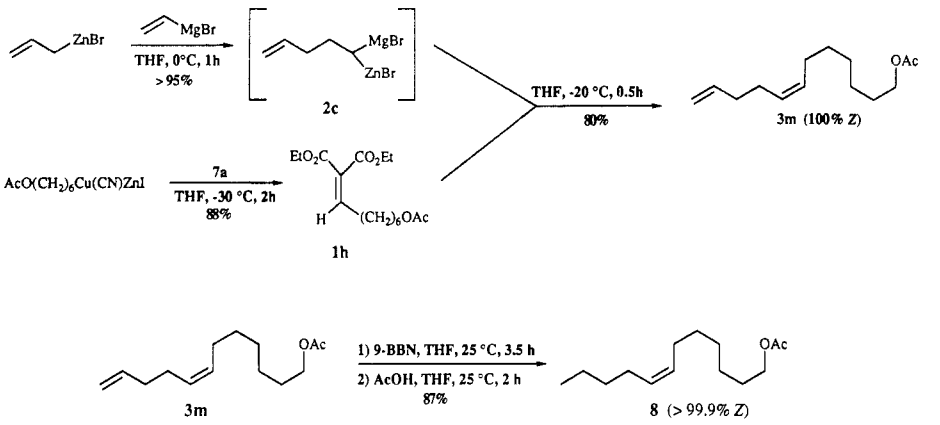
Scheme III



In conclusion, we have shown that the olefination of alkylidenemalonates **1** by 1,1-dimetalloalkanes **2** can accommodate a variety of functional groups and afford polyfunctional olefins **3** with fair to excellent *Z* stereoselectivities. Further studies are currently underway in our laboratories.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8818704) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supplementary Material Available: Typical procedures for the preparation of compounds **1**, **3**, and **7** as well as characterization data for compounds **1a–j**, **3a–m**, and **7a–c** (9 pages). Ordering information is given on any current masthead page.

Synthesis of the Novel Sarcosine and Proline (FK-525) Analogues of FK-506: Rearrangement of the Allylic Ester System

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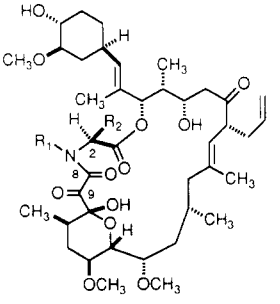
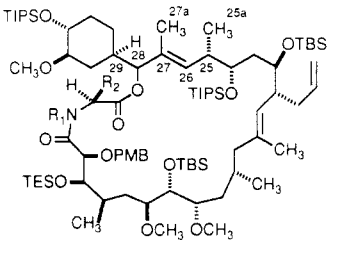
Summary: The novel sarcosine **2** and proline **3** (FK-525) analogues of FK-506 have been synthesized. Allylic rearranged products not observed in the pipecolinic acid series have been isolated from the amino acid formation/macrocyclization step.

The promising data now emerging from clinical studies in transplantation patients with the potent immunosuppressant FK-506[1] has resulted in intense interest in the search for analogues with enhanced efficacy. A systematic study of homologues modified at the tricarbonyl–amino acid linkage, while leaving the remainder of functionality about the macrocyclic array unperturbed, would provide valuable pharmacological information. In the accompanying article, we describe an efficient degradation of natural FK-506 to the selectively protected C_{10}–C_{34} synthetic intermediate **1**.[2] Herein, we demonstrate the use of **1** for the rapid entry into FK-506 amino acid homologues: the novel sarcosine derivative **2** and the proline derivative **3**, the latter isolated[3] from the same culture that produces FK-506. In addition, we report a striking dissimilarity in the amino acid formation/macrocyclization chemistry of the two analogues as compared to the pipecolinic acid (FK-506) series, i.e., the production of allylic rearranged macrocycles **15** and **17** (vide infra).



2 $R_1 = CH_3$, $R_2 = H$
3 R_1, $R_2 = (CH_2)_3$
FK-506 R_1, $R_2 = (CH_2)_4$



15 $R_1 = CH_3$, $R_2 = H$
17 R_1, $R_2 = (CH_2)_3$

Acylation of **1** with *N*-Boc-sarcosine (**4**, $R_1 = CH_3$, $R_2 = H$) and *N*-Boc-(*S*)-proline (**4**, R_1, $R_2 = (CH_2)_3$) under our previously established conditions[4] gave the esters **5**[5a,b] and **6**[5b] (Scheme I). Acetal hydrolysis then afforded the aldehydes **7** and **8** in 98% and 93% overall yields, respectively. Aldol condensation with **9** afforded the adducts **10**[5b]

(1) (a) Starzl, T. E.; Fung, J.; Venkataramman, R.; Todo, S.; Demetris, A. J.; Jain, A. *Lancet* **1989**, 1000–1004. (b) Thomson, A. W. *Immunol. Today* **1989**, *10*, 6–9. (c) Thomson, A. W. *Ibid.* **1990**, *11*, 35–36.

(2) Askin, D.; Joe, D.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.*, following paper in this issue. See following article for references to FK-506 isolation and biological activity.

(3) Hatanaka, H.; Kino, T.; Asano, M.; Goto, T.; Tanaka, H.; Okuhara, M. *J. Antibiot.* **1989**, *42*, 620–622.

(4) (a) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157–1159. (b) End game experimental procedures: Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998–3017.

(5) (a) Satisfactory ^1H NMR, ^{13}C NMR, and IR spectral data were obtained for all new compounds. NMR spectral assignments were made using COSY-45 and HETCOR 2-D experiments.[10,11] (b) Satisfactory combustion analysis (C, H, N to within 0.4% of theory) was obtained for this compound. (c) Satisfactory combustion analysis was obtained on the corresponding diol prior to Swern oxidation (Scheme III).

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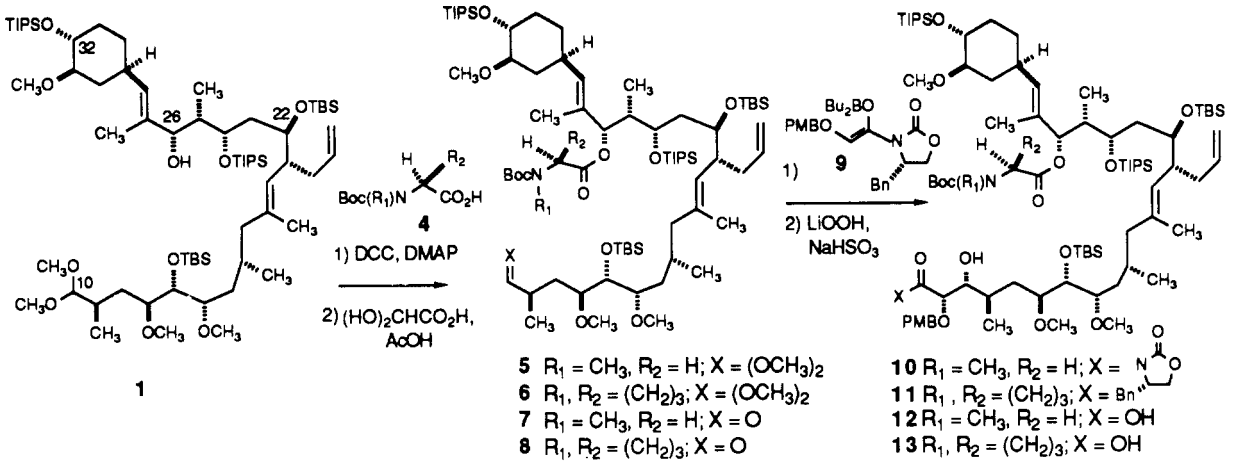
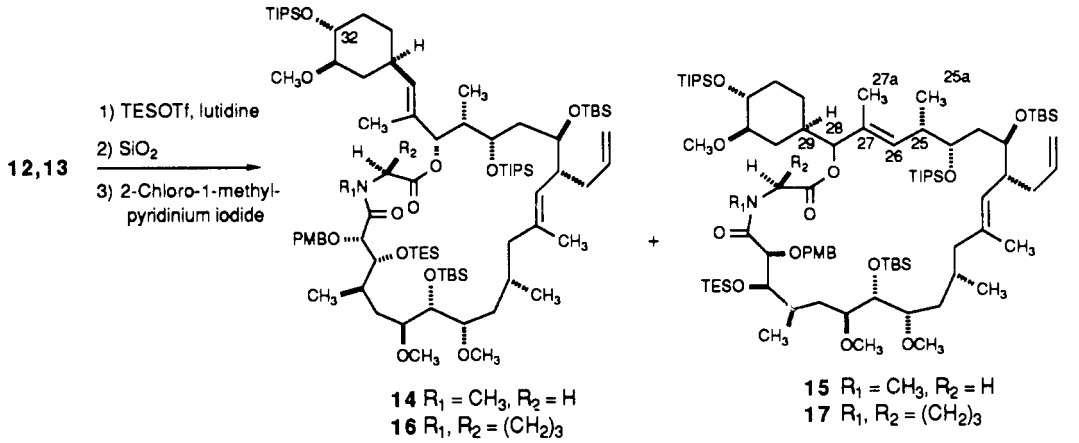
Scheme I



Scheme II



and 11[5b] in 78% and 87% yields, respectively. Conversion to the carboxylic acids **12** and **13** occurred by treatment with lithium hydroperoxide followed by reductive workup.

Exposure of the sarcosine series intermediate **12** to 4.5 equiv of triethylsilyl trifluoromethanesulfonate (TES-OTf) in the presence of 6 equiv of lutidine at 0 °C in CH_2Cl_2 followed by silica gel chromatography gave a mixture of amino acids[6] that were subjected to macrocyclization (Scheme II). The desired 23-membered macrocycle **14**[5b] was isolated in 34% overall yield. Additionally, *the rearranged 25-membered macrocycle* ***15***[7] *was produced in 5% yield.* Thus it appeared that the rearrangement had taken place in the amino acid formation step and not in the macrocyclization step. *In the proline series, the intermediate* ***13*** *afforded predominantly the rearranged 25-membered macrocycle* ***17*** *over the desired macrocycle* ***16***[5c] *when the silylation step was carried out at 0 °C*[4] (***17***:***16*** *= 60:40*). However, silylation with TES-OTf at −25 °C reduced the amount of rearranged product formed to less than 20% of the desired macrocycle. Since essentially no rearranged product was observed in the pipecolinic acid (FK-506) series, it appears that the rearrangement is dependent on the nature of the amino acid moiety. Interestingly, the rearranged products **15** and **17** are stereochemically homogeneous at the allylic ester center, although the stereochemistry could not be determined by NMR methods. The results appear to be consistent with a Lewis acid catalyzed [3,3]-sigmatropic rearrangement of the allylic ester system[8,9] prior to macrocyclization. The reason for the rearrangement propensity series of proline > sarcosine ≫ pipecolinic acid remains unclear in the absence of solution conformation data of the intermediates **12** and **13** and the corresponding pipecolinic acid (FK-506) series intermediate.

Two-step deblocking of the *p*-methoxybenzyl and triethylsilyl ethers of the desired macrocycles **14** and **16** (Scheme III), followed by Swern oxidation of the resulting diols, gave the corresponding tricarbonyl intermediates (52% and 49%, respectively). The tricarbonyl intermediates were then subjected to complete desilylation with concomitant hemiketal formation with 48% HF in CH_3CN to afford the C_{22}-dihydrosarcosine (FK-506 numbering) and C_{22}-dihydroproline derivatives **18** (87%) and **19** (89%), respectively. The three-step sequence of (a) C_{24},C_{32}-hydroxyl protection, (b) C_{22}-hydroxyl oxidation, and (c) deprotection then afforded the sarcosine analogue **2**[10]

(6) Examination of the crude amino acid mixture by ^1H NMR spectroscopy ($CDCl_3$) prior to exposure to the macrocyclization conditions revealed that two compounds were present.

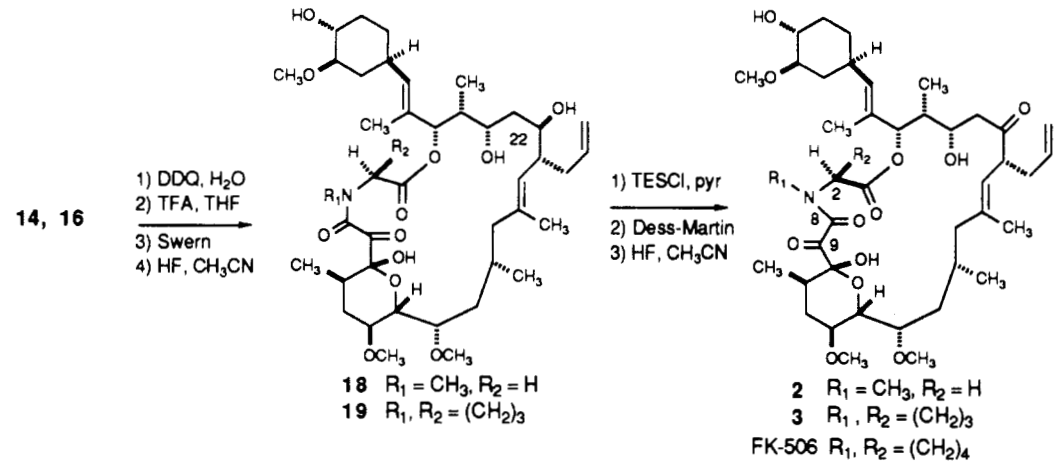
(7) 2-D NMR and NOE difference studies were used to characterize the rearranged compounds. In the COSY-45 experiment the spin system from the C_{25a} methyl to H_{26} could be assigned as well as the C_{27a} methyl (allylic coupling to H_{26}). In both compounds an NOE enhancement was observed from the C_{27a} methyl to H_{25}, thus defining the olefin geometry.

(8) Review: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579–586.

(9) A thermal [3,3] sigmatropic rearrangement of the allylic ester system of FK-506 has been observed by other workers at Merck: Ok, H.; Beattie, T.; Arison, B.; Ball, R.; Wyvratt, M.; manuscript submitted to *Tetrahedron Lett.*

(10) Carbon-13 NMR assignments for **2** (Major rotamer): (100.6 MHz, $CDCl_3$) 212.6 (C_{22}), 191.6 (C_9), 166.5, 166.3 (C_1, C_8), 139.7 (C_{19}), 135.4 (C_{21b}), 131.1 (C_{27}), 129.7 (C_{28}), 123.0 (C_{20}), 116.6 (C_{21c}), 98.5 (C_{10}), 84.2 (C_{31}), 77.5 (C_{15}), 77.2 (C_{26}), 74.0 (C_{13}), 73.5 (C_{32}), 71.7 (C_{14}), 69.2 (C_{24}), 57.7, 56.5, 56.3 ($3OCH_3$), 52.4 (C_{21}), 49.4 ($C_2(NCH_2)$), 48.6 (C_{18}), 44.8 (C_{23}), 40.5 (C_{25}), 36.9 (NCH_3), 35.8 (C_{16}), 35.0 (C_{21a}), 34.9 (C_{29}), 34.7 (C_{30}), 33.4 (C_{11}), 32.3 (C_{12}), 31.2 (C_{33}), 30.5 (C_{34}), 26.4 (C_{17}), 20.0 (C_{17a}), 16.0 (C_{11a}), 15.8 (C_{19a}), 14.3 (C_{27a}), 9.4 (C_{25a}). HRMS calcd for $C_{41}H_{65}O_{12}N$: 763.4505, found: 763.4522 (EI).

Scheme III



(26%) and the proline analogue 3[11] (35%). Compound 3 displayed identical ^1H and ^{13}C NMR spectral data[3] with material isolated by workers at Fujisawa. Interestingly, both 2 and 3 appear to exist in $CDCl_3$ with the C_8 carbonyl oriented syn to C_2 in the major rotamer,[12,13] which is opposite to the rotameric behavior observed in FK-506.[15]

The biological activity of the novel sarcosine analogue 2 will be reported elsewhere.

Acknowledgment. We thank Ms. J. Perkins, Mr. M. Valenciano, and Ms. J. Wu for performing combustion analysis and Dr. L. Colwell for high resolution mass spectroscopic measurements.

Supplementary Material Available: Copies of ^1H and/or ^{13}C NMR spectra for compounds **2**, **3**, **5–8**, **10**, **11**, **14**, **15**, **16** (diol derivative), **18**, and **19**, experimental procedures for the preparation of compounds **14–17** including COSY spectral data for **15** and **17** and NOE difference data on **17**, plus selected optical rotation data (30 pages). Ordering information is given on any current masthead page.

(11) Carbon-13 NMR assignments for **3** (major rotamer): (100.6 MHz, $CDCl_3$) 213.0 (C_{22}), 187.9 (C_9), 168.7, 162.5 (C_1, C_8), 140.4 (C_{19}), 135.4 (C_{21b}), 132.1 (C_{27}), 129.8 (C_{28}), 122.1 (C_{20}), 116.6 (C_{21c}), 99.1 (C_{10}), 84.2 (C_{31}), 78.4 (C_{26}), 76.5 (C_{15}), 73.6 (C_{13}), 73.5 (C_{32}), 71.2 (C_{14}), 69.0 (C_{24}), 59.9 (C_2), 57.6, 56.5, 56.2 ($3OCH_3$), 53.2 (C_{21}), 48.8 (C_{18}), 48.5 (C_5), 44.0 (C_{23}), 41.0 (C_{25}), 36.1 (C_{16}), 35.4 (C_{21a}), 34.8 (C_{29}), 34.7 (C_{30}), 32.9 (C_{11}), 32.6 (C_{12}), 31.2 (C_{33}), 30.6 (C_{34}), 28.4 (C_3), 25.7 (C_{17}), 25.4 (C_4), 18.7 (C_{17a}), 16.1 (C_{11a}), 15.6 (C_{19a}), 13.9 (C_{27a}), 9.7 (C_{25a}). HRMS calcd for $C_{43}H_{67}O_{12}N$: 789.4662, found: 789.4658 (EI).

(12) Carbon-13 chemical shift comparisons of the carbons flanking the amino acid nitrogen were used to determine the solution conformation of the C_8 carbonyl in FK-506 and **2**. In FK-506, C_6 is shielded in the major rotamer relative to the minor (δ_{C6}(major) = 39.1; δ_{C6}(minor) = 43.8), while C_2 shows just the opposite behavior, deshielded in the major (δ_{C2}(major) = 56.5; δ_{C2}(minor) = 52.6). Together with ^1H NMR chemical shift arguments, the major solution rotamer in FK-506 is assigned as having the C_8 carbonyl oriented toward C_6. Analogous ^{13}C chemical shift arguments can be applied to **2** except that the major rotamer has C_2 shielded relative to the minor (δ_{C2}(major) = 49.4; δ_{C2}(minor) = 51.7) and the major NCH_3 deshielded (δ_{NCH_3}(major) = 36.9; δ_{NCH_3}(minor) = 33.4). This leads to assignment of the C_8 carbonyl oriented toward C_2 in the major rotamer of **2**. However, since the ^1H chemical shift differences for the sarcosine protons are relatively small in the two rotamers of **2**, the solution conformation is assigned with less certainty than in FK-506.

(13) The ^{13}C NMR chemical shift arguments used to assign the rotamers in **2** could not be used for **3** because the chemical shift difference in the rotamers for C_2 and C_5 is less than 1 ppm. However, the ^{13}C chemical shifts of C_3 and C_4 in the proline ring can be diagnostic as to the orientation of the C_8 carbonyl.[14] The data are summarized as follows and are consistent with the same major rotamer as in **2** (**3**, major rotamer (δ_C): C_2 (59.9), C_3 (28.4), C_4 (25.4), C_5 (48.5); minor rotamer: C_2 (60.6), C_3 (31.6), C_4 (21.3), C_5 (48.0)).

(14) Thomas, W. A.; Williams, M. K. *J. Chem. Soc., Chem. Commun.* **1972**, 994.

(15) A report has recently appeared detailing the binding specificity of FK-506 rotamers to the FK-506 binding protein: Rosen, M. K., Standaert, R. F., Galat, A., Nakatsuka, M.; Schreiber, S. L. *Science* **1990**, *248*, 863–866.