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A Short High Yielding Synthesis of the Potent Anti-VZV Carbocyclic Nucleoside Analogue Carba-BVDU

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A SHORT HIGH YIELDING SYNTHESIS OF THE POTENT ANTI-VZV CARBOCYCLIC NUCLEOSIDE ANALOGUE CARBA-BVDU.

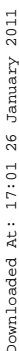
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Abstract. A short high yielding synthesis of the potent anti-varicella-zoster virus (VZV) carbocyclic nucleoside analogue carba-BVDU **1** starting from aminodiol **2** is described. Reaction of **2** with acyl carbamate **3** and subsequent ring closure under acidic conditions afforded 5-ethyl-2'-deoxy-4'a-carbauridine **5**. *In situ* acetylation of **5** afforded 3',5'-di-O-acetyl-5-ethyl-2'-deoxy-4'a-carbauridine **6** in 78% overall yield from **2**. Radical bromination of **6** with either bromine or NBS and subsequent treatment with triethylamine gave an efficient conversion to 3',5'-di-O-acetyl-5-(E)-(2-bromovinyl)-2'-deoxy-4'a-carbauridine **7**. Deacetylation of **7** afforded **1** in an overall 45-53% yield from **2**.

Introduction

The carbocyclic nucleoside analogue (+)-1-[(1*R*,3*S*,4*R*-3-hydroxy-4-(hydroxymethylcyclopentyl)-5-(*E*)-(2-bromovinyl)-1*H*,3*H*-pyrimidin-2,4-dione (5-(*E*)-(2-bromovinyl)-2'-deoxy-4'a-carbauridine, carba-BVDU, GR95168) **1** exhibits potent *in vitro* activity against varicella-zoster virus (VZV)¹ and is highly efficacious against simian VZV-induced disease in African green monkeys.² The original synthetic route to racemic **1**¹ and chiral **1**^{3,4,5} were not suitable for the synthesis of kilogram quantities of the chiral compound and therefore an efficient synthesis amenable to scale up was sought.



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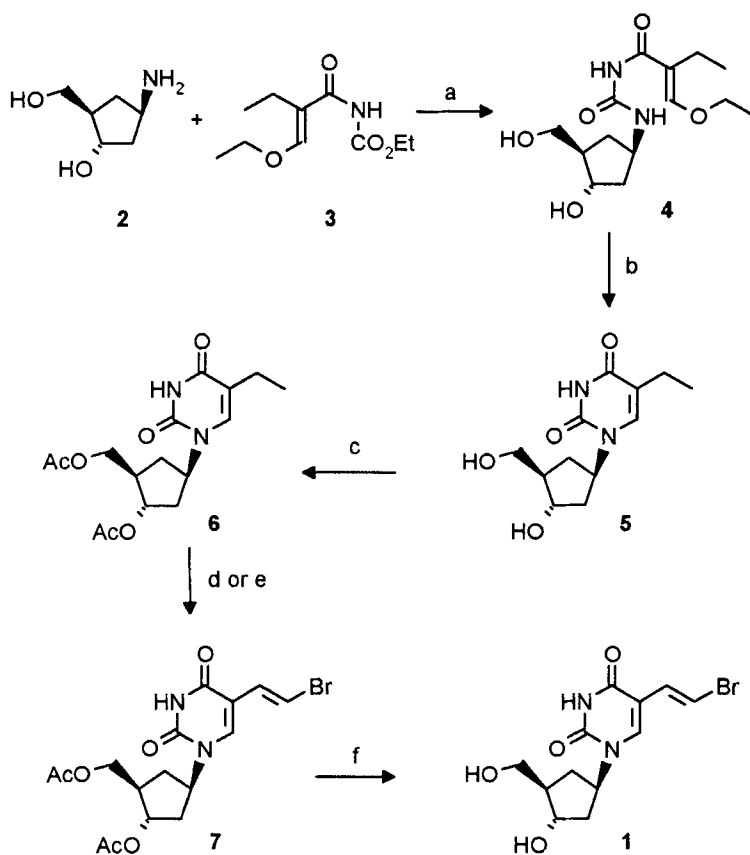
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Reagents: (a) NEt_3 , dioxane; (b) 2% 2N HCl in dioxane; (c) Ac_2O , DMAP, dioxane; (d) NBS, CHCl_3 or dioxane; (e) Br_2 , CHCl_3 ; (f) NaOH, EtOH or H_2O .

Scheme 1

triethylamine hydrochloride gave a solution of 4. Addition of 2M HCl (2% volume/volume) and heating at 90°C gave 5, which was treated with acetic anhydride and DMAP at 25°C to afford, after crystallization, 6 in 77.5% overall yield from 2.

Having established the synthesis of 6, we investigated the conversion of the 5-ethyl moiety of 6 into 5-bromovinyl moiety of 7 (Scheme 1). Reaction of 6 with NBS and AIBN in refluxing chloroform (Method A) gave a crude product (87% pure by HPLC) which crystallized from ethanol to give pure 7 in 51% yield (unoptimized). Although, addition of solid NBS to a refluxing solution of 6 in chloroform is acceptable on a small scale, this process is problematical on a manufacturing scale. The insolubility of NBS in

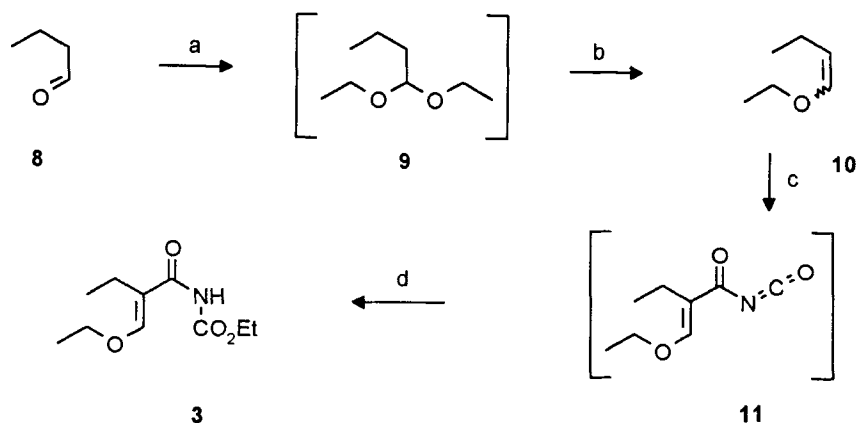
chloroform precluded the addition of a solution to the reaction and when all of the reagents were added before heating, a mixture resulted which contained only 2% of **7**. Alternative radical brominating agents N-bromoacetamide and 1,3-dibromo-5,5-dimethylhydantoin failed to yield **7**. However, slow addition of bromine to a refluxing solution of **5** in chloroform (Method B) gave an efficient conversion to **7** and a 246g input of **5** gave a 75% yield of **7** after crystallization.

Although, using chloroform as solvent gave high yields of **7**, there were concerns over future controls on its commercial use. A number of alternative solvents reported to be suitable for radical brominations using NBS¹¹ either did not afford **7** or gave mixtures of products including the corresponding 5,6-dibromo-5,6-dihydrouracil and 1,2-dibromovinyluracil derivatives. However, addition of a dioxane solution of NBS to **6** in dioxane at 60°C (Method C) gave **7** in an optimized yield of 84%, albeit 81% pure by HPLC. This material was found to be suitable for deacetylation to give **1**.

Deacetylation of **7**, obtained from the reaction using bromine in chloroform (Method B), using 2.5 M sodium hydroxide gave **1** in a 91% yield, representing an overall 53% yield for the conversion of **2** into **1**. Deacetylation of **7**, derived from the reaction using NBS in dioxane (Method C), using sodium hydroxide in ethanol gave a 71% yield of **1** (87% allowing for the purity of **7**). This alternative route gave an overall 45% yield for the synthesis of **1** from **2**.

To complete the process an efficient synthesis of acyl carbamate **3** was required. Vinyl ethers are reported to react with chlorocarbonyl isocyanate to give acryloyl isocyanates,¹² and subsequent quenching with alcohol affords the corresponding acyl carbamates. This approach was utilized to afford a route to **3** (Scheme 2). Reaction of butanal **8** with triethyl orthoformate in the presence of ammonium dihydrogen phosphate at 60°C gave the diethyl acetal **9**, which on further heating gave the vinyl ether **10** as a mixture of the *cis* and *trans* isomers. The ratio of the isomers of **10** formed depended on the reaction temperature and the rate of distillation of the product, however, the larger scale syntheses gave *cis-trans* isomer ratios of *ca* 2:1. This represented an efficient high yielding synthesis of **10** as most published syntheses of vinyl ethers involve isolation of the intermediate acetals.

Reaction of **10** with chlorocarbonyl isocyanate in dioxane followed by treatment with triethylamine gave the acyl isocyanate **11**. Isocyanate **11** was not isolated but quenched with ethanol to afford **3** as a crystalline solid in 69% yield from **10**. Variation of the *cis-trans* isomer ratio of **10** did not affect the outcome of this reaction as both isomers reacted to give a single isomer of **3**. This route represents an efficient two step synthesis of **3** in a 48% conversion from butanal.



Reagents: (a) HC(OEt)_3 , $\text{NH}_4\text{H}_2\text{PO}_4$, 60°C ; (b) 140°C ; (c) ClCONCO , dioxane, then Et_3N ; (d) EtOH .

Scheme 2

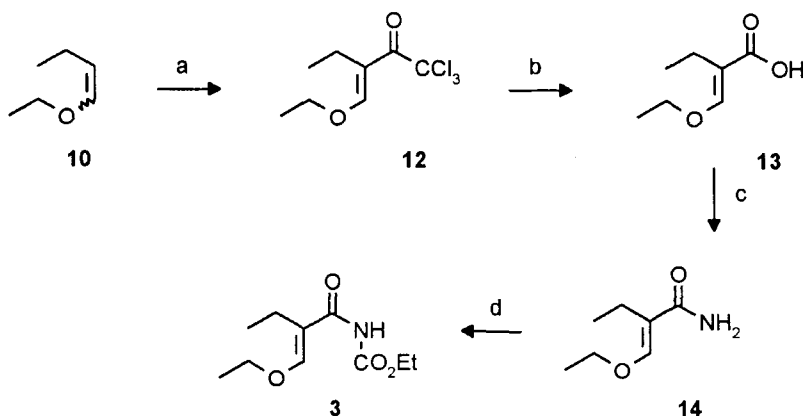
Because of a concern over the availability of commercial quantities of chlorocarbonyl isocyanate an alternative synthesis of **3** was developed (Scheme 3). Acid **13** has been reported to be synthesized by a number of methods^{13,14} but we found the following route to be the most efficient.¹⁵

Reaction of **10** with trichloroacetyl chloride in pyridine gave **12**, however, in this case only the *cis* isomer of **10** reacted. Hydrolysis of **12** under controlled conditions afforded the acid **13**. Attempts to couple **13** with ethyl carbamate failed to afford **3**, therefore, a two step procedure *via* amide **14** was investigated. Although, the conversion **14** into **3** failed under a variety of conditions, treatment of **14** with LDA in THF followed by reaction with ethyl chloroformate gave **3** in 73% yield. This process was suitable for scale up and yielded **3** in a 21% overall yield from butanal.

This route represents a considerable advance over the previous procedures used to synthesize **1**^{1,3,4,5} both in overall yield and the simplicity of the chemistry involved. Also the chemistry described could be adapted to efficiently synthesize a range of 1,5-disubstituted uracils.

Experimental Section

The ^1H NMR spectra for all compounds were recorded on a Bruker AM250 instrument and the chemical shifts are reported as part per million (ppm) relative to internal tetramethylsilane (TMS). During workup, organic solutions were dried over



Reagents: (a) Cl_3COCl , pyridine; (b) KOH , H_2O , PhCH_3 ; (c) (i) CDI , THF , (ii) NH_3 ; (d) (i) LDA , THF , (ii) EtO_2CCl .

Scheme 3

MgSO_4 and evaporated on a Büchi rotatory evaporator with a bath temperature of 40°C or below. Thin-layer chromatography was performed on silica plates (Merck Art. No. 5719), and flash column chromatography was carried out on silica (Merck Art. No. 9385). HPLC conditions, S5-ODS2 column; eluting with 25% acetonitrile in water; flow rate 2.0 mL min^{-1} ; detection: UV, 230nm. All dried solvents were purchased from the Aldrich Chemical Co. (Sureseal). Melting points are uncorrected.

(+)-1-[(1*R*,3*S*,4*R*)-3-Acetoxy-4-(acetoxymethylcyclopentyl]-5-ethyl-1*H*,3*H*-pyrimidin-2,4-dione (6).

A solution of **2** (319.6g, 1.91 mol), **3** (410.7g, 1.91 mol) and triethylamine (NEt_3) (277mL, 1.99 mol) in dioxane (2.1L) was heated at 100°C for 3h and then cooled. The suspension was filtered and the collected solid was washed with dioxane (0.42L). The filtrates were combined, 2M HCl (60mL) was added and the solution heated to 90°C for 13.5h. The pH of the reaction was maintained at *ca* 1 by the addition of 2M HCl . The reaction was cooled and concentrated to 2.1L. DMAP (53.3g, 0.436 mol) and acetic anhydride were added to the solution at a rate to maintain the temperature below 30°C . After 16h the reaction was cooled to $5\text{--}10^\circ\text{C}$ and ethanol (EtOH) (0.831L) was added in two portions. The reaction was concentrated to 2.1L and then partitioned between ethyl acetate (EtOAc) and 2N HCl . The separated aqueous layer was extracted with EtOAc .

The combined organic extracts were washed with saturated NaHCO_3 (x2) and saturated brine, dried and concentrated to 0.9L. To this solution was added isopropyl ether (IPE) (3.8L) to induce crystallization. The suspension was cooled to 5–10°C and left for 2h. The solid was collected and washed with IPE: EtOAc (4:1, 1L) and dried to afford **6** (499.9g, 77.5%). mp 67–69°C: $[\alpha]_D = +3.97^\circ$ (c 1.0, MeOH): IR (nujol) 1681, 1468 cm^{-1} : ^1H NMR (d_6 -DMSO) δ 1.04 (t, $J = 7.5$ Hz, 3H), 1.59 (m, 1H), 1.83–2.42 (m, 4H), 2.02 (s, 6H), 2.23 (m, 2H), 4.05 (m, 1H), 4.18 (m, 1H), 4.90 (m, 1H), 5.01 (m, 1H), 7.54 (s, 1H), 11.24 (s, 1H): UV (95% ethanol) 271 nm (ϵ 10630): Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_6$: C, 56.08; H, 6.55; N, 8.28%. Found: C, 56.11; H, 6.61; N, 8.33%.

(+)-1-[(1*R*,3*S*,4*R*)-3-Acetoxy-4-(acetoxymethylcyclopentyl)-5-(*E*)-(2-bromovinyl)-1*H*,3*H*-pyrimidin-2,4-dione (7).

Method A: NBS (528mg, 2.97 mmol) was added portionwise over 15 min to a solution of **6** (500mg, 1.48 mmol) and AIBN (3.5mg, 0.021 mmol) in chloroform (CHCl_3) (15mL) at reflux under N_2 . After 1.5h NEt_3 (0.41mL, 2.94 mmol) was added and the reaction refluxed for a further 30 min. The cooled reaction was washed with 2M HCl and saturated NaHCO_3 , dried and evaporated. The residue was crystallized from EtOH to afford **7** as white prisms (311mg, 51%, 95% by HPLC). mp 130–131°C: $[\alpha]_D = -5.3^\circ$ (c 0.75, DMSO): IR (nujol) 1711 and 1463 cm^{-1} : ^1H NMR (d_6 -DMSO) δ 1.56 (m, 1H), 1.88–2.44 (m, 4H), 2.02 (s, 6H), 4.03 (m, 1H), 4.17 (m, 1H), 4.92 (m, 1H), 5.01 (m, 1H), 6.87 (d, $J = 14$ Hz, 1H), 7.27 (d, $J = 14$ Hz, 1H), 7.99 (s 1H), 11.55 (s, 1H): UV (95% ethanol) 252 nm (ϵ 14060), 297 (ϵ 13280): Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{BrN}_2\text{O}_6$: C, 46.28; H, 4.61; N, 6.75; Br, 19.24%. Found: C, 46.17; H, 4.37; N, 6.61; Br, 19.30%.

Method B: Bromine (78.7mL, 1.54 mol) in CHCl_3 (3.7L) was added dropwise over 220 min to a solution of **6** (246.0g, 0.727 mol) and AIBN (7.38g 45 mmol) in CHCl_3 (3.7L) at reflux under N_2 . The bromine was added at a rate that maintained a pale orange color. After addition the reaction was heated for a further 10 min and then cooled. NEt_3 (246mL, 1.77 mol) was added over 5 min, maintaining the temperature below 50°C by cooling with cold water. After 30 min the reaction was washed with water, 2M HCl and water, dried and concentrated to 900mL by distillation at atmospheric pressure. Petrol (60/80, 1L) was added over 15 min to the solution at reflux and then allowed to slowly cool to 40°C. Further petrol (60/80, 250mL) was added over 15 min and the reaction allowed to cool to 25°C. The suspension was stirred for 16h and then cooled to 5°C for 5h. The solid was collected, washed with cold CHCl_3 : petrol (60/80) (1:1, 2 x 300mL) and dried to afford **7** (228.2g, 75%, 94% by HPLC).

Method C: A solution of NBS (13.0g, 73.0 mmol) in dioxane (120mL) was added over 35 min to a solution of **6** (8.0g, 23.6 mmol) in dioxane (40mL) at 60°C under N₂. After 40 min NEt₃ (10.5mL, 75.3 mmol) was added and the reaction heated at 60°C for a further 20 min. After cooling the mixture was partitioned between EtOAc and 2M HCl. The organic phase was washed with 2M HCl, 5% sodium metabisulphite solution and saturated NaHCO₃, dried and evaporated. A solution of the residue in EtOAc (50mL) was slowly added to vigorously stirred petrol (40-60, 1100ml). The filtered solid was washed with petrol and dried to afford **7** (8.22g, 84%, 81% by HPLC).

(+)-1-[(1*R*,3*S*,4*R*-3-Hydroxy-4-(hydroxymethylcyclopentyl)-5-(*E*)-(2-bromovinyl)-1*H*,3*H*-pyrimidin-2,4-dione (1**).**

Method using aqueous NaOH: **7** (129.4g, 0.31 mol) obtained using Method B was added to cooled 2.5M NaOH (520mL) and the solution stirred for 70 min at 20°C at a pH above 13. 6M HCl (78mL) was added and the solution heated to 75°C before additional 6M HCl (52mL) was added to give a final pH of 6.5. The slurry was cooled in ice, before the solid was collected, washed with cold water and dried at 45°C *in vacuo* to afford **1** (81.6g, 91%,). mp 188-189°C (dec): [α]_D = +4.4° (c 1.1, DMSO) :IR (nujol) 1660, 1460 cm⁻¹: ¹H NMR (d₆-DMSO) δ 1.38 (m, 1H), 1.7-2.2 (m, 4H), 3.44 (m, 2H), 3.99 (br. s, 1H), 4.62 (br. s, 1H), 4.74 (br. s, 1H), 4.96 (m, 1H), 6.90 (d, *J* = 13.8 Hz, 1H), 7.27 (d, *J* = 13.8 Hz, 1H), 7.93 (s, 1H), 11.51 (s, 1H): UV (95% ethanol) 253 nm (ε 13900), 299 (ε 13040): Anal. Calcd for C₁₂H₁₅BrN₂O₄: C, 43.52; H, 4.57; N, 8.46; Br 24.13%. Found: C, 43.27; H, 4.29; N, 8.16; Br 24.3%.

Method using ethanolic NaOH: A solution of **7** (8.0g, 19.3 mmol) obtained from Method C and NaOH (1.6g, 40.0 mmol) in EtOH (120mL) was stirred for 2h. The solution was then acidified with 2M HCl and evaporated. The residue was suspended in warm water (20mL) and then stored at 5°C for 16h. The solid was collected, washed with cold water and dried to give **1** (4.54g, 71%).

Ethyl butenylether (10**).**

A mixture of butanal **8** (4.05L, 45 mol), ammonium dihydrogen orthophosphate (500g), Celite J2 (33.0g) and triethyl orthoformate (7.5L, 45 mol) was heated at 60°C for 4h and then cooled to 40°C. *p*-Toluenesulfonic acid monohydrate (1.5g) was added and the reaction was heated at 60°C for 1h. Heating was continued and ethyl formate (3.44kg) was collected over 4.5h until the batch temperature reached 128°C (head temperature 56°C) and then *ca* 4L of distillate was collected over 6h (max. batch temp 140°C, max. head temp 80°C). The distillate was washed with 5% K₂CO₃ solution (6 x 1L) and dried

over MgSO_4 to afford **10** (3.17kg, 71%) as a colorless liquid. ^1H NMR (CDCl_3) δ 0.96 (m, 3H), (1.25 (m, 3H), 1.94 (m, 2H), 2.08 (m, 2H), 3.70 (m, 2H), 4.31 (d-t, $J = 7.5$, 7.5 Hz, 1H), 4.78 (d-t, $J = 7.5$, 12 Hz, 1H), 5.90 (d, $J = 7.5$ Hz, 1H), 6.22 (d, $J = 12$ Hz, 1H) The Z/E ratio was 2:1. The NMR indicated the presence of a trace of ethyl formate and ca 4 mole % of 1,1-diethoxybutane.

N-Ethoxycarbonyl-(E)-2-ethoxymethylene-butamide (**3**).

Method using chlorocarbonyl isocyanate: **10** (476mL, 3.7 mol) in dioxane (1.8L) was added over 20 min to a stirred solution of chlorocarbonyl isocyanate (229mL, 2.84 mol) in dioxane (2.8L) at 10°C . After a further 20 min, NEt_3 (396mL, 2.84 mol) in dioxane (3L) was added over 45 min and the reaction stirred for a further 15 min. During the addition a precipitate of $\text{NEt}_3 \cdot \text{HCl}$ formed. EtOH (184mL, 3.12 mol) was then added dropwise over 15 min followed by dioxane (6L) over 15 min. The resulting suspension was stirred for 20 min at 15°C , then filtered and the collected solid washed with dioxane (2L). The combined filtrates were concentrated to 900mL and then petrol (60-80, 900mL) was added to complete crystallization. The slurry was cooled to 5°C for 1h, filtered and the collected solid was washed with petrol: dioxane (5:1, 300mL) and dried to afford **3** (416.3g, 69%) as white prisms. mp $130\text{--}131^\circ\text{C}$: IR (nujol) 1748, 1524 cm^{-1} : ^1H NMR (d_6 -DMSO) δ 0.87 (t, $J = 7.5$ Hz, 3H), 1.22 (t, $J = 7.5$ Hz, 3H), 1.25 (t, $J = 7.5$ Hz, 3H), 2.13 (q, $J = 7.5$ Hz, 2H), 4.04 (q, $J = 7.5$ Hz, 2H), 4.10 (q, $J = 7.5$ Hz, 2H), 7.39 (s, 1H), 10.04 (br s, 1H). Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_4$: C, 55.80; H, 7.96; N, 6.51%. Found: C, 55.89; H, 8.14; N, 6.69%.

Method avoiding the use of chlorocarbonyl isocyanate: Ethyl chloroformate (1mL, 10.5 mmol) was added over period of 15 min to a solution of **14** (0.497g, 3.5 mmol) and LDA (2M in hexanes, 4.3mL, 8.6 mmol) in THF (13mL) at -10°C under N_2 . After 1h at -10°C the reaction was allowed to warm to 25°C , stirred for a further 1h and then quenched with aqueous NH_4Cl . The solution was extracted with EtOAc (x2) and the combined extracts were dried and evaporated. The residue was crystallized from EtOAc to afford **3** (0.547g, 73%, 99.6% by HPLC) as white prisms.

(E)-2-Ethoxymethylene-butamide (**14**).

A mixture of **10** (20.0g, 0.2 mol) and pyridine (16.2mL, 0.2 mol) was added to a cooled solution of trichloroacetyl chloride (36.4g, 0.2 mol) in CHCl_3 (100mL) at such a rate to keep the reaction temperature between $0\text{--}3^\circ\text{C}$. After addition the reaction was allowed to warm to 25°C and left for 16h. Water (50mL) was then added cautiously (strong exotherm) and then the mixture was stirred for 5 min. The layers were separated and the

organic phase was extracted with CHCl_3 . The combined organic phases were washed with 0.1M HCl, 0.1M KOH and water, evaporated and co-evaporated with toluene to afford crude **12** (24.6g). Water (5mL) was added to a cooled mixture of **12** (24.6g), toluene (100mL) and KOH (7.0g), followed by tetrabutylammonium hydrogen sulfate (0.1g) and then the mixture was heated to 90°C. After 2h the reaction was cooled and extracted with water (50ml) and dilute KOH (100mL). The aqueous layers were washed with toluene, combined and acidified with 5M HCl. The suspension was extracted with EtOAc and the combined extracts were washed with brine and stirred with charcoal (5g, Norit SX+). The mixture was filtered through celite and the filtrate evaporated to afford crude **13** (13.5g) as a dark brown solid. 1,1'-Carbonyldiimidazole (18.2g, 110 mmol) was added portionwise over 1 min to a solution of crude **13** (13.5g, 91.6 mmol) in THF (70mL) at 5°C. After 1h concentrated aqueous NH_3 (30mL) was added and the reaction stirred at 10°C for a further 1h. The reaction was then cooled to below 5°C and diluted with EtOAc (150mL). The reaction was adjusted to pH 3.5 by the addition of 6M HCl (110mL) at such a rate to maintain the temperature below 15°C. The phases were separated and the aqueous extracted with EtOAc. The combined organic extracts were dried and evaporated to afford **14** (10.1g, 35% from **10**). IR (nujol) 1660, 1460 cm^{-1} ; ^1H NMR (d_6 -DMSO) δ 0.87 (t, $J = 7.5$ Hz, 3H), 1.21 (t, $J = 7.5$ Hz, 3H), 2.13 (q, $J = 7.5$ Hz, 2H), 3.95 (q, $J = 7.5$ Hz, 2H), 6.79 (br s, 2H), 7.11 (s, 1H). Anal. Calcd for $\text{C}_7\text{H}_{13}\text{NO}_2$: C, 58.71; H, 9.15; N, 9.78%. Found: C, 58.80; H, 9.28; N, 9.84%.

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