A Rapid and Highly Diastereoselective Synthesis of Enantiomerically Pure (4*R*,5*R*)- and (4*S*,5*S*)-Isocytoxazone

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Abstract: A three-step protocol for the highly diastereoselective (>98%) synthesis of both (4*R*,5*R*)- and (4*S*,5*S*)-isocytoxazone from D- or L-tyrosine is reported. The diastereoselection was confirmed by X-ray crystallography. This synthesis is currently the highest yielding approach towards these enantiomerically pure biologically active oxazolidinones.

Key words: diastereoselective, cytoxazone, tyrosine, oxazolidinone, oxidation

During the course of screening for chemical immunomoderators from microbial metabolites, Osada found that an actinomycete strain (RK95-31) produced cytoxazone **1** (Figure 1), an oxazolidinone that interferes with cytokine IL-4, IL-10 and IgG production.[1] Several groups have synthesized (–)-cytoxazone **1** and (+)-*epi*-cytoxazone **2** (Figure 1),[2] and Šunjic has described the racemic syntheses of all of the stereoisomers and cogeners of isocytoxazone **3** (Figure 1); enantiomerically pure samples were isolated by preparative HPLC.[3] A theoretical study on the absolute configurations of **1** and **3** has been carried out by Berova, as have extensive X-ray crystallographic studies.[4]

Rozwadowska and Tomczak have recently reported the synthesis of (4*S*,5*S*)-(–)-isocytoxazone (**3**; Figure 1),[5] but the synthesis required seven synthetic steps, the last of which afforded a mixture of regioisomers in an overall yield of 8.1%. Prompted by these studies after reporting several routes to 1,3-amino diols[6] we herein report our efforts in this area, utilizing a rapid highly diastereoselective three-step process from Boc-protected D- or L-tyrosine.

Our original strategy towards (4*S*,5*S*)-isocytoxazone was similar to that of Rozwadowska, using diazotization as a key reaction step (Scheme 1).

Hydrogenation of the nitro group in the formate-protected amino diol **4** to give the corresponding amino compound **5** proved highly successful (99% yield). The subsequent diazotization reaction, however, was extremely poor, giving at best 15% yield in our hands (the reaction has previously been reported to give yields of up to 35%[7]). Further manipulation of product **6** afforded the 4-hydroxyphenyl-1,3-dioxane **7**. Methylation, after some experimentation, was achieved with caesium carbonate and dimethyl sulfate, producing the 4-methoxyformate **8**, but separation from by-products brought through from the initial diazotization reaction proved difficult (Scheme 2). Before this approach was abandoned, an interesting reaction reported by Quin and Macdiarmid was attempted, whereby direct conversion from an amine group to a methoxy group is possible using isoamyl nitrite in methanol (Scheme 3).[8] Unfortunately, when using our substrate, this led to a complex mixture of products, including loss of the formate protecting group.

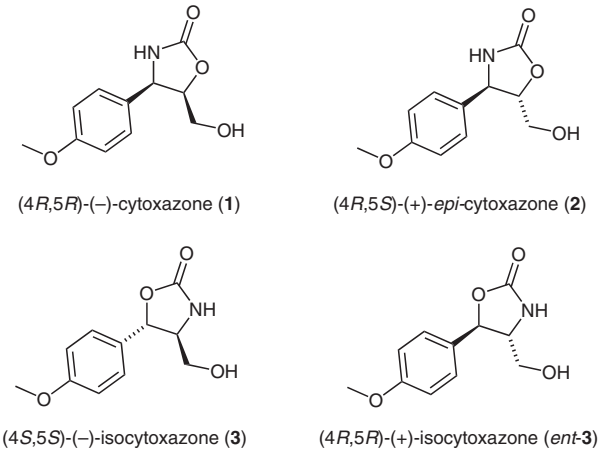
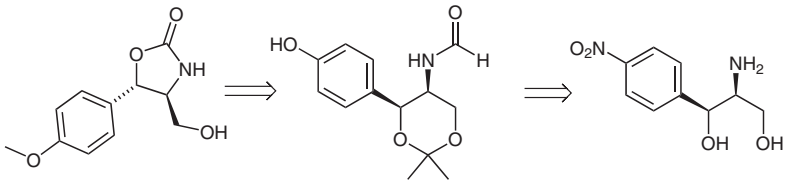


Figure 1 The cytoxazones



Scheme 1 Retrosynthetic route towards (4*S*,5*S*)-isocytoxazone

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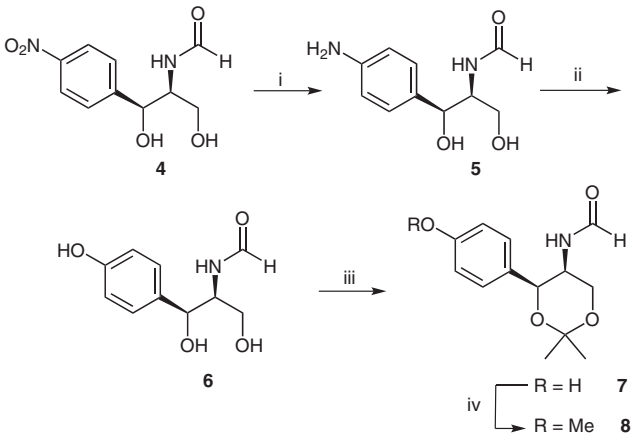
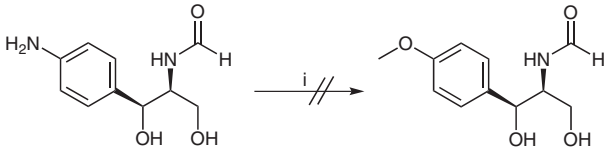


Scheme 2 Initial synthesis of the *p*-methoxyformate **8**. *Reagents and conditions*: (i) H_2/Pd, EtOH, r.t., 24 h, 99%; (ii) (a) $NaNO_2$, H_2SO_4; (b) pH 6, Δ, 15%; (iii) 2,2-DMP, acetone, CSA, r.t., 4 h, 72%; (iv) Cs_2CO_3, Me_2SO_4, CH_2Cl_2, 48 h, 72%.



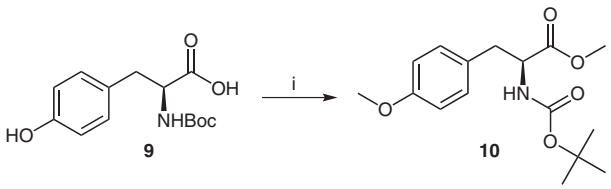
Scheme 3 Attempted direct incorporation of the methoxy group using Quin and Macdiarmid's method. *Reagents and conditions*: (i) (a) H_2SO_4, MeOH, $(CH_3)_2CHCH_2CH_2ONO$, 0 ºC, 3 h; (b) Δ, 1 h.

We next reasoned that (4*S*,5*S*)-isocytoxazone **3** could be prepared from commercially available Boc-D-tyrosine (Scheme 4).

We initially aimed to prepare the enantiomer of **3** (4*R*,5*R*)-isocytoxazone *ent*-**3** from the cheaper Boc-L-tyrosine (Schemes 5– 7). Methylation of the acid and phenol components within Boc-L-tyrosine with potassium hydroxide and iodomethane afforded **10**,[9] the required precursor to **11**.

Following the work of Ohfune,[10] the benzylic position of **10** was oxidized with potassium persulfate ($K_2S_2O_8$) and catalytic copper sulfate to form the oxazolidinone **11**[11] in a highly diastereoselective manner (diastereomeric ratio 98% *R* at C3) (Scheme 6).

The authors suggest that this high selectivity in cyclic carbamate formation arises because the reaction proceeds via the more stable conformer of benzyl cation intermediate **10b**. The conformer **10a** is more strained than **10b** due to steric interaction between the ester group and the *ortho* hydrogen atom. Intramolecular trapping of this cation by a carboxyl oxygen and subsequent release of the *tert*-butyl



Scheme 5 Formation of Boc-protected, dimethylated L-tyrosine **10**. *Reagents and conditions*: (i) MeI (2.2 equiv), KOH (2.2 equiv), DMF, 0 ºC to r.t., 3.5 h, 74%.

cation, which is believed to be more stable than the benzylic cation of **10**, is thought to be a driving force for the reaction. This was supported by Ohfune's observation that only poor yields were obtained from compounds containing other amino protecting groups, such as the Cbz group. Confirmation of the stereoselectivity was achieved from the X-ray crystal structure of compound **11**, as shown in Figure 2.

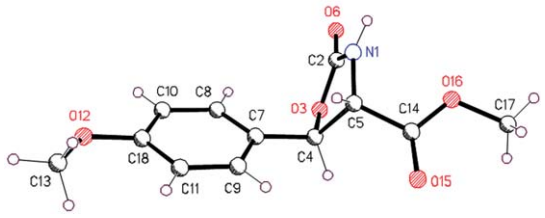
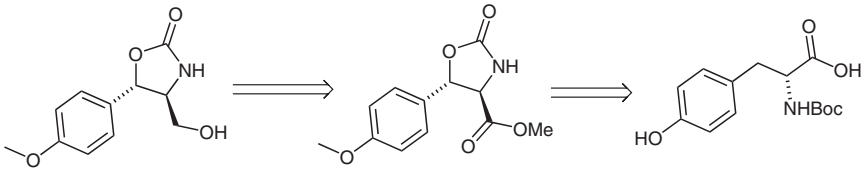


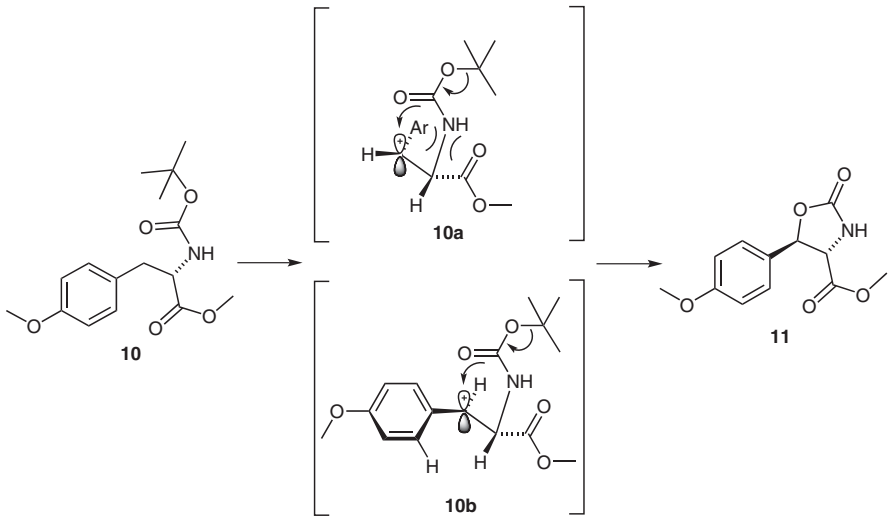
Figure 2 X-ray crystal structure of **11**[12]

Although this reaction is highly stereoselective, some problems were encountered during the synthesis. Yields tended to vary on scale-up of the reaction. Initially, the reaction on 4 mmol of substrate afforded 50% of the desired product (a good yield given the reported yield of 55%), but on increasing the scale to 26 mmol a drop in yield to 40% was observed. Optimum conditions were found when carrying the reaction out on a 16 mmol scale, a 52% yield of product was obtained. Attempts to drive the reaction to completion proved fruitless. Generally, increased reaction times and temperatures decreased the overall yield due to generation of higher levels of the side product 4-methoxy benzaldehyde (a product of over-oxidation).[10] Milder reaction conditions resulted in no product formation.

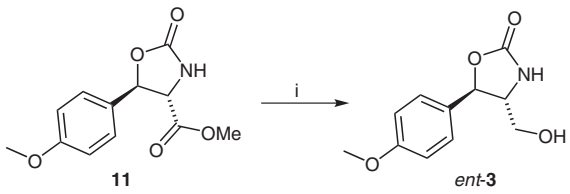
In order to afford the desired (4*R*,5*R*)-isocytoxazone *ent*-**3**[13] the carbamate **11** was then reduced; this was initially achieved with lithium aluminium hydride, but sodium borohydride provided a superior yield (91% compared to 77%), probably due to the ease of workup associated with the sodium borohydride reactions (Scheme 7). (4*S*,5*S*)-Isocytoxazone **3** was prepared by repeating this optimised



Scheme 4 A revised retrosynthetic route towards (4*S*,5*S*)-isocytoxazone from Boc-D-tyrosine



Scheme 6 Ohfune's cyclic carbamate formation. *Reagents and conditions*: $K_2S_2O_8$, $CuSO_4$, H_2O–MeCN (1:1), 70 °C, 3 h, 52%.



Scheme 7 Formation of (4*R*,5*R*)-isocytoxazone *ent*-**3**. *Reagents and conditions*: (i) $NaBH_4$, EtOH, 0 °C to r.t., 45 min, 91%.

sequence using D-tyrosine as the starting material, in an overall yield of 33%.[14]

In conclusion we have reported here the highly diastereoselective synthesis of (4*R*,5*R*)-isocytoxazone *ent*-**3** and (4*S*,5*S*)-isocytoxazone **3** in just three synthetic steps from D- or L-Boc-tyrosine, and confirmation of the stereoselection by X-ray crystallography. This is the shortest and most high yielding approach (35% overall yield compared to 8.1% overall yield reported previously) currently known for this class of biologically active oxazolidinones.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) ***O*-Methyl-*N*-*tert*-butoxycarbonyl-l-tyrosine Methyl Ester (10)**: A solution of *N*-*tert*-butoxycarbonyl-L-tyrosine (8.00 g, 28.5 mmol) in dimethylformamide (80 mL) was cooled using an ice bath, treated with freshly ground KOH (1.72 g, 31.3 mmol), and a cooled solution of iodomethane (1.95 mL, 31.3 mmol) in dimethylformamide (20 mL) was added dropwise over 5 min. The mixture was stirred at r.t. for 30 min, cooled using an ice bath, and additional KOH (1.72 g, 31.3 mmol) and a cooled solution of iodomethane (1.95 mL, 31.3 mmol) in dimethylformamide (20 mL) was added. The mixture was stirred for 3 h, poured onto ice (150 mL), and extracted with EtOAc (3 × 75 mL). The organic layers were washed with H_2O (3 × 50 mL), brine (2 × 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a colourless oil. Crystallization was achieved from EtOAc–light petroleum, to give **10** as colourless crystals (6.5 g, 74%); mp 52–53 ºC; $[\alpha]^{20}_D$ +58.9 (*c* 1.2, $CHCl_3$), lit.[15] $[\alpha]^{22}_D$ +59.2 (*c* 1.8, $CHCl_3$). IR (film): 2976, 1746, 1716, 1612, 1515, 1391, 1366, 1248, 1175,

1058, 1034 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 3.01–3.11 (m, 2 H), 3.71 (s, 3 H), 3.78 (s, 3 H), 4.53 (q, 1 H, *J* = 5.7 Hz), 5.00 (d, 1 H, *J* = 6.7 Hz), 6.82 (d, 2 H, *J* = 8.7 Hz), 7.03 (d, 2 H, *J* = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 37.6, 52.7, 54.7, 55.3, 79.9, 114.1, 128.1, 130.3, 155.1, 158.8, 172.4. HRMS: *m*/*z* calcd for $C_{16}H_{23}NO_5$: 309.1576; found: 309.1578.

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(11) **Methyl (4*S*,5*R*)-5-[4-Methoxyphenyl)-1,3-oxazolidin-2-one 4-Carboxylate (11)**: A solution of *O*-methyl-*N*-*tert*-butoxycarbonyl-L-tyrosine methyl ester (**10**; 5.00 g, 16.2 mmol) in MeCN (200 mL) was treated with a solution of $K_2S_2O_8$ (8.75 g, 32.4 mmol) in H_2O (210 mL) and a solution of $CuSO_4$ (0.52 g, 3.2 mmol) in H_2O (50 mL). The mixture was heated to 70 ºC for 3 h under a blanket of N_2, allowed to cool, and extracted with EtOAc (3 × 150 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark yellow oil. Column chromatography, eluting with EtOAc–light petroleum (1:10–1:1), afforded a colourless solid, which was recrystallised from EtOAc–light petroleum to give **11** as a colourless crystalline solid (2.10 g, 52%); mp 94–96 ºC; $[\alpha]^{20}_D$ +83.5 (*c* 1.15, $CHCl_3$). IR (film): 3316, 2956, 2362, 2337, 1762, 1613, 1515, 1382, 1250, 1224, 1026, 834, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 3.83 (s, 3 H), 4.31 (d, 1 H, *J* = 5.2 Hz), 5.56 (d, 1 H, *J* = 5.2 Hz), 6.81 (s, 1 H), 6.93 (d, 2 H, *J* = 4.8 Hz), 7.33 (d, 2 H, *J* = 4.8 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5, 55.7, 61.8, 79.9, 114.7, 127.5, 130.3, 158.6, 160.6, 170.7. HRMS: *m*/*z* [M^+] calcd for $C_{12}H_{13}NO_5$: 251.0794; found: 251.0794.

(12) Crystal data for **11**: $C_{12}H_{13}NO_5$, *M* = 251.23, monoclinic, *a* = 7.0103 (8), *b* =5.5734 (6), *c* = 15.6004 (18) Å, *U* = 602.01 (12) $Å^3$, space group $P2_1$, *Z* = 2, μ = 0.109 mm^{-1}, ρ_{calc} = 1.386 Mg/cm^3. 5035 data (1542 unique, R_{int} = 0.0157) collected on an Apex II diffractometer at 150 K. Solved by direct methods[16] and refined by full-matrix least squares on F^2. $R_1[I > 2\sigma(I)]$ = 0.0298 and wR_2 (all data) = 0.0745. Goodness of fit on F^2 = 1.079. CCDC No. 804096.

(13) **(4*R*,5*R*)-Isocytoxazone (*ent*-3)**: Methyl (4*S*,5*R*)-5-[4-methoxyphenyl]-1,3-oxazolidin-2-one 4-Carboxylate (**11**; 2.20 g, 8.8 mmol) was dissolved in EtOH (25 mL) and the solution was cooled using an ice bath. A solution of $NaBH_4$ (0.70 g, 19.3 mmol) in EtOH (8 mL) was added dropwise with stirring. After the addition was complete the ice bath was removed and the mixture was stirred for 45 min. The mixture was cooled to 0 ºC and concd HCl (1.5 mL) was added, followed by H_2O (15 mL). The EtOH was removed under reduced pressure and the remaining aqueous solution was extracted with EtOAc (3 × 50 mL). The combined organic solutions were dried ($MgSO_4$), and the solvents were removed to afford an off-white solid, which was recrystallized from EtOAc–light petroleum to give (4*R*,5*R*)-isocytoxazone (*ent*-**3**) as a colourless crystalline solid (1.75 g, 90%); mp 140–142 ºC; $[\alpha]^{20}_D$ +74.8 (*c* 1.08, acetone), lit.[3] $[\alpha]^{25}_D$ +70 (*c* = 0.4, MeOH). IR (nujol): 3239, 1725, 1614, 1514, 1459, 1376, 1251, 1174, 1062, 1016, 828 cm^{-1}. ^1H NMR (250 MHz, acetone-d_6): δ = 3.71–3.87 (m, 3 H), 3.86 (s, 3 H), 5.35 (d, 1 H, *J* = 5.3 Hz), 7.01 (d, 2 H, *J* = 8.6 Hz), 7.41 (d, 2 H, *J* = 8.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 63.1, 64.2, 80.4, 115.4, 128.7, 133.2, 159.6, 161.3. HRMS: *m*/*z* [M^+] calcd for $C_{11}H_{13}NO_4$: 223.0845; found: 223.0842.

(14) See the Supporting Information for the experimental data.

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