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Total Synthesis of (+)-Tautomycin

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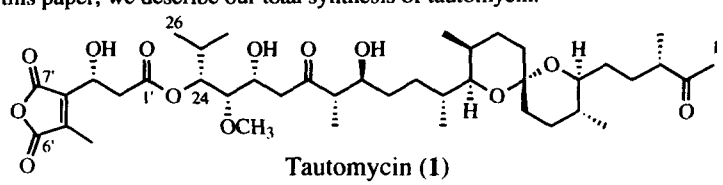
Abstract: A convergent stereocontrolled total synthesis of (+)-tautomycin (**1**), a specific inhibitor of protein serine/threonine phosphatases, has been achieved through an esterification of the C_1-$C_{7'}$ fragment A' **7 4** with the C_1-C_{26} fragment B' **7 6** by a modified Yamaguchi method and an aldol reaction of the C_{17}-C_{26} fragment C **5** with the C_1-C_{16} fragment D **6** using LDA as key steps. The fragments **5** and **6** have been constructed in a stereocontrolled manner, respectively. Copyright © 1996 Elsevier Science Ltd

Tautomycin (**1**), isolated by Isono and co-workers from a culture of *Streptomyces spiroverticillatus*, is an antifungal antibiotic.[1] It has been reported that **1** induces a morphological change (bleb formation) in human leukemia cells K562.[2] More recently, **1** has also been found to inhibit protein serine/threonine phosphatases (PPs) 1 and 2A specifically, and not to inhibit PP2C, similar to a well known tumor promoter, okadaic acid.[3] It is remarkable that tautomycin (**1**) inhibits strongly both phosphatases 1 and 2A, whereas okadaic acid, which is similar in its molecular size to **1**, inhibits PP2A much more strongly than PP1.

Determination of the structure of **1** as well as of the absolute configuration by X-ray analysis has not been achieved because of its non-crystallinity. Therefore, the structural determination of **1** was made on the basis of spectroscopic analysis of degradation products and their derivatives with the support of conformational calculation.[4] Its unique structure (with an ester linkage between the maleic anhydride moiety and the polyketide chain) and its interesting biological activities have encouraged synthetic studies on tautomycin,[5] and recently both Ichihara's group and Isobe's group have achieved total syntheses of **1**.[6,7]

We also took note of the remarkable biological activity of tautomycin on PPs and its unique structure, and started synthetic studies on tautomycin to hopefully provide non-natural derivatives of tautomycin as new biological tools for research on the PPs inhibition mechanism, and on the regulation of intracellular signal transduction. In this paper, we describe our total synthesis of tautomycin.[8]

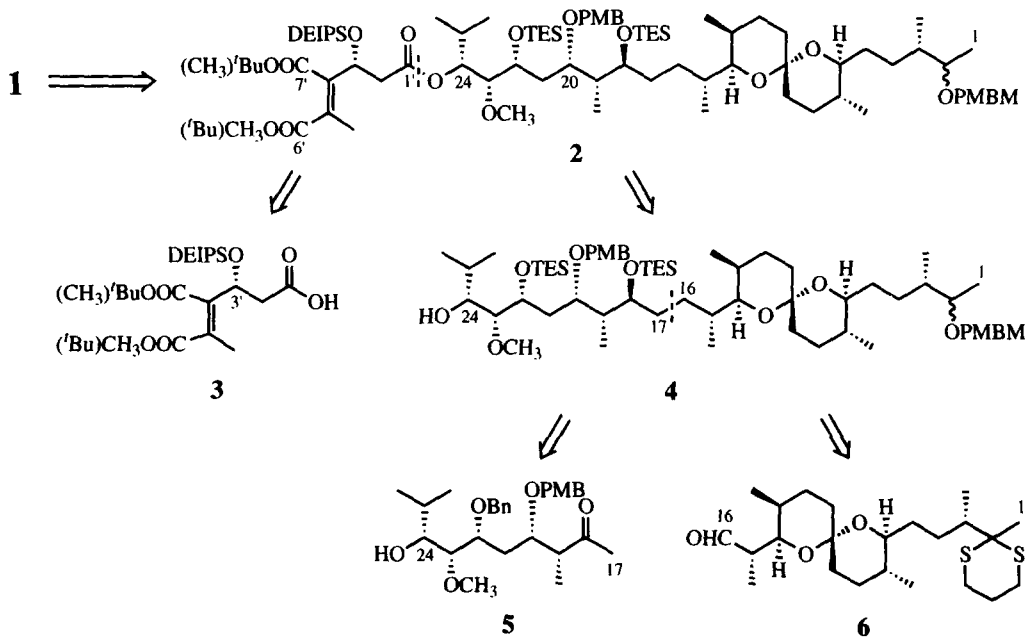


Tautomycin (**1**)

Retrosynthetic Plan

Examinations of the natural product have revealed its low chemical stability under various reaction conditions.[4] For instance, cleavage of the ester linkage and dehydration of the C_{21}-C_{22} bond occurs above pH 9, and a retro aldol reaction at the C_{18}-C_{19} bond and an epimerization at C_3 also occur above pH 10. Moreover, the maleic anhydride part of tautomycin (**1**) is a chemically unstable moiety, because 60% of which exists as the dicarboxylic acid in aqueous solvent at about pH 7. In consideration of their nature, the many functional groups have to be masked appropriately and deprotected under neutral or mildly acidic conditions at the final stage of the synthesis.

Our synthetic strategy toward **1** is summarized in **Scheme 1**. First, we decided to protect the hydroxy groups mainly as silyl ethers, for the reasons stated above. Moreover, we expected to prepare the carbonyl groups by oxidative deprotection of *p*-methoxybenzyl (PMB) groups with DDQ,[9] followed by oxidation of the resulting hydroxy groups; the maleic anhydride part was planned to be constructed from a more stable *t*-butyl methyl diester, or from a furan ring. Thus we chose the appropriately protected **2** as a key intermediate, which was expected to be synthesized from several fragments. Retrosynthetic disconnection of **2** at the ester linkage generated the C_1-C_7 fragment A **3** and the C_1-C_{26} fragment B **4**. It was planned to construct the latter through an aldol reaction using the C_{17}-C_{26} fragment C **5** and the C_1-C_{16} fragment D **6** as a key step. In the following sections, we describe our synthetic results and related discussions in detail.

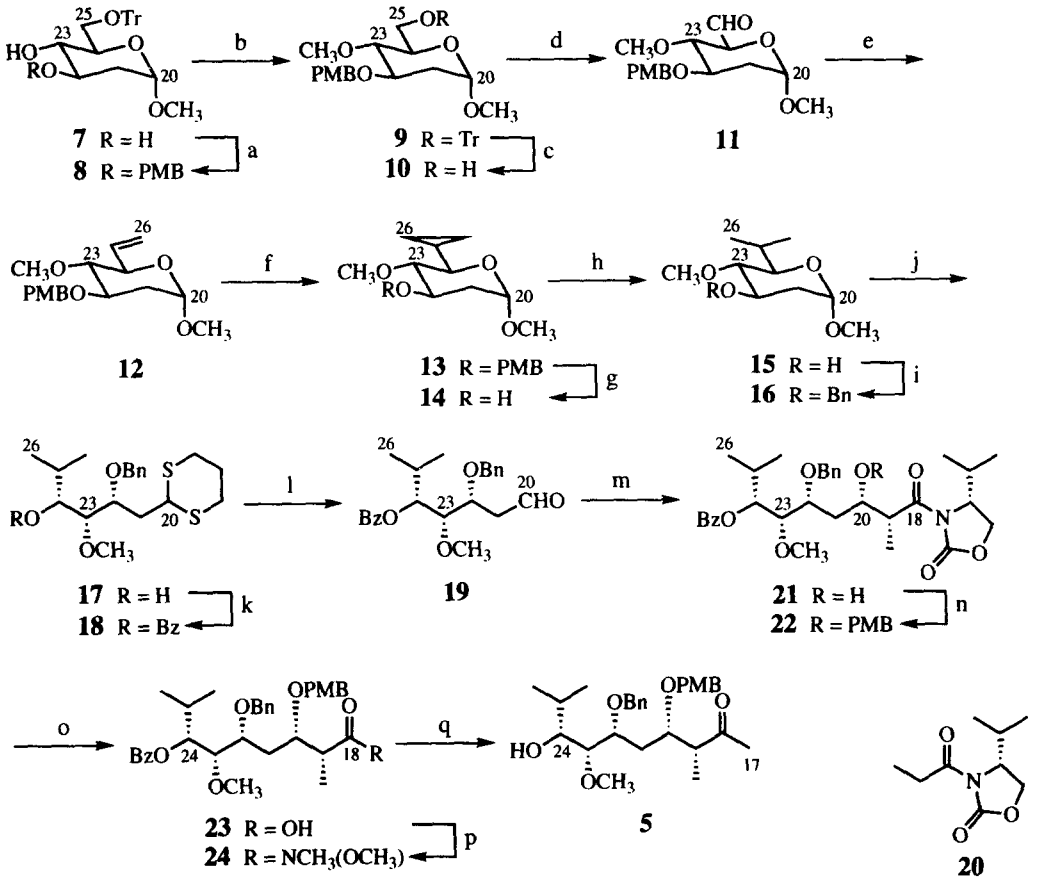


Scheme 1

Construction of the C_{17}-C_{26} Fragment C 5

As shown in **Scheme 2**, we selected the 2-deoxyglucose derivative **7**,[10] as a starting material for the synthesis of the fragment C **5**, because the six carbon atoms on **7** corresponded to the C_{20}-C_{25} positions of **5**. Namely, **7** has hydroxy groups with the correct absolute configurations at C_{22} and C_{23}, and it should be possible to convert the trityl ether to *gem*-dimethyl groups at C_{25}. Moreover, the acetal group would be thought as a masked form of both a carbonyl group at C_{20} and also a masked hydroxy group with the correct absolute configurations at C_{24}.

First the diol **7** was selectively mono-protected *via* the stannylene acetal,[11] followed by *O*-methylation and then cleavage of the trityl ether to give the alcohol **10**. The terminal isopropyl group was synthesized by a



Reagents and conditions : (a) *n*-Bu_2SnO, $PhCH_3$, reflux; CsF, PMBBr, DMF, r.t., 85% (conv. 93%); (b) NaH, CH_3I, THF, 0 °C to r.t., 97%; (c) HCO_2H-Et_2O-THF (4:3:1), r.t., 84%; (d) $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, -78 to 0 °C, 97%; (e) Zn, CH_2I_2, $Al(CH_3)_3$, THF, 0 °C, 76%; (f) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C; 99%; (g) DDQ, CH_2Cl_2-H_2O (18:1), r.t., 95%; (h) H_2, PtO_2, AcOH, 91%; (i) NaH, BnBr, THF-DMF, 0 °C to r.t., 100%; (j) $HS(CH_2)_3SH$, BF_3•OEt_2, CH_2Cl_2, 0 °C to r.t., 81%; (k) BzCl, Py, DMAP, CH_2Cl_2, 0 °C to r.t.; (l) NBS, $(CH_3)_2CO$-H_2O (19:1), -23 °C, 86% (2 steps); (m) **20**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 to 0 °C, 90%; (n) $Cl_3CC(NH)OPMB$, TfOH, Et_2O, r.t., 86%; (o) LiOOH, THF-H_2O (3 : 1), 0 °C to r.t.; (p) CH_3ONHCH_3•HCl, DEPC, Et_3N, DMF, 0 °C to r.t., 63% (2 steps); (q) CH_3Li, THF, -78 °C, 99%.

Scheme 2

formation-opening of a cyclopropane ring.[12] Namely, aldehyde **11**, given by Swern oxidation, was transformed to the olefin **12** using Nozaki reagent.[13] Unexpectedly, attempts at cyclopropanation using various Simmons-Smith type reactions did not afford satisfactory results. For example, using Et_2Zn and CH_2I_2, **13** was obtained only in low yield (46%) with several unidentified by-products. On the other hand, using the conditions of Suda,[14] cyclopropanation proceeded smoothly to yield **13** quantitatively. Although the cyclopropane ring of **13** was not opened by hydrogenolysis with Raney Ni (W2), after an oxidative cleavage of PMB group with DDQ, the cyclopropane ring in the resulting alcohol **14** was found to be regioselectively opened by hydrogenolysis with PtO_2 to give **15**.

According to our first synthetic plan, the C_{22} hydroxy group was planned to be protected as a silyl ether until the final stage of the total synthesis. TBS- or TES-protected alcohols, however, decomposed under the conditions of the following transformation of the acetal to acyclic intermediates. Thus, the C_{22} hydroxy group had to be protected as a Bn ether (**16**) temporarily. The Bn group proved to be the only protecting group which was stable under the conditions for transformation to **17** using 1,3-propanedithiol and $BF_3 \cdot Et_2O$. Protection of the resulting alcohol **17** as a Bz ester and cleavage of dithioacetal group with NBS[15] yielded the aldehyde **19**.

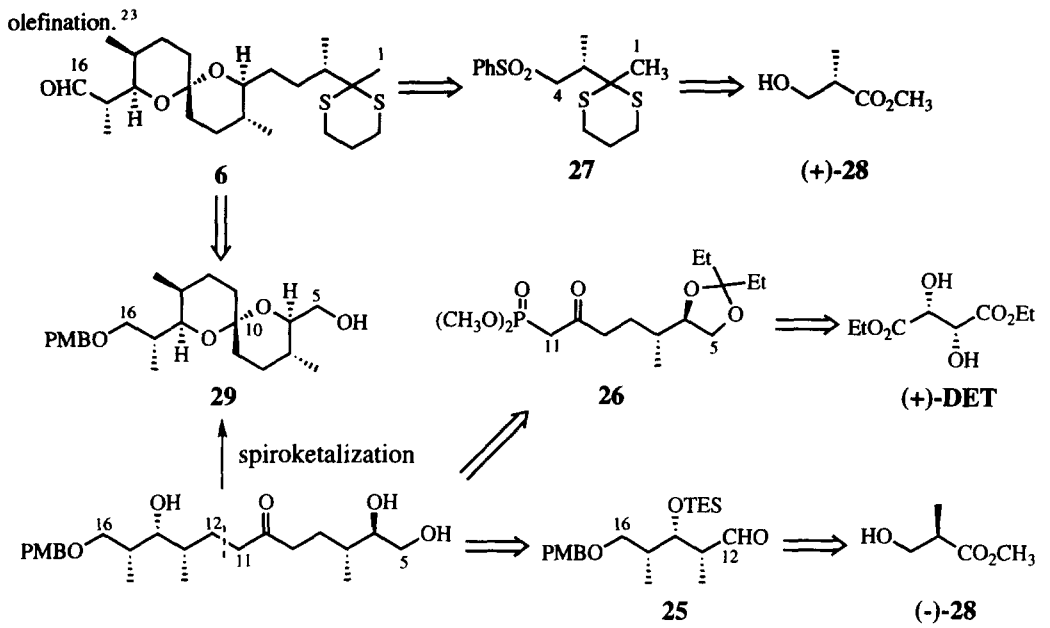
Construction of the C_{19} and C_{20} stereogenic centers was achieved by Evans' aldol reaction,[16] using the aldehyde **19** and the known oxazolidinone **20**, to yield the C_{18}-C_{26} unit **21** as a single diastereomer. The stereochemistry of the newly formed chiral centers was determined on the basis of the precedent[16] and the successful conversion to **1**. The resulting alcohol **21** was then protected as a PMB ether, giving **22**. After removal of the chiral auxiliary without cleavage of the Bz ester by selective hydrolysis using LiOOH,[17] the resulting carboxylic acid **23** was converted to the amide **24** using DEPC.[18] The amide **24** was treated with an excess of CH_3Li[19] to complete the synthesis of the hydroxyketone **5**, the C_{17}-C_{26} fragment C of **1**.

Construction of the C_1-C_{16} Fragment D 6

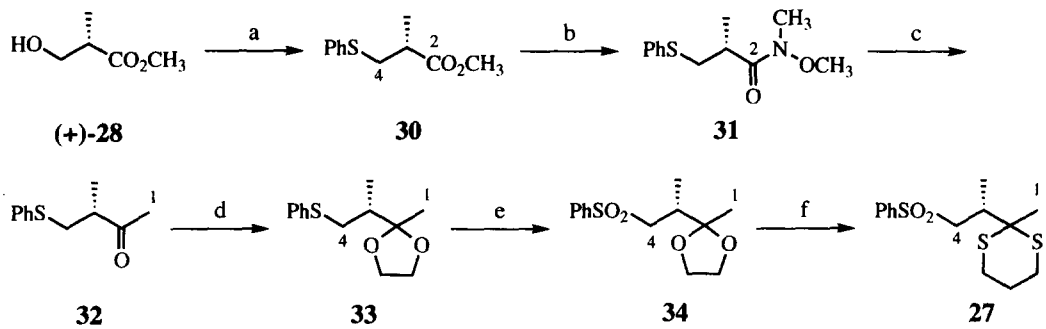
As shown in the retrosynthetic analysis outlined in **Scheme 3**, it was planned to construct the C_1-C_{16} fragment D **6** using a Horner-Emmons reaction and a Julia olefination[20] as key steps. When we started synthetic studies on tautomycin, the absolute configuration of the seven stereogenic centers which are present in **6** was unknown. We therefore selected chiral building groups of which the both enantiomers were commercially available as starting materials. Thus the C_{12}-C_{16} unit **25**, the C_5-C_{11} unit **26**, and the C_1-C_4 unit **27** were expected to be synthesizable from (-)-**28**, (+)-DET, and (+)-**28**, respectively.

The most important point regarding the synthesis of **6** is how to synthesize the characteristic spiroketal moiety in a stereocontrolled manner. Because the spiroketal **29** exists in the thermodynamically most stable form based on anomeric effect,[21] we thought that the corresponding keto-triol, which could be stereoselectively synthesized, would be easily spiroketalized in a stereoselective manner under acidic conditions.

The C_1-C_4 unit **27** was prepared as outlined in **Scheme 4**. The phenylsulfide **30**, which was obtained from (+)-**28**, was transformed to the Weinreb amide **31**.[22] On treatment with CH_3Li, **31** was converted to the methylketone **32**. After protection of the C_2 carbonyl group as an acetal (**33**), the resulting sulfide **33** was oxidized with *m*-CPBA to yield the sulfone **34** as a colorless solid. After recrystallization, acetal-exchange of the dioxolane **34** with 1,3-propanedithiol and $BF_3 \cdot Et_2O$ gave the dithiane **27**, the C_1-C_4 unit, in 79% yield from (+)-**28**. The sulfone **27** was recrystallized again to give the optically pure material for a subsequent Julia



Scheme 3

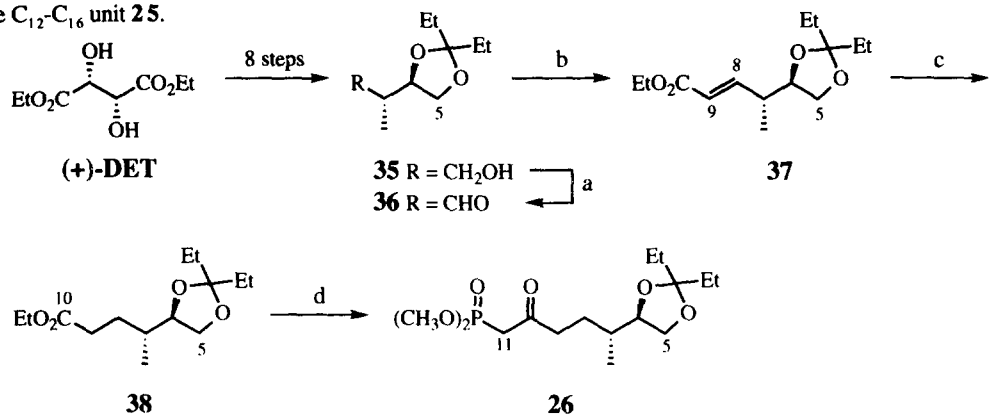


Reagents and conditions : (a) PhSSPh, *n*-Bu_3P, THF, 0 °C to r.t., 99%; (b) $Al(CH_3)_3$, CH_3ONHCH_3•HCl, CH_2Cl_2, reflux, 95%; (c) CH_3Li, THF, -78 °C, 99%; (d) $HO(CH_2)_2OH$, PPTS, PhH, reflux, 99%; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 100%; (f) $HS(CH_2)_3SH$, BF_3•OEt_2, CH_2Cl_2, 0 °C to r.t., 87%.

Scheme 4

Next the C_5-C_{11} unit **26** was prepared as shown in **Scheme 5**. (+)-DET was transformed to the alcohol **35** in a 8-step sequence of reactions,[24a] which we had utilized previously in a total synthesis of rhizoxin.[24b] The aldehyde **36**, obtained by Swern oxidation, was treated with potassium phosphonate generated from diisopropyl (ethoxycarbonylmethyl)phosphonate to yield α,β-unsaturated ester **37**. After the olefinic double bond had been reduced with Pd/C in an atmosphere of hydrogen, the resulting saturated ester **38** was transformed to the β-ketophosphonate **26**, the C_5-C_{11} unit, by treatment with lithium phosphonate generated from dimethyl

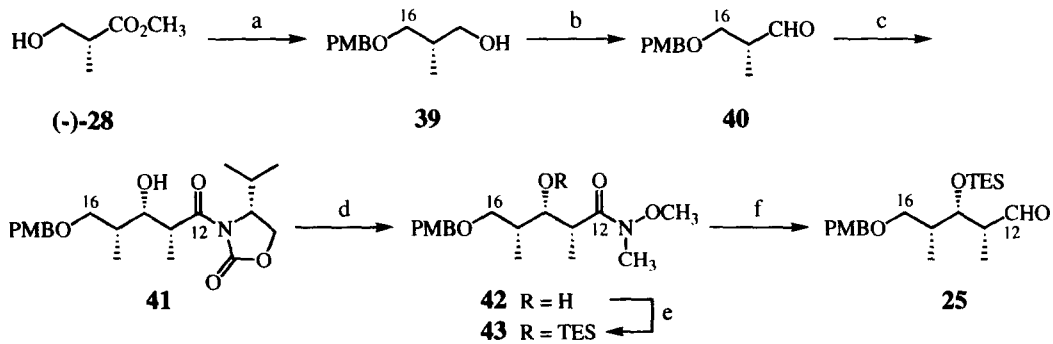
methylphosphonate. Because complete separation of **26** from excess dimethyl methylphosphonate proved to be impossible, a mixture of these phosphonates was used directly for the following Horner-Emmons reaction with the C_{12}-C_{16} unit **25**.



Reagents and conditions : (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C; (b) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, *t*-BuOK, THF, -78 °C to r.t., 93% (2 steps); (c) H_2, 10%-Pd/C, EtOH, r.t., 94%; (d) $(CH_3O)_2P(O)CH_3$, *n*-BuLi, THF, -78 °C, excellent yield.[25]

Scheme 5

For the synthesis of the C_{12}-C_{16} unit **25**, the most important point is how to construct the three consecutive stereogenic centers (C_{13}-C_{15}) in a stereocontrolled maner. Many reagent-controlled methods for the construction of this type of compound are known. For instance, a Sharpless epoxidation[26] followed by epoxide opening method, an Evans' aldol reaction,[16] or Brown's crotylborane method[27] may be cited as the most useful methods. In this case, as shown in **Scheme 6**, we decided to utilize an Evans' aldol reaction because of its advantages of a short number of steps and of its generally good diastereoselectivity. Protection of (-)-**28** as a PMB ether under acidic conditions and subsequent reduction with lithium aluminium hydride yielded the known alcohol **39**.[28] The aldehyde **40**, obtained by Swern oxidation of **39**, was treated with **20** under the standard conditions of Evans'



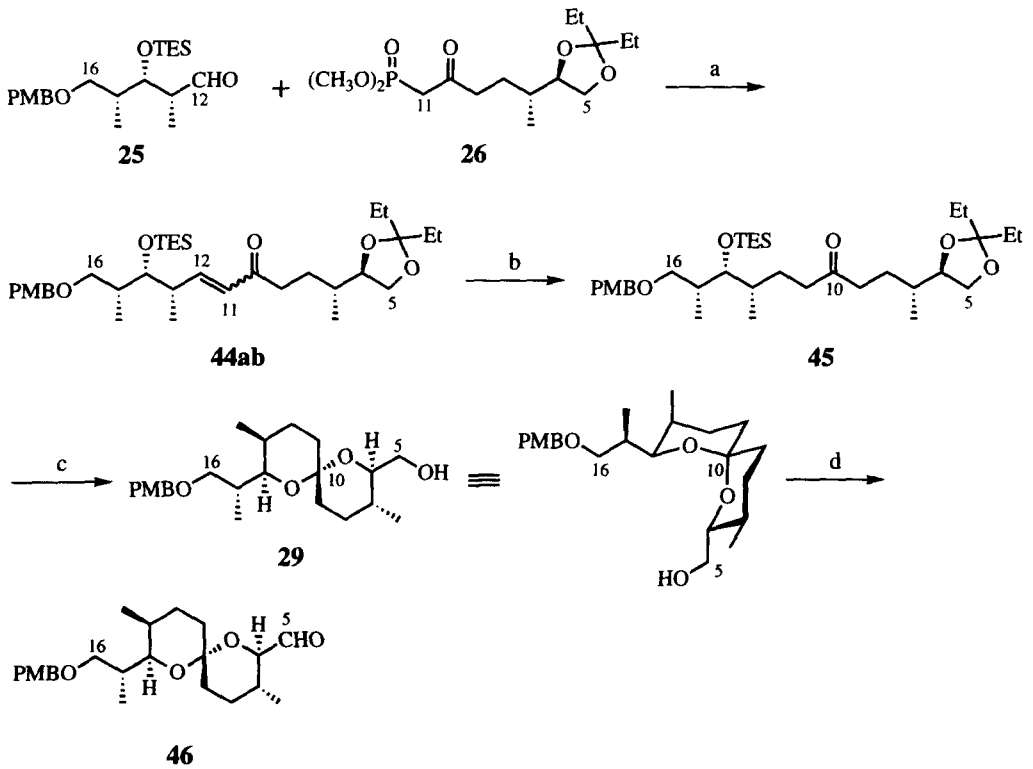
Reagents and conditions : (a) (1) $Cl_3CC(NH)OPMB$, PPTS, CH_2Cl_2, r.t., 93%; (2) $LiAlH_4$, Et_2O, 0 °C, 99%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C, 97%; (c) **20**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 to 0 °C; (d) $Al(CH_3)_3$, CH_3ONHCH_3•HCl, THF, -30 °C to r.t.; (e) TESCl, imidazole, DMF, r.t., 79% (*diastereoselection of the aldol reaction*, 89:11) (3 steps); (f) DIBAL-H, THF, -78 °C, 99%.

Scheme 6

aldol reaction to yield **41** as an inseparable mixture of diastereomers. The compound **41** was directly transformed to the amide **42** by treatment with $Al(CH_3)_3$ and $CH_3ONHCH_3{\cdot}HCl$.[29] The TES ether **43**, obtained from **42** by treatment with triethylchlorosilane and imidazole, was separated from its undesired diastereomer at this stage. As a result, **43** and its diastereomer was obtained in 79% overall yield by 3 steps from aldehyde **40** and with 89 : 11 *diastereoselection*. The stereochemistry of the newly formed chiral centers was again determined on the basis of the precedent[16] and the successful conversion to **1**. The amide **43** was reduced by DIBAL-H to afford the aldehyde **25**, the C_{12}-C_{16} unit.

With the three units **25**, **26** and **27** readily available, we attempted the crucial condensation reactions. First, a mild Horner-Emmons reaction, utilizing LiCl and DBU in CH_3CN, of the phosphonate **26** with the base sensitive aldehyde **25** was found to proceed smoothly without epmerization at C_{13} to give the corresponding enone **44ab** in a high *E*/*Z* ratio (*E* : *Z* = 93 : 1 by ^{1}H-NMR analysis) and in almost quantitative yield (**Scheme 7**).[30] The enone **44ab** was then converted to the ketone **45** without PMB cleavage by hydrogenation using Raney Ni (W2) in AcOEt. On the other hand, in the case of hydrogenation using Raney Ni (W2) in EtOH, overreduction occurred to yield the corresponding secondary alcohol.

We now had the protected keto-diol **45** as an open chain precursor of the C_5-C_{16} unit **29**. On treatment of

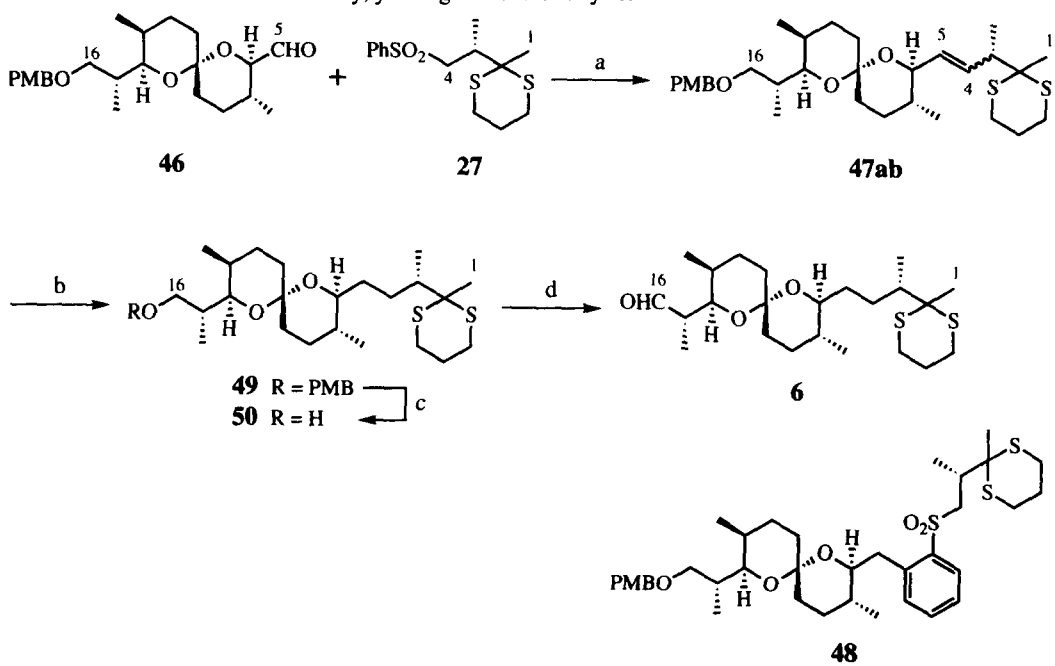


Reagents and conditions : (a) LiCl, *i*-Pr_2NEt, CH_3CN, r.t., 97% (*E* : *Z* = 93 : 1); (b) H_2, Raney Ni (W2), AcOEt, r.t., 100%; (c) CSA, CH_3OH, r.t., 98%; (d) $(COCl)_2$ DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C, 97%.

Scheme 7

45 with a catalytic amount of camphorsulfonic acid, the three hydroxy groups were, as expected, regenerated and spontaneous spiroketalization occurred in one pot, providing the alcohol **29** as a single product. Because the spectra data (^{1}H-NMR and ^{13}C-NMR) for **29** were consistent with those of the corresponding part of a degradation product of natural tautomycin **1**, the stereochemistry of **29** seemed likely to be the same as in the natural product, and was finally determined by the successful conversion to **1**. The C_5-C_{16} unit, aldehyde **46**, was then obtained by Swern oxidation of **29**.

We next attempted to complete the synthesis of the C_1-C_{16} fragment D **6** through a Julia olefination (**Scheme 8**). The sulfone **27** was treated with *n*-BuLi and the resulting lithium carbanion was coupled with the aldehyde **46**. Acetylation of the β-hydroxysulfone thus obtained and reductive elimination with Na-Hg gave the **47ab** in modest yield, as a mixture of stereoisomers. When the sulfone **27** was treated with 2 equiv of *n*-BuLi at -78 °C and then warmed to 0 °C to improve the reaction, the unexpected by-product **48** was produced in almost the same yield as **47ab** in a 3-step sequence. In general, a phenyl sulfone is converted to an α,α-dianion or an α,o-dianion with 2 equiv of *n*-BuLi.[31] Which of these is formed may be dependent upon substrate and reaction temperature. In our case, a mixture of the α,α-dianion and α,o-dianion was supposed to be formed even at 0 °C. Although the former would be converted over 3 steps to the desired α-alkylation product **47**, the latter would mainly be converted to the undesired *o*-alkylation product **48**. To avoid this side reaction, it was necessary to use just 1 equiv of *n*-BuLi so as to form the α-monoanion. Finally, addition of HMPA was found to increase the monoanion's reactivity, yielding **47ab** in 72% yield.



46 27 47ab 6 48

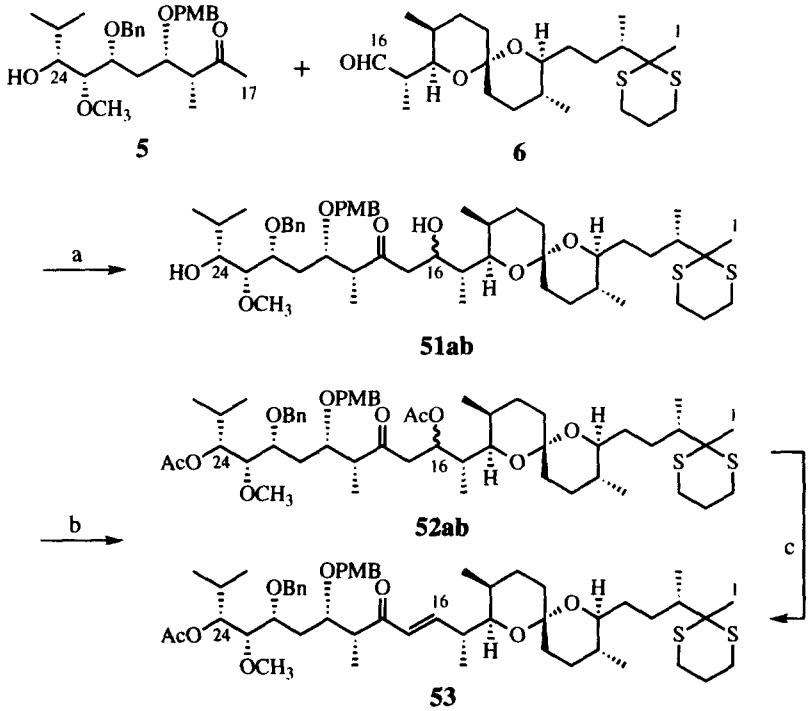
Reagents and conditions : (a) (1) **27**, *n*-BuLi (1 equiv), HMPA, THF, -78 to 0 °C then **46**, -78 to 0 °C; (2) Ac_2O, Py, DMAP, CH_2Cl_2, r.t.; (3) 5% Na-Hg, Na_2HPO_4, THF-CH_3OH (3:1), -20 °C, 72% (3 steps); (b) H_2, $(Ph_3P)_3RhCl$, PhH, r.t., 91 %; (c) DDQ, CH_2Cl_2-H_2O (18:1), r.t., 97%; (d) SO_3•Py, DMSO, Et_3N, r.t., 100%.

Scheme 8

We then addressed the efficient reduction of the olefin **47ab**. Reduction of **47ab** with diimide was our first choice, however, this reaction yielded only 49% of **49**. On the other hand, using Wilkinson's catalyst, which is known to be applicable to the reduction of an olefin containing a sulfur atom (such as the thioketal in **47ab**), the olefin **47ab** was successfully hydrogenated to yield **49** in 91% yield. Finally, oxidative cleavage of the PMB group with DDQ and SO_3•Py oxidation of the resulting alcohol **50** furnished aldehyde **6**, the C_1-C_{16} fragment D.

Construction of the C_1-C_{26} Fragment B 4

As shown in **Scheme 9**, the coupling of the C_{17}-C_{26} fragment C **5** and the C_1-C_{16} fragment D **6** was achieved by means of an aldol reaction. That is, the methylketone **5** was treated with 2 equiv of LDA at -78 °C, and aldol reaction of the resulting dianion with the aldehyde **6** furnished the coupling product **51ab** as a diastereomixture in 82% yield. The diol **51ab** was diacetylated, and the following β-elimination with DBU afforded the enone **53**.

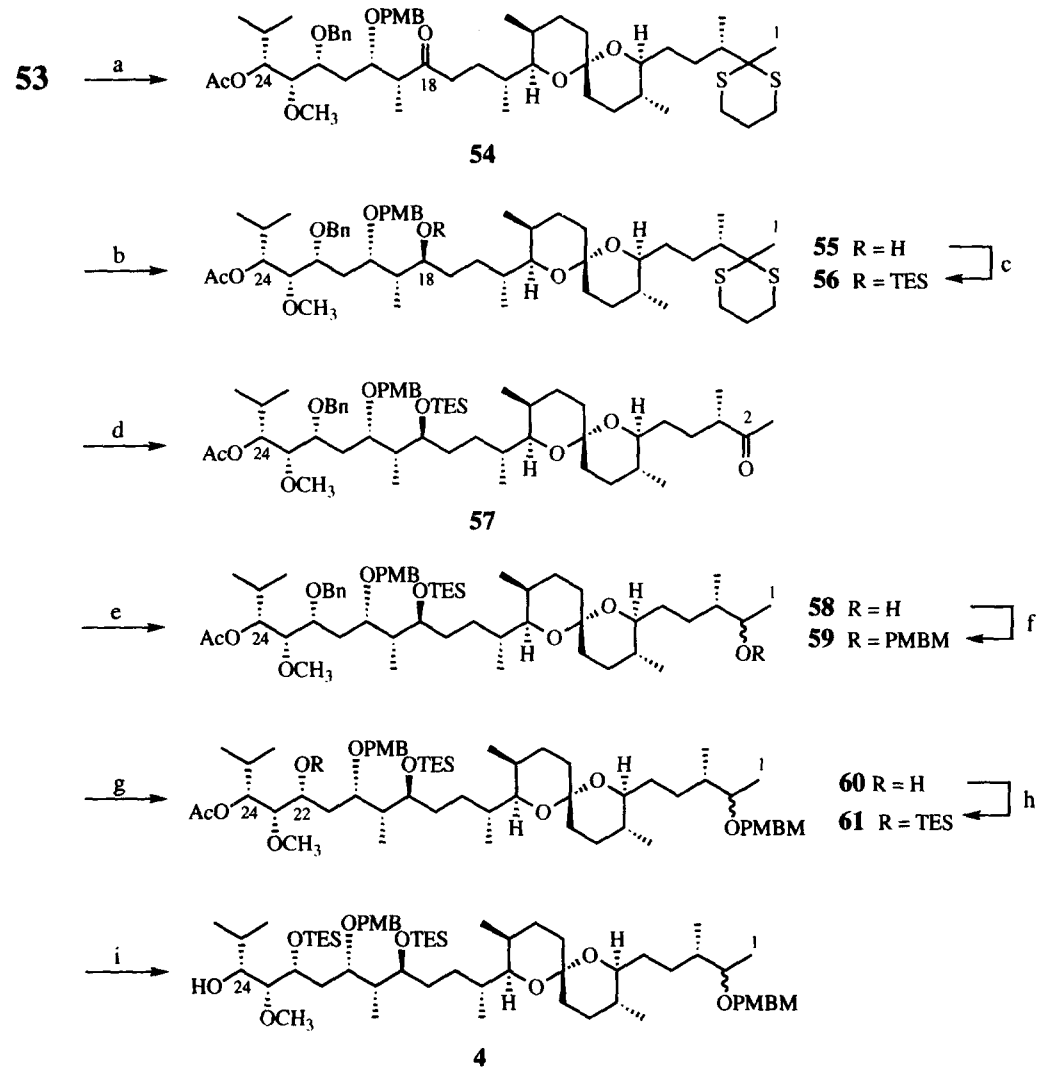


Reagents and conditions : (a) **5**, LDA (2 equiv), THF, -78 °C then **6**, 82%; (b) Ac_2O, DMAP, CH_2Cl_2, 0 °C to r.t.; (c) DBU, CH_2Cl_2, 0 °C to r.t., 98% (2 steps).

Scheme 9

Next we attempted further functional group manipulations including a key stereoselective reduction to complete the synthesis of the C_1-C_{26} fragment B (**Scheme 10**). Reduction of the enone **53** to the ketone **54** by hydrogenation with Wilkinson's catalyst turned out to be unsuccessful, perhaps due to its bulkiness and the

steric hindrance of the substituents in **53**. However, the desired 1,4-reduction was achieved under mild conditions using NaTeH[32] to give the ketone **54** quantitatively. Stereoselective reduction using bulky L-Selectride® then furnished the alcohol **55** as a mixture of inseparable epimers (2 : 1 selectivity). The major product was supposed to be the expected C_{18S} alcohol **55** based on asymmetric induction from the C_{19R} methyl group according to Cram's rule, and finally determined by the successful conversion to **1**. After TES-protection,



Reagents and conditions : (a) NaTeH, AcOH, EtOH, - 20 °C to r.t. (b) L-Selectride®, THF, -80 °C to -30 °C, 91% (2 steps) (*diastereoselection* 2 : 1); (c) TESOTf, *i*-Pr_2NEt, CH_2Cl_2, -40 °C, 89%; (d) NBS, $AgNO_3$, γ-collidine, CH_3CN-H_2O (17 : 3), 0 °C, 81%; (e) L-Selectride®, THF, -40 °C to -30 °C, 100%; (f) PMBMCl, *i*-Pr_2NEt, CH_2Cl_2, r.t., 89%; (g) H_2, Raney Ni (W2), EtOH, r.t., 80% (conv. 92%); (h) TESOTf, *i*-Pr_2NEt, CH_2Cl_2, -40 °C to -20 °C, 88%; (i) DIBAL-H, CH_2Cl_2, -78 °C, 100%.

Scheme 10

the diastereomers were readily separable.

It was next necessary to change protecting groups, in order to enable mild deprotection in the final stage of the synthesis. For cleavage of the dithioketal at C_2, reagents such as NBS, $Hg(ClO_4)_2$[33] and $PhI(OTFA)_2$[34] provided unsatisfactory results. However, using NBS, $AgNO_3$ and γ-collidine, the dithioketal **56** was converted to the ketone **57** in 81% yield with no epimerization at C_3. Selective reduction of the ketone **57** at C_2 was achieved using L-Selectride® to give **58** as an epimeric mixture. We used the diastereomixture **58** without separation, since the epimeric hydroxy group would be re-oxidized at a later stage of the synthesis. Surprisingly all attempts to protect **58** as a PMB ether failed. Protection with 4-methoxybenzyl 2,2,2-trichloroacetimidate under acidic conditions using reagents such as camphorsulfonic acid was impossible, because **58** includes acid-sensitive functional groups. Protection with PMB-Br using bases such as NaH, or the stronger KH and in combination with TBAI (used for the purpose of *in situ* generation of more reactive PMB-I) did not proceeded at all. We therefore selected a *p*-methoxybenzyloxymethyl (PMBM) group for protection of the alcohol **58**. The PMBM group was developed by Kozikowski,[35] and a PMBM ether can be formed easily from some secondary alcohols, and later deprotected with DDQ like a PMB ether. As expected, the desired PMBM ether **59** was obtained in 89% yield.

Next, benzyl ether **59** at C_{22} was deprotected by hydrogenolysis using Raney Ni (W2). The resulting alcohol **60** was protected as a TES ether to afford **61**. Methanolysis of the acetate **61** at C_{24} did not proceed, most likely due to steric hindrance, and reductive deprotection using DIBAL-H in THF at -78 °C was similarly unsuccessful. The expected reaction did, however, proceed at 0 °C albeit in low yield and with unknown by-products. We then examined solvent effects. Deprotection with DIBAL-H in pentane, which might conceivably have higher reactivity than in THF, did not give a satisfactory result even at -78 °C, also giving several more-polar by-products. Satisfactory reductive deprotection was finally achieved in CH_2Cl_2 at -78 °C and furnished the alcohol **4**, the C_1-C_{26} fragment B, in quantitative yield.

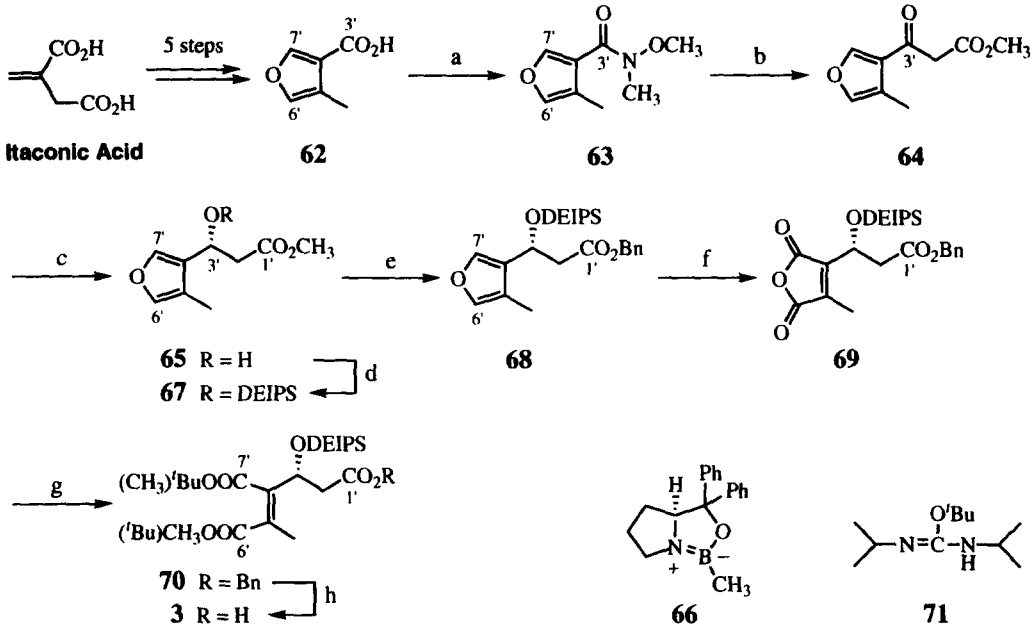
Construction of the C_1-C_7 Fragment A 3

The C_1-C_7 fragment A **3** was synthesized using an asymmetric reduction of β-keto ester as a key step (**Scheme 11**). By using the literature procedure[36] itaconic acid, a commercially available starting material, was transformed to the carboxylic acid **62** in a 5-step sequence of reactions. Using DEPC as a condensing reagent the carboxylic acid **62** was converted to the amide **63**, which was treated with the lithium enolate[37] of methyl acetate to yield the β-keto ester **64**.

The key asymmetric reduction was achieved by two methods. Asymmetric hydrogenation using Noyori's Ru-BINAP catalyst[38] yielded the alcohol **65** quantitatively in 86% ee.[39] Alternatively, asymmetric reduction using BH_3•THF and the oxazaborolidine catalyst **66** developed by Corey[40] also yielded **65** in 57% yield and with 92% ee. Optically pure **65** was obtained using chiral phase HPLC (Daicel Chiralcel OD, hexane : 2-PrOH = 9 : 1).

Protection of **65** as a diethylisopropylsilyl (DEIPS) ether furnished **67**,[6,41] which was transformed to the benzyl ester **68** via the carboxylic acid. The furan part of **68** was first treated with singlet oxygen,[42] and a subsequent PCC oxidation then furnished the maleic anhydride **69**. The maleic anhydride **69** was then planned to be converted to the much more stable *t*-butyl methyl diester **70** which could be re-converted to **69** under

acidic conditions.[6] Unexpectedly the half ester, given by methanolysis of **69**, could not be transformed to the *t*-butyl ester using *t*-BuOH, DCC and DMAP. On the other hand, an excellent esterificaion was achieved by treatment with the *t*-butylisourea **71** prepared from *t*-BuOH and 1,3-diisopropylcarbodiimide.[43] However, cleavage of DEIPS ether also occurred, and so, the resulting alcohol was therefore re-protected to yield the triester **70** as a mixture of isomers (9 : 1). Finally hydrogenolysis of the benzyl ester **70** with Pd/C under 1 atm pressure of hydrogen furnished the carboxylic acid **3**, the C_1-C_7 fragment A.



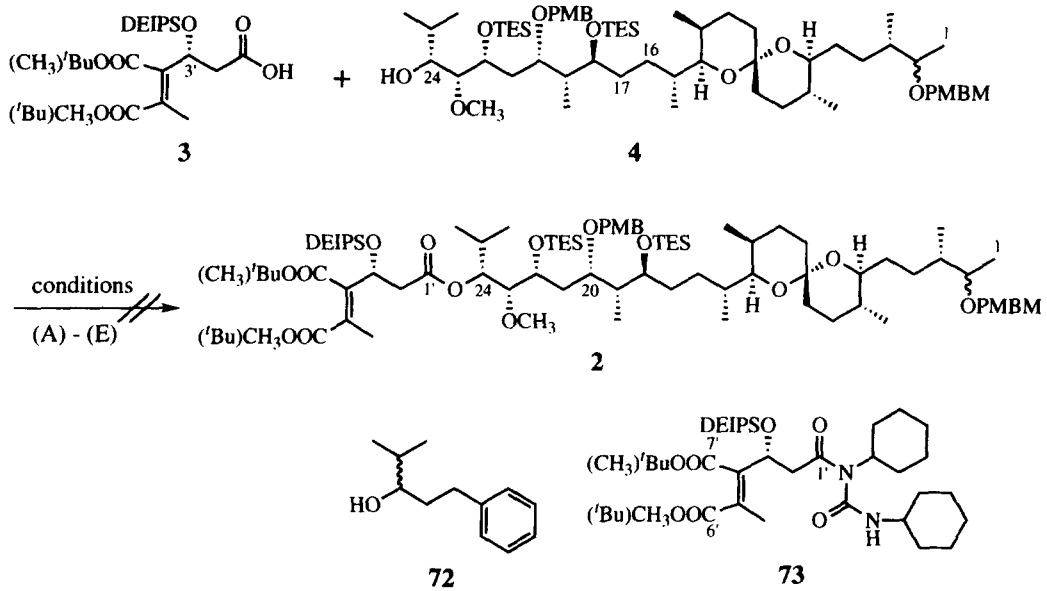
Reagents and conditions : (a) CH_3ONHCH_3•HCl, DEPC, Et_3N, DMF, 0 °C to r.t., 97%; (b) $AcOCH_3$, LDA, THF, -78 °C to 0 °C then HCl, 0 °C to r.t., 58% (conv. 73%); (c) (A) H_2, 100 atom, *cat.*(*S*)-BINAP-Ru(II), CH_3OH, 28 °C, 100%, 86% ee; (B) (*S*)-**66**, BH_3•THF, THF, 0 °C, 57% (conv. 67%), 92% ee; (d) DEIPSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 98%; (e) (1) LiOH, THF-H_2O (6 : 1), r.t.; (2) BnOH, DCC, DMAP, THF, r.t. 62% (2 steps); (f) (1) O_2, *hυ*, rose bengal, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (2) PCC, MS4A, CH_2Cl_2, r.t. 88% (2 steps); (g) (1) CH_3OH, Et_3N, 0 °C; (2) **70**, CH_2Cl_2, 40 °C; (3) DEIPSCl, imidazole, CH_2Cl_2, 0 °C to r.t. 66% (3 steps); (h) H_2, Pd/C, CH_3OH, r.t., 87%.

Scheme 11

Esterification with Two Fragments

As previously discussed, the C_1-C_7 fragment A **3** and the C_1-C_{26} fragment B **4** had been synthesized stereoselectively, and many of the functional groups of those fragments appropriately protected. We then examined a variety of methods for the esterification using these two fragments (**Scheme 12**). At first, model esterification using the carboxylic acid **3** and the model alcohol **72** (instead of **4**) was found to proceed in good yield using either (A) DCC-DMAP method, (B) Keck's method,[44] (C) modified Yamaguchi method,[45] (D) BOPCl method[46] or (E) DMC method.[47] Unfortunately, however, these procedures did not give satisfactory

results for coupling of the fragment **3** and **4**. For example, *N*-acyl transformation occurred to yield by-product **73** together with the recovered alcohol **4** by (A) DCC-DMAP method. This undesired transformation was suppressed by (B) Keck's method, together with the addition of DMAP•HCl; however, the expected coupling product **2** was never obtained. The other methods (C), (D) and (E) gave also recovered **4** without producing **2** at all. These unsatisfactory results appeared to be explicable on the grounds of severe steric hindrance.

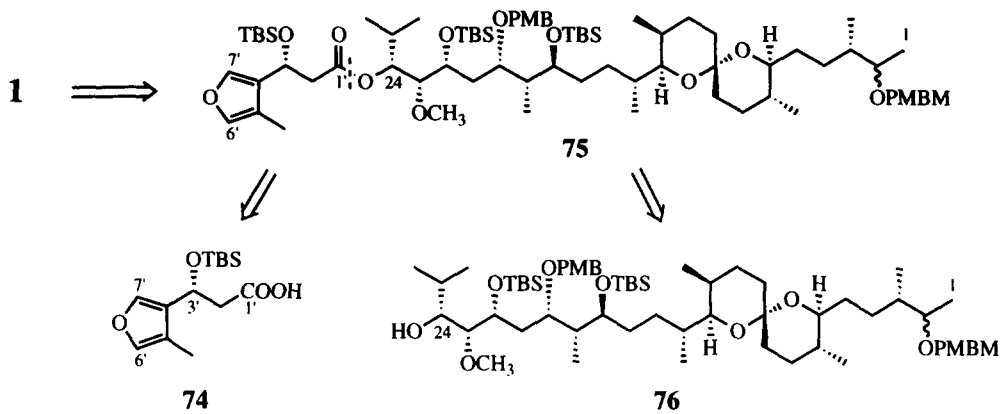


Reagents and conditions : (A) DCC, DMAP, THF, r.t.; (B) DCC, DMAP, DMAP•HCl, toluene, r.t. to 60 °C; (C) **3**, 2,4,6- trichlorobenzoyl chloride, Et_3N, toluene, r.t. then **4**, DMAP, toluene, 50 °C to 80 °C; (D) *N,N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride, Et_3N, DMAP, CH_2Cl_2, r.t. to 40 °C; (E) 2-chloro-1,3-dimethylimidazolinium chloride, DMAP, CH_2Cl_2, r.t. to 40 °C.

Scheme 12

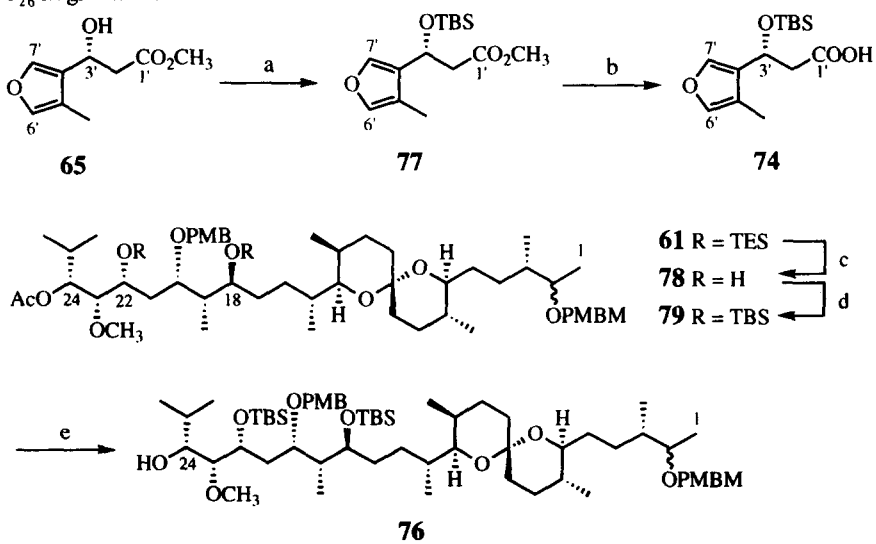
Total Synthesis

Having obtained unsatisfactory results as discussed above, we revised our strategy concerning the critical esterification. That is, **74** with its pre-synthesized furan ring was adopted as the new C_1-C_7 fragment for esterification instead of the much more bulky diester **3**. We expected that after esterification, total synthesis could be achieved through cleavage of the PMB and PMBM groups, followed by oxidation of the resulting diol, transformation of the furan moiety to the maleic anhydride, and final full deprotection of the silyl groups. For transformation of the furan moiety to maleic anhydride, however, the furan having two ketone groups could not be treated with singlet oxygen, since the ketone group was also reactive towards singlet oxygen. We thus chose Isobe's strategy,[7] which utilized NBS treatment, Jones oxidation, and PCC oxidation for the synthesis of the maleic anhydride. To this end the three hydroxy groups were protected as TBS ethers (instead of TES or DEIPS ethers) which would be stable to the conditions of Jones oxidation. Our final retrosynthesis of tautomycin **1** is summarized in **Scheme 13**.



Scheme 13

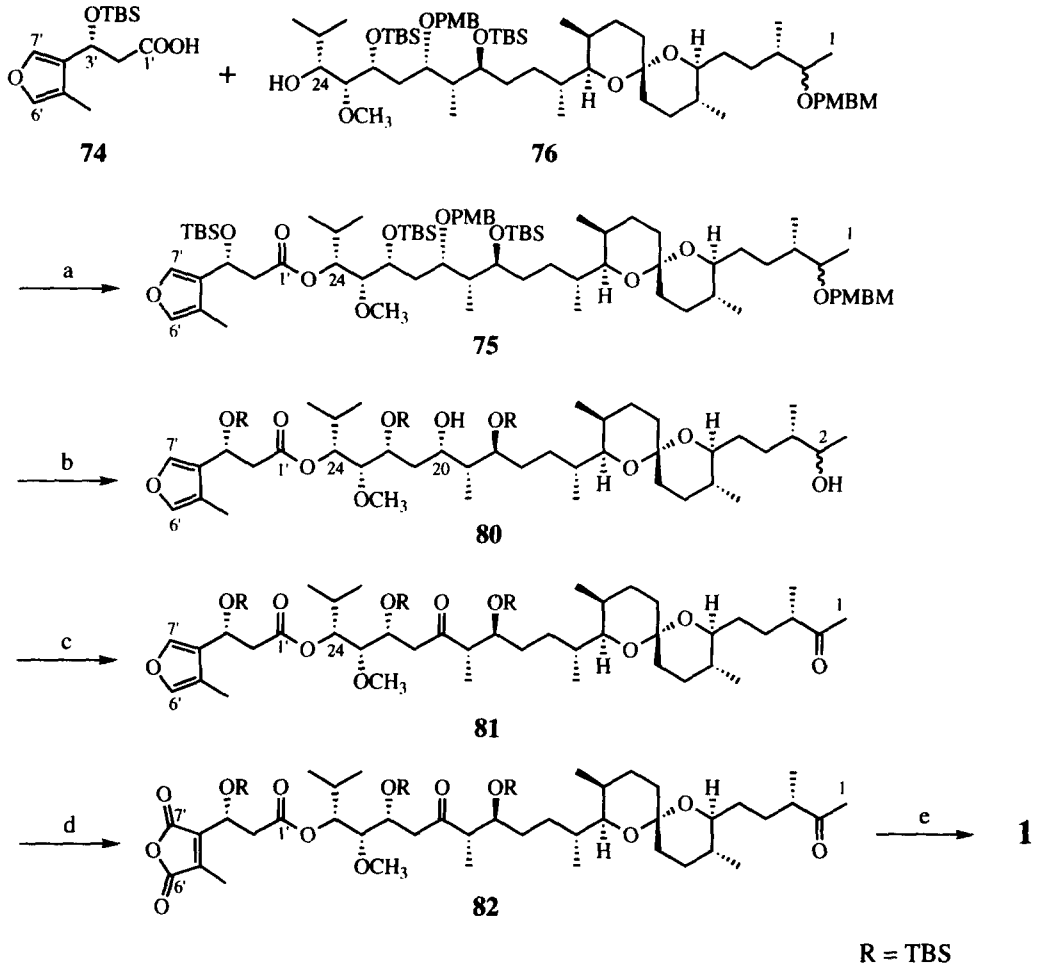
The new C_1-C_7 fragment **74** was synthesized by protection of **65** as a TBS ether followed by hydrolysis of the ester **77** (**Scheme 14**). In addition, the new C_1-C_{26} fragment **76** was synthesized from the TES ether **61**. When the TES groups of **61** were first deprotected with TBAF, an unexpected by-product, which we assumed to be produced through intramolecular migration of the acetyl group, was obtained along with the expected diol **78**. On the other hand, effective deprotection of the silyl groups was successfully achieved under the mildly acidic conditions using HF•Py, with suppression of undesired migration. The resulting alcohol was protected as a TBS diether to give **79**, and the following reductive deprotection with DIBAL-H furnished the alcohol **76**, the new C_1-C_{26} fragment B'.



Reagents and conditions : (a) TBSOTf, CH_2Cl_2, *i*-Pr_2NEt, 0 °C, 99%; (b) LiOH, THF-H_2O (6 : 1), r.t., 100%; (c) HF•Py, THF, 0 °C to r.t.; (d) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, -40 °C to 0 °C; (e) DIBAL-H, CH_2Cl_2, -78 °C, 75% (3 steps) (the migration product, 11%).

Scheme 14

With these new fragments in hand, the critical esterification was attempted toward total synthesis (**Scheme 15**). As a result, the most efficient conditions for the esterification were found to be a modified Yamaguchi method using a large excess of DMAP to afford the ester **75** in 72% yield (conv. 88%). The resulting ester **75** was then treated with DDQ for an oxidative cleavage of PMB and PMBM groups. However, deprotection using DDQ in CH_2Cl_2-H_2O (9 : 1) gave only a small amount of diol **80**, because the deprotection of the PMBM group at C_2 proceeded very slowly compared with that of PMB group at C_{20}, and in addition, an unexpected side reaction occurred. For suppressing this side reaction, cleavage in CH_2Cl_2-phosphate buffer pH 6.8 (9 : 1) was examined, and fortunately these conditions were found to furnish the diol **80** in 76% along with the mono-ol (deprotected only at C_{20}) in 10% yield. The diol **80** was oxidized with TPAP to afford diketone **81**.



Reagents and conditions : (a) **74**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, r.t. then **76**, DMAP, toluene, 50 °C, 72% (conv. 88%); (b) DDQ, CH_2Cl_2-phosphate buffer pH 6.8 (9 : 1), r.t., 76%; (c) TPAP, NMO, MS4A, CH_3CN, r.t., 87%; (d) (1) NBS, THF-phosphate buffer pH 7.0 (4 : 1), 0 °C; (2) Jones reagent, acetone, 0 °C, 62% (2 steps); (3) PCC, MS4A, CH_2Cl_2, r.t. 38%; (e) HF•Py, THF, r.t.[7]

Scheme 15

The diketone **81** was transformed to a mixture of the four isomeric furanones by treatment with NBS at 0 °C,[48] followed by Jones oxidation. The mixture of these isomers was oxidized using PCC to afford the maleic anhydride **82**. The synthetic **82** exhibited identical properties to those of the tris-TBS-tautomycin which was synthesized from natural tautomycin (TBSOTf, 2,6-lutidine, CH_2Cl_2, -30 °C to 0 °C). Finally full deprotection of the TBS groups of **82** was achieved using freshly prepared HF•Py to yield (+)-tautomycin (**1**).[7]

Conclusions

A total synthesis of (+)-tautomycin (**1**), a specific inhibitor of PPs, has been accomplished. The key features of the synthetic route to the each fragment are as follows. 1) The C_{17}-C_{26} fragment C **5** was prepared, in a highly selective manner, from the 2-deoxyglucose derivative **7** *via* a diastereoselective aldol reaction. 2) The C_1-C_{16} fragment D **6** was synthesized in a highly selective manner from the three units **25**, **26** and **27** by means of a Horner- Emmons reaction, a thermodynamically controlled spiroketalization and a Julia olefination, as *key* steps. The three units **25**, **26** and **27** were also obtained from (-)-**28**, (+)-DET, (+)-**28** respectively. 3) The C_1-C_{26} fragment B' **76** was synthesized *via* an aldol reaction between **5** and **6**, followed by stereoselective reduction using L-Selectride®, and then unification of protecting groups. 4) The C_1-C_7 fragment A' **74** was obtained *via* an asymmetric reduction (92% ee) of β-keto ester **64**, and finally 5) the esterification of **74** and **76** by means of a modified Yamaguchi method, followed by functional group manipulations, provided (+)-tautomycin (**1**).

Moreover this route may facilitate the preparation of non-natural derivatives and fragments of **1**, for use as new biological tools for research concerning the PPs inhibition mechanism and the associated regulation of intracellular signal transduction.

Experimental Part

General. Melting points are uncorrected. Optical rotations were measured on a JASCO DIP-140 polarimeter. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 diffraction grating infrared spectrophotometer. NMR spectra were recorded on a JEOL GSX-400 or a JEOL EX-270 spectrometer. Chemical shifts are reported in ppm on the δ scale relative to TMS (δ = 0.00 for ^{1}H-NMR) or using residual $CHCl_3$ (δ = 7.26 for ^{1}H-NMR and δ = 77.0 for ^{13}C-NMR) as an internal reference. EI-Mass spectra were measured on a JEOL JMS-DM303 or a JEOL JMS-SX-102A instruments. FAB-Mass spectra were mesured on a JEOL JMS-HX110 instrument. Flash column chromatography was carried out on Merck Art. 9385, Silica gel 60 (230-400 mesh ASTM). Thin layer chromatography was carried out on Merck Art. 5715, Silica gel 60 F_{254} plates. Solvents were dried rigorously and reagents were purified by standard methods. All experiments were performed under anhydrous conditions in an atmosphere of Ar, unless otherwise mentioned.

Methyl 2-deoxy-3-*O*-(4-methoxybenzyl)-6-*O*-trityl-α-D-*arabino*-hexopyranoside (8). A solution of methyl 2-deoxy-6-*O*-trityl-α-D-*arabino*-hexopyranoside **7** (3.21 g, 7.62 mmol) and dibutyltin oxide (2.22 g, 8.92 mmol) in toluene (50 ml) was azeotropically refluxed with stirring for 6 hr. The mixture was concentrated, and then pumped dry under reduced pressure for 1 hr. To this residue in DMF (90 ml) was added

cesium fluoride (2.52 g, 16.6 mmol) at room temperature and the resulting solution was stirred for 1 hr. To the reaction mixture was added 4-methoxybenzyl bromide (1.8 ml, 12.7 mmol). After being stirred for 12 hr, the whole reaction mixture was quenched with water and then diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 8) to give the alcohol **8** (3.51 g, 6.50 mmol; 85% (conv. 93%)) as a white foam and also the recovered starting material **7** (292 mg, 0.70 mmol). $[\alpha]^{24}_D$ +34.6 ° (*c* 0.99, $CHCl_3$); IR (KBr) 3445, 1559, 1458, 1247, 1052 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.31-7.19 (m, 11H), 6.86 (m, 2H), 4.83 (dd, *J* = 3.5, 0.7 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 3.78 (s, 3H), 3.74 (ddd, *J* = 11.7, 9.0, 4.9 Hz, 1H), 3.69 (ddd, *J* = 9.4, 5.5, 3.5 Hz, 1H), 3.56 (dd, *J* = 9.4, 9.0 Hz, 1H), 3.39 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.35 (s, 3H), 3.34 (dd, *J* = 9.9, 5.5 Hz, 1H), 2.51 (br s, 1H), 2.23 (ddd, *J* = 13.0, 4.9, 0.7 Hz, 1H), 1.63 (ddd, *J* = 13.0, 11.7, 3.5 Hz, 1H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 159.3, 144.0, 130.6, 129.4, 128.7, 127.8, 127.0, 113.9, 98.4, 86.8, 76.7, 72.3, 71.3, 70.5, 64.3, 55.2, 54.5, 34.8; Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found : C, 75.26; H, 6.77.

Methyl 2-deoxy-3-*O*-(4-methoxybenzyl)-4-*O*-methyl-6-*O*-trityl-α-D-*arabino*-hexopyranoside (9). To a solution of alcohol **8** (791 mg, 1.46 mmol) in THF (20 ml) were added sodium hydride (60% in oil, 98 mg, 2.45 mmol) and iodomethane (0.17 ml, 2.73 mmol) at 0 °C. After being stirred for 12 hr at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 8) to give the methyl ether **9** (788 mg, 1.42 mmol; 97%) as a white solid. mp 142-143 °C (recrystallized from AcOEt-hexane); $[\alpha]^{22}_D$ +66.8 ° (*c* 1.04, $CHCl_3$); IR (KBr) 3061, 2936, 2899, 2826, 1611, 1514, 1447, 1249, 1172, 1130, 1102, 1054 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 6H), 7.31-7.19 (m, 11H), 6.86 (m, 2H), 4.87 (dd, *J* = 3.7, 1.2 Hz, 1H), 4.56 (s, 2H), 3.79 (s, 3H), 3.78 (ddd, *J* = 11.5, 8.9, 5.2 Hz, 1H), 3.61 (ddd, *J* = 9.9, 4.4, 1.8 Hz, 1H), 3.40 (dd, *J* = 9.9, 1.8 Hz, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 3.31 (dd, *J* = 9.9, 8.9 Hz, 1H), 3.15 (dd, *J* = 9.9, 4.4 Hz, 1H), 2.24 (ddd, *J* = 13.0, 5.2, 1.2 Hz, 1H), 1.72 (ddd, *J* = 13.0, 11.5, 3.7 Hz, 1H); EI-MS *m/z* 311 (M^+-Tr); Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.90. Found : C, 75.82; H, 7.11.

Methyl 2-deoxy-3-*O*-(4-methoxybenzyl)-4-*O*-methyl-α-D-*arabino*-hexopyranoside (10). To a solution of trityl ether **9** (301 mg, 0.542 mmol) in THF/Et_2O (1 : 3, 13.3 ml) was added formic acid (13.3 ml) slowly at rt. After being stirred for 1 hr, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 1) to give the alcohol **10** (143 mg, 0.457 mmol; 84%) as a colorless oil. $[\alpha]^{22}_D$ +109.1 ° (*c* 1.38, $CHCl_3$); IR (neat) 3472, 2934, 2834, 1613, 1514, 1248, 1179, 1048 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.88 (m, 2H), 4.78 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.57 (s, 2H), 3.84 (ddd, *J* = 11.4, 9.2, 5.2 Hz, 1H), 3.83 (ddd, *J* = 11.9, 5.1, 3.7 Hz, 1H), 3.80 (s, 3H), 3.76 (ddd, *J* = 11.9, 7.7, 4.2 Hz, 1H), 3.59 (s, 3H), 3.54 (ddd, *J* = 9.5, 4.2, 3.7 Hz, 1H),

3.31 (s, 3H), 3.19 (dd, J = 9.5, 9.2 Hz, 1H), 2.23 (ddd, J = 13.1, 5.2, 1.2 Hz, 1H), 1.93 (dd, J = 7.7, 5.1 Hz, 1H), 1.60 (ddd, J = 13.1, 11.4, 3.6 Hz, 1H); EI-MS *m/z* 312 (M^+), 121 (PMB: base peak); Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found : C, 61.28; H, 7.78.

Methyl 2-deoxy-3-*O*-(4-methoxybenzyl)-4-*O*-methyl-α-D-*arabino*-hexodialdopyranoside (11). To a solution of oxalyl chloride (0.37 ml, 4.24 mmol) in CH_2Cl_2 (10 ml) was added DMSO (0.64 ml, 9.02 mmol) dropwise at -78 °C. After being stirred for 30 min at the same temperature, a solution of alcohol **10** (880 mg, 2.82 mmol) in CH_2Cl_2 (3 ml) was slowly added via cannula. After stirring for an additional 30 min at the same temperature, *N*,*N*-diisopropylethylamine (3.3 ml, 18.9 mmol) was added. The whole reaction mixture was allowed to warm to 0 °C over 1 h, and then poured into saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 3 : 2) to give the aldehyde **11** (845 mg, 2.72 mmol; 97%) as a colorless oil. IR (neat) 2935, 2835, 1739, 1613, 1514, 1248, 1209, 1180, 1110, 1048 cm^{-1}; EI-MS *m/z* 310 (M^+), 281 (M^+-CHO), 121 (PMB), 31 (OMe: base peak); Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found : C, 61.68; H, 6.94. This compound, which easily forms the monohydrate, was dried for 12 hr with P_2O_5 under reduced pressure for the subsequent olefination.

(2*R*, 3*S*, 4*R*, 6*S*)-3,6-Dimethoxy-4-(4-methoxybenzyl)oxy-2-vinyl-3,4,5,6-tetrahydro-2*H*-pyran (12). To a suspension of activated zinc dust (16.3 g, 250 mmol) in THF (150 ml) was added diiodomethane (6.70 ml , 83.2 mmol) at rt. After being stirred for 30 min, trimethylaluminium (1.02 *M* in hexane, 16.5 ml, 16.8 mmol) was added dropwise at 0 °C. After being stirred for additional 1 hr at rt, the mixture was cooled to 0 °C, and aldehyde **11** (6.46 g, 20.8 mmol) in THF (20 ml) was added via cannula. After being stirred for 1.5 hr at the same temperature, the whole reaction mixture was quenched with 2*N* aqueous NaOH, and filtered. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 9) to give the olefin **12** (4.87 g, 15.8 mmol; 76%) as a colorless oil. $[\alpha]^{22}_D$+100.4 ° (*c* 1.08, $CHCl_3$); IR (neat) 2934, 2902, 2833, 1613, 1514, 1370, 1248, 1181, 1116, 1049 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.87 (m, 2H), 5.97 (ddd, J = 17.3, 10.5, 6.2 Hz, 1H), 5.41 (ddd, J = 17.3, 1.6, 1.5 Hz, 1H), 5.26 (ddd, J = 10.5, 1.5, 1.4 Hz, 1H), 4.79 (dd, J = 3.7, 1.2 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 3.94 (dddd, J = 9.7, 6.2, 1.6, 1.4 Hz, 1H), 3.82 (ddd, J = 11.6, 8.8, 5.1 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 3H), 3.31 (s, 3H), 2.94 (dd, J = 9.7, 8.8 Hz, 1H), 2.22 (ddd, J = 13.2, 5.1, 1.2 Hz, 1H), 1.65 (ddd, J = 13.2, 11.6, 3.7 Hz, 1H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 159.1, 135.7, 130.9, 129.2, 117.4, 113.8, 98.4, 84.7, 76.6, 71.8, 71.7, 60.8, 55.3, 54.6, 35.7; EI-MS *m/z* 308 (M^+), 277 (M^+-OMe), 121 (PMB: base peak); EI-HRMS Calcd for $C_{17}H_{24}O_5$: 308.1624; Found : 308.1618.

(2*R*, 3*S*, 4*R*, 6*S*)-2-Cyclopropyl-3,6-dimethoxy-4-(4-methoxybenzyl)oxy-3,4,5,6-tetrahydro-2*H*-pyran (13). A solution of olefin **12** (635 mg, 2.06 mmol) and diazomethane (about 13.6 mmol) in Et_2O (20 ml) was divided into four parts (**a large scale experiment is very dangerous**). A

catalytic amount of $Pd(OAc)_2$ was added to each of them at 0 °C. The reaction mixture was filtered, and the filtrate was concentrated, and purified by silica gel flash chromatography (AcOEt/hexane, 1 : 9) to give the compound with cyclopropyl side chain **13** (659 mg, 2.04 mmol; 99%) as a pale yellow oil. $[\alpha]^{22}_D$ +86.0 ° (*c* 1.19, $CHCl_3$); IR (neat) 2934, 2898, 2833, 1614, 1514, 1248, 1124, 1052 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.87 (m, 2H), 4.73 (dd, *J* = 3.7, 1.2 Hz, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.73 (ddd, *J* = 11.4, 8.8, 5.2 Hz, 1H), 3.65 (s, 3H), 3.26 (s, 3H), 3.06 (dd, *J* = 9.5, 8.8 Hz, 1H), 2.87 (dd, *J* = 9.5, 7.9 Hz, 1H), 2.17 (ddd, *J* = 13.1, 5.2, 1.2 Hz, 1H), 1.62 (ddd, *J* = 13.1, 11.4, 3.7 Hz, 1H), 1.00 (m, 1H), 0.63 (m, 1H), 0.57-0.48 (m, 2H), 0.31 (m, 1H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 159.1, 131.1, 129.1, 113.8, 98.2, 86.1, 76.5, 74.4, 72.0, 60.8, 55.2, 54.4, 35.8, 13.2, 2.7, 1.7; EI-MS *m/z* 322 (M^+), 121 (PMB: base peak); Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found : C, 67.03; H, 8.15.

(2*R*,3*S*,4*R*,6*S*)-2-Cyclopropyl-3,6-dimethoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-ol (14). To a solution of PMB ether **13** (7.96 g, 24.7 mmol) in CH_2Cl_2 (90 ml) and water (5ml) was added DDQ (95%, 8.85 g, 37.0 mmol) at rt. After being stirred for 50 min, the reaction mixture was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 1) to give the alcohol **14** (4.72 g, 23.3 mmol; 95%) as a white solid. mp 82-83.5 °C (recrystallized from hexane); $[\alpha]^{22}_D$ +113.3 ° (*c* 1.00, $CHCl_3$); IR (KBr) 3384, 2941, 1443, 1390, 1126, 1103, 1072, 1044 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.75 (dd, *J* = 3.7, 0.9 Hz, 1H), 3.87 (m, 1H), 3.66 (s, 3H), 3.28 (s, 3H), 2.93 (dd, *J* = 9.2, 9.1 Hz, 1H), 2.79 (dd, *J* = 9.1, 8.8 Hz, 1H), 2.46 (br d, 1H), 2.12 (ddd, *J* = 13.1, 5.2, 0.9 Hz, 1H), 1.69 (ddd, *J* = 13.1, 11.8, 3.7 Hz, 1H), 0.99 (m, 1H), 0.70-0.50 (m, 3H), 0.34 (m, 1H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 98.2, 87.5, 74.8, 68.3, 60.9, 54.5, 37.2, 13.4, 3.0, 2.5; EI-MS *m/z* 171 (M^+-OMe), 74 ($CH_2CH(OMe)O$: base peak); Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found : C, 59.28; H, 9.20.

(2*R*,3*S*,4*R*,6*S*)-2-Isopropyl-3,6-dimethoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-ol (15). A solution of the compound with cyclopropyl side chain **14** (2.32 g, 11.5 mmol) and platinum (IV) oxide hydrate 308 mg (1.36 mmol) in AcOH (15 ml) was stirred vigorously under 1 atm pressure of hydrogen at rt for 5 days. The reaction mixture was filtered, and the filtrate was neutralized with saturated aqueous $NaHCO_3$ at 0 °C, and diluted wih AcOEt. The organic layer was separated, and the aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2) to give the compound with isopropyl side chain **15** (2.15 g, 10.5 mmol; 91%) as a white solid. mp 65-67 °C (recrystallized from AcOEt-hexane); $[\alpha]^{24}_D$ +154.9 ° (*c* 1.00, $CHCl_3$); IR (KBr) 3448, 2965, 2936, 1472, 1349, 1210, 1107, 1084, 1042 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.75 (dd, *J* = 3.8, 1.2 Hz, 1H), 3.96 (dddd, *J* = 11.5, 8.9, 5.1, 2.5 Hz, 1H), 3.57 (s, 3H), 3.38 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.29 (s, 3H), 2.93 (dd, *J* = 9.8, 8.9 Hz, 1H), 2.32 (d, *J* = 2.5 Hz, 1H), 2.10 (ddd, *J* = 13.0, 5.1, 1.2 Hz, 1H), 2.06 (dqq, *J* = 7.0, 7.0, 2.0 Hz, 1H), 1.65 (ddd, *J* = 13.0, 11.5, 3.8 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 98.1, 83.3, 73.8, 69.4, 60.4, 54.4, 37.4, 27.2, 20.4, 15.0; EI-MS *m/z* 204 (M^+), 173 (M^+-OMe), 161 (M^+-

$CHMe_2$), 74 ($CH_2CH(OMe)O$: base peak); Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found : C, 58.55; H, 10.00.

(2*R*, 3*S*, 4*R*, 6*S*)-4-Benzyloxy-2-isopropyl-3,6-dimethoxy-3,4,5,6-tetrahydro-2*H*-pyran (16). To a solution of alcohol **15** (2.11 g, 10.3 mmol) in THF (40 ml) were added DMF (10 ml) and NaH (60%, 680 mg, 17.0 mmol) and benzyl bromide (1.8 ml, 15.1 mmol) at 0 °C. After being stirred for 12 hr at rt, the reaction mixture was quenched with MeOH. After being stirred for an additional 1 hr, saturated aqueous NH_4Cl was added. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 12) to give the benzyl ether **16** (3.03 g, 10.3 mmol; 100%) as a colorless oil. $[\alpha]^{22}_D$+109.0 ° (*c* 1.22, $CHCl_3$); IR (neat) 2960, 2932, 1370, 1209, 1118, 1095, 1064 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H), 4.75 (dd, *J* = 3.8, 1.1 Hz, 1H), 4.63 (s, 2H), 3.82 (ddd, *J* = 11.5, 8.6, 5.2 Hz, 1H), 3.59 (s, 3H), 3.38 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.28 (s, 3H), 3.07 (dd, *J* = 9.8, 8.6 Hz, 1H), 2.23 (ddd, *J* = 13.1, 5.2, 1.1 Hz, 1H), 2.11 (dqq, *J* = 6.9, 6.9, 2.0 Hz, 1H), 1.60 (ddd, *J* = 13.1, 11.5, 3.8 Hz, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 138.8, 128.3, 127.6, 127.5, 98.1, 81.5, 77.9, 74.0, 71.8, 60.5, 54.3, 35.5, 27.0, 20.3, 15.1; MS *m/z* 294 (M^+), 263 (M^+-OMe), 251 (M^+-$CHMe_2$), 91 (Bn: base peak); Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found : C, 69.66; H, 8.77.

(3*R*, 4*R*, 5*R*)-5-Benzyloxy-6-(1,3-dithian-2-yl)-4-methoxy-2-methyl-3-hexanol (17). To a solution of benzyl ether **16** (307 mg, 1.04 mmol) in CH_2Cl_2 (10 ml) were added 1,3-propanedithiol (0.11ml, 1.10 mmol) and BF_3•Et_2O (0.13 ml, 1.06 mmol) at 0 °C. After being stirred for 24 hr at rt, the reaction mixture was quenched with 2*N* aqueous NaOH. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 7) to give the 1,3-dithiane **17** (313 mg, 0.845 mmol; 81%) as a colorless oil. $[\alpha]^{22}_D$+31.4 ° (*c* 1.14, $CHCl_3$); IR (neat) 3490, 2929, 2825, 1451, 1422, 1098 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 4.66 (s, 2H), 4.14 (m, 1H), 4.07 (dd, *J* = 8.6, 6.0 Hz, 1H), 3.56 (ddd, *J* = 8.2, 3.6, 3.4 Hz, 1H), 3.38 (s, 3H), 3.19 (dd, *J* = 8.1, 3.4 Hz, 1H), 3.09 (d, *J* = 3.6 Hz, 1H), 2.87-2.71 (m, 4H), 2.21-2.06 (m, 3H), 1.94-1.80 (m, 2H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 137.5, 128.6, 128.2, 78.7, 75.5, 74.8, 73.0, 58.4, 44.1, 35.5, 30.1, 29.7, 29.4, 26.0, 19.7, 15.8; EI-MS *m/z* 370 (M^+), 327 (M^+-$CHMe_2$), 91 (Bn: base peak); Anal. Calcd for $C_{19}H_{30}O_3S_2$: C, 61.58; H, 8.16. Found : C, 61.32; H, 8.33.

(1*R*, 2*S*, 3*R*)-3-Benzyloxy-4-formyl-1-isopropyl-2-methoxybutyl benzoate (19). To a solution of alcohol **17** (614 mg, 1.66 mmol) in CH_2Cl_2 (15 ml) were added pyridine (2.04 ml, 25.2 mmol), benzoyl chloride (1.88 ml, 16.2 mmol), and a catalytic amount of DMAP at 0 °C. After being stirred for 3 days at rt, the reaction mixture was quenched with 1*N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by

silica gel flash chromatography (AcOEt/hexane, 1 : 10) to give a mixture of the benzoyl ester **18** and benzoyl chloride. To a solution of NBS (2.49 g, 14.0 mmol) in acetone/water (95 : 5, 45 ml) was added a solution of the mixture (1,3-dithiane **18** and benzoyl chloride) in acetone/water (95 : 5, 17 ml) at -23 °C. After being stirred for 10 min at the same temperature, the reaction mixture was quenched with aqueous $Na_2S_2O_3$ and then diluted with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 6) to give the aldehyde **19** (545 mg, 1.42 mmol; 86% (2 steps)) as a yellow oil. IR (neat) 2965, 2933, 1722, 1452, 1314, 1272, 1099, 1071 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, *J* = 2.3, 1.2 Hz, 1H), 8.02 (m, 2H), 7.55 (m, 1H), 7.40 (m, 2H), 7.26-7.21 (m, 5H), 5.35 (dd, *J* = 7.7, 3.8 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.16 (ddd, *J* = 6.4, 5.2, 3.5 Hz, 1H), 3.54 (dd, *J* = 7.7, 3.5 Hz, 1H), 3.45 (s, 3H), 2.83 (ddd, *J* = 16.9, 5.2, 1.2 Hz, 1H), 2.79 (ddd, *J* = 16.9, 6.4, 2.3 Hz, 1H), 2.26 (dqq, *J* = 6.8, 6.8, 3.8 Hz, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); EI-MS *m/z* 221 (M^+-BnOCHCH$_2$CHO), 105 (Bz: base peak), 91 (Bn).

[3(2*R*, 3*S*, 5*R*, 6*S*, 7*R*), 4*R*]-3-(7-Benzoyloxy-5-benzyloxy-3-hydroxy-6-methoxy-2,8-dimethyl-1-oxononyl)-4-isopropyl-2-oxazolidinone (21). To a solution of (*R*)-(-)-4-isopropyl-3-propionyl-2-oxazolidinone **20** (0.48 ml, 2.84 mmol) in CH_2Cl_2 (10 ml) were added *n*-Bu_2BOTf (1.0 *M* in CH_2Cl_2, 3.4 ml, 3.40 mmol) and triethylamine (0.57 ml, 4.09 mmol) at 0 °C. After being stirred for 1 hr at 0 °C, the reaction mixture was cooled to -78 °C. To the cooled mixture was added aldehyde **19** (519 mg, 1.35 mmol) in CH_2Cl_2 (3 ml). After being stirred for 1.5 hr at -78 °C, the whole reaction mixture was gradually warmed to 0 °C, stirred for 0.5 hr at the same temperature, and then quenched with pH 7 phosphate buffer (6.5 ml) in MeOH (20 ml). After 5 min, 30 % H_2O_2/MeOH (1 : 1, 6.5 ml) was further added. The quenched solution was stirred for 1 h at 0 °C, and concentrated (bath temperature ≤ 30 °C). To the resulting mixture were added AcOEt and water. The organic layer was separated, and the aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 2 : 5) to give the alcohol **21** (694 mg, 1.22 mmol; 90%) as a white foam. $[\alpha]^{22}_D$ -25.1 ° (*c* 1.21, $CHCl_3$); IR (KBr) 3421, 1774, 1719, 1702, 1618, 1560, 1459 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.53 (m, 1H), 7.39 (m, 2H), 7.29-7.19 (m, 5H), 5.34 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.62 (d, *J* = 11.1 Hz, 1H), 4.51 (d, *J* = 11.1 Hz, 1H), 4.41 (ddd, *J* = 8.2, 3.9, 3.0 Hz, 1H), 4.23 (dd, *J* = 9.0, 8.2 Hz, 1H), 4.19 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.05 (m, 1H), 3.85 (m, 1H), 3.78 (dq, *J* = 6.9, 3.3 Hz, 1H), 3.60 (dd, *J* = 6.8, 3.9 Hz, 1H), 3.50 (s, 3H), 3.23 (d, *J* = 2.2 Hz, 1H), 2.34 (dqq, *J* = 7.0, 7.0, 3.9 Hz, 1H), 2.25 (dqq, *J* = 6.8, 6.7, 4.3 Hz, 1H), 1.95-1.83 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 176.3, 165.9, 153.6, 138.1, 132.8, 130.4, 129.7, 128.3, 128.2, 128.1, 127.5, 80.4, 77.6, 76.3, 72.5, 70.1, 63.3, 59.5, 58.3, 42.8, 34.8, 29.0, 28.4, 20.2, 17.8, 17.0, 14.7, 12.0; EI-MS *m/z* 570 (M^++H), 105 (Bz: base peak), 91 (Bn); Anal. Calcd for $C_{32}H_{43}NO_8$: C, 67.46; H, 7.61; N, 2.46. Found : C, 67.39; H, 7.49; N, 2.49.

[3(2*R*, 3*S*, 5*R*, 6*S*, 7*R*), 4*R*]-3-(7-Benzoyloxy-5-benzyloxy-6-methoxy-3-(4-methoxybenzyl)oxy-2,8-dimethyl-1-oxononyl)-4-isopropyl-2-oxazolidinone (22). To a solution of

alcohol **21** (450 mg, 0.790 mmol) in Et_2O (15 ml) were added 4-methoxybenzyl 2,2,2-trichloroacetimidate (0.34 ml, 1.64 mmol), 0.1 % (v/v) trifluoromethanesulfonic acid in Et_2O (0.21 ml, 0.237 mmol) at rt. After being stirred for 5 min at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 6) to give the PMB ether **22** (469 mg, 0.680 mmol; 86%) as a colorless oil. $[\alpha]^{22}_D$ -30.9 ° (*c* 1.11, $CHCl_3$); IR (neat) 2965, 1770, 1714, 1613, 1514, 1454, 1384, 1274, 1177, 1113 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.51 (m, 1H), 7.35 (m, 2H), 7.28-7.19 (m, 5H), 7.09 (m, 2H), 6.73 (m, 2H), 5.38 (dd, *J* = 7.7, 3.3 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.48 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 10.8 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.07 (ddd, *J* = 8.2, 3.8, 2.4 Hz, 1H), 4.03 (dq, *J* = 7.0, 6.8 Hz, 1H), 3.97 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.83-3.74 (m, 2H), 3.77 (s, 3H), 3.69 (dd, *J* = 9.0, 8.2 Hz, 1H), 3.60 (dd, *J* = 7.7, 3.2 Hz, 1H), 3.49 (s, 3H), 2.36-2.23(m, 2H), 2.12-1.98 (m, 2H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H) , 0.80 (d, *J* =6.8 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 174.9, 165.9, 159.0, 153.6, 138.6, 132.7, 130.6, 130.4, 129.8, 129.6, 128.3, 128.0, 127.2, 113.6, 79.8, 77.3, 76.2, 74.9, 71.7, 70.9, 62.9, 59.7, 58.6, 55.2, 41.6, 31.9, 29.0, 28.2, 20.3, 18.0, 16.6, 14.6, 13.9; EI-MS *m/z* 598 (M^+- Bn), 121 (PMB: base peak), 105 (Bz), 91 (Bn); Anal. Calcd for $C_{40}H_{51}NO_9$: C, 69.65; H, 7.43; N, 2.03. Found : C, 69.48; H, 7.66; N, 2.16.

(2*R*, 3*S*, 5*R*, 6*S*, 7*R*)-7-Benzoyloxy-5-benzyloxy-*N*,6-dimethoxy-3-(4-methoxybenzyl)-oxy-*N*,2,8-trimethylnonanamide (24). To a solution of the imide **22** (6.45 g, 9.36 mmol) in THF/water (3 : 1, 190 ml) were added 30% H_2O_2 (8.0 ml, 70.6 mmol) and lithium hydroxide monohydrate (790.3 mg, 18.8 mmol) at 0 °C. After being stirred for 11 hr at rt, the reaction mixture was quenched with 1.5*N* aqueous Na_2SO_3 (60 ml) at 0 °C. After addition of 1*N* aqueous HCl and AcOEt, the organic layer was separated, and the aqueous layer was extracted three times with AcOEt. The combined organic layers were dried (Na_2SO_4), and concentrated to give the carboxylic acid **23**, which was used without further purification. To a solution of the carboxylic acid and *N*,*O*-dimethylhydroxylamine hydrochloride (1.11 g, 11.3 mmol) in DMF (70 ml) were added diethylphosphoryl cyanide (1.6 ml, 10.5 mmol) and triethylamine (2.9 ml, 20.8 mmol) at 0 °C. After being stirred for 2 hr at rt, the reaction mixture was quenched with 1*N* aqueous HCl and AcOEt, and the organic layer was separated. The aqueous layer was further extracted three times with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 2 : 5) to give the amide **24** (3.69 g, 5.93 mmol; 63% (2 steps)) as a colorless oil. $[\alpha]^{23}_D$ -25.7 ° (*c* 0.96, $CHCl_3$); IR (neat) 2964, 1720, 1650, 1613, 1585, 1514, 1454, 1387, 1248, 1175, 1112 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.49 (m, 1H), 7.35 (m, 2H), 7.37-7.20 (m, 7H), 7.04 (m, 2H), 6.71 (m, 2H), 5.45 (dd, *J* = 8.0, 3.0 Hz, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 10.4 Hz, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.37 (d, *J* = 10.4 Hz, 1H), 3.76 (s, 3H), 3.78-3.70 (m, 2H), 3.58 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.14 (s, 3H), 3.12 (br m, 1H), 2.27 (dqq, *J* = 6.9, 6.9, 3.0 Hz, 1H), 2.01-1.94 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 175.9, 165.8, 159.1, 138.4, 132.8, 130.4, 130.3, 129.7, 129.3, 128.40, 128.36, 128.1, 127.4, 113.7, 80.1, 77.8, 76.2, 75.7, 72.6, 72.2, 61.4, 60.4, 55.2, 41.1, 34.4, 32.1, 28.8, 20.5, 16.6, 14.3; EI-MS *m/z* 622 (M^+), 121 (PMB: base peak), 105

(Bz), 91 (Bn) ; Anal. Calcd for $C_{36}H_{47}NO_8$: C, 69.54; H, 7.62; N, 2.25. Found : C, 69.25; H, 7.63; N, 2.43.

(3*R*, 4*S*, 6*R*, 7*R*, 8*R*)-6-Benzyloxy-8-hydroxy-7-methoxy-4-(4-methoxybenzyl)oxy-3,9-dimethyl-2-decanone (5). To a solution of amide **24** (71.6 mg, 0.115 mmol) in THF (2 ml) was added methyllithium (1.11 *M* in Et_2O, 0.52 ml, 0.572 mmol) dropwise at -78 °C. After being stirred for 20 min at the same temperature, the reaction mixture was added to a vigorously stirred mixture of saturated aqueous NH_4Cl and CH_2Cl_2 via cannula at 0 °C. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 1 : 8) to give the methyl ketone **5** (54.0 mg, 0.114 mmol; 99%) as a colorless oil. $[\alpha]^{25}_D$-12.1 ° (*c* 0.91, $CHCl_3$); IR (neat) 3063, 3031, 2959, 2933, 2346, 1710, 1612, 1586, 1514, 1455, 1365, 1202, 1249, 1177, 1095 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (m, 7H), 6.86 (m, 2H), 4.57 (s, 2H), 4.44 (m, 2H), 3.90 (m, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.57 (m, 1H), 3.37 (s, 3H), 3.22 (dd, *J* = 8.0, 2.7 Hz, 1H), 3.10 (br m, 1H), 2.78 (m, 1H), 2.04 (s, 3H), 2.01 (m, 1H), 1.92 (m, 1H), 1.87 (m, 1H), 1.14 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); FAB-MS *m/z* 473 (M^++H), 121 (PMB : base peak), 91 (Bn); FAB-HRMS Calcd for $C_{28}H_{41}O_6$ (M^++H) : 473.2903. Found : 473.2904.

(*R*)-Methyl 2-methyl-3-(phenylthio)propionate (30). To a solution of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate **(+)-28** (5.0 ml, 45.3 mmol) in THF (50 ml) were added diphenyl disulfide (15.4 g, 70.5 mmol) and tributylphosphine (13.8 ml, 70.5 mmol) at 0 °C. After being stirred for 24 hr at rt, the reaction mixture was concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 1 : 40) to give the sulfide **30** (9.40 g, 44.7 mmol; 99%) as a yellow oil. $[\alpha]^{24}_D$+64.3 ° (*c* 1.59, $CHCl_3$); IR (neat) 2976, 2951, 1732, 1583, 1480, 1455, 1436, 1211, 1165, 1025 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.29 (m, 2H), 7.20 (m, 1H), 3.67 (s, 3H), 3.27 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.93 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.70 (ddq, *J* = 7.2, 7.1, 7.0 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H); EI-MS *m/z* 210 (M^+); Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found : C, 62.55; H, 6.66.

(*R*)-*N*-Methoxy-*N*,2-dimethyl-3-(phenylthio)propionamide (31). To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (585 mg, 6.00 mmol) in CH_2Cl_2 (10 ml) was added trimethylaluminium (0.99 *M* in hexane, 6.0 ml, 5.94 mmol) dropwise at 0 °C. After being stirred for 1 hr at rt, to this suspension was added ester **30** (224 mg, 1.07 mmol) in CH_2Cl_2 (2 ml) at -20 °C, and then the whole reaction mixture was refluxed for 4 hr. The reaction mixture was added to a vigorously stirred mixture of 0.5 *N* aqueous HCl and CH_2Cl_2 (1 : 1, 200 ml) via cannula at 0 °C. The organic layer was separated, and washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 1 : 4) to give the amide **31** (242 mg, 1.01 mmol; 95%) as a yellow oil. $[\alpha]^{24}_D$+44.2 ° (*c* 1.23, $CHCl_3$); IR (neat) 2970, 2934, 1660, 1480, 1462, 1439, 1417, 1385 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.28 (m, 2H), 7.18 (m, 1H), 3.52 (s, 3H), 3.30 (dd, *J* = 13.1, 7.7 Hz, 1H), 3.18 (s, 3H), 3.11 (ddq, *J* = 7.7, 6.8, 6.5 Hz, 1H), 2.91 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.91 (dd, *J* = 13.1, 6.5 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 3H); EI-MS *m/z* 239 (M^+), 179 (M^+-N(Me)OMe), 151 (M^+-C(O)N(Me)OMe), 123 ($PhSCH_2$), 109 (PhS); Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found : C, 59.97; H, 7.44; N, 5.61.

(*R*)-3-Methyl-4-(phenylthio)-2-butanone (32). To a solution of amide **31** (4.85 g, 20.3 mmol) in THF (150 ml) was added methyllithium (1.4 *M* in Et_2O, 36.0 ml, 50.4 mmol) dropwise at -78 °C. After being stirred for 30 min at the same temperature, the reaction mixture was added to a vigorously stirred mixture of saturated aqueous NH_4Cl and THF (2 : 1, 200 ml) via cannula at 0 °C. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 12) to give the methyl ketone **32** (3.91 g, 20.1 mmol; 99%) as a pale yellow oil. $[\alpha]^{22}_D$ +37.8 ° (*c* 1.06, $CHCl_3$); IR (neat) 2970, 1718, 1583, 1480, 1458, 1438, 1420, 1358, 1159, 1024 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 4H), 7.20 (m, 1H), 3.25 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.86 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.77 (ddq, *J* = 7.1, 6.8, 6.8 Hz, 1H), 2.17 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 3H); EI-MS *m/z* 194 (M^+), 151 (M^+- MeCO), 123 ($PhSCH_2$), 109 (PhS), 85 (M^+-PhS); Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26. Found : C, 67.72; H, 7.33.

(*R*)-2-Methyl-2-[1-methyl-2-(phenylthio)ethyl]-1,3-dioxolane (33). To a solution of methyl ketone **32** (3.91 g, 20.1 mmol) in benzene (150 ml) was added ethylene glycol (5.0 ml, 89.7 mmol) and pyridinium *p*-toluenesulfonate (509 mg, 2.02 mmol) at rt. After refluxing azeotropically with stirring for 3 days, the reaction mixture was quenched with water at rt. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 40) to give the acetal **33** (4.74 g, 19.9 mmol; 99%) as a yellow oil. $[\alpha]^{22}_D$ -66.5 ° (*c* 1.07, $CHCl_3$); IR (neat) 2980, 2880, 1481, 1438, 1380, 1154, 1089, 1059, 1039 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.27 (m, 2H), 7.14 (m, 1H), 3.99-3.84 (m, 4H), 3.39 (dd, *J* = 12.8, 2.7 Hz, 1H), 2.53 (dd, *J* = 12.8, 10.7 Hz, 1H), 1.95 (ddq, *J* = 10.7, 6.9, 2.7 Hz, 1H), 1.29 (s, 3H), 1.13 (d, *J* = 6.9 Hz, 3H); EI-MS *m/z* 238 (M^+), 123 ($PhSCH_2$), 87 (M^+-$PhSCH_2CHCH_3$: base peak); Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found : C, 65.30; H, 7.40.

(*R*)-2-Methyl-2-[1-methyl-2-(phenylsulfonyl)ethyl]-1,3-dioxolane (34). To a solution of sulfide **33** (4.74 g, 19.9 mmol) in CH_2Cl_2 (100 ml) were added $NaHCO_3$ and *m*-chloroperbenzoic acid (80%, 10.7 g, 49.6 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The separated organic layer was washed with aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 1 : 3) to give the sulfone **34** (5.38 g, 19.9 mmol; 100%) as a white solid. mp 70-73 °C (recrystallized from AcOEt-hexane); $[\alpha]^{23}_D$ -23.0 ° (*c* 1.19, $CHCl_3$); IR (KBr) 2983, 2886, 1447, 1304, 1241, 1145, 1086, 1062 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 2H), 7.66 (m, 1H), 7.58 (m, 2H), 3.95-3.81 (m, 3H), 3.68 (m, 1H), 3.44 (dd, *J* = 14.1, 1.6 Hz, 1H), 2.88 (dd, *J* = 14.1, 10.2 Hz, 1H), 2.27 (ddq, *J* = 10.2, 6.9, 1.6 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.19 (s, 3H); EI-MS *m/z* 255 (M^+-Me), 141 ($PhSO_2$), 129 (M^+-$PhSO_2$), 87 (M^+-$PhSO_2CH_2CHCH_3$: base peak); Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71. Found : C, 57.51; H, 6.72.

(*S*)-2-Methyl-2-[1-methyl-2-(phenylsulfonyl)ethyl]-1,3-dithiane (27). To a solution of acetal **34** (515 mg, 1.91 mmol) in CH_2Cl_2 (20 ml) were added 1,3-propanedithiol (0.31 ml, 3.09 mmol) and boron trifluoride etherate (0.03 ml, 0.24 mmol) at 0 °C. After being stirred for 12 hr at rt, the reaction mixture was quenched with 6 *N* aqueous NaOH. The separated organic layer was washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 5) to give the sulfone **27** (526 mg, 1.66 mmol; 87%) as a white solid. mp 99-101 °C (recrystallized from AcOEt-hexane); $[\alpha]^{22}_D$ -92.8 ° (*c* 1.06, $CHCl_3$); IR (KBr) 2971, 2926, 1446, 1303, 1249, 1149, 1086 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.67 (m, 1H), 7.59 (m, 2H), 3.88 (m, 1H), 2.90 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.87-2.63 (m, 4H), 2.53 (m, 1H), 1.93 (m, 1H), 1.83 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.34 (s, 3H); EI-MS *m/z* 316 (M^+), 133 (M^+-$PhSO_2CH_2CHCH_3$: base peak); Anal. Calcd for $C_{14}H_{20}O_2S_3$: C, 53.13; H, 6.37. Found : C, 53.17; H, 6.54.

(2*E*, 4*R*, 5*R*)-Ethyl 5,6-(diethylmethylenedioxy)-4-methyl-2-hexenoate (37). DMSO (5.5 ml, 77.5 mmol) was added dropwise to a solution of oxalyl cholide (3.1 ml, 35.5 mmol) in CH_2Cl_2 (75 ml) at -78 °C. After being stirred for 30 min at the same temperature, a solution of (2*R*,3*R*)-3,4-diethylmethylenedioxy-2-methyl-butan-1-ol **35** (6.041 g, 32.1 mmol) in CH_2Cl_2 (15 ml) was slowly added via cannula. After stirring for an additional 30 min at the same temperature, triethylamine (22.0 ml, 158 mmol) was added. The whole reaction mixture was then allowed to warm to 0 °C over a 1 hr period, and poured into saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) concentrated to give the aldehyde **36**, which was used without further purification. To a suspension of potassium *tert*-butoxide (10.79 g, 96.2 mmol) in THF (150 ml) was added diisopropyl (ethoxycarbonylmethyl)phosphonate (23.0 ml, 96.7 mmol) at 0 °C, and the mixture was stirred for 2 hr at rt. The crude aldehyde **36**, in THF (15 ml), was then added to the mixture slowly via cannula at -78 °C. After being stirred for 40 min at rt, the reaction mixture was poured into saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15) to give the ester (7.63 g, 29.8 mmol; 93% (2 steps)) as a pale yellow oil. $[\alpha]^{25}_D$ +25.9 ° (*c* 1.20, $CHCl_3$); IR (neat) 2974, 2939, 2881, 1721, 1464, 1271, 1250, 1182, 1082, 1040 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.87 (dd, *J* = 15.9, 1.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.04 (dd, *J* = 7.7, 6.2 Hz, 1H), 3.98 (ddd, *J* = 7.6, 7.1, 6.2 Hz, 1H), 3.59 (dd, *J* = 7.7, 7.6 Hz, 1H), 2.49 (dddq, *J* = 7.4, 7.1, 6.9, 1.2 Hz, 1H), 1.64 (q, *J* = 7.5 Hz, 2H), 1.61 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); EI-MS *m/z* 256 (M^+), 227 (M^+-Et); Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found : C, 65.39; H, 9.21.

(4*R*,5*R*)-Ethyl 5,6-(diethylmethylenedioxy)-4-methylhexanoate (38). A suspension of α,β-unsaturated ester **37** (265 mg, 1.03 mmol) and Pd/C (10%, 34 mg) in EtOH (15 ml) was stirred vigorously under 1 atm pressure of hydrogen at rt for 1 day. The reaction mixture was filtered, and the filtrate was concentrated to give a residure which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 20) to give the ester **38** (251 mg, 0.97 mmol; 94%) as a colorless oil. $[\alpha]^{24}_D$ -5.93 ° (*c* 2.64, $CHCl_3$); IR (neat)

2973, 2938, 2881, 1736, 1464, 1258, 1178, 1079 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.2 Hz, 2H), 4.01 (dd, *J* = 7.7, 6.0 Hz, 1H), 3.81 (ddd, *J* = 8.5, 8.0, 6.0 Hz, 1H), 3.53 (dd, *J* =8.5, 7.7 Hz, 1H), 2.43 (ddd, *J* = 12.9, 9.6, 6.0 Hz, 1H), 2.35 (ddd, *J* = 15.9, 9.2, 6.5 Hz, 1H), 1.96 (m, 1H), 1.62 (q, *J* = 7.5 Hz, 2H), 1.60 (q, *J* = 7.5 Hz, 2H), 1.70-1.46 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 6.8 Hz, 3H); EI-MS *m/z* 259 (M^++H), 229 (M^+-Et), 213 (M^+-OEt); Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found : C, 64.83; H, 10.43.

Dimethyl [(5*R*,6*R*)-6,7-(diethylmethylenedioxy)-5-methyl-2-oxoheptyl]phosphonate (26). To a solution of dimethyl methylphosphonate (5.0 ml, 46.1 mmol) in THF (150 ml) was added *n*-butyllithium (1.65 *M* in hexane, 27.5 ml, 45.4 mmol) at -78 °C. After being stirred for 3 hr at the same temperature, a solution of ester **38** (5.02 g, 19.4 mmol) in THF (20 ml) was added to this solution slowly via cannula at -78 °C. After being stirred for 1 hr at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (MeOH/CH_2Cl_2, 1 : 40) to give an almost inseparable mixture of phosphonate **26** and dimethyl methylphosphonate (total 6.45 g) as a yellow oil. A small analytical sample of pure **26** was obtained, and the remainder used in the next step without further purification. $[\alpha]^{25}_D$ -9.02 ° (*c* 1.22, $CHCl_3$); IR (neat) 2969, 2881, 1716, 1463, 1260, 1177, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (dd, *J* = 7.7, 6.0 Hz, 1H), 3.79 (ddd, *J* = 8.5, 7.9, 6.0 Hz, 1H), 3.79 (d, *J* = 11.3 Hz, 6H), 3.52 (dd, *J* =8.5, 7.7 Hz, 1H), 3.13 (dd, *J* = 17.4, 13.7 Hz, 1H), 3.08 (d, *J* = 17.4, 13.8 Hz, 1H), 2.74 (ddd, *J* = 17.8, 8.4, 6.4 Hz, 1H), 2.70 (ddd, *J* = 17.8, 8.4, 6.6 Hz, 1H), 1.90 (m, 1H), 1.62 (q, *J* = 7.5 Hz, 2H), 1.62 (m, 1H), 1.60 (q, *J* = 7.5 Hz, 2H), 1.49 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); EI-MS *m/z* 307 (M^+-Et), FAB-MS *m/z* 337 (M^++H), 307 (M^+-Et), 251 (M^+-Et_2CO : base peak), 151 ($(MeO)_2P(O)CH_2CO$); FAB-HRMS Calcd for $C_{15}H_{30}O_6P$ (M^++H) : 337.1780. Found : 337.1770.

(*R*)-3-(4-Methoxybenzyl)oxy-2-methylpropanal (40). To a solution of oxalyl cholide (0.56 ml, 6.42 mmol) in CH_2Cl_2 (15 ml) at -78 °C, DMSO (0.98 ml, 13.8 mmol) was added dropwise. After being stirred for 30 min at the same temperature, a solution of (*S*)-3-(4-methoxybenzyl)oxy-2-methyl-1-propanol **39** (1.190 g, 5.66 mmol) in CH_2Cl_2 (5 ml) was slowly added via cannula at -78 °C. After being stirred for 30 min at the same temperature, triethylamine (4.0 ml, 28.7 mmol) was added, and the reaction mixture was then allowed to warm to 0 °C over 1 hr. The whole reaction mixture was poured into saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 9) to give the aldehyde **40** (1.14 mg, 5.49 mmol; 97%) as a yellow oil. IR (neat) 2935, 2858, 2837, 1723, 1613, 1514, 1463, 1302, 1248, 1174, 1095 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.6 Hz, 1H), 7.24 (m, 2H), 6.88 (m, 2H), 4.46 (d, *J* = 15.2 Hz, 1H), 4.45 (d, *J* = 15.2 Hz, 1H), 3.81 (s, 3H), 3.65 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.61 (dd, *J* = 9.3, 5.3 Hz, 1H), 2.65 (dddq, *J* = 7.2, 6.8, 5.3, 1.6 Hz, 1H), 1.12 (d, *J* = 7.2 Hz, 3H); EI-MS *m/z* 208 (M^+), 137 (OPMB), 121 (PMB).

(2*R*, 3*S*, 4*R*)-*N*-Methoxy-5-(4-methoxybenzyl)oxy-*N*,2,4-trimethyl-3-(triethylsilyl)oxypentanamide (43). To a solution of (*R*)-(-)-4-isopropyl-3-propionyl-2-oxazolidinone **20** (0.6 ml, 3.54 mmol) in CH_2Cl_2 (15 ml) were added *n*-Bu_2BOTf (1.0 *M* in CH_2Cl_2, 3.9 ml, 3.90 mmol) and triethylamine (0.6 ml, 4.30 mmol) at 0 °C. After being stirred for 1 hr at the same temperature, the reaction mixture was cooled to -78 °C and to this mixture was added aldehyde **40** (575 mg, 2.76 mmol) in CH_2Cl_2 (5 ml). After being stirred for 3 hr at -78 °C, the whole reaction mixture was gradually warmed to 0 °C, stirred for an additional 2 hr at the same temperature, and then quenched with pH 7 phosphate buffer (4 ml) in MeOH (20 ml). After 5 min, 30% H_2O_2/MeOH (1 : 1, 8 ml) was also added. The quenched solution was stirred for 1 hr at 0 °C, and concentrated below 30 °C. The resulting mixture was extracted three times with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 3 : 7) to give a mixture of the alcohol **41** and its diastereomer (1.03 g, 2.60 mmol; 94%) as a colorless oil. To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.55 g, 15.9 mmol) in THF (10 ml) was added trimethylaluminium (0.99 *M* in hexane, 16.0 ml, 15.8 mmol) dropwise at 0 °C. After being stirred for 1 h at rt, to this suspension was added the mixture of the diastereomers (1.03 g, 2.60 mmol) in THF (5 ml) at -20 °C, and the whole mixture was then stirred for 12 hr at rt. The reaction mixture was added to a vigorously stirred mixture of 0.5 *N* aqueous $NaHSO_4$ (100 ml) and CH_2Cl_2 (70 ml) via cannula at 0 °C. The organic layer was separated, and washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 2 : 3) to give a mixture of the amide **42**, its diastereomer and oxazolidinone (1.02 g) as a colorless oil. To a solution of the mixture (1.02 g) in DMF (15 ml) were added imidazole (488 mg, 7.16 mmol) and chlorotriethylsilane (0.9 ml, 5.36 mmol) at rt. After being stirred for 15 hr, the reaction mixture was quenched with water. The organic layer was separated, and washed with 0.5 *N* aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 1 : 9) to give the TES ether **43** (855 mg, 1.95 mmol; 75% (2 steps)) as a colorless oil, and also its diastereomer (106 mg, 0.24 mmol). The ratio of diastereoselectivity in the aldol reaction was thus 89 : 11 . $[\alpha]^{25}_D$ +2.95 ° (*c* 1.18, $CHCl_3$); IR (neat) 2957, 2910, 2876, 1660, 1514, 1460, 1248, 1113, 1087, 1052 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.87 (m, 2H), 4.41 (s, 2H), 4.04 (dd, *J* = 8.9, 2.0 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.40 (dd, *J* = 9.1, 6.5 Hz, 1H), 3.23 (dd, *J* = 9.1, 7.8 Hz, 1H), 3.15 (s, 3H), 3.07 (br m, 1H), 1.85 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.95 (m, 9H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.67-0.55 (m, 6H); EI-MS *m/z* 439 (M^+), 410 (M^+-Et), 121 (PMB); Anal. Calcd for $C_{23}H_{41}NO_5Si$: C, 62.83; H, 9.40, N, 3.19. Found : C, 62.79; H, 9.43, N, 3.23.

(2*R*,3*S*,4*R*)-5-(4-Methoxybenzyl)oxy-2,4-dimethyl-3-(triethylsilyl)oxypentanal (25). To a solution of the amide **43** (831 mg, 1.89 mmol) in THF (20 ml) was added diisobutylaluminium hydride (0.93 *M* in hexane, 5.1 ml, 4.72 mmol) dropwise at -78 °C. After being stirred for 80 min at the same temperature, the reaction mixture was added to a vigorously stirred mixture of 0.1 *N* aqueous potassium sodium tartrate and Et_2O via cannula at 0 °C, and the quenched solution was stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with

brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 12) to give the aldehyde **25** (712 mg, 1.87 mmol; 99%) as a colorless oil. IR (neat) 2955, 2910, 2876, 1722, 1514, 1248, 1091, 1036, 1010 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.1 Hz, 1H), 7.24 (m, 2H), 6.88 (m, 2H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.22 (dd, *J* = 5.1, 4.2 Hz, 1H), 3.81 (s, 3H), 3.37 (dd, *J* = 9.1, 7.1 Hz, 1H), 3.24 (dd, *J* = 9.1, 5.8 Hz, 1H), 2.53 (ddq, *J* = 6.9, 5.1, 1.1 Hz, 1H), 1.92 (dddq, *J* = 7.1, 7.0, 5.8, 4.2 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.59 (q, *J* = 7.9 Hz, 6H); EI-MS *m/z* 323 (M^+-CH(Me)CHO), 121 (PMB : base peak); Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found : C, 66.21; H, 9.56.

(2*R*,3*R*,9*S*,10*R*,11*R*)-1,2-(Diethylmethylenedioxy)-12-(4-methoxybenzyl)oxy-3,9,11-trimethyl-10-(triethylsilyl)oxy-7-dodecen-6-one (44ab). To a solution of phosphonate **26** (1.03 g, 3.07 mmol) in CH_3CN (25 ml) were added litium chloride (128 mg, 3.01 mmol), *N*,*N*-diisopropylethylamine (0.31 ml, 1.78 mmol), and aldehyde **25** in CH_3CN (5 ml) via cannula at rt. After being stirred for 36 hr, the reaction mixture was quenched with water and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 1 : 10 to CH_2Cl_2/MeOH, 1 : 40) to give the enone **44ab** (1.02 g, 1.73 mmol; 97%, *E* : *Z* = 93 : 1 (^{1}H-NMR analysis)) as a colorless oil and the recovered phosphonate **26** (0.45 g, 1.35 mmol). (*E*-olefin) $[\alpha]^{24}_D$ -10.7 ° (*c* 1.26, $CHCl_3$); IR (neat) 2961, 2877, 1514, 1461, 1248, 1173, 1081, 1057, 1039, 1010 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.88 (m, 2H), 6.84 (dd, *J* = 16.1, 7.9 Hz, 1H), 6.07 (dd, *J* = 16.1, 1.1 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.00 (dd, *J* = 7.6, 6.1 Hz, 1H), 3.814 (ddd, *J* = 8.6, 7.6, 6.1 Hz, 1H), 3.808 (s, 3H), 3.79 (dd, *J* = 6.8, 2.6 Hz, 1H), 3.53 (dd, *J* = 8.6, 7.6 Hz, 1H), 3.33 (dd, *J* = 9.0, 7.8 Hz, 1H), 3.19 (dd, *J* = 9.0, 6.1 Hz, 1H), 2.65 (ddd, *J* = 16.3, 9.4, 6.3 Hz, 1H), 2.59 (ddd, *J* = 16.3, 9.0, 6.4 Hz, 1H), 2.49 (dddq, *J* = 7.9, 6.8, 6.8, 1.1 Hz, 1H), 1.95-1.80 (m, 2H), 1.68-1.43 (m, 6H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.95 (m, 9H), 0.89 (t, *J* = 7,5 Hz, 3H), 0.88 (t, *J* = 7,5 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.59 (m, 6H); EI-MS *m/z* 590 (M^+), 561 (M^+-Et), 504 (M^+-Et_2O), 121 (PMB : base peak); Anal. Calcd for $C_{34}H_{58}O_6Si$: C, 69.11; H, 9.89. Found : C, 69.16; H, 10.02.

(2*R*,3*R*,9*S*,10*R*,11*R*)-1,2-(Diethylmethylenedioxy)-12-(4-methoxybenzyl)oxy-3,9,11-trimethyl-10-(triethylsilyl)oxy-6-dodecanone (45). A suspension of enone **44ab** (301 mg, 0.510 mmol) and a catalytic amount of Raney nickel (W2) in AcOEt (10 ml) was stirred vigorously under 1 atm pressure of hydrogen at rt for 1 hr. The reaction mixture was filtered, and the filtrate was concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15) to give the ketone **45** (302 g, 0.510 mmol; 100%) as a colorless oil. $[\alpha]^{21}_D$ -8.15 ° (*c* 1.02, $CHCl_3$); IR (neat) 2960, 1716, 1613, 1514, 1463, 1248, 1172, 1081 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.87 (m, 2H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.00 (dd, *J* = 7.7, 6.1 Hz, 1H), 3.80 (s, 3H), 3.79 (ddd, *J* = 8.4, 7.9, 6.1 Hz, 1H), 3.59 (dd, *J* = 5.2, 3.6 Hz, 1H), 3.51 (dd, *J* = 8.4, 7.7 Hz, 1H), 3.35 (dd, *J* = 8.9, 6.9 Hz, 1H), 3.20 (dd, *J* = 8.9, 6.3 Hz, 1H), 2.57-2.26 (m, 4H), 1.94 (dddq, *J* = 6.9, 6.8, 6.3, 3.6 Hz, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.65-1.40 (m, 7H), 1.33 (m, 1H), 0.95 (m, 9H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.881 (d, *J* = 6.8 Hz, 3H), 0.879 (t, *J* = 7,5 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.58 (m, 6H);

EI-MS *m/z* 563 (M^+-Et), 323 (PMBOCH$_2$CH(Me)CHOTES), 121 (PMB : base peak); Anal. Calcd for $C_{34}H_{60}O_6Si$: C, 68.87; H, 10.20. Found : C, 68.59; H, 10.27.

[2*R*, 3*R*, 6*R*, 8*R*,8(1*R*),9*S*]-[3,9-Dimethyl-8-[[1-methyl-2-(4-methoxybenzyl)oxy]ethyl]-1,7-dioxaspiro[5.5]undecan-2-yl]methanol (29). To a solution of ketone **45** (302 mg, 0.510 mmol) in MeOH (20 ml) was added a catalytic amount of *d*-camphor-10-sulfonic acid at rt. After being stirred for 20 hr, the reaction mixture was neutralized with triethylamine (ca. 1 ml), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 5) to give the alcohol **29** (197 mg, 0.501 mmol; 98%) as a colorless oil. $[\alpha]^{22}_D$ -52.6 ° (*c* 1.03, $CHCl_3$); IR (neat) 3478, 2930, 2872, 1613,1514, 1248, 1114, 1091, 1040, 1007 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.88 (m, 2H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.81 (s, 3H), 3.74 (ddd, *J* = 11.2, 7.2, 2.7 Hz, 1H), 3.54 (ddd, *J* = 11.2, 6.2, 4.8 Hz, 1H), 3.44 (dd, *J* = 10.0, 2.3 Hz, 1H), 3.37 (dd, *J* = 9.4, 4.5 Hz, 1H), 3.35 (ddd, *J* = 10.2, 6.2, 2.7 Hz, 1H), 3.21 (dd, *J* = 9.4, 6.7 Hz, 1H), 2.08 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.00 (m, 1H), 1.87 (dddq, *J* = 10.0, 6.7, 6.6, 4.5 Hz, 1H), 1.75-1.56 (m, 3H), 1.55-1.34 (m, 6H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); EI-MS *m/z* 392 (M^+), 271 (M^+-PMB), 121 (PMB : base peak); Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found : C, 70.16; H, 9.21.

[2*R*, 3*R*, 6*R*, 8*R*,8(1*R*),9*S*]-[3,9-Dimethyl-8-[[1-methyl-2-(4-methoxybenzyl)oxy]ethyl]-1,7-dioxaspiro[5.5]undecan-2-yl]carbaldehyde (46). To a solution of oxalyl chloride (50 μl, 573 μmol) in CH_2Cl_2 (10 ml) was added DMSO (90 μl, 1.27 mmol) dropwise at -78 °C. After being stirred for 30 min at the same temperature, a solution of alcohol **29** (197 mg, 501 μmol) in CH_2Cl_2 (3 ml) was slowly added via cannula. After being stirred for 30 min at the same temperature, triethylamine (0.37 ml, 2.65 mmol) was added. The mixture was then allowed to warm to 0 °C over 1 hr, and then poured into saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15) to give the aldehyde **46** (191 mg, 488 μmol; 97%) as a colorless oil. IR (neat) 2957, 2932, 1738, 1513, 1248, 1011 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 2.3 Hz, 1H), 7.23 (m, 2H), 6.88 (m, 2H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.43 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.35 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.22 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.05 (m, 1H), 1.85 (dddq, *J* = 10.0, 6.7, 6.4, 4.2 Hz, 1H), 1.77-1.35 (m, 9H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 5.9 Hz, 3H), 0.91 (d, *J* =7.0 Hz, 3H); EI-MS *m/z* 390 (M^+), 361 (M^+-CHO), 269 (M^+-PMB), 121 (PMB : base peak).

[2*R*,2(3*S*),3*R*, 6*R*, 8*R*,8(1*R*),9*S*]-3,9-Dimethyl-2-[3-(2-methyl-1,3-dithian-2-yl)-1-butenyl]-8-[[1-methyl-2-(4-methoxybenzyl)oxy]ethyl]-1,7-dioxaspiro[5.5]undecane (47ab). To a solution of sulfone **27** (246.7 mg, 0.78 mmol) in THF (5.5 ml) and HMPA (145 μl, 0.83 mmol) was added *n*-BuLi 460 μl (1.69 *M* in hexane, 460 μl, 0.78 mmol) dropwise at -78 °C. After being gradually warmed to 0 °C, the mixture was stirred for 30 min, and then recooled to -78 °C and treated with aldehyde **46** (153.5 mg, 393 μmol) in THF (2 ml) added slowly via cannula. After being stirred for 40 min at the same temperature, and then for an additional 25 min at 0 °C, the whole reaction mixture was poured into saturated

aqueous NH_4Cl, and the quenched mixture was extracted with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 6 to 1 : 2) to give the β-hydroxysulfone as a mixture of four diastereomers. To a solution of this β-hydroxysulfone in CH_2Cl_2 (10 ml) were added pyridine (0.45 ml, 5.56 mmol), acetic anhydride (0.45 ml, 4.77 mmol) and a catalytic amount of 4-dimethylaminopyridine at rt. After being stirred for 14 hr, the reaction mixture was quenched with 6 *N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15 to 1 : 2) to give the β-acetoxysulfone as a mixture of four diastereomers. To a solution of β-acetoxysulfone in THF (4.5 ml) and MeOH (1.5 ml) were added Na_2HPO_4 (700 mg) and sodium-mercury amalgam (5 %, 5 g, 10.9 mmol) at -20 °C. After being stirred for 1 hr at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl and Et_2O, and filtered through a pad of celite. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15 to 1 : 5) to give **47ab** (155 mg, 283 μmol; 72% (3 steps)) as a colorless oil. (*E*-olefin) $[\alpha]^{22}_D$ -67.8 ° (*c* 1.01, $CHCl_3$); IR (neat) 2935, 1613, 1514, 1454, 1422, 1377, 1302, 1248, 1172, 1087 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.87 (m, 2H), 5.68 (dd, *J* = 15.2, 8.7 Hz, 1H), 5.49 (dd, *J* = 15.2, 8.2 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 10.0, 8.2 Hz, 1H), 3.47 (dd, *J* = 10.0, 1.8 Hz, 1H), 3.40 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.23 (dd, *J* = 9.2, 6.9 Hz, 1H), 2.97-2.78 (m, 4H), 2.77 (dq, *J* = 8.7, 7.0 Hz, 1H), 2.08-1.82 (m, 4H), 1.57 (s, 3H), 1.74-1.29 (m, 9H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 159.0, 133.9, 131.8, 130.8, 128.9, 113.7, 96.0, 76.6, 73.0, 72.6, 72.0, 55.2, 52.9, 45.2, 35.9, 35.6, 34.7, 30.0, 28.1, 27.9, 26.6, 26.3, 25.3, 24.0, 18.1, 15.9, 15.5, 11.2; EI-MS *m/z* 548 (M^+), 133 (2-methyl-1,3-dithiane), 121 (PMB : base peak); EI-HRMS calcd for $C_{31}H_{48}O_4S_2$ (M^+): 548.2994; found : 548.3015.

[2*R*,2(3*S*),3*R*,6*R*,8*R*,8(1*R*),9*S*]-3,9-Dimethyl-2-[3-(2-methyl-1,3-dithian-2-yl)butyl]-8-[[1-methyl-2-(4-methoxybenzyl)oxy]ethyl]-1,7-dioxaspiro[5.5]undecane (49). A solution of **47ab** (110 mg, 200 μmol) and tris(triphenylphosphine)rhodium(I) chloride (39.1 mg, 43 μmol) in benzene (2 ml) was degassed, and stirred vigorously under 1 atm pressure of hydrogen at rt for 22 hr. The reaction mixture was directly purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15) to give **49** (107 mg, 194 μmol; 91%) as a colorless oil. $[\alpha]^{22}_D$ -55.4 ° (*c* 0.99, $CHCl_3$); IR (neat) 2930, 2873, 1513, 1248, 1091 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.87 (m, 2H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.38 (d, *J* = 11.9 Hz, 1H), 3.81 (s, 3H), 3.50 (dd, *J* = 10.3, 2.2 Hz, 1H), 3.39 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.24 (m, 1H), 3.22 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.90-2.72 (m, 4H), 2.10-1.93 (m, 4H), 1.92-1.81 (m, 2H), 1.56 (s, 3H), 1.73-1.24 (m, 14H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); EI-MS *m/z* 550 (M^+), 133 (2-methyl-1,3-dithiane), 121 (PMB); Anal. Calcd for $C_{31}H_{50}O_4S_2$: C, 67.59; H, 9.15. Found : C, 67.29; H, 9.06.

[2*R*,2[2*R*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-2-[3,9-Dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)-butyl]-1,7-dioxaspiro[5.5]undecane-2-yl]-1-propanol (50). To a solution of PMB ether **49** (275 mg, 500 μmol) in CH_2Cl_2 (18 ml) and water (1 ml) was added DDQ (95%, 184 mg, 768 μmol) at rt. After being stirred for 1 hr, the reaction mixture was filtered through a pad of celite, and the filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 7) to give the alcohol **50** (208 mg, 482 μmol; 97%) as a colorless oil. $[\alpha]^{22}_D$-85.8 ° (*c* 0.99, $CHCl_3$); IR (neat) 3451, 2923, 1454, 1382, 1275, 1254, 1230, 1094, 1022 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.66 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.63-3.55 (m, 2H), 3.23 (m, 1H), 2.99-2.89 (m, 2H), 2.82-2.74 (m, 2H), 2.16-1.97 (m, 4H), 1.94-1.71 (m, 3H), 1.64 (s, 3H), 1.70-1.22 (m, 11H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 95.8, 74.0, 72.2, 64.9, 55.1, 41.7, 37.4, 36.0, 35.1, 31.3, 30.3, 28.3, 28.0, 27.3, 26.8, 26.3, 25.6, 23.3, 18.0, 14.4, 13.9, 11.3 ; EI-MS *m/z* 430, (M^+), 371 (M^+-$HOCH_2CHCH_3$), 133 (2-methyl-1,3-dithiane); EI-HRMS Calcd for $C_{23}H_{42}O_3S_2$ (M^+): 430.2576; Found : 430.2549.

[2*S*,2[2*R*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-2-[3,9-Dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)-butyl]-1,7-dioxaspiro[5.5]undecane-2-yl]-1-propanal (6). To a solution of alcohol **50** (17.8 mg, 41.3 μmol) in DMSO (2 ml) were added triethylamine (70 μl, 502 μmol) and sulfur trioxide pyridine complex (35.4 mg, 222 μmol) at rt. After being stirred for 2 hr, the reaction mixture was quenched with 0.1 *N* aqueous $NaHSO_4$ and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15) to give the aldehyde **6** (17.7 mg, 41.3 μmol; 100%) as a colorless oil. $[\alpha]^{25}_D$ -7.7 ° (*c* 1.62, $CHCl_3$); IR (neat) 2931, 2875, 1724, 1456, 1382, 1231, 1096 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 3.5 Hz, 1H), 3.99 (dd, *J* = 10.0, 2.3 Hz, 1H), 3.21 (m, 1H), 2.97-2.87 (m, 2H), 2.82-2.74 (m, 2H), 2.55 (ddq, *J* = 10.0, 6.8, 3.5 Hz, 1H), 2.18-1.97 (m, 4H), 1.86 (m, 1H), 1.63 (s, 3H), 1.76-1.25 (m, 12H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); EI-MS *m/z* 428, (M^+), 371 (M^+-$OCHCHCH_3$), 133 (2-methyl-1,3-dithiane : base peak).

[2*R*,2[2*R*,3*S*,6*R*,8*S*,8(3*S*),9*R*],6*R*,7*S*,9*R*,10*S*,11*R*]-9-Benzyloxy-2-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-3,11-dihydroxy-10-methoxy-7-(4-methoxybenzyl)oxy-6,12-dimethyl-5-tridecanone (51ab). To a solution of LDA (4.34 mmol) in THF (25 ml) was added methylketone **5** (1.066 g, 2.12 mmol) in THF (5 ml) at -78 °C. After being stirred for 1 hr at the same temperature, to this solution was added aldehyde **6** (1.066 g, 2.12 mmol) in THF (5 ml) slowly via cannula at -78 °C. After being stirred for 1 hr at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl and CH_2Cl_2 at 0 °C. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 9 to 1 : 5) to give the β-hydroxyketone **51ab** (1.274 g, 1.41 mmol; 82%) as a colorless oil.

IR (neat) : 3498, 2931, 1706, 1612, 1513, 1455, 1422, 1380, 1302, 1249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.16 (m, 7H), 6.80 (m, 2H), 4.58-4.36 (m, 4H), 4.16-4.01(m, 2H), 3.83 (m, 1H), 3.75 (s, 3H), 3.80-3.61(m, 2H), 3.47 (m, 1H), 3.30 (s, 3H), 3.18-3.09 (m, 2H), 3.06-2.60 (m, 7H), 2.35-2.21(m, 1H), 2.10-1.20 (m, 21H), 1.56 (s, 1.2H), 1.49 (s, 1.8H), 1.09 (d, J = 6.6 Hz, 1.8H), 1.05 (d, J = 6.6 Hz, 1.8H), 1.08-1.02 (m, 2.4H), 0.92-0.77 (m, 15H); FAB-MS *m/z* 923 (M^++Na), 901 (M^++H), 121 (PMB: base peak); FAB-HRMS Calcd for $C_{51}H_{80}O_9S_2Na$ (M^++Na) : 923.5141 Found : 923.5131; Anal. Calcd for $C_{51}H_{80}O_9S_2$: C, 67.96; H, 8.95. Found: C, 68.07; H, 9.03.

[2*R*,2[2*R*,3*S*,6*R*,8*S*,8(3*S*),9*R*],3*E*,6*R*,7*S*,9*R*,10*S*,11*R*]-11-Acetoxy-9-benzyloxy-2-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-10-methoxy-7-(4-methoxybenzyl)oxy-6,12-dimethyl-3-tridecen-5-one (53). To a solution of β-hydroxyketone **51ab** (1.274 g, 1.41 mmol) in CH_2Cl_2 (50 ml) was added 4-dimethyaminopyridine (3.45 g, 28.2 mmol) and acetic anhydride (1.73 ml, 18.3 mmol) at 0 °C. After being stirred for 12 hr at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 7 to 1 : 5) to give a mixture of β-acetoxyketone **52ab** and enone **53** as a colorless oil. To a solution of the mixture in CH_2Cl_2 (45 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.39 ml, 2.61 mmol) at 0 °C. After being stirred for 1 hr at the same temperature, and then for an additional 1 hr at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 7) to give the enone **53** (1.274 g, 1.38 mmol; 98% (2 steps)) as a colorless oil. β-acetoxyketone **52ab**: IR (neat) : 2932, 1735, 1612, 1586, 1515, 1302 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 7H), 6.85 (m, 2H), 5.45 (m, 0.6H), 5.28 (m, 0.4H), 5.14-5.09 (m, 1H), 4.57-4.40 (m, 4H), 3.80 (s, 3H), 3.75 (m, 1H), 3.65 (m, 1H), 3.43 (s, 3H), 3.41-3.34 (m, 2H), 3.29 (m, 0.4H), 3.16 (m, 0.6H), 3.05-2.92 (m, 1H), 2.85-2.73 (m, 5H), 2.65 (m, 0.6H), 2.32 (m, 0.4H), 2.00 (s, 1.2H), 1.95 (s, 1.2H), 1.91 (s, 1.8H), 1.90 (s, 1.8H), 1.55 (s, 1.2H), 1.53 (s, 1.8H), 2.12-1.24 (m, 21H), 1.14-1.08 (m, 7.2H), 1.02-0.88 (m, 10.8H), 0.86 (d, J = 6.8Hz, 1.8H), 0.84 (d, J = 6.7Hz, 1.2H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 209.8, 209.5, 170.5, 170.3, 169.8, 159.1, 138.3, 130.3, 129.3, 129.0, 128.2, 128.1, 128.0, 127.54, 127.46, 113.7, 95.6, 79.8, 79.6, 77.2, 75.5, 75.4, 74.8, 74.7, 72.7, 72.5, 72.1, 71.8, 71.3, 71.0, 69.4, 65.8, 59.6, 55.3, 54.8, 54.6, 49.9, 49.5, 44.5, 36.1, 36.0, 35.0, 34.9, 32.9, 32.2, 30.1, 28.52, 28.48, 28.2, 28.1,27.6, 27.5, 26.7, 26.3, 26.1, 25.4, 23.2, 23.1, 21,0. 20.2, 18.1 ,16.6, 15.2, 14.7, 14.3, 12.7, 12.0 ,11.3, 11.0, 10.8; EI-MS *m/z* : 925(M^+-OAc), 133 (2-methyl-1,3-dithiane : base peak), 121(PMB), 43(Ac); Anal. Calcd for $C_{55}H_{84}O_{11}S_2$: C, 67.04; H, 8.59. Found: C, 67.25; H, 8.87. enone **53** (*E*-olefin) : $[\alpha]^{23}_D$ -37.9 ° (*c* 0.74, $CHCl_3$); IR (neat) : 2931, 1738, 1693, 1665, 1626, 1586, 1513, 1302cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.18 (m, 7H), 6.86-6.71 (m, 3H), 6.22 (d, J = 15.7Hz, 1H), 5.11 (dd, J = 7.5, 3.9Hz, 1H), 4.49 (m, 2H), 4.44 (m, 2H), 3.81 (m, 1H), 3.79 (s, 3H), 3.64 (dt, J = 6.5, 2.8Hz, 1H), 3.58 (dd, J = 10.3, 2.2Hz, 1H), 3.44 (s, 3H), 3.38 (dd, J = 7.3, 2.9Hz, 1H), 3.22 (dt, J = 9.7, 2.1Hz, 1H), 3.02-2.84 (m, 3H), 2.82-2.74 (m, 2H), 2.40 (m, 1H), 1.92 (s, 3H), 1.64 (s, 3H), 2.17-1.25(m, 20H), 1.18 (d, J = 7.0Hz, 3H), 1.13 (d, J = 6.6Hz, 3H),

1.10 (d, J = 7.0Hz, 3H), 0.94-0.89 (m, 6H), 0.85 (d, J = 7.0Hz, 3H), 0.84 (d, J = 6.6Hz, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 202.0, 170.3, 159.1, 149.0, 138.4, 130.5, 129.1, 129.0, 128.2, 128.1, 127.5, 113.7, 95.9, 79.8, 77.3, 75.5, 74.2, 73.6, 72.0,71.7, 59.7, 55.3, 54.9, 48.5, 42.0, 40.1, 35.9, 34.8, 33.5, 31.4, 30.2, 28.9, 28.5, 28.2, 27.1, 26.6, 26.3, 25.6, 23.5, 20.9, 20.2, 18.0, 17.6, 16.6, 14.0, 12.8, 10.7; EI-MS *m/z* : 925 (M^++H), 133 (2-methyl-1,3-dithiane, base peak), 121 (PMB), 43 (Ac); Anal. Calcd for $C_{53}H_{80}O_9S_2$: C, 68.80; H, 8.71. Found: C, 68.69; H, 8.71.

[2*R*,2[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*],5*S*,6*S*,7*S*,9*R*,10*S*,11*R*]-11-Acetoxy-9-benzyloxy-2-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-10-methoxy-7-(4-methoxybenzyl)oxy-6,12-dimethyl-5-tridecanol (55). A solution of tellurium (324 mg, 2.53 mmol) and sodium borohydride (217 mg, 5.80 mmol) in EtOH (3 ml) was refluxed for 30 min and then cooled to -20 °C. To this purple solution was added a mixed solution of degassed acetic acid and EtOH (1.2 : 5, 2.9 ml), and then enone **53** (350 mg, 0.377 mmol) in EtOH (2 ml) at the same temperature. After being stirred for 4 hr at rt, the reaction mixture was diluted with Et_2O and hexane, neutralized with triethylamine, and filtered through a pad of celite. The filtrate was concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 9) to give ketone **54** as a colorless oil. To a solution of ketone in THF (9 ml) was added L-Selectride® (1.0 *M* in THF, 1.32 ml, 1.32 mmol) at -80 °C. After being stirred for 24 hr at the same temperature, the reaction mixture was gradually warmed to -30 °C, and then quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue. To a solution of this residue in hexane was added ethanolamine (200 µl, 3.31 mmol) at 0 °C. After being stirred for 10 min at rt, the mixture was purified by silica gel flash chromatography (AcOEt/hexane, 1 : 9 to 1 : 6) to give a mixture of the alcohol **55** and its C_{18} epimer (317 mg, 0.341 mmol; 91% (2 steps)) as a colorless oil. ketone **54**: $[\alpha]^{23}_D$ -22.8 ° (*c* 0.90, $CHCl_3$); IR (neat) : 2932, 1739, 1711, 1613, 1586, 1456, 1372, 1302 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.14 (m, 7H), 6.85 (d, J = 8.1 Hz, 2H), 5.11 (dd, J = 7.3, 3.7 Hz, 1H), 4.51 (d, J = 5.2 Hz, 2H), 4.44 (m, 2H), 3.80 (s, 3H), 3.79 (m, 1H), 3.66 (m, 1H), 3.44 (s, 3H), 3.39 (dd, J = 7.3, 2.9 Hz, 1H), 3.33 (dd, J = 9.9, 1.8 Hz, 1H), 3.20 (m, 1H), 2.91-2.73 (m, 5H), 2.50-2.32 (m, 2H), 1.94 (s, 3H), 1.59 (s, 3H), 2.17-1.24 (m, 23H), 1.13 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.94-0.87 (m, 12H), 0.83 (d, J = 6.6 Hz, 3H); FAB-HRMS Calcd for $C_{53}H_{82}O_9S_2Na$ (M^++Na): 949.5298 Found : 949.5371. the mixture of alcohol **55** and its epimer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (m, 7H), 6.86-6.83 (m, 2H), 5.12 (dd, J = 7.3, 4.4 Hz, 0.7H), 5.07 (dd, J = 7.3, 4.0 Hz, 0.3H), 4.70-4.20 (m, 4H), 3.80 (s, 3H), 3.80-3.70 (m, 1.3H), 3.65-3.20 (m, 5.7H), 3.44 (s, 0.9H), 3.42 (s, 2.1H), 2.86-2.72 (m, 4H), 1.99 (s, 0.9H), 1.98 (s, 2.1H), 1.58 (s, 2.1H), 1.56 (s, 0.9H), 2.18-1.20 (m, 26H), 1.10 (d, J = 6.6 Hz, 3H), 1.06-0.81 (m, 18H); FAB-MS *m/z* 929 (M^++H), 121 (PMB: base peak), 43 (Ac); FAB-HRMS Calcd for $C_{53}H_{85}O_9S_2$ (M^++H) : 929.5635 Found : 929.5654.

[2*R*,2[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*],5*S*,6*S*,7*S*,9*R*,10*S*,11*R*]-11-Acetoxy-9-benzyloxy-2-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-10-methoxy-7-(4-methoxybenzyl)oxy-6,12-dimethyl-5-(triethylsilyl)oxytridecane (56). To a solution of a mixture of alcohol **55** and its epimer (174.6 mg, 188 µmol) in CH_2Cl_2 (12 ml) were added

diisopropylethylamine (980 µl, 5.63 mmol) and triethylsilyl trifluoromethanesulfonate (650 µl, 2.83 mmol) at -40 °C. After being stirred for 40 min at the same temperature, the reaction mixture was quenched with 1 *N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/benzene, 1 : 30) to give the TES ether **56** (119.8 mg, 115 µmol) and its C_{18} epimer (55.1 mg, 53 µmol) (89%) as a colorless oil. $[\alpha]^{22}_D$ -17.6 ° (*c* 0.89, $CHCl_3$); IR (neat) : 2931, 1740, 1514, 1457, 1374, 1243 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (m, 7H), 6.86 (d, *J* = 8.0 Hz, 2H), 5.13 (dd, *J* = 6.8, 4.0 Hz, 1H), 4.52-4.37 (m, 4H), 3.79 (s, 3H), 3.80-3.70 (m, 2H), 3.58 (m, 1H), 3.44 (s, 3H), 3.41 (m, 1H), 3.33 (m, 1H), 3.23 (m, 1H), 2.84-2.71 (m, 4H), 1.93 (s, 3H), 1.57 (s, 3H), 2.14-1.23 (m, 26H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 1.01-0.83 (m, 18H), 0.57 (q, *J* = 8.0 Hz, 6H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 170.3, 158.9, 138.6, 131.3, 128.8, 128.2, 127.9, 127.4, 113.7, 95.6, 80.3, 76.5, 76.1, 75.6, 75.0, 74.5, 74.1, 72.4, 70.7, 55.3, 54.8, 42.7, 41.8, 36.2, 35.3, 34.9, 33.4, 32.1, 30.9, 30.3, 28.6, 28.3, 27.7, 27.6, 26.8, 26.5, 26.3, 26.2, 25.5, 23.4, 21.0, 20.1, 18.1, 17.0, 16.7, 14.5, 11.0, 9.3, 7.2, 5.4; FAB-MS m/z 1043 (M^++H), 133 (2-methoxy-1,3-dithiane: base peak), 43 (acetyl); FAB-HRMS Calcd for $C_{59}H_{99}O_9SiS_2$ (M^++H) : 1043.6500 Found : 1043.6473.

[3*S*,5[2*S*,3*R*,6*R*,8*S*,8(1*R*,4*S*,5*S*,6*S*,8*R*,9*S*,10*R*),9*S*]]-5-[8-[10-Acetoxy-8-benzyloxy-9-methoxy-6-(4-methoxybenzyl)oxy-1,5,11-trimethyl-4-(triethylsilyl)oxy-dodecanyl]-3,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl]-3-methyl-2-pentanone (57). To a mixed solution of *N*-bromosuccinimide (58.6 mg, 0.33 mmol), silver nitrate (360.3 mg, 0.357 mmol) and 2,4,6-collidine (82 µl, 0.613 mmol) in CH_3CN and H_2O (4 : 1, 2 ml) was added dithiane **56** (55,1 mg, 52.8 µmol) at 0 °C. After being stirred for 10 min at the same tempurature, the reaction mixture was diluted with Et_2O and quenched with 10% aqueous $Na_2S_2O_3$. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed twice with saturated aqueous $KHSO_4$, then with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 10) to give the ketone **57** (40.6 mg, 42.6 µmol; 81%) as a colorless oil. $[\alpha]^{28}_D$ +1.4 ° (*c* 0.70, $CHCl_3$); IR (neat) : 2956, 1738, 1713, 1514, 1462, 1372, 1244 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 7H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.12 (dd, *J* = 4.2, 7.1 Hz, 1H), 4.60-4.37 (m, 4H), 3.80 (s, 3H), 3.74 (m, 1H), 3.69 (m, 1H), 3.58 (m, 1H), 3.44 (s, 3H), 3.42 (m, 1H), 3.26-3.15 (m, 2H), 2.55 (m, 1H), 2.13 (s, 3H), 1.93 (s, 3H), 2.14-1.19 (m, 23H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.99-0.87 (m, 24H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.57 (q, *J* = 8.1 Hz, 6H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 212.8, 170.3, 158.9, 138.6, 131.3, 128.8, 128.2, 127.8, 127.4, 113.7, 95.6, 80.2, 76.5, 76.1, 75.6, 75.3, 74.3, 74.1, 72.4, 70.6, 59.5, 55.3, 47.3, 42.8, 36.1, 35.3, 34.8, 33.3, 30.8, 30.6, 30.2, 29.1, 28.6, 28.1, 27.7, 26.8, 26.6, 21.0, 20.1, 18.0, 16.9, 16.7, 16.1, 10.9, 9.3, 7.1, 5.3; FAB-MS *m/z* 975 (M^++Na), 953 (M^++H), 281 (C_1-C_{14}); FAB-HRMS Calcd for $C_{56}H_{93}O_{10}Si$ (M^++H) : 953.6538 Found : 953.6479.

[3*S*,5[2*S*,3*R*,6*R*,8*S*,8(1*R*,4*S*,5*S*,6*S*,8*R*,9*S*,10*R*),9*S*]]-5-[8-[10-Acetoxy-8-benzyloxy-9-methoxy-6-(4-methoxybenzyl)oxy-1,5,11-trimethyl-4-(triethylsilyl)oxy-dodecanyl]-3,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl]-3-methyl-2-pentanol (58). To a solution of L-Selectride® (1.0 *M* in THF, 33 μl, 33 μmol) in THF (0.5 ml) was added ketone **57** (10.7 mg, 11.2 μmol) at -40 °C. After being stirred for 30 min with gradually warming to -30 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with a mixed solution of saturated aqueous $NaHCO_3$ and 30% aqueous H_2O_2, then with 10% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 10) to give the alcohol **58** (10.7 mg, 11.2 μmol; 100%) as a mixture of epimeric alcohols (colorless oil). IR (neat) : 3500, 2957, 1740, 1514, 1455, 1372, 1245 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 7H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.12 (dd, *J* = 7.0,4.0 Hz, 1H), 4.59-4.36 (m, 4H), 3.79 (s, 3H), 3.75-3.56 (m, 4H), 3.44 (s, 3H), 3.41 (m, 1H), 3.27 (m, 1H), 3.19 (m, 1H), 1.93 (s, 3H), 2.13-1.23 (m, 25H), 1.17-1.10 (m, 3H) , 0.99-0.82 (m, 30H), 0.57 (q, *J* = 8.1 Hz, 6H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 170.4, 158.9, 138.6, 131.3, 128.8, 128.2, 127.9, 127.4, 113.7, 95.7, 80.2, 76.5, 76.0, 75.5, 75.3, 75.2, 74.6, 74.5, 74.1, 72.4, 71.3, 71.2, 70.5, 59.5, 55.3, 42.8, 40.1, 39.9, 36.2, 35.3, 35.0, 34.8, 33.3, 30.7, 30.4, 30.2, 29.7, 28.7, 28.6, 28.13, 28.05, 27.7, 27.6, 26.7, 21.0, 20.4, 20.1, 19.7, 16.8, 16.7, 14.9, 14.2, 10.9, 9.3, 7.1, 5.3; FAB-MS *m/z* 955 (M^++H); FAB-HRMS Calcd for $C_{56}H_{95}O_{10}Si$ (M^++H) : 955.6695 Found : 955.6630.

[2*R*,2[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*],5*S*,6*S*,7*S*,9*R*,10*S*,11*R*]-11-Acetoxy-9-benzyloxy-2-[3,9-dimethyl-8-[4-[[(4-methoxybenzyloxy)methyl]oxy-3-methylpentyl]-1,7-dioxaspiro-[5.5]undecan-2-yl]-10-methoxy-7-(4-methoxybenzyl)oxy-6,12-dimethyl-5-(triethylsilyl)oxy-tridecane (59). To a solution of alcohol **58** (56.7 mg, 59.4 μmol) in CH_2Cl_2 (6 ml) were added diisopropylethylamine (580 μl, 3.33 mmol) and *p*-methoxybenzyloxymethyl chloride (ca. 1.2 mmol, in CH_2Cl_2 (0.5 ml)) at -20 °C. After being stirred for 20 hr at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt /hexane, 1 : 14) to give the PMBM ether **59** (59.5 mg, 52.8 μmol; 89%) as a colorless oil. IR (neat) : 2931, 1738, 1613, 1586, 1514, 1247 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (m, 9H), 6.87-6.83 (m, 4H), 5.12 (dd, *J* = 7.3, 4.4Hz, 1H), 4.77-4.70 (m, 2H), 4.59-4.48 (m, 4H), 4.38 (m, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.81-3.62 (m, 3H), 3.57 (m, 1H), 3.43 (s, 3H), 3.41 (m, 1H), 3.27 (m, 1H), 3.18 (m, 1H), 2.13-2.00 (m, 4H), 1.92 (s, 3H) , 1.90-1.26 (m, 20H), 1.16-1.09 (m, 3H), 0.99-0.86 (m, 27H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.57 (q, *J* = 7.7 Hz, 6H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 170.3, 159.2, 158.9, 138.6, 131.3, 130.2, 129.5, 129.4, 128.8, 128.2, 127.8, 127.4, 113.8, 113.7, 95.6, 92.9, 92.8, 80.2, 77.2, 76.5, 76.3, 76.1, 75.5, 75.2, 74.5, 74.1, 72.3, 70.6, 69.0, 59.5, 55.2, 42.8, 38.7, 38.0, 36.2, 35.4, 34.8, 33.3, 30.9, 30.6, 30.3, 28.9, 28.6, 28.2, 27.7, 26.7, 26.6, 21.0, 20.1, 18.1, 17.2, 16.9, 16.7, 15.7, 15.3, 14.4, 14.2, 10.9, 9.3, 7.1, 5.3; FAB-MS *m/z* 1143 (M^++K), 1127 (M^++Na); FAB-HRMS Calcd for $C_{65}H_{104}O_{12}SiNa$ (M^++Na): 1127.7195 Found : 1127.7155.

[3*R*,4*S*,5*R*,7*S*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-3-Acetoxy-12-[3,9-dimethyl-8-[4-[[(4-methoxybenzyloxy)methyl]oxy-3-methylpentyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-4-methoxy-7-(4-methoxybenzyl)oxy-2,8-dimethyl-9-(triethylsilyl)oxy-5-tridecanol (60). A suspension of TES ether **59** (56.7 mg, 50.3 μmol) and a catalytic amount of Raney Ni (W2) in EtOH (5 ml) was stirred vigorously under 1 atm pressure of hydrogen at rt for 48 hr. To this mixture was further added a catalytic amount of Raney Ni (W2) in EtOH (2 ml). After being stirred under 1 atm pressure of hydrogen for 24 hr, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 12 to 1 : 8) to give alcohol (40.9 mg, 40.3 μmol; 94%) as a colorless oil and also the recovered TES ether **60** (7.2 mg, 7.1 μmol). 80 % (conv. 92%). IR (neat) : 2933, 1740, 1613, 1586, 1514, 1248 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.23 (m, 4H), 6.87-6.83 (m, 4H), 5.12 (dd, *J* = 6.6, 4.8 Hz, 1H), 4.81-4.71 (m, 2H), 4.60-4.42 (m, 4H),3.794 (s, 3H), 3.786 (s, 3H), 3.80-3.62 (m, 4H), 3.47 (s, 3H), 3.27 (m, 1H), 3.18 (m, 1H), 3.12 (dd, *J* = 6.7, 2.6 Hz, 1H), 2.84 (m, 1H), 2.10-1.94 (m, 4H), 2.06 (s, 3H) , 1.85-1.22 (m, 20H), 1.17-1.11 (m, 3H), 0.99-0.87 (m, 27H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.59 (q, *J* = 7.9Hz, 6H); FAB-MS *m/z* 1037 (M^++Na); FAB-HRMS Calcd for $C_{58}H_{98}O_{12}SiNa$ (M^++Na) : 1037.6725 Found : 1037.6651.

[2*R*,2[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*],5*S*,6*S*,7*S*,9*R*,10*S*,11*R*]-11-Acetoxy-2-[3,9-dimethyl-8-[4-[[(4-methoxybenzyloxy)methyl]oxy-3-methylpentyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-10-methoxy-7-(4-methoxybenzyl)oxy-6,12-dimethyl-5,9-bis[(triethylsilyl)oxy]tridecane (61). To a solution of alcohol **60** (24.7 mg, 24.3 μmol) in CH_2Cl_2 (12 ml) were added diisopropylethylamine (170 μl, 976 μmol) and triethylsilyl trifluoromethanesulfonate (115 μl, 501 μmol) at -40 °C. After being stirred for 30 min with gradually warming to -20 °C, the reaction mixture was quenched with 1 *N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15) to give the TES ether **61** (24.2 mg, 21.4 μmol; 88%) as a colorless oil. IR (neat) : 3504, 2955, 1738, 1614, 1514, 1463, 1376, 1247 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 4H), 6.88-6.84 (m, 4H), 5.06 (dd, *J* = 7.3, 3.7 Hz, 1H), 4.79-4.71 (m, 2H), 4.59-4.52 (m, 2H), 4.42 (m, 2H), 3.91 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.79 (m, 1H), 3.70-3.63 (m, 2H), 3.42 (s, 3H), 3.32-3.25 (m, 2H), 3.18 (m, 1H), 2.00 (s, 3H), 2.17-1.24 (m, 24H), 1.17-1.09 (m, 3H) , 0.99-0.87 (m, 36H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.63 (q, *J* = 8.1 Hz, 6H), 0.60 (q, *J* = 8.1 Hz, 6H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 170.2, 159.2, 158.8, 131.4, 130.2, 129.5, 129.4, 128.6, 113.8, 113.6, 95.6, 93.0, 92.7, 81.7, 77.2, 76.6, 76.3, 75.7, 75.3, 74.5, 74.1, 70.8, 69.5, 69.0, 59.1, 55.3, 42.9, 38.7, 37.9, 36.5, 36.1, 35.5, 34.8, 30.9, 30.6, 30.4, 30.3, 29.7, 28.9, 28.6, 28.2, 27.7, 26.8, 26.7, 26.6, 21.0, 20.1, 18.0, 17.2, 16.9, 16.7, 15.6, 15.3, 14.4, 10.9, 9.2, 9.1, 7.0, 5.3; FAB-MS *m/z* 1152 (M^++Na); FAB-HRMS Calcd for $C_{64}H_{112}O_{12}Si_2Na$ (M^++Na): 1151.7590 Found : 1151.7481.

[3*R*,4*S*,5*R*,7*S*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-12-[3,9-Dimethyl-8-[4-[[(4-methoxybenzyloxy)methyl]oxy-3-methylpentyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-4-methoxy-7-(4-methoxybenzyl)oxy-2,8-dimethyl-5,9-bis[(triethylsilyl)oxy]-3-tridecanol (4). To a solution of ester **61** (3.39 mg, 3.0 μmol) in CH_2Cl_2 (150 μl) was added diisobutylaluminium hydride (0.93 *M* in hexane, 30 μl, 28 μmol) dropwise at -78 °C. After being stirred for 30 min at the same temperature, the reaction mixture was added to a vigorously stirred mixed solution of 0.5 *N* aqueous potassium sodium tartrate and Et_2O via cannula at 0 °C, and the quenched solution was stirred for 2 hr at rt. The organic layer was

separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by preparative thin layer chromatography (AcOEt/hexane, 1 : 4) to give the alcohol **4** (3.28 mg, 3.0 μmol; 100%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.22 (m, 4H), 6.88-6.84 (m, 4H), 4.79-4.69 (m, 2H), 4.56-4.38 (m, 4H), 4.14 (m, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.74-3.60 (m, 5H), 3.37 (s, 3H), 3.32-3.11 (m, 3H), 2.10-1.22 (m, 24H), 1.17-1.08 (m, 3H), 1.00-0.87 (m, 36H), 0.82 (d, J = 6.3Hz, 3H), 0.66 (q , J = 7.9 Hz, 6H), 0.60 (q, J = 8.0Hz, 6H). This compound was useless for the total synthesis.

***N*-Methoxy-*N*,4-dimethyl-3-furancarboxamide (63).** To a solution of carboxylic acid **62** (915 mg, 7.3 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (800 mg, 8.2 mmol) in DMF (20 ml) was added a mixture of diethylphosphoryl cyanide (1.3 ml, 8.0 mmol) and triethylamine (2.2 ml, 16.1 mmol) in DMF (5 ml) at 0 °C. After being stirred for 30 min at the same temperature, and then for an additional 30 min at rt, the reaction mixture was diluted with benzene and AcOEt, and then quenched with 5% aqueous HCl. The organic layer was separated, and washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 4) to give the amide **63** (1.20 g, 7.1 mmol; 97%) as a white solid. mp 39 °C (recrystallized from AcOEt-hexane); IR (KBr) 1637, 1534, 1382, 1230, 1140, 1047, 969, 863 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J =1.5 Hz, 1H), 7.21 (m, 1H), 3.66 (s, 3H), 3.32 (s, 3H), 2.21(d, J =1.1 Hz, 3H); ^{13}C-NMR (78.8 MHz, $CDCl_3$) δ 164.2, 146.3, 139.9, 121.9, 118.2, 60.9, 32.7, 9.5; EI-MS *m/z* 169 (M^+), 109 (M^+-N(OMe)Me); EI-HRMS Calcd for $C_8H_{11}O_3N$ (M^+) : 169.0739 Found : 169.0739.

Methyl 3-(4-methylfuryl)-3-oxopropionate (64). To a solution of LDA (9.9 mmol) in THF (15 ml) was added methyl acetate (0.79 ml, 9.9 mmol) dropwise at -78 °C. After being stirred for 20 min at the same temperature, to this solution was added amide **63** (1.20 g, 7.1 mmol) in THF (2 ml) slowly via cannula at -78 °C. After being stirred for 2 hr at the same temperature, the reaction mixture was poured into 1 *N* aqueous HCl and Et_2O at 0 °C. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15 to 1 : 6) to give the β-keto ester **64** (0.699 g, 3.8 mmol) as a colorless oil and the recovered amide (0.244 mg, 1.4 mmol). 58 % (conv. 73%). IR (neat) 3137, 2956, 1743, 1678, 1534, 1438, 1330, 1148, 1050, 874 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.02 (d, J =1.5 Hz, 1H), 7.23 (m, 1H), 3.77 (s, 2H), 3.76 (s, 3H), 2.21 (d, J = 1.0 Hz, 3H). ^{13}C-NMR (78.8 MHz, $CDCl_3$) δ 187.2, 167.5, 149.6, 141.6, 125.9, 120.4, 52.3, 47.4, 9.1; EI-MS *m/z* 182 (M^+), 109 (M^+-CH_2COOMe); EI-HRMS Calcd for $C_9H_{10}O_4$ (M^+): 182.0579 Found : 182.0579.

Methyl (*R*)-3-hydroxy-3-(4-methylfuryl)propionate (65). *Ru-BINAP method* : A solution of $[RuCl_2(benzene)]_2$ (5.0 mg) and (*S*)-BINAP (13.1 mg) in degassed DMF (0.5 ml) was warmed with stirring for 10 min at 100 °C and then pumped dry under reduced pressure (0.1 mmHg) at 50 °C. The residue (as a catalyst) and the β-keto ester **64** (181 mg, 1.0 mmol) were dissolved in degassed MeOH (2 ml) and the resulting mixture further degassed three times. After being stirred under 100 atm of hydrogen for 48 h, the whole reaction mixture was concentrated to give a residue which was then purified by silica gel flash

chromatography (AcOEt/hexane, 1 : 7) to give the alcohol **65** (184 mg, 1.0 mmol; 100%) as a colorless oil in 86% ee. (calculated by peak ratio (^{1}H-NMR) of MTPA ester). *BH_3-oxazaborolidine method* : To a solution of (*S*)-(-)-2-methyl-CBS-oxazaborolidine **66** (23.0 mg, 78 μmol) in THF (0.8 ml) was added BH_3•THF (1.0 *M* in THF, 75 μl, 75 μmol) dropwise at rt. To this mixture were added β-keto ester **64** (28.0 mg, 154 μmol) in THF (0.5 ml) and BH_3•THF (1.0 *M* in THF, 150 μl, 150 μmol) at 0 °C. After being stirred for 1 hr at the same temperature, the reaction mixture was diluted with Et_2O and 30% aqueous H_2O_2, and the mixture was stirred for an additional 30 min at room temperature. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with 10% $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 6) to give the alcohol **65** (16.2 mg, 88 μmol; 57%) as a colorless oil and the recovered keto ester (4.0 mg, 22 μmol). conv. 67%. 92% ee. (calculated by peak raio (^{1}H-NMR) of MTPA ester and by using analytical chiral phase HPLC (Daicel Chiralcel OD, hexane : 2-PrOH = 9 : 1)). Purification of the alcohol **65** was further performed by using preparative HPLC (Daicel Chiralcel OD, hexane : 2-PrOH = 9 : 1), and we used this optically pure **65** for the total synthesis of **1**. $[\alpha]^{22}_D$ +41.9 ° (*c* 0.84, $CHCl_3$, 100% ee); IR (neat) 3452, 2954, 1733, 1547, 1439, 1360, 1282, 1171, 1049, 876, 803 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 1H), 7.18 (m, 1H), 5.07 (m, 1H), 3.75 (s, 3H), 3.31 (d, *J* = 4.0 Hz, 1H), 2.7-2.9 (m, 2H), 2.06 (br-d, 3H); ^{13}C-NMR (78.8 MHz, $CDCl_3$) δ 173.2, 140.9, 140.0, 127.4, 119.3, 63.5, 52.4, 41.5, 8.9, EI-MS *m/z* 184 (M^+), 111 (M^+-CH_2COOMe); EI-HRMS Calcd for $C_9H_{12}O_4$ (M^+): 184.0736 Found : 184.0728.

Methyl (*R*)-3-(diethylisopropylsilyl)oxy-3-(4-methylfuryl)propionate (67). To a solution of alcohol **65** (13.9 mg, 75.5 μmol) in CH_2Cl_2 (1.3 ml) were added imidazole (13 mg, 191 μmol) and diethylisopropylchlorosilane (21 μl, 113 μmol) at 0 °C. After being stirred for 2 hr, the reaction mixture was quenched with water. The organic layer was separated, and washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by preparative thin layer silica gel chromatography (AcOEt/hexane, 1 : 4) to give the DEIPS ether **67** (23.0 mg, 73.7 μmol; 98%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.12 (m, 1H), 5.16 (dd, *J* = 8.6, 5.0 Hz, 1H), 3.66 (s, 3H), 2.81 (dd, *J* = 14.9, 8.6 Hz, 1H), 2.58 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.06 (d, *J* = 1.3 Hz, 3H), 1.02-0.84 (m, 13H), 0.65-0.52 (m, 4H). This compound was useless for the total synthesis of **1**.

Benzyl (*R*)-3-(diethylisopropylsilyl)oxy-3-(4-methylfuryl)propionate (68). To a solution of **67** (23.0 mg, 74 μmol) in THF/water (5 : 1, 1.8 ml) was added lithium hydroxide monohydrate (4.6 mg, 110 μmol) at rt. After being stirred for 48 hr, the reaction mixture was quenched with 0.3 *N* aqueous HCl at 0 °C and diluted with AcOEt. After being stirred for 30 min, the organic layer was separated, and the aqueous layer was extracted twice with AcOEt. The combined organic layers were dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2O/hexane, 1 : 2 to Et_2O only) to give the carboxylic acid (19.0 mg, 64 μmol) as a colorless oil. To a solution of carboxylic acid (19.0 mg, 64 μmol) in THF (2 ml) were added benzyl alcohol (23 μl, 0.22 mmol), 4-dimethylaminopyridine (7.0 mg, 57 μmol), and dicyclohexylcarbodiimide (17.1 mg, 83 μmol) at 0 °C. After being stirred for 5 hr at rt, the reaction mixture was diluted with hexane and filtered through a pad of celite. The filtrate was washed with 0.3*N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with AcOEt. The

combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 20) to give the benzyl ester (17.8 mg, 45.9 μmol; 62% (2 steps)) as a colorless oil. $[\alpha]^{28}_D$ +35.7 ° (*c* 1.09, $CHCl_3$); IR (neat) 2955, 2876, 1738, 1240, 1166, 1087, 1046 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 7.24 (m, 1H), 7.11 (m, 1H), 5.17 (dd, *J* = 8.6, 5.0 Hz, 1H), 5.09 (m, 2H), 2.86 (dd, *J* = 14.9, 8.6 Hz, 1H), 2.63 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.05 (d, *J* = 1.0 Hz, 3H), 0.96-0.82 (m, 13H), 0.62-0.58 (m, 4H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 170.8, 140.3, 139.9, 135.8, 128.5, 128.25, 128.18, 127.9, 118.5, 66.3, 64.7, 44.5, 17.1, 12.8, 8.7, 6.9, 6.8, 3.6, 3.4. This compound was useless for the total synthesis of **1**.

(*R*)-2-[2-Benzyloxycarbonyl-1-(diethylisopropylsilyl)oxyethyl]-3-methylmaleic anhydride (69). A solution of furan **68** (118.2 mg, 305 μmol), diisopropylethylamine (110 μl, 631 μmol) and a catalytic amount of rose bengal in CH_2Cl_2 (2.7 ml) was stirred under 1 atm pressure of oxygen with irradiation by a Hg lamp at 0 °C. The reaction mixture was then diluted with Et_2O and passed through a short silica gel flash chromatography column (Et_2O) to give 5-hydroxy-2,5-dihydro-2-furanone as a colorless oil. To a solution of the furanone in CH_2Cl_2 (7 ml) were added MS4A (500 mg) and pyridinium chlorochromate (200 mg, 930 μmol) at rt. After being stirred for 4 hr, the reaction mixture was diluted with Et_2O, and passed through a florisil® column (AcOH/Et_2O, 1 : 100) to give the maleic anhydride **69** (112.2 mg, 268 μmol; 88% (2 steps)) as a colorless oil. $[\alpha]^{26}_D$ +18.9 ° (*c* 0.43, $CHCl_3$); IR (neat) : 2956, 2878, 1770, 1738, 1253, 1170, 1101, 1015 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.16-5.08 (m, 3H), 2.89-2.84 (m, 2H), 2.12 (br-s, 3H), 0.99-0.87 (m, 13H), 0.68-0.56 (m, 4H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 169.2, 165.8, 164.3, 143.1, 142.6, 135.3, 128.7, 128.55, 128.51, 66.9, 64.1, 41.4, 17.0, 12.7, 10.0, 6.8, 3.4, 3.3. This compound was useless for the total synthesis of **1**.

Benzyl (4*Z*,3*R*)-4-(*tert*-butoxycarbonyl)-3-(diethylisopropylsilyl)oxy-5-(methoxycarbonyl)-4-hexenoate and Benzyl (4*Z*,3*R*)-5-(*tert*-butoxycarbonyl)-3-(diethylisopropylsilyl)oxy-4-(methoxycarbonyl)-4-hexenoate (70). To a solution of maleic anhydride **69** (5.8 mg, 13.8 μmol) in MeOH (1.0 ml) was added triethylamine (20 μl, 0.16 mmol) at 0 °C. After being stirred for 1 hr at the same temperature, the reaction mixture was quenched with 1 *N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated to give the half ester. To a solution of the half ester in CH_2Cl_2 (2.0 ml) was added *O*-*t*-butyl-*N*,*N*-diisopropylisourea **71** (70 μl, 0.27 mmol). After being refluxed 24 hr with stirring, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated. The residue was diluted with AcOEt, and the organic layer was washed with water, 1 *N* aqueous HCl and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by preparative thin layer chromatography (AcOEt/hexane, 1 : 4) to give the DEIPS deprotected triester (3.95 mg, 10.4 μmol; 75% (2 steps)) as a colorless oil. To a solution of the resulting alcohol (1.37 mg, 3.6 μmol) in CH_2Cl_2 (300 μl) were added imidazole (1.3 mg, 19 μmol) and diethylisopropylchlorosilane (1.7 μl, 9.2 μmol) in CH_2Cl_2 (20 μl) at 0 °C. After being stirred for 2.5 hr, the reaction mixture was quenched with water. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by preparative thin layer chromatography (AcOEt/hexane,

1 : 5) to give the DEIPS ether **70** (1.60 mg, 3.15 μmol; 87%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.18-5.12 (m, 3H), 3.73 (s, 2.7H), 3.72 (s, 0.3H), 3.01 (dd, *J* = 15.7, 8.8 Hz, 0.9H), 2.97 (dd, *J* = 15.6, 8.1 Hz, 0.1H), 2.77 (dd, *J* = 15.6, 4.8 Hz, 0.1H), 2.70 (dd, *J* = 15.7, 4.0 Hz, 0.9H), 1.95 (s, 0.3H), 1.93 (s, 2.7H), 1.50 (s, 0.9H), 1.46 (s, 8.1H), 0.96-0.85 (m, 13H), 0.65-0.54 (m, 4H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 170.8, 167.1, 167.1, 140.6, 135.7, 131.6, 128.5, 128.3, 81.8, 67.6, 66.51, 66.48, 52.08, 51.71, 42.5, 42.3, 28.1, 28.0, 27.9, 17.14, 17.08, 15.0, 12.8, 12.7, 6.9, 6.8, 3.5, 3.35, 3.27. This compound was useless for the total synthesis of **1**.

(4*Z*, 3*R*)-4-(*tert*-Butoxycarbonyl)-3-(diethylisopropylsilyl)oxy-5-(methoxycarbonyl)-4-hexenoic acid and (4*Z*,3*R*)-5-(*tert*-Butoxycarbonyl)-3-(diethylisopropylsilyl)oxy-4-(methoxycarbonyl)-4-hexenoic acid (3). A solution of triester **70** (1.29 mg, 2.54 μmol) and a catalytic amount of 10% Pd/C in MeOH (500 μl) was stirred vigorously under 1 atm pressure of hydrogen at rt for 30 min. The reaction mixture was diluted with $CHCl_3$, and filtered. The filtrate was concentrated to give the carboxylic acid (0.91 mg, 2.18 μmol; 87%) as a pale yellow oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.12 (m, 1H), 3.74 (s, 2.7H), 3.73 (s, 0.3H), 2.99-2.67 (m, 2H), 1.98 (s, 0.3H), 1.95 (s, 2.7H), 1.50 (s, 0.9H), 1.46 (s, 8.1H), 0.98-0.88 (m, 13H), 0.68-0.56 (m, 4H). This compound was useless for the total synthesis of **1**.

Methyl (*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methylfuryl)propionate (77). To a solution of alcohol **65** (52.0 mg, 283 μmol) in CH_2Cl_2 (2.5 ml) was added diisopropylethylamine (180 μl, 1.0 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (120 μl, 522 μmol) at 0 °C. After being stirred for 30 min, the reaction mixture was quenched with 1 *N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 12) to give the TBS ether (83.2 mg, 279 μmol; 99%) as a colorless oil. $[\alpha]^{28}_D$ +52.3 ° (*c* 0.65, $CHCl_3$); IR (neat) : 2929, 2856, 1741, 1087, 1046 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.13 (m, 1H), 5.13 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.68 (s, 3H), 2.80 (dd, *J* = 14.5, 9.2 Hz, 1H), 2.56 (dd, *J*= 14.5, 4.3 Hz, 1H), 2.05 (d, *J* = 1.3 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), -0.09 (s, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 171.5, 140.4, 139.8, 128.8, 127.9, 118.5, 64.9, 51.6, 44.3, 25.6, 18.0, 11.0, -4.8; EI-MS *m/z* 283 (M^+-CH_3); EI-HRMS Calcd for $C_{14}H_{23}O_4Si$ (M^+-CH_3) : 283.1366, Found : 283.1361.

(*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methylfuryl)propionic acid (74). To a solution of TBS ether **77** (6.0 mg, 20 μmol) in THF/water (5 : 1, 0.6 ml) was added lithium hydroxide monohydrate (1.3 mg, 30 μmol) at rt. After being stirred for 48 hr, the reaction mixture was quenched with 0.3 *N* aqueous HCl and diluted with AcOEt at 0 °C. After being stirred for 30 min, the organic layer was separated, and the aqueous layer was extracted twice with AcOEt. The combined organic layers were dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 2 to Et_2O only) to give the carboxylic acid **74** (5.7 mg, 20 μmol; 100%) as a colorless oil. $[\alpha]^{28}_D$ +41.5 ° (*c* 0.96, $CHCl_3$); IR (neat) : 2930, 2858, 1714, 1087 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.14 (m, 1H), 5.12 (dd, *J* = 8.6, 4.3 Hz, 1H), 2.83 (dd, *J* = 14.9, 8.6 Hz, 1H), 2.63 (dd, *J* = 14.9, 4.3 Hz, 1H), 2.05 (d, *J* = 1.0 Hz,

3H), 0.85 (s, 9H), 0.05 (s, 3H), -0.08 (s, 3H); ^{13}C-NMR (100.4 MHz, $CDCl_3$) δ 140.5, 139.9, 127.4, 118.3, 64.7, 43.8, 25.6, 18.0, 8.7, -4.8; EI-MS *m/z* 269 (M^+-Me), 227 (M^+-^{t}Bu) EI-HRMS Calcd for $C_{10}H_{15}O_4Si$ (M^+-^{t}Bu) : 227.0740, Found : 227.0746.

[3*R*,4*S*,5*R*,7*S*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-5,9-Bis-[(*tert*-butyldimethylsilyl)oxy]-12-[3,9-dimethyl-8-[4-[[(4-methoxybenzyloxy)methyl]oxy-3-methylpentyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-4-methoxy-7-(4-methoxybenzyl)oxy-2,8-dimethyl-3-tridecanol (76). To a solution of TES ether **61** (5.55 mg, 4.92 μmol) in THF (0.5 ml) was added hydrogen fluoride-pyridine (2 *mM* in THF; 0.10 ml, 0.20 mmol) at 0 °C. After being stirred for 24 hr at rt, hydrogen fluoride-pyridine (2 *mM* in THF; 0.15 ml, 0.30 mmol) was added to the mixture at 0 °C. After being stirred for an additional 36 hr at rt, the whole reaction mixture was diluted with Et_2O and aqueous $CuSO_4$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with aqueous $CuSO_4$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 2 : 5 to 1 : 2) to give a mixture of the desired diol **78** and the migration product (ca. 4.3 mg, 4.8 μmol) as a colorless oil. To a solution of the resulting mixture (ca. 4.3 mg, 4.8 μmol) in CH_2Cl_2 (0.7 ml) were added diisopropylethylamine (34 μl, 195 μmol) and *t*-butyldimethyllsilyl trifluoromethanesulfonate (26 μl, 113 μmol) at -40 °C. After being warmed to -20 °C for 30 min with stirring, the reaction mixture was quenched with 1 *N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 15 to 1 : 8) to give a mixture of the TBS ether **79** and the migration product (5.28 mg, 4.68 μmol) as a colorless oil. To a solution of the resulting mixture in CH_2Cl_2 (250 μl) was added diisobutylaluminium hydride (0.93 *M* in hexane, 50 μl, 47 μmol) dropwise at -78 °C. After being stirred for 30 min at the same tempurature, the reaction mixture was added to a vigorously stirred mixture of 0.5 *N* aqueous potassium sodium tartrate and Et_2O via cannula at 0 °C, and the quenched solution was stirred for 2 hr at rt. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by preparative thin layer chromatography (AcOEt/hexane, 1 : 4) to give the alcohol **76** (4.02 mg, 3.70 μmol; 75% (3 steps)) as a colorless oil. TBS ether **79**: IR (neat) : 2929, 1738, 1613, 1587, 1514, 1247 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.22 (m, 4H), 6.88-6.84 (m, 4H), 5.05 (dd, *J*= 7.0, 3.6 Hz, 1H), 4.80-4.72 (m, 2H), 4.60-4.35 (m, 4H), 3.90 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.73-3.61(m, 2H), 3.55 (m, 1H), 3.41 (s, 3H), 3.33 (dd, *J* = 7.0, 3.3Hz, 1H), 3.25 (m, 1H), 3.18 (m, 1H), 2.00 (s, 3H), 2.15-1.15 (m, 24H), 1.10-1.07 (m, 3H), 1.00-0.84 (m, 18H), 0.91 (s, 9H), 0.89 (s, 9H), 0.82 (d, *J* = 6.2Hz, 3H), 0.09 (s, 6H), 0.04 (s, 6H). alcohol **76**: IR (neat) : 3505, 2930, 1612, 1514, 1248 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.22 (m, 4H), 6.88-6.83 (m, 4H), 4.80-4.70 (m, 2H), 4.60-4.36 (m, 4H), 4.11 (m, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.74-3.58 (m, 5H), 3.36 (s, 3H), 3.29-3.12 (m, 3H), 2.10-1.24 (m, 24H), 1.17-1.10 (m, 3H), 1.00-0.86 (m, 18H), 0.91 (s, 9H), 0.89 (s, 9H), 0.81 (d, *J* = 6.2Hz, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.04 (s, 6H); FAB-MS *m/z* 1109 (M^++Na); FAB-HRMS Calcd for $C_{62}H_{110}O_{11}Si_2Na$ (M^++Na) : 1109.7482, Found : 1109.7400.

[3*R*,4*S*,5*R*,7*S*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-5,9-Bis[(*tert*-butyldimethylsilyl)oxy]-12-[3,9-dimethyl-8-[4-[[(4-methoxybenzyloxy)methyl]oxy-3-methylpentyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-4-methoxy-7-(4-methoxy-benzyl)oxyhydroxy-2,8-dimethyltridecan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methyl-3-furyl)propionate (75). To a solution of carboxylic acid **74** (12.39 mg, 43.6 μmol) in toluene (150 μl) were added triethylamine (0.588 *mM* in toluene, 100 μl, 58.8 μmol) and 2,4,6-trichlorobenzoyl chloride (0.523 *mM* in toluene, 100 μl, 52.3 μmol) at 0 °C. After stirring for 2 hr at rt, to this mixture were added alcohol **76** (10.43 mg, 9.6 μmol) and DMAP (21.0 mg, 172 μmol) at 50 °C. After being stirred for 12 hr at the same temperature, the reaction mixture was quenched with 1 *N* aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1 : 24) to give the ester **75** (9.28 mg, 6.8 μmol) as a pale yellow oil and also the recovered alcohol **76** (1.98 mg, 0.18 μmol). 72% (conv. 88%). IR (neat) 2930, 2857, 1738, 1614, 1587, 1514, 1463, 1249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (m, 5H), 7.09 (m, 1H), 6.88-6.81 (m, 4H), 5.14 (dd, *J* = 8.8, 3.7 Hz, 1H), 5.04 (dd, *J* = 5.9, 3.7 Hz, 1H), 4.80-4.72 (m, 2H), 4.59-4.41 (m, 2H), 4.44-4.32 (m, 2H), 3.85 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72-3.64 (m, 2H), 3.52 (m, 1H), 3.37 (s, 3H), 3.30 (dd, *J* = 5.9, 4.4 Hz, 1H), 3.25 (m, 1H), 3.18 (m, 1H), 2.79 (dd, *J* = 16.1, 8.8Hz, 1H). 2.49 (dd, *J* = 16.1, 3.7 Hz, 1H), 2.00 (m, 3H), 2.12-1.22 (m, 24H), 1.17-1.09 (m, 3H), 0.97-0.80 (m, 21H), 0.881 (s, 9H), 0.877 (s, 9H), 0.82 (s, 9H), 0.061 (s, 3H), 0.057 (s, 3H), 0.033 (s, 3H), 0.028 (s, 3H), 0.026 (s, 3H), -0.10 (s, 3H); FAB-HRMS Calcd for $C_{76}H_{132}O_{14}Si_3Na_1$ (M^++Na) : 1375.8826, Found : 1375.8781.

[3*R*,4*S*,5R,7*S*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-5,9-Bis[(*tert*-butyldimethylsilyl)oxy]-12-[3,9-dimethyl-8-[4-[4-hydroxy-3-methylpentyl]-1,7-dioxaspiro-[5.5]undecan-2-yl]-7-hydroxy-4-methoxy-2,8-dimethyltridecan-3-yl (3*R*)-3-(*tert*-butyl-dimethylsilyl)oxy-3-(4-methyl-3-furyl)propionate (80). To a solution of PMB ether **75** (14.1 mg, 10.4 μmol) in CH_2Cl_2 (700 μl) and phosphate buffer (pH7) (70 μl) was added DDQ (9.4 mg, 41.4 μmol) at 0 °C. After being stirred for 30 min at rt, this mixture was twice treated with additional DDQ (2.4 mg, 10.6 μmol) at 30 min intervals. After being stirred for an additional 30 min, the reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ and CH_2Cl_2 at 0 °C. The quenched mixture was filtered through a pad of celite, and the organic layer of the filtrate was separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was then purified by preparative thin layer chromatography (AcOEt/hexane, 1 : 4) to give the diol **80** (8.6 mg, 7.9 μmol; 76%) as a colorless oil and the mono-ol deprotected only at C_{20} (1.3 mg, 1.0 μmol; 10 %). IR (neat) 3411, 2930, 1742, 1463, 1374, 1247 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.11 (m, 1H), 5.16 (dd, *J* = 8.3, 4.3 Hz, 1H), 5.02 (dd, *J* = 5.5, 4.3 Hz, 1H), 4.11 (m, 1H), 3.99 (m, 1H), 3.72-3.59 (m, 2H), 3.38 (s, 3H), 3.42-3.13 (m, 3H), 2.82 (dd, *J* = 15.8, 8.3 Hz, 1H), 2.59 (dd, *J* = 15.8, 4.3 Hz, 1H), 2.35 (m, 1H), 2.05 (d. *J* = 0.9 Hz, 3H), 2.14-1.20 (m, 24H), 1.17-1.12 (m, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.95-0.81(m, 21H), 0.89 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.09-0.07 (m, 12H), 0.04 (s, 3H), -0.09 (s, 3H); FAB-MS *m/z* 1105 (M^++Na); FAB-HRMS Calcd for $C_{59}H_{114}O_{11}Si_3Na_1$ (M^++Na) : 1105.7567, Found : 1105.7592.

[3*R*, 4*S*, 5*R*, 8*S*, 9*S*, 12*R*, 12[2*S*, 3*S*, 6*R*, 8*S*, 8(3*S*), 9*R*]]-5,9-Bis[(*tert*-butyldimethylsilyl)oxy]-12-[3,9-dimethyl-8-[4-[3-methylpentyl-4-oxo]-1,7-dioxaspiro-[5.5]undecan-2-yl]-4-methoxy-2,8-dimethyl-7-oxotridecan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methyl-3-furyl)propionate (81). To a solution of the diol **80** (13.1 mg, 12.1 μmol), NMO (8.8 mg, 75 μmol) and MS4A in CH_3CN (1.3 ml) was added TPAP (6.6 mg, 19 μmol) at 0 °C. After being stirred for 1 hr at rt, the reaction mixture was diluted with CH_2Cl_2, then passed through a short column flash of silica gel (CH_2Cl_2) to give the diketone **81** (11.3 mg, 10.5 μmol; 87%) as a colorless oil. $[\alpha]^{26}_D$ +22.1 ° (*c* 0.24, $CHCl_3$); IR (neat) 2929, 1734, 1716, 1462, 1256 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.11 (m, 1H), 5.17 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.92 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.47 (m, 1H), 3.98 (m, 1H), 3.35 (s, 3H), 3.26 (m, 1H), 3.22 (dd, *J* = 7.2, 4.0 Hz, 1H), 3.17 (m, 1H), 2.82 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.56 (dd, *J* = 16.1, 4.4 Hz, 1H), 2.75-2.55 (m, 4H), 2.16 (s, 3H), 2.03 (m. 3H), 2.18-1.19 (m, 20H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.00-0.80 (m, 18H), 0.85 (s, 9H), 0.83 (s, 9H), 0.81 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), -0.02 (s, 3H), -0.09 (s, 3H); FAB-MS *m/z* 1101 (M^++Na); FAB-HRMS Calcd for $C_{59}H_{110}O_{11}Si_3Na_1$ (M^++Na) : 1101.7254, Found : 1101.7326.

Tris-*O*-(*tert*-butyldimethylsilyl)tautomycin (82). To a solution of furan **81** (3.3 mg, 3.1 μmol) in THF/pH 7 phosphate buffer (4 : 1, 0.5 ml) was added NBS (1.1 mg, 6.18 μmol) at 0 °C. After being stirred for 15 min at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with hexane/Et_2O (1 : 1). The organic layer was separated, and the aqueous layer was extracted twice with hexane/Et_2O (1 : 1). The combined organic layers were washed with saturated aqueous $NaHCO_3$, water and brine, then dried (Na_2SO_4) and concentrated to give the diol as a mixture of four isomers. To this diol in acetone (0.3 ml) was added Jones reagent (48.6 *μM* in acetone, 82 μl, 3.99 μmol) at 0 °C. After being stirred for 15 min at the same temperature, the reaction mixture was quenched with 2-PrOH (2 drops), and then pH 7 phosphate buffer. The quenched solution was extracted with Et_2O. The organic layer was separated, and washed with saturated aqueous $NaHCO_3$, and brine, then dried (Na_2SO_4) and concentrated to give to a residue which was then purified by preparative thin layer chromatography (AcOEt/hexane, 1 : 4) to give the 5-hydroxy-2,5-furanone (2.1 mg, 1.9 μmol; 62%) as a mixture of four isomers. To the mixture in CH_2Cl_2 were added MS4A (30 mg) and PCC (0.8 mg, 3.71 μmol). After being stirred for 3 hr, the reaction mixture was twice treated with additional PCC (0.8 mg, 3.71 μmol) at 3 hr intervals. After being stirred for an additional 12 hr, the reaction mixture was diluted with Et_2O, and passed through a pad of celite (Et_2O) to give a residue which was then purified by preparative thin layer chromatography (AcOEt/hexane/AcOH, 19 : 80 : 1) to give the maleic anhydride **82** (0.8 mg, 0.72 μmol; 38%) as a pale yellow oil. $[\alpha]^{24}_D$ +20.0 ° (*c* 0.04, $CHCl_3$); IR (neat) : 2955, 2926, 2854, 1772, 1737, 1714, 1462, 1095, 836, 777 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.16 (dd, *J* = 7.2, 5.7 Hz, 1H), 4.93 (dd, *J* = 7.3, 3.9 Hz, 1H), 4.46 (m, 1H), 3.97 (m, 1H), 3.36 (s, 3H), 3.28-3.13 (m, 3H), 2.87 (dd, *J* = 16.4, 7.3 Hz, 1H), 2.75-2.65 (m, 4H), 2.57 (m, 1H), 2.22 (s, 3H), 2.15 (s, 3H), 2.15-1.95 (m, 2H), 1.89 (m, 1H), 1.79-1.20 (m, 17H), 1.10 (d, *J* = 7.2 Hz, 3H), 0.99-0.79 (m, 18H), 0.86 (s, 9H), 0.85 (s, 9H), 0.82 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H); FAB-MS *m/z* 1131 (M^++Na), 1109 (M^++H); FAB-HRMS Calcd for $C_{59}H_{108}O_{13}Si_3Na$ (M^++Na) : 1131.6995, Found : 1131.6976. This compound was converted to **1** using freshly prepared HF•Py according to the literature procedure.[7]

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