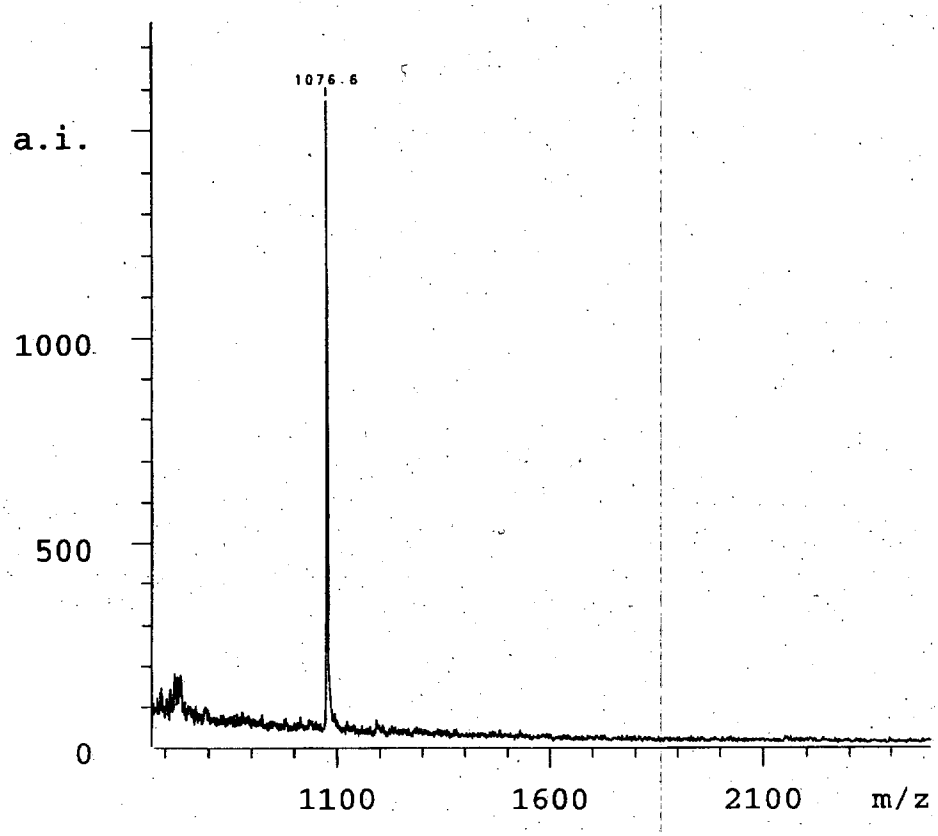


Figure S1. MALDI-TOF mass spectrum of HPLC-purified **1**.

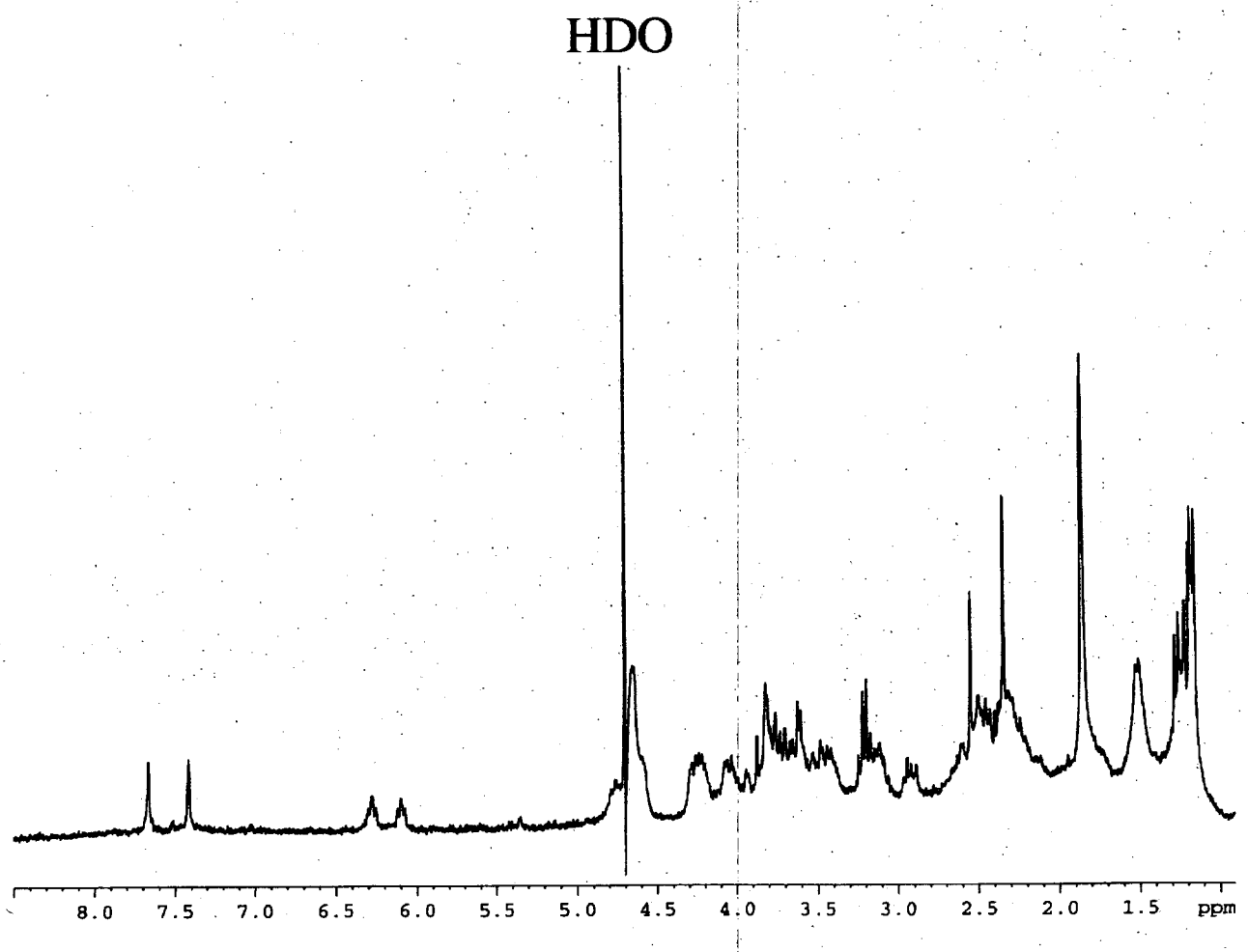


Figure S2. ^{1}H-NMR spectrum of **1** (300 MHz, D_2O, 22°C, water suppresion by presaturation).

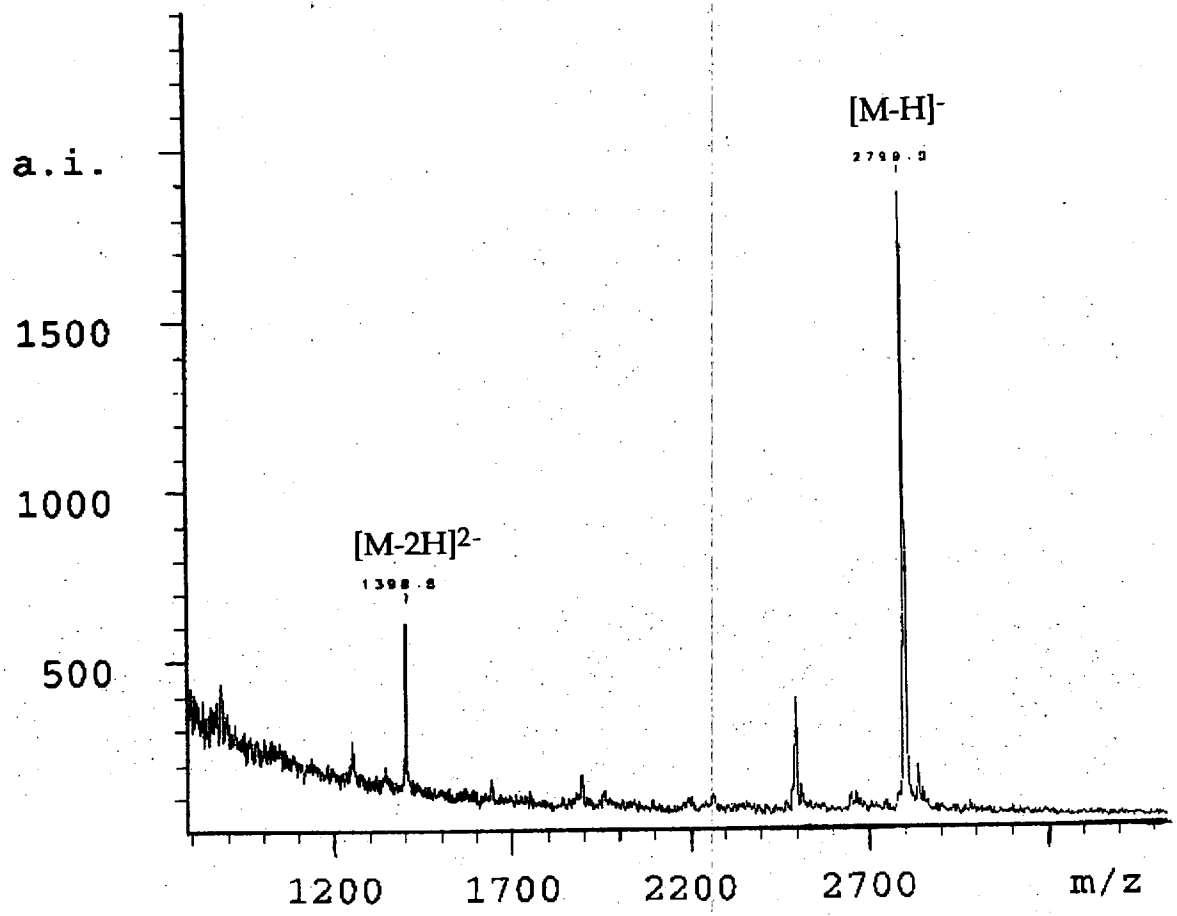


Figure S3. MALDI-TOF mass spectrum of *cyclo*-Glu-$(Ala)_2$-$(Leu)_4$-T*GCACG-DP-Lys as obtained after one HPLC injection under non-optimized conditions.

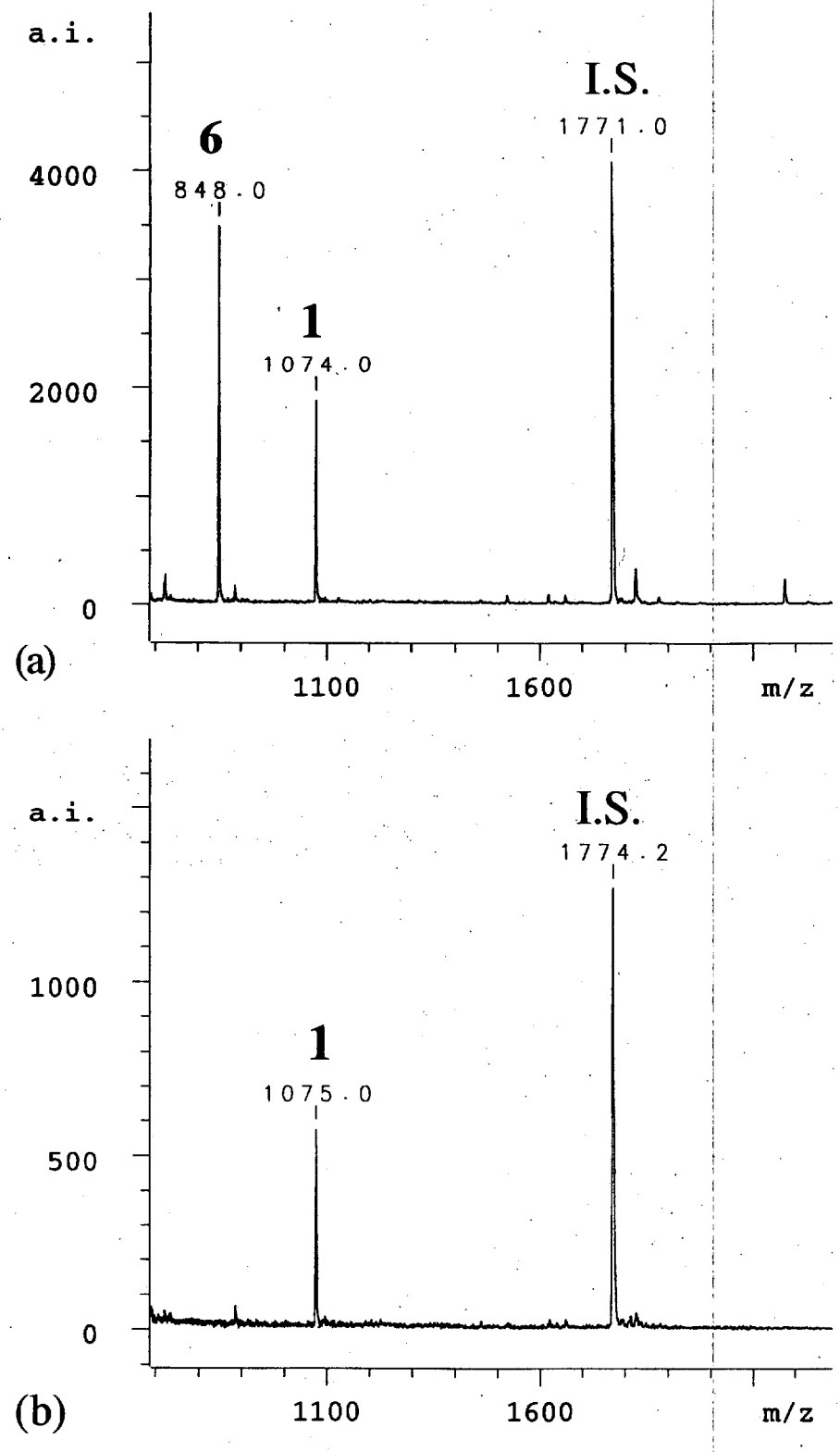
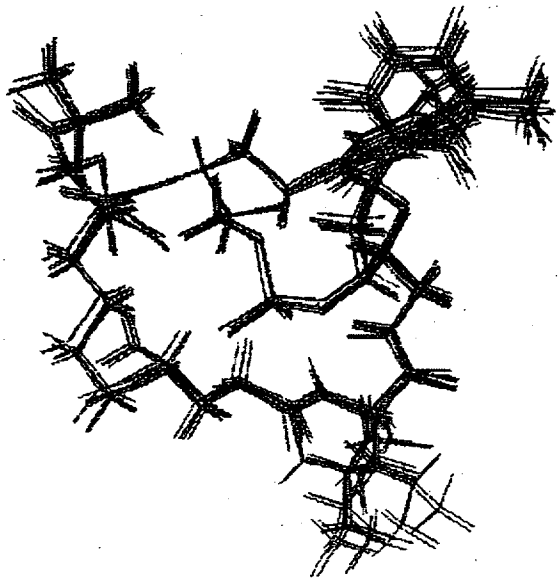
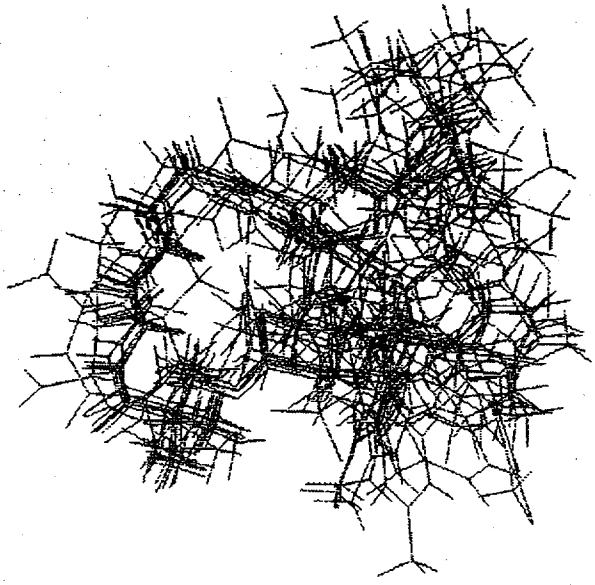


Figure S4. MALDI-TOF mass spectra of a mixture of **1** and DNA control compound 5'-T_PT_PT-3' (**6**), (a) prior to, and (b) after 50 h of exposure to a mixture of snake venom phosphodiesterase (E.C. 3.1.4.1) and calf spleen phosphodiesterase (E.C. 3.1.16.1) in ammonium acetate buffer at 25 °C. I.S. = internal standard 5'-GTCAAC-3' incorporated in the matrix preparation.



(a)



(b)

Figure S5: Force-field minimized structures obtained from a conformational search for hybrid **1**, performed with Macromodel using the Amber force field. In 1000 iterations (structures minimized) 207 structures within 50 kJ/mol of the lowest energy structure were found in a Monte Carlo search with 24 torsion angles resolution; (a) shows an overlay of the 10 lowest structures, which were at 541 ± 3 kJ/mol, and (b) shows an overlay of 10 of the 11 highest energy structures within the 50 kJ/mol window (-494 ± 1 kJ/mol), solely to give an impression of the diversity of conformations searched.

^{1}H-NMR for compound **1**.

(300 MHz, D_2O, 25¡C, selected resonances) δ 0.93/0.97 (2d, 2x3H, J = 5.3 Hz, CH_3-Leu2), 1.28/1.30 (2s, 2x3H, CH_3-DP5), 1.39 (m, 2H, Hβ/Hβ'-Aa), 1.65 (m, 2H, Hβ/Hβ'-Aa), 1.66 (m, 1H, CHγ-Leu2), 1.84/1.90 (2m, 2x1H, Hβ/Hβ'-Aa), 1.98/1.99 (2s, 2x3H, $CH_3$7-T), 2.43/2.61 (2m, 2x1H, H2'/H2''-T), 2.47/2.57 (2m, 2x1H, H2'/H2''-T), 4.17, 4.37, 4.38 (3m, 3x1H, Hα-Aa), 6.23 (tr, 1H, J = 6.7 Hz, H1'-T), 6.40 (tr, 1H, J = 7.1 Hz, H1'-T), 7.55 (s, 1H, H6-T), 7.79 (s, 1H, H6-T); DP = 3-hydroxy-2,2-dimethylpropionic acid residue, Aa = amino acid residue.