



# Stereoselective synthesis of 3,4-disubstituted pyroglutamates by ring transformation of 5-ylidene-1,3-dioxan-4-ones with *N*-(diphenylmethylene)-glycinate

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## Abstract

*N*-(Diphenylmethylene)-glycinate gives stereoselective conjugate addition to readily available (*E*) and (*Z*)-5-ylidene-1,3-dioxan-4-ones. Hydrolytic cleavage of the imine functionality of the resulting Michael-adducts causes ring transformation to new, optically active 3,4-disubstituted pyroglutamates. © 2000 Elsevier Science Ltd. All rights reserved.

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## 1. Introduction

Pyroglutamates are biologically important compounds, natural as well as synthetic members of this family exhibiting important pharmacological properties.<sup>1,2</sup> They are of further interest as conformationally constrained glutamate analogues.<sup>3</sup> Several syntheses of this class of compounds are known, among them the reactions of  $\alpha,\beta$ -unsaturated esters as C–C–C building blocks with protected  $\alpha$ -amino acid derivatives as C–N units. Imines derived from  $\alpha$ -amino esters turned out to be very useful in such syntheses.<sup>4–9</sup> Since the starting Michael-addition of the aminocarboxylate is stereoselective,<sup>4–10</sup> this approach is particularly useful for the asymmetric synthesis of pyroglutamates.<sup>6,7,9</sup> Chiral information to be exploited can be located in a substituent attached to the Michael-system<sup>7,9</sup> or in the imine of amino esters with chiral ketones.<sup>6,7,10</sup>

We report here the stereoselective synthesis of new 3,4-disubstituted pyroglutamates **4** and **5** applying 5-ylidene-1,3-dioxan-4-ones **1** as chiral Michael-systems. These dioxanones are readily available in (*E*) and (*Z*)-configuration from (*R*)-3-hydroxybutyrate, a monomer of naturally occurring poly-(*R*)-3-hydroxybutyrate (PHB), by acetalisation with pivalaldehyde and aldol reaction.<sup>11,12</sup> The dioxanones **1** were already applied in the synthesis of enantiopure 4-substituted

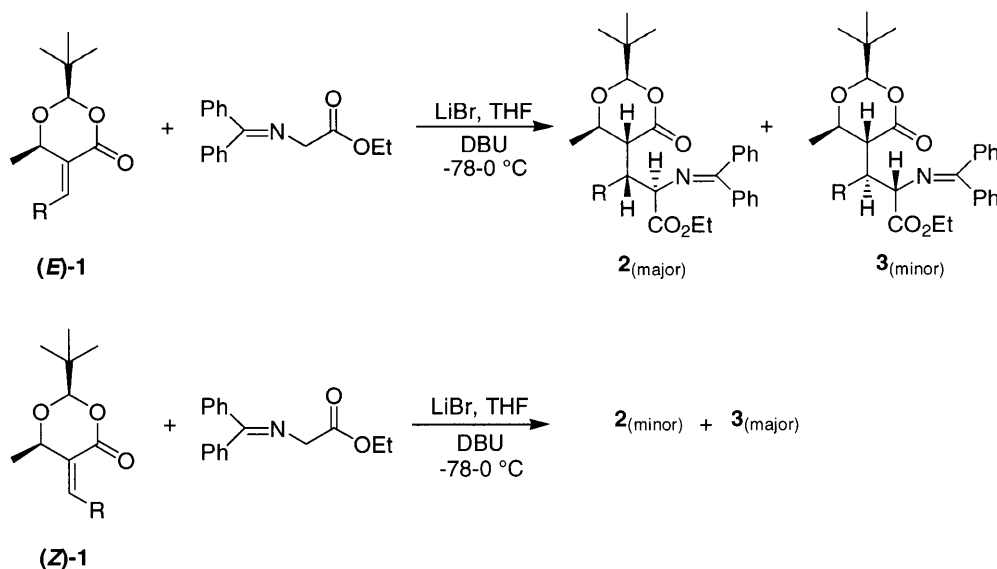
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3-(1-hydroxyethyl) pyrrolidine-2-ones using nitromethane as the C–N building block.<sup>13</sup> Michael-addition and subsequent reduction of the nitro to the amino group caused ring transformation by nucleophilic attack at the carbonyl carbon atom, opening the ring and splitting off pivalaldehyde.

## 2. Results and discussion

Reaction of ethyl *N*-(diphenylmethylene)-glycinate with (*E*) and (*Z*)-5-ylidene-1,3-dioxan-4-ones (*E*)-**1** and (*Z*)-**1** in the presence of DBU and LiBr gave the corresponding Michael-adducts **2** and **3** in high yields (Scheme 1; Table 1). Although three new stereogenic centres were created



Scheme 1.

Table 1  
Michael-adducts **2**, **3** and pyroglutamates **4** and **5**

Entry	R	Configuration of reactant <b>1</b>	Adducts <b>2</b> + <b>3</b> (% yield) <sup>a</sup>	dr <b>2</b> : <b>3</b>	Pyroglutamates <b>4</b> or <b>5</b> (% yield) <sup>b</sup>
1	CH <sub>3</sub>	<i>E</i>	<b>2a/3a</b> (82)	75:25	<b>4a</b> (98)
2	CH <sub>3</sub>	<i>Z</i>	<b>2a/3a</b> (80)	35:65	<b>5a</b> (97)
3	C <sub>2</sub> H <sub>5</sub>	<i>E</i>	<b>2b/3b</b> (78)	80:20	<b>4b</b> (97)
4	C <sub>2</sub> H <sub>5</sub>	<i>Z</i>	<b>2b/3b</b> (76)	30:70	<b>5b</b> (98)
5	(CH <sub>2</sub> ) <sub>2</sub> Ph	<i>E</i>	<b>2c/3c</b> (85)	90:10	<b>4c</b> (98)
6	(CH <sub>2</sub> ) <sub>2</sub> Ph	<i>Z</i>	<b>2c/3c</b> (82)	20:80	<b>5c</b> (97)
7	Ph	<i>E</i>	<b>2d/3d</b> (76)	95:05	<b>4d</b> (96)
8	Cyclohexyl	<i>E</i>	No reaction <sup>c</sup>	–	–

<sup>a</sup> Major isomer could be obtained in analytically pure form by flash chromatography.

<sup>b</sup> Obtained from pure adducts **2** or **3**, respectively.

<sup>c</sup> Starting material was completely recovered.

(dr 65:35 to 95:05), only two products could be detected in all the cases. The preferred mode of attack at **1** occurred from the bottom side, i.e. *re* for (*E*)-**1** and *si* for (*Z*)-**1** while the protonation always took place from the *si*-face (an overall *anti* addition to the exocyclic double bond).<sup>12</sup> Thus, diastereomer **2** is the major product starting from (*E*)-**1** and diastereomer **3** is the major product derived from (*Z*)-**1**. This *anti*-selective Michael-addition is assumed to proceed through a chelation-controlled transition state (Fig. 1).<sup>10</sup> The observed diastereoselectivities were lower in the reactions of (*Z*)-**1** compared with the corresponding (*E*) isomer. It is worth mentioning that cyclohexyl-substituted 5-ylidene-1,3-dioxan-4-one (*E*)-**1** (R=cyclohexyl) did not react at all under the conditions, being successful in all of the other cases. It is likely that the C–C double bond is sterically too congested by the secondary cyclohexyl substituent to allow a Michael-addition to occur. However, the generally high degree of substitution at the double bond of reactants **1** seems to be advantageous for the Michael-addition since less crowded Michael-systems can alternatively undergo 1,3-dipolar cycloaddition of the azomethine-ylide derived from  $\alpha$ -amino acids to the C–C double bond.<sup>10</sup>

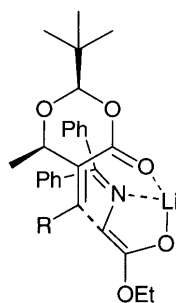
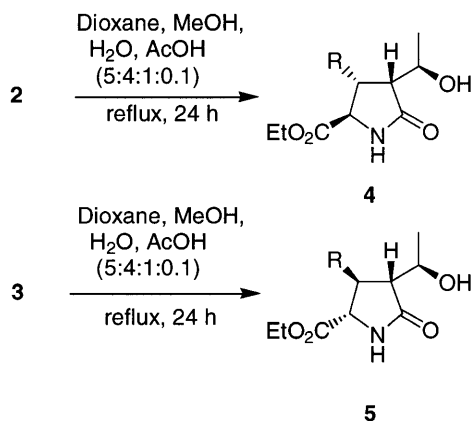


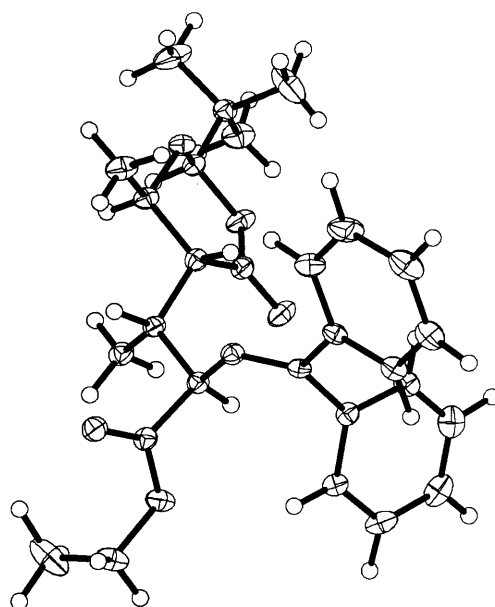
Figure 1. Chelation-controlled transition state model for the Michael-addition of *N*-(diphenylmethylene)-glycinate to (*E*)-5-ylidene-1,3-dioxan-4-one (*E*)-**1**

The major isomers **2** or **3** derived from (*E*)-**1** and (*Z*)-**1**, respectively, can easily be obtained in a diastereomerically pure state by simple flash chromatography or by crystallisation. They were further submitted to hydrolytic cleavage of the azomethine structure in order to deprotect the amino group. The resulting  $\alpha$ -amino esters could not be observed, but cyclised in almost quantitative yields to **4** or **5** by the nucleophilic attack of the amino group at the carbonyl carbon atom at position 4, opening the 1,3-dioxan-4-one ring and destruction of the acetal moiety by releasing pivalaldehyde (Scheme 2). The structures of products **2–5** were elucidated on the basis of X-ray crystal analysis of compounds **2a** (Fig. 2) and **3d** (Fig. 3). The absolute configurations of the pyroglutamates **4** and **5** can be concluded from their precursors **2** and **3**, respectively, and were confirmed by NMR experiments. The coupling constants in the <sup>1</sup>H NMR spectra of **4** and **5** were not useful for assignment of the relative configuration of substituents at positions 2, 3 and 4 (see Section 3). Thus 2D-NOESY correlations were applied to confirm the configuration in **4** and **5** (Fig. 4).

In summary, a straightforward access to new optically active pyroglutamates **4** and **5** from 5-ylidene-1,3-dioxanones **1** and ethyl *N*-(diphenylmethylene)-glycinate was developed as a two-step procedure by Michael-addition and hydrolytic cleavage of the azomethine. This method allows the stereoselective synthesis of either isomer by using either (*E*)-**1** or (*Z*)-**1** as reactant. Pyroglutamates **4** and **5** are promising candidates for reductive transformation into protein kinase C modulators.<sup>14</sup>

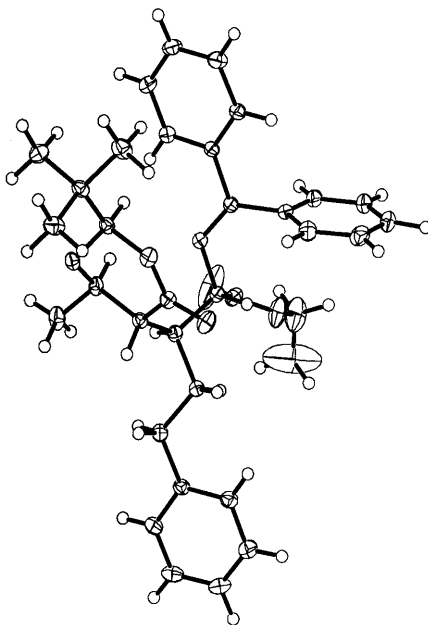
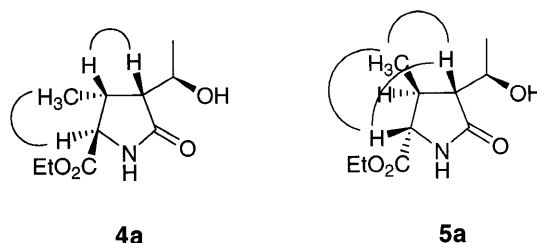


Scheme 2.

Figure 2. X-Ray crystal analysis of compound **2a**

### 3. Experimental

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker AC-300 in  $\text{CDCl}_3$  with TMS as internal standard. 2D NMR experiments include  $^1\text{H}$ - $^1\text{H}$  COSY, HMQC, NOESY and HMBC. Optical rotations were determined with a Perkin Elmer polarimeter 241 ( $c=1$ ,  $\text{CHCl}_3$ ,  $d=1$  mm). For preparative column chromatography silica (0.04–0.063 mm, Merck) was used. Starting glycinate and all other compounds used were purchased from Aldrich, Fluka or Merck. The ylidenedioxanones **1a–1e** were synthesised following or adapting literature procedures.<sup>11–13</sup>

Figure 3. X-Ray crystal analysis of compound **3c**Figure 4. Most significant cross peaks from the NOESY spectra of **4a** and **5a**

### 3.1. General procedure for the Michael-addition of ethyl N-(diphenylmethylene)-glycinate to chiral ylidenedioxonones (*E*)-**1** or (*Z*)-**1**

To a suspension of LiBr (0.105 g, 1.2 mmol) in dry THF (5 ml) was added a solution of imine (0.30 g, 1.1 mmol) in dry THF (5 ml) under argon atmosphere and stirring. After 15 min the solution was cooled to  $-78^{\circ}\text{C}$ . A solution of 5-ylidenedioxonone [(*E*)-**1** for the synthesis of **2** and (*Z*)-**1** for the synthesis of **3**] (1 mmol) in dry THF (5 ml) was added dropwise over 20 min. DBU (0.17 g, 1.1 mmol) was then added slowly. After stirring overnight, the reaction mixture was allowed to warm to  $0^{\circ}\text{C}$  and was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (10 ml). The organic phase was extracted with  $\text{Et}_2\text{O}$  (3 $\times$ 30 ml); combined organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to yield a pale yellow residue, which was purified by flash chromatography (silica gel, hexane– $\text{Et}_2\text{O}$ , 4:1).

3.1.1. Ethyl (2R,3R)-3-[(2R,5R,6R)-2-(*t*-butyl)-6-methyl-4-oxo-1,3-dioxan-5-yl]-2-[(diphenylmethylene)-amino]butanoate **2a**

Yield: 82%; mixture of **2a** and **3a**; dr 80:20; major isomer **2a**:  $R_f=0.44$  (hexane–Et<sub>2</sub>O, 4:1); colourless crystals, mp 112–113°C;  $[\alpha]_D^{20}=+185.2$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.86 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 0.89 (d,  $J=7.1$  Hz, 3H, CH<sub>3</sub>CH), 1.08 (t,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.42 (d,  $J=6.0$  Hz, 3H, CH<sub>3</sub>CHO), 2.45 (ddq,  $J=1.5, 10.2, 7.1$  Hz, 1H, CH<sub>3</sub>CH), 2.70 (dd,  $J=1.5, 9.8$  Hz, 1H, CHC=O), 3.75 (dq,  $J=9.8, 6.0$  Hz, 1H, CHO), 3.95 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.41 (d,  $J=10.2$  Hz, 1H, CHN), 4.78 (s, 1H, OCHO), 7.11–7.14 (m, 2H, ArH), 7.23–7.40 (m, 6H, ArH), 7.58–7.63 (m, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.06 (CH<sub>3</sub>CH), 14.05 (OCH<sub>2</sub>CH<sub>3</sub>), 20.20 (CH<sub>3</sub>CHO), 23.88 [C(CH<sub>3</sub>)<sub>3</sub>], 35.12 [C(CH<sub>3</sub>)<sub>3</sub>], 37.60 (CH<sub>3</sub>CH), 48.15 (CHC=O), 60.58 (OCH<sub>2</sub>), 68.15 (CHN), 74.23 (CHO), 107.78 (OCHO), 128.0, 128.03 ( $\times 2$ ), 128.22 ( $\times 2$ ), 128.59, 128.75 ( $\times 3$ ), 130.50 (CH, Ar), 136.04, 139.32 (C, Ar), 169.32 (C=N), 172.03, 172.05 (C=O). Anal. calcd for C<sub>28</sub>H<sub>35</sub>NO<sub>5</sub>: C, 72.23; H, 7.58; N, 3.01. Found: C, 72.20; H, 7.70; N, 2.99.

3.1.1.1. Crystal structure determination of compound **2a**<sup>15</sup>. A single crystal of **2a** with the dimensions 1.12×1.07×1.00 mm was measured on a STOE Stadi4 diffractometer using Mo K $\alpha$  radiation ( $\lambda=0.71073$  Å). Crystal data: C<sub>28</sub>H<sub>35</sub>NO<sub>5</sub>,  $M=465.57$ , orthorhombic space group  $P2_12_12_1$ ,  $a=9.2522$  (7),  $b=13.9982$  (17),  $c=20.165$  (5) Å,  $\beta=90^\circ$ ,  $V=2611.6$  (7) Å<sup>3</sup>,  $Z=4$ ,  $D_c=1.184$  g cm<sup>-3</sup>,  $F(000)=1000$ ,  $\mu$  (Mo K $\alpha$ )=0.081 mm<sup>-1</sup>. At 180 (2) K in the range of  $1.77<\theta<25.25^\circ$ , 2889 reflections were measured, 2690 were unique ( $R_{\text{int}}=0.0038$ ). The final residuals were  $wR_{2(\text{all})}=0.0797$  and  $R_{1(\text{obs})}=0.0317$ . The maximum and minimum peaks in the final difference map were 0.140 and -0.120 e Å<sup>-3</sup>, respectively.

3.1.2. Ethyl (2S,3S)-3-[(2R,5R,6R)-2-(*t*-butyl)-6-methyl-4-oxo-1,3-dioxan-5-yl]-2-[(diphenylmethylene)-amino]butanoate **3a**

Yield: 80%; colourless oil, mixture of **2a** and **3a**; dr 30:70; major isomer **3a**:  $R_f=0.48$  (hexane–Et<sub>2</sub>O, 4:1);  $[\alpha]_D^{20}=-134.2$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.58 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.05 (t,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.16 (d,  $J=7.1$  Hz, 3H, CH<sub>3</sub>CH), 1.30 (d,  $J=6.0$  Hz, CH<sub>3</sub>CHO), 2.29 (dd,  $J=1.1, 9.8$  Hz, 1H, CHC=O), 2.58 (m, 1H, CH<sub>3</sub>CH), 3.93 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.20 (d,  $J=9.04$  Hz, 1H, CHN), 4.44 (dq,  $J=9.8, 6.0$  Hz, 1H, CHO), 4.60 (s, 1H, OCHO), 7.10–7.13 (m, 2H, ArH), 7.21–7.39 (m, 6H, ArH), 7.55–7.58 (m, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.01 (OCH<sub>2</sub>CH<sub>3</sub>), 14.12 (CH<sub>3</sub>CH), 20.17 (CH<sub>3</sub>CHO), 23.50 [C(CH<sub>3</sub>)<sub>3</sub>], 34.39 [C(CH<sub>3</sub>)<sub>3</sub>], 37.31 (CH<sub>3</sub>CH), 52.66 (CHC=O), 60.72 (OCH<sub>2</sub>), 68.03 (CHN), 74.95 (CHO), 106.74 (OCHO), 127.49 ( $\times 2$ ), 128.10 ( $\times 2$ ), 128.35 ( $\times 2$ ), 128.61, 128.94 ( $\times 2$ ), 130.68 (CH, Ar), 135.87, 139.24 (C, Ar), 170.64 (C=N), 171.95, 172.27 (C=O). Anal. calcd for C<sub>28</sub>H<sub>35</sub>NO<sub>5</sub>: C, 72.23; H, 7.58; N, 3.01. Found: C, 72.12; H, 7.61; N, 2.92.

3.1.3. Ethyl (2R,3R)-3-[(2R,5R,6R)-2-(*t*-butyl)-6-methyl-4-oxo-1,3-dioxan-5-yl]-2-[(diphenylmethylene)-amino]pentanoate **2b**

Yield: 78%; mixture of **2b** and **3b**; dr 80:20; major isomer **2b**:  $R_f=0.48$  (hexane–Et<sub>2</sub>O, 4:1); colourless crystals, mp 75–76°C;  $[\alpha]_D^{20}=+134$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.83 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 0.88 (t,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.15 (t,  $J=7.1$  Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>), 1.17 (d,  $J=6.0$  Hz, 3H, CH<sub>3</sub>CHO), 1.62–1.72 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>), 2.31 (ddt,  $J=2.2, 10.2, 7.1$  Hz, 1H, CHCH<sub>2</sub>), 2.42 (dd,  $J=2.2, 9.8$  Hz, 1H, CHC=O), 3.93 (dq,  $J=9.8, 6.0$  Hz, 1H, CHO), 4.05 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.23 (d,  $J=6.8$  Hz, 1H, CHN), 4.75 (s, 1H, OCHO), 7.05–7.09 (m, 2H, ArH), 7.20–7.38 (m, 6H, ArH), 7.54–7.58 (m, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.35 (CH<sub>3</sub>CH<sub>2</sub>), 14.08

(OCH<sub>2</sub>CH<sub>3</sub>), 20.38 (CH<sub>3</sub>CHO), 23.57 (CH<sub>3</sub>CH<sub>2</sub>), 23.91 [C(CH<sub>3</sub>)<sub>3</sub>], 35.05 [C(CH<sub>3</sub>)<sub>3</sub>], 44.01 (CHCH<sub>2</sub>), 48.49 (CHC=O), 61.08 (OCH<sub>2</sub>), 66.59 (CHN), 73.46 (CHO), 107.18 (OCHO), 127.76 (×2), 128.05 (×2), 128.53 (×2), 128.81, 128.95 (×2), 130.42 (CH, Ar), 136.20, 139.44 (C, Ar), 169.30 (C=N), 171.0, 171.90 (C=O). Anal. calcd for C<sub>29</sub>H<sub>37</sub>NO<sub>5</sub>: C, 72.62; H, 7.78; N, 2.92. Found: C, 72.54; H, 7.61; N, 2.90.

3.1.4. Ethyl (2S,3S)-3-[(2R,5R,6R)-2-(*t*-butyl)-6-methyl-4-oxo-1,3-dioxan-5-yl]-2-[(diphenylmethylene)-amino]pentanoate **3b**

Yield: 80%; mixture of **2b** and **3b**; dr 75:25; major isomer **3b**: R<sub>f</sub>=0.51 (hexane–Et<sub>2</sub>O, 4:1); colourless oil; [α]<sub>D</sub><sup>20</sup> = –72.4 (*c* = 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.57 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 0.86 (t, *J* = 7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.05 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>), 1.29 (d, *J* = 6.4 Hz, 3H, CH<sub>3</sub>CHO), 1.40 and 1.72 (each m, 2×H, CH<sub>3</sub>CH<sub>2</sub>), 2.30 (ddt, *J* = 1.0, 8.6, 7.1 Hz, 1H, CHCH<sub>2</sub>), 2.39 (dd, *J* = 1.0, 9.8 Hz, 1H, CHC=O), 3.94 (q, *J* = 7.1 Hz, 2H, OCH<sub>2</sub>), 4.27 (d, *J* = 8.6 Hz, 1H, CHN), 4.45 (dq, *J* = 9.8, 6.4 Hz, 1H, CHO), 4.62 (s, 1H, OCHO), 7.12–7.15 (m, 2H, ArH), 7.24 (m, 1H, ArH), 7.30–7.44 (m, 4H, ArH), 7.49–7.57 (m, 2H, ArH), 7.73 (m, 1H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 12.09 (CH<sub>3</sub>CH<sub>2</sub>), 13.98 (OCH<sub>2</sub>CH<sub>3</sub>), 19.73 (CH<sub>3</sub>CHO), 23.50 [C(CH<sub>3</sub>)<sub>3</sub>], 25.26 (CH<sub>3</sub>CH<sub>2</sub>), 34.34 [C(CH<sub>3</sub>)<sub>3</sub>], 44.13 (CHCH<sub>2</sub>), 48.24 (CHC=O), 60.76 (OCH<sub>2</sub>), 67.13 (CHN), 74.97 (CHO), 106.67 (OCHO), 127.54, 128.07, 128.28 (×2), 128.55, 129.02 (×2), 130.05, 130.62, 132.40 (CH, Ar), 135.91, 139.42 (C, Ar), 170.73 (C=N), 172.08, 172.38 (C=O). Anal. calcd for C<sub>29</sub>H<sub>37</sub>NO<sub>5</sub>: C, 72.62; H, 7.78; N, 2.92. Found: C, 72.42; H, 7.74; N, 2.89.

3.1.5. Ethyl (2R,3R)-3-[(2R,5R,6R)-2-(*t*-butyl)-6-methyl-4-oxo-1,3-dioxan-5-yl]-2-[(diphenylmethylene)-amino]-5-phenylpentanoate **2c**

Yield: 85%; mixture of **2c** and **3c**; dr 90:10; major isomer **2c**: R<sub>f</sub>=0.52 (hexane–Et<sub>2</sub>O, 4:1); colourless oil; [α]<sub>D</sub><sup>20</sup> = +82.2 (*c* = 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.81 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.11 (d, *J* = 6.0 Hz, 3H, CH<sub>3</sub>CHO), 1.13 (t, *J* = 7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.97 and 2.19 (each m, 2×H, CH<sub>2</sub>CH<sub>2</sub>Ph), 2.36 (m, 1H, CHCH<sub>2</sub>), 2.48 (dd, *J* = 3.0, 9.8 Hz, 1H, CHC=O), 2.50–2.70 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ph), 3.91 (dq, *J* = 9.8, 6.0 Hz, 1H, CHO), 4.02 (q, *J* = 7.1 Hz, 2H, OCH<sub>2</sub>), 4.21 (d, *J* = 5.3 Hz, 1H, CHN), 4.70 (s, 1H, OCHO), 7.02–7.09 (m, 5H, ArH), 7.14–7.38 (m, 8H, ArH), 7.53–7.57 (m, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.10 (OCH<sub>2</sub>CH<sub>3</sub>), 20.30 (CH<sub>3</sub>CHO), 23.94 [C(CH<sub>3</sub>)<sub>3</sub>], 32.14 (CH<sub>2</sub>CH<sub>2</sub>Ph), 33.72 (CH<sub>2</sub>CH<sub>2</sub>Ph), 35.08 [C(CH<sub>3</sub>)<sub>3</sub>], 41.81 (CHCH<sub>2</sub>), 48.89 (CHC=O), 61.16 (OCH<sub>2</sub>), 66.46 (CHN), 73.47 (CHO), 107.22 (OCHO), 125.91, 127.74 (×2), 128.09 (×2), 128.38 (×2), 128.49 (×2), 128.60 (×2), 128.87, 129.03 (×2), 130.52 (CH, Ar), 136.17, 139.36, 141.69 (C, Ar), 169.07 (C=N), 171.17, 171.79 (C=O). Anal. calcd for C<sub>35</sub>H<sub>41</sub>NO<sub>5</sub>: C, 75.65; H, 7.44; N, 2.52. Found: C, 75.47; H, 7.50; N, 2.57.

3.1.6. Ethyl (2S,3S)-3-[(2R,5R,6R)-2-(*t*-butyl)-6-methyl-4-oxo-1,3-dioxan-5-yl]-2-[(diphenylmethylene)-amino]-5-phenylpentanoate **3c**

Yield: 86%; mixture of **2c** and **3c**; dr 20:80; major isomer **3c**: R<sub>f</sub>=0.50 (hexane–Et<sub>2</sub>O, 4:1); colourless crystals, mp 104–105°C; [α]<sub>D</sub><sup>20</sup> = –97.8 (*c* = 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.60 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.05 (t, *J* = 7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.23 (d, *J* = 6.0 Hz, 3H, CH<sub>3</sub>CHO), 1.73 and 2.13 (each m, 2×H, CH<sub>2</sub>CH<sub>2</sub>Ph), 2.41–2.51 (m, 3×H, CHCH<sub>2</sub>, CHC=O and CH<sub>2</sub>CH<sub>2</sub>Ph), 2.69 (m, 1H, CH<sub>2</sub>CH<sub>2</sub>Ph), 3.93 (q, *J* = 7.1 Hz, 2H, OCH<sub>2</sub>), 4.28 (d, *J* = 7.9 Hz, 1H, CHN), 4.41 (dq, *J* = 9.8, 6.0 Hz, 1H, CHO), 4.65 (s, 1H, OCHO), 7.05–7.38 (m, 13H, ArH), 7.52–7.56 (m, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.01 (OCH<sub>2</sub>CH<sub>3</sub>), 19.78 (CH<sub>3</sub>CHO), 23.56 [C(CH<sub>3</sub>)<sub>3</sub>], 33.57 (CH<sub>2</sub>CH<sub>2</sub>Ph), 34.11 (CH<sub>2</sub>CH<sub>2</sub>Ph), 34.41 [C(CH<sub>3</sub>)<sub>3</sub>], 41.58 (CHCH<sub>2</sub>), 48.95 (CHC=O), 60.91

(OCH<sub>2</sub>), 67.08 (CHN), 74.78 (CHO), 106.71 (OCHO), 125.88, 127.51 (×2), 128.09 (×2), 128.30 (×2), 128.33 (×2), 128.36 (×2), 128.61, 129.06 (×2), 130.65 (CH, Ar), 135.93, 139.37, 141.40 (C, Ar), 170.50 (C=N), 171.92, 172.57 (C=O). Anal. calcd for C<sub>35</sub>H<sub>41</sub>NO<sub>5</sub>: C, 75.65; H, 7.44; N, 2.52. Found: C, 75.36; H, 7.29; N, 2.52.

**3.1.6.1. Crystal structure determination of compound 3c<sup>15</sup>.** A single crystal of **2a** with the dimensions 0.80×0.56×0.48 mm was measured on a STOE Ipds diffractometer using Mo K $\alpha$  radiation ( $\lambda=0.71073$  Å). Crystal data: C<sub>35</sub>H<sub>41</sub>NO<sub>5</sub>,  $M=555.69$ , monoclinic space group  $P2_1$ ,  $a=9.459$  (3),  $b=17.438$  (4),  $c=9.625$  (4) Å,  $\beta=100.1^\circ$ ,  $V=1563.6$  (9) Å<sup>3</sup>,  $Z=2$ ,  $D_c=1.180$  g cm<sup>-3</sup>,  $F(000)=596$ ,  $\mu$  (Mo K $\alpha$ )=0.078 mm<sup>-1</sup>. At 180 (2) K in the range of  $2.15<\theta<25.94^\circ$ , 5722 reflections were measured, 3132 were unique ( $R_{\text{int}}=0.0214$ ). The final residuals were  $wR_{2(\text{all})}=0.1017$ , and  $R_{1(\text{obs})}=0.0377$ . The maximum and minimum peaks in the final difference map were 0.284 and  $-0.253$  e Å<sup>-3</sup>, respectively.

**3.1.7. Ethyl (2R,3S)-3-[(2R,5R,6R)-2-(*t*-butyl)-6-methyl-4-oxo-1,3-dioxan-5-yl]-2-[(diphenylmethylene)-amino]-3-phenylpropanoate 2d**

Yield: 76%; mixture of **2d** and **3d**; dr 95:05; major isomer **2d**:  $R_f=0.46$  (hexane–Et<sub>2</sub>O, 4:1); colourless crystals, mp 53–55°C;  $[\alpha]_D^{20}=+115.0$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.61 (t,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 0.71 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.46 (d,  $J=6.0$  Hz, 3H, CH<sub>3</sub>CHO), 3.11 (dd,  $J=3.0, 9.4$  Hz, 1H, CHC=O), 3.51–3.58 (m, 3H, OCH<sub>2</sub> and CHPh), 3.69 (dq,  $J=9.4, 6.0$  Hz, 1H, CHO), 3.98 (s, 1H, OCHO), 5.08 (d,  $J=10.9$  Hz, 1H, CHN), 7.16–7.41 (m, 13H, ArH), 7.63–7.71 (m, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.50 (OCH<sub>2</sub>CH<sub>3</sub>), 19.95 (CH<sub>3</sub>CHO), 23.72 [C(CH<sub>3</sub>)<sub>3</sub>], 34.73 [C(CH<sub>3</sub>)<sub>3</sub>], 48.56 (CHPh), 50.94 (CHC=O), 60.09 (OCH<sub>2</sub>), 66.89 (CHN), 73.68 (CHO), 107.22 (OCHO), 127.77, 128.04 (×2), 128.10 (×2), 128.18 (×2), 128.49 (×2), 128.62, 128.80 (×2), 129.89 (×2), 130.54 (CH, Ar), 136.26, 137.07, 139.48 (C, Ar), 169.64 (C=N), 171.47, 172.68 (C=O). Anal. calcd for C<sub>33</sub>H<sub>37</sub>NO<sub>5</sub>: C, 75.12; H, 7.07; N, 2.65. Found: C, 75.03; H, 7.24; N, 2.58.

**3.2. General procedure for the transformation of Michael-adducts 2 and 3 to pyroglutamates 4 or 5**

The solution of Michael-adducts **2** or **3** (1 mmol) in a mixture of MeOH, H<sub>2</sub>O, dioxane and AcOH (4:1:5:0.1) (20 ml) was refluxed for 20 h. After cooling to room temperature the solvents were removed under reduced pressure and the residue was mixed with saturated aqueous NaHCO<sub>3</sub> solution (5 ml). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×30 ml); combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give colourless oil. Products were purified by flash chromatography (silica gel, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>).

**3.2.1. (–)-Ethyl (2R,3R,4R)-4-[(1R)-1-hydroxyethyl]-3-methyl-5-oxo-2-pyrrolidinecarboxylate 4a**

Yield: 98%; colourless oil;  $R_f=0.40$  (5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{20}=-82.9$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.06 (d,  $J=7.1$  Hz, 3H, CH<sub>3</sub>CH), 1.23 (d,  $J=6.4$  Hz, 3H, CH<sub>3</sub>CHO), 1.24 (t,  $J=7.1$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.03 (dd,  $J=7.5, 9.0$  Hz, 1H, CHC=O), 2.48 (m, 1H, CHCH<sub>3</sub>), 3.81 (dq,  $J=7.5, 6.4$  Hz, 1H, CHO), 4.10 (d,  $J=9.4$  Hz, 1H, CHN), 4.17 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 5.23 (br s, 1H, OH), 6.50 (br s, 1H, NHC=O); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.26 (OCH<sub>2</sub>CH<sub>3</sub>), 15.71 (CH<sub>3</sub>CH), 21.30 (CH<sub>3</sub>CHO), 35.31 (CHCH<sub>3</sub>), 52.43 (CHC=O), 58.73 (CHN), 61.50 (OCH<sub>2</sub>),



68.70 (CHO), 171.09 (OC=O), 180.14 (NC=O). Anal. calcd for C<sub>10</sub>H<sub>17</sub>NO<sub>4</sub>: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.78; H, 7.99; N, 6.48.

### 3.2.2. (+)-Ethyl (2S,3S,4R)-4-[(1R)-1-hydroxyethyl]-3-methyl-5-oxo-2-pyrrolidinecarboxylate **5a**

Yield: 97%; colourless oil;  $R_f=0.42$  (5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{20}=+19.1$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.20 (d,  $J=6.4$  Hz, 3H, CH<sub>3</sub>CH), 1.24 (t,  $J=7.1$  Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>O), 1.30 (d,  $J=6.4$  Hz, CH<sub>3</sub>CHO), 1.96 (dd,  $J=6.0, 8.3$  Hz, 1H, CHC=O), 2.16 (m, 1H, CHCH<sub>3</sub>), 3.71 (d,  $J=5.3$  Hz, 1H, CHN), 4.56 (dq,  $J=8.3, 6.4$  Hz, 1H, CHO), 4.16 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.56 (br s, 1H, OH), 6.67 (br s, 1H, NHC=O); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.12 (OCH<sub>2</sub>CH<sub>3</sub>), 19.94 (CH<sub>3</sub>CH), 20.89 (CH<sub>3</sub>CHO), 37.04 (CHCH<sub>3</sub>), 54.36 (CHC=O), 61.07 (CHN), 61.82 (OCH<sub>2</sub>), 68.95 (CHO), 171.35 (OC=O), 178.72 (NC=O). Anal. calcd for C<sub>10</sub>H<sub>17</sub>NO<sub>4</sub>: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.74; H, 8.02; N, 6.45.

### 3.2.3. (–)-Ethyl (2R,3R,4R)-3-ethyl-4-[(1R)-1-hydroxyethyl]-5-oxo-2-pyrrolidinecarboxylate **4b**

Yield: 97%; colourless oil;  $R_f=0.40$  (5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{20}=-81.4$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.92 (t,  $J=7.1$  Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>), 1.23 (t,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.26 (d,  $J=6.0$  Hz, 3H, CH<sub>3</sub>CHO), 1.28 and 1.55 (each m, 2×H, CH<sub>2</sub>), 2.14 (dd,  $J=6.4, 8.3$  Hz, 1H, CHC=O), 2.33 (m, 1H, CHCH<sub>2</sub>), 3.82–3.85 (m, 2H, CHO and OH), 4.16 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.22 (d,  $J=9.0$  Hz, 1H, CHN), 6.80 (br s, 1H, NHC=O); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  11.92 (CH<sub>3</sub>CH<sub>2</sub>), 14.15 (OCH<sub>2</sub>CH<sub>3</sub>), 21.38 (CH<sub>3</sub>CHO), 22.99 (CH<sub>3</sub>CH<sub>2</sub>), 43.0 (CHCH<sub>2</sub>), 50.99 (CHC=O), 58.16 (CHN), 61.45 (OCH<sub>2</sub>), 68.47 (CHO), 171.21, 171.92 (OC=O), 179.79 (NC=O). Anal. calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>4</sub>: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.52; H, 8.42; N, 6.05.

### 3.2.4. (+)-Ethyl (2S,3S,4R)-3-ethyl-4-[(1R)-1-hydroxyethyl]-5-oxo-2-pyrrolidinecarboxylate **5b**

Yield: 98%; colourless oil;  $R_f=0.43$  (5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{20}=+18.7$  ( $c=1.75$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.94 (d,  $J=7.5$  Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>), 1.22 (d,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.23 (d,  $J=6.0$  Hz, 3H, CH<sub>3</sub>CHO), 1.54–1.69 (m, 2H, CH<sub>2</sub>), 2.03 (dd,  $J=5.3, 7.1$  Hz, 1H, CHC=O), 2.22 (m, 1H, CHCH<sub>2</sub>), 2.95 (br s, 1H, OH), 3.78 (dq,  $J=7.1, 6.0$  Hz, 1H, CHO), 3.79 (d,  $J=4.1$  Hz, 1H, CHN), 4.15 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 7.05 (br s, 1H, NHC=O); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  10.73 (CH<sub>3</sub>CH<sub>2</sub>), 14.07 (OCH<sub>2</sub>CH<sub>3</sub>), 20.71 (CH<sub>3</sub>CHO), 27.95 (CH<sub>3</sub>CH<sub>2</sub>), 42.88 (CHCH<sub>2</sub>), 52.29 (CHC=O), 59.38 (CHN), 61.53 (OCH<sub>2</sub>), 69.27 (CHO), 171.43, 172.56 (OC=O), 178.76 (NC=O). Anal. calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>4</sub>: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.65; H, 8.38; N, 6.02.

### 3.2.5. (–)-Ethyl (2R,3R,4R)-4-[(1R)-1-hydroxyethyl]-5-oxo-3-phenethyl-2-pyrrolidinecarboxylate **4c**

Yield: 98%; colourless oil;  $R_f=0.47$  (5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{20}=-71.6$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.1.20 (d,  $J=6.4$  Hz, 3H, CH<sub>3</sub>CHO), 1.23 (d,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.56 and 1.88 (each m, 2×H, CH<sub>2</sub>CH<sub>2</sub>Ph), 2.18 (dd,  $J=6.4, 9.0$  Hz, 1H, CHC=O), 2.41 (m, 1H, CHCH<sub>2</sub>), 2.55 and 2.73 (each m, 2×H, CH<sub>2</sub>CH<sub>2</sub>Ph), 3.67 (br s, 1H, OH), 3.78 (t,  $J=6.4$  Hz, 1H, CHO), 4.17 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.25 (d,  $J=7.9$  Hz, 1H, CHN), 6.79 (br s, 1H, NHC=O), 7.06–7.15 (m, 3H, ArH), 7.19–7.24 (m, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.15 (OCH<sub>2</sub>CH<sub>3</sub>), 21.23 (CH<sub>3</sub>CHO), 31.77 (CH<sub>2</sub>CH<sub>2</sub>Ph), 33.37 (CH<sub>2</sub>CH<sub>2</sub>Ph), 40.52 (CHCH<sub>2</sub>), 50.82 (CHC=O), 58.11 (CHN), 61.45 (OCH<sub>2</sub>), 68.40 (CHO), 126.21, 128.21 (×2), 128.56 (×2) (CH, Ar), 140.94 (C, Ar),

171.18 (OC=O), 179.76 (NC=O). Anal. calcd for C<sub>17</sub>H<sub>23</sub>NO<sub>4</sub>: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.67; H, 7.64; N, 4.52.

### 3.2.6. (+)-Ethyl (2S,3S,4R)-4-[(1R)-1-hydroxyethyl]-5-oxo-3-phenethyl-2-pyrrolidine-carboxylate **5c**

Yield: 98%; colourless oil;  $R_f=0.50$  (5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{20}=+17.3$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.122 (d,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.24 (d,  $J=6.4$  Hz, 3H, CH<sub>3</sub>CHO), 1.83–1.95 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>Ph), 2.05 (dd,  $J=4.5, 6.0$  Hz, 1H, CHC=O), 2.38 (m, 1H, CHCH<sub>2</sub>), 2.57 and 2.75 (each m, 2×H, CH<sub>2</sub>CH<sub>2</sub>Ph), 3.77 (dq,  $J=6.4, 6.0$  Hz, 1H, CHO), 3.86 (d,  $J=3.4$  Hz, 1H, CHN), 4.16 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.23 (br s, 1H, OH), 7.10–7.15 (m, 3H, ArH), 7.19–7.25 (m, 2H, ArH), 6.79 (br s, 1H, NHC=O); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.10 (OCH<sub>2</sub>CH<sub>3</sub>), 20.73 (CH<sub>3</sub>CHO), 32.89 (CH<sub>2</sub>CH<sub>2</sub>Ph), 37.66 (CH<sub>2</sub>CH<sub>2</sub>Ph), 41.61 (CHCH<sub>2</sub>), 53.29 (CHC=O), 60.19 (CHN), 61.99 (OCH<sub>2</sub>), 69.45 (CHO), 126.18, 128.30 (×2), 128.53 (×2) (CH, Ar), 140.98 (C, Ar), 172.69 (OC=O), 178.38 (NC=O). Anal. calcd for C<sub>17</sub>H<sub>23</sub>NO<sub>4</sub>: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.78; H, 7.60; N, 4.60.

### 3.2.7. (–)-Ethyl (2R,3S,4R)-4-[(1R)-1-hydroxyethyl]-5-oxo-3-phenyl-2-pyrrolidinecarboxylate **4d**

Yield: 96%; colourless oil;  $R_f=0.58$  (5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{20}=-85.6$  ( $c=1$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.95 (d,  $J=5.6$  Hz, 3H, CH<sub>3</sub>CHO), 1.23 (d,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.62 (t,  $J=8.3$  Hz, 1H, CHC=O), 3.63 (dq,  $J=8.3, 5.6$  Hz, 1H, CHO), 3.68 (dd,  $J=6.2, 8.3$  Hz, 1H, CHPh), 4.12 (d,  $J=6.2$  Hz, 1H, CHN), 4.19 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>), 4.60 (br s, 1H, OH), 6.58 (br s, 1H, NHC=O), 7.21–7.26 (m, 5H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.13 (OCH<sub>2</sub>CH<sub>3</sub>), 20.88 (CH<sub>3</sub>CHO), 47.07 (CHPh), 50.01 (CHC=O), 61.66 (CHN), 62.02 (OCH<sub>2</sub>), 65.56 (CHO), 127.79 (×2), 127.91, 128.89 (×2) (CH, Ar), 138.51 (C, Ar), 171.07 (OC=O), 180.14 (NC=O). Anal. calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub>: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.82; H, 6.99; N, 4.96.

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## References

- (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113. (b) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117.
- Valeria D'Auria, M.; Zampella, A.; Pa'loma, L. G.; Minale, L.; Debitus, C.; Roussakis, C.; Le Bert, V. *Tetrahedron* **1996**, *52*, 9589.
- Dyer, J.; Keeling, S.; Moloney, M. G. *J. Chem. Soc., Chem. Commun.* **1998**, 461.
- For a review, see: Feringa, B. L.; Jansen, J. F. G. A. In *Stereoselective Synthesis*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1996; E-21, Vol. 4, p. 2104.
- Pachaly, P.; Kang, H.-S.; Wahl, D. *Arch. Pharm. (Weinheim)* **1991**, *324*, 989.
- Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875.

7. (a) Tatsukawa, A.; Dan, M.; Ohbatake, M.; Kawatake, K.; Fukata, T.; Wada, E.; Kanemasa, S.; Kakei, S. *J. Org. Chem.* **1993**, *58*, 4221. (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2172. (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747.
8. Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411.
9. (a) Pyne, S. G.; Safaei-G., J.; Schafer, K.; Javidan, A.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1998**, *51*, 137. (b) Javidan, A.; Schafer, K.; Pyne, S. G. *Synlett* **1997**, 100.
10. Tatsukawa, A.; Kawatake, K.; Kanemasa, S.; Rudzinski, J. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2525 and references cited therein.
11. Seebach, D.; Imwinkelried, R. *Helv. Chim. Acta* **1987**, *70*, 448.
12. Amberg, W.; Seebach, D. *Chem. Ber.* **1990**, *123*, 2413.
13. Bartels, A.; Jones, P. G.; Liebscher, J. *Tetrahedron: Asymmetry* **1997**, 1545.
14. Qiao, L.; Wang, S.; George, C.; Lewin, N. E.; Blumberg, P. M.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 6629.
15. Full details have been deposited at the Cambridge Crystallographic Data Centre, CCDC reference number CCDC 149977 (**2a**) and CCDC 149978 (**3c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.