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β-Cyclodextrin mediated sterioselective total synthesis of (+)-cytoxazone and (-)-5-*epi*-cytoxazone

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ABSTRACT

β-Cyclodextrin mediated stereoselective synthesis of a potent cytokine modulator cytoxazone has been achieved from 2,3-isopropylidene D-glyceraldehyde involving the Grignard reaction, reduction of azide to aminodiol and finally cyclization of N-*Boc* diol, synthesis of (+)-cytoxazone and (-)-5-*epi*-cytoxazone is described.

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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] Cytoxazone (1) containing a 4,5-disubstituted 2-oxazolidinone ring was isolated from the fermentation broth of Streptomyces sp. in low yield[2] and its absolute configuration has been determined by X-ray crystallographic analysis and CD-spectroscopy. As the importance of cytoxazone, synthesis of recemic mixture of this natural product has been reported in the literature,[3-5] however the sterio-selective synthesis is significant in natural product synthesis.[6-9] Our approach for the sterio-selective synthesis of (-)-cytoxazone and 5-*epi*-cytoxazone in the presence of β-cyclodextrin[10] 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 (85%), and 5a (15%) based on HPLC analysis. The diastereomeric mixture treated with PDC, DCM, Ac_2O converted to corresponding ketone (6). And reaction of 6 with sodium borohydride in presence of β-cyclodextrin gave exclusively (5a) 99% yield. The diastereomers 5 and 5a were also separated by silica gel column chromatography. Compound 5 was converted to corresponding mesylate (7), which on further treatment with sodium azide in acetone gave azide (8) in excellent yield 98%. Reduction of azide 8 with lithium aluminum hydride gave the amine (9) which was protected with di-*tert*-butyldicarbonate gave 1,2,5,6-Di-O-isopropylidene-α-D-mannitol (13), it was further treatment with sodium azide in presence of DMF in nitrogen atmosphere underwent cyclization and gave the title compound 1.

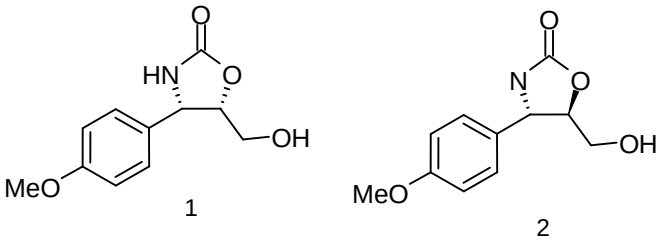
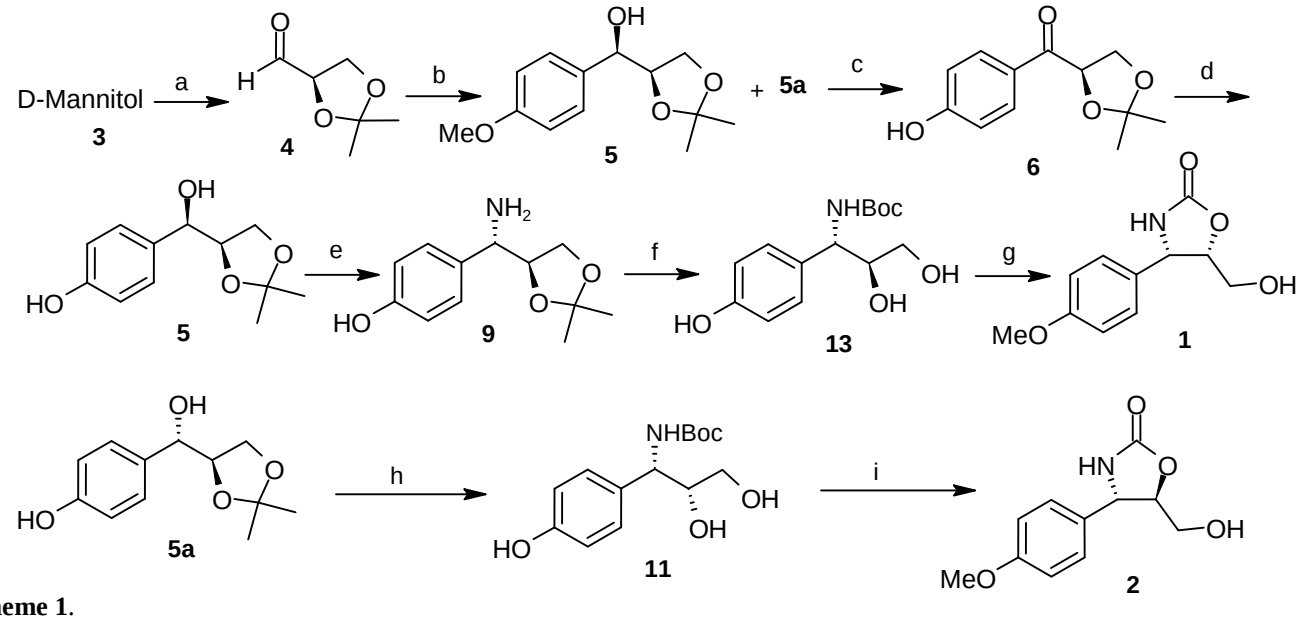


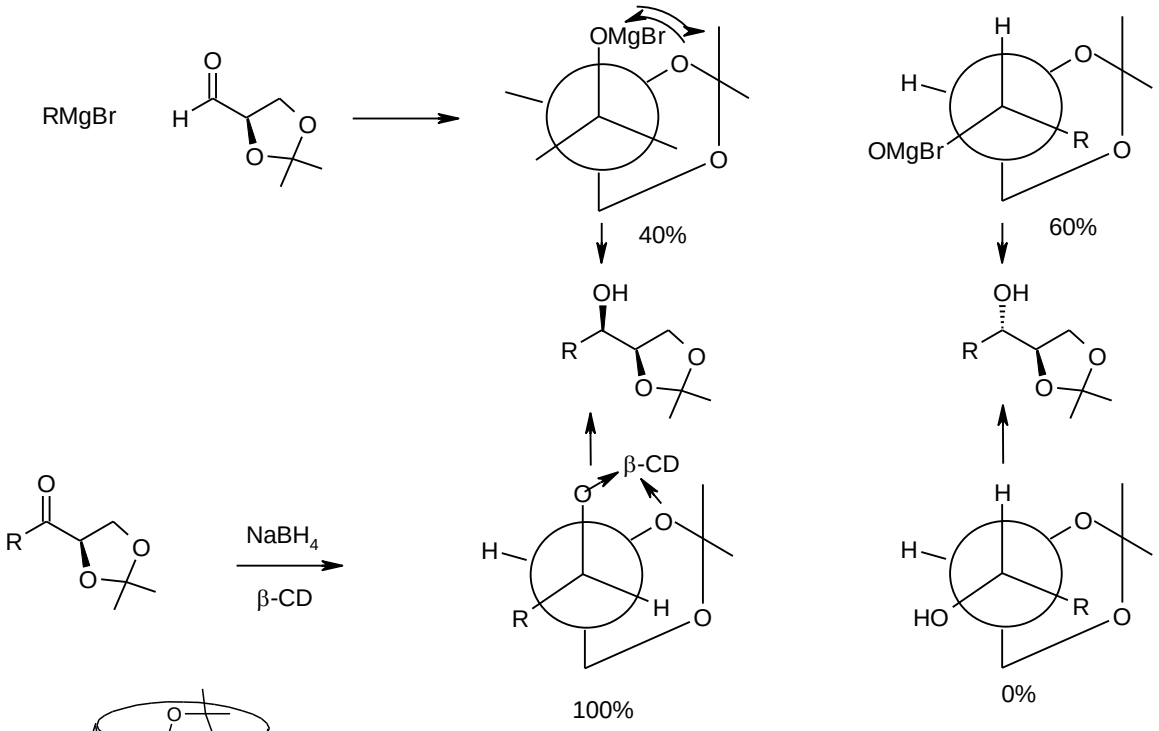
Figure 1.

To a solution of anhydrous $ZnCl_2$ (60 g) in dry acetone (300 mL) was added in one portion finely powdered D-mannitol (10 g). The mixture was stirred for 3 h at 20 °C. The stirring was continued further for 12 h at room temperature. The reaction mixture is then poured into a solution of potassium carbonate (70 g) in water (70 mL) which is extracted with diethyl ether (300 mL). The mixture is stirred for 0.5 h when the organic layer is filtered and washed under vacuum to remove zinc carbonate, and the combined filtrates evaporated

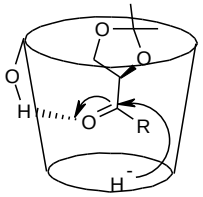


Scheme 1.

a) (i) Dri acetone, $ZnCl_2$, K_2CO_3. (ii) $NaIO_4$, $NaHCO_3$, DCM. (b) *p*-MeOPhMgBr, dri THF, rt. c) (i) PDC, DCM, Ac_2O. (d) $NaBH_4$, β-CD. 0.1 mol% e) (i) Mesylchloride, Et_3N, DCM, rt. (ii) NaN_3, dry acetone, reflux. (iii) LAH, DCM, rt. f) (i) Boc_2O, DCM, DMAP, rt (g) NaH, DMF h) Mesylchloride, Et_3N, DCM, rt (ii) NaN_3, dry acetone, reflux. (iii) Triphenyl phosphine (iv) Boc_2O, DCM, DMAP, rt (i) NaH, DMF



β-CD =



Scheme 2.

to dryness on a rotary evaporator. The dry residue is successively extracted with hexane (5 x 50 mL) and combined extracts slowly cooled and filter to give the product in 55% yield (7.9 g). m.p 119 ^{o}C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ, 1.37 (s, 6H), 1.40 (s, 6H), 2.49 (br d, 2H), 3.68-3.72 (m, 2H), 3.96-3.99 (m, 2H), 4.05-4.10 (m, 2H), 4.12-4.19 (m, 2H).

FABMS (M+ 1):263

(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) was added $NaIO_4$ (8.94 g, 42.01 mmol), saturated aqueous $NaHCO_3$ (0.5 mL) and stirred for 3 h. After completion of the reaction, the reaction mixture was extracted into dichloromethane (3 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give (R)-2,3-*O*-isopropylidene glyceradehyde (4) in 81% yield (1.59 g, 19.91 mmol). This was immediately reacted with *p*-methoxyphenyl magnesiumbromide (3.90 g, 18.57 mmol) in dry THF (20 mL) under nitrogen atmosphere for 3 h at room temperature. After completion of the reaction, the reaction was quenched with saturated ammonium chloride solution (15 mL) and extracted into ethyl acetate (3 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give a crude diastereomeric mixture of 5 (85%) and 5a (15%). 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 85 % yield.

[α]D25 9.27 (c 1, $CHCl_3$),

^{1}H NMR($CDCl_3$, 200 MHz): δ 1.37 (s, 3H), 1.48 (s, 3H), 3.64 (dd, *J* = 5.5, 8.5 Hz, 1H, Ha-31), 3.74 (dd, *J* = 5.5, 8.5 Hz, 1H, Hb-31), 3.80 (s, 3H, OMe), 4.18 (dd, *J* = 5.5, 8.0 Hz, 1H, H-21), 4.48 (d, *J* = 6 Hz, 1H, H-11), 6.84 (d, *J* = 7Hz, 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 (7): To an ice cooled solution of compound 4 (2.80 g, 13.08 mmol) in dry dichloromethane (15 mL) and PDC (3.76 g, 10 mmol), Ac_2O (10 mmol) and stirred at room temperature for 0.5 h. After completion of the reaction water was added to the reaction mixture and extraction done with dichloromethane (3 x 20 mL). The crude reaction mixture was further reduced with $NaBH_4$, β-CD. 0.1 mol% in THF After completion of the reaction water was added to the reaction mixture and extraction done with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. It was further reacted with triethyl amine (5.46 mL, 39.25 mmol), and methanesulphonyl chloride (0.9 mL, 14.39 mmol) and stirred at room temperature for 3 h. After completion of the reaction water was added to the reaction mixture and extraction done with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give mesylate 6 (3.50 g) in 85%, 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 (8): To a solution of compound 7 (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 h. After completion of the reaction, acetone was removed under reduced pressure, water was added and the contents extracted into 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): δ, 1.39 (s, 3H), 1.5 (s, 3H), 3.58 (dd, *J* = 5.6, 10.0 Hz, 1H, Ha-31), 3.68 (dd, *J* = 5.6, 10.0 Hz, 1H, Hb-31), 3.8 (s, 3H, OMe), 3.92 (dd, *J* = 5.6, 8.5 Hz, 1H, H-21), 4.3 (d, *J* = 6 Hz, 1H, H-11), 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 (9): To an ice cooled solution of compound 8 (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 h, 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 9 (0.94 g 3.96 mmol) in 70% yield.

^{1}H NMR ($CDCl_3$, 200 MHz): δ, 1.38 (s, 3H), 1.43 (s, 3H), 3.59 (dd, *J* = 6, 8 Hz, 1H, Ha-31), 3.68 (dd, *J* = 6, 8 Hz, 1H, Hb-31), 3.8 (s, 3H, OMe), 3.84 (d, *J* = 6 Hz, 1H, H-21), 4.1 (dd, *J* = 6, 8 Hz, IH, H-11), 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*-sopropylidene-3-*p*-methoxyphenyl-1,2-propanediol (10): To an ice cooled solution of compound 9 (0.8 g, 3.37 mmol) in dry dichloromethane (15 mL) was 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 h, water was added, extracted into dichloromethane (3 x 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 eluting with ethyl acetate hexane (2:8) to give the title compound 10 (0.93 g) in 82% yield. [α]D25 –7.76 (c 1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.31 (s, 3H), 1.39 (s, 9H),1.48 (s, 3H), 3.7 (dd, *J* = 5, 8 Hz, 1H, Ha-31),3.78 (s, 3H, OMe) 3.91 (dd, *J* = 5, 8 Hz, 1H, Hb-31), 4.28 (m, 1H, H-21), 5.17 (d, *J* = 8 Hz, 1H, H-11), 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 (11): To a solution of compound 10 (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 h. 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 11 which was purified by silica gel column to give pure diol 11 (0.46 g) 76% yield. M.p.125-128 ^{o}C, [α]D25 1.09 (c 1, $CHCl_3$), 1H NMR ($CDCl_3$, 200 MHz), δ 1.41(s , 9H), 3.48 (d, *J* = 7Hz, 2H, Ha-31, Hb-31), 3.61 (m, 1H,

H-21), 3.77 (s, 3H, OMe), 3. 8.2-3.89 (m, 1H, H-11), 6.8 (d, *J* = 8Hz, 2H, Ar), 7.24 (d, *J* = 8 Hz, 2H, Ar). FABMS (m/z): 320 $(M + Na)^+$.

(2*R*,3*R*)-3-*tert*–Butoxycarbonylamino-3-*p*-methoxyphenyl-1,2-di-4-nitrobenzoate (12): To a stirred solution of compound 11 (0.220 g 0.74 mmol) in dry THF (15 mL) were added triphenyl phosphine (0.98 g 0.37 mmol), *p*-nitrobenzoic acid (0.61 g, 3.68 mmol) and diethylazadicarboxylate in 5 mL THF (0.20 mL, 1.12 mmol). Reaction mixture was allowed to stir at room temperature for 24 h, under nitrogen atmosphere. THF was removed under vacuo and to crude compound water was added extracted in ethylacetate (3 x 20 mL) dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product 12 which was purified by silica gel column to give pure protected compound 12.

[α]D25 -3.99 (c 0.5 , MeOH),

^{1}H NMR ($CDCl_3$, 200 MHz)): δ, 1.45 (s, 9H), 3.80 (s, 3H), 4.48-4.58 (m, 1H,), 4.69-4.78 (m, 1H,), 4.97-5.05 (m, 1H,), 5.10-5.20 (m, 1H), 5.80 (br d, 1H) 6.83-6.90 (d, *J* = 8Hz, 2H, Ar), 7.24-7.30 (d, *J* = 8 Hz, 2H, Ar) 8.02-8.19 (m, 4H, Ar), 8.11-8.36 (m, 4H, Ar), FABMS (m/z): 582 $(M + 1)^+$.

(2*R*, 3*R*)-3-*tert*–Butoxycarbonylamino-3-*p*-methoxyphenyl-1,2-propanediol (13): To compound 12 (0.015 g, 0.257 mmol) in THF (2.5 mL) and water (7.5 mL) was added LiOH (0.037 g, 0.154 mmol) at 0 ºC. Reaction mixture was allowed to stir at room temperature for 2 h after that THF was removed under vacuo and to crude compound water was added extracted into ethylacetate (3 x 15 mL) dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product 12 which was purified by silica gel column to give pure protected compound 13 in 81% yield m.p.115-116ºC, [α]D25 -51.2 (c 1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.44 (s, 9H), 2.31 (br s,1H), 2.96 (br s,1H), 3.62-3.72 (m, 2H), 3.73-3.81 (m, 1H), 3.82 (s, 3H), 4.59 (ddd,1H), 5.02 (br s, 1H), 6.89 (d, 2H, *J* = 8.5Hz), 7.25 (d, 2H *J* = 8.5Hz).

(4*R*,5*R*)–5-Hydroxymethyl–4-(4-methoxyphenyl)-2-oxazolidinone (1): To a solution of compound 13 (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 nitrogen atmosphere for 2 h. 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 (2), which was purified by silica gel column chromatography using ethyl acetate hexane (4:6) to give pure 5-*epi*-cytoxazone (2) (0.067 g) in 90% as a white solid (-)- cytoxazone.

m.p.118-120 ºC,

[α]D25 -71.0 (c, 1.32, MeOH)

^{1}H NMR (DMSO-d6, 200MHz): δ, 2.96 (m, 2H), 3.76 (s, 3H), 4.62-4.79 (m, 1H), 4.84 (t, 1H, *J* = 5Hz), 4.90 (D, 1H, *J* = 8 Hz), 6.94 (d, 2H, *J* = 8.5Hz), 7.15 (d, 2H, *J* = 8.5Hz), 13C NMR (acetone-d6, 50 MHz), δ160.27, 159.22, 129.86, 128.62, 114.23 ,81.11, 62.17, 57.48, 55.19. EIMS (m/z): 223 (M^+).

(4*R*,5*S*)–5-Hydroxymethyl–4-(4-methoxyphenyl)-2-oxazolidinone (2): To a solution of compound 11 (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 nitrogen atmosphere for 2 h. 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 (2), which was purified by silica gel column chromatography using ethyl acetate hexane (4:6) to give pure 5-*epi*-cytoxazone (2) (0.067 g) in 90% as a white solid. (+)-5-*epi*- cytoxazone, m.p.155-158ºC [α]D25 70.10 (c, 1.32, MeOH), ^{1}H NMR (DMSO, 200MHz), δ 3.61 (dd, *J* = 5, 8Hz, 1H,Ha-6), 3.75 (dd, *J* = 5, 8Hz, 1H, Hb-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* = 8Hz, 2H, Ar), 7.28 (d, *J* = 8Hz, 2H,Ar), 7.65 (br d, *J* = 8 Hz, 1H, H-3). ^{13}C NMR (DMSO, 50 MHz), δ 55.0, 57.0, 83.75, 114.0, 128.0, 133.0, 158.0, 159.0; EIMS (m/z): 223 (M^+).

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