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An efficient synthesis of (+)-*epi*-cytoxazone via asymmetric organocatalysis

Sung-Gon Kim [a,*], Tae-Ho Park [b]

[a] *Department of Chemistry, College of Natural Science, Kyonggi University, San 94-6, Iui-dong, Yeongtong-gu, Suwon 443-760, Republic of Korea*
[b] *Medicinal Science Division, Korea Research Institute of Chemical Technology, PO Box 107, Yuseong-gu, Daejeon 305-600, Republic of Korea*

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ABSTRACT

The catalytic enantioselective synthesis of (+)-*epi*-cytoxazone has been accomplished in four steps from *p*-methoxybenzaldehyde *N*-Boc-imine with good diastereo- and enantioselectivity. This approach involves asymmetric Mannich reaction of an aldehyde with *N*-Boc-imine using the novel 2-pyrrole-derived imidazolidinone as an organocatalyst.

1. Introduction

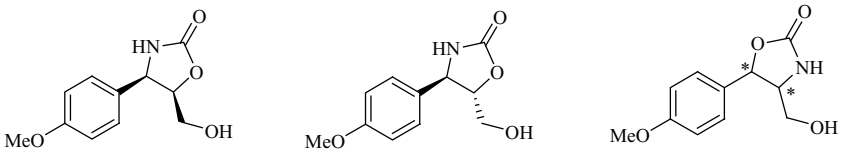
(−)-Cytoxazone **1**, containing a novel 4,5-disubstituted-2-oxazolidinone moiety, is a microbial metabolite isolated from *Streptomyces*, which shows cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells.[1] Since Th2 cells play a role in mediating the immune response to allergens, cytoxazone its stereoisomers might be lead compounds for the development of therapeutic agents for asthma and atopic dermatitis, and have attracted considerable attention from synthetic chemists. A variety of synthetic methods including (−)-cytoxazone and its stereoisomers (+)-*epi*-cytoxazone and isocytoxazone have been reported (Fig. 1).[2] In several of the synthetic approaches, the α-hydroxy β-amino functionalities are used as key intermediates, which can be indirectly introduced in two ways: either by the enantioselective Sharpless epoxidation,[3] dihydroxylation,[4] and aminohydroxylation[5] into cinnamic acid derivatives or by the enantioselective and diastereoselective C–C bond formation between building blocks involving the Petasis reaction,[6] aldol reaction,[7] and imino-1,2-Wittig rearrangement.[8]

Herein, as part of a program for the synthesis of biologically active natural products based on asymmetric organocatalysis,[9] we report a short and efficient synthesis of (+)-*epi*-cytoxazone including the direct asymmetric synthesis of an α-hydroxy β-amino alcohol.

2. Results and discussion

Our synthetic approach toward the target molecule is based on the organocatalytic asymmetric Mannich reaction of aldehydes with *N*-Boc-imines, which have recently been developed by List and Córdova independently (Scheme 1).[10] This direct asymmetric Mannich reaction using (*S*)-proline as an organocatalyst is a highly effective carbon–carbon bond forming reaction that affords *syn*-selective and enantioselective β-amino aldehydes. We employed their organocatalytic Mannich reaction in the synthesis of (+)-*epi*-cytoxazone.

In an initial use of (*S*)-proline as the organocatalyst,[11] we found that the Mannich reaction between *p*-methoxybenzaldehyde *N*-Boc-imine **4**[12] and benzyloxyacetaldehyde **9** afforded the corresponding β-amino aldehyde **10** in high yield with excellent enantioselectivity (Table 1). However, the product had poor diastereoselectivity (2:1 *syn*:*anti*) and the diastereomers could not be separated by column chromatography even after hydrolysis to the β-amino alcohol. Hence, we decided to investigate various organocatalysts in order to obtain high diastereoselectivity in this



(-)-cytoxazone **1** (+)-*epi*-cytoxazone **2** isocytoxazone **3**

Figure 1. Cytoxazone and its stereoisomers.

* Corresponding author. Tel.: +82 31 249 9631; fax: +82 31 249 9639.
E-mail address: sgkim123@kgu.ac.kr (S.-G. Kim).

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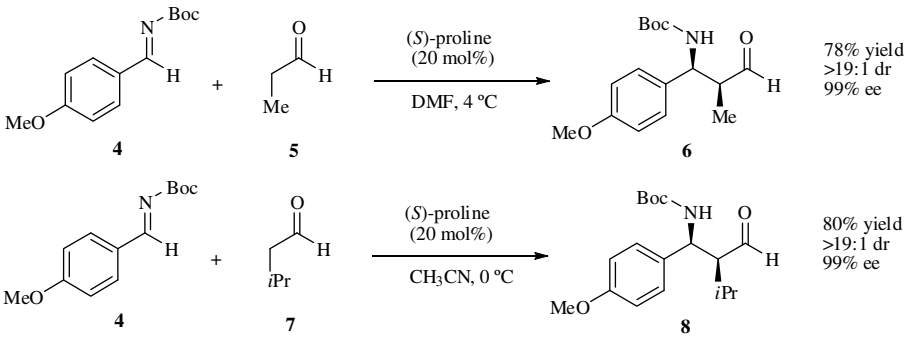
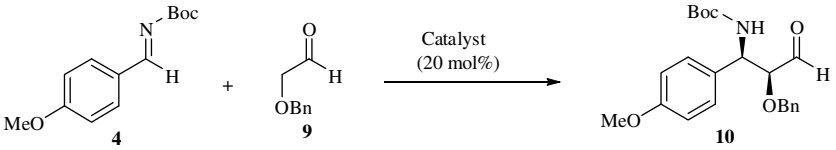


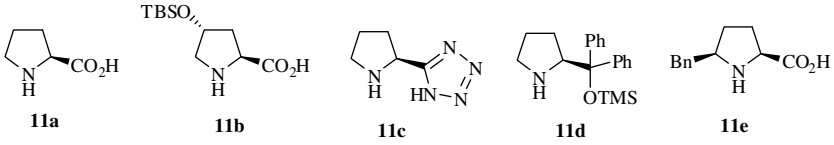
Scheme 1. Proline-catalyzed Mannich reaction of aldehydes with *N*-Boc-imine.

Table 1
Organocatalytic Mannich reaction of α-benzyloxyacetaldehyde with *p*-methoxybenzaldehyde *N*-Boc-imine



Entry	Catalyst	Solvent	Temp (°C)	Yield[a] (%)	dr (*syn*:*anti*)[b]	ee (%) *syn*[c]	ee (%) *anti*[c]
1	**11a**	DMF	rt	80	2:1	98	99
2	**11a**	DMF	0	84	3:1	99	99
3	**11b**	DMF	rt	—[d]	2:1	98	95
4	**11c**	DMF	rt	—[d]	3:2	67	68
5	**11d**	$CHCl_3$	0	77	1:1	48	60
6	**11e**	DMF	rt	42	1:4	21	62

[a] Yield of isolated product.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H).
[d] Not determined.



Mannich reaction. *trans*-4-*tert*-Butyldimethylsilyloxy-(*S*)-proline **11b** showed the same level of diastereomeric ratio and ee's with (*S*)-proline (entry 3). In the cases of (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole **11c** and (*S*)-2-(diphenyl-trimethylsilanyloxymethyl)pyrrolidine **11d**, their diastereo- and enantioselectivity were lower than the case of (*S*)-proline (entries 4 and 5). Even though diastereoselectivity was increased in the case of (2*S*,5*R*)-5-benzyl-pyrrolidine-2-carboxylic acid **11e**[13] when used as a catalyst, the enantioselectivity was not satisfied.

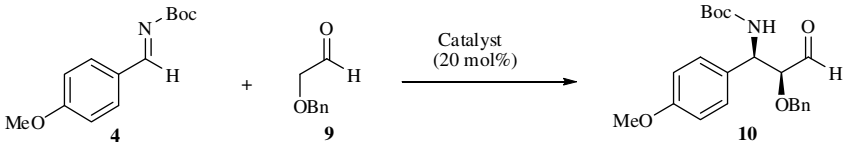
Next, we turned our attention to the imidazolidinone catalyst as the organocatalyst for the Mannich reaction between *p*-methoxybenzaldehyde *N*-Boc-imine **4** and benzyloxyacetaldehyde **9**, which has not been applied to the asymmetric Mannich reactions until now (Table 2). This Mannich reaction was successful with imdazolidinone **11f**·TFA but gave poor diastereo- and enantioselectivity (entry 1). In contrast, the imidazolidinone **11h**·TFA slightly increased the diastereoselectivity (entry 3, 3:1 dr) although with a low enantioselectivity. Hence, a heteroaromatic group at the C(5) position in the imidazolidinone was considered to effect the stereocontrol in this Mannich reaction and new 2-pyrrole-derived imidazolidinones **11i** and **11j** were elaborated. As expected, new 2-pyrrole-derived imidazolidinone **11j** afforded satisfactory levels of diastereo- and enantioselectivity maintaining a good yield (entry 5, 90% yield, 4:1 *syn*:*anti*, 82% ee). After extensive optimization of reaction conditions, including screening reaction media, temperature, and acid additives, we found that the use of $CHCl_3$ as a solvent and TCA as an additive at −30 °C gave the best result (entry 7, 78% yield, 8:1 *syn*:*anti*, 94% ee).

Having the requisite β-amino aldehyde **10** in hand, we carried out the synthesis of (+)-*epi*-cytoxazone (Scheme 2). β-Amino aldehyde **10** was reduced with sodium borohydride to afford β-amino alcohol **12** in 98 % yield. Deprotection of **12** by hydrogenolysis of the benzyl group afforded the desired diol **13** in 91% yield. Finally, treatment of compound **13** with sodium hydride in THF led to regioselective cyclization to give (+)-*epi*-cytoxazone **2** in 85% yield $\{[\alpha]_D^{23} = +32.8$ (*c* 0.6, MeOH)$\}$.[3b,7] The physical and spectroscopic data of **2** are in full agreement with the literature data.

3. Conclusion

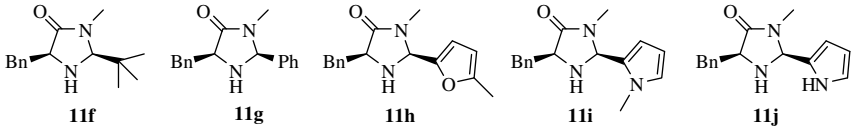
In conclusion, we have completed a short and efficient synthesis of (+)-*epi*-cytoxazone, based on the organocatalytic asymmetric Mannich reaction between *p*-methoxybenzaldehyde *N*-Boc-imine and benzyloxyacetaldehyde using the novel 2-pyrrole-derived

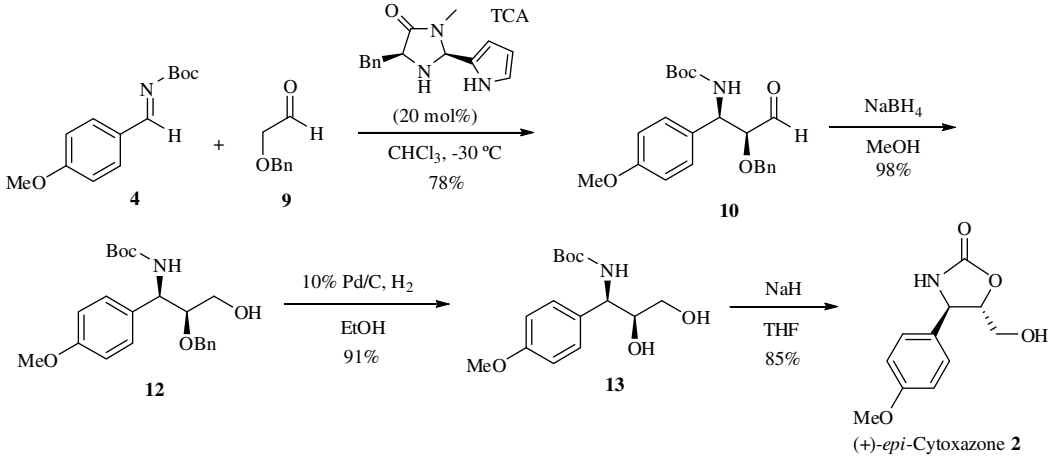
Table 2
Organocatalytic Mannich reaction of α-benzyloxyacetaldehyde with *p*-methoxybenzaldehyde *N*-Boc-imine using imidazolidinone catalysts



Entry	Catalyst	Solvent	Temp (°C)	Yield[a] (%)	dr (*syn*:*anti*)[b]	ee (%) *syn*[c]	ee (%) *anti*[c]
1	**11f** + TFA	$CHCl_3$	rt	91	2:1	43	44
2	**11g** + TFA	$CHCl_3$	rt	72	2:1	43	0
3	**11h** + TFA	$CHCl_3$	rt	84	3:1	45	0
4	**11i** + TFA	$CHCl_3$	rt	78	5:2	26	10
5	**11j** + TFA	$CHCl_3$	rt	90	4:1	82	45
6	**11j** + TFA	$CHCl_3$	−30	80	5:1	89	—[d]
7	**11j** + TCA	$CHCl_3$	−30	78	8:1	94	—[d]

[a] Yield of isolated product.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H).
[d] Not determined.





Scheme 2. Asymmetric synthesis of (+)-*epi*-cytoxazone.

imidazolidinone as an organocatalyst. The enantioselective synthesis of (+)-*epi*-cytoxazone was achieved in four steps from *p*-methoxybenzaldehyde *N*-Boc-imine (59% yield, 94% ee). The applications of the other organocatalytic asymmetric reactions of 2-pyrrole-derived imidazolidinone are now in progress and will be presented in due course.

4. Experimental

4.1. General methods

Commercial reagents were used without further purification. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. All organic solvents were distilled prior to use. Chromatographic purification of the products was accomplished using forced-flow chromatography on ICN 60 32–64 mesh Silica Gel 63. Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm Silica Gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching and anisaldehyde stain. Melting points were determined on a Tomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Jasco 610 FT-IR spectrometer using KBr salt plates, and reported in terms of frequency of absorption (cm^{-1}). Mass spectra and elemental analysis data were obtained from the Korea Research Institute of Chemical Technology Facility. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm). HPLC analysis was performed on a Shimadzu LC-20 A Prominence HPLC using the following Chiralcel columns: AD (25 cm) and AD guard (5 cm), as noted.

4.2. (2*S*,5*S*)-5-Benzyl-3-methyl-2-pyrrole-imidazolidine-4-one 11j

To a solution of (*S*)-phenylalanine methyl amide (3.00 g, 16.8 mmol) and pyrrol-2-carboxaldehyde (1.40 g, 14 mmol) in THF (25 mL) was added samarium(III) trifluoromethanesulfonate hydrate (410 mg, 0.84 mmol) and powdered 4 Å molecular sieves (4.5 g). After stirring for 52 h at room temperature, the reaction mixture was filtered, concentrated, and purified by flash column chromatography (60% EtOAc/hexane) to afford the title compound as a pale yellow oil in 42% yield (1.50 g, 5.88 mmol) and the faster eluting (2*R*,5*S*)-isomer as a pale yellow oil in 35% yield (1.25 g, 4.9 mmol). $[\alpha]_D^{25} = -145.1$ (*c* 0.7, $CHCl_3$); IR (KBr): 3412, 3293, 2923, 2857, 1686, 1478, 1450, 1402, 1334, 1273, 1098, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.44 (m, 5H), 7.16 (br s, 1H), 6.54 (dd, *J* = 3.0, 4.2 Hz, 1H), 6.16 (dd, *J* = 4.2, 6.0 Hz, 1H), 6.06 (dd, *J* = 3.0, 6.0 Hz, 1H), 5.32 (s, 1H), 4.02 (t, *J* = 4.6 Hz, 1H), 3.31 (dd, *J* = 4.8, 13.8 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 137.8, 130.6, 128.9, 128.7, 127.1, 119.6, 109.4, 108.2, 70.6, 59.7, 38.0, 30.0; HRMS (M+) calcd for $C_{15}H_{17}N_3O^+$: 255.1372; found, 255.1366.

4.3. (1*R*,2*S*)-[2-Benzyloxy-3-hydroxy-1-(4-methoxyphenyl)-propyl]-carbamic acid *tert*-butyl ester 12

To a solution of (4-methoxybenzylidene)-carbamic acid *tert*-butyl ester **4** (59 mg, 0.25 mmol), (2*S*,5*S*)-5-benzyl-3-methyl-2-pyrrole-imidazolidine-4-one **11j** (10.2 mg, 0.050 mmol), and 1 M trichloroacetic acid (50 μL, 0.050 mmol) in chloroform (0.5 mL) at −30 °C was added benzyloxyacetaldehyde **9** (75 mg, 0.50 mmol). After stirring for 36 h at this temperature, the reaction mixture was allowed to warm 0 °C, after which were added methanol (1 mL) and an excess of sodium borohydride. After 15 min, the remaining sodium borohydride was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (10% EtOAc/Hexanes then 30% EtOAc/hexanes) to afford the title compound as a white solid (75 mg, 78%). The ratio of the *syn*- and *anti*- product was determined by ^1H-NMR spectra. The enantiomeric excess of products was measured by HPLC analysis. mp 174–175 °C; $[\alpha]_D^{23} = -18.6$ (*c* 0.6, $CHCl_3$); IR (KBr): 3374, 2977, 2934, 1682, 1513, 1456, 1296, 1249, 1169, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.41 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.36 (d, *J* = 9.3 Hz, 1H), 4.95 (br s, 1H), 4.28 (dd, *J* = 11.1, 30.3 Hz, 2H), 3.81 (s, 3H), 3.55–3.77 (m, 3H), 3.13 (br s, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 157.2, 138.0, 128.7, 128.6, 128.3, 128.1, 128.0, 114.1, 82.7, 80.3, 73.8, 61.7, 55.5, 53.6, 28.6; Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 67.98; H, 7.77; N, 3.54. HPLC (Chiralcel AD-H, 7.5% isopropanol/hexanes, 1 mL/min); t_{minor} = 16.7 min, t_{major} = 20.0 min, 94% ee.

4.4. (1*R*,2*S*)-[2,3-Dihydroxy-1-(4-methoxyphenyl)-propyl]-carbamic acid *tert*-butyl ester 13

To a solution of (1*R*,2*S*)-[2-benzyloxy-3-hydroxy-1-(4-methoxyphenyl)propyl]-carbamic acid *tert*-butyl ester **12** (395 mg, 1.02 mmol) in EtOH (60 mL) were added 10% Pd/C (0.2 w/w, 60 mg) and 1 drop of 4 M HCl in dioxane. After stirring for 2 h under an H_2 atmosphere, Pd/C was filtered out and the reaction solvent was evaporated in vacuo. The residue was purified by flash column chromatography (70% EtOAc in hexanes) to afford the title compound as a white solid (275 mg, 91%). mp 141–142 °C; $[\alpha]_D^{23} = -36.1$ (c 1.0, $CHCl_3$); IR (KBr): 3385, 2976, 2934, 1688, 1613, 1512, 1367, 1298, 1248, 1170, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.22 (d, *J* = 8.1 Hz, 1H), 4.76 (br s, 1H), 3.92 (m, 1H), 3.80 (s, 3H), 3.54 (dd, *J* = 6.3, 6.6 Hz, 2H), 2.75 (br s, 1H), 2.66 (br s, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.0, 132.2, 129.2, 114.4, 79.5, 76.3, 64.9, 55.9, 54.3, 28.5; Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.27; H, 8.05; N, 4.65.

4.5. (4*R*,5*S*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)-oxazolidin-2-one [(+)-*epi*-cytoxazone] 2

To a solution of (1*R*,2*S*)-[2,3-dihydroxy-1-(4-methoxyphenyl)-propyl]-carbamic acid *tert*-butyl ester **13** (60 mg, 0.27 mmol) in THF (1 mL) was added NaH (14 mg, 0.32 mmol, 60% in mineral oil) at 0 °C. After stirring for 2 h at this atmosphere, the reaction mixture was allowed to warm at room temperature and stirred for an additional 2 h and quenched with H_2O, and then extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (30% EtOAc/hexanes then) to afford the title compound as a white solid (45 mg, 85%). mp 161–162 °C; $[\alpha]_D^{23} = +32.8$ (*c* 0.6, MeOH); IR (KBr): 3285, 2944, 2930, 1752, 1723, 1510, 1255, 1026 cm^{-1}; ^1H NMR (300 MHz, DMSO-D_6) δ 8.01 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.17 (br s, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.12 (m, 1H), 3.73 (s, 3H), 3.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.0, 131.9, 129.1, 114.6, 82.5, 61.4, 57.3, 54.8.

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