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Stereoselective synthesis of (−)-cytoxazone and (+)-*epi*-cytoxazone

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Abstract—Optically pure (−)-cytoxazone was synthesized, starting from methyl *p*-methoxycinnamate, in six steps and in 31% overall yield. The required *anti*-aminoalcohol configuration was established by combining Sharpless asymmetric aminohydroxylation with the configurational inversion of the intermediate amidoalcohol via an oxazoline. The synthesis of (+)-*epi*-cytoxazone is also described.

Cytoxazone **1** is a natural product isolated in 1998 from a fermentation broth of *Streptomyces* sp.[1,2] The strong, yet selective, immunosuppressive activity of this oxazolidinone derivative (it exerts cytokine modulation activity through selective inhibition of the Th2 cell signalling pathway), indicated a possible therapeutic application and consequently induced the substantial interest of synthetic organic chemists. Several total syntheses have been reported, based on asymmetric synthesis, as well as on the separation of the racemic product. The enantioselective approaches to biologically active (−)-**1** have relied on Sharpless asymmetric dihydroxylation,[3,4] asymmetric aldol reaction with the internal boron reagent[5] and substrate-controlled addition of organometallics to chiral aldehydes.[6,7] The imino-Wittig rearrangement route,[8] as well as the azide opening of a glycidic ester,[9] afforded the racemic compound. The stereoisomer of **1**—*epi*-cytoxazone—**2**, has also been synthesized,[3,7,9,10] as well as regioisomeric derivatives required for SAR studies.[11]

The inevitable synthetic predecessors of cytoxazone (and *epi*-cytoxazone) are 1,2-aminoalcohols, which have been the subject of thorough synthetic studies,[12] due to the frequent presence of this structural subunit in natural products, biologically active compounds and chiral ligands for catalytic asymmetric synthesis.[13] During the last few years, asymmetric oxidations of alkenes have emerged as the most efficient methods for the stereoselective synthesis of 1,2-difunctionalized compounds, where the recently developed Sharpless asymmetric aminohydroxylation reaction (AA) occupies a prominent place.[14,15] However, the AA process does not offer a universal entry into all types of aminoalcohols, and has been used more frequently in the synthesis of *syn*-aminoalcohols than for the *anti*-isomers. This is due to the fact that AA reactions with *Z*-alkenes appear to give products of lower optical purity; in addition, *Z*-alkenes are more difficult to obtain than *E*-alkenes, and sometimes show proclivity towards isomerization. Therefore, all the syntheses of cytoxazone described so far have used indirect methods to establish the required vicinal aminoalcohol functionality.

We endeavoured to develop an efficient enantioselective synthesis of (−)-cytoxazone **1**, as well as of (+)-*epi*-cytoxazone **2**, based on the AA protocol, that would afford both molecules in the least number of steps, in high yield and with the highest level of optical purity. Our approach is delineated in Scheme 1. Retrosynthetic inversion of the configuration at C-5 of the target molecule **1** proceeds via oxazoline **3**, and gives amidoalcohol **4**, a common synthetic precursor of both **1** and **2**. In turn, **4** should be obtained directly by AA of the easily available cinnamic ester **5**. The epimer **2** does not require the correction of stereochemistry at C-5, and should be obtained in a few steps, by routine functional group manipulations of the AA product **4**.

Thus, the synthetic plan for cytoxazone **1** called for a tactical combination of reactions: AA and inversion of configuration. Among the many methods that can effect

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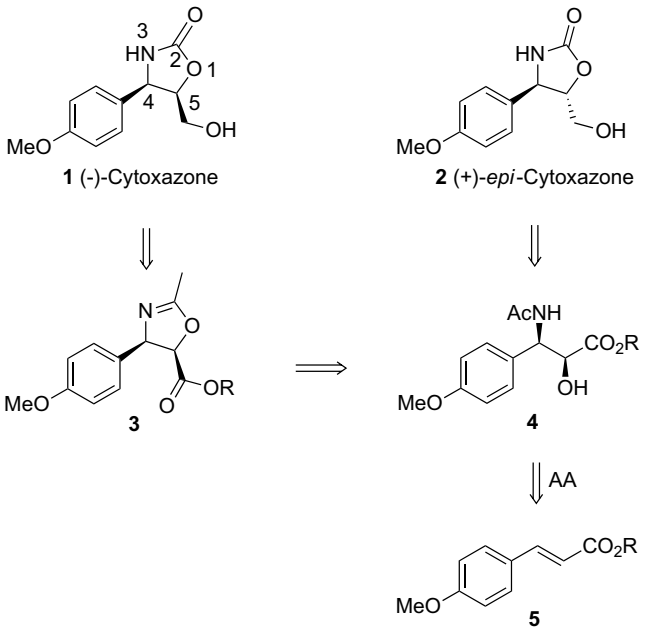
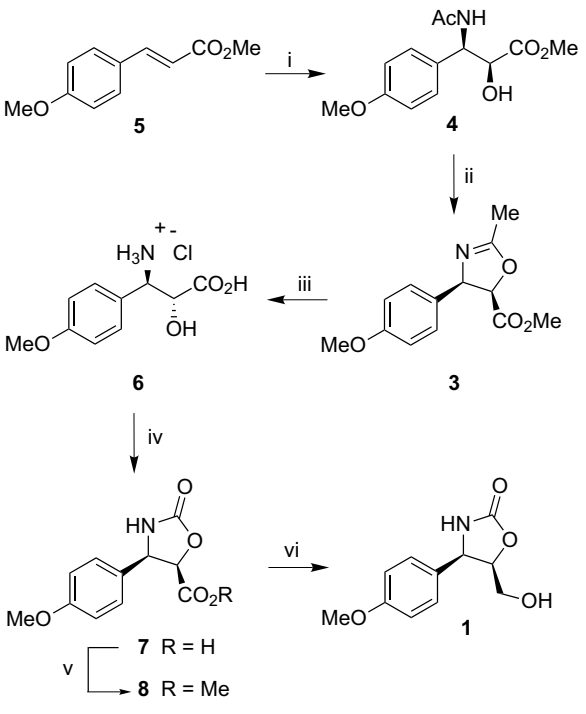


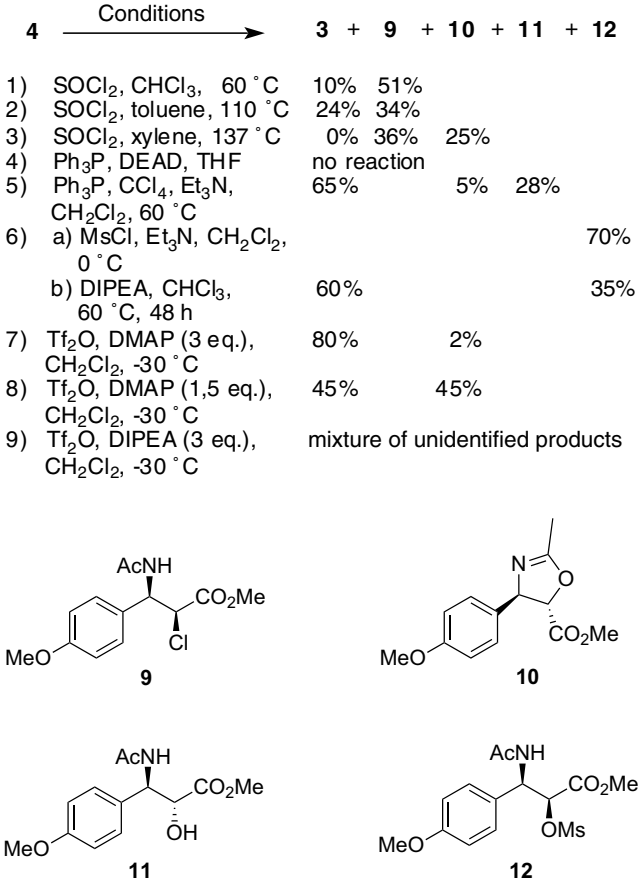
Scheme 1. Retrosynthetic analysis of (−)-cytoxazone and (+)-*epi*-cytoxazone.

the latter transformation, we opted for intramolecular reactions. These were expected to offer at least two advantages: to facilitate the suppression of unwanted, bimolecular reactions and to contribute to the atom economy of the process, as the protective group at nitrogen would also have the role as internal nucleophile. The fact that the AA reaction works best with unencumbered *N*-haloamides as nitrogen sources[16] further narrowed the range of isomerization reactions to those applicable directly to vicinal hydroxy amides of type **4**, pointing to oxazoline **3** as a synthetic intermediate.[17] A similar approach was used in stereoselective transformations of a β-phenyl isoserine derivative.[18]

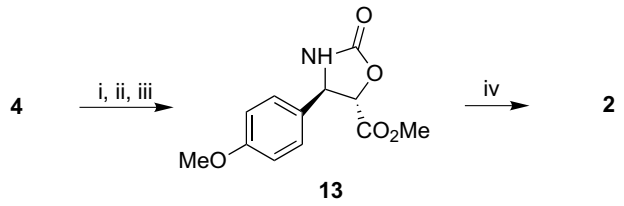
The synthesis of **1** proceeded as displayed in Scheme 2. Sharpless asymmetric aminohydroxylation of **5** with $(DHQD)_2PHAL$ afforded amido alcohol **4** in 72% yield.[19] The next step—oxazoline ring closure—comprised a short study aimed towards examining comparatively the efficiency of various procedures (Scheme 3). Thionyl chloride was reported to cyclize *anti*-amidoalcohols into oxazolines;[20] however, under identical conditions ($CHCl_3$, 60 °C) the *syn*-amidoalcohol **4** gave chloro derivative **9** (the product of an S_Ni reaction) as the main product. At higher temperatures the ratio of products was in favour of the oxazoline, but isomerization to the *trans*-oxazoline **10** was also observed. Surprisingly, triphenylphosphine/diethyl azodicarboxylate failed to promote any reaction.[21] Triphenylphosphine/carbon tetrachloride[22] effected the desired transformation in 93% yield (a mixture of 65% of **3** and 28% of **11**), but the product was contaminated with 5% of the *trans*-oxazoline. We also examined a two-step



Scheme 2. Total synthesis of (−)-cytoxazone. Reagents and conditions: (i) $K_2[OsO_2(OH)_4]$ (4 mol%), BrNHAc, $(DHQD)_2PHAL$ (1 mol%) $LiOH{\cdot}H_2O$, *t*-BuOH, 4 °C, 20 h, 72%; (ii) Tf_2O, DMAP, CH_2Cl_2, 80%; (iii) 12% HCl, Δ, 1.5 h; (iv) $ClCO_2CCl_3$, NaOH, H_2O, 0 °C; (v) CH_2N_2, THF, 72% from **3**; (vi) $NaBH_4$, THF, 0 °C, 75%.



Scheme 3. Configurational inversion of amidoalcohol **4** under various conditions.



Scheme 4. Synthesis of (+)-*epi*-cytoxazone. Reagents and conditions: (i) 10% HCl, Δ, 4 h; (ii) $ClCO_2CCl_3$, NaOH, H_2O, 0 °C; (iii) CH_2N_2, THF, 63% from **4**; (iv) $NaBH_4$, THF, 0 °C, 80%.

procedure including the conversion of alcohol **4** into a mesylate **12**, followed by cyclization.[23] The previously reported procedure proved unsuitable, affording a mixture of isomerized hydroxyester **11** (in low yield) and unreacted starting compound **4**. The use of DIPEA as base, under anhydrous conditions, improved the yield of **3** (60%), but the reaction time was long and conversion incomplete (35% recovered **12**). The best results were obtained when the isomerization was performed via the in situ formed triflate,[24] using 3 equiv of DMAP as base:[25] under these conditions oxazoline **3** could be isolated in 80% yield. Lowering the amount of DMAP, or using DIPEA instead, proved unsatisfactory. Further synthetic steps involved acidic hydrolysis of oxazoline **3** to hydroxy amino acid **6**, its conversion into cyclic carbamate **7** by diphosgene, and the esterification to **8** with diazomethane. We found that it was more convenient experimentally not to isolate/purify the intermediates **6** and **7**, but to proceed directly to the ester **8**, which was isolated in 72% yield (over three steps). Reduction of **8** with sodium borohydride afforded (−)-cytoxazone **1** (75%) whose physical properties were identical to those of the natural product.[26]

epi-Cytoxazone **2** was synthesized from the common intermediate **4** as delineated in Scheme 4. Submission of amidoalcohol **4** to the sequence of reactions already described for cytoxazone (hydrolysis/cyclization/esterification), gave the methyl ester **13** (63% over three steps), whose reduction with sodium borohydride furnished the optically pure *epi*-cytoxazone **2** (80%).[26]

To summarize, optically pure (−)-cytoxazone **1** has been synthesized in six steps and in 31% overall yield, starting from readily available methyl *p*-methoxycinnamate. (+)-*epi*-Cytoxazone **2** was also synthesized, starting from the same precursor, in five steps and 36% overall yield. In terms of overall yield, number of steps and operational simplicity, both syntheses compare favorably with those previously described. The inversion of stereochemistry of amidoalcohols via oxazolines contributes to the versatility of the well-known Sharpless AA reaction and allows for its efficient application to the synthesis of *anti*-1,2-aminoalcohol derivatives.

Acknowledgements

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