Supplementary material

Design and Synthesis of all Diastereomers of Cyclic Pseudo-Dipeptides as Mimic of Cyclic CXCR4 Pentapeptide Antagonist.

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Experimental and analytical data

Methyl (R)-2-(N-Boc-amino)-5-(triisopropylsilyloxy) pentanoate D-6 [ Boc-D-Hnv(TIPS)-OMe ]: Product was prepared on the same way as L-6 from methyl (R)-2-(N-Boc-amino)-5-hydroxypentanoate (8.60 g, 34.5 mmol) to give as an inseparable mixture (88/12) of D-6 and TIPSOH (14.0 g, 88%). MS (FAB+) : m/z = 404 (M + H+).

(R)-2-(N-Boc-amino)-5-(triisopropylsilyloxy)pentan-1-ol D-7 : Product was prepared on the same way as L-7 from D-6 containing 12% of TIPSOH (8.60 g, 21.3 mmol) to give D-7 (7.00 g, 99%). 1H NMR (CDCl3) δ identical to L-7. [α]D 22 +4.4 (c=1.0, CHCl 3), MS (FAB+) m/z 376 (M + H+), 398 (M + Na+); HRMS calcd for C19H42NO4Si+ (MH+) 376.2883, found 376.2886.

(N)-1-Allyl-2-Boc-N1-(o-nitrobenzenesulfonyl)-5-(triisopropylsilyloxy)pentane-1,2-diamine D-8 : Reaction was done on the same way as for L-8 using alcohol D-7 (7.00 g, 18.6 mmol) to furnish product D-8 (7.45 g, 66%). MS (FAB+) m/z 599 (M+); HRMS calcd for C28H49N3O7SSi+ (M+) 599.3060, found 599.3065. [α]D 20 +21.6° (c=1.00)

Methyl (S)-2-[N-Allyl-(4-benzyloxyphenyl)acetamido]-5-(triisopropylsilyloxy)pentanoate 13b : Amine L-10 (3.00 g, 8.73 mmol), 2-(4-benzyloxyphenyl)acetic acid 12 (4.23 g, 2 eq) and HATU (6.64 g, 2 eq) were dissolved in DMF (85 ml). Et3N (3.6 ml, 3 eq) was added dropwise and the reaction was stirred for 3 h at rt. The reaction was partitioned between ether and HCl 0.5M solution. Aqueous phase was extracted twice with ether. Combined organic phases were successively washed with water and brine, dried over MgSO4 and concentrated. Oil was purified by flash chromatography using hexane/EtOAc (90/10 to 80/20) to furnish 13b (4.25 g, 86%). 1H NMR (CDCl3) δ 7.44-7.28 (m, 5H), 7.15 (m, 2H), 6.92 (m, 2H), 5.78 (ddt, 1H, Jd1 = 17.6 Hz, Jd2 = 12.2 Hz, Jt = 5.1 Hz), 5.20 (m, 2H), 5.04 (s, 2H), 4.80 (dd, 1H, J = 5.8 Hz, J = 8.8 Hz), 3.98 (dd, 1H, J = 5.9 Hz, J = 17.6 Hz), 3.84 (dd, 1H, J = 5.4 Hz, J = 17.8 Hz), 3.65 (m, 7H), 2.06 (m, 1H), 1.84 (m, 1H), 1.53 (m, 2H), 1.05 (m, 21H). 13C (CDCl3) δ 172.1, 171.9, 157.7, 137.0, 134.3, 129.1, 129.8, 128.5, 127.9, 127.4, 127.0, 117.3, 115.0, 70.0, 62.7, 57.5, 51.9, 49.3, 40.1, 29.8, 25.6, 18.0, 11.9. FTIR (cm⁻1) 2943, 2865, 1739, 1649, 1612, 1510, 1455, 1240, 1176, 1103. MS (FAB+) m/z 568 (M + H+); HRMS calcd for C33H50NO5Si+ (MH+) 568.3453, found 568.3449.

(S)-2-[N-Allyl-(4-benzyloxyphenyl)acetamido]-5-(triisopropylsilyloxy)pentanoic acid 3b : Ester 13b (4.25 g, 7.48 mmol) was dissolved in THF/H2O/MeOH (3/1/1, 75 ml), cooled down to 0°C and treated with LiOH·H2O (942 mg, 3 eq). The reaction was stirred for 3 h at 0°C and was diluted with EtOAc and 0.5 M HCl solution. Aqueous phase was extracted with EtOAc. Combined
organic phases were washed with brine, dried over MgSO₄ and concentrated. Oil was purified by flash chromatography using hexane/EtOAc (90/10 to 60/40) to furnish 3b (2.83 g, 68%). ¹H NMR (CDCl₃) δ 7.44-7.29 (m, 5H), 7.14 (m, 2H), 6.92 (m, 2H), 5.76 (dd, 1H, J₁₁ = 17.8 Hz, J₁₂ = 12.2 Hz, J₂₂ = 5.4 Hz), 5.23 (m, 2H), 5.07 (s, 2H), 4.48 (dd, 1H, J = 6.8 Hz, J = 8.0 Hz), 4.03 (dd, 1H, J = 5.8 Hz, J = 17.3 Hz), 3.86 (dd, 1H, J = 5.6 Hz, J = 17.3 Hz), 3.70 (m, 4H), 2.15 (m, 1H), 1.96 (m, 1H), 1.57 (m, 2H), 1.05 (m, 21H). MS (FAB⁺) m/z 554 (M + H⁺); HRMS calcd for C₃₂H₄₈NO₅Si⁺ (M⁺) 554.3296, found 554.3304.

(2RS)-2-[N-allyl-(4-benzyloxyphenyl)propanamido]-N-[(2R)-1-(N-allyl-o-nitrophenylsulfonamido)-5-trisopropylsilyloxypentan-2-yl]-5-triisopropylsilyloxypentanamide (2RS,2'R)-(16/17) : Protocol was similar to the one used for the synthesis of 14/15 with d-8 (2.35 g, 3.92 mmol) and gave d-4 (1.84 g, 94%). Acid 3a (1.62 g, 2.85 mmol) and amine d-4 (1.85 g, 1.3 eq) were coupled as described for the synthesis of 14/15 to give 16/17 (2.72 g, 91%) as a 1:1 mixture of two diastereomers. MS (FAB⁺) m/z 1049 (M + H⁺), 1071 (M + Na⁺); HRMS calcd for C₅₆H₈₉N₄O₉SSi₂⁺ (M⁺) 1049.5889, found 1049.5894.

(2R)- and (2S)-2-[N-Allyl-(4-benzyloxyphenyl)acetamido]-N-[(2R)-1-(N-allyl-o-nitrophenylsulfonamido)-5-triisopropylsilyloxypentan-2-yl]-5-triisopropylsilyloxypentanamide (2R,2'R)-20 and (2S,2'R)-21 : Acid 3b (1.35 g, 2.44 mmol) and amine d-4 (1.58 g, 1.3 eq) were coupled as described for the synthesis of 14/15. Purification by flash chromatography using hexane/EtOAc (75/25) furnished two diastereomers (2R,2'R)-20 (0.937 g, 37%) and (2S,2'R)-21 (1.35 g, 53%). First to elute (2R,2'R)-20 : ¹H NMR (CDCl₃) δ identical to (2S,2'S)-18. MS (FAB⁺) m/z 1035 (M + H⁺), 1057 (M + Na⁺); HRMS calcd for C₅₅H₈₇N₄O₉Si₂⁺ (M⁺) 1035.5727, found 1035.5741; Second to elute (2S,2'R)-21 : ¹H NMR (CDCl₃) δ identical to (2R,2'S)-19. MS (FAB⁺) m/z 1035 (M + H⁺), 1057 (M + Na⁺); HRMS calcd for C₅₅H₈₇N₄O₉Si₂⁺ (M⁺) 1035.5732, found 1035.5745.

(2R,5R,6E)-2,5-Bis(3-(triisopropylsilyloxy)propyl)-1-[3-(4-benzyloxyphenyl)propionyl]-7-(o-nitrobenzenesulfonyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5R,6E)-24 and its (2S,5R,6E)-isomer 25: (2R,2'S)-16/17 (2.70 g, 2.57 mmol) was dissolved in DCM (850 ml, 3 mM). Solution was degassed for 5 min by bubbling argon, Grubbs II cat (400 mg, 0.18 eq) was then added. Reaction was stirred for 12 h under reflux. Volatile was removed and products were purified by flash chromatography using hexane/EtOAc (90/10 to 60/40) and furnished two diastereomers (2R,5R,6E)-24 (0.990 g, 38%) and (2S,5R,6E)-25 (0.913 g, 35%). First to elute : (2R,5R,6E)-24 : ¹H NMR (CDCl₃) δ identical to (2S,5S,6E)-22, MS (FAB⁺) m/z 1021 (M⁺), 977 (M⁺ - iPr). Second to elute : (2S,5R,6E)-25 : ¹H NMR (CDCl₃) δ identical to (2R,5S,6E)-23, MS (FAB⁺) m/z 1021 (M⁺), 977 (M⁺ - iPr).

(2S,5S,6E)-2,5-Bis(3-(triisopropylsilyloxy)propyl)-1-(4-benzyloxyphenylacetyl)-7-o-nitrobenzenesulfonyl-1,4,7-triazacycloundec-9-en-3-one (2S,5S,6E)-26 : Protocol similar to 24/25 using (2S,2'S)-18 (1.1 g, 1.06 mmol) which furnished after purification (2S,5S,6E)-26 (740 mg, 69%): ¹H NMR (CDCl₃, 1.5 to 1 mixture of 2 rotamers) δ 7.92 (dd, 1H maj, J = 7.8 Hz, J = 1.5 Hz), 7.83 (dd, 1H min, J = 7.3 Hz, J = 1.9 Hz), 7.74-7.58 (m, 3H), 7.48-7.36 (m, 5H), 7.33 (m, 1H), 7.15 (m, 2H), 6.93 (d, 2H maj, J = 8.5 Hz), 6.23 (d, 1H, J = 6.1 Hz), 5.56 (m, 2H maj + 1H min), 5.39 (m, 1H min), 5.21 (d, 1H min, J = 11.5 Hz), 5.14 (t, 1H maj, J = 7.7 Hz), 5.06 (m, 1H min + 2H maj), 4.69 (d, 1H min, J = 16.8 Hz), 4.33 (d, 1H maj, J = 12.7 Hz), 4.17 (m, 1H min), 4.06 (d, 1H maj, J = 19.3 Hz), 3.93 (d, 1H min, J = 14.2 Hz), 3.80-3.66 (m, 8H), 3.31 (m, 2H), 3.17 (m, 1H), 2.00-1.30 (m, 8H), 1.05 (m, 42H). MS (FAB⁺) m/z 1007 (M⁺), 963 (M⁺ - iPr).

(2R,5S,6E)-2,5-Bis(3-(triisopropylsilyloxy)propyl)-1-(4-benzyloxyphenylacetyl)-7-o-
nitrobenzenesulfonfonyl-1,4,7-triazacycloundec-9-en-3-one (2R,5S,6E)-27 : Protocol similar to 24/25 using (2R,2'S)-19 (1.2 g, 1.16 mmol) which furnished after purification (2R,5S,6E)-27 (755 mg, 65%): \(^1\)H NMR (CDCl₃, 1 to 1 mixture of 2 rotamers) \(\delta\) 7.99-7.92 (m, 1H), 7.69 (m, 2H), 7.61 (m, 1H), 7.44-7.27 (m, 6H), 7.17 (d, 1H, \(J = 8.5\) Hz), 7.06 (d, 1H, \(J = 8.3\) Hz), 6.94 (d, 1H, \(J = 8.8\) Hz), 5.76 (d, 0.5H, \(J = 7.1\) Hz), 5.55 (m, 1H), 5.45 (m, 1H), 5.20 (t, 0.5H, \(J = 7.7\) Hz), 5.07 (m, 2H), 4.63 (d, 0.5H, \(J = 14.4\) Hz), 4.20 (t, 0.5H, \(J = 7.5\) Hz), 4.05 (d, 0.5H, \(J = 17.5\) Hz), 3.86 (d, 1H, \(J = 14.1\) Hz), 3.77 (d, 1H, \(J = 14.6\) Hz), 3.70-3.41 (m, 8H), 3.24 (m, 2H), 1.92-1.74 (m, 2H), 1.50-1.32 (m, 6H), 1.05 (m, 42H). MS (FAB\(^-\)) \(m/z\) 1007 (M\(^+\)), 963 (M\(^+\) - iPr).

(2R,5R,6E)-2,5-Bis[(trisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-o-nitrobenzenesulfonfonyl-1,4,7-triazacycloundec-9-en-3-one (2R,5R,6E)-28 : Protocol similar to 24/25 using (2R,2'R)-20 (0.832 g, 0.80 mmol) which furnished after purification (2R,5R,6E)-28 (0.576 g, 71%): \(^1\)H NMR (CDCl₃) \(\delta\) identical to (2S,5S,6E)-26. MS (FAB\(^-\)) \(m/z\) 1007 (M\(^+\)), 963 (M\(^+\) - iPr).

(2S,5R,6E)-2,5-Bis[(trisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-o-nitrobenzenesulfonfonyl-1,4,7-triazacycloundec-9-en-3-one (2S,5R,6E)-29 : Protocol similar to 24/25 using (2S,2'R)-21 (1.2 g, 1.17 mmol) which furnished after purification (2S,5R,6E)-29 (0.783, 67%): \(^1\)H NMR (CDCl₃) \(\delta\) identical to (2R,5S,6E)-27. MS (FAB\(^-\)) \(m/z\) 1007 (M\(^+\)), 963 (M\(^+\) - iPr).

(2R,5S,6E)-2,5-Bis[(trisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5S,6E)-31 : Protocol similar to the one used for (2S,5S,6E)-30 using (2R,5S,6E)-23 (919 mg, 0.90 mmol) which furnished after purification (2R,5S,6E)-31 (718 mg, 80%): \(^1\)H NMR (CDCl₃) \(\delta\) 7.82 (m, 3H), 7.68 (s, 1H), 7.47-7.28 (m, 8H), 7.15 (m, 2H), 6.89 (m, 2H), 5.31-5.17 (m, 2H), 5.01 (m, 3H), 4.22 (br s, 1H), 3.99 (dd, 1H, \(J = 6.0\) Hz, \(J = 14.6\) Hz), 3.86 (s, 2H), 3.81 (m, 2H), 3.67 (m, 4H), 3.45 (m, 1H), 3.05 (m, 2H), 2.89 (m, 1H), 2.04 (t, 2H, \(J = 7.1\) Hz), 2.38 (dd, 1H, \(J = 7.6\) Hz, \(J = 13.9\) Hz), 1.88 (m, 1H), 1.63 (m, 4H), 1.39 (m, 3H), 1.04 (m, 42H). MS (FAB\(^+\)) \(m/z\) 1004 (M + H\(^+\)), 960 (M\(^+\) - i-Pr); HRMS calec for C₆₀H₉₀N₉O₆Si₂\(^{+}\) (MH\(^+\)) 1004.6349, found 1004.6349.

(2R,5R,6E)-2,5-Bis[(trisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5R,6E)-32 : Protocol similar to the one used for (2S,5S,6E)-30 using (2R,5R,6E)-24 (967 mg, 0.95 mmol) which furnished after purification (2R,5R,6E)-32 (412 mg, 44%): \(^1\)H NMR (CDCl₃) \(\delta\) identical to (2S,5S,6E)-30. MS (FAB\(^-\)) \(m/z\) 1004 (M + H\(^+\)), 960 (M\(^+\) - i-Pr); HRMS calec for C₆₀H₉₀N₉O₆Si₂\(^{+}\) (MH\(^+\)) 1004.6368, found 1004.6362.

(2S,5R,6E)-2,5-Bis[(trisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5R,6E)-33 : Protocol similar to the one used for (2S,5S,6E)-30 using (2S,5R,6E)-25 (838 mg, 0.82 mmol) which furnished after purification (2S,5R,6E)-33 (518 mg, 65%): \(^1\)H NMR (CDCl₃) \(\delta\) identical to (2R,5S,6E)-31. MS (FAB\(^-\)) \(m/z\) 1004 (M + H\(^+\)), 960 (M\(^+\) - i-Pr); HRMS calec for C₆₀H₉₀N₉O₆Si₂\(^{+}\) (MH\(^+\)) 1004.6368, found 1004.6374.

(2S,5S,6E)-2,5-Bis[(trisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5S,6E)-34 : Protocol similar to the one used for (2S,5S,6E)-30 using (2S,5S,6E)-26 (730 mg, 0.72 mmol) which furnished after purification (2S,5S,6E)-34 (451 mg, 63%): \(^1\)H NMR showed a complex mixture of rotamers and/or conformers in CDCl₃. MS (FAB\(^-\)) \(m/z\) 990 (M + H\(^+\)), 946 (M\(^+\) - i-Pr); HRMS calec for C₉₈H₈₈N₉O₆Si₂\(^{+}\) (MH\(^+\))
(2R,5S,6E)-2,5-Bis[3-(trisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5S,6E)-35 : Protocol similar to the one used for (2S,5S,6E)-30 using (2R,5S,6E)-27 (772 mg, 0.77 mmol) which furnished after purification (2R,5S,6E)-35 (505 mg, 66%) : ¹H NMR showed a complex mixture of rotamers and/or conformers in CDCl₃. MS (FAB⁺) m/z 990 (M⁺ + H⁺), 946 (M⁺ – i-Pr); HRMS calcd for C₅₉H₈₈N₃O₆Si₂⁺ (MH⁺) 990.6211, found 990.6205.

(2R,5R,6E)-2,5-Bis[3-(trisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5R,6E)-36 : Protocol similar to the one used for (2S,5S,6E)-30 using (2R,5R,6E)-28 (569 mg, 0.56 mmol) which furnished after purification (2R,5R,6E)-36 (319 mg, 57%) : ¹H NMR (CDCl₃) δ identical to 34. MS (FAB⁺) m/z 990 (M⁺ + H⁺), 946 (M⁺ – i-Pr); HRMS calcd for C₅₉H₈₈N₃O₆Si₂⁺ (MH⁺) 990.6211, found 990.6205.

(2S,5R,6E)-2,5-Bis[3-(trisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5R,6E)-37 : Protocol similar to the one used for (2S,5S,6E)-30 using (2S,5R,6E)-29 (800 mg, 0.79 mmol) which furnished after purification (2S,5R,6E)-37 (535 mg, 68%) : ¹H NMR (CDCl₃) δ identical to 35. MS (FAB⁺) m/z 990 (M⁺ + H⁺), 946 (M⁺ – i-Pr); HRMS calcd for C₅₉H₈₈N₃O₆Si₂⁺ (MH⁺) 990.6211, found 990.6199.

(2R,5S,6E)-2,5-Bis(3-hydroxypropyl)-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5S,6E)-39 : Protocol similar to (2S,5S,6E)-38 using (2R,5S,6E)-31 (728 mg, 0.72 mmol) which furnished after purification (2R,5S,6E)-39 (372 mg, 74%) : ¹H NMR (CDCl₃) δ 7.81 (m, 3H), 7.68 (s, 1H), 7.45-7.28 (m, 8H), 7.14 (m, 2H), 6.90 (m, 2H), 5.81 (d, 1H, J = 9.5 Hz), 5.24 (m, 1H), 5.17 (t, 1H, J = 7.1 Hz), 5.10 (m, 1H), 5.01 (s, 2H), 4.23 (br s, 1H), 3.99 (dd, 1H, J = 6.8 Hz, J = 14.9 Hz), 3.87 (s, 2H), 3.81 (m, 2H), 3.61 (m, 4H), 3.43 (dd, 1H, J = 8.8 Hz, J = 16.6 Hz), 3.17 (dd, 1H, J = 8.0 Hz, J = 13.9 Hz), 3.00 (m, 1H), 2.89 (m, 1H), 2.62 (m, 2H), 2.51 (dd, 1H, J = 7.1 Hz, J = 14.1 Hz), 2.00 (m, 2H), 1.75 (m, 1H), 1.65-1.41 (m, 7H). MS (FAB⁺) m/z 692 (M⁺ + H⁺); HRMS calcd for C₄₂H₅₀N₃O₆ (MH⁺) 692.3700, found 692.3697.

(2R,5R,6E)-2,5-Bis(3-hydroxypropyl)-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5R,6E)-40 : Protocol similar to (2S,5S,6E)-38 using (2R,5R,6E)-32 (382 mg, 0.38 mmol) which furnished after purification (2R,5R,6E)-40 (188 mg, 72%) : ¹H NMR (CDCl₃) δ identical to (2S,5S,6E)-38. MS (FAB⁺) m/z 692 (M⁺ + H⁺); HRMS calcd for C₄₂H₅₀N₃O₆ (MH⁺) 692.3700, found 692.3708.

(2S,5R,6E)-2,5-Bis(3-hydroxypropyl)-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5R,6E)-41 : Protocol similar to (2S,5S,6E)-38 using (2S,5R,6E)-33 (485 mg, 0.48 mmol) which furnished after purification (2S,5R,6E)-41 (240 mg, 72%) : ¹H NMR (CDCl₃) δ identical to (2R,5S,6E)-39. MS (FAB⁺) m/z 692 (M⁺ + H⁺); HRMS calcd for C₄₂H₅₀N₃O₆ (MH⁺) 692.3700, found 692.3697.

(2S,5S,6E)-2,5-Bis(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5S,6E)-42 : Protocol similar to (2S,5S,6E)-38 using (2S,5S,6E)-34 (451 mg, 0.45 mmol) which furnished after purification (2S,5S,6E)-42 (182 mg, 59%) : ¹H NMR showed a complex mixture of rotamers and/or conformers in CDCl₃ at 20°C or 40°C or in DMSO at 20°C or 60°C. Purity was verified by RP-HPLC on 4.6 x 250 mm COSMOSIL 5C₁₈-AR-II column at 1 ml/min in water/acetonitrile both containing 0.1%TFA [90/10
(2R,5S,6E)-2,5-Bis-(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5S,6E)-43: Protocol similar to (2S,5S,6E)-38 using (2R,5S,6E)-35 (505 mg, 0.51 mmol) which furnished after purification (2R,5S,6E)-43 (340 mg, 98%): 1H NMR showed a complex mixture of rotamers and/or conformers in CDCl3 (at 20°C or 40°C) or in DMSO (at 20°C or 60°C). Purity was verify by RP-HPLC on the same way as 42, rt = 16.18, purity up to 96%. MS (FAB+) m/z 678 (M + H+); HRMS caled for C41H48N3O6+ (MH+) 678.3543, found 678.3554.

(2R,5R,6E)-2,5-Bis-(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5R,6E)-44: Protocol similar to (2S,5S,6E)-38 using (2R,5R,6E)-36 (315 mg, 0.32 mmol) which furnished after purification (2R,5R,6E)-44 (194 mg, 90%): 1H NMR identical to 42. Purity was verify by RP-HPLC on the same way as 42, rt = 16.13, purity up to 95%. MS (FAB+) m/z 678 (M + H+); HRMS caled for C41H48N3O6+ (MH+) 678.3543, found 678.3541.

(2S,5R,6E)-2,5-Bis-(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5R,6E)-45: Protocol similar to (2S,5S,6E)-38 using (2S,5R,6E)-37 (315 mg, 0.32 mmol) which furnished after purification (2S,5R,6E)-45 (286 mg, 78%): 1H NMR identical to 43. Purity was verify by RP-HPLC on the same way as 42, rt = 16.13, purity up to 98%. MS (FAB+) m/z 678 (M + H+); HRMS caled for C41H48N3O6+ (MH+) 678.3543, found 678.3551.

(2R,5S,6E)-2,5-Bis-(3-guanidinopropyl)-1-[3-(4-hydroxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5S,6E)-55: Protocol similar to (2S,5S,6E)-54 using (2R,5S,6E)-39 (150 mg, 0.22 mmol) which furnished protected bis-guanidine 47 (approx 90 mg) as a mixture with Ph3PO and after deprotection and purification (2R,5S,6E)-55 (28 mg, 19%). MS (FAB+) m/z 684 (M + H+); HRMS caled for C37H50N5O4+ (MH+) 684.3986, found 684.3992. [α]D 23° +71 (c=0.1, AcOH)

(2R,5R,6E)-2,5-Bis-(3-guanidinopropyl)-1-[3-(4-hydroxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5R,6E)-56: Protocol similar to (2S,5S,6E)-54 using (2R,5R,6E)-40 (112 mg, 0.16 mmol) which furnished protected bis-guanidine 48 (approx 55 mg) as a mixture with Ph3PO and after deprotection and purification (2R,5R,6E)-56 (29 mg, 26%). MS (FAB+) m/z 684 (M + H+); HRMS caled for C37H50N5O4+ (MH+) 684.3986, found 684.3993. [α]D 24° +49 (c=0.1, AcOH)

(2S,5S,6E)-2,5-Bis-(3-guanidinopropyl)-1-(N-(3-(4-(hydroxy)phenyl)propionyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5S,6E)-57: Protocol similar to (2S,5S,6E)-54 using (2S,5R,6E)-41 (150 mg, 0.22 mmol) which furnished protected bis-guanidine 49 (approx 25 mg) as a mixture with Ph3PO and starting material which was resubmitted to give 49 (approx 47 mg) as a mixture with Ph3PO. After deprotection and purification (2S,5R,6E)-57 (14 mg, 10%) and a less pure fraction of 57 (12 mg, purity = 70%) were obtained. MS (FAB+) m/z 684 (M + H+); HRMS caled for C37H50N5O4+ (MH+) 684.3986, found 684.3973. [α]D 21° +67 (c=0.05, AcOH)

(2S,5S,6E)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5S,6E)-58: Protocol similar to (2S,5S,6E)-54 using
(2S,5S,6E)-42 (150 mg, 0.22 mmol) in THF/toluene/DMF solution (6/1/1 : 4 ml) which furnished protected bis-guanidine 50 (approx 108 mg) as a mixture with Ph3PO. After deprotection and purification (2S,5S,6E)-58 (59 mg, 40%) was obtained. MS (FAB+) m/z 670 (M + H+) HRMS calcd for C36H48N9O4+ (MH+) 670.3829, found 670.3822. [α]24D −31 (c=0.1, AcOH)

(2R,5S,6E)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5S,6E)-59 : Protocol similar to (2S,5S,6E)-54 using (2R,5S,6E)-43 (150 mg, 0.22 mmol) which furnished protected bis-guanidine 51 (approx 70 mg) as a mixture with Ph3PO. After deprotection and purification (2R,5S,6E)-59 (28.5 mg, 19%) was obtained. MS (FAB+) m/z 670 (M + H+); HRMS calcd for C36H48N9O4+ (MH+) 670.3829, found 670.3821. [α]25D −39 (c=0.1, AcOH)

(2R,5R,6E)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2R,5R,6E)-60 : Protocol similar to (2S,5S,6E)-54 using (2R,5R,6E)-44 (150 mg, 0.22 mmol) in THF/toluene/DMF solution (6/1/1 : 4 ml) which furnished protected bis-guanidine 52 (approx 106 mg) as a mixture with Ph3PO. After deprotection and purification (2R,5R,6E)-60 (40.5 mg, 27%) was obtained. MS (FAB+) m/z 670 (M + H+); HRMS calcd for C36H48N9O4+ (MH+) 670.3829, found 670.3820. [α]25D +32 (c=0.1, AcOH)

(2S,5R,6E)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2S,5R,6E)-61 : Protocol similar to (2S,5S,6E)-54 using (2S,5R,6E)-45 (150 mg, 0.22 mmol) which furnished protected bis-guanidine 53 (approx 40 mg) as a mixture with Ph3PO. After deprotection and purification (2S,5R,6E)-61 (22 mg, 15%) was obtained. MS (FAB+) m/z 670 (M + H+); HRMS calcd for C36H48N9O4+ (MH+) 670.3829, found 670.3835. [α]23D +39 (c=0.1, AcOH)