Diastereomeric **2a** was separated by preparative thick-layer chromatography (20% EtOAc–hexane, developed 2–3 times) for characterization purposes.

Higher R_f diastereomer (R_f 0.29, 20% EtOAc–hexane): $[\alpha]^{25}_D$ = −20.5° (*c* = 1.07, $CHCl_3$); ^1H NMR δ 7.89 (apparent dd, 2 H, *J* = 8.5 Hz, *J* = 1.4 Hz, *o*-ArH), 7.64 (tt, 1 H, *J* = 7.4 Hz, *J* = 1.3 Hz, *p*-ArH), 7.56 (apparent t, 2 H, *J* = 7.6 Hz, *m*-ArH), 4.18 (d, 1 H, *J* = 3.4 Hz, SCHS), 3.92 (dd, 1 H, *J* = 5.7 Hz, *J* = 1.3 Hz, TBSOC*H*), 3.33 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.27–3.31 (overlapping apparent d, 1 H, *J* = 10.1 Hz, *anti*-TBSOCHC*H*OMe, and m, 1 H, $PhSO_2CH$Me), 3.08 (ddd, 1 H, *J* = 9.3 Hz, *J* = 5.7 Hz, *J* = 2.4 Hz, *syn*-TBSOCHC*H*OMe), 2.76–2.96 (m, 4 H, $SCH_2CH_2CH_2S$), 2.06–2.17 (m, 2 H, one of SCH_2CH_2 and SCHC*H*Me), 2.02 (ddd, 1 H, *J* = 13.1 Hz, *J* = 8.4 Hz, *J* = 4.3 Hz, one of $PhSO_2CHCH_2$), 1.78–1.86 (m, 2 H, one of SCH_2CH_2 and $PhSO_2CHCH_2CH$Me), 1.68 (ddd, 1 H, *J* = 15.1 Hz, *J* = 8.8 Hz, *J* = 2.2 Hz, one of SCHCHC*H2*), 1.46–1.55 (m, 2 H, one of $SCHCHCH_2$ and one of $PhSO_2CHCH_2CHCH_2$), 1.22–1.30 (m, 2 H, one of $PhSO_2CHCH_2CHCH_2$ and one of $PhSO_2CHCH_2$), 1.24 (d, 3 H, *J* = 6.9 Hz, $PhSO_2CHCH_3$), 1.11 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 0.98 (d, 3 H, *J* = 6.7 Hz, $PhSO_2CHCH_2CHCH_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); IR (thin film) 2950, 2930, 2890, 1460, 1445, 1305, 1150, 1090, 840, 735 cm^{-1}.

Lower R_f diastereomer (R_f 0.23, 20% EtOAc–hexane): $[\alpha]^{25}_D$ = −39.0° (*c* = 1.27, $CHCl_3$); ^1H NMR δ 7.89 (apparent dd, 2 H, *J* = 8.2 Hz, *J* = 1.3 Hz, *o*-ArH), 7.66 (tt, 1 H, *J* = 7.5 Hz, *J* = 1.3 Hz, *p*-ArH), 7.57 (apparent t, 2 H, *J* = 7.6 Hz, *m*-ArH), 4.17 (d, 1 H, *J* = 3.5 Hz, SCHS), 3.86 (dd, 1 H, *J* = 6.1 Hz, *J* = 1.3 Hz, TBSOC*H*), 3.37 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.25 (br d, 1 H, *J* = 10.3 Hz, *anti*-TBSOCHC*H*OMe), 3.07–3.15 (overlapping ddd, 1 H, *J* = 9.4 Hz, *J* = 6.3 Hz, *J* = 3.3 Hz, *syn*-TBSOCHC*H*OMe, and m, 1 H, $PhSO_2CH$Me), 2.78–2.96 (m, 4 H, $SCH_2CH_2CH_2S$), 2.08–2.16 (m, 2 H, one of SCH_2CH_2 and SCHC*H*Me), 1.80–1.89 (m, 1 H, one of SCH_2CH_2), 1.72–1.79 (m, 1 H, $PhSO_2CHCH_2CH$Me), 1.69 (ddd, 1 H, *J* = 15.1 Hz, *J* = 8.8 Hz, *J* = 2.2 Hz, one of $SCHCHCH_2$), 1.59–1.62 (m, 2 H, $PhSO_2CHCH_2$), 1.51 (ddd, 1 H, *J* = 15.1 Hz, *J* = 10.5 Hz, *J* = 4.6 Hz, one of $SCHCHCH_2$), 1.38–1.48 (m, 2 H, $PhSO_2CHCH_2CHCH_2$), 1.28 (d, 3 H, *J* = 6.8 Hz, $PhSO_2CHCH_3$), 1.13 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.86 (d, 3 H, *J* = 6.6 Hz, $PhSO_2CHCH_2CHCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); IR (thin film) 2940, 2920, 2880, 1455, 1440, 1300, 1245, 1140, 1085, 835, 755 cm^{-1}.

Diastereomeric mixture: EIMS *m/e* (relative intensity) 618 (1), 561 (50), 529 (3), 455 (4), 423 (2), 381 (2), 349 (7), 269 (33), 205 (100); CIHRMS calcd for $C_{30}H_{54}O_5SiS_3$ 619.2982, found 619.2970.

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Supplementary Material Available: Characterizations of intermediates in the sequences going from **25** → **20** and from **29** → **32** (3 pages). Ordering information is given on any current masthead page.

A Formal Synthesis of FK-506. Exploration of Some Alternatives to Macrolactamization

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The coupling of the previously described subunits **2**, **3**, and **4** is described. The C_{28}–C_{27} *E*-double bond is fashioned from a sulfurane induced dehydration of alcohol **11**. The C_{19}–C_{20} *E*-double bond was constructed via a modified Julia process culminating in a reductive elimination of a vicinal trifluoracetoxy sulfone (see **22** → **23** → **24** and **25**). The synthesis of intermediates anticipating potential macrolactonization are also described.

Introduction

The extraordinary immunosuppressive properties of FK-506 (**1**), as well as its novel structure, have engendered a great deal of interest in its clinical potential, mechanism of action, and chemistry.[1-3] Not surprisingly, considerable attention has also been directed to its synthesis. Though many approaches to the total synthesis problem have been recorded,[4] only one comprehensive solution has been achieved. Earlier this year a group of scientists at the Merck, Sharpe and Dohme Research Laboratories reported the total synthesis of FK-506.[5] In the terminal stage of this landmark effort, systems of the type **7** (including the specific compound **7c**) were converted to FK-506 by insertion of a two carbon (glycolate) fragment, followed by macrolactamization. Such compounds were also identified as strategic goals in our synthetic effort.

In earlier papers in this issue,[6] we described straightfoward routes to properly matched, enantiomerically pure, subunits **2**, **3**, and **4**. Herein we describe in detail the

(1) (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (b) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249. (c) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T., Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, *40*, 1256. (d) Hatanaka, H.; Iwami, M.; Kino, T.; Goto, T.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 1586. (e) Coleman, R. S.; Danishefsky, S. J. *Heterocycles* **1989**, *28*, 157. (f) Askin, D.; Reamer, R. A.; Jones, T. K.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989**, *30*, 671. (g) Askin, D.; Reamer, R. A.; Joe, D.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989**, *30*, 6121.

(2) Starzl, T. E.; Todo, S.; Fung, J.; Demetris, A. J.; Venkataramman, R.; Jain, A. *Lancet* **1989**, 1000.

(3) (a) Siekierka, J. J.; Hung, S. H. Y.; Poe, M.; Lin, C. S.; Sigal, N. H. *Nature* **1989**, *341*, 755. (b) Harding, M. W.; Galat, A.; Uehling, D. E.; Schreiber, S. L. *Nature* **1989**, *341*, 758.

(4) For a comprehensive listing of synthetic efforts as of this writing refer to footnote 3 within ref 6b.

(5) For the total synthesis of FK-506, see: Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. D.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157.

(6) (a) Linde, R. G. II; Egbertson, M.; Coleman, R. S.; Jones, A. B.; Danishefsky, S. J. *J. Org. Chem.*, preceding. (b) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.*, preceding.

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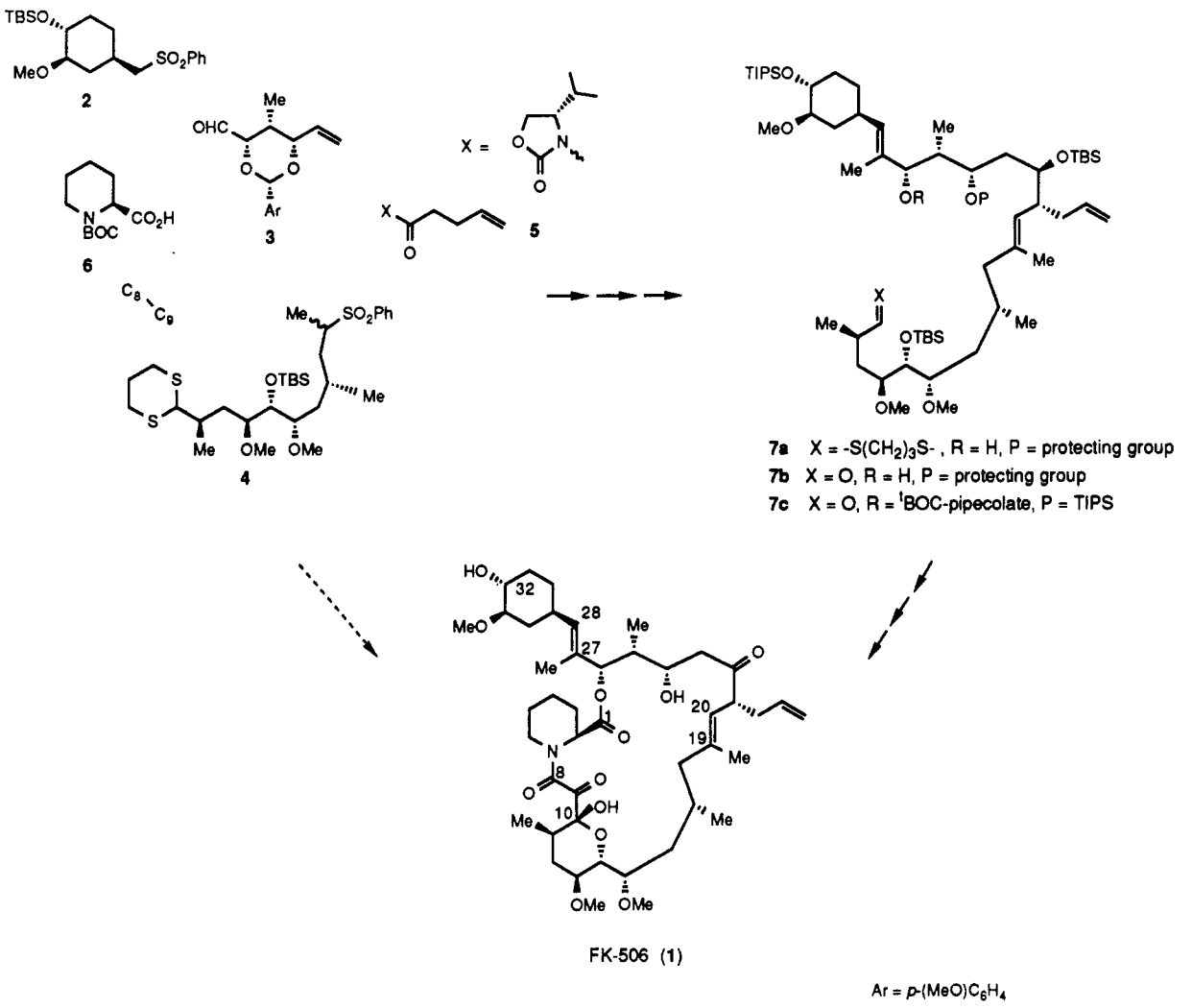
Scheme I



coupling and melding of these units with two additional and simple building blocks, **5** and **6**, leading to a stereoselective synthesis of **7c**. Given the conversion of this compound to FK-506,[5] the work constitutes, in a formal sense, a total synthesis of the latter.

We have also begun to explore new options to reach the macrocyclic substructure of **1** for purposes of both total synthesis and analogue synthesis. Potential candidate substrates for such departures have been developed from systems of the type **7**. A survey report on these investigations is also provided below.

Discussion of Results

The lithium salt **2a**, generated from **2**,[6a] reacted with aldehyde **3**[6b] in THF at −78 °C. The resultant product mixture **8**, when treated with the Dess–Martin periodinane,[7] afforded keto sulfone diastereomers **9**. Upon reduction of this mixture with lithium naphthalenide, there was obtained the homogeneous ketone **10** in 60% overall yield. Many approaches were explored to introduce the C_{27}–C_{28} double bond via compound **10**. Also, variants of this system, with differing blocking groups at the C_{24} and C_{26} oxygens, were developed. Eventually we settled upon a two-step sequence starting with the reaction of **10** with methylmagnesium bromide. The resultant carbinol, **11**, when subjected to the action of the Burgess reagent,[8] afforded an 80% yield of a 6:1.5:1 ratio of olefin isomers, **12**. The major product was the desired C_{27}–C_{28} *E* isomer. The minor products were presumed to be the disubstituted (ΔC_{27a}–C_{27}) and enol ether (ΔC_{26}–C_{27}) isomers. For purposes of converging with compound **7c** it was useful to cleave the *tert*-butyldimethylsilyl (TBS) group and to install a triisopropylsilyl (TIPS) group on the cyclohexyl moiety (**12** → **13**). Separation of the major component was not practical at this stage. Accordingly, mixture **13** was carried further. Selective hydroboration of the vinyl group was readily achieved through the action of 9-BBN (THF; 0 °C). Oxidation with alkaline hydrogen peroxide followed by silica gel chromatography afforded homogeneous **14** in 62% yield from mixture **13**. After oxidation, again with the Dess–Martin periodinane,[7] aldehyde **15** was in hand (see Scheme II).

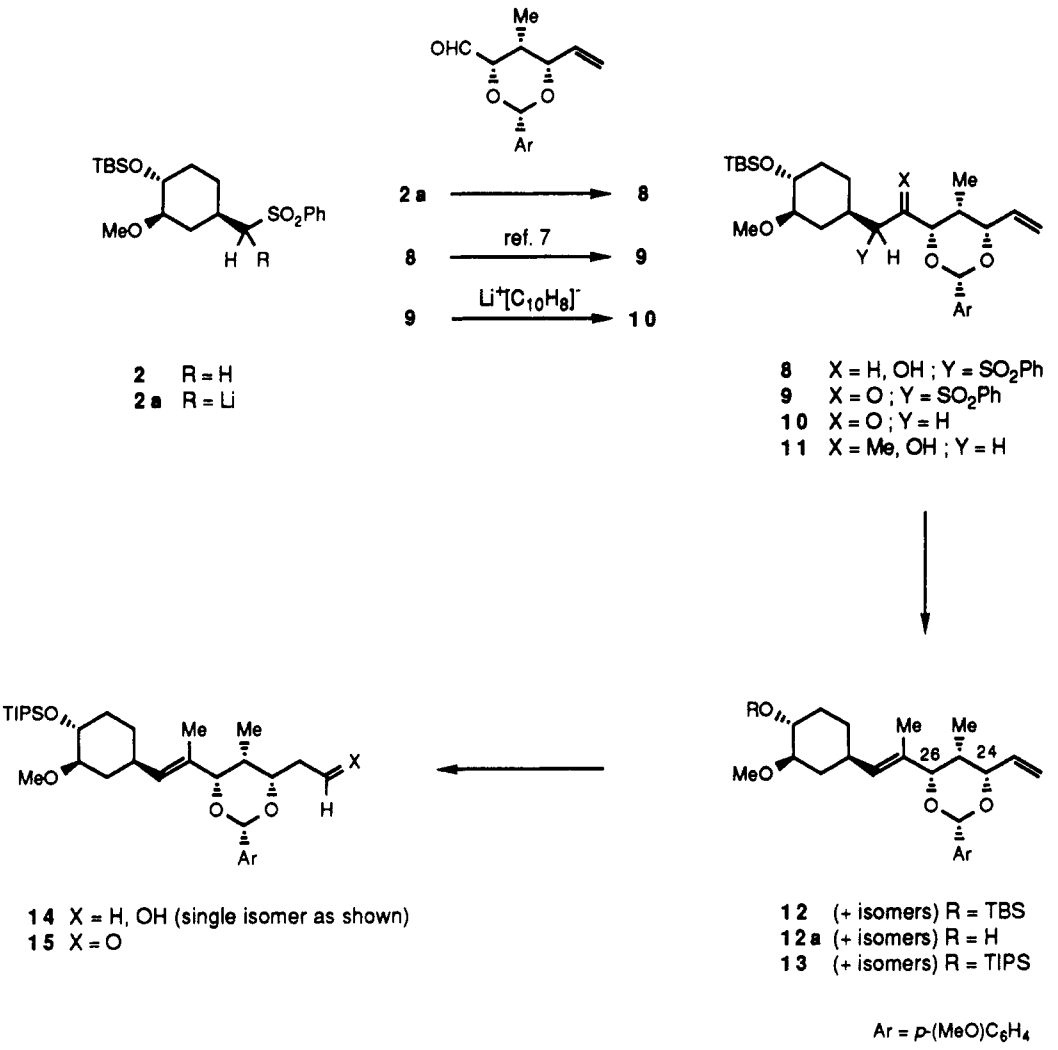
Various possibilities were explored for condensing either C_2(acetate) or C_5(pentenoate) fragments with aldehyde **15**. Several silyl enol ethers and silyl ketene acetals were evaluated. None of these attempts led to useful stereoselectivity margins in serviceable yields. Instead, we took recourse in the very reliable oxazolidone chemistry pioneered by Evans and associates.[9] Not only did this

(7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(8) (a) Burgess, E. M.; Penton, H. R. *Org. Synth.* **1977**, *56*, 40. (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(9) (a) Evans, P. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (c) For a review, see: Evans, D. *Aldrichchimica Acta* **1982**, *15*, 23.

Scheme II



methodology allow us to install an α-branched C_5 fragment as one consolidated unit, but it enabled the imposition of predictable (*S*) stereochemistry at carbon 21. Given the erythro (or syn) nature of aldol products derived from the condensation of boron enolates with aldehydes,[9,10] the resultant configuration at carbon 22 would be defined to be *R*. Of course, the configuration at C_{22} is not of importance per sé since this carbon center is destined to emerge as a ketone. However, as a practical matter, access to stereochemically homogeneous intermediates of predictable configuration is a considerable advantage in a multistep synthesis.

The 4-butenoyloxazolidinone (**5**)[11] was prepared in the usual way from 4-pentenoyl chloride with the oxazolidinone derived from the (*S*)-valinol.[9] The imide **5** was treated with dibutylborontriflate in the presence of Hünig's base. The enolborinate so formed, was subjected to reaction with aldehyde **15** (methylene chloride −78 °C → room temperature). The resultant carbinol **16** was converted to its *tert*-butyldimethylsilyl derivative **17** (90% from **15**) through the action of TBSOTf/2,6-lutidine. Reaction of **17** with lithium benzyl oxide accomplished its transformation to benzyl ester **18** in 87% yield. Reduction of the ester with DIBAL-H followed by oxidation (Swern)[12] of **19** afforded the key aldehyde **20** (88%). This aldehyde was to be coupled with the other major fragment, the dithianasulfone **4**.[6c]

The required α-lithio sulfone derivative was generated through reaction of **4** with *n*-butyllithium (THF; −78 °C). To this solution was added the aldehyde **20**. The components combined smoothly to yield what was clearly a stereoisomeric mixture of β-hydroxy sulfones corresponding to **21**. Attempts to reductively eliminate[13] the vicinal hydroxyl and phenylsulfonyl linkages under several conditions (sodium–ammonia; lithium naphthalenide) were carried out. While fully characterized products were not obtained, it was clear that the phenylsulfonyl group was being cleaved. However ^{1}H NMR analysis indicated that the vinyl group of the allyl function was no longer present. It was presumed that the interaction of the radical anionoid species arising from reductive cleavage of the phenylsulfonyl linkage with the vinyl group (possibly by electron transfer or cyclization) was faster than expulsion of the hydroxyl function.

This line of conjecture, which was not undergirded by hard structural data, did nonetheless serve to suggest a solution. *It was proposed that if the leaving group pro-*

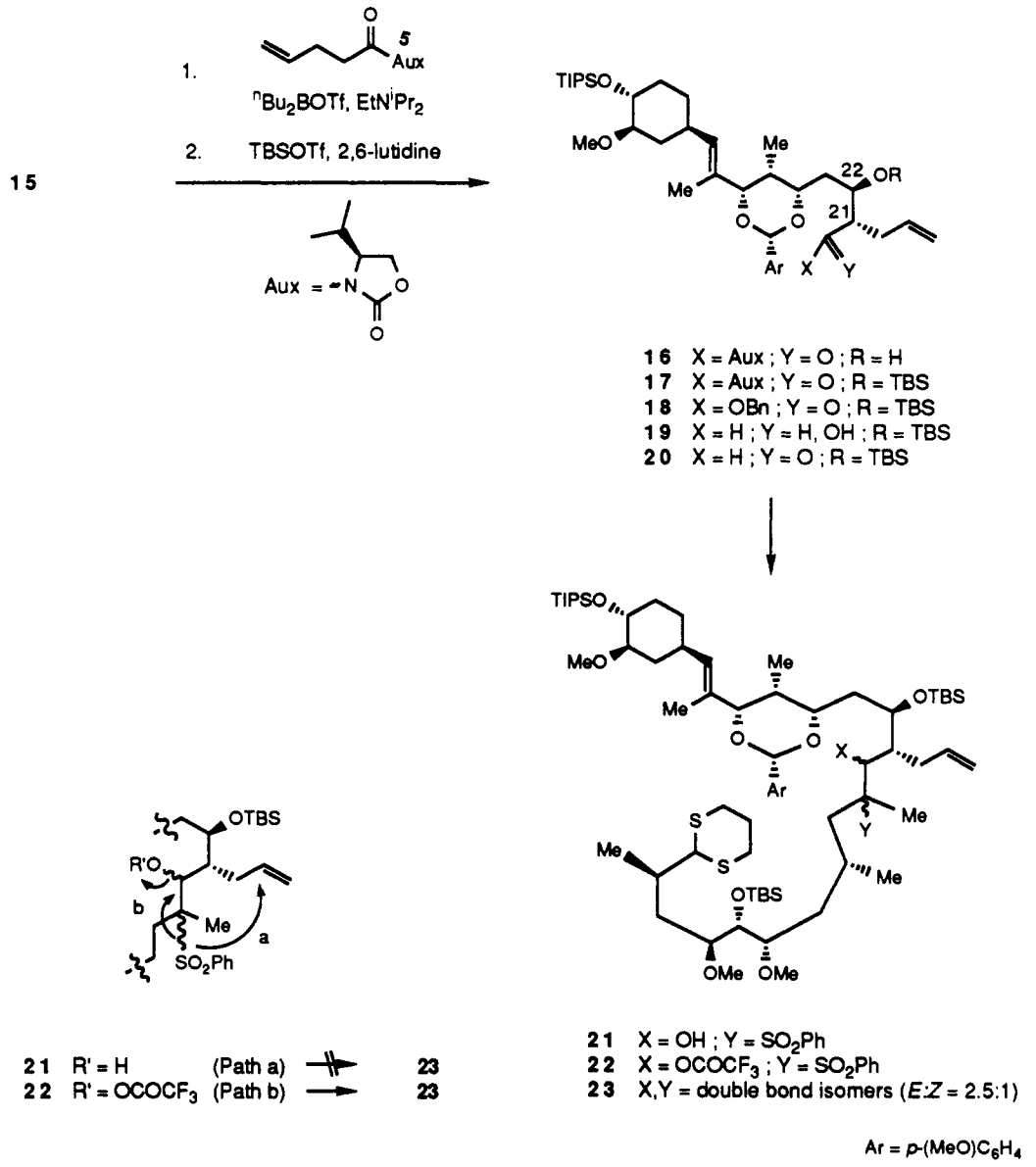
(10) (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

(11) See supplemental material for the preparation and characterization of oxazolidinone **5**.

(12) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(13) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.

Scheme III



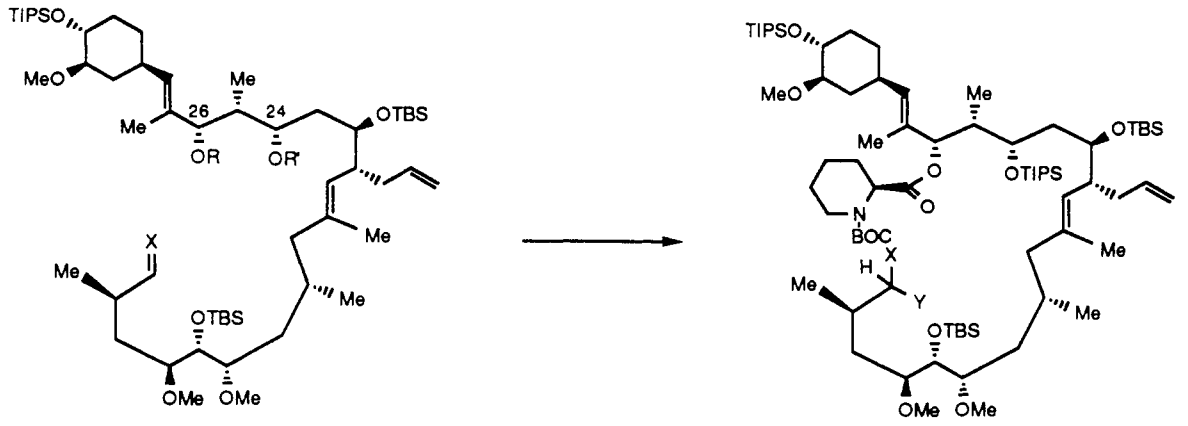
pensity at C_{20} were increased, β-elimination with formation of a C_{19}–C_{20} double bond might then be competitive with the presumed engagement of the C_{19} radical anion with the proximal vinyl group. Several attempts to acetylate or benzoylate the secondary alcohol function were unsuccessful. Accordingly we turned to trifluoroacetylation. Indeed, treatment of mixture **21** with trifluoroacetic anhydride (pyridine–DMAP–methylene chloride; room temperature) afforded trifluoroacetates **22**. When this mixture was subjected to the action of lithium naphtalenide (THF; −20 °C), the trisubstituted olefin was smoothly generated. The overall yield for this modified Julia sequence (**20** → mixture **23**)[13] was ca. 65%.

Detailed proton and carbon NMR analysis indicated that **23** was an *E*:*Z* mixture, with the former predominating. Separation of the geometric isomers was not possible at this stage. We estimate this ratio to be 2.5:1 based on ^{1}H NMR data and chromatographic separation of geometric isomers at a later stage of synthesis (vide infra).

Liberation of the C_{24}–C_{26} diol from its *p*-methoxybenzylidene blocking group is attended by serious difficulties that have not been satisfactorily solved at this writing. The cyclic acetal linkage has proven to be surprisingly stable to a variety of mildly acidic conditions. It had been anticipated that conditions would be available, wherein the deprotection would be achieved, while the arrangement of silyl blocking groups was preserved. Unfortunately in practice only partial selectivity could be realized. The optimal conditions which we were able to define involved treatment of isomer mixture **23** with PPTS in 1:1 2-propanol–acetonitrile at 70 °C. ^{1}H NMR analysis indicated the emergence of diol mixture **24**:**25** and still more polar products presumed to be disilylated versions of **24**:**25**. In a typical run, after a 26-h reaction time, diol **24** derived from the series was obtained in 33% yield. The C_{19}–C_{20} *Z* diol, **25**, was isolated in 11% yield, and starting material **23** was recovered to the extent of 28%. While this result constitutes a serious impediment to the flow of synthetic material, there was some small consolation in that **24** and **25** were readily separated by chromatography on silica gel. The major compound could be selectively silyated at the C_{24} alcohol, through the agency of triisopropylsilyl triflate and 2,6-lutidine, to provide an 80% yield of compound **26**.

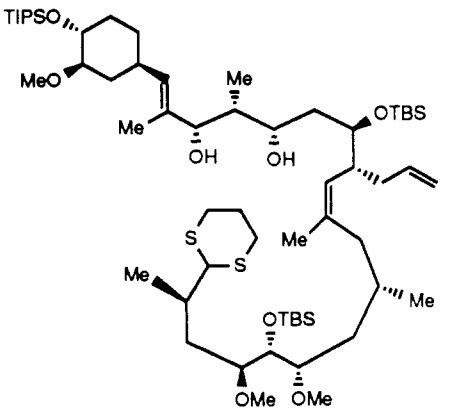
At this stage, the C_{26} alcohol could be acylated with any of several derivatives of L-pipecolic acid. For purposes of reaching specific compound **7c**, the C_{26} alcohol was acy-

Scheme IV



24 R = R' = H ; X = -S(CH$_2$)$_3$S-
26 R = H ; R' = TIPS ; X = -S(CH$_2$)$_3$S-
27 R = ^{t}BOC-pipecolate ; R' = TIPS ; X = -S(CH$_2$)$_3$S-

28 X = Y = OMe
7c X,Y = O



25

lated with compound **6**.[14] Reaction was carried out in methylene chloride with DCC–DMAP at −20 °C. There was thus obtained compound **27** in 70% yield.

Treatment of **27** with silver(I) nitrate–*N*-chlorosuccinimide and 2,6-lutidine in the presence of 1:1 methanol–THF afforded the crude dimethyl acetal **28** (Scheme IV). Finally **7c** was obtained by reaction of **28** with PPTS in methylene chloride (80%). The identity of compound **7c** was established by comparison with the highly detailed ^{1}H NMR spectrum of the corresponding aldehyde generated in the Merck synthesis.[5] The ^{1}H and ^{13}C NMR spectra of **27** were also identical with the Merck spectra.

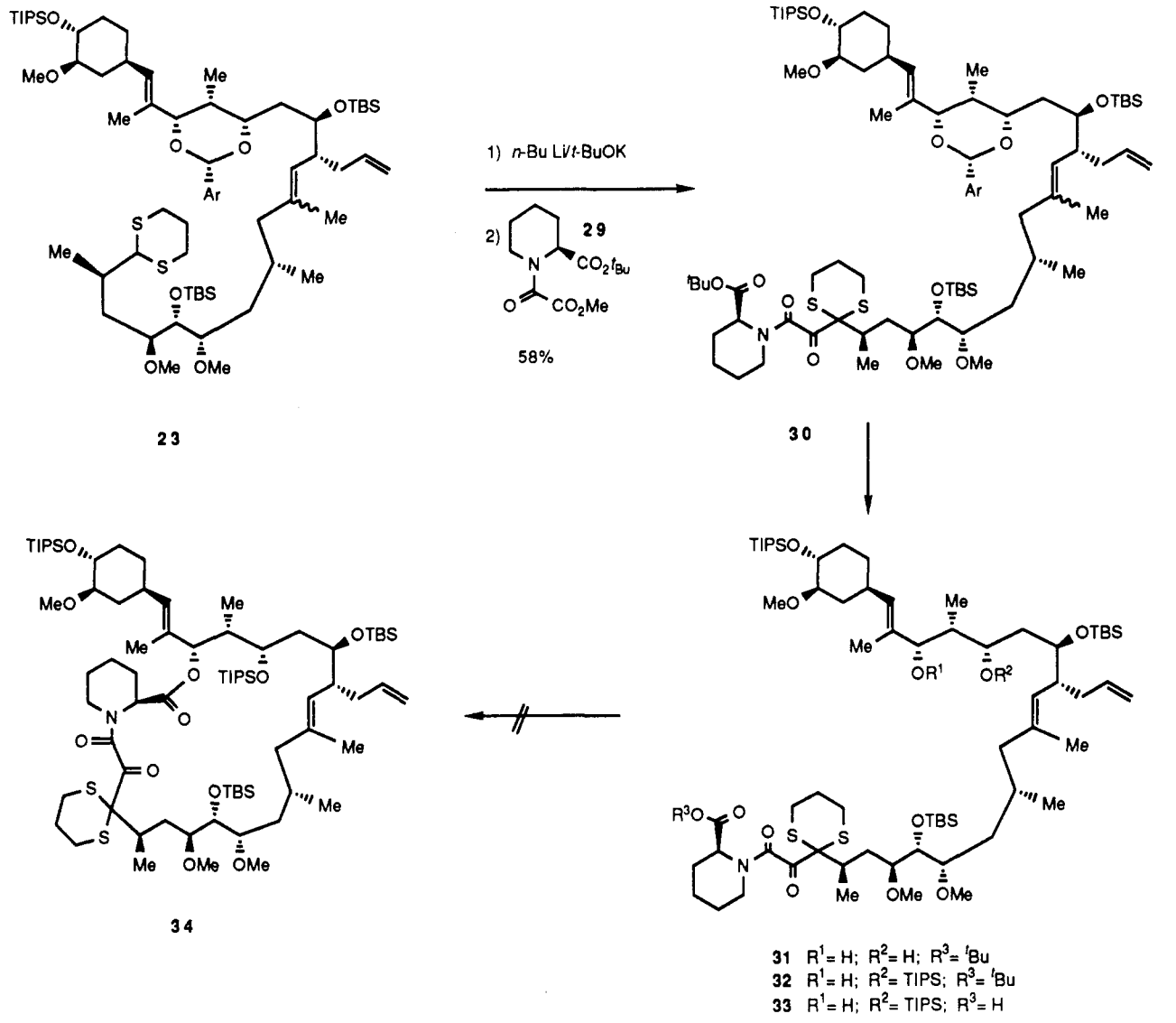
The possibility of reaching the FK-506 macrocycle by macrolactonization was also pursued. It was hoped that acylation of a metallodithiane derivative with an oxalylpipecolyl fragment would be possible and would allow us to rapidly assemble a seco-acid candidate. We first investigated the acylation of olefin mixture **23** with the compound **29**.[23]

In grappling with the problem we were much aided by a model study carried out by Melissa Egbertson.[15] These studies established the feasibility of metallation of 2-substituted dithianes with the LICKOR super base system developed by Schlosser.[16] Using this methodology it was found that deprotonation could be accomplished at temperatures as low as −78 °C.

Application to the case at hand involved generation of a solution of superbase using equimolar amounts of potassium *tert*-butoxide (triply sublimed) and *n*-butyllithium in a pentane–hexane–THF solvent. Reaction of this system with dithiane mixture **23**, followed by acylation with ester **29** (−78 °C, 20 min), afforded a 58% yield of **30**. As was the case with isomer **23** separation of the C$_{19}$–C$_{20}$ *E*:*Z* isomers was not possible at this stage. The separation was achieved after the benzylidene group was cleaved under

(14) Johnson, R. L.; Rajakumar, G.; Yu, K.-L.; Mishra, R. K. *J. Med. Chem.* **1986**, *29*, 2104.
(15) For a further account of this work, see: Melissa S. Egbertson, Doctoral Dissertation, Yale University, 1988.
(16) (a) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741. (b) Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627.
(17) Yield based upon a 2.5:1 ratio of olefin isomers in the starting material.
(18) (a) Keck, G. E.; Boden, E. D.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896. (b) White, J. D.; Amedio, J. C., Jr. *J. Org. Chem.* **1989**, *54*, 736. (c) Boden, E. D.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.
(19) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(20) Inanga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc.* **1979**, *52*(7), 1989.
(21) (a) Findlay, J. A.; White, P. S.; Swindells, D. C. N. *Can. J. Chem.* **1978**, *56*, 7491. (b) Findlay, J. A.; Radics, L. *Can. J. Chem.* **1980**, *58*, 579. (c) Findlay, J. A.; Liu, J.-S.; Burnell, D. J.; Nakashima, T. T. *Can. J. Chem.* **1982**, *60*, 2046. (d) Sehgal, S. N.; Baker, H.; Vezina, C. *J. Antibiot.* **1975**, *28*, 727. (e) Martel, R. R.; Klicius, J.; Galet, S. *Can. J. Physiol. Pharmacol.* **1977**, *55*, 48. (f) Calne, R. Y.; Lim, S.; Samaan, A.; Collier, D. St. J.; Pollard, S. G.; White, D. J. G.; Thiru, S. *Lancet* **1989**, 227. (g) Morris, R. E.; Meiser, B. M. *Med. Sci. Res.* **1989**, *17*, 609.
(22) Yamagiwa, S.; Hoshi, N.; Sato, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 214.
(23) For preparation of, and/or spectral data for, this compound see the supplemental material.

Scheme V



conditions very similar to those employed for **23**. The major *E* isomer **31** (obtained in 46% theoretical[17] yield) underwent monosilylation at C_{24} through the action of TIPSOTf/2,6-triflate lutidine. Under these conditions the *tert*-butyl ester **32** was stable. When compound **32** was treated with TMSOTf/2,6-lutidine in THF under reflux, followed by cleavage of the trimethylsilyl groups through the action of HCl, the homogeneous seco-acid **33** was in hand. *This compound is thus the first variation of an FK-506 seco hydroxy acid which has been reported.*

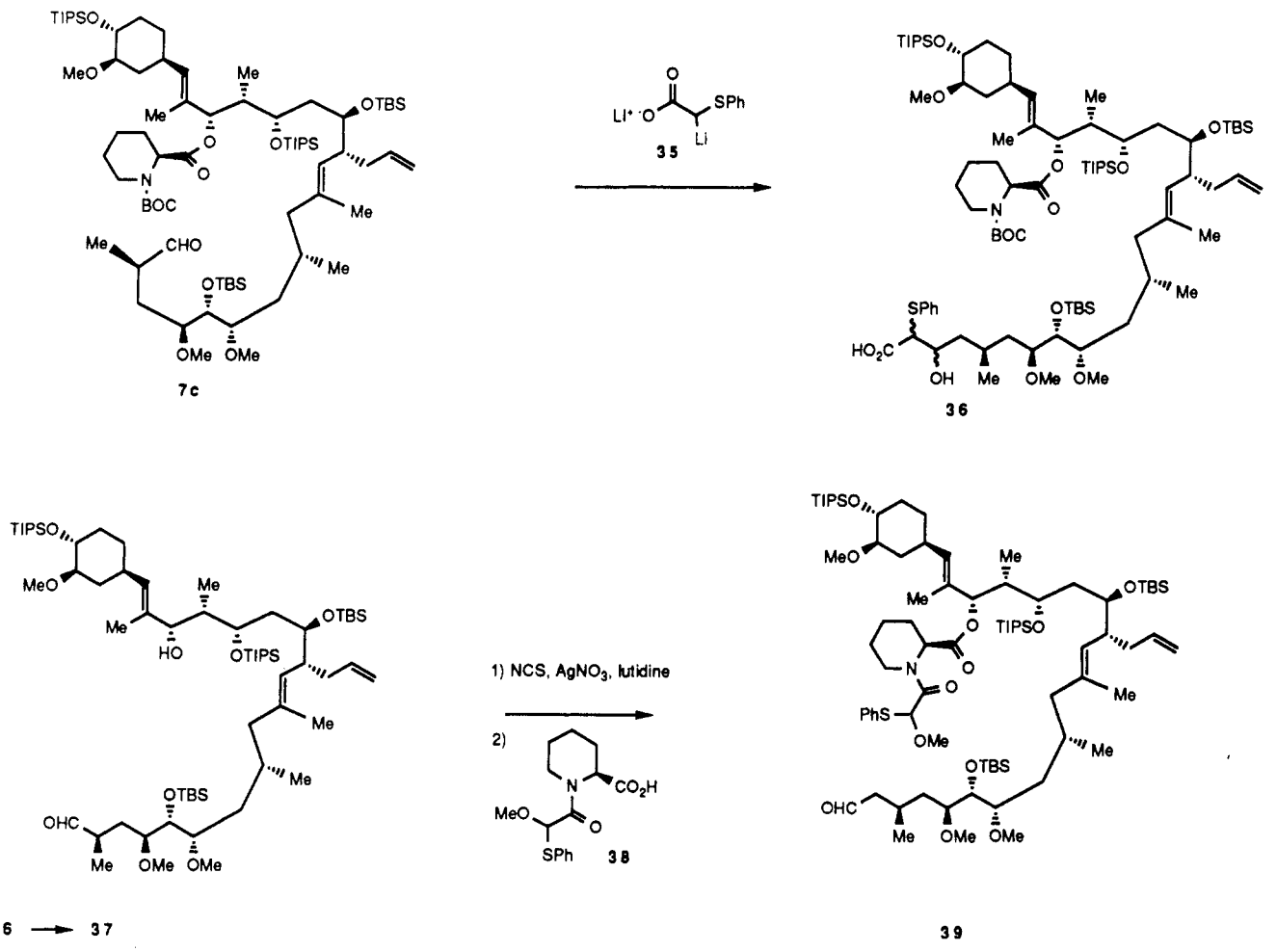
Attempts were undertaken to achieve macrolactonization of **33** under several conditions (involving the use of DCC–DMAP,[18] pyridinium salts,[19] or mixed anhydride[20] methods of dehydration). Several of these runs resulted in the formation of apparently neutral products. However, in screening the ^1H NMR spectra of these reaction mixtures, and partially purified components, we could garner no encouragement for claiming the formation of macrolactone **34**. Particularly conspicuous by its absence was any indication that the hydroxyl function at C_{26} had become acylated, or that the carboxyl at C_1 had become esterified.

Of course these macrolactonizations were attempted with only one substrate (**33**) in which an oxalyl residue had been interpolated between the nitrogen and C_{10}. The failure of macrolactonization may be due to an unfortunate choice of substrate wherein the absence of the hemiacetal linkage and the presence of the α-dicarbonyl linkage may individually or in combination be detrimental. Therefore these findings should not be construed as foreclosing the possibilities of macrolactonization in the FK-506 series.

While it is still our intention to survey the possibility of macrolactonization with different C_8–C_{10} permutations, we have also begun to examine alternative possibilities for macrocyclization. The hope is to eventually produce substitution variants in the C_8–C_9 sector of FK-506 for purposes of evaluating biological activity. This region of the molecule, common to another immunomodulating metalbolite, rapamycin,[21] is structurally most novel and is generally credited with a major role in biological function. Reaction of aldehyde **7c** with dianion **35**[22] did produce acid **36** as a diastereomeric mixture in 78% yield.

Another exploratory route to novel congeners started with deprotection of the C_{10} aldehyde at the stage of compound **26** with silver(I) nitrate–*N*-chlorosuccinimide, as before. There was thus obtained hydroxy aldehyde **37**. Examination of the ^1H NMR spectrum of this material indicated no evidence for the presence of the hemiacetal tautomer. It has been possible to acylate the alcohol function in **37** with N-acylated pipecolic acid derivative **38**.[23] In this way the C_9–C_{10} seco system **39** has been produced (see Scheme VI).

Scheme VI



In summary, linkage with a late intermediate (**7c**) in the total synthesis of FK-506[5] has been accomplished. A key element of success involved the reduction of a C_{20}–C_{19} hydroxy sulfone in the presence of competing functionality by formation of the C_{20}-trifluoroacetate. New routes to novel analogs and some possible "end game" variations for reaching FK-506 itself have been charted. Studies intended to follow up these leads as well as other avenues for molecular modification in this fascinating system continue to be of interest in our laboratory.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded on a Nicolet 5-SX FTIR or a Perkin-Elmer 1420 spectrophotometer. Low-resolution (EI) mass spectroscopy was determined on a Hewlett-Packard 5985 mass spectrometer. Low-resolution (CI, FAB) and high-resolution (CI, FAB) mass spectroscopy were determined on a Kratos MS80RFA spectrometer. High-field ^1H NMR spectra were recorded on a Bruker 490 MHz or Bruker 250-MHz instrument in $CDCl_3$, with $CHCl_3$ (7.27 ppm) as an internal reference. Microanalyses were performed by Robertson Laboratories, Inc. Flash chromatography was performed on EM Kieselgel 60 (230–400 mesh). Nomenclature for new compounds was supplied by Chemical Abstracts Service.

All reactions were carried out under a positive pressure of N_2 unless otherwise noted. Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) was freshly distilled from P_2O_5 before use. Benzene (PhH), toluene ($PhCH_3$), and acetonitrile (CH_3CN) were freshly distilled from CaH_2, while methanol (MeOH) and 2-propanol (^{i}PrOH) were freshly distilled from magnesium turnings activated with iodine. Hünig's base, triethylamine, and 2,6-lutidine were distilled from CaH_2 and stored over KOH. Anhydrous methyl sulfoxide (DMSO) and pyridine were purchased from Aldrich Chemical Co. Dess–Martin periodinane was either purchased from the Aldrich Chemical Co. or prepared according to the known procedure.

[2*S*-[2α,4α(1*S,3*S**,4*S**),5α,6α]]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxycyclohexyl]-1-[6-ethenyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-ethanone (10).** Sulfone **2**[6a] (3.26 g, 8.15 mmol), was dissolved in THF (50 mL) and cooled to −78 °C. ^{n}BuLi (5.3 mL of 1.6 N solution in hexane, 8.51 mmol) was added dropwise, and the mixture was stirred at −78 °C for 20 min. A solution of aldehyde **3**[6b] (1.95 g, 7.4 mmol) in THF (10 mL) was added dropwise. After 20 min at −78 °C (TLC; 25% EtOAc/hexanes) the reaction was quenched by addition of saturated aqueous ammonium chloride solution and allowed to warm to room temperature. The resulting mixture was extracted with EtOAc (3×), and the combined organic layers washed with brine (1×), dried over $MgSO_4$, filtered, and concentrated to give a crude mixture of hydroxy sulfones **8** (4.85 g). This mixture was dissolved in CH_2Cl_2 (60 mL) and stirred at room temperature. Pyridine (0.59 mL, 7.3 mmol) was added, followed by portionwise addition of Dess–Martin periodinane (3.74 g, 8.8 mmol). After 2 h at room temperature (TLC; 25% EtOAc/hexanes) Et_2O was added, and the mixture was stirred for 5 min. The resulting suspension was poured into a stirred mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (5:1 v/v). After 15 min the organic layer was separated, and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. ^{n}Heptane was added to the residue, the mixture was concentrated, and the process was repeated. The crude keto sulfone **9** so obtained was dissolved in THF (60 mL) and cooled to −78 °C. A solution of lithium naphthalenide (1.0 N in THF; prepared by addition of lithium (2.1 g, 0.3 mol) to a solution of naphthalene (15.9 g, 0.15 mol) in THF (150 mL) followed by ultrasonication for 1 h) was added dropwise until the reaction mixture maintained the dark green color of the

naphthalenide solution. The mixture was stirred for an additional 10 min at −78 °C before quenching with saturated aqueous ammonium chloride solution and allowing to warm to room temperature. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine (1×), dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (10% EtOAc/hexanes) gave **10** (2.23 g, 58% over the three steps), as a clear oil: $[\alpha]^{25}_D$ = −75.1° (*c* 1.25, $CHCl_3$); ^1H NMR δ 7.48 (2 H, d, *J* = 8.7 Hz, ArH (*m*-OMe)), 6.94 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.82 (1 H, ddd, *J* = 17.3, 10.8, 4.7 Hz, C*H*=CH_2), 5.58 (1 H, s, C*H*Ar), 5.34 (1 H, dt, *J* = 17.3, 1.6 Hz, *cis*-CH=C*H*H), 5.23 (1 H, dt, *J* = 10.8, 1.6 Hz, *trans*-CH=C*H*H), 4.48 (1 H, m, OC*H*CH=CH_2), 4.30 (1 H, d, *J* = 2.6 Hz, OCHC=O), 3.84 (3 H, s, ArOMe), 3.40–3.35 (4 H, m, C*H*OTBS, and 3.40 s, CHO*Me*), 2.95 (1 H, ddd, *J* = 11.2, 8.5, 4.5 Hz, C*H*OMe), 2.61 (1 H, dd, *J* = 18.3, 6.0 Hz, C*H*HC=O), 2.47 (1 H, dd, *J* = 18.3, 7.0 Hz, C*H*HC=O), 2.16 (1 H, m, C*H*(CH_3)), 2.08 (1 H, m, MeOCHC*H*H), 1.95 (1 H, m, C*H*CH_2C=O), 1.83 (1 H, m, TBSOCHC*H*H), 1.64 (1 H, m, TBSOCHCH_2C*H*H), 1.38 (1 H, m, TBSOCHC*H*H), 1.05–0.78 (14 H, m, MeOCHC*H*H, TBSOCH$_2$C*H*H, CH_3, and 0.90, s, ^{t}Bu), 0.08 (3 H, s, CH_3Si), 0.06 (3 H, s, CH_3Si); IR (CH_2Cl_2 solution), 2930, 2855, 1714, 1616, 1518, 1463, 1394, 1303, 1249, 1107, 1033, 836 cm^{-1}; CILRMS *m*/*e* (relative intensity) 461 (9.6), 383 (100), 365 (11.5), 351 (58.6), 325 (54.8), 251 (16.1), 219 (45.8), 137 (77.8), 89 (15.0); CIHRMS calcd for $C_{29}H_{47}O_6Si$ 519.3143, found 519.3142.

Anal. Calcd for $C_{29}H_{46}O_6Si$: C, 67.14; H, 8.94. Found: C, 67.17; H, 9.05.

[2*S*-[2α,4α[*E*(1*S,2*S**,4*S**)],5α,6α]]-(1,1-Dimethylethyl)[[4-[2-[6-ethenyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-1-propenyl]-2-methoxycyclohexyl]oxy]dimethylsilane (12).** Methylmagnesium bromide (2.1 mL of 3.0 N solution in Et_2O, 6.3 mmol) was added to a solution of ketone **10** (2.2 g, 4.2 mmol) in THF (30 mL) at 0 °C. After 15 min (TLC: 25% EtOAc/hexanes) the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with EtOAc (3×), and the combined organic fractions were washed with brine (1×), dried over $MgSO_4$, filtered, and concentrated. The crude **11** was dissolved in PhH (50 mL) and warmed to 40 °C. Burgess' salt (1.5 g, 6.3 mmol) was added in one portion. After 4 h (TLC; 10% EtOAc/hexanes) the mixture was concentrated. Purification by chromatography (5% EtOAc/hexanes) gave the olefin mixture **12** as a clear oil (1.67 g, 76%). A small amount was purified further by a second chromatography to allow characterization of the major isomer **12**: $[\alpha]^{25}_D$ = −37.9° (*c* 0.62, CH_2Cl_2); ^1H NMR δ 7.48 (2 H, d, *J* = 8.7 Hz, ArH (*m*-OMe)), 6.91 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.87 (1 H, ddd, *J* = 17.3, 10.8, 5.0 Hz, C*H*=CH_2), 5.61 (1 H, s, C*H*Ar), 5.37 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)), 5.33 (1 H, dt, *J* = 17.3, 1.6 Hz, *cis*-CH=C*H*H), 5.19 (1 H, dt, *J* = 10.8, 1.6 Hz, *trans*-CH=C*H*H), 4.48 (1 H, m, OC*H*CH=CH_2), 4.26 (1 H, bs, OC*H*C(Me)=CH), 3.82 (3 H, s, ArOMe), 3.42 (4 H, m, TBSOC*H*, and 3.42, s, CHO*Me*), 2.97 (1 H, ddd, *J* = 12.9, 8.5, 4.5 Hz, C*H*OMe), 2.31 (1 H, m, C*H*CH=C(Me)), 1.95 (1 H, m, MeOCHC*H*H), 1.86 (1 H, m, TBSOCHC*H*H), 1.76 (1 H, m, C*H*(Me)), 1.63–1.56 (4 H, m, TBSOCHCH_2C*H*H, and 1.62, s, CH=C(*Me*)), 1.38 (1 H, m, TBSOCHC*H*H), 1.17–1.02 (2 H, m, TBSOCHCH_2C*H*H and MeOCHC*H*H), 0.91 (9 H, s, ^{t}Bu), 0.82 (3 H, d, *J* = 6.9 Hz, CH(*Me*)), 0.08 (6 H, m, Me_2Si); IR (CH_2Cl_2 solution) 2932, 2855, 1615, 1518, 1249, 1105, 1032, 909, 835 cm^{-1}; CILRMS *m*/e (relative intensity) 517 (3.2), 459 (3.7), 381 (11.1), 349 (12.2), 325 (22.1), 313 (58.2), 293 (10.1), 281 (13.9), 255 (47.6), 223 (15.8), 137 (100.0), 121 (16.9), 89 (15.6); CIHRMS calcd for $C_{30}H_{49}O_5Si$ 517.3351, found 517.3334.

[2*S*-[2α,4α[*E*(1*S,2*S**,4*S**)],5α,6α]]-[[4-[2-[6-Ethenyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-1-propenyl]-2-methoxycyclohexyl]oxy]tris(1-methylethyl)silane (13).** Silyl ether **12** (1.55 g, 3.08 mmol) was dissolved in THF (30 mL) at room temperature, and tetra-*n*-butylammonium fluoride (6.16 mL of a 1 N solution in THF, 6.16 mmol) was added. After 20 h (TLC: 25% EtOAc/hexanes) the mixture was concentrated to approximately one-fifth of its original volume and filtered through a short column of silica gel, eluting with 25% EtOAc/hexanes. The filtrate was concentrated to a pale yellow oil. This residue was redissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. 2,6-Lutidine (2.2 mL, 18.48 mmol) and DMAP (113 mg, 0.92 mmol) were added followed by triisopropylsilyl triflate (1.7 mL, 6.6 mmol). After 2 h (TLC: 25% EtOAc/hexanes) the mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 10% EtOAc/hexanes) gave silyl ether **13** (1.60 g, 95%) as a clear oil: $[\alpha]^{25}_D$ = −54.5° (*c* 1.49, $CHCl_3$); ^1H NMR δ 7.48 (2 H, d, *J* = 8.7 Hz, ArH (*m*-OMe)), 6.91 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.88 (1 H, ddd, *J* = 15.8, 10.8, 5.0 Hz, C*H*=CH_2), 5.61 (1 H, s, C*H*Ar), 5.38 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)), 5.34 (1 H, dt, *J* = 17.4, 1.6 Hz, *cis*-CH=C*H*H), 5.20 (1 H, dt, *J* = 10.7, 1.6 Hz, *trans*-CH=C*H*H), 4.49 (1 H, m, OC*H*CHCH=CH_2), 4.27 (1 H, s, OC*H*C(Me)=CH), 3.82 (3 H, s, ArOMe), 3.57 (1 H, ddd, *J* = 10.9, 8.4, 4.8 Hz, TIPSOC*H*), 3.41 (3 H, s, CHO*Me*), 2.99 (1 H, ddd, *J* = 11.2, 8.3, 4.4 Hz, C*H*OMe), 2.33 (1 H, m, C*H*CH=C(Me)), 1.98 (2 H, m, TIPSOCHC*H*H and MeOCHC*H*H), 1.77 (1 H, m, C*H*(Me)), 1.63–1.58 (4 H, m, TIPSOCHCH$_2$C*H*H, and 1.62, s, CH=C(*Me*)), 1.41 (1 H, ddd, *J* = 24.0, 13.9, 3.5 Hz, TIPSOCHC*H*H), 1.24–0.98 (23 H, m, TIPSOCHCH_2C*H*H, MeOCHC*H*H, (Me_2C*H*)$_3$Si, and 1.09, s, (Me_2CH)$_3$Si), 0.83 (3 H, d, *J* = 6.9 Hz, CH(*Me*)); IR (thin film) 2925, 2850, 1610, 1515, 1455, 1245, 1105, 1030, 825, 810, 675 cm^{-1}; CILRMS *m*/*e* (relative intensity) 559 (1.4), 558 (0.8), 557 (1.7), 515 (5.6), 419 (10.4), 391 (15.8), 355 (47.6), 323 (40.3), 311 (100.0), 279 (79.8), 145 (14.5), 137 (66.1), 121 (45.5); CIHRMS calcd for $C_{33}H_{55}O_5Si$ 559.3818, found 559.3809.

[2*S*-[2α,4α,5α,6α[*E*(1*S,3*S**,4*S**)]]]-6-[2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxycyclohexyl]-1-methylethenyl]-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane-4-ethanol (14).** The olefin mixture **13** (930 mg, 1.8 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. A solution of 9-BBN (7.2 mL of 0.5 N solution in THF, 3.6 mmol) was added. After 4 h (TLC: 25% EtOAc/hexanes, consumption of starting material) the reaction mixture was quenched at 0 °C by slow addition of 1 N aqueous sodium hydroxide solution (20 mL), followed by slow addition of 30% aqueous hydrogen peroxide solution (3 mL) also at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. Saturated aqueous sodium sulfite solution was added, and the mixture was extracted with EtOAc (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (25 → 50% EtOAc/hexanes) gave the homogeneous alcohol **14** (700 mg, 73%) as a clear oil: $[\alpha]^{25}_D$ = −49.0° (*c* 1.25, $CHCl_3$); ^1H NMR δ 7.43 (2 H, d, *J* = 8.7, ArH (*m*-OMe)), 6.89 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.58 (1 H, s, C*H*Ar), 5.37 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)), 4.23 (1 H, bs, OC*H*C(Me)=CH), 4.15 (1 H, dt, *J* = 9.5, 2.5 Hz, OC*H*CH$_2$), 3.90–3.75 (5 H, m, CH_2OH, and 3.81, s, ArOMe), 3.96 (1 H, ddd, *J* = 10.8, 8.4, 4.8 Hz, TIPSOC*H*), 3.41 (3 H, s, *Me*OCH), 2.99 (1 H, ddd, *J* = 11.2, 8.4, 4.4 Hz, MeOC*H*), 2.32 (1 H, m, C*H*CH=C(Me)), 2.20–2.00 (4 H, m, CH_2CH$_2$OH, MeOCHC*H*H, and TIPSOCHC*H*H), 1.80–1.65 (5 H, m, C*H*(Me), TIPSOCHCH$_2$C*H*H, and 1.61, s, CH=C(*Me*)), 1.41 (1 H, m, TIPSOCHC*H*H), 1.20–0.95 (23 H, m, MeOCHC*H*H, TIPSOCHCH$_2$C*H*H, (Me_2C*H*)$_3$Si, and 1.08, s, (*Me*2CH)$_3$Si), 0.86 (3 H, d, *J* = 6.9 Hz, CH(*Me*)); IR (thin film) 3450, 2930, 2855, 1610, 1510, 1455, 1245, 1135, 1105 cm^{-1}; LRMS *m*/*e* (relative intensity) 533 (6.6), 379 (19.5), 323 (12.1), 311 (35.5), 279 (28.0), 235 (23.2), 217 (13.3), 161 (19.7), 135 (66.5), 121 (100.0); CIHRMS calcd for $C_{33}H_{57}O_6Si$ 577.3926, found 577.3929.

Anal. Calcd for $C_{33}H_{56}O_6Si$: C, 68.71; H, 9.78. Found: C, 68.75; H, 9.82.

[2*S*-[2α,4α,5α,6α[*E*(1*S,3*S**,4*S**)]]]-2-(4-Methoxyphenyl)-6-[2-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-5-methyl-1,3-dioxane-4-acetaldehyde (15).** Alcohol **14** (1.0 g, 1.87 mmol) was dissolved in CH_2Cl_2 (20 mL) at room temperature. Pyridine (227 mL, 2.80 mmol) was added followed by the Dess–Martin periodinane (1.19 g, 2.80 mmol). After 1.5 h (TLC: 50% EtOAc/hexanes) Et_2O was added, and the mixture was stirred for 5 min. The resulting suspension was poured into a stirred mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (5:1, v/v). After 15 min the organic layer was separated, and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. ^{n}Heptane was added to the residue, the mixture was reconcentrated, and the process was repeated. Purification

of the residue by chromatography (20% EtOAc/hexanes) gave the aldehyde **15** (858 mg, 86%) as a clear oil: $[\alpha]^{25}_D$ = −45.8° (*c* 0.31, CH_2Cl_2); ^1H NMR δ 9.85 (1 H, bs, C*H*=O), 7.42 (2 H, d, *J* = 8.7 Hz, ArH (*m*-OMe)), 6.90 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.60 (1 H, s, C*H*Ar), 5.39 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)), 4.52 (1 H, m, OC*H*CH_2CHO), 4.28 (1 H, s, OC*H*C(Me)=CH), 3.81 (3 H, s, ArOMe), 3.57 (1 H, ddd, *J* = 11.0, 8.5, 4.8 Hz, TIPSOC*H*), 3.41 (3 H, s, *Me*OCH), 2.99 (1 H, ddd, *J* =11.3, 8.4, 4.4 Hz, MeOC*H*), 2.85 (1 H, ddd, *J* = 17.0, 8.6, 1.7 Hz, C*H*HCHO), 2.51 (1 H, ddd, *J* = 17.0, 4.6, 1.8 Hz, C*H*HCHO), 2.33 (1 H, m, C*H*CH=C(Me)), 1.97 (2 H, m, TIPSOCHC*H*H and MeOCHC*H*H), 1.75 (1 H, m, C*H*(Me)), 1.61–1.54 (4 H, m, TIPSOCHCH_2C*H*H, and 1.61, s, CH=C(*Me*)), 1.39 (1 H, m, TIPSOCHC*H*H), 1.20–1.00 (23 H, m, MeOCHC*H*H, TIPSOCHCH_2C*H*H, (Me_2C*H*)$_3$Si, and 1.08, s, (*Me*$_2$CH)$_3$Si), 0.85 (3 H, d, *J* = 6.9 Hz, CH(*Me*)); IR (CH_2Cl_2 solution) 2941, 2934, 2865, 1729, 1518, 1249, 1140, 1107, 1039 cm^{-1}; EILRMS *m/e* (relative intensity) 531 (16.1), 363 (14.2), 311 (93.0), 279 (53.6), 233 (20.5), 145 (94.4), 136 (100.0), 121 (69.2), 89 (38.2), 75 (48.1); CIHRMS calcd for $C_{33}H_{55}O_6Si$ 575.3771, found 575.3806.

Anal. Calcd for $C_{33}H_{54}O_6Si$: C, 68.95; H, 9.47. Found: C, 69.06; H, 9.70.

[2*S*-[2α,4α[*S[*R**(*R**)]],5α,6α[*E*(1*S**,3*S**,4*S**)]]]-3-[2-[1-Hydroxy-2-[2-(4-methoxyphenyl)-6-[2-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-5-methyl-1,3-dioxan-4-yl]ethyl]-1-oxo-4-pentenyl]-4-(1-methylethyl)-2-oxazolidinone (16) and [2*S*-[2α,4α[*S**[*R**(*R**)]],5α,6α[*E*(1*S**,3*S**,4*S**)]]]-3-[2-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[2-(4-methoxyphenyl)-6-[2-[3-methoxy-4-[[tris(methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-5-methyl-1,3-dioxan-4-yl]ethyl]-1-oxo-4-pentenyl]-4-(1-methylethyl)-2-oxazolidinone (17).** Di-*n*-butylboron triflate (1.6 mL, 1.57 mmol) was added dropwise to a solution of oxazolidinone **5**[11] (330 mg, 1.57 mmol) in CH_2Cl_2 (5 mL) at 0 °C. Hünig's base (340 μL, 1.93 mmol) was then added directly, and the mixture was stirred at 0 °C for 30 min before transferring dropwise via cannula to a solution of the aldehyde **15** (300 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After 10 min at −78 °C the mixture was allowed to warm to room temperature. After 40 min (TLC: 25% EtOAc/hexanes) an aqueous pH 7 phosphate buffer solution (1.0 mL) was added followed by MeOH (1.0 mL) and 30% aqueous hydrogen peroxide solution (1.0 mL). After stirring for 1 h the mixture was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. (The residue could be purified by chromatography (10→25% EtOAc/hexanes) at this stage to provide the secondary alcohol **16** as a clear oil, vide infra.) The crude residue was dissolved in CH_2Cl_2 (7.5 mL) and cooled to 0 °C. 2,6-Lutidine (496 μL, 4.16 mmol) and *tert*-butyldimethylsilyl triflate (298 μL, 1.3 mmol) were added in succession. After 2 h (TLC: 25% EtOAc/hexanes) the mixture was quenched by addition of an aqueous pH 7 phosphate buffer solution and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (10% EtOAc/hexanes) gave the silylated aldol adduct **17** (423 mg, 90%) as a clear oil: $[\alpha]^{25}_D$ = +6.1° (*c* 0.67, $CHCl_3$); ^1H NMR δ 7.42 (2 H, d, *J* = 8.5 Hz, ArH (*m*-OMe)), 6.88 (2 H, d, *J* = 8.5 Hz, ArH (*o*-OMe)), 5.81 (1 H, m, C*H*=CH_2), 5.50 (1 H, s, C*H*Ar), 5.25 (1 H, d, *J* = 8.9 Hz, CH=C(Me)), 5.03 (1 H, d, *J* = 17.2 Hz, *cis*-CH=C*H*H), 4.99 (1 H, d, *J* = 10.4 Hz, *trans*-CH=C*H*H), 4.19–4.11 (5 H, m, CHN, CH_2OC=O, OC*H*C(Me)=CH, and OC*H*CH_2CHOTBS), 3.85 (1 H, dd, *J* = 9.0, 2.3 Hz, C*H*OTBS), 3.82 (3 H, s, ArOMe), 3.54 (1 H, m, TIPSOC*H*), 3.40 (3 H, s, CHO*Me*), 3.36 (1 H, t, *J* = 8.6 Hz, C*H*C(O)N), 2.97 (1 H, m, C*H*OMe), 2.55 (2 H, m, CH_2CH=CH_2), 2.25 (2 H, m, C*H*CH=C(Me) and Me_2C*H*C), 1.93 (3 H, m, C*H*HCHOTBS, TIPSOCHC*H*H, and MeOCHC*H*H), 1.73 (1 H, m, C*H*HCHOTBS), 1.62–1.52 (5 H, m, C*H*(Me), TIPSOCHCH_2C*H*H and 1.57, s, CH=C(*Me*)), 1.37 (1 H, ddd, *J* = 24.0, 13.2, 3.1 Hz, TIPSOCHC*H*H), 1.12–0.96 (23 H, m, MeOCHC*H*H, TIPSOCHCH_2C*H*H, (Me_2C*H*)$_3$Si, and 1.07, s, (*Me*$_2$CH)$_3$Si), 0.92 (9 H, s, ^tBu), 0.81 (4 H, d, *J* = 6.9 Hz, *Me*CH(Me) and C*H*(Me)CHO), 0.76 (3 H, d, *J* = 6.8 Hz, *Me*CH(Me)), 0.08 (6 H, s, Me_2Si); IR (thin film) 2935, 2865, 1780, 1695, 1615, 1515, 1460, 1385, 1250, 1115, 840 cm^{-1}; FABLRMS (TECDME) *m/e* (relative intensity) 900 (28.8), 764 (19.2), 720 (20.8), 443 (49.9), 398 (16.2), 354 (62.7), 311 (100.0), 266 (54.7); FABHRMS calcd for $C_{50}H_{86}NO_9Si_2$ 900.5844, found 900.5819.

Anal. Calcd for $C_{50}H_{85}NO_9Si_2$: C, 66.70; H, 9.51. Found: C, 66.48: H, 9.80.

For the aldol adduct **16**: $[\alpha]^{25}_D$ = +7.2° (*c* 0.32, $CHCl_3$); ^1H NMR δ 7.39 (2 H, d, *J* = 8.7 Hz, ArH (*m*-OMe)), 6.88 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.86 (1 H, m, C*H*=CH_2), 5.57 (1 H, s, C*H*Ar), 5.35 (1 H, bd, *J* = 9.1 Hz, C*H*=C(Me)), 5.10 (1 H, bd, *J* = 17.2 Hz, *cis*-CH=C*H*H), 5.02 (1 H, bd, *J* = 10.1 Hz, *trans*-CH=C*H*H), 4.45 (1 H, m), 4.24–4.11 (6 H, m), 3.81 (3 H, s, ArOMe), 3.57 (1 H, m, TIPSOC*H*), 3.41 (3 H, s, CHO*Me*), 3.18 (1 H, bs, OH), 2.99 (1 H, ddd, *J* = 12.3, 8.3, 4.2 Hz, MeOC*H*), 2.63 (1 H, m, C*H*HCHCH=CH_2), 2.43 (1 H, m, C*H*HCH=CH_2), 2.32 (2 H, m, C*H*CH=C(Me) and Me_2C*H*CH), 2.05–1.92 (3 H, m, C*H*HCH(OH), MeOCHC*H*H, and TIPSOCHC*H*H), 1.68 (1 H, m, C*H*HCH(OH)), 1.63–1.57 (5 H, m, C*H*(Me), TIPSOCHCH_2-C*H*H, and CH=C(*Me*)), 1.39 (1 H, ddd, *J* = 24.8, 13.6, 3.3 Hz, TIPSOCHC*H*H), 1.13–1.01 (23 H, m, TIPSOCHCH_2C*H*H, MeOCHC*H*H, (Me_2C*H*)$_3$Si, and 1.08, s, (*Me*$_2$CH)$_3$Si), 0.90 (3 H, d, *J* = 7.0 Hz, *Me*CH(Me)), 0.86 (3 H, d, *J* = 6.6 Hz, OCHCH-(*Me*)), 0.85 (3 H, d, *J* = 5.3 Hz, *Me*CH(Me)); IR (thin film) 3500, 2929, 2866, 1779, 1694, 1614, 1519, 1385, 1249, 1107 cm^{-1}; FABLRMS (TECDME) *m/e* (relative intensity) 786 (37.9), 768 (22.5), 742 (22.1), 650 (100.0), 632 (24.8), 600 (16.9), 443 (80.2); FABHRMS (NOBA + NaI) calcd for $C_{44}H_{71}O_9NNaSi$ 808.4798, found 808.4843.

Anal. Calcd for $C_{44}H_{71}NO_9Si$: C, 67.22; H, 9.10; N, 1.78. Found: C, 67.16; H, 9.17; N, 1.67.

[2*S*-[2α,4α(αR*,βS*),5α,6α[*E*(1*S,3*S**,4*S**)]]]-β-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-(4-methoxyphenyl)-6-[2-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-5-methyl-α-2-propenyl-1,3-dioxane-4-butanoic Acid Phenylmethyl Ester (18).** Benzyl alcohol (250 μL, 2.4 mmol) was dissolved in THF (10 mL) and cooled to 0 °C, and ^{n}BuLi (1.69 mL of a 1.39 N solution in hexanes, 2.35 mmol) was added dropwise. After 30 min the mixture was transferred dropwise via cannula to a solution of the silylated aldol adduct **17** (430 mg, 0.48 mmol) in THF (4 mL) at 0 °C. After 2 h at 0 °C the mixture was allowed to warm to room temperature and stirred for an additional 1 h, (TLC: 25% EtOAc/hexanes). Saturated aqueous ammonium chloride solution was added, and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine (1×), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 10% EtOAc/hexanes) gave the benzyl ester **18** (367 mg, 87%) as a clear oil: $[\alpha]^{25}_D$ = −26.7° (*c* 0.93, $CHCl_3$); ^1H NMR δ 7.42 (2 H, d, *J* = 8.7 Hz, ArH (*m*-OMe)), 7.30 (5 H, s, Ph), 6.81 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.76 (1 H, m, C*H*=CH_2), 5.50 (1 H, s, C*H*Ar), 5.35 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)), 5.13 (1 H, d, *J* = 12.5 Hz, C*H*HPh), 5.03 (1 H, d, *J* = 17.1 Hz, *cis*-CH=C*H*H), 4.97 (2 H, m, C*H*HPh and *trans*-CH=C*H*H), 4.15 (2 H, m, TBSOC*H* and OC*H*C(Me)=CH), 4.05 (1 H, m, OC*H*CH_2CHOTBS), 3.79 (3 H, s, ArOMe), 3.57 (1 H, ddd, *J* = 11.4, 8.9, 4.8 Hz, TIPSOC*H*), 3.40 (3 H, s, CHO*Me*), 2.98 (1 H, m, MeOC*H*), 2.78 (1 H, m, C*H*CO_2Bn), 2.41 (2 H, m, CH_2CH=CH_2), 2.33 (1 H, m, C*H*CH=C(Me)), 1.98 (3 H, m, C*H*HCHOTBS, MeOCHC*H*H, and TIPSOCHC*H*H), 1.71 (1 H, dt, *J* = 14.7, 5.3 Hz, C*H*HCHOTBS), 1.59 (5 H, m, C*H*(Me), TIPSOCHCH_2C*H*H, and 1.58, s, CH=C(*Me*)), 1.39 (1 H, ddd, *J* = 24.4, 13.3, 3.6 Hz, TIPSOCHC*H*H), 1.10 (23 H, m, TIPSOCHCH_2C*H*H, MeOCH-C*H*H, (Me_2C*H*)$_3$Si, and 1.08, s, (M_2CH)$_3$Si), 0.89 (9 H, s, ^tBu), 0.78 (3 H, d, *J* = 6.8 Hz, CH(*Me*)), 0.06 (3 H, s, MeSi), 0.04 (3 H, s, MeSi); IR (thin film) 2935, 2860, 1730, 1615, 1520, 1460, 1250, 1110, 835 cm^{-1}; FABLRMS (TECDME) *m/e* (relative intensity) 880 (20.9), 879 (16.9), 835 (19.0), 743 (23.3), 443 (97.6), 377 (35.5), 346 (46.9), 311 (100.0), 267 (62.2); FABHRMS calcd for $C_{51}H_{83}O_8Si_2$ 879.5629, found 879.5621.

Anal. Calcd for $C_{51}H_{82}O_8Si_2$: C, 69.66; H, 9.40. Found: C, 69.66; H, 9.21.

[2*S*-[2α,4α(αR*,βS*)5α,6α[*E*(1*S,3*S**,4*S**)]]]-β-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-(4-methoxyphenyl)-6-[2-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-5-methyl-α-2-propenyl-1,3-dioxane-4-butanal (20).** Benzyl ester **18** (345 mg, 0.39 mmol) was dissolved in toluene (4.0 mL) and cooled to −78 °C. Diisobutylaluminum hydride (1.18 mL of a 1 N solution in hexanes,

1.18 mmol) was added dropwise. After 30 min (TLC: 25% EtOAc/hexanes) the reaction was quenched by dropwise addition of MeOH (300 mL) at −78 °C followed by addition of a saturated aqueous sodium potassium tartrate solution. The mixture was allowed to warm to room temperature and stirred for 1.5 h before extracting with EtOAc (3×). The combined organic extracts were washed with brine (1×), dried over $MgSO_4$, filtered, and concentrated to give a crude mixture of primary alcohol **19** and aldehyde **20**.

DMSO (237 μL, 3.31 mmol) was added dropwise to a solution of oxalyl chloride (137 μL, 1.56 mmol) in CH_2Cl_2 (4.0 mL) at −78 °C. After 20 min at −78 °C a solution of **19** and **20**, in CH_2Cl_2 (1.0 mL), was added dropwise to this mixture. After an additional 1 h at −78 °C triethylamine (650 μL, 4.68 mmol) was added, and the mixture was allowed to warm to room temperature. Water was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 10% EtOAc/hexanes gave aldehyde **20** (267 mg, 88%) as a clear oil: $[\alpha]^{25}_D$ = −24.9° (*c* 1.42, $CHCl_3$); ^1H NMR δ 9.78 (1 H, d, *J* = 1.5 Hz, C*H*=O), 7.42 (2 H, d, *J* = 8.7 Hz, ArH (*m*-OMe)), 6.90 (2 H, d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.80 (1 H, m, C*H*=CH_2), 5.51 (1 H, s, C*H*Ar), 5.36 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)), 5.09 (2 H, m, CH=CH_2), 4.25 (1 H, q, *J* = 5.9 Hz, TBSOC*H*), 4.17 (1 H, bs, OC*H*C(Me)=CH), 4.04 (1 H, m, OC*H*CH_2CHOTBS), 3.82 (3 H, s, ArOMe), 3.57 (1 H, ddd, *J* = 10.8, 8.4, 4.8 Hz, TIPSOC*H*), 3.41 (3 H, s, CHO*Me*), 2.99 (1 H, m, MeOC*H*), 2.62 (1 H, m, C*H*CHO), 2.55 (1 H, m, C*H*HCH=CH_2), 2.28 (2 H, m, C*H*HCH=CH_2 and C*H*CH=C(Me)), 1.95 (3 H, m, C*HHCHOTBS*, MeOCH*CH*H, and TIPSOCI*CH*H), 1.72 (1 H, dt, *J* = 14.3, 5.5 Hz, C*H*HCHOTBS), 1.62 (5 H, m, C*H*(Me), TIPSOCHCH_2C*H*H, and 1.60, s, CH=C(*Me*)), 1.39 (1 H, ddd, *J* = 24.3, 13.4, 3.6 Hz, TIPSOCHC*H*H), 1.09 (23 H, m, TIPSOCHCH_2C*H*H, MeOCHC*H*H, ($Me_iCH)_3$Si, and 1.08, s, ($Me_2CH)_3$Si), 0.91 (9 H, s, ^tBu), 0.81 (3 H, d, *J* = 6.8 Hz, CH(*Me*)), 0.09 (3 H, s, MeSi), 0.08 (3 H, s, MeSi); IR (thin film) 2920, 2850, 1720, 1615, 1515, 1455, 1250, 1105 cm^{-1}; FABLRMS (thioglycerol) *m/e* 745, 613, 563, 443, 407, 379, 335, 319.

Anal. Calcd for $C_{44}H_{76}O_7Si_2$: C, 68.35; H, 9.91. Found: C, 68.07; H, 10.03.

[2*S*-[2α,4α[5*S,6*S**,7*E*,10*R**,12*R**,13*S**(1*R**,3*S**)],5α,6α-[*E*(1*S**,3*S**,4*S**)]]]-13-[4-(1,3-Dithian-2-yl)-1-methoxy-3-methylbutyl]-12-methoxy-5-[[2-(4-methoxyphenyl)-6-[2-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-5-methyl-1,3-dioxan-4-yl]methyl]-2,8,10,16-tetramethyl-6-(2-propenyl)-4,14-dioxa-3,15-disilaheptadec-7-ene (23).** Sulfone **4**[6c] (237 mg, 0.38 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. ^{n}BuLi (278 mL of a 1.39 N solution in hexanes, 0.38 mmol) was added dropwise, and the mixture was stirred at −78 °C for 20 min. A solution of the aldehyde **20** (212 mg, 0.27 mmol) in THF (1.0 mL) was added dropwise. After a further 20 min (TLC: 25% EtOAc/hexanes) the reaction was quenched by addition of saturated aqueous ammonium chloride solution and allowed to warm to room temperature. The mixture was extracted with EtOAc (3×), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (10 → 30% EtOAc/hexanes) gave an uncharacterized mixture of hydroxy sulfones **21** (336 mg, 88%).

A mixture of these hydroxy sulfones (382 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (4.0 mL) at room temperature. Pyridine (222 μL, 2.75 mmol), 4-(dimethylamino)pyridine (11 mg, 0.09 mmol), and trifluoroacetic anhydride (194 μL, 1.38 mmol) were added in succession. After 1.5 h (TLC: 5% EtOAc/$PhCH_3$) the reaction mixture was concentrated and purified by chromatography to give an uncharacterized mixture of trifluoroacetates **22**. This mixture was dissolved in THF (3 mL) and cooled to −20 °C. A solution of lithium naphthalenide (0.4 N in THF; prepared by addition of lithium (22 mg, 3.14 mmol) to a solution of naphthalene (205 mg, 1.60 mmol) in THF (4.0 mL) followed by ultrasonication for 1 h) was added dropwise until the reaction mixture remained dark green. The mixture was stirred for an additional 10 min at −20 °C before quenching with saturated aqueous ammonium chloride solution and allowing to warm to room temperature. The resulting mixture was extracted with EtOAc (3×), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 10% EtOAc/hexanes) gave an inseparable mixture of olefin isomers **23** (229 mg, 68% overall, two steps) as a clear gum. Selected data for the olefin mixture: ^1H NMR δ 7.42 (2 H, 2 d, *J* = 8.7 Hz, ArH (*m*-OMe)), 6.88 (2 H, 2 d, *J* = 8.7 Hz, ArH (*o*-OMe)), 5.74 (1 H, m, C*H*=CH_2), 5.51 ($^2/_3$ H, s, C*H*Ar, major isomer), 5.48 ($^1/_3$ H, s, C*H*Ar, minor isomer), 5.37 (1 H, m, C*H*=C(Me)CO), 5.19 ($^1/_3$ H, d, *J* = 8.8 Hz, C*H*=C(Me)CH_2, minor isomer), 5.04–4.88 ($^8/_3$ H, m, C*H*=C(Me)CH_2, major isomer, and CH=CH_2), 4.22–4.13 (2 H, m, C*H*$(S)_2$ and OC*H*C(Me)=CH), 4.05 ($^2/_3$ H, m, OC*H*CH_2, major isomer), 3.98 ($^1/_3$ H, m, OC*H*CH_2, minor isomer), 3.89 (1 H, m, TBSOC*H*CH(OMe)), 3.83–3.71 (4 H, m, TBSOC*H*CH_2, and 3.81, s, ArOMe), 3.57 (1 H, m, TIPSOC*H*), 3.45 (2 H, s, OMe, major isomer), 3.44 (1 H, s, OMe, minor isomer), 3.40 (3 H, s, OMe), 3.33 (3 H, s, OMe), 3.26 (1 H, bd, *J* = 9.4 Hz, MeOC*H*CH_2CH(Me)CH_2), 3.17 (1 H, m, MeOC*H*CH_2CH(Me)CH$(S)_2$), 3.02–2.78 (5 H, m, MeOC*H*CH(OTIPS), SCH_2, and SCH_2), 2.53 ($^2/_3$ H, m, C*H*CH_2CH=CH_2, major isomer), 2.46 ($^1/_3$ H, m, C*H*CH_2CH=CH_2, minor isomer), 1.70 (1 H, s, CH<<ΔbdC(*Me*)CH_2, minor isomer), 1.60 (3 H, s, CH=C(*Me*)CH(O)), 1.52 (2 H, s, CH=C-(*Me*)CH_2, major isomer), 1.08 (s, ($Me_2CH)_3$Si), 0.91 (s, ^tBuSi); FABLRMS *m/e* (relative abundance) 1233 (32.7), 1176 (46.0), 1098 (44.3), 731 (100.0); FABHRMS calcd for $C_{68}H_{124}O_9S_2Si_3$ 1232.7994, found 1232.8018.

[1*R*-[1α(1*E*,3*S,4*R**,5*S**,7*R**,8*R**,9*E*,12*S**,14*S**,15*R**,16*S**,18*R**),3α,4β]]-7,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-19-(1,3-dithian-2-yl)-14,16-dimethoxy-1-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-2,4,10,12,18-pentamethyl-8-(2-propenyl)-1,9-nonadecadiene-3,5-diol (24).** The olefin mixture **23** (45 mg, 0.037 mmol) was dissolved in 2-propanol (5 mL), and acetonitrile (5 mL) was added. A solution of pyridinium *p*-toluenesulfonate (9.2 mg, 0.037 mmol) in acetonitrile (150 μL) was added, and the mixture was warmed to 70 °C. After 26 h (TLC: 25% EtOAc/hexanes) the mixture was allowed to cool to room temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and concentration. Water was added to the residue, and the mixture was extracted with EtOAc (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue gave recovered starting material **23** (12.6 mg, 28%), minor diol **25** (4.5 mg, 11%), and the homogeneous diol **24** (13.4 mg, 33%) as a clear oil: $[\alpha]^{25}_D$ = −19.0° (*c* 0.72, $CHCl_3$); ^1H NMR δ 5.72 (1 H, m, C*H*=CH_2), 5.34 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)CH(OH)), 5.04–4.98 (2 H, m, C*H*=C(Me)CH_2 and *cis*-CH=C*H*H), 4.95 (1 H, d, *J* = 10.1 Hz, *trans*-CH=C*H*H), 4.19 (2 H, d, *J* = 2.3 Hz, CH$(S)_2$ and HOC*H*C(Me)=CH), 4.00 (1 H, bd, *J* = 8.2 Hz, HOC*H*CH_2CHOTBS), 3.89 (1 H, d, *J* = 6.3 Hz, TBDSOC*H*CH(OMe)), 3.84 (1 H, m, TBSOC*H*CHCH=C-(Me)), 3.58 (1 H, m, TIPSOC*H*), 3.47 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.34 (3 H, s, OMe), 3.27 (1 H, d, *J* = 10.1 Hz, C*H*-(OMe)CH_iCH(Me)CH$(S)_2$), 3.17 (1 H, m, C*H*(OMe)CH_iCH-(Me)CH_2), 2.98 (1 H, m, MeOC*H*CH(OTIPS)), 2.93 (1 H, d, *J* = 12.3 Hz, SC*H*H), 2.89–2.80 (3 H, m, SC*H*H and SCH_2), 2.57 (1 H, m, C*H*CH_2CH=CH_2), 2.35–2.07 (5 H, m), 2.00–1.89 (3 H, m), 1.89–1.79 (2 H, m), 1.79–1.68 (2 H, m), 1.65–1.50 (9 H, m, including 1.59, s, CH=C(*Me*)CHOH) and CH=C(*Me*)CH_2), 1.43–1.32 (3 H, m), 1.18–0.96 (28 H, m, including 1.13, d, *J* = 7.0 Hz, CH-(*Me*)C$(S)_2$, and 1.09, s, ($Me_2CH)_3$Si), 0.92 (9 H, s, ^tBu), 0.90 (9 H, s, ^tBu), 0.84 (3 H, d, *J* = 6.7 Hz, CH(*Me*)), 0.82 (3 H, d, *J* = 7.0 Hz, CH(*Me*)), 0.10 (12 H, m, Me_2Si and Me_2Si); IR (CH_2Cl_2 solution) 3510 (br), 2930, 2863, 1461, 1381, 1104, 836 cm^{-1}; FABLRMS (NOBA + NaI) *m/e* (relative intensity) 1138 (45.4), 966 (27.0), 909 (30.0), 732 (29.3), 699 (73.9), 667 (42.0), 599 (35.2), 567 (100.0), 521 (447); FABHRMS calcd for $C_{60}H_{118}NaO_8S_2Si_3$ 1137.7478, found 1137.7468.

Anal. Calcd for $C_{60}H_{118}O_8S_2Si_3$: C, 64.59; H, 10.67. Found: C, 64.81; H, 10.37.

[1*R*-[1α(1*E*,3*S,4*R**,5*S**,7*R**,8*R**,9*E*,12*S**,14*S**,15*R**,16*S**,18*R**),3α,4β]]-7,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-19-(1,3-dithian-2-yl)-14,16-dimethoxy-1-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-2,4,10,12,18-pentamethyl-8-(2-propenyl)-5-[[tris(1-methylethyl)silyl]oxy]-1,9-nonadecadien-3-ol (26).** Diol **24** (20 mg, 17.9 μmol) was dissolved in CH_2Cl_2 (500 μL) at room temperature. 2,6-Lutidine (10.5 μL, 89.5 μmol) and triisopropylsilyl triflate (12.0 μL, 44.8 μmol) were added successively. After 20 min (TLC: 10%

EtOAc/hexanes) the reaction was quenched by addition of saturated aqueous sodium bicarbonate solution. The mixture was extracted with CH_2Cl_2 (3×), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 10% EtOAc/hexanes) gave silyl ether **26** (17.0 mg, 75%) as a clear oil: $[\alpha]^{25}_D$ = −9.6° (*c* 0.75, $CHCl_3$); ^1H NMR δ 5.72 (1 H, m, CH=CH_2), 5.42 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)CH(OH)), 5.01–4.94 (3 H, m, CH=C*H*$_2$ and C*H*=C(Me)CH_2), 4.37 (1 H, m, TIPSOC*H*CH(Me)), 4.25 (1 H, s, C*H*(OH)C(Me)=CH), 4.19 (1 H, d, *J* = 3.3 Hz, C*H*$S)_2$), 3.91 (1 H, dd, *J* = 6.1, 1.1 Hz, C*H*(OTBS)CH(OMe)), 3.87 (1 H, m, OH), 3.56 (2 H, m, TIPSOC*H*CH(OMe) and TBSOC*H*CHCH=C(Me)), 3.47 (3 H, m, OMe), 3.41 (3 H, m, OMe), 3.34 (3 H, m, OMe), 3.28 (1 H, bd, *J* = 9.8 Hz, C*H*(OMe)CH_2CH(Me)CH$(S)_2$), 3.19 (1 H, m, C*H*(OMe)CH_2CH(Me)CH_2), 2.98 (1 H, ddd, *J* = 11.5, 8.4, 4.3 Hz, MeOC*H*CH(OTIPS)), 2.93 (1 H, br dd, *J* = 12.2, 1.3 Hz, SC*H*H), 2.84 (3 H, m, SC*H*H and SCH_2), 2.44 (1 H, m, TBSOCHC*H*CH=C(Me)), 2.35–2.20 (3 H, m), 2.19–2.06 (2 H, m), 2.02–1.89 (3 H, m), 1.89–1.72 (5 H, m), 1.66–1.48 (9 H, m, including 1.60, s, CH=C(*Me*), and 1.58, s, CH=C(*Me*)), 1.48–1.34 (2 H, m), 1.20–1.00 (49 H, m), 0.92 (9 H, s, ^tBu), 0.90 (9 H, s, ^tBu), 0.83 (3 H, d, *J* = 6.6 Hz, CH(*Me*)), 0.77 (3 H, d, *J* = 7.0 Hz, CH(*Me*)), 0.10 (3 H, s, MeSi), 0.09 (3 H, s, MeSi), 0.07 (3 H, s, MeSi), 0.05 (3 H, s, MeSi); IR (CH_2Cl_2 solution) 2928, 2865, 1460, 1382, 1103, 838 cm^{-1}; FABLRMS (NOBA, MeOH–NaI) *m/e* (relative intensity) 1296 (41.5), 1214 (3594), 889 (30.4), 855 (40.3), 829 (32.7), 656 (33.2)8, 553 (100.0), 521 (64.4); FABHRMS calcd for $C_{69}H_{138}NaO_8S_2Si_4$ 1293.8817, found 1293.8799.

Anal. Calcd for $C_{69}H_{138}O_8S_2Si_4$: C, 65.15; H, 10.94. Found: C, 64.94; H, 10.71.

[1*R*-[1α[*E*[1*S(*S**),2*S**,3*S**,5*R**,6*R**,7*E*,10*S**,13*R**,14*S**,16*R**]],3α,4β]]-2-[5,13-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-(1,3-dithian-2-yl)-12,14-dimethoxy-1-[2-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-2,8,10,16-tetramethyl-6-(2-propenyl)-3-[[tris(1-methylethyl)silyl]oxy]-7-heptadecenyl]-1,2-piperidinedicarboxylic Acid 1-(1,1-Dimethylethyl ester) (27).** Alcohol **26** (21 mg, 16.5 μmol) was dissolved in CH_2Cl_2 (350 μL) and cooled to −20 °C. A solution of ^{t}BOC-pipecolic acid[14] (38 mg, 0.165 mmol) in CH_2Cl_2 (100 μL) was added, followed by a solution of 4-(dimethylamino)pyridine (4 mg, 33 μmoL) in CH_2Cl_2 (50 μL). Finally a solution of dicyclohexylcarbodiimide (34 mg, 0.165 mmol) in CH_2Cl_2 (75 μL) was added. After 12 h at −20 °C (TLC: 5% EtOAc/$PhCH_3$) Et_2O was added, and the resulting suspension was filtered through Celite, eluting with Et_2O. Silica gel was added to the filtrate, and the slurry was concentrated to dryness. The material was loaded directly onto a chromatography column and eluted with 5 → 10% EtOAc/hexanes to give the ester **27** (20 mg, 81%) as a clear oil. Spectroscopic data was identical with that supplied by Merck and Co., Inc.[5]

[1*R*-[1α[*E*[1*R(*S**),2*S**,3*S**,5*R**,6*R**,7*E*,10*S**,12*S**,13*R**,14*S**,16*R**]],3α,4β]]-2-[5,13-Bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-12,14-dimethoxy-1-[2-[3-methoxy-4-[[tris-(1-methylethyl)silyl]oxy]cyclohexyl]-1-methylethenyl]-2,8,10,16-tetramethyl-18-oxo-6-(2-propenyl)-3-[[tris(1-methylethyl)silyl]oxy]-7-octadecenyl]-1,2-piperidinedicarboxylic Acid 1-(1,1-Dimethylethyl ester) (7c).** Dithiane **27** (20 mg, 13.4 μmol) was dissolved in 1:1 THF/MeOH (200 μL) and added rapidly to a stirred suspension of *N*-chlorosuccinimide (9.0 mg, 67.0 μmol), silver nitrate (14.0 mg, 80.4 μmol), and 2,6-lutidine (15.0 μL, 134.0 μmol) in 1:1 THF/MeOH (500 μL) at room temperature. After 15 min (TLC: 5% EtOAc/$PhCH_3$) the reaction was quenched by the addition of saturated aqueous sodium sulfite solution. After 1 min saturated aqueous sodium carbonate solution was added and, after a further minute, brine. The mixture was filtered through celite, eluting with 1:1 hexanes/CH_2Cl_2. The filtrate was partitioned and the aqueous phase extracted with 1:1 hexanes/CH_2Cl_2 (2×). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification of the residue by chromatography (10 → 25% EtOAc/hexanes) gave a clear oil **28** which was dissolved in CH_2Cl_2 (500 μL) at room temperature in an open vessel. Pyridinium *p*-toluenesulfinate (17 mg, 67.0 μmol) was added and the mixture stirred for 2 h. The reaction mixture was poured directly onto a chromatography column and eluted with 10 → 25% EtOAc/hexanes to give the aldehyde **7c** (14 mg, 75%) as a clear oil. Spectroscopic data was identical to that supplied by Merck and Co., Inc.[5]

[1*R*-[1α[1(*S),2*R**,4*S**,5*R**,6*S**,8*S**,10*E*,12*R**,13*R**,15*S**,16*R**,17*S**,18*E*],3α,4β]]-1-[[2-[5,13-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-15,17-dihydroxy-4,6-dimethoxy-19-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-2,8,10,16,18-pentamethyl-12-(2-propenyl)-10,18-nonadecadienyl]-1,3-dithian-2-yl]oxoacetyl]-2-piperidinecarboxylic Acid 1,1-Dimethylethyl Ester (31).** Freshly sublimed (3×) potassium *tert*-butoxide (12.6 mg, 112 μmol) was stirred in dry pentane (500 μL) at 0 °C, and ^{n}BuLi (81 μL of a 1.39 N solution in hexanes, 112 mmol) was added. After 1 h at 0 °C the mixture was cooled to −78 °C, and a solution of the dithiane mixture **23** (69 mg, 56 μmol) in THF (400 μL) was added slowly. After 20 min at −78 °C a solution of the pipicolyl oxalate **29**[23] (45 mg, 168 μmol) in THF (100 μL) was added. After a further 20 min (TLC: 25% EtOAc/hexanes) the reaction was quenched by addition of saturated aqueous ammonium chloride solution and allowed to warm to room temperature. The mixture was extracted with EtOAc (3×), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 10% EtOAc/hexanes) gave recovered starting material (11 mg, 16%) and a mixture of the olefin isomers of masked tricarbonyl compound **30** (40 mg, 58% based on recovered **31** and 48% forward) as a clear oil (an uncharacterized mixture of C_{19}–C_{20} olefin isomers and amide bond rotamers).[23]

A mixture of the olefin isomers of masked tricarbonyl compound **30** (33 mg, 0.022 mmol) was dissolved in 2-propanol (3 mL), and acetonitrile (3 mL) was added. A solution of pyridinium *p*-toluenesulfonate (7.3 mg, 0.029 mmol) in acetonitrile (100 μL) was added, and the mixture was warmed to 75 °C. After 25 h (TLC: 25% EtOAc/hexanes) the mixture was allowed to cool to room temperature and saturated aqueous sodium bicarbonate solution (300 μL) was added. The resulting mixture was concentrated, diluted with water, and extracted with EtOAc (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 20% EtOAc/hexanes) gave recovered starting material (10 mg, 30%), the diol of the minor olefin isomer (3.7, mg, 12%), and the diol of the major olefin isomer (7.4 mg, 24%; 52% theoretical,[17] based on recovered **30**) as a clear oil: mixture of rotamers (2.5:1); ^1H NMR (selected data for the major rotamer) δ 5.73 (1 H, m, C*H*=CH_2), 5.34 (1 H, d, *J* = 9.1 Hz, C*H*=C(Me)CH(OH)), 5.19 (1 H, bd, *J* = 5.0 Hz, C*H*$CO_2{}^tBu$), 5.04–4.97 (2 H, m, *cis*-CH=C*H*H and C*H*=C(Me)CH_2), 4.95 (1 H, d, *J* = 10.1 Hz, *trans*-CH=C*H*H), 4.19 (1 H, s, C*H*(OH)C(Me)=CH), 4.01 (1 H, bd, *J* = 7.1 Hz, C*H*(OH)CH_2), 3.83 (2 H, m, TBSOC*H* and TBSOC*H*), 3.66 (1 H, bd, *J* = 11.1 Hz, NC*H*H), 3.57 (1 H, ddd, *J* = 10.9, 8.4, 4.9 Hz, TIPSOC*H*), 3.45 (3 H, s, MeO), 3.40 (3 H, s, MeO), 3.39–3.29 (4 H, m, NC*H*H, and 3.31 s, MeO), 3.25 (1 H, bd, *J* = 9.9 Hz, MeOC*H*CH_2CH(Me)C$(S)_2$), 3.21 (1 H, m, MeOC*H*CH_2CH(Me)CH_2), 3.02–2.83 (3 H, m), 2.71–2.54 (4 H, m), 1.59 (6 H, s, CH=C(*Me*) and CH=C(*Me*)), 1.48 (9 H, s, $CO_2{}^tBu$), 1.22 (3 H, d, *J* = 6.8 Hz, CH(*Me*)C$(S)_2$), 1.08 (18 H, s, $(Me_2CH)_3Si$), 0.92 (9 H, s, ^tBuSi), 0.90 (9 H, s, ^tBuSi), 0.85–0.80 (6 H, m, CH(*Me*) and CH(*Me*)), 0.11–0.08 (12 H, m, Me_2Si and Me_2Si); unobscured resonances for minor rotamer δ 4.49 (bd, *J* = 12.9 Hz), 4.32 (d, *J* = 4.6 Hz), 3.46 (s), 3.32 (s), 3.12–3.03 (t, *J* = 11.5 Hz), 1.51 (s).

[1*R*-[1α[1(*S),2*R**,4*S**,5*R**,6*S**,8*S**,10*E*,12*R**,13*R**,15*S**,16*S**,17*S**,18*E*]3α,4β]]-1-[[2-[5,13-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-hydroxy-4,6-dimethoxy-19-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-2,8,10,16,18-pentamethyl-12-(2-propenyl)-15-[[tris(1-methylethyl)silyl]oxy]-10,18-nonadecadienyl]-1,3-dithian-2-yl]oxocetyl]-2-piperidinecarboxylic Acid 1,1-Dimethylethyl Ester (32).** Diol **31** (6.4 mg, 4.7 μmol) was dissolved in CH_2Cl_2 (500 μL) at room temperature. 2,6-Lutidine (1.3 μL, 11.4 μmol) and triisopropylsilyl triflate (1.5 μL, 5.7 μmol) were added in succession. After 20 min further amounts of 2,6-lutidine (4 μL, 35 μmol) and triisopropylsilyl triflate (2 μL, 7.6 μmol) were added. After a further 25 min (TLC: 20% EtOAc/hexanes) the reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and extracted with EtOAc (3×). The combined organic extracts were washed with saturated copper sulfate solution and then brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (5 → 10%

EtOAc/hexanes) gave the alcohol **32** (5.5 mg, 77%) as a clear oil: ^{1}H NMR (selected data for major isomer) δ 5.72 (1 H, m, C*H*=CH_2), 5.42 (1 H, d, J = 8 Hz, C*H*=C(Me)CH(OH)), 5.20 (1 H, d, J = 6 Hz, C*H*CO_2*t*Bu), 5.02-4.92 (3 H, m, CH=CH_2 and C*H*=C(Me)CH_2), 4.38 (1 H, bd, J = 8 Hz, TIPSOC*H*CH(Me)), 4.26 (1 H, s, C*H*(OH)), 3.88 (2 H, m, TBSOC*H*CH(OMe) and OH), 3.68 (1 H, bd, J = 10 Hz, NC*H*H), 3.55 (2 H, m, TIPSOC*H*CH(OMe) and TBSOC*H*CH_2), 3.45 (3 H, s, MeO), 3.42 (3 H, s, MeO), 3.37 (1 H, m, NC*H*H), 3.33 (3 H, s, MeO), 3.29 (1 H, d, J = 9 Hz, MeOC*H*CH_2CH(Me)C(S)$_2$), 3.21 (1 H, m, MeOC*H*CH_2CH(Me)-CH_2), 2.99 (3 H, m), 2.67 (3 H, m), 2.45 (1 H, m, C*H*CH=C-(Me)CH_2), 1.59 (6 H, s, CH=C(*Me*) and CH=C(*Me*)), 1.49 (9 H, s, CO_2*t*Bu), 1.21 (3 H, d, J = 8 Hz), 1.11 (s, (Me_2CH)$_3$Si), 1.10 (s, (Me_2CH)$_3$Si), 0.94 (s, *t*BuSi), 0.91 (s, *t*BuSi), 0.82 (d, J = 7 Hz), 0.78 (d, J = 7 Hz), 0.13-0.06 (12 H, m, Me_2Si and Me_2Si).

[1*R*-[1α[1(*S),2*R**,4*S**,5*R**,6*S**,8*S**,10*E*,12*R**,13*R**,15*S**,16*S**,17*S**,18*E*],3α,4β]]-1-[[2-[5,13-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-hydroxy-4,6-dimethoxy-19-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-2,8,10,16,18-pentamethyl-12-(2-propenyl)-15-[[tris(1-methylethyl)silyl]oxy]-10,18-nonadecadienyl]-1,3-dithian-2-yl]oxoacetyl]-2-piperidinecarboxylic acid (33).** *tert*-Butyl ester **32** (5.5 mg, 3.6 μmol) was dissolved in THF (300 μL) at room temperature. 2,6-Lutidine (18 μL, 150 μmol) and trimethylsilyl triflate (21 μL, 109 μmol) were added successively. After 0.5 h at room temperature the mixture was heated to reflux. After 1 h further amounts of 2,6-lutidine (10 μL, 83 μmol) and TMSOTf (10 μL, 52 μmol) were added. After a further 1 h at reflux the reaction mixture was allowed to cool to room temperaure and 1 N aqueous hydrochloric acid was added followed by EtOAc. The organic layer was separated, and the aqueous layer was reextracted with EtOAc (2×). The combined organic extracts were washed with 1 N aqueous hydrochloric acid, then brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (EtOAc → 5% MeOH/EtOAc) on 4% KH_2PO_4 impregnated silica gel gave the carboxylic acid **33** (4.8 mg, 87%) as a clear oil: ^{1}H NMR (selected data for major rotamer) δ 5.71 (1 H, m, C*H*=CH_2), 5.41 (1 H, d, J = 8 Hz, C*H*=C(Me)CH(OH)), 5.37 (1 H, bs, C*H*CO_2H), 5.00 (1 H, d, J = 15 Hz, *cis*-C*H*=CH_2), 4.95 (1 H, d, J = 9 Hz, *trans*-C*H*=CH_2), 4.90 (1 H, d, J = 12 Hz, C*H*=C(Me)CH_2), 4.38 (1 H, bd, J = 10 Hz, TIPSOC*H*CH(Me)), 4.28 (1 H, s, C*H*(OH)), 3.79 (1 H, d, J = 7 Hz, TBSOC*H*CH(OMe)), 3.75 (1 H, bd, J = 15 Hz, NC*H*H), 3.61 (1 H, m, TIPSOC*H*CH(OMe)), 3.50-3.33 (m, including 3.43, s, MeO), 3.29 (3 H, s, MeO), 3.25-3.13 (m), 3.07 (1 H, m, MeOC*H*CH(OTIPS)), 3.02-2.81 (m), 2.70-2.61 (m), 1.61 (s, CH=C(*Me*) and CH=C-(*Me*)), 1.21 (d, J = 7 Hz, CH(*Me*)), 0.83 (d, J = 8 Hz, CH(*M*)), 0.75 (d, J = 8 Hz, CH(*Me*)); IR (CH_2Cl_2 solution) 3500 (br), 2928, 2862, 1739, 1694, 1642, 1461, 1385, 1251, 1190, 1105, 1001, 881, 834, 775 cm^{-1}.

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Supplementary Material Available: Experimental procedures for **5**, **29**, **36**, **37**, **38**, and **39**, and ^{1}H NMR spectra for **24**, **26**, **30**, **31**, **33**, **36**, **37**, **38**, **39** (16 pages). Ordering information is given on any current masthead page.

Antineoplastic Agents. 206. Structure of the Cytostatic Macrocyclic Lactone Combretastatin D-2[1]

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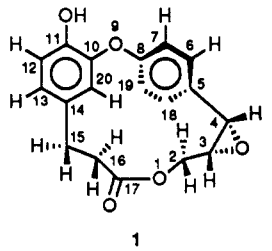
The South African tree *Combretum caffrum* (Combretaceae) has been found to contain two new and cytostatic (P388 lymphocytic leukemia) macrocyclic lactones designated combretastatin D-1 (**1**, ED_{50} 3.3 μg/mL) and D-2 (**2**, ED_{50} 5.2 μg/mL). With the X-ray crystal structure of combretastatin D-1 (**1**) serving as an unequivocal reference point ^{13}C NMR and high field (400 MHz) ^{1}H NMR spectral techniques were employed to assign structure **2** to combretastatin D-2.

The South African tree *Combretum caffrum* (Combretaceae) has been found to produce two *cis*-stilbenes, combretastatins A-1 and A-4, that strongly inhibit growth of the P-388 lymphocytic leukemia cell line (PS system) and tubulin polymerization.[2] Recently, we reported[3] the isolation and structure determination of an unexpected 17-membered macrocyclic lactone designated combretastatin D-1 (**1**) from the same plant. We now summarize the



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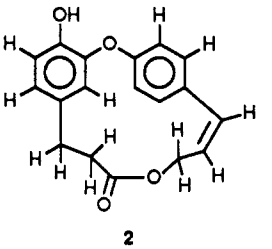

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isolation and structural elucidation of another PS cell line inhibitory member of this unusual series of macrocyclic lactones named combretastatin D-2 (**2**) along with chemical

(1) For the preceding paper, see: Pettit, G. R.; Singh, S. B.; Hogan, F.; Burkett, D. *J. Med. Chem.* In press.

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