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Total Synthesis of FK-506. Part 1: Construction of the C16-C34 Fragment† [1]

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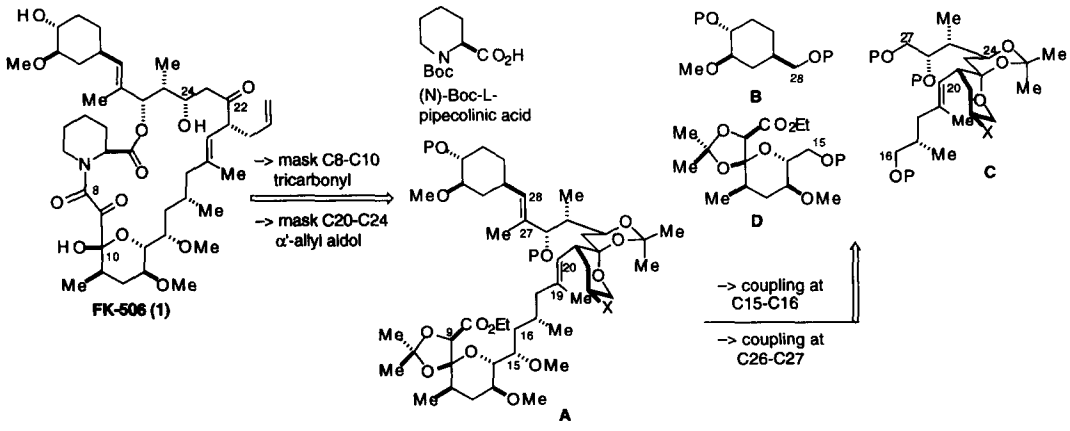
Abstract. *The C23-C27 1,3-diol was constructed via either Brown's crotylation – osmylation or regio- and stereoselective opening of an 2,3-anhydro-β-ribofuranoside derived from D-xylofuranose. Lewis acid catalyzed epoxide opening with a protected lithiofurfural alcohol followed by oxidative spiroketalization established the C21-C24 spiroketal as a masked α'-allyl aldol. The C19-C20 tri-substituted olefin was synthesized via zirconium catalyzed carboalumination – in situ transmetalation with a higher order cuprate, followed by stereoselective conjugate addition to a spiroenone. The C27-C28 tri-substituted olefin was formed either via coupling of a methyl cuprate with an enoltriflate, mediated by sonication, or via direct coupling between the C17-aldehyde and the C28-vinyl magnesium bromide.* © 1997 Elsevier Science Ltd.

FK-506 (**1**) was isolated from the fermentation broth of *Streptomyces tsukubaensis* No. 9993 by Goto and coworkers. Both *in vitro* and *in vivo* assays with mice indicated that it strongly inhibits immune responses and that it is ca. 100 times more potent than cyclosporin A (CsA).[2] Chemical and biological studies

Scheme 1



† 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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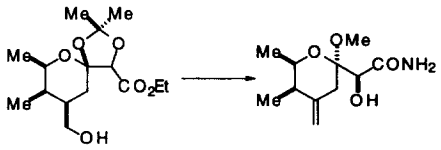
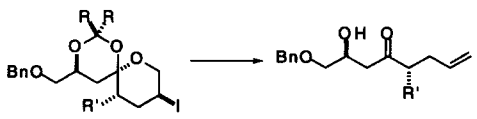
involving both CsA and FK-506 (and the structurally related metabolite Rapamycin) have enriched our understanding of cellular signaling mechanisms at the molecular level.[3] The structure of FK-506 was established via chemical, spectroscopic and X-ray analyses.[4] Embedded in this unique 21 membered macrolide are several distinct structural motifs (cf. Scheme 1). Foremost among these is the α,β-diketoamide group (C8-C10, FK-506 numbering), known as the tricarbonyl region, which was shown to have a remarkable propensity for C-C bond cleavage.[5] The β-hydroxy carbonyl grouping (C22-C24), coupled with a δ-(α'-allyl)-oxygen function, renders the molecule labile to degradation under both basic and acidic conditions.[6] FK-506 also contains two trisubstituted olefins, the construction of which in the context of natural product syntheses has proven nontrivial (vide infra).

Its unique structure and biological activity profile as well as its enormous potential in organ transplantation has made FK-506 an important synthetic target. To date many synthetic efforts have been recorded.[7,8,9] In this and the following paper we disclose our first successful synthesis of FK-506.

Synthetic Planning. Based on consideration of the structural features of FK-506 as discussed earlier, our synthetic approach has evolved around the following concepts: 1) A lower oxidation state at C9 (e.g. a C9-OH analog) would effectively render that center less electrophilic, therefore conferring manageable chemical stability on the tricarbonyl region. This hypothetical α-hydroxy β-ketoamide acetal motif bears remarkable resemblance to what is present in the natural product pederin, a vesicant component isolated from certain species of beetles. In their synthetic studies of pederin, the Meinwald group had employed an acetonide protected intermediate that was subsequently converted to the α-hydroxy β-ketoamide acetal (eq 1).[10] It was therefore decided to adopt this protocol in our retrosynthesis of the tricarbonyl unit (cf. **A**, Scheme 1). 2) In designing a proper surrogate for the sensitive aldol region (C22-C24), we noticed the presence of an allyl group at the α'-position (C21) in **1**. Ideally, a protecting group for this functionality incorporates both the allyl group and the β-hydroxy ketone. Removal of this protecting group should proceed in such a manner as to generate the desired aldol system at the correct oxidation state. Such a methodology was developed in these laboratories that delivers α'-allyl aldol systems via fragmentation of functionalized spiroketals (eq 2).[11] 3) The macrocycle of **1** was to be constructed via the amide bond formation in light of the discovery by the Merck group that lactonization resulted in epimerization at the C2 position of the pipecolinic acid moiety,[8(b)] and the difficulty encountered by Danishefsky's group in an attempted macrolactonization.[9(a)] Thus, on the basis of the



(1)



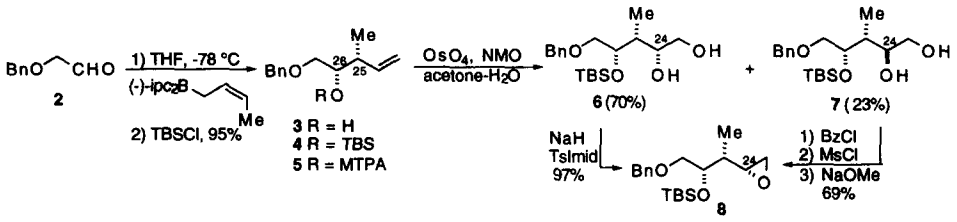
(2)

above analysis, **A** was formulated as the key intermediate in our synthesis. Further bond dissections at C15-C16 and C27-C28 defined the synthetic subunits **B**, **C**, and **D** (Scheme 1). The synthesis and subsequent assembly of **B** and **C** leading to the C16-C34 backbone of **1** are described in this paper. Further advancement to the key intermediate **A** and the eventual completion of the total synthesis will be discussed in the subsequent article.

Synthesis of the C16-C27 Fragment. Perusal of this segment (cf. **C**, Scheme 1) reveals three distinct structural domains. Namely the linker domain (C16-C20), the spiroketal domain (C21-C24), and the '1,3-diol' domain (C23-C27). It was envisioned that the 1,3-diol region would be constructed first, followed by sequential additions of the spiroketal and the linker synthons.

Our original approach to the C23-C27 diol was to use an enantioselective crotylation to establish the absolute stereochemistry at C25 and C26 (Scheme 2). Thus, benzyloxy acetaldehyde **2**[12] was treated at -78 °C with Brown's (*Z*)-crotyl diisopinocampheyl borane[13] to give the homoallylic alcohol **3**, which was inseparable from the derived chiral auxiliary isopinocampheol. Direct silylation with TBSCl led to an easily separable mixture of silyl ethers from which the product **4** was isolated in 70% yield. The optical purity of **4** was assessed using Mosher's technology in the following manner. Desilylation (TBAF) followed by Mosher ester formation (MTPACl) provided **5**.[14] The 470 MHz ^{19}F NMR spectrum of the crude product revealed a diastereomer ratio of ~ 20:1, corresponding to ≥ 90% ee for the crotylation product.

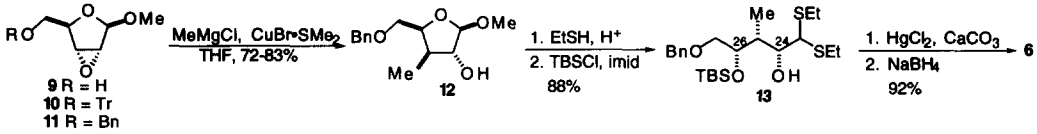
Scheme 2



In order to introduce the C24 asymmetric center dihydroxylation of the olefin bond in **4** was examined. The best result was obtained with the OsO_4/NMO system,[15] affording diols **6** and **7** with a ratio of 3:1. The major isomer was assigned the C24-(*R*) stereochemistry by analogy to previous results.[16] The low stereoselectivity for the dihydroxylation was partly compensated by the fact that both isomers were separately converted to the desired C24-(*R*)-epoxide **8**. However, chromatographic separation of diols **6** and **7** proved tedious and, on large scales (≥ 10 g), even formidable. We also briefly explored the possibility of a directed epoxidation of the homoallylic alcohol derivatives **3** and **4**. When **4** was subjected to the $VO(acac)_2$-TBHP system, a 1:1 mixture of epoxides were obtained. Under similar conditions, the alcohol **3** was converted to an intractable mixture.[17], Attempts to utilize the C26-OH in **3** in applying either the iodo

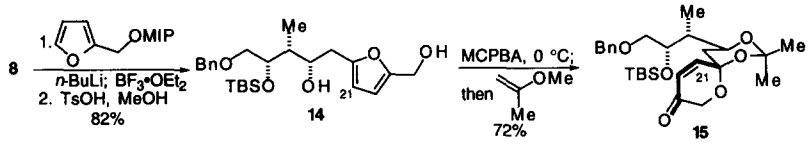
lactonization or the oxidative cyclization strategy (e.g. via its phosphates) proved fruitless.[18] In view of these disappointing results, a different synthetic route was designed that would allow for the practical preparation of the diol **6** in a highly stereoselective fashion.[19]

Scheme 3



The new approach was based on the results of Jenkin and Wilton that MeMgCl reacts with 2,3-anhydro-β-ribofuranoside **10** regio- and stereo- selectively at the 3-position (ether/reflux, 140 h, 57% yield, Scheme 3).[20] Given the identical stereochemical relationship between **6** and **12**, it was of interest for us to apply this method to the corresponding benzyl ether **11**,[21] which was readily prepared in 89-100% yield from alcohol **9** under modified conditions.[22] In line with the literature report, the reaction between MeMgCl and epoxide **11** was sluggish and low yielding. It was eventually found that in the presence of $CuBr•SMe_2$,[23] the reaction proceeded smoothly at room temperature in THF to afford the desired alcohol **12** in 72-83% yield.[24] Thiol acetal formation (EtSH, concd HCl)[25] followed by selective silylation of C26-OH provided **13** in 88% overall yield. Next, the dithioacetal was cleaved under carefully controlled conditions ($HgCl_2$, $CaCO_3$, aq CH_3CN)[26] and the resulting unstable aldehyde was immediately reduced to afford the diol **6** in 92% combined yield. Thus, starting from the readily available D-xylofuranose, the C23-C27 diol region was obtained in multi-gram quantity. Direct epoxide formation was accomplished by using Fraser-Reid's condition (Tosylimidazole, NaH) to give **8** (cf. Scheme 2) in 97% yield.[27] At this juncture, introduction of the spiroketal domain via the epoxide opening at C23 was explored.

Scheme 4

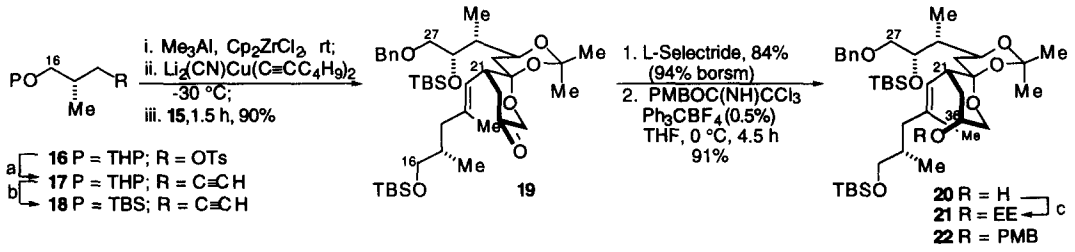


Based on previously developed methodology, the epoxide **8** was treated with the 1-methoxyisopropyl (MIP) protected lithio furfuryl alcohol in the presence of $BF_3•OEt_2$ catalyst (Scheme 4).[28] The resulting alcohol was surprisingly stable, more so than the deprotected diol, towards weak acids (e.g., PPTs, NH_4Cl) despite the labile nature of the MIP protecting group. As a result, crude bulk material was stored at this stage.

After cleaving the MIP group with a catalytic amount of TsOH in MeOH, the diol **14** was isolated in 82% yield. The crucial spiroketalization was effected using DeShong's methodology.[29] Thus, furan **14** was treated with 1.2 equivalents of MCPBA followed by in situ trapping of the enedione-diol-acetal with 2-methoxy propene in the presence of HCl to give 77% of a 15:1 mixture of spiroenones. The major anomer was assigned as **15** based upon steric and stereoelectronic considerations.[30] Although the formation of this inseparable mixture was of some concern at the time, the two were easily separated at a later stage in the synthesis.

The presence of an enone function in **15** offered the immediate opportunity for the introduction of the linker domain (C16-C20) at C21. Toward this end alkyne **18** (Scheme 5) was prepared in 80% yield from the known precursors **16**[31] and **17**,[32] under modified conditions. Subsequent Negishi carboalumination (Me_3Al, Cp_2ZrCl_2),[33] in situ transmetalation with a mixed higher order cuprate,[34] and conjugate addition to enone **15** afforded, in one pot, the complete C16-C27 skeleton (**19**) in excellent yield (90%). Thus the stereochemistry of both C21[35] and the C19-C20 trisubstituted olefin[36] was secured in the desired fashion during this operation. Subsequent reduction of the C36 carbonyl with L-Selectride[37] occurred exclusively from the equatorial face, leading to the alcohol **20** in 84% yield in addition to 10% of recovered starting material. A minor isomer created at C22 during the spiroketalization reaction (cf. Scheme 4), having lower Rf on TLC, was easily separated in this step.

Scheme 5

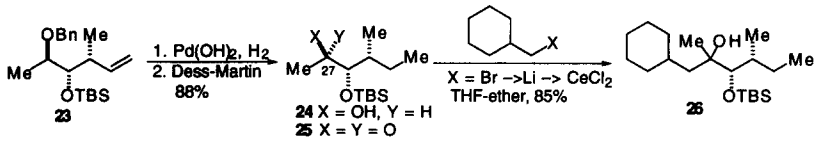


(a) HC≡CLi•eda, DMSO, 10-15 °C, 90%. (b) (i) TsOH, MeOH; (ii) TBSOTf, Et_3N, 80%. (c) Ethyl vinyl ether, TsOH, 100%

At this stage, the issue of selecting a protecting group for the C36-OH emerged. Our synthetic plan dictates that this group must (1) sustain various reaction conditions on route to the end of the synthesis (notably organometallic coupling, catalytic hydrogenation, both acidic and basic desilylations, and ester hydrolysis in strongly basic media at high temperature); (2) be removable under conditions amenable to the spiroketal, the silyl (TBS and BDPS) and the macrolactone functions. Several protecting groups were evaluated, including the methoxyisopropyl (MIP) –unstable during the removal of the C27-benzyl group, the MEM –removal of which resulted in destruction of the spiroketal function, and the 1-ethoxyethyl (EE). The EE group, while cleavable under mildly acidic conditions, has the disadvantage of generating a

diastereoisomeric mixture of products upon alcohol protection. Nevertheless the ethoxyethyl ether **21** had the desired stability, and therefore, was used in exploratory studies despite the complicated ^{1}H and ^{13}C NMR spectra associated with it (vide infra). Further experimentation eventually led us to the choice of *p*-methoxy benzyl (PMB) ether to protect the C36-OH. Due to the sterically hindered nature of the axial C36-OH and the diverse functionality within the molecule (**20**), realization of a suitable method for the formation of the desired PMB ether demanded much effort. For example, standard alkylation using PMBX (X = Cl, Br)[38] under various conditions provided at best irreproducible yields of the product, especially when the reaction was carried out on larger (≥ 1 mmol) scales. Acid catalyzed (TfOH or BF_3•ether) benzylation with *p*-methoxybenzyl trichloroacetimidate resulted in extensive destruction of the spiroketal function.[39] Fortunately it was found that trityl tetrafluoroborate (0.5% mol) brought about the desired reaction affording **22** in 91% yield,[40] provided that low temperature and minimum reaction time were maintained.[41] At this juncture, both termini of the spiroketal **22** are functionally suitable for further homologations. The relatively inert nature of the cyclohexyl motif strongly suggested that the C27-C34 subunit be installed prior to the masked tricarbonyl-containing subunit. Two successful approaches to the fusion of the cyclohexyl fragment are addressed below.

Scheme 6



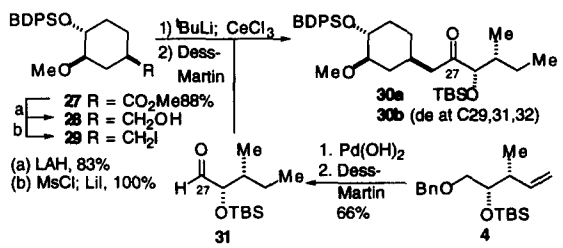
Coupling of a Cyclohexyl Methyl Anion with C27-Aldehyde. It was envisioned earlier that the C27-C28 olefin bond could be accessible through addition of a C28-anion to a C27-ketone followed by dehydration. As a model system, ketone **25** (Scheme 6) was prepared from the previously synthesized olefin **23**[16] via hydrogenolysis (to **24**) followed by Dess-Martin periodinane[42] oxidation. The ketone **25** was treated at -78 °C with several equivalents of cyclohexyl methyl cerium, which was generated by lithium-halogen exchange[43] followed by transmetalation[44] from cyclohexyl methyl bromide. An instantaneous reaction occurred to produce the addition product **26** in 85% yield. Other organometallics such as cyclohexyl methyl lithium and magnesium bromide were also successful in the addition reactions with ketone **25**.

With the initial success of the model studies, these reaction conditions were extended to the substituted cyclohexane **29**, which was prepared from the known ester **27** (cf. Scheme 7).[45] Surprisingly the positive results obtained with the unsubstituted cyclohexane were not realized with this substrate. Analysis of the reaction products indicated that the iodide had undergone lithium-halogen exchange quantitatively, but the ketone **25** was recovered unchanged. It was initially believed that quenching of the anion had occurred via

proton abstraction either intramolecularly, or from the solvent. This was found not to be the case however as the corresponding cerium reagent underwent clean addition to benzaldehyde under identical conditions. Subsequently many other organometallic derivatives of the iodide **29** were prepared (e.g. Li, Ce, Mg, Zr), but were found to be unreactive toward ketone **25** under a variety of conditions.[46]

These experiments indicate that inherent structural qualities of both the nucleophilic and electrophilic components of the reaction contribute to the failure of the addition. The oxygenated cyclohexane ring system may be involved in the formation of aggregates, thus reducing its reactivity as compared to the unsubstituted cyclohexane ring. However, addition of cosolvents to the reaction mixtures did not alter the outcome. The low reactivity of iodide **29** as compared with cyclohexyl methyl bromide was further exemplified by the sluggish rate at which iodide **29** reacted with elemental magnesium. Typically, formation of the Grignard reagent required sonication of the reaction mixture for several hours in order to effect complete metalation. Additionally, the negative results using ketone **25** suggested that a more reactive functionality was needed when used in conjunction with the substituted cyclohexane ring.

Scheme 7



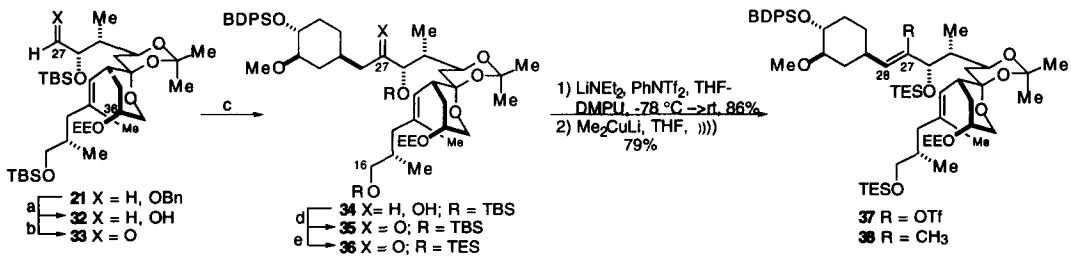
After the disappointing results from the model system, it was decided to attempt the C27-C28 bond forming reaction on a more activated C27 aldehyde (Scheme 7). Towards this end, olefin **4** was subjected to sequential hydrogenolysis–oxidation, leading to the saturated aldehyde **31** in good yield. This aldehyde was found to be an exceptional substrate for the addition of the racemic organocerium derived from the iodide **29**. The reaction occurred instantaneously at -78 °C and afforded the desired mixture of alcohols, which were subsequently oxidized to ketones **30a** and **30b** for spectral analysis.

In light of these superior results, it was felt that the chances for extending this methodology to the fully elaborated C27 aldehyde **33** (Scheme 8) were excellent. However, removal of the benzyl group in **21** presented a delicate problem. In model systems it was discovered that dissolving metal reductions such as Li/NH_3 resulted in migration of the silyl protective group from the C26 alcohol to the C27 alcohol. A catalytic hydrogenation procedure that would retain the integrity of the C19-C20 double bond was therefore explored for the reductive removal of the benzyl group. For this purpose, the procedure of Yonemitsu[47] was followed. Hydrogenation of the benzyl ether **21** in the presence of W-2 Raney nickel afforded a more polar product as judged from TLC. Analysis of the product (**32**), which was isolated in 97% yield, indicated that the desired benzyl reduction had occurred and that the double bond had remained intact. This selective deprotection followed by oxidation of the alcohol afforded the desired aldehyde **33**.

The first organometallic species to be explored was the organolithium derived from **29**. Addition of a -78 °C solution of the nucleophile to aldehyde **33** produced a mixture of the desired adduct **34**, along with several unidentifiable by-products. When the reaction temperature was lowered to -100 °C, a 72% yield (96% based on recovered **33**) of alcohol **34** was obtained. The aldehyde also underwent successful additions with the corresponding organocerium and organomagnesium reagents, but required additional equivalents of the nucleophile. The diastereomeric alcohol products were, as a rule, directly oxidized to ketone **35** to aid spectral analysis.

The conversion of ketone **35** to the olefin **38** was the final transformation needed for completion of the right side of FK-506. Concurrent work[8(d)] in this laboratory had shown that once the C27-C28 olefin was introduced, deprotection of the C26-TBS protecting group was impossible. It was therefore decided to replace the C26-TBS with the more labile triethylsilyl (TES) protecting group at this point, which could be removed under the Merck conditions.[8(b)] Thus ketone **35** was subjected to various acidic hydrolysis conditions. However, cleavage of the silyl groups was complicated by competitive deprotection of the ethoxyethyl ether. Eventually a procedure involving TBAF in THF along with 4Å molecular sieves as a drying agent was employed for convenient cleavage of both C16- and C26-TBS protecting groups. After reprotection of the resultant diol as the TES ether (**36**) the stage was set for the introduction of the C27-vinyl methyl substituent.

Scheme 8



(a) W-2 Raney-Ni, H_2, EtOH, 97%. (b) Dess-Martin, 83%. (c) **29**, ^{t}BuLi, -100 °C, 72% (+ 24% **33**). (d) Dess-Martin, 82%. (e) i. TBAF, 4Å MS; ii. TES, Imid, 77%

The most meritorious approach for the introduction of the desired methyl group appeared to be that of McMurry, which proceeded by the coupling of an organocopper with an enol triflate.[48] Attempted formation of the C27-enol triflate under standard conditions by deprotonation of ketone **36** with LDA was found to be unsuccessful. A more acceptable procedure was developed using lithium diethyl amide as the base. Treatment of the ketone with an excess of this reagent (20 equiv) followed by addition of DMPU and then N-phenyltriflimide provided enol triflate **37** in excellent yield. Although ^{13}C NMR spectrum of the product was

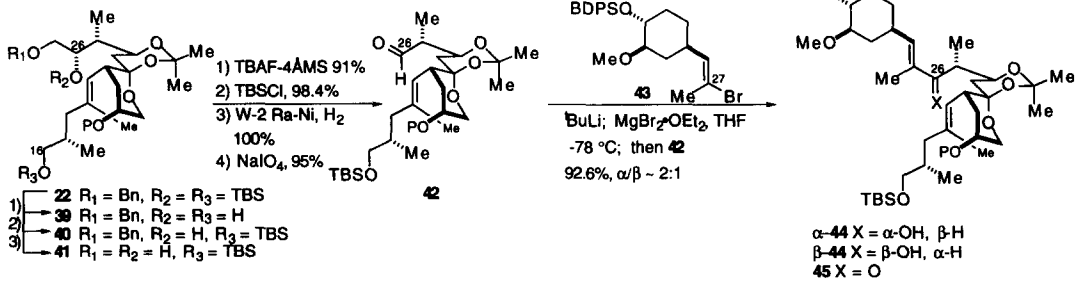
complicated due to the presence of the EE protecting group, it was clear that only one geometrical enol triflate had been formed in the reaction. This was confirmed by analysis of the 470 MHz ^{19}F NMR spectrum which showed only two resonances of equal heights. The product was assigned as the (*Z*)-enol triflate based on the proposed rationale for the stereoselectivities observed in ketone and ester enolizations.[49]

The organocuprate coupling reaction, although well precedented in a similar system,[50] did not proceed as expected. Reaction of Me_2CuLi, generated from various sources of copper salts,[51] with enol triflate **37** did not occur to any appreciable extent. Furthermore, the use of higher order organocuprates resulted in recovery of ketone **36**. After much experimentation it was found that sonication[52] of the cuprate reaction mixture effected a clean conversion of enol triflate **37** to olefin **38** in 79% yield. *It is remarkable that the reactive cuprate reagent sustained this unconventional reaction condition (sonication for up to 8 h) which was essential to the success of this synthetic route.*

It soon became obvious to us that the crucial sonication during the methylation had posed a severe limitation on our ability to carry out large scale couplings. In view of the non-convergent nature of our synthetic design, a practical method for the C27-C28 olefin bond construction was desired.

Coupling of a Cyclohexyl Vinyl Anion with a C26 Aldehyde. The new approach was based on the fact that both vinyl bromide **43**[53] and PMB-ether **22** were accessible in large quantities (Scheme 9). It is conceivable that coupling between a C27 vinyl anion and a C26 aldehyde would constitute a rapid construction of the entire C16-C34 skeleton. Although adopting this methodology at this stage of our synthesis would necessitate the annihilation of the C26 chiral center, we were nevertheless attracted by its convergent nature. In this regard, the TBS groups of the PMB ether **22** were removed using TBAF – 4Å molecular sieves to afford the diol **39** in 91% yield. Reprotection of the C16-OH (TBSCl, Et_3N, DMAP, THF, 55 °C, 98.4% of **40**) and chemoselective debenzylation at the C27 hydroxy (W-2 Raney nickel, H_2, EtOH) afforded the vicinal diol **41** in quantitative yield. Cleavage of the diol with sodium periodate provided the requisite aldehyde **42** in 95% yield.

Scheme 9 (P=PMB)



The vinyl bromide **43** was lithiated (*t*-BuLi, -78 °C) followed by transmetalation to the vinyl Grignard ($MgBr_2 \cdot OEt_2$). Upon addition of the aldehyde **42**, a 2:1 mixture of adducts were isolated in 93% yield. The two isomers were easily separated by flash chromatography and the major product (α-**44**, 60% isolated yield) was shown to possess the desired α-C26-OH configuration.[54] The alcohols (either β- or mixture of α- and β-) were easily oxidized to enone **45** using the Dess-Martin periodinane in the hope that the C26-carbonyl group could be selectively reduced to the desired α-isomer. Unfortunately all attempts were met with disappointing results: the best α/β ratio ever achieved was about 1:1.[55] When vinyl bromide **43** was converted to either the corresponding lithium or cerium species, subsequent couplings with aldehyde **42** afforded inferior isomer ratios. Direct inversion of the β-C26-OH under Mitsunobu conditions was not successful, probably due to steric hindrance.[56] While an effective means by which the net optical yield of alcohol α-**44** would be improved seemed elusive at this point, the described route did provide large quantities of the desired C26-isomer for further elaboration.

In summary, we have successfully synthesized the C16-C34 fragment of the FK-506 backbone. The two trisubstituted olefin bonds were constructed stereospecifically via zirconium and copper based chemistry. A novel organocuprate-enoltriflate coupling mediated by sonication was developed for the vinyl methylation at C27. The α'-allyl aldol moiety was masked as a spiroketal with a strategic substitution on C36. The introduction of the masked tricarbonyl domain and the ultimate unravelling of the allyl aldol functionality in the context of total synthesis of FK-506 will be described in the following article.

Experimental Section

General. Combustion analyses were performed by Spang Microanalytical Laboratory (Star Rt. 142, Eagle Harbor, Michigan, 49951) or by QTI (Quantitative Technologies Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888) or, at the University of Virginia's Chemistry Department. High resolution fast atom bombardment (FAB) mass spectral data were obtained on a VG 70VSE mass spectrometer by linear voltage scanning with resolution (*m/Dm*) of ca. 10,000 using the sodium adducts of polyethylene glycol (PEG) as reference peaks. Sample were dispersed in dithiothreitol-dithioerythritol (3:1) to which PEG-1000, and NaCl had been added. Data were acquired and processed on a VG OPUS workstation. Infrared spectra were obtained with either a Perkin-Elmer model 1310 or a Nicolet model DX-FTIR. Polystyrene was used as the reference standard. NMR spectra were recorded on a General Electric QE-300, a GN-300, or an Omega 500 spectrometer using the solvent indicated. Chemical shifts are reported in ppm (δ), relative to chloroform at 7.26 for ^1H and 77.0 for ^{13}C, or to other indicated solvents. Data are reported as follows: chemical shift, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m =

multiplet and b = broad), coupling constants (Hertz) and integration. Melting points are reported uncorrected. Optical rotations were measured at room temperature in a 1-dm or in a 0.1-dm cell on a Jasco DIP-360 polarimeter or a Perkin Elmer 243B Polarimeter. All silica gel used for flash column chromatography[57] was E. Merck silica gel 60 (70-230 mesh ASTM).

Unless otherwise noted, chemicals were obtained from commercial suppliers and used without further purification. Dry solvents were distilled shortly before use from an appropriate drying agent under nitrogen. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. DMF was distilled from P_2O_5. *n*-Hexane, toluene, benzene, CH_2Cl_2, 2,6-lutidine, $(i\text{-Pr})_2NH$, Et_2NH, Et_3N, Hexamethyldisilazane (HMDS), DME, and hexamethylphosphoramide (HMPA) were distilled from CaH_2 prior to use. Anhydrous methanol was distilled from $Mg(OMe)_2$. Molecular sieves were oven-dried (130 °C). Alkyllithiums were titrated by the method of Watson and Eastham.[58] Lithium amides were titrated according to the method of Ireland and Meissner.[59] All glassware, syringes, and needles were dried at 130 °C for at least 12 hours and cooled under argon prior to use. Reactions were normally carried out under a nitrogen or argon atmosphere. HPLC analysis was carried out using a Waters model 510 pump and a model 990 photodiode array detector. Preparative separations were achieved using an Alltech Econosil Silica 10mm column with dimensions of 250 x 22.5 mm. Gas chromatography was performed on a HP 5890A gas chromatography using a 30 m x 0.32 mm Alltech Superox FA polyethylene glycol ester column.

(3*R*, 4*S*)-4-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3-methyl-5-phenylmethoxy-1-pentene (4). To a solution of potassium *t* -butoxide (22.4 g, 0.200 mol) in THF (100 mL) at -78 °C was added *cis* -2-butene (22.4 g, 0.400 mol), followed by a solution of *n* -butyl lithium (2.5 M in hexanes, 80 mL, 0.200 mol). The solution was allowed to warm to -45 °C for 15 min and then cooled to -78 °C whereupon a solution (-)-β-methoxy-diisopinocamphenylborane (63.3 g, 0.200 mol) in ether (225 mL) was added. The solution was stirred for 30 min and then borontrifluoride etherate (30.0 mL, 0.244 mol) was added, followed by a solution of benzyloxyacetaldehyde (20.0 g, 0.133 mol) in ether (200 mL). The reaction mixture was stirred at -78 °C for 3 h and then NaOH (2N, 200mL) and H_2O_2 (30%, 50 mL) were added. The biphasic mixture was heated to reflux for 3 h and then allowed to cool to room temperature. The layers were separated and the aqueous layer was extracted with ether (2 x 200 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 15:85) afforded the product and isopinocamphenol.

The crude product was dissolved in DMF (400 mL) followed by the addition of imidazole (36.22 g, 0.532 mol) and TBSCl (30.06 g, 0.200 mol). Subsequently DMAP (0.5 g) was added and the mixture was stirred for 12 h before the addition of water (500 mL). The mixture was extracted with hexane (5 x 200 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on

silica gel (ethyl acetate-cyclohexane 0:100-5:95) afforded the olefin (29.9 g, 70%): $[\alpha]_D$ +3.5° (*c* 0.6, $CHCl_3$); IR (neat) 3050, 2940, 2920, 2840, 1660, 1400, 1355, 1245, 1095, 1020, 830, 720, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.23 (m, 5 H), 5.91-5.80 (m, 1 H), 5.07-4.98 (m, 2 H), 4.56-4.48 (m, 2 H) 3.77 (q, 1 H, *J* = 5 Hz), 3.48 (dd, 1 H, *J* = 5, 10 Hz), 3.39 (dd, 1 H, *J* = 6,10 Hz), 2.48-2.38 (m, 1 H), 1.02 (d, 3 H, *J* = 7 Hz), 0.91 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.1, 138.9, 128.7, 128.1, 127.9, 114.5, 75.3, 73.7, 73.6, 41.5, 26.3, 18.7, 14.7, -3.7, -4.3. Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.24; H, 10.22.

(2*S*, 3*R*)-3-methyl-1-phenylmethoxy-4-penten-2-ol (3). To a solution of silyl ether **4** (1.02 g, 3.18 mmol) in THF (20 mL) was added a solution of TBAF (1.0 M in THF, 9.5 mL, 9.5 mmol), and the solution was stirred for 12 h at ambient temperature. Water (50 mL) was added and the mixture was extracted with ether (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 10:90) afforded the alcohol (0.58 g, 88%): $[\alpha]_D$ +21.6° (*c* 0.7, $CHCl_3$); IR (neat) 3430, 3040, 3010, 2950, 2840, 1650, 1485, 1440, 1355, 1090, 905, 735, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.12 (m, 5 H), 5.80-5.69 (m, 1 H), 5.09-5.00 (m, 2 H), 4.54 (s, 2 H), 3.67-3.62 (m, 1 H), 3.56 (dd, 1 H, *J* = 3, 9 Hz), 3.34 (dd, 1 H, *J* = 8, 9 Hz), 2.47 (bs, 1 H), 2.40-2.29 (m, 1 H), 1.09 (d, 3 H, *J* = 6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.8, 138.5, 128.9, 128.2, 115.5, 73.9, 73.8, 73.2, 41.6, 16.1. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.75; H, 8.88.

(α*S*)-α-methoxy-α-trifluoromethyl-benzeneacetic acid, (*2S, 3R*)-3-methyl-1-phenylmethoxy-4-penten-2-ol ester (5). To a solution of alcohol **3** (0.098 g, 0.475 mmol) in pyridine (3 mL) was added a trace of DMAP followed by the Mosher-acid chloride (0.57 g, 2.26 mmol), and the mixture was stirred 36 h at room temperature. Water (1 mL) was added followed by the addition of ether (50 mL). The mixture was washed with 2 N HCl (4 x 30 mL), and saturated aqueous $NaHCO_3$ (2 x 30 mL). The solvent was evaporated to afford a crude product which was pure by TLC analysis: ^{19}F NMR (470 MHz, $CDCl_3$) δ 22.18, 21.77 (ratio-19.6:1).

(2*R*, 3*R*, 4*S*)-4-[(1,1-Dimethylethyl)dimethylsilyl-oxy]-5-phenylmethoxy-3-methylpentan-1,2-diol (6) and **(2*S*, 3*R*, 4S)-4-[(1,1-Dimethylethyl)dimethylsilyl-oxy]-5-phenylmethoxy-3-methyl-pentan-1,2-diol (7)**. To a solution of the olefin **4** (1.99 g, 6.21 mmol) in acetone:water (10:1, 20 mL) was added N-methylmorpholine-N-oxide (1.09 g, 9.31 mmol) followed by a 0.2 M solution of osmium tetroxide (0.6 mL, 0.12 mmol) in benzene. The suspension was stirred for 16 h at room temperature and then the solvent was evaporated. The residue was partitioned between 75 mL each of CH_2Cl_2 and brine, and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were

dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 20:80) afforded the major isomer **6** (1.34 g, 61%), a mixture of isomers (0.58 g, 26%), and the minor isomer **7** (0.14 g, 6%).

(**6**): vide infra.

(**7**): $[\alpha]_D$ +3.6° (*c* 0.8, $CHCl_3$); IR (neat) 3350, 2910, 2820, 1725, 1710, 1690, 1675, 1445, 1420, 1395, 950, 730, 620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5 H), 4.55 (d, 1 H, *J* = 12 Hz), 4.48 (d, 1 H, *J* = 12 Hz), 4.13-4.09 (m, 1 H), 4.04 (d, 1 H, *J* = 3 Hz), 3.70-3.42 (m, 4 H), 2.64 (bs, 1 H), 1.96-1.88 (m, 1 H), 0.89 (s, 9 H), 0.84 (d, 3 H, *J* = 7 Hz), 0.11 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.5, 128.8, 128.1, 75.0, 74.3, 73.8, 72.2, 65.5, 33.0, 26.2, 18.5, 12.6, -4.0, -4.7. Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.33; H, 9.66.

(1*R*, 1'*R*, 2'*S*)-1-[1-methyl-2-[(*tert*-butyldimethylsilyl)-oxy]-3-phenylmethoxy-propyl]-oxirane (8) From 7: To a solution of the diol **7** (0.488 g, 1.376 mmol) in pyridine (5 mL) at 0 °C was added DMAP (0.01 g) followed by benzoyl chloride (0.192 mL, 1.65 mmol). The reaction was stirred at 0 °C for 1 h and was quenched by the addition of water (0.5 mL). The mixture was poured into cold HCl (2.0 N, 50 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried (K_2CO_3) and evaporated to afford the benzoate which was dissolved in 5 mL of pyridine.

Subsequently, methanesulfonyl chloride (0.213 mL, 2.752 mmol) and DMAP (0.01G) were added. The reaction mixture was stirred for 12 h at room temperature and was quenched by the addition of water (0.5 mL). The mixture was poured into HCl (2.0 N, 50 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried (K_2CO_3) and evaporated to afford the diester which was dissolved in 10 mL of anhydrous methanol.

The solution was cooled to 0 °C and was added a methanolic solution of sodium methoxide (5.4 M, 2.6 mL, 14.0 mmol). The reaction was stirred for 30 min at 0 °C and then quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic phases were dried (K_2CO_3) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 4:96) afforded a mixture of the product and methyl benzoate. Kugelrohr distillation (120 °C 0.5 mmHg) of the mixture afforded the pure epoxide **8** (0.321 g, 69%).

Methyl 3-deoxyl-3-*C*-methyl-5-*O*-benzyl-β-D-xylofuranoside (12). In a flame-dried 1-L, three-necked round-bottomed flask fitted with an addition funnel and a magnetic stirring bar, methyl 2,3-anhydro-5-*O*-benzyl-β-D-ribofuranoside (**11**, 21.5 g, 91.0 mmol) and $CuBr{\bullet}SMe_2$ (75.0 g, 364 mmol) were added. The flask was charged with anhydrous THF (300 mL) under argon and cooled with an ice bath. A 3 M solution of MeMgCl in THF (243 mL, 729 mmol) was transferred to the addition funnel and was added dropwise to the

vigorously stirred reaction mixture. During the addition the initially milky-white color changed to golden yellow, orange, blue and finally to green. The cooling bath was removed and the end of the addition and the resulting dirty gray mixture was stirred at room temperature for 56 h. The reaction contents were slowly poured into an ice-NH_4Cl (120 g) sludge followed by the addition of ethyl acetate. After being stirred for 1 h, the mixture was filtered through a Celite pad and the residue was rinsed with ethyl acetate several times. The aqueous phase was separated and extracted three times. The combined organic phase was washed with saturated NH_4Cl solution, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica (10-30% ethyl acetate in hexanes) afforded the pure product as a colorless oil (19.2 g, 83%): $[\alpha]_D$ -36.3° (*c* 1.30, $CHCl_3$); IR (neat) 3400 (OH), 1690, 1570, 1345, 1200 (ketal), 1110, 1050, 1000, 835, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 4.78 (d, 1 H, *J* = 1.5 Hz), 4.58 (d, 1 H, *J* = 12 Hz), 4.54 (d, 1 H, *J* = 12 Hz), 4.45 (q, 1 H, *J* = 6.6 Hz), 3.88 (b, 1 H), 3.54 (d, 2 H, *J* = 6.0 Hz), 3.37 (s, 3 H), 2.69 (b, 1 H), 2.26 (m, 1 H), 1.03 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.1, 128.2, 127.6, 127.5, 110.3, 82.4, 80.3, 73.3, 70.5, 55.4, 42.1, 11.6. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.46; H, 8.10.

(2*R*, 3*S*, 4*S*)-1,1-Bis(ethylthio)-3-methyl-4-[(*tert*-butyldimethylsilyl)-oxy]-5-phenylmethoxy-pentane-2-ol (13). *In a well ventilated hood*, methyl 3-deoxy-3-C-methyl-5-*O*-benzyl-β-D-xylofuranoside (**12**, 61.0 g, 242 mmol) and ethanethiol (145 mL) were placed in a 500-mL round-bottomed flask containing a magnetic stirring bar. To this was added a solution of HCl (concd, 15 mL) which induced an exothermic reaction. The solution was stirred at room temperature for 1 h before powdered $NaHCO_3$ was slowly added until the gas evolution subsided. After the excess ethanethiol was condensed into a cold trap (-78 °C) under water-aspirator vacuum, CH_2Cl_2 was added and the mixture was dried with $MgSO_4$. Filtration and concentration yielded the crude dithioacetal as a yellow oil (82.0 g, 98%). It was dissolved in anhydrous DMF (150 g) and then treated sequentially with imidazole (35.0 g, 515 mmol), DMAP (catalytic amount) and TBSCl (39.0 g, 258 mmol). The mixture was stirred at room temperature for 14 h and was then poured into a mixture of ice water (1.5 L) and petroleum ether (500 mL). The aqueous layer was separated and extracted with petroleum ether (5 x 150 mL), the combined organic phase was washed once with H_2O, saturated NaCl solution, and dried with Na_2SO_4. Filtration, concentration and chromatography on silica (0-7% ethyl acetate in petroleum ether) yielded the alcohol as an oil (94.0 g, 88% in two steps): $[\alpha]_D$ +30.6° (*c* 1.3, $CHCl_3$); IR (neat) 3460, 3020, 2950, 2920, 2880, 2840, 1500, 1380, 1370, 1300, 1250, 1200, 1100, 1070, 1020, 1000, 970, 830, 805, 770, 730, 690, 615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5 H), 4.53, (bs, 2 H), 3.90 (q, 1 H, *J* = 4.8 Hz), 3.84 (s, 2 H), 3.54 (d, 2 H, *J* = 4.8 Hz), 3.13 (s, 1 H), 2.66 (m, 4 H), 2.37 (m, 1 H), 1.26 (m, 6 H), 0.94 (d, 3 H, *J* = 7.2 Hz), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$)

δ 138.2, 128.2, 127.6, 127.4, 74.7, 73.3, 72.7, 71.3, 56.9, 39.0, 25.9, 24.6, 23.6, 18.1, 14.5, 14.3, 8.3, -4.2, -4.9. Anal. Calcd for $C_{23}H_{42}O_3S_2Si$: C, 60.21; H, 9.23; S, 13.98. Found: C, 60.16; H, 9.23; S, 13.96.

(2*R*, 3*R*, 4*S*)-4-[(1,1-Dimethylethyl)dimethylsilyl-oxy]-5-phenylmethoxy-3-methyl-pentane-1,2-diol (6). In a 5-L, three-necked rounded-bottomed flask equipped with a mechanical stirrer $HgCl_2$ (272 g, 1.00 mol), $CaCO_3$ (121 g, 1.21 mol), CH_3CN (500 mL) and H_2O (350 mL) were mixed and flushed with nitrogen. An argon flushed solution of the dithioacetal **13** (183 g, 0.399 mol) in CH_3CN (200 mL) was added to the flask through a glass funnel and the residue was rinsed with additional solvent (3 x 100 mL). The endothermic reaction was allowed to proceed with vigorous stirring at room temperature for 2 h when TLC monitoring indicated that the starting material was still present. CH_3CN and H_2O (100 mL of each) were added and the mixture was stirred for an additional 1.5 h before an aqueous solution of $Na_2S{\bullet}9H_2O$ (51.0 g, 0.212 mol) in water (400 mL) was slowly added. The resulting brown mixture was filtered through a Celite pad and the solid residue was rinsed with ethyl acetate until no more product could be detected from the filtrate by TLC. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic phase was concentrated and the resulting oily residue was mixed with THF (850 mL) and H_2O (120 mL). A magnetic stirring bar was placed in the solution which was then flushed with nitrogen and cooled with an ice bath. Solid $NaBH_4$ (31.0 g, 0.819 mol) was added to the solution in small batches. The mixture was then stirred at room temperature for 3.5 h. After the addition of MeOH (50 mL) the solvents were evaporated. The residue was treated with MeOH (500 mL), stirred for 20 min and then concentrated. This sequence was repeated with MeOH (200 mL), NH_4Cl (saturated, 150 mL) and finally with H_2O (150 mL). The residue was partitioned between ethyl acetate and diluted NH_4Cl solution. After separation and extraction of the aqueous layer (3 x), the organic phase was dried ($MgSO_4$), filtered and concentrated. Filter chromatography on a 2-L funnel (12 x 145 cm silica) starting with 8% ethyl acetate in petroleum ether afforded the diol (**6**) as an oil (130 g, 92% over two steps): $[\alpha]_D$ +3.5° (*c* 1.2, $CHCl_3$); IR (neat) 3430, 2910, 2820, 1725, 1705, 1690, 1685, 1495, 1470, 1245, 945, 835, 770, 620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5 H), 4.53 (s, 2 H), 3.95-3.84 (m, 2 H), 3.64-3.42 (m, 4 H), 3.35 (bs, 1 H), 1.84-1.75 (m, 1 H), 0.91 (d, 3 H, J = 7 Hz), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.1, 128.9, 128.2, 128.1, 74.9, 74.1, 72.7, 72.4, 65.9, 39.8, 26.3, 18.5, 9.5, -3.8, -4.6. Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.46; H, 9.72.

(1*R*, 1'*R*, 2'*S*)-1-[1-methyl-2-[(*tert*-butyldimethylsilyl)-oxy]-3-phenylmethoxy-propyl]-oxirane (8). In a 5-L three-necked round-bottomed flask equipped with a 1-L addition funnel and a magnetic stirring bar, NaH (95%, 28.0 g, 1.11 mol) and anhydrous THF (2000 mL) were mixed under argon. A solution of the diol **6** (130 g, 367 mmol) in THF (400 mL) was prepared in the addition funnel and was added dropwise to the flask cooled at 0 °C. The suspension was stirred for 20 min at 0 °C, before a solution of tosyl imidazole

(128.0 g, 576 mmol) in THF (400 mL) was slowly added in drops through the addition funnel, resulting in gas evolution. The mixture was stirred for 9 h at room temperature and was poured into a mixture of 1:1 saturated NaCl solution and ice (4 L). The mixture was extracted with ether (3 x) and the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-petroleum ether 10:90) afforded 104 g of the epoxide plus recovered starting material which, after resubmitted to the above reaction conditions, yielded an additional 16 g of product (total 120 g, 97%): $[\alpha]_D$ -5.4° (*c* 0.7, $CHCl_3$); IR (neat) 3010, 2940, 2910, 2840, 1445, 1350, 1245, 1070, 1020, 825, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5 H), 4.53 (d, 1 H, *J* = 12 Hz), 4.48 (d, 1 H, *J* = 12 Hz), 3.90 (dd, 1 H, *J* = 5, 9 Hz), 3.48-3.41 (m, 2 H), 2.93-2.90 (m, 1 H), 2.73 (dd, 1 H, *J* = 4, 5 Hz), 2.57 (dd, 1 H, *J* = 3, 5 Hz), 1.53-1.48 (m, 1 H), 1.03 (d, 3 H, *J* = 7 Hz), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.6, 128.8, 128.1, 73.8, 73.6, 72.9, 55.5, 47.2, 40.6, 26.3, 18.6, 11.7, -3.7, -4.5. Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H; 9.58. Found: C, 67.86; H, 9.53.

(α*S*, 1'*R*, 2'*S*)-α-[1-methyl-2-[(*tert*-butyldimethylsilyl)-oxy]-3-phenylmethoxy-propyl]-5-hydroxymethyl-2-furanethanol (14). To a solution of the MIP furfuryl ether (1.229 g, 7.220 mmol) in 20 mL of THF at -78 °C was added a solution of *n*-butyl lithium (2.5 M in hexanes, 2.9 mL, 7.2 mmol). The solution was allowed to warm to -30 °C for 20 min and then was cooled to -78 °C. A solution of the epoxide (**8**, 0.486 g, 1.444 mmol) in 5 mL of THF was added followed by the addition of borontrifluoride etherate (0.36 mL, 2.93 mmol). The reaction mixture was stirred at -78 °C for 30 min and then poured into 100 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were dried (K_2CO_3) and evaporated. Chromatography on silica gel (ethyl acetate-cyclohexane 10:90) afforded the MIP alcohol which was dissolved in a mixture of THF-H_2O (10:1, 11 mL).

Subsequently,pyridinium *p*-toluenesulfonate (0.10 g) was added and the solution was stirred for 3 h. Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (K_2CO_3) and evaporated to afford the diol **14** (0.501 g, 82%): $[\alpha]_D$ -7.3° (*c* 2.6, $CHCl_3$); IR (neat) 3340, 2920, 2900, 2830, 1540, 1440, 1355, 1235, 1075, 995, 820, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5 H), 6.17 (d, 1 H, *J* = 3 Hz), 6.02 (d, 1 H, *J* = 3 Hz), 4.54 (s, 2 H), 4.52 (s, 2 H), 4.08-4.19 (m, 1 H), 3.92 (dd, 1 H, *J* = 4, 9 Hz), 3.51 (dd, 1 H, *J* = 4, 10 Hz), 3.43 (dd, 1 H, *J* = 5,10 Hz), 3.14 (bs, 1 H), 2.84 (dd, 1 H, *J* = 8, 18 Hz), 2.74 (dd, 1 H, *J* = 6, 15 Hz), 1.83-1.74 (m, 1 H), 0.93 (d, 3 H, *J* = 7 Hz), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.0, 153.3, 138.2, 128.8, 128.2, 75.3, 74.0, 72.5, 71.3, 57.9, 41.0, 34.3, 26.3, 18.5, 7.9, -3.7, -4.5. Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.32; H, 8.81. Found: C, 66.49; H, 8.76.

(4*S*, 6*R*, 1'*R*, 2'*S*)-2,2-Dimethyl-4-[1-methyl-2-[(*tert*-butyldimethylsilyl)-oxy]-3-phenylmethoxy-propyl]-1,3,7-trioxa-spiroundec-10-en-9-one (15). To a solution of the furan **14** (0.213 g, 0.490 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added MCPBA (85%, 0.119 g, 0.588 mmol) and the reaction mixture was stirred for 1 h at 0 °C. Subsequently, 2-methoxypropene (4 mL) and concd. Hcl (0.02 mL) were added. The solution was stirred at 0 °C for 2 h and then 30 mL of NaOH (2 N) was added. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and then the combined organic phases were dried (K_2CO_3), and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 5:95) afforded the enone (0.185 g, 77%). On larger scale reactions starting from the oxirane (**8**, 35-104 g) through the sequence epoxide opening – MIP-deprotection (TsOH in *MeOH*) – oxidation – spiroketalization, overall yields of ≥50% were achieved: $[\alpha]_D$ +14.3° (*c* 1.4, $CHCl_3$); IR (neat) 2940, 2910, 2860, 2830, 1690, 1605, 1440, 1365, 1240, 1065, 940, 820, 765, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5 H), 6.64 (d, 1 H, *J* = 10 Hz), 6.05 (d, 1 H, *J* = 10 Hz), 4.50 (s, 2 H), 4.41 (d, 1 H, *J* = 17 Hz), 4.27-4.20 (m, 1 H), 4.05 (d, 1 H, *J* = 17 Hz), 3.94-3.89 (m, 1 H), 3.49-3.39 (m, 2 H), 1.86 (dd, 1 H, *J* = 3, 12 Hz), 1.77-1.65 (m, 2 H), 1.55 (s, 3 H), 1.36 (s, 3 H), 0.95 (d, 3 H, *J* = 7 Hz), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.8, 149.2, 138.7, 128.7, 128.1, 128.0, 127.4, 100.1, 93.7, 73.7, 73.3, 72.0, 66.6, 65.9, 41.9, 37.6, 31.1, 26.3, 23.6, 18.6, 9.6, -3.5, -4.5. Anal. Calcd for $C_{27}H_{42}O_6Si$: C, 66.09; H, 8.63. Found: C, 66.13; H, 8.93.

(4*S*)-4-methyl-5-[(*tert*-butyldimethylsilyl)-oxy]-pentyne (18). A solution of (2'*R*)-2-[2-methyl-3-[(*p*-toluenesufonyl)-oxy]-propoxy]tetrahydrapyran **16** (52.5 g, 160 mmol) in anhydrous DMSO (30 mL) was added dropwise through an addition funnel to a solution of lithium acetylide•eda complex (90%, 25.0 g, 244 mmol) in anhydrous DMSO (70 mL) cooled at 10 °C under argon. Efficient stirring was kept during the addition so as to maintain the reaction temperature between 10-15 °C. The funnel was rinsed with additional DMSO (15 mL) and the cooling bath was removed after 10 min. Ice water was slowly added after 2 h. The mixture was extracted with capacious amount of ether which was back extracted (3 x) with water. Evaporation and chromatography on silica (10% ethyl acetate in hexanes) afforded the pure THP protected alkyne **17** as a brown oil (26.0 g, 90%).

The alkyne thus obtained (66.0 g, 362 mmol) was dissolved in MeOH (1.5 L) containing a spatula tip of TsOH and the solution was stirred at 40-50 °C overnight.[60] The solvent was evaporated and the residue was partitioned between ether (1.4 L) and H_2O (0.5 L). The aqueous layer was separated and further extracted with ether. The combined ether solution was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. Flash filter chromatography of the residue on silica (5% ethyl acetate in hexanes) afforded ca. 48 g of the alcohol which was treated with anhydrous ether (1.5 L) and Et_3N (160 mL, 1.15 mol). The solution under argon was cooled with an ice bath, and was treated via cannula with TBSOTf, prepared from TBSCl (83.0 g, 533 mmol) and TfOH (47.0 mL, 533 mmol).[61] The mixture was stirred for 6 h at room

temperature and was then treated with ice water. The ether layer was separated and washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. Flash filter chromatography on silica (5% ethyl acetate in hexanes) afforded the pure silyl ether (61.4 g, 79.8%): Bp 60 °C (16 mmHg); $[\alpha]_D$ -15.5° (*c* 1.1, $CHCl_3$); IR (neat) 3300, 2960, 2920, 2860, 2110, 1465, 1385, 1255, 1095, 1030, 830, 780, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.61-3.44 (m, 2 H), 2.29 (ddd, 1 H, *J* = 3, 6, 17 Hz), 2.12 (ddd, 1 H, *J* = 3, 7, 17 Hz), 1.93 (dd, 1 H, *J* = 3, 3, Hz), 1.89-1.74 (m, 1 H), 0.97 (d, 3 H, *J* = 7 Hz), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 83.5, 69.5, 67.1, 35.6, 26.3, 22.5, 18.7, 16.3, -5.0. Anal. Calcd for $C_{12}H_{24}OSi$: C, 67.86; H, 11.39. Found: C, 67.65; H, 11.50.

[4*S*, 6*R*, 11*R*, 4'*S*, 1''*R*, 2''*S*, 1'*E*]-2,2-Dimethyl-11-[2,4-dimethyl-5-[(*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-[1-methyl-2-[*tert*-butyldimethylsilyl)oxy]-3-phenylmethoxy-propyl]-1,3,7-trioxaspiroundecan-9-one (19). To a solution of zirconocene dichloride (1.50 g, 5.12 mmol) in 35 mL of dichloroethane was added a 2 M solution of trimethylaluminum in toluene (26.8 mL, 53.6 mmol) followed by a solution of the alkyne **18** (1.62 g, 7.64 mmol) in dichloroethane (10 mL). The reaction mixture was stirred for 3 h at room temperature when ^1H NMR of an aliquot (quenched by D_2O) indicated the absence of the alkyne. The solvent and excess trimethylaluminum was condensed to a cold trap (-78 °C) under reduced pressure (0.2 mmHg) and the residue was dried under high vacuum for 5 h. Anhydrous ether (10 mL) was added and the supernatant was used for the next step.

A solution of 1-hexyne (1.80 mL, 15.7 mmol) in anhydrous THF (15 mL) at -30 °C was treated with a 2.5 M solution of *n*-BuLi (6.30 mL, 15.7 mmol) in hexane. This was then cannulated to a flask (-30 °C) containing flame-dried CuCN (0.690 g, 7.70 mmol), followed by THF rinsing (10 mL). The cooling bath was temporarily removed to allow the yellow mixture turn into a clear solution. The vinylalan solution prepared earlier was then cannulated to the cooled cuprate solution, the residue left being washed with ether (2 x 10 mL). The reaction mixture was stirred at -23 °C for 15 min, then a solution of the enone **15** (2.50 g, 5.10 mmol) in ether (10 mL) was added over 15 min. The reaction was stirred for 45 min at -23 °C and then a mixture of saturated aqueous NH_4Cl and concd NH_4OH (9:1, 100 mL) was added. The biphasic mixture was stirred for 1 h at room temperature and the layers were separated. The aqueous layer was extracted with ether (5 x 50 mL) and the combined organic phases was dried (K_2CO_3) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-hexanes 3.5:96.5) afforded the ketone (3.30 g, 90%) as an oil. On large-scale reactions employing 16.0–53.0 g of the enone, yields of the product ranged from 80 to 86%: $[\alpha]_D$ +21.4° (*c* 1.4, $CHCl_3$); IR (neat) 2930, 2900, 2820, 1715, 1445, 1360, 1240, 1190, 1070, 990, 820, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5 H), 5.10 (d, 1 H, *J* = 10 Hz), 4.57 (d, 1 H, *J* = 12 Hz), 4.47 (d, 1 H, *J* = 12 Hz), 4.20-4.11 (m, 2 H), 3.94-3.84 (m, 2 H), 3.48-3.39 (m, 2 H), 3.38 (d, 2 H, *J* = 6 Hz), 3.01 (dd, 1 H, *J* =

6, 16 Hz), 2.93-2.88 (m, 1 H), 2.26-2.11 (m, 2 H), 1.82-1.50 (m, 5 H), 1.59 (s, 3 H), 1.53 (s, 3 H), 1.38 (s, 3 H), 0.93 (d, 3 H, J = 7 Hz), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.76 (d, 3 H, J = 7 Hz), 0.03 (s, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.9, 138.7, 137.8, 99.7, 97.5, 73.7, 73.6, 72.0, 68.9, 68.7, 66.6, 45.3, 44.2, 41.9, 41.5, 35.8, 34.3, 31.3, 26.4, 26.3, 23.8, 18.8, 18.6, 16.9, 16.4, 9.8, -3.5, -4.7, -4.9. Anal. Calcd for $C_{40}H_{70}O_7Si_2$: C, 66.81; H, 9.81. Found: C, 66.91; H, 9.86.

[4*S*, 6*R*, 9*R*, 11*R*, 4'*S*, 1"*R*, 2"*S*, 1'*E*]-2,2-Dimethyl-11-[2,4-dimethyl-5-[(*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-[1-methyl-2-[t-butyldimethylsilyl)-oxy]-3-phenylmethoxy-propyl]-1,3,7-trioxaspiroundecan-9-ol (20). To a solution of the ketone **19** (62.0 g, 86.3 mmol) in THF (1 L) at -78 °C was added a 1 M solution of L-Selectride in THF (125 mL, 125 mmol). The solution was stirred for 2 h at -78 °C and then allowed to warm to 0 °C overnight. Water (800 mL) and sodium perborate (96.0 g, 624 mmol) were added and the suspension was stirred for 2 h at ambient temperature. The mixture was extracted with ether and the combined organic phases was dried ($MgSO_4$), and evaporated. Chromatography on silica (5–10% ethyl acetate in petroleum ether) afforded the desired alcohol (52.0 g, 84%) in addition to recovered starting material (6.7 g, 10%): $[\alpha]_D$ +18.9° (c 0.9, $CHCl_3$); IR (neat) 3410, 2910, 2880, 1440, 1355, 1230, 1065, 940, 810, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5 H), 5.46 (d, 1 H, J = 9 Hz), 4.52 (d, 1 H, J = 12 Hz), 4.47 (d, 1 H, J = 12 Hz), 4.17-4.11 (m, 1 H), 3.96-3.89 (m, 2 H), 3.75 (bs, 1 H), 3.59 (d, 1 H, J = 12 Hz), 3.51-3.36 (m, 5 H), 2.47-2.38 (m, 1 H), 2.33 (dt, 1 H, J = 4, 14 Hz), 2.22 (dd, 1 H, J = 4, 13 Hz), 1.86-1.78 (m, 1 H), 1.75-1.54 (m, 4 H), 1.59 (s, 3 H), 1.52 (s, 3 H), 1.32 (s, 3 H), 1.27-1.18 (m, 1 H), 0.92-0.90 (m, 12 H), 0.88 (s, 9 H), 0.81 (d, 3 H, J = 7 Hz), 0.07 (s, 3 H), 0.04 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.1, 136.5, 128.7, 128.1, 127.9, 126.5, 99.2, 97.8, 73.7, 73.6, 72.4, 69.0, 66.2, 66.0, 65.8, 44.5, 41.9, 41.8, 36.5, 34.5, 32.4, 31.4, 26.4, 23.8, 18.8, 18.6, 16.7, 16.5, 10.0, -3.5, -4.5, -4.9. Anal. Calcd for $C_{40}H_{72}O_7Si_2$: C, 66.62; H, 10.06. Found: C, 66.47; H, 9.92.

[4*R*, 6*R*, 9*R*, 11*R*, 1'*R*, 4"*S*, 1"'*R*, 2"'*S*, 1"(E)]-2,2-Dimethyl-9-(1-ethoxy-1-methyl-methoxy)-11-[2,4-dimethyl-5-[[(1,1-dimethy-lethyl)dimethylsilyl]-oxy]-1-pentenyl]-4-[2-[[(1,1-dimethylethyl)-dimethylsilyl]-oxy]-1-methyl-3-phenylmethoxy-propyl]-1,3,7-trioxa-spiroundecane and **[4*R*, 6*R*, 9*R*, 11*R*, 1'*S*, 4"*S*, 1"'*R*, 2"'*S*, 1"(E)]-2,2-Dimethyl-9-(1-ethoxy-1-methyl-methoxy)-11-[2,4-dimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-1-pentenyl]-4-[2-[[(1,1-di-methylethyl)dimethylsilyl]-oxy]-1-methyl-3-phenylmethoxy-propyl]-1,3,7-trioxaspiroundecane (21).** To a solution of the alcohol **20** (0.033 g, 0.046 mmol) in ethyl vinyl ether (0.5 mL) was added p-toluene sulfonic acid (0.002 g), and the solution was stirred for 20 min at room temperature. The reaction mixture was quenched by the addition of 2 N NaOH (10 mL), and then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phased were dried (K_2CO_3) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 15:85) afforded the

ethoxyethyl ether (0.036 g, 100%): $[\alpha]_D$ +21.4° (*c* 2.2, $CHCl_3$); IR (neat) 2940, 2910, 2840, 1445, 1365, 1245, 1080, 940, 825, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5 H), 5.41-5.35 (m, 1 H), 4.79-4.71 (m, 1 H), 4.54-4.45 (m, 2 H), 4.22-4.09 (m, 1 H), 4.00-3.81 (m, 2 H), 3.75-3.68 (m, 1 H), 3.64-3.28 (m, 7 H), 2.48-2.38 (m, 1 H), 2.19-2.02 (m, 2 H), 1.87-1.52 (m, 6 H), 1.56 (s, 3 H), 1.49 (s, 3 H), 1.32-1.22 (m, 3 H), 1.20 (s, 3 H), 1.19-1.13 (m, 3 H), 0.91-0.84 (m, 21 H), 0.82 (d, 3 H, *J* = 6 Hz), 0.05-0.02 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9, 138.8, 133.5, 128.7, 128.1, 127.9, 127.8, 127.5, 127.3, 99.2, 99.1, 98.6, 98.4, 98.1, 97.6, 73.7, 73.2, 72.6, 69.1, 68.9, 68.0, 67.7, 65.8, 65.2, 65.0, 63.5, 60.0, 59.3, 44.4, 42.4, 42.3, 41.9, 35.3, 34.8, 34.6, 34.5, 31.4, 31.3, 28.8, 26.4, 24.1, 23.9, 20.8, 20.7, 18.8, 18.6, 17.0, 16.8, 16.6, 15.9, 15.8, 10.2, 10.1, -3.5, -3.6, -4.4, -4.5, -4.9. Anal. Calcd for $C_{44}H_{80}O_8Si_2$: C, 66.62; H, 10.16. Found: C, 66.88; H, 10.32.

[4*R*, 6*R*, 9*R*, 11*R*, 4'*S*, 1''*R*, 2''*S*, 1'*E*]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-5-[*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-[1-methyl-2-[(*tert*-butyldimethylsilyl)-oxy]-3-phenylmethoxy-propyl]-1,3,7-trioxa-spiroundecane (22). To a cooled (0 °C) solution of the alcohol **20** (39.5 g, 54.9 mmol) and *p*-methoxybenzyl trichloroacetimide (31.0 g, 109 mmol) in anhydrous THF (220 mL) under argon was added a catalytic amount of Ph_3CBF_4 (90 mg, 0.27 mmol). The reaction mixture was stirred at 0 °C for 4 h and was quenched with Et_3N (2 mL). The solvent was evaporated and the residue was stirred with hexanes (300 mL). The mixture was filtered and washed with hexanes (3 x 100 mL). The combined hexanes solution was concentrated and the residue was chromatographed on silica (5% ethyl acetate in petroleum ether) to afford the PMB-ether (42.0 g, 91%): $[\alpha]_D$ +30.3° (*c* 1.45, $CHCl_3$); IR (neat) 2950, 2920, 2880, 2840, 1600, 1505, 1455, 1370, 1245, 1090, 1025, 955, 830, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5 H), 7.24 (d, 2 H, *J* = 7.4 Hz), 6.85 (d, 2 H, *J* = 7.4 Hz), 5.50 (d, 1 H, *J* = 10.2 Hz), 4.50 (bs, 2 H), 4.48 (d, 1 H, *J* = 11.7 Hz), 4.36 (d, 1 H, *J* = 10.7 Hz), 4.20-4.15 (m, 1 H), 3.92-3.86 (m, 2 H), 3.80 (s, 3 H), 3.66 (bd, 1 H, *J* = 12.9 Hz), 3.49-3.37 (m, 4 H), 3.32 (dd, 1 H, *J* = 9.6, 6.6 Hz), 2.46-2.39 (m, 1 H), 2.16-2.05 (m, 2 H), 1.81-1.74 (m, 1 H), 1.72-1.55 (m, 3 H), 1.59 (s, 3 H), 1.49 (s, 3 H), 1.30 (s, 3 H), 1.36-1.22 (m, 2 H), 0.92-0.90 (overlapped, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.78 (d, 3 H, *J* = 6.3 Hz), 0.068 (s, 3 H), 0.046 (s, 3 H), 0.29 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9, 138.5, 133.3, 130.9, 129.0, 128.2, 127.6, 127.4, 126.9, 113.6, 98.6, 98.0, 73.2, 72.5, 70.6, 69.3, 68.6, 65.0, 63.4, 55.2, 43.9, 41.5, 41.4, 35.0, 34.1, 31.0, 28.1, 26.0, 23.5, 18.3, 18.2, 16.4, 16.1, 9.7, -4.0, -4.9, -5.3. Anal. Calcd for $C_{48}H_{80}O_8Si_2$: C, 68.53; H, 9.58. Found: C, 68.62; H, 9.44.

(2 *R*, 3 *S*, 4 *R*)-3-[(1,1-Dimethylethyl)dimethylsilyl-oxy]-4-methyl-2-hexanol (24). To a solution of the olefin **23** (5.09 g, 15.2 mmol) in absolute ethanol (160 mL) was added palladium hydroxide (0.25 g), and the suspension was shaken for 6 h under H_2 atmosphere (45 psi) in a Parr apparatus. The suspension was

filtered over a short pad of silica gel and the filtrate was evaporated to an oily residue. Kugelrohr distillation afforded 3.74 g (100%) of the desired alcohol: Bp 80 °C (16 mmHg); $[\alpha]_D$ -4.2° (*c* 1.0, $CHCl_3$); IR (neat) 3390, 2950, 2930, 2850, 1455, 1375, 1250, 1055, 1015, 835, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37-3.28 (m, 1 H), 3.47 (t, 1 H *J* = 4 Hz), 1.98 (d, 1 H *J* = 4 Hz), 1.69-1.48 (m, 1 H), 1.44-1.31 (m, 1 H), 1.30-1.12 (m, 1 H; d, 3 H *J* = 6 Hz), 0.92-0.85 (m, 6 H; s 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 79.1, 70.6, 37.1, 27.7, 26.4, 18.8, 18.6, 15.0, 12.4, -3.6, -3.9. Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.36; H, 11.98.

(3 *S*, 4 *R*)-3-[(1,1-Dimethylethyl)dimethylsilyl-oxy]-4-methyl-2-hexanone (25). To a solution of the alcohol **24** (0.190 g, 0.771 mmol) in CH_2Cl_2 (10 mL) was added the Dess-Martin periodinane reagent (0.424 g, 1.002 mmol), and the reaction mixture was stirred for 3 h at room temperature. The solution was poured into 100 mL of ether, to which 50 mL each of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ were added. The biphasic solution was stirred for 30 min and then the layers were separated. The aqueous layer was extracted with ether (2 x 50 mL), and then the combined organic phases were dried ($MgSO_4$) and evaporated to an oil. Kugelrohr distillation (100 °C, 16 mmHg) afforded the ketone (0.165 g, 88%): Bp 100 °C (16 mmHg); $[\alpha]_D$ -30.6° (*c* 1.3, $CHCl_3$); IR (neat) 2950, 2930, 2860, 1720, 1460, 1345, 1250, 1135, 1060, 865, 840, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (d, 2 H *J* = 4 Hz), 2.12 (s, 3 H), 1.71-1.60 (m, 1 H), 1.58-1.33 (m, 1 H), 1.21-1.07 (m, 1 H), 0.92 (s, 9 H), 0.92-0.84 (m, 6 H) 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 213.0, 82.5. 39.9, 26.6, 26.2, 18.6, 14.3, 12.2, -4.6, -4.7. Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.55. Found: C, 64.05; H, 11.35.

[α*R* (1*S*, 2*R*)]-α-[1-[(1,1-Dimethyethyl)dimethylsilyl-oxy]-2-methyl-butyl]-α-methyl-cyclohexane ethanol (26). In a 50 mL 2 neck round bottom flask was placed ceriumtrichloride heptahydrate (0.180 g, 0.481 mmol) and the flask was heated to 140 °C under high vacuum (0.2 mmHg) for 2 h. Argon was introduced and then the flask was cooled to 0 °C at which time THF (5 mL) was added. The suspension was stirred for 3 h at room temperature. In a separate flask a solution of cyclohexylmethyl bromide (0.70 mL, 0.50 mmol) at -78 °C in hexane:ether (3:2, 3 mL) was treated with a solution of *t*-BuLi (1.7 M in pentane, 0.60 mL, 1.02 mmol). The solution was stirred for 1 h at -78 °C. The cerium trichloride suspension was cooled to -78 °C and then the organolithium solution was added *via* cannulation to afford a bright orange suspension. This suspension was stirred for 1 h at -78 °C and then a solution of the ketone **25** (0.34 g, 0.14 mmol) in THF (2.0 mL) was added. The reaction mixture was stirred for 20 min before methanol (0.5 mL) was added. The mixture was allowed to warm to 0 °C whereby it was quenched by the addition saturated aqueous NH_4Cl (20 mL). The mixture was extracted with ether (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$),

and evaporated. Chromatography of the residue afforded the alcohol (0.41 g, 85%): $[\alpha]_D$ -3.4° (*c* 1.2, $CHCl_3$); IR (neat) 3540, 2960, 2920, 2850, 1510, 1370, 1255, 1115, 1055, 815, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 1 H), 2.02 (s, 1 H), 1.91-1.86 (m, 1 H), 1.72-1.17 (overlapping series of multiplets, 16 H), 1.12 (s, 3 H), 0.92-0.80 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 83.3, 76.5, 44.2, 36.5, 36.3, 35.9, 33.7, 30.4, 27.1, 26.9, 26.8, 26.7, 24.7, 19.1, 14.9, 12.9, -2.7, -3.9. Anal. Calcd for $C_{20}H_{42}O_2Si$: C, 70.11; H, 12.36. Found: C, 70.10; H, 12.25.

(1*R*, 3*R*, 4*R*)-4-[(1,1-Dimethylethyl)diphenylsilyl)-oxy]-3-methoxy-cyclohexanemethanol (28). To a suspension of LAH (0.753 g, 19.8 mmol) in ether (50 mL) at 0 °C was added a solution of the ester **27** (4.23 g, 9.91 mmol) in ether (75 mL) over 45 min. The reaction mixture was stirred for 1 h at 0 °C and then quenched via careful addition of aqueous sodium potassium tartrate solution (0.5 M, 100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), and evaporated to an oil which upon silica gel chromatography (ethyl acetate-cyclohexane, 20:80) afforded the alcohol (3.28 g, 83%): $[\alpha]_D$ -17.9° (*c* 1.4, $CHCl_3$); IR (neat) 3320, 3040, 3020, 2900, 2830, 2790, 1575, 1445, 1415, 1370, 1075, 805, 730, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77-7.72 (m, 4 H), 7.42-7.35 (m, 6 H), 3.62-3.54 (m, 1 H), 3.40 (d, 2 H *J* = 6 Hz), 3.33 (s, 3 H), 3.16-3.08 (m, 1 H), 2.14-2.10 (m, 1 H), 1.80-1.69 (m, 2 H), 1.60-1.48 (m, 2 H), 1.44-1.30 (m, 1 H), 1.08 (s, 9 H), 0.89-0.74 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.5, 136.4, 135.5, 134.8, 129.8, 127.8, 84.4, 76.0, 67.9, 57.6, 33.3, 32.8, 27.5, 27.4, 27.0, 19.8. Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60. Found: C, 72.07; H, 8.73.

(1*R*, 3*R*, 4*R*)-4-[(1,1-Dimethylethyl)diphenylsilyl)-oxy]-1-(iodomethyl)-3-methoxy-cyclohexane (29). To a solution of the alcohol **28** (3.06 g, 7.68 mmol) in THF (50 mL) at 0 °C was added triethylamine (2.7 mL, 19.2 mmol), followed by methanesulfonyl chloride (0.89 mL, 11.52 mmol). The reaction mixture was stirred at 0 °C for 1 h and then quenched by addition of saturated aqueous $NaHCO_3$ (200 mL). The mixture was extracted with ether (4 x 100 mL), dried ($MgSO_4$), and evaporated.

The residue was dissolved in THF (75 mL) and cooled to 0 °C. Subsequently LiI (10.0 g, 74.7 mL) was added and the mixture was heated to reflux for 2 h. The reaction was allowed to cool to room temperature and whereby H_2O (100 mL) was added. The mixture was extracted with ether (4 x 100 mL), dried ($MgSO_4$), and evaporated to afford an oil (3.90 g, 100%) which was pure by TLC analysis: $[\alpha]_D$ -16.0° (*c* 1.0, $CHCl_3$); IR (neat) 3060, 3040, 2920, 2850, 1465, 1445, 1420, 1360, 1190, 1155, 1105, 860, 820, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.72 (m, 4 H), 7.42-7.38 (m, 6 H), 3.60-3.52 (m, 1 H), 3.33 (s, 1 H), 3.15-3.07 (m, 1 H), 3.05 (d, 2 H *J* = 6 Hz), 2.21-2.17 (m, 1 H), 1.74-1.63 (m, 2 H), 1.54-1.26 (m, 2 H), 1.06 (s, 9

H), 0.94-0.79 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.4, 136.3, 135.4, 134.7, 129.8, 84.1, 75.5, 57.8, 38.6, 36.4, 32.9, 30.8, 27.4, 19.8, 14.0. Anal. Calcd for $C_{24}H_{33}O_2Si$: C, 56.69; H, 6.54. Found: C, 56.72; H, 6.52.

(2*S*, 3*R*)-2-[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3-methyl-pentanal (31). To a solution of the benzyl ether **4** (2.15 g, 6.70 mmol) in EtOH (50 mL) was added $Pd(OH)_2$ (0.125 g, 0.89 mmol), the suspension was then shaken on a Parr apparatus under H_2 atmosphhere (40 psi) for 2 h. The mixture was filtered over a short pad of silica gel and the filtrate was evaporated to an oil which was dissolved in dry CH_2Cl_2 (30 mL).

Subsequently, the Dess-Martin periodinane reagent (3.41 g, 8.04 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. The mixture was poured into ether (200 mL) and then saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (100 mL each) were added. The mixture was stirred until two clear layers were formed and the layers were separated. The aqueous layer was extracted with ether (2 x 100) mL and the combined organic phases were dried (K_2CO_3) and evaporated. Cromatography of the residue on silica gel (ethyl acetate-cyclohexane 10:90) afforded an impure product which was distilled in a Kugelrohr apparatus (100 °C, 16 mmHg) to afford the aldehyde (1.20 g, 66%): $[\alpha]_D$ -22.9° (*c* 2.1, $CHCl_3$); IR (neat) 2940, 2910, 2840, 1725, 1445, 1370, 1240, 1130, 1065, 825, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1 H), 3.87 (d, 1 H, J = 2 Hz), 1.79-1.73 (m, 1 H), 1.50-1.43 (m, 1 H), 1.27-1.17 (m, 1 H), 0.94-0.86 (m, 15 H), 0.05 (m, 3 H), 0.03 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.8, 80.8, 38.8, 26.1, 18.6, 14.1, 12.2, -4.1, -4.7. Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.64; H, 11.47.

(3*S*, 4*R*, 1'*R*, 3'*R*, 4'*R*)-1-[4'-[(1,1-Dimethylethyl)diphenyl-silyl-oxy]-3'-methoxy-cyclohexyl]-3-[(1,1-dimethylethyl)dimethyl-silyl-oxy]-4-methyl-2-hexanone (30α) and **(3*S*, 4*R*, 1'*S*, 3'*S*, 4'*S*)-1-[4'-[(1,1-Dimethylethyl)diphenyl-silyl-oxy]-3'-methoxy-cyclohexyl]-3-[(1,1-dimethylethyl)dimethyl-silyl-oxy]-4-methyl-2-hexanone (30β).** Ceriumtrichloride heptahydrate (0.074 g, 0.300 mmol) was heated to 140 °C under a 0.2 mmHg vacuum for 2 h. The flask was allowed to cool to room temperature whereby THF (4 mL) was added. The suspension was stirred for 2 h and then a solution of the aldehyde **31** (0.023 g, 0.100 mmol) in THF (3 mL) was added. The mixture was stirred for 1 h and then cooled to -78 °C. In a separate flask a solution of the racemic iodide **29** (0.146 g, 0.287 mmol) in hexane (1.8 mL) and ether (1.2 mL) at -78 °C was treated with a solution of *t* -butyl lithium (1.8 M in pentane, 0.32 mL, 0.58 mmol), and the solution was stirred for 30 min at -78 °C. The presumed organolithium was cannulated into the aldehyde suspension and the reaction mixture was stirred for 1 h at -78 °C. Methanol (0.2 mL) was added and the mixture was allowed to warm to room temperature before the addition of saturated aqueous NH_4Cl (20 mL). The mixture was

extracted with ether (3 x 50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 4:96) afforded a mixture of alcohols (0.51 g, 84%) which was carried on without further analysis.

To a solution of the alcohol (0.034 g, 0.056 mmol) in dry CH_2Cl_2 (3 mL) was added the Dess-Martin periodinane reagent (0.034 g, 0.080 mmol), and the reaction mixture was stirred for 1.5 h at room temperature. Ether (20 mL) was added, followed by 10 mL each of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was stirred until two clear layers were formed, and then the layers were separated. The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. Preparative TLC of the residue on silica gel (ethyl acetate-cyclohexane 10:90) afforded the ketone (0.030 g, 88%): IR (neat) 3050, 3020, 2940, 2910, 2860, 1700, 1450, 1415, 1370, 1090, 830, 770, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79-7.72 (m, 4 H), 7.47-7.32 (m, 6 H), 3.84 (d, 1 H, J = 4 Hz), 3.57-3.49 (m, 1 H), 3.32 (s, 1.5 H), 3.31 (s, 1.5 H), 3.15-3.07 (m, 1 H), 2.45-2.25 (m, 2 H), 2.04-1.98 (m, 1 H), 1.95-1.82 (m, 1 H), 1.66-1.59 (m, 2 H), 1.52-1.24 (m, 4 H), 1.11-1.02 (m, 11 H), 0.90-0.84 (m, 12 H), 0.81-0.78 (m, 3 H), 0.00-0.02 (m, 6 H). Anal. Calcd for $C_{36}H_{58}O_4Si_2$: C, 70.77; H, 9.57. Found: C, 70.87; H, 9.42.

[4*R*, 6*R*, 9*R*, 11*R*, 1'*R*, 4"*S*, 1'"*R*, 2'"*S*, 1"(E)]-2,2-Dimethyl-9-(1-ethoxy-1-methyl-methoxy)-11-[2,4-dimethyl-5-[(1,1-dimethy-lethyl)dimethylsilyl-oxy]-1-pentenyl]-4-[2-[(1,1-dimethylethyl)-dimethylsilyl-oxy]-1-methyl-3-propanol]-1,3,7-trioxa-spiroundecane and **[4*R*, 6*R*, 9*R*, 11*R*, 1'*S*, 4"*S*, 1'"*R*, 2'"*S*, 1"(E)]-2,2-Dimethyl-9-(1-ethoxy-1-methyl-methoxy)-11-[2,4-dimethyl-5-[(1,1-dimethyl-ethyl)dimethylsilyl-oxy]-1-pentenyl]-4-[2-[(1,1-dimethylethyl)-dimethylsilyl-oxy]-1-methyl-3-propanol]-1,3,7-trioxaspiroundecane (32)**. To a solution of the benzyl ether **21** (0.121 g ,0.152 mmol) ethanol (2 mL) was added W-2 Raney nickel (~ 0.12 g) and the suspension was stirred under a hydrogen atmosphere for 12 h. The mixture was filtered over a short bed of silica gel and the filtrate was evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 15:85) afforded the alcohol (0.104 g, 97%): $[\alpha]_D$ +36.7° (*c* 0.9, $CHCl_3$); IR (neat) 3430, 2910, 2840, 1720, 1400, 1365, 1240, 940, 825, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (d, 0.5 H, J = 9 Hz), 5.39 (d, 0.5 H, J = 10 Hz), 4.80-4.72 (m, 1 H), 4.43-4.27 (m, 1 H), 3.99 (dd, 0.5 H, J = 2, 12 Hz), 3.89 (dd, 0.5 H, J = 2, 12 Hz), 3.77-3.27 (m, 9 H), 2.50-2.35 (m, 2 H), 2.20-2.05 (m, 2 H), 1.83-1.47 (m, 11 H), 1.42-1.21 (m, 7 H), 1.20-1.12 (m, 3 H), 0.93-0.86 (m, 21 H), 0.83 (d, 3 H, J = 6 Hz), 0.07-0.02 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 134.0, 133.8, 127.1, 99.2, 98.6, 98.4, 97.3, 75.4, 75.2, 68.9, 68.8, 67.5, 65.2, 64.7, 64.2, 63.9, 60.1, 59.2, 44.4, 42.4, 42.2, 42.0, 41.9, 35.2, 34.6, 34.4, 31.3, 31.1, 28.2, 26.3, 24.0, 23.8, 20.8, 20.6, 18.7, 18.5, 17.2, 17.0, 16.6, 16.5, 15.8, 15.7, 11.0, -4.0, -4.2, -4.9. Anal. Calcd for $C_{37}H_{74}O_8Si_2$: C, 63.20; H, 10.61. Found: C, 63.11; H, 10.82.

[4*R*, 6*R*, 9*R*, 11*R*, 1'*R*, 4"*S*, 1'"*R*, 2'"*S*, 1"(E)]-2,2-Dimethyl-9-(1-ethoxy-1-methyl-methoxy)-11-[2,4-dimethyl-5-[(1,1-dimethy-lethyl)dimethylsilyl-oxy]-1-pentenyl]-4-[2-[(1,1-dimethylethyl)-dimethylsilyl-oxy]-1-methyl-3-propanal]-1,3,7-trioxa-spiroundecane and **[4*R*, 6*R*, 9*R*, 11*R*, 1'*S*, 4"*S*, 1'"*R*, 2'"*S*, 1"(E)]-2,2-Dimethyl-9-(1-ethoxy-1-methyl-methoxy)-11-[2,4-dimethyl-5-[(1,1-dimethy-lethyl)dimethylsilyl-oxy]-1-pentenyl]-4-[2-[(1,1-dimethylethyl)-dimethylsilyl-oxy]-1-methyl-3-propanal]-1,3,7-trioxaspiroundecane (33)**. To a solution of the alcohol **32** (0.103 g, 0.146 mmol) in CH_2Cl_2 (3 mL) was added the Dess-Martin periodinane reagent (0.093 g, 0.219 mmol) and the solution was stirred for 1 h at room temperature. The mixture was poured into ether (50 mL) and then saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (25 mL each) were added. The mixture was stirred until two clear layers were formed and then the layers were separated. The aqueous phase was extracted with ether (3 x 25 mL) and then the combined organic phases were dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 3:97) afforded the aldehyde (0.086 g, 83%): $[\alpha]_D$ +38.3° (*c* 1.8, $CHCl_3$); IR (neat) 2940, 2920, 2880, 2840, 1725, 1455, 1370, 1250, 1090, 950, 835, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48-9.45 (m, 1 H), 5.44 (d, 1 H, *J* = 10 Hz), 4.79-4.71 (m, 1 H), 4.53-4.36 (m, 1 H), 3.99 (dd, 0.5 H, *J* = 2, 12 Hz), 3.91-3.83 (m, 1.5 H), 3.72 (d, 1 H, *J* = 2 Hz), 3.66-3.25 (m, 5 H), 2.47-2.35 (m, 1 H), 2.21-2.01 (m, 2 H), 1.92-1.44 (m, 11 H), 1.41 (s, 3 H), 1.36-1.20 (m, 7 H), 1.18-1.12 (m, 3 H), 0.95-0.85 (m, 21 H), 0.82 (d, 3 H, *J* = 6 Hz), 0.05-0.01 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.2, 202.9, 133.9, 133.6, 127.4, 127.2, 99.4, 98.4, 98.2, 97.0, 79.3, 79.2, 68.9, 68.7, 67.3, 67.2, 65.2, 63.7, 63.2, 62.8, 59.9, 59.1, 44.4, 43.3, 43.1, 42.2, 42.0, 34.9, 34.6, 34.4, 31.3, 30.8, 27.8, 27.3, 26.2, 26.0, 23.9, 23.8, 20.8, 20.6, 18.7, 18.5, 17.2, 17.0, 16.5, 15.8, 15.7, 9.8, 9.7, -4.1, -4.2, -4.5, -4.9. Anal. Calcd for $C_{37}H_{74}O_8Si_2$: C, 63.20; H, 10.61. Found: C, 63.11; H, 10.82.

Ketone (35). To a solution of the iodide **29** (0.042 g, 0.084 mmol) in hexane:ether (2:3, 7 mL) at -78 °C was added a solution of *t* -butyl lithium (1.8 M in pentane, 0.10 mL, 0.18 mmol). The solution was stirred for 30 min at -78 °C and then ether (7 mL) was added. The organolithium solution was slowly cannulated over 5 min into a solution (-100 °C) of the aldehyde **33** (0.025 g, 0.036 mmol) in ether (7 mL), and the reaction mixture was stirred for 30 min at -100 °C. Methanol (0.5 mL) was added and the solution was allowed to warm to room temperature before the addition of saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 2:98-3:97) afforded the alcohol **34** (0.028 g, 72%) and the starting aldehyde (0.006 g, 24%).

The mixture of alcohols (**34**) was dissolved in CH_2Cl_2 (1.5 mL) and the Dess-Martin periodinane reagent(0.044 g, 0.104 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, and

then 25 mL of ether was added. Subsequently 10 mL each of saturated aqueous $NaHCO_3$ and saturated $Na_2S_2O_3$ was added. The mixture was stirred until two clear layers were formed and then the layers were separated. The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 2:98-4:96) afforded the ketone (0.023 g, 82%): $[\alpha]_D$ +8.1° (*c* 1.6, $CHCl_3$); IR (neat) 2940, 2910, 2880, 2840, 1710, 1455, 1370, 1245, 1090, 950, 830, 770, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82-7.65 (m, 4 H), 7.39-7.30 (m, 6 H), 5.48 (d, 1 H, *J* = 10 Hz), 4.78-4.69 (m, 1 H), 4.06-3.90 (m, 2 H), 3.69 (bs, 1 H), 3.60-3.24 (m, 10 H), 3.12-3.03 (m, 1 H), 2.47-2.33 (m, 2 H), 2.27-1.93 (m, 5 H), 1.16-1.10 (m, 3 H), 1.02 (s, 9 H), 0.79 (d, 3 H, *J* = 6 Hz), 0.02-⁻0.07 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.4, 136.4, 136.3, 135.6, 134.9, 133.8, 133.4, 129.7, 127.8, 127.7, 127.5, 127.2, 99.4, 98.3, 98.1, 97.3, 84.5, 79.8, 79.4, 76.1, 69,1, 68.9, 67.5, 65.4, 65.0, 64.9, 63.4, 59.8, 59.2, 57.6, 44.6, 44.3, 42.1, 36.4, 36.3, 35.2, 34.9, 34.7, 34.5, 33.8, 33.7, 31.3, 31.0, 27.4, 26.4, 26.2, 23.9, 23.8, 20.8, 20.6, 19.8, 18.6, 18.5, 17.1, 16.9, 16.6, 15.8, 10.1, -4.0, -4.1, -4.5, -4.9. Anal. Calcd for $C_{61}H_{104}O_{10}Si_3$: C, 67.73; H, 9.69. Found: C, 67.51; H, 9.71.

Ketone (36). To a solution of the bis-*t*-butyldimethylsilyl ether **35** (0.162 g, 0.150 mmol) in THF (5 mL) was added activated powered 4Å molecular sieves (1.2 g) followed by a solution of TBAF (1.0 M, 0.33 mL, 0.33 mmol) in THF. The suspension was stirred for 45 min at room temperature and then saturated aqueous $NaHCO_3$ (50 mL) was added. The mixture was extracted with ether (4 x 50 mL) and then the combined organic phases were dried ($MgSO_4$) and evaporated. The reaction was repeated on a 0.340 g (0.315 mmol) scale to afford an additional crop of the crude diol.

The combined crude diols were dissolved in DMF (10 mL) and then imidazole (0.253 g, 3.712 mmol) was added. Subsequently TESCl (0.234 mL, 1.392 mmol) was added and the reaction mixture was stirred for 14 h at room temperature. Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with ether (4 x 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 2:98-10:90) afforded the silyl ether (0.386 g, 77%): $[\alpha]_D$ +11.4° (*c* 1.4, $CHCl_3$); IR (neat) 2950, 2920, 2870, 1715, 1375, 1100, 1005, 955, 815, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.67 (m, 4 H), 7.42-7.30 (m, 6 H), 5.42 (d, 1 H, *J* = 10 Hz), 4.79-4.71 (m, 1 H), 4.06 (d, 1 H, *J* = 6 Hz), 3.96 (dd, 0.5 H, *J* = 2, 12 Hz), 3.85 (dd, 0.5 H, *J* = 2, 13 Hz), 3.72 (d, 1 H, *J* = 1 Hz), 3.29 (s, 3 H), 3.14-3.06 (m, 1 H), 2.48-2.26 (m, 2 H), 2.21-2.11 (m, 1 H), 2.07-2.01 (m, 1 H), 1.18-1.12 (m, 3 H), 1.05 (s, 9 H), 0.62-0.52 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.6, 211.5, 136.4, 136.3, 135.6, 134.9, 133.8, 133.5, 129.7, 99.4, 98.4, 98.2, 98.0, 97.3, 84.5, 79.7, 79.4, 76.1, 68.9, 68.7, 67.5, 65.5, 65.1, 63.3, 59.8, 59.2, 57.6, 44.7, 44.4, 44.3, 42.1, 36.4, 35.0, 34.7, 34.6, 33.7, 31.1, 31.1, 31.0, 28.1, 27.4,

23.9, 23.8, 20.8, 20.6, 19.8, 16.9, 16.8, 16.5, 15.8, 15.7, 10.0, 7.3, 5.4, 4.9. Anal. Calcd for $C_{61}H_{104}O_{10}Si_3$: C, 67.73; H, 9.69. Found: C, 67.88; H, 9.70.

Enol Triflate (37). To a solution of diethylamine (0.78 mL, 7.50 mmol) of in hexane (7 mL) at 0 °C was added a solution of *n*-butyl lithium (2.5 M, 2.0 mL, 5.0 mmol) in hexanes and the solution was stirred for 15 min at 0 °C. The solvent was evaporated *in vacuuo* (0.02 mmHg) and the white residue was dried under high vacuum (0 °C, 0.2 mmHg) for 30 min. THF (50 mL) was added to afford a 0.1 M solution of lithium diethylamide.

To the lithium diethylamide solution (9.2 mL, 0.92 mmol) at -78 °C was added a solution of the ketone **36** (0.050 g, 0.046 mmol) in THF (2 mL). The solution was stirred for 1 h before the addition of DMPU (0.14 mL). The reaction mixture was stirred for 1 h at -78 °C whereby N-phenyl triflimide (0.412 g, 1.15 mmol) was added. The reaction mixture was allowed to warm to room temperature and stir for 1 h before the addition of saturated aqueous $NaHCO_3$ (25 mL). The mixture was extracted with ether (4 x 20 mL) and then the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 0.5:95.5-2:98) afforded 0.49 g (86%) of the enol triflate: $[\alpha]_D$ +10.7° (*c* 1.4, $CHCl_3$); IR (neat) 3060, 3040, 2960, 2930, 2870, 1455, 1410, 1375, 1210, 1140, 1100, 1005, 955, 820, 740, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79-7.72 (m, 4 H), 7.43-7.36 (m, 6 H), 5.47 (d, 1 H, *J* = 10 Hz), 5.32-5.22 (m, 1 H), 4.82-4.73 (m, 1 H), 4.27-4.21 (m, 1 H), 4.05-3.83 (m, 2 H), 3.75 (bs, 1 H), 3.13 (s, 3 H), 3.20-3.10 (m, 1 H), 1.20-1.15 (m, 3 H), 1.09 (s, 9 H), 0.66-0.56 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.4, 136.5, 136.4, 135.4, 133.9, 133.4, 129.8, 129.7, 127.8, 127.7, 127.4, 127.1, 126.6, 99.1, 98.2, 98.1, 97.8, 97.2, 83.9, 75.3, 72.6, 72.0, 68.9, 68.7, 67.3, 65.3, 65.1, 63.2, 59.7, 59.0, 57.8, 44.4, 42.1, 41.9, 40.9, 40.7, 35.4, 35.3, 34.6, 34.4, 33.5, 33.2, 31.3, 30.8, 30.2, 28.0, 27.4, 24.2, 20.8, 20.6, 19.8, 16.9, 16.7, 16.3, 15.8, 8.7, 7.2, 5.1, 4.9.

Diene (38). To a suspension of CuI (1.08 g, 5.67 mmol) in THF (17 mL) at 0 °C was added a solution of methyl lithium (1.4 M, 6.1 mL, 8.51 mmol) in ether and the mixture was stirred at 0 °C until a clear solution was formed. Subsequently, a solution of the enol triflate **37** (0.343 g, 0.283 mmol) in THF (10 mL) was added and the mixture was sonicated (Branson 1200) for 4 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl-NH_4OH solution (9:1, 60 mL), and the mixture was extracted with ether (4 x 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-cyclohexane 2:98-4:96) afforded the olefin (0.240 g, 79%) and an unidentifiable product (0.041 g): $[\alpha]_D$ +10.0° (*c* 1.1, $CHCl_3$); IR (neat) 3060, 3040, 2950, 2920, 2870, 1455, 1370, 1100, 1005, 945, 810, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79-7.71 (m, 4 H), 7.44-7.32 (m, 6 H), 5.42 (d, 1 H, *J* = 10 Hz), 5.01-4.97 (m, 1 H), 4.97-4.73 (m, 1 H), 3.99-3.80 (m, 2 H), 3.75-3.68 (m, 1 H), 3.61-3.40 (m, 6 H),

3.32 (s, 3 H), 3.31-3.22 (m, 1 H), 3.18-3.10 (m, 1 H), 2.46-2.35 (m, 1 H), 2.30-2.02 (m, 3 H), 2.20-1.92 (m, 1 H), 1.19-1.13 (m, 3 H), 0.63-0.49 (m, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.5, 136.4, 135.9, 135.8, 135.7, 134.9, 133.6, 133.4, 132.4, 132.2, 129.7, 127.7, 127.4, 127.3, 99.9, 98.3, 98.1, 96.8, 84.7, 80.7, 80.4, 77.6, 76.2, 68.7, 68.4, 67.4, 67.0, 65.1, 64.4, 64.2, 63.7, 59.8, 59.0, 57.7, 44.6, 42.3, 42.0, 36.1, 36.0, 35.4, 34.6, 34.4, 34.2, 31.3, 31.1, 30.7, 27.4, 24.4, 20.8, 20.5, 19.8, 17.4, 17.1, 16.5, 16.4, 15.8, 15.7, 11.6, 11.3, 9.7, 7.4, 7.2, 5.4, 4.9. Anal. Calcd for $C_{62}H_{106}O_9Si_3$: C, 68,97; H, 9.89. Found: C, 68.95; H, 9.77.

[4*R*, 6*R*, 9*R*, 11*R*, 4'*S*, 1''*R*, 2''*S*, 1'*E*]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-5-hydroxyl-1-pentenyl]-4-[1-methyl-2-hydroxyl-3-phenylmethoxy-propyl]-1,3,7-trioxa-spiroundecane (39). To a solution of the bis-silyl ether **22** obtained above (42.0 g, 50 mmol) in 400 mL of THF was added a solution of TBAF (1 M in THF, 180 mL, 180 mmol) and 4Å molecular sieves (8.0 g). The mixture was stirred at room temperature for 2 days and then was filtered, and the residue was washed with THF three times. THF was evaporated and the residue was partitioned between ethyl acetate and saturated NH_4Cl solution and the aqueous layer was extracted three times with ethyl acetate. The combined organic phase was dried (Na_2SO_4), concentrated and chromatographed on silica (30% ethyl acetate in hexanes) to afford the diol as an oil (28 g, 91 %): $[\alpha]_D$ +39.4° (*c* 1.4, $CHCl_3$); IR (neat) 3420, 2920, 2850, 1600, 1500, 1450, 1370, 1300, 1240, 1200, 1170, 1100, 1030, 980, 950, 870, 820, 730, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (bs, 5 H), 7.24 (d, 2 H, *J* = 7.1 Hz), 6.35 (d, 2 H, *J* = 7.1 Hz), 5.54 (d, 1 H, *J* = 10.2 Hz), 4.57 (d, 1 H, *J* = 12.0 Hz), 4.52 (d, 1 H, *J* = 12.0 Hz), 4.46 (d, 1 H, *J* = 12.3 Hz), 4.37 (d, 1 H, *J* = 12.0 Hz), 4.23 (bd, 1 H, *J* = 10.2 Hz), 4.03 (bs, 1 H), 3.91 (d, 1 H, *J* = 10.1 Hz), 3.70 (s, 3 H), 3.71 (d, 1 H, *J* = 12.0 Hz), 3.46 (d, 4 H, *J* = 10.1 Hz), 3.34-3.29 (m, 1 H), 2.80 (b, 1 H, O*H*), 2.45-2.40 (m, 1H), 2.12-1.99 (m, 2 H), 1.90-1.60 (m, 4 H), 1.62 (s, 3 H), 1.55 (s, 3 H), 1.32 (s, 3 H), 1.40-1.25 (m, 2 H), 0.91 (d, 3 H, *J* = 6.9 Hz), 0.86 (d, 3 H, *J* = 6.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.7, 138.7, 134.5, 131.4, 129.8, 129.1, 128.4, 128.3, 127.6, 114.3, 99.5, 98.6, 74.0, 73.4, 72.9, 71.3, 70.1, 68.9, 68.6, 64.2, 55.9, 45.1, 42.4, 39.6, 35.2, 34.4, 31.6, 30.4, 28.5, 24.3, 17.8, 16.9, 8.4. Anal. Calcd for $C_{36}H_{52}O_8$: C, 70.56; H, 8.55. Found: C, 70.43; H, 8.80.

[4*R*, 6*R*, 9*R*, 11*R*, 4'*S*, 1''*R*, 2''*S*, 1'*E*]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-5-[(*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-[1-methyl-2-hydroxyl-3-phenylmethoxy-propyl]-1,3,7-trioxa-spiroundecane (40). To a solution of the diol **39** (4.88 g, 8.00 mmol) in anhydrous THF (30 mL) was added anhydrous Et_3N (2.40 mL, 17.2 mmol), TBSCl (1.33 g, 8.54 mmol) and DMAP (100 mg, 0.819 mmol). After being stirred at 55 °C for 24 h under argon, the mixture was treated with an additional amount of TBSCl (0.14 g, 0.899 mmol) and was stirred for 12 h. The mixture was cooled to room temperature, diluted with 100 mL of ether, and filtered through a Celite pad. The residue was washed with

additional ether (3 x 30 mL) and the combined filtrate was concentrated. The resulting crude material was chromatographed on silica (6-15% ethyl acetate in hexanes) to afford the primary silyl ether (5.70 g, 98%) as an oil: $[\alpha]_D$ +40.3° (*c* 1.2, $CHCl_3$); IR (neat) 3450, 2950, 2920, 2840, 1600, 1500, 1450, 1370, 1245, 1090, 1030, 950, 830, 770, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5 H), 7.24 (d, 2 H, *J* = 9.0 Hz), 6.85 (d, 2 H, *J* = 8.4 Hz), 5.52 (d, 1 H, *J* = 10.5 Hz), 4.57 (d, 1 H, *J* = 12.0 Hz), 4.52 (d, 1 H, *J* = 12.3 Hz), 4.48 (d, 1 H, *J* = 12.3 Hz), 4.36 (d, 1 H, *J* = 12.0 Hz), 4.34-4.29 (m, 1 H), 4.03-4.00 (m, 1 H), 3.92 (dd, 1 H, *J* = 2.7, 12.0 Hz), 3.79 (s, 3 H), 3.70 (d, 1 H, *J* = 12.3 Hz), 3.48-3.39 (m, 4 H), 3.29 (dd, 1 H, *J* = 6.6, 9.6 Hz), 2.86 (d, 1 H, *J* = 1.5 Hz), 2.47-2.40 (m, 1 H), 2.13-2.04 (m, 2 H), 1.80-1.50 (m, 4 H), 1.60 (s, 3 H), 1.56 (s, 3 H), 1.41 (d, 3 H, *J* = 12.3 Hz), 1.35-1.26 (m, 1 H), 1.32 (s, 3 H), 0.91 (d, 3 H, *J* = 7.2 Hz), 0.88 (s, 9 H), 0.79 (d, 3 H, *J* = 6.0 Hz), 0.02 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9, 138.1, 133.7, 130.7, 129.0, 128.3, 127.7, 127.6, 126.6, 113.6, 98.7, 98.0, 73.4, 73.3, 72.4, 70.4, 69.3, 68.5, 68.4, 63.7, 55.2, 43.9, 41.7, 38.6, 34.6, 34.0, 30.1, 27.7, 25.9, 23.6, 18.3, 16.6, 16.1, 7.0, -5.3. Anal. Calcd for $C_{42}H_{66}O_8Si$: C, 69.38; H, 9.15. Found: C, 69.26; H, 9.29.

[4*R*, 6*R*, 9*R*, 11*R*, 4'*S*, 1''*R*, 2''*S*, 1'*E*]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-5-[(*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-(1-methyl-2,3-dihydroxylpropyl)-1,3,7-trioxa-spiroundecane (41). Commercial W-2 Raney® nickel (35.0 g) was stirred vigorously with anhydrous ethanol (50 mL) for 2 min and allowed to settle down. The cloudy supernatant was then decanted and the washing was repeated five times. The washed Raney Ni was immediately covered with ethanol (50 mL) and was treated with the benzyl-ether **40** (12.0 g, 16.6 mmol) in ethanol (150 mL total). The mixture was flushed three times with hydrogen and stirred under a hydrogen balloon for 24 h. The mixture was filtered through a Celite pad and the nickel residue (which was covered with K_2CO_3 in order to prevent it from being exposed to the air) was washed with capacious amount of THF. The filtrate was concentrated and the resulting residue was flashed through a short silica pad (10-50% ethyl acetate in hexanes) to afford the vicinyl diol (10.7 g, 100%) as an oil: $[\alpha]_D$ +41.5° (*c* 1.3, $CHCl_3$); IR (neat) 3340, 2950, 2920, 2840, 1605, 1510, 1460, 1375, 1295, 1245, 1200, 1090, 1030, 960, 880, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 2 H, *J* = 8.4 Hz), 6.84 (d, 2 H, *J* = 8.7 Hz), 5.53 (d, 1 H, *J* = 10.5 Hz), 4.48 (d, 1 H, *J* = 10.7 Hz), 4.35 (bd, 2 H, *J* = 10.7 Hz), 3.92 (dd, 1 H, *J* = 2.1, 12.3 Hz), 3.84 (b, 1 H), 3.79 (s, 3 H), 3.74-3.63 (m, 2 H), 3.54-3.49 (m, 1 H), 3.45-3.38 (m, 2 H), 3.28 (dd, 1 H, *J* = 6.6, 9.6 Hz), 2.87 (bs, 1 H), 2.47-2.41 (m, 1 H), 2.24 (b, 1 H), 2.13-2.04 (m, 2 H), 1.78-1.67 (m, 3 H), 1.60 (s, 6 H), 1.52 (dd, 1 H, *J* = 2.1, 13.2 Hz), 1.42 (d, 1 H, *J* = 10.7 Hz), 1.35 (s, 3 H), 0.92 (d, 3 H, *J* = 6.9 Hz), 0.88 (s, 9 H), 0.79 (d, 3 H, *J* = 6.3 Hz), 0.02 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.0, 133.8, 130.7, 129.0, 126.5, 113.6, 98.9, 97.9, 75.3, 70.3, 69.3, 68.4, 68.2, 64.8, 63.7,

55.2, 43.9, 41.6, 39.0, 34.6, 34.1, 30.9, 27.5, 25.9, 23.6, 18.3, 16.6, 16.1, 7.7, -5.3. Anal. Calcd for $C_{35}H_{60}O_8Si$: C, 66.00; H, 9.49. Found: C, 65.91; H, 9.60.

[4*R*, 6*R*, 9*R*, 11*R*, 4'*S*, 1''*R*, 2''*S*, 1'*E*]-2,2-Dimethyl-9-(*p*-methoxyphenylmethoxy)-11-[2,4-dimethyl-5-[(*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-(1-methyl-2-ethanal)-1,3,7-trioxa-spiroundecane (42). To a solution of the diol **41** (8.70 g, 13.7 mmol) in THF (85 mL) was added H_2O (30 mL) and $NaIO_4$ (8.8 g, 41.1 mmol) under nitrogen. The mixture was stirred at room temperature for 1.5 h and was then partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted three times and the combined CH_2Cl_2 solution was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated to yield a yellow oil (7.84 g, 95%): $[\alpha]_D$ +16.0° (*c* 1.4, $CHCl_3$); IR (neat) 2950, 2920, 2840, 1720, 1605, 1505, 1455, 1375, 1295, 1245, 1195, 1165, 1090, 1030, 955, 870, 835, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1 H), 7.23 (d, 2 H, *J* = 7.4 Hz), 6.84 (d, 2 H, *J* = 7.4 Hz), 5.52 (d, 1 H, *J* = 10.5 Hz), 4.55 (dd, 1 H, *J* = 3.9, 11.1 Hz), 4.48 (d, 1 H, *J* = 11.7 Hz), 4.35 (d, 1 H, *J* = 11.7 Hz), 3.93 (dd, 1 H, *J* = 12.0 Hz), 3.79 (s, 3 H), 3.71 (d, 1 H, *J* = 12.3 Hz), 3.44-3.37 (m, 2 H), 3.31-3.26 (dd, 1 H, *J* = 6.9, 9.6 Hz), 2.42-2.36 (m, 2 H), 2.13-2.08 (m, 2 H), 1.76-1.60 (m, 4 H), 1.58 (s, 6 H), 1.42-1.25 (m, 1 H), 1.32 (s, 3 H), 1.06 (d, 3 H, *J* = 6.9 Hz), 0.88 (s, 9 H), 0.78 (d, 3 H, *J* = 6.3 Hz), 0.02 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.0, 158.9, 133.9, 129.0, 126.4, 113.6, 99.0, 97.7, 70.3, 69.3, 68.4, 64.8, 63.7, 55 2, 50.3, 43.8, 41.6, 34.6, 34.0, 30.8, 27.5, 25.9, 23.4, 18.3, 16.5, 16.1, 7.9, -5.3. Anal. Calcd for $C_{34}H_{56}O_7Si$: C, 67.51; H, 9.33. Found: C, 67.33; H, 9.30.

[4*R*, 4[1*S*, 2*R/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-[(*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-[1,3-dimethyl-2-hydroxy-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]cyclohex-1-yl]-3-butenyl]-1,3,7-trioxa-spiroundecane (β/α-44). To a solution of the vinyl bromide **43** (10.2 g, 21 mmol), previously dried over P_2O_5 under vacuum for 12 h, in anhydrous THF (85 mL) at - 78 °C was added *t*-BuLi (1.76 M in pentane, 24.0 mL, 42.2 mmol) under argon. The solution was stirred at -78 °C for 30 min during which precipitate formed. A freshly prepared 1 M solution of $MgBr_2$•ether (24 mL, 24 mmol) in ether was added to the reaction mixture and stirring was continued for 20 min. A solution of the previously prepared aldehyde **42** (9.0 g, 15 mmol, dried over P_2O_5 under vacuum for 12 h) in THF (40 mL) was cooled at -78 °C and cannulated to the vinyl Grignard formed above, followed by THF rinsing (4 x 10 mL). The reaction mixture was stirred at -78 °C for 2 h before a solution of NH_4Cl (4.5 g, 84 mmol) in 40 mL of H_2O was added. The mixture was allowed to warm to room temperature and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 three times and the combined organic solution was dried (K_2CO_3), concentrated and

chromatographed on silica (5-10% ethyl acetate in hexanes) to afford the desired α-isomer (9.0 g, 60%), a mixed fraction (0.4 g, 2.6%) and finally the β-isomer (4.5 g, 30%) as foaming oils.

The α-isomer (α-**44**): $[\alpha]_D$ 15.8° (*c* 1.3, $CHCl_3$); IR (neat) 3800, 2930, 2850, 1510, 1455, 1425, 1375, 1360, 1245, 1200, 1140, 1105, 1030, 950, 840-820, 775, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.70 (m, 4 H), 7.42-7.34 (m, 6 H), 7.24 (d, 2 H, *J* = 7.5 Hz), 6.80 (d, 2 H, *J* = 7.5 Hz), 5.54 (d, 1 H, *J* = 10.5 Hz), 5.23 (d, 1 H, *J* = 8.7 Hz), 4.48 (d, 1 H, *J* = 11.7 Hz), 4.35 (d, 1 H, *J* = 11.7 Hz), 4.33-4.29 (overlapped, 1 H), 4.10 (bs, 1 H), 3.91 (d, 1 H, *J* = 11.4 Hz), 3.79 (s, 3 H), 3.71 (d, 1 H, *J* = 12.3 Hz), 3.61-3.53 (m, 1 H), 3.44-3.39 (m, 2 H), 3.35-3.24 (m, 1 H), 3.32 (s, 3 H), 3.17-3.09 (m, 1 H), 2.90 (s, 1 H, O*H*), 2.45-2.42 (m, 1 H), 2.32-2.22 (m, 1 H), 2.12-2.08 (m, 2 H), 1.79-1.66 (m, 4 H), 2.19-1.26 (m, 5 H), 1.60 (s, 3 H), 1.55 (s, 3 H), 1.52 (s, 3 H), 1.33 (s, 3 H), 1.06 (s, 9 H), 1.05-0.85 (m, 1 H), 0.88 (s, 9 H), 0.81-0.79 (2 bs, 7 H), 0.02 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9, 136.0, 135.9, 135.2, 134.4, 133.6, 133.5, 130.7, 129.5, 129.3, 129.2, 128.9, 127.3, 127.2, 126.7, 113.6, 98.8, 97.9, 84.3, 79.2, 75,7, 70.3, 69.3, 69.0, 68.3, 63.7, 57.2, 55.2, 44,0, 41.6, 38.7, 36.2, 35.4, 34.9, 34.0, 33.8, 30.9, 30.6, 27.4, 27.0, 25.9, 23.8, 19.4, 18.3, 16.7, 16.0, 13.4, 5.8, -5.3. Anal. Calcd for $C_{60}H_{92}O_9Si_2$: C, 71.10; H, 9.15. Found: C, 71.01; H, 8.91.

The β-isomer (β-**44**): $[\alpha]_D$ -61.8° (*c* 1.9, $CHCl_3$); IR (neat) 3480, 2940, 2920, 2840, 1505, 1460-1420, 1370, 1240, 1100, 1070, 1030, 940, 830-810, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.7 (m, 4 H), 7.40-7.30 (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), 5.16 (d, 1 H, *J* = 8.1 Hz), 4.48 (d, 1 H, *J* = 11.7 Hz), 4.39 (b, 1 H), 4.33 (1 H, d, *J* = 11.7 Hz), 3.94-3.75 (m, 2 H), 3.80 (s, 3 H), 3.68-3.65 (m, 2 H), 3.59-3.51 (m, 1 H), 3.42-3.38 (m, 2 H), 3.35-3.26 (m, 1 H), 3.31 (s, 3 H), 3.16-3.08 (m, 1 H), 2.457-2.35 (m, 1 H), 2.30-2.15 (m, 1 H), 1.95-1.91 (m, 1 H), 1.85-1.64 (m, 5 H), 1.62-1.21 (m, 4 H), 1.60 (s, 3 H), 1.54 (s, 3 H), 1.51 (s, 3 H), 1.33 (s, 3 H), 1.06 (s, 9 H), 0.95-0.85 (m, 1 H), 0.88 (s, 9 H), 0.81-0.78 (2s, 7 H), 0.02 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9, 136.0, 135.9, 135.2, 134.6, 134.4, 133.7, 131.0, 130.6, 129.2$_4$, 129.1$_9$, 129.0, 127.3, 127.2, 126.5, 113.6, 98.9, 97.9, 84.2, 80.2, 75.6, 70.1, 69.2, 68.4, 67.0, 63.8, 57.1, 55.2, 43.7, 41.5, 37.8, 36.0, 34.4, 34.2, 33.7, 33.4, 31.0, 30.7, 27.2, 27.0, 26.0, 23.6, 19.3, 18.3, 16.5, 16.2, 12.2, 12.0, -5.3. Anal. Calcd for $C_{60}H_{92}O_9Si_2$: C, 71.10; H, 9.15. Found: C, 70.91; H, 9.24.

[4*R*, 4[1*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-[(*tert*-butyldimethylsilyl)-oxy]-1-pentenyl]-4-[1,3-dimethyl-4-[3-methoxy-4-[(*tert*-butyldiphenylsilyl)oxy]-cyclo-hex-1-yl]-3-buten-2-one-1-yl]-1,3,7-trioxa-spiroundecane (45). To a solution of the α- and β-alcohol mixture **44** (150 mg, 0.148 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was added the Dess-Martin periodinane (90.0 mg, 0.21 mmol). The cloudy

solution was stirred at room temperature for 2 h and was then diluted with ether (15 mL). Saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10%, 5 mL) were added and the mixture was stirred to a clear biphasic solution. The aqueous layer was separated and extracted with ether (3 x) and the combined ether solution was concentrated. The residue thus obtained was chromatographed on silica (5% ethyl acetate in hexanes) to afford the ketone (151 mg, 100%) as an oil: $[\alpha]_D$ +15.4° (*c* 0.9, $CHCl_3$); IR (neat) 3060, 2950, 2920, 2840, 1655, 1605, 1505, 1450, 1420, 1370, 1295, 1245, 1135, 1100, 1075, 1030, 955, 840-815, 770, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.71 (m, 4 H), 7.44-7.34 (m, 6 H), 7.23 (d, 2 H, *J* = 8.4 Hz), 6.85 (d, 2 H, *J* = 9.0 Hz), 6.27 (d, 1 H, *J* = 9.0 Hz), 5.38 (d, 1 H, *J* = 10.2 Hz), 4.46 (d, 1 H, *J* = 11.7, Hz), 4.35 (d, 1 H, *J* = 11.7 Hz), 4.21-4.11 (m, 1 H), 3.89 (dd, 1 H, *J* = 1.8, 12.3 Hz), 3.79 (s, 3 H), 3.65-3.56 (m, 2 H), 3.42-3.28 (m, 2 H), 3.36 (s, 3 H), 3.19-3.13 (m, 2 H), 2.45-2.35 (m, 2 H), 2.11-1.95 (m, 4 H), 1.80-0.70 (m, 13 H), 1.74 (s, 3 H), 1.55 (s, 3 H), 1.53 (s, 3 H), 1.30 (s, 3 H), 1.07 (s, 9 H), 0.89 (s, 9 H), 0.74 (d, 3 H, *J* = 6.6 Hz), 0.03 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.0, 159.0, 145.2, 136.1, 136.0, 135.9, 134.9, 134.2, 133.8, 130.7, 129.4, 129.3, 129.0, 127.4, 127.3, 126.4, 113.6, 99.0, 98.0, 83.6, 75.0, 70.5, 69.4, 68.6, 67.5, 63.6, 57.3, 55.2, 44.3, 43.5, 41.8, 36.0, 34.8, 34.4, 34.1, 33.0, 30.9, 29.4, 28.3, 27.0, 26.0, 23.6, 19.3, 18.3, 16.3, 16.2, 14.1, 11.6, -5.3. Anal. Calcd for $C_{60}H_{90}O_9Si_2$: C, 71.24; H, 8.97. Found: C, 71.16; H, 9.09.

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REFERENCES

1. (a) This project was completed in August 1993 and was presented at seminars by REI at Harvard (October, 1993) and by LL at Columbia (October, 1994). (b) Taken in part from the PhD Thesis of TDR, University of Virginia, 1991.
2. (a) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiotics* **1987,** *40,* 1249. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Toshimi, Y.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochia, T. *J. Antibiotics* **1987,** *40,* 1256.
3. See, for example: Belshaw, P. J.; Meyer, S. D.; Johnson, D. D.; Romo, D.; Ikeda, Y.; Andrus, M.; Alberg, D. G.; Schulz, L. W.; Clardy, J.; Schreiber, S. L. *Synlett* **1994,** 381.
4. (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. *J. Am. Chem. Soc.* **1987,** *109,* 5031. (b) Taga, T.; Tanaka, H.; Goto, T.; Tada, S. *Acta Cryst.* **1987,** *C43,* 751.

5. (a) Fisher, M. J.; Chow, K.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1991,** *56,* 2900. (b) Askin, D.; Reamer, R. A.; Jone, T. K.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989,** *30,* 671. (c) Askin, D.; Reamer, R. A.; Joe, D.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989,** *30,* 6121. (d) Baumann, K.; Oberhauser, B.; Grassberger, M. A.; Haidl, G.; Schulz, G. *Tetrahedron Lett.* **1995,** *36,* 2231.

6. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hashimoto, M.; Hatanaka, H.; Kino, T.; Goto, T.; Okuhara, M. *Transplantation Proceedings* **1987,** *19(5),* Suppl. 6, 11. (b) ref. 4(a)

7. (a) For a compilation of the eariler synthetic studies, see: White, J. D.; Toske, S. G.; Yakura, T. *Synlett* **1994,** 591 and references cited therein. (b) Jarowicki, K.; Kocienski, P.; Norris, S.; O'shea, M.; Stocks, M. *Synthesis* **1995,** 195. (c) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995,** *60,* 7230.

8. Total synthesis: (a) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989,***111,* 1157. (b) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G.; *J. Am. Chem. Soc.* **1990,** *112,* 2998. (c) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990,***112,* 5583. (d) Ireland, R. E.; Gleason, G. L.; Geganas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996,** *61,* 6856.

9. Formal synthesis: (a) Jones, B. A.; Villalobos, A.; Linde, R. G.; Danishefsky, S. J. *J. Org. Chem.* **1990,** *55,* 2786. (b) Gu, R.; Sih, C. J. *Tetrahedron Lett.* **1990,** *31,* 3287. (c) Smith, A. B. III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett.* **1994,** *35,* 4271.

10. Adams, M. A.; Duggan, A. J.; Smolanoff, J.; Meinwald, J. *J. Am. Chem. Soc.* **1979,** *101,* 5364.

11. Ireland, R. E.; Wipf, P.; Miltz, W.; Vanasse, B. *J. Org. Chem.* **1990,** *55,* 1423.

12. Shiao, M.; Yang, C.; Lee, S.; Wu, T. *Synth. Commun.* **1988,** *18,* 359.

13. (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989,** *54,* 1570. For reviews, see: (b) Hoffmann, R. W. *Angew. Chem. Int. Ed. Eng.* **1982,** *21,* 555; (c) Roush, W. R. *J. Org. Chem.* **1991,** *56,* 4151. (d) Roush, W. R. in *Comprenhensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon: New York, 1990; Vol. 2, p1.

14. (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969,** *34,* 2543. (b) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991,** *32,* 7165.

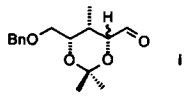
15. For a review, see: Schröder, M. *Chem. Rev.* **1980,** *80,* 187.

16. Ireland, R. E.; Wipf, P.; Roper, T, D. *J. Org. Chem.* **1990,** *55,* 2284.

17. (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1978,** *95,* 6136. (b) Tsuzuki, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1978,** 989. (c) Fukuyama, T.; Vranrsic, B.; Negri, O. P.; Kishi, Y. *Tetrahedron Lett.* **1978,** 2741. (d) Mihelich, E. D.; Daniels, K.; Erickhoff, D. J. *J. Am. Chem. Soc.* **1981,** *103,* 7690

18. Bartlett, P. A. *Tetrahedron* **1980,** *36,* 2.

19. It should be pointed out that Stork's *ancillary stereocontrol* strategy should be applicable in terms of correcting the C24 stereochemistry via, for example, structure **i**: Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982,** *104,* 4686.



i

20. Jenkins, S. R.; Walton, E. *Carbohyd. Res.* **1973,** *26,* 71.
21. (a) Wright, J. A.; Taylor, N. F. *Carbohyd. Res.* **1968,** *6,* 347. (b) Anderson, C. D.; Goodman, L.; Baker, B. R. *J. Am. Chem. Chem.* **1958,** *80,* 5237. (c) Opening of the epoxide ring of 2,3-anhydro-D-ribofuranosides (either α- or β-anomer) by nitrogen or sulfur based nucleophilic reagents resulted in nearly exculsive attack at the C3 position (see ref (b) and references cited there in). In the case of MeMgCl as nucleophile, it was found that the α-anomer led to the formation of the 3-*chloro*-derivative as the major product and a third compound that was consistent with 2-methyl derivative (see ref. 20). For this reason the α-anomer of **11** was converted to the β-anomer (MeOH, BF_3•ether, 50 °C, 78%).
22. For benzylation conditions, see: Czernecki, S.; Geogoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976,** 3535.
23. Theis, A. B.; Townsend, C. A. *Synth. Commun.* **1981,** *11,* 157.
24. In a related system high order cuprate $Me_2Cu(CN)Li_2$ was employed to open the epoxide of methyl 2,3-anhydro-5-deoxy-α-L-lyxofuranoside: Fleet, G. W. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983,** *24,* 3657.
25. Zinner, H. *Chem. Ber.* **1950,** *83,* 275.
26. Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979,** *101,* 7104.
27. Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974,** 203.
28. (a) Ireland, R. E.; Wipf, P.; Miltz, W.; Vanasse, B. *J. Org. Chem.* **1990,** *55,* 1423. (b) Ref. 16.
29. DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988,** *110,* 1901.
30. For recent reviews on the synthesis of spiroenones, see, Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. in *The Total Synthesis of Natural Products;* ApSimon, J. Ed.; Wiley: New York, 1992; Vol. 8, p 533.
31. (a) Mori, K.; Senda, S. *Tetrahedron* **1985,** *41,* 541. (b) Mori, K. *Tetrahedron* **1983,** *39,* 3107.
32. Baker, R.; Brimble, M.; Margaret, A. *Tetrahedron Lett.* **1986,** *27,* 3311.

33. (a) Rand, C. L.; van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981,** *46,* 4093. (b) Negishi, E.; van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985,** *107,* 6639. (c) A similar approach had been reported by Smith and coworkers: Smith, A. B.; Hale, K. J. *Tetrahedron Lett.* **1989,** *30,* 1037.

34. (a) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990,** *55,* 1425. (b) Ref. 28(a). (c) For a review on organocuprate chemistry via transmetallations, see, Wipf, P. *Synthesis* **1993,** 537.

35. For stereochemistry of vinyl cuprate addition to enones, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985,** *26,* 6015. (b) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983,** *24,* 2231.

36. For a comment on the nontriviality of C19-C20 double bond construction, see, Ragen, J. A.; Standaert, R. F.; Schreiber, S. L. in *Strategies and Tactics in Organic Synthesis*; Lindberg, T. Ed.; Academic: New York, Vol. 3, **1991,** Chapter 11, p 418.

37. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972,** *94,* 7159.

38. For the preparation of PMBBr: McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988,** *53,* 1947.

39. Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc. Perkin Trans. 1* **1985,** 2247.

40. Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988,** *29,* 4139.

41. Longer reaction times or more catalyst resulted in decomposition of the spiroketal unit. For oxidative deketalizations, see: Barton, D. H. R.; Magnus, F. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc. Perkin Trans. 1* **1972,** 542.

42. (a) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993,** *58,* 2899. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991,** *113,* 7277 and references cited therein.

43. Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990,** *55,* 5404

44. Imamoto, T.; Kusomoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. J. *J. Org. Chem.* **1984,** *49,* 3904.

45. Ireland, R. E.; Highsmith, T. K.; Gegnas, L. D.; Glleason, J. L. *J. Org. Chem.* **1992,** *57,* 5071.

46. For a successful addition of a similar Grignard reagent to a C27-methyl ketone, see: Rao, A. V. R.; Chakraborty, T. K.; Sankaranayanan, D.; Purandare, A. V. *Tetrahedron Lett.* **1991,** *32,* 547.

47. Horita, K.; Yoshida, T.; Tamaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986,** *42,* 3021.

48. (a) McMurry, J. E.; Scott, W. J.; *Tetrahedron Lett.* **1980,** *21,* 4313. (b) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988,** *21,* 47

49. (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991,** *56,* 650. (b) Ireland. R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976,** *98,* 2868. (c) Also, see: Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984,** *25,* 495.

50. Smith, A. B.; Hale, K. J. *Tetrahedron Lett.* **1989,** *30,* 6963.

51. Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987,** *28,* 4251.
52. For a recent review, see, Einhorn, K.; Einhorn, J.; Luche, J. *Synthesis* **1989,** 787.
53. (a) Ref. 45. (b) Ragan, J. A.; Nakatsuka, M.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Org. Chem.* **1989,** *54,* 4267.
54. Both α- and β-**44** were converted to the C16,C26-bis-triethylsilyl C36-ethoxyethyl ether through the following sequence: (1) TBAF, THF; (2) TESCl (xs), Pyr, DMAP; (3) DDQ, CH_2Cl_2-H_2O; (4) Ethyvinyl ether, TsOH. Comparision of the ^{13}C and ^{1}H NMR spectra of each sample with those of **38** (cf. Scheme 8) indicates that the sample derived from the major isomer possesses the desired α-OH at C26.
55. The following conditions led to only the β-iosmer: (a) $NaBH_4$, $CeCl_3$, MeOH, -78 °C. (b) $LiBH_4$, $EuCl_3$, MeOH-ether, -70 °C; cf. Kishi and coworkers, *J. Am. Chem. Soc.* **1989,** *111,* 7525. Conditions that led to the formation of more β-isomer (>2:1): (c) $LiBH_4$, THF, -78-0 °C. (d) DIBALH, PhMe, -78 °C. (e) RedAl, THF or PhMe, rt. (f) LAH, $MgBr_2$, ether, -78 °C; cf. Tamura, Y.; Annoura, H.; Fujioka, H. *Tetrahedron Lett.* **1987,** *28,* 5681. (g) LAH-SiO_2, ether, rt; cf. Kamitori, K.; Hojo, M.; Masuda, R.; Izumi, T.; Inoue, T. *Synthesis* **1983,** 387. (h) $ZnBH_4$, ether, 0 °C; cf. Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984,** *32,* 1411. Also ref. 9(b)). Conditions that led to the formation of ≤2:1 β, α-isomer: (i) LAH, ether, -78 or -100 °C (2:1) (j) LAH, $CeCl_3$, THF, -78 °C (2:1); cf. Fukuzawa, S.-i.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* **1986,** 1929. (k) LAH, LiBr, ether, -78 °C (2:1 plus what seemed to be a 1,3-allylic rearranged product). (l) LAH, LiI, ether, -78 °C (2:1), -100 °C (1:1); cf. Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M.*Tetrahedron Lett.* **1988,** *29,* 5419. The asymmetric catalyst system (*S*)-α,α-diphenyl-*B*-butyloxazoborolidine-catecholborane-PhMe did not react with enone **45** (-78 °C to rt), see: (m) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990,** *31,* 611.
56. Hughes, D. L. in *Org. Reactions*; Wiley: New York, 1992; Vol. 42, Chapter 2.
57. (a) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** 43, 2923. (b) Rigby, W.; Hunt, B. J. *Chem. Ind. (London)* **1967,** 1868.
58. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967,** *9,* 165. For a newer method, see, Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980,** 87.
59. Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991,** *56,* 4566.
60. Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977,** *42,* 3772.
61. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. *Tetrahedron Lett.* **1981,** *22,* 3455.

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