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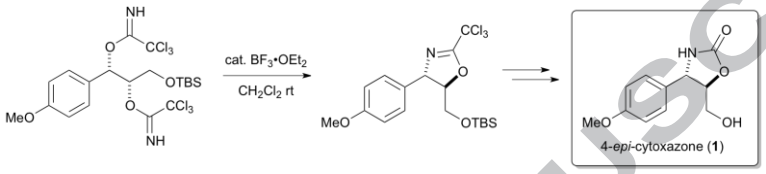

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ABSTRACT

A short and efficient method for synthesizing *epi*-cytoxazone *via* the corresponding oxazoline intermediate was developed. The formation of the oxazoline ring, which proceeds through an S_N1 mechanism to ensure that the *trans*-oxazoline stereochemistry is retained, was induced by intramolecular benzylic substitution of a 1,2-bis-trichloroacetimidate, starting from the known enantiomerically pure diol.

Cytoxazone is a microbial metabolite which was originally isolated from a *Streptomyces* species in a soil sample collected in the Hiroshima Prefecture.[1] This compound has been identified as a selective cytokine modulator that inhibits cytokine production *via* the signaling pathway of Th2 cells, but not of Th1 cells.[1] Inhibitors of Th2-dependent cytokine production have significant potential for use as potent chemotherapeutic agents in immunotherapy. Thus, owing to the potent biological activity of cytoxazone, the development of methods for synthesizing it and its stereoisomers has become a subject of intense research interest.[2] Several methods for synthesizing cytoxazone and its isomers (Fig. 1) have been reported since the first independent reports on the total synthesis of cytoxazones by Nakata's group and Mori's group.[3] It was reported that there is no significant difference between the stereoisomers in terms of their bioactivity.[4] This interesting observation motivated us to develop a scalable and practical synthetic route for its isomer, *epi*-cytoxazone.[5]

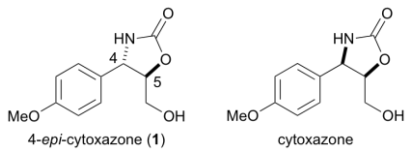

Figure 1. Structures of cytoxazone and 4-*epi*-cytoxazone.

In our attempt to synthesize *epi*-cytoxazone, we developed a novel nitrogen-introducing intramolecular cyclization process using a trichloroacetimidate. Trichloroacetimidates are well-known leaving groups, and, in particular, efficient glycosyl donors during glycosylation. Moreover, several useful reactions involving the use of trichloroacetimidates for the introduction of a nitrogen functional group, wherein the nitrogen atom of the trichloroacetimidate acts as a nucleophile, have been reported. These include (1) the electrophile-promoted intramolecular aminations of trichloroacetimidates derived from allylic and homoallylic alcohols,[6] (2) the acid-promoted intramolecular epoxide opening of trichloroacetimidates,[7] (3) an Overman rearrangement, in which the trichloroacetimidate also acts as the leaving group,[8] and (4) the intramolecular conjugate additions of trichloroacetimidates.[9] In addition to these reactions, intramolecular allylic substitution by bis-trichloroacetimidate during the synthesis of staurosporine was reported by Danishefsky and co-workers.[10] This reaction can be viewed as a vinylogous intramolecular Schmidt glycosylation reaction.[11] Recently, a few examples of similar reactions were also reported.[12] On the other hand, dihydrooxazine ring formation *via* intramolecular benzylic substitution by 1,3-bis-trichloroacetimidates has also been reported.[13] In addition, intramolecular propargylic substitution by 1,2-bis-trichloroacetimidates was also reported very recently.[14] However, to the best of our knowledge, oxazoline ring formation *via* intramolecular benzylic substitution by 1,2-bis-trichloroacetimidates has not been reported previously. Herein, we describe a simple and effective method for the synthesis of 4-*epi*-cytoxazone (4*S*,5*R*)-**1** *via* oxazoline formation by intramolecular benzylic substitution using bis-trichloroacetimidates.

Based on the retrosynthetic analysis as shown in Scheme 1, we envisaged that 4-*epi*-cytoxazone **1** could be obtained from the

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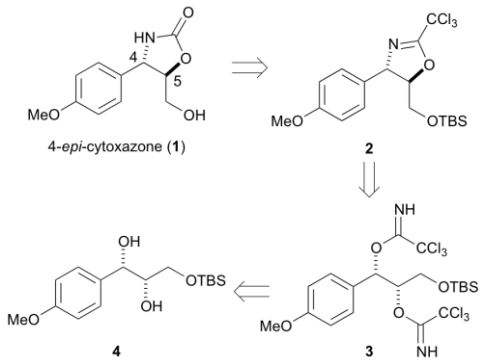
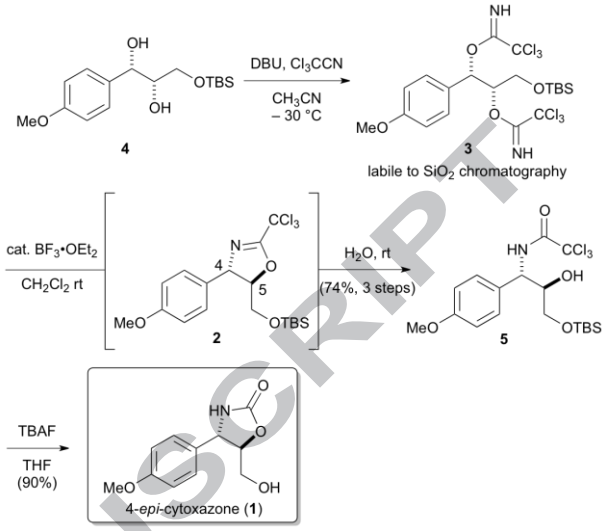
preceding compound **2** containing an oxazoline moiety. The *trans*-oxazoline intermediate **2** could, in turn, be obtained by the key intramolecular benzylic substitution of the corresponding bis-trichloroacetimidate **3**. Trichloroacetimidate **3** can be prepared from the known chiral starting diol **4**[3b] *via* Sharpless asymmetric dihydroxylation (AD).[15]



Scheme 1. Retrosynthetic analysis of 4-*epi*-cytoxazone **1**.

The starting diol (2*S*,3*S*)-**4**[16] was obtained by Sharpless AD from the corresponding *O*-TBS-allyl alcohol using $(DHQ)_2PHAL$ as the chiral ligand (AD-mix-α), in keeping with a previous study.[3b] Diol **4** was then transformed into the corresponding bis-trichloroacetimidate **3** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and excess trichloroacetonitrile in acetonitrile. When the resulting crude bis-trichloroacetimidate **3** was subjected to silica gel chromatography, the purified product collected in the expected fraction eluted as a single spot on the TLC plate. This product was evidently the desired one, namely, bis-trichloroacetimidate **3**, but contained a substantial amount of oxazoline **2**. This implied that cyclization to oxazoline **2** had occurred unexpectedly during the chromatography of bis-trichloroacetimidate **3**. To improve conversion, we increased the standing time in silica gel. However, the transformation was not complete even after several hours. Furthermore, oxazoline **2**[17] could not be separated from bis-trichloroacetimidate **3**. It was previously reported that, in the case of the oxazoline ring, a small coupling constant (6 Hz) corresponds to the *trans* form while a large one (9 Hz) corresponds to the *cis* form.[18] Therefore, the relatively small coupling constant ($J_{H\text{-}4,5}$ = 6.9 Hz) of compound **2** implied that it possessed the desired *trans* stereochemistry.

As a preliminary attempt at acid-promoted oxazoline formation using the thus-obtained bis-trichloroacetimidate **3**, which included oxazoline **2**, the cyclization reaction was examined with a catalytic amount of methanesulfonic acid (MsOH) or BF_3•OEt_2. The desired product, trichloroacetamide **5**, was obtained successfully in moderate yield (MsOH: 57%; BF_3•OEt_2: 77%); this was probably formed by the hydrolysis of oxazoline **2** during the reaction. Accordingly, a one-pot transformation reaction was carried out, wherein a crude sample of bis-trichloroacetimidate **3** was reacted with catalytic BF_3•OEt_2 in dry CH_2Cl_2, and the resulting reaction mixture was successively treated with excess H_2O. This afforded trichloroacetamide **5** in high yield (74% over 3 steps from diol **4**), as shown in Scheme 2. It is worth noting that BF_3•OEt_2 was less effective as a catalyst for dihydrooxazine ring formation.[13] The stereoselectivity of this cyclization reaction, which proceeds through an S_N1 mechanism, can be explained using the transition state (TS) models in Figure 2. Owing to steric hindrance between the side-chain (R) and the *p*-methoxyphenyl group, the *cis*-TS model is less favorable than the *trans*-TS one. Therefore, it is likely that the cyclization reaction proceeds as per the *trans*-TS model to produce *trans*-oxazoline **2**.



Scheme 2. Synthesis of 4-*epi*-cytoxazone **1**.

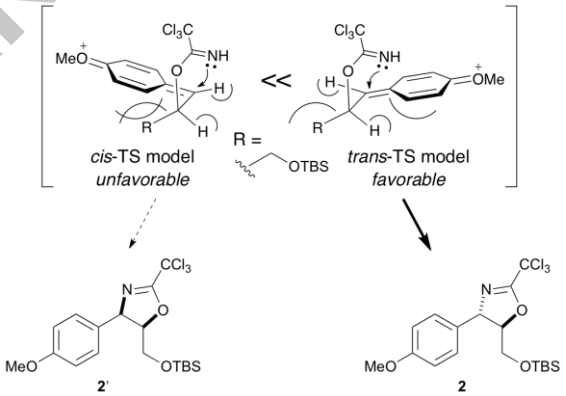


Figure 2. Proposed transition state models for intramolecular benzylic substitution.

Finally, trichloroacetamide **5** was transformed into 4-*epi*-cytoxazone **1** in 90% yield using tetrabutylammonium fluoride (TBAF). During this one-pot transformation, the TBS group was deprotected first, as observed using TLC. This was followed by the formation of the oxazolidinone ring.[19] The spectroscopic properties of the obtained 4-*epi*-cytoxazone **1** were consistent with those reported in the literature. {$[\alpha]^{25.3}$ –32.3 (*c* 0.998, MeOH); cf. lit.3a $[\alpha]^{28}$ –30.4. (*c* 1.01, MeOH); antipode: lit.5a $[\alpha]^{23}$ +28.6 (*c* 1.0, MeOH)}.

In conclusion, 4-*epi*-cytoxazone **1** was successfully synthesized from 1,2-bis-trichloroacetimidate using intramolecular benzylic substitution as the key reaction. The proposed synthetic route is short and efficient, that is, it only involves 4 steps (total yield of 67%) starting from a known enantiomerically pure diol and can be scaled to allow for gram-scale synthesis. Furthermore, in addition to being suitable for synthesizing 4-*epi*-cytoxazone, the proposed strategy can also be employed for synthesizing other types of molecules containing oxazolidinone or amino alcohol moieties in their structures. For example, the importance of the 1,2-aminoalcohol motif in synthetic chemistry is underlined by its occurrence in a vast range of natural products and other biologically active compounds.[20]

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Supplementary Material

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Highlights

- A short and efficient synthesis of *epi*-cytoxazone (total 67% yield in 4 steps).
- Oxazoline formation by an intramolecular substitution of bis-trichloroacetimidate.
- Removal of TBS and oxazolidinone formation was performed by a one-step procedure.

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