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Enantioselective synthesis of (−)-cytoxazone and (+)-*epi*-cytoxazone, novel cytokine modulators via Sharpless asymmetric epoxidation and L-proline catalyzed Mannich reaction

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Abstract—A short and efficient enantioselective synthesis of (−)-cytoxazone and its stereoisomer (+)-*epi*-cytoxazone, novel cytokine modulators, has been described with good yield and enantioselectivity. Ti-catalyzed Sharpless asymmetric epoxidation of allyl alcohol and L-proline catalyzed three-component Mannich reaction constitute the key steps in introducing stereogenicity into the molecule.

1. Introduction

Cytoxazone **1**, containing a novel 4,5-disubstituted-2-oxazolidinone moiety was isolated[1] from *Streptomyces* sp., and its absolute configuration was unambiguously established by asymmetric synthesis.[2] (−)-Cytoxazone [(−)-**1**] exhibits cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells. Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Since Th2 cells play a role in mediating the immune response to allergens, cytoxazone **1** could be a useful lead compound for the development of therapeutic agents for atopic dermatitis and asthma.

Due to its potential bioactivity and the simple structure, several methods of synthesizing (−)-cytoxazone (**1**) have been accomplished.[3] The stereoisomer of (−)-cytoxazone (**1**), (+)-*epi*-cytoxazone (**2**) has also been synthesized.[4] In this paper, we wish to report a short enantioselective synthesis of (−)-cytoxazone and its stereoisomer (+)-*epi*-cytoxazone in good yields by employing Ti-catalyzed Sharpless asymmetric epoxidation of allyl alcohol and L-proline catalyzed Mannich reaction, respectively, as the key steps in introducing stereogenic centers into the molecule.

2. Results and discussion

Retrosynthetic analysis of cytoxazone (**1**) reveals that amino alcohol **3** could be visualized as a key intermediate (Fig. 1).

The key intermediate (*Z*)-olefinic ether (**8**) was obtained in three steps: (i) Sonogashira coupling (cat. $Pd(PPh_3)_4$ (0.5 mol %), cat. CuI (10 mol %), Et_2NH, 25 °C, 96%) of 4-iodoanisole with propargyl alcohol to give aryl propargyl alcohol **6** in 96% yield; (ii) acetylenic alcohol **6** was protected with TBS chloride to give TBS ether **7**, which was

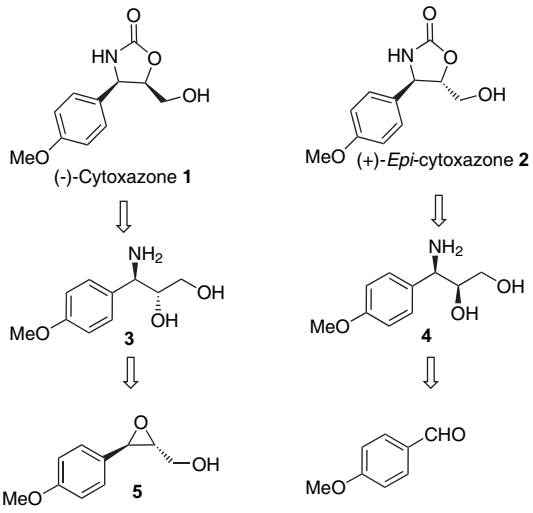

Figure 1. Retrosynthesis of (−)-cytoxazone (**1**) and (+)-*epi*-cytoxazone (**2**).

Keywords: Asymmetric synthesis; Aminohydroxylation; Epoxidation; Mannich reaction; Oxidation; Ozonolysis.
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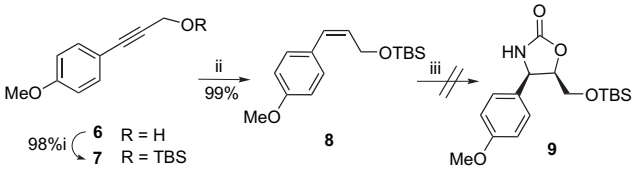
stereospecifically reduced with Lindlar catalyst to obtain (*Z*)-olefinic ether **8** in 99% yield. However, several attempts to functionalize (*Z*)-olefinic ether **8** with Os-catalyzed asymmetric aminohydroxylation (AA) failed despite employing various reaction conditions (Scheme 1).[5]



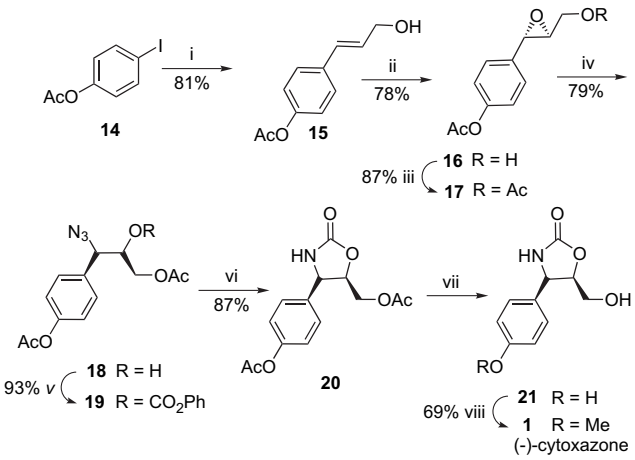
Scheme 1. Reagents and conditions: (i) TBSCl, Et_3N, CH_2Cl_2, 0–25 °C, 98%; (ii) Lindlar catalyst (5% Pd on $CaCO_3$ with Pb poisoned), dry hexane, H_2 (1 atm), 25 °C, 99 %; (iii) cat. K_2OsO_6, $(DHQD)_2PHAL$, Urethane, *tert*-BuOCl or 1,3-dichoro-5,5-dimethyl hydantoin, aq 10% NaOH, *n*-PrOH, 25 °C, 24 h.

After failing to functionalize aminohydroxylate (*Z*)-olefinic ether **8**, we then turned our attention to functionalize (*E*)-allyl alcohol **11**.

Accordingly, we subjected (*E*)-allyl alcohol **11** to Ti-catalyzed asymmetric epoxidation (AE) under standard reaction conditions;[6] here again, all our attempts to obtain chiral epoxide **12** failed. The reason may be due to the positive inductive effect of methoxy group present on an aromatic ring, which facilitates the opening of epoxide ring, thus deactivating the Ti-catalyst by forming metal chelate **13** (Scheme 2).

In order to eliminate this positive inductive effect due to OMe group, we changed our strategy by replacing electron-rich OMe group on the aromatic ring with electron-deficient OAc group. This protecting group can be further deprotected easily during the course of the synthesis (Scheme 3).

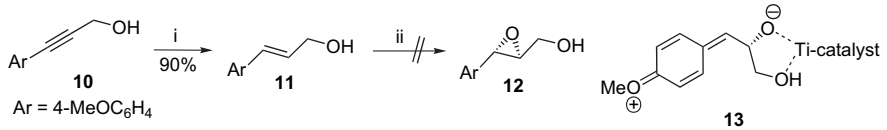
4-Iodophenol was protected as its acetyl derivative **14** (Et_3N, CH_2Cl_2, 25 °C). The Pd-catalyzed arylation of allyl alcohol with **14** gave the *trans*-allylic alcohol **15** in 81% yield.[7] The allylic alcohol **15** was subjected to Sharpless asymmetric epoxidation [(+)-DIPT, $Ti(O^iPr)_4$, anhyd TBHP, 25 °C] to give the chiral epoxide **16** in 78% yield and 92.5% ee (determined by chiral HPLC using Chiralcel OD-H® column). The alcohol **16** was acetylated (CH_3COCl, Et_3N, DMAP (cat.), CH_2Cl_2, 25 °C) to give epoxy acetate **17** in 86% yield. The nucleophilic opening of the epoxide at the benzylic position with N_3 was achieved (NaN_3, NH_4Cl (cat.), THF, 25 °C) to give azido alcohol **18** in 88% yield. We then followed reported procedure[8] for the conversion of azido alcohol **18** to the corresponding oxazolidinone **21** in two steps by alcohol protection followed by reductive cyclization with triphenylphosphine. Basic hydrolysis of both acetate groups in MeOH gave the phenol **21** which was directly subjected to



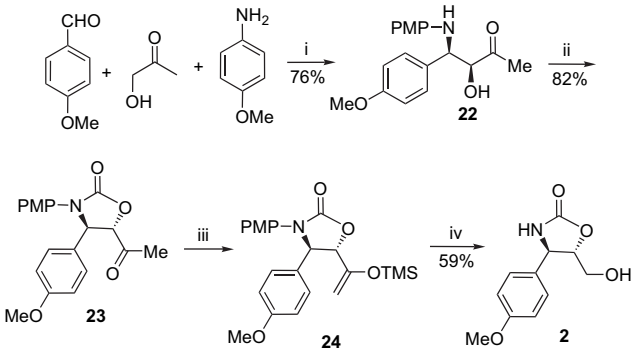
Scheme 3. Reagents and conditions: (i) allyl alcohol (3 equiv), AgOAc (1 equiv), cat. $Pd(OAc)_2$ (5 mol %), cat. PPh_3 (10 mol %), DMF, 70 °C, 16 h, 81%; (ii) anhyd 5.4 M TBHP in CH_2Cl_2, 4 Å Molecular sieves, cat. $Ti(O^iPr)_4$ (10 mol %), cat. (+)-DIPT (12 mol %), CH_2Cl_2, −20 °C, 20 h, 78%; (iii) AcCl, Et_3N, cat. DMAP (10 mol %), CH_2Cl_2, 25 °C, 87%; (iv) NaN_3, cat. NH_4Cl (30 mol %), THF/H_2O (2:1), 50 °C, 3 h, 79%; (v) PhOCOCl, pyridine, CH_2Cl_2, −5 to 25 °C, 1 h, 93%; (vi) PPh_3 (4 equiv), THF/H_2O (10:1), 50 °C, 2 h, 87%; (vii) aq $NaHCO_3$, MeOH, reflux, 1 h; (viii) NaH, MeI, THF, 0–25 °C, 3 h, 69%, 83% ee.

methylation with methyl iodide in the presence of NaH to afford (−)-cytoxazone (**1**) in 65% yield and 83% ee [determined by HPLC using Chirasphere® column and optical rotation].

Based on the retrosynthetic analysis of (+)-*epi*-cytoxazone **2** (Fig. 1), amino alcohol **4** is the key intermediate, which can be obtained from L-proline catalyzed asymmetric Mannich reaction (Scheme 4).[9] Thus, 4-methoxybenzaldehyde was condensed with hydroxyacetone and *p*-anisidine in the presence of 30 mol % L-proline, to obtain chiral amino alcohol **22** in 76% yield with *syn*/*anti* ratio 2:1. Efforts to improve the diastereomeric ratios were not successful despite replacing OMe group with electron withdrawing groups such as OAc or OMs on the aromatic nucleus. However, the required diastereomer was separated by simple column chromatographic purification. Amino alcohol **22** was then protected with triphosgene to give oxazolidinone **23** in 82% yield. Attempts to convert methyl ketone in **23** to the corresponding carboxylic acid via haloform reaction were not fruitful. Alternately, we tried to prepare kinetically controlled silyl enol ether **7** from oxazolidinone **23** so that enol ether **24** could be further easily converted to *epi*-cytoxazone (**2**) by ozonolysis with reductive work up. However, all attempts to isolate enol ether **24** in pure form resulted in the isolation of the starting ketone **23**. Then we subjected in situ generated silyl enol ether for ozonolysis without purification. Reductive work up of ozonide and PMP deprotection with CAN gave (+)-*epi*-cytoxazone **2** in 59% yield and 81% ee.



Scheme 2. Reagents and conditions: (i) LAH, THF, 0 °C, 3 h, 90%. (ii) $Ti(O^iPr)_4$ (10 mol %), (+)-DIPT (12 mol %), anhydrous TBHP, CH_2Cl_2, −20 °C, 24 h.



Scheme 4. Reagents and conditions: (i) *p*-anisidine (1.1 equiv), hydroxyacetone (10 equiv), cat. L-proline (20 mol %), DMSO, 25 °C, 24 h, 76%; (ii) triphosgene, Et_3N, CH_2Cl_2, −10 to 25 °C, 82%; (iii) Li-HMDS, TMSCl, THF, −78 °C; (iv) (a) O_3, PPh_3, CH_2Cl_2, −78 °C; (b) $NaBH_4$, MeOH, 25 °C; (c) CAN, CH_3CN, 5 h, (59% in three steps), 81% ee.

3. Conclusion

In conclusion, we have achieved a simple and efficient asymmetric synthesis of (−)-cytoxazone (**1**) using asymmetric epoxidation of allylic alcohol (AE) in the presence of $Ti(O^iPr)_4$ as a catalyst and (+)-DIPT as ligand with a overall yield of 23%, and optical purity of 83% ee (by HPLC) in nine steps starting from readily available 4-iodophenol. We have also achieved asymmetric synthesis of (+)-*epi*-cytoxazone (**1**) using L-proline catalyzed Mannich reaction with overall yield of 37%, and optical purity of 81% in six steps starting from readily available *p*-anisaldehyde.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Melting points were uncorrected. HPLC analyses were performed on a chiral column (Chiralcel OD-H® and Chirasphere®). Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on a Shimadzu FTIR-8400 spectrometer. ^1H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL-300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020B-70 eV mass spectrometer. Elemental analysis was carried out on a Carlo Erba EA 110B CHNS-O analyzer.

4.2. Preparation of 3-(4-methoxyphenyl)prop-2-yn-1-ol (6)

A two-necked 100 ml RB flask was charged with *p*-iodoanisole (4.68 g, 20 mmol), propargyl alcohol (1.68 g, 30 mmol), CuI (0.40 g, 2 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), and diethylamine (50 ml). The resulting mixture was stirred at 25 °C for 6 h. Then the reaction was diluted with ethyl acetate (80 ml), washed with 10% HCl (10 ml), water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give black colored thick oil. This crude product was purified on column chromatography using 20% ethyl acetate in pet. ether as eluent to afford pure **6** (3.10 g, 96%) as pale yellow colored solid.

Yield: 96%; mp: 74–75 °C; IR ($CHCl_3$, cm^{-1}): 669, 757, 833, 1033, 1172, 1215, 1249, 1292, 1463, 1510, 1606, 2856, 2927, 3018, 3421; ^1H NMR (200 MHz, $CDCl_3$): δ 2.61 (br s, 1H), 3.78 (s, 3H), 4.48 (s, 2H), 6.79 (d, J=9.0 Hz, 2H), 7.34 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.42, 55.13, 85.38, 85.90, 113.83, 114.57, 133.06, 159.59; LRMS *m*/*z* (% rel intensity): 162 (M+, 100), 145 (33), 131 (40), 108 (30), 102 (33), 91 (57), 77 (30), 63 (43); Analysis: $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21; found C, 74.17; H, 6.14 %.

4.3. Preparation of (3-(4-methoxyphenyl)prop-2-ynyloxy)(*tert*-butyl)dimethylsilane (7)

To a stirred solution of alcohol **6** (2.46 g, 15.2 mmol) in dry CH_2Cl_2 (25 ml), Et_3N (2.29 g, 22.7 mmol) and *tert*-butyldimethylsilyl chloride (2.75 g, 18.2 mmol) were added portion wise at 0 °C. This mixture was then brought to room temperature and stirred for 12 h and then quenched with MeOH. It was poured into water and extracted with EtOAc. The organic phase was washed with aq $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$ and purified over column chromatography using pet. ether as eluent to afford pure **7** (4.11 g, 98%) as yellow colored oil.

Yield: 98%; IR ($CHCl_3$, cm^{-1}): 776, 845, 1125, 1230, 1522, 1605; ^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.78 (s, 9H), 3.61 (s, 3H), 4.34 (s, 2H), 6.61 (d, J=8.9 Hz, 2H), 7.15 (d, J=8.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.23, 18.03, 25.62, 51.94, 54.64, 84.62, 86.26, 113.62, 114.90, 132.70, 159.37; LRMS *m*/*z* (% rel intensity): 276 (M^+, 5), 261 (3), 231 (3), 219 (65), 205 (5), 189 (80), 174 (5), 159 (5), 145 (100), 130 (15), 115 (10), 102 (20), 94 (20), 75 (15), 57 (10), 41 (12); Analysis: $C_{16}H_{24}O_2Si$ requires C, 69.51; H, 8.75; found C, 69.47; H, 8.70%.

4.4. Preparation of (*Z*)-(4-methoxycinnamyloxy)(*tert*-butyl)dimethylsilane (8)

To a 50 ml two-necked RB flask equipped with a condenser and a balloon filled with H_2 at 1 atm was added Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with lead, 1.4 g), silyl ether **7** (2.76 g, 10 mmol), quinoline (2.6 g, 21 mmol), and 45 ml of dry *n*-hexane. The resulting mixture was stirred at room temperature under H_2 (1 atm) for 1 h. When starting material was consumed (monitored by TLC), the reaction mixture was filtered through sintered funnel. After distilling off hexane, we obtained 2.75 g (99%) of pure (*Z*)-olefin **8** as yellow colored oil.

Yield: 99%; IR ($CHCl_3$, cm^{-1}): 534, 617, 650, 668, 814, 837, 909, 938, 960, 983, 1006, 1035, 1085, 1175, 1216, 1253, 1302, 1361, 1405, 1442, 1464, 1471, 1511, 1575, 1607, 1681, 2401, 2857, 2897, 2931, 2956, 3019, 3443; ^1H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.84 (s, 9H), 3.76 (s, 3H), 4.37 (d, J=5.9 Hz, 2H), 5.61 (q, J=5.9 Hz, 1H), 6.34 (d, J=12.0 Hz, 1H), 6.79 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.18, 18.25, 25.87, 55.08, 60.36, 113.51, 129.04, 129.49, 130.00, 130.76, 158.55; LRMS *m*/*z* (% rel intensity): 278 (M^+, 5), 222 (15), 221 (50), 205 (5), 189 (5), 175 (10), 166 (5), 147 (100), 131 (45), 115 (75), 103 (65), 91 (90), 75

(90), 57 (80), 41 (90); Analysis: $C_{16}H_{26}O_2Si$ requires C, 69.01; H, 9.41; found C, 69.00; H, 9.35%.

4.5. Preparation of (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (11)

LAH (0.29 g, 7.8 mmol) was taken in THF (23 ml) and the slurry was cooled to 0 °C in an ice bath under nitrogen atmosphere. To this mixture, alcohol **6** (1.60 g, 9.88 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 30 min. After completion of reaction (monitored by TLC), ice-cold water (20 ml) was added and extracted with ether (3×30 ml). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution, and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether/EtOAc (3:1) as eluent to furnish **11** as colorless solid (1.18 g).

Yield: 73%; IR ($CHCl_3$, cm^{-1}): 761, 890, 1098, 1375, 1452, 1504, 2989, 3010, 3409, 3610; ^1H NMR (200 MHz, $CDCl_3$): δ 1.60 (br s, 1H), 3.81 (s, 3H), 4.28 (d, J=6.0 Hz, 2H), 6.17–6.30 (m, 1H), 6.52–6.60 (d, J=16.0 Hz, 1H), 6.84 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.13, 63.58, 113.90, 126.29, 127.54, 129.42, 130.67, 159.15; Analysis: $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37; found C, 73.12; H, 7.80%.

4.6. Preparation of 4-((*E*)-3-hydroxyprop-1-enyl)phenyl acetate (15)

A mixture of 4-iodophenyl acetate (7.89 g, 30 mmol) and allyl alcohol (3.48 g, 60 mmol) was stirred for 16 h in the presence of the AgOAc (5.01 g, 30 mmol), PPh_3 (0.78 g, 3 mmol), and $Pd(OAc)_2$ (0.33 g, 1.5 mmol) at 70 °C in 50 ml DMF. The reaction mixture was filtered through sintered funnel and washed with aq HCl (15 ml), water (15 ml), aq $NaHCO_3$ (15 ml), and brine (15 ml) sequentially. The crude allyl alcohol was purified by column chromatography using pet. ether/EtOAc (3:1) as eluent to furnish 4.65 g of **15** as colorless solid.

Yield: 81%; mp: 81–83 °C (crystallized from EtOH); IR ($CHCl_3$, cm^{-1}): 504, 524, 692, 755, 872, 970, 1016, 1087, 1151, 1196, 1332, 1414, 1503, 1600, 1677, 1714, 2869, 2939, 3029, 3366; ^1H NMR (200 MHz, $CDCl_3$): δ 1.67 (br s, 1H), 2.38 (s, 3H), 4.32 (d, J=4.9 Hz, 2H), 6.27–6.40 (m, 1H), 6.57 (d, J=15.9 Hz, 1H), 7.20 (d, J=8.7 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.74, 61.84, 121.52, 127.15, 128.01, 129.76, 135.84, 147.80, 169.28; LRMS m/z (% rel intensity): 192 (M^+, 5), 174 (3), 150 (50), 131 (10), 121 (10), 107 (100), 94 (60), 76 (30), 65 (15), 50 (20); Analysis: $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.29; found C, 68.61; H, 6.18%.

4.7. Preparation of 4-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)phenyl acetate (16) using Sharpless asymmetric epoxidation

A 100 ml two-necked RB flask was charged with 4 Å molecular sieves (1 g), 20 ml CH_2Cl_2, and cooled at −25 °C. Then $Ti(O^iPr)_4$ (0.59 ml, 0.568 g, 2 mmol) and L-(+)-DIPT (0.53 ml, 0.585 g, 2.5 mmol) was added sequentially and the mixture was stirred for 10 min before the addition of allyl alcohol **15** (3.84 g, 20 mmol). Finally, a 5.4 M anhydrous TBHP solution in CH_2Cl_2 (7.6 ml, 41 mmol) was added and the resulting mixture was stirred at −20 °C for 20 h. After completion of reaction (monitored by TLC), 10% aq tartaric acid (20 ml) was added and the aqueous layer solidifies. After 1 h the reaction was brought to room temperature and stirring was continued until the aqueous layer becomes clear. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether/EtOAc (3:1) as eluent to furnish epoxide **16** as white solid (3.23 g).

Yield: 78%; mp: 96 °C (crystallized from EtOH); $[\alpha]_D^{25}$ +23.59 (*c* 1.3, $CHCl_3$); HPLC: 92.5% ee, Chiralcel OD-H®, λ=254 nm, 5% 2-propanol/hexane, 1 ml/min, retention time: (*R*,*R*) 10.81 min, (*S*,*S*) 15.716 min; IR ($CHCl_3$, cm^{-1}): 527, 605, 703, 736, 784, 872, 971, 1045, 1152, 1175, 1200, 1232, 1369, 1417, 1504, 1605, 1740, 2939, 3029, 3060, 3499; ^1H NMR (200 MHz, $CDCl_3$): δ 2.04 (br s, 1H), 2.39 (s, 3H), 3.78–4.08 (m, 4H), 7.25–7.37 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.75, 54.67, 60.89, 62.63, 122.11, 127.22, 136.13, 148.81, 149.23, 170.11; Analysis: $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81; found C, 63.38; H, 5.78%.

4.8. Preparation of 4-((2*S*,3*S*)-3-(acetoxymethyl)oxiran-2-yl)phenyl acetate (17)

The mixture of epoxy alcohol **16** (2.08 g, 10 mmol), acetyl chloride (0.858 g, 11 mmol), Et_3N (1.52 g, 15 mmol), and DMAP (0.122 g, 10 mol %) in dry CH_2Cl_2 (10 ml) was stirred at room temperature. After the reaction was complete (TLC, 2 h), the solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (10 ml) and was extracted with ethyl acetate (2×25 ml). The organic layer was washed with saturated $NaHCO_3$ (2×15 ml) and brine (15 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product, which was purified by column chromatography to afford 2.17 g (87%) of epoxy ester **17** as colorless gum.

Yield: 87%; IR ($CHCl_3$, cm^{-1}): 526, 604, 702, 735, 783, 871, 970, 1016, 1044, 1109, 1152, 1175, 1200, 1232, 1369, 1418, 1504, 1605, 1740, 1913, 2939, 3029, 3062, 3499; ^1H NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.40 (s, 3H), 3.20–3.25 (m, 1H), 3.84 (d, J=2.0 Hz, 1H), 4.07–4.16 (m, 1H), 4.44–4.51 (m, 1H), 7.22 (d, J=9.1 Hz, 2H), 7.30 (d, J=7.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.55, 20.76, 55.45, 59.29, 63.67, 122.09, 127.15, 129.71, 135.57, 148.93, 170.51; Analysis: $C_{13}H_{14}O_5$ requires C, 50.34; H, 4.93; found C, 50.28; H, 4.89%.

4.9. Preparation of (2*R*,3*R*)-3-azido-2-hydroxy-3-(4-acetoxyphenyl)propyl acetate (18)

To a solution of NaN_3 (0.29 g, 5.2 mmol) and NH_4Cl (0.054 g, 1 mmol) in water (5 ml), a solution of epoxy ester **17** (0.775 g, 3.1 mmol) in THF (10 ml) was added. The reaction mixture was stirred at 50 °C for 3 h. Cooled to room temperature and the solution was extracted with EtOAc and washed with water (50 ml), dried over anhydrous

Na_2SO_4. Upon evaporation of the solvent, the crude product was purified by column chromatography over silica gel (EtOAc/pet. ether, 2:8) yielding 0.717 g (79%) of azido alcohol **18** as yellow colored solid.

Yield: 79%; mp: 61 °C; $[\alpha]_D^{25}$ −9.16 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 527, 604, 668, 757, 873, 908, 970, 1018, 1044, 1108, 1151, 1176, 1217, 1332, 1371, 1417, 1503, 1603, 1735, 2108, 2401, 2939, 3022, 3472; ^1H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.38 (s, 3H), 2.66 (br s, 1H), 3.98–4.09 (m, 1H), 4.15 (d, *J*=2.5 Hz, 1H), 4.17 (d, *J*=1.4 Hz, 1H), 4.63 (d, *J*=6.3 Hz, 1H), 7.31 (d, *J*=8.7 Hz, 2H), 7.43 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.62, 20.76, 64.79, 66.09, 72.03, 122.27, 129.40, 135.17, 148.96, 169.12, 171.21; Analysis: $C_{13}H_{15}N_3O_5$ requires C, 53.24; H, 5.16; N, 14.33; found C, 53.15; H, 5.10; N, 14.30%.

4.10. Preparation of (1*R*,2*R*)-3-acetoxy-1-azido-1-(4-acetoxyphenyl)propan-2-yl phenyl carbonate (19)

To a solution of azido alcohol **18** (0.469 g, 1.6 mmol) and pyridine (0.14 ml, 1.7 mmol) in CH_2Cl_2 (20 ml), a solution of phenylchloroformate (0.22 ml, 0.28 g, 1.7 mmol) in CH_2Cl_2 (1 ml) was added at −5 °C over10 min. After stirring at −5 °C for 1 h, the reaction mixture was poured into water. The organic layer was washed with 1% H_3PO_4, then with 3% $NaHCO_3$, and dried over anhydrous Na_2SO_4. Upon evaporation of the solvent, 0.614 g of gummy azido ester **19** was obtained as brown colored gum.

Yield: 93%; IR (KBr, cm^{-1}): 602, 670, 761, 873, 1045, 1109, 1150, 1175, 1245, 1510, 1610, 1760, 2100, 2955; ^1H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.37 (s, 3H), 4.16–4.20 (m, 2H), 4.45–4.56 (m, 1H), 4.63 (d, *J*=6.3 Hz, 1H), 7.12–7.48 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.64, 20.75, 64.81, 66.11, 72.05, 122.32, 124.95, 129.44, 135.22, 148.98, 152.24, 159.73, 166.65, 171.37; Analysis: $C_{20}H_{19}N_3O_7$ requires C, 58.11; H, 4.63; N, 10.16; found C, 58.05; H, 4.60; N, 10.10%.

4.11. Preparation of ((4*R*,5*R*)-4-(4-acetoxyphenyl)-2-oxooxazolidin-5-yl)methyl acetate (20)

Azido ester **19** (0.454 g, 1.1 mmol) and PPh_3 (1.18 g, 4.5 mmol) were dissolved in THF (20 ml) and water (2 ml). The reaction mixture was heated at 50 °C for 2 h. Evolution of N_2 was observed during the first 1 h of the reaction. Solvent was evaporated; the solid residue was dissolved in EtOAc (20 ml), washed with brine (10 ml), and dried over anhydrous Na_2SO_4. Crude product was purified by column chromatography and recrystallized from $CHCl_3$ to obtain 0.280 g (87%) of oxazolidinone **20** as gray colored solid.

Yield: 87%; mp: 103 °C (crystallized from $CHCl_3$); $[\alpha]_D^{25}$ −54.82 (*c* 0.8, $CHCl_3$); IR (KBr, cm^{-1}): 971, 1025, 1043, 1051, 1173, 1233, 1367, 1514, 1605, 1712, 1720, 1740, 2938, 3228, 3255, 3475; ^1H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.34 (s, 3H), 3.14–3.16 (m, 2H), 4.66–4.78 (m, 1H), 4.92 (d, *J*=8.2 Hz, 1H), 7.13–7.25 (m, 4H), 8.11 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.64, 20.75, 56.86, 67.49, 80.55, 121.51, 128.59, 132.73, 148.66, 159.92, 170.10, 171.15; Analysis: $C_{14}H_{15}NO_6$ requires C, 57.34; H, 5.16; N, 4.78; found C, 57.28; H, 5.12; N, 4.69%.

4.12. Preparation of (4*R*, 5*R*)-5-hydroxymethyl-4-(4-methoxyphenyl)-oxazolidin-2-one: (−)-cytoxazone (1)

A mixture of oxazolidinone **20** (0.237 g, 0.81 mmol), and 10% aq $NaHCO_3$ (2 ml) in methanol (5 ml) was heated under reflux for 1 h. After the reaction was complete (TLC), solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (5 ml) and was extracted with ethyl acetate (2×5 ml). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product **21**, which without purification, was then added to THF (5 ml) containing NaH (60% suspension in paraffin) (0.034 g, 0.85 mmol) at 0 °C and stirred for 1 h. To this mixture was further added MeI (0.12 g, 0.85 mmol) at 0 °C and then stirred at room temperature for 3 h. After the reaction was complete, the reaction mixture was diluted with water (3 ml) and extracted with diethyl ether (2×5 ml). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product, which was purified by column chromatography and recrystallized from MeOH to afford the required (−)-cytoxazone **1** in 69% (0.124 g) yield as colorless solid.

Yield: 69%; mp: 117–120 °C (crystallized from MeOH), (lit.[1] 118–121 °C); $[\alpha]_D^{25}$ −60.16 (*c* 0.3, MeOH), (lit.[1] $[\alpha]_D^{25}$ −71 (*c* 0.1, MeOH)); HPLC: 83% ee, Chirasphere®, λ=254 nm, 5% 2-propanol/hexane, 1 ml/min, retention time: (*S*,*S*) 16.776 min, (*R*,*R*) 21.001 min; IR (KBr, cm^{-1}): 450, 766, 965, 997, 1026, 1041, 1050, 1177, 1215, 1236, 1254, 1398, 1514, 1615, 1712, 1720, 2948, 3228, 3255, 3352, 3476; ^1H NMR (200 MHz, DMSO-d_6): δ 2.95–2.97 (m, 2H), 3.75 (s, 3H), 4.62–4.73 (m, 1H), 4.82 (t, *J*=5.0 Hz, 1H), 4.90 (d, *J*=4.9 Hz, 1H), 6.91 (d, *J*=8.8 Hz, 2H), 7.15 (d, *J*=8.8 Hz, 2H), 7.92 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.17, 56.82, 61.93, 80.48, 113.79, 128.17, 129.45, 158.81, 160.09; Analysis: $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found C, 59.17; H, 5.80; N, 6.19%.

4.13. Preparation of (3*S*,4*R*)-4-(4-methoxyphenylamino)-3-hydroxy-4-(4-methoxyphenyl)butan-2-one (22)

A mixture of L-proline (0.23 g, 2 mmol), *p*-anisidine (1.35 g, 11 mmol), *p*-anisaldehyde (1.36 g, 10 mmol), and hydroxyacetone (2 ml) in DMSO (10 ml), was stirred at 25 °C for 24 h. After completion of reaction, aq saturated NH_4Cl (10 ml) was added and the mixture was extracted with ethyl acetate. Upon evaporation of the solvent, crude product was purified by column chromatography on silica gel (EtOAc/pet. ether, 3:4) yielding required Mannich product (**22**) 2.39 g (76%) as yellow oil.

Yield: 76%; $[\alpha]_D^{25}$ −1.28 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1092, 1237, 1346, 1513, 1709, 2360, 2916, 3269; ^1H NMR (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 4.42 (d, *J*=2.20 Hz, 1H), 4.91 (d, *J*=2.0 Hz, 1H), 6.54–6.63 (m, 2H), 6.72–6.81 (m, 2H), 6.96–7.05 (m, 2H), 7.35–7.44 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.79, 55.62, 56.12, 60.14, 81.32, 114.15, 115.24, 115.76, 128.60, 131.58,

140.00, 152.77, 159.44, 207.98; Analysis: $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44; found C, 68.50; H, 6.80; N, 4.39%.

4.14. Preparation of (4*R*,5*S*)-5-acetyl-3,4-bis(4-methoxyphenyl)oxazolidin-2-one (23)

The Mannich product **22** (0.315 g, 1 mmol), in dry CH_2Cl_2 (20 ml) was cooled to −20 °C and to this Et_3N (506 mg, 5 mmol) and triphosgene (297 mg, 1 mmol) was added. The mixture was warmed to room temperature, stirred for 3 h, and quenched with aq NH_4Cl (10 ml). After extraction with CH_2Cl_2 (20 ml), the organic layer was dried over Na_2SO_4 and concentrated to furnish crude *trans*-oxazolidinone **23**, which was further purified by column chromatography (EtOAc/pet. ether, 5:3) yielding 0.28 g (82%) of white solid.

Yield: 82%; mp: 106–108 °C (crystallized from EtOH); $[\alpha]_D^{25}$ −18.14 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 740, 807, 927, 1035, 1099, 1179, 1248, 1367, 1452, 1513, 1612, 1726, 2860, 2934, 3228, 3300; ^1H NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.66 (s, 3H), 3.74 (s, 3H), 4.58 (d, *J*=4.8 Hz, 1H), 5.41 (d, *J*=4.8 Hz, 1H), 6.55–6.59 (m, 2H), 6.71–6.82 (m, 2H), 6.95–7.06 (m, 2H), 7.37–7.46 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.72, 55.24, 55.97, 62.43, 83.12, 114.16, 115.24, 115.76, 128.87, 129.19, 129.34, 137.77, 157.00, 204.55; Analysis: $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.61; N, 4.10; found C, 66.77; H, 5.56; N, 4.04%.

4.15. Preparation of (4*R*,5*S*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one: (+)-*epi*-cytoxazone (2)

To a 1 M solution of lithium hexamethyldisilylamide (1.6 ml, 1.6 mmol) at −78 °C under an argon atmosphere was added chlorotrimethylsilane (0.64 ml, 4.88 mmol) dropwise. A cold (−78 °C) solution of oxazolidinone **23** (0.275 g, 0.8 mmol) in THF (2 ml) was then added dropwise. After being stirred for 25 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred for 30 min and then concentrated in vacuum. After drying ($MgSO_4$) and removal of the solvent in vacuum, the crude silyl enol ether **24** was used directly in the next step without further purification because it partly rearranged to ketone **23** during attempted purification. A solution of this crude silyl enol ether **24** in MeOH (15 ml) and CH_2Cl_2 (10 ml) was cooled to −78 °C, and ozone was bubbled through this solution for 45 min. Triphenylphosphine (0.223 g, 0.885 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated in vacuum, and the residue was dissolved in absolute EtOH (4 ml), $CaCl_2$ (0.15 g, 1.35 mmol) and $NaBH_4$ (0.16 g, 4 mmol) was added, and the reaction mixture was stirred for 20 min at 25 °C. The excess of reducing agent was destroyed by the addition of satd NH_4Cl (0.5 ml) and then EtOH was evaporated; the residue was then dissolved in CH_3CN (5 ml) at 0 °C which was then treated with cerium ammonium nitrate (2.2 g, 4 mmol) in water (3 ml). The mixture was stirred for 5 min, treated with 10 ml of satd aq $NaHCO_3$, warmed to 25 °C, and treated with solid Na_2SO_3 (0.126 g, 1 mmol). The reaction mixture was extracted with ethyl acetate (3×6 ml), dried, and concentrated to furnish after column chromatography pure (+)-*epi*-cytoxazone (**2**) as colorless solid in (0.105 g) 59% yield and 81% ee.

Yield: 59%; mp: 159–160 °C (crystallized from MeOH), (lit.[4b] 158–160 °C); $[\alpha]_D^{25}$ +22.89 (*c* 0.4, MeOH), (lit.[4b] $[\alpha]_D^{25}$ +28.6 (*c* 1, MeOH)); HPLC: 81% ee, Chiracel OD-H®, λ=280 nm, 15% 2-propanol/hexane, 0.8 ml/min, retention time: (*R*,*S*) 14.32 min, (*S*,*R*) 15.28 min; IR (KBr, cm^{-1}): 830, 1025, 1240, 1510, 1720, 2920, 3290; ^1H NMR (200 MHz, DMSO-d_6): δ 3.62–3.66 (m, 1H), 3.75 (s, 3H), 3.80–3.84 (m, 1H), 4.43–4.47 (m, 1H), 4.78 (d, *J*=5.9 Hz, 1H), 6.93 (d, *J*=8.7 Hz, 2H), 7.2 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.41, 57.12, 62.23, 85.58, 114.81, 128.73, 131.52, 159.77, 161.00; Analysis: $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found C, 59.14; H, 5.72; N, 6.22%.

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