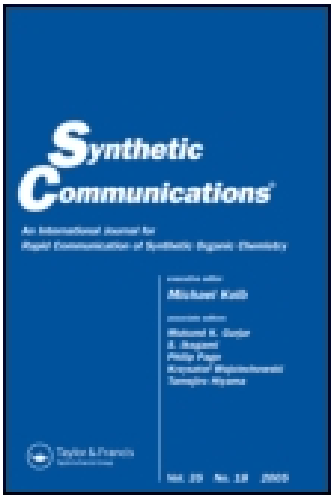

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 31 Oct 2011.Published online: 29 May 2012.

To cite this article: Kollapudi Chandra Babu, Rapolu Naveen Reddy, Salluri Yellamanda Rao, Palnati Venkateshwarlu & Gutta Madhusudhan (2012) New, Efficient, and High-Yielding Asymmetric Synthesis of (4S,5S)-Cytoxazone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:17, 2624-2631, DOI: 10.1080/00397911.2011.563450

To link to this article: http://dx.doi.org/10.1080/00397911.2011.563450

Synthetic Communications®, 42: 2624–2631, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.563450

NEW, EFFICIENT, AND HIGH-YIELDING ASYMMETRIC SYNTHESIS OF (4*S*,5*S*)-CYTOXAZONE

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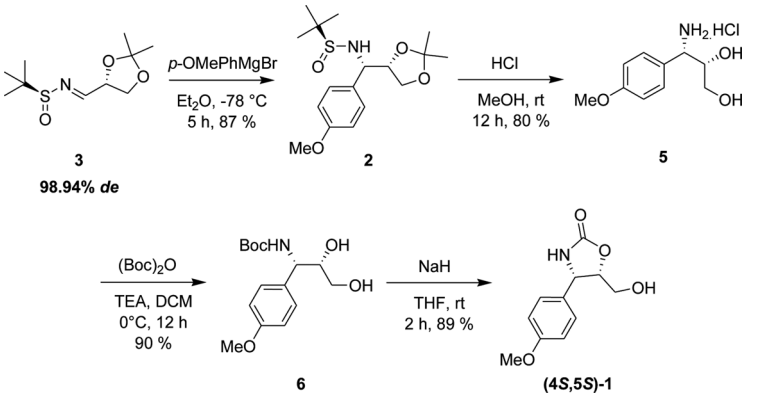
GRAPHICAL ABSTRACT



Abstract *A new approach for the asymmetric synthesis of (4S,5S)-cytoxazone* ***1*** *in five steps and in 48% overall yield starting from commercially available (R)-epichlorohydrin has been described. The key step include stereoselective 1,2-addition of p-methoxyphenyl magnesium bromide (p-OMePhMgBr) to chiral N-sulfinimine derived from (R)-glyceraldehyde acetonide and (S)-t-BSA, which gave corresponding sulfinamide* ***2*** *with high diastereoselectivity. Deprotection of the t-butylsulfonyl group and 1,3-dimethyl acetal in a single step followed by N-Boc protection and subsequent carbonylation yields the targeted (4S,5S)-cytoxazone* ***1****.*

Keywords Chiral *N*-sulfinimine; (*R*)-glyceraldehyde acetonide; (4*R*5*R*)-cytoxazone; (4*S*5*S*)-cytoxazone; stereoselective 1,2-addition

Received December 28, 2010.
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INTRODUCTION

(4*R*,5*R*)-Cytoxazone **1** is a microbial metabolite[1] isolated from *Streptomyces* sp.,[2] which has been identified as a selective modulator of Th2 cytokine secretion. Inhibitors of Th2-dependent cytokine production have potential as potent chemotherapeutic agents in the field of immunotherapy. (4*R*,5*R*)-Cytoxazone **1** is different from known immunomodulators such as FK 506 and rapamycin with respect to structure and biological activity. As such, **1** should be a useful tool for understanding signalling pathways in Th2 cells. Because of its potent biological activity and relatively simple structure, the development of efficient asymmetric routes to cytoxazone and its stereoisomers has been the subject of intense synthetic interest. A variety of synthetic routes to **1** have been previously reported in 10% to 51% overall yield, including chemoenzymatic resolution,[3] imino 1,2-Wittig rearrangement,[4] addition of Grignard reagents to a protected imine,[5] Sharpless asymmetric dihydroxylation and regio- and stereoselective introduction of azide,[6,7] asymmetric aminohydroxylation[8] and asymmetric aldol reactions.[9] Most of these reported methods are for the synthesis of (4*R*,5*R*)-**1** only but are limited for getting (4*S*,5*S*)-**1** directly.[10] Naito et al. synthesized (4*S*,5*S*)-**1** staring from (*R*)-α-hydroxy oxime ether in five steps and 9% overall yield by diastereoselective imino 1,2-Wittig rearrangement.[10]

RESULTS AND DISCUSSION

Herein we report the synthesis of (4*S*,5*S*)-**1** starting from (*R*)-glyceraldehyde acetonide. We have previously demonstrated stereoselective addition of phenylmagnesium bromide (PhMgBr) to *N*-sulfinimine derived from (*R*)-glyceraldehyde acetonide and (*S*)-*t*-BSA with high diastereoselectivity followed by deprotection of the *t*-butylsulfonyl group and 1,3-dimethyl acetal in a single step, resulting in the corresponding *syn*-β-amino alcohol. The amine functionality of obtained β-amino-alcohol was protected as *N*-Boc derivative and finally proceeded to 2-oxazolidinone ring formation.[11] It was envisaged that this methodology would allow an efficient and stereoselective asymmetric synthesis of (4*S*,5*S*)-cytoxazone **1** via synthetic elaboration of the *N*-sulfinimine **3** derived from (*R*)-glyceraldehyde acetonide and (*S*)-*t*-BSA by the stereoselective addition of *p*-methoxyphenylmagnesium bromide (*p*-OMePhMgBr) (Fig. 1).

In this context, (*R*)-glyceraldehyde acetonide is regarded as a common starting material, which has previously been synthesized by us in four steps and in 31% overall yield starting from commercially available (*R*)-epichlorohydrin.[11] Previously, (*R*)-glyceraldehyde acetonide was also elaborated to (*S,E*)-*N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide **3** by the reaction of (*R*)-glyceraldehyde acetonide with (*S*)-*t*-butylsulfinamide [(*S*)-*t*-BSA] using $CuSO_4$ in dichloromethane at room temperature with 98.94% de (Scheme 1).[11]

The chiral α-hydroxy-*N*-sulfinimines have recently received much attention as important precursors and intermediates for the preparation of a wide variety of natural products and drugs.[12] Furthermore, they can be easily converted into chiral β-amino alcohols and 2-oxazolidinones. Therefore, development of methodologies for the stereoselective synthesis of chiral 3-amino-1,2-propanediol followed by carbonylation to 2-oxazolidinones is of considerable interest.[8,13]

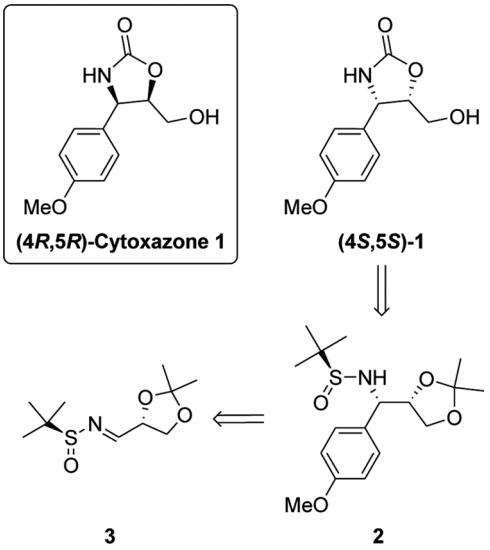
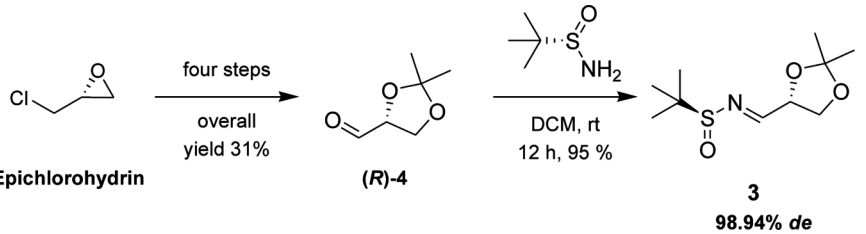


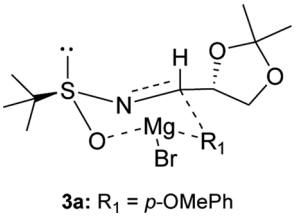
Figure 1. Retrosynthetic analysis for (4*S*,5*S*)-**1**.

1,2-Addition of phenylmagnesium bromide to benzyl imine derivative of (*S*)-**4** is reported in the literature.[5] Chiral α-hydroxy-*N*-sulfinimine **3** on treatment with *p*-OMePhMgBr in Et_2O at −78 °C gave the (*S*)-*N*-((*S*)-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)(*p*-methoxyphenyl)methyl)-2-methylpropane-2-sulfinamide **2** with 87% yield. It is apparent that 1,2-addition of *p*-OMePhMgBr to chiral sulfinimine **3** proceeds via transition state **3a** (Fig. 2).[14]

When tetrahydrofuran (THF), CH_2Cl_2, and toluene were used as the solvent, no increased in yield was observed (Table 1, entries 2, 3, and 4). Deprotection of the *t*-butylsulfonyl group and 1,3-dimethyl acetal in compound **2** was performed in a single step in acidic media (MeOH · HCl) to give the corresponding *syn*-β-aminoalcohol **5**. The amine functionality in **5** was protected as *N*-Boc derivative **6**. The next step in the sequence is the formation of the 2-oxazolidinone. The *N*-Boc protective group was advantageously utilized for the formation of 2-oxazolidinone ring, thereby avoiding the protection and deprotection of primary hydroxyl group.



Scheme 1. Synthesis of (*R*)-glyceraldehyde acetonide **4** and (*S,E*)-*N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide **3** staring from (*R*)-epichlorohydrin.



3a: R_1 = *p*-OMePh

Figure 2. Transition state **3a**.

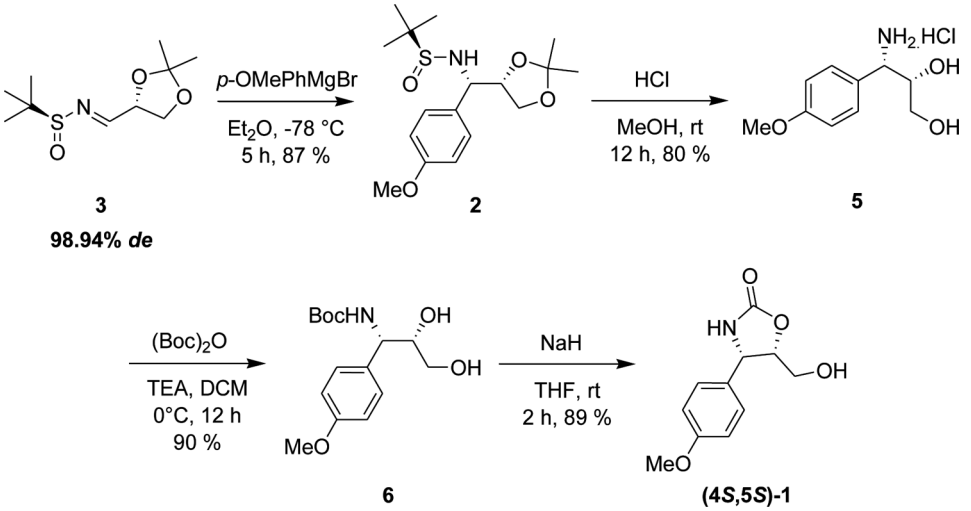
Table 1. 1,2-Addition of *p*-OMePhMgBr to chiral α-hydroxy-*N*-sulfinimine **3**

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	Et_2O	−78	5–6	87 (0)
2	THF	−78	15	25 (42)
3	Toluene	−78	15	35 (50)
4	CH_2Cl_2	−78	15	17 (60)

[a]Yields in parentheses are for recovered starting materials.

Thus, compound **6** on treatment with NaH in THF cyclized regioselectively to targeted (4S,5S)-cytoxazone **1**. The entire strategy is outlined in Scheme 2.

(4S,5S)-Cytoxazone **1** has been confirmed to exist in *threo* configuration by characteristic H4 and H5 signals that appear in ^{1}H NMR spectra and was in agreement with reported values.[10] Because the absolute stereochemistry of (*R*)-**4** and *t*-BSA were known, the identity of the stereocenters of the **1** has been elucidated and confirmed to be (4*S*,5*S*).



Scheme 2. Synthesis of (4*S*,5*S*)-**1**.

CONCLUSION

As a conclusion, an efficient method has been developed for the preparation of (4S,5S)-**1** in five steps and in 48% overall yield starting from (*R*)-glyceraldehyde acetonide. The key step includes stereoselective 1,2-addition of *p*-methoxyphenyl magnesium bromide (*p*-OMePhMgBr) to chiral *N*-sulfinimine derived from (*R*)-glyceraldehyde acetonide and (*S*)-*t*-BSA. The synthetic strategy detailed herein is equally applicable to the synthesis of the (4*R*,5*R*)-, (4*R*,5*S*)-, and (4*S*,5*R*)-stereoisomers of cytoxazone using the diastereoselective 1,2-addition of *p*-methoxyphenyl magnesium bromide (*p*-OMePhMgBr), and the application of this strategy to a variety of related natural products is currently under way in our laboratories.

EXPERIMENTAL

Melting points were determined on a Buchi 540 melting-point apparatus and are uncorrected. Furier transform–infrared (FT-IR) spectra were recorded as KBr pellet on a Nicolet 380 FT-IR instrument Thermo Electron Corporation Spectrum One), and ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on a Varian 400-MHz spectrometer using dimethylsulfoxide (DMSO-d_6), $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on an Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375 °C. All the organic extracts were dried over sodium sulfate after workup. The dry reactions were carried out under a nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. Thin-layer chromatograpy (TLC) was performed on precoated silica-gel plates, which were visualized using ultraviolet (UV) light and sulfuric acid/ethanol (5:95) charring. Flash column chromatography was carried out on silica gel (230–400 mesh) unless otherwise stated.

(*S*)-*N*-((*S*)-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)(*p*-methoxyphenyl) methyl)-2-methyl Propane-2-sulfinamide (2)

A solution of *p*-methoxyphenylmagnesium bromide (186.2 mL, 0.257 mol, 3.0 M solution in Et_2O) was added dropwise to a solution of chiral *N*-sulfinimine **3** (50.0 g, 0.214 mol) in Et_2O (200 mL) over a period of 30 min at −78 °C under an argon atmosphere. After being stirred for 5 h at −78 °C, the reaction mixture was allowed to come to room temperature and poured into a saturated aqueous NH_4C1 solution (300 mL). Both the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 300 mL). The combined organics was dried over anhydrous $MgSO_4$, and solvent was removed in vacuo. Purification of the obtained residue by flash column chromatography (EtOAc–*n*-hexane, 1:3) afforded **2** as a pale yellow liquid (63.6 g, yield 87%). IR (KBr) ν_{max} cm^{-1}: 3285, 1463, 1061; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.05 (s, 9H), 1.22 (s, 3H), 1.32 (s, 3H), 3.73 (s, 3H), 3.91–4.06 (m, 2H), 4.21 (dd, 1H), 4.30 (m, 1H), 5.24 (d, 1H, ex. D_2O), 6.86 (d, 2H), 7.26 (d, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 25.0, 26.5, 55.1, 60.5. 65.8, 78.0, 108.8, 113.4, 129.0, 131.9, 158.3; ESI-MS: m/z (%) 221 (80), 342 ($M^+ + 1$,

100); $[\alpha]_D^{28} = +86.4$ (*c* 1, EtOH). Elemental anal. calcd for $C_{17}H_{27}NO_4S$: C, 59.80; H, 7.97; N, 4.10; S, 9.39. Found: C, 59.72; H, 7.85; N, 4.21; S, 9.09.

(2*S*,3*S*)-3-Amino-3-(4-methoxyphenyl)propane-1,2-diol Hydrochloride (5)

A solution of MeOH-HCl (10%) (88.0 mL, 0.292 mol) was added dropwise to a solution of protected chiral amine **2** (50.0 g, 0.146 mol) in methanol (100 ml) over a period of 30 min. The solution was stirred for 12 h at room temperature and was then concentrated in vacuo. The amine hydrochloride was obtained as a white solid after precipitation from ether and was used without further purification of compound **5** (27.3 g, yield: 80%), mp 219 °C (dec.); IR (KBr) ν_{max} cm^{-1}: 3343, 3085, 3036, 1612, 1492, 1386, 1063, 553; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.22 (dd, 2H), 3.77 (s, 3H), 3.96 (m, 2H), 4.29 (d, 1H), 6.93–6.99 (d, 2H), 7.37–7.40 (d, 2H), 8.34 (s, 2H); ^{13}C NMR (100 MHz, D_2O) δ: 57.0, 58.0, 63.9, 72.5, 129.5, 130.6, 131.1, 133.9; ESI-MS: *m*/*z* (%) 163 (100), 198 ($M^+ + 1$, 20); $[\alpha]_D^{25} = +3.7°$ (*c* 1.05, MeOH).

tert-Butyl (1*S*,2*S*)-2,3-Dihydroxy-1-(4-methoxyphenyl)propyl Carbamate (6)

TEA (27.1 g, 0.268 mol) and $(Boc)_2O$ (26.0 g, 0.128 mol) were added slowly to a solution of β-amino alcohol **5** (25.0 g, 0.107 mol) in DCM (100.0 mL), under argon atmosphere at 0°C. After the reaction mixture was stirred at rt for 12 h, the organic extractions were dried over $MgSO_4$ and concentrated in vacuo to give compound **6** (28.6 g, yield: 90%) as a white solid, which was recrystallized from EtOAc–hexane; mp 116–118 °C; IR (KBr) ν_{max} cm^{-1}: 3371, 1684; ^{1}H NMR (300 MHz, DMSO) δ: 1.35 (s, 9H), 3.22 (d, 2H), 3.60 (d, 1H), 3.72 (s, 3H), 4.44–4.66 (m, 3H), 6.84 (d, 2H), 7.17 (d, 2H); ^{13}C NMR (DMSO, 75 MHz) δ: 28.9, 55.6, 57.6, 62.4, 85.8, 115.0, 128.4, 133.9, 158.9; 160.6; ESI-MS: *m*/*z* 298 ($M^+ + 1$, 100%); $[\alpha]_D^{25} = +51.0$ (*c* 0.65, $CHC1_3$).

(4*S*,5S)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one (1)

Sodium hydride (3.21 g, 1.0 mol, (60% w/w in mineral) was added to a solution of compound **6** (25.0 g, 0.0840 mol) in anhydrous THF (100 mL) at room temperature, and the mixture was stirred under a nitrogen atmosphere for 2 h. The reaction mixture was concentrated, CH_2Cl_2 was added, and the mixture was washed with aqueous saturated NH_4Cl solution and brine and dried over $MgSO_4$. The organic layer was concentrated by rotary evaporation, and the residue was purified by flash column chromatography to give compound **1** (16.7 g, yield: 89%) as a white solid; mp 121–123 °C; IR ν_{max} (KBr) cm^{-1}: 3453, 2969, 1718, 1556, 1247, 1039, 861; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.19 (m, 2H), 3.80 (s, 1H), 3.82 (s, 3H), 4.82 (d, 1H), 6.08 (d, 1H), 6.94–6.99 (d, 2H), 7.24–7.28 (d, 2H); ^{13}C NMR (75 MHz, DMSO) δ: 55.1, 56.2, 61.0, 80.0, 113.7, 128.0, 129.3, 158.7, 159.0; ESI-MS: *m*/*z* 222 ($M^+ - 1$, 100); $[\alpha]_D^{30} = +74.4$ (*c* 0.86, MeOH). Elemental anal. calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.10; H, 5.78; N, 6.15.

ACKNOWLEDGMENT

Financial support from the Inogent Laboratories Private Limited (A GVK BIO Company) is gratefully acknowledged.

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