 (*c* 1, $CHCl_3$), $^1$H NMR ($CDCl_3$, 200 MHz), $\delta$ 1.41 (s, 9H), 3.20 (d, $J = 7$ Hz, 2H, $H_a$-$3^1$, $H_b$-$3^1$), 3.61 (m, 1H, H-$2^1$), 3.77 (s, 3H, OMe), 3. 8.2–3.89 (m, 1H, H-$1^1$), 6.8 (d, $J = 8$ Hz, 2H, Ar), 7.24 (d, $J = 8$ Hz, 2H, Ar). FABMS (*m*/*z*): 320 $(M + Na)^+$.

**(4*R*,5*S*)-5-Hydroxymethyl-4-(4-methoxyphenyl)-2-oxazolidinone (1).** To a solution of compound **10** (0.1 g, 0.336 mmol) in dry THF (10 mL) was added sodium hydride (0.016 g, 0.67 mmol) at room temperature, and the mixture was stirred under $N_2$ atmosphere for 2 hr. After completion of the reaction, the solvent was removed, water was added, extracted with ethyl acetate, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give 5-*epi*-cytoxazone (**1**), which was purified by silica gel column chromatography using ethyl acetate : hexane (4 : 6) to give pure 5-*epi*-cytoxazone (**1**) (0.067 g) in 90% yield as a white solid. (+)-5-*epi*-cytoxazone, m.p. 155–158°C $[\alpha]_D^{25}$ 70.1°C (*c*, 1.32, MeOH), $^1$H NMR (DMSO, 200 MHz), $\delta$ 3.61 (dd, $J = 5$, 8 Hz, 1H, $H_a$-6), 3.75 (dd, $J = 5$, 8 Hz, 1H, $H_b$-6), 3.81 (s, 3H, OMe), 4.21 (m, 1H, H-5), 4.73 (d, $J = 7$ Hz, 1H, H-4), 6.89 (d, $J = 8$ Hz, 2H, Ar), 7.28 (d, $J = 8$ Hz, 2H,Ar), 7.65 (br d, $J = 8$ Hz, 1H, H-3). $^{13}$C NMR (DMSO, 50 MHz), $\delta$ 55.0, 57.0, 83.75,

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114.0, 128.0, 133.0, 158.0, 159.0. EIMS ($m/z$): 223 ($M^+$) [Literature[10] values for (+)-5-*epi*-cytoxazone: m.p. 143–144°C, $^1$H NMR (acetone-$d_6$), $\delta$ 3.15–3.26 (m, 3H), 3.80 (s, 3H), 4.82 (ddd, 1H),5.03 (d, 1H, $J = 8.0$ Hz), 6.94 (d, 2H, $J = 8.5$ Hz), 6.96 (br s, 1H), 7.24 (d, 2H, $J = 8.5$ Hz), $^{13}$C NMR (acetone-$d_6$), $\delta$ 54.9, 57.2, 61.9, 113.9, 128.3, 129.6, 158.8, 159.9].

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