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Total Synthesis of FK-506. Part 2: Completion of The Synthesis† [1]

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Abstract: *The C15-C16 bond of FK-506 was formed via sulfone anion coupling followed by chelation controlled reduction of the C15 ketone. Efficient methylation of the C15-OH was accomplished by a combination of Me_3OBF_4-4Å molecular sieves in the presence of Proton Sponge®. A procedure was developed to avoid epimerization at the C2 position of the pipecolinate section during alkaline hydrolysis. A reductive fragmentation of the C21-C24 [6,6]-spiroketal iodide using active Zn/Ag-graphite delivered the α'-allyl aldol section. The C9-C10 [5,6]-spiroketal acetonide was de-blocked via a novel β-elimination, using a combination of LiHMDS-Mg(HMDS)$_2$ in HMPA-DME (1:1), to afford an enediol acetal, which was oxidized with dimethyl dioxirane to generate the C8-C10 α, β-diketoamide acetal function. Final desilylations completed the total synthesis of FK-506.*
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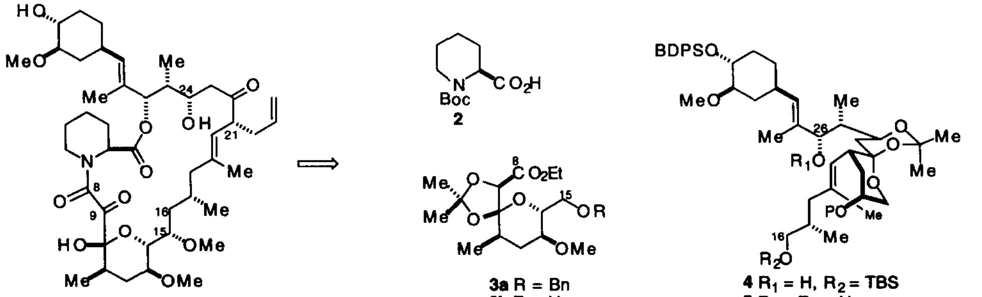
In the preceding paper we have presented the synthesis of the C16-C34 fragment **4** of FK-506, wherein the C21-C24 α'-allyl aldol function was embeded in a novel [6,6]-spiroketal. To complete the entire FK-506 skeleton, it remained that the L-pipecolinic acid derivative **2** and the C8-C15 fragment **3**[2] where the [5,6]-spiroketal serves as the latent C8-C10 tricarbony function were to be assembled (Scheme 1. Since the C26-OH in **4** is unprotected, it would serve as an attractive starting point for the introduction of a protected pipecolinic acid. By doing so, however, the resulting rotamers about the (N)-Boc bond would complicate

Scheme 1 (P = PMB)



FK-506 (**1**)

2

3a R = Bn
3b R = H

4 R_1 = H, R_2 = TBS
5 R_1 = R_2 = H

† Dedicated to Professor Gilbert Stork on the occasion of his seventy fifth birthday and fiftieth anniversary of creative excellence in chemistry.
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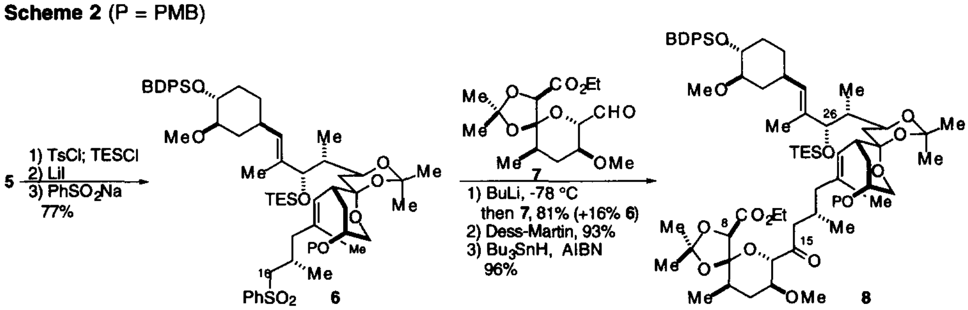
any spectroscopic analyses of reaction products thereafter. Precaution must also be taken in subsequent operations so as to avoid the use of alkaline or basic conditions that would epimerize the C2-stereo-center of the ester linkage. Given the labile nature of the C2-H and the involvement of carbanions in the C15-C16 bond formation protocol (vide infra), the C8-C15 fragment was chosen to be installed first. This was to be accomplished via addition of a C16 anion to the C15 aldehyde.

Installation of the C8-C15 Subunit. Although there are several plausible methods for the generation of the C16 carbanion, the most prudent course of action would be the use of a sulfone as an anion precursor.[3] This protocol would allow the recovery of any of the precious C16-C34 fragment that remained unreacted or quenched by adventitious proton sources. To this end silyl ether **4** was converted to diol **5** (TBAF) in 93% yield. Tosylation at C16 followed by the protection of the C26-OH as its TES ether was achieved in a one pot operation. Sequential treatment of the resulting C16 tosylate with LiI and sodium benzenesulfinate afforded the desired sulfone **6** in 76% yield over three steps (Scheme 2). For the crucial coupling, it was essential to azeotrope each component repeatedly with toluene prior to the reaction in order to obtain reproducible results. Thus, a solution of the sulfone **6** was treated at -78 °C with 1 equivalent of *n*-BuLi to form a yellow solution of the anion. This was then allowed to react with 1 equivalent of the freshly prepared aldehyde **7**[4] to afford a mixture of the diastereomeric sulfone alcohols in 81% isolated yield in addition to 16%

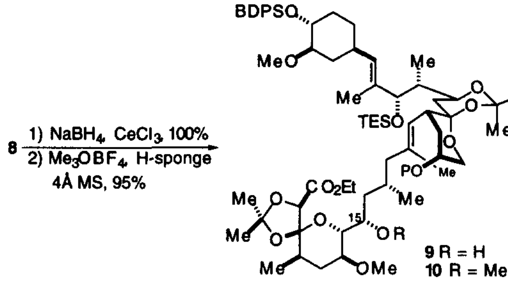
Scheme 2 (P = PMB)

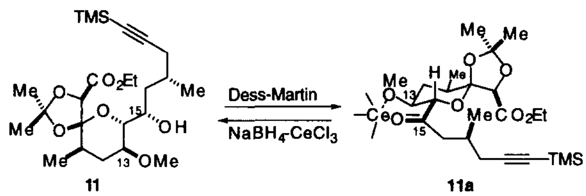


of recovered sulfone **6**. Following Smith's procedure,[5] the coupling products were oxidized (Dess-Martin, 92%) to the ketosulfone, which was in turn treated with excess Bu3SnH and with small batches of AIBN (up to 1 equiv) in boiling toluene to afford the desired ketone **8**. It was found that during chromatographic purification the C26-TES group in **8** was partially cleaved. This was most likely caused by the presence of the Lewis acidic Sn(IV) residue. Addition of pyridine (1 molar equiv to Bu3SnH) to the crude reaction mixture prior to chromatography effectively suppressed this process and afforded ketone **8** in 96% yield.

The stereocenter at C15 was the last chiral center to be established for the total synthesis of FK-506. Although literature reports on related systems indicated several reagents that might be used, ketone **8** presented an additional chemoselectivity problem due to the presence of the C8 ester function. Reduction using L-Selectride failed largely because of the decomposition of the C9-C10 [3,5]-spiroketal upon workup. It was then found that ketone **8** was reduced cleanly under the Luche conditions to a single isomer in quantitative yield (Scheme 3). The stereochemistry of the C15-OH was assigned to be the desired α-isomer **9** based upon the following observation. When the known alcohol **11**[6] (eq 1) was oxidized (Dess-Martin) and then reduced under the Luche conditions ($NaBH_4$-$CeCl_3$),[7] the same alcohol **11** was isolated as the only product in excellent yield, demonstrating that the reduction of the C15 ketone had occurredin in the desired fashion. The excellent diastereoselectivity observed in this reduction could be attributed to the involvement of a six-membered cerium(III) chelate with the C15 carbonyl and the C13 methoxy group (cf. **11a**). Addition of hydride to this complex from the less hindered β-face would give arise to the observed selectivity.[8]

Scheme 3 (P = PMB)



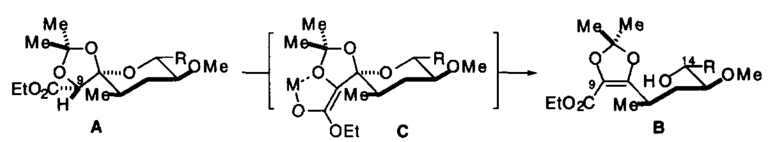


(1)

The formation of the C15-OH methyl ether proved to be surprisingly difficult. When MeOTf (10 equiv) and 2,6-di-*t*-butyl pyridine (20 equiv) were employed, the reaction was extremely slow and significant amounts of decomposition occurred. The best result was obtained when the reaction was stopped after 3 days to afford 64% of **10** and 13% of recovered alcohol **9**. While other reagents such as CH_2N_2 or MeI-Ag_2O proved to be ineffective towards methylation, the use of MeI-NaH resulted in complete destruction of the substrate. Attention was then turned to the use of Meerwein's trimethyl oxonium salt (Me_3OBF_4) in conjunction with Proton Sponge® in CH_2Cl_2.[9] Although the reaction using this protocol proceeded much faster than that using MeOTf, it again seemed stopped at about 50% conversion (e.g., 44% of **10** plus 35% of **9** were isolated after 5 h). It thus appeared that (1) the forward methylation reaction was inhibited by the reaction by-products and that (2) the decomposition of starting material occurred in the presence of these by-products. One possible scenario would be that the C15-OH was involved in the formation of a 1:1 complex with the by-product amine salts, perhaps through hydrogen bonding, in such a way that it became less accessible for the methylating reagents. Due to the Lewis acidic nature of the reagents used, slow decomposition of the spiroketal functions was to be expected with longer reaction time. After considerable effort, it was found that inclusion of 4Å molecular sieves dramatically improved the outcome of the methylation reaction. Hence when a mixture of the alcohol **9**, Proton Sponge® (7 equiv), and 4Å MS (1.3 equiv w/w) in CH_2Cl_2 was treated with Me_3OBF_4 (5.7 equiv) under argon, the reaction went to completion in ca. 30 min and the desired methyl ether **10** was isolated in >95% yield (Scheme 3).[10]

Model Studies on the Tricarbonyl Formation. As we alluded earlier the newly introduced [4,5]-spiroketal subunit was designed to serve as a precursor to the C9-C10 diketone moiety. Various methods on constructing the labile tricarbonyl function have been reported in the FK-506 literature.[11] In the total syntheses by the Merck[12] and Harvard[13] groups, both relied on a bis-oxidation of a C9-C10 dihydroxyamide to achieve that key function. In our original plan it was hoped that the C9-C10 acetonide could be cleaved at a later stage, and that the resulting C9-OH would undergo oxidation to furnish the tricarbonyl function. Initial model studies from this laboratory indicated that hydrolysis of the C9-C10 spiroketal acetonide section required refluxing in a mixture of acetic and sulfuric acids. Such conditions would be prohibitive in the framework of the present synthesis due to the presence of other functionalities in the molecule, especially the C21-C24 [6,6]-spiroketal that must be carried toward the end of the synthesis.

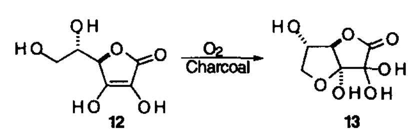
A solution to this problem was found in the C8-ester appendage. It was recognized that an anionic fragmentation or elimination process initiated by deprotonation at C9 (cf. **A**, eq 2) would unlock the [5,6]-spiroketal framework (cf. **B**) and thereby allow differentiation of this subunit from other acetals. Although there are two oxygens that can undergo the β-elimination process,



(2)

only the C-O bond in the pyran ring is capable of achieving an orientation perpendicular to the intermediate enolate (cf. **C**), a proper geometry for elimination. The acetonide C-O bond, on the contrary, lies in the plane of the enolate and is not properly disposed to fragmentation.

It is well known that the enediol in ascorbic acid **12** is easily oxidized to a hydrated tricarbonyl hemiketal **13** by various reagents, including bromine or oxygen over activated charcoal (eq 3).[14] By analogy, it was reasoned that the protected C9-C10 enediol intermediate derived from the proposed β-elimination (cf. **B**) might be similarly oxidized to the desired tricarbonyl in FK-506. Confirmation of this conjecture is presented in the following model studies.

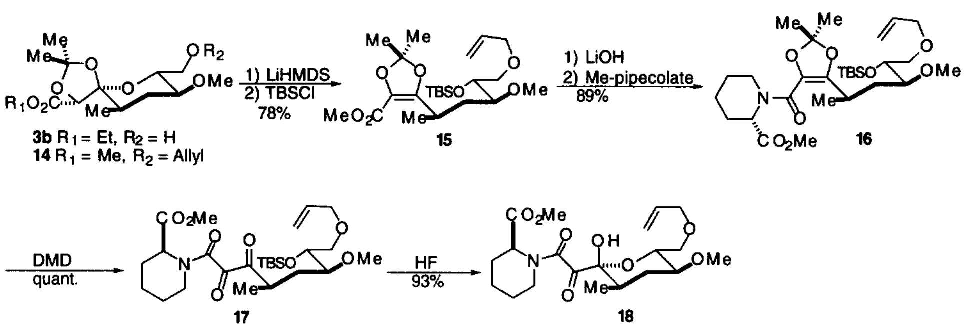


(3)

In designing a model system, we hoped that the following issues would be addressed. (1) The feasibility of blocking and deblocking of the C14 alcohol. Once the enediol acetal was formed via β-elimination, the C14-OH must be protected should the oxidation of the former be carried out at a later stage. (2) The generation, and reactivity towards oxidation, of a protected *amide* enediol from an *ester* enediol.[15] (3) The selective oxidation of an enediol acetal in the presence of olefin bonds. Since the reactivity of the enediol acetal (cf. eq

2) is expected to be attenuated by the electron withdrawing carboxyl group and by the steric hinderance of the substituents, it was of concern whether the C21 allyl moiety in FK-506 would be epoxidized during the enediol acetal oxidation. Starting with the known spiroketal **3a**, the benzyl group was cleaved to give **3b** and an allyl group was introduced at C15 (NaH, allyl bromide) (Scheme 4). Unfortunately, ester hydrolysis also occurred during this operation. Therefore the resultant acid was esterified with diazomethane to give the corresponding methyl ester **14**. β-Elimination was accomplished by the use of LiHMDS in THF-HMPA at 0 °C to give the enediol acetal intermediate which was immediately silylated with TBSCl to give the more stable silyl ether **15** in 79% over two steps. The use of HMPA was essential for the elimination step: the reaction was very slow otherwise and was complicated by decomposition of the product. Ester hydrolysis followed by amide formation provided **16** in 89% overall yield from **15**.

Scheme 4



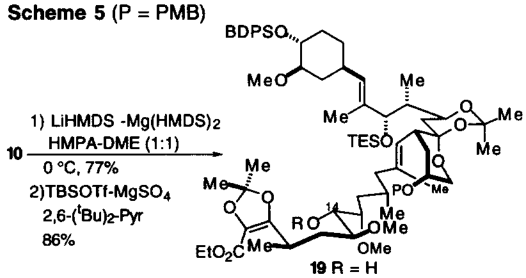
In an earlier study, we found that dimethyl dioxirane (DMD) reacts cleanly with ester enediol acetal while other oxidants such as NBS or O_2/charcoal were ineffective.[16] Treatment of **16** in CH_2Cl_2 with 1.05 equivalent of DMD at -25 °C gave a yellow solution, characteristic of formation of vicinal tricarbonyls. After removal of the solvents, ^{13}C NMR spectroscopy of the crude product showed four individual carbonyl signals at 199.56, 185.44, 170.91, and 166.22 ppms, as expected for the desired product **17**. Finally, removal of the silyl protecting group with HF in acetonitrile furnished the α,β-diketoamide hemiketal **18** cleanly in 93% yield over the two-step process. These results demonstrates that the C14-OH can be protected to afford a more stable enediol acetal and that the latter can be selectively oxidized without competition from the terminal olefin. A final notable observation in this system was that the enediol and tricarbonyl amides **16** and **17** both appeared to exist as predominantly one amide rotamer. In contrast the hemiketal **18**, like the parent FK-506, is comprised of a mixture of cis and trans rotamers.

Assembly of the Macrocycle. Having established the feasibility of a novel elimination–oxidation sequence to reach the C8-C14 section of FK-506, we promptly applied this methodology to the key intermediate **10**. Motivation behind this action stems from our concern that the strongly basic conditions used in the β-elimination step was likely to cause epimerization at the C2 center of the pipecolinic acid moiety, should the latter be introduced prior to the deketalization. As shall be seen such concern was well founded due to ambiguities, at this stage of the synthesis, in detecting the C2-epimerization by spectroscopic means.

Accordingly ester **10** was subjected to the β-elimination conditions defined earlier (3 equiv LiHMDS, 25% HMPA-THF, 0 °C). TLC analysis of this reaction indicated that the reaction was much slower and that the formation of the desired product was accompanied by the accumulation of decomposition products. Furthermore, it was found that after a period of building up, the product fraction started reverting back to a spot with an Rf identical to that of the starting material. In fact the recyclization process was so favorable that when a reaction mixture, consisting ~1:1 starting material and the product, was let stand at -15 °C overnight, the product disappeared completely. The new mixture consisted mainly of starting material, plus a new component with an intermediate Rf value. Analysis of the ^{1}H NMR spectrum of the new compound suggested that it is the C9-epimer of the starting material **10**.[17]

Clearly, under these conditions enolization followed by β-elimination of ester **10** did occur to generate the desired product **19** (Scheme 5) as its C14-lithium oxide. However, structural biases imposed by the entire C8-C34 backbone apparently favored the undesired cyclization, especially with longer reaction time and at higher temperature. It was reasoned that metal ions capable of forming stronger oxygen chelates might stabilize the elimination product, and therefore, facilitate the desired forward reaction. At the same time the increased "Lewis-acidic" character of the ions should not compromise the bacisity of the amide base. Systematic studies along this line of thinking eventually led us to the realization of an optimized set of conditions. Thus ester **10** was allowed to react with a mixture of LiHMDS (~ 80 equiv) and MgHMDS (ca. 6 equiv) in 1:1 HMPA-DME at 0 °C.[18] After 20 min, the reaction was quickly quenched with 2 equivalents of aq HOAc at this temperature. Regular workup and purification on silica gel afforded the metastable alcohol **19** in 70-80% yield (Scheme 5). Subsequent silylation of the resultant C14-OH proved troublesome, most likely as a result of the enediol alcohol's propensity to undergo cyclization as well as decomposition. Nevertheless, the desired product **20** could be isolated in 86% yield when a combination of TBSOTf-MgSO4 was used.

Scheme 5 (P = PMB)

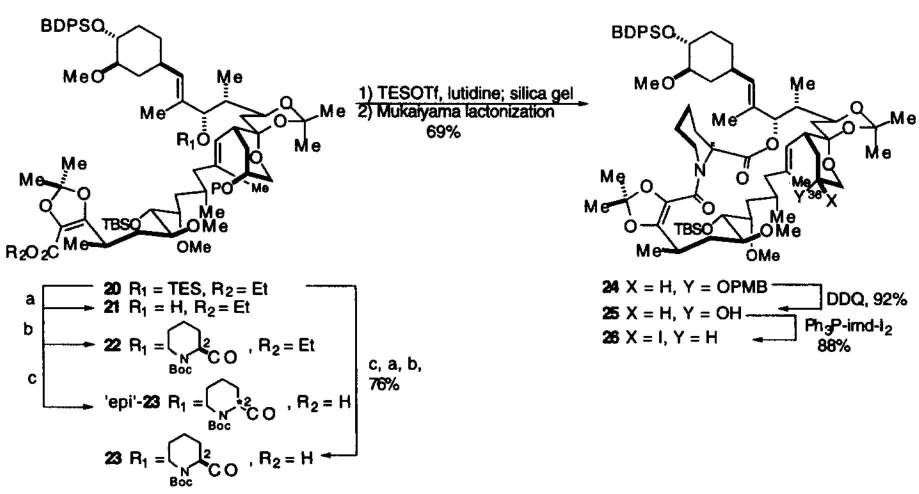


19 R = H
20 R = TBS

At this stage, the Merck protocol[12] was used for the introduction of the pipecolinic ester and the subsequent macrolactamization (Scheme 6). Removal of the C26-TES group (1.4% trifluoroacetic acid in 6:1

THF-H_2O, 99% yield to alcohol **21**) and formation of the pipecolinate **22** at -15 °C (88% yield) were carried out without incident. Saponification of the C8 ethyl ester with alkaline bases at room temperature was not successful, probably due to the inherent vinylogous carbonate-like character as well as the lower reactivity conferred by the ethyl group of the ester function. Fortunately clean hydrolysis was achieved when **22** was heated at 100 °C with 30 equivalents of NaOH in aqueous dioxane for 3 hours, leading to 89% of the acid '*epi*-**23**'. It was remarkable that the pipecolinate ester group was not hydrolyzed under such a harsh condition. However, it was not clear whether the C2 stereocenter had been epimerized during the alkaline hydrolysis (cf. * at C2 in the structure of '*epi*-**23**'). Such a possibility could not be excluded based on analysis of the ^{1}H and ^{13}C NMR data of acid '*epi*-**23**', due to complications arising from the presence of both cis and trans rotamers about the N-BOC bond. Furthermore, when treated with EtOH in the presence of DCC, DMAP•HCl,[19] '*epi*-**23**' was converted to an ethyl ester whose ^{1}H NMR was identical to that of **22**. On the other hand, when the hydrolysis of **22** was conducted with NaOD and D_2O under the same condition, the characteristic broad peaks assigned to the C2 proton for 'epi-**23**' at δ 4.84 and δ 4.67 ppms were suppressed in the ^{1}H NMR spectrum, *indicating that enolization-deuterization had occurred at this center.* Although it remained unclear as to whether a *net epimerization* had taken place,[20] it was desirable to explore an alternative route by which the possibility of C2-enolization would be avoided.

Scheme 6 (P = PMB)



(a) TFA, 99%. (b) **2**, DCC/DMAP, -15 °C, 88%. (c) NaOH, 100 °C, 89%.

In this regard, ester **20** was first subjected to hydrolysis followed by deprotection of the C26-TES ether. The resulting C26-hydroxy C8-carboxylic acid was added slowly to a mixture of N-Boc-pipecolinic acid (**2**), DCC, and DMAP at -20 °C to afford the desired product as a mixed anhydride (with **2**). Brief hydrolysis of the reaction mixture (NaOH-THF-H_2O, rt) followed by purification provided the acid **23** in 76% overall yield. Since no strong alkaline conditions were employed after the introduction of the pipecolinate fragment, we were confident that the acid **23** derived from this sequence possessed the desired stereochemistry at C2. Finally cleavage of the (N)-Boc group with TESOTf[21] followed by macrolactamization under Mukaiyama's condition (2-chloro-methyl pyridinium iodide, Et_3N, DMAP) afforded the macrolactam **24** in 69% overall yield.[22]

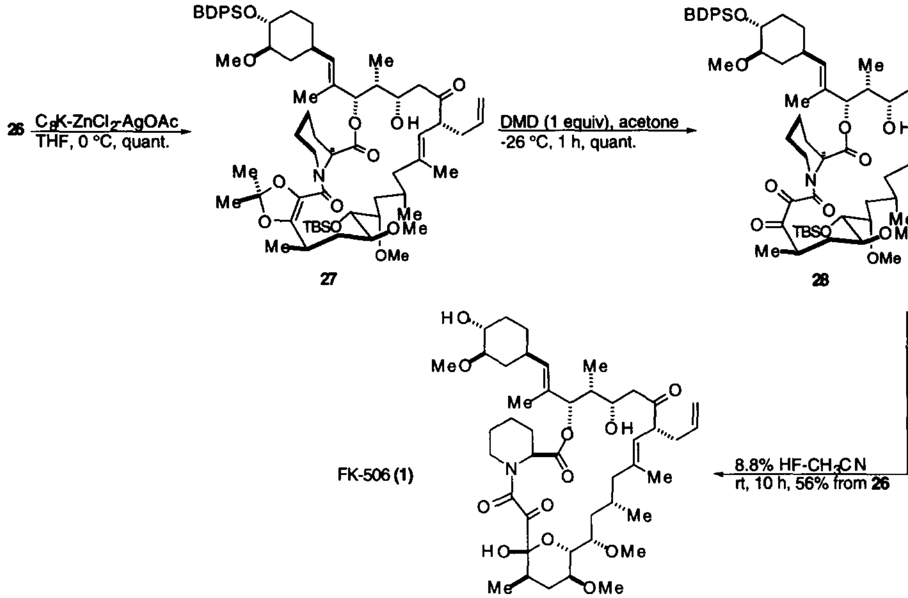
With the complete FK-506 skeleton in hand, the ultimate test for our strategic generation of the two most demanding sections of the molecule was in order. Prior to any further action, we were faced with the option of two possible pathways leading to the final target: namely the order of the sequence by which the tricarbonyl and the α-allyl aldol components were to be generated. Should the C9, C10-dicarbonyl be generated first, the resulting electron deficient tricarbonyl moiety must survive the strongly reductive fragmentation condition that was to be employed for the subsequent α-allyl aldol formation. On the other hand, forming the α'-allyl aldol unit first would necessarily prohibit any uses of extreme pH media or of reagents incompatible with either the C22-C24 aldol group or the C21 olefin bonds. Fortunately the latter constraint was compatible with the mild oxidant DMD, and as a result, constituted the basis for the remaining reaction sequence.

Reductive Fragmentation of [6,6]-Spiroketal. The C36-PMB ether of **24** was cleaved under Yonemitsu's conditions (DDQ, 1.9:0.1 CH_2Cl_2-H_2O) to give the alcohol **25** in 92% yield.[23] The success of this step was a direct consequence of the carefully chosen C36 protecting group (cf. discussion in the preceding paper). The oxidation potential of the PMB group was low enough to warrant the survival of the enediol acetal function during the PMB removal. In fact some decomposition was observed when **24** was subjected to either a slight excess of the oxidizing agent or longer reaction times. Next, the conversion of the C36-OH to the corresponding iodide was undertaken. This reaction turned out to be extremely chaotic under standard reaction conditions, most likely due to the heterogeneity of the reaction and the instability of the enediol acetal in the presence of iodine. It was eventually found that by carefully titrating a solution of alcohol **25** in the presence of excess Ph_3P and imidazole, in toluene at 70 °C, with aliquots of an iodine solution, reproducible yields of the desired iodide **26** (88% isolated yield) was realized.[24]

For the crucial reductive fragmentation, a suspension of zinc/silver-graphite in THF was readily prepared according to Fürstner's procedure,[25] and to this suspension was added a solution of the iodide **26**. After 1 hour at 0 °C, a polar product corresponding to the desired α-allyl aldol **27** was isolated in nearly quantitative yield (Scheme 7). Although this type of fragmentation had been applied to related systems previously in these laboratories, this was the first time such an operation was carried out efficiently when a labile cyclic enediol acetal function was present as a spectator.

Oxidative Fragmentation to the Tricarbonyl and Completion of the Total Synthesis. For the selective oxidation of the enediol acetal, the prescribed reagent DMD served the purpose admirably. Thus,

Scheme 7



when **27** was treated with 1 equivalent of dimethyl dioxirane in acetone at -26 °C, a deep yellow solution was formed. Upon evaporation of the acetone solvent, the tricarbonyl **28** was obtained in quantitative yield. ^{13}C NMR spectrum of this material showed no acetal resonances, indicating that hydration of the tricarbonyl was negligible. Given, *a priori*, possible unfavorable conformational bias within the macrocycle and the dense substitution flanking the enediol acetal moiety, the remarkably selective oxidation and smooth fragmentation of the putative bicyclic[3,1,0]-2,4,6-trioxohexane intermediate to the diketoamide was a most welcome event.[26] The final step of the synthesis involved treatment of **28** with a solution of HF (8.8%) in aqueous acetonitrile[27] in a polypropylene tube[13] at room temperature to effect the desilylation first at C14 (~ 2 h, by TLC) and then at C32, thus furnishing the final product FK-506 (**1**) in 56% yield over three steps from **26**. The synthetic material was identical with a sample of the natural product ($[\alpha]_D$, mp, ^1H & ^{13}C NMR, IR, and TLC mobility).

The present synthesis demonstrated the utility of spiroketals, along with strategically planted polar functionalities, in the protecting and eventual unmasking of important functional groups, specifically, the α'-allyl aldol and the tricarbonyl functions in FK-506. Because the spiroketals are considerably more stable than their destined functionalities, variation of the FK-506 skeleton should be possible along the synthetic pathway to provide analogs for the elucidation of mechanisms of cell signalling processes. Equally noteworthy is the application of the hydro(carbo)-zirconations coupled with transmetallations in the stereospecific construction of trisubstituted olefins.

Experimental Section

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-(2,4-dimethyl-5-hydroxy-penten-1-yl]-4-[1,3-dimethyl-2-hydroxy-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (5). To a solution of the silyl ether **4** (1.97 g, 1.95 mmol) in anhydrous THF (5 mL) was added TBAF (1.02 g, 3.90 mmol). The yellow solution was stirred at room temperature for 12 h and was then quenched with HOAc (0.15 mL, 2.62 mmol). The solution was concentrated and the residue was chromatographed on silica (20% ethyl acetate in hexanes) to afford the diol (1.63 g, 93%) as an oil: $[\alpha]_D$ +14.3° (*c* 1.0, $CHCl_3$); IR (neat) 3580-3200, 2930, 2870, 2850, 1500, 1450, 1425, 1375, 1365, 1245, 1200, 1100, 1065, 1030, 985-950, 875-840, 820, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77-7.71 (m, 4 H), 7.40-7.34 (m, 6 H), 7.25 (d, 2 H, *J* = 8.4 Hz), 6.86 (d, 2 H, *J* = 8.4 Hz), 5.56 (d, 1 H, *J* = 10.2 Hz), 5.22 (d, 1 H, *J* = 9.0 Hz), 4.46, (d, 1 H, *J* = 11.4 Hz), 4.37 (d, 1 H, *J* = 11.7 Hz), 4.27 (d, 1 H, *J* = 11.7 Hz), 4.10 (bs, 1 H), 3.92 (bd, 1 H, *J* = 12.3 Hz), 3.79 (s, 3 H), 3.72 (d, 1 H, *J* = 12.3 Hz), 3.62-3.53 (m, 1 H), 3.46-3.30 (m, 3 H), 3.33 (s, 3 H), 3.18-3.10 (m, 1 H), 2.84 (s, 1 H), 2.47-2.42 (m, 1 H), 2.34-2.23 (m, 1 H), 2.15-2.02 (m, 2 H), 1.96-1.26 (m, 10 H), 1.62 (s, 3 H), 1.55 (s, 3 H), 1.53 (s, 3 H), 1.33 (s, 3 H), 1.07 (s, 9 H), 1.05-0.85 (m, 2 H), 0.84 (d, 3 H, *J* = 11.4 Hz), 0.82 (d, 3 H, *J* = 12.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9, 135.9, 135.8, 135.0, 134.3, 133.7, 133.6, 130.5, 129.4, 129.1_8, 129.1_5, 128.9, 127.2, 127.1_7, 126.8, 113.5, 98.8, 97.8, 84.2, 78.4, 78.3, 75.6, 70.4, 69.3, 68.6, 67.9, 63.4, 57.1, 55.1, 44.0, 41.5, 38.8, 36.1, 35.0, 34.8, 33.7, 30.8, 30.6, 27.6, 26.9, 23.7, 19.2, 16.8, 16.2, 13.3, 6.2, 6.1. Anal. Calcd for $C_{54}H_{78}O_9Si$: C, 72.12; H, 8.74. Found: C, 71.76; H, 9.04.

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-5-(phenysulfonyl)-1-pentenyl]-4-[1,3-dimethyl-2-[(triethylsilyl)-oxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)-oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (6). To a solution of the diol **5** (1.63 g, 1.80 mmol) in dry CH_2Cl_2 (7.0 mL) was added pyridine (5.0 mL, anhydrous), TsCl (0.420 g, 2.16 mmol) and a catalytic amount of DMAP. The solution was stirred for 8 h at room temperature, more TsCl (0.050 g, 0.26 mmol) was added and stirring was continued for 8 h. The reaction mixture was cooled to 0 °C and TESCl (0.60 mL, 3.6 mmol) was syringed dropwise. After being stirred at room temperature over night, the mixture was cooled to 0 °C and quenched with a cold solution of $NaHCO_3$ (5 mL). It was then partitioned between ether and H_2O. The aqueous layer was separated and extracted with ether (4 x). The combined ether phase was washed three times with a solution of $CuSO_4$ (3 x), once with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to afford 2.5 g of the crude tosylate (100%). It was then dissolved in anhydrous THF (20 mL) and cooled to 0 °C. LiI (2.4 g, 18 mmol) was slowly added to the stirred solution (exothermic!) under argon. A reflux condenser was fitted to the reaction flask and the cooling bath was replaced with an oil bath preheated to 60 °C. After 4.5 h, the deep red solution was concentrated on a rotary evaporator and the resulting residue was transferred with ether (100 mL) into a separation funnel. The ether solution was washed with saturated $NaHCO_3$ solution and then an aqueous solution of $Na_2S_2O_3$ (10%). The aqueous washings were back extracted once and the combined organic phases was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The crude iodide was then dissolved in anhydrous DMF (15 mL) and sodium benzenesulfinate (3.0 g, 18 mmol) was added. The mixture was heated to 65 °C for 4 h and was then cooled to room temperature. Ether (150 mL) and water (50 mL) were added and the layers were separated. The aqueous phase was extracted with ether (3 x 50 mL), and the combined organic phases were washed with H_2O, then saturated NaCl solution, dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (10% ethyl acetate-hexanes) afforded the sulfone **6** (1.56 g, 76.6%) as an oil: $[\alpha]_D$ +4.1° (*c* 1.2, $CHCl_3$); IR (neat) 3040, 2960, 2930, 2870, 1605, 1580, 1505, 1460-1440, 1420, 1375, 1315, 1300, 1245, 1140, 1105, 1085-1070, 1055, 1030, 980, 955, 910, 875, 870, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 2 H, J = 6.9 Hz), 7.75-7.70 (m, 4 H), 7.62-7.54 (m, 3 H), 7.40-7.33 (m, 6 H), 7.19 (d, 2 H, J = 8.4 Hz), 6.83 (d, 2 H, J = 8.4 Hz), 5.20 (d, 1 H, J = 11.2 Hz), 4.97 (d, 1 H, J = 9.0 Hz), 4.40 (d, 1 H, J = 11.7 Hz), 4.31 (d, 1 H, J = 11.7 Hz), 3.87-3.78 (m, 3 H), 3.79 (s, 3 H), 3.60 (d, 1 H, J = 12.6 Hz), 3.57-3.50 (m, 1 H), 3.37 (bs, 1 H), 3.33 (s, 3 H), 3.16-3.08 (m, 1 H), 2.99 (dd, 1 H, J = 3.6, 14.1), 2.37-2.15 (m, 3 H), 2.09-1.93 (m, 5 H), 1.74-1.60 (m, 2 H), 1.50 (s, 3 H), 1.47 (s, 3 H), 1.38-1.18 (m, 4 H), 1.33 (s, 3 H), 1.25 (s, 3 H), 1.05 (s, 9 H), 1.04 (overlapped, 3 H), 0.94-0.70 (m, 5 H), 0.91 (t, 9 H, J = 7.8 Hz), 0.54 (q, 6 H, J = 7.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.0, 140.3, 136.0, 135.9, 135.3, 135.2, 134.4, 133.5, 132.0, 131.6, 130.7, 129.3. 129.2, 129.0, 128.9_6, 127.6, 127.3, 127.2, 113.6, 98.5, 97.4, 84.2, 80.2, 75.7, 70.2, 69.2, 63.6, 63.5, 61.7, 57.2, 55.2, 48.0, 41.7, 40.4, 35.7, 34.9, 33.8, 30.9, 30.6, 27.2, 27.0, 26.4, 24.0, 20.2, 19.3, 15.4, 11.0, 9.3, 7.0, 5.0. Anal. Calcd for $C_{66}H_{96}O_{10}SSi_2$: C, 69.68; H, 8.51; S, 2.82. Found: C, 69.59; H, 8.53; S, 2.79.

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11[1*E*, 4S, 6(4*R*, 5*S*, 7*S*, 8*R*, 10*S*)]]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-6-(2,2,10-trimethyl-4-ethoxycarbonyl-8-methoxy-1, 3, 6-trioxa-spirodecan-7-yl)-6-oxo-1-hexenyl]-4-[1,3-dimethyl-2-[(triethylsilyl)-oxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (8). *Preparation of aldehyde* **7**: a solution of the corresponding C15-alcohol **3b** (2.0 g, 6.2 mmol, vide infra) in CH_2Cl_2 (20 mL) was treated with the Dess-Martin periodinane (4.0 g, 9.4 mmol) and the mixture was stirred for 1 h at room temperature. Ether (30 mL), saturated $NaHCO_3$ (10 mL) and a 10% aqueous $Na_2S_2O_3$ (10 mL) were added and the mixture was stirred for 10 min. The layers were separated and the aqueous layer was extracted with ether (3 x). The ether solution was washed once with saturated NaCl solution, dried ($MgSO_4$), concentrated and chromatographed on silica (20–40% ethyl acetate in hexanes) to afford the unstable aldehyde (~1.7 g, 5.3 mmol) which was dried azeotropically in toluene (4 x 5 mL) at room temperature and used immediately in the following step.

The sulfone **6** (6.0 g, 5.3 mmol) was placed in a 250-mL round-bottomed flask and dried azeotropically in toluene (4 x 25 mL) at room temperature. Anhydrous THF (50 mL) was added under argon and the solution was cooled to -78 °C. A 2.3 M solution of *n*-BuLi (2.30 mL, 5.29 mmol) in hexane was added via syringe, resulting in an orange solution. After being stirred for 10 min, a THF (10 mL) solution of the previously prepared aldehyde **7** at -78 °C was cannulated to the reaction flask. The mixture was stirred for 40 min before an aqueous solution of NH_4Cl (saturated, 10 mL) was added. The mixture was then allowed to warm to room temperature and was treated with more aqueous NH_4Cl (saturated, 30 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 60 mL). The combined organic solution was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica (20–40% ethyl acetate in hexanes) afforded the sulfone alcohol (6.2 g, 81%) as a mixture of diastereoisomers in addition to recovered sulfone **6** (1.0 g, 16 %).

The sulfone alcohol (4.3 mmol) was dissolved in CH_2Cl_2 (40 mL) and was then treated with the Dess-Martin periodinane (2.8 g, 6.6 mmol) and pyridine (0.53 mL, 6.6 mmol). The mixture was stirred for 2 h at room temperature before ether (100 mL), saturated $NaHCO_3$ (40 mL) and 10 % aqueous $Na_2S_2O_3$ (20 mL) were added. After 30 min, the layers were separated and the aqueous layer was extracted with ether (3 x). The ether solution was washed once with saturated NaCl solution, dried ($MgSO_4$), concentrated and chromatographed on silica (15–20% ethyl acetate in hexanes) to afford the sulfone ketone (5.7 g, 92%) as a mixture of diastereoisomers.

The sulfone ketone (3.9 mmol) was dissolved in toluene (40 mL, H_2SO_4 washed before distilled over $LiAlH_4$) and was heated to reflux (120 °C) under argon followed by the addition of Bu_3SnH (4.8 mL, 17.8 mmol). Aliquots of AIBN (~60 mg, 0.36 mmol) were added to the reaction mixture in every 5 min until the reaction went to completion (total ~45 min). The solution was immediately cooled to room temperature followed by the slow addition of 1.5 mL of pyridine (exothermic!). The cooled mixture was directly loaded onto a silica column (packed with petroleum ether) and chromatographed (0-20% ethyl acetate in petroleum ether) to afford the ketone **8** (4.98 g, 96%) as a foaming solid: $[\alpha]_D$ +14.3° (*c* 1.0, $CHCl_3$); IR (neat) 2920, 1760, 1720, 1505, 1460-1420, 1370, 1330, 1290, 1240, 1200, 1100, 1090-1060, 1025, 1000, 950, 875-850, 820, 740, 720, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.70 (m, 4 H), 7.40-7.32 (m, 6 H), 7.22 (d, 2 H, J = 8.4 Hz), 6.84 (d, 2 H, J = 8.4 Hz), 5.49 (d, 1 H, J = 10.5 Hz), 4.97 (d, 1 H, J = 8.7 Hz), 4.56 (s, 1 H), 4.46 (d, 1 H, J = 12.0 Hz), 4.32 (d, 1 H, J = 12.0 Hz), 4.25-4.13 (m, 2 H), 3.96 (d, 1 H, J = 9.6 Hz), 3.91-3.75 (m, 3 H), 3.80 (s, 3 H), 3.61-3.49 (m, 2 H), 3.39-3.25 (m, 2 H), 3.32 (s, 3 H), 3.28 (s, 3 H), 3.16-3.08 (m, 1 H), 2.40-1.90 (m, 8 H), 1.77-1.63 (m, 2 H), 1.60-0.80 (m, 11 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.50 (s, 3 H), 1.43 (s, 3 H), 1.34 (s, 3 H), 1.25 (t, 3 H, J = 7.2 Hz), 1.24 (s, 3 H), 1.05 (s, 9 H), 1.02 (d, 3 H, J = 8.7 Hz), 0.89 (t, 9 H, J = 8.1 Hz), 0.87 (d, 3 H, J = 6.6 Hz), 0.75 (d, 3 H, J = 6.0 Hz), 0.51 (q, 6 H, J = 8.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.9, 167.5, 158.9, 136.0, 135.9, 135.4, 135.2, 134.4, 133.1, 131.9, 130.8, 129.2, 129.1$_8$, 128.9, 127.5, 127.3, 127.2, 113.6, 112.8, 106.5, 98.4, 97.8, 84.2, 80.1, 79.6, 76.9, 75.7, 74.4, 70.2, 69.2, 63.8, 63.5, 61.1, 57.2, 56.4, 55.2, 47.4, 41.6, 40.5, 35.7, 35.3, 34.9, 33.7, 33.1, 33.0, 30.8, 30.6, 27.8, 27.4, 26.9, 26.8, 26.3, 24.0, 23.4, 19.3, 19.2, 16.0, 15.7, 14.2, 11.0, 9.2, 6.9, 4.9. Anal. Calcd for $C_{75}H_{114}O_{15}Si_2$: C, 68.67; H, 8.76. Found: C, 68.45; H, 8.90.

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11[1*E*, 4S, 6*S*, 6(4*R*, 5*S*, 7*R*, 8*R*, 10*S*)]]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-6-(2,2,10-trimethyl-4-ethoxycarbonyl-8-methoxy-1, 3, 6-trioxa-spirodecan-7-yl)-6-hydroxy-1-hexenyl]-4-[1,3-dimethyl-2-[(triethylsilyl)-oxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (9). To a solution of the ketone **8** (1.50 g, 1.14 mmol) in methanol-ether (2:1, 60 mL) was added $CeCl_3 \cdot 7H_2O$ (855 mg, 2.29 mmol) and the mixture was stirred to a clear solution before it was cooled to -78 °C under argon. Powdered $NaBH_4$ (435 mg, 11.4 mmol) was added and the mixture was stirred for 3 h at -78 °C when TLC monitoring indicated the absence of starting material. Water (5 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was partitioned between ethyl acetate and water, the aqueous layer was separated, and extracted with more ethyl acetate (3 x). The combined organic phase was washed with aqueous saturated NH_4Cl solution, dried ($MgSO_4$) and concentrated. Chromatography (10–30% ethyl acetate in hexanes) afforded the desired alcohol **9** (1.50 g, 100%) as a foaming oil: $[\alpha]_D$ +21.0° (*c* 1.1, $CHCl_3$); IR (neat) 3500 (w), 2970, 1760, 1720, 1450, 1370, 1240, 1200, 1160, 1100, 1080, 1030, 1000, 980, 965, 870, 820, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.71 (m, 4 H), 7.40-7.34 (m, 6 H), 7.23 (d, 2 H, J = 8.4 Hz), 6.84 (d, 2 H, J = 8.4 Hz), 5.51 (d, 1 H, J = 10.5 Hz), 4.98 (d, 1 H, J = 8.7 Hz), 4.58 (s, 1 H), 4.48 (d, 1 H, J = 12.0 Hz), 4.33 (d, 1 H, J = 12.0 Hz), 4.27-4.15 (m, 2 H), 3.95-3.80 (m, 4 H), 3.79 (s, 3 H), 3.60 (d, 1 H, J = 12.3 Hz), 3.54-3.43 (m, 3 H), 3.39-3.30 (m, 2 H), 3.36 (s, 3 H), 3.32 (s, 3 H), 3.17-3.09 (m, 1 H), 2.44-2.35 (m, 1 H), 2.24-1.90 (m, 7 H), 1.85-1.64 (m, 3 H), 1.60-0.80 (m, 10 H), 1.59 (s, 3 H), 1.56 (s, 3 H), 1.51 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.30 (t, 3 H, J = 7.2 Hz), 1.25 (s, 3 H), 1.06 (s, 9 H), 1.02 (d, 3 H, J = 6.3 Hz), 0.90 (t, 9 H, J = 7.8 Hz), 0.88 (overlapped, 3 H). 0.80 (d, 3 H, J = 6.3 Hz), 0.52 (q, 6 H, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.0, 158.9, 136.0, 135.9, 135.4, 135.2, 134.4, 133.6, 131.8, 130.8, 129.2, 129.1$_8$, 128.9, 127.3, 127.2, 113.6, 112.7, 106.3, 98.4, 97.8, 84.2, 80.0, 79.9, 75.7, 75.2, 73.8, 70.1, 69.2, 67.7, 63.9, 63.4, 61.1, 57.2, 56.3, 55.2, 47.1, 42.3, 41.6, 40.6, 35.7, 35.3, 34.9, 33.7, 33.4, 32.8, 30.9, 30.6, 27.9, 27.8, 27.5, 27.0, 24.0, 19.7, 19.3, 16.0, 15.9, 14.3, 11.0, 9.2, 6.9, 4.9. Anal. Calcd for $C_{75}H_{116}O_{15}Si_2$: C, 68.56; H, 8.90. Found: C, 68.28; H, 9.03.

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11[1*E*, 4S, 6*S*, 6(4*R*, 5*S*, 7*R*, 8*R*, 10*S*)]]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-6-(2,2,10-trimethyl-4-ethoxycarbonyl-8-methoxy-1, 3, 6-trioxa-spirodecan-7-yl)-6-methoxy-1-hexenyl]-4-[1,3-dimethyl-2-[(triethylsilyl)-oxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (10). The alcohol **9** thus obtained (1.50 g, 1.14 mmol) was dissolved in anhydrous CH_2Cl_2 (45 mL) followed by the addition of Proton Sponge® (1.50 g, 7.00 mmol), molecular sieves (4Å beads, 2.0 g) and finally Me_3OBF_4 (850 mg, 5.70 mmol). The mixture under argon was vigorously stirred at room temperature for 50 min and then filtered through a fritted funnel. After the residue on the funnel was washed with ethyl acetate (6 x 60 mL), the combined organic phase was washed with H_2O (1 x), aqueous $CuSO_4$ (10%, 2 x), dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica (5–15% ethyl acetate) then afforded the methyl ether **10** (1.45 g, 95.5%) as a foaming oil: $[\alpha]_D$ +15.1° (*c* 0.92, $CHCl_3$); IR (neat) 2920, 2880, 1760, 1730-1705, 1505, 1450, 1420, 1370, 1295, 1240, 1195, 1160, 1100, 1050, 1030, 1000-975, 950, 870, 815, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.70 (m, 4 H), 7.40-7.33 (m, 6 H), 7.22 (d, 2 H, *J* = 8.4 Hz), 6.84 (d, 2 H, *J* = 8.4 Hz), 5.50 (d, 1 H, *J* = 10.5 Hz), 4.98 (d, 1 H, *J* = 8.7 Hz), 4.54 (s, 1 H), 4.48 (d, 1 H, *J* = 12.3 Hz), 4.34 (d, 1 H, *J* = 12.0 Hz), 4.18 (q, 2 H, *J* = 6.9 Hz), 3.92-3.80 (m, 3 H), 3.79 (s, 3 H), 3.66-3.46 (m, 4 H), 3.38-3.25 (m, 2 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 3.29 (s, 3 H), 3.17-3.09 (m, 1 H), 2.45-2.35 (m, 1 H), 2.21-1.94 (m, 7 H), 1.75-0.80 (m, 13 H), 1.60 (s, 3 H), 1.54 (s, 3 H), 1.51 (s, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.28 (t, 3 H, *J* = 7.2 Hz), 1.25 (s, 3 H), 1.06 (s, 9 H), 1.00 (d, 3 H, *J* = 6.0 Hz), 0.90 (t, 9 H, *J* = 8.1 Hz), 0.88 (overlapped, 3 H), 0.76 (d, 3 H, *J* = 6.0 Hz), 0.52 (q, 6 H, *J* = 7.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.1, 158.9, 136.0, 135.9, 135.4, 135.2, 134.4, 133.6, 131.8, 130.8, 129.2_3, 129.2, 128.9, 127.3, 127.2, 113.6, 112.5, 106.6, 98.4, 97.9, 84.3, 80.1, 80.0, 75.8, 75.7, 75.1, 73.8, 70.1, 69.2, 63.9, 63.4, 61.1, 57.2, 55.9, 55.2, 47.3, 41.6, 40.6, 37.6, 35.7, 35.3, 34.9, 33.7, 33.0, 30.9, 30.6, 29.7, 28.1, 27.6, 27.4, 27.0, 26.9_8, 24.0, 19.3_3, 19.2_9, 16.1, 15.9, 14.1, 11.1, 9.2, 6.9, 4.9. Anal. Calcd for $C_{76}H_{118}O_{15}Si_2$: C, 68.74; H, 8.96. Found: C, 68.60; H, 9.04.

[4R,5S,7R,8S,10R]-7-Hydroxymethyl-4-carbomethoxy-8-methoxy-2,2,10-trimethyl-1,3,6-tiioxaspirodecane (3b): A solution of benzyl ether **3a** (1.49g, 3.65 mmol) and a 20% dispersion of $Pd(OH)_2$ on carbon (100 mg) in abs. ethanol (15 mL) was allowed to stir under a hydrogen atmosphere (1 atm) for 8 h. The reaction was filtered through celite and the solids washed with EtOAc. The solution was concentrated *in vacuo* and the residue was chromatographed on silica gel with ethyl acetate/hexanes (10% to 30%) as eluent to give alcohol **3b** (1.15 g, 99%): $[\alpha]^{28}_D$ +97.3° (*c* 1.3, $CHCl_3$); IR (neat) 3450, 2930, 1760, 1450, 1370, 1200, 1095, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 1H), 4.24 (q, 2H, *J* = 7.2 Hz), 3.60-3.80 (m, 3H), 3.56 (s, 3H), 3.19 (m, 1H), 2.11 (m, 2H), 1.87 (dd, 1H, *J* = 6.3, 6.3 Hz, 1.59 (s, 3H), 1.49 (m, 1H), 1.42 (s, 3H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.03 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.35, 113.07, 106.50, 79.94, 75.61, 73.90, 63.33, 61.52, 56.77, 33.79, 33.50, 28.30, 27.35, 16.46, 14.72. Anal: Calcd. for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23; Found: C, 56.36; H, 8.25.

[4R,5S,6R,8S,9R]-7-Allyloxymethyl-4-carbomethoxy-8-methoxy-2,2,10-trimethyl-1,3,6-tiioxaspirodecane (14): To a solution of alcohol **3b** (398 mg, 1.25 mmol) in THF (10 mL) at 0°C was added sodium hydride (79 mg, 3.29 mmol) and the mixture was allowed to stir for 10 min. To the reaction was added allyl bromide (325 µL, 3.76 mmol) and the reaction was allowed to stir at RT overnight. The reaction was quenched by addition of water at 0 °C and was partitioned between ether and water. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel with EtOAc/hexanes (20%) as eluent to give the ethyl ester (90 mg, 20%). The aqueous layer was acidified and extracted with several portions of ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the acid (309 mg, 75%). A solution of the acid (244 mg) in ether was treated with excess diazomethane in ether untill nitrogen evolution had ceased. The solvents were removed in vacuo and the residue was chromatographed on silica gel with EtOAc/hexanes (20%) as eluent to give the methyl ester **14** (254 m, 100%): $[\alpha]^{28}_D$ +82.3° (*c* 1.0, $CHCl_3$); IR (neat): 2980, 2940, 1770, 1735, 1450, 1375, 1300, 1210, 1110, 975, 920, 875, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.21 (dd, 1H, *J* = 17.1, 1.5 Hz), 5.09 (dd, 1H, *J* = 10.2, 1.5 Hz), 4.53 (s, 1H), 3.94 (m, 1H), 3.70 (s, 3H), 3.63 (m, 1H), 3.55 (m, 2H), 3.31 (s, 3H), 3.21 (m, 1H), 2.08 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H), 1.38 (m, 1H), 0.98 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.97, 135.54, 116.49, 113,01, 106.83, 80.16, 74.56, 74.43, 72.74, 69.58, 56.98, 52.41, 33.86, 28.00, 27.46, 16.46. Anal. Calcd. for $C_{17}H_{28}O_7$: C, 59.29; H8.19. Found C, 59.57; H, 8.23.

[4(1R,3S,4R)]-4-(5-Allyloxy-3-methoxy-1-methyl-4-tertbutyldimethylsilyloxy)-5-carbomethoxy-2,2-dimethyl-1,3-dioxol-4-ene (15): To a solution of spiroketal **14** (137 mg, 0.398 mmol) in THF (2.0 mL) and HMPA (0.5 mL) at -78 °C was added a 0.78 M solution of LiHMDS (1.27 mL, 0.995 mmol) in DME. The reaction was stirred at -78 °C for 30 min, and then warmed to 0 °C. After 20 min, the reaction was quenched by addition of NH_4Cl (sat.), diluted with ether and washed with H_2O. The aqueous layer was back-extracted and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo.

The crude product (157 mg) was dissolved in DMF (3 mL) and treated with imidazole (162 mg, 2.37 mmol), TBSCl (180 mg, 1.19 mmol), and a catalytic amount of DMAP. The reaction was stirred at RT for 18 hr. The reaction was diluted with ether and washed with H_2O. The aqueous layer was back extracted and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/hexanes (5% to 10%) as eluent to give the enediol ester **15** (145 mg, 79%): $[\alpha]^{28}_D$ +6.3° (*c* 0.3, $CHCl_3$); IR (neat): 2960, 2930, 2860, 1710, 1660, 1440, 1375, 1355, 1325, 1250, 1185, 1125, 1015, 840, 815, 780, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.22 (d, 1H, J = 17.4 Hz), 5.12 (d, 1H, J = 10.5 Hz), 3.92 (d, 2H, J = 5.4 Hz), 3.85 (m, 1H), 3.77 (s, 3H), 3.49 (m, 1H), 3.35 (m, 2H), 3.32 (s, 3H), 3.06 (d, 1H, J = 10.5 Hz) 1.66 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.51 (m, 1H), 1.13 (d, 3H, J = 6.9 Hz), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.79, 154,38, 135,16, 126.30, 117.02, 115.00, 81.83, 73.17, 72.62, 72.38, 58.83, 51.83, 35.04, 27.43, 26.24, 25.86, 25.54, 19.55, 18.55, -4.22, -4.45. Anal. Calcd. for $C_{23}H_{42}O_7Si$: C, 60.23; H, 9.23. Found C, 60.03; H, 9.32

Enediol Amide (16): To a solution of enediol ester **15** (100 mg, 0.218 mmol) in MeOH (2 mL) was added $LiOH{\bullet}H_2O$ (250 mg, 5.95 mmol). The reaction was stirred at rt for 24 hr, at which point additional $LiOH{\bullet}H_2O$ (250 mg) was added. After an additional 4 hr, the reaction was acidified by the addition of 10% NaH_2PO_4, and the product was extracted with two portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give 97 mg (100%) of crude acid. The acid was combined with methyl pipecolate hydrochloride (59 mg, 0.327 mmol) and the mixture diluted with CH_2Cl_2 (10 mL). To the mixture was added NEt_3 (300 μL, 2.15 mmol), 2-chloro-N-methylpyridinium iodide (111 mg, 0.436 mmol), and a catalytic amount of DMAP. The reaction was stirred for 18 hr and then partitioned between EtOAc and NH_4Cl (satd). The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and the residue chromatographed on silica gel with EtOAc/hexanes (10% to 20%) as eluent to give enediol amide **16** (111 mg, 89%): $[\alpha]^{28}_D$ -41.0° (*c* 0.9, $CHCl_3$). IR (neat): 2940, 2860, 1745, 1620, 1430, 1380, 1290, 1250, 1200, 1145, 1105, 1020, 975, 840, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.24 (dd, 1H, J = 17.1, 1.5 Hz), 5.13 (dd, 1H, J = 10.5, 1.2 Hz), 5.06 (d, 1H, J = 4.5 Hz), 4.28 (bm), 1H), 3.94 (d, 2H, J = 5.4 Hz), 3.84 (m, 1H), 3.69 (s, 3H), 3.25-3.47 (m, 3H) 3.37 (s, 3H), 3.11 (m, 1H), 3.05 (bs), 1H), 2.20 (d, 1H, J = 14.4 Hz), 1.65 (m, 4H), 1.54 (s, 3H), 1.48 (s, 3H), 1.3-1.5 (m, 3H), 1.14 (d, 3H, J = 6.9 Hz), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.33, 162.57, 151.03, 135.34, 128.29, 116.87, 114.16, 81.91, 73.78, 72.60, 72.58, 59.26, 52.41, 35.28, 27.37, 26.30, 25.86, 25.46, 21.68, 19.47, 18.60, -4.17, -4.40. Anal. Calcd. for $C_{29}H_{51}NO_8Si$: C, 61.13; H, 9.02; N, 2.46. Found C, 61.16; H, 9.13; N, 2.42.

Tricarbonyl (17): To a solution of enediol amide **16** (61.6 mg, 0.108mmol) in CH_2Cl_2 (2 mL) at -45 °C was a solution of dimethyldioxirane (0.055 M, 2.06 mL, 0.113 mmol) in acetone (cf. ref. 16b). After 30 min, the reaction was warmed to -25 °C and after 2 hr, the solvents were removed in vacuo to give the crude tricarbonyl **17** (59 mg, 100%): $[\alpha]^{28}{}_D$ +37.3° (*c* 0.6, $CHCl_3$). IR (neat): 2940, 2860, 1740, 1710, 1640, 1445, 1360, 1250, 1100, 840, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.27 (bs, 1H), 5.24 (d, 1H, *J* = 16.2 Hz), 5.15 (d, 1H, *J* = 10.5 Hz), 4.46* (d, 1H, *J* = 13.8 Hz), 4.28* (d, 1H, *J* = 4.2 Hz), 3.94 (d, 2H, *J* = 5.4 Hz), 3.89 (m, 1H), 3.76 (s, 3H), 3.38 (m, 5H), 3.15 (m, 1H), 3.12 (s, 3H), 2.97* (m, 1H), 2.30 (d, 1H, *J* = 13.8 Hz), 2.18 (m, 1H), 1.89 (m, 1H), 1.62-1.78 (m, 3H), 1.36-1.53 (m, 1H), 1.13 (d, 3H, *J* = 6.9 Hz), 0.87 (s, 9H), 0.06, (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.56, 185.44, 170.91, 166.22, 135.13, 117.25, 80.22*, 80.08, 72.65, 72.38*, 72.27, 57.70, 56.81*, 52.92, 51.94, 44.26, 39.91*, 37.11*, 36.66, 34.30, 27.85, 26.83, 26.25, 25.56, 24.73*, 21.34*, 21.41, 18.55, 16.12*, 15.84, -4.10, -4.49 (* in advanced intermediates indicate resonances for minor rotamers).

Model α,β-Diketoamide Hemiketal (18): To a solution of the crude tricarbonyl **17** (59 mg, 0.108 mmol) in MeCN (3 mL) was added a solution of HF (3 M, 2 mL) in MeCN. The reaction was stirred for 2 hr and was then quenched by the slow addition of $NaHCO_3$ (satd). The product was extracted with ether, and the aqueous was back-extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and the residue chromatographed on silica gel with EtOAc/hexanes (25% to 30%) as eluent to give α,β-diketoamide hemiketal **18** (41.4 mg, 93%): $[\alpha]^{28}{}_D$ +3.1° (*c* 0.4, $CHCl_3$); IR (neat) 3350, 2940, 1740, 1640, 1450, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.25 (d, 1H, *J* = 1.5 Hz), 5.21 (d, 1H, *J* = 9 Hz), 5.13 (dd, 1H, *J* = 10.5, 1.2 Hz), 4.35-4.47 (m, 1.5H), 4.20 (bs), 0.5H, 3.95 (m, 3H), 3.81 (m, 1H), 3.75 (s, 3H), 3.49-3.69 (m, 3H), 3.33 (s, 3H), 3.27 (m, 1H), 3.15 (m, 1H), 2.88 (t, 0.5H), 2.12-2.40 (m, 2.5H), 2.04 (dt, 1H, *J* = 12.0, 4.2 Hz), 1.35-1.88 (m, 7H), 0.96 (d, 1.5H, *J* = 6.6 Hz), 0.90 (d, 1.5H *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.71, 195.55, 177.44, 170.80, 166.90, 165.77, 135.29, 135.03, 117.25, 98.68, 98.25, 75.17, 74.75, 73.49, 71.61, 70.46, 69.99, 57.11, 56.81, 56.73, 53.08, 52.86, 51.90, 45.08, 39.51, 35.21, 34.56, 32.35, 32.22, 27.31, 26.87, 25.30, 24.72, 21.45, 21.42, 16.22, 16.02. Anal. Calcd. for $C_{20}H_{31}NO_8$: C, 58.10; H, 7.56. Found C, 57.93; H, 7.52; N, 3.25.

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S, 6*S*, 7*R*, 8*S*, 10*R*)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4,10-trimethyl-6,8-dimethoxy-7-hydroxy-10-(2,2-dimethyl-4-ethoxycarbonyl-1,3-dioxolen-5-yl)-1-decenyl]-4-[1,3-dimethyl-2-[(triethylsilyl)-oxy]-4-[3-methoxy-4-[(*tert*-butyl-diphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (19). In a 50-mL, three-necked round-bottomed flask under argon was added a solution of LHMDS (0.78 M, 8.0 mL, 6.24 mmol),[28] in HMPA-DME (1:1) followed by a solution of MeMgBr (3.0 M , 0.160 mL, 0.480 mmol) in ether. The solution was stirred at room temperature for 10 min before it was cooled with an ice-water bath. A cooled (0 °C) solution of the bis-spiroketal ester **10** (100 mg, 0.0753 mmol) in HMPA-DME (1:1, 5.6 mL) was cannulated in drops to the cooled, well stirred base solution while the tip of the cannula was immersed into the base liquid during the addition. The starting material residue was rinsed with additional mixed solvent HMPA-DME (1:1, 3 x 0.8 mL) and was cannulated quickly to the reaction flask (total addition time: ~ 5 min). The mixture was vigorously stirred for 18 min at the ice bath temperature and was then quickly poured into a stirred mixture of NH_4Cl (2 g), HOAc (0.76 mL, 13.9 mmol) and ice-water (40 mL) cooled with an ice bath. The reaction flask was rinsed with ether (total of 100 mL) and the quenched mixture was stirred for 10 min. The aqueous layer was separated and extracted with ether (3 x 30 mL). The combined ether solution was washed with saturated NH_4Cl solution, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica (0–15% ethyl acetate in hexanes) yielded the alcohol **19** (76.7 mg, 77%) as a foaming oil: $[\alpha]_D$ +16.3° (*c* 0.67, $CHCl_3$); IR (neat) 2920, 2860, 1700, 1650, 1600, 1500, 1450, 1420, 1375, 1315, 1290, 1240, 1170, 1100, 1070, 1025, 975, 950, 905, 870, 815, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.70 (m, 4 H), 7.40-7.34 (m, 6 H), 7.23 (d, 2 H, *J* = 8.7 Hz), 6.84 (d, 2 H, *J* = 8.4 Hz), 5.53 (d, 1 H, *J* = 10.2 Hz), 4.97 (d, 1 H, *J* = 8.7 Hz), 4.47 (d, 1 H, *J* = 12.0 Hz), 4.33 (d, 1 H, *J* = 12.0 Hz), 4.28 (q, 2 H, *J* = 7.2 Hz), 3.95-3.75 (m, 2 H), 3.79 (s, 3 H), 3.65-3.50 (m, 3 H), 3.40-3.29 (m, 3 H), 3.36 (s, 3 H), 3.35 (s, 3 H), 3.32 (s, 3 H), 3.17-3.06 (m, 3 H), 2.45-2.35 (m, 1 H), 2.34-2.10 (m, 2 H), 2.10-2.09 (m, 7 H), 1.85-1.15 (m, 14 H), 1.58 (bs, 6 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.18 (d, 3 H, *J* = 6.9 Hz), 1.05 (s, 9 H), 0.90 (t, 9 H), 0.85 (overlapped, 3 H), 0.81 (d, 3 H), 0.52 (q, 6 H, *J* = 8.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.1, 158.9, 154.0, 136.0, 135.9, 135.4, 135.2, 134.4, 133.2, 131.9, 130.8, 129.2$_3$, 129.2, 129.0, 127.5, 127.3, 127.2, 125.8, 114.5, 113.6, 98.5, 97.8, 84.2, 80.1, 79.9, 77.4, 75.7, 73.2, 70.2, 69.2, 63.8, 63.5, 60.4, 58.3, 57.3, 57.2, 55.2, 48.2, 41.6, 40.6, 36.5, 35.7, 34.9, 34.8, 33.7, 30.9, 30.6, 27.3, 27.1, 27.0, 25.5, 25.1, 24.0, 19.7, 19.4, 19.3, 15.7, 14.4, 11.0, 9.2, 6.9, 4.9. Anal. Calcd for $C_{76}H_{118}O_{15}Si_2$: C, 68.74; H, 8.96. Found: C, 68.57; H, 9.05.

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S, 6*S*, 7*R*, 8*S*, 10*R*)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4,10-trimethyl-6,8-dimethoxy-7-[(*tert*-butyldimethylsilyl)oxy]-10-(2,2-dimethyl-4-ethoxycarbonyl-1,3-dioxolen-5-yl)-1-decenyl]-4-[1,3-dimethyl-2-[(triethylsilyl)-oxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (20). To a solution of the alcohol **19** (205 mg, 154 μmol) in anhydrous CH_2Cl_2 (1.2 mL) was added 2,6-di-(*tert*-butyl)pyridine (360 μL, 1.60 mmol), $MgSO_4$ (200 mg), TBSOTf (255 μL, 1.54 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temperature for 1 h before an aqueous $NaHCO_3$ (50% saturated, 2 mL) was slowly added. The mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic phase was dried (K_2CO_3) and concentrated. Chromatography on silica (5–15% ethyl acetate in hexanes) of the residue afforded the TBS-ether **20** (191 mg, 86%) as a foaming oil: $[\alpha]_D$ -1.75° (*c* 1.14, $CHCl_3$); IR (neat) 2940, 2910, 2860, 2840, 1700, 1645, 1600, 1500, 1450, 1415, 1365, 1310, 1240, 1170, 1100, 1070, 1025, 975, 950, 870, 825, 770, 755, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80-7.70 (m, 4 H), 7.55-7.35 (m, 6 H), 7.23 (d, 2 H, *J* = 8.4 Hz), 6.84 (d, 2 H, *J* = 8.4 Hz), 5.53 (d, 1 H, *J* = 10.2 Hz), 4.99 (d, 1 H, *J* = 8.7 Hz), 4.49 (d, 1 H, *J* = 12.0 Hz), 4.35 (d, 1 H, *J* = 12.0 Hz), 4.34-4.25 (m, 2 H), 3.95-3.80 (m, 3 H), 3.78 (s, 3 H), 3.70-3.51 (m, 3 H), 3.40-3.33 (m, 1 H), 3.39 (s, 3 H), 3.29 (s, 3 H), 3.25 (s, 3 H), 3.18-3.05 (m, 3 H), 2.45-2.36 (m, 1 H), 2.26-2.23 (m, 2 H), 2.10-2.06 (m, 1 H), 2.00-1.94 (m, 1 H), 1.78-1.20 (m, 13 H), 1.59 (s, 6 H), 1.52 (s, 6 H), 1.36 (s, 3 H), 1.32 (t, 3 H), 1.26 (s, 3 H), 1.17 (d, 3 H, *J* = 7.2 Hz), 1.06 (s, 9 H), 0.93-0.80 (m, 18 H), 0.90 (s, 9 H), 0.43 (q, 6 H, *J* = 7.8 Hz), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.0, 158.9, 153.9, 135.9, 135.8, 135.3, 135.1, 134.3, 133.6, 131.8, 130.7, 129.2, 129.1_8, 128.9, 127.2_4, 127.2, 127.1, 126.0, 114.4, 113.5, 98.4, 97.8, 84.2, 81.0, 80.0, 79.9, 75.7, 73.1, 70.1, 69.2, 63.8, 63.4, 60.3, 58.5, 57.3, 57.2, 55.1, 46.6, 41.6, 40.6, 38.1, 35.6, 35.4, 34.9, 34.7, 33.7, 30.8. 30.6, 27.8, 27.5, 26.9, 26.8, 25.9, 25.7, 25.0, 23.9, 20.1, 19.4, 19.3, 18.2, 15.9, 14.4, 11.0, 9.2, 6.9, 4.9, -4.6, -4.7. Anal. Calcd for $C_{82}H_{132}O_{15}Si_3$: C, 68.29; H, 9.23. Found: C, 68.08; H, 9.40.

[4*R*, 4[1*S*, 2*S*, 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S, 6*S*, 7*R*, 8*S*, 10*R*)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4,10-trimethyl-6,8-dimethoxy-7-[(*tert*-butyldimethylsilyl)oxy]-10-(2,2-dimethyl-4-ethoxycarbonyl-1,3-dioxolen-5-yl)-1-decenyl]-4-[1,3-dimethyl-2-hydroxy-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (21). A solution of the C26-TES ether **20** (182 mg, 126 μmol) in THF-H_2O-TFA (6:1:0.1, 3 mL) was stirred for 1 h at room temperature and quenched with saturated $NaHCO_3$ solution at 0 °C. The aqueous solution was extracted with ether (3 x) and the combined organic phase was dried (K_2CO_3), concentrated, and chromatographed on silica (3–15% ethyl acetate in hexanes) to afford the alcohol **21** (167 mg, 100%) as a foaming oil: $[\alpha]_D$ +1.40° (*c* 0.71, $CHCl_3$); IR (neat) 3460, 2920, 2840, 1700, 1645, 1505, 1460-1440, 1420, 1370, 1315, 1240, 1170, 1105, 1020, 945, 825, 775-735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.68 (m, 4 H), 7.42-7.32 (m, 6 H), 7.22 (d, 2 H, *J* = 7.4 Hz), 6.84 (d, 2 H, *J* = 7.4 Hz), 5.53 (d, 1 H, *J* = 10.5 Hz), 5.22 (d, 1 H, *J* = 7.7 Hz), 4.48 (d, 1 H, *J* = 12.0 Hz), 4.37 (d, 1 H, *J* = 12.0 Hz), 4.35-4.20 (m, 2 H), 4.08 (b, 1 H), 3.92-3.80 (m, 2 H), 3.78 (s, 3 H), 3.70 (d, 1 H, *J* = 12.0 Hz), 3.60-3.52 (m, 2 H), 3.41 (m, 1 H), 3.38 (s, 3 H), 3.32 (s, 3 H), 3.25 (s, 3 H), 3.15-3.04 (m, 3 H), 2.84 (s, 1 H), 2.45-2.40 (m, 1 H), 2.26-2.22 (m, 2 H), 2.12-2.04 (m, 1 H), 1.94-1.90 (m, 1 H), 1.80-1.20 (m, 22 H), 1.58 (s, 6 H), 1.51 (s, 6 H), 1.16 (d, 3 H, *J* = 6.9 Hz), 1.05 (s, 9 H), 0.96-0.83 (m, 3 H), 0.90 (s, 9 H), 0.79 (2 bs, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.1, 158.9, 153.9, 136.0, 135.9, 135.2, 134.4, 134.0, 133.5, 130.7, 129.5, 129.2_4, 129.2, 128.8, 127.3, 127.2, 126.8, 126.0, 114.4, 113.6, 98.8, 98.0, 84.3, 81.0, 80.8, 79.0, 75.7, 73.2, 70.2, 69.3, 68.9, 63.5, 60.3, 58.5, 57.4, 57.2, 55.2, 46.8, 41.5, 38.7, 38.2, 36.2, 35.2, 34.9, 34.7, 33.7, 30.9, 30.6, 28.0, 27.7, 27.0, 26.8, 25.9, 25.8, 25.0, 23.7, 20.0, 19.4, 19.3, 18.2, 16.0, 14.4, 13.3, 5.8, -4.6, -4.7. Anal. Calcd for $C_{76}H_{118}O_{15}Si_2$: C, 68.74; H, 8.96. Found: C, 68.71; H, 9.02.

[4*R*, 4[1*S*, 2*S*, 2(2*S*) 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S, 6*S*, 7*R*, 8*S*, 10*R*)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4,10-trimethyl-6,8-dimethoxy-7-[(*tert*-butyldimethylsilyl)oxy]-10-(2,2-dimethyl-4-ethoxycarbonyl-1,3-dioxolen-5-yl)-1-decenyl]-4-[1,3-dimethyl-2-[*N*-(*tert*-butoxycarbonyl)-piperidine-2-carbonyloxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)-oxy]-cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (22). To a cooled (-78°C) solution of the alcohol **21** (51.0 mg, 38.4 μmol) in anhydrous CH_2Cl_2 (3.0 mL) under argon was added (*N*)-Boc-L-pipecolinic acid (88.0 mg, 384 μmol), DCC (88.0 mg, 426 μmol) and a catalytic amount of DMAP. The mixture was allowed to stand in a freezer (-15 °C) for 20 h with occasional shaking. The resulting yellow mixture was diluted with hexanes (6 mL) and filtered through a Celite pad. After further washings (3 x) of the residue, the combined filtrate was concentrated and the crude mixture was purified on preparative TLC plates (15% ethyl acetate in hexanes) to yield the pipecolinate (52 mg, 88%) as a foaming oil: $[\alpha]_D$ -18.5° (*c* 1.24, $CHCl_3$); IR (neat) 2920, 2850, 1730, 1690, 1650, 1505, 1450, 1370, 1315, 1245, 1175, 1150, 1105, 1030, 990, 955, 925, 870, 830, 810, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.70 (m, 4 H), 7.40-7.33 (m, 6 H), 7.22 (d, 2 H, *J* = 7.4 Hz), 6.83 (d, 2 H, *J* = 7.4 Hz), 5.51 (d, 1 H, *J* = 9.9 Hz), 5.22 (d, 1 H, *J* = 7.4 Hz), 5.16-5.12 (m, 1 H), 4.83 (b, 0.5 H), 4.70 (b, 0.5 H), 4.48 (d, 1 H, *J* = 12.3 Hz), 4.34 (d, 1 H, *J* = 12.3 Hz), 4.32-4.20 (m, 2 H), 4.03-3.80 (m, 4 H), 3.78 (s, 3 H), 3.71 (s, 0.5 H), 3.62-3.52 (m, 3 H), 3.39 (s, 3 H), 3.28 (s, 3 H), 3.24 (s, 3 H), 3.13-3.06 (m, 3 H), 2.94-2.80 (m, 1 H), 2.45-2.00 (m, 4 H), 1.91-1.51 (m, 20 H), 1.40-1.15 (m, 31 H), 1.04 (s, 9 H), 0.95-0.70 (m, 11 H), 0.89 (s, 9 H), 0.08 (2s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9, 170.8, 161.1, 158.9, 155.6, 155.2, 153.9, 136.0, 135.9, 135.5, 135.1, 134.8, 134.3, 133.9, 130.7, 130.3, 129.2, 128.9, 127.3, 127.2, 126.9, 126.0, 114.4, 113.6, 98.7, 97.8, 84.1, 82.1, 81.6, 81.0, 79.9, 79.7, 79.6, 75.5, 73.2, 70.1, 70.0, 69.2, 64.1, 63.7, 63.5, 60.3, 58.5, 57.4, 57.0, 55.2, 54.8, 53.8, 46.7, 42.0, 41.6, 40.9, 38.3, 38.1, 35.7, 34.9, 34.7, 33.6, 30.8, 30.3, 28.3, 27.9, 27.5, 27.4, 27.0, 26.8, 25.9, 25.8, 25.0, 24.7, 23.8, 20.7, 20.5, 20.1, 19.4, 19.3, 18.2, 15.9, 14.4, 11.8, 11.7_6, 9.4, 9.2, -4.6. -4.8. Anal. Calcd for $C_{87}H_{135}O_{18}NSi_2$: C, 67.89; H, 8.84; N, 0.91. Found: C, 67.57; H, 8.88; N, 1.05.

[4*R*, 4[1*S*, 2*S*, 2(2*R*) 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S, 6*S*, 7*R*, 8*S*, 10*R*)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4,10-trimethyl-6,8-dimethoxy-7-[(*tert*-butyldimethylsilyl)oxy]-10-(2,2-dimethyl-4-hydroxycarbonyl-1,3-dioxolen-5-yl)-1-decenyl]-4-[1,3-dimethyl-2-[*N*-(*tert*-butoxycarbonyl)-piperidine-2-carbonyloxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)-oxy]-cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (*epi*-23). To a solution of the ester **22** (88.0 mg, 57.0 μmol) in dioxane (0.75 mL, passed through a short pad of basic alumina before use) was added a solution of 3 N solution of NaOH (0.55 mL, 1.65 mmol) and H_2O (0.35 mL). The solution was stirred at 100 °C for 8 h and cooled to room temperature. The base was neutralized with 1 M solution of $NaHSO_4$ and the mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic phase was washed with saturated NH_4Cl solution, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica (20–80% ethyl acetate in hexanes) yielded the acid (77 mg, 89%) whose ^{1}H and ^{13}C NMR resonances are identical to those of the acid directly prepared from **20** (*vide infra*): $[\alpha]_D$ -12.5° (*c* 1.2, $CHCl_3$).

When the above reaction was performed with NaOD (prepared from Na and D_2O) and D_2O in place of NaOH and H_2O under the same condition, the ^{1}H NMR resonances of the product showed all but the two broad signals at δ 4.84 (b, 0.5 H) and δ 4.67 (b, 0.5 H) corresponding to the *a*-proton on the pipecolinic ring.

[4*R*, 4[1*S*, 2*S*, 2(2*S*) 3*E*, 4(1*R*, 3*R*, 4*R*)], 6*R*, 9*R*, 11*R*, 11(1*E*, 4S, 6*S*, 7*R*, 8*S*, 10*R*)]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4,10-trimethyl-6,8-dimethoxy-7-[(*tert*-butyldimethylsilyl)oxy]-10-(2,2-dimethyl-4-hydroxycarbonyl-1,3-dioxolen-5-yl)-1-decenyl]-4-[1,3-dimethyl-2-[*N*-(*tert*-butoxycarbonyl)-piperidine-2-carbonyloxy]-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)-oxy]-cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (23). To a solution of the ethyl ester **20** (368 mg, 255 μmol) in dioxane (30 mL, passed through a short pad of basic alumina before use) was added a 3 N solution of NaOH (2.5 mL, 7.5 mmol) and H_2O (2.5 mL). The solution was stirred at 100 °C for 8 h and the resulting yellow solution was cooled with an ice bath. The base was neutralized with $NaHSO_4$ (1 M, 2.5 mL) and the mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic phase was washed with saturated NH_4Cl solution and concentrated. The residue was dissolved in THF (6.0 mL), H_2O (1.0 mL) and trifluoroacetic acid (0.1 mL) were added slowly. The mixture was stirred for 1.5 h at room temperature and was quenched with aqueous $NaHCO_3$ (saturated, 1.5 mL) at 0 °C. The mixture was extracted with ether (4 x) and the organic phase was washed once with saturated NH_4Cl solution, dried (K_2CO_3), concentrated, and chromatographed on silica (ethyl acetate in hexanes, 25%, 100 mL; 30%, 60 mL; 40%, 50 mL) to afford the hydroxy acid (265 mg, 80%) which was dissolved in anhydrous CH_2Cl_2 (2.5 mL).

A solution containing (*N*)-Boc-L-pipecolinic acid **2** (240 mg, 1.04 mmol), DCC (210 mg, 1.02 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (5.0 mL) was cooled to -25 °C (CCl_4-dry ice bath) under argon. The hydroxy acid solution prepared above was added via a syringe pump to the stirred reaction mixture over 3 h while the cooling bath temperature was maintained between -25 °C and -15 °C. After the addition the syringe was rinsed with additional CH_2Cl_2 (3 x 0.2 mL) and the reaction flask was placed in a freezer (-15 °C) overnight. The yellow mixture was diluted with hexanes (10 mL), filtered through a Celite pad and the residue was washed with more hexanes (5 x 10 mL). The filtrate was concentrated and the resulting oily solid was dissolved in 15 mL of THF. Water (4.4 mL) and a 3 N solution of NaOH (0.60 mL, 1.8 mmol) were added and the mixture was stirred for 40 min at room temperature. The basic mixture was neutralized with 1 M solution of $NaHSO_4$ (1.8 mL, 1.8 mmol) and the THF was evaporated. The residue was partitioned between CH_2Cl_2 and saturated NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x). The organic phase was dried (Na_2SO_4), concentrated and the residue was chromatographed on silica (ethyl acetate in hexanes, 8% up) to afford the pure acid **23** (292 mg, 76% overall) as a foaming oil: $[\alpha]_D$ -13.7° (*c* 0.8, $CHCl_3$); IR (neat) 3060, 2910, 2840, 1730, 1690, 1640, 1500, 1450, 1420, 1370, 1290, 1240, 1175, 1150, 1135, 1100, 1030, 990, 950, 920, 870, 830, 770, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.60 (m, 4 H), 7.40-7.30 (m, 6 H), 7.22 (d, 2 H, J = 7.7 Hz), 6.84 (d, 2 H, J = 7.4 Hz), 5.51 (d, 1 H, J = 9.9 Hz), 5.22 (d, 1 H, J = 7.4 Hz), 5.15-5.12 (m, 1 H), 4.84 (b, 0.5 H), 4.67 (b, 0.5 H), 4.48 (d, 1 H, J = 12.0 Hz), 4.34 (d, 1 H, J = 12.0 Hz), 4.10-3.80 (m, 4 H), 3.79 (s, 3 H), 3.63-3.50 (m, 3 H), 3.39 (s, 3 H), 3.29 (s, 3 H), 3.26 (s, 3 H), 3.15-3.05 (m, 3 H), 2.94-2.84 (m, 1 H), 2.42-2.06 (m, 4 H), 1.91-1.50 (m, 20 H), 1.40-1.15 (m, 28 H), 1.05 (s, 9 H), 0.95-0.70 (m, 11 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9, 165.3, 159.0, 156.5, 155.5, 155.3, 136.0, 135.9, 135.4, 135.1, 134.8, 134.4, 133.9, 130.7, 130.3, 129.2, 128.9, 127.3, 127.2, 126.9, 125.6, 115.0, 113.8, 113.6, 98.7, 97.8, 84.1, 82.1, 81.6, 81.1, 80.1, 80.0, 79.8, 79.7, 75.5, 73.0, 70.0, 69.2, 64.2, 63.7, 63.5, 58.5, 57.4, 57.0, 55.2, 54.8, 53.8, 46.7, 42.0, 41.6, 41.0, 38.3, 38.1, 35.7, 35.1, 35.0, 34.8, 33.6, 30.8, 30.4, 29.7, 28.3, 27.9, 27.8, 27.6, 27.5, 27.0; 26.8, 26.6, 25.9, 25.7, 25.5, 25.1, 24.9, 24.7, 23.8, 20.7, 20.5, 20.1, 19.3, 18.2, 16.0, 11.8, 11.7_8, 9.4, 9.2, -4.5, -4.7. Anal. Calcd for $C_{85}H_{131}O_{18}NSi_2$: C, 67.56; H, 8.74; N, 0.93. Found: C, 67.53; H, 8.96; N, 0.96.

Macrolactam (24). A solution of the acid **23** (33.0 mg, 21.8 µmol) in anhydrous CH_2Cl_2 (3.0 mL) at 0 °C was treated with 2,6-lutidine (50.0 µL, 430 µmol) and TESOTf (75.0 µL, 332 µmol) under argon. The solution was stirred with cooling for 2 h and the solvent was evaporated. The residue was transferred (with CH_2Cl_2 rinsings) to a short column of silica gel (5 x 1 cm) and aged for 2 h. The column was eluted with CH_2Cl_2/hexanes (50%, to remove the silyl by-products), followed by CH_2Cl_2, then MeOH/CH_2Cl_2 (0.5, 0.75, 1.0%, to remove excess 2,6-lutidine) and finally with MeOH/CH_2Cl_2 (2.5–8%) to afford the amino acid which was azeotroped with THF three times to remove the methanol residue. The amino acid thus obtained was dissolved in anhydrous CH_2Cl_2 (2.0 mL) followed by the addition of Et_3N (250 µL, 1.79 mmol). This was added over 2 h via a syringe pump into a solution of methyl-2-chloropyridinium iodide (55.0 mg, 218 µmol) and Et_3N (100 µL, 717 µmol) in anhydrous CH_2Cl_2 (50 mL) under vigorous stirring. The resulting orange solution was stirred at room temperature for 12 h and extracted three times with water. The aqueous washings were combined and back extracted once with CH_2Cl_2. The combined organic phase was washed with aqueous saturated NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica (5–15% ethyl acetate in hexanes) to afford the macrolactam **24** (21.0 mg, 69%) as a foaming oil: $[\alpha]_D$ -20.5° (*c* 1.36, $CHCl_3$); IR (neat) 2930, 2850, 1730, 1650, 1600, 1580, 1505, 1460-1430, 1425, 1370, 1280, 1245, 1195-1170, 1130, 1100, 1070, 1030, 980, 960, 875-845, 835-815, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.60 (m, 4 H), 7.45-7.30 (m, 6 H), 7.22 (d, 2 H, *J* = 7.8 Hz), 6.84 (d, 2 H, *J* = 8.1 Hz), 5.43 (d, 1 H, *J* = 9.6 Hz), 5.20-5.12 (m, 2 H), 5.01 (b, 1 H), 4.45 (d, 1 H, *J* = 11.7 Hz), 4.29 (d, 1 H, *J* = 11.7 Hz), 4.23-4.15 (m, 1 H), 4.05-3.90 (m, 1 H), 3.85 (d, 1 H, *J* = 11.7 Hz), 3.79 (s, 3 H), 3.76-3.50 (m, 3 H); 3.40-3.36 (m, 4 H), 3.29 (s, 3 H), 3.24 (s, 3 H), 3.20-2.90 (m, 4 H), 2.40-2.35 (m, 1 H), 2.25-2.15 (m, 2 H), 2.14-1.20 (m, 40 H), 1.04 (s, 9 H), 0.96-0.50 (m, 11 H), 0.90 (s, 9 H), 0.07 (ds, 6 H) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 161.3, 159.0, 151.3, 135.9, 135.2, 134.4, 133.1, 131.7, 130.8, 129.1 (2 x s), 127.3, 126.8, 113.6, 113.5, 98.6, 97.8, 84.1, 82.2, 81.0, 80.2, 75.5, 74.6, 70.3, 69.2, 64.8, 63.8, 58.5, 57.1, 56.4, 55.2, 52.7, 48.2, 44.3, 41.5, 39.0, 38.1,. 35.9, 34.8, 34.0, 33.9, 30.8, 30.5, 30.0, 29.7, 29.3, 28.2, 27.2, 27.0, 26.6, 26.4, 26.0, 25.1, 23.8, 21.3, 19.3, 18.5, 18.3, 15.4, 13.0, 10.1, -4.4. Anal. Calcd for $C_{80}H_{121}O_{15}NSi_2$: C, 68.98; H, 8.76; N, 1.01. Found: C, 68.67; H, 8.75; N, 0.97.

C36-Alcohol (25). To a solution of the C36-PMB ether **24** (15.0 mg, 10.7 μmol) in CH_2Cl_2 (1.9 mL) was added H_2O (0.1 mL) and DDQ (6.0 mg, 26.4 μmol). The mixture was vigorously stirred at room temperature for 50 min and was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The aqueous layer was extracted (3 x) and the combined organic phase was dried (K_2CO_3), concentrated. The residue was chromatographed on silica (15% ethyl acetate in hexanes) to afford the alcohol (12.6 mg, 92%) as a foaming oil: $[\alpha]_D$ -25.4° (*c* 1.30, $CHCl_3$); IR (neat) 3520-3360, 2920, 2880, 2840, 1730 (b), 1600, 1460-1420, 1370, 1280, 1245, 1190, 1135, 1100, 980, 970-950, 830-810, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.72 (m, 4 H), 7.42-7.32 (m, 6 H), 5.37 (d, 1 H, *J* = 9.6 Hz), 5.18 (b, 1 H), 5.08-4.95 (m, 2 H), 4.26 (bd, 1 H, *J* = 12.9 Hz), 3.97-3.93 (m, 1 H), 3.91 (dd, 1 H, *J* = 1.5, 13.8 Hz), 3.69 (b, 2 H), 3.57-3.53 (m, 2 H), 3.37 (bs, 3 H), 3.31 (bs, 3 H), 3.28 (bs, 3 H), 3.22-3.19 (m, 1 H), 3.15-3.00 (m, 4 H), 2.45-2.35 (m, 1 H), 2.25-2.05 (m, 3 H), 1.95-1.10 (m, 39 H), 1.05 (s, 9 H), 0.92-0.75 (m, 11 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.0, 161.5, 151.9, 136.6, 135.9, 135.8, 135.0, 134.3, 131.3, 129.2_2, 129.1_7, 127.2_4, 127.1_9, 126.9, 125.4, 113.4, 98.8, 97.4, 84.0, 81.8, 78.5, 75.5, 75.2, 65.9, 65.8, 65.0, 58.5, 57.2, 57.1, 52.5, 47.1, 43.7, 41.3, 39.2, 38.5, 36.0, 35.0, 34.7, 33.5, 31.9, 30.8, 30.5, 29.6, 29.3, 29.0, 27.9, 27.4, 26.9, 26.6, 26.0, 25.6, 25.0, 23.7, 22.6, 21.3, 21.1, 19.3, 18.4, 18.2, 16.8, 14.0, 13.3, 10.2, -4.3, -4.5. Anal. Calcd for $C_{72}H_{113}O_{14}NSi_2$: C, 67.94; H, 8.95; N, 1.10. Found: C, 68.21; H, 9.00; N, 1.05.

C36-Iodide (26). A toluene solution (2.5 mL) containing the C36-alcohol **25** (89.0 mg, 70 μmol), triphenyl phosphine (166 mg, 629 μmol) and imidazole (45 mg, 661 μmol) was heated to 70 °C. To this was added *slowly* a solution of iodine (10 mg/100 μmol) in 100-μL aliquots via a syringe in such a way that the syringe tip was immersed underneath the solution so the iodine color discharged immediately upon mixing. A total of 300 μL of the iodine solution was added over a period of 10 min (in some cases more iodine need to be added, over a longer period, to ensure a complete reaction) and the mixture was stirred for another 20 min before it was cooled to room temperature. The mixture was directly chromatographed on silica (0–5% ethyl acetate in hexanes) to afford the iodide **26** (85 mg, 88%) plus a small amount of the starting alcohol **25** (3.8 mg, 4%): $[\alpha]_D$ -11.6° (*c* 0.86, $CHCl_3$); IR (neat) 3060, 3040, 2920, 2840, 1750-1725, 1650, 1610, 1420, 1370, 1280, 1200, 1130, 1100, 1000, 980, 955, 870, 830, 770, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.70 (m, 4 H), 7.40, 7.33 (m, 6 H), 5.30 (d, 1 H, *J* = 9.0 Hz), 5.22 (b, 1 H), 5.07 (d, 1 H, *J* = 8.7 Hz), 4.95 (b, 1 H), 4.40-4.27 (m, 1 H), 4.17 (d, 1 H, *J* = 12.9 Hz), 3.96 (t, 1 H, *J* = 11.1 Hz), 3.90-3.76 (m, 1 H), 3.75-3.62 (m, 1 H), 3.60-3.46 (m, 1 H), 3.36 (s, 3 H), 3.30 (s, 6 H), 3.15-3.02 (m, 3 H), 2.75-2.60 (m, 1 H), 2.36 (d, 1 H, *J* = 9.6 Hz), 2.30-2.00 (m, 2 H), 2.04-1.26 (m, 39 H), 1.33 (s, 3 H), 1.17 (d, 3 H, *J* = 6.9 Hz), 1.05 (s, 9 H), 0.90 (s, 9 H), 0.86-0.90 (m, 6 H), 0.78 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.8, 161.4, 151.4, 137.0, 136.0, 135.9, 135.0, 134.3, 131.7, 131.3, 129.3, 129.2, 127.3, 127.2, 122.0, 113.4, 98.0, 96.4, 84.1, 82.1, 80.5, 79.0, 75.5, 74.0, 67.4, 65.8, 58.1, 57.2, 56.0, 52.4, 47.0, 44.1, 39.3, 38.3, 37.6, 36.0, 35.2, 34.8, 33.6, 30.8, 30.5, 29.7, 29.6, 29.3, 28.4, 28.1, 27.9, 27.6, 27.0, 26.5, 26.3, 26.0, 25.8, 25.5, 25.2, 24.9, 23.5, 22.8, 22.6, 21.4. 21.2, 19.3, 19.1, 18.6, 18.4, 18.3, 16.5, 14.1, 13.2, 10.3, -4.3, -4.6. Anal. Calcd for $C_{72}H_{112}IO_{13}NSi_2$: C, 62.54; H, 8.16; N, 1.01. Found: C, 62.78; H, 8.19; N, 1.01.

α'-Allyl Aldol (27). In a 25-mL three-necked round-bottomed flask equipped with a reflux condenser under argon, graphite (116 mg, 1.21 mmol of C_8) was heated at 150 °C for 15 min followed by the addition of potassium (47 mg, 1.20 mmol). The mixture was vigorously stirred at 150 °C for 15 min and was cooled to room temperature. A suspension of $ZnCl_2$ (flame dried, 82 mg, 6.02 mmol) and AgOAc (8.0 mg, 48 μmol) in THF (2 mL) was cannulated to the C_8K mixture followed by additional rinsings (2 x 1 mL). The mixture was heated to reflux for 30 min and was cooled with an ice bath. To this cooled mixture was added a solution of the iodide **26** (23 mg, 17.0 μmol) in THF (3.0 mL) followed by additional rinsings (3 x 1 mL). The mixture was stirred for 1 h and was filtered through a pad of Celite into a flask containing aqueous NH_4Cl (saturated, 2 mL). The residue was further washed with THF (30 mL total) and the filtrate was concentrated. The resulting mixture was partitioned between ethyl acetate and aqueous saturated NH_4Cl solution and the aqueous layer was extracted three times. The combined organic phase was concentrated and chromatographed on silica (5–15% ethyl acetate in hexanes) to afford the α'-allyl aldol (22 mg, 110%): $[\alpha]_D$ -105° (*c* 2.0,

$CHCl_3$); IR (neat) 3540-3340, 3060, 3040, 2910, 2840, 1730-1690, 1680-1580, 1450-1410, 1370, 1275, 1240, 1180, 1135, 1110-1060, 975, 835-805, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.65 (m, 4 H), 7.42-7.30 (m, 6 H), 5.75-5.60 (m, 1 H), 5.16 (b, 1 H), 5.11-4.90 (m, 5 H), 4.24 (d, 1 H, J = 13.5 Hz), 3.85-3.75 (m, 2 H), 3.36-3.50 (m, 2 H), 3.45-3.20 (m, 1 H), 3.37 (bs, 3 H), 3.31 (s, 3 H), 3.25 (s, 3 H), 3.15-3.00 (m, 4 H), 2.85-2.72 (m, 2 H), 2.45-2.12 (6 H), 1.95 (d, 1 H, J = 12.0 Hz), 1.84-1.20 (m, 25 H), 1.26 (s, 3 H), 1.15 (d, 3 H, J = 7.2 Hz), 1.05 (s, 9 H), 0.95-0.80 (m, 9 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.6, 170.2, 161.4, 152.1, 140.0, 136.0, 135.9, 135.3, 135.1, 134.4, 131.2, 129.3, 129.2, 127.3, 127.2, 122.8, 116.5, 113.4, 84.0, 81.7, 81.5, 78.7, 75.4, 74.6, 68.5, 58.6, 57.2, 56.8, 53.2, 52.7, 46.6, 44.4, 43.8, 39.5, 38.1, 35.9, 35.5, 34.7, 34.4, 33.4, 30.5, 29.6, 29.3, 29.2, 28.3, 27.0, 26.6, 26.0, 25.7, 25.1, 24.8, 22.6, 21.3, 20.6, 19.3, 18.3, 17.3, 14.2, 13.5, 9.4, -4.5, -4.7. HRMS calcd for $C_{69}H_{107}NaNO_{12}Si_{12}$ (M^++Na) 1220.7230, found 1220.7218.

Tricarbonyl (28). To a sample of the α'-allyl aldol **27** (29 mg, 24 μmol) cooled to -50 °C was added a solution of dimethyl dioxirane in acetone (8.5 mM, 2.8 mL, 23.8 μmol). The solution was stirred for one minute before it was placed in a freezer (-26 °C). Additional dimethyl dioxirane was added after 75 min (0.5 mL, 4.2 μmol) and 100 min (0.2 mL, 1.7 μmol) of reaction times (based on TLC monitoring). The solvent was evaporated after 130 min when TLC showed only the presence of product spot which is polar and less UV active than is the starting material. The yellow residue (29 mg, 100%) thus obtained showed the following analytical data. One milligram of the material was sent for HRMS and the rest was used directly for the next step: $[\alpha]_D$ -127° (c 1.4, $CDCl_3$); IR (neat) 3540-3340, 3050-2980, 2940, 2900, 2820, 1730-1710, 1690, 1625, 1440-1410, 1370-1340, 1240, 1180, 1130, 1100-1080, 1070, 900, 830-800, 765, 720, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78-7.60 (m, 4 H), 7.40-7.34 (m, 6 H), 5.75-5.62 (m, 1 H), 5.17-4.80 (m, 6 H), 4.45-4.38 (m, 1 H), 4.00-3.94 (m, 1 H), 3.78-3.73 (m, 1 H), 3.60-3.00 (m, 8 H), 3.40, 3.37, 3.31, 3.26, 3.20, 3.16, (6s, 9 H, 3-CH_3), 2.89-2.76 (m, 1 H), 2.50-1.10 (m + s, 32 H), 1.05 (s, 9 H), 1.00-0.70 (m, 6 H), 0.90 (s, 9 H), 0.79 (d, 3 H, J = 6.0 Hz), 0.09, 0.073, 0.067 (3s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.1, 210.3, 200.2, 185.3, 168.8, 168.6, 165.7, 139.4, 135.9, 135.5, 135.1, 134.3, 133.2, 132.9, 131.0, 129.2, 127.3, 123.1, 122.9, 116.5, 84.0, 81.6, 81.2, 80.7, 80.3, 79.7, 78.8, 75.4, 74.5, 74.1, 68.3, 67.9, 59.4, 59.0, 57.2, 57.0, 56.9, 56.0, 53.1, 53.0, 51.7, 47.1, 46.5, 46.0, 45.5, 43.9, 40.0, 39.2, 39.0, 38.9, 37.5, 36.1, 36.0, 35.8, 35.1, 34.9, 34.7, 34.5, 34.1, 33.6, 33.5, 32.0, 30.4, 29.6, 27.9, 27.0, 26.0, 25.8, 25.1, 24.2, 22.8, 21.1, 20.6, 20.4, 19.7, 19.3, 18.4, 18.3, 16.8, 16.7, 16.5, 15.9, 14.0, 12.7, 12.6, 9.2, 9.1, 1.0, -4.3, -4.2, -4.4. HRMS calcd for $C_{66}H_{101}NaNO_{12}Si_2$ (M^++Na) 1178.6760, found 1178.6725 .

FK-506 (1). The tricarbonyl compound obtained earlier **28** (28 mg) was transferred into a polypropylene tube and was dissolved in CH_3CN (2.45 mL) followed by addition of an aqueous solution of

HF (48%, 0.55 mL). The mixture, which became deep yellow, was stirred at room temperature for 10 h before it was cooled with an ice bath. The mixture was carefully quenched with ice-cold saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2 (5 x). The combined organic phase was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica (40–80% ethyl acetate in hexanes) afforded an oil which solidified upon standing (10.5 mg, 54% isolated, 56% based on the loss from the HRMS sample, over three steps from the iodide): Mp 126-129 °C (lit. 127-129 °C); $[\alpha]^{23}_D$ -86±1° (*c* 1.0, $CHCl_3$; lit. -84.4/*c* 1.02,[29] -85/*c* 0.2 (ref. 13), -84.1/*c* 0.63 (27 °C, ref. 12); TLC (ethyl acetate in hexanes 80%, then reverse develop with 30%, 50%), IR, ^1H NMR (300 MHz, 500 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz and 125 MHz, $CDCl_3$) of the synthetic sample were identical to those of a natural sample in every respects. The ^{13}C NMR (500 MHz) data is recorded below in view of the incomplete literature data: 212.7, 212.5, 196.1, 192.6, 168.9, 168.7, 165.8, 164.6, 139.7, 138.9, 135.5, 135.3, 132.4, 131.7, 129.7, 129.6, 122.6, 122.4, 116.6, 98.6, 97.0, 84.1, 77.8, 77.2, 76.5, 75.1, 73.6, 73.5, 72.8, 72.2, 70.0, 68.9, 57.5, 56.9, 56.6, 56.3, 56.1, 52.9, 52.7, 48.5, 48.4, 43.9, 43.2, 40.4, 39.8, 39.2, 35.6, 35.4, 35.1, 34.8, 34.7, 34.6, 33.6, 32.9, 32.7, 32.5, 31.2, 30.6, 27.6, 26.2, 26.0, 24.6, 24.5, 21.1, 20.8, 20.4, 19.4, 16.2, 16.0, 15.8, 14.2, 14.1, 9.8, 9.5.

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HMDSH, see experimental part. Initially $MgBr_2$•ether was used but the results were irreproducible for reasons that are not clear. Control experiments indicated that $Mg(HMDS)_2$ as well as $Mg[N(^iPr)_2]_2$ alone (80 equiv) did not effect elimination at all. In fact if more than 10 equivalents of $Mg(HMDS)_2$ were used with LiHMDS (80 equiv), the reaction became very slow.

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