

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

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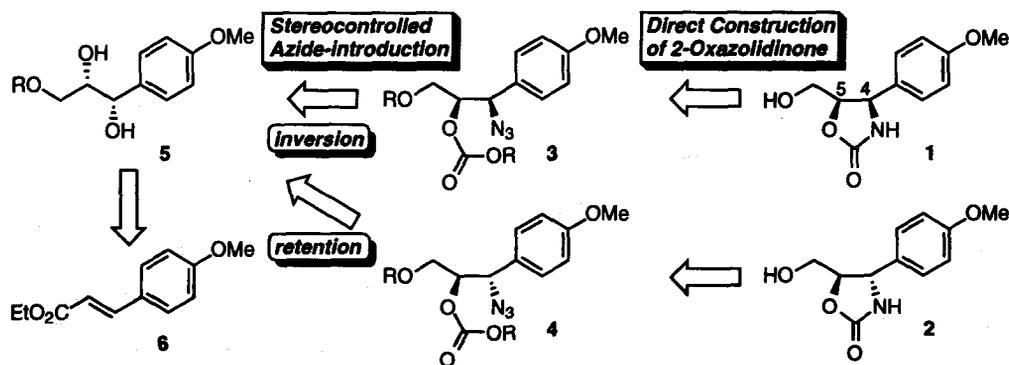
Abstract

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. © 1999 Elsevier Science Ltd. All rights reserved.

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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].

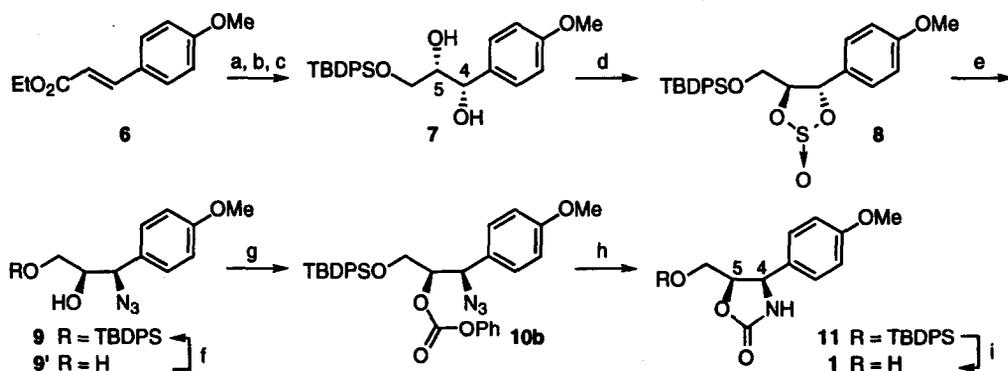
Our synthetic strategy for cytoxazone (**1**) and 4-*epi*-cytoxazone (**2**) is summarized in Scheme 1. Although 2-oxazolidinone rings are typically synthesized from the corresponding amino



Scheme 1

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*)-Cytosaxone (**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/H₂O gave an optically pure diol (93%, 99% ee) [6], which was subjected to reduction with NaBH₄ followed by protection with *t*-butyldiphenylsilyl chloride (TBDPSCI) to afford (4*S*,5*S*)-diol **7** (cytosaxone 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 SOCl₂ in the presence of Et₃N [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 LiN₃ in DMF at 70 °C to afford azide alcohol **9** (74%) and desilylated azide diol **9'** (24%), which was quantitatively converted to **9** by TBDPSCI/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 ClCO₂Ph/pyridine. The construction of the oxazolidinone ring was performed in one pot; *i.e.*, upon treatment of **10b** with Ph₃P in THF/H₂O, 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*)-cytosaxone (**1**) in 96% yield. The ¹H NMR spectrum and the optical rotation of the synthetic **1** were identical with those of natural cytosaxone (**1**) [12]. Therefore, the absolute



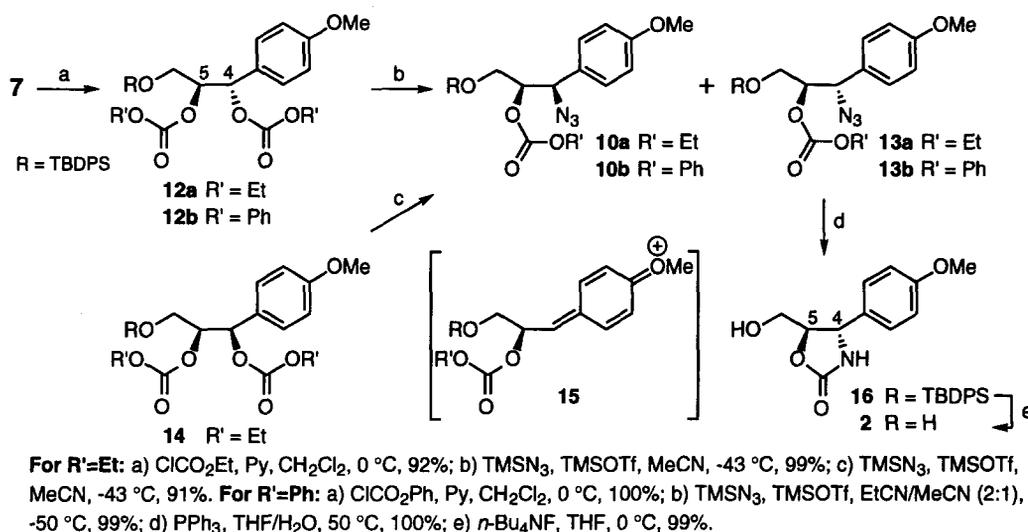
a) AD-mix- α , *t*-BuOH/H₂O (1:1), r.t., 93% (99%ee); b) NaBH₄, THF, 0 °C, 66%; c) TBDPSCI, imidazole, DMF, 0 °C, 99%; d) SOCl₂, Et₃N, CH₂Cl₂, 0 °C, 99%; e) LiN₃, DMF, 70 °C, **9**: 74%, **9'**: 24%; f) TBDPSCI, imidazole, DMF, 0 °C, 100%; g) ClCO₂Ph, Py, CH₂Cl₂, r.t., 96%; h) PPh₃, THF/H₂O, 50 °C, 90%; i) *n*-Bu₄NF, 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 ClCO₂Et/pyridine, was treated with TMSN₃ (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 ClCO₂Ph/pyridine. Thus, the treatment of **12b** with TMSN₃ (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 PPh₃ in THF/H₂O 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.



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

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- [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); ¹³C 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; [α]²⁶_D -75.7 (c 1.00, MeOH) [lit. [1], [α]²³_D -71 (c 0.1, MeOH)]; Anal. Calcd for C₁₁H₁₃NO₄: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.21; H, 5.87; N, 6.35.
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- [15] When ethyl carbonate **13a** was employed in the azide reduction using PPh₃, 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); ¹³C 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; [α]²⁸_D -30.4 (c 1.01, MeOH); Anal. Calcd for C₁₁H₁₃NO₄: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.93; H, 5.88; N, 6.20.