

# Synthesis of trifluoromethyl-containing depsipeptides *via* OH insertion of rhodium carbenoid into the carboxylic group of N-protected $\alpha$ -amino acids

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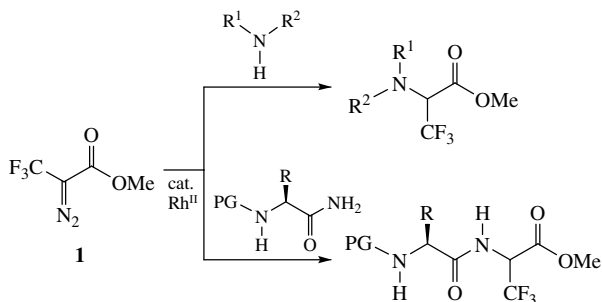
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A new approach to trifluoromethyl-depsipeptides involving the formation of a COO–CH(CF<sub>3</sub>)CO link by a metal carbene insertion reaction into the COOH group of N-protected amino acids has been developed.

Modification of peptides and proteins by incorporation of fluorinated amino acids is a modern strategy in drug discovery.<sup>1</sup> In this context, trifluoromethyl (Tfm) substituted  $\alpha$ -amino acids attract considerable attention<sup>2</sup> due to unique properties of the trifluoromethyl group, such as high electronegativity, electron density, steric hindrance and hydrophobic character.<sup>3</sup> The advantages of peptides modified by Tfm amino acid include enhanced proteolytic stability and affinity to lipid bilayer membranes, as well as stabilization of secondary structures<sup>4</sup> owing to the ability of fluorine to form hydrogen bonds.<sup>5</sup> On the other hand, the replacement of the native peptide bond (CONH) in peptidomimetic structures by different functions or atoms has been currently used for the optimisation of their biological profiles.<sup>6</sup> Among biologically active peptidomimetics, depsipeptides bearing a COO function instead of CONH take up one of the most noticeable places.<sup>7</sup> However, to the best of our knowledge, fluorinated depsipeptides are unexplored compounds until now.

Earlier, we have developed an effective pathway to trifluoroalanine derivatives based on NH insertion reactions of fluorinated carbene generated *in situ* from methyl 3,3,3-trifluoro-2-diazo-propionate **1**<sup>8</sup> under rhodium(II) and copper(0) catalysis.<sup>9</sup> This method allows us to obtain dipeptides with the C-terminal position of trifluoroalanine (Scheme 1). Here, we report a new approach to Tfm depsipeptide synthesis, which involves the formation of a COO–CH(CF<sub>3</sub>)CO link by a metal carbene insertion reaction into the COOH group of N-protected amino acids.



PG = protecting group

Scheme 1

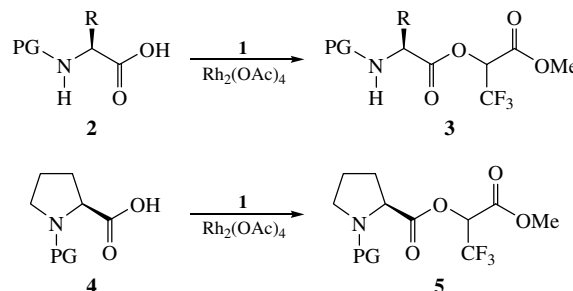
Reactions involving the OH insertion of metallocarbenoid intermediates derived from corresponding diazocarbonyl compounds have been investigated under copper or rhodium catalysed conditions.<sup>10</sup> There are few examples of insertion into carboxylic acids.<sup>11</sup> However, they have received nearly no attention as a synthetic route to  $\alpha$ -oxy carboxylic acid derivatives, including depsipeptides.

Thus, we found that diazo compound **1** readily reacts with different N-protected  $\alpha$ -amino acids at room temperature in anhydrous methylene chloride or toluene for 5–10 h in the presence of catalytic amounts (2–3 mol%) of Rh<sub>2</sub>(OAc)<sub>4</sub> to afford regioselectively the corresponding OH-insertion products with moderate to good yields (Scheme 2, Table 1). The variation of substituents (R) and protecting groups in starting L-amino acids does not essentially affect the diastereoselectivity of the process;

Table 1 Formation of depsipeptides from N-protected amino acids.

Amino acid	PG	R	Depsipeptide	Yield (%)
<b>2a</b>	PhC(O)	Me	<b>3a</b>	40
<b>2b</b>	PhC(O)	Ph	<b>3b</b>	70
<b>2c</b>	PhC(O)	Bu <sup>s</sup>	<b>3c</b>	73
<b>2d</b>	PhC(O)	Bu <sup>i</sup>	<b>3d</b>	45
<b>2e</b>	Phth	Bu <sup>i</sup>	<b>3e</b>	68
<b>2f</b>	Phth	Bu <sup>s</sup>	<b>3f</b>	58
<b>2g</b>	Phth	Me	<b>3g</b>	87
<b>4a</b>	Cbz		<b>5a</b>	78
<b>4b</b>	Boc		<b>5b</b>	76

in all cases, isolated depsipeptides **3**, **5** were the mixtures of diastereomers in a ratio of about 1:1. They can be easily separated by column chromatography on silica gel.<sup>†</sup>



Scheme 2

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<sup>†</sup> Typical procedure for the synthesis of depsipeptides. A solution of diazo compound **1** (4.5 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was added dropwise to a solution of **2f** (3.0 mmol) and dirhodium tetraacetate (2 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The reaction mixture was stirred at room temperature for 8 h. After evaporation of the solvent under a reduced pressure, the residue (a 1:1 mixture of diastereomers, as determined by <sup>19</sup>F NMR spectroscopy; yield, 58%) was separated by column chromatography on silica gel (eluent: ethyl acetate–hexane, 1:5). *Diastereomer A*: yield, 25%, oil, R<sub>f</sub> 0.22, [ $\alpha$ ]<sub>D</sub><sup>25</sup> –13.4 (c 1.37, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 0.89 (t, 3H, Me, <sup>3</sup>J<sub>HH</sub> 7.2 Hz), 1.09 (m, 1H, CH<sub>2</sub>), 1.15 (d, 3H, Me, <sup>3</sup>J<sub>HH</sub> 7.9 Hz), 1.59 (m, 1H, CH<sub>2</sub>), 2.58 (m, 1H, CH), 3.85 (s, 3H, OMe), 4.85 (d, 1H, CHN, <sup>3</sup>J<sub>HH</sub> 8.1 Hz), 5.41 (q, 1H, CH–CF<sub>3</sub>, <sup>3</sup>J<sub>HF</sub> 6.9 Hz), 7.76 (m, 2H, Ph), 7.88 (m, 2H, Ph). <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$ : 4.78 (d, 3F, CF<sub>3</sub>, <sup>3</sup>J<sub>FF</sub> 6.9 Hz). MS, m/z: 401 [M]<sup>+</sup>. *Diastereomer B*: yield, 13%, oil, R<sub>f</sub> 0.16, [ $\alpha$ ]<sub>D</sub><sup>25</sup> –3.5 (c 0.86, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 0.87 (t, 3H, Me, <sup>3</sup>J<sub>HH</sub> 7.4 Hz), 1.07 (m, 1H, CH<sub>2</sub>), 1.14 (d, 3H, Me, <sup>3</sup>J<sub>HH</sub> 6.8 Hz), 1.60 (m, 1H, CH<sub>2</sub>), 2.62 (m, 1H, CH), 3.75 (s, 3H, OMe), 4.83 (d, 1H, CHN, <sup>3</sup>J<sub>HH</sub> 8.7 Hz), 5.56 (q, 1H, CH–CF<sub>3</sub>, <sup>3</sup>J<sub>HF</sub> 7.2 Hz), 7.77 (m, 2H, Ph), 7.90 (m, 2H, Ph). <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$ : 4.88 (d, 3F, CF<sub>3</sub>, <sup>3</sup>J<sub>FF</sub> 7.2 Hz). Found (%): C, 52.32; H, 4.89; N, 3.69. Calc. for C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>6</sub> (%): C, 52.44; H, 4.62; N, 3.60.

**5a**: oil, mixture of diastereomers (1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.65–2.01 (m, 4H, 2CH<sub>2</sub>), 3.39 (m, 1H, CH), 3.79 (m, 2H, CH<sub>2</sub>), 3.88 (br. s, 3H, OMe), 5.02 (m, 1H, CH), 5.18 (m, 2H, OCH<sub>2</sub>), 7.79 (m, 5H, Ph). <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$ : 6.89 (m, 3F, CF<sub>3</sub>). Found (%): C, 52.55; H, 4.78; N, 3.79. Calc. for C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>6</sub> (%): C, 52.44; H, 4.62; N, 3.60.

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