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A CONCISE SYNTHESIS OF (-)-CYTOXAZONE

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Abstract – A concise, stereoselective synthesis of (-)-cytoxazone 1 was described. A key feature is highly diastereoselective reduction of the amino ketone to give the *anti*-amino alcohol directly, which is 2-oxazolidinone precursor.

INTRODUCTION

(-)-Cytoxazone **1** is a microbial metabolite containing a novel 4,5-disubstituted- 2-oxazolidinone moiety which was isolated from *Streptomyces sp*. in 1998 (Figure 1).[1] (-)-Cytoxazone exhibits cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.[2] Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Since Th2 cells play a major role in mediating the immune response to allergens, (-)-cytoxazone could be a useful lead compound for the development of therapeutic agents for atopic dermatitis and asthma.

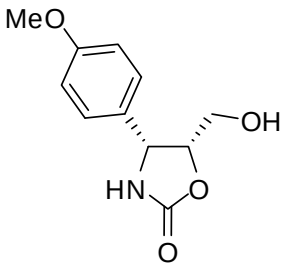

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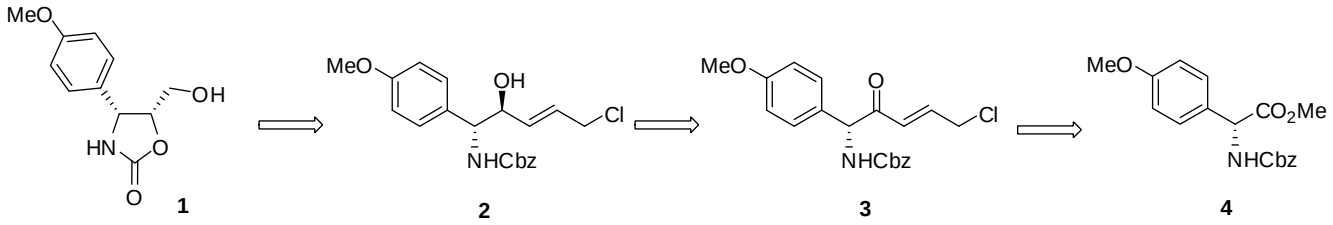
Figure 1. Structure of (-)-cytoxazone **1**

Due to its potent bioactivity and relatively simple structure, the development of efficient routes to (-)-cytoxazone and its stereoisomers has been the focus of intense synthetic interest. Following the first syntheses, more than 30 other syntheses of the natural product and its stereoisomers have been reported.[3] The synthetic precursors of (-)-cytoxazone and its stereoisomers are 1,2-aminoalcohols, which have been the subject of thorough synthetic efforts in recent years. Most of the syntheses of (-)-cytoxazone described so far have made use of indirect methods to establish the *anti*-amino alcohol functionality. In this paper, we wish to report a short and straightforward synthetic route to (-)-cytoxazone **1** in good yield by employing highly diastereoseclective reduction of an amino ketone as the key step in introducing stereogenic center into the molecule.

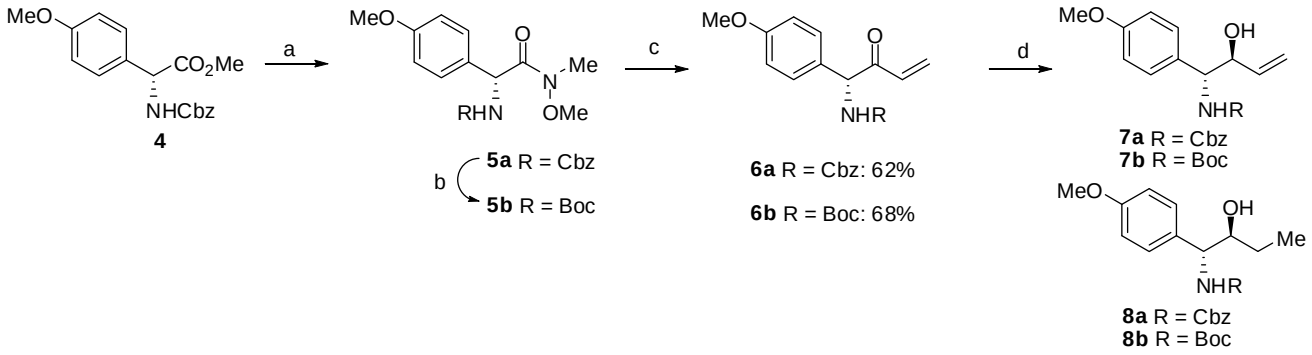


Scheme 1. Retrosynthetic analysis

Retro-synthetic analysis of the title compound **1** was shown in Scheme 1. The target 2-oxazolidinone moiety could be prepared from 1,2-*anti*-amino alcohol **2** via ozonolysis, subsequent reduction, and cyclization. And also compound **2** may be yielded by the diastereoselective reduction of aminoketone **3**. Compound **3** could be got easily from ester **4** in few steps. The ester **4** was prepared from *D*-4-hydroxyphenylglycine according to the known procedure.[4]

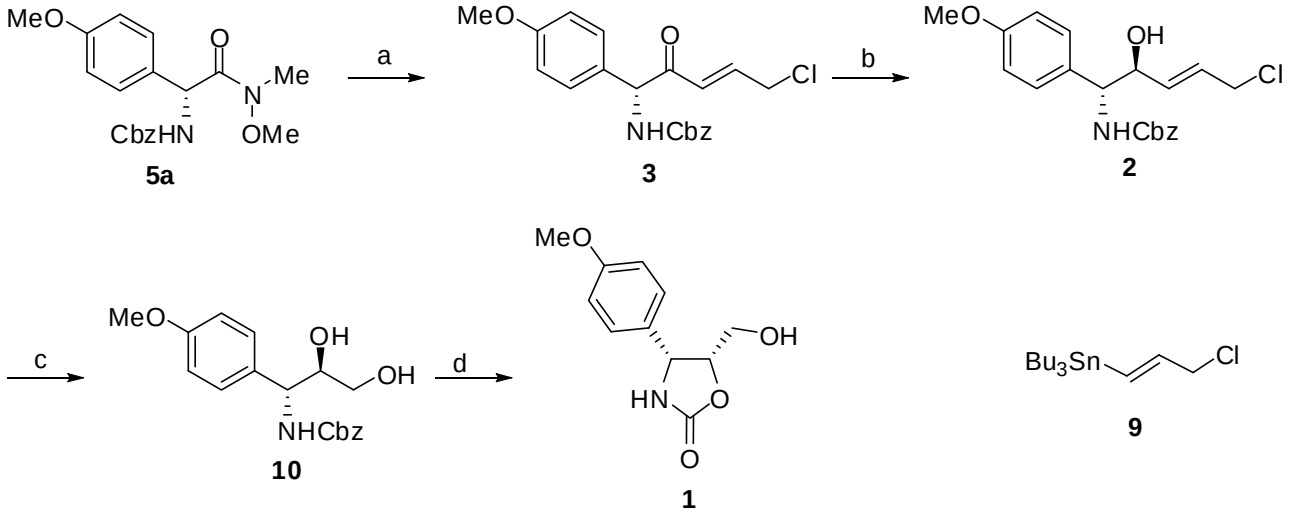
RESULTS AND DISCUSSION

The synthesis of **1** commenced with preparation of the Weinreb amide **5** from the ester **4** by treatment with *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminum (77% yield) (Scheme 2).[5] Reaction of the Weinreb amide **5a** with vinylmagnesium bromide in THF at 0 °C gave α,β-unsaturated amino ketone **6a** in 62% yield. We have recently investigated the *anti*-selective reduction of *N*-protected α,β-unsaturated ketone with various reducing agents, and we found that reaction with lithium tri-*tert*-butoxyaluminum hydride in ethanol at -78 °C gave the desired 1,2-*anti*-amino alcohol derivative as the major compound in good yield with excellent stereoselectivity.[6] It is noteworthy that under this reaction condition, the reduction of enone **6a**,**b** unexpectedly afforded the corresponding saturated alcohol **8a**,**b** with *anti*-stereochemistry that resulted from 1,4-addition followed by stereoselective reduction along with a small amount of desired unsaturated alcohol **7a**,**b**.[7]



Scheme 2. Reagents and conditions: a) NH(OMe)Me·HCl, Me_3Al, CH_2Cl_2, 0 °C-rt, 77%. b) Pd/C, H_2, Boc_2O, MeOH + hexanes, 78%. c) vinylmagnesium bromide, THF, 0 °C. d) $LiAlH(OBu\text{-}t)_3$, EtOH, -78 °C.

Therefore, the Weinreb amide **5a** was reacted with vinyltin derivative **9** and MeLi in THF at -78 °C gave α,β-unsaturated ketone **3** in 90% yield (Scheme 3).Treatment of obtained aminoketone **3** with lithium tri-*tert*-butoxyaluminum hydride in ethanol at -78 °C gave the desired aminoalcohol **2** as the major compound in good yield (80%) with high stereoselectivity (*anti/syn* >10:1 by ^{1}H-NMR).[8] For completion of the synthesis of (-)-cytoxazone **1**, the conversion of alkene **2** into the terminal primary alcohol **10** was achieved in 78% yield by ozonolysis of the double bond followed by sodium borohydride reduction. Finally, the regioselective intramolecular cyclization of aminodiol **10** using sodium hydride in THF at 0 °C, led to formation of (-)-cytoxazone **1** in 80% yield. The spectroscopic data for synthetic **1** showed good agreements with those reported. The optical rotation of **1**, $[\alpha]_D^{25}$ -70.35 (*c* 1.0, MeOH), compared to the reported value,[3a] $[\alpha]_D^{25}$ -70.3 (*c* 1.0, MeOH), confirms the identity of the absolute configuration.



Scheme 3. Reagents and conditions: a) **9**, MeLi, THF, -78 °C, 90%. b) $LiAlH(OBu\text{-}t)_3$, EtOH, -78 °C, 80%. c) O_3, MeOH, -78 °C then $NaBH_4$, MeOH, 0 °C, 78% for 2 steps. d) NaH, THF, 0 °C-rt, 80%.

CONCLUSION

In summary, we reported a concise and direct synthetic route to (-)-cytoxazone **1**. The key step in this procedure is highly diastereoselective reduction of α,β-unsaturated ketone **3**, led to *anti*-amino alcohol, which was converted to 2-oxazolidinone ring system under unique conditions.

EXPERIMENTAL

1.1. General methods

Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^{1}H NMR spectra were recorded at Varian inova FT-NMR 500 MHz in $CDCl_3$ and DMSO-d_6. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ and DMSO-d_6. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on a Bruker FT-IR spectrometer. Mass spectra were recorded on Mass spectrometer (Agilent MSD Trap SL). Flash chromatography was executed with Merck Kiesegel 60 (230-400 mesh) using mixtures of ethyl acetate and hexane as eluants. Ethyl acetate (EtOAc) and hexane were dried and purified by distillation prior to use. Tetrahydrofuran (THF) was distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

1.2. (*R*)-Benzyl 2-(methoxy(methyl)amino)-1-(4-methoxyphenyl)-2-oxoethylcarbamate 5a

To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (6.32 g, 64.83 mmol) in CH_2Cl_2 (200 mL) was added trimethylaluminum (2 M solution in hexane, 32.40 mL, 64.83 mmol) at 0 ^{o}C (Caution: CH_4-evolution). The mixture was stirred for 30 min at rt. Subsequently, a solution of methyl ester **4** (7.12 g, 21.61 mmol) in CH_2Cl_2 (200 mL) was added dropwise. The mixture was stirred at rt for 1h then the reaction mixture was cooled to 0 ^{o}C and carefully quenched with 10% aqueous sodium potassium tartrate (25 mL). After being stirred for 1h at rt, the resulting suspension was filtered through celite pad, washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give the crude product, which upon purification gave the Weinreb amide **5a** (5.40 g, 77%) as a colorless oil; R_f = 0.3 (EtOAc / hexanes = 1 / 1); IR (neat) ν_{max}: 1042, 1178, 1250, 1515, 1660, 1716, 2360, 3326 cm^{-1}; $[\alpha]_D^{25}$ -93.07 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.18 (s, 3H), 3.47 (s, 3H), 3.79 (s, 3H), 5.05 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 5.72 (d, *J* = 6.5 Hz, 1H), 6.12 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.28-7.34 (m, 7H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.54, 55.11, 55.47, 61.38, 67.02, 114.41, 128.25, 128.27, 128.69, 129.24, 130.09, 136.64, 155.71, 159.72, 171.32; HRMS (FAB$^+$) (M^+ +H) m/z calcd for $C_{19}H_{23}N_2O_5$ 359.1607 found 359.1610.

1.3. (*R,E*)-Benzyl 5-chloro-1-(4-methoxyphenyl)-2-oxopent-3-enylcarbamate 3

Vinyltin **9** (4.83 g, 13.22 mmol) was dissolved in dry THF (40 mL) and cooled to -78 ^{o}C. MeLi (1.6M solution in hexanes, 8.27 mL, 13.22 mmol) was added dropwise. The mixture was stirred for 30 min at the same temperature. Subsequently, a solution of Weinreb amide **5a** (1.58 g, 4.41 mmol) in dry THF (30 mL) was added dropwise and stirring was allowed to continue for 30 min, after which time TLC analysis indicated complete reaction. The reaction was quenched by sat. aqueous NH_4Cl (50 mL) then warmed to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layer washed with sat. aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried with $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. The resulting substance was purified to give the amino ketone **3** (1.51 g, 90%) as a white solid; Mp 93 ^{o}C; R_f = 0.5 (EtOAc / hexanes = 1 / 3); IR (neat) ν_{max}: 1030, 1252, 1508, 1636, 1698, 3649, 3750 cm^{-1}; $[\alpha]_D^{25}$ -179.90 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3H), 4.09 (d, *J* = 5.0 Hz, 2H), 5.04 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.47 (d, *J* = 6.0 Hz, 1H), 6.20 (d, *J* = 5.5 Hz, 6.35 (d, *J* = 15.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.97 (dd, *J* = 6.0, 6.0, 15.0 Hz, 1H), 7.24-7.34 (m, 7H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.83, 55.53, 63.24, 67.17, 114.93, 114.99, 127.83, 128.32, 128.36, 128.73, 129.78, 136.50, 114.86, 155.59, 160.19, 193.59; HRMS (FAB$^+$) (M^+ +H) m/z calcd for $C_{20}H_{21}NO_4Cl$ 374.1159, found 374.1160.

1.4. Benzyl (1*R*,2*S*,*E*)-5-chloro-2-hydroxy-1-(4-methoxy-phenyl)pent-3-enyl-carbamate 2

To a solution of amino ketone **3** (644 mg, 1.72 mmol) in EtOH (20 mL) was added lithium tri-*tert*-butoxyaluminum hydride (1N solution in THF, 3.45 mL, 3.45 mmol) at –78 ^{o}C. After the reaction mixture was stirred at the same temperature for 4 h, 10% aqueous solution of citric acid (20 mL) was added. The resulting mixture was warmed to rt and extracted with EtOAc (20 mL X 3). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude products. Which was purified to give amino alcohol **2** (517 mg, 80%, ratio *anti:syn* > 10:1 by ^{1}H-NMR) as a white solid, Mp 139 ^{o}C; R_f = 0.3 (EtOAc / hexanes = 1 / 2); IR (neat) ν_{max}: 1248, 1541, 1685, 2361, 3649, 3750 cm^{-1}; $[\alpha]_D^{25}$ -5.23 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.82 (s, 3H), 3.99 (d, *J* = 6.5 Hz, 2H), 4.45 (d, *J* = 4.5 Hz, 1H), 4.81 (br, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12 Hz, 1H), 5.50 (d, *J* = 8.0 Hz, 1H), 5.66 (dd, *J* = 6.0, 15.0 Hz, 1H), 5.85 (m, 1H), 6.88-6.91 (m, 2H), 7.20-7.21 (m, 2H), 7.28-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 44.11, 55.52, 59.42, 67.28, 74.55, 114.27, 114.45, 128.42, 128.44, 128.76, 128.83, 129.12, 133.04, 136.46, 156.32, 159.54; HRMS (FAB$^+$) (M^+ +H) m/z calcd for $C_{20}H_{23}NO_4Cl$ 376.1316, found 376.1317.

1.5. Benzyl (1*R*,2*R*)-2,3-dihydroxy-1-(4-methoxyphenyl)propylcarbamate 10

A solution of the alkene **2** (517 mg 1.38 mmol) in MeOH (50 mL) was cooled to -78 ^{o}C. Ozone was

passed through the solution until starting material had been consumed (TLC analysis). The resulting blue solution was purged with oxygen for 10 min, and sodium borohydride (78 mg, 2.07 mmol) was then added. After the mixture had been stirred at rt for 30 min, sat. aqueous NH_4Cl was added. The reaction mixture was extracted with EtOAc, and washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure, followed by purification by silica gel chromatography afforded the diol **10** (356 mg, 78%) as a white solid, Mp 85 ^oC; R_f = 0.2 (EtOAc / hexanes = 1 / 1); IR (neat) ν_{max}: 1030, 1246, 1456, 1698, 2360, 3648, 3750 cm^{-1}; $[\alpha]_D^{25}$ -27.80 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.82-2.93 (br, 2H), 3.53-3.59 (m, 1H), 3.64-3.66 (m, 1H), 3.80 (s, 3H), 3.81-3.86 (m, 1H), 4.75 (dd, *J* = 6.5, 8.5 Hz, 1H), 5.09 (dd, *J* = 12.0, 26.5 Hz, 2H), 5.71 (br, 1H), 6.87-6.90 (m, 2H), 6.24-7.34 (m, 7H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.53, 56.99, 63.51, 67.39, 74.06, 114.49, 128.17, 128.41, 128.76, 129.19, 130.86, 136.39, 156.79, 159.54; HRMS (FAB^+) (M^+ +H) m/z calcd for $C_{18}H_{22}NO_5$ 332.1498, found 332.1494.

1.6. (-)-Cytoxazone: (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one 1

To a solution of compound **10** (282 mg, 0.85 mmol) in anhydrous THF (8.5 mL) was added sodium hydride (102 mg, 2.55 mmol, 60% w/w in mineral oil) at rt and the mixture was stirred under a nitrogen atmosphere for 2 h. The reaction mixture was concentrated, CH_2Cl_2 was added, washed with saturated aqueous NH_4Cl solution, brine and dried over Na_2SO_4. The organic layer was concentrated by rotary evaporation and the residue was purified by flash column chromatography to give **1** (153mg, 80%) as a white solid; Mp 124-127 ^oC; R_f = 0.1 (EtOAc / hexanes = 3 / 1); IR (neat) ν_{max}: 688, 954, 1023, 1100, 1250, 1514, 1725, 1741, 2324, 2962, 3250 cm^{-1}; $[\alpha]_D^{25}$ -70.35 (c 1.0, MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 2.95-2.99 (m, 2H), 3.75 (s, 3H), 4.69-4.73 (m, 1H), 4.79 (t, *J* = 5.2 Hz, 1H), 4.91 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H) 8.03 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 55.81, 56.94, 61.76, 80.77, 114.38, 128.17, 128.72, 129.97, 159.45, 159.72; HRMS (FAB^+) (M^+ +H) m/z calcd for $C_{11}H_{14}NO_4$ 224.0923, found 224.0920.

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7. In the reductive reaction of enone **6a,b** with LiAlH(OBu-*t*)$_3$ in EtOH at -78 ^{o}C, it is not selective only 1,2-reduction but also 1,4-reduction reaction happened. The ^{1}H-NMR chart of reaction product show the ethyl protons of compound **8a,b** and small peaks of vinyl protons of compound **7a**,**b**. The yield of each compounds (**7a**, **7b**, **8a**, and **8b**) could not indentified. For related reference, see: T. Yamamoto, H. Hasegawa, T. Hakogi, and S. Katsumura, *Org. Lett*., 2006, **8**, 5569.
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