perturbation of the IR spectrum of 1 indicates the direct interaction of 1 and CO_2, and thus diffusion cannot be the rate-limiting factor. The observed photochemical reactivity is in accordance with the photochemistry of excited 1 in polycrystalline alcohols at 77 K.[16] Under these conditions O–H insertion (typical reaction of singlet carbenes) is faster than C–H insertion (triplet reaction), and thus electronically excited triplet carbene 1 reacts like a singlet carbene. An alternative explanation, the reaction of "hot" ground states produced by irradiation, cannot be ruled out by the present experiments.

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Studies of the Immunosuppressive Agent FK-506: Synthesis of an Advanced Intermediate

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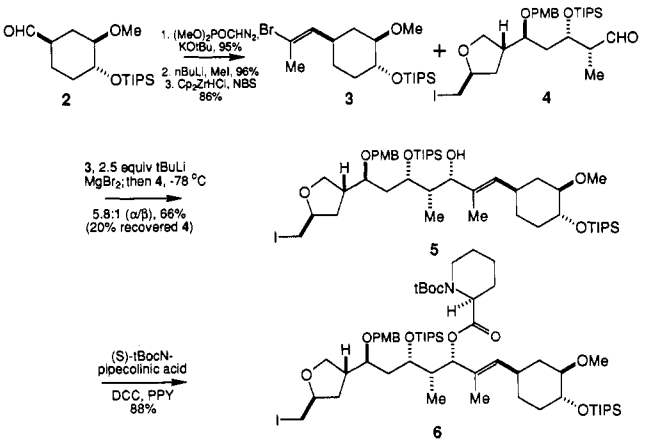
Summary: The addition of a vinyl anion that corresponds to C_{27} of the immunosuppressant FK-506 to an aldehyde that corresponds to C_{26} results in a coupling process that is stereoselective and convergent and allows for the direct attachment of the C_{26}-pipecolinate moiety. The pipecolinate is shown to be compatible with conditions required to achieve a subsequent coupling reaction.

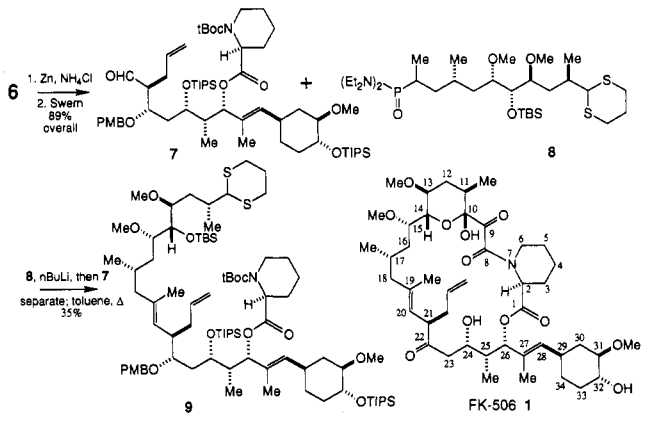
Sir: Several recent reports have described synthetic efforts[1] relating to the immunosuppressive and antiautoimmune agent, FK-506 (1),[2,3] including the first total synthesis.[4] Synthetic procedures such as these have the potential for helping to define the topographical relationship between this unusual ligand and its receptor(s). Our recent isolation and characterization of an FK-506 binding protein, termed fujiphilin, and an FK-506 associated cyclophilin[5] variant, termed mimphilin, provide hope that this goal may soon be realized.[6–8]

The target molecules of our research program in the FK-506 area require an efficient method to couple the cyclohexyl moiety of the natural product to a carbon chain through the C_{27}–C_{28} trisubstituted olefin spacer found in FK-506. Reported methods to achieve this objective utilized a Peterson olefination[1b,c] and a Burgess reagent mediated elimination of a tertiary alcohol.[1k] Herein we report an alternative coupling sequence that is convergent and stereoselective and allows for the attachment of the C_{26}-pipecolinate moiety without recourse to protecting-group chemistry at C_{26}.

Scheme I



Scheme II



The aldehyde 2 (Scheme I) was prepared by Swern oxidation of the corresponding alcohol whose synthesis (TIPS = H) was described in an earlier report.[1g] Homologation to the vinyl bromide proceeded in three steps. The direct conversion of the aldehyde function in 2 into a terminal acetylene was achieved according to the procedure of Gilbert[9] ($(MeO)_2POCHN_2$, KOtBu, 95% yield). Methylation of the acetylene (nBuLi, MeI, 96% yield) was fol-

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lowed by a stereo- and regioselective hydrozirconation reaction[10] that gave rise to the vinyl bromide **3** in 86% yield after treatment of the vinylzirconium intermediate with *N*-bromosuccinimide (NBS).

The union of **3** and the previously reported **4** (TIPS = TBS)[1k,11] required considerable experimentation in order to find conditions that resulted in an efficient and stereoselective outcome. First, the reaction of **3** with 2.5 equiv of tBuLi resulted in halogen–metal exchange. The resultant alkenyllithium was sequentially treated with 1.0 equiv of magnesium bromide and aldehyde **4**. The coupling resulted in the predominant formation of α-carbinol **5** together with the readily separable diastereomeric β-carbinol (α:β = 5.8:1) in 66% yield, with 20% yield of recovered **4**. Evidence that the major diastereomer corresponded to that of a Cram-selective addition was obtained by a chemical correlation[12] with material prepared by the previously described route.[1k]

The acylation of **5** occurred smoothly at −20 °C with (*S*)-tBOC-*N*-pipecolinic acid, DCC, and 4-pyrrolidinopyridine to provide **6** in 88% yield. When the same conditions were used with racemic tBOC-*N*-pipecolinic acid, the reaction yielded two readily separable (silica gel (sg) chromatography) isomeric products, thereby confirming that epimerization at C_2 did not occur in the reaction with the nonracemic amino acid derivative.

In order to evaluate the compatibility of the pipecolinate ester toward conditions required to introduce the C_{19}–C_{20} olefin, the coupling of **7** and phosphonamide **8**[1j] was examined (Scheme II). Treatment of **6** with zinc dust in the presence of ammonium chloride unmasked the C_{21} allyl side chain. Swern oxidation of the resulting primary alcohol gave aldehyde **7** in 89% overall yield from **6**. The reaction of the α-lithio derivative of **8** with **7** resulted in the formation of readily separable diastereomeric adducts in nearly quantitative yield. The more rapidly eluting (R_f = 0.5 (sg); 2:1 hexane/ethyl acetate) and major pair of diastereomers underwent stereospecific elimination to the trans olefin **9** (yield of **9** from **7** = 35%) upon heating in toluene.[13,14] The more polar and minor diastereomeric pair (R_f = 0.3 (sg); 2:1 hexanes/ethyl acetate) produced the C_{19}–C_{20} cis isomer (not shown) under similar conditions. We are currently investigating methods to convert the polar pair of diastereomers into **9** in order to improve upon the coupling efficiency.

Spectroscopic and chemical analyses of **9** provided evidence that the olefination conditions did not result in appreciable epimerization of the stereocenter on the pipecolinate ring and thereby suggest that the early and direct introduction of this moiety, as detailed in the present paper, will be of utility in studies relating to the synthesis of FK-506.

Supplementary Material Available: ^{1}H NMR spectra for all compounds (16 pages). Ordering information is given on any current masthead page.

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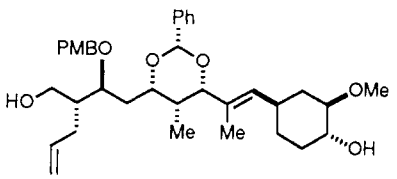
(11) The stereochemistry at the carbon bearing the iodomethyl group of the tetrahydrofuran has not been determined and is arbitrarily rendered with the β-configuration. This stereocenter is removed upon treatment of **6** with Zn/NH_4Cl.

(12) Compound **5** was converted into diol **10** by the following sequence: (i) Zn, NH_4Cl, EtOH; (ii) Bu_4NF, THF, (iii) PhCHO, TsOH, benzene. The 500-MHz ^{1}H NMR spectra of both **10** and its derived bisacetate (Ac_2O, Et_3N, DMAP, CH_2Cl_2) were identical with the spectra of the corresponding materials prepared by the previously described route.[1k]



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(14) The assignment of the C_{19}–C_{20} olefin geometry is based on the characteristic resonances of the C_{19} methyl substituent in (*E*)-**9** (16.0 ppm) and (*Z*)-**9** (23.5 ppm) as observed in related systems.[4]

Synthesis of the Macrolactone Alkaloid (+)-Usaramine via Necic Acid Coupling to a Pyrrolizidine Borane

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Summary: The protected necic acid **19**, prepared from (*R*)-(+)-β-citronellol, was converted to the *Crotalaria* alkaloid (+)-usaramine (**2**) by regioselective coupling to the pyrrolizidine borane **22**.

Sir: The dilactones integerrimine (**1**), usaramine (**2**), and its geometrical isomer retrorsine (**3**) are members of a broadly distributed family of pyrrolizidine alkaloids (PAs) that have been shown to possess powerful hepatotoxic and carcinogenic properties.[1] Earlier investigations of the chemistry of macrolactone PAs[2] that included syntheses of **1**[3] and related systems[4] have laid the groundwork for approaches to more highly functionalized members of the group. Recently, a flexible route to the necic acid of **1** was opened from (*R*)-(+)-β-citronellol (**4**)[5] that, in principle, can be extended to **2** and **3**. We now describe the first

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