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Stereoselective synthesis of cytoxazone and its analogues

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Abstract—A variety of synthetic routes to (−)-cytoxazone **1**, a cytokine modulator isolated from *Streptomyces* cultures, and its stereomers **2** and regioisomers **3** have been reviewed.

Contents

1. Introduction

(−)-Cytoxazone **1**, a potent cytokine modulator, is a naturally occurring 4,5-disubstituted 2-oxazolidinone, isolated from cultures of the *Streptomyces* species by Osada et al.[1] in 1998. Its structure and the (4*R*,5*R*)-absolute configuration was unambiguously established by NMR and CD spectroscopy, X-ray measurements[2] and by its first total asymmetric syntheses, reported in 1999 by Nakata et al.[3] and Mori and Seki.[4]

Following the first syntheses, more than 30 other syntheses of the natural product and its stereoisomers, for example, **2** and regioisomers, for example, **3** have been reported so far (Fig. 1).

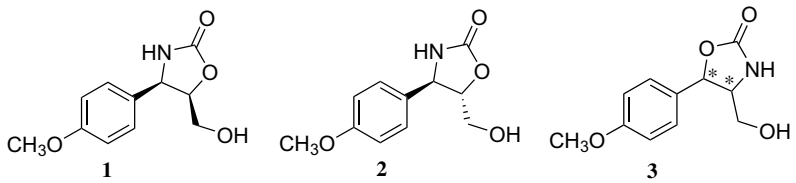

Figure 1.

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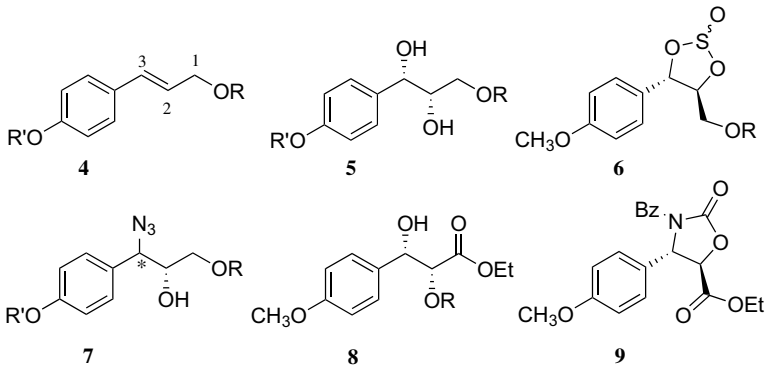


Figure 2.

The synthesis of cytoxazone and its analogues appears to be attractive to many research teams, not only in view of the possibility of developing novel immunotherapeutic agents, but also because the 4,5-disubstituted 2-oxazolidinone ring system provides an interesting objective for various asymmetric synthesis strategies.

2. Synthetic strategies

Since the oxazolidinone ring is conveniently built of amino alcohols, in all the approaches that have been applied to the synthesis of cytoxazone and its analogues, substituted chiral nonracemic β-amino alcohols have been used as key intermediates. Thus, efforts have been made to prepare the corresponding β-amino alcohols in high enantiomeric excess. This has been accomplished either by enantioselective introduction of the hydroxy and amino functionalities into prochiral cinnamic acid derivatives, or by construction of the carbon framework by the formation of a carbon–carbon bond between two building blocks (chiral pool approach included). Commercially available 2-amino-1-methylthiophenyl-1,3-propanediol has also been used as a substrate in the synthesis of a sulfur analogue of **2**.

Finally, to complete the synthesis of (−)-cytoxazone **1** and its isomers, the chiral nonracemic key intermediates prepared, *syn*- and *anti*-α-hydroxy-β-amino(azido) cinnamic acid (alcohol) derivatives, were subjected to standard functional group manipulations, including cyclization of either *N*-Boc derivatives or, directly by exposure of amino alcohols to phosgene equivalents. Chemical and enzymatic resolutions of racemic cytoxazone and epimer have also been performed.

2.1. The synthesis using cinnamic acid derivatives as substrates[†]

In the synthesis, *E*-4-methoxycinnamic acid derivatives, such as esters, amides, or cinnamic alcohol were used as substrates. The β-amino alcohol functionality was then introduced either via two-step procedures involving catalytic asymmetric Sharpless dihydroxylation, or epoxidation followed by azidolysis, or straightforwardly by Sharpless aminohydroxylation. A one-pot amidation/oxidation and epoxidation/azidolysis process was applied to cinnamic acid derivatives as well.

In the first syntheses[3,4] of (−)-cytoxazone **1**, in which 4-methoxycinnamic alcohol derivatives **4** (R = TBDPS, TBS, R′ = CH_3) were used, the two stereogenic centers were generated by catalytic asymmetric dihydroxylation of the olefinic double bond using AD mix-α. To convert the (2*S*,3*S*)-triols-**5** (R = TBDPS, TBS, R′ = CH_3) into the corresponding amino diols a regioselective substitution of benzylic hydroxyl with nitrogen nucleophile needed to be carried out. This was best achieved with azide ions via cyclic sulfites **6** (R = TBDPS, TBS)[3,4] leading to azido diol (2*R*,3*R*)-**7** (R = H, R′ = CH_3) with high diastereoselectivity and with complete inversion of the configuration at C-3 (Fig. 2). Conversion of azido diols (2*R*,3*R*)-**7** (R = H, R′ = CH_3) to the natural product (−)-**1** was achieved in two ways. According to the Nakata approach[3] the construction of the oxazolidinone ring was accomplished by reductive cyclization (PPh_3/THF/H_2O) of *O*-phenoxycarbonylated (2*R*,3*R*)-**7** (R = TBDPS, R′ = CH_3) (called in this paper 'Nagata cyclization') and the final removal of the TBDPS-protecting group (*n*-Bu_4NF/THF). In the Mori approach,[4] the azide was first hydrogenated ($HCOONH_4$/Pd–C) and the amino diol obtained was cyclized with diethyl carbonate/K_2CO_3, and then TBS-deprotected with *n*-Bu_4NF/THF.

The preparation of the diastereomeric azido diol (2*R*,3*S*)-**7** (R = H, R′ = CH_3), needed for the synthesis of (+)-5-*epi*-cytoxazone **2**, was achieved by treatment of diethyl carbonate of triol **5** (R = TBDPS, R′ = CH_3) with $TMSN_3$/TMSOTf at −50 °C, proceeding with retention of configuration.[3]

In their synthesis of 4-*epi*-cytoxazone *ent*-**2**, Ko et al.[5] applied dihydroxy ester (2*R*,3*S*)-**8** (R = H), homochiral with triol (2*S*,3*S*)-**5**, as a substrate, which was prepared by asymmetric dihydroxylation of ethyl 4-methoxycinnamate using AD mix-α. A cyclic iminocarbonate rearrangement of *syn*-diols to *syn*-amino alcohols[6] occurring in a three-

[†] The numbering system of the β-amino-α-hydroxy-propanol chain corresponds to that of cinnamic alcohol.

step one-pot procedure under the action of Bu_2SnO/BzNCS/LiI reagent mixture, was applied as the key process. In this manner, an intermediate oxazolidinone **9** was produced with retention of configuration of both stereocenters due to a double inversion taking place in the ring opening (LiI)/recyclization process of the intermediate *N*-benzoyliminocarbonate. *N*-Debenzoylation and $NaBH_4$ reduction of **9** furnished 4-*epi*-cytoxazone *ent*-**2** (Fig. 2).

In another synthesis[7] enantiomeric dihydroxy ester *ent*-**8** (R = H) was transformed into epoxy ester **10** via the corresponding 2-tosyloxy derivative *ent*-**8** (R = Ts) (Fig. 3). After epoxide ring opening with sodium azide in CH_3CN and the Nakata cyclization,[3] followed by $NaBH_4$ reduction, (−)-cytoxazone **1** was produced (as claimed by the Barua et al.[7]); however, the correctness of their reasoning has given serious doubts.

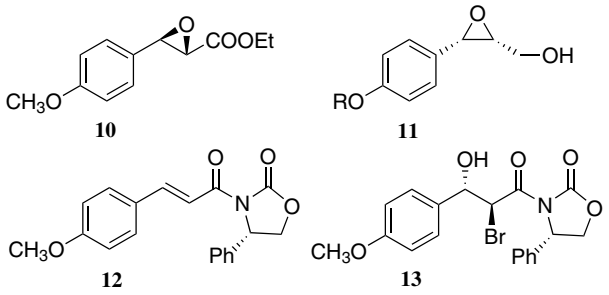


Figure 3.

(2*R*,3*S*)-Epoxy alcohol **11** (R = Ac), prepared from the corresponding cinnamic alcohol **4** (R = H, R′ = Ac) by Sharpless asymmetric epoxidation, was the key intermediate in the synthesis of (−)-cytoxazone **1**, reported by Sudalai and Paraskar.[8a] Compound **11** (R = Ac) was *O*-acetylated and transformed into azido diol (2*R*,3*R*)-**7** (R = R′ = Ac) by nucleophilic opening of the epoxide ring with N_3^- ions, occurring with inversion of the configuration at the benzylic carbon. Conversion of (2*R*,3*R*)-**7** (R = R′ = Ac) into (−)-**1** was achieved following the Nakata cyclization[3] (*O*-phenoxycarbonylation, reductive PPh_3 induced cyclization), hydrolysis of both *O*-acetyl groups and *O*-methylation (NaH/CH_3I). In the synthesis of (±)-**1**, (±)-**11** was applied by Sugai et al.[8b]

In a diastereoselective synthesis of (−)-cytoxazone **1**, also performed by Sudalai et al.'s group,[9] epoxy alcohol **11** (R = CH_3) was used as an intermediate (Fig. 3). It was prepared from chiral 4-methoxycinnamic acid amide **12**, incorporating a chiral oxazolidinone moiety as the amine part. In the next step, oxidative bromohydroxylation ($NaIO_4$/LiBr/H^+) afforded bromohydrin **13**, which after reductive removal of the chiral auxiliary ($LiBH_4$) and exposure to 10% NaOH gave epoxy alcohol **11** (R = CH_3), which in turn was converted into azido diol (2*R*,3*R*)-**7** (R = H, R′ = CH_3), (NaN_3/NH_4Cl). The synthesis was completed by azide reduction (H_2, 10% Pd/C), *N*-*t*-butoxycarbonylation and cyclization (NaH/THF).

Ohshima and Shibasaki et al.[10] described a synthesis in which a catalytic asymmetric epoxidation of 4-methoxycinnamic acid amides, employing TBHP as an oxidant and Sm–(−)-BINOL–$Ph_3AsR{=}O$ complex as a catalyst, was performed and to the in situ formed epoxide Me_3SiN_3 was added, producing *anti*-azido hydroxy amide **14** (Fig. 4). This was isolated in high yield, with complete regioselectivity and with enantioselectivity up to 99%. Reduction and *N*-*t*-butoxycarbonylation (H_2/Pd–C, Boc_2O) of azide **14** followed by amide reduction and cyclization (NaH/THF) gave (−)-cytoxazone **1**.

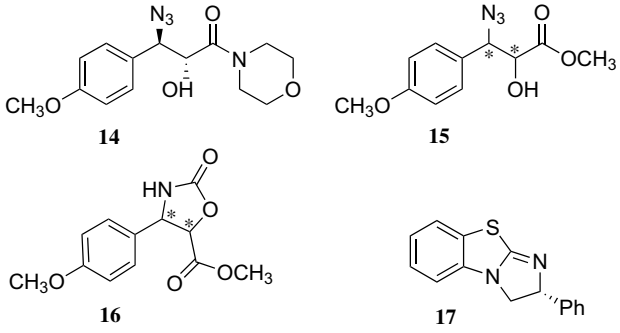


Figure 4.

Sunjic et al.,[11] by opening of the epoxide ring in commercially available racemic methyl 4-methoxyphenylglycidate with sodium azide, prepared racemic *anti*-α-hydroxy-β-azido ester (±)-**15**, which was elaborated to racemic cytoxazone (±)-**1** via *cis*-oxazolidinone (±)-**16**, prepared from (±)-**15** by the Nakata cyclization[3] and ester group reduction ($NaBH_4/CaCl_2$) (Fig. 4). Racemic cytoxazone was then resolved by *Penicillium camemberi* lipase to supply both enantiomers: (−)-**1** and (+)-*ent*-**1**. Resolution of racemic *epi*-cytoxazone (±)-**2**, which was synthesized from the common intermediate *cis*-(±)-**16** upon its epimerization at C-5 with potassium hydroxide, was achieved with *Candida antarctica* lipase.

Kinetic resolution of racemic oxazolidinone (±)-**16** by highly enantioselective catalytic *N*-acylation with propionic anhydride catalyzed by chiral imidazobenzothiazole **17**, afforded enantiomerically pure (4*R*,5*R*)-**16**, a (−)-cytoxazone **1** precursor.[12]

In another approach to the synthesis of cytoxazone **1** and (+)-*epi*-cytoxazone **2** Sudalai et al.[13] used both enantiomeric (*R*)- and (*S*)-amino diols **18** (R = H), prepared by L- and D-proline-catalyzed asymmetric α-amino-oxilation of 2-methoxyphenyl propanal, respectively, followed by reduction ($NaBH_4$ then H_2/10% Pd/C) (Fig. 5). On treatment with chlorosulfonyl isocyanate, (*R*)-**18** (R = H) was converted into sulfonate ester (*R*)-**18** (R = SO_2NH_2), which after TBS-protection of the secondary hydroxyl, was subjected to Rh-catalyzed intramolecular C–H amination to afford insertion product **19**. Then *O*-debenzylation, *N*-*t*-butoxycarbonylation (Boc_2O/Et_3N) and hydrolysis afforded *N*-Boc amino alcohol **20**, which could be easily cyclized to (−)-**1**. Treating (*S*)-diol **18** (R = TBS) with trichloroacetyl isocyanate resulted in carbamate **18** (R = $CONH_2$), which could be cyclized ($K_2CO_3/CH_3OH/H_2O$) to (+)-**2**, upon TBS-deprotection.

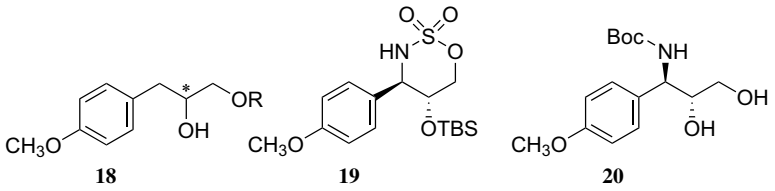


Figure 5.

Asymmetric aminohydroxylation of 4-methoxycinnamic acid methyl ester, which led to *syn*-α-hydroxy-β-amido ester (2*S*,3*R*)-**21** (R = Ac), has been reported by Saicic et al.[14] (Fig. 6). It was converted into (+)-5-*epi*-cytoxazone **2** by hydrolysis of the *N*-acetyl group, oxazolidinone ring formation with diphosgene, and final ester reduction ($NaBH_4$). Epimerization at C-2 in (2*S*,3*R*)-**21** (R = Ac) was achieved via oxazolidine **22**, obtained with inversion of configuration, which took part during cyclization between the *N*-acetyl substituent and in situ generated *O*-triflate ester. Compound **22** was then hydrolyzed (HCl) to give *anti*-α-hydroxy-β-amido ester (2*R*,3*R*)-**21** (R = H), used in the synthesis of (−)-**1**.

Simultaneous introduction of the two functional groups into 4-methoxycinnamic acid *t*-butyl ester was accomplished by Davies et al.[15] Addition of chiral lithium *N*-benzyl-*N*-α-methylbenzylamide followed by in situ CSO-oxidation gave *anti*-α-hydroxy-β-amino ester **23** in high yield and with 98% de (Fig. 6). Compound **23** was subjected to a series of functional group transformations, involving double *N*-debenzylation (H_2/$Pd(OH)_2$), cyclization with diphosgene and ester reduction (TFA, EtOCOCl/$NaBH_4$), to afford (−)-cytoxazone **1**.

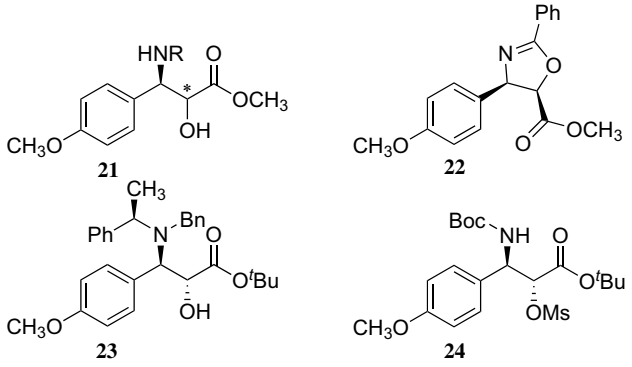


Figure 6.

O-Mesyl *N*-Boc derivative **24**, obtained from *N*-deprotected *anti*-ester **23**, on cyclization in DMF underwent epimerization at C-2, and after reduction of the ester group (Superhydride®) yielded (+)-*epi*-cytoxazone **2**.

2.2. Synthesis by a carbon–carbon bond forming strategy

Various synthetic strategies have been applied to prepare the key intermediates, the chiral nonracemic 3-amino-1,2-diols, by employing a C–C bond forming methodology. Several methods rely on the chiral pool approach, making use of commercially available amino acids or carbohydrates, while others have involved diastereoselective synthesis, using building blocks with chiral auxiliaries attached to the nitrogen atom. Enantioselective syntheses applying asymmetric nitro aldol and Mannich-type reactions were also performed.

A chiral pool approach starting with D-(−)-4-hydroxyphenylglycine has been reported by Rao et al.[16] and by Saicic et al.[17] (Scheme 1). Both research groups used aldehyde **25** (R = Boc,[16] Bz[17]) as the key building block (Scheme 1), which was prepared from the amino acid by functional group transformations involving *O*-methylation and reduction/oxidation processes. This compound was then subjected to homologation either by the addition of vinyl magnesium bromide[16] or by a cyanohydrin reaction.[17]

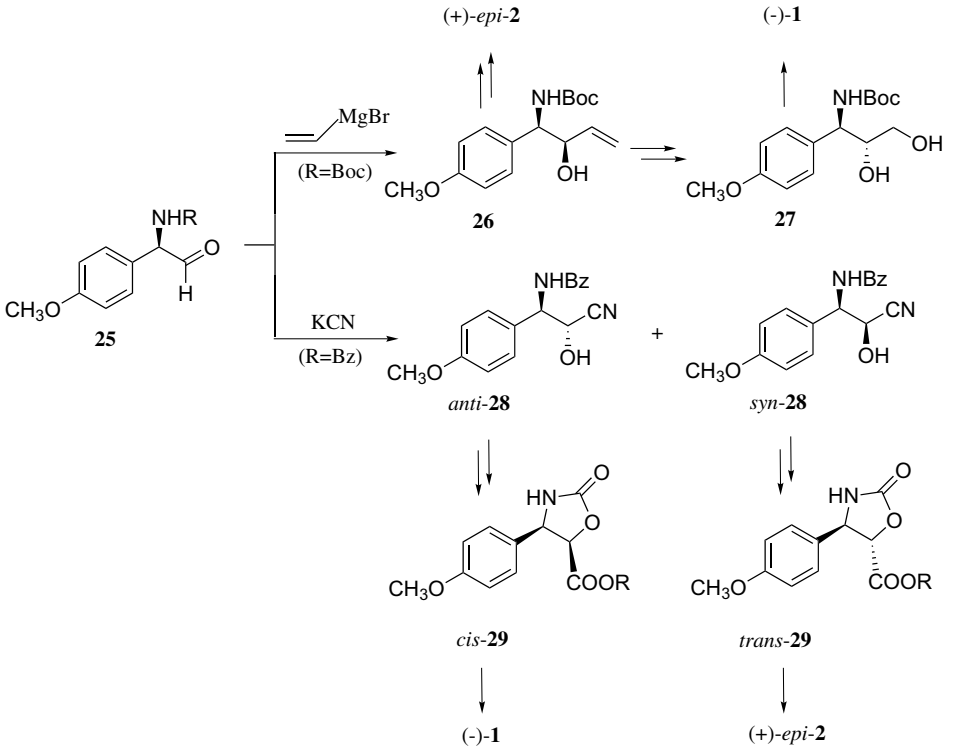
The addition of a vinyl Grignard reagent[16] to the in situ generated aldehyde **25** (R = Boc) afforded *syn*-amino alcohol **26** with an (*R*)-configuration of both stereocenters. This was then cyclized and subjected to ozonolysis/reduction to complete the synthesis of (+)-5-*epi*-cytoxazone **2**. (−)-Cytoxazone **1** was synthesized from the same intermediate *syn*-**26** via *N*-Boc *anti*-amino diol **27**, prepared by epimerization at C-2 under Mitsunobu reaction conditions and ozonolysis.

The cyanohydrin reaction[17] of aldehyde **25** (R = Bz) resulted in a 1:1.5–2.0 mixture of diastereomeric *anti*- and *syn*-α-hydroxy-β-amino nitriles **28**. These were separated by chromatography, hydrolyzed and each of the corresponding *cis*- and *trans*-diastereomeric acids **29** (R = H) was elaborated into (−)-**1** and (+)-**2**, respectively, by $NaBH_4$ reduction of their methyl esters **29** ($R = CH_3$).

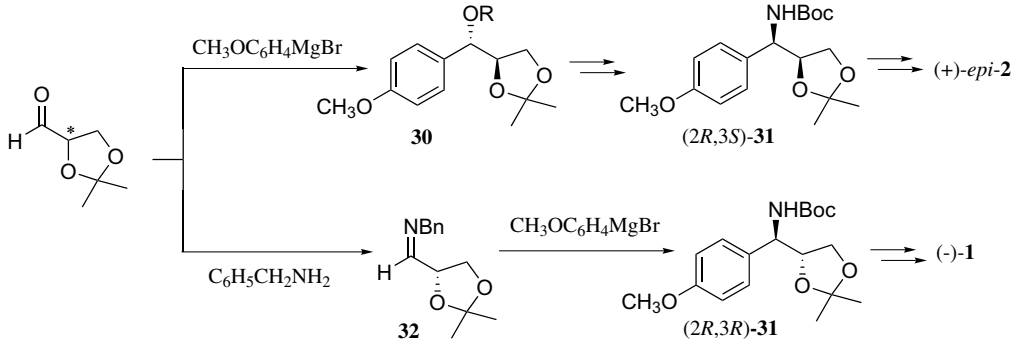
Both enantiomers of D- and L-glyceraldehyde have been used for the synthesis of (−)-cytoxazone (**1**) and its 5-epimer (+)-**2**, respectively (Scheme 2).

Venkateswarlu et al.[18] via addition of 4-methoxyphenyl magnesium bromide to D-glyceraldehyde isopropylidene, obtained *anti*-triol (2*R*,3*R*)-**30** (R = H). This was then converted into *syn*-amino diol (2*R*,3*S*)-**31** in high yield by a stepwise procedure in which the nitrogen functionality was introduced by azidolyzis (NaN_3/acetone) via OMs derivative **30** ($R = OCH_3$) followed by azide reduction (LAH/THF) and *N*-*t*-butoxycarbonylation (Boc_2O/Et_3N/DCM). Cyclization to give (+)-*epi*-cytoxazone **2** was carried under standard conditions (Scheme 2).

Previously, Rao et al.[19] used L-glyceraldehyde benzylidene amine **32** and the same Grignard reagent, 4-



Scheme 1.



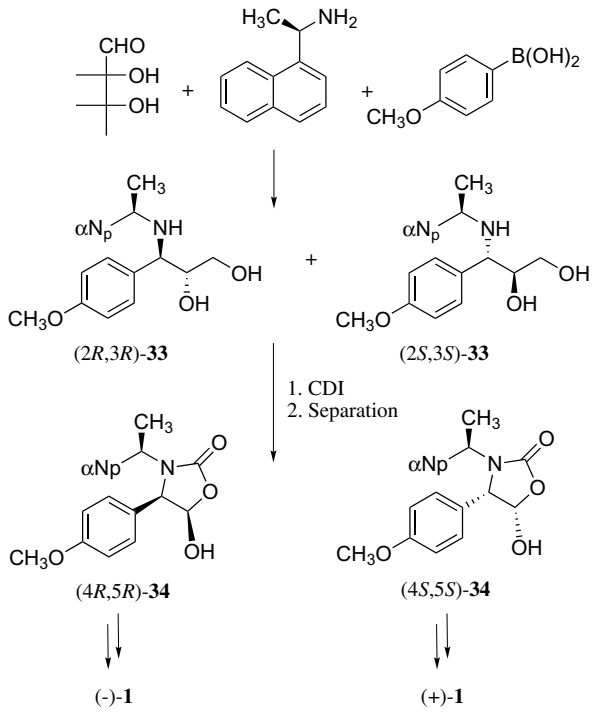
Scheme 2.

$CH_3OC_6H_4MgBr$, to prepare *anti*-amino diol (2*R*,3*R*)-**31** with good stereoselectivity, which after *N*-*t*-butoxycarbonylation, *N*-debenzylation (Pd/C, HCl) and cyclization, was converted into (−)-**1** (Scheme 2).

A diastereoselective synthesis of both enantiomers (−)- and (+)-cytoxazone, **1** and *ent*-**1**, was reported by Sugiyama and Ishii et al.[20] by a three-component Petasis reaction (Scheme 3). In this reaction racemic D,L-glyceraldehyde and (*R*)-1-(naphthyl)ethylamine were coupled with 4-methoxyphenyl boronic acid to afford a 50:50 mixture of *anti*-diastereomeric amino diols (2*R*,3*R*)-**33** and (2*S*,3*S*)-**33**. The coupling products, under the action of phosgene reagent (CDI), were cyclized to diastereomeric *cis*-oxazolidinones (4*R*,5*R*)-**34** and (4*S*,5*S*)-**34**, which after chromatographic separation followed by *N*-deprotection, supplied both cytoxazones (−)-**1** and *ent*-**1**, respectively.

4-Anisaldehyde and its imines, chiral **38**[22] and **50**[25] and achiral **40**,[23] have also found applications as substrates in the synthesis of the natural product and stereoisomers employing carbon–carbon bond forming methodology.

Recently, Smitha and Reddy[21] described the synthesis of (+)-*epi*-cytoxazone **2** using epoxy alcohol **36** as a crucial intermediate (Fig. 7). It was prepared by enantioselective Sharpless epoxidation of racemic allylic alcohol **35**, prepared from anisaldehyde and vinylmagnesium bromide. Under Mitsunobu reaction conditions the benzylic hydroxy group in **36** was substituted with azide ions with inversion of the configuration and after hydrolytic opening of the epoxide ring (NaOH/*t*-BuOH), reduction of the azide group and *N*-Boc formation (Boc_2O/THF), *syn*-amino diol **37** was prepared and cyclized to (+)-*epi*-cytoxazone **2**.



Scheme 3.

Bentley et al.[22] used a SmI_2 induced reductive cross-coupling reaction of chiral *t*-butanesulfinyl imine **38** with benzyloxyacetaldehyde to construct the amino diol carbon chain (Fig. 7). The major *anti*-isomer **39** was produced in high yield and with 25:1 dr. Removal of the chiral auxiliary (HCl/CH_3OH), *O*-deprotection and treatment with triphosgene gave (−)-cytoxazone **1**.

A highly enantio- and diastereoselective Mannich-type reaction of *N*-Boc anisaldimine **40** and hydroxy ketone **41**, catalyzed by Et_2Zn/(*S*,*S*)-BINOL complex, leading to *syn*-ketone **42**, was carried out by Shibasaki et al.[23] (Scheme 4). To cleave the ketone function in the cyclization product **43**, the Bayer–Villiger oxidation was applied and the resulting ester **44** reduced, to yield (−)-4-*epi*-cytoxazone *ent*-**2**.

The enantiomeric analogue of ketone **42**, the keto amino alcohol **45**, was synthesized by Sudalai and Paraskar[8] in an L-proline-catalyzed enantioselective Mannich reaction between 4-anisaldehyde, hydroxyacetone, and 4-anisidine (Scheme 5). Reaction with triphosgene supplied the cyclic product **46**, which via its enol ether **47**, was converted into (+)-*epi*-cytoxazone **2** upon ozonolysis/reduction and final *N*,*O*-deprotection.

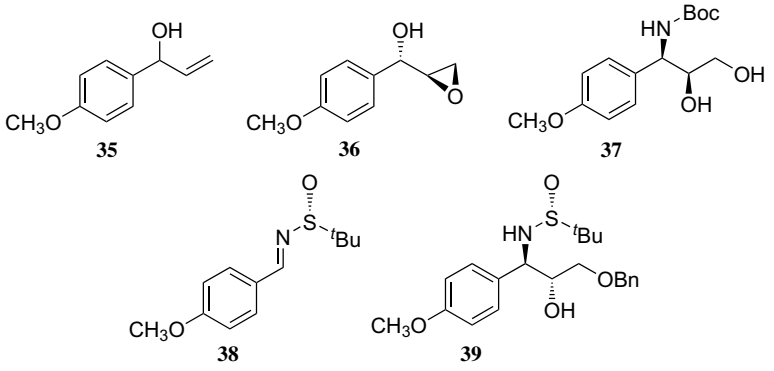
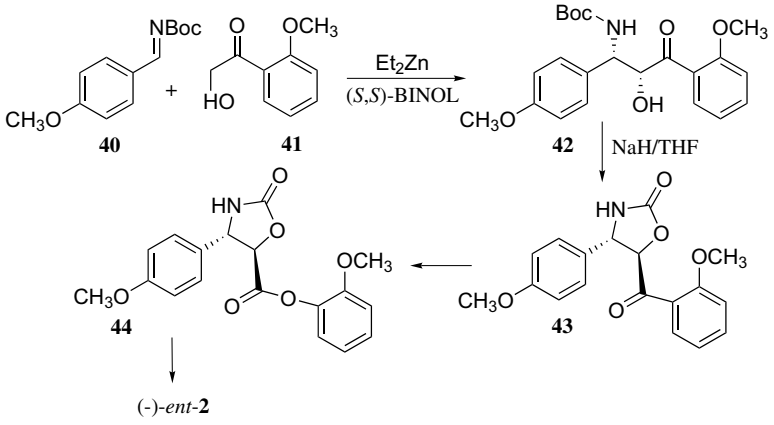
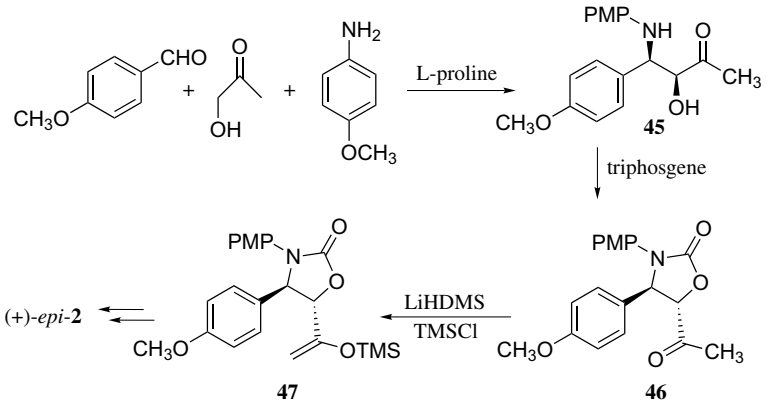


Figure 7.



Scheme 4.



Scheme 5.

The enantio- and *syn*-selective nitroaldol reaction between 4-methoxy-α-nitrotoluene and *O*-TBS protected hydroxyacetaldehyde, catalyzed by guanidine–thiourea **48** organocatalyst, was used by Nagasawa et al.[24] in the synthesis of 4-*epi*-cytoxazone *ent*-**2**. Reduction ($NiCl_2/NaBH_4$) of the addition product **49**, followed by CDI-cyclization and *O*-deprotection completed the synthesis (Fig. 8).

β-Lactam **51**, prepared from (*R*)-anisaldimine **50** and *O*-acethoxy acetic acid chloride, was used as a substrate by Turos et al.[25] in the synthesis of (−)-cytoxazone **1** and (+)-*epi*-cytoxazone **2** (Scheme 6).

Methanolysis of **51** with Me_3SiCl/MeOH yielded *syn*-hydroxy amino ester **52**, which after *N*-debenzylation and *N*-Boc group introduction was epimerized at C-2 under Mitsunobu reaction conditions to afford, after reduction ($NaBH_4$/MeOH) amido diol **53**. This amino diol **53**, identical with *N*-Boc amino diol **20** reported earlier,[9] was

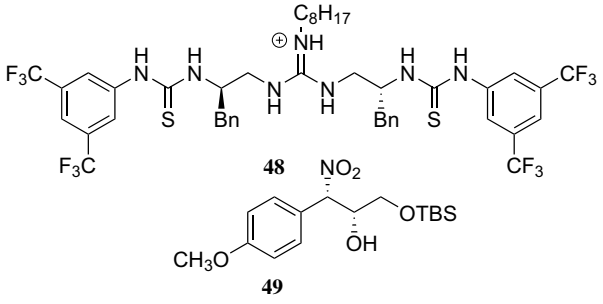
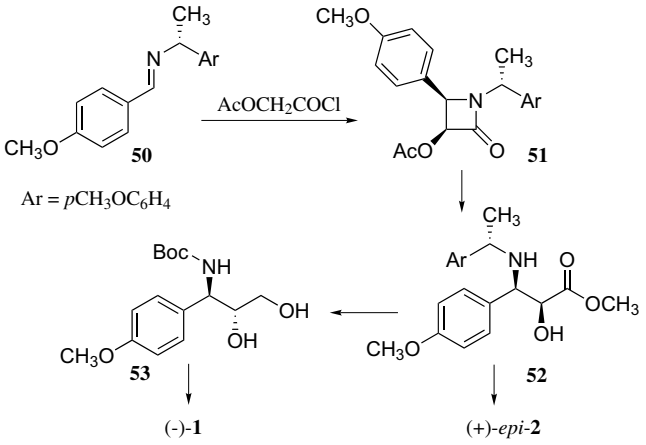


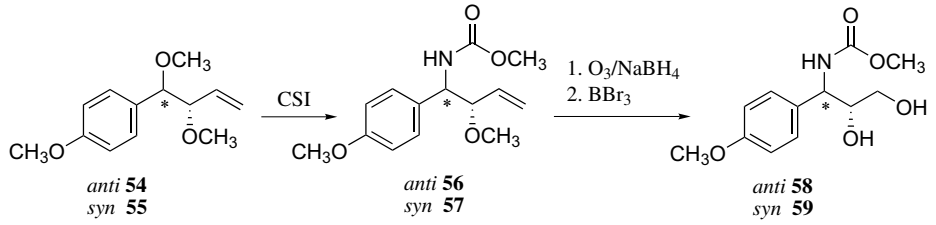
Figure 8.



Scheme 6.

next cyclized to (−)-**1**. In a second series of experiments, the intermediate *syn*-hydroxy amino ester **52** was converted into (+)-**2** in a three-step synthesis involving triphosgene cyclization, *N*-debenzylation ($(NH_4)Ce(NO_2)/CH_3CN$), and ester reduction ($NaBH_4$).

(−)-Cytoxazone **1** and (−)-*epi*-cytoxazone *ent*-**2** were synthesized by Jung et al.,[26,27] according to a synthetic strategy based on regio- and diastereoselective amination of *O*-methylated 1,2-diols: *anti*-**54** and *syn*-**55**, respectively, using chlorosulfonyl isocyanate (CSI) (Scheme 7). The diols were prepared from anisaldehyde: the *anti*-**54** in reaction with allyl(di*iso*propyloamino)dimethylsilane, while the *syn*-**55** with allylmethyl ether, with both reactions catalyzed by chiral boron reagents. After *O*-methylation (NaH/CH_3I)



Scheme 7.

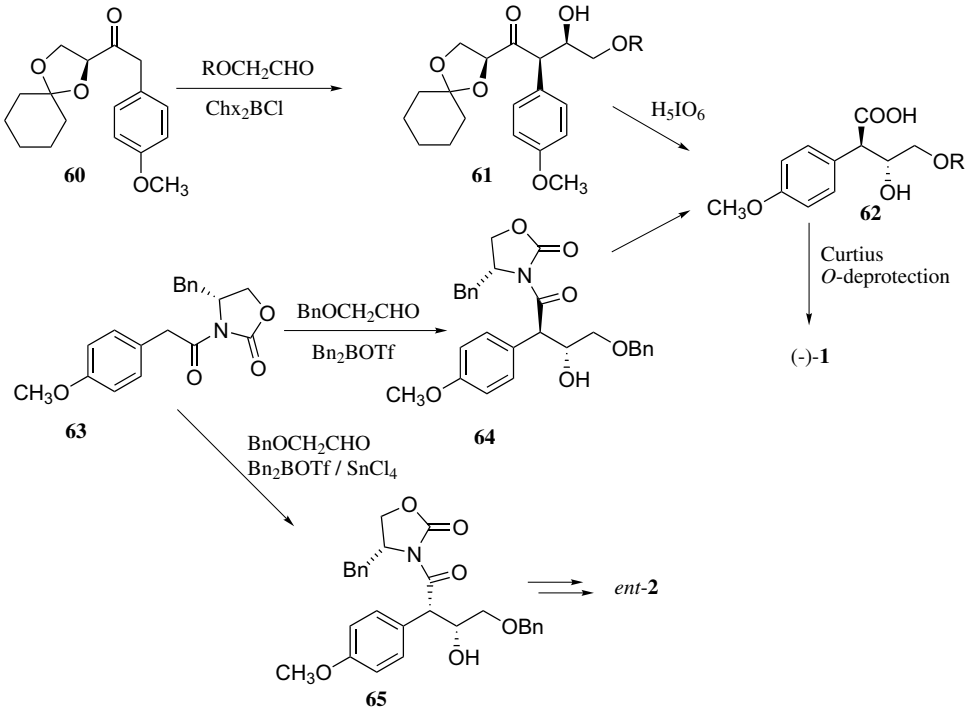
and treatment with CSI diastereomeric carbamates *anti*-**56** and *syn*-**57** were obtained with retention of the configuration, and after cleavage of the vinyl group with $O_3/NaBH_4$ and the methoxyl with BBr_3, the thus formed carbamate diols *anti*-**58** and *syn*-**59** were cyclized to (−)-**1** and (+)-**2**, respectively.

A synthetic strategy employing stereoselective boron aldol reaction to produce hydroxy acid **62** followed by Curtius rearrangement of acid azide has been applied for the synthesis of cytoxazone and isomers by two research teams.[28,29]

The reaction between *O*-protected hydroxy acetaldehyde and the boron enolate of chiral ketone **60**, prepared from L-erythrulose and 4-methoxyphenyl magnesium bromide, was performed by Carda and Marco et al.[28] (Scheme 8). The aldol product **61** (R = TPS, Bn) was converted into (−)-cytoxazone (−)-**1** via *anti*-hydroxy acid **62**, prepared from **61** by oxidative cleavage of the diol function and Curtius rearrangement of acid azide, during which the oxazolidinone ring was simultaneously formed due to intramolecular capture of the isocyanate group by the hydroxy function.

A similar approach, employing the aldol reaction/Curtius rearrangement sequence was applied by Carter et al.[29] for the synthesis of all four stereoisomers of natural cytoxazone to study the influence of the stereochemical configuration on their biological activity. The boron enolate of the known substrate **63**, containing an (*R*)-4-benzyloxazolidinone moiety as a chiral auxiliary, was reacted with benzyloxy acetaldehyde to give *anti*-aldol product **64** (95:5 dr) (Scheme 8). The *syn*-isomer **65** (75:25 dr) was produced when the same reaction was carried out in the presence of $SnCl_4$. Both diastereomers, *anti*-**64** and *syn*-**65** were then transformed into (−)-cytoxazone **1** and (−)-4-*epi*-cytoxazone *ent*-**2**, respectively. The *anti*-isomer **64**, after removal of the chiral auxiliary, gave *anti*-hydroxy acid **62** (R = Bn) which on Curtius rearrangement/cyclization of the acid azide and final *O*-debenzylation afforded (−)-**1**. The *syn*-**65** diastereomer was used in the synthesis of (−)-*ent*-**2**, following the same reaction sequence. The corresponding enantiomers, (+)-cytoxazone *ent*-**1** and (+)-5-*epi*-cytoxazone **2** were synthesized according to the same reaction sequence, starting from epimeric substrate *ent*-**63** with (*S*)-4-benzyloxazolidinone chiral auxiliary.

Following their earlier investigation on the application of racemic imino 1,2-Wittig rearrangement of hydroximates to 2-hydroxy oxime ethers[30,31] to the synthesis of racemic cytoxazone (±)-**1**, Naito et al. carried out an asymmetric synthesis of (+)-cytoxazone *ent*-**1** by the same methodology[32] (Fig. 9). In this approach, the asymmetric induction was carried out by an (*S*)-(2-hydroxy-1-phenyl)ethyl auxiliary attached to the oximate oxygen **66**, which upon treatment with LDA underwent diastereoselective rearrangement to give (*R*) hydroxy ester **67**. This was then converted into oxazolidinone **68** by $NaBH_3CN$ stereoselective reduction of the C=N double bond, reductive (LAH) removal of the *N*-substituent, *N*-*t*-butoxycarbonylation and cyclization. The final step involved the ozonolysis/reduction of the vinyl substituent. It should be noted that racemic cytoxazone (±)-**1** and its epimer (±)-**2**, prepared earlier by the same authors, were efficiently resolved by separation of their esters with (−)-camphanic acid.[30,31]



Scheme 8.

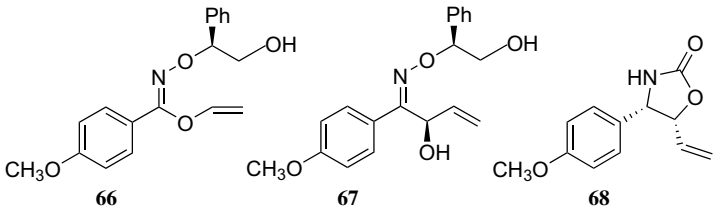


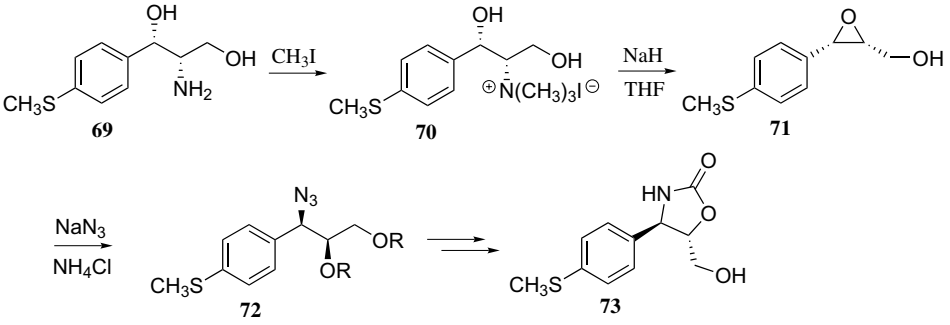
Figure 9.

2.3. The synthesis using (2*S*,3*S*)-2-amino-1,3-diol as a substrate

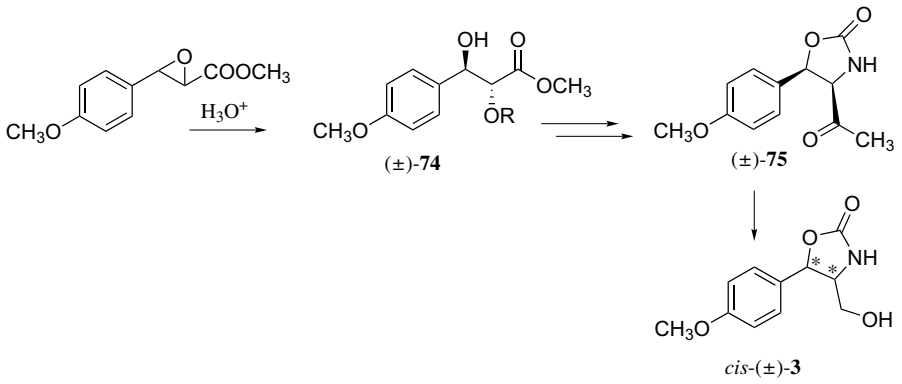
In another chiral pool approach, commercially available (+)-thiomicamine **69**, a waste product of thiamphenicol antibiotic manufacture, has been used as a substrate in the synthesis of **73**, a sulfur analogue of (+)-5-*epi*-cytoxazone **2**, by Rozwadowska.[33] In this synthesis, in order to reverse the position of the amino and benzylic hydroxy groups in **69**, epoxide (2*R*,3*S*)-**71** was prepared from methiodide **70** in quantitative yield and with complete inversion of configuration at C-2, and used as the key intermediate (Scheme 9). Upon treatment with sodium azide, *syn*-azidodiol **72** (R = H) was formed regioselectively and with inversion of configuration at C-3. Its di-*O*-phenoxycarbonyl derivative **72** (R = COOPh) was then cyclized following a known procedure[14] and hydrolyzed to afford enantiomerically pure (4*R*,5*S*)-(+)-**73** in high overall yield.[33]

2.4. The synthesis of isocytoxazones

Several structural analogues of cytoxazone such as *cis*- and *trans*-regioisomers **3**, called isocytoxazones, including those differing in substituents at the aromatic ring, have been synthesized. Sunjic et al.[34] were able to obtain all four stereoisomers of isocytoxazone **3** by separation of the racemic *cis*- and *trans*-diastereomers by preparative HPLC with chiral stationary phase. Similar to their earlier synthesis,[14] *trans*-4-methoxyphenylglycidate was used as a substrate in this synthesis (Scheme 10). The acid-catalyzed hydrolytic opening of the epoxide ring supplied the *anti*-diol ester (±)-**74** (R = H), which was then subjected to standard operations. Azidolysis of the α-hydroxy group via nosyl ester **74** (R = Ns), followed by the Nakata cyclization[3] gave *cis*-oxazolidinone (±)-**75**, and after ester reduction, *cis*-isocytoxazone (±)-**3** was produced. To prepare *trans*-isocytoxazone (±)-**3**, the intermediate *cis*-oxazolidinone (±)-**75** was epimerized under basic conditions and reduced.



Scheme 9.



Scheme 10.

The absolute configuration of the pure enantiomers of isocytoxazone obtained by HPLC separation was established on the basis of a correlation between the experimental and calculated specific rotations, the latter obtained among others by ab initio calculations of the enantiomers' ORD spectra recorded at different wavelengths.[35] In this way, the (4*R*,5*S*)-configuration was predicted for the dextrarotatory enantiomer *cis*-(+)-**3**, while (4*S*,5*S*)-for the dextrarotatory *trans*-(+)-**3** enantiomer.

Several structural analogues of isocytoxazone **3**, *trans*-(4*S*,5*S*)-oxazolidinones **77** (R = H),[36] and **77** (R = SCH_3, NO_2),[37] differing in the type of substituents at the aromatic ring, have been prepared from commercially available (2*S*,3*S*)-2-amino-3-aryl-1,3-propanediols **76** (R = H, SCH_3, NO_2), respectively (Fig. 10). The oxazolidinone ring was closed between the benzylic hydroxyl and the amine functionality either directly under action of phosgene reagents or via the corresponding *N*-alcoxycarbonyl derivatives in a base-catalyzed intramolecular process. All the (4*S*,5*S*)-oxazolidinones **77** were determined to be levorotatory compounds unlike the (4*S*,5*S*)-**3**, described in the study by Sunjic et al. for which dextrarotatory rotation was predicted.[35] The (4*S*,5*S*)-configuration of **77** followed from the (2*S*,3*S*)-stereochemistry of the starting aminodiols **76**, from the ^{1}H NMR study ($J_{H\text{-}4/H\text{-}5}$ ca. 5 Hz) and X-ray crystal analysis of **77** (R = SCH_3).[37]

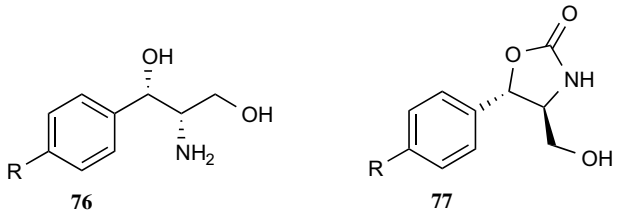


Figure 10.

3. Conclusion

(−)-Cytoxazone **1** and its analogues have been the subject of many synthetic studies because of their potent cytokine modulating activity[1,23] and possible use as novel immunotherapeutic agents. In this article, a variety of asymmetric synthesis strategies applied have been reported to present a wide range of possible routes to this class of compounds. In several of the synthetic approaches, cinnamic acid derivatives were used as substrates and the α-hydroxy β-amino functionalities were introduced in a crucial step via enantioselective Sharpless epoxidation, dihydroxylation, and aminohydroxylation. Using the C–C bond forming approach, achiral and chiral building blocks were transformed into the target compounds in diastereoselective and enantioselective processes involving, for example, addition of carbon nucleophiles to anisaldehyde imines, asymmetric aldol reactions, imino 1,2-Wittig rearrangement, etc. Commercially available 2-amino-1,3-diols were used for the synthesis of the analogues as well. In most of the syntheses, the final products were prepared in good to excellent yields and with high enantiomeric purity. In addition to the total asymmetric synthesis, the chemical and enzymatic resolutions of racemic derivatives of cytoxazone have also been performed. The synthesis of these simple molecules has encountered a great deal of interest amongst many research teams, because the 4,5-disubstituted 2-oxazolidinone system is an interesting objective revealing a broad spectrum of asymmetric synthesis.

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