The Total Synthesis of Herbimycin A

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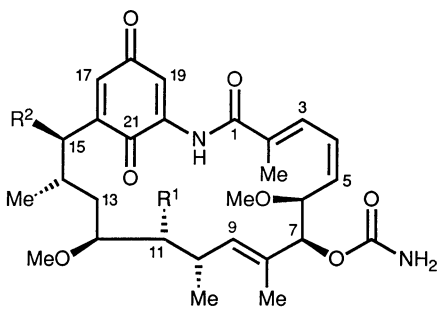
The first total synthesis of herbimycin A (**1**), the benzoquinonoid ansamycin antibiotic, is described. (2*E*,4*S*,5*R*,6*S*,8*S*)-5,6-Dimethoxy-9-(4-methoxybenzyl)oxy-2,4,8-trimethyl-2-nonenal (**40**), corresponding to the C7—C15 portion of the ansa-chain of **1**, was prepared from methyl 3,4-anhydro-2-deoxy-2-*C*-methyl-6-*O*-(triphenylmethyl)-α-D-altropyranoside (**16**), which had been previously prepared from methyl α-D-mannopyranoside according to our developed procedure, by using a regioselective epoxide opening [bis(1,2-dimethylpropyl)borane–$NaBH_4$] and a stereoselective hydroboration (BH_3·SMe_2) as the key steps. This aldehyde **40** was subjected to the Brown's diastereo- and enantioselective allylation conditions [[(*Z*)-3-methoxyallyl]diisopinocampheylborane] to afford the desired *syn* 3-methoxy-1,5-dodecadien-4-ol derivative. Subsequent three-step conversion of this alcohol furnished the synthesis of the C5—C15 ansa-chain aldehyde, (2*S*,4*S*,5*R*,6*S*,7*E*,9*S*,10*S*)-9-[(*t*-butyldimethylsilyl)oxy]-4,5,10-trimethoxy-2,6,8-trimethyl-7,11-dodecadienal (**7**). Union of **7** and the lithiated aromatic chromophore, prepared from *N*-(triphenylmethyl)-3-bromo-2,5-dimethoxyaniline and butyllithium, provided the coupling product, which was transformed to herbimycin A (**1**) through elongation of the C1—C4 carbon unit and macrolactamization. This fully enantiospecific synthesis elucidates the absolute stereochemistry of **1**.

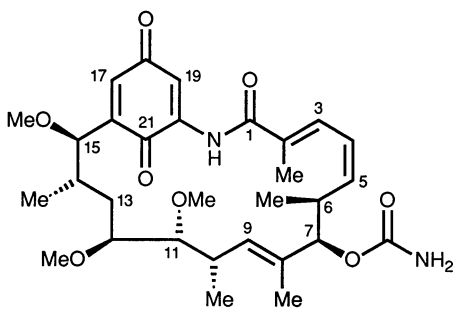
The benzoquinonoid ansamycin antibiotic herbimycin A (**1**)[1] was isolated in 1979 from the fermentation broth of *Stereptmyces hygroscopicus* strain AM-3672. The structure was elucidated by spectroscopic and biosynthetic means[1b] and the relative configuration of **1** was established by X-ray crystallographic analysis.[1c] Further investigation of the same culture broth led to the discovery of the structurally related compounds, herbimycin B (**2**) and herbimycin C (**3**),[1d,1e] whose structures were determined on the basis of spectroscopic studies in comparison with herbimycin A. Herbimycin A exhibits herbicidal,[1a,1d] anti-tabocco mosaic virus,[1d] and antitumor activities.[1e] We wish to describe in this full account[2] the details of the first total synthesis of herbimycin A (**1**) and elucidate the absolute stereochemistry of **1** as depicted in Fig. 1. The total synthetic studies of the closely related ansamycin antibiotic macbecin I (**4**), which has the methyl substituent instead of the methoxyl substituent on C6 in herbimycin A (**1**), has recently been accomplished by several groups.[3]

Results and Discussion

Retrosynthetic Analysis. Figure 2 reveals the plan for the synthesis of herbimycin A (**1**). It was divided into the aromatic chromophore portion and the aliphatic ansa-chain portion. We anticipated that the C15–C16 bond could be formed in a Cram-selective manner by coupling the aromatic lithium compound **5** (X=Li) and the α-methyl-substituted aldehyde. The important option is selection of an aldehyde suitable for this coupling. Two candidates were elected for requisite aldehyde, the C9—C15 aldehyde **6** and the C5—C15 aldehyde **7**. The C1—C4 conjugated (*E*,*Z*)-diene portion would be constructed by a stepwise elongation with the Still's reagent **8**[4] and the Wittig reagent **9**. The crucial macrolactamization would be realized by the activated ester method using bis(2-oxo-3-oxazolidinyl)-phosphinic chloride. This reagent was developed by Palomo-Coll[5] and applied to macrolactamization in macbecin I synthesis by Baker[3a] and then used in our



1 : Herbimycin A R^1 = OMe, R^2 = OMe
2 : Herbimycin B R^1 = OH, R^2 = H
3 : Herbimycin C R^1 = OH, R^2 = OMe



4 : Macbecin I

Fig. 1.

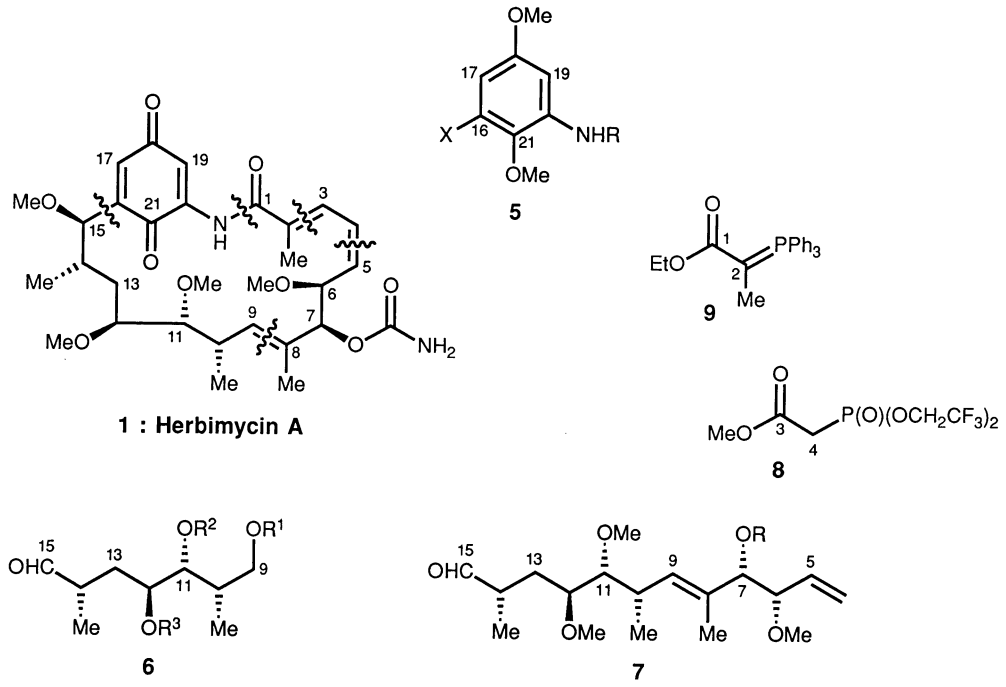
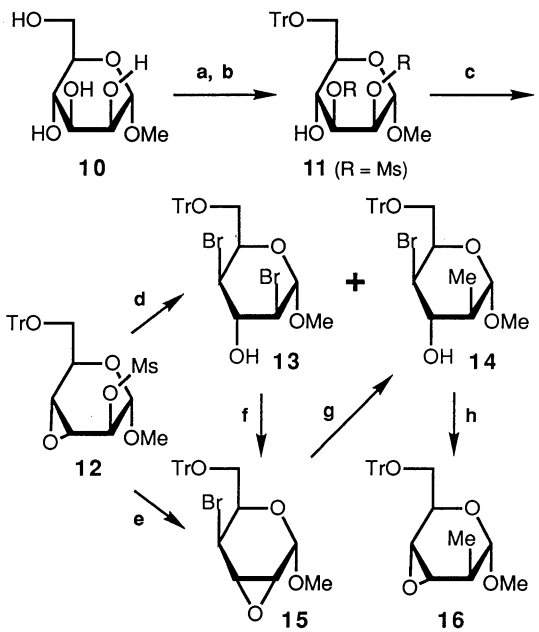


Fig. 2.

total synthesis of rifamycin W.[6] Finally, oxidative demethylation of two methoxyl groups on para-position in the aromatic portion would complete the synthesis. We first began the synthesis of the C9—C15 aldehyde **6** starting from methyl α-D-mannopyranoside.

Synthesis of the C9—C15 Segment. We have previously reported[7] the preparation of the epoxide **16** from methyl α-D-mannopyranoside (**10**) by the sequence shown in Scheme 1. We reinvestigated the C2-methyl group (corresponding to the C14-methyl group in **1**) introduction to the bromo epoxide **15** and found that the treatment of **15** with an etherial methylmagnesium bromide in CH_2Cl_2 gave the desired methylated product **14** in 86% yield along with the 12% yield of dibromide **13**. The yield improvement of this sequence of reactions (**12**→**15**→**14**→**16**) made the preparation of **16** more convenient.

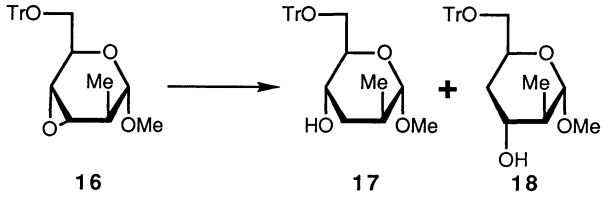
The first crucial step for the synthesis of the C9—C15 segment was the regioselective epoxide opening of **16** to establish the necessary stereochemical relationships at C12 and C13.[8] A number of conditions to achieve this requirement were examined and the relevant data on these reactions are summarized in Table 1. Epoxide opening with $LiBH_4$ and diisobutylaluminum hydride (DIBAL) afforded the undesired C3-alcohol **18** and the desired C4-alcohol **17** in a ratio of 3.4 : 1 (Entries 1 and 2). These structures were confirmed by analyzing their ^1H NMR spectra (see Experimental section). By comparison, $BH_3{\cdot}SMe_2$ complex mediated epoxide opening of **16** afforded a 2.3 : 1 ratio of products favoring the desired C4-alcohol **17** (Entry 3). It is well-known[9] that the reaction is faster when a catalytic amount of $NaBH_4$ is added along with the borane reagent (Entries 3, 4 and 5, 6). A more bulky reagent dicyclohexylborane-mediated epoxide opening gave satisfactory result with a 5.7—6.0 : 1 ratio of products favoring the desired C4-alcohol **17** (Entries 5 and 6). The best choice of the reagent was disiamylborane which is an appropriately



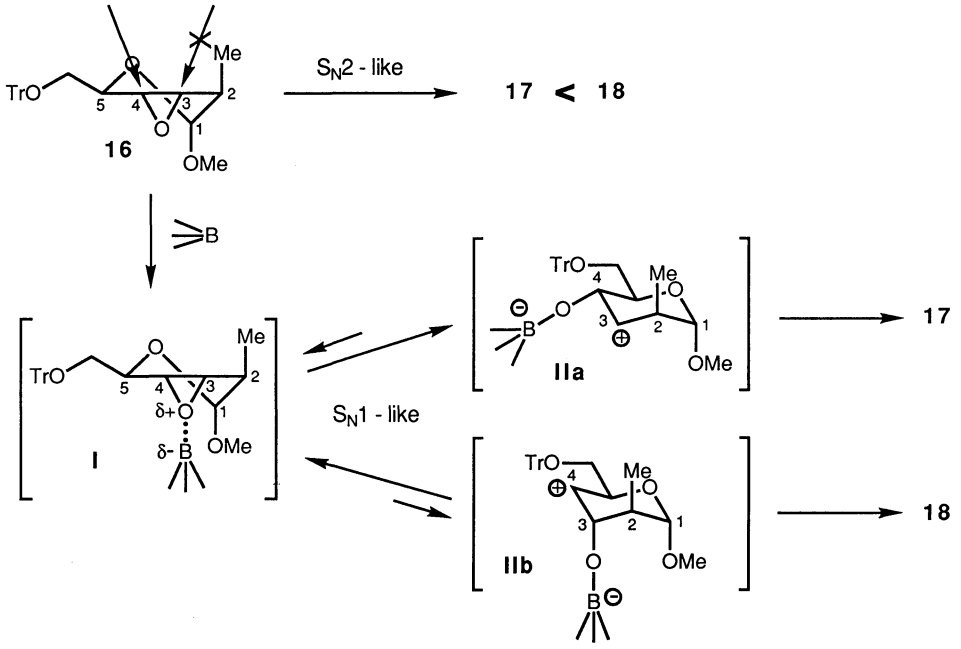
(a) TrCl, 4-dimethylaminopyridine, py, 25°C, 24 h; (b) MsCl, 25°C, 8 h; (c) NaOMe/MeOH, dioxane, 25°C, 14 h, 73% from **10**; (d) MeMgBr/ether, *t*-BuBr, CH_2Cl_2, 25°C, 3 h, 82%, **13** : **14** = 1 : 2; (e) LiBr, dioxane, 110°C, 3 d, 80%; (f) NaOMe/MeOH, 85%; (g) MeMgBr/ether, CH_2Cl_2, 25°C, 1 h, 98%, **13** : **14** = 1 : 7; (h) NaH, DME, 0°C, 1 h, 89%.

Scheme 1.

Table 1. Reductive Opening of the Epoxide **16**



Entry	Conditions	Reaction time / h	Ratio, **17**:**18**	Yield of **17** / %
1	$LiBH_4$ (4 equiv), THF, 25°C	21	1 :3.4	21
2	DIBAL (4 equiv), toluene, 25°C	24	1 :3.4	20
3	BH_3·SMe_2 (12 equiv), THF, 25°C	115	2.3:1	47
4	BH_3·SMe_2 (12 equiv), $NaBH_4$ (0.25 equiv), THF, 25°C	20	2.3:1	50
5	Dicyclohexylborane (10 equiv), THF, 25°C	48	5.7:1	60
6	Dicyclohexylborane (10 equiv), $NaBH_4$ (0.25 equiv), THF, 25°C	19	6.0:1	68
7	Bis(1,2-dimethylpropyl)borane (8 equiv), $NaBH_4$ (0.25 equiv), THF, 25°C	18	6.0:1	83

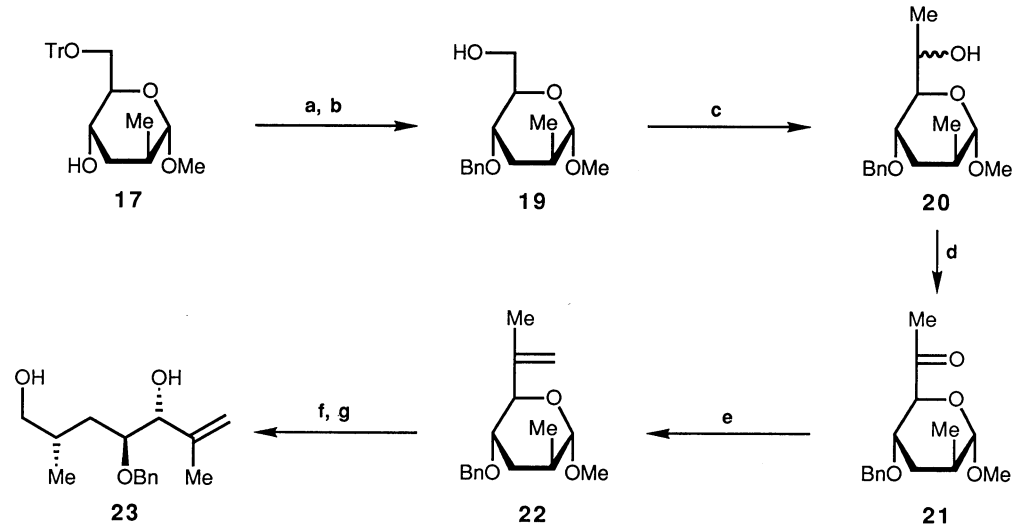


Scheme 2.

bulky reagent and can be worked up more easily than dicyclohexylborane (Entries 6 and 7), providing the 83% isolated yield of **17**.

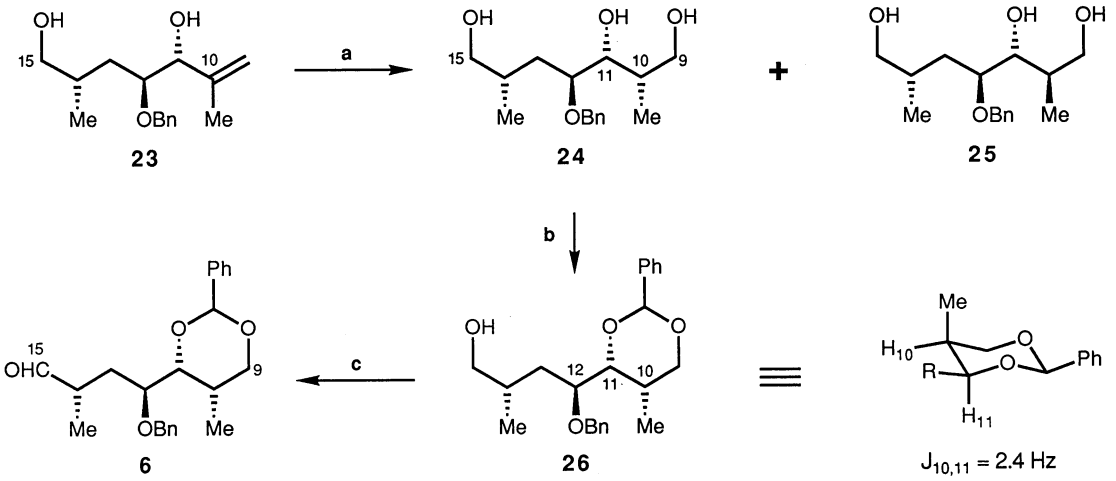
The regioselectivity of this reaction might be explained as follows (Scheme 2). ^1H NMR spectrum of the epoxide **16** shows that it exists in a half-chair conformation as depicted in Scheme 2 ($J_{1,2}$=2.4 Hz). Approach of hydride reagent to the C3 position might be interrupted by the C2-methyl substituent. As a consequence, the nucleophilic $LiBH_4$ and DIBAL react by an S_N2-like mechanism, leading to the trans-diaxial opened C3-hydroxyl compound **18** predominantly.[10] On the other hand, BH_3 and dialkylborane reagents first coordinate to the epoxide oxygen (**16**→**I**) and then the carbonium ion (**IIa** or **IIb**) would be produced. Thus, the S_N1-like mechanism begins to take over and the equilibrium might be preferred to **IIa** because the equatorial alkoxyborane **IIa** is considered to be more stable than the axial alkoxyborane **IIb**. Therefore, the desired C4-hydroxyl compound **17** dominated over the C3-hydroxyl compound **18**.[10]

Benzylation of **17** with benzyl bromide and NaH in DMF followed by de-*O*-tritylation with 0.1% HCl–MeOH afforded the primary alcohol **19** in 86% yield (Scheme 3).[11] Swern oxidation of **19** in CH_2Cl_2 at −78°C—−45°C to afford the unstable aldehyde which



(a) BnBr, NaH, DMF, 0°C, 1 h; (b) 0.1% HCl - MeOH, 25°C, 2 h, 86% from **17**; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, - 78 ~ - 45°C, then MeMgBr, THF - ether, - 78°C, 1 h; (d) PCC, MS 3AP, CH_2Cl_2, 25°C, 3 h, 80% from **19**; (e) Ph_3PCH_3Br, *n* - BuLi, ether, 25°C, 20 h; (f) 50% aq AcOH, 105°C, 1.5 h; (g) $NaBH_4$, EtOH, 25°C, 1 h, 85% from **21**.

Scheme 3.



(a) dicyclohexylborane, THF, 25°C, 1 h, then H_2O_2 - aq NaOH, 65.5% of **25** (**24** : **25** = 1 : 4.5) or BH_3•SMe_2, THF, 25°C, 1 h, then H_2O_2 - aq NaOH, 83% of **24** (**24** : **25** = 5 : 1); (b) $PhCH(OMe)_2$, CSA, CH_2Cl_2, 25°C, 1 h, 90%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 99%

Scheme 4.

was treated, after dilution of the reaction mixture with THF,[12] with an etherial methylmagnesium bromide to give the diastereomeric mixture of alcohol **20**.[13] Oxidation of **20** with pyridinium chlorochromate (PCC) in the presence of molecular sieves 3A powder (MS 3AP) in CH_2Cl_2 gave the ketone **21** in 80% overall yield from **19**.[14] Wittig olefination of **21** with methylidenetriphenylphosphorane prepared from methyltriphenylphosphonium bromide and butyllithium in ether gave the alkene **22**, which was treated successively with 50% aqueous acetic acid at 105°C and $NaBH_4$ in EtOH to afford the alkenediol **23** in 85% overall yield from **21**.

The next crucial step for the construction of the C9—C15 segment was the stereoselective hydroboration of the alkenediol **23** in order to establish the necessary *syn* relationships at C10 and C11. It has been reported[15] that the bulky organoborane reagents exhibited impressive stereoselectivity giving the *anti* isomer in hydroboration of the terminal alkenol like **23**. Moreover, simple allyl alcohols undergo hydroboration with little or no stereoselectivity by BH_3•THF complex.[15a] By comparison, rhodium-catalyzed hydroboration (catecholborane and Rh complex) of the terminal alkenol gives the *syn* isomer predominantly.[16] In our compound **23**, the hydroboration using dicyclohexylborane in THF and the subsequent aqueous alkaline hydroperoxide workup gave the undesired *anti* compound **25** and the desired *syn* compound **24** in 65.5 and

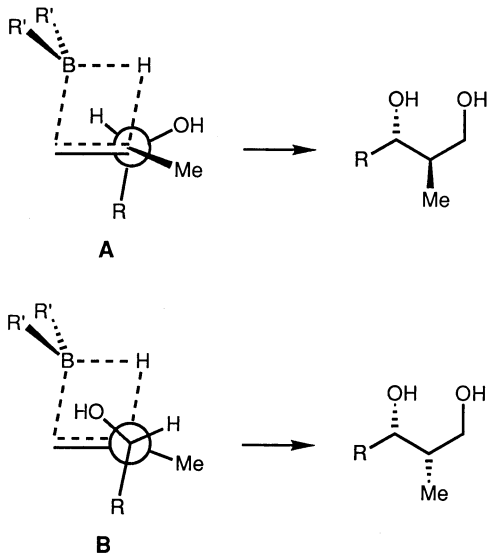


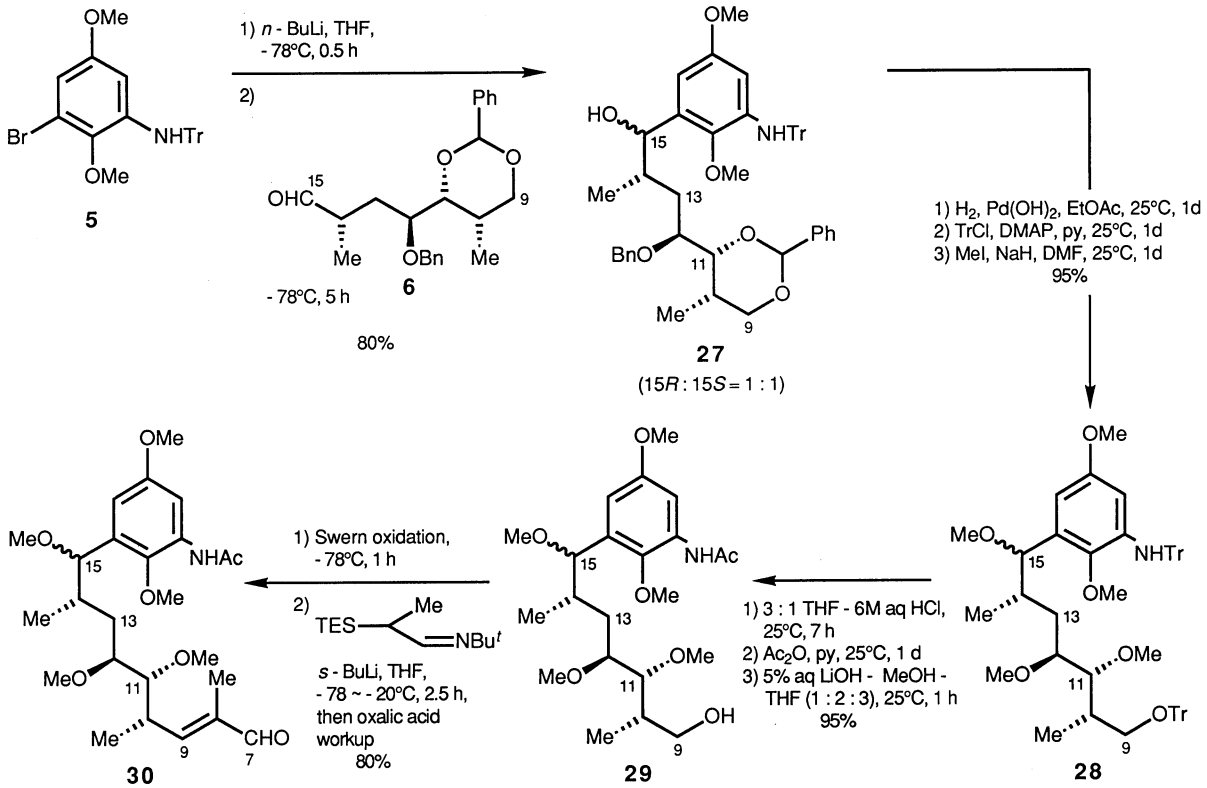
Fig. 3.

14.5% yield, respectivelly. The configuration at the newly created C10-stereocenter was determined at the next stage (vide infra). On the other hand, hydroboration of **23** using $BH_3 \cdot SMe_2$ in THF and the subsequent workup gave the desired **24** in 83% yield along with the 16.5% yield of its C10-epimer **25**. The Houk's[17] and Burgess's[16e,f] theoretical studies indicate that hydroboration with the dialkylborane reagent proceed via the transition state model **A** where the alkyl substituent, the hydroxyl group, and hydrogen lie *anti*, *outside,* and *inside*, respectivily, giving the *anti* isomer predominantly (Fig. 3). They described that a secondary interaction between a σ-orbital from the asymmetric center and the alkene π-orbital is maximum when the alkyl group occupies the *anti* position and via that orientation the major product will be produced. The *syn* compound **24** may probably be obtained via the transition state model **B** having the "OH-*inside*, H-*outside*, R-*anti*" position. The Houk's theoretical computational calculations[17] suggests that the transition state model **B** is more favorable than model **A** (calculations were performed with R=Et and R'=Me), but the energy difference between them is only 0.1 kcal mol^{-1}. Therefore, the exact reason of our selectivity is not yet clear. Other conformational factors may play the key role in our stereoselective hydroboration with $BH_3 \cdot SMe_2$.[18]

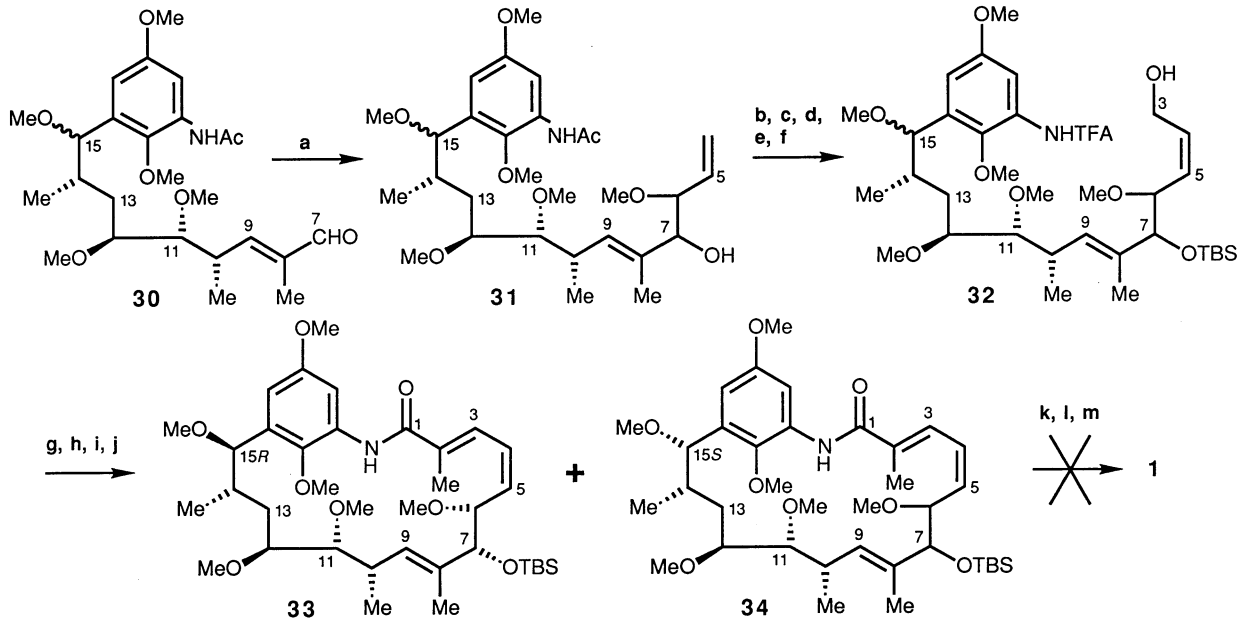
The triol **24** was subjected to benzylidenation with benzaldehyde dimethyl acetal in CH_2Cl_2 in the presence of a catalytic amount of *dl*-10-camphorsulfonic acid (CSA) to give **26**. The C10-configuration was determined at this stage by analyzing the coupling constants ($J_{10,11}$=2.4 Hz, $J_{11,12}$=8.2 Hz) of the ^1H NMR spectrum of the benzylidene derivative **26**, whose benzylidene ring has the rigid chair conformation.[19] Swern oxidation of **26** furnished the C9—C15 segment **6**.

Initial Results. With the C9—C15 segment in hand, we turned our attention to the coupling reaction of **6** with the aromatic segment. The aromatic segment **5** (X=Br) was prepared from the known[20] 3-bromo-2,5-dimethoxyaniline by tritylation with triphenylmethyl chloride in pyridine in 98% yield. Lithiation of **5** with butyllithium in THF at −78 °C and to this was added the aldehyde **6**. After workup, the coupling product **27** was obtained as an 1 : 1 mixture of the C15-diastereomeric alcohols in 80% yield (Scheme 5). As these C15-epimers could not be separated, the following transformations have been carried out as a mixture until the macrolactamization stage. Hydrogenolysis of **27** and selective re-tritylation of the resulting aminotetraol followed by *O*-methylation gave **28** in 95% yield. A subsequent three-step conversion transformed **28** to the primary alcohol **29** in 95% yield. Swern oxidation and the resulting aldehyde was subjected to the Corey–Schlessinger's olefination conditions[21] to afford the α,β-unsaturated aldehyde **30** as a single product in 80% yield.[22]

The stage was now set for us to examine the effective construction of the C6/C7 stereogenic centers. The use of allylic organometallic compounds appeared to be an especially promising route to achieve this goal. Yamamoto[23] discovered that the Lewis acid-mediated reaction of crotylstannanes with aldehydes produces the *syn* homoallylic alcohol. Later, Keck,[24a] and Koreeda[24b] reported that the Lewis acid-mediated additions of 3-methoxyallylstannanes to aldehydes are *syn* selective. We first applied the latter procedure. Treatment of the C15-diastereomeric (1 : 1) mixture of the aldehyde **30** with 1-methoxy-3-(tributylstannyl)-1-propene in the presence of $BF_3 \cdot OEt_2$ provided an inseparable 1 : 1 mixture of the allylated product **31** in 70% yield. This result indicates that the reaction of each C15-diastereomer of **30** proceeded with an high stereoselectivity. $TiCl_4$ was also effective to this coupling,[25] providing the same mixture of products (1 : 1) in 60% yield. The stereochemistry at the newly created C6/C7 centers was tentatively assigned *syn* by considering generallity of this type of reactions,[23,24] but could not be determined correctly at this stage. Other Lewis acids[25] including $MgBr_2$, $SnCl_4$, and ZnI_2 were extremely less effective and no coupling products were obtained. In addition, treatment of the aldehyde **30** with Brown's[26] (+)- or (−)-[(*Z*)-3-methoxyallyl]diisopinocampheylborane gave no coupling products. Since the allylated product **31** also could not be separated at this stage, they were subjected to the straightforward transformation shown in Scheme 6, providing the cyclization products **33** and **34**, which were easily separated by silica-gel column chromatography. Each of them was led to the final product by three-step conversion (Scheme 6), but unfortunately they were not identical with **1**! It is not clear why the Keck's or Koreeda's protocol proceeded with a high stereoselectivity to give only the undesired stereoisomers and the Brown's one did not proceed. But the following assumption might be helpful to an explanation for these



Scheme 5.



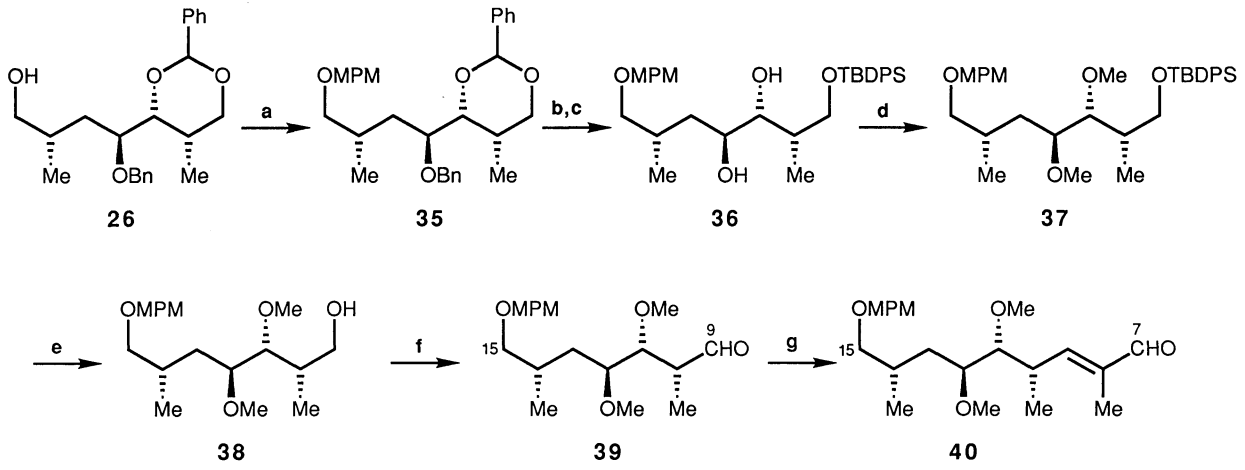
(a) (n - Bu)$_3$SnCH$_2$CH = CHOMe, BF_3•OEt_2, CH_2Cl_2, - 78 ~ - 20°C, 10 h, 70%; (b) t - butyldimethylsilyl trifluoromethanesulfonate, 2,6 - lutidine, CH_2Cl_2, 0°C, 1 d, 85%; (c) OsO_4 - KIO_4, 50% aq THF, 25°C, 10 h, 70%; (d) **8**, KN(SiMe$_3$)$_2$, 18 - crown - 6, THF, - 78°C, 1 h, 90%; (e) DIBAL, toluene, - 78°C, 5 h; (f) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 25°C, 2 h, then pH 7 phosphate buffer, MeOH, 25°C, 15 min, 70% (two steps); (g) MnO_2, CH_2Cl_2, 25°C, 10 h, 80%; (h) **9**, CH_2Cl_2, 40°C, 2 d, 100%; (i) LiOH, 2 : 2 : 1 THF - MeOH - water, 25°C, 24 h; (j) bis(2 - oxo - 3 - oxazolidinyl)phosphinic chloride, (i - Pr)$_2$EtN, toluene, 85°C, 1 d, **33** (25% for three steps) and **34** (25% for three steps); (k) TBAF, THF, 25°C, 2 d; (l) NaOCN, TFA, CH_2Cl_2, 25°C, 1 d; (m) AgO, 1M aq HNO_3, dioxane, 25°C, 5 h, 80% (three steps).

Scheme 6.

results. It might be assumed that the α,β-unsaturated aldehyde **30** in its ground state exists in the conformation in which the aromatic portion occupies the position covering one side of the conjugated system in **30**. As a result, the reagents attack the formyl group from the other side, giving only one diastereomer. On the other hand, if the Brown's methoxyallylation of aldehyde proceeds via a mechanism involving a six-membered early transition state,[27] the bulky Brown's reagents and **30** do not adopt such a transition state because of the crowded surroundings, resulting in no reaction. This strategy was abandoned and we focused our attention on the construction of the C6/C7 stereogenic centers prior to the coupling with the aromatic segment. Toward this goal, the synthesis of the C7—C15 aldehyde **40** was undertaken.

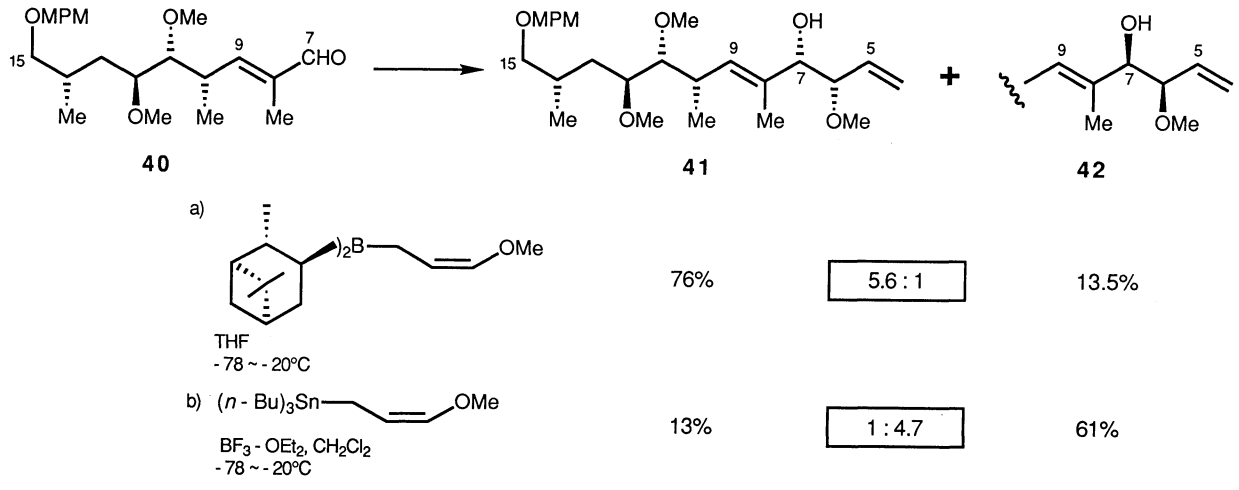
Synthesis of the C5—C15 Segment. Treatment of **26** with 4-methoxybenzyl chloride (MPMCl) and NaH in DMF followed by hydrogenation of the resulting **35** with 1 atm of hydrogen in the presence of Raney Ni-W4 gave the triol (Scheme 7). After protection of the primary alcohol as its *t*-butyldiphenylsilyl (TBDPS) ether, the resulting **36** was methylated with methyl iodide and NaH in DMF to give **37**, which was desilylated with tetrabutylammonium fluoride (TBAF) to give **38** in 80% overall yield from **26**. Dess-Martin oxidation[28] of **38** in CH_2Cl_2 gave the C9-aldehyde **39**, which was subjected to the Corey–Schlessinger's olefination conditions[21] with *N*-[2-(triethylsilyl)propylidene]-*t*-butylamine and *s*-butyllithium in THF at −78 to −20°C and aqueous oxalic acid workup to afford the (*E*)-unsaturated aldehyde **40** as a single product in 85% yield from **38**.

With the C7—C15 segment now in hand, the construction of the necessary stereogenic centers at C6 and C7 was undertaken. As illustrated in Scheme 8, the aldehyde **40** was treated with [(*Z*)-3-methoxyallyl]-diisopinocampheylborane,[26] which was prepared from (−)-α-pinene, in THF at −78 to −20°C to afford the



(a) MPMCl, NaH, DMF, 25°C, 16 h; (b) H_2, Raney Ni - W4, EtOH, 25°C, 24 h; (c) TBDPSCl, Imid, DMF, 25°C, 20 h; (d) MeI, NaH, DMF, 25°C, 2 h; (e) TBAF, THF, 25°C, 17 h, 80% from **26**; (f) Dess - Martin periodinane, CH_2Cl_2, 25°C, 2 h; (g) *N* - [2 - (triethylsilyl)-propylidene] - *t* - butylamine, *s* - BuLi, THF, - 78 ~ - 20°C, 4.5 h, oxalic acid workup, 85% from **38**.

Scheme 7.



Scheme 8.

desired **41** in 76% yield along with the 13.5% yield of the separable diastereomeric *syn*-diol **42**. The configurations at the C6 and C7 stereocenters in **41** and **42** were presumed to be the illustrated ones in analogy to the well-established Brown's precedent.[26] In contrast, the coupling using 1-methoxy-3-(tributylstannyl)-1-propene and $BF_3 \cdot OEt_2$ in CH_2Cl_2 at −78 to −20 °C[24] showed the opposite stereochemistry, giving the undesired **42** predominantly (**41**:**42**=1:4.7). The synthesis of the required ansa-chain aldehyde **7** was completed in 75% overall yield by protection of the C7-hydroxyl group in **41** as its *t*-butyldimethylsilyl (TBS) ether, deprotection of MPM ether by DDQ, and Swern oxidation of the resulting **43** (Scheme 9).

Coupling of the C5—C15 Segment and the Aromatic Chromophore. The coupling of the aldehyde **7** and the aromatic chromophore was realized (Scheme 9) by addition of **7** to the lithiated reagent prepared from **5** and butyllithium in THF at −78 °C to produce the coupling product **44** and its C15-epimer **45** in comparable ratio (91% combined yield), which were easily separated by silica-gel column chromatography. The compound of high R_f-value on TLC was assumed to be the desired one having the 15*R*-configuration by comparison of ^1H NMR spectrum with those of the Baker's synthetic intermediates of macbecin I.[3a,29] This assumption was confirmed by the success of the total synthesis.

To overcome this unpleasant selectivity, it was necessary to recycle the undesired 15*S*-epimer. We examined the oxidation–reduction recycling process in the preliminary case of **27**. The corresponding ketone, prepared from **27** by Dess–Martin oxidation,[28] was

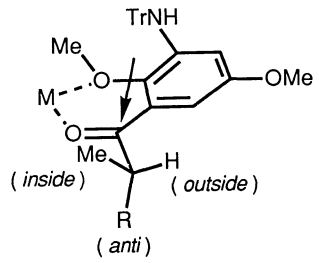
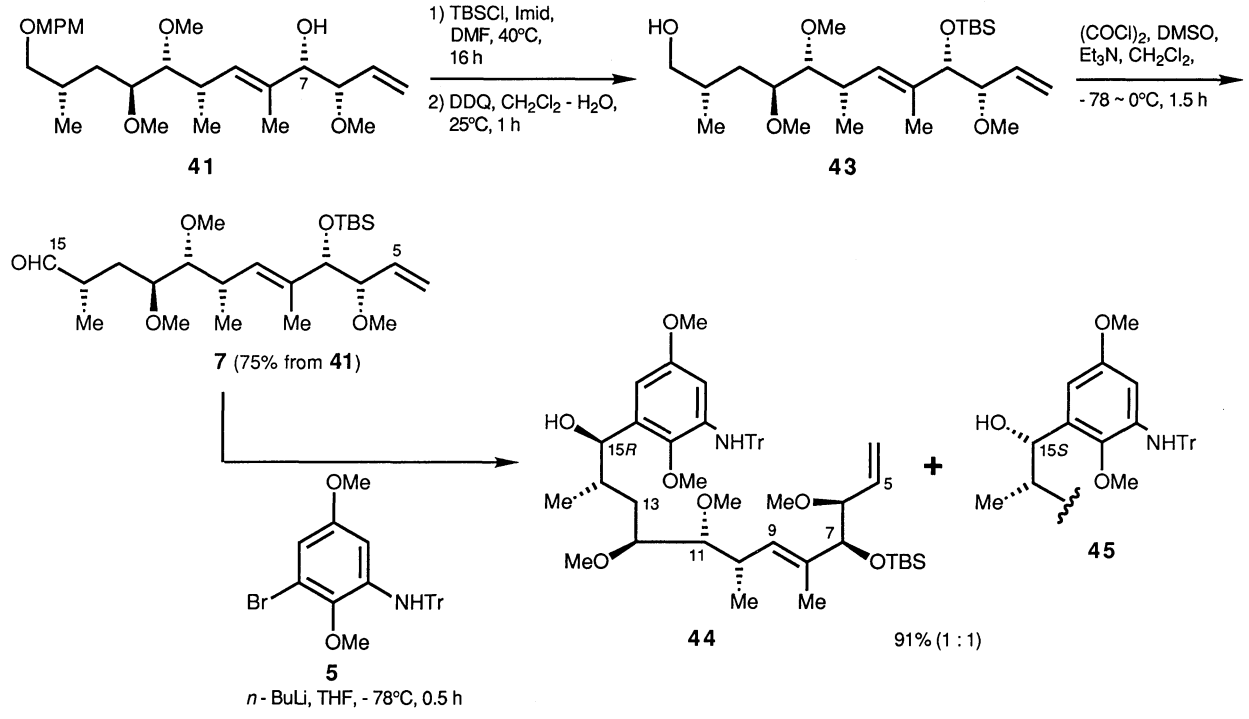


Fig. 4.

subjected to a variety of reduction conditions including aluminum-containing reducing agents, boron-containing reducing agents, (+)- and (−)-BINAL-H,[30] and (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane-$LiAlH_4$.[31] However, the undesired 15*S*-epimer was always produced predominantly (1—5:1 ratio).[32] Presumably this unexpected selectivity may be explained in an analogous fashion to the Coutt and Kallmerten's explanation.[3b] As depicted in Fig. 4, hydride reduction occurrs through the transition-state model which has the largest substituent (R), methyl, and hydrogen occupying the *anti*, *inside*, and *outside* posistions, respectively. This model is in agreement with the Felkin–Anh[33] and the Houk[34] model. Finally, we found that the reduction with a chiral reagent prepared from $LiAlH_4$ and (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (Chirald)[35] gave a 2:1 mixture of the 15*R*- and 15*S*-epimers. Although the selectivity was not satisfactory, it was pleasant that the desired 15*R*-epimer dominated over the 15*S*-epimer. It is noteworthy to

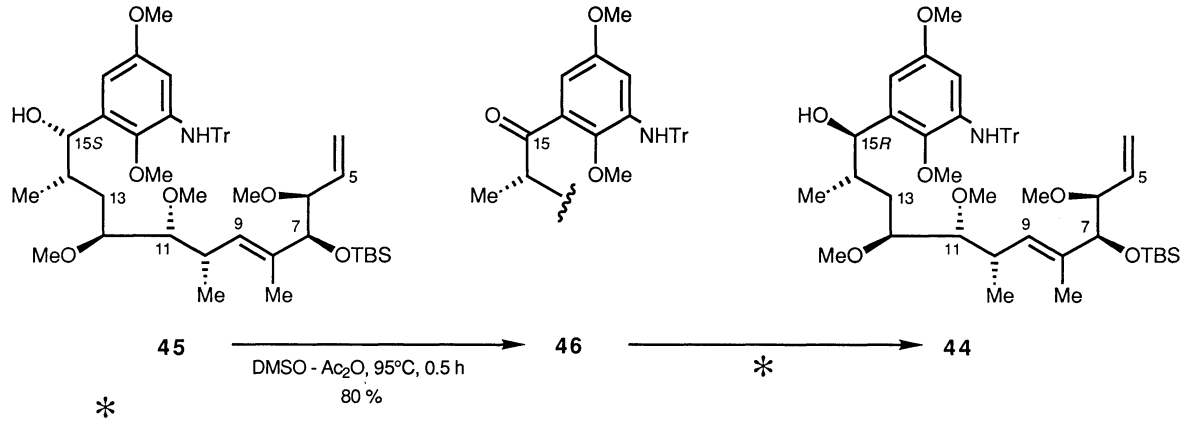


Scheme 9.

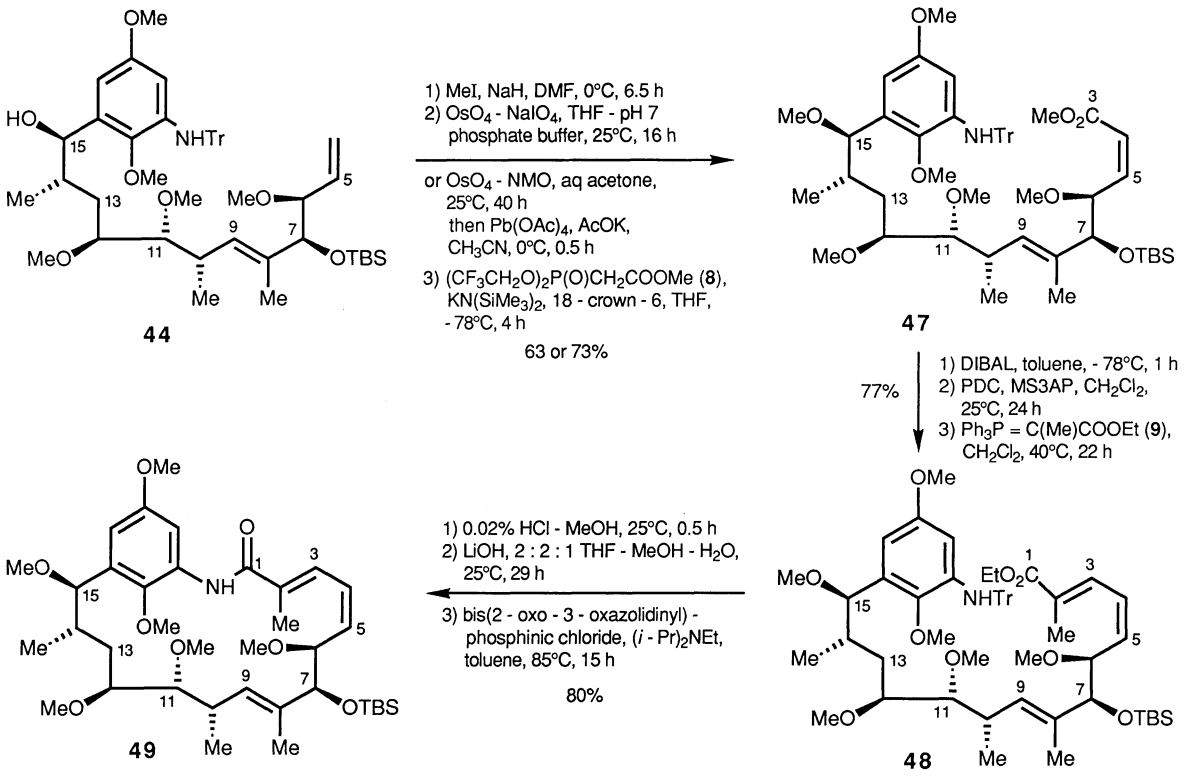
describe that the concentration of THF is essential in this reduction. Less than 5% THF in ether is necessary to obtain the 15*R*-epimer as a major product. If none or more THF was used in this reaction, the undesired 15*S*-epimer became to dominate over the 15*R*-epimer. Although a rationale for the selectivity remains obscure, the incorporation of THF molecules as external ligands in the $LiAlH_4$-Chirald complex may be the key role.[36] In light of these findings, we attempted the reduction of **46**, which was derived from **45** by DMSO–acetic anhydride oxidation, with the selected reducing agents (Table 2). Fortunately, the reduction of **46** with $LiAlH_4$-Chirald in 1% THF–ether at −78 °C gave **44** and **45** in 64 and 16% yields, respectively (the ratio of **44**:**45**=4:1).

Final Stage. *O*-Methylation of **44** with methyl iodide and NaH in DMF (quantitative conversion) followed by selective cleavage of the terminal olefin with OsO_4–$NaIO_4$

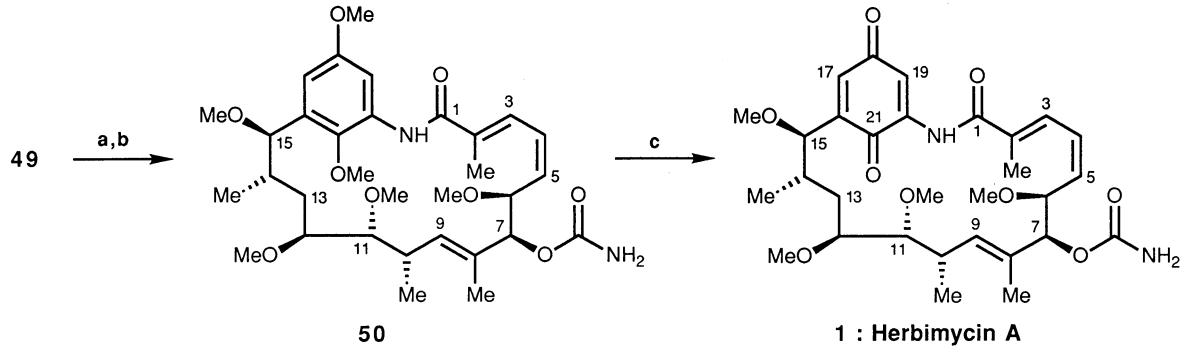
Table 2. Stereoselective Reduction of the Ketone **46**



Entry	Conditions	Ratio of **44**:**45**	Combined yield
1	$LiAlH_4$, ether, −78 °C, 0.5 h	1:2.4	80%
2	$LiBEt_3H$, THF, −78 °C, 3 h	1:2.5	100%
3	$LiBH_4$, 0 °C, 2 h	1:1.6	100%
4	$LiAlH_4$–Chirald, 1% THF–ether, −78 °C, 25 h	4:1	80%



Scheme 10.



(a) TBAF, THF, 25°C, 48 h; (b) NaOCN, TFA, CH_2Cl_2, 25°C, 17 h; (c) AgO, 1M aq HNO_3, dioxane, 25°C, 2.5 h, 91% for three steps.

Scheme 11.

in THF–pH 7 phosphate buffer (76% yield) or with OsO_4–4-methylmorpholine *N*-oxide (NMO) in aqueous acetone and subsequent $Pb(OAc)_4$ treatment (88% yield) gave the C5-aldehyde (Scheme 10). This was transformed to the target herbimycin A (**1**) by conceptually similar route to the Baker's macbecin I synthesis.[2a] Still's olefination[4] of this aldehyde with **8** and potassium bis(trimethylsilyl)amide in the presence of 18-crown-6 in THF at −78°C gave the (*Z*)-unsaturated ester **47** in 83% yield as a sole product. Further elaboration of **47** into **48** was accomplished in 77% yield by DIBAL reduction in toluene and pyridinium dichromate (PDC) oxidation[37] of the resulting allylic alcohol followed by Wittig olefination with **9** in CH_2Cl_2. Exposure of **48** to an acidic (0.02% HCl–MeOH, 25°C, 0.5 h) and a basic (LiOH, 2:2:1 THF–MeOH–H_2O, 25°C, 29 h) conditions furnished the amino acid, which was cyclized using bis(2-oxo-3-oxazolidinyl)phosphinic chloride and *N*-ethyldiisopropylamine[3a,5,6] in toluene at 85°C for 15 h to afford **49** in 80% yield from **48**. Desilylation of **49** with TBAF in THF followed by carbamoylation with sodium cyanate and trifluoroacetic acid in CH_2Cl_2[38] afforded **50** (Scheme 11). Finally, oxidative de-*O*-methylation of **50** with AgO and 1 M aqueous HNO_3 in dioxane[6,39] gave herbimycin A (**1**) in 91% yield from **49**. All data (^{1}H NMR, IR, UV, $[\alpha]_D$, and TLC mobilities) were identical with those of natural herbimycin A.[40] This goal indicates that the absolute configuration of herbimycin A is depicted in Fig. 1.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter in chloroform unless otherwise noted. IR spectra were recorded on a BIO RAD DIGILAB FTS-65 spectrometer and ^{1}H NMR spectra were on either a JEOL GSX270 or a JEOL GSX400 spectrometer in $CDCl_3$ using TMS as internal standard unless otherwise noted. Mass spectra were recorded on a JEOL JMS-DX302 mass spectrometer. Silica-gel TLC and column chromatography were performed on Merck TLC 60F-254 and Merck Kieselgel 60 or Daisogel IR-60, respectively. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, organic solvents were purified and dried by the appropriate procedure, and evaporation and concentration were carried out under reduced pressure below 30°C, unless otherwise noted.

Methyl 4-Bromo-2,4-dideoxy-2-*C*-methyl-6-*O*-triphenylmethyl-α-D-idopyranoside (14) and Methyl 2,4-Dibromo-2,4-dideoxy-6-*O*-triphenylmethyl-α-D-idopyranoside (13). To a stirred solution of **15** (9.91 g, 20.6 mmol) in dry CH_2Cl_2 (50.0 ml) was added dropwise at 0°C 3 M methylmagnesium bromide (1 M=1 mol dm^{-3}) in ether (34.3 ml, 103 mmol). After 0.75 h at room temperature, saturated aqueous NH_4Cl was added to the ice-cooled reaction mixture and the new mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (410 g) with 20:1 benzene–ethyl acetate to afford **14** (8.77 g, 86%) and **13** (1.39 g, 12%) as colorless foams. The spectroscopic data of these samples were identical with those of the authentic samples.[7]

Methyl 2,3-Dideoxy-2-*C*-Methyl-6-*O*-(triphenylmethyl)-α-D-*arabino*-hexopyranoside (17) and Methyl 2,4-Dideoxy-2-*C*-methyl-6-*O*-(triphenylmethyl)-α-D-*arabino*-hexopyranoside (18). To a stirred solution of 10 M BH_3·SMe_2 (31.2 ml. 312 mmol) in dry THF (332 ml) at 0°C was added dropwise 2-methyl-2-butene (66.1 ml, 624 mmol). After 1.5 h at 0°C, $NaBH_4$ (370 mg, 9.78 mmol) and a solution of **16** (16.3 g, 39.1 mmol) in dry THF (81.4 ml) were added and the mixture was stirred at room temperature for 20 h. The reaction mixture was cooled at 0°C and water (100 ml), 3 M aqueous NaOH (250 ml), and 30% aqueous H_2O_2 (150 ml) were added successively and the mixture was heated at 60°C for 2 h. The mixture was cooled to ambient temperature and extracted with ether (150 ml×3). The extracts were washed with water (150 ml×2) and saturated aqueous NaCl (100 ml), dried, and concentrated. The residue was chromatographed on silica gel (1 kg) with 25:1 chloroform–ethyl acetate to afford **17** (13.6 g, 83%) and **18** (2.21 g, 13.5%) as colorless syrups.

17: R_f=0.27 (20:1 chloroform–ethyl aceate); $[\alpha]_D^{25}$ +30.5° (*c* 0.76); ^{1}H NMR (270 MHz) δ=1.04 (3H, d, *J*=7.5 Hz, 2-Me), 1.68 (1H, ddd, J_{gem}=12.6 Hz, $J_{2,3eq}$=3.3 Hz, and $J_{3eq,4}$=5.0 Hz, H-3eq), 1.82 (1H, ddd, $J_{2,3ax}$=4.8 Hz and $J_{3ax,4}$=10.5 Hz, H-3ax), 1.92—2.05 (1H, m, H-2), 2.44 (1H, d, *J*=3.5 Hz, OH), 3.33 (1H, dd, J_{gem}=9.5 Hz and $J_{5,6}$=6.0 Hz, H-6), 3.34 (3H, s, OMe),

3.43 (1H, dd, $J_{5,6'}$=4.6 Hz, H-6'),3.60 (1H, ddd, $J_{4,5}$=9.3 Hz, H-5), 3.68—3.80 (1H, m, H-4), 4.32 (1H, br s, H-1), 7.20—7.35 and 7.43—7.48 (15H, m, 3×Ph). Found: C, 77.36; H, 7.21%. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22%.

18: R_f=0.47 (20:1 chloroform–ethyl acetate); ^{1}H NMR (270 MHz) δ=1.01 (3H, d, J=7.5 Hz, 2-Me), 1.52—1.61 (1H, m, H-4eq), 1.73 (1H, ddd, J_{gem}=13.8 Hz, $J_{2,4ax}$=2.7 Hz, and $J_{4ax,5}$=12.2 Hz, H-4ax), 1.95—2.06 (1H, m, H-2), 3.09 (1H, dd, J_{gem}=9.8 Hz and $J_{5,6}$=4.2 Hz, H-6), 3.23 (1H, dd, $J_{5,6'}$=6.3 Hz, H-6'), 3.44 (3H, s, OMe), 3.68—3.77 (1H, m, H-3), 3.78 (1H, d, J=9.6 Hz, OH), 4.08—4.19 (1H, m, H-5), 4.60 (1H, br s, H-1), 7.19—7.34 and 7.44—7.50 (15H, m, 3×Ph).

Methyl 4-*O*-Benzyl-2,3-didoxy-2-*C*-methyl-α-D-*arabino*-hexopyranoside (19). To a stirred solution of **17** (3.56 g, 8.51 mmol) in dry DMF (53.4 ml) at 0°C was added NaH (410 mg, 10.3 mmol; 60% dispersion in mineral oil). After 15 min at 0°C, benzyl bromide (1.21 ml, 10.2 mmol) was added and the mixture was stirred at 0°C for 1 h. Methanol (1 ml) was added and the mixture was stirred for 20 min. Water (50 ml) was then added and the mixture was extracted with hexane (130 ml×2). The extracts were washed with water (130 ml) and saturated aqueous NaCl (75 ml), dried, and concentrated. The residual syrup [5.37 g; R_f=0.48 (20:1 benzene–ethyl acetate)] was dissolved in 0.1% HCl–MeOH (161 ml) and stood at room temperature for 2 h. The reaction mixture was neutralized with triethylamine and concentrated. The residue was dissolved in ethyl acetate (40 ml) and this was washed with water (20 ml) and saturated aqueous NaCl (20 ml), dried, and concentrated. The residue was chromatographed on silica gel (147 g) with 2:1 hexane–ethyl acetate to afford **19** (1.95 g, 86%) as a colorless syrup. This sample consists of a 6:1 mixture of α- and β-anomers: R_f=0.12 (10:1 benzene–ethyl acetate); ^{1}H NMR (270 MHz) δ=1.03 (3H, d, J=7.4 Hz, 2-Me), 1.78—2.08 (4H, m, H-2, 3ax, 3eq, and OH), 3.35 (3H, s, OMe), 3.57—3.88 (4H, m, H-4, 5, 6, and 6'), 4.36 (1H, d, $J_{1,2}$=1.6 Hz, H-1), 4.44 and 4.61 (each 1H, ABq, J=11.6 Hz, OCH_2Ph), and 7.27—7.38 (5H, m, Ph) [for β-anomer: 0.97 (3H, d, J=7.4 Hz, 2-Me), 3.49 (3H, s, OMe), 4.47 and 4.58 (each 1H, ABq, J=11.6 Hz, OCH_2Ph), and 4.50 (1H, d, $J_{1,2}$=2.4 Hz, H-1)]. Found: C, 67.47; H, 8.11%. Calcd for $C_{15}H_{22}O_4$: C, 67.57; H, 8.33%.

Methyl 4-*O*-Benzyl-2,3,7-trideoxy-2-*C*-methyl-α-D-*arabino*-heptopyranosid-6-ulose (21). A solution of DMSO (4.26 ml, 60.1 mmol) in dry CH_2Cl_2 (64 ml) was added to a stirred solution of oxalyl dichloride (2.62 ml, 30.0 mmol) in dry CH_2Cl_2 (38.6 ml) to −78°C. After 15 min at −78°C, a solution of **19** (4.00 g, 15.0 mmol) in dry CH_2Cl_2 (32 ml) was added dropwise and the resulting suspension was stirred at −78°C for 45 min. After addition of triethylamine (12.5 ml, 90.0 mmol), the mixture was gradually warmed to −45°C. After 1.5 h at −45°C, the reaction mixture was recooled to −78°C and dry THF (143 ml) was added and to this was added 3 M MeMgBr in ether (50.1 ml, 150 mmol). After 1 h at −78°C, saturated aqueous NH_4Cl (300 ml) was added and the mixture was warmed to ambient temperature. The mixture was extracted with ethyl acetate (150 ml×3) and the extracts were washed with saturated aqueous NaCl (100 ml), dried, and concentrated. The residue was chromatographed on silica gel (252 g) with 3:1 hexane–ethyl acetate to afford **20** (3.67 g, 87%) as a colorless syrup [A portion of this sample was rechromatographed on silica gel with the same solvent system to afford a major α-glycoside whose C6-configuration was not determined: R_f=0.42 (2:1 hexane–ethyl acetate); ^{1}H NMR (270 MHz) δ=1.04 (3H, d, J=7.4 Hz, 2-Me), 1.28 (3H, d, J=6.4 Hz, 6-Me), 1.76—1.94 (2H, m, H-3ax and 3eq), 1.95—2.07 (1H, m, H-2), 1.98 (1H, d, J=9.4 Hz, OH), 3.34 (3H, s, OMe), 3.43 (1H, dd, $J_{4,5}$=9.8 Hz and $J_{5,6}$=2.0 Hz, H-5), 3.76 (1H, ddd, $J_{3ax,4}$=15.0 Hz and $J_{3eq,4}$=5.4 Hz, H-4), 4.06 (1H, ddq, H-6), 4.38 (1H, d, $J_{1,2}$=1.6 Hz, H-1), 4.48 and 4.61 (each 1H, ABq, J=11.4 Hz, OCH_2Ph), and 7.25—7.36 (5H, m, Ph)]. To a stirred solution of **20** (3.16 g, 11.3 mmol) in dry CH_2Cl_2 (63 ml) at room temperature were added MS 3AP (8.74 g) and PCC (7.28 g, 33.8 mmol). After 3 h at room temperature, the reaction mixture was diluted with ether and the resulting suspension was transferred to a column filled with silica gel (100 g). The column was eluted with ether and the eluant was concentrated. The residue was chromatographed on silica gel (310 g) with 5:1 hexane–ethyl acetate to afford **21** (2.48 g, 79%) and its β-anomer (408 mg, 13%) as colorless syrups.

21: R_f=0.53 (5:1 hexane–ethyl acetate); $[\alpha]_D^{25}$ 124° (*c* 0.96); IR ($CHCl_3$) 1722 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.03 (3H, d, J=7.4 Hz, 2-Me), 1.69 (1H, ddd, J_{gem}=12.8 Hz, $J_{2,3eq}$=5.2 Hz, and $J_{3eq,4}$=4.6 Hz, H-3eq), 1.90 (1H, ddd, $J_{2,3ax}$=4.6 Hz and $J_{3ax,4}$=8.4 Hz, H-3ax), 1.96—2.07 (1H, m, H-2), 2.23 (3H, s, 3×H-7), 3.41 (3H, s, OMe), 3.79 (1H, ddd, $J_{4,5}$=8.4 Hz, H-4), 4.17 (1H, d, H-5), 4.37 (1H, d, $J_{1,2}$=3.4 Hz, H-1), 4.47 and 4.57 (each 1H, ABq, J=11.8 Hz, OCH_2Ph), and 7.24—7.34 (5H, m, Ph). Found: C, 68.94; H, 7.66%. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

***β*-Anomer of 21:** R_f=0.49 (5:1 hexane–ethyl acetate); ^{1}H NMR (270 MHz) δ=0.93 (3H, d, J=7.4 Hz, 2-Me), 1.63—1.73 (1H, m, H-3), 1.82—1.93 (1H, m, H-3'), 2.12—2.22 (1H, m, H-2), 2.23 (3H, s, 3×H-7), 3.47 (3H, s, OMe), 3.88—3.97 (2H, m, H-4 and 5), 4.49 and 4.56 (each 1H, ABq, J=11.8 Hz, OCH_2Ph), 4.51 (1H, d, $J_{1,2}$=2.6 Hz, H-1), and 7.29—7.35 (5H, m, Ph).

Methyl 4-*O*-Benzyl-2,3,6,7-tetradeoxy-2,6-di-*C*-methyl-α-D-*arabino*-hept-6-enopyranoside (22). To a stirred suspension of methyltriphenylphosphonium bromide (28.4 g, 79.5 mmol) in dry ether (568 ml) at 0°C was added 1.55 M butyllithium in hexane (51.3 ml, 79.5 mmol). After 15 min at 0°C, a solution of **21** (5.53 g, 19.9 mmol) in dry ether (111 ml) was added dropwise and the mixture was stirred at room temperature for 20 h. Water (450 ml) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ether (450 ml×3) and the combined organic layers were washed with saturated aqueous NaCl (450 ml), dried, and concentrated. The residue was chromatographed on silica gel (550 g) with 30:1 benzene–ethyl acetate to afford **22** (5.12 g, 93%) as a colorless syrup: R_f=0.80 (3:1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +95.0° (*c* 1.04); ^{1}H NMR (270 MHz) δ=1.05 (3H, d, J=7.4 Hz, 2-Me), 1.79 (3H, s, 6-Me), 1.80 (1H, ddd, J_{gem}=12.6 Hz and $J_{2,3eq}$=$J_{3eq,4}$=4.5 Hz, H-3eq), 1.92 (1H, ddd, $J_{2,3ax}$=5.0 Hz and $J_{3ax,4}$=9.9 Hz, H-3ax), 1.97—2.08 (1H, m, H-2), 3.35 (3H, s, OMe), 3.58 (1H, ddd, $J_{4,5}$=9.3 Hz, H-4), 4.03 (1H, d, H-5), 4.35 (1H, d, $J_{1,2}$=1.8 Hz, H-1), 4.47 and 4.54 (each 1H, ABq, J=11.7 Hz, OCH_2Ph), 5.01 and 5.11 (each 1H, each br s, H-7 and 7'), and 7.25—7.33 (5H, m, Ph). Found: C, 73.52; H, 8.37%. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%.

(2*S*,4*S*,5*R*)-4-Benzyloxy-2,6-dimethyl-6-heptene-1,5-diol (23). A solution of **22** (4.69 g, 17.0 mmol) in 50 (v/v)% aqueous acetic acid (47 ml) was heated at 105°C for 1.5 h. The reaction mixture was cooled to ambient temperature, concentrated, and co-evaporated with toluene (3 times). The

residue (4.45 g) was dissolved in ethanol (75.5 ml) and cooled to 0°C. $NaBH_4$ (772 mg, 20.4 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was treated with CG-50 in ethanol and the insoluble materials were filtered and washed with ethanol. The combined filtrate and washings were concentrated. The residue was chromatographed on silica gel (450 g) with 1 : 1 hexane–ethyl acetate to afford **23** (4.08 g, 91%) as a colorless syrup: R_f=0.19 (3 : 2 benzene–ethyl acetate); $[\alpha]_D^{25}$ −35.5° (*c* 0.80); ^{1}H NMR (270 MHz) δ=0.83 (3H, d, *J*=6.6 Hz, 2-Me), 1.19 (1H, ddd, J_{gem}=14.2 Hz, $J_{2,3}$=8.4 Hz, and $J_{3,4}$=2.4 Hz, H-3), 1.67 (1H, ddd, $J_{2,3'}$=5.0 Hz and $J_{3',4}$=10.4 Hz, H-3'), 1.70 (3H, s, 6-Me), 1.73—1.87 (2H, m, H-2 and OH), 2.30 (1H, d, *J*=2.0 Hz, OH), 3.37—3.53 (2H, m, H-1 and 1'), 3.63 (1H, ddd, $J_{4,5}$=2.8 Hz, H-4), 4.41 (1H, br s, H-5), 4.54 and 4.71 (each 1H, ABq, *J*=11.2 Hz, OCH_2Ph), 4.95 and 5.14 (each 1H, each br s, H-7 and 7'), and 7.30—7.38 (5H, m, Ph). Found: *m*/*z* 265.1780. Calcd for $C_{16}H_{25}O_3$: M+1, 265.1801.

(2*S*,3*R*,4*S*,6*S*)-4-Benzyloxy-2,6-dimethyl-1,3,7-heptanetriol (24) and Its 2*R*-Epimer (25). To a stirred solution of **23** (1.20 g, 4.54 mmol) in dry THF (24 ml) at 0°C was added dropwise 10 M BH_3·SMe_2 (0.910 ml, 9.10 mmol). After 1 h at room temperature, water (15 ml), 3 M aqueous NaOH (1.5 ml), and 30% aqueous H_2O_2 (0.5 ml) were carefully added to the ice-cooled reaction mixture. After 1 h at 60°C, the mixture was cooled to ambient temperature and extracted with ether (25 ml×6). The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (193 g) with 1 : 10 hexane–ethyl acetate to afford **24** (1.07 g, 83%) and **25** (0.210 g, 16.5%) as colorless syrups.

24: R_f=0.44 (2 : 3 hexane–ethyl acetate); $[\alpha]_D^{25}$ +7.6°, $[\alpha]_{365}^{25}$ +12.4° (*c* 0.37); ^{1}H NMR (270 MHz) δ=0.94 (3H, d, *J*=6.6 Hz, 6-Me), 1.02 (3H, d, *J*=6.6 Hz, 2-Me), 1.53 (1H, ddd, J_{gem}=14.8 Hz, $J_{4,5}$=3.8 Hz, and $J_{5,6}$=7.6 Hz, H-5), 1.81 (1H, ddd, $J_{4,5'}$=7.0 Hz and $J_{5',6}$=4.8 Hz, H-5'), 1.88—2.02 (2H, m, H-6 and OH), 2.03—2.10 (1H, m, H-2), 2.21 and 3.11 (each 1H, each br s, 2×OH), 3.37—3.78 (4H, m, 2×H-1 and 2×H-7), 3.66 (1H, ddd, $J_{3,4}$=7.0 Hz, H-4), 3.86—3.93 (1H, m, H-3), 4.54 and 4.60 (each 1H, ABq, *J*=11.2 Hz, OCH_2Ph), and 7.28—7.37 (5H, m, Ph). Found: C, 67.94; H, 9.05%. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28%.

25: R_f=0.38 (2 : 3 hexane–ethyl acetate); ^{1}H NMR (270 MHz) δ=0.83 (3H, d, *J*=7.0 Hz, 6-Me), 0.88 (3H, d, *J*=6.6 Hz, 2-Me), 1.25 (1H, ddd, J_{gem}=14.2 Hz, $J_{4,5}$=2.8 Hz, and $J_{5,6}$=8.8 Hz, H-5), 1.72 (1H, t, *J*=5.4 Hz, OH), 1.73—1.93 (3H, m, H-2, 5', and 6), 2.74 (1H, d, *J*=2.0 Hz, 3-OH), 3.08 (1H, dd, *J*=4.2 and 7.8 Hz, OH), 3.43—3.53 (2H, m, H-1, 1' or H-7, 7'), 3.59 (1H, ddd, $J_{3,4}$=2.8 Hz and $J_{4,5}$=10.4 Hz, H-4), 3.63—3.71 (2H, m, H-7, 7' or H-1, 1'), 3.87 (1H, ddd, $J_{2,3}$=9.0 Hz, H-3), 4.51 and 4.65 (each 1H, ABq, *J*=11.4 Hz, OCH_2Ph), and 7.32—7.39 (5H, m, Ph).

(2*S*,4*S*,5*R*,6*S*)-5,7-(Benzylidenedioxy)-4-benzyloxy-2,6-dimethyl-1-heptanol (26). To a stirred solution of **24** (1.00 g, 3.54 mmol) in dry CH_2Cl_2 (20.0 ml) at 0°C were added benzaldehyde dimethyl acetal (0.531 ml, 3.54 mmol) and CSA (82.2 mg, 0.354 mmol). After 1 h at room temperature, the reaction mixture was neutralized with triethylamine and washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated. The residue was chromatographed on silica gel (200 g) with 2 : 1 hexane–ethyl acetate to afford **26** (1.18 g, 90%) as a colorless syrup: R_f=0.78 (1 : 8 hexane–ethyl acetate); $[\alpha]_D^{25}$ 0.00°, $[\alpha]_{365}^{25}$+5.9° (*c* 0.34); ^{1}H NMR (270 MHz) δ=0.98 (3H, d, *J*=6.6 Hz, 2-Me), 1.24 (3H, d, *J*=6.6 Hz, 6-Me), 1.62 (1H, ddd, J_{gem}=14.5 Hz, $J_{2,3}$=8.2 Hz, and $J_{3,4}$=3.9 Hz, H-3), 1.65 (1H, t, *J*=6.0 Hz, 1-OH), 1.77 (1H, ddd, $J_{2,3'}$=5.0 Hz and $J_{3',4}$=6.4 Hz, H-3'), 1.89—2.02 (2H, m, H-2 and 6), 3.53 (1H, dd, $J_{1,2}$=2.8 Hz, H-1), 3.59 (1H, dd, $J_{1',2}$=2.9 Hz, H-1'), 3.73 (1H, ddd, $J_{4,5}$=8.2 Hz, H-4), 3.93 (1H, dd, $J_{5,6}$=2.2 Hz, H-5), 4.11 (1H, dd, J_{gem}=11.2 Hz and $J_{6,7}$=1.7 Hz, H-7), 4.24 (1H, dd, $J_{6,7'}$=2.4 Hz, H-7'), 4.59 and 4.67 (each 1H, ABq, *J*=11.0 Hz, OCH_2Ph), 5.51 (1H, s, C*H*Ph), and 7.25—7.50 (10H, m, 2×Ph). Found: C, 74.51; H, 8.13%. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%.

6*R*-Epimer of 26. 6*R*-Epimer of **26** was prepared from **25** exactly as described above for the preparation of **26** from **24**: R_f=0.85 (1 : 8 hexane–ethyl acetate); ^{1}H NMR (270 MHz) δ=0.83 (3H, d, *J*=6.6 Hz, 6-Me), 0.86 (3H, d, *J*=6.6 Hz, 2-Me), 1.22—1.29 (1H, m, OH), 1.39 (1H, ddd, J_{gem}=14.2 Hz, $J_{2,3}$=7.8 Hz, and $J_{3,4}$=2.2 Hz, H-3), 1.78—1.88 (1H, m, H-2), 1.92 (1H, ddd, $J_{2,3'}$=5.6 Hz and $J_{3',4}$=10.4 Hz, H-3'), 1.98—2.13 [1H, m, H-6 (after irradiation of 0.83 ppm, multiplet changes to ddd. $J_{5,6}$=10.5 Hz)], 3.42—3.53 (2H, m, H-1 and 5), 3.52 (1H, dd, J_{gem}=8.8 Hz and $J_{6,7ax}$=10.4 Hz, H-7ax), 3.68—3.77 (2H, m, H-1' and 4), 4.12 (1H, dd, $J_{6,7eq}$=4.6 Hz, H-7eq), 4.58 and 4.78 (each 1H, ABq, *J*=11.6 Hz, OCH_2Ph), 5.44 (1H, s, C*H*Ph), 7.27—7.39 and 7.45—7.52 (10H, m, 2×Ph).

(2*S*,3*R*,4*S*,6*S*)-1,3-(Benzylidenedioxy)-4-benzyloxy-7-[4-(methoxybenzyl)oxy]-2,6-dimethylheptane (35). To a stirred solution of **26** (250 mg, 0.675 mmol) in dry DMF (2.5 ml) at 0°C was added NaH (54.0 mg, 1.35 mmol; 60% dispersion in minaral oil). After 1 h at 0°C, 4-methoxybenzyl chloride (0.183 ml, 1.35 mmol) was added at 0°C and the mixture was stirred at room temperature for 16 h. Ethanol was added to the ice-cooled reaction mixture and the new mixture was poured into water and extracted with hexane. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (33 g) with 8 : 1 hexane–ethyl acetate to afford **35** (331 mg, 100%) as a colorless syrup: R_f=0.40 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +2.0°, $[\alpha]_{365}^{25}$+8.8° (*c* 0.50); ^{1}H NMR (270 MHz) δ=0.99 (3H, d, *J*=6.5 Hz, 6-Me), 1.22 (3H, d, *J*=6.6 Hz, 2-Me), 1.56 (1H, ddd, J_{gem}=14.5 Hz, $J_{4,5}$=3.6 Hz and $J_{5,6}$=9.6 Hz, H-5), 1.82 (1H, ddd, $J_{4,5'}$=6.8 Hz and $J_{5',6}$=4.5 Hz, H-5'), 1.88—1.97 (1H, m, H-2), 2.04—2.17 (1H, m, H-6), 3.24 (1H, dd, J_{gem}=9.4 Hz and $J_{6,7}$=6.8 Hz, H-7), 3.32 (1H, dd, $J_{6,7'}$=6.0 Hz, H-7'), 3.68 (1H, ddd, $J_{3,4}$=8.2 Hz, H-4), 3.78 (3H, s, OMe), 3.87 (1H, dd, $J_{2,3}$=2.4 Hz, H-3), 4.02 (1H, dd, J_{gem}=10.5 Hz and $J_{1,2}$=1.8 Hz, H-1), 4.08 (1H, dd, $J_{1',2}$=2.2 Hz, H-1'), 4.42 (2H, s, CH_2 of MPM), 4.53 and 4.64 (each 1H, ABq, *J*=11.4 Hz, OCH_2Ph), 5.46 (1H, s, C*H*Ph), 6.83 and 7.22 (each 2H, each d, *J*=9.0 Hz, aromatic protons of MPM), and 7.28—7.48 (10H, m, 2×Ph). Found: C, 75.67; H, 7.75%. Calcd for $C_{31}H_{38}O_5$: C, 75.89; H, 7.81%.

(2*S*,3*R*,4*S*,6*S*)-1-[(*t*-Butyldiphenylsilyl)oxy]-7-[(4-methoxybenzyl)oxy]-2,6-dimethyl-3,4-heptanediol (36). A mixture of **35** (331 mg, 0.675 mmol), Raney Ni-W4, and ethanol (16.5 ml) was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 24 h. The insoluble materials were filtered and washed with ethanol. The combined filtrate and washings were concentrated and the residual triol (211 mg) was dissolved in dry DMF (4.2 ml). To this were added imidazole (91.9 mg, 1.35 mmol) and *t*-butylchlorodiphenylsilane (0.228 ml, 0.877 mmol) at room temperature. After 19.5 h at room temperature, ethanol and water were added and the mixture was

extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (37 g) with 3 : 1 hexane–ethyl acetate to afford **36** (342 mg, 92%) as a colorless syrup: R_f=0.44 (2 : 1 hexane–ethyl acetate); $[\alpha]_D^{25}$ −9.6°, $[\alpha]_{365}^{25}$ −25.8° (*c* 0.52); ^{1}H NMR (270 MHz) δ=0.92 (3H, d, *J*=6.6 Hz, 6-Me), 1.06 (9H, s, *t*-butyl), 1.07 (3H, d, *J*=6.6 Hz, 2-Me), 1.37 (1H, ddd, J_{gem}=14.4 Hz, $J_{4,5}$=9.6 Hz, and $J_{5,6}$=7.0 Hz, H-5), 1.84 (1H, ddd, $J_{4,5'}$=1.6 Hz and $J_{5',6}$=5.2 Hz, H-5′), 1.91—1.98 (1H, m, H-2), 2.01—2.10 (1H, m, H-6), 3.21 (1H, d, *J*=2.5 Hz, 3-OH), 3.22 (1H, dd, J_{gem}=$J_{6,7}$=9.0 Hz, H-7), 3.42 (1H, dd, $J_{6,7'}$=4.4 Hz, H-7′), 3.53—3.61 (1H, m, H-4), 3.67 (1H, ddd, $J_{2,3}$=2.5 Hz and $J_{3,4}$=7.6 Hz, H-3), 3.68 (1H, dd, J_{gem}=10.2 Hz and $J_{1,2}$=4.4 Hz, H-1), 3.80 (1H, br s, 4-OH), 3.80 (3H, s, OMe), 3.81 (1H, dd, $J_{1',2}$=3.4 Hz, H-1′), 4.47 (2H, s, CH_2 of MPM), 6.87 and 7.24 (each 2H, each d, *J*=9.0 Hz, aromatic protons of MPM), 7.35—7.47 and 7.64—7.68 (10H, m, 2×Ph). Found: C, 72.26; H, 8.70%. Calcd for $C_{33}H_{46}O_5Si$: C, 71.96; H, 8.42%.

(2*S*,3*R*,4*S*,6*S*)-1-[(*t*-Butyldiphenylsilyl)oxy]-7-[(4-methoxybenzyl)oxy]-3,4-dimethoxy-2,6-dimethylheptane (37). To a stirred solution of **36** (340 mg, 0.617 mmol) and methyl iodide (0.231 ml, 3.71 mmol) in dry DMF (6.8 ml) at 0°C was added protionwise NaH (61.9 mg, 1.55 mmol; 60% dispersion in mineral oil). After 2 h at room temperature, methanol was added to the ice-cooled reaction mixture. The mixture was poured into water and extracted with hexane. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (28 g) with 8 : 1 hexane–ethyl acetate to afford **37** (332 mg, 93%) as a colorless syrup: R_f=0.60 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +5.2°, $[\alpha]_{365}^{25}$+20.3° (*c* 0.62); ^{1}H NMR (270 MHz) δ=0.90 (3H, d, *J*=6.5 Hz, 6-Me), 0.94 (3H, d, *J*=6.5 Hz, 2-Me), 1.06 (9H, s, *t*-butyl), 1.15 (1H, ddd, J_{gem}=14.0 Hz, $J_{4,5}$=2.8 Hz, and $J_{5,6}$=10.0 Hz, H-5), 1.66 (1H, ddd, $J_{4,5'}$=10.2 Hz, and $J_{5',6}$=3.6 Hz, H-5′), 1.80—1.92 (1H, m, H-2), 1.92—2.06 (1H, m, H-6), 3.20 (1H, dd, J_{gem}=9.0 Hz and $J_{6,7}$=7.6 Hz, H-7), 3.33 (1H, dd, $J_{6,7'}$=5.4 Hz, H-7′), 3.36 (3H, s, OMe), 3.36—3.43 (1H, m, H-4), 3.43 (3H, s, OMe), 3.48 (1H, dd, $J_{2,3}$=$J_{3,4}$=4.2 Hz, H-3), 3.50 (1H, dd, J_{gem}=10.0 Hz and $J_{1,2}$=5.2 Hz, H-1), 3.58 (1H, dd, $J_{1',2}$=6.6 Hz, H-1′), 3.80 (3H, s, OMe), 4.43 (2H, s, CH_2 of MPM), 6.86 and 7.25 (each 2H, each d, *J*=9.0 Hz, aromatic protons of MPM), 7.33—7.45 and 7.63—7.68 (10H, m, 2×Ph). Found: C, 72.72; H, 8.44%. Calcd for $C_{35}H_{50}O_5Si$: C, 72.62; H, 8.71%.

(2*S*,3*R*,4*S*,6*S*)-3,4-Dimethoxy-7-[(4-methoxybenzyl)oxy]-2,6-dimethyl-1-heptanol (38). To a stirred solution of **37** (315 mg, 0.544 mmol) in dry THF (6.3 ml) at room temperature was added 1 M TBAF in THF (2.17 ml, 2.17 mmol). After 17 h at room temperature, the reaction mixture was concentrated and the residue was dissolved in ethyl acetate. This was washed with water and saturated aqueous NaCl, dried, and concentrated. The residue was chromatgraphed on silica gel (17 g) with 3 : 1 hexane–acetone to afford **38** (174 mg, 94%) as a colorless syrup: R_f=0.31 (3 : 1 hexane–acetone); $[\alpha]_D^{25}$ +2.1°, $[\alpha]_{365}^{25}$ +11.6° (*c* 0.57); ^{1}H NMR (270 MHz) δ=0.98 (3H, d, *J*=6.8 Hz, 6-Me), 1.00 (3H, d, *J*=6.8 Hz, 2-Me), 1.26 (1H, ddd, J_{gem}=14.2 Hz, $J_{4,5}$=3.0 Hz, and $J_{5,6}$=9.6 Hz, H-5), 1.69 (1H, ddd, $J_{4,5'}$=9.2 Hz and $J_{5',6}$=4.0 Hz, H-5′), 1.88—2.08 (2H, m, H-2 and 6), 1.97 (1H, t, *J*=5.4 Hz, OH), 3.24 (1H, dd, J_{gem}=9.2 Hz and $J_{6,7}$=6.8 Hz, H-7), 3.30 (1H, dd, $J_{2,3}$=$J_{3,4}$=4.2 Hz, H-3), 3.35 (1H, dd, $J_{6,7'}$=6.0 Hz, H-7′), 3.39 (3H, s, OMe), 3.44 (3H, s, OMe), 3.44 (1H, ddd, H-4), 3.58 (1H, dd, $J_{1,2}$=2.4 Hz, H-1), 3.61 (1H, dd, $J_{1',2}$=1.4 Hz, H-1′), 3.81 (3H, s, OMe), 4.44 (2H, s, CH_2 of MPM), 6.86 and 7.26 (each 2H, each d, *J*=8.4 Hz, aromatic protons of MPM). Found: C, 67.20; H, 9.17%. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47%.

(2*E*,4*S*,5*R*,6*S*,8*S*)-5,6-Dimethoxy-9-[(4-methoxybenzyl)-oxy]-2,4,8-trimethyl-2-nonenal (40). To a stirred solution of **38** (175 mg, 0.514 mmol) in dry CH_2Cl_2 (5.25 ml) at 0°C was added Dess–Martin periodinane (iodine(V) compound as an oxidizing reagent, 327 mg, 0.771 mmol).[28] After 2 h at room temperature, ether and 5 : 1 (v/v) saturated aqueous $NaHCO_3$–$Na_2S_2O_3$ were added and the mixture was vigorously stirred for 10 min. The mixture was extracted with ethyl acetate and the extracts were washed with saturated aqueous NaCl, dried, and concentrated to afford the crude aldehyde **39** [174 mg, 100%; R_f=0.42 (3 : 1 hexane–acetone); ^{1}H NMR (270 MHz) δ=0.97 (3H, d, *J*=6.5 Hz, 6-Me), 1.18 (3H, d, *J*=7.0 Hz, 2-Me), 1.32 (1H, ddd, J_{gem}=14.0 Hz, $J_{4,5}$=2.8 Hz, and $J_{5,6}$=9.6 Hz, H-5), 1.67 (1H, ddd, $J_{4,5'}$=8.8 Hz and $J_{5',6}$=3.8 Hz, H-5′), 1.93—2.09 (1H, m, H-6), 2.63 (1H, ddq, $J_{1,2}$=1.6 Hz and $J_{2,3}$=4.5 Hz, H-2), 3.22—3.36 (3H, m, H-4, 7, and 7′), 3.33 (3H, s, OMe), 3.36 (3H, s, OMe), 3.57 (1H, dd, $J_{3,4}$=5.4 Hz, H-3), 3.80 (3H, s, OMe), 4.44 (2H, s, CH_2 of MPM), 6.87 and 7.25 (each 2H, each d, *J*=8.8 Hz, aromatic protons of MPM), and 9.07 (1H, d, H-1)]. To a stirred solution of *N*-[2-(triethylsilyl)propylidene]-*t*-butylamine (1.75 g, 7.70 mmol) in dry THF (26.0 ml) at 0°C was added 1.09 M *s*-butyllithium in cyclohexane (7.06 ml, 7.70 mmol). After 0.5 h at room temperature, the mixture was cooled to −78°C and to this was added a solution of the above aldehyde **39** (174 mg) in dry THF (1.70 ml). The reaction mixture was warmed to −20°C during 2.5 h and stirred at the same temperature for 2 h. Water (9.6 ml) was added and to this was added citric acid to make the pH of the mixture ca. 4.5. Ethyl acetate and saturated aqueous NaCl were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried and concectrated. The residue was chromatographed on silica gel (20 g) with 3 : 1 hexane–ethyl acetate to afford **40** (165 mg, 85%) as a colorless syrup: R_f=0.64 (3 : 1 hexane–ethyl acetate); ^{1}H NMR (270 MHz) δ=0.87 (3H, d, *J*=6.5 Hz, 8-Me), 1.08—1.18 (1H, m, H-7), 1.14 (3H, d, *J*=6.5 Hz, 4-Me), 1.64—1.75 (1H, m, H-7′), 1.75 (3H, s, 2-Me), 1.88—2.02 (1H, m, H-8), 2.78—2.92 (1H, m, H-4), 3.16—3.26 (2H, m, H-5 and 6), 3.21 (1H, dd, J_{gem}=9.6 Hz and $J_{8,9}$=7.2 Hz, H-9), 3.31 (1H, dd, $J_{8,9'}$=5.8 Hz, H-9′), 3.37 (3H, s, OMe), 3.49 (3H, s, OMe), 3.80 (3H, s, OMe), 4.42 (2H, s, CH_2 of MPM), 6.34 (1H, d, $J_{3,4}$=10.2 Hz, H-3), 6.86 and 7.24 (each 2H, each d, *J*=9.0 Hz, aromatic protons of MPM), and 9.42 (1H, s, H-1).

(3*S*,4*S*,5*E*,7*S*,8*R*,9*S*,11*S*)-12-[(4-Methoxybenzyl)oxy]-3,8,9-trimethoxy-5,7,11-trimethyl-1,5-dodecadien-4-ol (41) and Its (3*R*,4*R*)-Epimer (42). To a stirred solution of 1 M allyl methyl ether in THF (4.52 ml, 4.52 mmol) at −78°C was added 1.09 M *s*-butyllithium in cyclohexane (3.32 ml, 3.62 mmol). After 0.5 h at −78°C, 1 M (+)-B-methoxydiisopinocampheylborane, derived from (−)-α-pinene,[26] in THF (3.62 ml, 3.62 mmol) was added and the mixture was further stirred at −78°C for 1 h. BF_3·OEt_2 (0.455 ml, 3.62 mmol) was then added and a solution of **40** (171 mg, 0.452 mmol) in dry THF (1.71 ml) was added at −78°C and the mixture was stirred at −78°C for 2 h. The reaction mixture was gradually warmed to −20°C during 2 h. The mixture was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried,

and concentrated. The residue was chromatographed on silica gel (20 g) with 3 : 1 hexane–ethyl acetate to afford **41** (155 mg, 76%) and **42** (27.5 mg, 13.5%) as colorless syrups.

41: R_f=0.35 (3 : 1 chloroform–ethyl acetate); $[\alpha]_D^{25}$ +36.3° (*c* 0.49); ^{1}H NMR (270 MHz) δ=0.90 (3H, d, *J*=6.6 Hz, 11-Me), 1.03 (3H, d, *J*=6.6 Hz, 7-Me), 1.11 (1H, ddd, J_{gem}=15.0 Hz, *J*=9.8 and 2.3 Hz, H-10), 1.60 (3H, d, *J*=1.2 Hz, 5-Me), 1.64 (1H, ddd, *J*=10.4 Hz and 4.0 Hz, H-10′), 1.88—2.01 (1H, m, H-11), 2.37—2.52 (1H, m, H-7), 2.84 (1H, d, *J*=1.8 Hz, OH), 3.08 (1H, dd, *J*=8.2 and 2.6 Hz, H-8), 3.14—3.21 (2H, m, H-9 and 12), 3.33 (3H, s, OMe), 3.34 (s, 3H, OMe),3.34—3.39 (1H, m, H-12′), 3.46 (3H, s, OMe), 3.51 (1H, dd, $J_{2,3}$=7.8 Hz and $J_{3,4}$=8.4 Hz, H-3), 3.80 (3H, s, OMe), 3.84 (1H, dd, H-4), 4.43 (2H, s, C*H*$_2$ of MPM), 5.24 (1H, dd, J_{gem}=1.6 Hz and $J_{1,2}$=10.0 Hz, H-1), 5.26 (1H, dd, $J_{1',2}$=17.6 Hz, H-1′), 5.29 (1H, d, $J_{6,7}$=10.0 Hz, H-6), 5.53 (1H, ddd, H-2), 6.87 and 7.25 (each 2H, each d, *J*=8.6 Hz, aromatic protons of MPM). Found: C, 69.40; H, 9.07%. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.39%.

42: R_f=0.31 (3 : 1 chloroform–ethyl acetate); ^{1}H NMR (270 MHz) δ=0.91 (3H, d, *J*=6.6 Hz, 11-Me), 0.97 (3H, d, *J*=6.6 Hz, 7-Me), 1.11 (1H, ddd, J_{gem}=14.4 Hz, $J_{9,10}$=1.8 Hz, and $J_{10,11}$=10.6 Hz, H-10), 1.59 (3H, d, *J*=1.2 Hz, 5-Me), 1.68 (1H, ddd, $J_{9,10'}$=4.0 Hz and $J_{10',11}$=5.8 Hz, H-10′), 1.88—2.05 (1H, m, H-11), 2.38 (1H, m, H-7), 2.79 (1H, d, *J*=2.0 Hz, OH), 3.14 (1H, dd, $J_{7,8}$=2.6 Hz and $J_{8,9}$=8.2 Hz, H-8), 3.19 (1H, dd, *J*=9.2 and 7.4 Hz, H-12), 3.27 (1H, ddd, H-9), 3.33 (3H, s, OMe), 3.34—3.39 (1H, m, H-12′), 3.35 (3H, s, OMe), 3.48 (1H, dd, $J_{2,3}$=7.8 Hz and $J_{3,4}$=8.4 Hz, H-3), 3.49 (3H, s, OMe), 3.80 (3H, s, OMe), 3.83 (1H, dd, H-4), 4.43 (2H, s, C*H*$_2$ of MPM), 5.21 (1H, dd, J_{gem}=2.0 Hz and $J_{1,2}$=17.6 Hz, H-1), 5.24 (1H, dd, $J_{6,7}$=10.0 Hz, H-6), 5.25 (1H, dd, $J_{1',2}$=11.2 Hz, H-1′), 5.55 (1H, ddd, H-2), 6.87 and 7.25 (each 2H, each d, *J*=8.8 Hz, aromatic protons of MPM).

(2*S*,4*S*,5*R*,6*S*,7*E*,9*S*,10*S*)-9-[(*t*-Butyldimethylsilyl)oxy]-4,5,10-trimethoxy-2,6,8-trimethyl-7,11-dodecadien-1-ol (43). To a stirred solution of **41** (175 mg, 0.388 mmol) in dry DMF (3.5 ml) at 0 °C were added imidazole (106 mg, 1.55 mmol) and *t*-butylchlorodimethylsilane (176 mg, 1.17 mmol). After 18 h at room temperature, methanol and water were added and the mixture was extracted with hexane. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (22 g) with 10 : 1 hexane–ethyl acetate to afford a colorless syrup (199 mg, 91%), which was dissolved in 20 : 1 (v/v) CH_2Cl_2–water (6.0 ml). DDQ (120 mg, 0.529 mmol) was added and the mixture was stirred vigorously for 1 h at room temperature. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The residue was chromatographed on silica gel (7.9 g) with 3 : 1 hexane–ethyl acetate to afford **43** (152 mg, 97%) as a colorless syrup: R_f=0.24 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +6.0°, $[\alpha]_{365}^{25}$ +29.2° (*c* 0.50); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.01 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.87 (9H, s, *t*-butyl), 0.91 (3H, d, *J*=6.6 Hz, 2-Me),1.02 (3H, d, *J*=6.6 H, 6-Me), 1.25—1.38 (1H, m, H-3), 1.54 (3H, d, *J*=1.2 Hz, 8-Me), 1.54—1.64 (1H, m, H-3′), 1.60—1.72 (1H, m, H-2), 2.37 (1H, ddq, $J_{5,6}$=9.2 Hz and $J_{6,7}$=10.0 Hz, H-6), 2.83 (1H, t, *J*=6.2 Hz, OH), 3.14 (1H, dd, $J_{4,5}$=1.4 Hz, H-5), 3.22 (1H, ddd, $J_{3,4}$=9.2 Hz and $J_{3',4}$=1.4 Hz, H-4), 3.30 (3H, s, OMe), 3.34—3.42 (2H, m, H-1 and 1′), 3.36 (3H, s, OMe), 3.48 (1H, br dd, $J_{9,10}$=7.2 Hz and $J_{10,11}$=10.4 Hz, H-10), 3.50 (3H, s, OMe), 3.89 (1H, d, H-9), 5.07 (1H, dd, H-7), 5.14 (1H, dd, J_{gem}=2.0 Hz and $J_{11,12}$=7.6 Hz, H-12), 5.21 (1H, ddd, $J_{11,12'}$=17.6 Hz and $J_{10,12'}$=1.2 Hz, H-12′), and 5.52 (1H, ddd, H-11). Found: C, 64.42; H, 10.49%. Calcd for $C_{24}H_{48}O_5Si$: C, 64.82; H, 10.88%.

(2*S*,4*S*,5*R*,6*S*,7*E*,9*S*,10*S*)-9-[(*t*-Butyldimethylsilyl)oxy]-4,5,10-trimethoxy-2,6,8-trimethyl-7,11-dodecadienal (7). A solution of DMSO (0.118 ml, 1.66 mmol) in dry CH_2Cl_2 (0.47 ml) was added at −78 °C to a stirred solution of oxalyl dichloride (0.0724 ml, 0.830 mmol) in dry CH_2Cl_2 (1.05 ml). After 15 min at −78 °C, a solution of **43** (123 mg, 0.277 mmol) in dry CH_2Cl_2 (0.98 ml) was added dropwise and the resulting suspension was stirred at −78 °C for 45 min. After addition of triethylamine (0.345 ml, 2.48 mmol), the mixture was gradually warmed to 0 °C during 45 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (6.1 g) with 8 : 1 hexane–ethyl acetate to afford **7** (107 mg, 88%) as a colorless syrup: R_f=0.63 (3 : 1 hexane–ethyl acetate); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.01 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.88 (9H, s, *t*-butyl), 1.02 (3H, d, *J*=6.4 Hz, Me), 1.04 (3H, d, *J*=6.6 Hz, Me), 1.31 (1H, ddd, J_{gem}=14.6 Hz, $J_{2,3}$=5.8 Hz and $J_{3,4}$=2.4 Hz, H-3), 1.53 (3H, d, *J*=1.6 Hz, 8-Me), 2.05 (1H, ddd, $J_{2,3'}$=8.8 Hz and $J_{3',4}$=10.4 Hz, H-3′), 2.25—2.42 (2H, m, H-2 and 6), 3.09 (1H, dd, $J_{4,5}$=1.8 Hz and $J_{5,6}$=9.6 Hz, H-5), 3.14 (1H, ddd, H-4), 3.23 (3H, s, OMe), 3.30 (3H, s, OMe), 3.46 (1H, dd, $J_{9,10}$=7.4 Hz and $J_{10,11}$=7.6 Hz, H-10), 3.50 (3H, s, OMe), 3.89 (1H, d, H-9), 5.06 (1H, d, $J_{6,7}$=10.0 Hz, H-7), 5.20 (1H, dd, J_{gem}=1.8 and $J_{11,12}$=9.6 Hz, H-12), 5.21 (1H, dd, $J_{11,12'}$=17.6 Hz, H-12′), 5.50 (1H, ddd, H-11), and 9.45 (1H, d, $J_{1,2}$=4.0 Hz, H-1).

***N*-(Triphenylmethyl)-3-bromo-2,5-dimethoxyaniline (5).** To a solution of 3-bromo-2,5-dimethoxyanline[20] (1.32 g, 5.71 mmol) in dry CH_2Cl_2 (13.2 ml) at 0 °C were added triethylamine (1.20 ml, 8.61 mmol) and triphenylmethyl chloride (1.60 g, 5.74 mmol). After at room temperature for 24 h, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (271 g) with 20 : 1 hexane–ethyl acetate to afford **5** (2.63 g, 97%), as colorless crystals: R_f=0.63 (5 : 1 hexane–ethyl acetate); mp 192.5—193 °C (chloroform–hexane); ^{1}H NMR (270 MHz) δ=3.30 (3H, s, OMe), 3.85 (3H, s, OMe), 5.58 and 6.26 (each 1H, each d, *J*=2.4 Hz, aromatic protons), 5.83 (1H, br s, NH), and 7.18—7.36 (15H, m, Tr). Found: C, 68.15; H, 5.03; N, 2.88%. Calcd for $C_{27}H_{24}BrNO_2$: C, 68.36; H, 5.10; N, 2.95%.

(1*R*,2*S*,4*S*,5*R*,6*S*,7*E*,9*S*,10*S*)-9-[(*t*-Butyldimethylsilyl)oxy]-1-[2,5-dimethoxy-3-[(triphenylmethyl)amino]phenyl]-4,5,10-trimethoxy-2,6,8-trimethyl-7,11-dodecadien-1-ol (44) and Its 1*S*-Epimer (45). To a stirred solution of **5** (155 mg, 0.327 mmol) in dry THF (2.23 ml) at −78 °C was added 1.65 M butyllithium in hexane (0.347 ml, 0.573 mmol). After 0.5 h at −78 °C, a solution of **7** (48.2 mg, 0.109 mmol) in dry THF (0.48 ml) was added and the mixture was stirred at −78 °C for 2 h. Methanol (0.1 ml) was added and the mixture was warmed to ambient temperature. Saturated aqueous NH_4Cl was added the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (13.7 g) with 3 : 1 hexane–ethyl acetate to afford **44** (41.5 mg, 45.5%) and **45** (41.5 mg, 45.5%) as colorless syrups.

44: R_f=0.22 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +10.6° $[\alpha]_{435}^{25}$ +22.6° (*c* 0.47); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.02

(3H, s, SiMe), 0.07 (3H, s, SiMe), 0.80 (3H, d, J=6.6 Hz, 2-Me), 0.88 (9H, s t-butyl), 1.00 (3H, d, J=6.6 Hz, 6-Me), 1.20—1.31 (1H, m, H-3), 1.54 (3H, d, J=1.2 Hz, 8-Me), 1.65—1.79 (1H, m, H-3′), 1.98—2.10 (1H, m, H-2), 2.33—2.48 (1H, m, H-6), 2.70 (1H, d, J=4.6 Hz, OH), 3.11 (1H, dd, $J_{4,5}$=2.4 Hz and $J_{5,6}$=9.0 Hz, H-5), 3.21—3.28 (1H, m, H-4), 3.29 (3H, s, OMe), 3.33 (3H, s, OMe), 3.34 (3H, s, OMe), 3.45 (3H, s, OMe), 3.48 (1H, dd, $J_{9,10}$=7.4 Hz and $J_{10,11}$=7.6 Hz, H-10), 3.79 (3H, s, OMe), 3.89 (1H, d, H-9), 4.86 (1H, dd, $J_{1,2}$=4.6 Hz, H-1), 5.11 (1H, d, $J_{6,7}$=10.0 Hz, H-7), 5.14 (1H, dd, J_{gem}=2.0 Hz and $J_{11,12}$=10.2 Hz, H-12), 5.19 (1H, dd, $J_{11,12'}$=17.6 Hz, H-12′), 5.54 (1H, ddd, H-11), 5.56 and 6.19 (each 1H, each d, J=2.6 Hz, aromatic protons), 5.61 (1H, br s, NH), and 7.17—7.38 (15H, m, Tr); M^+, 837.

45: R_f=0.17 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +2.0°, $[\alpha]_{546}^{25}$ +3.8° (c 0.89); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.02 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.64 (3H, d, J=6.6 Hz, 2-Me), 0.88 (9H, s, t-butyl), 1.03 (3H, d, J=6.6 Hz, 6-Me), 1.29—1.42 (1H, m, H-3), 1.54 (3H, s, J=1.2 Hz, 8-Me), 1.74—1.86 (1H, m, H-3′), 2.00—2.13 (1H, m, H-2), 2.33—2.48 (1H, m, H-6), 3.15 (1H, dd, $J_{4,5}$=1.4 Hz and $J_{5,6}$=9.0 Hz, H-5), 3.25—3.33 (1H, m, H-4), 3.29 (3H, s, OMe), 3.31 (3H, s, OMe), 3.39 (3H, s, OMe), 3.47 (1H, dd, $J_{9,10}$=7.4 Hz and $J_{10,11}$=7.6 Hz, H-10), 3.52 (3H, s, OMe), 3.81 (3H, s, OMe), 3.89 (1H, d, H-9), 3.96 (1H, d, J=3.4 Hz, OH), 4.53 (1H, dd, $J_{1,2}$=9.6 Hz, H-1), 5.08 (1H, d, $J_{6,7}$=10.0 Hz, H-7), 5.17 (1H, dd, J_{gem}=2.0 Hz and $J_{11,12}$=10.2 Hz, H-12), 5.20 (1H, dd, $J_{11,12'}$=17.6 Hz, H-12′), 5.51 (1H, ddd, H-11), 5.56 and 6.09 (each 1H, each d, J=2.6 Hz, aromatic protons), 5.70 (1H, br s, NH), and 7.17—7.38 (15H, m, Tr).

Oxidation of 45 to the Ketone 46. A solution of **45** (100 mg, 0.119 mmol) in 3: 1 (v/v) DMSO–acetic anhydride (4.0 ml) was heated at 95°C for 0.5 h. After cooling to ambient temperature, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (10 g) with 8 : 1 hexane–acetone to afford the ketone **46** (80.0 mg, 80%) as a pale yellow foam: R_f=0.40 (5 : 1 hexane–acetone); IR ($CHCl_3$) 1684, 1593, 1495, 1361, and 1249 cm^{-1}; ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.02 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.88 (9H, s, t-butyl), 0.98 (3H, d, J=6.6 Hz, 6-Me), 1.09 (3H, d, J=6.8 Hz, 2-Me), 1.31—1.41 (1H, m, H-3), 1.52 (3H, s, 8-Me), 1.60—1.69 (1H, m, H-3′), 2.03—2.17 (1H, m, H-2), 2.33—2.48 (1H, m, H-6), 3.09 (1H, dd, $J_{4,5}$=2.4 Hz and $J_{5,6}$=9.0 Hz, H-5), 3.18 (1H, ddd, $J_{3,4}$=2.4 Hz and $J_{3',4}$=10.2 Hz, H-4), 3.25 (3H, s, OMe), 3.29 (3H, s, OMe), 3.34 (3H, s, OMe), 3.43 (3H, s, OMe), 3.47 (1H, dd, $J_{9,10}$=7.4 Hz and $J_{10,11}$=7.6 Hz, H-10), 3.78 (3H, s, OMe), 3.88 (1H, d, H-9), 5.09 (1H, d, $J_{6,7}$=10.0 Hz, H-7), 5.12 (1H, dd, J_{gem}=2.0 Hz and $J_{11,12}$=10.2 Hz, H-12), 5.19 (1H, dd, $J_{11,12'}$=17.6 Hz, H-12′), 5.52 (1H, ddd, H-11), 5.74 and 6.22 (each 1H, each d, J=2.6 Hz, aromatic protons), 5.83 (1H, br s, NH), and 7.17—7.38 (15H, m, Tr).

LiAlH$_4$-Chirald Reduction of Ketone 46. To a solution of 1.0 M $LiAlH_4$ in THF (0.054 ml, 0.054 mmol) in ether (3.4 ml) was added at −78°C a solution of Chirald (40.0 mg, 0.141 mmol) in dry ether (0.6 ml). After 20 min at −78°C, a solution of **46** (15.0 mg, 0.0179 mmol) in dry ether (0.45 ml) was added and the mixture was stirred at −78°C for 24 h. The reaction mixture was quenched with wet ether and the mixture was warmed to ambient temperature. The insoluble materials were filterd with Celite and washed with ether. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (1.5 g) with 3 : 1 hexane–ethyl acetate to afford **44** (9.6 mg, 64%) and **45** (2.4 mg, 16%) as colorless syrups.

Methyl (2*Z*,4*S*,5*S*,6*E*,8*S*,9*R*,10*S*,12*S*,13*R*)-5-[(*t*-Butyldimethylsilyl)oxy-13-[2,5-dimethoxy-3-[(triphenylmethyl)amino]phenyl]-4,9,10,13-tetramethoxy-6,8,12-trimethyl-2,6-tridecadienoate (47). To a stirred solution of **44** (58.0 mg, 0.0692 mmol) and methyl iodide (0.0129 ml, 0.208 mmol) in dry DMF (1.16 ml) at 0°C was added NaH (5.5 mg, 0.14 mmol, 60% dispersion in mineral oil). After 6.5 h at 0°C, methanol and water were added and the mixture was extracted with hexane. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (6 g) with 5 : 1 hexane–ethyl acetate to afford a glass of methyl ether (59.0 mg, 100%) [R_f=0.62 (3 : 1 hexane–ethyl acetate); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.01 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.81 (3H, d, J=6.6 Hz, 11-Me), 0.88 (9H, s, t-butyl), 0.99 (3H, d, J=6.6 Hz, 7-Me), 1.20—1.36 (1H, m, H-10), 1.54 (3H, s, 5-Me), 1.58—1.73 (1H, m, H-10), 1.90—2.06 (1H, m, H-11), 2.34—2.50 (1H, m, H-7), 3.07 (1H, dd, $J_{7,8}$=9.0 Hz and $J_{8,9}$=2.4 Hz, H-8), 3.14—3.22 (1H, m, H-9), 3.23 (3H, s, OMe), 3.27 (3H, s, OMe), 3.29 (3H, s, OMe), 3.33 (3H, s, OMe), 3.44 (3H, s, OMe), 3.47 (1H, dd, $J_{2,3}$=7.6 Hz and $J_{3,4}$=7.4 Hz, H-3), 3.78 (3H, s, OMe), 3.87 (1H, d, H-4), 4.31 (1H, d, $J_{11,12}$=4.6 Hz, H-12), 5.10 (1H, dd, J_{gem}=2.0 Hz and $J_{1,2}$=10.2 Hz, H-1), 5.12 (1H, dd, $J_{6,7}$=10.0 Hz, H-6), 5.17 (1H, dd, $J_{1',2}$=17.6 Hz, H-1′), 5.53 (1H, ddd, H-2), 5.57 and 6.09 (each 1H, each d, J=3.0 Hz, aromatic protons), 5.64 (1H, br s, NH), and 7.17—7.38 (15H, m, Tr)]. To a stirred solution of the methyl ether (37.6 mg, 0.0441 mmol) in 2 : 1 (v/v) acetone–water (1.13 ml) at room temperature were added 1 (w/v)% aqueous OsO_4 (0.0336 ml, 0.00132 mmol) and 4-methylmorpholine N-oxide (15.5 mg, 0.132 mmol). After 40 h at room temperature, 10% aqueous $Na_2S_2O_3$ was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was dissolved in dry acetonitrile (0.94 ml) and to this were added at 0°C potassium acetate (24.2 mg, 0.247 mmol) and lead tetraacetate (21.6 mg, 0.0485 mmol). After 0.5 h at 0°C, insoluble materials were filtered and washed with acetonitrile. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (3.8 g) with 5 : 1 hexane–acetone to afford a glass of aldehyde (33.2 mg, 88%). This aldehyde was also obtained by treatment of the methyl ether with OsO_4–$NaIO_4$ in 1 : 1 (v/v) THF–pH 7 phosphate buffer (prepared from aqueous KH_2PO_4 and Na_2HPO_4) at room temperature for 16 h in 76% yield. [R_f=0.37 (3 : 1 hexane–ethyl acetate); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.02 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.83 (3H, d, J=6.6 Hz, 10-Me), 0.89 (9H, s, t-butyl), 1.00 (3H, d, J=6.4 Hz, 6-Me), 1.20—1.35 (1H, m, H-9), 1.62 (3H, s, 4-Me), 1.62—1.72 (1H, m, H-9′), 1.90—2.05 (1H, m, H-10), 2.42—2.55 (1H, m, H-6), 3.06 (1H, dd, $J_{6,7}$=8.0 Hz and $J_{7,8}$=3.2 Hz, H-7), 3.11—3.19 (1H, m, H-8), 3.23 (3H, s, OMe), 3.27 (3H, s, OMe), 3.32 (3H, s, OMe), 3.41 (3H, s, OMe), 3.43 (3H, s, OMe), 3.57 (1H, dd, $J_{1,2}$=2.2 Hz and $J_{2,3}$=6.0 Hz, H-2), 3.78 (3H, s, OMe), 4.24 (1H, d, H-3), 4.30 (1H, d, $J_{10,11}$=5.7 Hz, H-11), 5.25 (1H, d, $J_{5,6}$=10.0 Hz, H-5), 5.56 and 6.08 (each 1H, each d, J=3.0 Hz, aromatic protons), 5.63 (1H, br s, NH), 7.17—7.38 (15H, m, Tr), and 9.61 (1H, d, H-1)]. To a solution of **8** (61.4 mg, 0.193 mmol) and 18-crown-6 (255 mg,

0.965 mmol) in dry THF (3.86 ml) was added at −78°C 0.5 M potassium bis(trimethylsilyl)amide in toluene (0.370 ml, 0.185 mmol). After 0.5 h at −78°C, a solution of the above aldehyde (33.0 mg, 0.0386 mmol) in dry THF (0.66 ml) was added and the mixture was stirred at −78°C for 1 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The extracts were washed with aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (3.5 g) with 6:1 hexane–ethyl acetate to afford **47** (29.2 mg, 83%) as a colorless glass: R_f=0.63 (3:1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +49.3° (*c* 0.15); IR ($CHCl_3$) 1721, 1599, 1503, 1359, and 1201 cm^{-1}; ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=0.00 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.79 (3H, d, *J*=6.6 Hz, 12-Me), 0.88 (9H, s, *t*-butyl), 0.99 (3H, d, *J*=6.4 Hz, 8-Me), 1.23—1.37 (1H, m, H-11), 1.60 (3H, d, *J*=1.6 Hz, 6-Me), 1.60—1.72 (1H, m, H-11′), 1.89—2.03 (1H, m, H-12), 2.37—2.53 (1H, m, H-8), 3.09 (1H, dd, $J_{8,9}$=8.4 Hz and $J_{9,10}$=2.0 Hz, H-9), 3.15—3.23 (1H, m, H-10), 3.22 (3H, s, OMe), 3.28 (3H, s, OMe), 3.29 (3H, s, OMe), 3.32 (3H, s, OMe), 3.44 (3H, s, OMe), 3.64 (3H, s, OMe), 3.78 (3H, s, OMe), 4.02 (1H, d, $J_{4,5}$=5.6 Hz, H-5), 4.32 (1H, d, $J_{12,13}$=5.2 Hz, H-13), 4.89 (1H, dd, $J_{3,4}$=8.6 Hz, H-4), 5.20 (1H, d, $J_{7,8}$=10.0 Hz, H-7), 5.57 and 6.08 (each 1H, d, *J*=3.0 Hz, aromatic protons), 5.64 (1H, br s, NH), 5.89 (1H, d, $J_{2,3}$=11.6 Hz, H-2), 5.79 (1H, dd, H-3), and 7.17—7.38 (15H, m, Tr). Found: C, 70.88; H, 7.97; N, 1.62%. Calcd for $C_{54}H_{75}NO_9Si$: C, 71.25; H, 8.30; N, 1.54%.

Ethyl (2*E*,4*Z*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-7-[(*t*-Butyldimethylsilyl)oxy]-15-[2,5-dimethoxy-3-[(triphenylmethyl)amino]phenyl]-6,11,12,15-tetramethoxy-2,8,10,14-tetramethyl-2,4,8-pentadecatrienoate (48). To a stirred solution of **47** (29.1 mg, 0.0320 mmol) in dry toluene (1.46 ml) at −78°C was added 1.0 M DIBAL in toluene (0.113 ml, 0.113 mmol). After 1 h at −78°C, 1:1 (v/v) methanol–toluene (0.0456 ml) and 1:1 (v/v) water–methanol (0.0300 ml) were added and the mixture was stirred at room temperature for 1 h. The insoluble materials were filtered and the filtrate was washed with toluene. The filtrate and washings were concentrated and the residue was chromatographed on silica gel (3 g) with 2:1 hexane–ethyl acetate to afford the allylic alcohol (25.1 mg, 89%) as a colorless glass [R_f=0.17 (3:1 hexane–ethyl acetate); ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=0.03 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.82 (3H, d, *J*=6.6 Hz, 12-Me), 0.89 (9H, s, *t*-butyl), 0.99 (3H, d, *J*=6.6 Hz, 8-Me), 1.23—1.38 (1H, m, H-11), 1.54 (3H, d, *J*=1.6 Hz, 6-Me), 1.58—1.73 (1H, m, H-11′), 1.89—2.05 (1H, m, H-12), 2.22 (1H, t, *J*=6.0 Hz, OH), 2.38—2.55 (1H, m, H-8), 3.08 (1H, dd, $J_{8,9}$=8.4 Hz and $J_{9,10}$=3.2 Hz, H-9), 3.17—3.25 (1H, m, H-10), 3.22 (3H, s, OMe), 3.27 (3H, s, OMe), 3.29 (3H, s, OMe), 3.32 (3H, s, OMe), 3.43 (3H, s, OMe), 3.77 (3H, s, OMe), 3.91 (1H, dd, $J_{3,4}$=8.6 Hz and $J_{4,5}$=7.0 Hz, H-4), 4.03 (1H, d, H-5), 4.15 (2H, dd, $J_{1,2}$=6.5 Hz, H-1), 4.32 (1H, d, $J_{12,13}$=5.0 Hz, H-13), 5.14 (1H, d, $J_{7,8}$=10.0 Hz, H-7), 5.27 (1H, dd, $J_{2,3}$=11.4 Hz, H-3), 5.56 and 6.08 (each 1H, each d, *J*=3.0 Hz, aromatic protons), 5.63 (1H, br s, NH), 5.83 (1H, dt, H-2), and 7.17—7.38 (15H, m, Tr)]. This (24.9 mg, 0.0282 mmol) was dissolved in dry CH_2Cl_2 (1.25 ml) and to this were added MS 3AP (63.7 mg) and PDC (53.1 mg, 0.141 mmol) at 0°C. After 2 h at 0°C, the reaction mixture was dilute with ether and the resulting suspension was transferred to a column filled with silica gel (1 g). The column was eluted with ether and the eluant was concentrated. The residue was chromatographed on silica gel (2.5 g) with 4:1 hexane–ethyl acetate to afford the allyl aldehyde (23.8 mg, 96%) as a colorless syrup [R_f=0.58 (5:2 hexane–ethyl acetate); ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=0.03 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.80 (3H, d, *J*=6.6 Hz, 12-Me), 0.88 (9H, s, *t*-butyl), 0.99 (3H, d, *J*=6.6 Hz, 8-Me), 1.21—1.35 (1H, m, H-11), 1.53 (3H, d, *J*=1.6 Hz, 6-Me), 1.59—1.73 (1H, m, H-11′), 1.91—2.04 (1H, m, H-12), 2.40—2.54 (1H, m, H-8), 3.08 (1H, dd, $J_{8,9}$=8.0 Hz and $J_{9,10}$=2.6 Hz, H-9), 3.14—3.23 (1H, m, H-10), 3.23 (3H, s, OMe), 3.27 (3H, s, OMe), 3.32 (3H, s, OMe), 3.33 (3H, s, OMe), 3.44 (3H, s, OMe), 3.77 (3H, s, OMe), 4.10 (1H, d, $J_{4,5}$=6.0 Hz, H-5), 4.30 (1H, d, $J_{12,13}$=5.2 Hz, H-13), 4.39 (1H, dd, $J_{3,4}$=8.6 Hz, H-4), 5.22 (1H, d, $J_{7,8}$=10.0 Hz, H-7), 5.56 and 6.08 (each 1H, each d, *J*=3.0 Hz, aromatic protons), 5.63 (1H, br s, NH), 6.05 (1H, dd, $J_{1,2}$=8.0 Hz and $J_{2,3}$=11.8 Hz, H-2), 6.29 (1H, dd, H-3), 7.17—7.38 (15H, m, Tr), and 10.11 (1H, d, H-1). Contaminated (*E*)-isomer: δ=6.29 (1H, dd, $J_{1,2}$=8.4 Hz and $J_{2,3}$=16.0 Hz, H-2), 6.66 (1H, dd, $J_{3,4}$=5.2 Hz, H-3), and 9.53 (1H, d, H-1)]. This (15.8 mg, 0.0179 mmol) was dissolved in dry CH_2Cl_2 (0.474 ml) and to this was added 1-(ethoxycarbonyl)ethylidenetriphenylphosphorane **9** (17.8 mg, 0.0538 mmol). The mixture was heated at 40°C for 16 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel (2 g) with 4:1 hexane–ethyl acetate to afford **48** (15.6 mg, 90%) as a colorless glass: R_f=0.55 (3:1 hexane–ethyl acetate); $[\alpha]_D^{25}$ +41.7° (*c* 0.46); IR ($CHCl_3$) 1700, 1599, 1503, 1361, and 1253 cm^{-1}; ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=0.03 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.78 (3H, d, *J*=6.6 Hz, 14-Me), 0.87 (9H, s, *t*-butyl), 0.98 (3H, d, *J*=6.6 Hz, 10-Me), 1.21—1.34 1H, m, H-13), 1.30 (3H, t, *J*=7.0 Hz, CH_2*Me*), 1.51 (3H, s, 8-Me), 1.59—1.72 (1H, m, H-13′), 1.84 (3H, s, 2-Me), 1.87—2.03 (1H, m, H-14), 2.34—2.51 (1H, m, H-10), 3.07 (1H, dd, $J_{10,11}$=8.0 Hz and $J_{11,12}$=2.2 Hz, H-11), 3.13—3.24 (1H, m, H-12), 3.22 (3H, s, OMe), 3.26 (3H, s, OMe), 3.28 (3H, s, OMe), 3.32 (3H, s, OMe), 3.44 (3H, s, OMe), 3.78 (3H, s, OMe), 4.00 (1H, d, $J_{6,7}$=6.4 Hz, H-7), 4.11 (1H, dd, $J_{5,6}$=10.0 Hz, H-6), 4.21 (2H, q, *J*=7.0 Hz, CH_2Me), 4.32 (1H, d, $J_{14,15}$=4.6 Hz, H-15), 5.16 (1H, d, $J_{9,10}$=10.0 Hz, H-9), 5.48 (1H, dd, $J_{4,5}$=10.5 Hz, H-5), 5.57 and 6.08 (each 1H, each d, *J*=3.0 Hz, aromatic protons), 5.63 (1H, br s, NH), 6.43 (1H, dd, $J_{3,4}$=11.0 Hz, H-4), 7.16—7.38 (15H, m, Tr), and 7.51 (1H, d, H-3). Found: C, 71.96; H, 8.47; N, 1.61%. Calcd for $C_{58}H_{81}O_9Si$: C, 72.24; H, 8.47; N, 1.45%.

Macrolactam 49. A solution of **48** (17.3 mg, 0.0179 mmol) in 0.02% HCl–MeOH (0.865 ml) was stirred at room temperature for 0.5 h. The reaction mixture was neutralized with triethylamine and concentrated. The residue was dissolved in 2:2:1 (v/v/v) THF–MeOH–water (0.52 ml) and to this was added LiOH (4.3 mg, 0.18 mmol). After 24 h at room temperature, 10% aqueous NaH_2PO_4 was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residual amino carboxylic acid [R_f=0.21 (5:1 benzene–acetone); ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=0.02 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.80 (3H, d, *J*=6.6 Hz, 14-Me), 0.87 (9H, s, *t*-butyl), 0.98 (3H, d, *J*=6.6 Hz, 10-Me), 1.23—1.37 (1H, m, H-13), 1.52 (3H, s, 8-Me), 1.62—1.75 (1H, m, H-13′), 1.89 (3H, s, 2-Me), 1.89—2.02 (1H, m, H-14), 2.35—2.51 (1H, m, H-10), 3.06 (1H, dd, $J_{10,11}$=8.4 Hz and $J_{11,12}$=2.2 Hz, H-11), 3.18—3.24 (1H, m, H-12), 3.24 (3H, s, OMe), 3.26 (3H, s, OMe), 3.30 (3H, s, OMe), 3.44 (3H, s, OMe), 3.71 (3H, s, OMe), 3.73 (3H, s, OMe), 3.98 (1H, d, $J_{6,7}$=6.4 Hz, H-7), 4.09 (1H, dd, $J_{5,6}$=10.5 Hz, H-6), 4.35 (1H, d, $J_{14,15}$=4.6 Hz, H-15), 5.16 (1H, d, $J_{9,10}$=10.0 Hz, H-9), 5.56 (1H, dd, $J_{4,5}$=10.5 Hz, H-5), 6.23

and 6.29 (each 1H, each d, J=3.0 Hz, aromatic protons), 6.45 (1H, dd, $J_{3,4}$=12.0 Hz, H-4), and 7.62 (1H, d, H-3)] was dissolved in dry toluene (12.4 ml) and to this were added *N*-ethyldiisopropylamine (0.0312 ml, 0.179 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic choloride (13.7 ml, 0.0538 mmol). The reaction mixture was heated at 85°C for 15 h. After cooling to ambient temperature, 10% aqueous NaH_2PO_4 (1.5 ml) was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (2 g) with 6 : 1 benzene–acetone to afford **49** (9.7 mg, 80%) as a colorless glass: R_f=0.39 (5 : 1 benzene–acetone); $[\alpha]_D^{25}$ +23.1° (*c* 0.13); IR ($CHCl_3$) 3381, 1654, 1594, 1523, and 1364 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ=−0.05 (3H, s, SiMe), −0.02 (3H, s, SiMe), 0.45—0.55 (1H, m, H-13), 0.61 (3H, d, J=6.8 Hz, 14-Me), 0.81 (9H, s, *t*-butyl), 0.88 (3H, d, J=6.2 Hz, 10-Me), 0.93 (3H, s, 8-Me), 1.37—1.52 (1H, m, H-13), 1.85 (3H, s, 2-Me), 1.92—2.20 (2H, m, H-10 and 14), 2.77—2.86 (1H, m, H-12), 3.01 (3H, s, OMe), 3.11 (1H, dd, J=9.0 Hz and 1.8 Hz, H-11), 3.16 (3H, s, OMe), 3.21 (3H, s, OMe), 3.39 (3H, s, OMe), 3.43 (3H, s, OMe), 3.47 (1H, d, $J_{6,7}$=4.6 Hz, H-7), 3.64 (1H, dd, $J_{5,6}$=10.5 Hz, H-6), 3.68 (3H, s, OMe), 4.33 (1H, d, $J_{14,15}$=5.2 Hz, H-15), 4.90 (1H, d, $J_{9,10}$=10.5 Hz, H-9), 4.94 (1H, dd, $J_{4,5}$=10.5 Hz, H-5), 5.96 (1H, d, $J_{3,4}$=11.5 Hz, H-3), 6.14 (1H, dd, H-4), 6.44 (1H, d, J=3.2 Hz, H-19), 6.63 (1H, d, J=3.2 Hz, H-17), and 9.35 (1H, s, NH). Found: m/z 675.4142. Calcd for $C_{37}H_{61}NO_8Si$: M, 675.4162.

Macrocyclic Carbamate (50). To a stirred solution of **49** (5.1 mg, 0.0075 mmol) in dry THF (0.153 ml) at room temperature was added 1 M TBAF in THF (0.0748 ml, 0.0748 mmol). After 20 h at room temperature, another TBAF (0.0748 mol, 0.0748 mmol) was added and the mixture was further stirred at room temperature for 24 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1 g) with 2 : 1 benzene–acetone to afford the C7-alcohol (4.2 mg, 100%) as a colorless glass [R_f=0.22 (4 : 1 benzene–acetone); ^1H NMR (270 MHz, DMSO-d_6) δ=0.48—0.59 (1H, m, H-13), 0.61 (3H, d, J=6.8 Hz, 14-Me), 0.90 (3H, d, J=6.2 Hz, 10-Me), 0.94 (3H, s, 8-Me), 1.33—1.49 (1H, m, H-13), 1.86 (3H, s, 2-Me), 1.97—2.19 (2H, m, H-10 and 14), 2.79—2.89 (1H, m, H-12), 3.02 (3H, s, OMe), 3.08 (1H, d, J=9.0 Hz, H-11), 3.16 (3H, s, OMe), 3.21 (3H, s, OMe), 3.39 (3H, s, OMe), 3.43 (3H, s, OMe), 3.52 (1H, dd, $J_{5,6}$=10.0 Hz and $J_{6,7}$=3.6 Hz, H-6), 3.68 (3H, s, OMe), 4.32 (1H, d, $J_{14,15}$=5.2 Hz, H-15), 4.50 (1H, d, H-7), 4.91 (1H, d, $J_{9,10}$=10.0 Hz, H-9), 4.95 (1H, dd, $J_{4,5}$=11.5 Hz, H-5), 5.98 (1H, d, $J_{3,4}$=11.5 Hz, H-3), 6.17 (1H, dd, H-4), 6.44 (1H, d, J=2.6 Hz, H-19), 6.60 (1H, d, J=2.6 Hz, H-17), and 9.34 (1H, br s, NH)]. To a stirred solution of the above alcohol (4.0 mg, 0.0071 mmol) in dry CH_2Cl_2 (0.32 ml) at 0°C were added 90% sodium cyanate (12.3 mg, 0.171 mmol) and trifluroacetic acid (0.0130 ml, 0.171 mmol). After 17 h at room temperature, water was added and the mixture was extracted with ethyl acetate. The extracts were washed with 5% aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1 g) with 2 : 1 chloroform–acetone to afford macrocyclic carbamate **50** (3.9 mg, 91%) as a colorless glass: R_f=0.20 (2 : 1 chloroform–acetone); $[\alpha]_D^{25}$ +32.8° (*c* 0.39); IR ($CHCl_3$) 3545, 3428, 3381, 1731, 1668, 1586, 1524, 1369, and 1317 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ=0.50—0.61 (1H, m, H-13), 0.61 (3H, d, J=6.8 Hz, 14-Me), 0.87 (3H, d, J=6.2 Hz, 10-Me), 0.96 (3H, br s, 8-Me), 1.37—1.52 (1H, m, H-13), 1.87 (3H, s, 2-Me), 1.97—2.20 (2H, m, H-10 and 14), 2.79—2.91 (1H, m, H-12), 2.99 (3H, s, OMe), 3.12 (1H, d, J=9.0 Hz, H-11), 3.17 (3H, s, OMe), 3.23 (3H, s, OMe), 3.39 (3H, s, OMe), 3.45 (3H, s, OMe), 3.69 (3H, s, OMe), 3.74—3.89 (1H, m, H-6), 4.35 (1H, d, J=5.2 Hz, H-15), 4.77 (1H, d, J=9.0 Hz, H-7), 4.93—5.06 (1H, m, H-5), 5.06 (1H, d, J=10.4 Hz, H-9), 5.91—6.08 (1H, m, H-3), 6.24 (1H, t, J=11.0 Hz, H-4), 6.28 (2H, br s, NH_2), 6.46 (1H, d, J=2.8 Hz, aromatic proton), 6.63 (1H, br s, aromatic proton), and 9.34 (1H, br s, NH).

Herbimycin A (1). To a stirred solution of **50** (3.4 mg, 0.0056 mmol) in 1,4-dioxane (0.47 ml) at room temperature were added AgO (2.8 mg, 0.0226 mmol) and 1 M aqueous HNO_3 (0.0224 ml, 0.0224 mmol). After 2.5 h at room temperature, 1 : 1 (v/v) saturated aqueous $NaHCO_3$–NaCl was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1 g) with 3 : 1 chloroform–acetone to afford herbimycin A (**1**) (3.2 mg, 100%) as yellow crystals: R_f=0.54 (2 : 1 chloroform–acetone); mp 231—232°C [mp of natural herbimycin A: 231—232°C, lit,[1a] 230°C]; mixed mp 231—232°C; $[\alpha]_D^{25}$ +122° (*c* 0.20) [$[\alpha]_D^{25}$ of natural herbimycin A: +126° (*c* 0.30), lit,[1a] $[\alpha]_D^{20}$ +137° (*c* 1.0)]; UV (MeOH) λ_{max} nm (ε) 271 (19300) and 396 (2080) [λ_{max} nm (ε) of natural herbimycin A: 271 (20700) and 397 (2560), lit,[1a] 270 (20090) and 392.5 (1650)]; IR ($CHCl_3$) 3545, 3430, 3367, 1734, 1696, 1660 (sh), 1649, 1611, 1100, and 1077 cm^{-1} [IR ($CHCl_3$) of natural herbimycin A: 3545, 3430, 3367, 1735, 1696, 1660 (sh), 1648, 1611, 1099, and 1077 cm^{-1}, lit,[1a] 3530, 3410, 3350, 1730, 1690, 1655, 1645, 1600, 1095, and 1070 cm^{-1}]; ^1H NMR (400 MHz) δ=0.83 (3H, d, J=6.6 Hz, 14-Me), 1.10 (3H, d, J=6.6 Hz, 10-Me), 1.65 (3H, s, 8-Me), 1.70—1.82 (1H, m, H-13), 2.02 (3H, s, 2-Me), 2.58—2.72 (1H, m, H-10), 3.32 (3H, s, OMe), 3.35 (3H, s, OMe), 3.54 (3H, s, OMe), 3.44—3.54 (2H, m, H-11 and 12), 4.47—4.54 (2H, m, H-6 and 15), 4.43 (2H, br s, NH_2), 5.43—5.56 (1H, m, H-9), 5.60—5.72 (1H, m, H-7), 5.87 (1H, dd, $J_{4,5}$=11.2 Hz and $J_{5,6}$=6.8 Hz, H-5), 6.51 (1H, dd, $J_{3,4}$=11.2 Hz, H-4), 6.63 (1H, t, J=1.3 Hz, H-17), 6.97 (1H, d, H-3), 7.35 (1H, d, J=2.6 Hz, H-19), and 8.81 (1H, br s, NH).

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