8.002, 7.998, 7.801, 7.797, 7.789, 7.784, 7.783, 7.778, 7.772, 7.764, and 7.761. This spectrum was simulated with the following chemical shifts and coupling constants: $\nu_a = \delta$ 8.018, $\nu_b = \delta$ 7.780, $J_{AB} = 7.6$ Hz, $J_{AB'} = 1.2$ Hz, $J_{BB'} = 6.7$ Hz, and $J_{AA'} = 0.8$ Hz (Figure 3). The $^1$H-NMR spectrum of the collected diadduct fractions was complex (more than 100 transitions from $\delta$ 7.5–8.2) resulting from the many regiochemical possibilities for adding a second benzyne molecule to [$C_{60}$ + $C_6H_4$].

The $^{13}$C[$^1$H]-NMR spectrum (Figure 4) showed 19 transitions. A tabulation of the peaks is given in the figure caption. The $C_{2v}$ structure, corresponding to benzyne addition across the pyracyclene bonds, should give rise to 20 peaks in the spectrum; seven independent carbon atoms sit on mirror planes and 13 have unit occupancy. Correspondence between the proposed structure and the NMR spectrum would be achieved if the missing line, one of the expected weak signals, is isochronous with the peak at $\delta$ 143.30, thus contributing to its unique intensity. Symmetry considerations force us to conclude that addition occurs across bonds between fused six-membered rings. The coupled spectrum reveals that the peaks at $\delta$ 124.22 and $\delta$ 130.76 correspond to carbons carrying the protons. The signal at $\delta$ 78.75 is assigned to the quaternary bridgehead carbons of the fullerene cage which are the sites of attachment of the benzyne moiety. The upfield value confirms that the structure is the closed, rather than the open [10]annulene, isomer.[15] Complete analysis of the connectivity via the INADEQUATE sequence is in progress.[16]

The monoadduct of $C_{60}$ and benzyne is yellow in color; the UV/vis spectrum in *n*-hexane showed $\lambda_{max}$ at 320 nm with a weak visible band at 428 nm. The FTIR spectrum (KBr pellet) showed C–H absorption bands at 2924 and 2854 cm$^{-1}$. Additional frequencies were recorded at 1458, 1278, and 1024 cm$^{-1}$.

In one anomalous reaction of benzyne and buckminsterfullerene, we observed two AA'BB' spin systems in the aromatic region for the separated product that gave rise to a predominant ion (*m/z* 796) in the mass spectrometer. The major product showed eight major transitions at $\delta$ 7.627, 7.620, 7.616, 7.609, 7.480, 7.473, 7.468, and 7.462. We are investigating the possibility that even the monoaddition of benzyne to $C_{60}$ may be regiononspecific and subtly dependent on reaction conditions.

The isolated monoaddition product, corresponding to the downfield AA'BB' spin system, crystallized from $CS_2$ as dark red spars (mp >400 °C). Structure analysis by X-ray diffraction is in progress.

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## Synthesis of the 9,10-Acetonide of 9-Dihydro-FK-506[1]

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*Summary:* The synthesis of the analog FKANAL (I) of the immunosuppressant FK-506 in which the central features are the spiroenone system B which masks the $\alpha$-allyl aldol portion of FK-506 and the spiroketal D which mimics the $\alpha$-keto amide portion is described.

In the course of work directed toward the total synthesis of the immunosuppressant FK-506,[2] it appeared that the spiroketal I (FKANAL[3]) might be a close, stable analog of the natural product itself. Many of the salient features that effect the binding[4] of FK-506 to its receptor FKBP are preserved in this analog and the effector domain[4] remains identical to that of the natural product. The synthesis of this material became the first target of this work and this goal has now been achieved.

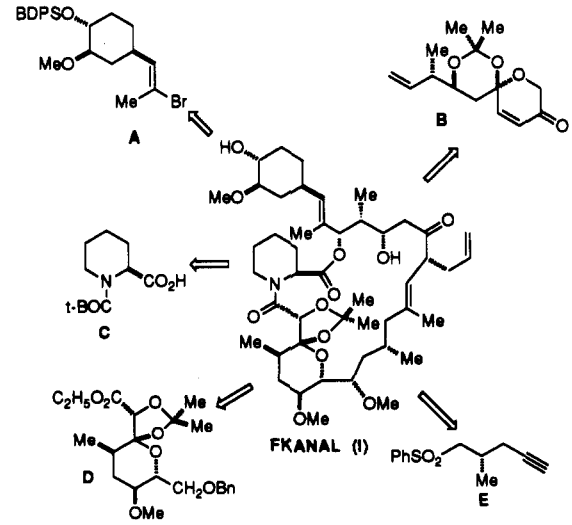


**Figure 1.** Parts for the synthesis of FK-506 analog.

The main features of the retrosynthetic plan for the analog I are the vinyl bromide A, the spiroenone B, and the spiroketal D (Figure 1). The assemblage of these parts

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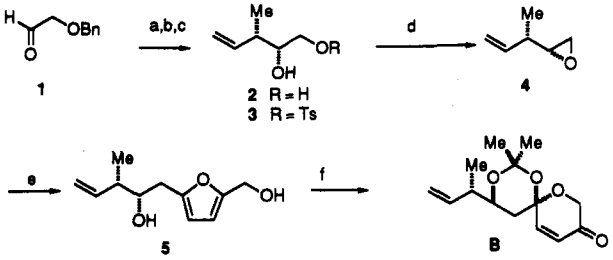
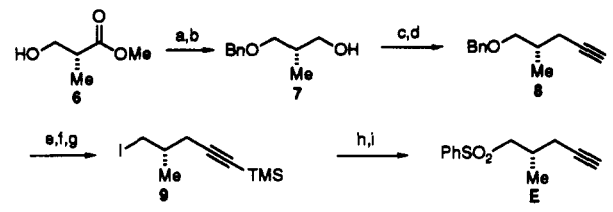
**Scheme I. Synthesis of Spiroenone B[a]**



[a] Conditions: (a) (*Z*)-crotyldiisopinocampheylborane (derived from (-)-α-pinene), THF, -78 °C, then $H_2O_2$, NaOH; (b) Li, $NH_3$, -78 °C, (80%, 2 steps); (c) TsCl, pyridine, 25 °C; (d) NaH, $Et_2O$, 0 °C; (e) 5-lithiofurfuryl methoxyisopropyl ether, $BF_3$·$OEt_2$, THF, -78 °C, then HCl, THF/$H_2O$, 25 °C (55% 3 steps); (f) MCPBA, $CH_2Cl_2$, 0 °C, then $CH_2C(OCH_3)CH_3$, HCl, 0 → 25 °C (70%).

**Scheme II. Synthesis of the Linker E[a]**



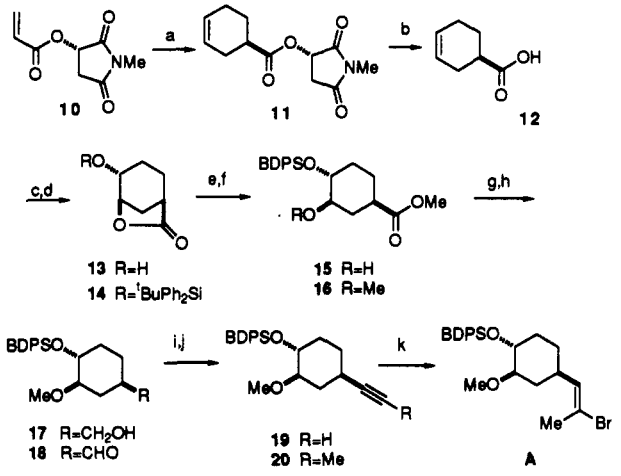
[a] Conditions: (a) $Cl_3CC(=NH)OBn$, TfOH, hexane/$CH_2Cl_2$, rt; (b) $LiAlH_4$, $Et_2O$, 0 °C, (93%, 2 steps); (c) TsCl, DMAP, Pyr (82%); (d) HCCLi-EDA, DMSO, rt (83%); (e) BuLi, TMSCl, THF, -78 → rt; (f) LiDBB, THF, -78 °C, (82%, 2 steps); (g) $Ph_3P$, $I_2$, imidazole, $CH_2Cl_2$, rt, (86%); (h) $PhSO_2Na$, DMF, 65 °C; (i) TBAF, THF, rt (83%; 2 steps).

together with the linking units L-(-)-pipecolic acid C and the acetylenic sulfone E follows the sequence B + E → BE + D → BED + A → BEDA + C → BEDAC + lactamization/fragmentation/deblocking → FKANAL (I). This strategy is synthetically quite flexible, for by modification of any of these small parts a different FK-506 analog may be prepared by application of a similar reaction sequence.

The synthesis of the spiroenone B follows the precedence established in earlier work from these laboratories[5] (Scheme I). Thus, crotylation of benzylglycolaldehyde 1 according to the procedure of Brown[6] and then lithium/ammonia debenzylation afforded an 80% overall yield of the diastereomerically pure diol 2. The oxide 4, readily prepared from this diol 2 but generally not isolated, gave the new diol 5 in 55% overall yield after treatment with 5-lithiofurfuryl methoxyisopropyl ether and then mild hydrolysis. Oxidation of this furan according to the procedure of DeShong[7] and then acetonide formation gave the desired spiroenone B in 70% overall yield.

The sulfone E was prepared on a large scale in 37% overall yield from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate as shown in Scheme II. This sulfone E was used for carboalumination and then conjugate addition to the spiroenone B (Scheme IV). This process, carried out in the fashion established earlier[8] that was so successful with other conjugated enones, led to the saturated ketone 21 in 82% yield. After reduction of the ketone 21, the hydroxyl group was blocked and the new sulfone 23 was isolated in 93% yield.

**Scheme III. Synthesis of Vinyl Bromide A[a]**



[a] Conditions: (a) 1,3-butadiene, $TiCl_4$, $CH_2Cl_2$, 0 °C (85%); (b) LiOH, $H_2O_2$, THF, 0 °C (98%); (c) MCPBA, $CCl_4$, 0 °C → 25 °C, then $Et_3N$, $SiO_2$, 70 °C (65%); (d) $^tBuPh_2SiCl$, imidazole, DMF, 25 °C (90%); (e) MeOH, $NaHCO_3$, 25 °C; (f) MeOTf, 2,6-di$^t$BuPyr, $CH_2Cl_2$, 25 °C (98%, 2 steps); (g) $LiAlH_4$, $Et_2O$, 0 °C (100%); (h) $(COCl)_2$, DMSO; $NEt_3$, $CH_2Cl_2$, -78 °C (93%); (i) NaH, $N_2CHP(O)(OMe)_2$, THF, -78 °C (83%); (j) *n*-BuLi, MeI, THF, -78 °C (86%); (k) $Cp_2Zr(H)Cl$, THF, 40 °C, then *N*-bromosuccinimide (83%).

At this juncture, the previously prepared spiroketal ester D[9] was converted to the corresponding aldehyde by hydrogenolysis of the benzyl ether and then oxidation of the resulting alcohol. Condensation of this aldehyde with the lithium salt of the sulfone 23 led in 74% yield to a mixture of the expected four diastereoisomeric hydroxy sulfones 24. Oxidation of these hydroxy sulfones 24 and then removal[10] of the sulfone grouping afforded the stereoisomerically pure ketone 26 in 84% overall yield. Completion of this phase of the synthesis was then readily accomplished by chelate-controlled reduction[11] of the ketone group and methylation of the resulting alcohol 27. The BED portion 28 thus formed was available in 67% yield after the recovered alcohol 27 was recycled through the methylation process.

For the next stage it was necessary to prepare the vinyl bromide portion A. After exploration of several routes for the formation of the cyclohexyl portion of the vinyl bromide A in enantiopure fashion, the use of the Diels-Alder condensation sequence (Scheme III) proved to be the most efficient. Condensation between butadiene and the acryloyl ester of (*S*)-*N*-methyl-2-hydroxysuccinimide (10) (Helmchen procedure[12]) afforded the crystalline adduct 11 on a large scale in 85% yield. The 98% enantiomerically pure acid 12, obtained after removal of the chiral auxiliary, was then oxidized with MCPBA. After the resulting mixture of epoxides was directly lactonized by treatment with triethylamine and silica gel, the hydroxy lactone 13[2c,13a] from the α-epoxide was isolated in 65% overall yield. Conversion of this hydroxy lactone 13 to the desired vinyl bromide A then follows precedence from the work of others.[2c,13]

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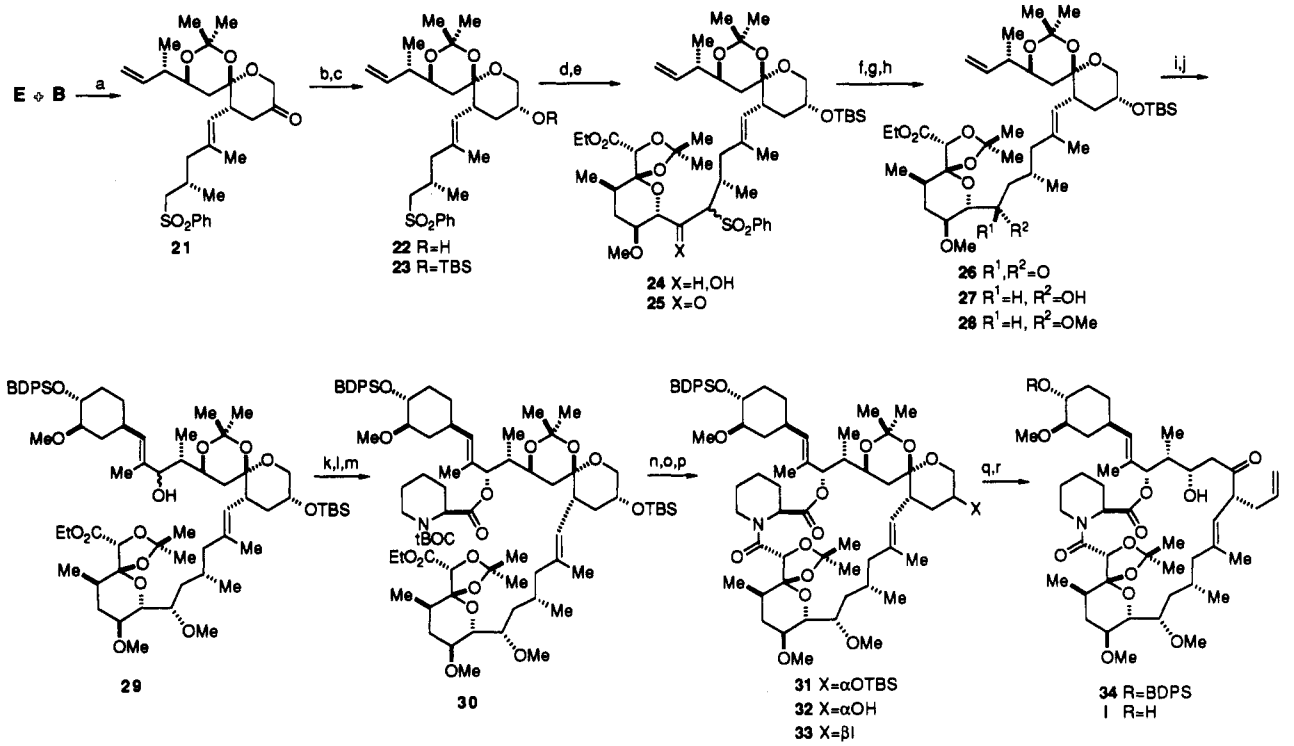
**Scheme IV. Synthesis of FKANAL (I)[a]**




[a] Conditions: (a) (i) A, $Me_3Al$, $Cp_2ZrCl_2$, $ClCH_2CH_2Cl$, rt; (ii) $C_4H_9$ CCLi (2 equiv), CuCN (1 equiv), THF, $Et_2O$, −23 °C; (iii) spiroenone B, THF, −23 °C (82%); (b) Li(ˢBu)$_3$BH, THF, −78 °C; $H_2O_2$, NaOH (100%); (c) TBSCl, imidazole, DMAP, DMF, rt (93%); (d) (i) benzyl ether D, $H_2$, $Pd(OH)_2$, EtOH, (99%); (ii) $COCl_2$, DMSO; $NEt_3$, $CH_2Cl_2$, −78 °C (96%); (iii) **23**, BuLi, THF, −78 °C (74%); (e) Dess–Martin periodinane, $CH_2Cl_2$; (f) $Bu_3SnH$, AIBN, PhMe, reflux (84%); (g) $CeCl_3 \cdot 7H_2O$, MeOH, rt → 78 °C; $NaBH_4$, (84%); (h) MeOTf, 2,6-diᵗBuPyr, $CH_2Cl_2$, (80%, 49% conversion); (i) $OsO_4$, NMO, THF, $H_2O$; $NaIO_4$ (90%); (j) vinyl bromide A, ᵗBuLi, THF; $MgBr_2$, −78 °C (57%); (k) Dess–Martin periodinane, $CH_2Cl_2$, (78%); (l) $CeCl_3 \cdot 7H_2O$, MeOH, rt → 78 °C; $NaBH_4$, (99%); (m) ᵗBOC-pipecolic acid, DCC, DMAP, $CH_2Cl_2$, −15 °C, 24 h (100%); (n) (i) LiOH, THF/$H_2O$; (ii) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C; (iii) HOAc, THF/$H_2O$; (iv) 2-chloro-1-methylpyridinium iodide, $NEt_3$, $CH_2Cl_2$, reflux (68%); (o) TBAF (5 equiv), THF, 0 °C (57%); (p) $Ph_3P$, $I_2$, imidazole, PhMe, 70 °C (96%); (q) $C_8K$, $ZnCl_2 \cdot AgOAc$, THF, rt (84%); (r) 5%HF/MeCN, rt (64%, 51% conversion).

With the vinyl bromide A in hand, the coupling with the BED unit **28** was explored (Scheme IV). Cleavage of the terminal olefin in the BED unit **28** with osmium tetraoxide/sodium periodate easily revealed the aldehyde which was used directly in the Grignard reaction with the magnesium derivative of the vinyl bromide A. Attempts to better control the stereochemical outcome of this condensation were unsuccessful and as a result the mixture (1:2) of epimeric alcohols **29** was oxidized and then reduced under chelation control[11] to give the desired (*S*)-oriented hydroxyl function. Finally, addition of the last building block, *N*-*t*-BOC-pipecolic acid C, was efficiently accomplished[2c] through the coupling of this (*S*) alcohol with the acid C in the presence of DCC/DMAP. With all the parts of the analog I now together, it remained to close the macrolactam ring of the BEDAC unit **30** and then remove the various blocking groups.

After saponification of the ester grouping and cleavage of the *N*-*t*-BOC blocking group in the BEDAC intermediate **30**, the resulting amino acid was cyclized in 68% overall yield through a modification of the Merck group's conditions[2c] for a similar such lactamization. The resulting macrocycle **31** was then ready for fragmentation[5] to reveal the desired α-allyl aldol portion of the molecule. The silylated hydroxyl group of the spiroketal acetonide **31** was first converted to the iodide **33** which was fragmented according to previously described[5] procedures with potassium–graphite doped with zinc chloride/silver acetate.[14] This fragmentation process was realized in a very satisfactory manner and the α-allyl aldol system **34** was readily available. Finally, removal of the last silyl blocking group gave the desired FKANAL (I) analog in 64% yield after the recovered starting material was recycled once. This analog I is currently undergoing biological testing and the results will be reported elsewhere. In the meantime, further synthetic work is underway to modify this synthetic sequence so as to prepare FK-506 itself.

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**Supplementary Material Available:** Experimental details and characterization data (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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