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Stereoselective syntheses of cytoxazone, a novel cytokine modulator, and its stereoisomers

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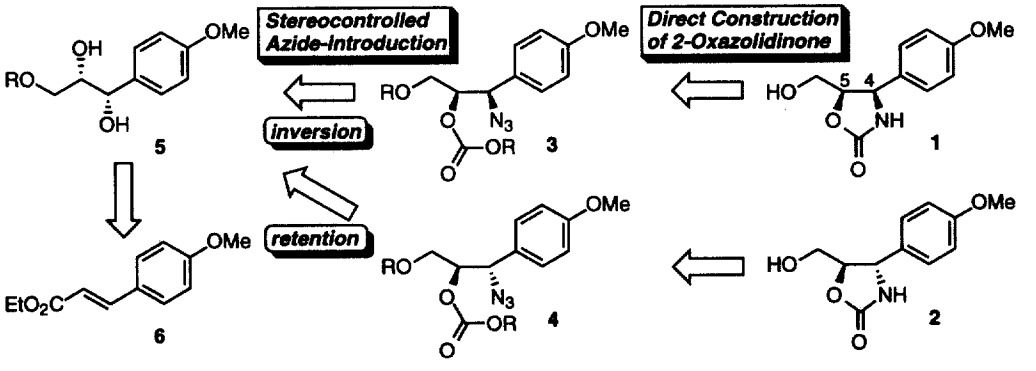
Abstract

Cytoxazone, a novel cytokine modulator, and its stereoisomers were stereoselectively synthesized *via* stereocontrolled introduction of an azide group and direct construction of the 2-oxazolidinone ring from an azide carbonate by reductive cyclization.

Keywords: Oxazolidinones; Stereocontrol; Azides; Sharpless asymmetric dihydroxylation

Cytoxazone (**1**), produced by *Streptomyces* sp., is a novel cytokine modulator, which interferes with the cytokine IL-4, IL-10 and IgG production by selective inhibition of the signaling pathway of Th2 cells [1]. The structure of **1** includes a 4,5-disubstituted 2-oxazolidinone ring, which is rare in microbial metabolites. The absolute configuration of **1** was determined to be 4*R*,5*R* on the basis of the comparison of the CD spectra with those of (*R*)- and (*S*)-4-phenyl-2-oxazolidinones. In this paper, we report the enantioselective total syntheses of cytoxazone (**1**), 4-*epi*-cytoxazone (**2**), and their enantiomers, and the establishment of the absolute configuration of natural cytoxazone [2].

Our synthetic strategy for cytoxazone (**1**) and 4-*epi*-cytoxazone (**2**) is summarized in Scheme 1. Although 2-oxazolidinone rings are typically synthesized from the corresponding amino



Scheme 1

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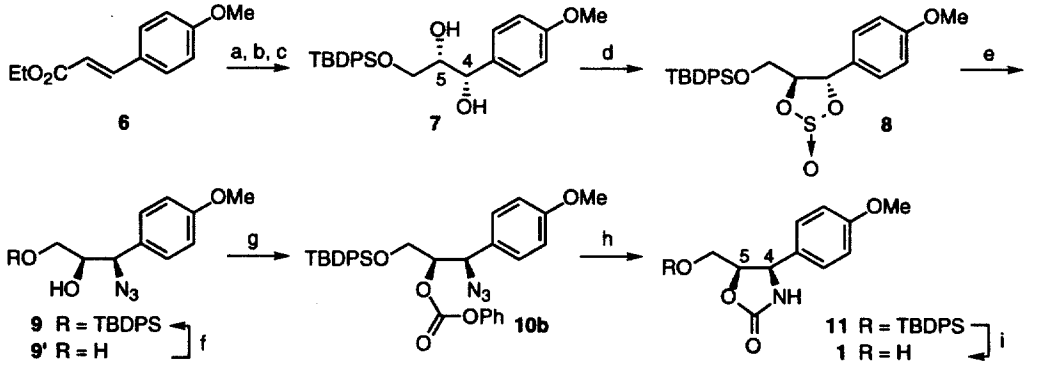
alcohols [3], our synthesis of the 2-oxazolidinone ring in **1** and **2** is designed on direct construction from azide carbonates **3** and **4** by reduction of azide to amine and subsequent cyclization. The key step for the syntheses of **1** and **2** is the regio- and stereoselective introduction of an azide group into a common synthetic intermediate diol **5** to give β-azide **3** and α-azide **4**, respectively. The diol **5** would be obtained from ethyl *p*-methoxycinnamate (**6**) with high enantioselectivity by the Sharpless catalytic asymmetric dihydroxylation [4].

(4*R*,5*R*)-Cytoxazone (**1**) was synthesized starting from ethyl *p*-methoxycinnamate (**6**) [5] as shown in Scheme 2. The asymmetric dihydroxylation of **6** with AD-mix-α in *t*-BuOH/H_2O gave an optically pure diol (93%, 99% ee) [6], which was subjected to reduction with $NaBH_4$ followed by protection with *t*-butyldiphenylsilyl chloride (TBDPSCl) to afford (4*S*,5*S*)-diol **7** (cytoxazone numbering) in 65% yield. Neither *p*-methoxycinnamyl alcohol nor its silyl ether derivative was appropriate for the synthesis of **7**, because these asymmetric dihydroxylations proceeded with low enantiomeric excess [7]. For regioselective introduction of an azide group into the diol **7** with inversion of stereochemistry, we investigated a nucleophilic substitution of a cyclic sulfite [8]. The treatment of **7** with $SOCl_2$ in the presence of Et_3N [9] produced cyclic sulfite **8** in 99% yield as a 1.4:1 diastereomeric mixture due to the stereogenic sulfur atom. The sulfite **8** was treated with LiN_3 in DMF at 70 °C to afford azide alcohol **9** (74%) and desilylated azide diol **9'** (24%), which was quantitatively converted to **9** by TBDPSCl/imidazole treatment. In this azide substitution reaction, complete regio- and stereoselectivities were achieved. To construct the 2-oxazolidinone ring, the azide alcohol **9** was converted to phenyl carbonate **10b** by treatment with $ClCO_2Ph$/pyridine. The construction of the oxazolidinone ring was performed in one pot; *i.e.*, upon treatment of **10b** with Ph_3P in THF/H_2O, the azide reduction and cyclization took place simultaneously to give the desired 2-oxazolidinone **11** in 90% yield [10]. Finally, removal of the TBDPS group of **11** with tetrabutylammonium fluoride gave (4*R*,5*R*)-cytoxazone (**1**) in 96% yield. The ^1H NMR spectrum and the optical rotation of the synthetic **1** were identical with those of natural cytoxazone (**1**) [12]. Therefore, the absolute



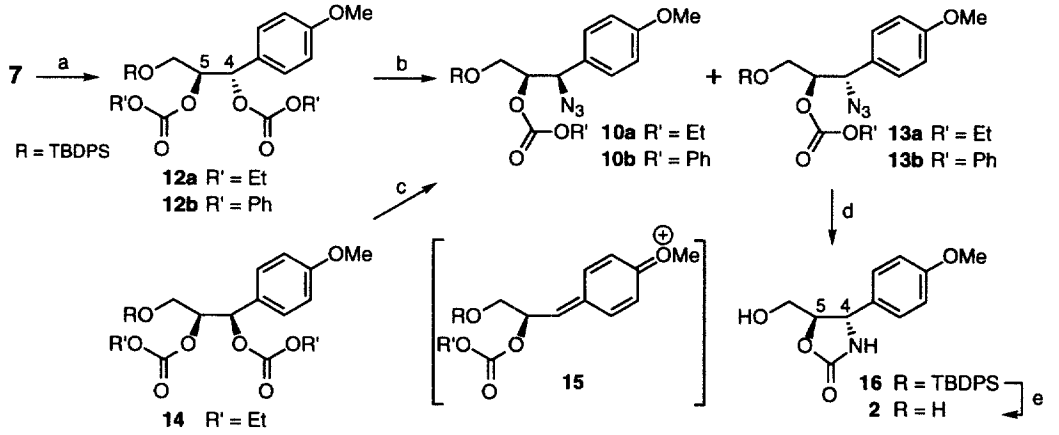
a) AD-mix-α, *t*-BuOH/H_2O (1:1), r.t., 93% (99%ee); b) $NaBH_4$, THF, 0 °C, 66%; c) TBDPSCl, imidazole, DMF, 0 °C, 99%, d) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 99%; e) LiN_3, DMF, 70 °C, **9**: 74%, **9'**: 24%; f) TBDPSCl, imidazole, DMF, 0 °C, 100%, g) $ClCO_2Ph$, Py, CH_2Cl_2, r.t., 96%; h) PPh_3, THF/H_2O, 50 °C, 90%; i) *n*-Bu_4NF, THF, 0 °C, 96%.

Scheme 2

configuration of cytoxazone was established synthetically.

We next examined the synthesis of 4-*epi*-cytoxazone (**2**) from the common intermediate **7** (Scheme 3). For this purpose the introduction of an azide group at the C-4 position of **7** requires retention of stereochemistry, which is usually achieved by a stepwise double inversion process of bromination and azidation [13,14]. We have developed an efficient one-step method for the stereoselective azidation. Thus, (4*S*,5*S*)-di(ethylcarbonate) **12a**, prepared from (4*S*,5*S*)-diol **7** with $ClCO_2Et$/pyridine, was treated with $TMSN_3$ (6 eq.) in the presence of TMSOTf (2 eq.) in MeCN at -43 °C to afford a 6:1 mixture of the desired α-azide **13a** and its β-isomer **10a**. In order to investigate this stereoselective reaction, the stereoisomer (4*R*,5*S*)-di(ethylcarbonate) **14** was also subjected to the same reaction conditions, which gave almost the same result as that of **12a**, giving the α-azide **13a** as the predominant isomer. These results show that the present stereoselective azidations proceed without stereospecificity through the same oxonium ion **15** as a reaction intermediate. After several attempts to improve the stereoselectivity, the best result for the azidation was obtained using (4*S*,5*S*)-di(phenylcarbonate) **12b**, prepared from **7** with $ClCO_2Ph$/pyridine. Thus, the treatment of **12b** with $TMSN_3$ (6 eq.) in the presence of TMSOTf (2 eq.) in EtCN/MeCN (2:1) at -50 °C gave a 9.5:1 mixture of α-azide **13b** and β-azide **10b** in 99% yield. The desired α-azide **13b** was treated with PPh_3 in THF/H_2O to give 2-oxazolidinone **16** [15], which was successfully converted to 4-*epi*-cytoxazone (**2**) in 99% yield by using tetrabutylammonium fluoride [16].

Utilizing the developed synthetic routes, we have also synthesized *ent*- and 5-*epi*-cytoxazones, the enantiomers of **1** and **2**, respectively, by use of AD-mix-β in the asymmetric dihydroxylation.



For R'=Et: a) $ClCO_2Et$, Py, CH_2Cl_2, 0 °C, 92%; b) $TMSN_3$, TMSOTf, MeCN, -43 °C, 99%; c) $TMSN_3$, TMSOTf, MeCN, -43 °C, 91%. **For R'=Ph:** a) $ClCO_2Ph$, Py, CH_2Cl_2, 0 °C, 100%; b) $TMSN_3$, TMSOTf, EtCN/MeCN (2:1), -50 °C, 99%; d) PPh_3, THF/H_2O, 50 °C, 100%; e) *n*-Bu_4NF, THF, 0 °C, 99%.

Scheme 3

In summary, we have accomplished the stereoselective syntheses of cytoxazone (**1**), 4-*epi*-cytoxazone (**2**), and their enantiomers by the stereocontrolled introduction of an azide group

and the direct construction of the 2-oxazolidinone ring from an azide carbonate. The biological activities of cytoxazone and its stereoisomers are under investigation. Work on the syntheses of cytoxazone derivatives is also in progress.

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References and Notes

[1] (a) Kakeya H, Morishita M, Kobinata K, Osono M, Ishizuka M, Osada H. J. Antibiot. 1998; 51: 1126-1128. (b) Kakeya H, Morishita M, Koshino H, Morita T, Kobayashi K, Osada H. J. Org. Chem. 1999; 64: 1052-1053.

[2] Sakamoto Y, Shiraishi A, Nakata T, Kakeya H, Osada H. 74th Spring Meeting of the Japan Chemical Society, 1998: Abstract 3E737.

[3] For reviews, see: (a) Ager DJ, Prakash I, Schaad DR. Chem. Rev. 1996; 96: 835-875. (b) Dyen ME, Swern D. ibid. 1967; 67: 197-246.

[4] (a) Sharpless KB, Amberg W, Bennani YL, Crispino GA, Hartung J, Jeong K-S, Kwong H-L, Morikawa K, Wang Z-M, Xu D, Zhang X-L. J. Org. Chem. 1992; 57: 2768-2771. For a review, see: (b) Kolb HC, VanNieuwenhze MS, Sharpless KB. Chem. Rev. 1994; 94: 2483-2547.

[5] Ethyl *p*-methoxycinnamate (**6**) is commercially available from Tokyo Kasei Co., Ltd.

[6] The optical purity of the resulting diol ester was determined chromatographically with a Chiralcel OJ HPLC column (Daicel Chemical Technologies).

[7] A similar result was reported, see: Lohray BB, Kalantar TH, Kim BM, Park CY, Shibata T, Wai JSM, Sharpless KB. Tetrahedron Lett. 1989; 30: 2041-2044.

[8] (a) Lohray BB, Ahuja JR. J. Chem. Soc., Chem. Commun. 1991; 95-97. (b) Kim BM, Sharpless KB. Tetrahedron Lett. 1990; 31: 4317-4320. For a review, see: (c) Lohray BB. Synthesis 1992; 1035-1052. See also ref. 3b and references cited therein.

[9] Kim BM, Sharpless KB. Tetrahedron Lett. 1989; 30: 655-658.

[10] It is not obvious whether this oxazolidinone formation proceeds stepwise *via* hydrolysis of the resulting iminophosphorane to an amine followed by nucleophilic cyclization or, alternatively, *via* the Staudinger-aza-Wittig cyclization [11] followed by hydrolysis of the resulting oxazoline.

[11] For a review, see: Molina P, Vilaplana MJ. Synthesis 1994, 1197-1218.

[12] The physical data for synthetic cytoxazone (**1**): mp 122-123 °C; IR (KBr) 3482, 3255, 1713, 1515, 1253, 1177, 1050, 1028, 997 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 7.23 (d, J = 8.8 Hz, 2H), 6.95 (br s, 1H, NH), 6.93 (d, J = 8.8 Hz, 2H), 5.01 (d, J = 8.3 Hz, 1H), 4.81 (ddd, J = 8.3, 8.3, 4.4 Hz, 1H), 3.83 (dd, J = 6.4, 4.9 Hz, 1H, OH), 3.79 (s, 3H), 3.22 (ddd, J = 11.7, 8.3, 4.9 Hz, 1H), 3.17 (ddd, J = 11.7, 6.4, 4.4 Hz, 1H); ^{13}C NMR (150.8 MHz, acetone-d_6) δ 160.6, 159.5, 130.2, 129.0, 114.6, 81.4, 62.5, 57.8, 55.5; $[\alpha]^{26}_D$ -75.7 (*c* 1.00, MeOH) [lit. [1], $[\alpha]^{23}_D$ -71 (*c* 0.1, MeOH)]; Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.21; H, 5.87; N, 6.35.

[13] (a) Koskinen AMP, Karvinen EK, Siirilä JP. J. Chem. Soc., Chem. Commun. 1994; 21-22. (b) Wang Z-M, Kolb HC, Sharpless KB. J. Org. Chem. 1994; 59: 5104-5105. (c) Harada N, Hashiyama T, Ozaki K, Yamaguchi T, Ando A, Tsujihara K. Heterocycles 1997; 44: 305-318.

[14] An efficient epoxide-opening substitution reaction on a *p*-methoxybenzylic carbon with retention was reported, see: Hashiyama T, Inoue H, Konde M, Takeda M. J. Chem. Soc., Perkin Trans. I 1984; 1725-1732.

[15] When ethyl carbonate **13a** was employed in the azide reduction using PPh_3, the migration of the ethoxycarbonyl group took place to form a non-cyclic carbamate at the C-4 position (53%). The resulting carbamate was also converted to the 2-oxazolidinone **16** with NaH in THF at room temperature (68%).

[16] The physical data for 4-*epi*-cytoxazone (**2**): mp 161.5-162.5 °C; IR (KBr) 3253, 3147, 1740, 1724, 1515, 1252, 1101, 1022, 832 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 7.32 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.92 (br s, 1H, NH), 4.78 (d, J = 6.4 Hz, 1H), 4.31 (dd, J = 6.4, 5.4 Hz, 1H, OH), 4.24 (ddd, J = 6.4, 4.4, 3.9 Hz, 1H), 3.81 (ddd, J = 12.2, 5.4, 3.9 Hz, 1H), 3.79 (s, 3H), 3.70 (ddd, J = 12.2, 6.4, 4.4 Hz, 1H); ^{13}C NMR (150.8 MHz, acetone-d_6) δ 160.6, 159.0, 133.9, 128.4, 115.0, 85.6, 62.4, 57.6, 55.6; $[\alpha]^{28}_D$ -30.4 (*c* 1.01, MeOH); Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.93; H, 5.88; N, 6.20.