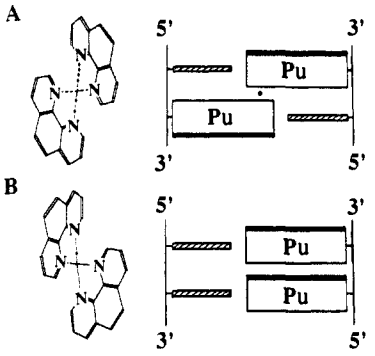

Figure 2. An illustration of the basis for the enantioselective cleavage by $Rh(phen)_2phi^{3+}$ at propeller-twisted sites on DNA. Shown schematically in A is the 5'-pyr-pur-3' step, with the purine bases propeller twisted either upward (in the top base pair) or downward (in the bottom base pair), matching the disposition of the Δ isomer, and pyrimidines oriented perpendicular to the helical axis. The C_2 axis along the dyad is marked by the ●. The Λ isomer, with the opposite orientation of ancillary ligands, would clash with the pyrimidine bases. In B are shown the disposition of ancillary phenanthroline ligands in the Λ isomer, also viewed along the intercalative dyad axis, and the schematic illustration of a 5'-pyr-pyr-3' step, which lacks a C_2 axis along the dyad direction. Because of the absence of this C_2 axis, enantiomeric discrimination does not accompany intercalation into the 5'-pyr-pyr-3' sequence.

nucleotide symmetry of DNA helices may provide an indirect, sequence-selective element that is important in the recognition of sites by proteins.

Acknowledgment. We are grateful to the National Institutes of Health and the National Foundation for Cancer Research for their financial support. We also thank T. Shields for his excellent technical assistance.

Registry No. d(CGCGAATTCGCG), 77889-82-8; Λ-$Rh(phen)_2phi^{3+}$, 130192-92-6; Δ-$Rh(phen)_2phi^{3+}$, 130192-93-7; *rac*-$Rh(phen)_2phi^{3+}$, 121174-96-7.

Supplementary Material Available: An autoradiogram showing cleavage by $Rh(phen)_2phi^{3+}$ enantiomers on a fragment rich in homopyrimidine-homopurine tracts (2 pages). Ordering information is given on any current masthead page.

Solution Structure of FK 506 from Nuclear Magnetic Resonance and Molecular Dynamics

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The conformation of the highly active immunosuppressant FK 506[1-3] (Figure 1) has been examined by high-resolution NMR and NOE restrained molecular dynamics simulations. All of the ^1H and ^{13}C resonances were assigned by using a combination of 2D NMR techniques[4,5] including TOCSY,[6] E. COSY,[7] ROESY,[8]

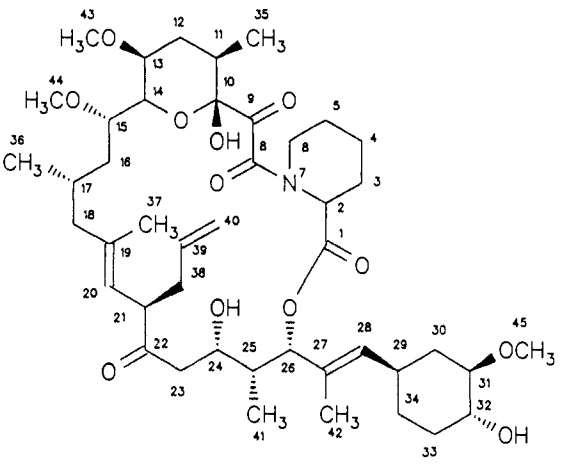

Figure 1. Constitution of FK 506 illustrating the numbering of the atoms.

Table I. Averages and Standard Deviations of Dihedrals of FK 506 from Molecular Dynamics and X-ray Structure[a]

	cis		trans		
torsion	av	SD	av	SD	X-ray
O2-1-2-3	-63	15	75	33	72
1-2-3-4	-80	7.7	-116	11	-76
2-3-4-5	-51	8.0	-51	8.2	-52
3-4-5-6	51	7.7	58	12	56
4-5-6-N7	-51	8.0	-43	19	-53
5-6-N7-2	53	8.4	47	11	50
6-N7-2-3	-51	7.2	-50	7.6	-47
6-N7-8-9	3	8.3	-178	6.1	1
7-8-9-10	-90	6.9	-98	8.5	-95
8-9-10-11	-47	8.8	134	8.7	-28
9-10-11-12	166	6.9	158	9.0	164
10-11-12-13	-53	6.6	-50	7.3	-54
11-12-13-14	56	5.8	53	7.3	58
12-13-14-15	178	5.8	-173	8.1	-175
13-14-15-16	174	7.4	-175	8.2	-178
14-15-16-17	60	10	58	8.4	68
15-16-17-18	-163	8.5	-140	16	172
16-17-18-19	100	27	151	12	66
17-18-19-20	165	18	174	18	-132
18-19-20-21	174	14	165	12	-168
19-20-21-22	-102	20	-106	16	-141
20-21-22-23	39	40	83	37	137
21-22-23-24	-66	31	-13	46	-118
22-23-24-25	-175	8.3	157	25	59
23-24-25-26	-117	13	73	6.7	-168
24-25-26-27	-89	8.2	177	7.4	56
25-26-27-28	-136	10	-72	8.1	-128
26-27-28-29	180	9.9	176	10	180
27-28-29-30	125	19	116	28	100
28-29-30-31	176	6.9	179	8.2	175
29-30-31-32	-52	6.9	-53	7.6	-56
30-31-32-33	52	7.2	53	7.6	62
31-32-33-34	-52	7.6	-53	7.7	-62
32-33-34-29	53	7.6	53	7.5	59
33-34-29-30	-54	7.2	-53	7.4	-55

[a] The dihedrals are defined by using the numbering of the heavy atoms from the Cambridge Data Bank. The values are given in degrees.

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(4) All NMR spectra were recorded at -30 or 27 °C on an AMX 600 (600 MHz) spectrometer equipped with ASPECT X32 and 3000 computers. A sample of FK 506 (20 mg) was dissolved in 0.5 mL of deuterated chloroform to give a final concentration of approximately 25 mM for each of the two configurational isomers.

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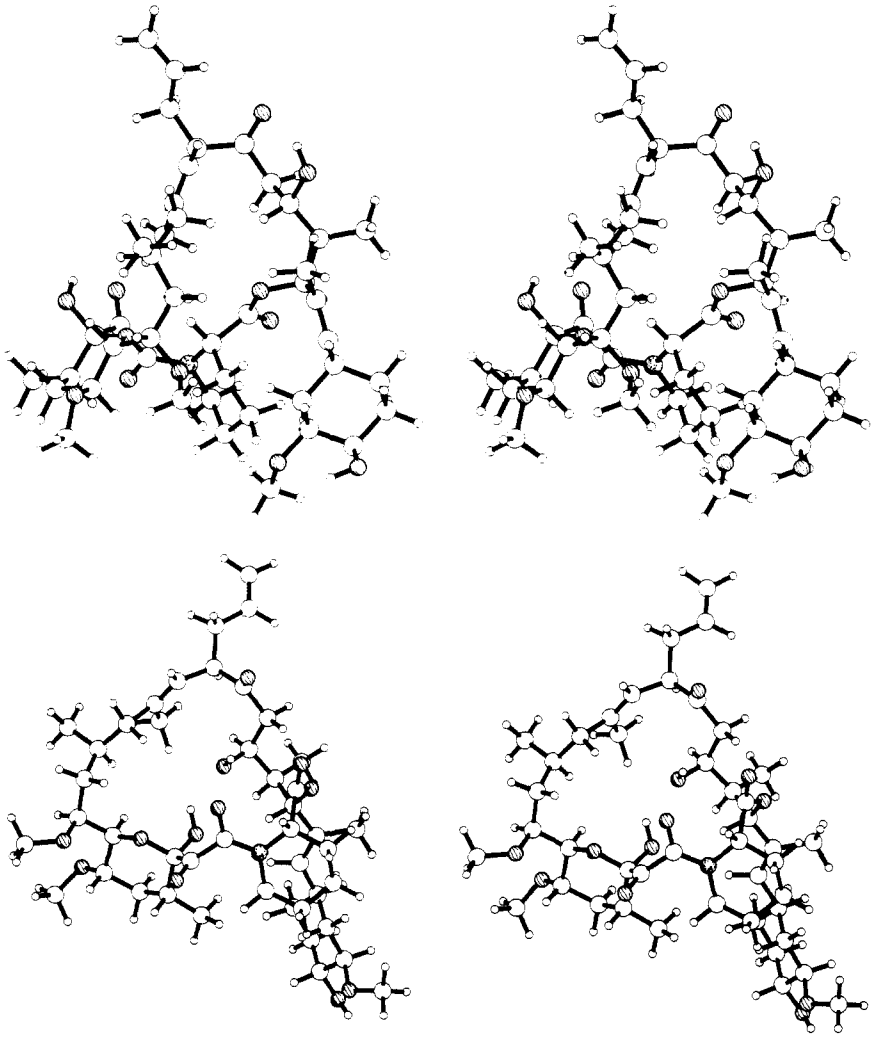

Figure 2. Stereostructure of low-energy conformations of FK 506 from NOE-restrained molecular dynamics. Above: conformation containing a cis peptide bond between atoms 7 and 8. Below: conformation with a trans peptide bond.

NOESY,[9] and ^{1}H detected H,C COSY (HMQC).[10] Two isomers with a ratio of 2:1 were observed in $CDCl_3$ solution. The isomers were assigned as cis and trans configurations about the single amide bond. Indeed, ROESY spectra measured at 27 °C in $CDCl_3$ revealed weak cross peaks due to chemical exchange. The assignment of the resonances started with C40; the ^{13}C resonance was identified from the HMQC experiment as the only methylene at low field. The spin system from H40 to C19-Me was assigned via homonuclear coupling from TOCSY experiments with various mixing times (16, 40, and 80 ms). The correlation between C19-Me and $(H18)_2$ was obtained through the ROESY spectrum. Again, using the TOCSY experiments in conjunction with the HMQC, it was possible to trace out the proton and carbon chemical shifts solely on the basis of scalar couplings from $(C18)_2$ to C11-Me. The remaining spin systems, H23-H26, H27Me-H34, and H2-H6, were identified in a similar manner. The assignment of the methoxy signals was based on the trivial ROESY correlations to neighboring protons.

Intramolecular proton-proton distances were defined from NOESY spectra recorded at -30 °C and used as constraints in molecular dynamics calculations.[11] The NOEs from the major and minor species were applied to both the cis and trans configurational isomers. Of the 48 NOE restraints used for the major isomer, 20 are unique (i.e., not found in the minor isomer). During the molecular dynamics simulation, the energy for the distance restraints was always 3 kcal/mol greater for the trans isomer compared to the cis isomer. There are three NOEs that are of particular importance with regard to this assignment; H2-H16, H2-H18, and H2-H23. These NOEs are across the 21-membered-ring system restricting the conformation of the ring and as determined from the NOE-restrained molecular dynamics are better suited to the cis structure; the trans configuration causes the ring system to adopt a more extended array and, therefore, cannot meet the distance restraints of the major isomer.

For the minor isomer, there were 49 NOE restraints, of which 21 are unique. The application of the experimental restraints to the cis and trans isomers produced clearly defined results: the energy of the distance restraints was always at least 5 kcal/mol greater for the cis isomer than the trans isomer. In addition, the total potential energy (without consideration of the distance restraints) was on average 10 kcal/mol greater for the cis config-

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(11) The computer simulations were carried out in vacuo by using the DISCOVER software package from BIOSYM (Hagler, A. T. In *The Peptides*; Udenfriend, S., Meienhofer, J., Hruby, V., Eds.; Academic Press: Orlando, FL, 1985; pp 214-296) on Silicon Graphics 4D/240SX and 4D/70GTB computers. The distance restraints were calculated from a comparison with the volume of the NOEs from geminal protons (distance 1.78 Å) using the two-spin approximation. The NOE-restrained molecular dynamics simulations were carried out at 500 K for a duration of 100 ps. The NOE restraints were applied by using a skewed biharmonic constraining function with maximum force constants of 185 and 20 kcal/(mol·Å^2) for upper and lower bounds, respectively.

urational isomer. This clearly indicates that the experimentally determined conformational parameters measured for the minor component are better suited to the trans configurational isomer.

The average values and standard deviations of the torsions during the NOE-restrained simulations are given in Table I. The torsions listed for the cis and trans isomers are from the application of the NOEs measured for the major and minor components, respectively. There are only two positions in the ring system that show significant differences: The torsion between atoms C9 and C10 changes by 180° while the C17–C18 torsion swivels by approximately 60° to compensate. These changes are reflected in the differences of the ^{13}C chemical shifts of the carbons involved in these torsions.[12]

Outside of the macrocyclic system, the molecular dynamics simulations suggest that the orientation of the six-membered ring (atoms 29–34) is different in the cis and trans isomers. The torsions 24–25 and 25–26 project the six-membered ring in opposite directions with regard to the plane of the macrocycle. This difference is illustrated by the minimum-energy structures for the cis and trans conformers taken from the NOE-restrained molecular dynamics simulations (Figure 2).

The conformation of the cis isomer in solution is similar to the X-ray structure through most of the molecule (see Table I). There are significant differences at the torsions between atoms 21–22, 22–23, 23–24, 24–25, and 25–26. This produces an extended and relatively "flat" structure within the crystal with the six-membered ring projecting out in the plane of the macrocycle. This flat orientation likely arises from the packing forces within the crystal. The importance of the orientation of this exocyclic portion is currently being investigated.

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(12) The differences in the chemical shifts of the carbons between the two isomers (major to minor) are +4.65, +1.15, −3.54, +1.63, −0.94, and +2.53 ppm for carbons C6, C8, C9, C10, C11, and C16, respectively. There are only minor differences (<0.5 ppm) in the chemical shifts of the remaining carbons.

Synthetic Studies on Quassinoids: Total Synthesis of (±)-Chaparrinone

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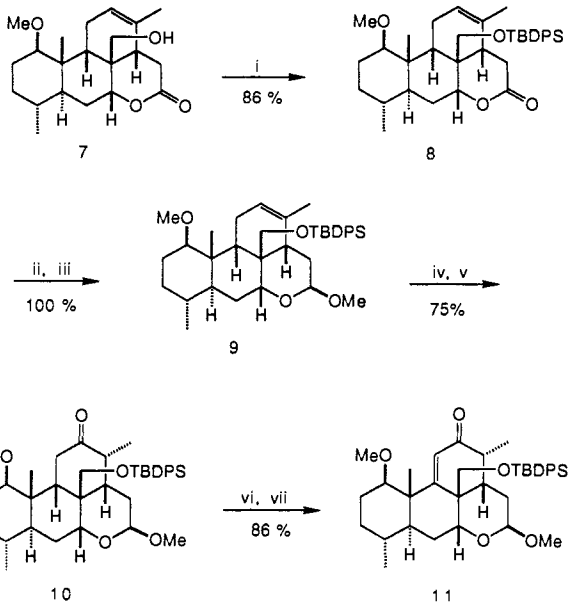
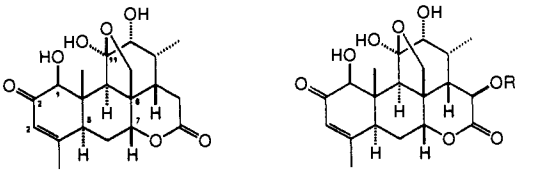
The C(8), C(11) bridged hemiketal structural array and the ring-A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit bearing a methyl group at C(4) found in chaparrinone (**1**) are structural features common to a large number of quassinoids.[1] These structural fragments appear to be essential for the rich array of pharmacological properties associated with quassinoids.[2] To date all efforts to prepare chaparrinone (**1**) and related quassinoids [cf. glaucarubinone (**2**)] have met with no success, in part, due to the incompatibility of the methods that have been developed independently for construction of the ring-A functionality[3] and the ring-C hemiketal array.[4] We detail herein the first total synthesis of (±)-chaparrinone featuring a new protocol for the elaboration of ring A which is compatible with functionality present in ring C.

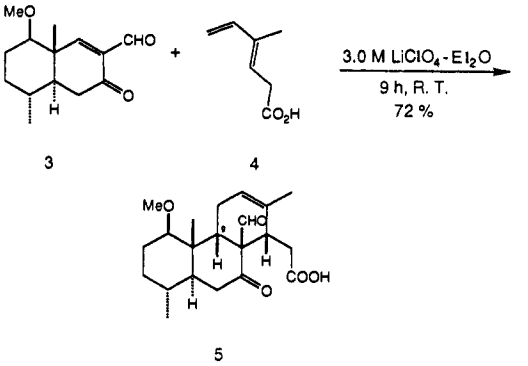
Scheme I. Preparation of Tetracyclic Enone **11**[a]



[a](i) TBDPSCl, imidazole, DMF; (ii) *i*-Bu_2AlH, THF, −78 °C; (iii) MeOH, concentrated HCl, THF; (iv) B_2H_6, THF, 0 °C; 3 N NaOH, 30% H_2O_2; (v) PCC, NaOAc, CH_2Cl_2; (vi) LDA, THF, −78 °C → 0 °C; TMSCl, −78 °C; (vii) $Pd(OAc)_2$, Na_2CO_3, CH_3CN, 45 °C.



Our strategy for constructing the ABC carbocyclic ring system of **1** was based on a Diels–Alder approach which necessitates, at some point in the synthesis, the inversion of configuration at C(9) (cf. structure **5**). Toward this end, exposure (9 h) of dienophile



3[5] to 5.0 equiv of dienoic acid **4** in 3.0 M $LiClO_4$–diethyl ether[6] at ambient temperature gave rise in 72% yield to crystalline keto acid **5**, mp 161.5–163.0 °C. Attempts to carry out the [4 + 2] cycloaddition in refluxing toluene required 2 days and gave rise to only a 20% yield of **5**, with the major product (60%) being the

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