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Metadata Record: https://dspace.lboro.ac.uk/2134/13582

Version: Accepted for publication

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

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Received: The date will be inserted once the manuscript is accepted.

Abstract: A three step protocol for the highly diastereoselective (>98%) synthesis of both (4R,5S)- and (4S,5S)-iso-cytoxazone 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 immunomodulators from microbial metabolites, Osada found that an actinomycete strain (RK95-31) produced cytoxazone 1, an oxazolidinone that interferes with cytokine IL-4, IL-10 and IgG production. 1 Several groups have synthesised (–)cytoxazone 1 and (+)-epi-cytoxazone 2;2 and Šujić has described the racemic syntheses of all of the stereoisomers and cogeners of iso-cytoxazone 3; 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 they have extensive X-ray crystallographic studies.4 Rozwadowska and Tomczak have recently reported the synthesis of (4S,5S)-(–)-iso-cytoxazone 3,5 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 diols6 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 (4S,5S)-iso-cytoxazone was similar to that of Rozwadowska, using diazotization as a key reaction step (Scheme 1).

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

[Scheme image]

Scheme 2 Initial synthesis of the p-methoxy formate 8.

[Scheme image]
We next reasoned that (4S,5S)-iso-cytosazone 3 could be prepared from commercially available Boc-(D)-tyrosine (Scheme 4).

We initially aimed to prepare the enantiomer of 3 (4R,5R)-iso-cytosazone ent-3 from the cheaper Boc-(L)-tyrosine (Schemes 5, 6 and 7). Methylation of the acid and phenol components within Boc-(L)-tyrosine with potassium persulfate (K₂S₂O₈) was oxidized with potassium persulfate (K₂S₂O₈) and catalytic copper sulfate to form the oxazolidinone was oxidized with potassium persulfate (K₂S₂O₈) and catalytic copper sulfate to form the oxazolidinone 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 cation, which is believed to be more stable than the benzyl 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.

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). Milder reaction conditions resulted in no product formation.

In order to afford the desired (4R,5R)-iso-cytosazone ent-3 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 work-up associated with the sodium borohydride reactions, (Scheme 7). 

Reagents and Conditions: i: a) H₂SO₄, MeOH, (CH₃)₂CHCH₂CH₂ONO, 0 °C, 3 h; b) Δ, 1 h.

Scheme 3 Attempted direct incorporation of the methoxy group using Quin and Macdiarmid’s method.

We initially aimed to prepare the enantiomer of 3 (4R,5R)-iso-cytosazone ent-3 from the cheaper Boc-(L)-tyrosine (Schemes 5, 6 and 7). Methylation of the acid and phenol components within Boc-(L)-tyrosine with potassium persulfate (K₂S₂O₈) was oxidized with potassium persulfate (K₂S₂O₈) and catalytic copper sulfate to form the oxazolidinone in a highly diastereoselective manner (diastereomeric ratio ≥ 98 % R at C3) (Scheme 6).

Reagents and Conditions: i: a) Mel (2.2 eq.), KOH (2.2 eq.), DMF, 0 °C-r.t. 3.5 h, 74 %.

Scheme 5 Formation of Boc-protected, dimethylated (L)-tyrosine 10.

Following the work of Ohfune, the benzylic position of 10 was oxidized with potassium persulfate (K₂S₂O₈) and catalytic copper sulfate to form the oxazolidinone 11 in a highly diastereoselective manner (diastereomeric ratio ≥ 98 % R at C3) (Scheme 6).

Reagents and Conditions: a) H₂SO₄, MeOH, (CH₃)₂CHCH₂CH₂ONO, 0 °C, 3 h; b) Δ, 1 h.

Scheme 4 A revised retrosynthetic route towards (4S,5S)-iso-cytosazone from Boc-D-tyrosine.

Reagents and Conditions: i: a) Mel (2.2 eq.), KOH (2.2 eq.), DMF, 0 °C-r.t. 3.5 h, 74 %.

Scheme 5 Formation of Boc-protected, dimethylated (L)-tyrosine 10.

Figure 2 X-ray crystal structure of 11.

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). Milder reaction conditions resulted in no product formation.

In order to afford the desired (4R,5R)-iso-cytosazone ent-3 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 work-up associated with the sodium borohydride reactions, (Scheme 7). 

Reagents and Conditions: K₂S₂O₈, CuSO₄, H₂O/MeCN (1:1), 70 °C, 3h, 52%.
In conclusion we have reported here the highly diastereselective synthesis of \((4R,5R)\)-iso-cytocazone ent-3 and \((4S,5S)\)-iso-cytocazone 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.

Acknowledgment

The authors would like to thank Loughborough University for funding and Research Councils UK for a RCUK fellowship to B.R.B.

References


(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 potassium hydroxide (1.72 g, 31.3 mmol), and a cooled solution of iodomethane (1.95 ml, 31.3 mmol) in dimethylformamide (20 ml) added dropwise over 5 min. The mixture was stirred at room temperature for 30 min, cooled using an ice bath, and additional potassium hydroxide (1.72 g, 31.3 mmol) and a cooled solution of iodomethane (1.95 ml, 31.3 mmol) in dimethylformamide (20 ml) added. The mixture was stirred for 3 h, poured onto ice (150 ml), and extracted with ethyl acetate (3 x 75 ml). The organic layers were washed with water (3 x 50 ml), brine (2 x 50 ml) and dried (MgSO\(_4\)). The solvent was removed under reduced pressure to afford a colourless oil. Crystallization was achieved from ethyl acetate/light petroleum, to give 10 as colourless crystals (6.5 g, 74%); m.p. 52-53°C; \(\delta^1\)H \(\ddot{N}M\) \(=\)58.9 (c 1.2, CHCl\(_3\)), lit. \(\delta^1\)H \(\ddot{N}M\) \(=\)59.2, c 1.8, CHCl\(_3\)). 

(10) Crystal data for 11: \(C_3H_3NO\_2\) \(M\) = 251.23, monoclinic, \(a\) = 7.0103(8), \(b\) = 5.5734(6), \(c\) = 15.6004(18) \(\AA\), \(U\) = 602.01(12) \(\AA\) \(^3\), space group \(P2_1\), \(Z\) = 2, \(\mu\) = 0.109 mm\(^{-1}\), \(\rho_{calc}\) = 1.386 Mg cm\(^{-3}\), 5035 data (1542 unique, \(R_{int}\) = 0.0157) collected on an Apex II diffractometer at 150K. Solved by direct methods and refined by full-matrix least-squares on \(F^2\). \(R_1(> 2\sigma(F)) = 0.0298\) and \(wR_2(\text{all}) = 0.0745\). Goodness of fit on \(F^2\) = 1.079. CCDC No. 804096.

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white solid, which was recrystallized from ethyl acetate/light petroleum to give (4R,5R)-iso-cytoxazone ent-3 as a colourless crystalline solid (1.75 g, 90%); m.p. 140-142 °C; [α]D⁰ +74.8 (c 1.08, CH₃COCH₃, lit.); [α]D⁰ +70 c 0.4, MeOH); ν max (nujol)/cm⁻¹ 3239, 1725, 1614, 1514, 1459, 1376, 1251, 1174, 1062, 1016, 828; δH (250 MHz; acetone-d₆) 3.71-3.87 (3 H, m), 3.86 (3 H, s), 5.35 (1 H, d, J 5.3 Hz), 7.01 (2 H, d, J 8.6 Hz), 7.41 (2 H, d, J 8.6 Hz); δC (100 MHz; CDCl₃) 56.0, 63.1, 64.2, 80.4, 115.4, 128.7, 133.2, 159.6, 161.3; m/z 223.0842; C₁₁H₁₃NO₄ (M⁺) requires 223.0845.

(14) See the supplementary material for the experimental data.
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