Supplementary material

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

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Expetimental 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 ($CDCl_3$) δ identical to L-**7**. $[\alpha]_D^{22}$ +4.4 (c=1.0, $CHCl_3$), MS (FAB^+) *m/z* 376 ($M + H^+$), 398 ($M + Na^+$); HRMS calcd for $C_{19}H_{42}NO_4Si^+$ (MH^+) 376.2883, found 376.2886.

(*R*)-N^1-Allyl-N^2-Boc-N^1-(*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 $C_{28}H_{49}N_3O_7SSi^+$ (M^+) 599.3060, found 599.3065. $[\alpha]_D^{20}$ +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). Et_3N (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 $MgSO_4$ 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 ($CDCl_3$) δ 7.44-7.28 (m, 5H), 7.15 (m, 2H), 6.92 (m, 2H), 5.78 (ddt, 1H, J_{d1} = 17.6 Hz, J_{d2} = 12.2 Hz, J_t = 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). ^{13}C ($CDCl_3$) δ 172.1, 171.9, 157.7, 137.0, 134.3, 129..9, 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 $C_{33}H_{50}NO_5Si^+$ (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/H_2O/MeOH (3/1/1, 75 ml), cooled down to 0°C and treated with $LiOH·H_2O$ (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 $MgSO_4$ and concentrated. Oil was purified by flash chromatography using hexane/EtOAc (90/10 to 60/40) to furnish **3b** (2.83 g, 68%). ^{1}H NMR ($CDCl_3$) δ 7.44-7.29 (m, 5H), 7.14 (m, 2H), 6.92 (m, 2H), 5.76 (ddt, 1H, J_{d1} = 17.8 Hz, J_{d2} = 12.2 Hz, J_t = 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 $C_{32}H_{48}NO_5Si^+$ (MH^+) 554.3296, found 554.3304.

(2*RS*)-2-[*N*-Allyl-3-(4-benzyloxyphenyl)propanamido]-*N*-[(2*R*)-1-(*N*-allyl-*o*-nitrophenylsulfonamido)-5-triisopropylsilyloxypentan-2-yl]-5-triisopropylsilyloxypentanamide (2*RS*,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 $C_{56}H_{89}N_4O_9SSi_2^+$ (MH^+) 1049.5889, found 1049.5894.

(2*R*)- and (2*S*)-2-[*N*-Allyl-(4-benzyloxyphenyl)acetamido]-*N*-[(2*R*)-1-(*N*-allyl-*o*-nitrophenylsulfonamido)-5-triisopropylsilyloxypentan-2-yl]-5-triisopropylsilyloxypentanamide (2*R*,2'*R*)-20 and (2*S*,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 (2*R*,2'*R*)-**20** (0,937 g, 37%) and (2*S*,2'*R*)-**21** (1.35 g, 53%). First to elute (2*R*,2'*R*)-**20** : ^{1}H NMR ($CDCl_3$) δ identical to (2*S*,2'*S*)-**18**. MS (FAB$^+$) *m*/*z* 1035 (M + H$^+$), 1057 (M + Na$^+$); HRMS calcd for $C_{55}H_{87}N_4O_9Si_2S^+$ (MH^+) 1035.5727, found 1035.5741; Second to elute (2*S*,2'*R*)-**21** : ^{1}H NMR ($CDCl_3$) δ identical to (2*R*,2'*S*)-**19**. MS (FAB+) *m*/*z* 1035 (M + H$^+$), 1057 (M + Na$^+$); HRMS calcd for $C_{55}H_{87}N_4O_9SSi_2^+$ (MH^+) 1035.5732, found 1035.5745.

(2*R*,5*R*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(*o*-nitrobenzenesulfonyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-24 and its (2*S*,5*R*,6*E*)-isomer 25: (2*RS*,2'*R*)-**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 (2*R*,5*R*,6*E*)-**24** (0.990 g, 38%) and (2*S*,5*R*,6*E*)-**25** (0.913 g, 35%). First to elute : (2*R*,5*R*,6*E*)-**24** : ^{1}H NMR ($CDCl_3$) δ identical to (2*S*,5*S*,6*E*)-**22**, MS (FAB$^+$) *m*/*z* 1021 (M$^+$), 977 (M$^+$ - *i*Pr). Second to elute : (2*S*,5*R*,6*E*)-**25** : ^{1}H NMR ($CDCl_3$) δ identical to (2*R*,5*S*,6*E*)-**23**, MS (FAB$^+$) *m*/*z* 1021 (M$^+$), 977 (M$^+$ - *i*Pr).

(2*S*,5*S*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-*o*-nitrobenzenesulfonyl-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*S*,6*E*)-26 : Protocol similar to **24**/**25** using (2*S*,2'*S*)-**18** (1.1 g, 1.06 mmol) which furnished after purification (2*S*,5*S*,6*E*)-**26** (740 mg, 69%) : ^{1}H NMR ($CDCl_3$, 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$^+$ - *i*Pr).

(2*R*,5*S*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-*o*-

nitrobenzenesulfonyl-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*S*,6*E*)-27 : Protocol similar to **24**/**25** using (2*R*,2'*S*)-**19** (1.2 g, 1.16 mmol) which furnished after purification (2*R*,5*S*,6*E*)-**27** (755 mg, 65%): ^{1}H NMR ($CDCl_3$, 1 to 1 mixture of 2 rotamers) δ 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^+ - *i*Pr).

(2*R*,5*R*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-*o*-nitrobenzenesulfonyl-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-28 : Protocol similar to **24**/**25** using (2*R*,2'*R*)-**20** (0.832 g, 0.80 mmol) which furnished after purification (2*R*,5*R*,6*E*)-**28** (0.576 g, 71%): ^{1}H NMR ($CDCl_3$) δ identical to (2*S*,5*S*,6*E*)-**26**. MS (FAB$^+$) *m*/*z* 1007 (M^+), 963 (M^+ - *i*Pr).

(2*S*,5*R*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-*o*-nitrobenzenesulfonyl-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*R*,6*E*)-29 : Protocol similar to **24**/**25** using (2*S*,2'*R*)-**21** (1.2 g, 1.17 mmol) which furnished after purification (2*S*,5*R*,6*E*)-**29** (0.783, 67%): ^{1}H NMR ($CDCl_3$) δ identical to (2*R*,5*S*,6*E*)-**27**. MS (FAB$^+$) *m*/*z* 1007 (M^+), 963 (M^+ - *i*Pr).

(2*R*,5*S*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*S*,6*E*)-31 : Protocol similar to the one used for (2*S*,5*S*,6*E*)-**30** using (2*R*,5*S*,6*E*)-**23** (919 mg, 0.90 mmol) which furnished after purification (2*R*,5*S*,6*E*)-**31** (718 mg, 80%) : ^{1}H NMR ($CDCl_3$) δ 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 calcd for $C_{60}H_{90}N_3O_6Si_2^+$ (MH^+) 1004.6368, found 1004.6349.

(2*R*,5*R*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-32 : Protocol similar to the one used for (2*S*,5*S*,6*E*)-**30** using (2*R*,5*R*,6*E*)-**24** (967 mg, 0.95 mmol) which furnished after purification (2*R*,5*R*,6*E*)-**32** (412 mg, 44%) : ^{1}H NMR ($CDCl_3$) δ identical to (2*S*,5*S*,6*E*)-**30**. MS (FAB$^+$) *m*/*z* 1004 (M + H$^+$), 960 (M^+ – *i*-Pr); HRMS calcd for $C_{60}H_{90}N_3O_6Si_2^+$ (MH^+) 1004.6368, found 1004.6362.

(2*S*,5*R*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*R*,6*E*)-33 : Protocol similar to the one used for (2*S*,5*S*,6*E*)-**30** using (2*S*,5*R*,6*E*)-**25** (838 mg, 0.82 mmol) which furnished after purification (2*S*,5*R*,6*E*)-**33** (518 mg, 65%) : ^{1}H NMR ($CDCl_3$) δ identical to (2*R*,5*S*,6*E*)-**31**. MS (FAB$^+$) *m*/*z* 1004 (M + H$^+$), 960 (M^+ – *i*-Pr); HRMS calcd for $C_{60}H_{90}N_3O_6Si_2^+$ (MH^+) 1004.6368, found 1004.6374.

(2*S*,5*S*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*S*,6*E*)-34 : Protocol similar to the one used for (2*S*,5*S*,6*E*)-**30** using (2*S*,5*S*,6*E*)-**26** (730 mg, 0.72 mmol) which furnished after purification (2*S*,5*S*,6*E*)-**34** (451 mg, 63%) : ^{1}H NMR showed a complex mixture of rotamers and/or conformers in $CDCl_3$. MS (FAB$^+$) *m*/*z* 990 (M + H$^+$), 946 (M^+ – *i*-Pr); HRMS calcd for $C_{59}H_{88}N_3O_6Si_2^+$ (MH^+)

990.6211, found 990.6222.

(2*R*,5*S*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*S*,6*E*)-35 : Protocol similar to the one used for (2*S*,5*S*,6*E*)-**30** using (2*R*,5*S*,6*E*)-**27** (772 mg, 0.77 mmol) which furnished after purification (2*R*,5*S*,6*E*)-**35** (505 mg, 66%) : ^{1}H NMR showed a complex mixture of rotamers and/or conformers in $CDCl_3$. MS (FAB^+) *m*/*z* 990 ($M + H^+$), 946 ($M^+ - i$-Pr); HRMS calcd for $C_{59}H_{88}N_3O_6Si_2^+$ (MH^+) 990.6211, found 990.6217.

(2*R*,5*R*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-36 : Protocol similar to the one used for (2*S*,5*S*,6*E*)-**30** using (2*R*,5*R*,6*E*)-**28** (569 mg, 0.56 mmol) which furnished after purification (2*R*,5*R*,6*E*)-**36** (319 mg, 57%) : ^{1}H NMR ($CDCl_3$) δ identical to **34**. MS (FAB^+) *m*/*z* 990 ($M + H^+$), 946 ($M^+ - i$-Pr); HRMS calcd for $C_{59}H_{88}N_3O_6Si_2^+$ (MH^+) 990.6211, found 990.6205.

(2*S*,5*R*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*R*,6*E*)-37 : Protocol similar to the one used for (2*S*,5*S*,6*E*)-**30** using (2*S*,5*R*,6*E*)-**29** (800 mg, 0.79 mmol) which furnished after purification (2*S*,5*R*,6*E*)-**37** (535 mg, 68%) : ^{1}H NMR ($CDCl_3$) δ identical to **35**. MS (FAB^+) *m*/*z* 990 ($M + H^+$), 946 ($M^+ - i$-Pr); HRMS calcd for $C_{59}H_{88}N_3O_6Si_2^+$ (MH^+) 990.6211, found 990.6199.

(2*R*,5*S*,6*E*)-2,5-Bis(3-hydroxypropyl)-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*S*,6*E*)-39 : Protocol similar to (2*S*,5*S*,6*E*)-**38** using (2*R*,5*S*,6*E*)-**31** (728 mg, 0.72 mmol) which furnished after purification (2*R*,5*S*,6*E*)-**39** (372 mg, 74%) : ^{1}H NMR ($CDCl_3$) 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 $C_{42}H_{50}N_3O_6^+$ (MH^+) 692.3700, found 692.3697.

(2*R*,5*R*,6*E*)-2,5-Bis(3-hydroxypropyl)-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-40 : Protocol similar to (2*S*,5*S*,6*E*)-**38** using (2*R*,5*R*,6*E*)-**32** (382 mg, 0.38 mmol) which furnished after purification (2*R*,5*R*,6*E*)-**40** (188 mg, 72%) : ^{1}H NMR ($CDCl_3$) δ identical to (2*S*,5*S*,6*E*)-**38**. MS (FAB^+) *m*/*z* 692 ($M + H^+$); HRMS calcd for $C_{42}H_{50}N_3O_6^+$ (MH^+) 692.3700, found 692.3708.

(2*S*,5*R*,6*E*)-2,5-Bis(3-hydroxypropyl)-1-[3-(4-benzyloxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*R*,6*E*)-41 : Protocol similar to (2*S*,5*S*,6*E*)-**38** using (2*S*,5*R*,6*E*)-**33** (485 mg, 0.48 mmol) which furnished after purification (2*S*,5*R*,6*E*)-**41** (240 mg, 72%) : ^{1}H NMR ($CDCl_3$) δ identical to (2*R*,5*S*,6*E*)-**39**. MS (FAB^+) *m*/*z* 692 ($M + H^+$); HRMS calcd for $C_{42}H_{50}N_3O_6^+$ (MH^+) 692.3700, found 692.3697.

(2*S*,5*S*,6*E*)-2,5-Bis(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*S*,6*E*)-42 : Protocol similar to (2*S*,5*S*,6*E*)-**38** using (2*S*,5*S*,6*E*)-**34** (451 mg, 0.45 mmol) which furnished after purification (2*S*,5*S*,6*E*)-**42** (182 mg, 59%) : ^{1}H NMR showed a complex mixture of rotamers and/or conformers in $CDCl_3$ (at 20°C or 40°C) or in DMSO (at 20°C or 60°C). Purity was verify by RP-HPLC on 4.6 x 250 mm COSMOSIL 5C_{18}-AR-II column at 1 ml/min in water/acetonitrile both containing 0.1%TFA [90/10

(0 min), 40/60 (10 min), 10/90 (30 min), 5/95 (35 min)], rt = 16.13, purity up to 91%. MS (FAB^+) *m*/*z* 678 ($M + H^+$); HRMS calcd for $C_{41}H_{48}N_3O_6^+$ (MH^+) 678.3543, found 678.3554.

(2*R*,5*S*,6*E*)-2,5-Bis-(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*S*,6*E*)-43 : Protocol similar to (2*S*,5*S*,6*E*)-**38** using (2*R*,5*S*,6*E*)-**35** (505 mg, 0.51 mmol) which furnished after purification (2*R*,5*S*,6*E*)-**43** (340 mg, 98%) : ^1H NMR showed a complex mixture of rotamers and/or conformers in $CDCl_3$ (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 calcd for $C_{41}H_{48}N_3O_6^+$ (MH^+) 678.3543, found 678.3544.

(2*R*,5*R*,6*E*)-2,5-Bis-(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-44 : Protocol similar to (2*S*,5*S*,6*E*)-**38** using (2*R*,5*R*,6*E*)-**36** (315 mg, 0.32 mmol) which furnished after purification (2*R*,5*R*,6*E*)-**44** (194 mg, 90%) : ^1H NMR identical to **42**. Purity was verify by RP-HPLC on the same way as **42**, rt = 16.17, purity up to 95%. MS (FAB^+) *m*/*z* 678 ($M + H^+$); HRMS calcd for $C_{41}H_{48}N_3O_6^+$ (MH^+) 678.3543, found 678.3541.

(2*S*,5*R*,6*E*)-2,5-Bis-(3-hydroxypropyl)-1-(4-benzyloxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*R*,6*E*)-45 : Protocol similar to (2*S*,5*S*,6*E*)-**38** using (2*S*,5*R*,6*E*)-**37** (315 mg, 0.32 mmol) which furnished after purification (2*S*,5*R*,6*E*)-**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 calcd for $C_{41}H_{48}N_3O_6^+$ (MH^+) 678.3543, found 678.3551.

(2*R*,5*S*,6*E*)-2,5-Bis(3-guanidinopropyl)-1-[3-(4-hydroxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*S*,6*E*)-55 : Protocol similar to (2*S*,5*S*,6*E*)-**54** using (2*R*,5*S*,6*E*)-**39** (150 mg, 0.22 mmol) which furnished protected bis-guanidine **47** (approx 90 mg) as a mixture with Ph_3PO and after deprotection and purification (2*R*,5*S*,6*E*)-**55** (28 mg, 19%). MS (FAB^+) *m*/*z* 684 ($M + H^+$); HRMS calcd for $C_{37}H_{50}N_9O_4^+$ (MH^+) 684.3986, found 684.3992. $[\alpha]_D^{23}$ −71 (c=0.1, AcOH)

(2*R*,5*R*,6*E*)-2,5-Bis(3-guanidinopropyl)-1-[3-(4-hydroxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-56 : Protocol similar to (2*S*,5*S*,6*E*)-**54** using (2*R*,5*R*,6*E*)-**40** (112 mg, 0.16 mmol) which furnished protected bis-guanidine **48** (approx 55 mg) as a mixture with Ph_3PO and after deprotection and purification (2*R*,5*R*,6*E*)-**56** (29 mg, 26%). MS (FAB^+) *m*/*z* 684 ($M + H^+$); HRMS calcd for $C_{37}H_{50}N_9O_4^+$ (MH^+) 684.3986, found 684.3993. $[\alpha]_D^{24}$ +49 (c=0.1, AcOH)

(2*S*,5*R*,6*E*)-2,5-Bis-(3-guanidinopropyl)-1-(*N*-(3-(4-(hydroxy)phenyl)propionyl)-7-(*N*-(2-naphthylacetyl))-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*R*,6*E*)-57 : Protocol similar to (2*S*,5*S*,6*E*)-**54** using (2*S*,5*R*,6*E*)-**41** (150 mg, 0.22 mmol) which furnished protected bis-guanidine **49** (approx 25 mg) as a mixture with Ph_3PO and starting material which was resubmitted to give **49** (approx 47 mg) as a mixture with Ph_3PO. After deprotection and purification (2*S*,5*R*,6*E*)-**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 calcd for $C_{37}H_{50}N_9O_4^+$ (MH^+) 684.3986, found 684.3973. $[\alpha]_D^{21}$ +67 (c=0.05, AcOH)

(2*S*,5*S*,6*E*)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*S*,6*E*)-58 : Protocol similar to (2*S*,5*S*,6*E*)-**54** using

(2*S*,5*S*,6*E*)-**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 Ph_3PO. After deprotection and purification (2*S*,5*S*,6*E*)-**58** (59 mg, 40%) was obtained. MS (FAB^+) *m*/*z* 670 ($M + H^+$); HRMS calcd for $C_{36}H_{48}N_9O_4^+$ (MH^+) 670.3829, found 670.3822. $[\alpha]_D^{24}$ −31 (c=0.1, AcOH)

(2*R*,5*S*,6*E*)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*S*,6*E*)-59 : Protocol similar to (2*S*,5*S*,6*E*)-**54** using (2*R*,5*S*,6*E*)-**43** (150 mg, 0.22 mmol) which furnished protected bis-guanidine **51** (approx 70 mg) as a mixture with Ph_3PO. After deprotection and purification (2*R*,5*S*,6*E*)-**59** (28.5 mg, 19%) was obtained. MS (FAB^+) *m*/*z* 670 ($M + H^+$); HRMS calcd for $C_{36}H_{48}N_9O_4^+$ (MH^+) 670.3829, found 670.3821. $[\alpha]_D^{25}$ −39 (c=0.1, AcOH)

(2*R*,5*R*,6*E*)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*R*,5*R*,6*E*)-60 : Protocol similar to (2*S*,5*S*,6*E*)-**54** using (2*R*,5*R*,6*E*)-**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 Ph_3PO. After deprotection and purification (2*R*,5*R*,6*E*)-**60** (40.5 mg, 27%) was obtained. MS (FAB^+) *m*/*z* 670 ($M + H^+$); HRMS calcd for $C_{36}H_{48}N_9O_4^+$ (MH^+) 670.3829, found 670.3820. $[\alpha]_D^{25}$ +32 (c=0.1, AcOH)

(2*S*,5*R*,6*E*)-2,5-Bis(3-guanidinopropyl)-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (2*S*,5*R*,6*E*)-61 : Protocol similar to (2*S*,5*S*,6*E*)-**54** using (2*S*,5*R*,6*E*)-**45** (150 mg, 0.22 mmol) which furnished protected bis-guanidine **53** (approx 40 mg) as a mixture with Ph_3PO. After deprotection and purification (2*S*,5*R*,6*E*)-**61** (22 mg, 15%) was obtained. MS (FAB^+) *m*/*z* 670 ($M + H^+$); HRMS calcd for $C_{36}H_{48}N_9O_4^+$ (MH^+) 670.3829, found 670.3835. $[\alpha]_D^{23}$ +39 (c=0.1, AcOH)