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Concise synthesis of the Taxol side chain and demethoxy-4-*epi*-cytoxazone *via* oxazoline formation through intramolecular benzylic substitution of a bis-trichloroacetimidate ☆

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ABSTRACT

A concise and efficient method for synthesizing the Taxol side chain *via* the corresponding oxazoline intermediate was developed. The oxazoline ring is formed *via* an S_N1 mechanism to ensure that the *trans*-oxazoline stereochemistry is retained. This process was induced by intramolecular benzylic substitution of a 1,2-bis-trichloroacetimidate, which was obtained from a known, enantiomerically pure diol. Demethoxy-4-*epi*-cytoxazone was also obtained from the intermediary *trans*-oxazoline **3b**.

Introduction

Chiral β-amino α-hydroxy acid moieties are frequently found in various biologically important compounds and natural products [1], and also serve as chiral ligands and auxiliaries for asymmetric synthesis [2]. For example, the side chain present in the anticancer drug Taxol and its derivatives is the most well-known example of a chiral β-amino α-hydroxy acid; therefore the synthesis of Taxol analogues has attracted considerable attention [3]. Extensive efforts have been made to develop enantioselective routes for the synthesis of optically active β-amino α-hydroxy acids. Successful approaches include the following: Sharpless asymmetric aminohydroxylation [4], Sharpless asymmetric dihydroxylation [5], ring-opening of chiral epoxides [6], asymmetric nitroaldol reactions [7], asymmetric 1,3-dipolar cycloaddition [8], asymmetric Mannich reactions [9], and other synthetic strategies [10]. Although these methods are currently available for the enantioselective synthesis of chiral β-amino α-hydroxy acids, including vicinal amino alcohol moieties, simple and efficient approaches toward these classes of compounds are still greatly desired.

In our attempt to synthesize the Taxol side chain (**1**), we applied our nitrogen-introducing method that employs an intramolecular cyclization process using a trichloroacetimidate. Trichloroacetimidates are well-known leaving groups and can serve as efficient glycosyl donors for glycosylation reactions. Moreover, several useful reactions involving the use of trichloroacetimidates for the introduction of a nitrogen functionality have been reported, wherein the trichloroacetimidate nitrogen atom acts as a nucleophile. These include (1) electrophile-promoted intramolecular aminations of trichloroacetimidates derived from allylic and homoallylic alcohols [11], (2) acid-promoted intramolecular epoxide-opening reactions of trichloroacetimidates [12], (3) Overman rearrangements in which trichloroacetimidates also act as leaving groups [13], (4) rearrangement of benzylic trichloroacetimidates to benzylic trichloroacetamides [14], and (5) intramolecular conjugate additions of trichloroacetimidates [15]. In addition to these reactions, intramolecular allylic substitution by a bis-trichloroacetimidate during the synthesis of staurosporine was reported by Danishefsky [16]. This reaction can be viewed as a vinylogous intramolecular Schmidt glycosylation reaction [17]. A few examples of other, similar reactions have also been reported [18]. Furthermore, intramolecular benzylic substitutions by 1,3-bis-trichloroacetimidates have reportedly provided dihydrooxazine ring systems [19], while 1,2-bis-trichloroacetimidates have induced intramolecular propargylic substitutions [20]. Recently, we reported the synthesis of 4-*epi*-cytoxazone *via* oxazoline formation that proceeded through the intramolecular benzylic substitution of 1,2-bis-trichloroacetimidates [21]. We were not only interested in

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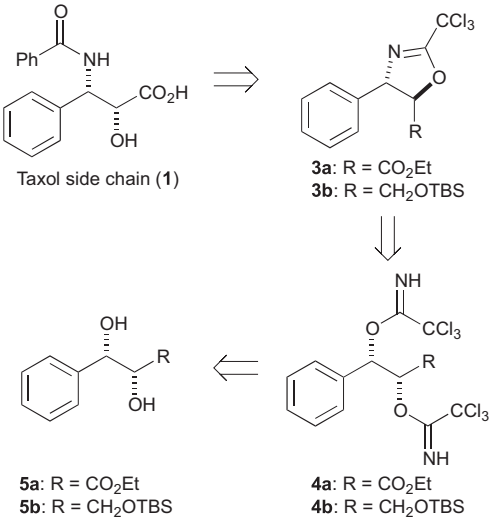
demonstrating the usefulness of this method, but also in evaluating the effect it had on the reactivity of the benzene ring substituents and the functional groups adjacent to the trichloroacetimidate moiety.

Herein, we report a concise and effective route for the synthesis of **1** (Fig. 1), which was developed by investigating the reactivity of bis-trichloroacetimidates. Additionally, we detail the synthesis of demethoxy-4-*epi*-cytoxazone (**2**) from an intermediary compound (**3b**). Cytoxazone is a microbial metabolite originally isolated from a *Streptomyces* species [22]. It has been identified as a selective cytokine modulator that inhibits cytokine production *via* the signaling pathway of Th2 cells, but not Th1 cells [22]. Inhibitors of Th2-dependent cytokine production have significant potential for use as potent chemotherapeutic agents for immunotherapy. Therefore, various methods for the synthesis of cytoxazone and its derivatives have been reported [23].

The purpose of this study was to utilize trichloroacetimidate-mediated functionalization to introduce a nitrogen functionality during the stereoselective synthesis of β-amino α-hydroxy acids with 1,2-amino alcohol moieties, such as **1**.

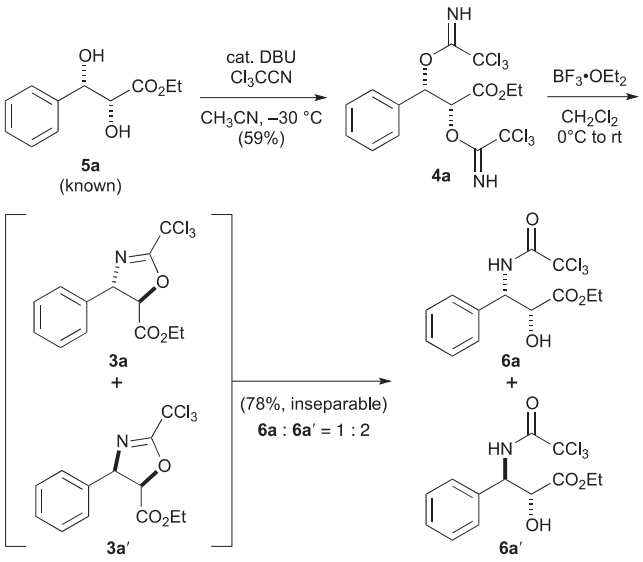


Scheme 1. Retrosynthesis of **1**.

Results and discussion

Based on the retrosynthetic analysis of **1**, as shown in Scheme 1, we envisaged that **1** could be obtained from compounds **3a** or **3b** bearing an oxazoline moiety. The desired *trans*-oxazoline intermediates **3a** or **3b** could be obtained by the key intramolecular benzylic substitution of the corresponding bis-trichloroacetimidates **4a** or **4b**, respectively. These trichloroacetimidates can be prepared from known chiral diols **5a** or **5b**, respectively, which can be obtained by Sharpless asymmetric dihydroxylation (AD).

Due to its ester moiety, diol **5a** is more similar in structure to **1** than diol **5b** is; therefore, we decided to start our synthetic studies with this compound (Scheme 2). The starting diol, (2*R*,3*S*)-**5a** [24], was obtained by Sharpless AD from the corresponding α,β-unsaturated ester (ethyl cinnamate) using dihydroquinine phthalazine ($(DHQ)_2PHAL$) as the chiral ligand (denoted as the AD-mix-α protocol). First, diol **5a** was transformed into the corresponding bis-trichloroacetimidate **4a** by treatment with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and an excess amount of trichloroacetonitrile in acetonitrile at a low temperature. Bis-trichloroacetimidate **4a** was stable on silica gel; however, the yield was only moderate (up to 59%) and could not be improved. In fact, using a stoichiometric amount of DBU considerably decreased the yield. Subsequent cyclization was performed using Lewis acids (BF_3•OEt_2 or trimethylsilyl trifluoromethanesulfonate (TMSOTf)). The reactivity of bis-trichloroacetimidate **4a** was low, as expected, and the starting bis-imidate remained practically unchanged under conditions employing a catalytic amount of BF_3•OEt_2. The desired cyclization was found to proceed with a catalytic amount of TMSOTf or a stoichiometric amount of BF_3•OEt_2. However, the oxazoline rings of the resultant **3a** and **3a′** were easily hydrolyzed during the reaction to afford the corresponding isomers **6a** and **6a′** [25], which could not be separated, in moderate yield (up to 78%). Unfortunately, the selectivities of the desired **6a** and its isomer **6a′** were quite low (ca. 1:2 to 1:1) [26].



Scheme 2. Synthetic protocol beginning from diol **5a**.

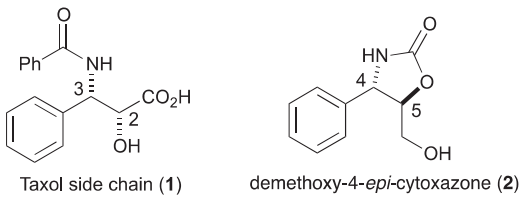
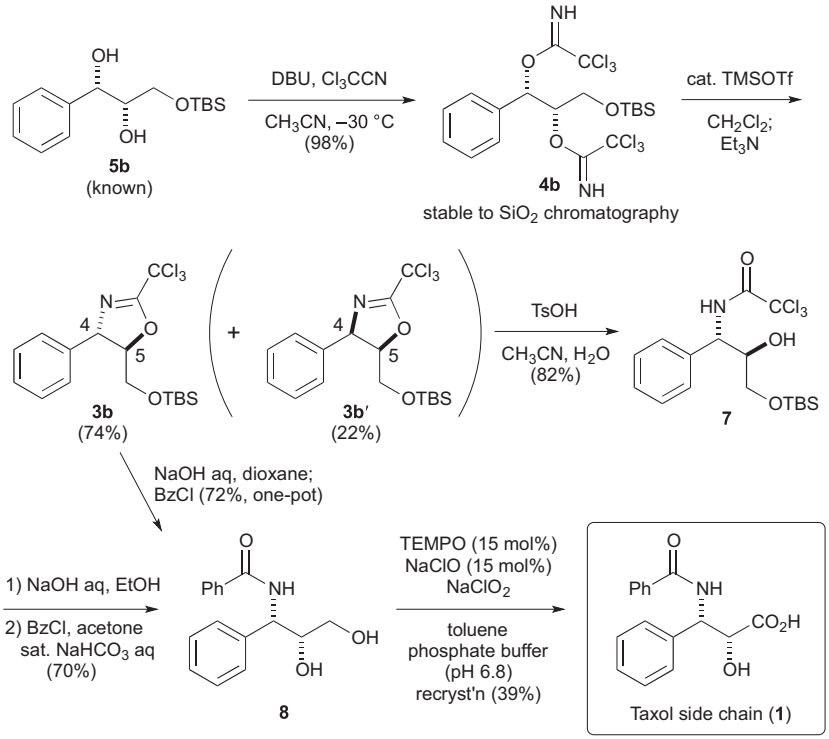


Fig. 1. Structures of the Taxol side chain (**1**) and demethoxy-4-*epi*-cytoxazone (**2**).

Due to the low-yielding trichloroacetimidation, poorly selective cyclization, and inseparable isomer products, we attempted the same synthesis but with diol (2*S*,3*S*)-**5b** [27,28], as shown in Scheme 3. Diol **5b** was also easily obtained by Sharpless AD from the corresponding *O*-TBS-allyl alcohol using the AD-mix-α protocol.

Diol **5b** was treated with a stoichiometric amount of DBU and an excess amount of trichloroacetonitrile in acetonitrile at low temperature to afford bis-trichloroacetimidate **4b**. The corresponding *p*-methoxy-isomer of **4b** was not stable on silica gel, thus it was prone to cyclizing into an oxazoline during silica-gel chromatography [21]. In stark contrast, **4b** was fairly stable on silica gel and was obtained in high yield (98%) after typical silica-gel chromatography [14].

Bis-trichloroacetimidate **4b** was then cyclized to form the corresponding oxazoline (**3b**) by treatment with Lewis acids. Specifically, treatment of **4b** with a catalytic amount (0.4 eq) of



Scheme 3. Synthesis of **1**.

BF_3•OEt_2 resulted in the recovery of almost all the starting bis-imidate, while this same treatment resulted in complete conversion of the *p*-methoxy isomer [21,14]. However, treatment of **4b** with a stoichiometric amount (1.1 eq) of BF_3•OEt_2 resulted in the formation of oxazoline **3b** with moderate selectivity (ca. 3:1) along with a substantial amount of hydrolyzed trichloroacetamide **7**. The addition of water to the reaction mixture did not improve the yield of the trichloroacetamide, and further treatment with triethylamine was not effective in preventing ring-opening.

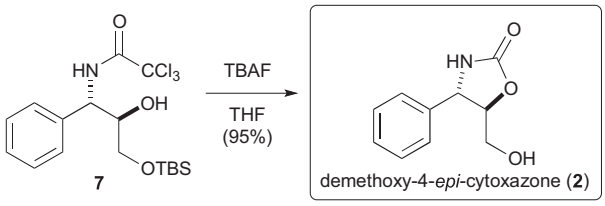
Next, we attempted to use TMSOTf, which has been reported as a good Lewis acid in the reactions of the bis-trichloroacetimidates of alkynyl-glycinols [20]. Consequently, **4b** was treated with a catalytic amount (0.4 eq) of TMSOTf followed by quenching with triethylamine [20], which afforded the corresponding oxazoline (**3b**) with good selectivity (ca. 3.4:1) and in a relatively high yield (combined, 96%) without any ring-opening occurring. Fortunately, the *trans* (**3b**) and *cis* (**3b′**) isomers were easily separated due to the former being less polar than the latter. This resulted in **3b** and **3b′** being isolated in 74% and 22% yield, respectively. Regarding the oxazoline rings of these isomers, it was reported that a small coupling constant (~6–7 Hz) corresponds to the *trans* isomer while a large coupling constant (~9–10 Hz) represents the *cis* form [21,29]. Therefore, the relatively small coupling constant ($J_{H\text{-}4,5}$ = 6.9 Hz) that we observed for **3b**, the major compound, implies that it exhibits *trans* stereochemistry, while the large coupling constant ($J_{H\text{-}4,5}$ = 10.1 Hz) noted for **3b′**, the minor compound, suggests that it has a *cis* configuration.

The mechanism of this reaction seems to be the same as that reported for a methoxy-substituted substrate, where an S_N1-type reaction and the steric repulsion of the substituents exclusively give the *trans*-oxazoline product (sterically retained) [21]. In the absence of the methoxy group (**4b**), the intermediary carbocation might not be stably generated, and the isomeric ratio may become poor due to the mixture of compounds presumably generated from the S_N2 mechanism. In the case of the 1,2-bis-trichloroacetimidates of alkynyl-glycinols [20], the reactions generally proceed *via* an S_N2 mechanism; however, when the substituent at the end of the alkyne is a Ph group, an S_N1-type reaction occurs. The occurrence of the S_N1-type reaction is suppressed by adding the electron-withdrawing chlorine substituent to the Ph group.

With the target intermediary oxazoline (**3b**) in hand, the next step was to transform it into *N*-benzoylated diol **8**, the exact precursor of **1**. Acidic hydrolysis of *trans*-oxazoline **3b** with aqueous HCl and successive *N*-benzoylation was unsuccessful. However, partial hydrolysis of the oxazoline ring of **3b** was successfully performed with *p*-TsOH in wet CH_3CN to give to trichloroacetamide **7** (82% yield), which was then hydrolyzed under basic conditions and successively *N*-benzoylated to give diol **8** in 70% yield (2 steps). Upon examining the alkaline hydrolysis of oxazoline **3b** or trichloroacetamide **7**, we noted that **2**, which is relatively resistant to alkaline hydrolysis, was obtained as a byproduct in low yield. Therefore, we performed the same hydrolysis under stronger conditions that employed 1,4-dioxane as a co-solvent. Consequently, the alkaline hydrolysis and *N*-benzoylation of **3b** could be successfully executed in a one-pot reaction to give the target diol (**8**) in good yield (72%). Diol **8** has been reported as a decomposition product of the reaction of Taxol with sodium borohydride [30], and the melting point and ^{1}H NMR spectrum of **8** obtained from that reaction were consistent with those observed for our diol (**8**). This confirmed our isolation of the desired product.

Finally, the selective oxidation of **8** with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) [31] afforded the crude product (**1**), which was directly recrystallized (avoiding column chromatography) to give the pure product as fine needle-like crystals in 39% yield. The spectroscopic properties (^{1}H and ^{13}C NMR) of **1** obtained in this work were consistent with those of the known compound reported in the literature [6(c),8a,10a].

Additionally, intermediate trichloroacetamide **7** was transformed into **2** (Scheme 4). We successfully obtained **2** in 95% yield through a one-step process involving the treatment of **7** with



Scheme 4. Synthesis of **2**.

tetrabutylammonium fluoride (TBAF).[21,32] The spectroscopic properties (^{1}H and ^{13}C NMR) of **2** obtained in our work were consistent with those reported for the racemate of **2** in the literature [33].

Conclusion

We successfully synthesized the Taxol side chain (**1**) and demethoxy-4-*epi*-cytoxazone (**2**) using a protocol where the introduction of a stereoselective nitrogen functional group *via* 1,2-bis-trichloroacetimidate was the key reaction. This facile synthetic route requires only four steps to isolate **1** (20%) from the known, enantiomerically pure diol **5b**. Not only can our strategy construct β-amino α-hydroxy acid derivatives and other compounds possessing oxazoline rings, oxazolidinone rings, or amino alcohol moieties, but it can do so without an azide reagent. This is significant as azides are potentially toxic and hazardous. Furthermore, the 1,2-amino alcohol motif is present in various natural products and other biologically active compounds [34]; thus, its fabrication using a simple protocol such as the one reported here is very beneficial. There are currently no reports on the bioassays of **2**, but it has been reported that there is no significant difference between its four stereoisomers in terms of their bioactivity [35]. Due to the interesting biological activity of the *p*-methoxy and non-substituted forms of cytoxazone, we plan to conduct bioassays on these compounds in future studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153095.

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