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Synthesis of Derivatives of FK 506 and FR 900520: Modifications at the Binding Domain

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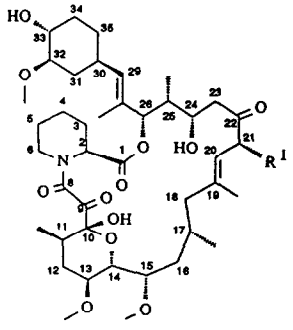
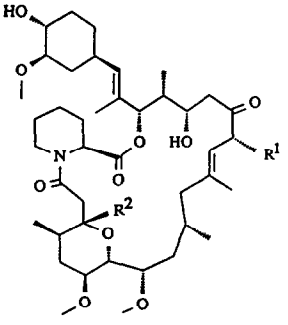
Abstract: The synthesis of 9-deoxo-FK 506 (13a), 9-deoxo-FR 900520 (13b), 9-deoxo-10(R)-deoxy-FR 900520 (14) and its 10(S) isomer 15 is described. Radical deoxygenation/elemination of the 9-dihydro-9,10-thiocarbonates 5a,5b,6a and 6b gave the 9,10 unsaturated compounds 7a (7b) or 8a (8b) which were further transferred by hydration or hydrogenation. Different E/Z ratios of 7a (7b) were obtainted when nBu_3SnH or $[(CH_3)_3Si]_3SiH$ in combination with AIBN or Et_3B were used, allowing the selective preparation of both isomers. Two possible reaction mechanisms are discussed.

FK 506 (1a) and its 21-ethyl analog FR 900520 (also known as *ascomycin*[1]) (1b) are potent immunosuppressive agents which act as inhibitors of signal transduction pathways that lead to T lymphocyte activation. Both compounds bind with high affinity to a specific cytoplasmic protein FKBP[2]. Schreiber et al.[3] suggest in a recent paper, that the target for the complex between FKBP and FK 506 is calcineurin, a serine/threonine phosphatase and that binding to it affects T-cell receptor and IgE receptor signaling in mast cells. NMR[4] and X-ray[5] studies of the FK 506-FKBP complex show that the left half (binding domain) of the FK 506 molecule is bound to FKBP, whereas the right half sticks out of the protein and can act as effector element. The characteristic difference between bound and unbound FK 506 is a *cis* amide bond in unbound FK 506 while in the complex the bond is *trans*[6] due to a hydrogen bond between the oxygen at C(8) and Tyr(82)-OH of FKBP.



1a : FK 506, R^1 = allyl
1b : FR 900520, R^1 = Et



13a : R^1 = allyl, R^2 = OH
13b : R^1 = Et, R^2 = OH
14 : R^1 = Et, R^2 = H

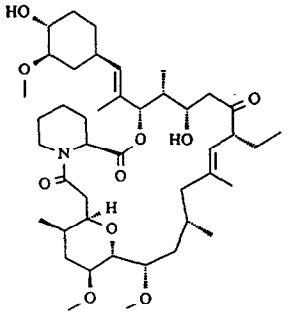


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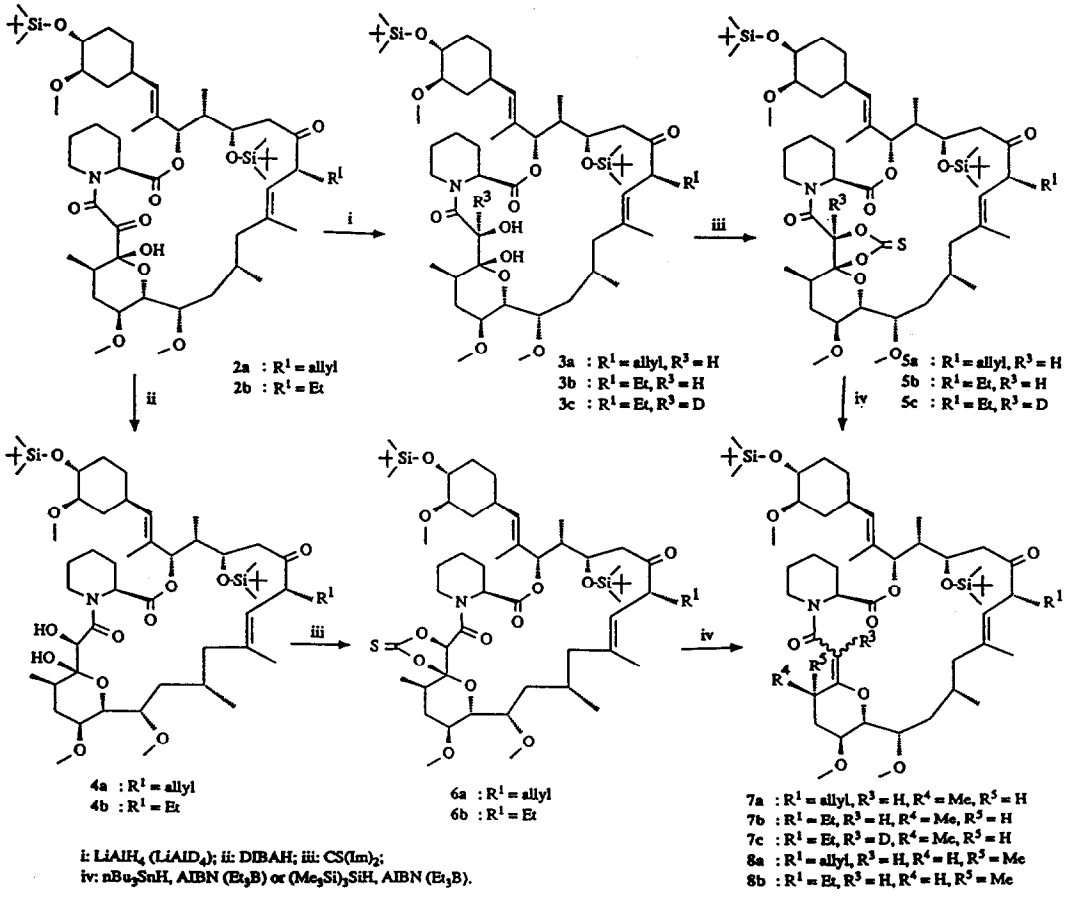
Figure 1.

With respect to the tricarbonyl system a further hydrogen bond is observed between the C(10) hemiketal hydroxyl and Asp(37)CO_2^- whereas the orthogonality of the adjacent carbonyls at C(8) and C(9) in FK 506 is maintained in the complex. Although there are no hydrogen bonds to the C(9) keto oxygen, there are three ϵ-hydrogens from the aromatic residues Tyr(26), Phe(36) and Phe(99) in contact with this atom, responsible for an aromatic C-H-O stabilizing interaction.

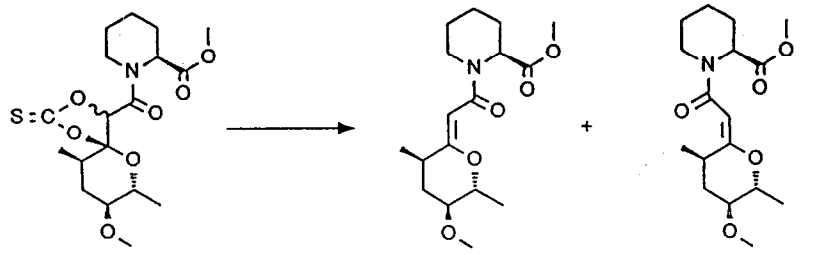
In the course of our derivation program on FK 506 and FR 900520 we became interested in the influence of chemical modifications of the region C(9)-C(11) on the binding of FKBP and the immunosuppressive activity (Figure 1).

As shown in Scheme 1,the treatment of the 24,33-bis-t.-butyl-dimethylsilyl (tBDMS) ether of FK 506 (2a) and FR 900520 (2b) with lithium aluminum hydride afforded the 9(S)-dihydroderivates 3a and 3b whereas with diisobutylaluminum hydride (DIBAH) the corresponding 9(R)-dihydroderivates 4a and 4b were obtained. The two isomeric 9-dihydroderivatives could efficiently be transformed with 1,1'-thiocarbonyl-diimidazole into the 9,10-thiocarbonates 5a (5b) and 6a (6b). The configuration at C(9) of the thiocarbonates and thereby of the precursor alcohols was determined by NMR measurements. In 6a, 6b a NOE is observed from H-9 to H-11 and to the hydrogens of the methyl group. Reaction of the 9,10-thiocarbonates with tributyltin hydride or tris(trimethylsilyl)silane[7] in combination with a radical starter generated the 9,10 unsaturated compounds 7a or 7b as mixtures of E and Z-isomers, separable be column chromatography. Assignment of geometry was done by NOE experiments. A NOE of the methyl group at C(11) to H-9 could be measured only for the Z-isomer.



Scheme 1.

Table 1. Radical Deoxygenation-Elimination of 9-(H_2)-Thiocarbonates 5a, 5b, 6a, 6b



5a, 5b 9(S)
6a, 6b 9(R)

E + Z

7a, 7b

		E/Z Ratio[a] of Products 7a,7b (total yield[b] in parenthesis)			
Method	Conditions[c]	Substrate 5a	5b	6a	6b
A	nBu_3SnH, AIBN, reflux	2:1 (78%)	1:1 (83%)	1:1 (92%)	1:1.2 (86%)
B	nBu_3SnH, Et_3B, RT	10:1 (55%)	5:1 (47%)	10:1 (34%)	10:1 (53%)
C	$(Me_3Si)_3SiH$, AIBN, 80°C[d]		1:1.4 (93%)		1:10 (73%)
D	$(Me_3Si)_3SiH$, Et_3B, RT	3:2 (6%[e])	1:2.5 (44%)		1:2.4 (64%)
G	nBu_3SnH, Et_3B, 80°C		2.6:1 (72%)		3:2 (61%)
H	$(Me_3Si)_3SiH$, Et_3B, 80°C		1:1.5 (59%)		1:5 (71%)

[a] determined by integration of characteristic ^{1}H-NMR signals [b] yield of isolated products after chromatography [c] all reactions were run in toluene [d] with 5a as substrate 38% of 10 were obtained [e] +54% of 10

As shown in Table 1 the E/Z ratio of 7a (7b) strongly depended on the reagents and conditions used, allowing selective preparation of each isomer (compare *method B* and *C*). The configuration at C(9) of the starting thiocarbonate did not play a significant role for the E/Z ratio of 7a or 7b when tributyltin hydride was used, irrespective of whether AIBN or triethylborane[8] served as radical starter. However, the E/Z ratio of 7b differs significantly in the reaction of the two isomeric thiocarbonates 5b and 6b with tris(trimethylsilyl)silane when AIBN was used as radical starter, but not, when tris(trimethylsilyl)silane was used together with triethylborane.

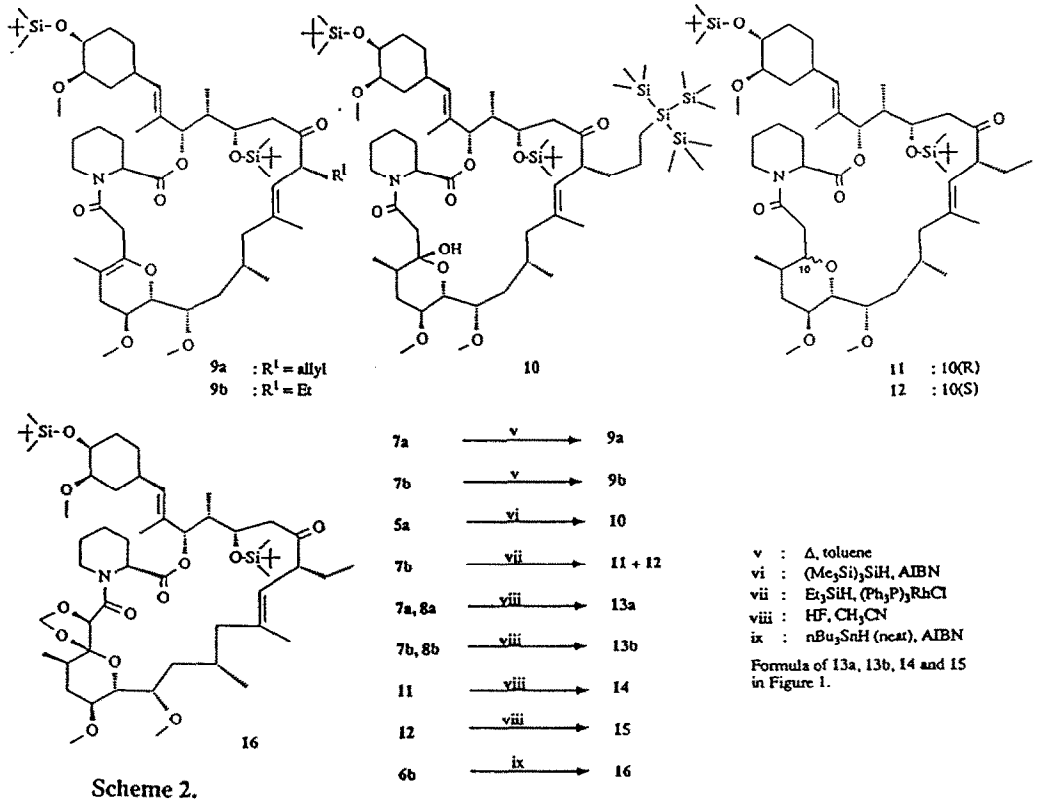
In FK 506 derivative 5a, the exocyclic double bond was affected to a high degree by radical addition of the reagent leading to 10, when tris(trimethylsilyl)silane was used in combination with AIBN or triethylborane.

A dependence of the E/Z ratio on the reaction temperature applied in the triethylborane initiated reactions (*method B, D* versus *method G, H*) is observed with a tendency toward the values for the ratio E/Z in *method A, C*.

Prolonged heating of 6a or 6b with tributyltin hydride/ AIBN in toluene under reflux resulted, beside the formation of the 9,10 double bond, in a partial epimeriation at C(11) (compound 8a or 8b) (Scheme 1). Treatment of 7b with tributyltin hydride/ AIBN in refluxing toluene for 15 hours gave a mixture of 11-epi compound 8b (45% yield) and starting material 7b, whereas refluxing of 7a or 7b in toluene without reagents only resulted in a double bond shift from C(9)-C(10) to C(10)-C(11) (compound 9a in 90% yield or compound 9b in 66% yield) (Scheme 2). This hydrogen shift could be performed with both isomers separately or with a mixture of both. The rate for the hydrogen shift was dependent on the geometry of the starting material and was about twice for the E-isomer than for the corresponding Z-isomer.

Reduction of the 9,10 double bond of 7b with triethylsilane/ Wilkinson catalyst[9] resulted in two iso-

meric compounds 11 and 12. The ratio of the two products depended on the geometry of the starting material. The hydrogenation of the 9,10 double bond of the E-isomer of 7b under the conditions described above gave a 20/1 mixture of 11/12, whereas from the Z-isomer of 7b a 1/6.5 mixture of 11/12 was obtained. The configuration at C(10) of the two products was determined by COSY measurements. The hydrogen at C(10) of the 10(R) isomer 11 is in axial position, representing formal substitution of -OH by -H, keeping the shape of the original carbon backbone intact, which is not the case for the 10(S) isomer 12 (Scheme 2).

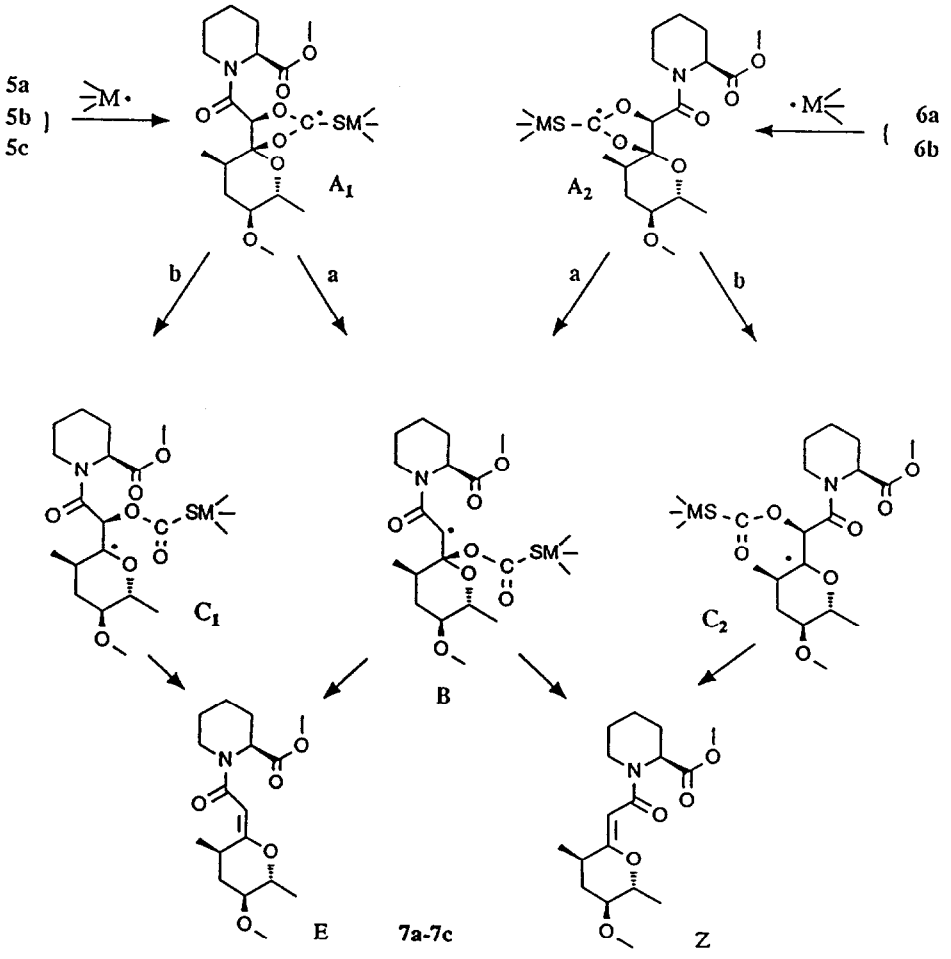


Scheme 2.

Deprotection of 7a (7b) with HF in acetonitrile proceeded with simultaneous addition of water to the 9,10 double bond leading to 9-deoxo-derivative 13a (13b). When 8a or 8b were treated with HF, besides deprotection and hydration, a complete isomerization at C(11) surprisingly occurred resulting in 13a (13b). Concomitant hydration was also found when the same reaction conditions were applied for deprotection of 9a (9b) leading to 13a (13b). Finally, deprotection of 11 and 12 gave the bis-deoxygenated compounds 14 and 15 (Figure 3).

As already mentioned, an unexpected pattern of E/Z ratios of compound 7a (7b) was found, when different methods for radical deoxygenation/ elimination[10] of the isomeric thiocarbonates 5a (5b) and 6a (6b) were used, which rases the question of the mechanism involved in these reactions. These limited data do not allow a complete and satisfactory mechanistic interpretation, but we will discuss here two possible mechanisms. To clarify, that the 9,10 unsaturated compounds 7a, 7b are not simply produced by elimination of water from a 9-deoxo-compound, we synthesized the deuterated compound 5c by reduction of 2b with lithium aluminum deuteride to 3c, which was transferred to 5c as described for 3b. Subjection of 5c to the methods described above resulted in no detectable loss of deuterium, indicating that neither a dehydration of an intermediate 9-deoxo-compound nor an epimerization at C(9) during the formation of 7c occurred. On the other hand, when tributyltin hydride was substituted by tributyltin deuteride, no incorporation of deuterium was observed. Evidently, tributyltin hydride and tris(trimethylsilyl)silane propagate the radical chain reaction

but do not act as H-radical donors in the present cases. Only, when 6b is treated in neat tributyltin hydride at 100°C with catalytical amount of AIBN, reduction of the thiocarbonyl to the methylidene derivative 16 group occurred[11]. This product could not be detected when the reaction was done in neat tris(trimethylsilyl)silane.



Scheme 3.

As shown in Scheme 3, two different reaction pathways (a and b) can be anticipated. Following the Barton and McCombie mechanism[12], the attack of a tributylstannyl or tris(trimethylsilyl)silyl radical on the thioxo sulfur of 5a-5c, forming the radical intermediates A_1 and A_2, is common for both reaction pathways. At this stage A_1 and A_2 can undergo different ß-cleavages, either at C(9), resulting in radical intermediate B (*path* a), or at C(10), leading to the radical intermediates C_1 and C_2 (*path* b). Further radical elimination results in formation of E and Z-isomers of **7a-7c**. Regarding the examples in the literature[13] about free radical deoxygenation of thiocarbonates, there is no clear correlationship for regioselectivity in product formation, when secondary and tertiary centers are involved. Steric and stereo-electronic factors often alter the course of the reaction. In our case we have not only to distinguish between a secondary (B) and a tertiary radical (C_1, C_2), we have also to take into account the electronic factors exerted by the neighbouring groups. Stabilization by the carbonyl at C(8) results in an electrophilic radical (B) and vice versa by the pyran oxygen in a nucleophilic radical (C_1 or C_2). A carbonyl group should stabilize a radical better than an oxygen group[14], but other factors like bond angle strains[15] can render the situation more complex, making a prediction difficult,

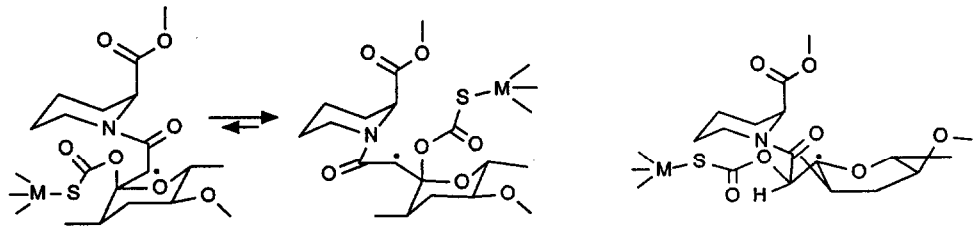
which of the two reactions pathways is preferred.

In *reaction path* a, we expect a reaction proceeding via radical intermediate B. The assumption of a collapse in the steric arrangement at C(9) would explain why the configuration at C(9) in the starting material is not important, as observed in *method A* (Table 1). In *method C*, the dependence of the E/Z value on the starting material, as well as the selectivity in formation of the Z-isomer of 7b, when 6b was the starting material, cannot satisfactory be explained by reaction through *path* a and in this case we assume a reaction via *path* b.

In *reaction path* b, we anticipate a reaction via two distinct intermediates C_1 or C_2. In each of the two, the configuration at C(9) of the original starting material is retained. To explain the above mentioned selectivity in Z-isomer formation of 7b, when applying *method C* to 6b, we have to assume the existence of radical C_2 in a definite conformation, which reacts further by elimination of a $R_3MSCOO\cdot$ radical (R=Bu, M=Sn, or R=$(CH_3)_3Si$, M=Si) under stereo-electronic control to form the Z-isomer of 7b. To allow maximum orbital overlap, a radical intermediate C_2 is formulated (Scheme 4), in which the pyrane ring is in a boat form[16]. Further stabilization can be expected by a ß-CO-bond effect[17] of the oxygen in the substituent at C(9). When 5b is the substrate this mechanism fails. Instead of the expected high preponderance of the E isomer, a 1:1.4 mixture of E and Z-isomer is obtained. At the moment this result can only be attributed to steric hindrance in the transition state, overwhelming the stereo-electronic factors and resulting in unselective radical elimination.

When using *method B*, the E-isomer is selectively formed. As discussed earlier, we would estimate that the reaction proceeds mainly via *path* a. The E-isomer selectivity could be either a result of a polar effect[18] exerted by triethylborane, which is present in excess in the reaction mixture, on the transition state in radical formation, or the result of the lower reaction temperature as compared to *method A*, leading to a preferred conformation of radical B. In principle, α amide radicals can be present in four different isomeric forms, two geometric (E and Z) isomers, as indicated in Scheme 4, together with the two rotameric forms resulting from restricted rotation around the amide bond[19]. Fischer et al.[20] have measured rotation barriers about a partial double bond (•C-C=O ⇄ C=C-O•) in selected α amide radicals with the technique of muon spin rotation. The authors suggest that the dominant radical conformer possesses Z orientation and the barrier separating E and Z-conformer is in excess of 11 kcal/mol. Regarding the amide bond (CO-N), a considerable barrier to rotation should be expected also for α amide radicals (~18-20 kcal/mol for amides), but no experimental data are available as yet.

Due to the complexity of the situation and the paucity of physical data we are unable at the moment to give a better founded mechanistic picture of the reaction sequences. Further studies like ESR measurements on fragments would be necessary to get a deeper insight into the reaction mechanism.



Scheme 4.

In the FKBP binding assay, compounds 13a and 13b bind about four times weaker than FK 506, indicating that the unusual interaction of the keto carbonyl with the aromatic ring systems of the three neighbouring amino acids of FKBP, mentioned earlier, is not very strong. The other structure modifications described in this paper give a more pronounced decrease in binding constants.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 250 MHz (Bruker WM 250) and at 500 MHz (Bruker AMX 500). All mass spectra are fast atom bombardment (FAB) spectra. They were recorded on a VG 70-SE instrument (VG Analytical) operating at 8kV accelerating voltage. UV spectra were obtained with a Beckman DK-2A spectrometer. Column chromatography was accomplished on silica gel 60 (0.063 - 0.2 mm, Merck) under hydrostatic pressure or on commercially available colums (Lobar Fertigsäule, filled with LiChroprep Si 60, 0.04 - 0.063 mm, Merck) using pressures up to 5 bars. Thin layer chromatography was performed on HPTLC plates pre-coated with silica gel 60 F254 (Merck). The spots were visualized by either quenching of UV fluorescence (λmax = 254 nm) or by staining with Kierberger reagent, followed by heat. The purity of the products was checked by high-performance liquid chromatography (Beckman 114M) on a column (125x4.6 mm) of CPS Hypersil CN (Merck) with a water acetonitrile gradient and a Beckman 165 UV detector (220nm). Tetrahydrofuran (THF) was obtained dry and oxygen free by distillation from $LiAlH_4$ under argon atmosphere. All other solvents were reagent grade quality and if necessary were dried by storing over molecular sieves (0.4 nm). Tri-n-butyltin deuteride was prepared analogous to a literature procedure[21] from $(Bu_3Sn)_2O$ and $LiAlD_4$. All other reagents were from commercial sources and used as obtained.

24,33-Bis-(t.butyl-dimethylsilyl)-9(S)-dihydro-FK 506 (3a): To a solution of 1.02 g (1 mmol) of 2a in 8 ml anhydrous THF, 0.1 g (2.6 mmol) $LiAlH_4$ were added in small portions under stirring at 0°C and after addition the reaction mixture was brought to room temperature and stirring was continued for further 2.5 h. The reaction was quenched by adding ethyl actate and saturated NH_4Cl solution, the organic phase was separated and the aqueous phase extracted three times with ethyl acetate. After washing 3 times with water and drying over Na_2SO_4 of the united organic phases the solvent was evaporated and the residue was purified by column chromatography (SiO_2, hexane / ethyl acetate = 2/1 leading to 450 mg (45%) of a colourless foam. ^1H-NMR ($CDCl_3$), mixture of conformers: 5/2; major conformer δ -0.04, 0.02, 0.06, 0.08 (4s, $2Si(CH_3)_2$), 0.76 (d, J=5Hz, 17-CH_3), 1.00 (d, J=7.5Hz, 11-CH_3), 2.95 (ddd, J_1=5Hz, J_2=8Hz, J_3=10Hz, H-32), 3.05 (dd, J_1=2.5Hz, J_2=10Hz, H-13), 3.16 (dt, J_1=5Hz, J_2=10Hz, H-21), 3.37, 3.39, 3.41 (3s, $3xOCH_3$), 3.55 (m, H-15), 3.80 (dd, J_1=2Hz, J_2=10Hz, H-14), 3.90 (d, J=10Hz, 9-OH), 4.21 (m, H-24), 4.46 (d, J=10Hz, H-9), 4.95 (dd, J_1=2Hz, J_2=17Hz, H-38), 4.96 (s, H-26), 5.07 (dd, J_1=2Hz, J_2=17Hz, H-38), 5.11 (d, J=10Hz, H-29), 5.14 (d, J=5Hz, H-2), 5.33 (d, J=2Hz, 10-OH), 5.70 (ddt, J_1=6Hz. J_2=10Hz, J_3=17Hz, H-37); minor conformer δ 3.74 (dd, J_1=2Hz, J_2=10Hz, H-14), 4.52 (d, J=14Hz, H-6e). ^{13}C-NMR ($CDCl_3$), major conformer δ -4.5, -4.8, -5.1 ($2Si(CH_3)_2$), 11.1 (25-CH_3), 14.1 (28-CH_3), 16.0, 16.2 (11-CH_3, 19-CH_3), 18.2 (17-CH_3), 21.7 (C_4), 25.1 (C_5), 25.9 ($2SiC(CH_3)_3$), 26.0 (C_{17}), 26.7 (C_3), 30.8 (C_{35}), 32.3 (C_{12}), 32.9 (C_{34}), 33.8 (C_{30}, C_{31}), 34.9 (C_{36}), 35.3, 36.4 (C_{11}, C_{12}), 41.6 (C_{25}), 43.9 (C_6), 44.2 (C_{23}), 48.4 (C_{18}), 53.4 (C_2), 54.1 (C_{21}), 56.1, 57.0, 57.9 ($3xOCH_3$), 68.5 (C_{24}), 71.2 (C_9), 72.1 (C_{14}), 74.0 (C_{13}), 75.1 (C_{33}), 76.8 (C_{15}), 78.0 (C_{26}), 84.1 (C_{32}), 99.5 (C_{10}), 115.8 (C_{38}), 122.3 (C_{20}), 130.8 (C_{29}), 132.9 (C_{38}), 136.1 (C_{37}),140.3 (C_{19}), 169.6 (C_1), 173.3 (C_8), 209.5 (C_{22}); minor conformer δ -4.3, -4.4 ($2Si(CH_3)_2$), 10.6 (25-CH_3), 12.8 (28-CH_3), 15.4, 16.2 (11-CH_3, 19-CH_3), 20.2 (C_4), 24.9 (C_5), 25.7 ($2SiC(CH_3)_3$), 25.9 (C_{17}), 27.9 (C_3), 30.6 (C_{35}), 40.8 (C_6), 52.6 (C_{21}), 55.8, 56.2, 57.0 ($3xOCH_3$), 97.5 (C_{10}), 116.4 (C_{38}), 123.5 (C_{20}), 128.2 (C_{29}), 132.6 (C_{28}), 135.7 (C_{37}), 138.6 (C_{19}), 170.2 (C_1), 171.3 (C_8).

24,33-Bis-(t.butyl-dimethylsilyl)-9(S)-dihydro-FR 900520 (3b): 1.02 g (1 mmol) of 2b were treated with $LiAlH_4$ as above leading to 472 mg (47%) of 3b in form of a colourless foam. ^1H-NMR ($CDCl_3$), mixture of two conformers: 5/2; major conformer δ -0.04, 0.02, 0.06, 0.08 (4s, $2Si(CH_3)_2$), 0.76 (d, J=5Hz, 17-CH_3), 1.00 (d, J=7.5Hz, 11-CH_3), 2.95 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.05 (dd, J_1=2.5Hz, J_2=10Hz, H-13), 3.16 (dt, J=5Hz, J=10Hz, H-21), 3.37, 3.39, 3.41 (3s, $3xOCH_3$), 3.54 (d, J=10Hz, H-15), 3.80 (dd, J_1=2Hz, J_2=10Hz, H-14), 4.14 (d, J=12.5Hz, H-6e), 4.21 (m, H-2, H-24), 4.46 (d, J=7.5Hz, H-9), 4.84 (d, J=10Hz, H-20), 5.10 (s, H-26), 5.11 (d, J=10Hz, H-29), 5.14 (d, J=5Hz, H-2), 5.32 (d, J=2Hz, 10-OH); minor conformer δ 3.76 (dd, J_1=2Hz, J_2=10Hz, H-14), 4.52 (d, J=14Hz, H-6e), 4.92 (d, J=10Hz, H-20).

24,33-Bis-(t.butyl-dimethylsilyl)-9(S)-deutero-hydro-FR 900520 (3c): 1.02 g of 2b were treated with 3 equiv. of $LiAlD_4$ in a similar way as described for the preparation of 3b leading to 140 mg (14%) of starting material 2b and 310 mg (31%) of 3c (colourless foam). The ^1H-NMR spectrum is the same as described for 3b with the exception, that the signal at 4.46 is absent.

24,33-Bis-(t.butyl-dimethylsilyl)-9(R)-dihydro-FK 506 (4a): 25 g (24.2 mmol) of 2a were dissolved in 120 ml anhydrous THF and cooled to -78°C. 36 ml (36 mmol) of a 20% solution of DIBAH in hexane were

added dropwise to this solution and stirring was continued for further 15 minutes at this temperature. Excess of reagent was destroyed by careful addition of 0.1 N HCl and the precipitate was filtered off. The organic phase was diluted with ethyl acetate and washed 3x with water. After drying over Na_2SO_4 the solvent was evaporated and 20.3 g (81%) of a colourless solid were obtained. Although the dehydro compound could be purified at this stage by column chromatography, it proved advantageous to use the crude product in the next step without further purification. An analytical sample was prepared by column chromatography (SiO_2, CH_2Cl_2 / CH_3OH = 20/1) and obtained in form of a colourless foam. ^{1}H-NMR ($CDCl_3$) δ -0.03, 0.05, 0.08, 0.1 (4s, 2x$Si(CH_3)_3$), 0.84 (d, J=5Hz, 17-CH_3), 1.13 (d, J=5Hz, 11-CH_3), 2.96 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.34, 3.37, 3.41 (3s, 3xOCH_3), 3.53 (dd, J_1=2Hz, J_2=8Hz, H-15), 3.79 (dd, J_1=2Hz, J_2=8Hz, H-14), 3.87 (d, J=15Hz, H-6e), 4.29 (m, H-24), 4.39 (d, J=12Hz, H-9), 4.83 (d, J=5Hz, H-2), 4.96 (dd, J_1=2Hz, J_2=17Hz, H-38), 4.97 (d, J=9Hz, H-20), 5.01 (dd, J_1=2Hz, J_2=17Hz, H-38), 5.16 (d, J=10Hz, H-29), 5.19 (s, H-26), 5.73 (ddt, J_1=6Hz, J_2=10Hz, J_3=17Hz, H-37). ^{13}C-NMR ($CDCl_3$) δ -4.4, -4.5, -5.8, -5.0 (2$Si(CH_3)_2$), 9.9 (25-CH_3), 14.7 (28-CH_3), 16.4, 16.9 (11-CH_3, 19-CH_3), 18.4 (17-CH_3), 20.9 (C_4), 24.3 (C_{17}), 25.8 (2$SiC(CH_3)_3$), 26.2 (C_3), 30.9 (C_{12}), 33.8 (C_{34}), 34.7, 34.9 (C_{30}, C_{31}), 35.4 (C_{36}), 36.7, 37.9 (C_{11}, C_{12}), 41.4 (C_{25}), 43.3 (C_6), 44.7 (C_{23}), 48.3 (C_{18}), 53.1 (C_2), 53.7 (C_{21}), 56.2, 57.3, 58.0 (3xOCH_3), 69.7, 70.8, 71.1 (C_9, C_{14}, C_{24}), 73.8 (C_{13}), 75.2 (C_{33}), 75.5, 76.1 (C_{15}, C_{26}), 84.1 (C_{32}), 98.1 (C_{10}), 115.9 (C_{38}), 121.6 (C_{20}), 128.3 (C_{29}), 132.8 (C_{28}), 136.4 (C_{37}), 139.6 (C_{19}), 168.7 (C_1), 173.5 (C_e), 210.9 (C_{22}).

24,33-Bis-(t.butyl-dimethylsilyl)-9(R)-dihydro-FR 900520 (4b): 12 g (11.75 mmol) were treated with DIBAH as above leading to 9.84 g (82 %) of 4b (colourless solid). ^{1}H-NMR ($CDCl_3$) δ -0.03, 0.05, 0.08, 0.1 (4s, 2x$Si(CH_3)_2$), 0.84 (d, J=5Hz, 17-CH_3), 1.13 (d, J=5Hz, 11-CH_3), 2.35 (dd, J_1=1.5Hz, J_2=15.5Hz, H-23), 2.51 (dd, J_1=8Hz, J_2=15.5Hz, H-23), 2.96 (ddd, J_1=4Hz, J_2=8Hz, J_3=11Hz, H-32), 3.05 (d, J=11Hz, 9-OH), 3.16 (m, H-21), 3.35, 3.38, 3.42 (3s, 3xOCH_3), 3.54 (m, H-13), 3.80 (dd, J_1=2Hz, J_2=10Hz, H-14), 4.28 (m, H-24), 4.38 (d, J=11Hz, H-9), 4.83 (d, J=5Hz, H-2), 4.96 (d, J=9Hz, H-20), 5.12 (d, J=10Hz, H-29), 5.18 (s, H-26), 6.21 (d, J=1Hz, 10-OH).

General procedure for the preparation of 9-dihydro-9,10-thiocarbonates (5a-5c, 6a and 6b): To a solution of the 24,33-disilylated 9-dihydro compound (1 equiv.) in 1,2-dichloroethane (30 ml/g of 9-dihydro compound), 1,1'-thiocarbonyldiimidazole (2 equiv.) is added in portions under stirring. After completion of reaction (2-18 h), the solvent was removed under vacuo and the obtained residue purified by column chromatography (SiO_2, hexane/ethyl acetate = 2/1) to afford spectroscopically pure thiocarbonates (5a-5c, 6a and 6b).

24,33-Bis-(t.butyl-dimethylsilyl)-9(S)-dihydro-FK 506-9,10-thiocarbonate (5a) :The standard procedure afforded the product as a colourless foam (1.42 g, 91%) from 1.5 g 3a. ^{1}H-NMR ($CDCl_3$) δ 0.04, 0.06, 0.07 (3s, 2$Si(CH_3)_2$), 1.09 (d, J=7.5Hz, 11-CH_3), 2.95 (ddd, J_1=4Hz, J_2=9Hz, J_3=12Hz, H-32), 3.30, 3.40 (2s, 3xOCH_3), 3.62 (dd, J=5Hz, J=11Hz, H-15), 3.75 (d, J=9Hz, H-14), 4.12 (m, H-24), 4.54 (d, J=13Hz, H-6e), 4.88 (s, H-2), 4.91 (d, J=10Hz, H-20), 4.96 (dd, J_1=2Hz, J_2=17Hz, H-38), 5.02 (dd, J_1=2Hz, J_2=17Hz, H-38), 5.30 (d, J=9Hz, H-29), 5.46 (d, J=4Hz, H-26), 5.67 (ddt, J_1=6Hz, J_2=10Hz, J=17Hz, H-37). ^{13}C-NMR ($CDCl_3$) δ -4.3, -4.4, -4.5, -4.8 (2$Si(CH_3)_2$), 10.9 (25-CH_3), 12.1 (28-CH_3), 14.7, 15.1 (C_{11}, C_{19}), 20.0 (17-CH_3), 20.5 (C_4), 24.7 (C_5), 25.8 (2$SiC(CH_3)_3$), 26.0 (C_{17}), 28.0 (C_3), 30.5 (C_{35}), 32.2 (C_{12}), 32.9 (C_{16}), 33.8 (C_{34}), 34.9 (C_{30}, C_{31}), 35.7 (C_{36}), 36.2 (C_{11}), 40.0 (C_{25}), 40.7 (C_6), 45.5 (C_{23}), 48.8 (C_{18}), 52.6 (C_{21}), 54.7 (C_2), 56.4, 57.4, 57.7 (3xOCH_3), 69.8 (C_{24}), 71.9 (C_{14}), 74.4 (C_{13}), 75.0 (C_{33}), 76.5 (C_{15}), 79.3 (C_{26}), 84.0 (C_{32}), 85.3 (C_9), 111.8 (C_{10}), 116.7 (C_{38}), 124.2 (C_{20}), 132.3 (C_{28}), 134.8 (C_{29}), 135.3 (C_{37}), 137.7 (C_{19}), 161.4 (C_8), 169.0 (C_1), 188.5 (C=S), 209.5 (C_{22}).

24,33- Bis-(t.butyl-dimethylsilyl)- 9(S)-dihydro- FR 900520- 9,10- thiocarbonate (5b): The standard procedure afforded the product as a colourless foam (1.43 g, 92%) from 1.5 g 3b. ^{1}H-NMR ($CDCl_3$) δ 0.05, 0.08, 0.09 (3s, 2$Si(CH_3)_2$), 2.26 (dd, J_1=7Hz, J_2=18Hz, H-23), 2.61 (dd, J_1=5Hz, J_2=18Hz, H-23), 2.87 (m, H-6a), 2.96 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.30, 3.38 (2s, 3xOCH_3), 3.62(dd, J_1=4Hz, J_2=8Hz, H-15), 3.75 (dd, J_1=1Hz, J_2=8Hz, H-14), 4.10 (m, H-24), 4.54 (d, J=15Hz, H-6e), 4.87 (dd, J_1=2.5Hz, J_2=10Hz, H-2), 4.92 (d, J=10Hz, H-20), 5.12 (s, H-9), 5.15 (d, J=9Hz, H-29), 5.42 (d, J=5Hz, H-26).

24,33- Bis- (t.butyl-dimethylsilyl)- 9(S)-deutero- hydro- FR 900520- 9,10- thiocarbonate (5c): The standard procedure afforded the product as a colourless foam (118 mg, 65%) from 180 mg 3c. The H-NMR spectrum is the same as described for 5b with the exception that the signal at 5.12 is absent.

24,33-Bis-(t.butyl-dimethylsilyl)-9(R)-dihydro-FK 506-9,10-thiocarbonate (6a): The standard procedure afforded the product as a colourless foam (8.57 g, 82%) from 10 g 4a. H-NMR ($CDCl_3$) δ 0.06, 0.09, 0.11 (3s, $2Si(CH_3)_2$), 2.66 (d, J=5Hz, 2H-23), 2.96 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.30, 3.40, 3.42 (3s, $3xOCH_3$), 3.68 (dd, J_1=1Hz, J_2=8Hz, H-14), 3.86 (dt, J_1=5Hz, J_2=7.5Hz, H-21), 4.36 (q, J=4Hz, H-24), 4.80 (m, H-2), 5.28 (s, H-26), 5.48 (s, H-9). ^{13}C-NMR ($CDCl_3$) δ -4.6, -4.8, -4.9 ($2Si(CH_3)_2$), 9.7 (25-CH_3), 14.5 (11-CH_3, 19-CH_3), 15.5 (28-CH_3), 20.2 (C_4), 20.5 (17-CH_3), 23.3 (C_5), 24.8 (C_{17}), 25.6 (C_3), 25.7, 25.8 ($2SiC(CH_3)_3$), 30.8 (C_{35}), 31.3 (C_{16}), 31.8 (C_{12}), 33.6 (C_{34}), 34.7 (C_{30}), 36.5 (C_{30}), 36.6 (C_{11}), 37.0 (C_{31}), 41.1 (C_{25}), 42.9 (C_6), 45.9 (C_{23}), 48.6 (C_{18}), 51.5 (C_{21}), 53.4 (C_2), 56.3, 56.6, 57.7 ($3xOCH_3$), 69.8 (C_{24}), 72.1 (C_{14}), 74.1 (C_{13}), 75.0 (C_{33}), 75.3 (C_{15}), 75.7 (C_{26}), 79.7 (C_9), 84.0 (C_{32}), 111.2 (C_{10}), 115.9 (C_{38}), 122.5 (C_{20}), 128.0 (C_{29}), 132.2 (C_{28}), 136.3 (C_{37}), 139.0 (C_{19}), 162.2 (C_8), 169.2 (C_1), 189.3 (C=S), 211.7 (C_{22}).

24,33- Bis-(t.butyl-dimethylsilyl)- 9(R)-dihydro- FR 900520- 9,10-thiocarbonate (6b): The standard procedure afforded the product as a colourless foam (12.61 g, 88%) from 13.81 g 4b. ^{1}H-NMR ($CDCl_3$) δ 0.06, 0.09, 0.11 (3s, $2Si(CH_3)_2$), 2.65 (d, J=6Hz,H-23), 2.68 (d, J=4Hz, H-23), 2.96 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.30, 3.39, 3.42 (3s, $3xOCH_3$), 3.53 (dd, J_1=2.5Hz, J_2=9Hz, H-15), 3.69 (dd, J_1=1Hz, J_2=8Hz, H-14), 4.37 (m, H-24), 4.79 (dd, J_1=2Hz, J_2=5.5Hz, H-2), 4.92+4.97 (d, J=10Hz, d, J=12Hz, H-20, H-29), 5.27 (s, H-26), 5.48 (s, H-9).

General procedure for the radical deoxygenation/ elimination of the thiocarbonates:

Method A: nBu_3SnH, AIBN

1 Equiv. of the chosen thiocarbonate was dissolved in dry toluene (20 ml/g of thiocarbonate), heated under reflux and treated by dropwise addition with 2 equiv. of nBu_3SnH and a catalytical amount of AIBN. Heating was continued until the reaction was almost complete (10 min - 2 h). After cooling to room temperature the solvent was evaporated in vacuo and the residue purified by column chromatography (SiO_2, hexane/ethyl acetate = 2/1) leading to the desired unsaturated compound. If necessary, E and Z isomer were separated by column chromatography (SiO_2, dichloromethane/acetone = 20/1).

Method B: nBu_3SnH, Et_3B (room temperature)

To a solution of 1 equiv. of the chosen thiocarbonate in dry benzene (20 ml/g of thiocarbonate), 3.5 equiv. of nBu_3SnH and 3.5 equiv. of Et_3B in form of a 1.0 molar solution in hexane were added dropwise under stirring. The reaction was kept for 18 hours at room temperature and afterword the solvent was evaporated in vacuo. Purification of the obtained row material was performed in the same way as described under method A.

Method C: $[(CH_3)_3Si]_3SiH$, AIBN

1 Equiv. of the chosen thiocarbonate was dissolved in dry toluene (20 ml/g of thiocarbonate), heated to 80°C and treated with 3 equiv. of $[(CH_3)_3Si]_3SiH$ and a catalytical amount of AIBN. Heating was continued until the reaction was complete (30 min - 2 h). Work up and purification were performed in the same way as described in method A.

Method D: $[(CH_3)_3Si]_3SiH$, Et_3B (room temperature)

1 equiv. of thiocarbonate in dry benzene (20 ml/g of thiocarbonate) was treated with 3 equiv. of $[(CH_3)_3Si]_3SiH$ and 3 equiv. of Et_3B (1.0 M in hexane) and was worked up after completion of reaction (18 h) as described in method A.

Method E: nBu_3SnD, AIBN

The reaction was performed as described in method A with the exception that nBu_3SnD was used instead of nBu_3SnH.

Method F: nBu_3SnD, Et_3B

The reaction was performed as described in method B with the exception that nBu_3SnD was used instead of nBu_3SnH.

Method G: nBu_3SnH, Et_3B (80°C)

The reaction was performed as described in method B with the exception that it was run at 80°C instead of room temperature.

Method H: $[(CH_3)_3Si]_3SiH$, Et_3B (80°C)

The reaction was performed as described in method C with the exception that it was run at 80°C instead of room temperature.

24,33-Bis-(t.butyl-dimethylsilyl)-Δ^9-FK 506 (7a): Following method A the product (920 mg, 92%, E/Z = 1/1) was obtained as a colourless foam from **6a** (1.076 g, 1 mmol). As indicated in Table 1, 7a was also

prepared on gramme scale by the methods B and D. E and Z-isomer can be separated, if desired by column chromatography (dichloromethane/ acetone = 10/1). UV (EtOH) λ=222nm, log ε = 4.14, λ=251nm, log ε = 3.82; E-isomer ^{1}H-NMR ($CDCl_3$) δ 0.02, 0.04, 0.07, 0.08 (4s, 2Si(CH_3)$_2$), 1.38 (d, J=6.5Hz, 11-CH_3), 2.38 (dd, J_1=5.5Hz, J_2=16.5Hz, H-23), 2.75 (dd, J_1=6.5Hz, J_2=16.5Hz, H-23), 2.97 (m, H-21, H-32), 3.36, 3.41 (2s, 3xOCH_3), 3.41 (m, H-15, H-33), 3.68 (m, H-13), 3.92 (dd, J_1=1Hz, J_2=8Hz, H-14), 4.05 (m, H-24), 4.52 (d, J=13Hz, H-6e), 4.65 (dd, J_1=1Hz, J_2=4Hz, H-2), 4.90 (d, J=10Hz, H-20), 4.97 (dd, J_1=2Hz, J_2=7Hz, H-38), 5.05 (dd, J_1=2Hz, J_2=17Hz, H-38), 5.15 (d, J=5Hz, H-26), 5.21 (d, J=10Hz, H-29), 5.38 (s, H-9), 5.70 (ddt, J_1=6Hz, J_2=10Hz, J_3=17Hz, H-37). ^{13}C-NMR ($CDCl_3$) δ -4.0, -4.37, -4.48, -4.72 (2Si(CH_3)$_2$), 10.2 (25-CH_3), 12.6 (28-CH_3), 15.9 (19-CH_3), 20.7 (11-CH_3), 20.9 (17-CH_3), 21.0 (C_4), 24.7 (C_5), 25.9 (2SiC(CH_3)$_3$), 27.5 (C_3), 27.8 (C_{11}), 28.5 (C_{17}), 30.2 (C_{12}), 30.8 (C_{35}), 33.9 (C_{34}), 34.7 (C_{16}), 34.9 (C_{30}), 35.1 (C_{31}), 36.3 (C_{36}), 38.7 (C_{25}), 39.7 (C_6), 46.5 (C_{23}), 48.8 (C_{18}), 53.0 (C_{21}), 56.2, 56.4, 57.8 (3xOCH_3), 69.4 (C_{24}), 73.8 (C_{14}), 75.2 (C_{33}), 76.0 (C_{13}), 78.5 (C_{15}), 79.7 (C_{26}), 84.2 (C_{32}), 96.2 (C_9), 116.4 (C_{38}), 123.6 (C_{20}), 131.6 (C_{28}), 133.4 (C_{29}), 135.7 (C_{37}), 138.8 (C_{19}), 167.8 (C_8), 170.2 (C_1), 172.1 (C_{10}), 208.4 (C_{22}). Z-isomer ^{1}H-NMR ($CDCl_3$) δ 0.02, 0.07, 0.09 (3s, 2Si(CH_3)$_2$), 0.84, 0.89 (2s, 2SiC(CH_3)$_3$), 1.11(d, J=7.5Hz, 11-CH_3), 2.54 (dd, J_1=9Hz, J_2=15Hz, H-23), 2.95 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.13 (dt, H_1=2.5Hz, H_2=12.5Hz, H-6a), 3.14 (dt, H_1=5Hz, H_2=12.5Hz, H-21), 3.37 (m, H-33), 3.41, 3.42 (2s, 3xOCH_3), 3.56 (m, H-15), 3.59 (dd, J_1=1Hz, J_2=8Hz, H-14), 3.66 (m, H-13), 3.79 (d, J=11Hz, H-6e), 4.24 (ddd, J_1=1Hz, J_2=4.5Hz, J_3=7.5Hz, H-24), 4.92 (dd, J_1=2Hz, J_2=10Hz, H-38), 4.98 (d, J=7.5 Hz, H-24), 4.92 (dd, J_1=2Hz, J_2=10Hz, H-38), 4.98 (d, J=7.5Hz, H-29), 5.0 (dd, J_1=2Hz, J_2=15Hz, H-38), 5.20 (d, J=5Hz, H-2), 5.21 (s, H-26), 5.37 (s, H-9), 5.40 (d, J=10Hz, H-20), 5.74 (ddt, J_1=6Hz, J_2=10Hz, J_3=17Hz, H-37). ^{13}C-NMR ($CDCl_3$) δ -4.4, -4.5, -4.7, -5.0 (2Si(CH_3)$_2$), 10.1 (25-CH_3), 14.6 (28-CH_3), 17.1 (19-CH_3), 17.7 (11-CH_3), 17.9 (17-CH_3), 21.6 (C_4), 25.3 (C_5), 25.9 (2SiC(CH_3)$_3$), 26.3 (C_{17}), 27.0 (C_3), 31.0 (C_{35}), 32.5 (C_{12}), 33.9 (C_{34}), 34.0 (C_{11}), 35.0 (C_{30}), 35.7 (C_{31}), 36.7, 36.8 (C_{16}, C_{36}), 41.5 (C_{25}), 43.8, 43,9 (C_{23}, C_{26}), 47.7 (C_{18}), 52.0 (C_2), 54.3 (C_{21}), 56.5, 57.3, 57.9 (3xOCH_3), 72.0 (C_{24}), 73.6 (C_{14}), 75.2 (C_{33}), 75.3 (C_{13}), 76.3 (C_{15}), 81.4 (C_{26}), 84.2 (C_{32}), 102.5 (C_9), 115.6 (C_{38}), 121.0 (C_{20}), 128.9 (C_{29}), 133.1 (C_{28}), 136.7 (C_{37}), 140.0 (C_{19}), 163.5 (C_{10}), 169.3 (C_1), 210.8 (C_{22}).

24,33-Bis-(t.butyl-dimethylsilyl)-Δ^9-FR 900520 (7b): Following method A, the product (1.13 g, 83%, E/Z = 1/1) was obtained as a colourless foam from **5b** (1.27 g, 1.19 mmol). E-isomer ^{1}H-NMR ($CDCl_3$) δ 0.02, 0.04, 0.07, 0.08 (4s, 2Si(CH_3)$_2$), 1.38 (d, J=6.5Hz, 11-CH_3), 1.69 (m, H-12), 1.95 (m, H-12), 2.38 (dd, J_1=5.5Hz, J_2=16.5Hz, H-23), 2.68 (dd, J_1=6.5Hz, J_2=16.5Hz, H-23), 2.94 (m, H-33), 3.01 (d, J=13Hz, H-6a), 3.21 (m, H-21), 3.36, 3.41 (2s, 3xOCH_3), 3.41 (m, H-15, H-33), 3.63 (m, H-11), 3.70 (m, H-13), 3.92 (dd, J_1=1Hz, J_2=8Hz, H-14), 4.06 (m, H-24); 4.53 (d, J=13Hz, H-6e), 4.66 (dd, J_1=1Hz, J_2=4Hz, H-2), 4.93 (d, J=10Hz, H-20), 5.21 (d, J=10Hz, H-29), 5.28 (d, J=5Hz, H-26), 5.35 (s, H-9); Z-isomer ^{1}H-NMR ($CDCl_3$) δ 0.02, 0.07, 0.09 (3s, 2Si(CH_3)$_2$), 1.07 (d, J=7.5Hz,11-CH_3), 2.49 (dd, J_1=9Hz, J_2=15Hz, H-23), 2.91 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.03 (dt, J_1=7Hz, J_2=10Hz, H-6a), 3.12 (dt, J_1=3Hz, J_2=10Hz, H-21), 3.36 (s, 3xOCH_3), 3.55 (m, H-15), 3.57 (dd, J_1=1Hz, J_2=8Hz, H-14), 3.65 (m, H-13), 3.74 (d, J=10Hz, H-6e), 4.18 (m, H-24), 4.96 (d, J=9Hz, H-29), 5.32 (d, J=11Hz, H-2), 5.33 (s, H-9).

24,33-Bis-(t.butyl-dimethylsilyl)-9-deutero-Δ^9-FR 900520 (7c): Following method B, the product (35 mg, 38%, E/Z =5/1) was obtained as a colourless foam from **5c** (98 mg, 0.092 mmol). The ^{1}H-NMR data are the same as described for **7b** (E-isomer) with the exception that the signal at 5.35 is absent.

24,33-Bis-(t.butyl-dimethylsilyl)-Δ^9-11-epi-FK 506 (8a): A solution of 3 g (2.79 mmol) of **6a** in 60 mL of dry toluene was heated under reflux and treated by dropwise addition of 48 ml (5.57 mmol) of nBu_3SnH and a catalytical amount of AIBN. Heating was continued for 4 h and afterwards the reaction mixture was worked up as described in method A. Separation by column chromatography (SiO_2, hexane/ethyl acetate = 2/1) yielded 874 mg (29%) of starting material **6a**, 483 mg (24%) of an E/Z mixture (7/3) of **8a** (colourless foam) and 1.23 g (44%) of **7a**. ^{1}H-NMR ($CDCl_3$) E-isomer δ 0.81 (d, J=7Hz, 25-CH_3), 0.97 (d, J=6.5Hz, 17-CH_3), 1.27 (d, J=7Hz, 11-CH_3), 2.90 (m, H-6a), 2.94 (m, H-32), 3.36, 3.42, 3.44 (3s, 3xOCH_3), 3.52 (dd, J_1=5Hz, J_2=17 Hz, H-15), 3.76 (m, H-13, H-16), 4.10 (m, H-24), 4.49(d, J=13Hz, H-6e), 4.63 (d, J=5Hz, H-2), 4.89 (d, J=10Hz, H-20), 4.97 (dd, J_1=2Hz, J_2=10.5Hz, H-38), 5.01 (dd, J_1=2Hz, J_2=17Hz, H-38), 5.17 (d, J=6Hz, H-26), 5.23 (d, J=8.5Hz, H-29), 5.54 (s, H-9), 5.66 (ddt, J_1=6Hz, J_2=10Hz, J_3=17Hz, H-37); Z-isomer δ 0.72 (d, J=7Hz, 25-CH_3), 1.33 (d, J=7Hz, 11-CH_3), 2.45 (H-23), 3.08 (m, H-6a), 3.36, 3.38, 3.40 (3s, 3xOCH_3), 3.86 (m, H-13), 3.93 (d, J=13Hz, H-6e), 4.22 (m, H-24), 5.07 (d, J=9Hz, H-20), 5.34 (d, J=9.5Hz, H-29), 5.44 (d, J=4Hz, H-2), 5.66 (dd, J_1=6Hz, J_2=10Hz, J=17Hz, H-37). ^{13}C-NMR ($CDCl_3$) E-isomer δ -4.2, -4.3, -4.5, -4.7 (4Si(CH_3)$_2$), 10.0 (25-CH_3), 14.4 (28-CH_3), 16.3 (19-CH_3), 20.7 (C_4), 20.9 (11-CH_3), 21.2 (17-CH_3), 24.7 (C_5), 25.9 (2SiC(CH_3)$_3$), 26.0 (C_3), 27.8 (C_{17}), 30.8 (C_{35}), 32.0, 32.9, 33.0,

33.9 (C_{11}, C_{12}, C_{16}, C_{34}), 35.0 (C_{36}), 36.3 (C_{31}), 38.8 (C_6), 40.2 (C_{25}), 46.7 (C_{23}), 49.2 (C_{18}), 53.1 (C_{21}), 56.2 (C_2), 56.3, 57.9, 58.0 (3xOCH_3), 70.0 (C_{13}), 75.1 (C_{33}), 76.0 (C_{26}), 77.6 (C_{15}), 82.3 (C_{14}), 84.1 (C_{32}), 100.2 (C_9), 116.5 (C_{38}), 123.3 (C_{20}), 131.6 (C_{28}), 135.4 (C_{29}), 135.6 (C_{37}), 138.9 (C_{19}), 167.4 (C_8), 169.8 (C_1), 172.9 (C_{10}), 209.1 (C_{22}); Z-isomer δ 10.1 (25-CH_3), 12.8 (28-CH_3), 16.5 (19-CH_3), 20.6 (C_4), 21.5 (17-CH_3), 24.6 (C_5), 26.4 (C_3), 27.9 (C_{17}), 30.5 (C_{35}), 34.9 (C_{36}), 35.1 (C_{11}), 37.6 (C_{31}), 41.7 (C_{25}), 45.4 (C_6), 47.6 (C_{23}), 48.8 (C_{18}), 51.5 (C_2), 52.3 (C_{21}), 56.6, 57.1, 57.9 (3xOCH_3), 69.3 (C_{24}), 81.6 (C_{14}), 84.2 (C_{32}), 99.6 (C_9), 116.9 (C_{38}), 124.0 (C_{20}), 130.1 (C_{29}), 132.6 (C_{28}), 166.8 (C_8), 170.2 (C_1), 170.4 (C_{10}), 208.7 (C_{22}).

24,33-Bis-(t.butyl-dimethylsilyl)-Δ^9-11-epi-FR 900520 (8b): A solution of 1.5 g (1.52 mmol) **7b** (E-isomer) in 20 ml of dry toluene was heated under reflux and treated with 0.8 ml (3.03 mmol) of nBu_3SnH and a catalytical amount of AIBN. Heating was continued for 15 h. After cooling to room temperature the solvent was evaporated in vacuo. Separation by column chromatography (SiO_2,dichloromethane/ acetone = 10/1) gave 678 mg (45%) of an E/Z (2/1) mixture of **8b** (colourless foam) and 351 mg (23%) of recovered **7b**. ^{1}H-NMR ($CDCl_3$) E-isomer δ 0.81 (d, J=7Hz, 25-CH_3), 0.97 (d, J=6.5Hz, 17-CH_3), 1.27 (d, J=6.5Hz, 11-CH_3), 2.45 (d, J=6Hz, H-23), 2.60 (dd, J_1=5Hz, J_2=17.5Hz, H-23), 2.90 (m, H-6a), 2.94 (m, H-32), 3.36, 3.42, 3.44 (3s, 3xOCH_3), 3.52 (dd, J_1=5Hz, J_2=17Hz, H-15), 3.76 (m, H-13), 4.12 (m, H-24), 4.52 (d, J=13Hz, H-6e), 4.65 (d, J=5Hz, H-2), 4.94 (dd, J_1=10Hz, J_2=10Hz, H-20), 5.23 (d, J=5Hz, H-26), 5.24 (d, J=8.5Hz, H-29), 5.52 (s, H-9); Z-isomer δ 0.81 (d, J=7Hz, 25-CH_3), 0.97 (d, J=6.5Hz, 17-CH_3), 1.27 (d, J=6.5Hz, 11-CH_3), 3.09 (m, H-6a), 3.36, 3.38, 3.40 (3s, 3xOCH_3), 3.88 (m, H-13), 3.97 (d, J=13Hz, H-6e), 4.23 (m, H-24), 5.07 (d, J=9Hz, H-20), 5.32 (s, H-9), 5.36 (d, J=9.5Hz, H-29), 5.47 (d, J=4Hz, H-2).

24,33-Bis-(t.butyl-dimethylsilyl)-Δ^{10}-FK 506 (9a): 50 mg (0.05 mmol) of **7a** (E-isomer) were dissolved in 2 ml of dry toluene and heated under reflux for 6 h. Afterwards the reaction solution was cooled to room temperature and the solvent evaporated in vacuo. The residue was purified by filtration over SiO_2 (hexane/ethyl acetate = 2/1) leading to 45 mg (90%) of **9a** as a colourless foam. ^{1}H-NMR ($CDCl_3$), mixture of two conformers: 4/1; major conformer δ -0.05, 0.03, 0.08, 0.09 (4s, 2Si(CH_3)$_2$), 1.74 (s, 11-CH_3), 2.46+2.58 (AB-system, J=10Hz, 2H-9), 2.73 (dd, J_1=5.5Hz, J_2=15Hz, H-12), 2.96 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.09 (d, J=15Hz, H-6a), 3.40, 3.42, 3.44 (3s, 3xOCH_3), 3.58 (d, J=15Hz, H-6e), 3.62 (dd, J_1=1Hz, J_2=10Hz, H-14), 3.72 (dd, J_1=2Hz, J_2=7.5Hz, H-13), 4.22 (m, H-24), 4.94 (dd, J_1=2Hz, J_2=10Hz, H-38), 5.01 (dd, J_1=2Hz, J_2=17Hz, H-38), 5.02 (d, J=10Hz, H-20), 5.11 (d, J=5Hz, H-2), 5.12 (s, H-26), 5.16 (d, J=8Hz, H-29), 5.70 (ddt, J_1=6Hz, J_2=10Hz, J_3=17Hz, H-37); minor conformer δ 3.32, 3.41, 3.43 (3s, 3xOCH_3), 4.09 (m, H-24), 4.50 (d, J=12.5Hz, H-6e), 4.83 (m, H-2), 4.87 (m, H-20), 5.29 (d, J=8Hz, H-29), 5.38 (d, J=5Hz, H-26). ^{13}C-NMR ($CDCl_3$), major conformer δ -4.6, -4.7, -4.8, -5.0 (2Si(CH_3)$_2$), 10.1 (25-CH_3), 14.5 (28-CH_3), 16.7 (19-CH_3), 17.4 (17-CH_3), 18.8 (11-CH_3), 21.6 (C_4), 25.0 (C_4), 25.8 (2SiC(CH_3)$_3$), 26.7 (C_{17}), 30.9 (C_{35}), 33.8 (C_{34}), 34.2 (C_{16}), 34.5 (C_{12}), 34.9 (C_{30}, C_{31}), 35.6 (C_{36}), 36.5 (C_9), 41.3 (C_{25}), 43.1 (C_6), 44.2 (C_{23}), 48.2 (C_{18}), 52.8 (C_2), 54.1 (C_{21}), 56.3, 57.3, 57.6 (3xOCH_3), 69.9 (C_{24}), 71.5 (C_{14}), 72.5 (C_{13}), 75.1 (C_{33}), 76.2 (C_{15}), 76.8 (C_{26}), 84.1 (C_{32}), 104.8 (C_{11}), 115.9 (C_{38}), 121.9 (C_{20}), 129.3 (C_{29}), 132.7 (C_{28}), 136.2 (C_{37}), 140.0 (C_{19}), 143.1 (C_{10}), 168.9 (C_8), 169.0 (C_1), 210.3 (C_{22}).

24,33-Bis-(t.butyl-dimethylsilyl)-Δ^{10}-FR 900520 (9b): From E-isomer: 600 mg (0.6 mmol) of **7b** (E-isomer) in 15 ml of dry toluene were heated under reflux for 24 h. Afterwards the reaction solution was evaporated in vacuo and the residue purified by column chromatography (SiO_2, dichloromethane/acetone = 20/1) yielding 395 mg (66%) of **9b** as a colourless foam. From Z-isomer: 50 mg (0.005 mmol) of **7b** (Z-isomer) in 5 ml of dry toluene were heated under reflux for 48 h. Afterwards the reaction solution was evaporated in vacuo and the residue purified by column chromatography (SiO_2, hexane/ ethyl acetate = 3/1) yielding 32 mg (64%) of **9b** as a colourless foam. ^{1}H-NMR ($CDCl_3$), mixture of two conformers: 2.5/1; major conformer δ -0.05, 0.03, 0.07, 0.09 (4s, 2Si(CH_3)$_2$), 1.74 (s, 11-CH_3), 2.36+2.50 (AB-system, J=15Hz, 2H-9), 2.73 (dd, J_1=5.5Hz, J_2=15Hz, H-12), 2.96 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.10 (m, H-6a), 3.40, 3.42, 3.44 (3s, 3xOCH_3), 3.58 (d, J=15Hz, H-6e), 3.62 (dd, J_1=1Hz, J_2=10Hz, H-14), 3.65 (m, H-15, H-33), 3.72 (dd, J_1=2Hz, J_2=7.5Hz, H-13), 4.20 (m, H-24), 5.01 (d, J=10Hz, H-20), 5.12 (2d, J_1=5Hz, J_2=8Hz, H-2, H-29), 5.13 (s, H-26); minor conformer δ 3.55 (dd, J_1=1Hz, J_2=10Hz, H-14), 4.07 (m, H-24), 4.49 (d, J=12.5 Hz, H-6e), 4.82 (m, H-2), 4.91 (d, J=10Hz, H-20), 5.29 (d, J=8Hz, H-29), 5.35 (d, J=5.5Hz, H-26).

24,33-Bis-(t.butyl-dimethylsilyl)-9-deoxo-36-hydro-37-(tris-trimethylsilyl)-silyl- FK 506 (10): 146 mg (0.14 mmol) of thiocarbonate **5a** were treated with 0.13 ml of [(CH_3)$_3$]$_3$SiH and a catalytical amount of AIBN in 8 ml of toluene for 40 min. as described in method C. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate = 2/1) leading to 70 mg (38%) of **10**. ^{1}H-NMR ($CDCl_3$) δ -0.06, 0.01, 0.06, 0.08 (4s, 2Si(CH_3)$_2$), 0.12 (s, Si(CH_3)$_3$), 0.72 (d, J=5.5Hz, 17-CH_3), 0.97 (d, J=5.5Hz, 25-CH_3),

1.95 (m, H-12), 2.28 (m, H-23), 2.50 (dd, J_1=10Hz, J_2=15Hz, H-23), 2.56+2.67 (AB-system, J=15Hz, 2H-9), 2.95 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.10 (dt, J_1=5Hz, J_2=10Hz, H-21), 3.22 (dt, J_1=5Hz, J_2=10Hz, H-6a), 3.37, 3.38, 3.41 (3s, 3xOCH_3), 3.57 (m, H-15), 3.68 (d, J=10Hz, H-6e), 3.92 (dd, J_1=2Hz, J_2=10Hz, H-14), 4.18 (m, H-24), 4.93 (d, J=4Hz, H-2), 4.95 (d, J=6.5Hz, H-29), 5.12 (s, H-26). ^{13}C-NMR ($CDCl_3$) δ -4.5, -4.7, -5.0 (2Si(CH_3)$_2$), 1.1 (3Si(CH_3)$_3$), 8.0 (C_{37}), 10.0 (25-CH_3), 14.8 (28-CH_3), 15.5 (19-CH_3), 16.8 (11-CH_3), 17.8 (17-CH_3), 18.3 (C_{36}), 21.2 (C_4), 24.5 (C_5), 25.4 (C_{17}), 25.9 (2SiC(CH_3)$_3$), 26.7 (C_3), 31.0 (C_{35}), 32.8 (C_{12}), 33.9 (C_{34}), 35.0 (C_{30}, C_{31}), 36.8 (C_{16}), 37.4 (C_{11}), 38.5 (C_9), 41.6 (C_{25}), 42.5 (C_6), 43.9 (C_{23}), 48.5 (C_{18}), 52.6 (C_2), 54.5 (C_{21}), 56.2, 57.6, 58.0 (3xOCH_3), 70.4 (C_{24}), 72.4 (C_{14}), 74.4 (C_{13}), 75.7 (C_{33}), 76.6 (C_{26}), 76.8 (C_{15}), 84.2 (C_{32}), 98.5 (C_{10}), 121.9 (C_{20}), 128.3 (C_{29}), 133.2 (C_{28}), 140.9 (C_{19}), 168.9 (C_1), 173.5 (C_8), 212.0 (C_{22}).

24,33-Bis-(t.butyl-dimethylsilyl)-9-deoxo-10(R)-deoxy-FR 900520 (11) and 24,33-Bis-(t.butyl-dimethylsilyl)-9-deoxo-10(S)-deoxy-FR 900520 (12): From E-isomer: To a solution of 810 mg (0.82 mmol) of 7b (E-isomer) in 4 ml of Et_3SiH, 24 mg of $(Ph_3P)_3RhCl$ were added and heated under an atmosphere of argon at 50°C (bath temperature) for 20 h. After cooling to room temperature the reaction solution was consecutively treated with 15 ml of methanol and 30 mg of K_2CO_3 and stirring was continued for one hour. The reaction mixture was filtered, the solvent evaporated and the residue taken up in toluene and evaporated again. Separation of the resulting mixture was performed by column chromatography (SiO_2, hexane/ethyl acetate=2/1) leading to 216 mg (22%) of 11 (colourless foam), 32 mg (4%) of 12 (colourless foam) and 21 mg (3%) of starting material 7b. From Z-isomer: To a solution of 500 mg (0.51 mmol) of 7b (Z-isomer) in 4 ml of Et_3SiH, 20 mg of $(Ph_3P)_3RhCl$ were added and heated at 50°C (bath temperature) for 28 h. Work up was the same as described for the E-isomer. Column chromatography (SiO_2, hexane/ ethyl acetate = 2/1) yielded 223 mg (45%) of 11 (colourless foam) and 162 mg (32%) of 12 (colourless foam). 11: ^{1}H-NMR ($CDCl_3$) δ -0.07, 0.01, 0.07, 0.08 (4s, 2Si(CH_3)$_2$), 1.14 (q, J=11Hz, H-12a), 1.56 (d, J=7.5Hz, H-11), 2.22 (d, J=15.5Hz, H-23), 2.30 (m, H-12e), 2.41 (dd, J_1=1Hz, J_2=15Hz, H-9), 2.55 (dd, J_1=9.5Hz, J_2=15.5Hz, H-23), 2.57 (dd, J_1=10Hz, J_2=15Hz, H-9), 2.96 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.08 (d, J=12.5Hz, H-6a), 3.22 (dd, J_1=2Hz, J_2=9Hz, H-14), 3.35, 3.38, 3.40 (3s, 3xOCH_3), 3.46 (ddd, J_1=5Hz, J_2=10Hz, J_3=11Hz, H-13), 3.51 (ddd, J_1=2Hz, J_2=4Hz, J_3=11.5Hz, H-15), 3.62 (dt, J_1=1Hz, J_2=9Hz, H-10), 3.74 (d, J=12.5Hz, H-6e), 4.19 (ddd, J_1=1.5Hz, J_2=5Hz, J_3=10Hz, H-24), 4.96 (d, J=8Hz, H-20), 4.97 (s, H-2), 5.16 (s, H-26), 5.18 (d, J=8Hz, H-29). ^{13}C-NMR ($CDCl_3$) δ -4.5, -4.7, -5.0 (2Si(CH_3)$_2$), 10.0 (25-CH_3), 11.6 (C_{37}), 14.8 (28-CH_3), 16.5 (19-CH_3), 17.5 (11-CH_3), 18.0 (17-CH_3), 21.7 (C_4), 22.3 (C_5), 24.9 (C_{36}), 25.8 (2SiC(CH_3)$_3$), 26.2 (C_3), 26.9 (C_{17}), 31.0 (C_{35}), 33.8 (C_{34}), 34.3 (C_{11}), 34.9 (C_{30}), 35.3 (C_9), 36.1 (C_{16}), 36.7 (C_{31}), 38.4 (C_{12}), 41.7 (C_{25}), 42.5 (C_6), 43.9 (C_{23}), 48.3 (C_{18}), 52.8 (C_2), 56.3 (C_{21}), 56.4, 57.4, 58.0 (3xOCH_3), 72.5 (C_{24}), 74.3 (C_{13}), 75.2 (C_{33}), 75.4 (C_{26}), 76.5 (C_{15}), 79.8 (C_{14}), 80.7 (C_{10}), 84.2 (C_{32}), 121.5 (C_{20}), 128.3 (C_{29}), 133.2 (C_{28}), 141.0 (C_{19}), 169.1, 170.7 (C_1, C_8), 211.9 (C_{22}). 12: H^1-NMR ($CDCl_3$) δ -0.05, 0.03, 0.06, 0.08 (4s, 2Si(CH_3)$_2$), 1.40 (dd, J_1=5Hz, J_2=9Hz, H-36), 1.76 (d, J=4Hz, H-25), 1.80 (dd, J_1=5Hz, J_2=9Hz, H-36), 2.08 (m, H-11), 2.30 (dd, J_1=3Hz, J_2=16Hz, H-23), 2.43 (dd, J_1=8.5Hz, J_2=16Hz, H-23), 2.59 (dd, J_1=4.5 Hz, J_2=14Hz, H-9), 2.73 (dd, J_1=11.5Hz, J=$_2$14Hz, H-9), 2.94 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.07 (dt, J_1=5Hz, J_2=9Hz, H-21), 3.25 (d, J=11.5Hz, H-6a), 3.26 (d, J=11.5Hz, H-6a), 3.34, 3.38, 3.40 (3s, 3xOCH_3), 3.44 (d, J=9Hz, H-15), 3.63 (dd, J_1=2Hz, J_2=9Hz, H-14), 3.64 (d, J=11.5Hz, H-6e), 4.17 (ddd, J_1=4.5Hz, J_2=5Hz, J_3=11.5Hz, H-10), 4.21 (ddd, J_1=3Hz, J_2=4Hz, J_3=8.5Hz, H-24), 5.02 (d, J=9Hz, H-29), 5.17 (d, J=10Hz, H-20), 5.18 (s, H-26), 5.22 (d, J=7Hz, H-2). ^{13}C-NMR ($CDCl_3$) δ -4.5, -4.7, -4.9 (2Si(CH_3)$_2$), 10.0 (25-CH_3), 11.7 (C_{37}), 14.4 (28-CH_3), 17.1 (19-CH_3), 17.2 (11-CH_3), 18.5 (17-CH_3), 21.6 (C_4), 22.6 (C_{36}), 25.4 (C_5), 25.8 (2SiC(CH_3)$_3$), 26.1 (C_{17}), 26.9 (C_3), 30.9 (C_{11}), 31.0 (C_{35}), 31.5 (C_9), 32.7 (C_{12}), 33.9 (C_{34}), 34.9 (C_{30}), 35.4 (C_{16}), 36.7 (C_{31}), 41.2 (C_6), 44.0 (C_{25}), 44.3 (C_{23}), 47.9 (C_{18}), 52.4 (C_{21}), 56.1 (C_2), 56.2, 57.3, 58.0 (3xOCH_3), 71.3 (C_{24}), 71.7 (C_{14}), 73.8 (C_{10}), 74.6 (C_{13}), 75.2 (C_{33}), 76.1 (C_{26}), 76.6 (C_{15}), 84.2 (C_{32}), 121.9 (C_{20}), 129.3 (C_{29}), 133.1 (C_{28}), 139.8 (C_{19}), 169.4, 170.0 (C_1, C_8), 211.3 (C_{22}).

General procedure for deprotection:

A solution of 1 mmol of the desired bis-silylated compound in 20 ml acetonitrile was treated with 0.4 ml 40% HF at 0°C, followed by warming to room temperature. When the reaction was complete the reaction mixture was diluted with ethyl acetate and washed with water until neutral. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. The obtained material was purified by column chromatography using ethyl acetate or a mixture of dichloromethane/diisopropyl ether/methanol =10/4/1 as eluent.

9-Deoxo-FK 506 (13a): The standard procedure afforded the product as a colourless foam (220 mg,

94%) from 300 mg **7a**. ^{1}H-NMR ($CDCl_3$) δ 0.77 (d, J=6Hz, 25-CH_3), 0.89 (d, J=7.5Hz, 11-CH_3), 0.96 (d, J=5Hz, 17-CH_3), 2.25 (dd, J_1=10Hz, J_2=17Hz, H-23), 2.52+2.69 (AB-system, J=15Hz, 2H-9), 2.65 (d, J=17Hz, H-23), 3.01 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.19 (dd, J_1=2Hz, J_2=12.5 Hz, H-6a), 3.38, 3.42 (2s, 3xOCH_3), 3.54 (m, H-15), 3.55 (d, J=2Hz, 24-OH), 3.72 (dd, J_1=2.5Hz, J_2=12.5Hz, H-6e), 3.87 (dd, J_1=2Hz, J_2=10Hz, H-14), 4.02 (m, H-24), 4.98 (d, J=5Hz, H-2), 5.00 (d, J=10Hz, H-20), 5.02 (dd, J_1=2Hz, J_2=10.5Hz, H-38), 5.06 (dd, J_1=2Hz, J_2=15Hz, H-38), 5.12 (d, J=2.5 Hz, H-29), 5.21 (s, H-26), 5.72 (ddt, J_1=6Hz, J_2=10Hz, J_3=17Hz, H-37), 7.09 (s, 10-OH). ^{13}C-NMR ($CDCl_3$) δ 9.8 (25-CH_3), 14.4 (28-CH_3), 15.7 (19-CH_3), 16.8 (11-CH_3), 18.7 (17-CH_3), 20.7 (C_4); 24.4 (C_5), 25.8 (C_{17}), 26.6 (C_3), 30.7 (C_{35}), 31.3 (C_{34}), 32.6 (C_{12}), 34.9 (C_{30}, C_{31}), 35.8 (C_{36}), 36.3 (C_{16}), 37.3 (C_{11}), 38.5 (C_{25}), 40.5 (C_9), 42.5 (C_{23}), 42.6 (C_6), 48.4 (C_{18}), 52.6 (C_2), 53.4 (C_{21}), 56.0, 56.5, 57.6 (3xOCH_3), 69.3 (C_{24}), 70.7 (C_{14}), 73.5 (C_{33}), 74.4 (C_{13}), 76.7 (C_{15}), 77.0 (C_{26}), 84.2 (C_{32}), 98.4 (C_{10}), 116.5 (C_{38}), 121.4 (C_{20}), 128.9 (C_{29}), 132.4 (C_{28}), 135.4 (C_{37}), 141.1 (C_{19}), 169.3 (C_1), 173.9 (C_8), 214.0 (C_{22}). FAB MS: 772 $(M\text{-}OH)^+$, 790 $(MH)^+$.

9-Deoxo-FR 900520 (13b): The standard procedure afforded the product as a colourless foam (235 mg, 75%) from 400 mg **7b**. ^{1}H-NMR ($CDCl_3$) δ 0.78 (d, J=6Hz, 25-CH_3), 0.95 (d, J=5.5Hz, 17-CH_3), 2.23 (dd, J_1=11Hz, J_2=17Hz, H-23), 2.51+2.69 (AB-system, J=16Hz, 2H-9), 2.67 (d, J=1.5Hz, 33-OH), 2.68 (d, J=17Hz, H-23), 3.00 (ddd, J_1=4Hz, J_2=9Hz, J_3=11Hz, H-32), 3.14 (q, J=7Hz, H-21), 3.22 (dd, J_1=3Hz, J_2=12Hz, H-6a), 3.37, 3.42 (2s, 3xOCH_3), 3.53 (m, H-15), 3.65 (d, J=2Hz, 24-OH), 3.71 (d, J=12Hz, H-6e), 3.87 (dd, J_1=2Hz, J_2=9.5Hz, H-14), 4.00 (m, H-24), 4.87 (dd, J_1=2Hz, J_2=6Hz, H-2), 4.98 (d, J=9Hz, H-20), 5.07 (d, J=8.5Hz, H-29), 5.22 (s, H-26), 7.09 (d, J=1.5Hz, 10-OH). ^{13}C-NMR ($CDCl_3$) δ 9.8 (C_{25}), 11.8 (C_{37}), 14.5 (28-CH_3), 15.5 (19-CH_3), 16.9 (11-CH_3), 18.8 (17-CH_3), 20.7 (C_4), 24.4 (C_{36}), 24.9 (C_{25}), 25.7, 26.6 (C_3, C_{17}), 30.7 (C_{35}), 31.2 (C_{34}), 32.6 (C_{12}), 34.8 (C_{30}, C_{31}), 36.2 (C_{16}), 37.2 (C_{11}), 38.5 (C_{23}), 40.3 (C_{25}), 41.8 (C_9), 42.6 (C_6), 48.5 (C_{18}), 52.5 (C_2), 55.4 (C_{21}), 56.1, 56.6, 57.7 (3xOCH_3), 69.6 (C_{24}), 70.7 (C_{14}), 73.5 (C_{33}), 74.3 (C_{13}), 76.4 (C_{15}), 77.0 (C_{26}), 84.2 (C_{32}), 98.5 (C_{10}), 122.0 (C_{20}), 128.7 (C_{29}), 132.4 (C_{28}), 141.1 (C_{19}), 169.4 (C_1), 174.0 (C_8), 215.3 (C_{22}). FAB MS: 760 $(M\text{-}OH)^+$, 778 $(MH)^+$.

9-Deoxo-10(R)-deoxy-FR 900520 (14): The standard procedure afforded the product as a colourless foam (80 mg, 50%) from 210 mg of **11**. ^{1}H-NMR ($CDCl_3$), mixture of two conformers: 3/2; major conformer δ 0.79 (d, J=6Hz, 25-CH_3), 0.95 (d, J=7Hz, 17-CH_3), 2.37 (dd, J_1=1Hz, J_2=16Hz, H-9), 2.60 (dd, J_1=10Hz, J_2=16Hz, H-9), 3.00 (m, H-32), 3.17 (dd, J_1=2Hz, J_2=9Hz, H-14), 3.35, 3.36, 3.40 (3s, 3xOCH_3), 3.58 (dt, J_1=2Hz, J_2=9Hz,H-10), 3.98 (m, H-24), 4.90 (dd, J_1=1Hz, J_2=4.5Hz, H-2), 4.98 (d, J=9Hz, H-29), 5.08 (d, J=8.5Hz, H-20), 5.19 (s, H-26); minor conformer δ 4.48 (d, J=13Hz, H-6e), 4.62 (d, J=5Hz, H-2), 4.83 (d, J=10Hz, H-29), 5.05 (d, J=9Hz, H-20), 5.22 (s, H-26). ^{13}C-NMR ($CDCl_3$), major conformer δ 9.8 (25-CH_3), 11.8 (C_{37}), 14.6 (28-CH_3), 15.8 (19-CH_3), 17.6 (11-CH_3), 19.4 (17-CH_3), 21.1 (C_4), 23.4 (C_5), 25.1 (C_{36}), 26.0 (C_3), 26.8 (C_{17}), 30.6 (C_{35}), 31.2 (C_{34}), 34.1 (C_{11}), 34.8 (C_{30}, C_{31}), 35.4, 36.6, 38.1 (C_9, C_{12}, C_{16}), 40.1 (C_{25}), 41.6 (C_6), 42.6 (C_{23}), 48.6 (C_{18}), 52.8 (C_2), 55.4 (C_{24}), 56.3, 56.5, 57.4 (3xOCH_3), 69.8 (C_{24}), 73.5 (C_{33}), 74.3 (C_{13}), 76.0 (C_{15}), 77.2 (C_{26}), 79.7 (C_{14}), 80.4 (C_{10}), 84.2 (C_{32}), 121.8 (C_{20}), 128.4 (C_{29}), 132.5 (C_{28}), 141.2 (C_{19}), 169.6 (C_1), 171.3 (C_8), 215.3 (C_{22}). FAB MS: 744 $(M\text{-}OH)^+$, 762 $(MH)^+$.

9-Deoxo-10(S)-deoxy-FR 900520 (15): The standard procedure afforded the product as a colourless foam (59 mg, 80%) from 96 mg of **12**. ^{1}H-NMR ($CDCl_3$) δ 2.08 (m, H-11), 2.28 (dd, J_1=9.5Hz, J_2=17Hz, H-23), 2.53 (dd, J_1=4Hz, J_2=15Hz, H-9), 2.66 (dd, J_1=2.5Hz, J_2=17Hz, H-23), 2.67 (dd, J_1=10.5 Hz, J_2=15Hz, H-9), 2.72 (s, 33-OH), 3.01 (ddd, J_1=4Hz, J_2=8Hz, J_3=11Hz, H-32), 3.14 (dt, J_1=6.5 Hz, J_2=9Hz, H-21), 3.32 (dd, J_1=3Hz, J_2=12.5Hz, H-6a), 3.35, 3.38, 3.40 (3s, 3xOCH_3), 3.47 (dd, J_1=4Hz, J_2=9.5Hz, H-15), 3.51 (dd, J_1=2Hz, J_2=9Hz, H-14), 3.72 (d, J=12.5Hz, H-6e), 3.96 (m, H-24), 4.26 (dt, J_1=4.5Hz, J_2=10Hz, H-10), 5.04 (d, J=9Hz, H-29), 5.05 (d, J=10Hz, H-20), 5.16 (d, J=2Hz, H-26), 5.18 (d, J=5.5Hz, H-2). FAB MS: 744 $(M\text{-}OH)^+$, 762 $(MH)^+$.

24,33-Bis-(t.butyl-dimethylsilyl)-9(R)-dihydro-FR 900520-9-10- methylidene acetal (16): 200 mg (0.19 mmol) of **6b** were dissolved in 2 ml of nBu_3SnH, a catalytical amount of AIBN was added and the reaction solution was heated for 3 h at 100°C. The reaction mixture was diluted after cooling to room temperature with 2 ml of hexane and poured on a column filled with SiO_2 and equilibrated with hexane. nBu_3SnH was washed from the column with hexane and the residue was chromatographed with hexane/ ethyl acetate = 2/1. 126 mg (62%) of **17** as a colourless foam and 49 mg (26%) of **7b** (E/Z = 2.8/1) were obtained. ^{1}H-NMR ($CDCl_3$) mixture of two conformers: 5/1; major conformer δ -0.02, 0.04, 0.05, 0.07 (4s, 2$Si(CH_3)_2$), 1.01 (d, J=6.5Hz, 11-CH_3), 1.61 (28-CH_3), 1.68 (s, 19-CH_3), 2.66 (dd, J_1=1Hz, J_2=4.5Hz, H-23), 2.94 (ddd, J_1=5Hz, J_2=8Hz, J_3=11Hz, H-32), 3.30 (m, H-6a), 3.26, 3.36, 3.40 (3s, 3xOCH_3), 3.47 (m, H-6e, H-13, H-15), 3.54 (dd, J_1=1.5Hz, J_2=9.5Hz, H-14), 3.57 (m, H-21), 4.31 (m, H-24), 4.85 (d, J=8.5Hz, H-2), 4.93 (d, J=9Hz,

H-29), 4.95 (s, H-9), 4.99 (d, J=5Hz, H-20), 5.16, 5.47 (2s, -O-CH_2-O-), 5.18 (s, H-26); minor conformer δ 4.07 (m, H-24), 4.46 (d, J=14Hz, H-6e), 4.60 (s, H-9), 4.70 (d, J=9Hz, H-20), 4.84, 4.99 (2s, -O-CH-O-), 5.12 (d, J=8.5Hz, H-29), 5.28 (m, H-2, H-26). ^{13}C-NMR ($CDCl_3$) major conformer δ 10.0 (25-CH_3), 11.7 (C_{37}), 14.7 (28-CH_3), 15.5 (11-CH_3), 16.2 (19-CH_3), 20.5 (17-CH_3), 21.0 (C_4), 23.6 (C_5), 24.9 (C_{17}), 25.8 (2Si(CH_3)$_3$), 25.9 (C_{36}), 26.0 (C_3), 31.0 (C_{35}), 32.1 (C_{16}), 32.7 (C_{34}), 33.9 (C_{12}), 34.9 (C_{30}), 36.0 (C_{11}), 36.8 (C_{31}), 40.8 (C_{25}), 41.4 (C_6), 46.0 (C_{23}), 49.2 (C_{18}), 53.1 (C_2), 53.9 (C_{21}), 56.3, 56.8, 58.0 (3xOCH_3), 70.6 (C_{24}), 73.3 (C_{13}), 73.5 (C_{14}), 74.6 (C_{26}), 75.2 (C_{33}), 76.4 (C_{15}), 77.3 (C_9), 84.2 (C_{32}), 96.8 (-O-CH_2-O-), 105.5 (C_{10}), 123.1 (C_{20}), 128.1 (C_{29}), 132.4 (C_{28}), 138.2 (C_{19}), 167.7 (C_8), 169.4 (C_1), 212.9 (C_{22}). FAB MS: 902 $(M\text{-OtBDMS})^+$, 1034 $(MH)^+$.

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