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The synthesis of (4*S*,5*S*)-(−)-*iso*cytoxazone

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ABSTRACT

(4*S*,5*S*)-(−)-*Iso*cytoxazone, which is needed for a configurational study, was synthesized from the commercially available (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol in which the *p*-nitro substituent was replaced by a *p*-methoxyl group; the thus prepared *p*-methoxyphenyl amino diol was cyclized via an *N*-Boc derivative.

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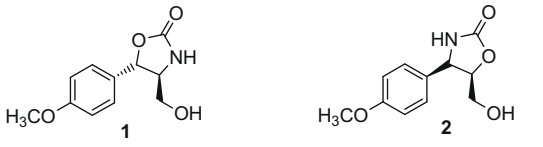
1. Introduction

*Iso*cytoxazone **1**, its structural isomer, the potent cytokine modulator (−)-cytoxazone **2**, and their stereoisomers have recently received much attention because of their pronounced biological activity and pharmacological potential.[1,2] On the other hand, the relatively simple 4,5-disubstituted 1,3-oxazolidinone structure of **1** and **2** has attracted much attention of synthetic chemists, who have undertaken much effort to pursue the development of efficient asymmetric synthesis of this class of compounds.[3] Recently, this heterocyclic system has been chosen as the subject of a methodological study on the development of tools for configurational assignments of organic compounds, based on the ab initio calculations of ORD spectra[4,5] (Fig. 1).



(4*S*,5*S*)-(-)-*iso*cytoxazone **1** (4*R*,5*R*)-(-)-cytoxazone **2**

Figure 1.

The absolute configuration of natural (4*R*,5*R*)-(−)-cytoxazone **2** has been assigned on the basis of comparative CD data analysis/X-ray measurements,[6] as well as by several total syntheses.[3] The stereochemistry of *iso*cytoxazones has recently been investigated by Rossini, Berova et al.,[5] who have chosen *iso*cytoxazone and cytoxazone stereoisomers for the ab initio calculations of the ORD spectra. All four stereoisomers of **1**, needed for this study, were supplied by Sunjic et al.[7] They were prepared by preparative chiral HPLC resolution of racemic *cis* and *trans* diastereoisomeric *iso*cytoxazones, synthesized form epoxy cinnamic acid ester.[7]

On the basis of the ab initio calculations with the use of B3LYP/6-31G(d) method of the ORD spectra measured at four different wavelength, the authors[5] established the (4*S*,5*S*) absolute configuration of the dextrorotatory enantiomer of *trans-iso*cytoxazone. However, several *trans iso*cytoxazone analogues with the (4*S*,5*S*) stereochemistry, which differ only in the type of *p*-substituents at the aromatic ring, such as hydrogen,[8] nitro-,[9] and methylthio,[10] have been found to show the negative sign of the rotation. This inconsistency called for clarification. To solve this problem a stereoselective synthesis of (4*S*,5*S*)-*iso*cytoxazone **1** has been undertaken.

This paper reports on the synthesis of (4*S*,5*S*)-(−)-*iso*cytoxazone **1**, in which (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **3** (R = NO_2) with the established (*S*,*S*) configuration was applied as the starting material. The sequence of reactions leading to **1**, via methoxyphenyl amino diol **8**, the key intermediate, is shown in Scheme 1.

2. Results and discussion

In analogy to our earlier work,[10] in which (1*S*,2*S*)-(+)-thiomicamine **3** (R = CH_3S) was efficiently transformed into the methylthio analogue **1** ($CH_3O{=}CH_3S$) of (4*S*,5*S*)-(−)-*iso*cytoxazone **1**, we have used (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **3** (R = NO_2), a waste product of chloramphenicol antibiotic manufacture, as the starting material. The crucial point of this approach, the synthesis of methoxyphenyl amino diol **8**, involved the replacement of the nitro substituent by a methoxyl group. It was realized via diazotization/iodination of the corresponding diamine **5**, a reduction product of **4**, followed by Cu-catalyzed cross-coupling of iodide **6** with methyl alcohol (Scheme 1).

To avoid any complication during the diazotization step, a suitable protecting group for the primary aliphatic amine was needed. Among the amine protecting groups tested, such as *N*- phthaloyl, *N*-Boc, and *N*-Cbz, the *N*,*N*-dibenzyl protection turned out to be

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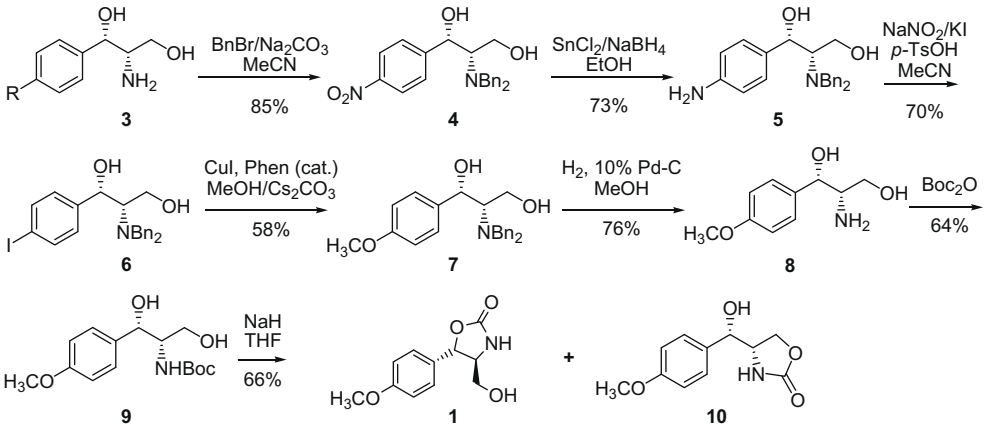

Scheme 1. Transformation of (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **3** (R = NO_2) into (4*S*,5*S*)-(−)-*iso*cytoxazone **1**.

the best choice. Unlike the other protecting groups, it was stable under subsequent reactions conditions, and provided crystalline intermediates, all isolated as single diastereomers.

The synthesis started with *N*,*N*-dibenzylation of nitrophenyl amino diol **3** (R = NO_2) with benzyl bromide and sodium carbonate at reflux in acetonitrile, according to the procedure described for the benzylation of a similar 2-amino-1,3-diol **3** (R = H),[11] to give the protected **4** in 85% yield (mp 154.5–156.5 °C, $[\alpha]_D$ = +73.5).

For the reduction of the nitro substituent in compound **4**, the $NaBH_4/SnCl_2{\cdot}2H_2O$ reducing system, known to effectively reduce aromatic nitro groups in the presence of other reducible functionalities,[12] was used to obtain aminophenyl amino diol **5** in 73% yield (mp 136.5–138.5 °C, $[\alpha]_D$ = +94.7), with no observed cleavage of the *N*-benzyl protecting groups.

Next, the intermediacy of iodo derivative **6** en route to a methoxyl-substituted product was considered. Iodide **6** was prepared in 70% yield (mp 108.5–110 °C, $[\alpha]_D$ = +65.1), by a convenient one-step diazotization–iodination procedure described by Krasnokutskaya et al.,[13] involving sequential treatment of amine **5** with KI, $NaNO_2$, and TsOH in acetonitrile.

The crucial step of the synthesis, the cross-coupling of iodide **6** with methyl alcohol, was best achieved by applying the efficient Buchwald[14,15] modification of the Ullmann ether synthesis. Thus, the Cu-catalyzed reaction, in the presence of 1,10-phenanthroline[14] or 3,4,7,8-tetramethyl-1,10-phenanthroline[15] and Cs_2CO_3, was carried out in a sealed ampule at 90 °C for 24 h to afford the *N*-protected methoxyphenyl amino diol **7** (mp 119–120 °C, $[\alpha]_D$ = +86.3). In this experiment, irrespective of the ligand used, similar results (60% and 58%) were obtained.

The key intermediate of the synthesis, (1*S*,2*S*)-(+)-2-amino-1-(4-methoxyphenyl)-1,3-propanediol **8**, was then obtained quantitatively by catalytic hydrogenolysis of the dibenzyl protecting groups in **7**, performed in methanol at 5 atm pressure of hydrogen using Pearlman's catalyst. The mp (127.5–130 °C) and the specific rotation ($[\alpha]_D$ +32.5 in 2 M aq HCl) of a sample of **8** crystallizing with 0.5 molecules of water, which was difficult to remove, as well as the spectroscopic characteristics corresponded well to those reported for its enantiomer, *ent*-**8** (mp 132–133 °C), $[\alpha]_D$ = −28 (in 2 M aq HCl).[16]

The final step of the synthesis, the construction of the oxazolidinone ring, was performed according to a typical procedure applied in many syntheses of oxazolidinones from amino alcohols, that is, the NaH-induced cyclization of the corresponding *N*-Boc derivatives. Accordingly, the *N*-Boc amino diol **9**, (gum, $[\alpha]_D$ = +27.9), was synthesized under solvent- and catalyst-free conditions as inspired by Jia's procedure,[17] in which methoxyphenyl amino diol **8** was ground with Boc_2O in a mortar at room temperature, and cyclized using standard conditions of NaH/THF. The desired regioisomer, (4*S*,5*S*)-*iso*cytoxazone **1**, was produced as the major product. Part of it precipitated in pure form from the crude product mixture when dissolved in DCM. An additional amount of **1** (total yield 66%) was separated from mother liquors by column chromatography, along with trace amounts of its regioisomer **10**. The structure of **10** (HR MS *m*/*z*: 223.08366) could be deduced from the ^{1}H NMR spectroscopic data analysis. When measured in DMSO-d_6, the hydroxyl proton signal appeared as a doublet (δ, 5.62, J = 4.4 Hz) and disappeared upon treatment with D_2O indicating the presence of a secondary alcohol functionality, while in the spectrum of **1**, the absorption of the hydroxyl group proton was seen as a triplet (δ, 5.10, J = 5.2 Hz), confirming a primary alcohol structure.

Over the course of this study, (4*S*,5*S*)-(−)-*iso*cytoxazone **1** was characterized by mp 145–146 °C (crystallized from ethyl acetate) and $[\alpha]_D$ = −72.5 (*c* 1.025, acetone) which corresponded well to those of the (4*R*,5*R*)-(+)-enantiomer, *ent*-**1**, mp 140–142 °C (crystallized from ethyl acetate/light petroleum), $[\alpha]_D$ = +74.8 (*c* 1.08, acetone), synthesized from the L-tyrosine.[16]

3. Conclusion

In conclusion, the synthesis of (4*S*,5*S*)-(−)-*iso*cytoxazone **1** has been performed using (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **3** (R = NO_2) as the starting material. The (1*S*,2*S*) stereochemistry of the amino diol **3** (R = NO_2) has been preserved during the synthesis, and the target compound (4*S*,5*S*)-**1** was found to be the levorotatory enantiomer. This finding, which contradicts the results reported earlier,[5] implies that caution should be taken when interpreting the results of this type of theoretical investigations when applied to conformationally flexible molecules.

4. Experimental

4.1. General methods

Melting points were determined on a Koffler block and are uncorrected. NMR spectra: Varian Gemini 300, with TMS as the internal standard. Mass spectra (EI): AM D402. Optical rotation: Perkin-Elmer polarimeter 242B at 20 °C. Elemental analysis: Vario EL III. Analytical HPLC: Waters HPLC system with Mallinkrodt-Baker Chiralcel OD-H column. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel 60_{254} for TLC. (2*S*,3*S*)-(+)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol was purchased from Aldrich Chemical Co. and was used as received.

4.1.1. (1*S*,2*S*)-(+)-2-*N*,*N*-Dibenzylamino-1-(4-nitrophenyl)-1,3-propanediol 4

To a mixture of (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **3** (R = NO_2) (2.12 g, 10 mmol) and K_2CO_3 (4.13 g, 30 mmol) in acetonitrile (40 ml) benzyl bromide (2.36 ml, 20 mmol) was added and the mixture was stirred at reflux for 8 h, then left at room temperature for 16 h. Water (50 ml) was added to this mixture and stirring was continued for 30 min. The crystalline precipitate was filtered off, washed with water (50 ml), and dried in air to afford TLC-pure **4**, 3.55 g (85%). Mp 154.5–156.5 °C (from ethanol) [lit.[18] mp 156–158 °C], $[\alpha]_D$ = +73.5 (*c* 1.05, methanol). ^{1}H NMR ($CDCl_3$) δ: 8.10–8.01 (m, 2H), 7.39–7.25 (m 12H), 4.77 (s, 1H, disappears on treatment with D_2O), 4.70 (d, *J* = 9.6 Hz, 1H), 4.10 (d, *J* = 13.1 Hz, 2H), 3.75–3.66 (m, 4H), 2.82 (ddd, *J* = 4.1, 6.5, 9.6 Hz, 1H), 1.50 (s, 1H, disappears on treatment with D_2O). ^{13}C NMR ($CDCl_3$) δ: 150.0, 147.4, 138.5, 129.7, 128.8, 128.6, 127.8, 127.5, 123.5, 77.4, 77.0, 76.6, 69.8, 64.9, 58.5, 54.5. EI MS *m*/*z* (%): 361 (1), 240 (55), 181 (5), 150 (2), 148 (2), 91 (100). Anal. Calcd for $C_{23}H_{24}N_2O_4$ (329): C, 70.38; H, 6.17; N, 7.14. Found: C, 70.37; H, 5.94; N, 7.15.

4.1.2. (1*S*,2*S*)-(+)-2-*N*,*N*-Dibenzylamino-1-(4-aminophenyl)-1,3-propanediol 5

A mixture of nitro compounds **4** (5.25 g, 13.4 mmol) and $SnCl_2 \cdot H_2O$ (15.12 g, 67 mmol) in ethanol (100 ml) was heated at 60 °C for 1 h with stirring. Next $NaBH_4$ (255 mg, 67 mmol) in ethanol (80 ml) was introduced dropwise over 10 min and the mixture was kept at 60 °C for another 1 h. After being cooled to ca. 10 °C water (100 ml) was added followed by neutralization with 15% NaOH. Ethanol was evaporated and the residue was extracted with ethyl ether until the Dragendorff test was negative (ca. 500 ml). The ether solution was dried and concentrated to give a white solid (4.8 g, 92%), which was digested with ethyl ether to give pure amine **5** (3.51 g, 73%), mp 136.5–138.5 °C. $[\alpha]_D$ = +94.7 (*c* 1.03, methanol). ^{1}H NMR ($CDCl_3$) δ: 7.37–7.23 (m, 10H), 6.04–6.89 (m, 2H), 6.56 (m, 2H), 4.47 (d, *J* = 9.9 Hz, 1H), 4.02 (d, *J* = 13.2 Hz, 2H, + 1H which disappears upon treatment with D_2O), 3.75 (d, *J* = 13.2 Hz, 2H), 3.60 (s, 1H, disappears upon treatment with D_2O), 3.54 (dd, *J* = 7.5, 11.5 Hz, 2H), 3.40 (dd, *J* = 4.4, 11.5 Hz, 2H), 2.90 (ddd, *J* = 4.4, 7.5, 9.7 Hz, 1H), 1.87 (br s, 1H, disappears on treatment with D_2O). ^{13}C NMR ($CDCl_3$) δ: 146.2, 139.1, 131.5, 129.3, 128.5, 127.9, 127.2, 115.1, 77.4, 77.0, 76.6, 71.7, 65.0, 59.0, 54.3. EI MS *m*/*z* (%): 363 (0.2), 240 (58), 223 (6), 181 (5), 120 (4), 91 (100). Anal. Calcd for $C_{23}H_{26}N_2O_2$ (362)·¼H_2O: C, 75.28; H, 7.15; N, 7.63. Found: C, 75.77; H, 7.18; N, 7.48.

4.1.3. (1*S*,2*S*)-(+)-2-*N*,*N*-Dibenzylamino-1-(4-iodophenyl)-1,3-propanediol 6

To a suspension of amine **5** (1.09 g, 3 mmol) and *p*-TsOH·H_2O (1.72 g, 9 mmol) in acetonitrile (12 ml), a solution of $NaNO_2$ (414 mg, 6 mmol) and KI (1.25 g, 7.5 mmol) in water (1.8 ml) was added dropwise. The reaction mixture was stirred for 10 min at 10 °C, then at room temperature for 2 h. Water (500 ml) was added and stirring was continued for 30 min, after which the mixture was neutralized with 10% $NaHCO_3$, followed by the addition of satd $Na_2S_2O_3$ (3 ml) and extracted with ethyl ether, until the Dragendorff test was negative. The organic phase was dried and concentrated to give iodide **6** as a yellowish foam (1.2 g, 84%), which was purified by column chromatography [silica gel (1:10), hexane/ethyl acetate (9:1)] to afforded pure **6** (0.99 g, 70%), mp 108.5–110 °C (from methanol), $[\alpha]_D$ = +65.1 (*c* 1.1, methanol). ^{1}H NMR ($CDCl_3$) δ: 7.60–7.56 (m, 2H), 7.38–7.27 (m, 10H), 6.89–6.86 (m, 2H), 4.52 (d, *J* = 9.8 Hz, 1H), 4.42 (s, 1H, disappears upon treatment with D_2O), 4.06 (d, *J* = 12.9 Hz, 2H), 3.75 (d, *J* = 12.9 Hz, 2H), 3.62 (dd, *J* = 7.6, 11.5 Hz, 1H), 3.50 (dd, *J* = 3.8, 11.5 Hz, 1H), 2.83 (ddd, *J* = 3.8, 7.6, 9.8 Hz 1H), 1.54 (br s, 1H, disappears upon treatment with D_2O). ^{13}C NMR ($CDCl_3$) δ: 141.9, 138.8, 137.5, 129.3, 128.9, 128.6, 127.4, 93.3, 77.4, 77.0, 76.6, 70.6, 64.9, 58.9, 54.4. EI MS, *m*/*z* (%): 241 (14), 240 (75), 232 (2), 231 (2), 181 (6), 91 (100). Anal. Calcd for $C_{23}H_{24}NO_2I$ (473): C, 58.34; H, 5.11; N, 2.96. Found: C, 58.36; H, 4.64; N, 2.76. HR MS *m*/*z*: 472.07700. Calcd for [M^+−1]: 472.07736.

4.1.4. (1*S*,2*S*)-(+)-2-*N*,*N*-Dibenzylamino-1-(4-methoxyphenyl)-1,3-propanediol 7

An ampule equipped with magnetic stirring bar was filled with iodide **6** (1.42 g, 3 mmol), CuI (28 mg, 0.15 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (72 mg, 0.3 mmol), and Cs_2CO_3 (1.17 g, 3.5 mmol) in anhydrous methanol (3 ml). After being sealed it was placed in oil bath at 90 °C for 24 h, then cooled to room temperature, opened and the solution was decanted from inorganic material, which was washed several times with methanol. The organic solution was filtered through a pad of Celite, after which water (12 ml) was added to the filtrate, methanol evaporated and the water solution was extracted with ethyl ether until the Dragendorff test was negative. The ethereal solution was dried and concentrated to give 1.1 g of oily residue, from which 0.66 g (58%) of pure **7** was obtained by column chromatography separation [silica gel (1:15), hexane/ethyl acetate (85:15)]. Mp 119–120 °C (from ethanol), $[\alpha]_D$ = +88.9 (*c* 1.01, methanol). ^{1}H NMR ($CDCl_3$) δ: 7.34–7.25 (m, 10H), 7.09–7.04 (m, 2H), 6.82–6.77 (m, 2H), 4.54 (d, *J* = 9.8 Hz, 1H), 4.11 (s, 1H, disappears upon treatment with D_2O), 4.05 (d, *J* = 12.9 Hz, 2H), 3.76 (d, *J* = 12.9 Hz, 2H), 3.75 (s, 3H), 3.63 (dd, *J* = 7.6, 11.5 Hz, 1H), 3.45 (dd, *J* = 4.4, 11.5 Hz, 1H), 2.92 (ddd, *J* = 4.4, 7.7, 9.8 Hz, 1H), 1.69 (s, 1H, disappears upon treatment with D_2O). ^{13}C NMR ($CDCl_3$) δ: 159.3, 139.8, 133.9, 129.3, 128.5, 128.1, 127.3, 112.9, 77.4, 77.0, 76.6, 71.3, 65.1, 59.0, 55.2, 54.3. EI MS *m*/*z* (%): 376 (0.2), 241 (13), 240 (77), 181 (6), 147 (5), 135 (3), 91 (100). Anal. Calcd for $C_{24}H_{27}NO_3$ (377)·¼H_2O: C, 75.46; H, 7.12; N, 3.67. Found: C, 75.63; H, 6.90; N, 3.54.

4.1.5. (1*S*,2*S*)-(+)-2-Amino-1-(4-methoxyphenyl)-1,3-propanediol 8

To a solution of dibenzylated amine **7** (480 mg, 1.27 mmol) in dry methanol (12 ml), 20% $Pd(OH)_2$–C (254 mg) was added and the mixture was hydrogenated under 5 atm hydrogen for 9 h. The catalyst was removed by filtration through Celite, washed with methanol and the filtrate was concentrated under reduced pressure to afford a crystalline solid (250 mg, 91%), which was digested with ethyl ether to give pure amino diol **8** (210 mg, 76 %), containing 0.5 molecules of water of crystallization. Mp 127.5–130 °C, $[\alpha]_D$ = +32.5 (*c* 1.15, 2 M HCl) [lit.[16] for *ent*-**8**, mp 132–134 °C (from methanol/ethyl ether), $[\alpha]_D$ = −28.3 (*c* 1.06, 2 M HCl)].

^{1}H NMR ($CDCl_3$) δ: 7.29–7.24 (m, 2H), 6.92–6.87 (m, 2H), 4.46 (d, *J* = 7.1 Hz, 1H), 3.77 (s, 3H), 3.42 (dd, *J* = 4.4, 10,7 Hz, 1H), 3.27 (dd, *J* = 6.5, 10.7, 1H), 2.88 (ddd, *J* = 4.4, 6.6, 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 160.7, 136.0, 128.8, 114.8, 75.4, 64.0, 59.9, 55.7. EI MS *m*/*z* (%): 180 (10), 162 (6), 160 (18), 149 (47), 148 (7), 137 (35), 134 (60), 121 (43), 118 (9), 117 (10), 109 (35), 107(12), 106 (14), 105 (8), 94 (42), 79 (33), 78 (24), 77 (67), 75 (9), 60 (99). Anal Calcd for $C_{10}H_{15}NO_3$ (197)·1/2H_2O: C, 58.02; H, 7.29; N, 6.76. Found: C, 58.18; H, 6.96; N, 6.51.

4.1.6. (1*S*,2*S*)-(+)-2-^{t}Butoxycarbonylamino-1-(4-methoxyphenyl)-1,3-propanediol 9

Amino diol **8** (197 mg, 1 mmol) and Boc_2O (327 mg, 1.5 mmol) were placed in an agate mortar and ground from time to time, while monitoring the progress of the reaction by TLC. After 3 h, the mixture was dissolved in ethyl ether, transferred into separatory funnel and washed with 1% HCl. The ether solution was dried and concentrated to give crude product, which was purified by column chromatography [silica gel (1:15), hexane/ethyl acetate

(70:30)] to yield pure **9** as a gum (189 mg, 64%), $[\alpha]_D$ = +27.9 (*c* 1.0, methanol). ^{1}H NMR ($CDCl_3$) δ: 7.29–7.27 (m, 2H), 6.89–6.85 (m, 2H), 5.26 (br s, 1H, disappears upon treatment with D_2O), 4.90 (d, *J* = 3.5 Hz, 1H), 3.79 (s, 3H), 3.79–3.73 (m, 3H), 3.49, 2.99 and 1.96 (3 br s, 1H each, disappear upon treatment with D_2O), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 159.1, 156.6, 133.3, 127.3, 113.7, 79.9, 77.4, 77.0, 76.6, 73.9, 63.8, 57.1, 55.2, 28.2. EI MS *m*/*z* (%): 224 (26), 211 (23), 206 (36), 198 (30), 194 (39), 185 (21), 180 (99), 175 (35), 137 (46), 115 (24), 109 (34), 60 (23), 57 (36). Anal. Calcd for $C_{15}H_{23}NO_5$ (297)·1/4H_2O: C, 59.68; H, 7.85; N, 4.64. Found: C, 59.70; H, 7.74; N, 4.40.

4.1.7. (4*S*,5*S*)-(−)-4-Hydroxymethyl-5-(4-methoxyphenyl)-oxazolidin-2-one [(4*S*,5*S*)-(−)-*Iso*cytoxazone] 1

N-Boc derivative **9** (190 mg, 0.63 mmol) in dry THF (8 ml) was treated with NaH (40 mg, 1 mmol, 60% dispersion in mineral oil) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 2 h, during which the presence of two products in ca. 1:1 ratio and the starting material was observed by TLC. The reaction was completed after being left in a refrigerator overnight with the product of lower R_f prevailing. To the mixture, methanol and 20% NH_4Cl were added, and the organic solvents were evaporated under reduced pressure. The aqueous phase was extracted with ethyl acetate, and the organic extract was dried and concentrated to yield an oily residue, which when dissolved in DCM deposited pure *iso*cytoxazone **1** (59 mg). An additional amount of **1** (37 mg, total yield 66%) was obtained from mother liquors by column chromatography separation [silica gel (1:30), DCM/methanol (50:2)]. Mp 145–146 °C (ethyl acetate), $[\alpha]_D$ = −72.5 (*c* 1.025, acetone) [lit.[16] for *ent*-**1**: mp 140–142 °C (ethyl acetate/petroleum), $[\alpha]_D$ = +74.8 (*c* 1.08, acetone)]. HPLC (hexane/isopropanol 65:35, 0.5 ml/min., λ = 226.1, t_R = 15.59 min). ^{1}H NMR (DMSO-d_6) δ: 7.82 (s, 1H, disappears upon treatment with D_2O), 7.32–7.27 (m, 2H), 6.99–6.88 (m, 2H), 5.22 (d, *J* = 5.2 Hz, 1H), 5.10 (t, *J* = 5.2 Hz, 1H, disappears upon treatment with D_2O), 3.76 (s, 3H), 3.57 (dd, *J* = 4.9, 9.6 Hz,1H), 3.47 (t, *J* = 4.9 Hz, 2H). EI MS *m*/*z* (%): 223 (11), 162 (3), 149 (6), 148 (15), 137 (100), 135 (15), 109 (22), 94 (11), 77 (15). HR MS *m*/*z*: 223.08455. Calcd for $C_{11}H_{13}NO_4$ [M^+]: 223.08446.

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