

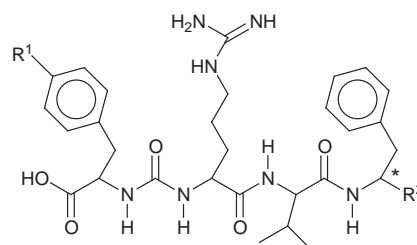
# First efficient synthesis of $\alpha$ -MAPI

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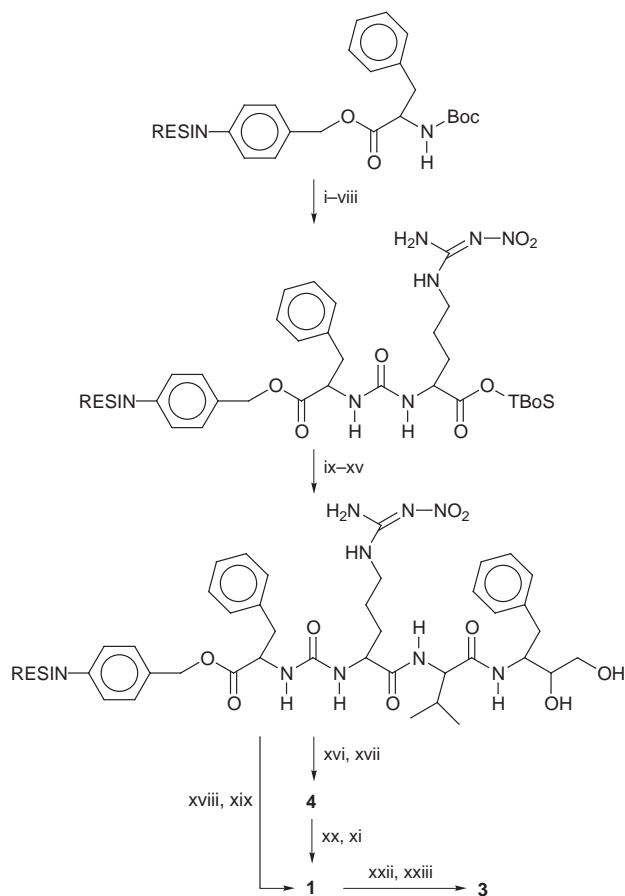
$\alpha$ -MAPI **1** and its analogues have been synthesised using *tert*-butoxysilyl protected amino acids in conjunction with a solid-phase N $\rightarrow$ C assembly; the terminal aldehyde group of the peptide is generated from a C-modified amino acid containing a *gem*-diol.

MAPI (*microbial alkaline proteinase inhibitor*) is a mixture of three compounds,  $\alpha$ -,  $\beta$ - and  $\gamma$ -MAPI possessing similar activity which are produced by *streptomyces nigrescens* WT-27.<sup>1–3</sup> The unique features of these peptides are that they contain terminal carboxy and aldehyde groups and a ureido (–NH–CO–NH–) function. Furthermore,  $\alpha$ -MAPI **1** has been shown to inhibit



**Table 1** Configuration data for **1–6**

Compound	R <sup>1</sup>	R <sup>2</sup>	Config. at *
<b>1</b> $\alpha$ -MAPI	H	CHO	<i>S</i>
<b>2</b> $\beta$ -MAPI	H	CHO	<i>R</i>
<b>3</b> Mer-N5075A	H	CH <sub>2</sub> OH	<i>S</i>
<b>4</b> $\alpha$ -MAPI-diol	H	CHOHCH <sub>2</sub> OH	<i>S</i>
<b>5</b> GE20372A	OH	CHO	<i>S</i>
<b>6</b> GE20372B	OH	CHO	<i>R</i>



**Scheme 1** Reagents and conditions: i, CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  1 min); ii, 50% TFA–CH<sub>2</sub>Cl<sub>2</sub> (5 and 25 min); iii, CH<sub>2</sub>Cl<sub>2</sub> (4  $\times$  1 min); iv, CDI (78 mg, 0.48 mmol), CH<sub>2</sub>Cl<sub>2</sub>, 30 min; v, repeat iii; vi, remove 2–3 mg resin for ninhydrin assay; vii, Arg–TBos (223 mg, 0.48 mmol), CH<sub>2</sub>Cl<sub>2</sub>, 120 min; viii, repeat iii; ix, 25% TFA–CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  5 min); x, repeat iii; xi, Val–TBos (172 mg, 0.48 mmol); BOP–HOBT–DIPEA (1 : 1 : 1 : 3 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 120 min; xii, repeat iii, xiii, repeat ix, x; xiv, Phe-diol (87 mg)–BOP–HOBT–DIPEA (1 : 1 : 1 : 3 equiv.), DMF, 120 min; xv, DMF (2  $\times$  1 min), CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  1 min); xvi, HF; xvii, RP–HPLC; xviii, NaIO<sub>4</sub>, MeOH, 90 min; xix, repeat xv–xvii; xx, NaIO<sub>4</sub>, MeOH–H<sub>2</sub>O (80%, 2 ml), 45 min; xxi, repeat xvii; xxii, NaBH<sub>4</sub>, MeOH, 30 min, AcOH; xxiii, repeat xvii. The solvent used was 10 ml throughout for 200 mg of resin.

HIV-I protease.<sup>4</sup> Recently, a closely related family of tetrapeptides **3**, **5** and **6** which inhibit HIV-protease has been reported.<sup>5–7</sup> It is hoped that these compounds may ultimately lead to the development of effective anti-proteolytic drugs for the treatment of AIDS. There is no report on the synthesis of **1** and **2**. Therefore, the synthesis of these compounds and their analogues is of paramount importance.

Our recently reported<sup>8</sup> new approach for the assembly of peptides on solid-phase from N $\rightarrow$ C direction was extended for the synthesis of  $\alpha$ -MAPI **1** and its analogues **3** and **4** as illustrated in Scheme 1.

Boc-Phe-Merrifield resin was treated with TFA to remove the Boc group. The resin was thoroughly washed (CH<sub>2</sub>Cl<sub>2</sub>) and incubated with *N,N'*-carbonyldiimidazole (CDI). The reaction was monitored by ninhydrin assay.<sup>9</sup> Arginine-(N<sup>G</sup>-NO<sub>2</sub>)-*tert*-*tert*-butoxysilyl ester<sup>8</sup> (TBos)<sup>†</sup> was added and the mixture was shaken for 2 h. The removal of *tert*-*tert*-butoxysilyl group was accomplished in quantitative yield with 25% TFA. The peptide chain was further elongated by coupling valine-*tert*-*tert*-butoxysilyl ester followed by the deprotection of the ester group as before. Finally, the resulting peptidyl-resin was coupled to phenylalanine diol<sup>10</sup> in DMF to give the required peptidyl-resin. The peptide was then cleaved from the resin using liquid HF<sup>11</sup> and after preparative RP–HPLC followed by lyophilisation gave  $\alpha$ -MAPI-diol **4** in 75% yield.<sup>§</sup> Analytical and spectral data are in agreement with the assigned structure.<sup>¶</sup>

The diol **4** was smoothly oxidized with NaIO<sub>4</sub> to give  $\alpha$ -MAPI **1**. The extent of reaction completeness was monitored by RP–HPLC and mass spectrometry. The oxidation was complete in 45 min. RP–HPLC purification afforded  $\alpha$ -MAPI **1** in 84% yield<sup>§</sup> and gave the expected spectral data.<sup>¶</sup> The oxidation of the diol was also carried out on the solid-phase to give the aldehyde **1** in good yield.

$\alpha$ -MAPI **1** was treated with NaBH<sub>4</sub> and gave after purification the expected alcohol **3** in 64% yield.¶ Further work in this area is continuing.

## Notes and References

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‡ All amino acids described in this work are of L-configuration. TBoS refers to the tri-*tert*-butoxysilyl group.

§ Analytical and preparative reversed-phase HPLC (RP-HPLC) experiments were performed on a Gilson 715 instrument equipped with a multi-wave length detector (Applied Biosystems 759A) and two slave 306 pumps. Retention times are given for gradient elution using the following conditions: Column, Vydac C<sub>18</sub> (10  $\mu$ m, 0.46 and 2.2  $\times$  25 cm); eluent A, 0.1% (v/v) TFA in H<sub>2</sub>O; eluent B, 0.1% (v/v) TFA in acetonitrile, gradient, 0% B over 2 min, 0–80% B over 32 min; flow rate 1 ml min<sup>-1</sup> (analytical) and 10 ml min<sup>-1</sup> (preparative); absorbance, 216 nm. Molecular weight determinations were carried out by electrospray (ES) Micromass Quattro II mass spectrometer.

¶ All compounds reported herein are white solids and exhibited satisfactory analytical and spectral data. *Selected data* for  $\alpha$ -MAPI-diol **4**: single peak, retention time, 16.5 min HPLC; ESMS, *m/z* 628 [M + H]<sup>+</sup>. *Selected data* for  $\alpha$ -MAPI **1**: single peak, retention time, 16.8 min HPLC; mp 211–213 °C (decomp.) (lit.,<sup>2</sup> 204–205 °C); [ $\alpha$ ]<sub>D</sub><sup>24</sup> 22.2 (c 0.9, AcOH) (lit.,<sup>2</sup> –18); ESMS, *m/z* 596 [M + H]<sup>+</sup> and 614 [M + H<sub>2</sub>O]<sup>+</sup>, hemi-acetal;  $\delta$ <sub>H</sub> (360 MHz, [2H<sub>7</sub>]DMF) 0.79 (d, 3H, *J* 6.7 CH–CH<sub>3</sub>, Val), 0.81 (d, 3H, *J* 6.9, CH–CH<sub>3</sub>, Val), 1.5–1.75 (m, 4H, CH–CH<sub>2</sub>–CH<sub>2</sub>, Arg), 2.08 (h, 1H, *J* 6.55, CH[CH<sub>3</sub>]<sub>2</sub>, Val), 3.0–3.35 (m, 4H, 2  $\times$  CH<sub>2</sub>, Phe), 3.6 (2H, obscured by solvent, –CH<sub>2</sub>–NH, Arg), 4.3–4.6 (m, 4H, 4  $\times$  methines), 6.5 (d, 1H, *J* 8), 6.7 (d, 1H, *J* 7.8), 7.2 (m, 10H, 2  $\times$  C<sub>6</sub>H<sub>5</sub>, Phe), 7.55 (br), 7.85 (d, 1H, *J* 8.6), 8.5 (d, 1H, *J* 7.1), 9.58 (s, 1H, CHO). *Selected data* for alcohol **3**: single peak, retention time, 16.8 min HPLC; mp 155 °C, softens and 180–182 °C, (decomp. lit.,<sup>5</sup> 182 °C); [ $\alpha$ ]<sub>D</sub><sup>24</sup> –24.0 (c 0.5, AcOH) (lit.,<sup>5</sup> –24.4); ESMS, *m/z* 598 [M + H]<sup>+</sup>;

<sup>1</sup>H NMR (360 MHz) and <sup>13</sup>C NMR (90 MHz) gave expected chemical shift values.

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