Asymmetric Synthesis of the Decalin Part of Azadirachtin

by

Naoki Kanoh

Dissertation

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Abbreviations

Ac	acetyl
BHT	2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene)
BINAL-H	2,2'-dihydroxy-1,1'-binaphtylaluminium hydride - lithium ethoxide complex
Bn	benzyl
b.p.	boiling point
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron impact
FAB	fast atom bombardment
HPLC	high performance liquid chromatography
HR	high resolution
IBX	*o*-iodobenzoic acid
IMDA	intramolecular Diels-Alder
IR	infrared spectrum
LDA	lithium diisopropylamide
LR	low resolution
LUMO	lowest unoccupied molecular orbital
m.p.	melting point
MPM	*p*-methoxybenzyl
MS	molecular sieves
MS	mass spectrum
Ms	methanesulfonyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
N-PSP	*N*-(phenylseleno)phthalimide
p-BrBz	*p*-bromobenzoyl

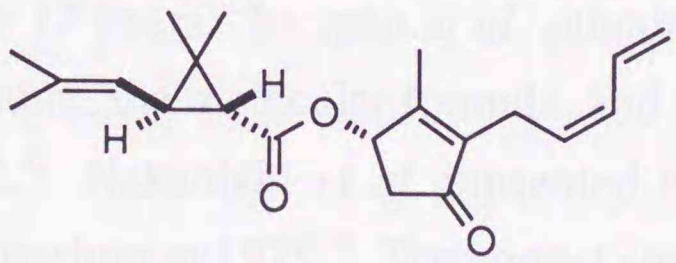
PDC	pyridinium dichromate
*p*MP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
PTS	*p*-toluenesulfonic acid
RI	reflactive index
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
t_R	retention time
Triton® B	benzyltrimethylammonium hydroxide, 40 wt.% solution in MeOH

CONTENTS

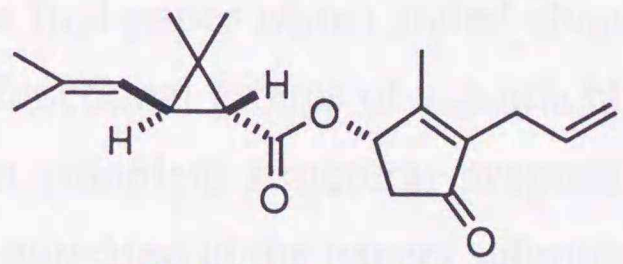
Introduction[3)]

The worldwide food problem is getting serious as population continues to increase in the world. To relieve this problem, it becomes important to furnish crops from diminishing farmland as much as possible. In 1988, more than half of the worldwide expenditure on agrochemicals, some $4000 million, was devoted to insecticides in an effort to resist the continuous attack of over half a million different herbivorous insect species. While there are many kinds of chemically synthesized insecticides such as organochlorines, organophosphates, and dinitrophenols, nowadays, their strong toxicities and broad spectra frequently cause destruction of other beneficial species including the pest's natural enemies, and pollution of the environment.

Environmentally acceptable methods to protect crops have been required. It has been well-known that plants have their inherent protection systems such as production of chemical substances against insect attack. This class of second metabolites provides the science with a rich pool of biologically active compounds. Pyrethrin I[1)] is a representative molecule in these compounds, and it's derivatives and structurally related synthetic compounds, which are known as pyrethroids,[2)] have well been investigated and provided a great success as to hold one third of world-use insecticides (Figure 1).



Pyrethrin I (natural)



Allethrin (synthetic)

Fenvalerate (synthetic)

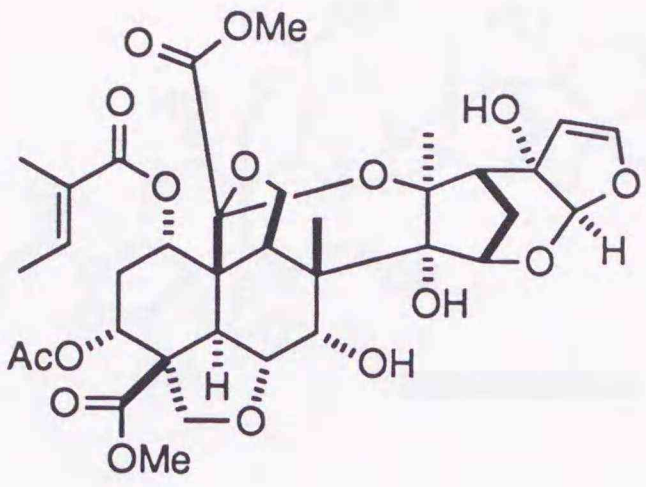
Figure 1. Natural pyrethrin and synthetic pyrethroids.

Related to the self-defence of plants, the Indian neem tree, *Azadirachta Indica* A. Juss, had been well known for its activity against insects. The properties were featured in ancient Sanskrit writings. The leaves are used to protect grains and clothes from insects and the seed oil used as an insecticide and medicine for the treatment of leprosy, skin diseases, and malaria. Particularly, its insect antifeedant activity has drawn the attention and has been investigated thus far.

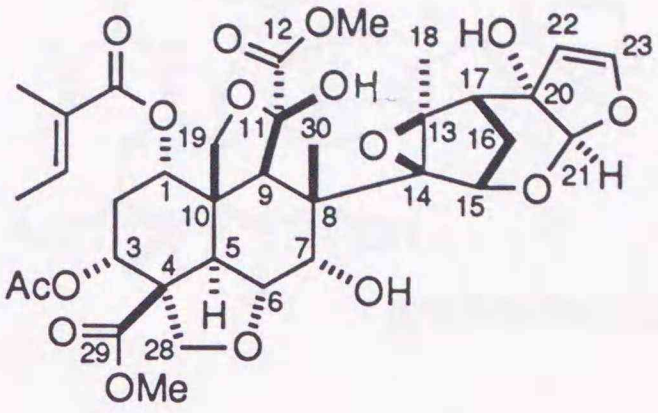
Until 1993, many commercial products were registered and available including Margosan-O® (W. R. Grace & Co., Cambridge, MA, U. S. A.); Azatin (Agridyne Technologies, Salt Lake City, UT, U. S. A.); Bioneem and Neemesis (Ringer Corp., Minneapolis, MN, U. S. A.); Safer's ENI (Safer Ltd., Victoria, B.C., Canada, incorporated into Ringer corp. as of 1993); Wellgro and RD-Repelin (ITC Ltd., Andhra Pradesh, India); Neemguard (Gharda Chemicals, Bombay, India); Neemark (West Coast Herbochem, Bombay, India); and Neemazal (Trifolio M GmBH, D-6335 Lahnau 2, Germany).

Although many different formulations of the neem have been used, the main and common component is azadirachtin[3](**1**) (azadirachtin A) which belongs to C-*seco*-limonoid group of triterpenoids. It was isolated from the seeds of the neem tree by Butterworth and Morgan in 1968 as a substance which inhibits feeding in the desert locust (*Schistocerca gregaria*).[4] The structure determination of the compound had cost considerable endeavor by many different groups for some 17 years. Morgan *et al.* submitted the first paper which stated about the structure, the molecular formula, and some functional groups of azadirachtin in 1972.[5] Nakanishi *et al.* presented the first complete structural proposal for azadirachtin in 1975.[6] The correct structure appeared in the papers submitted in the middle 80's by Ley *et al.*[7] and Kraus *et al.*,[8] and the full details were finally described by them and Nakanishi's group in 1987.[9] (Figure 2)

Determination of the absolute configuration of azadirachtin was accomplished by Ley *et al.* in 1992 by using the advanced Mosher method and X-ray crystallographic analysis of the MTPA derivatives of the degradation products.[10]



Nakanishi's azadirachtin



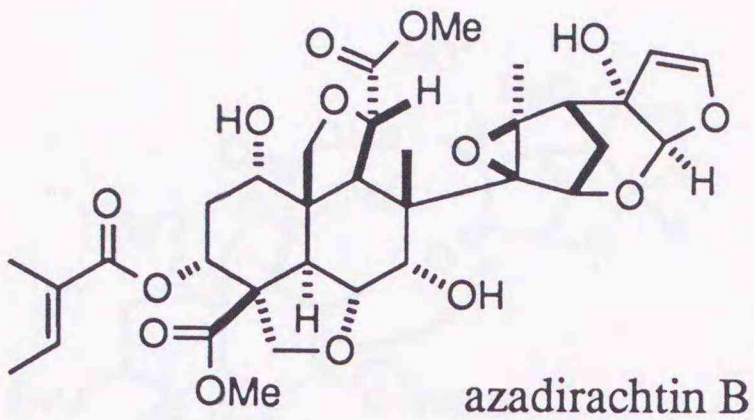
Established structure of azadirachtin (**1**)

Figure 2

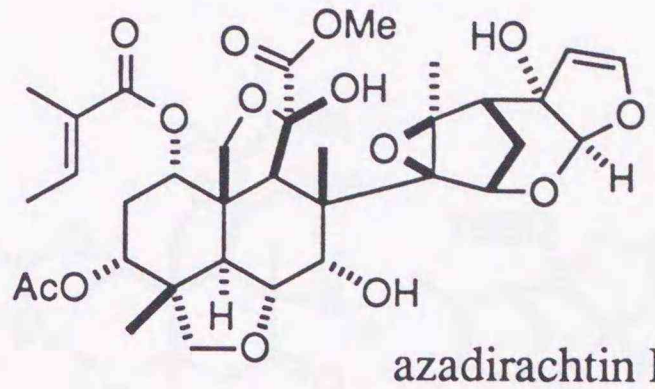
Several compounds related closely to azadirachtin were also isolated from the neem tree, although contents of these compounds were not as much as that of azadirachtin and the antifeedant activities of these compounds are rather low. 3-Tigloylazadirachtol (azadirachtin B) is presented at a concentration up to 20% of that of azadirachtin, and other azadirachtins (C-I) occur at much lower concentrations.[3a] (Figure 3)

Numerous research of azadirachtin have revealed its strong antifeedant, insect growth regulatory and reproductive effects for some 30 years although very little has been known of its biochemical mode of action at the cellular level.[3b] One approach to understand these mechanisms from the viewpoint of organic chemists is to investigate chemical properties of azadirachtin. In addition to this reason, the complexity of this molecule including a plethora of oxygen functionalities has paid attention of the world's synthetic chemists.

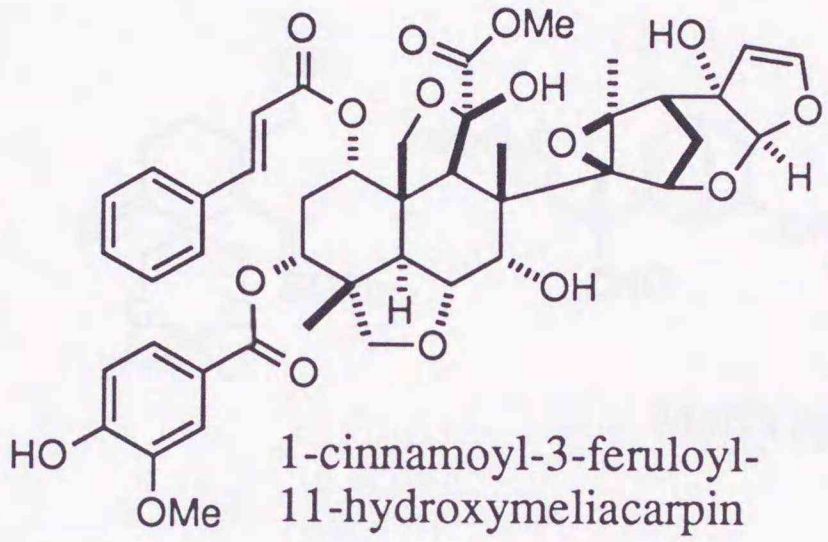
Several synthetic approaches toward the total synthesis of this molecule have been reported (Figure 4). All groups except for Mori's group have selected the convergent strategies in which the target molecule was disconnected at C_8-C_{14} (azadirachtin numbering) bond retrosynthetically. Shibasaki's group mentioned an aldol strategy to construct C_8-C_{14} bond.[11] Mori and Watanabe[12] have a conceptually different approach towards azadirachtin which involves the formation of the requisite bond at a rather early stage. Recently, Ley *et al.* developed a radical approach to bring together to form the crucial C_8-C_{14} bond.[13]



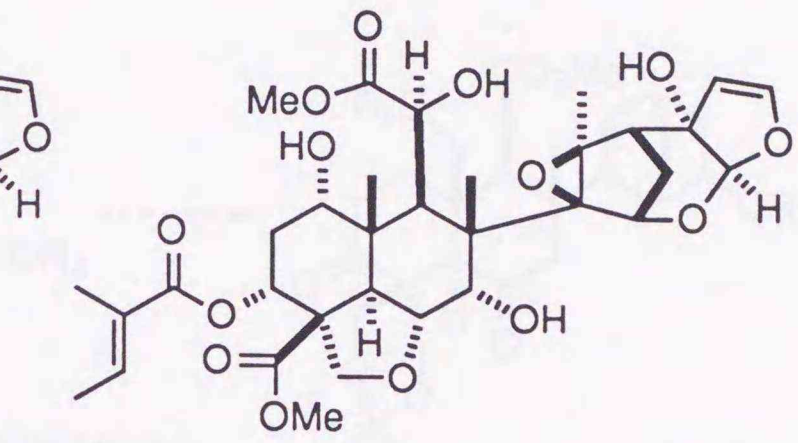
azadirachtin B



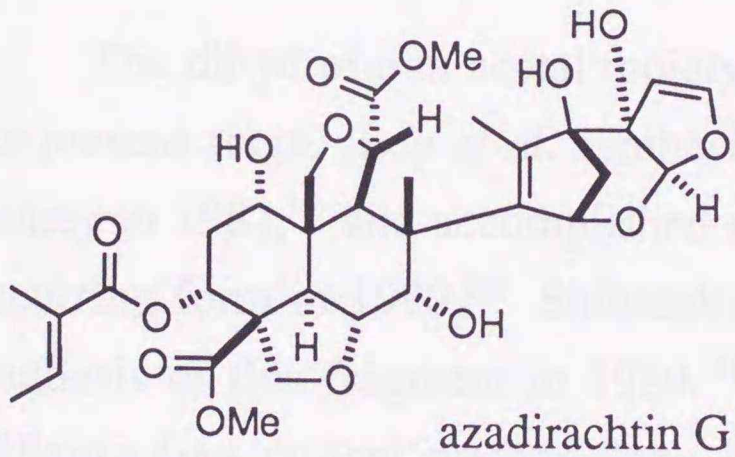
azadirachtin D



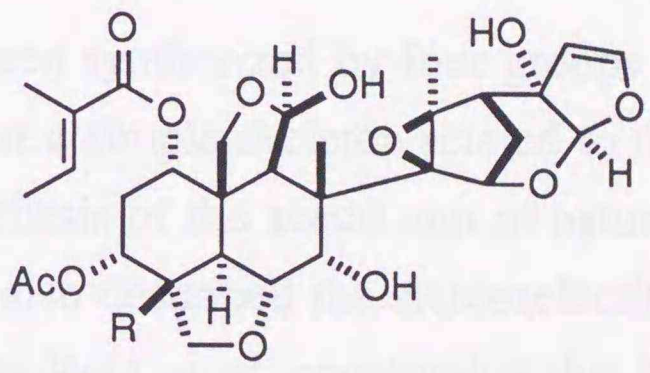
1-cinnamoyl-3-feruloyl-
11-hydroxymeliacarpin



azadirachtin F

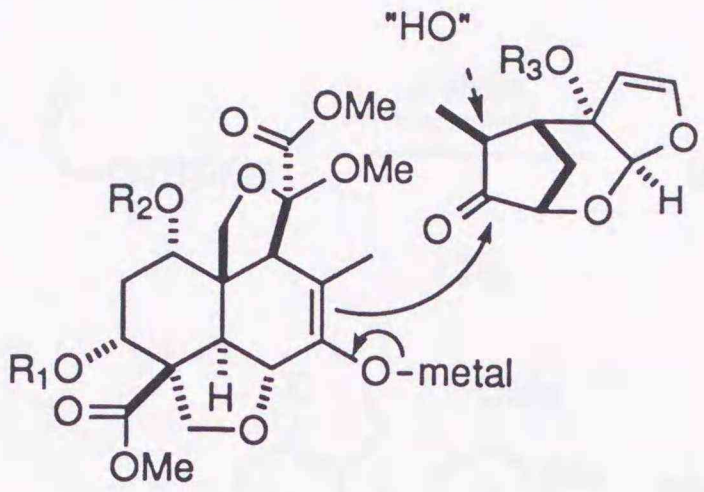


azadirachtin G

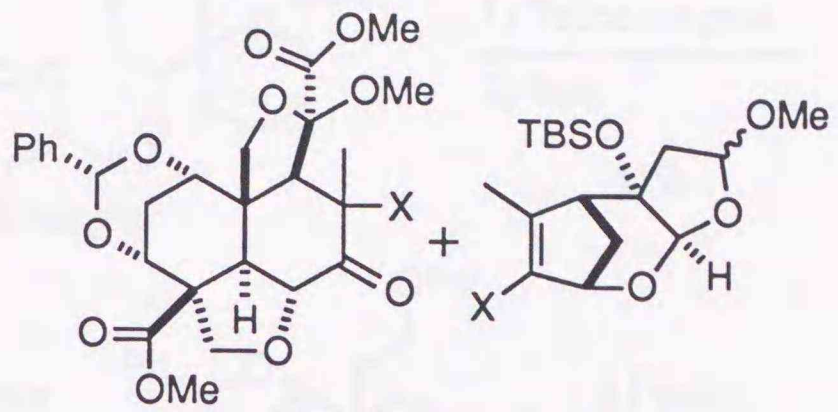


azadirachtin H; R = CH_3
azadirachtin I; R = CO_2Me

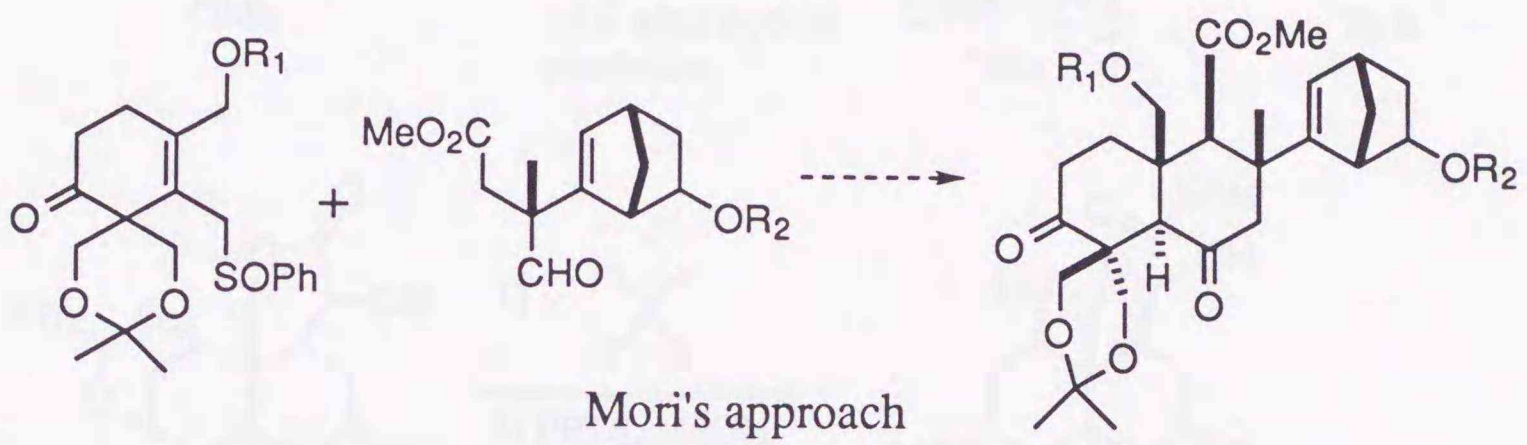
Figure 3



Shibasaki's approach



Ley's approach

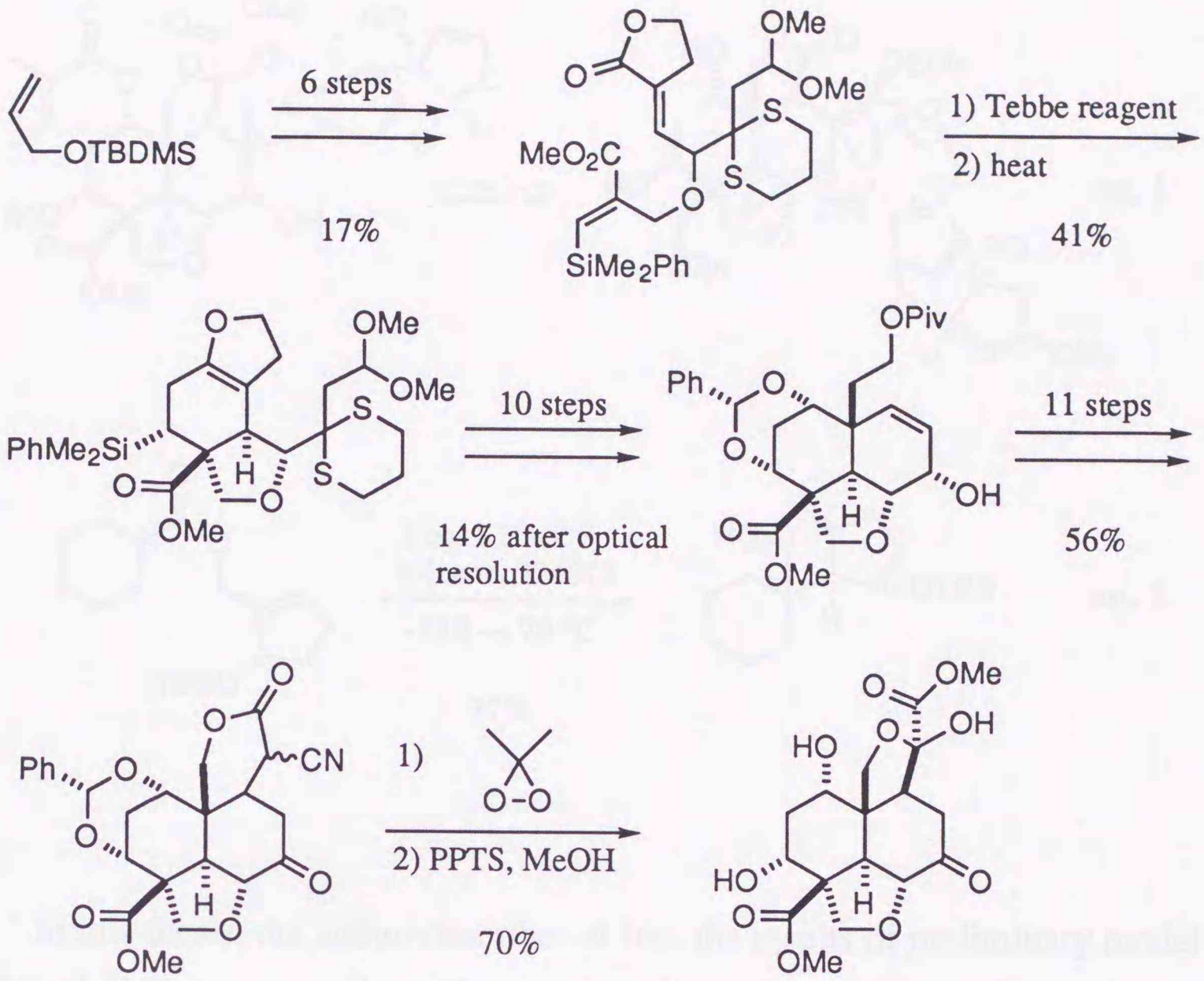


Mori's approach

Figure 4

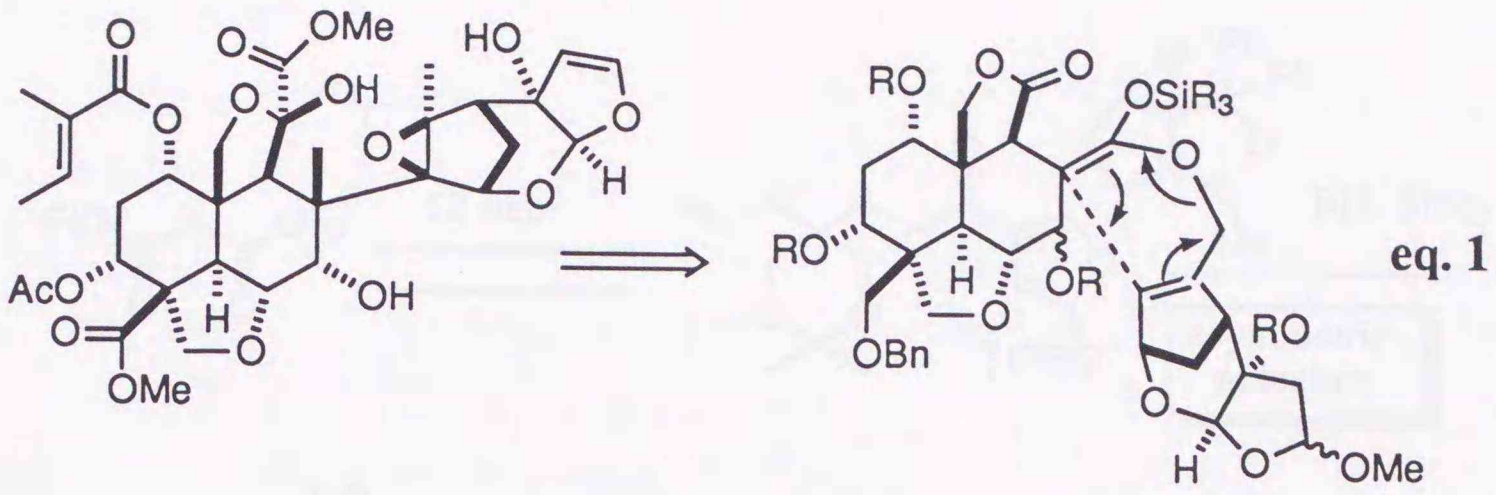
The dihydrofuran acetal moiety had been synthesized by four groups at the present stage. Ley *et al.* synthesized first a simple skeleton related to the moiety in 1987,[14] and accomplished the synthesis of the acetal unit in natural occurring form in 1990.[15] Shibasaki *et al.* also described the stereoselective synthesis of this fragment in 1989.[11] Fraser-Reid *et al.* constructed this by utilizing free radical methodology in 1994.[16] Recently, Mori *et al.* also accomplished its enantioselective synthesis.[17]

As compared with these acetal unit synthesis, only one group reported the synthesis of decalin fragment of azadirachtin. Ley *et al.* have accomplished the first synthesis of the decalin moiety of this molecule (Scheme 1).[18] Their route features two intramolecular reactions; IMDA reaction using a phenyldimethylsilyl group as a stereocontrol substituent,[19] and an oxidative rearrangement to construct the tetrahydrofuran hemiacetal moiety.

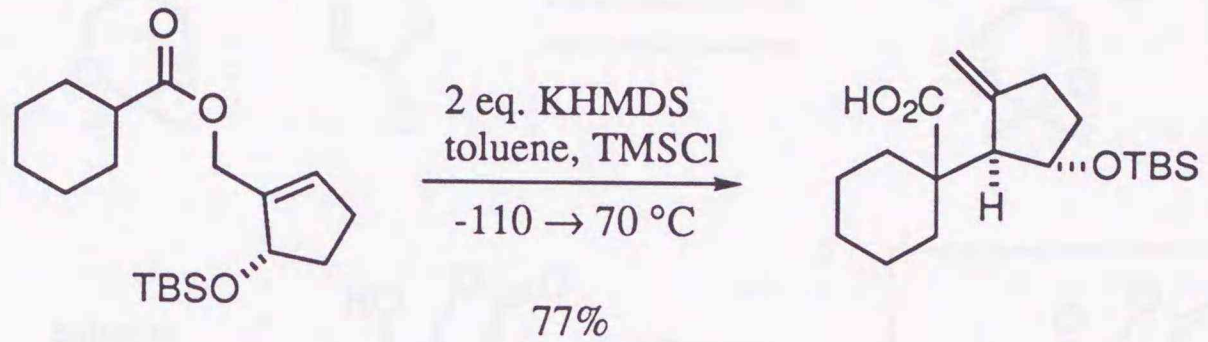


Scheme 1. The synthetic route of the decalin fragment by Ley *et al.*[18)]

Although the syntheses of both fragments were accomplished, further coupling study and the total synthesis have not been reported thus far. Under these situations, our group has started a project for the total synthesis of azadirachtin individually. IMDA reaction and Ireland's ester enolate Claisen rearrangement (eq. 1) are key steps in our synthetic plan. In preliminary model experiments, the Claisen process has been succeeded in a good yield (eq. 2).[20)]

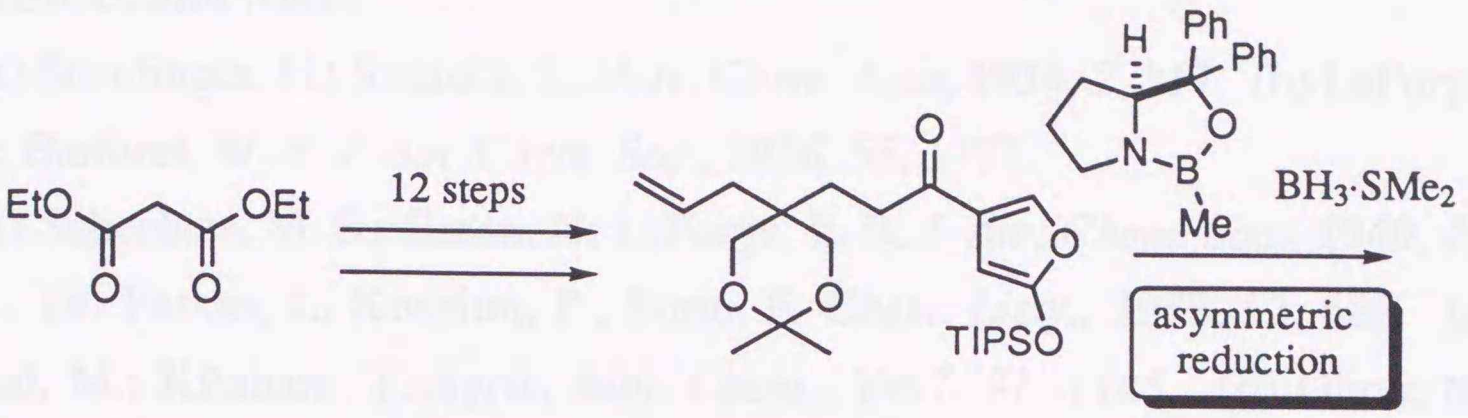


eq. 1



eq. 2

In this thesis, the author describes at first the results of preliminary model studies of IMDA process[21] in Chapter 1 and an asymmetric synthesis of the IMDA adduct in Chapter 2. In Chapter 3, the synthesis of the decalin part of azadirachtin is described. The author also mentions the strategy to construct the tetrahydrofuran hemiacetal part in the decalin moiety in Chapter 4. In Scheme 2, the abstract of the author's established synthetic route and strategy of the decalin part are revealed.



Scheme 2-1. Established synthetic route of the decalin part.

Scheme 2-2. Model study on construction of the acetal part.

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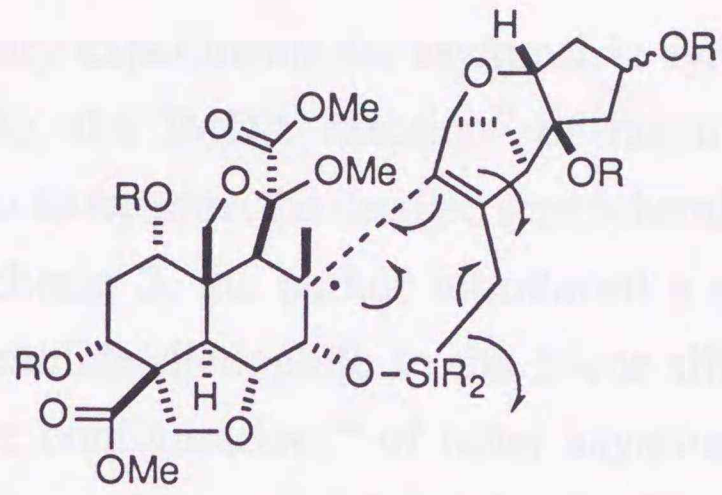
Watanabe, H. '7th International Congress of Pesticide Chemistry' Hansburg, Book of Abstract, 1990, vol. 1, p 251.

(13) Their approach is depicted as below; Private communication (1995).



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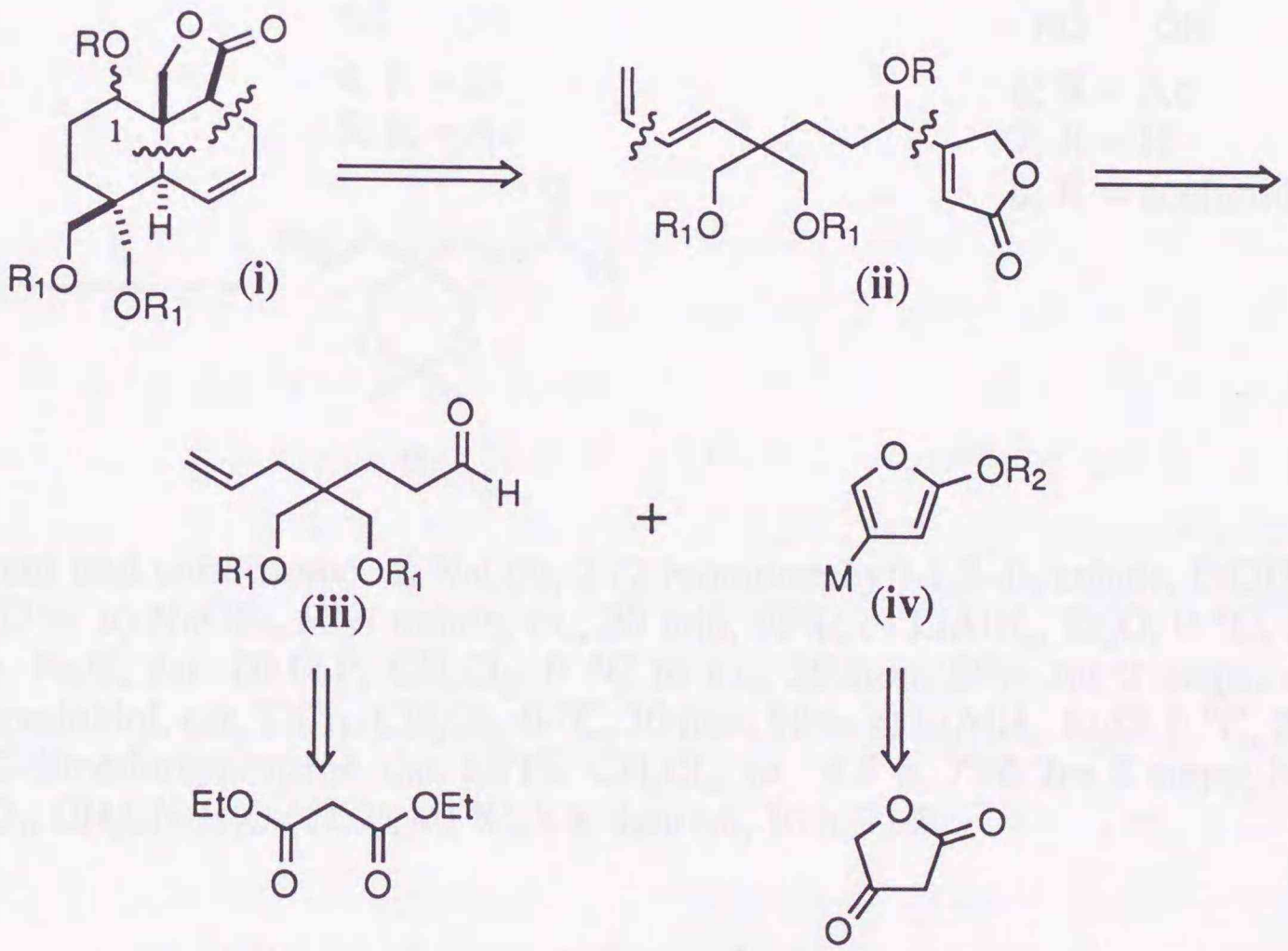
Chapter 1

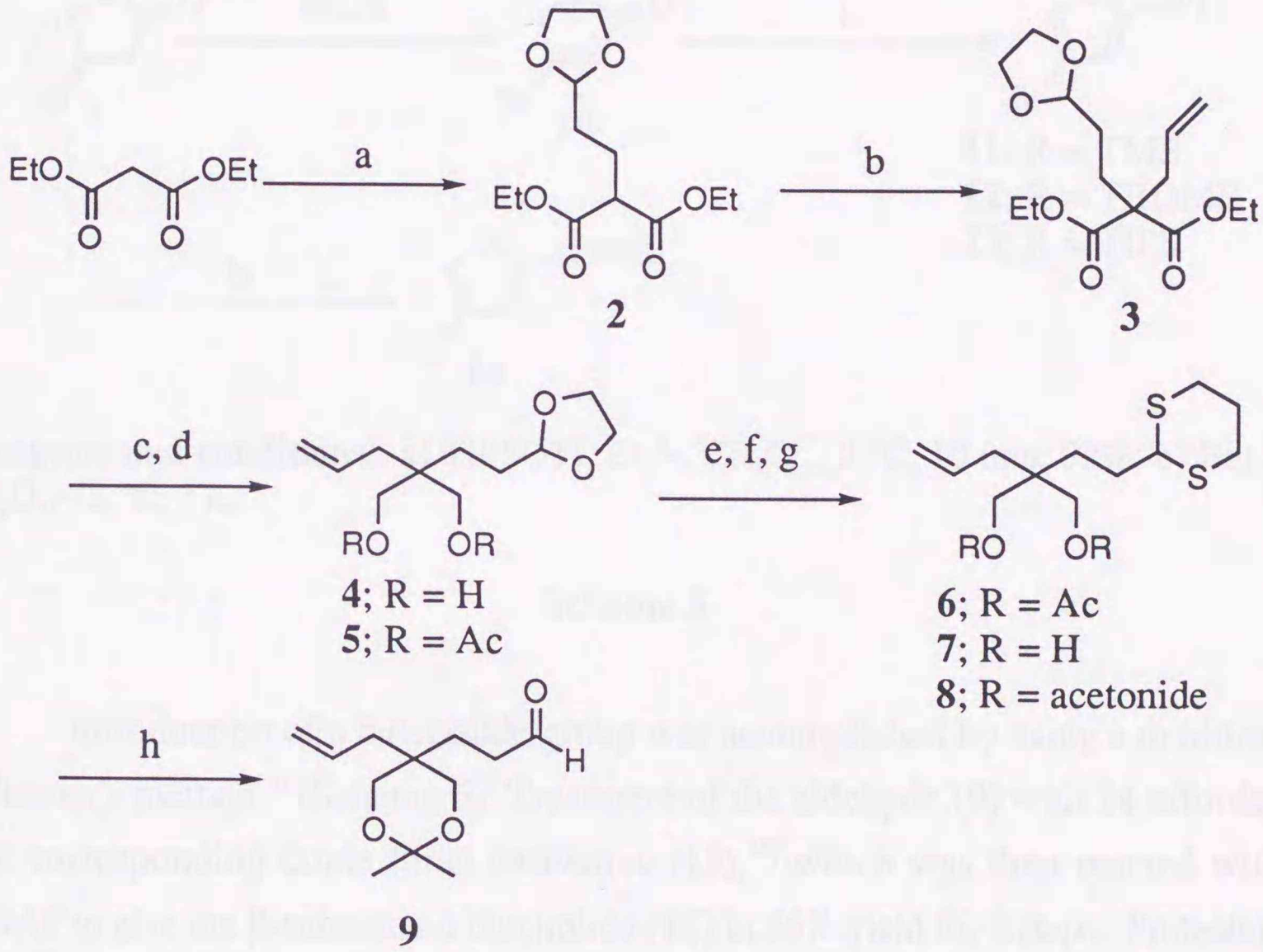
Construction of the Tricyclic *trans*-Decalin Framework of Azadirachtin *via* Intramolecular Diels-Alder Reaction.[1)]

As preliminary experiments for asymmetric synthesis of the decalin part of azadirachtin (**1**), the IMDA reaction[2)] of racemic trienes was initially investigated in order to examine the detailed stereochemical aspects of the adducts. As depicted in Scheme 3, the author introduced a secondary alkoxyl group adjacent to a butenolide dienophile in the triene (**ii**) expecting the effect to control the relative configurations[3)] of other asymmetric carbons in adducts. Our hopeful product would be *trans*-fused decalin (**i**), although the configuration of the alkoxyl group at C_1 (azadirachtin numbering) in one of the adducts might be contrary to the case of **1**. The author intended to prepare the racemic triene (**ii**) from the aldehyde (**iii**) and the 4-metallofuran (**iv**), which could be obtained from commercially available diethyl malonate and tetronic acid, respectively.



Scheme 3. Our synthetic plan for the decalin (**i**).

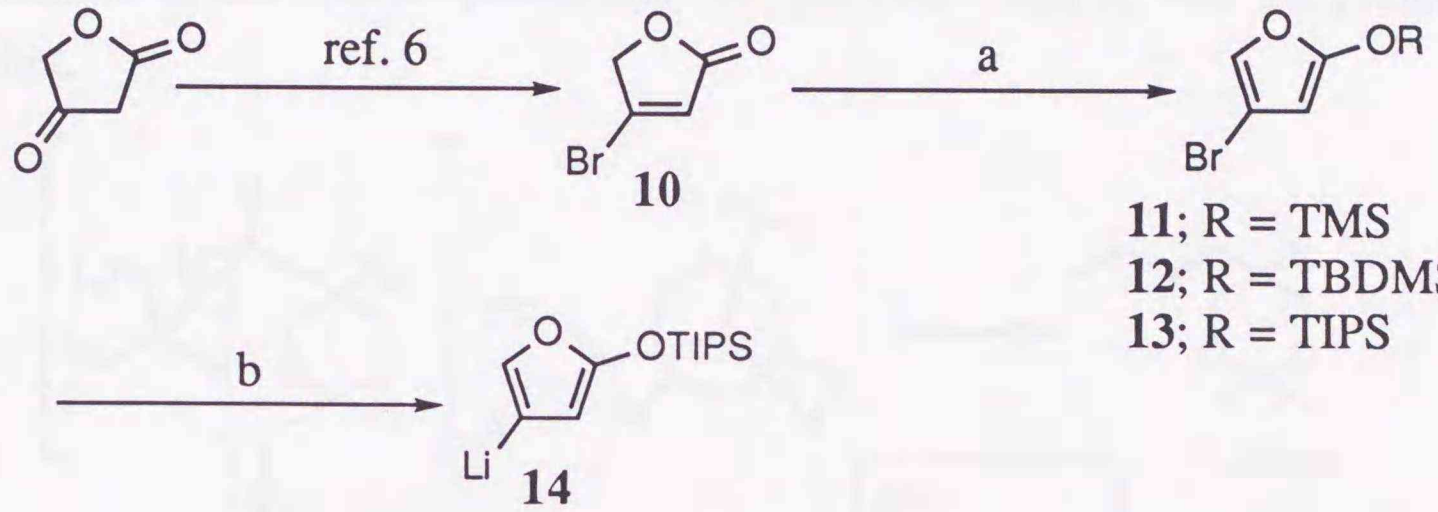
Preparation of the aldehyde (**9**) commenced with twice alkylation of ethyl malonate to afford the diester (**3**) in 69% for 2 steps (Scheme 4). This compound was reduced with $LiAlH_4$ to afford the crude diol (**4**), which subsequently gave the diacetate (**5**) in 89% for 2 steps. The acetal exchange of the compound afforded the dithiane derivative (**6**) in 98%, followed by removal of the acetyl group[4] and protection of the diol as its acetonide to yield the dithiane derivative (**8**) in 73% for 2 steps. Cleavage of the dithiane ring using $MeI/CaCO_3$[5] led to the aldehyde (**9**) in 71% yield.



Reagent and conditions: a) NaOEt, 2-(2-bromomethyl)-1,3-dioxolane, EtOH, 5 °C, 1 h, 73%; b) NaOEt, allyl iodide, r.t., 20 min, 95%; c) $LiAlH_4$, Et_2O, 0 °C, 5 h; d) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C to r.t., 35 min, 89% for 2 steps; e) 1,3-propanedithiol, cat. $TiCl_4$, CH_2Cl_2, 0 °C, 30 min, 98%; f) $LiAlH_4$, Et_2O, 0 °C, 20 min; g) 2,2-dimethoxypropane, cat. PPTS, CH_2Cl_2, r.t., 4.5 h, 73% for 2 steps; h) MeI, $CaCO_3$, CH_3CN-H_2O (11:2), 40 °C, 8 h, then r.t., 10 h, 71%.

Scheme 4

The 4-lithiofuran derivative (**14**) was prepared as described in Scheme 5. Tetronic acid was converted to 4-bromo-2,5-dihydro-2-furanone (**10**) by the method developed by Jas.[6] 4-bromo-2-[(trimethylsilyl) oxy]furan (**11**) and its TBS and TIPS derivatives (**12**[6] and **13**) were then synthesized from **10** in good yields. While these compounds could be converted to their lithio derivatives, **13** was selected for the large scale synthesis because it is the most stable for storage.[7] This compound was treated with butyllithium[8] to give **14** prior to use.



Reagents and conditions: a) TIPSOTf, Et_3N, CH_2Cl_2, 0 °C, 10 min, 92%; b) BuLi, Et_2O, -78 °C, 1 h.

Scheme 5

Introduction of a butenolide group was accomplished by using a modified Wiesner's method.[9] (Scheme 6) Treatment of the aldehyde (**9**) with **14** afforded the corresponding crude furan derivative (**15**),[10] which was then reacted with TBAF to give the β-substituted butenolide (**16**) in 56% yield for 2 steps. Protection of the secondary alcohol as its TBS ether (**17**) followed by dihydroxylation with OsO_4 and cleavage of the resulting diol afforded the aldehyde (**18**) in 73% yield for 3 steps. Coupling of **18** with 1 eq. of vinylmagnesium bromide provided a 1:1 diastereomeric mixture of the allylic alcohols (**19**) along with the recovered starting material.[11] Unfortunately, **18** was not vanished even though Grignard reagent was further added, and **18** and **19** were hardly separable even by careful chromatography of fine silica gel. Therefore, the author had to reduce **18** to separate from **19**.[12] The resulting alcoholic mixture (**19**) was converted to methyl carbonates (**20**) in quantitative yield based on 71% conversion. The

E-selective diene formation from **20** was accomplished by using the Tsuji method.[13] The Pd^0-catalyzed diene formation of this substrate proceeded smoothly in high *E*-selectivity (>98:1) to give the triene (**21**) in 70 to 84% yield.[14]

This unprecedented high selectivity is thought to be due to the steric bulkiness of the adjacent 1,3-dioxane moiety in the σ-allyl palladium intermediate (Figure 5); the conformer **A** is preferred than conformer **B** because non-bonding interaction in the conformer **B** is severe. Thus, the *E*-diene, produced by *syn*-elimination of the hydride-palladium from the conformer **A**, was the preferred product.

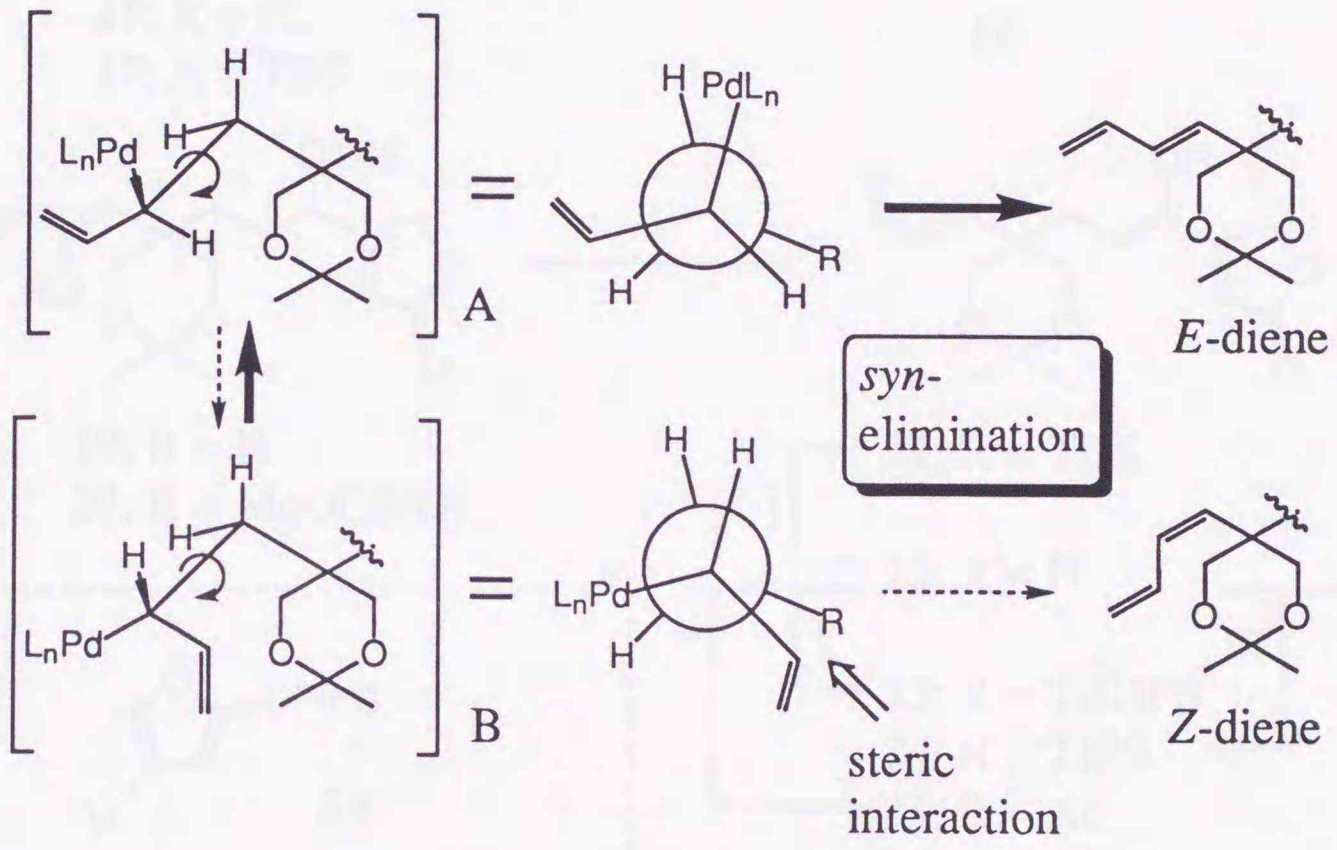
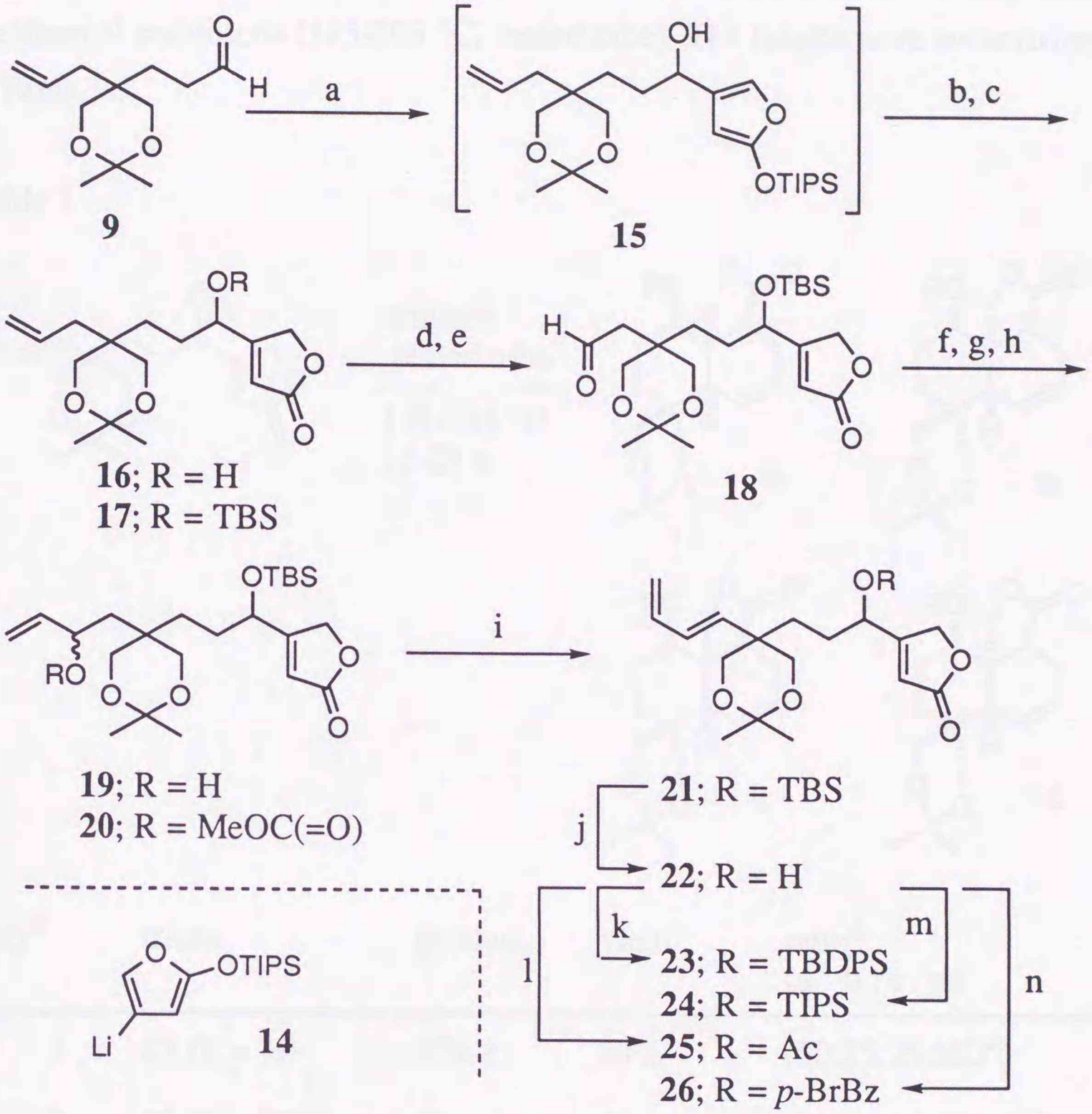


Figure 5

Finally, the protective group on allylic alcohol was detached to afford alcohol (**22**) in good yield. Then, **22** was converted to the other IMDA precursors (**23-26**)[15] in order to estimate the electrostatic and steric effects on protecting groups of the secondary hydroxyl group.

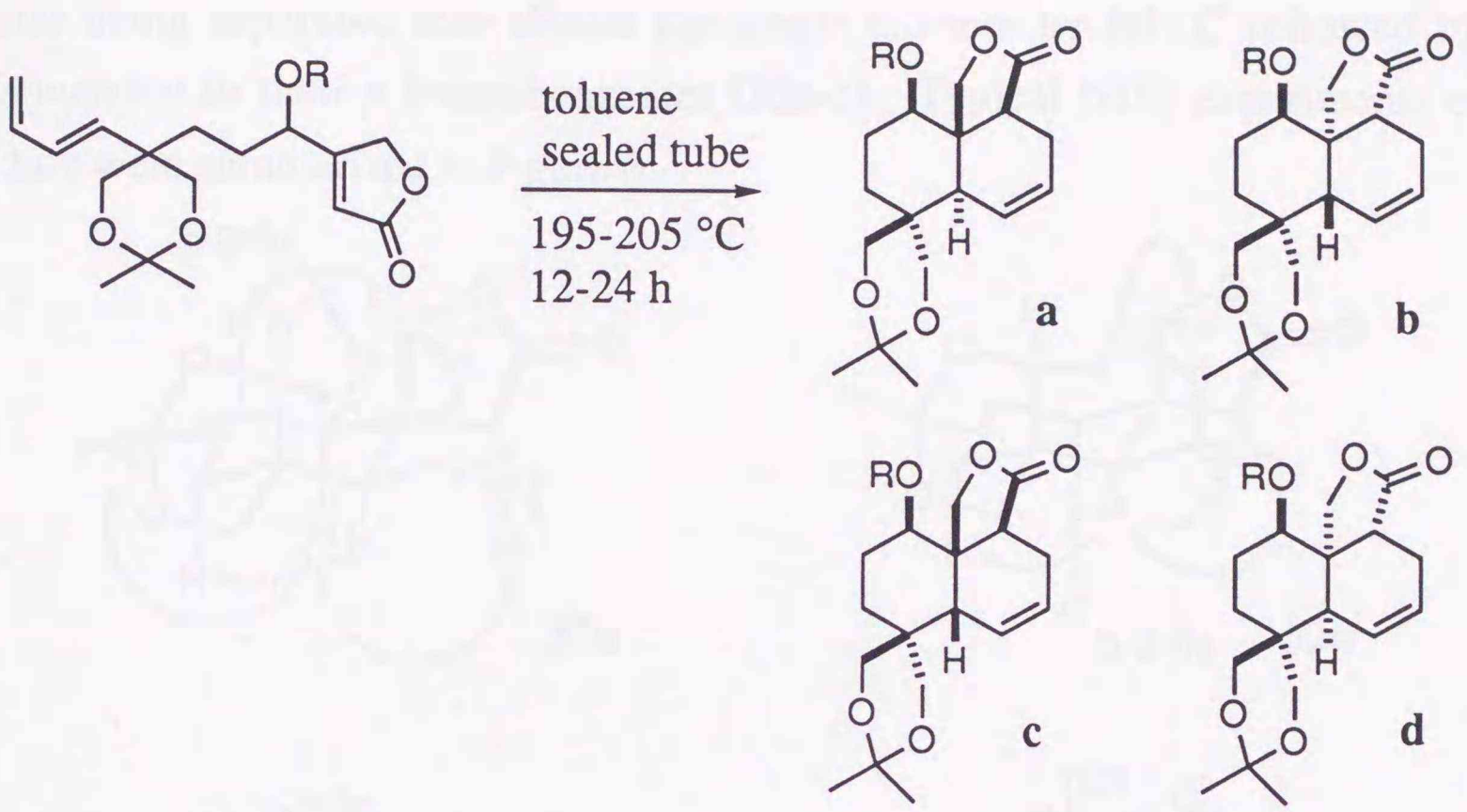


Reagents and conditions: a) **14**, Et_2O, -78 °C, 1 h; b) TBAF, THF, 0 °C, 15 min, 56% for 2 steps; c) TBSCl, imidazole, DMF, r.t., 10 h, 76%; d) cat. OsO_4, NMO, H_2O-*t*-BuOH-THF (1:2:2), r.t., 13 h; e) $NaIO_4$, MeOH-H_2O (4:3), 0 °C, 20 min, 97% for 2 steps; f) vinylmagnesium bromide, THF, -78 °C, 20 min; g) $NaBH_4$, EtOH, 0 °C, 20 min, 56% for 2 steps; h) methyl chloroformate, pyridine, CH_2Cl_2, 0 °C, 1 h, 90 min, then r.t., 40 min, 100% (71% conversion); i) cat. $Pd(PPh_3)_4$, Et_3N, THF, 55 °C, 40 min, 70-84%; (*E*:*Z* = >98:2); j) TBAF, THF, 0 °C, 12 min, 98%; k) TBDPSCl, imidazole, DMF, r.t., 42 h, 78%; l) Ac_2O, pyridine, CH_2Cl_2, r.t., 10 h, 93%; m) TIPSCl, imidazole, DMF, r.t., 58%; n) *p*-BrBzCl, pyridine, r.t., 3 h, 91%.

Scheme 6

The IMDA reactions of these precursors (**21-26**) were carried out under the thermal conditions (195-205 °C, sealed tube). The results were summarized in Table 1.

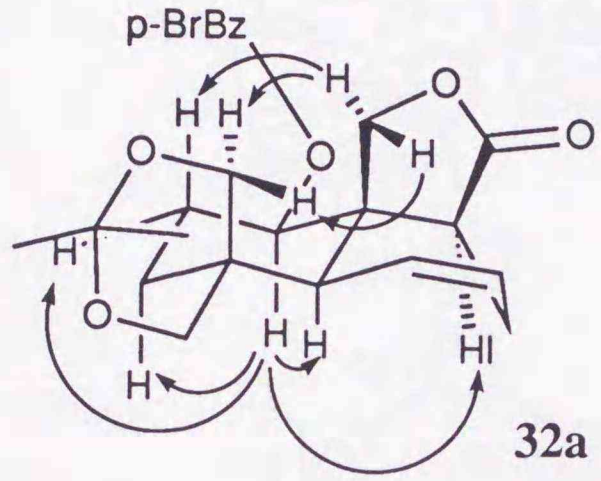
Table 1

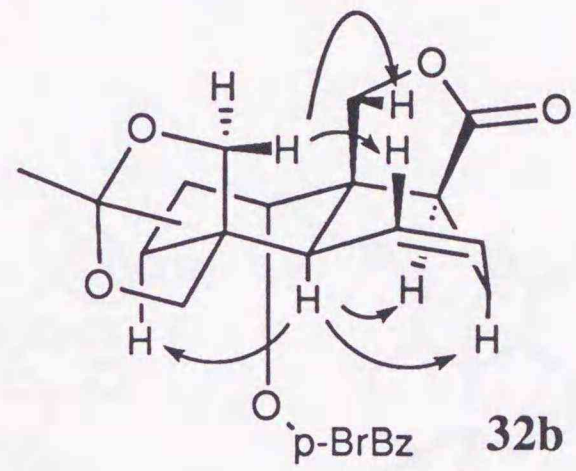


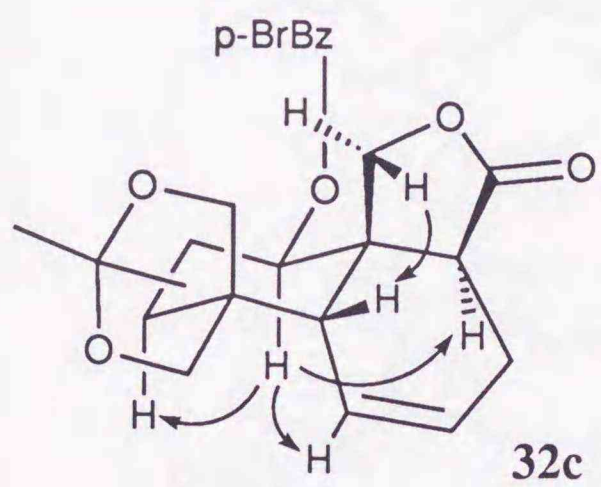
entry[a)]	triene	product	yield[b)]	ratio[c)] (**a** : **b** : **c** : **d**)
1	**22** (R = H)	**27a-c**	87%	(50:25:25:ND[d)])
2	**21** (R = TBS)	**28a-d**	81%	(35:44:15:5)
3	**23** (R = TBDPS)	**29a-d**	76%	(49:27:23:2)
4	**24** (R = TIPS)	**30a-d**	crude[e)]	(42:30:22:5)
5	**25** (R = Ac)	**31a-d**	83%	(58:14:25:2)
6	**26** (R = *p*-BrBz)	**32a-d**	83%	(59:15:24:2)

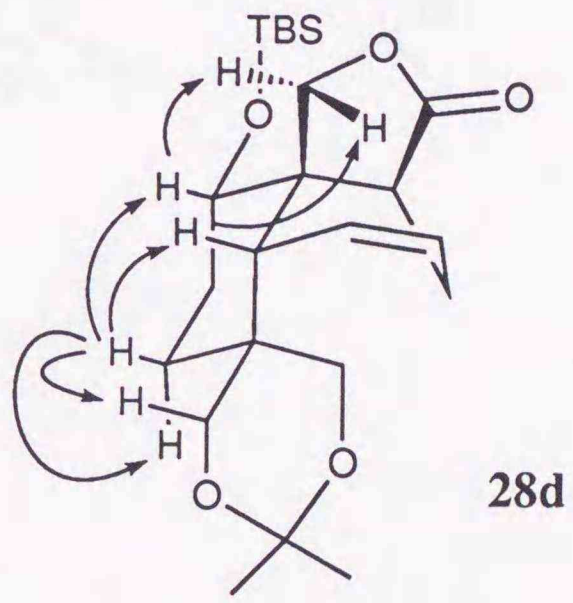
a) For reaction procedures, see experimental section; b) Isolated yield of diastereomixture; c) The ratios were determined by ^{1}H-NMR (400 MHz); d) This diastereomer was not detected by both ^{1}H-NMR (400 MHz) and HPLC analyses; e) The yield of the crude mixture was 96%.

Thermolysis of **22** gave rise to a mixture of three diastereoisomers,[16] and structures (**27a-c**) (entry 1) of which were determined after leading to their TBS derivatives (**28a-c**), respectively (*vide infra*). Thermolysis of the other precursors (**21**, **23-26**) afforded the products as a mixture of four diastereoisomers (entries 2-6). Structures of the adducts (**28a-c**) were confirmed by careful NMR analyses after being separated into almost the single isomers by HPLC followed by conversion to their *p*-bromobenzoates (**32a-c**). Typical NOE experiments of **32a-c** were summarized in Figure 6.









; NOE

Figure 6. The observance of NOEs in **32a-c**, and **28d**.

On the other hand, the structure of the adduct **28a**, which could be recrystallized from benzene to afford a single crystal, was definitively confirmed by X-ray diffraction analysis.[17] (Figure 7). The adduct **28d**, moreover, was afforded as a single diastereomer by HPLC separation, and the structure could be determined by the NMR analysis. The NOEs observed in the adduct **28d** are also depicted in Figure 6. In the respective cases of the adducts given from **23**,

24, and **25**, the structures were deduced from similarity of their pattern for olefinic and oxygenated methine protons in their ^{1}H-NMR spectra .

The author also attempted Lewis acid catalyzed IMDA reactions of **21** (Et_2AlCl or $EtAlCl_2$ in CH_2Cl_2).[18] But unfortunately, cyclization did not occur and only decomposition was observed in each case.

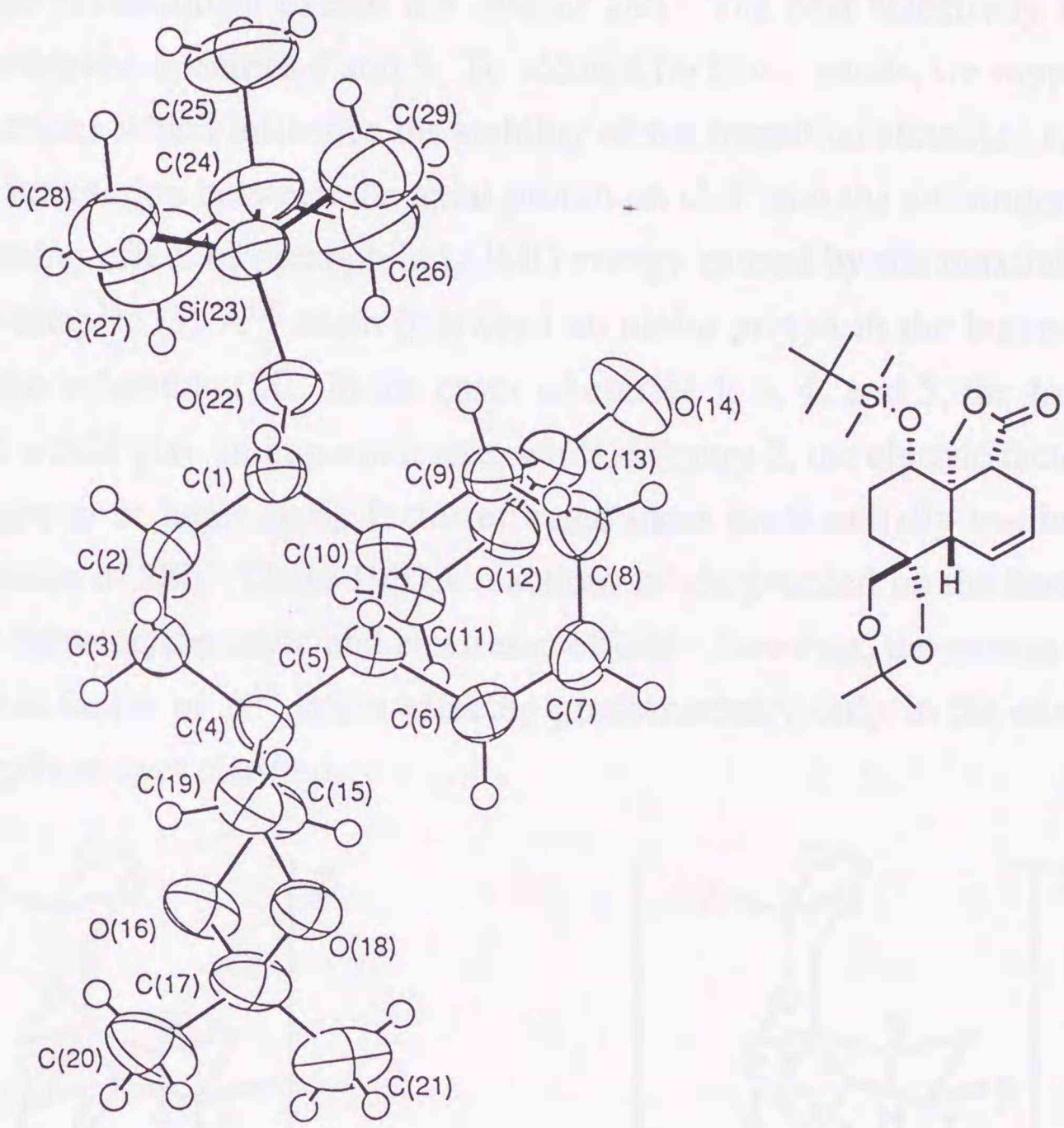
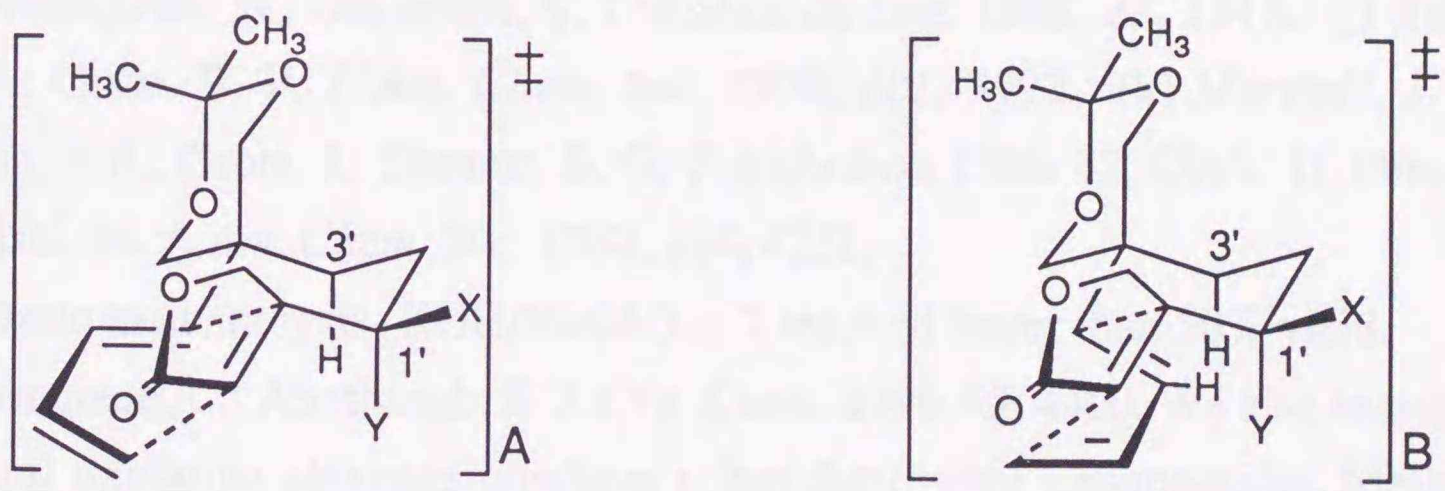


Figure 7. ORTEP figure for **28a**.

These results imply that these triene systems are generally suitable for formation of the *trans*-decalins (type **a** and **b**) rather than the undesired *cis*-decalins (**c** and **d**). They could be rationalized as follows: since an electron-withdrawing carbonyl group on a dienophile exists on a terminal position, the reaction would probably proceeds through 6-membered pseudo chair-like transition states **A** and **B** from the concept of "concerted but asynchronous" reaction pathway

(Figure 8).[19] In the transition state **B**, which leads to *cis*-decalins, the severe nonbonding interaction between a diene and axial substituents at C-1' and C-3' would be there, while there is no such interaction in the transition state **A** which gives *trans*-decalins. Accordingly, the transition state **A** would be preferred. Among the *trans*-decalin adducts, experimental results showed that the type **a** adducts were predominant except the case of **28b**. The best selectivity for **a** series was achieved in entries 4 and 5. To account for these results, we supposed three interactions which influence the stability of the transition state **A**: *i.e.*, (1) 1,3-diaxial interaction between the axial proton on C-3' and the substituent Y; (2) the lowering effect of dienophile LUMO energy caused by the maximizing $\sigma^*_{C\text{-}O}$-π^* overlap[3a]; (3) $A^{1,3}$ strain beetween an olefin proton in the butenolide group and the substituent X. In the cases of entries 1, 3, 4, and 5, the former steric effect would play an important role, while, in entry 2, the electric factor of the TBSO group or latter steric factor effected more preferentially leading to much formation of **28b**. These IMDA reactions might proceed on the basis of the balance between the steric and electronic effects. However, the reason why the electronic factor or $A^{1,3}$ strain effected predominantly only in the case of TBSO group is not yet clarified.



X, Y = H or OR

Figure 8

In conclusion, the author prepared the several racemic trienes, and found that the thermolysis of these compounds proceed to give the favored *trans*-decalins as the major products, while their stereoselectivities were not so high. The

author decided to use the adduct **27a** for further synthetic studies because it could be separated rather easily as a single isomer from the other diastereomers by silica gel column chromatography, while the products from other trienes could hardly be separated.

References and Notes

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(3) (a) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (b) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186. (c) Müller, G.; Jas, G. *Tetrahedron Lett.* **1992**, *33*, 4417. (d) Nemoto, H.; Satoh, A.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 10159. (e) Roush, W.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (f) Roush, W. R.; Coe, J. W. *Tetrahedron Lett.* **1987**, *28*, 931. (g) Boeckman Jr., R. K.; Barta, J. E. *J. Org. Chem.* **1985**, *50*, 3421. (h) Roush, W. R.; Kageyama, M. *Tetraedron Lett.* **1985**, *26*, 4327. (i) Ichihara, A.; Kawagishi, H.; Tokugawa, N.; Sakamura, S. *Tetrahedron Lett.* **1986**, *27*, 1347. (j) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992. (k) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893. (l) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251.

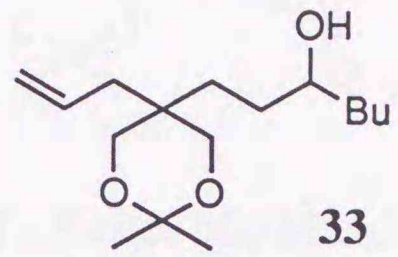
(4) Basic methanolysis (KOH/MeOH) of **7** resulted lower than 50% yield.

(5) Vargeese, C.; Abushanab, E. *J. Org. Chem.* **1990**, *55*, 4400. We also examined several oxidative cleavage conditions, but these were unsuccessful. Methods examined include NBS, CH_3CN-H_2O (4:1), 0 °C; $Hg(ClO_4)_2 \cdot 3H_2O$, $CaCO_3$, THF-H_2O (10:3), r.t.; and $(CF_3CO_2)_2IPh$, CH_3CN-H_2O (11:2), 45 °C.

(6) Jas, G. *Synthesis* **1991**, 965.

(7) Even this compound decomposed slowly when it was stored for a few weeks at -20 °C (See experimental section). We purified the compound by silica gel chromatography using hexane as an eluate, and dried *in vacuo* for several hours prior to use.

(8) As mentioned in Chapter 2, the remaining butyllithium reacts as an alkylating reagent to give **33** as a side product. But, this side reaction was eliminated by use of 2 eq. of *t*-butyllithium as a base.

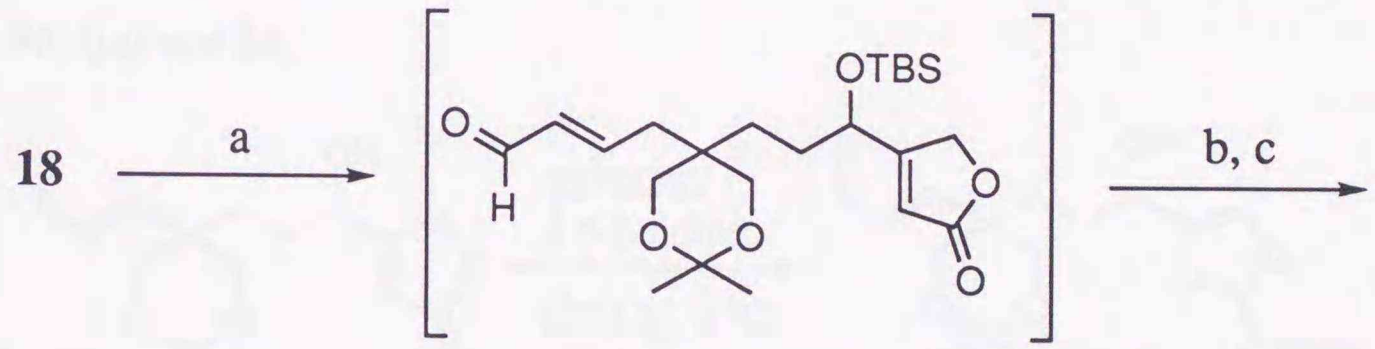


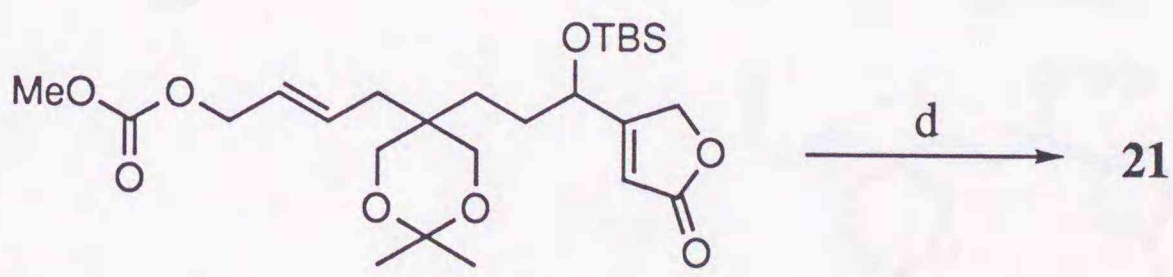
33

(9) Marini-Bettolo, R.; Tsai, C. S. J.; Tsai, T. Y. R.; Wiesner, K. *Heterocycles* **1981**, *15*, 305.

(10) Purification of **15** by silica gel chromatography resulted in a partial cleavage of the TIPS ether.

(11) Numerous other attempts to introduce the C-2 group, such as the use of $CeCl_3$ with vinylmagnesium bromide, and the use of lithium acetylide instead of vinylmagnesium bromide, were examined, but the author could not improve the reaction results. Another synthetic scheme was also examined, while this approach resulted in rather low total yield (*vide infra*).

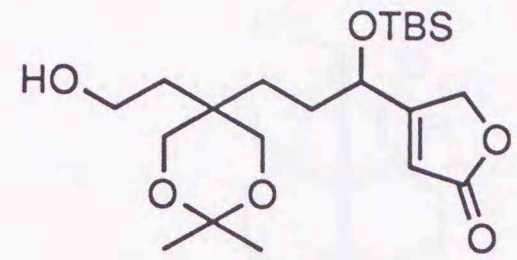




Reagents and conditions: a) (triphenylphosphonylidene)acetaldehyde, benzene, reflux, 1 day; b) $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 30 min; c) methyl chloroformate, pyridine, CH_2Cl_2, 0 °C, 30 min; d) cat. $Pd(PPh_3)_4$, Et_3N, THF, 55 °C, 40 min, 31% for 4 steps.

(12) Unfortunately, oxidation of the recovered alcohol **34** afforded **18** in quite

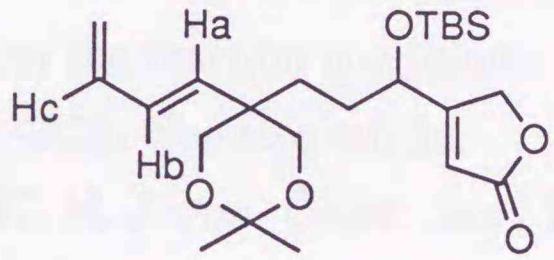
low yield. (34% and 15% for PDC and Swern oxidation, respectively.)



34

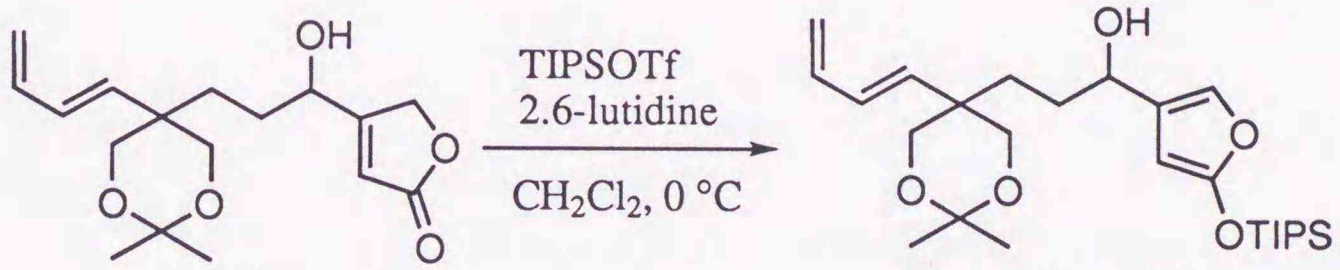
(13) a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075. b) Mandai, T.; Matsumoto, T.; Nakao, Y.; Teramoto, H.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1992**, *33*, 2549.

(14) The diene part of **21** probably exists in *s-cis* conformation in nonpolar solvent such as C_6D_6 on the basis of ^{1}H-NMR analysis. Other trienes were also thought to tend to form the same conformation.

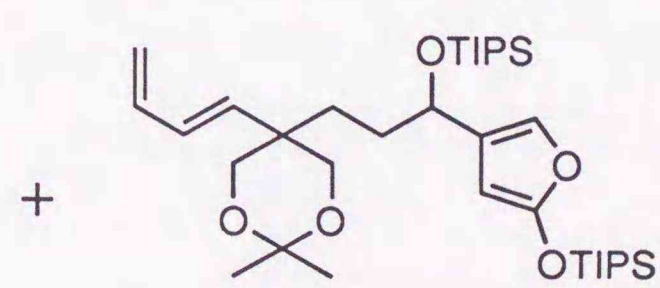


21 $J_{Ha\text{-}Hb} = 16.8$ Hz, $J_{Hb\text{-}Hc} = 11.1$ Hz

(15) When we treated **22** with TIPSOTf instead of TIPSCl, the product were **35** and **36**, but not **24**.



22 **35** 48%



36 31%

(16) It has to be mentioned that the thermolysis of **22** sometimes produced a small amount of **37** when the reaction was repeated in order to keep a sufficient amount of **27a**.

37

(17) The author would like to thank Dr. K. Kinoshita and Ms. K. Yamashita, Institute for Life Science Research, Asahi Chemical Industry, Co. Ltd., for their kind analysis of the X-ray of **28a**.

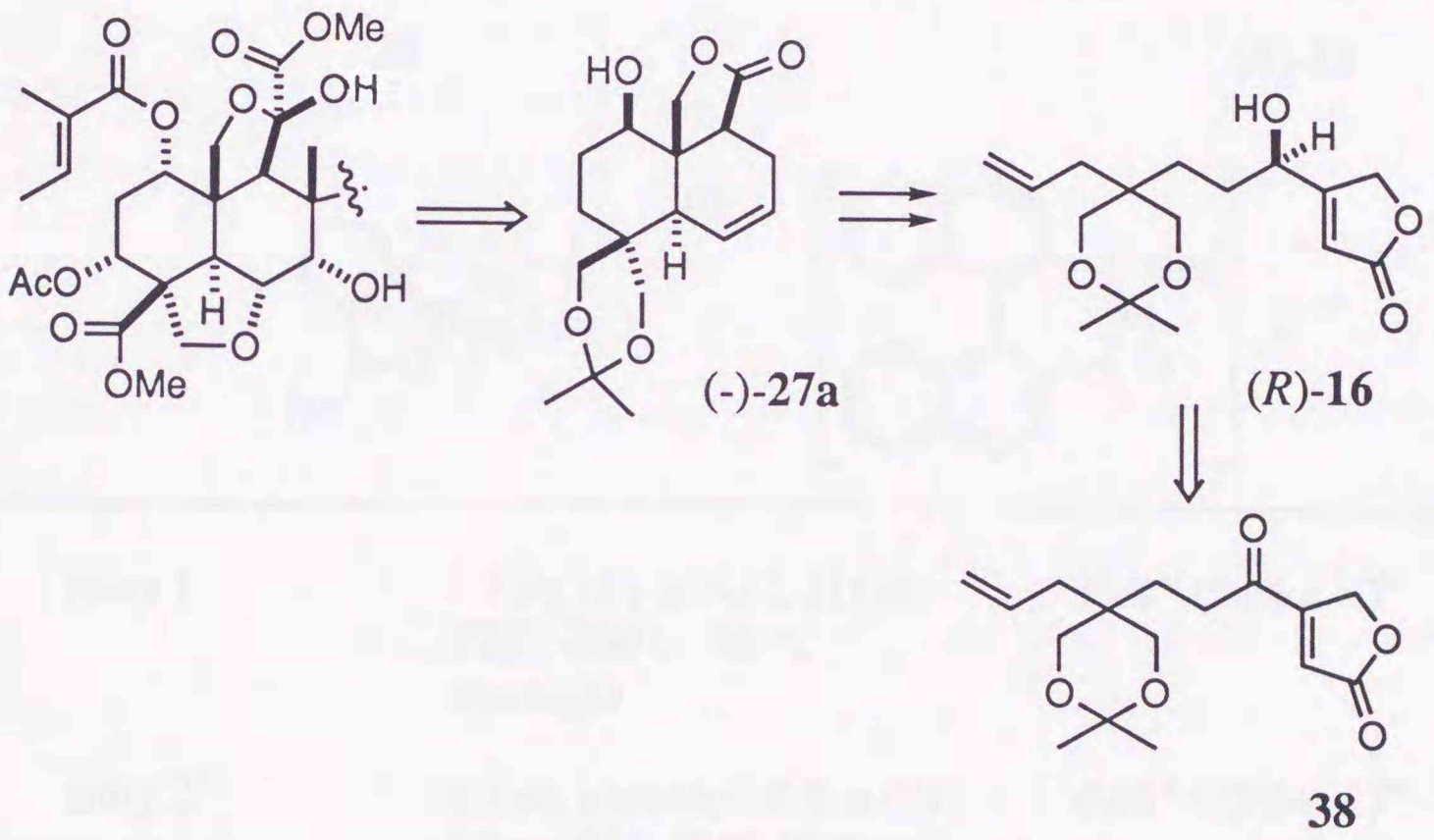
(18) To my knowledge, Lewis acid catalyzed IMDA reactions are better in the point of diastereoselectivity than the thermal reaction if the triene would not be decomposed under the reaction conditions; Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825. See also ref. 3a.

(19) (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. (b) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297. See also ref. 2b.

Chapter 2

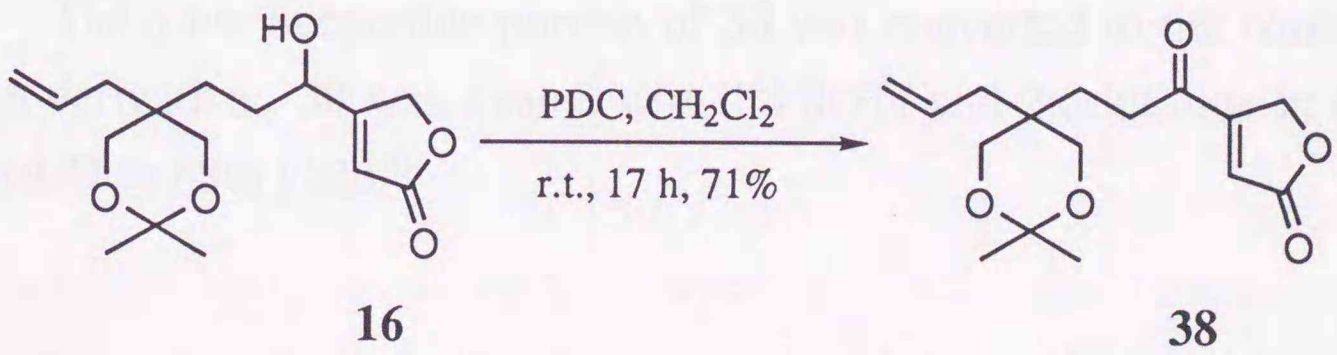
Preparation of the Optically Active Decalin Compound (-)-(27a) by using Catalytic Asymmetric Reduction.

On the basis of the results described in the previous chapter, (*R*)-**16** could be a synthetic precursor for the naturally occurring azadirachtin. The author considered that the chiral center of (*R*)-**16** would be introduced by the asymmetric reduction of **38**, which could be obtained from a racemic sample of **16** (Scheme 7). Therefore, we examined the asymmetric reduction of **38** at first.



Scheme 7. Synthetic plan for the chiral decalin.

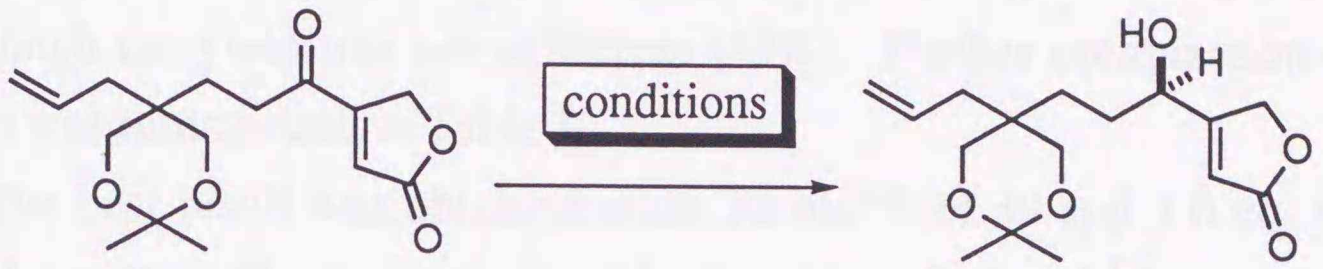
38 was prepared by PDC oxidation of **16** in 71% yield (eq. 3). We also examined other conditions such as Swern, MnO_2, TPAP,[1)] and IBX[2)] oxidations, but these reactions did not work well.



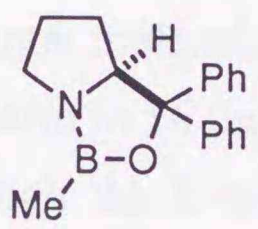
16 **38** **eq. 3**

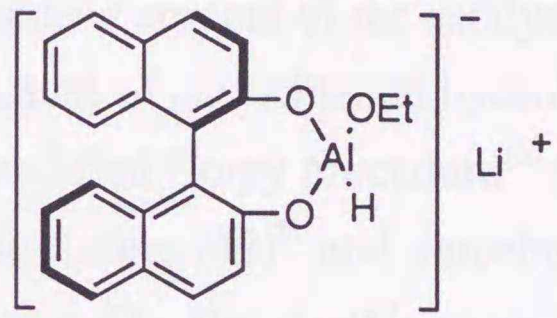
The asymmetric reduction of **38** were then examined. The BINAL-H[3] reduction and the oxazaborolidine catalyzed reduction,[4,5] which were developed by Noyori *et al.* and Corey *et al.*, respectively, were utilized (Table 2). However, both the yields and the optical purities of the resulting **16** were insufficient under both conditions.

Table 2



38 (*R*)-**16**

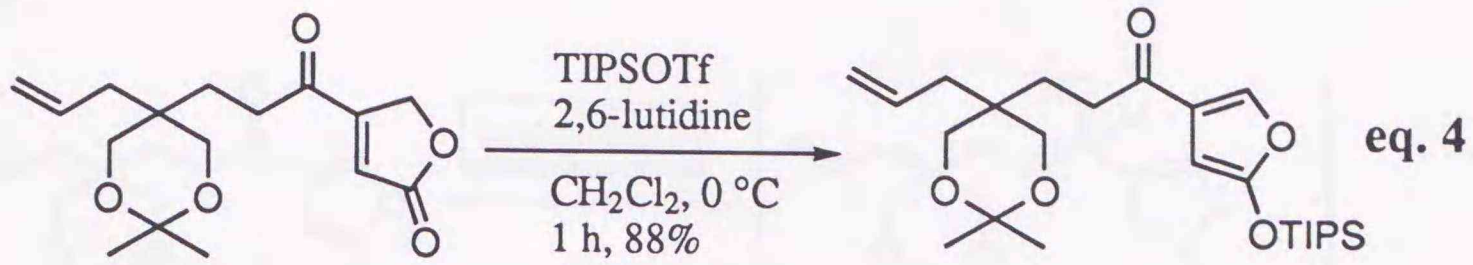
39; 

40; 

entry 1	1.3 eq. (*R*)-BINAL-H (**40**) THF, -100 to -78 °C overnight	13%[a] (52% e.e.)[b]
entry 2	0.5 eq. oxazaborolidine (**39**) 1.5 eq. BH_3·THF, THF 0 °C, 40 min	69%[a] (23% e.e.)[b]

a) Isolated yields. b) Values in parenthesis denote enantiomeric excess, and these values were determined by 400 MHz ^{1}H-NMR after leading to their MTPA esters.[6] The configuration of the resulting hydroxyl group in **16** was determined to be *R* by the advanced Mosher Method.[6,7]

Then, the butenolide portion of **38** was converted to the corresponding furan derivative. **38** was treated with TIPSOTf and 2,6-lutidine in CH_2Cl_2 to afford **41** in 88% yield.[8]



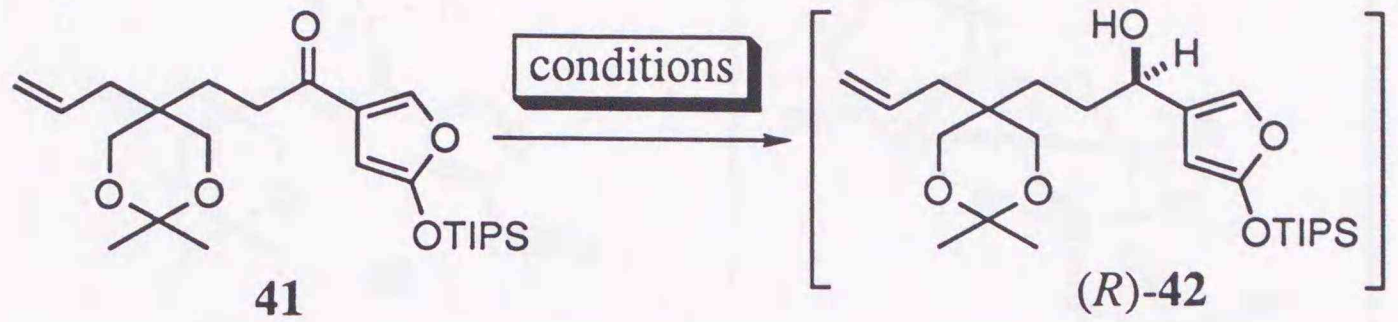
38 **41** **eq. 4**

Contrary to the previous results, **41** was reduced by the Corey procedure followed by treatment with TBAF to afford (*R*)-**16** in a high optical purity (93% e.e.) though the yield was not sufficient (53%). Further optimization of this reaction was summarized in Table 3.

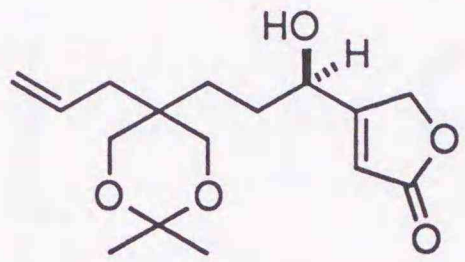
The best result was obtained when 30 mol% of **39** and 1.0 eq. of neat $BH_3 \cdot SMe_2$ complex[9] were used as a reductant (entry 3), in which case the yield and the optical purity of the resulting (*R*)-**16** amounted to 100% and 97%, respectively. Prolonged reaction time and reduced amount of the catalyst caused decrease of the target molecule, probably because of an incidental hydroboration of the terminal olefin in **16** (entry 2). The modified Corey procedure[10] was also examined, in which the B-*n*-butyl oxazaborolidine (**42**)[5] and catecholborane were used in toluene at low temperature (entry 4). But, in this case, both the optical purity and isolated yield of the resulting product were unsatisfactory. A combination of catalyst **39** and catecholborane also gave insufficient results (entry 5).

These results could be rationalized by applying Corey's hypothesis[11] as follows: coordination of **41** to the catalyst might occur strongly by using lone pair *a*, because the resulting three component complex allows the maximum π-electron donation from an electron rich 4-furanyl group to the electron deficient carbonyl carbon (Figure 9). In addition to this stereoelectronic effect, the larger furanyl group should tend to be in an equatorial position in the transition state. Thus, intracomplex hydride transfer would almost occur through a six-membered chair like transition state $\mathbf{C_1}$ to give an optically pure alcohol. On the other hand, the coordination of lone pair *a* in **38** to the catalyst would not be stabilized since π-electron donation from the electron deficient butenolide group should not be strong. As a result, the $\mathbf{C_1}$-like transition state would not be sufficiently stabilized and loss of enantioface selectivity would occur in this case.

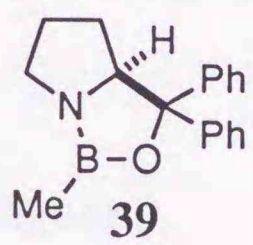
Table 3



41 (*R*)-**42**



(*R*)-**16**



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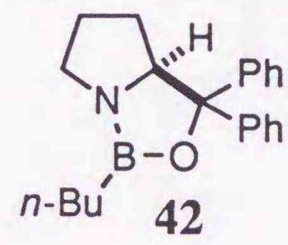
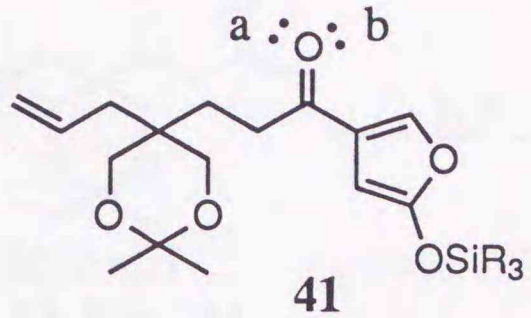


42

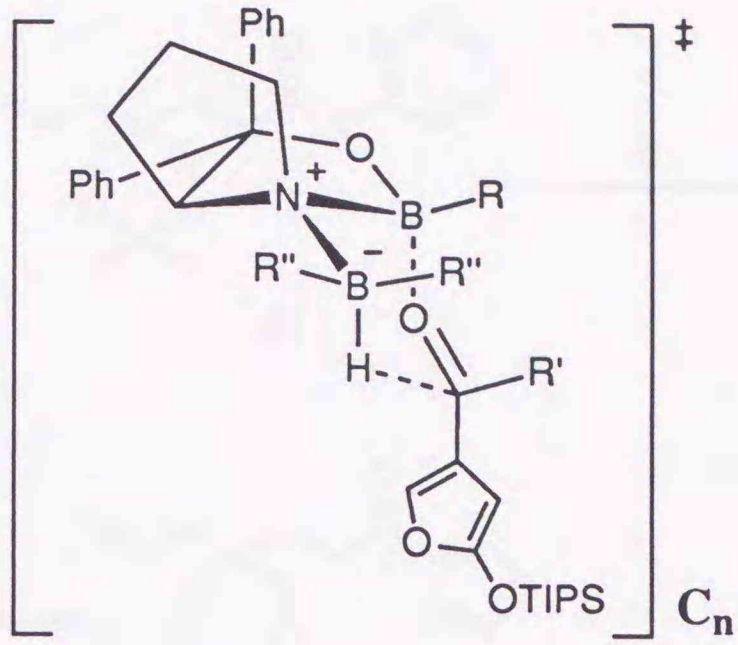
entry	catalyst (mol%)	borane[a)] (eq.)	solv.	temp. (°C)	reaction time	yield[b)] (%)
1	**39** (10)	BH_3·THF (1.4)[c)]	THF	0	40 min	57 (93)
2	**39** (15)	BH_3·SMe (0.7)	THF	-10	25 min	83 (97)
3	**39** (30)	BH_3·SMe (1.0)	THF	-10	10 min	100 (97)
4	**42** (15)	catecholborane (1.9)	toluene	-80	41 h	14[d)] (52)
5	**39** (15)	catecholborane (1.9)	toluene	-80	36 h	66 (83)

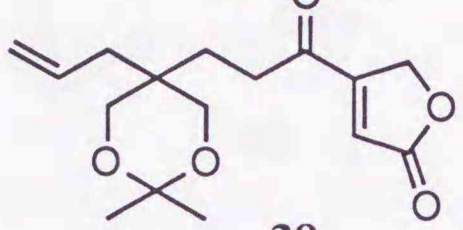
a) The borane reagents used were purchased from Aldrich Chemical Co., Inc. b) Isolated yield of **16**. Values in parenthesis denote optical purities. c) The BH_3·THF was added in two portions (2 × 0.7 eq.). d) The starting material was recovered in 41%.

The low reactivity and enantioselectivity in entry 4 was also explained as follows: 1,3-diaxial interaction in the transition state $\mathbf{C_2}$ would be so severe that this transition state is no longer favored and intercomplex hydrogen transfer should be competed.



41





38

TS C_1; R = Me, R"= H

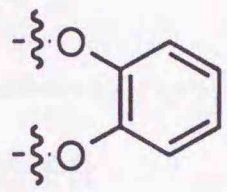
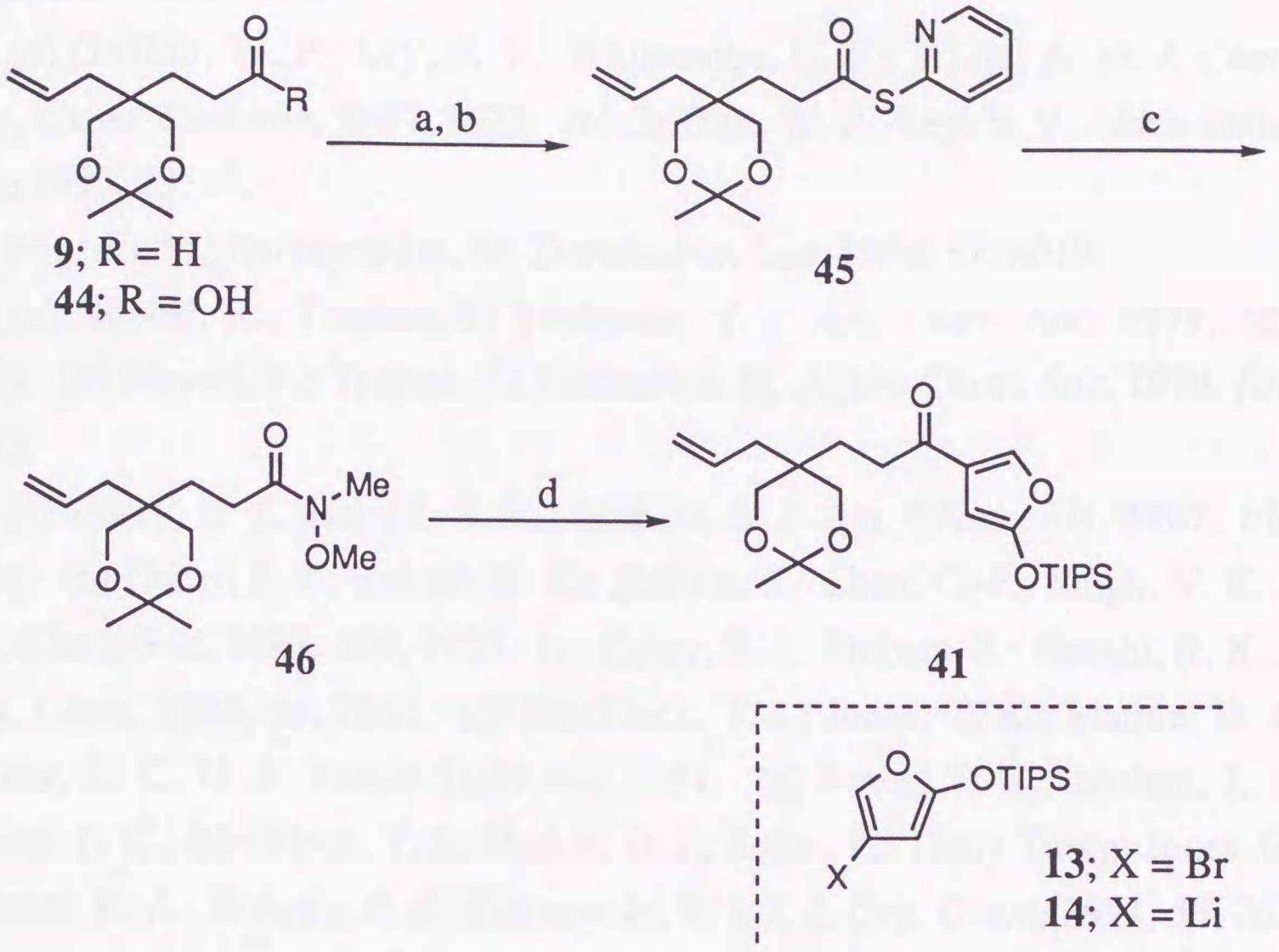
TS C_2; R = Bu, R" = 

Figure 9

The compound **16** became available in the optically active form, although the synthetic scheme toward **16** was roundabout. Therefore, an alternative efficient synthetic route was developed as shown in Scheme 8. The synthesis commenced with $NaClO_2$ oxidation of **9**. The resulting carboxylic acid (**44**) was treated with 2,2-dipyridyl disulfide and Ph_3P to afford **45** in 96% yield for 2 steps. At first, this compound was used in a coupling reaction with lithiofuran (**14**) by applying the procedure developed by Mukaiyama *et al.*,[12] but an overreaction occurred and a small amount of tertiary alcohol was formed. The author had also attempted to convert **13** to coressponding Grignard reagent in order to follow the original Mukaiyama procedure, but **13** was inert in the presence of Mg and activator. Furthermore, a reaction of **45** with **14** in the presence of $MgBr_2$ also gave insufficient result. This method was then given up and an alternative Weinreb's method[13] was examined as follows. An amidation of **45** afforded **46** in quantitative yield. Unlike the precedent results, the coupling reaction of **46** with **14** proceeded to give **41** in 97% yield based on the recovered starting material (33%) and no side reaction occurred.



9; R = H
44; R = OH

45

46

41

13; X = Br
14; X = Li

Reagents and conditions: a) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-buene, *t*-BuOH-H_2O (3:1), 0 °C, 1 h; b) PPh_3, 2,2'-dipyridyl disulfide, CH_2Cl_2, r.t., 40 min, 96% for 2 steps; c) *N*,*O*-dimethylhydroxylamine hydrochloride, Et_3N, CH_2Cl_2, r.t., 40 min, 100%; d) **14**, Et_2O, -78 °C, 97% based on 67% conversion.

Scheme 8

Optically active (*R*)-**16** was then converted to (-)-**27a** as described in the previous chapter, while some minor changes were carried. It is pertinent to mention some comments in the synthesis of optically active (-)-**27a.** First, no racemization occurred in these procedures. Second, the IMDA reaction of **22** was carried out by using a catalytic amount of BHT in an autoclave when this reaction was carried in a grams scale. Third, the adduct **27a** could be purified further by recrystallization to give pure sample which had almost a perfect optical purity (>99% e.e.).

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(1) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. (b) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

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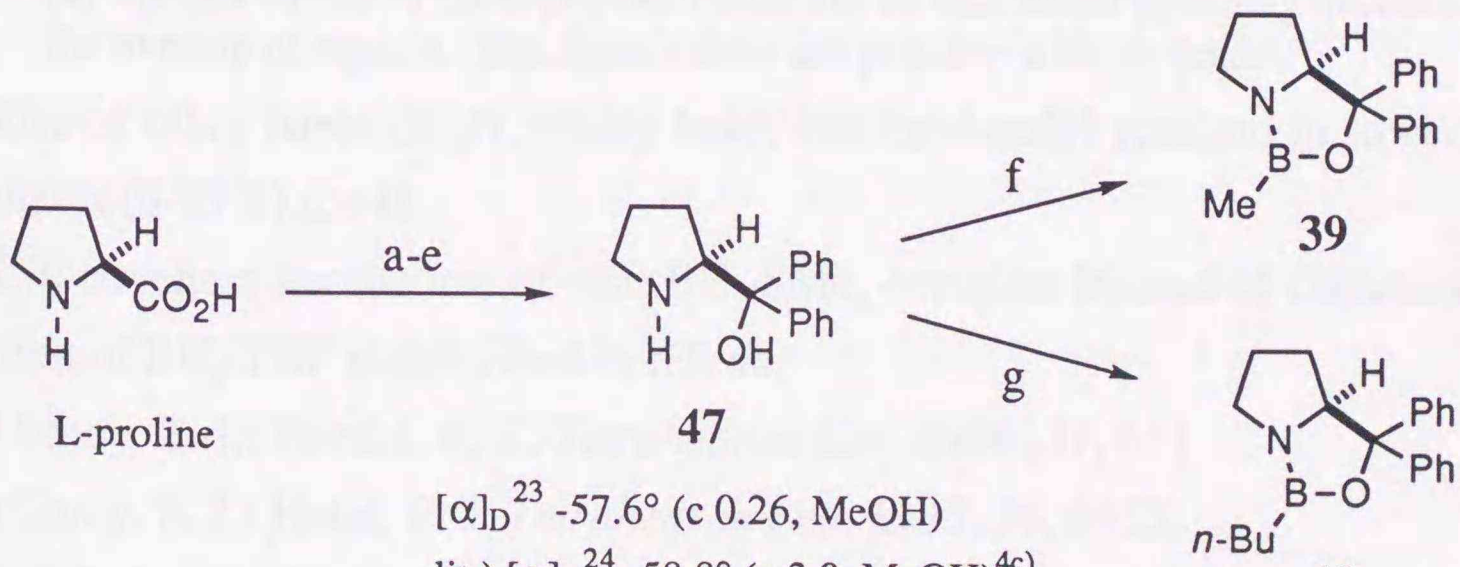
(4) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) Blacklock, T. J.; Jones, T. K.; Mathre, D. J.; Xavier, L. C. U. S. Patent 5,039,802 1991. (e) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Tracy Turner Jones, E.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763. (f) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Tracy Turner Jones, E.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751. (g) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Vanhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324.

(5) The oxazaborolidine catalysts was prepared from L-proline as follows:



L-proline

47

$[\alpha]_D^{23}$ -57.6° (c 0.26, MeOH)

lit.) $[\alpha]_D^{24}$ -58.8° (c 3.0, MeOH)[4c)]

$[\alpha]_D^{21}$ -54.3° (c 0.261, MeOH)[4f)]

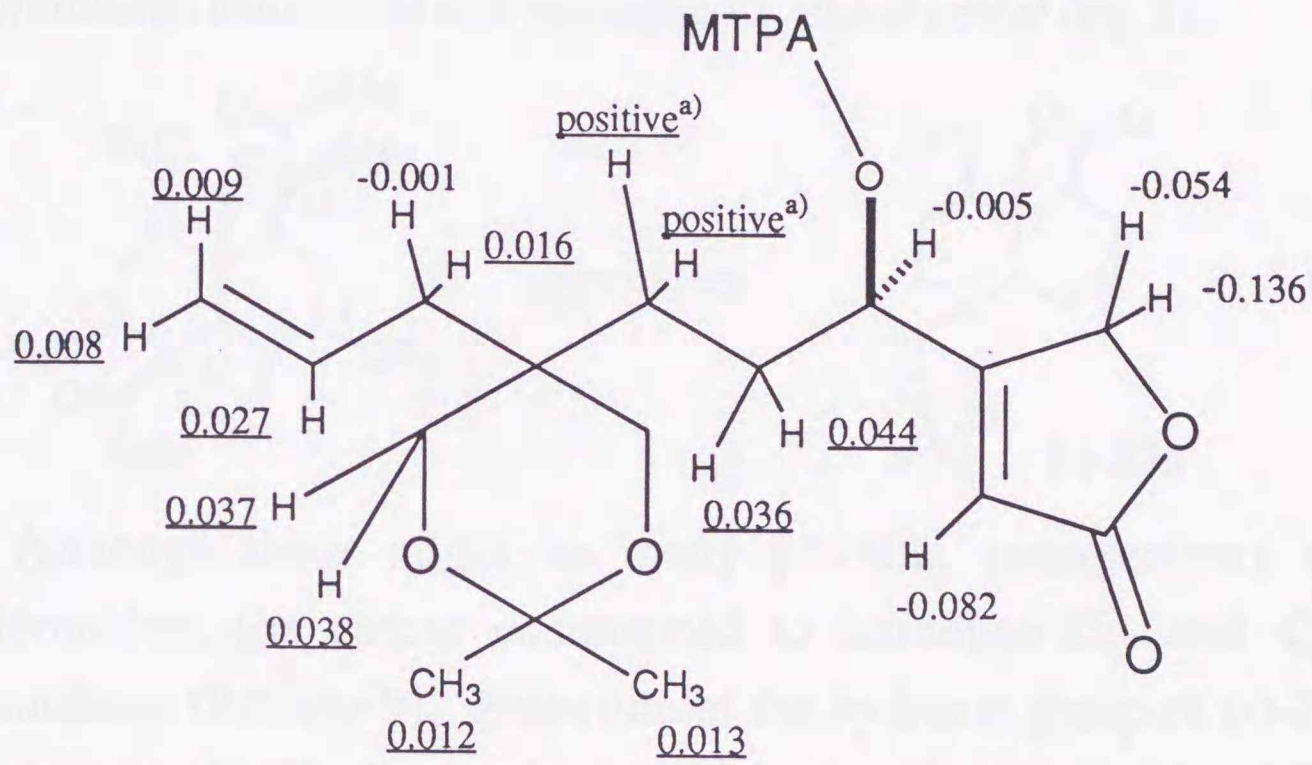
mp. 79-80.5 °C[4c)]

lit.) 79-79.5 °C[4f)]

Reagents and conditions: a) $SOCl_2$, MeOH, 0 °C to r.t., 2 h; b) $ClCO_2Et$, $NaHCO_3$, H_2O-dioxane (1:1), r.t., 1 h, 96% for 2 steps; c) excess PhMgBr, THF, 0 °C, 4 h, 99%; d) KOH, MeOH-H_2O (5:2), reflux, 37 h, 97%; e) recrystallized from hexane; f) trimethylboroxine, toluene, r.t., 30 min, then reflux, 2 h; toluene addition and concentration; g) $BuB(OH)_2$, toluene, Dean-Stark, reflux, 5 h, then concentration.

(6) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(7) $\Delta\delta$ values (ppm) obtained for (*R*) and (*S*)-MTPA esters of **16**. The data are obtained from the spectra measured using $CDCl_3$ as a solvent. $\Delta\delta = \delta_S - \delta_R$.



(a) The $\Delta\delta$ values of these protons could not be calculated precisely because of the overlap of signals. But these values are positive with no doubt.

(8) Use of other bases (Et_3N, Hünig base, and imidazole) resulted in lowering the yields (0-29%) for **41**.

(9) Effectiveness for the use of neat $BH_3 \cdot SMe_2$ complex instead of commercial solution of $BH_3 \cdot THF$ is described in ref. 4e.

(10) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

(11) Corey, E. J.; Hetal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.

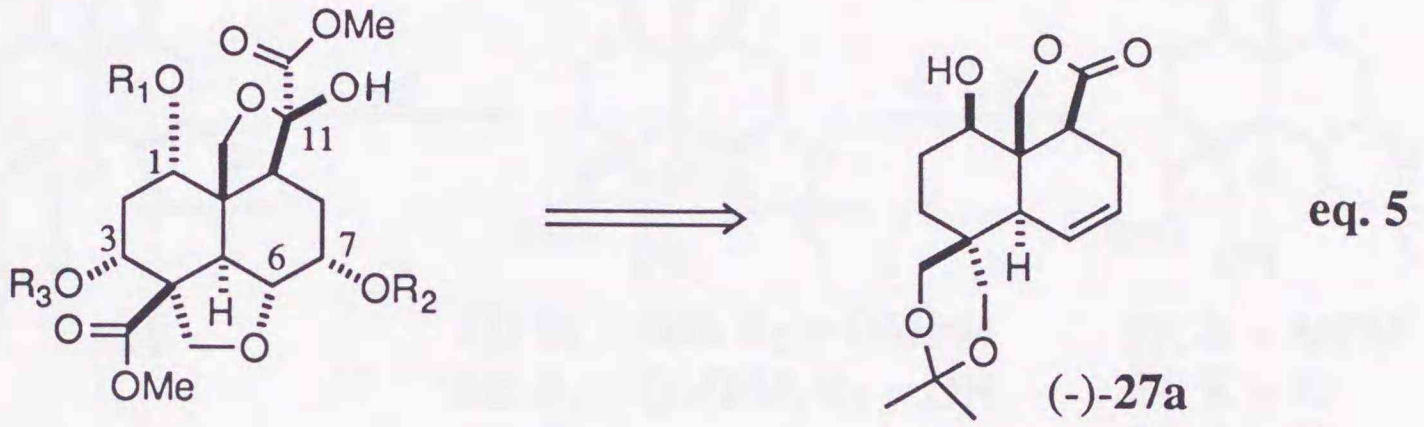
(12) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763.

(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Chapter 3

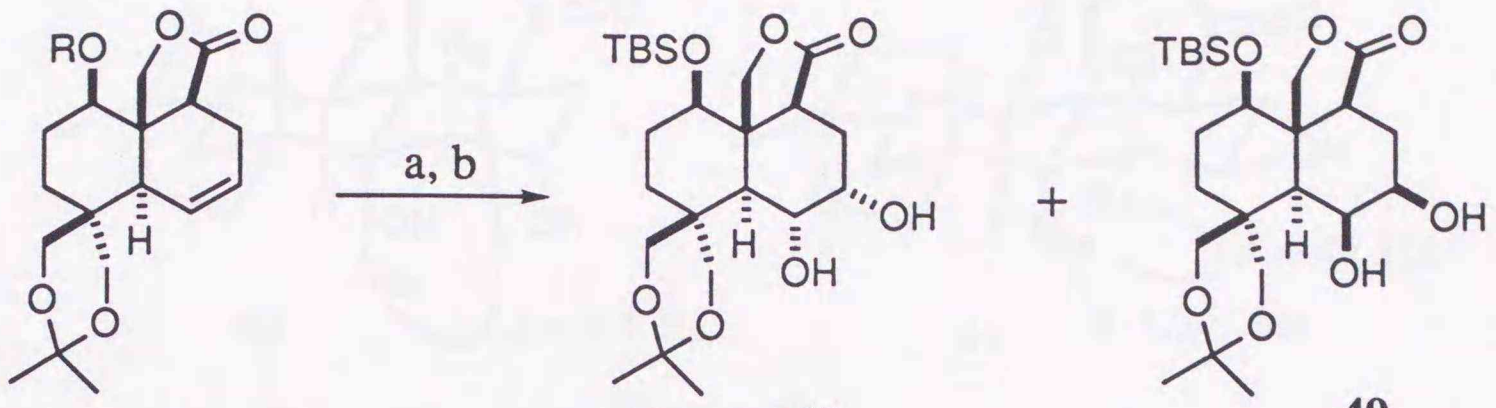
Synthesis of the Tetracyclic Decalin Portion of Natural Azadirachtin.

In order to construct the highly functionalized tetracyclic decalin portion of azadirachtin from (-)-**27a**, several key transformations must be executed: (1) the stereoselective introduction of C_3-alkoxyl group; (2) the stereoselective introduction of C_7- and C_6-oxygen functionalities (azadirachtin numbering) and tetrahydrofuran ring formation; (3) the stereoselective construction of the tetrahydrofuran hemiacetal unit including C_{11} chiral center (eq. 5).



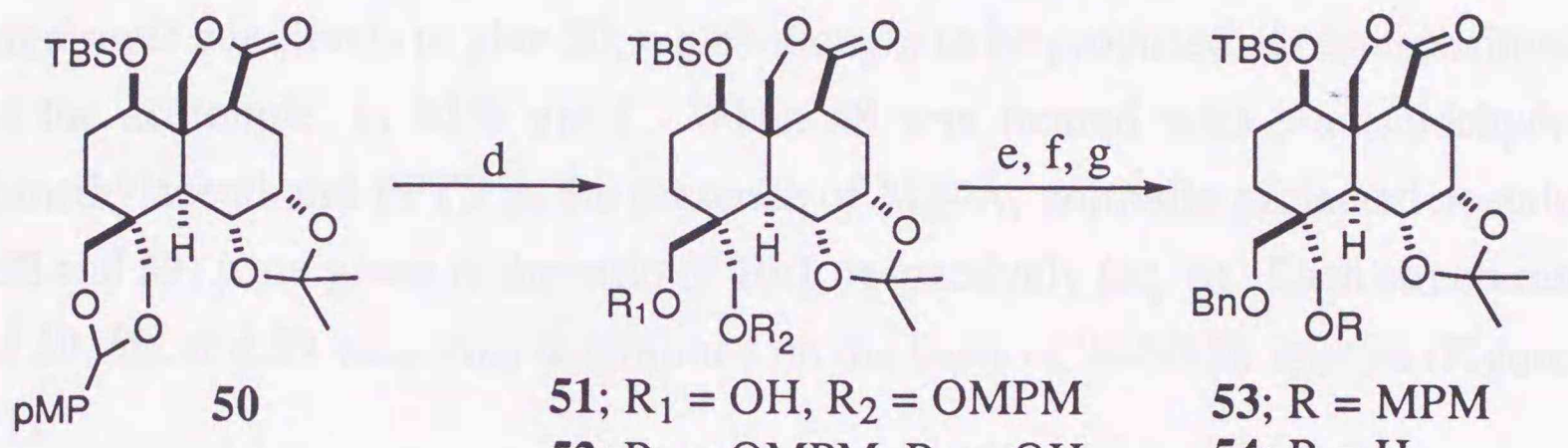
(-)-**27a** **eq. 5**

Although there might be many possible arrangements of these transformation, the author commenced to introduce C_7- and C_6-oxygen functionalities (Scheme 9). Protection of the hydroxyl group of (-)-**27a** as its TBS ether give (-)-**28a** in quantitative yield. The dihydroxylation of (-)-**28a** by using a catalytic amount of OsO_4 in the presence of NMO afforded diols (**48** and **49**) in the ratio of ca. 4:1. The respective stereochemistry of the diols was obviously determined on the basis of ^{1}H-NMR data (Figure 10). The coupling constants between C_6-H and C_{6a}-H in **48** indicated that both of these protons occupied axial positions. On the other hand, C_{6a}-H signal of **49** appeared as broad singlet and the coupling constant between C_6-H and C_{6a}-H was less than 1 Hz. These data showed C_6-H to be in an equatorial position.



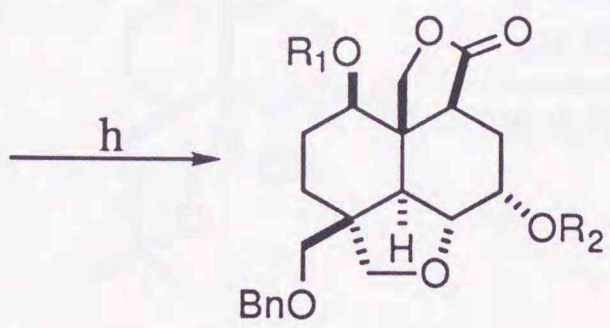
(-)-**27a**; R = H
(-)-**28a**; R = TBS

c



51; R_1 = OH, R_2 = OMPM
52; R_1 = OMPM, R_2 = OH
(6.2:1 inseparable mixture)

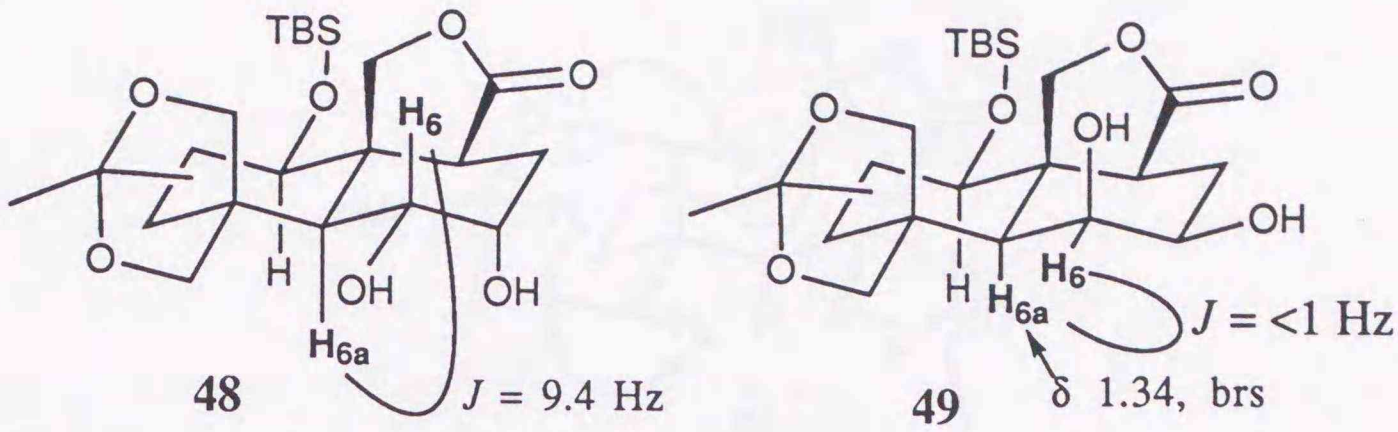
53; R = MPM
54; R = H
55; R = Ms



56; R_1 = TBS, R_2 = H
57; R_1 = R_2 = H

Reagents and conditions: a)TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 90 min, 100%; b) cat. OsO_4, NMO, THF-H_2O-*t*-BuOH (2:1:2), r.t., 23 h, 75% for **48**, 20% for **49**; c) PPTS, benzene, reflux, 1 h, then *p*-anisaldehyde, 2 h, 81%; d) $NaBH_3CN$, TfOH, MS4Å, DMF, r.t., 12 h, 77% (86% based on recovered **50**); e) BnBr, NaH, TBAI, THF, r.t., 27 h, 93%; f) DDQ, CH_2Cl_2-H_2O (20:1), r.t., 2 h, 86%; g) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 100%; h) PTS·H_2O, ethylene glycol-THF (1:20), 50 °C, 31 h, 87% for **56**, 13% for **57** (91% conversion).

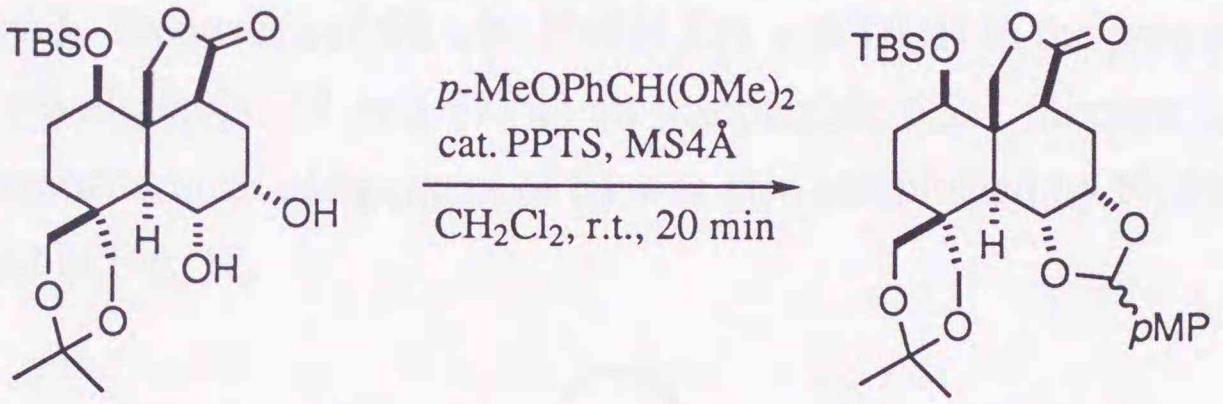
Scheme 9



48 **49**

Figure 10

The major isomer (**48**) was treated with *p*-anisaldehyde and PPTS under azeotropic conditions to give **50**, which thought to be produced *via* transposition of the acetonide, in 81% yield. When **48** was treated with *p*-anisaldehyde dimethylacetal and PPTS in the presence of MS4Å, normally protected acetals (**58** and **59**) were given in the ratio of 10:1, respectively (eq. 6). Each structures of **50**, **58**, and **59** were also determined on the basis of ^{1}H-NMR spectra (Figure 11).



48

58; α-*p*MP (79%)
59; β-*p*MP (8%)

eq. 6

The NOEs observed between $C_{2'}$-H and $C_{4'}$-H and between $C_{2'}$-H and $C_{6'}$-H in **50** are consistent with the structure depicted in Figure 11. In the same way, the observation of NOEs between a benzyl proton and C_5-H, and between a benzyl proton and C_6-H for **58** , and these between a benzyl proton and C_4-H for **59** confirmed the indicated stereochemical assignment.

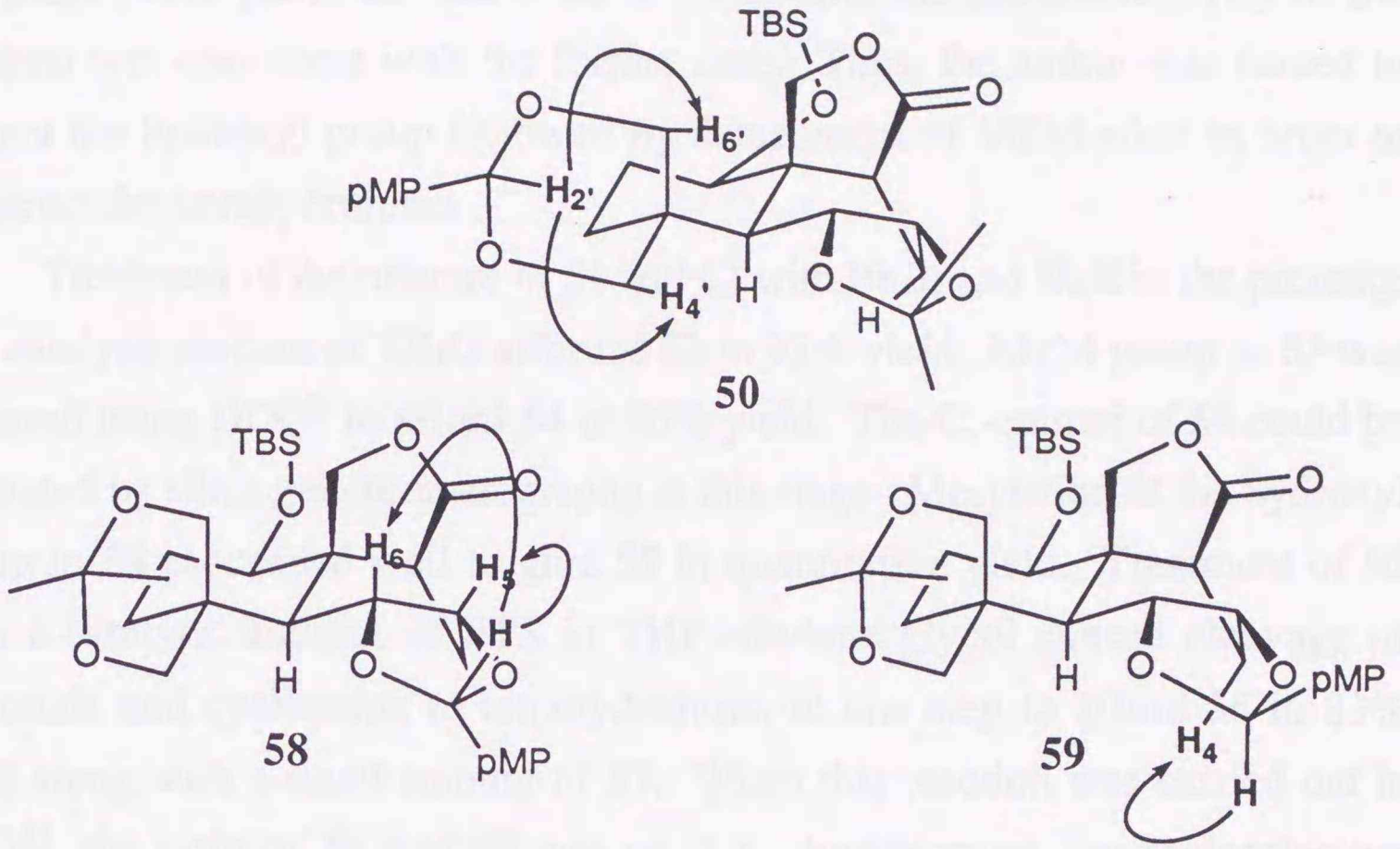


Figure 11

Reductive opening of the *p*-methoxybenzylidene acetal[1)] was then examined. Treatment of **50** with $NaBH_3CN$ and TfOH in the presence of MS3Å gave two alcohols (**51** and **52**) as an inseparable 6.2:1 mixture in 80% yield. The stereochemical assignment of **51** was also established by NOEs observed as depicted in Fig. 12.

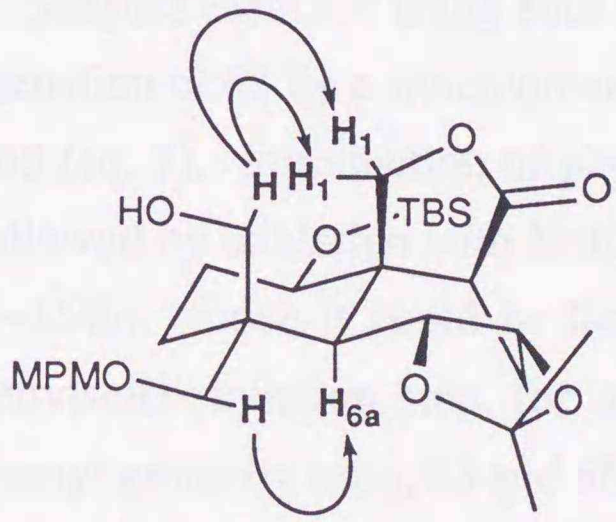


Figure 12

The author also attempted to cleave the acetal ring by using TMSOTf and acetonitrile[1)] instead of TfOH and DMF, but the yield and selectivity were not

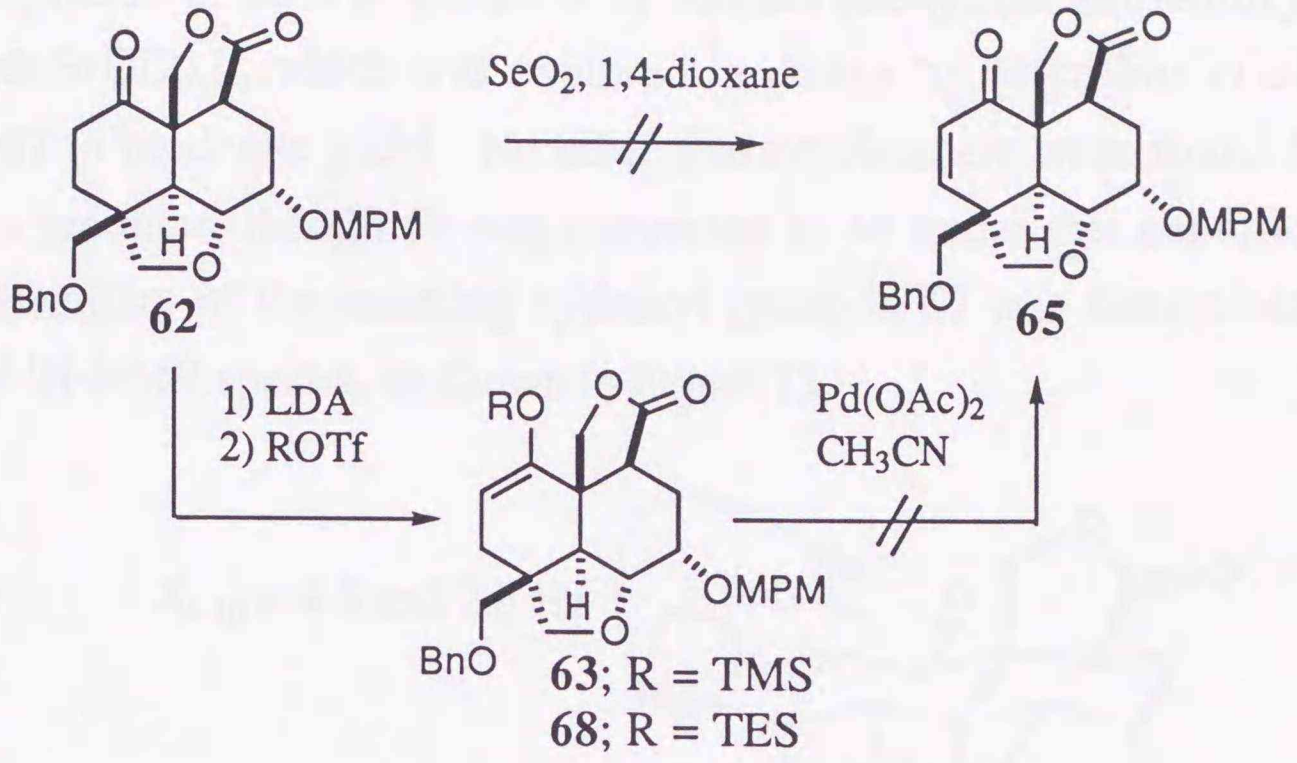
sufficient (45% yield, **51** : **52** = ca. 2 : 1), while the stereoselectivity of the reaction was consistent with the former case. Thus, the author was forced to protect the hydroxyl group followed by detachment of MPM ether in order to construct the tetrahydrofuran.

Treatment of the mixture of **51** and **52** with BnBr and NaH in the presence of a catalytic amount of TBAI afforded **53** in 93% yield. MPM group in **53** was removed using DDQ[2] to afford **54** in 86% yield. The C_7-epimer of **54** could be separated by silica gel chromatography at this stage. Mesylation of the hydroxyl group in **54** proceeded well to give **55** in quantitative yield. Treatment of **55** with a catalytic amount of PTS in THF-ethylene glycol caused cleavage of acetonide and cyclization to tetrahydrofuran in one step to afford **56** in 83% yield along with a small amount of **57**. When this reaction was carried out in MeOH, the ratio of **56** and **57** was ca. 1:1. Furthermore, the regioselective silylation of **57** was difficult because of lack of the solubility in solvents such as CH_2Cl_2.

Protection of the hydroxyl group in **56** as its MPM ether followed by TBAF treatment proceeded to give **61** in 67% yield for 2 steps (Scheme 10). The hydroxyl group in **61** was oxidized with PDC to afford **62** in 84% yield.

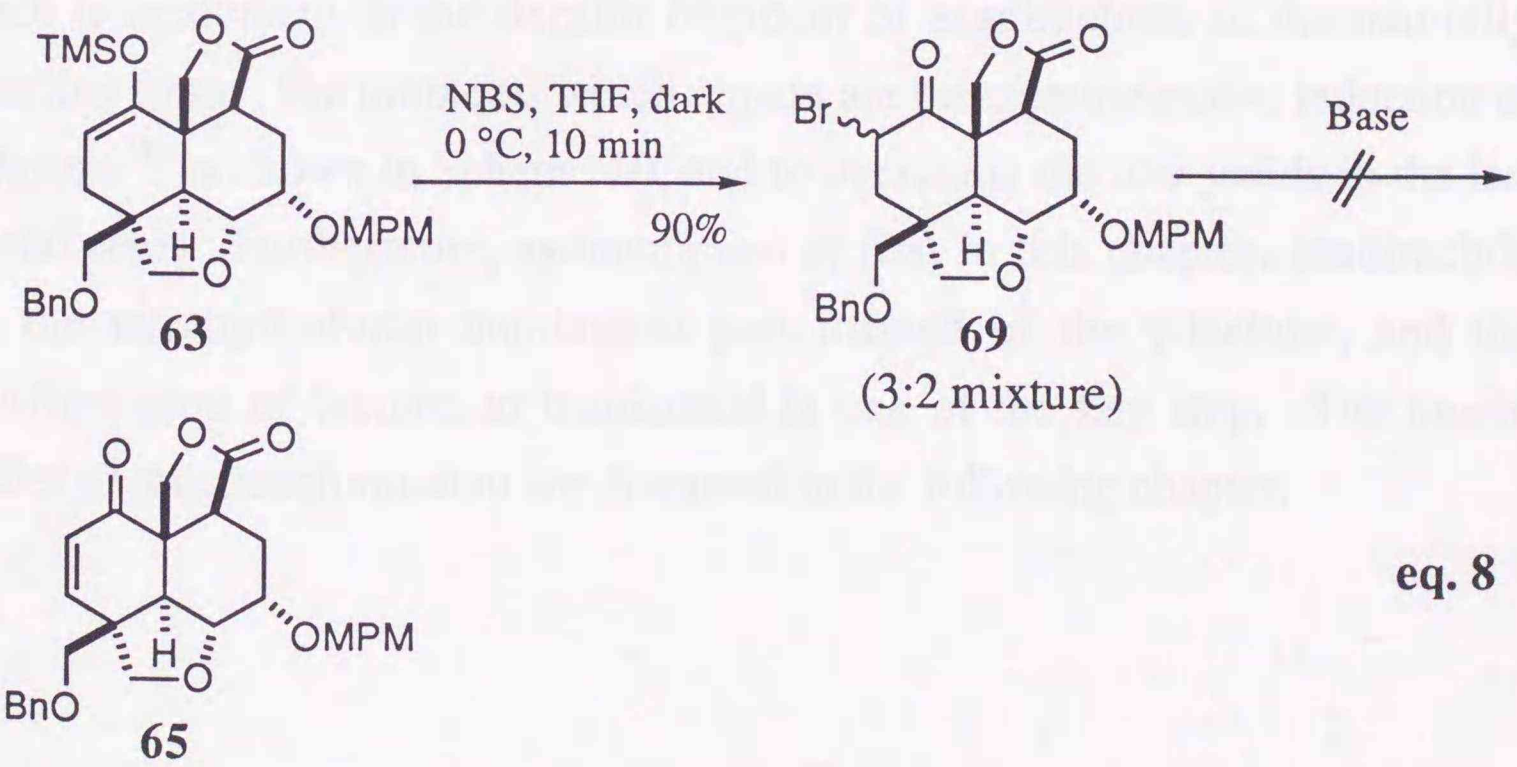
Then, the author attempted to derive α,β-unsaturated ketone **65** from **62** at this stage in order to introduce C_3 oxygen function. But, this transformation was highly problematic. Saegusa method[3] using enol silyl ethers (**63** or **68**) as substrates, and dehydrogenation of **62** by a stoichiometric amount of SeO_2 gave only a trace amount of **65** (eq. 7). Introduction of phenylselenenyl group into **62** *via* lithium enolate followed by oxidation with $NaIO_4$ afforded **65**, while the overall yield was low (~15%). Since it could be thought that the low yield originated from the phenylselenenylation step, the author also attempted to introduce the phenylselenenyl group by using **63** and **68** as substrates. However, a reaction of **63** with PhSeBr,[4] and that of **68** with PhSeBr in the presence of TBAF[5] gave a protonated ketone (**62**) as a major product, while **65** was not obtained. Fortunately, when *N*-PSP[6] was used as a selenenylation reagent instead of PhSeBr, a selenenylated product (**64**) was obtained along with **65**, which would probably be produced by air-oxidation of **64**. Oxidative removal

of phenylseslenenyl group in **64** was accomplished by using $NaIO_4$ to afford 65 in 87% yield.



eq. 7

The author, on the other hand, attempted to construct the enone system by α-bromination of ketone followed by elimination of HBr. While the bromination[7] of **63** by using NBS proceeded smoothly in 10 minutes to gave **69** as a 3:2 mixture of diastereomer in 90% yield, the elimination step, unfortunately, did not proceed at all and it gave a complex mixture (eq. 8).

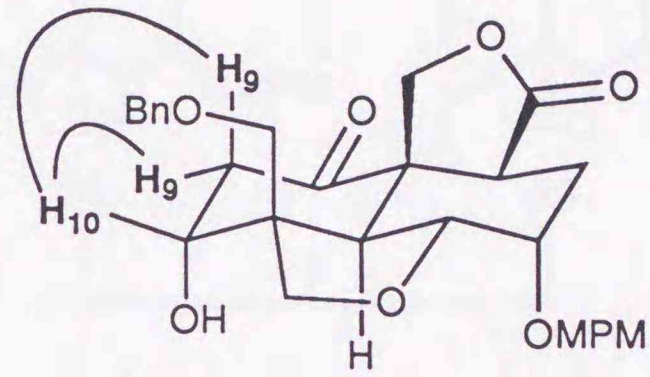


eq. 8

The resulting enone system in **65** was then oxidized to α,β-epoxy ketone by using the procedure developed by Miyashita *et al.*[8] Treatment of **65** with TBHP in the presence of TBAF afforded **66** in moderate yield. Use of H_2O_2

instead of TBHP only decomposed the starting material, and Grieco's procedure[9] (TBHP, Triton® B, THF) also gave decomposed products. Regioselective opening of the epoxide in **66** was achieved by sodium phenylseleno(triethoxy)borate, $Na^+[PhSeB(OEt)_3]^-$, which was explored in details by Miyashita *et al.*,[10,11] to afford **67** in moderate yield. No other diastereoisomers were found from the reaction products, though **67** was converted to **65** under this condition. The stereochemistry of the resulting hydroxyl group in **67** was determined on the basis of ^{1}H-NMR spectra, as shown in Figure 13.

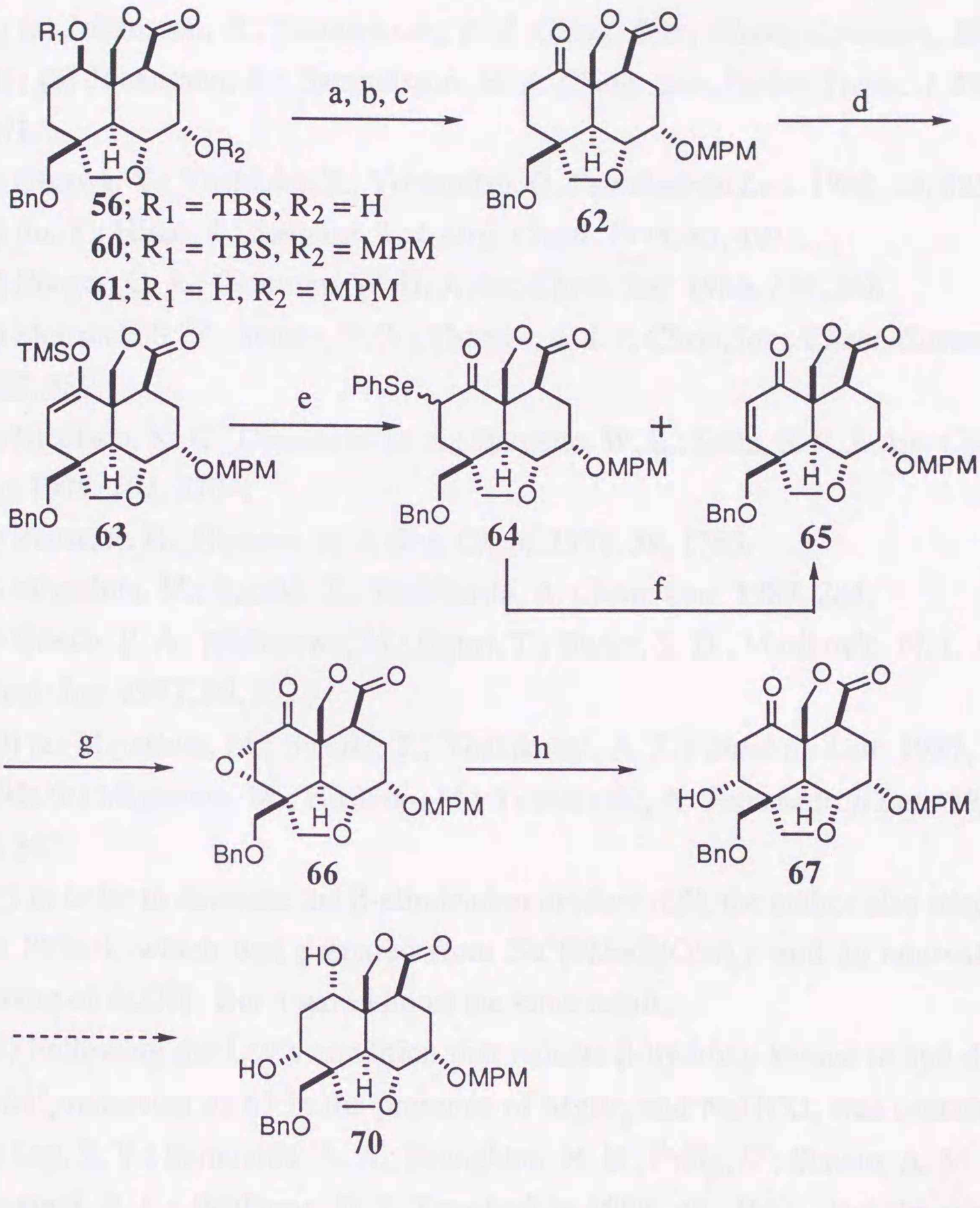
$J_{9\text{-}10}$ = 4.0 and 2.8 Hz



67

Figure 13

Thus, the author has constructed the important synthetic intermediate **67**, which is equivalent to the decalin fragment of azadirachtin, in the naturally occurring form. The problems which remain are the stereoselective reduction of C_1 ketone[12] as shown in Scheme 10, and to overcome the low yields in the last several steps. Furthermore, as mentioned at first in this chapter, azadirachtin has the tetrahydrofuran hemiacetal part instead of the γ-lactone, and the transformation of lactone to hemiacetal is one of the key step. The model studies of this transformation are discussed in the following chapter.



Reagents and conditions; a) MPM trichloroacetimidate, TfOH, Et_2O, r.t., 22 h, 70%; b) TBAF, THF, 0 °C to r.t., 12 h, 95%; c) PDC, MS3Å, CH_2Cl_2, r.t., 12 h, 84%; d) LDA, **62**, THF, -78 °C, 1 h, then TMSOTf, -78 °C, 25 min, 66% (78% based on recovered **62**); e) *N*-PSP, TMSOTf, THF, 0 °C to r.t., 2 h, 18% for **64**, 31% for **65**; f) $NaIO_4$, MeOH-H_2O (4:1), r.t., 8 h, 87%; g) TBHP, TBAF, DMSO, r.t., 50% (90% conversion); h) $Na^+[PhSeB(OEt)_3]^-$, AcOH, EtOH, r.t., 20 min, 56% for **67**, 39% for **65**

Scheme 10

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(1) (a) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201; (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc.,Perkin Trans. 1* **1984**, 2371.

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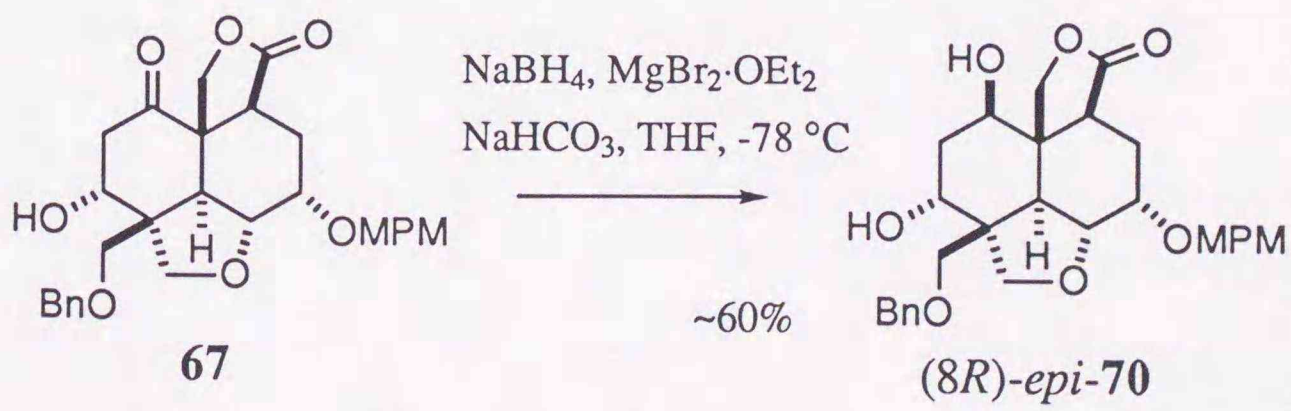
(10) (a) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293; (b) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron Lett.* **1988**, *29*, 347.

(11) In order to decrease the β-elimination product (**65**), the author also tried to use PhSeH, which was prepared from $Na^{+}[PhSeB(OEt)_3]^{-}$ and an equivalent amount of AcOH. But it gave almost the same result.

(12) Following the Ley's condition that reducts β-hydroxy ketone to syn diol, $NaBH_4$ reduction of **67** in the presence of $MgBr_2$ and $NaHCO_3$ was executed: see Ley, S. V.; Somovilla, A. A.; Broughton, H. B.; Craig, D.; Slawin, A. M. Z.; Toogood, P. L.; Williams, D. J. *Tetrahedron* **1989**, *45*, 2143. But the major product isolated was anti diol ((8*R*)-*epi*- **70**) in this case.



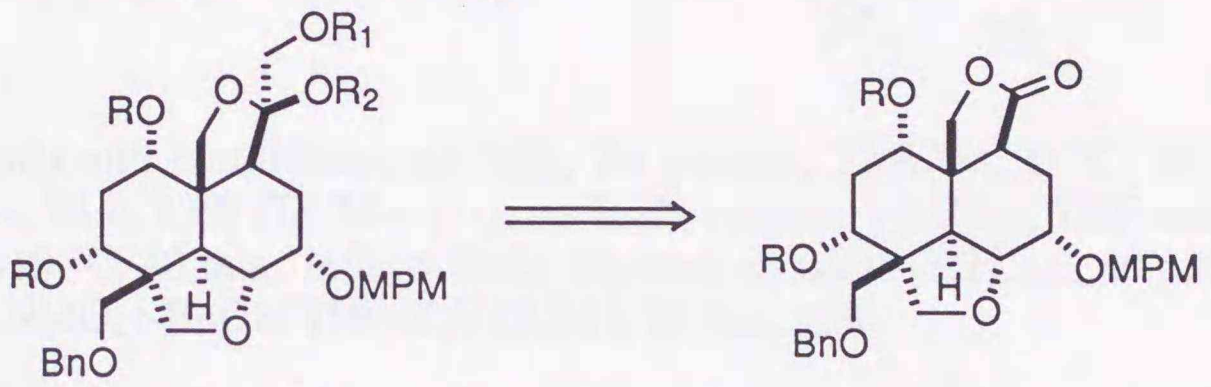
67 (8*R*)-*epi*-**70**

^{1}H-NMR data for (8*R*)-*epi*- **70** (400 MHz, C6D6), δ7.33-7.35 (2H, m, J_{ortho} = 8.4 Hz, two of $MeOC_6H_4CH_2$), 7.12-7.24 (5H, m, $C_6H_5CH_2$), 6.88 (2H, m, J_{ortho} = 8.4 Hz, two of $MeOC_6H_4CH_2$), 4.83, 4.57 (each 1H, d, J = 11.7 Hz, $MeOC_6H_4CH_2$), 4.23, 4.18 (each 1H, d, J = 11.9 Hz, $C_6H_4CH_2$), 4.15 (1H, d, J = 7.5 Hz, one of C_1-*H* or one of $BnOCH_2$), 4.05 (1H, brd, J = 9.0 Hz, one of C_7-*H*), 3.93 (1H, brd, J = 7.5 Hz, one of C_1-*H* or one of $BnOCH_2$), 3.84 (1H, brs, C_{10}-*H*), 3.80 (1H, brs, C_3-*H*), 3.56 (1H, d, J = 9.0 Hz, one of C_7-*H*), 3.50 (1H, m, C_8-*H*), 3.43 (1H, dd, J = 2.2, 12.5 Hz, C_{2a}-*H*), 3.35 (3H, s, $CH_3OC_6H_4$), 3.09 (1H, d, J = 9.2 Hz, one of C_1-*H* or one of $BnOCH_2$), 2.96 (1H, d, J = 12.5 Hz, C_{10b}-*H*), 2.76 (1H, brd, J = 9.2 Hz, one of C_1-*H* or one of $BnOCH_2$), 2.49 (1H, brdd, J = 5.9, 14.6 Hz, one of C_4-*H*), 2.33 (1H, ddd, J = 3.7, 5.9, 14.6 Hz, C_{4a}-*H*), 1.52 (1H, brt, J = 13.6 Hz, C_9-*H*), 1.29 (1H, m, C_9-*H*), and 1.05 (1H, dt, J = 2.2, 14.6 Hz, one of C_4-*H*).

Chapter 4

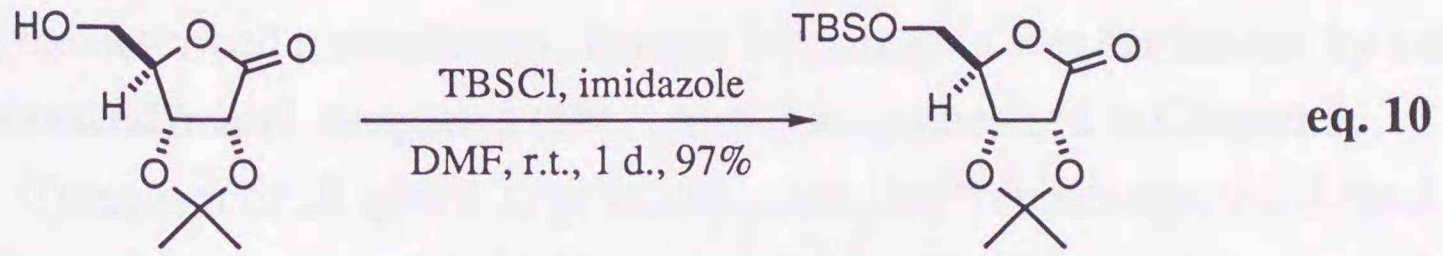
Model Study on Construction of the Tetrahydrofuran Hemiacetal Unit of Azadirachtin by Using Methylenation-Oxidation Strategy.

As described in Chapter 3, construction of the tetrahydrofuran hemiacetal unit in azadirachtin molecule is thought to be among the key transformations toward the total synthesis. The author planned to construct this part, starting from the corresponding γ-lactone, by methylenation of the carbonyl group followed by dihydroxylation of the exo methylene group, and undertook a model study in order to investigate the strategy.



eq. 9

Ribonolactone derivative (**72**) was chosen as the first model compound. Compound **72** was prepared by protection of the primary hydroxyl group of **71** (eq. 10), which was given by acetonide formation of 2,3-diol of ribonolactone.[1)]

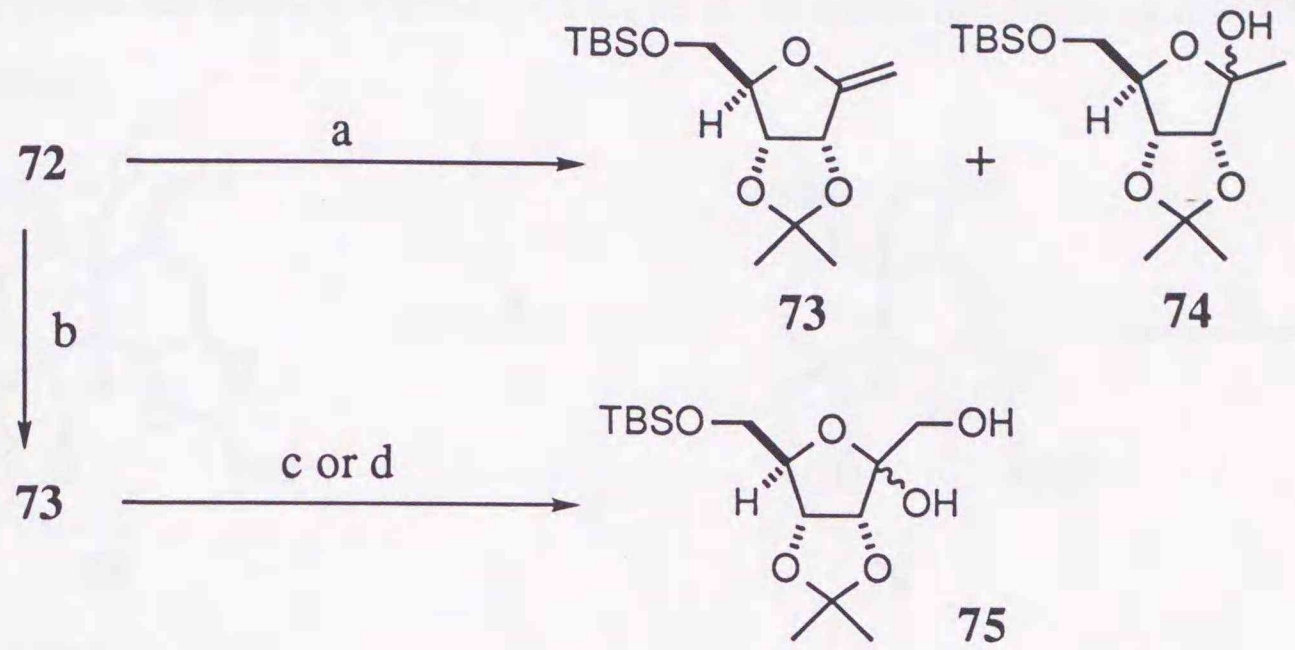


71 **72**

eq. 10

The methylenation reaction was then examined (Scheme 11). The author applied at first the procedure developed by Takai *et al.*[2)] to **72**. Although enol ether (**73**) was given from this procedure, nearly a half amount of **73** had been converted to hemiacetal (**74**) during the methylenation reaciton. However, this side reaction was suppressed when Tebbe reagent[3)] was used as an olefin metathesis reagent. Treatment of **72** with 1.5 eq. of Tebbe reagent in the presence of 2.2 eq. of pyridine at low temperature (-40 °C to -10 °C) afforded **73** in 76% yield.[4)] The next dihydroxylation was achieved by OsO_4 to afford **75** in 99% yield.

Catalytic dihydroxylation (0.1 eq. OsO_4, 1.2 eq. NMO) was also gave satisfactory results. The ratio of the resulting two diastereomers was varied between 5:1 and 3:1, while the relative stereochemistry of each compounds was not determined.



Reagents and conditions; a) $TiCl_4$, Zn powder, TMEDA, 0 °C, 70 min, then **72**, CH_2Br_2, 24 h, 63% (**73**:**74** = 1:1); b) Tebbe reagent, pyridine, THF-toluene (1:1), -45 °C to -10 °C, 40 min, 76%; c) OsO_4, benzene-pyridine (1:2), r.t., 40 min, 99%; d) cat. OsO_4, NMO, *t*-BuOH-THF-H_2O (2:2:1), 70 min, 92%

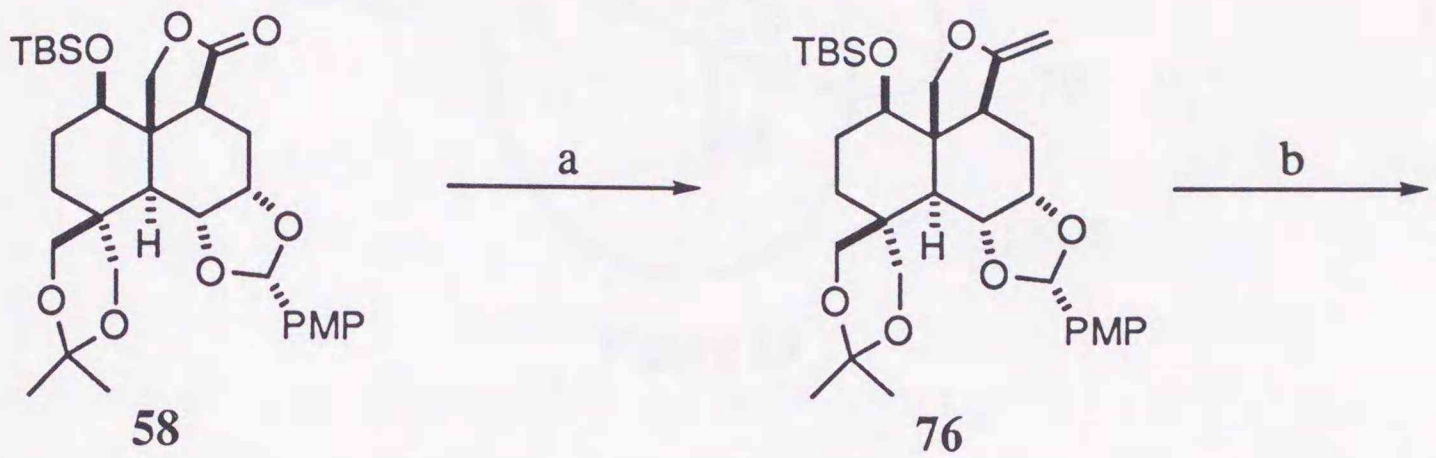
Scheme 11

Thus, the author was able to obtain hemiacetal (**75**) from lactone (**72**) by using the described methodology. Further investigation was carried out by using the advanced model compound (**58**), which was synthesized in Chapter 3.

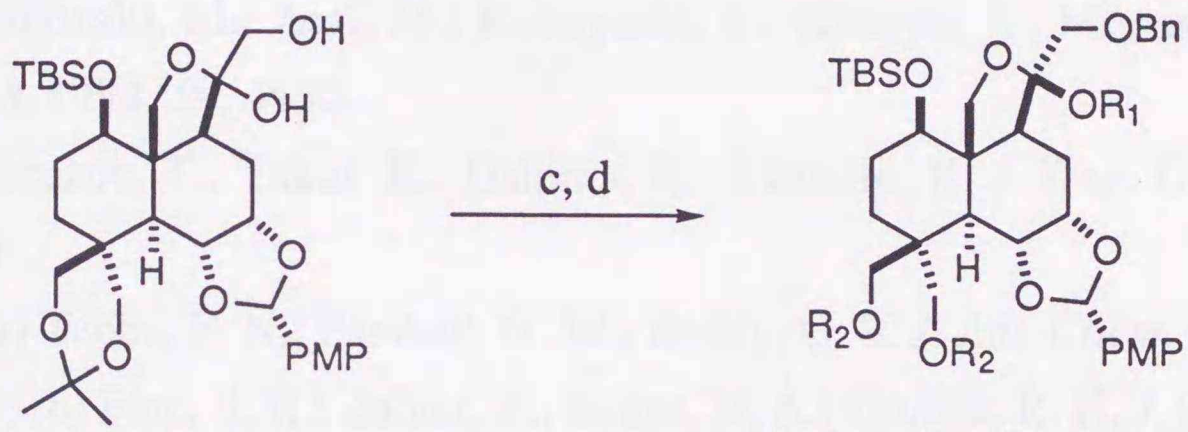
Treatment of **58** with a large excess amount of Tebbe reagent followed by dihydroxylation by using OsO_4 provided **77** in 72-90% yield for two steps (Scheme 12).[5] It should be noted that the olefin transfer reaction did not proceed when Tebbe regent was added up to 2 eq. for **58**, with which the former model compound (**72**) reacted to give the enol ether (**73**). The ratio of diastereomers for the hydroxyhemiacetal (**77**) was varied between 7:2 and 5:3. It is also noted that the major diastereomer isomerized to be the minor one even in neutral solvent such as C_6D_6.

The mixture of **77** was treated with excess BnBr and NaH in the presence of TBAI to afford **78** in 80% as a single isomer. The relative stereochemistry at

C_3 could not be determined in this compound. Acetal exchange of **78** using PPTS and MeOH afforded **79** as 7.5:1 mixture of diastereomer at C_3 in up to 69% yield. Observed NOEs for the major diastereomer **79** as depicted in Figure 13 confirmed the stereochemistry of C_3 as *S*, which is the same as that of natural azadirachtin.



58 **76**

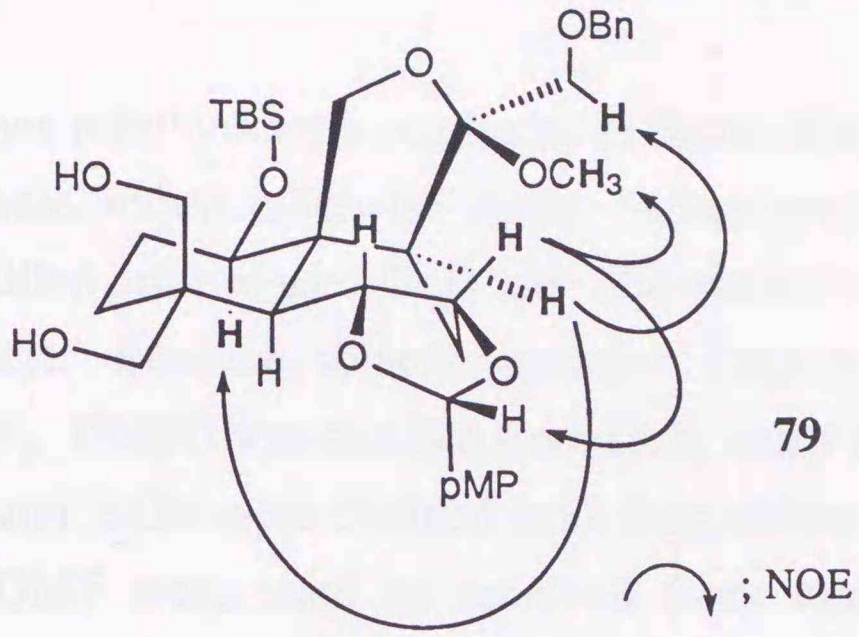


77

78; R_1 = Bn, R_2 = acetonide
79; R_1 = Me, R_2 = H

Reagents and conditions; a) excess Tebbe reagent, pyridine, toluene-THF (2:1), -45 °C to 0 °C; b) OsO_4, benzene-pyridine (6:1), r.t., 26 h, 77% for 2 steps; c) BnBr, NaH, TBAI, THF, 0 °C to r.t., 31 h, 80%; d) cat. PPTS, MeOH, r.t., 1 h, 69%.

Scheme 12



79

Figure 13

References and Notes

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(2) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410.

(3) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611; (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

(4) The small amount of acetal **74** was produced when reaction temperature was raised up to room temperature.

(5) In this procedure, complete purification of **76** was difficult because **76** was held in a viscous residue after work up. Therefore, almost purified **76** contained cyclopentadienyl derivatives and the oxidant used in the next step had to be added to excess.

Experimental section

All anhydrous reactions were conducted in flame-dried glasswares under an argon atmosphere, unless otherwise stated. All solvents except DMF and *t*-BuOH were distilled prior to use. Et_2O and THF were distilled from sodium benzophenone ketyl. Benzene, toluene, pyridine, CH_3CN and CH_2Cl_2 were distilled from CaH_2. DMSO was distilled from CaH_2 under reduced pressure (5 mmHg). MeOH and EtOH were distilled from magnesium turnings. *t*-BuOH and anhydrous DMF were used as received from commercial sources. Chromatography and extraction were carried out by using normal reagent-grade solvents. All reagents were used as received unless noted.

All reactions were monitored by thin-layer chromatography with precorted silica gel plates (E. Merck, Silica gel 60 F_{254} Art. 5715 and 5554), and compounds were visualized with ultraviolet light and/or ethanolic *p*-anisaldehyde (*p*-anisaldehyde/96% H_2SO_4/EtOH, 1:1:18, then heat). For chromatography was utilized silica gel (YMC, YMCGEL SIL-60-230/70W and SIL-60-400/230W). HPLC were run with Waters Associates 6000A liquid chromatography equipped with Waters Associates differential reflactometer R401.

Melting points were measured on Yanagimoto Seisakusyo Micro melting point apparatus (Serial No. 989) and uncorrected. Optical Rotations were recorded on JASCO model DIP-360 digital polarimeter in appropriate solvents. Low- and high resolution mass spectra were obtained on JEOL JMS-DX303, JEOL HX110, JEOL JMS-AX500, and JEOL JMS-SX102A spectrometers. Infrared spectra were measured on Hitachi model 270-30 infrared spectrometer in noted state.

^{1}H-NMR spectra were measured on JEOL JNM-FX270 (270 MHz), JNM-EX400 (400 MHz) and JNM-α400 (400 MHz) spectrometers. Chemical shifts are reported in δ units (ppm); coupling constants are reported in Hz. Splitting patterns were designed as "s, d, t, q, m, and br"; these symbols indicate "singlet, doublet, triplet, quartet, multiplet, and broad", respectively. Tetramethylsilane (δ0.00) was used as an internal reference for spectra measured in $CDCl_3$, and residual benzene (δ7.20) in C_6D_6. ^{13}C-NMR spectra were measured at 100 MHz

on JNM-α400 spectrometer, and residual $CHCl_3$ (δ77.0) was used as internal standard.

Ethyl 2-[2'-(1'', 3''-dioxolan-2''-yl)ethyl]malonate (2)

To sodium metal (23.9 g, 1.04 mol) was slowly added ethanol (440 mL) at 0 °C and the mixture was stirred at the same temperature for 1 h. Diethyl malonate (155 mL, 1.02 mol) was added to the resulting solution of sodium ethoxide *via* syringe. Then, the reaction mixture turned into white solid and was heated at 55 °C until it melt completely. 2-(2-bromoethyl)-1,3-dioxolane (170.6 g, 0.94 mol) was added to the mixture over 35 min. After 25 min, the reaction mixture was concentrated *in vacuo*, then extracted with EtOAc (3×500 mL). The combined organic extracts were washed with sat. aq. NH_4Cl, water and brine, dried over anhydrous $MgSO_4$, filtrated through cotton, concentrated *in vacuo*, and distilled *in vacuo* to afford **2** (178.7 g, 0.69 mol, 73%) as a colorless liquid: b.p., 156-161°C/3 mmHg; ^{1}H-NMR (270 MHz, $CDCl_3$), δ4.89 (1H, t, J = 4.6 Hz), 4.20 (4H, q, J = 7.3 Hz), 3.81-4.00 (4H, m), 3.41 (1H, t, J = 7.6 Hz), 2.03 (2H, m), 1.72 (2H, m), and 1.27 (6H, t, J = 7.3 Hz); IR (neat), ν_{max} 2984, 2892, 1734, 1452, 1372, 1258, 1228, 1146, 1028, 946, and 860 cm^{-1}; EI-LR-MS, m/z 260 (M^+, 0.1%), 215 (4), 171 (11), 149 (6), 99 (14), 73 (100), 69 (8), 57 (11), 45 (18), and 41 (11); EI-HR-MS, calcd. for $C_{12}H_{20}O_6$ 260.1260, found 260.1227; TLC (hexane/EtOAc, 1:1), R_f 0.46.

Ethyl 2-allyl-2-[2'-(1'', 3''-dioxolan-2''-yl)ethyl]malonate (3)

Ethanol (50 mL) was slowly added to sodium (1.45 g, 63 mmol) at ambient temperature, and this mixture was stirred until it became a homogeneous solution. To the solution was added **2** (13 g, 50 mmol) in ethanol (20 mL) *via* syringe and the mixture was stirred for 30 min. Allyl iodide (6 mL, 65.7 mmol) was added dropwise *via* syringe. After 20 min, the reaction was quenched with sat. aq. NH_4Cl (4 mL), and then concentrated *in vacuo*. The residue was added to water, extracted with EtOAc (2×300 mL), and the combined organic extracts were washed successively with water and brine, dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification by silica gel

column chromatography (230/70W, 100 g, EtOAc/hexane 5:1) afforded **3** (14.2 g, 47.3 mmol, 95%) as a pale yellow oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.66 (1H, ddt, J = 17.1, 9.6, 7.6 Hz), 5.11 (1H, brd, J = 17.1 Hz), 5.09 (1H, brd, J = 9.6 Hz), 4.86 (1H, t, J = 4.6 Hz), 4.18 (4H, q, J = 7.3 Hz), 3.80-4.00 (4H, m), 2.64 (2H, d, J = 7.6 Hz), 2.00 (2H, m), 1.59 (2H, dt, J = 12.5, 4.6 Hz), and 1.24 (6H, t, J = 7.3 Hz); IR (neat), ν_{max} 3080, 2984, 2884, 1734, 1664, 1450, 1370, 1270, 1210, 1192, 1146, and 1034 cm^{-1}; EI-LR-MS, m/z 300 (M^+, 0.1%), 299 (0.4), 255 (4), 199 (7), 153 (9), 99 (22), 86 (4), 73 (100), 57 (3), 45 (14), and 41 (6); EI-HR-MS, calcd. for $C_{15}H_{24}O_6$ 300.1573, found 300.1595; TLC (hexane/EtOAc, 5:1), R_f 0.34.

2-Allyl-2-[2'-(1'', 3''-dioxolan-2''-yl)ethyl]-1,3-propanediol (4)

To a vigorously stirred Et_2O (400mL) was slowly added $LiAlH_4$ (5 g, 0.13 mol) at 0 °C. A solution of **3** (33 g, 0.11 mol) in Et_2O (50 mL) was added over 10 min *via* syringe to the resulting suspension at the same temperature. (Gray clayey compound was formed during the addition.) The reaction mixture was stirred at ambient temperature for 100 min, and then additional amounts of $LiAlH_4$ (total 1.5 g, 39 mmol) were added over 3 h. To the reaction mixture was slowly added EtOAc until exothermal reaction ceased, and then 2 M aq. NaOH (20 mL) was added. The resulting mixture was stirred further 20 min (white precipitate was formed during this period), and filtrated through Celite pad. The filtrate was concentrated and dried *in vacuo* to afford crude **4** (24.03 g) as a pale yellow oil. This material was used without further purification: ^{1}H-NMR (270 MHz, $CDCl_3$), δ6.81 (1H, ddt, J = 15.5, 11.2, 7.3 Hz), 5.10 (1H, brd, J = 15.5 Hz), 5.09 (1H, brd, J = 11.2 Hz), 4.86 (1H, t, J = 4.6 Hz), 3.80-4.04 (4H, m), 3.57 (4H, s), 2.46 (2H, brs), 2.03 (2H, brd, J = 7.3 Hz), and 1.42-1.72 (4H, m); IR (neat), ν_{max} 3432, 3076, 2888, 1642, 1416, 1230, 1130, 1036, 946, 920, and 868 cm^{-1}; EI-LR-MS, m/z 216 (M^+, 0.1%), 215 (0.4), 154 (2), 123 (3), 106 (6), 99 (8), 86 (9), 73 (100), 67 (8), 57 (15), 45 (34), and 41 (16); EI-HR-MS, calcd. for $C_{11}H_{20}O_4$ 216.1362, found 216.1352; TLC (hexane/EtOAc, 1:1), R_f 0.14.

2-[3',3'-Bis(acetoxymethyl)hex-5-enyl]-1,3-dioxolane (5)

To a stirred solution of crude **4** (5.00 g, 23.1 mmol), Ac_2O (5.0 mL, 53.0 mmol), and Et_3N (10 mL, 71.7 mmol) in CH_2Cl_2 (30 mL) was added DMAP (130 mg, 1.06 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature, stirred for 35 min, and then poured into water. The aqueous layer was extracted with CH_2Cl_2 (2×125 mL). The combined organic extracts were washed successively with sat. aq. NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtrated through cotton, and then concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (230/70W, 150 g, hexane/EtOAc 7:1-2:1) afforded **5** (6.18 g, 20.6 mmol, 89% for 2 steps) as a colorless oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.75 (1H, ddt, J = 16.8, 10.2, 7.6 Hz), 5.11 (1H, brd, J = 10.2 Hz), 5.08 (1H, brd, J = 16.8 Hz), 4.82 (1H, t, J = 4.6 Hz), 3.93 (4H, s), 3.82-3.99 (4H, m), 2.11 (2H, brd, J = 7.6 Hz), 2.06 (6H, s), 1.56-1.70 (2H, m), and 1.43-1.49 (2H, m); IR (neat), ν_{max} 3076, 2960, 1746, 1742, 1368, 1232, 1132, 1040, 946, 920, and 878 cm^{-1}; EI-LR-MS, m/z 300 (M^+, 0.07%), 299 (0.4), 167 (0.9), 136 (0.9), 118 (1.3), 101 (1.1), 87 (12.5), 73 (100), 45 (15), and 43 (44.2); EI-HR-MS, calcd. for $C_{15}H_{24}O_6$ 300.1573, found 300.1565; TLC (hexane/EtOAc, 1:1), R_f 0.50.

2-[3',3'-Bis(acetoxymethyl)hex-5-enyl]-1,3-dithiane (6)

To a cooled (0 °C) and vigorously stirred solution of **5** (21.9 g, 73.0 mmol) and 1,3-propanedithiol (9.0 mL, 89.6 mmol) in CH_2Cl_2 (150 mL) was added $TiCl_4$ (2.0 mL, 18.2 mmol) over 5 min *via* syringe. The reaction mixture turned into bright red solution instantaneously, then became a yellowish-white suspension, and finally faded into white color. After 13 min, an additional amount of $TiCl_4$ (2.0 mL, 18.2 mmol) was added to the reaction mixture. The mixture became yellowish-white again, and was stirred additional 9 min. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), allowed to warm to room temperature, and then poured into water (100 mL), extracted with EtOAc (2×300 mL). The combined organic extracts were washed successively with water and brine (each 100 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel column

chromatography (230/70W, 500 g, hexane/EtOAc 7:1-2:1) afforded **6** (24.65 g, 71.2 mmol, 98%) as a pale yellow oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.74 (1H, ddt, J = 16.5, 10.2, 7.6 Hz), 5.13 (1H, brd, J = 10.2 Hz), 5.10 (1H, brd, J = 16.5 Hz), 3.98 (1H, t, J = 6.3 Hz), 3.92 (4H, s), 2.80-2.94 (4H, m), 2.10 (2H, brd, J = 7.6 Hz), 2.07 (6H, s), and 1.54-1.93 (6H, m); IR (neat), ν_{max} 2936, 1738, 1426, 1366, 1246, 1042, 910, and 870 cm^{-1}; EI-LR-MS, m/z 346 (M^+, 17%), 287 (9), 213 (7), 145 (23), 132 (12), 119 (71), 106 (30), 73 (17), and 43 (100); EI-HR-MS, calcd. for $C_{12}H_{26}O_4S_2$ 346.1273, found 346.1284; TLC, (hexane:EtOAc, 1:1) R_f 0.60.

2-Allyl-2-[2'-(1'',3''-dithian-2''-yl)ethyl]-1,3-propanediol (7)

To a cooled (0 °C) and vigorously stirred suspension of $LiAlH_4$ (4.09 g, 107.6 mmol) in Et_2O (100 mL) was added **6** (11.29 g, 32.63 mmol) dropwise in Et_2O (100 mL) over 21 min. The reaction mixture was stirred at the same temperature for 1.5 h, then quenched with water (4 mL), and stirred for 30 min. Then, 4 M aq. NaOH (4 mL) was added to the mixture. The mixture was stirred for 30 min, and water (8 mL) was added again. The resulting mixture was stirred at room temperature for 1 h, and filtrated through Celite pad. The filtrate was concentrated *in vacuo* to afford crude **7** (7.17 g) as white crystals. This material was used without further purification: m.p., 86-88 °C; ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.81 (1H, ddt, J = 16.5, 10.9, 7.6 Hz), 5.12 (1H, brd, J = 16.5 Hz), 5.11 (1H, brd, J = 10.9 Hz), 3.99 (1H, t, J = 6.9 Hz), 3.58 (4H, brs), 2.80-2.94 (4H, m), and 1.51-2.18 (10H, m); IR ($CHCl_3$), ν_{max} 3632, 3460, 3076, 1640, 1426, 1278, 1036, 922, and 866 cm^{-1}; EI-LR-MS, m/z 262 (M^+, 25%), 187 (21), 145 (24), 119 (100), 106 (42), 73 (32), 45 (44), and 41 (78); EI-HR-MS, calcd. for $C_{12}H_{22}O_2S_2$ 262.1062, found 262.1066; TLC (hexane/EtOAc, 1:1), R_f 0.14.

5-Allyl-5-[2'-(1'',3''-dithian-2''-yl)ethyl]-2,2-dimethyl-1,3-dioxane (8)

A solution of crude **7** (7.17 g), 2, 2-dimethoxypropane (5 mL, 40.6 mmol), and PPTS (359 mg, 1.43 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature. After 4 h, an additional amount of 2, 2-dimethoxypropane (1.0

mL, 8.13 mmol) was added. The reaction mixture was stirred further 30 min, and then mixed with sat. aq. $NaHCO_3$ (10 mL). The organic layer was washed successively with water and brine (each 10 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (230/70W, 100 g, hexane/EtOAc 7:1-4:1) afforded **8** (7.22 g, 23.9 mmol, 73% for 2 steps) as a colorless oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.76 (1H, ddt, J = 9.6, 17.5, 7.5 Hz), 5.12 (1H, brd, J = 17.5 Hz), 5.11 (1H, brd, J = 9.6 Hz), 3.98 (1H, t, J = 6.3 Hz), 3.56 (4H, s), 2.80-2.94 (4H, m), 2.17 (2H, brd, J = 7.5 Hz), 2.06 (1H, m), 1.50-1.92 (5H, m), and 1.40 (6H, s); IR (neat), ν_{max} 2992, 2940, 2860, 1456, 1424, 1372, 1202, 1156, 1092, 914, and 834 cm^{-1}; EI-LR-MS, m/z 302 (M^+, 17%), 287 (21), 213 (24), 132 (40), 119 (58), 106 (26), 91 (28), 79 (50), 43 (100); EI-HR-MS, calcd. for $C_{15}H_{26}O_2S_2$ 302.1375, found 302.1397; TLC (hexane/EtOAc, 1:1), R_f 0.74.

3-(5'-Allyl-2',2'-dimethyl-1',3'-dioxan-5'-yl)propanal (9)

To a stirred suspension of **8** (19.91 g, 65.9 mmol), $CaCO_3$ (13.19 g, 131.8 mmol) in CH_3CN (600 mL) and water (110 mL) was added methyl iodide (55 mL, 0.883 mol) *via* syringe. The resulting mixture was warmed to 40 °C, and stirred for 8 h, then allowed to cool to room temperature for 10 h. The mixture was concentrated *in vacuo* to a volume of ca.100 mL. The residue was extracted with Et_2O (3×300 mL), and the combined organic extracts were washed successively with 10% aq. $Na_2S_2O_3$, water, and brine (each 50 mL). The combined aqueous layers were extracted further thrice with Et_2O (each 100 mL). The organic layers were dried over anhydrous $MgSO_4$, filtrated, concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 100 g, hexane/Et_2O 1:1) afforded **9** (9.90 g, 46.7 mmol, 71%) as a pale yellow oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ9.79 (1H, t, J = 1.7 Hz), 5.72 (1H, ddt, J = 16.0, 10.9, 7.6 Hz), 5.11 (1H, d, J = 10.9 Hz), 5.10 (1H, d, J = 16.0 Hz), 3.63 ,3.55 (each 2H, d, J = 11.9 Hz), 2.46 (2H, dt, J = 1.7, 7.9 Hz), 2.10 (2H, brd, J = 7.6 Hz), 1.73 (2H, m), 1.41 and 1.40 (each 3H, s); IR (neat), ν_{max} 2992, 2940, 2864, 2720, 1726, 1640, 1454, 1372, 1256, 1198, 1156, 1098, 1078, 1034, 998, 920, and 830 cm^{-1}; EI-LR-MS, m/z 197 (48.5%, M^+-Me), 155 (6.6), 137 (7.1), 93

(26.7), 67 (48.3), 59 (35.3), 43 (100); EI-HR-MS, calcd. for $C_{11}H_{17}O_3$ (M^+-Me), 197.1178, found 197.1161; TLC (hexane/EtOAc, 1:1), R_f 0.57.

4-Bromo-2-[(triisopropylsilyl)oxy]furan (13)

To a cooled (0 °C) solution of 4-bromo-2,5-dihydro-2-furanone (**10**) (31.51 g, 193.3 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (31 mL, 222.4 mmol) and TIPSOTf (55 mL, 204.6 mmol) *via* syringe. The resulting solution was stirred for 10 min, then diluted with Et_2O (200 mL), and washed successively with sat. aq. NH_4Cl and sat. aq. $NaHCO_3$ (each 50 mL). The organic layer was diluted with further Et_2O (100mL), washed with water and brine (each 50 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (230/70W, 250 g, hexane) afforded **13** (56.95 g, 178.5 mmol, 92%) as a pale yellow liquid. On a small scale reaction, **13** was provided as a colorless liquid. This material was slowly decomposed and turned into orange brown liquid on storage at -20 °C: ^{1}H-NMR (270 MHz, $CDCl_3$), δ6.83 (1H, d, J = 1.3 Hz), 5.24 (1H, d, J = 1.3 Hz), 1.18-1.31 (3H, m), and 1.09 (18H, d, J = 6.9 Hz); IR (neat), ν_{max} 3168, 2952, 2872, 1614, 1466, 1358, 1272, 1100, 958, and 920 cm^{-1}; EI-LR-MS, 320 (M^+, 30%), 318 (M^+, 29), 249 (3), 147 (3), 207 (7), 205 (7), 115(100), 87 (65), 73 (74), and 59 (84); EI-HR-MS, calcd. for $C_{13}H_{23}O_2SiBr$ 318.0651, found 318.0651; TLC (hexane/EtOAc, 5:1), R_f 0.74.

4-[3'-(5''-Allyl-2'',2''-dimethyl-1'',3''-dioxan-5''-yl)-1'-hydroxypropyl]-2,5-dihydro-2-furanone (16)

To a cooled (-78 °C) and stirred solution of **13** (1.60 g, 5.02 mmol) in Et_2O (10 mL) was added *n*-BuLi (1.64 M in hexane, 2.5 mL, 4.10 mmol) *via* syringe and the mixture was stirred for 1 h. To the resulting orange brown solution of **14** were added a solution of **9** (0.70 g, 3.30 mmol) in Et_2O (2 mL) *via* syringe along with Et_2O rinse (2 mL), and the reaction mixture was stirred for 1 h and quenched with sat. aq. NH_4Cl (5 mL), then allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with water and brine (each 10 mL), dried

over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo* to afford crude **15** (2.11 g) as a yellowish brown oil. This material was dissolved in THF (10 mL), and cooled (0 °C). TBAF (1.0 M solution in THF, 5 mL, 5.0 mmol) was added to the stirred yellowish brown solution *via* syringe. The resulting dark brown solution was stirred for 15 min, and then poured into sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with water and brine (each 5 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 40 g, hexane/EtOAc 2:1-1:2) afforded **16** (551 mg, 1.86 mmol, 56% for 2 steps) as a brown oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.98 (1H, brs), 5.71 (1H, ddt, J = 16.5, 10.2, 7.9 Hz), 5.12 (1H, brd, J = 10.2 Hz), 5.11 (1H, brd, J = 16.5 Hz), 4.88 (2H, brs), 4.63 (1H, brt, J = 5.6 Hz), 3.64 (2H, d, J = 11.9 Hz), 3.52 (2H, d, J = 11.9 Hz), 2.06 (2H, d, J = 8.2 Hz), 1.47-1.85 (4H, m), 1.42 (3H, s), and 1.39 (3H, s); IR (neat), ν_{max} 3432, 2940, 2864, 1778, 1748, 1640, 1454, 1374, 1262, 1198, 1094, 924, 893, and 832 cm^{-1}; FAB-LR-MS, m/z 297 (M^++1, 29%), 289 (18), 239 (11), 219 (12), 154 (100), 136 (74), 107 (26), 91 (20), 69 (24), and 55 (22); FAB-HR-MS, calcd. for $C_{16}H_{26}O_5$ (M^++1) 297.1702, found 297.1728; TLC (hexane/EtOAc, 1:2), R_f 0.34.

(1'*R*)-4-[3'-(5''-Allyl-2'',2''-dimethyl-1'',3''-dioxan-5''-yl)-1'-hydroxy-propyl]-2,5-dihydro-2-furanone (+)-(16)

To the cold (-10 °C) solution of oxazaborolidine (1.0 M toluene solution, 0.30 mL, 0.30 mmol) in THF (5 mL) was added neat $BH_3 \cdot SMe_2$ complex (ca. 10.1 M, 0.1 mL, 1.05 mmol) *via* syringe, and the resulting solution was stirred for 10 min. To the solution was added **40** (449.6 mg, 1.00 mmol) in THF (2.5 mL) *via* syringe along with THF wash (2.5 mL). The reaction mixture was stirred for 10 min at the same temperature, then quenched by the cautious addition of sat. aq. NH_4Cl (2 mL), allowed to warm to room temperature, and concentrated *in vacuo*. The aqueous residue was extracted with Et_2O (3×5 mL). The combined organic layers were washed with water and brine (each 3 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in*

vacuo to afford crude **42**. This material was dissolved in THF (5 mL) and cooled to 0 °C. To the solution was added TBAF (1.0 M solution in THF, 1.0 mmol) *via* syringe and the resulting yellowish brown solution was stirred for 10 min at the same temperature, then sat. aq. NH_4Cl (10 mL) was added to the solution. The resulting mixture was allowed to warm to room temperature, and concentrated *in vacuo*. The aqueous residue was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 10 g, hexane/EtOAc 1:1-1:2) afforded (+)-**16** (306.2 mg, 1.00 mmol, 100% for 2 steps) as a brown oil; $[\alpha]_D^{24}$ +4.2° (c 1.47, $CHCl_3$). Caution: The value of optical rotation of this material lacked reproducibility. Optical purity of this material was estimated to be 97% e.e. from Mosher method.

4-[1'-(*tert*-Butyldimethylsilyl)oxy-3'-(5''-allyl-2'',2''-dimethyl-1'',3''-dioxan-5''-yl)propyl]-2,5-dihydro-2-furanone (17)

A solution of **16** (559.7 mg, 1.89 mmol), TBSCl (327.3 mg, 2.17 mmol), and imidazole (155.3 mg, 2.28 mmol) in DMF (2 mL) was stirred at room temperature for 10 h. Purification of the reaction mixture by silica gel chromatography (230/70W, 40 g, hexane/EtOAc 5:1-1:1) afforded **17** (588.2 mg, 1.43 mmol, 76%) as a colorless oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.93 (1H, dt, J = 2.0, 1.5 Hz), 5.69 (1H, ddt, J = 16.9, 10.8, 7.7 Hz), 5.10 (1H, brd, J = 10.8 Hz), 5.08 (1H. brd, J = 16.9 Hz), 4.80 (2H, d, J = 1.5 Hz), 4.63 (1H, brt, J = 6.2 Hz), 3.60 (2H, dd, J = 11.6, 1.7 Hz), 3.50 (2H, d, J = 11.6 Hz), 2.07 (2H, d, J = 7.7 Hz), 1.37-1.67 (4H, m), 1.40, 1.38 (each 3H, s), 0.91 (9H, s), 0.10, and 0.04 (each 3H, s); IR (neat), ν_{max} 2992, 2932, 2856, 1780, 1752, 1642, 1454, 1372, 1260, 1198, 1092, 1030, 916, 884, and 836 cm^{-1}; FAB-LR-MS, m/z 411 (M^++1, 30%), 395 (31), 353 (21), 295 (19), 221 (27), 147 (22), 136 (20), and 73 (100); FAB-HR-MS, calcd. for $C_{22}H_{39}O_5Si$ 411.2567, found 411.2560; TLC (hexane/EtOAc, 1:1), R_f 0.61.

(1'*R*)-4-[1'-(*tert*-Butyldimethylsilyl)oxy-3'-(5''-allyl-2'',2''-dimethyl-1'',3''-dioxan-5''-yl)propyl]-2,5-dihydro-2-furanone (+)-(17)

$[\alpha]_D^{22}$ +14.2° (c 0.98, $CHCl_3$).

2-[5'-[3''-(*tert*-Butyldimethylsilyl)oxy-3''-(2''',5'''-dihydro-2'''-oxofuran-4'''-yl)propyl]-2',2'-dimethyl-1',3'-dioxan-5'-yl]ethanal (18)

To a cloudy solution of **17** (188.8 mg, 0.46 mmol) and NMO (65.0 mg, 0.56 mmol) in THF (2.5 mL) and water (1.25 mL) was added OsO_4 (19.7 mM solution in *t*-BuOH, 2.5 mL, 0.049 mmol) *via* syringe, then the resulting homogeneous solution was stirred at room temperature for 13 h. The excess oxidizer was quenched by adding $NaHSO_3$ (175 mg). The mixture was stirred for a additional 5 h, filtrated through Celite pad, and concentrated *in vacuo* to afford crude diol (244.5 mg) as a pale yellow oil. The material was dissolved in MeOH (4 mL) and stirred at 0 °C. A solution of $NaIO_4$ (121.0 mg, 0.566 mmol) in water (3 mL) was added to the solution, and the resulting mixture was stirred at the same temperature for 20 min, then filtrated through Celite pad, and concentrated *in vacuo*. The residue was poured into water (10 mL), extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 4 g, hexane/EtOAc 3:1-1:1) afforded **18** (184.6 mg, 0.45 mmol, 97% for 2 steps) as a colorless oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ9.88 (1H, t, J = 1.8 Hz), 5.93 (1H, m), 4.79 (2H, d, J = 1.5 Hz), 4.62 (1H, brt, J = 4.4 Hz), 3.69 (2H, d, J = 11.5 Hz), 3.65 (2H, d, J = 11.5 Hz), 2.58 (2H, d, J = 1.8 Hz), 1.35-1.70 (4H, m), 1.42, 1.41 (each 3H, s), 0.91 (9H, s), 0.04, and 0.09 (each 3H, s); IR (neat), ν_{max} 2992, 2932, 2856, 1780, 1752, 1644, 1464, 1374, 1260, 1200, 1086, 1026, 938, and 836 cm^{-1}; EI-LR-MS, m/z 397 (M^+-CH_3, 3%), 355 (2), 337 (2), 297 (23), 253 (11), 205 (14), 177 (20), 149 (18), 131 (21), 95 (29), 75 (100), 59 (28), and 43 (51); FAB-HR-MS, calcd. for $C_{21}H_{36}O_6Si$ 412.2281, found 412.2254; TLC (hexane/EtOAc, 2:3), R_f 0.49.

(3''*R*)-2-{5'-[3''-(*tert*-Butyldimethylsilyl)oxy-3''-(2''',5'''-dihydro-2'''-oxofuran-4'''-yl)propyl]-2',2'-dimethyl-1',3'-dioxan-5'-yl}ethanal (+)-(18)

$[\alpha]_D^{23}$ +14.6° (c 1.01, $CHCl_3$).

(1'*S,2'''*S**)-4-[1'-(*tert*-Butyldimethylsilyl)oxy-3'-[5''-(2'''-hydroxybut-3'''-enyl)-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]propyl]-2,5-dihydro-2-furanone (19a) and its C-1' Epimer (19b)**

To a cooled (-78 °C) and stirred solution of **18** (17.28 g, 41.9 mmol) in THF (250 mL) was added vinylmagnesium bromide (1.0 M solution in THF, 47.0 mL, 47.0 mmol) over 5 min *via* syringe, and the reaction mixture was stirred at the same temperature for 14 min, then quenched with sat. aq. NH_4Cl (150 mL), concentrated *in vacuo* until THF was almost distilled off. The residue was extracted with EtOAc (3×200 mL), and the combined organic extracts were washed with brine (100 mL). The brine layer was extracted again with EtOAc (100 mL). Then combined organic layers were dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo* to afford crude **19**. This material was dissolved in EtOH (200 mL) and stirred at 0 °C. To the solution was added $NaBH_4$ (491.2 mg, 13.0 mmol), and the resulting mixture was stirred for 20 min. The reaction mixture was quenched by slow addition of sat. aq. NH_4Cl (50 mL), concentrated *in vacuo*, poured into water (100 mL), and extracted with EtOAc (3×200 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 250 g, hexane/EtOAc 4:1-1:2) afforded **19** (as a 1:1 mixture of diastereomers, 10.27 g, 23.3 mmol, 56% for 2 steps) as a pale yellow oil followed by almost pure alcohol **34** (This material contained ca. 12% of a structure unknown compound, total 5.34 g, 12.9 mmol, ca. 27%) as a viscous pale yellow oil. **19**: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.94 (1H, m), 5.88 (1H, ddd, J = 17.3, 11.6, 6.9 Hz), 5.24 (1H, dt, J = 17.3, 0.9 Hz), 5.09 (1H, dt, J = 11.6, 0.8 Hz), 4.81 (2H, m), 4.66 (1H, m), 4.41 (1H, m), 3.55-3.76 (4H, m), 1.30-1.67 (6H, m), 1.42, 1.41 (each 3H, s), 0.92 (9H, s), 0.10, and 0.05 (each 3H, s); IR (neat),

ν_{max} 3464, 2932, 2856, 1780, 1752, 1642, 1464, 1372, 1258, 1146, 1084, 936, and 838 cm^{-1}; FAB-LR-MS, m/z 440 (M^+, 4%), 425 (11), 383 (24), 365 (11), 251 (51), 136 (39), 75 (100), and 59 (26); FAB-HR-MS, calcd. for $C_{23}H_{40}O_6Si$ 440.2594, found 440.2565; TLC (PhH/CH_3CN, 3:1), R_f 0.57.

(1'*R*,2'''*S*)-4-[1'-(*tert*-Butyldimethylsilyl)oxy-3'-[5''-(2'''-hydroxybut-3'''-enyl)-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]propyl]-2,5-dihydro-2-furanone (+)-(19a) and its C-2''' Epimer (+)-(19b)

$[\alpha]_D^{23}$ +13.0° (c 1.32, $CHCl_3$).

(1'*S,2'''*S**)-4-[1'-(*tert*-Butyldimethylsilyl)oxy-3'-[5''-(2'''-methoxycarbonyloxy-but-3''-enyl)-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]propyl]-2,5-dihydro-2-furanone (20a) and its C-1' Epimer (20b)**

To a cooled (0 °C) and stirred solution of **19** (758.5 mg. 1.70 mmol) and pyridine (0.70 mL, 8.65 mmol) in CH_2Cl_2 (10 mL) was added methyl chloroformate (0.52 mL, 6.73 mmol) over 16 min *via* syringe, during which time the mixture became yellowish-white suspension and gas was evolved. The resulting mixture was stirred at the same time for 70 min, allowed to warm to room temperature over 40 min, then quenched with sat. aq. NH_4Cl (10 mL), and extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue with silica gel column chromatography (400/230W, 23 g, hexane/EtOAc 4:1-1:1) afforded **20** (as a 1:1 mixture of diastereomers, 604.0 mg, 1.20 mmol, 71%) as a pale yellow oil followed by recovered **19** (233.0 mg, 0.53 mmol, 31%). **20**: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.97 (1/2H, dt, J = 1.5, 1.0 Hz), 5.94 (1/2H, q, J = 1.0 Hz), 5.79 (1H, ddt, J = 5.5, 10.0, 16.5 Hz), 5.29 (1H, brd, J = 16.5 Hz), 5.15-5.33 (2H, m), 4.86 (2H, m), 4.74 , 4.60 (each, 1/2H, m), 3.76 (3H, s), 3.48-3.66 (4H, m), 1.48-1.80 (6H, m), 1.39, 1.37 (each 3H, s), 0.92, 0.91 (each 9/2H, s), 0.11 (3H, s), 0.06, and 0.05 (each 3/2H, s); IR (neat), ν_{max} 2956, 1780, 1754, 1446, 1264, 1094, 838, and 778 cm^{-1}; FAB-LR-MS, m/z 499 (M^++1, 1.5%), 423 (100), 365 (41), 233 (27), 215 (18), and 73 (89); FAB-HR-MS, calcd. for $C_{25}H_{43}O_8Si$ (M^++1) 499.2728,

found 499.2747; TLC (PhH/CH_3CN, 3:1), R_f 0.60.

(1'*R*,2'''*S*)-4-[1'-(*tert*-Butyldimethylsilyl)oxy-3'-[5''-(2'''-methoxy-carbonyloxy-but-3''-enyl)-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]propyl]-2,5-dihydro-2-furanone (+)-(20a) and its C-2''' Epimer (+)-(20b)

$[\alpha]_D^{24}$ +8.6° (c 1.13, $CHCl_3$).

4-[3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]-1'-[(*tert*-butyldimethylsilyl)oxy]propyl]-2,5-dihydro-2-furanone (21)

To a warmed (40 °C) and stirred pale yellow solution of tetrakis(triphenylphosphino)palladium(0) (2.48 g, 2.15 mmol) and Et_3N (5.5 mL, 39.5 mmol) in THF (300 mL) was added a solution of **20** (9.85 g, 19.8 mmol) in THF (30 mL) *via* cannula along with THF (30 mL) wash. The solution was warmed to 55 °C over 40 min, allowed to cool to room temperature, filtrated through a short column of Florisil, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (230/70W, 150 g, hexane/EtOAc 5:1) afforded **21** (6.44 g, 15.2 mmol, 77%) as a pale yellow oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ6.28 (1H, dt, *J* = 17.6, 11.1 Hz), 6.02 (1H, dd, *J* = 11.1, 16.8 Hz), 5.94 (1H, m), 5.37 (1H, d, *J* = 16.8 Hz), 5.19 (1H, brd, *J* = 17.6 Hz), 5.09 (1H, brd, *J* = 11.1 Hz), 4.80 (2H, d, *J* = 2.3 Hz), 4.66 (1H, m), 3.78, 3.55 (each 2H, d, J = 12.3 Hz), 2.50-2.75 (4H, m), 1.42, 1.39 (each 3H, s), 0.92 (9H, s), 0.10, and 0.05 (each 3H, s); IR (neat), ν_{max} 2992, 2952, 1780, 1754, 1644, 1474, 1372, 1256, 1198, 1080, 1008, and 838 cm^{-1}; EI-LR-MS, m/z 422 (M^+, 0.3%), 407 (5.6), 307 (11.0), 277 (60.6), 94 (46.3), 75 (100), and 67 (75.5); EI-HR-MS, calcd. for $C_{23}H_{38}O_5Si$ 422.2488, found 244.2462; TLC (hexane/EtOAc, 2:1), R_f 0.50.

(1'*R*)-4-[3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]-1'-[(*tert*-butyldimethylsilyl)oxy]propyl]-2,5-dihydro-2-furanone (-)-(21)

$[\alpha]_D^{19}$ -1.9° (c 1.20, benzene).

4-[3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]-1'-hydroxypropyl]-2,5-dihydro-2-furanone (22)

To a stirred and cooled (0 °C) solution of **21** (1.46 g, 3.45 mmol) in THF (30 mL) was added TBAF (1.0 M solution in THF, 3.8 mL, 3.8 mmol). The resulting reddish brown solution was stirred at the same temperature for 12 min, then poured into sat. aq. NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2×40 mL). The combined organic layers were washed with water and brine (each 20 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 25 g, hexane/EtOAc 2:1-1:2) afforded **22** (1.04 g, 3.37 mmol, 98%) as a yellow oil: ^{1}H-NMR (270 MHz, C_6D_6), δ6.26 (1H, dt, J = 16.7, 9.7 Hz), 5.98 (1H, brdd, J = 15.9, 10.5 Hz), 5.56 (1H, brs), 5.15, 5.15 (each 1H, d, J = 16.7 Hz), 5.04 (1H, d, J = 10.3 Hz), 4.15, 4.13 (each 1H, d, J = 16.0 Hz), 3.75 (1H, m), 3.61 (2H, dd, J = 3.2, 11.3 Hz), 3.43 (2H, m), 1.50-1.70 (2H, m), 1.45, 1.31 (each 3H, s), and 1.05-1.30 (2H, m); IR (neat), ν_{max} 3448, 2944, 2868, 1780, 1746, 1642, 1454, 1374, 1260, 1198, 1080, 896, and 830 cm^{-1};EI-LR-MS, m/z 308 (M^+, 0.04%), 293 (7.2), 220 (20.6), 94 (100), 79 (83.3), and 43 (47.2); EI-HR-MS, calcd. for $C_{17}H_{24}O_5$ 308.1623, found 308.1618; TLC (hexane/EtOAc, 1:2) R_f 0.26.

(1'*R*)-4-[3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]-1'-hydroxypropyl]-2,5-dihydro-2-furanone (+)-(22)

$[\alpha]_D^{22}$ +1.1° (c 2.30, benzene).

4-[3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]-1'-[(*tert*-butyldiphenylsilyl)oxy]propyl]-2,5-dihydro-2-furanone (23)

A solution of **22** (35.0 mg, 0.114 mmol), TBDPSCl (45 μL, 0.173 mmol), and imidazole (16.4 mg, 0.241 mmol) in DMF (0.5 mL) was stirred at room temperature for 42 h. Direct purification of the reaction mixture by silica gel chromatography (230/70W, 5 g, hexane/EtOAc 7:1-3:1) afforded **23** (46.0 mg, 0.089 mmol, 78%) as a colorless oil: ^{1}H-NMR (400 MHz, C_6D_6), δ7.26-7.73

(10H, m), 6.22 (1H, dt, J = 16.8, 10.6 Hz), 5.88 (1H, dd, J = 10.6, 16.0 Hz), 5.78 (1H, q, J = 1.2 Hz), 5.13 (1H, dd, J = 0.8, 16.8 Hz), 5.04 (1H, d, J = 16.0 Hz), 5.03 (1H, dd, J = 0.8, 10.6 Hz), 4.41 (1H, brt, J = 5.2 Hz), 4.37 (1H, dd, J = 1.6, 17.6 Hz), 4.11 (1H, brd, J = 17.6 Hz), 3.55 (2h, dd, J = 7.2, 11.6 Hz), 3.39, 3.32 (each 1H, dd, J = 1.6, 11.6 Hz), 1.28-1.75 (4H, m), 1.43, 1.29 (each 3H, s), and 1.12 (9H, s); IR (neat), ν_{max} 2940, 1780, 1752, 1434, 1372, 1260, 1198, 1112, 1078, 1008, and 702 cm^{-1}; EI-LR-MS, m/z 546 (M^+, 0.4%), 489 (6.0), 431 (33.8), 401 (35.7), 199 (100), 91 (30.8), and 67 (62.7); EI-HR-MS, calcd. for $C_{33}H_{42}O_5Si$ 546.2801, found 546.2794; TLC (hexane/EtOAc, 1:2), R_f 0.77.

4-[3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]-1'-(triisopropylsilyl)oxypropyl]-2,5-dihydro-2-furanone (24)

A solution of **22** (13.6 mg, 44.1 μmol), TIPSCl (15μL, 70.1 μmol) and imidazole (7.7 mg, 113.1μmol) in DMF (0.3 mL) was stirred at room temperature for 13 h, them heated to 70 °C. Then, further TIPSCl (50 μL, 233.6 μmol) and imidazole (27.1 mg, 398.1 μmol) were added, and the reaction mixture was stirred for further 22 h. Direct purification of the mixture by silica gel chromatography (230/70W, 7 g, hexane/EtOAc 7:1-3:1) afforded **24** (11.9 mg, 25.6 μmol, 58%) as a colorless oil: ^{1}H-NMR (400 MHz, C_6D_6), δ6.25 (1H, dt, J = 17.1, 10.5 Hz), 5.95 (1H, dd, J = 10.5, 15.9 Hz), 5.87 (1H, t, J = 1.3 Hz), 5.16 (1H, dd, J = 17.1, 1.5 Hz), 5.13 (1H, dd, J = 15.9, 1.8 Hz), 5.04 (1H, dd, J = 10.5, 1.5 Hz), 4.53 (2H, dt, J = 17.6, 1.3 Hz), 4.43 (1H, brs), 4.32 (1H, d, J = 17.6 Hz), 3.60 (2H, dd, J = 3.3, 11.7 Hz), 3.43 (2H, d, J = 11.7 Hz), 1.25-1.75 (4H, m), 1.44, 1.29 (each 3H, s), and 0.88-1.05 (21H, m); IR (neat), ν_{max} 2948, 2868, 1782, 1754, 1466, 1674, 1198, 1080, 1032, and 882 cm^{-1}; EI-LR-MS, m/z 464 (M^+, 0.4%), 363 (20.5), 333 (50.1), 131 (38.8), 75 (58.3), and 67 (100); EI-HR-MS, calcd. for $C_{26}H_{44}O_5Si$ 464.2958, found 464.2953; TLC (hexane/EtOAc, 1:2), R_f 0.80.

4-[1'-Acetoxy-3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]propyl]-2,5-dihydro-2-furanone (25)

A solution of **22** (11.6 mg, 37.7 μmol), Ac_2O (35 μL, 0.371 mmol), and pyridine (45 μL, 0.556 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 10 h, and then concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 2 g, hexane/EtOAc 3:1-2:1) afforded **25** (12.3 mg, 35.1 μmol, 93%) as a pale yellow oil: ^{1}H-NMR (400 MHz, C_6D_6), δ6.23 (1H, dt, *J* = 17.0, 10.3 Hz), 5.91 (1H, dd, *J* = 10.3, 16.0 Hz), 5.61 (1H, m), 5.30 (1H, brt, *J* = 5.9 Hz), 5.14 (1H, brd, *J* = 17.0 Hz), 5.08 (1H, d, *J* = 16.0 Hz), 5.03 (1H, brd, *J* = 10.3 Hz), 4.03 (2H, m), 3.58 (2H, dd, *J* = 11.7, 2.2 Hz), 3.39 (2H, d, *J* = 11.7 Hz), 1.59-1.64 (2H, m), 2.00 (3H, s), 1.44 (3H, s), 1.30-1.44 (2H, m), and 1.29 (3H, s); IR (neat), ν_{max} 2940, 1782, 1756, 1646, 1456, 1374, 1234, 1158, 1080, and 832 cm^{-1}; EI-LR-MS, m/z 350 (M^+, 0.1%), 335 (8.6), 262 (16.5), 202 (23.9), 79 (30.8), and 43 (100); EI-HR-MS, calcd. for $C_{19}H_{26}O_6$ 350.1730, found 350.1713; TLC (hexane/EtOAc, 1:1), R_f 0.51.

4-[3'-[5''-[(1'''*E*)-1''',3'''-Butadienyl]-2'',2''-dimethyl-1'',3''-dioxan-5''-yl]-1'-(*p*-bromophenylcarbonyl)oxypropyl}-2,5-dihydro-2-furanone (26)

To a solution of **22** (11.7 mg, 37.7 μmol) in pyridine (0.5 mL) was added *p*-BrBzCl (48.0 mg, 0.219 mmol) at room temperature. The resulting mixture was stirred for 3 h, then poured into water (5 mL), and extracted with EtOAc (3×5 mL). The combined organic layers were washed with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, water, and brine (each 2 mL), dried over anhydrous $MgSO_4$, filtrate through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 2g, hexane/EtOAc 5:1-3:1) afforded **26** (16.9 mg, 34.4 μmol, 91%) as a pale yellow oil: ^{1}H-NMR (400 MHz, C_6D_6), δ7.72 (2H, brd, *J* = 8.6 Hz), 7.25 (2H, d, *J* = 8.6 Hz), 6.23 (1H, dt, *J* = 17.2, 10.4 Hz), 5.91 (1H, dd, *J* = 10.4, 16.0 Hz), 5.68 (1H, m), 5.53 (1H, brt, *J* = 5.5 Hz), 5.12 (1H, d, *J* = 17.2 Hz), 5.09 (1H, d, *J* = 16.0 Hz), 5.02 (1H, brd, *J* = 10.4 Hz), 4.10 (2H, m), 3.58 (2H, brd, *J* = 11.7 Hz), 3.40 (2H, brd, *J* = 11.7 Hz), 1.52-1.73 (2H, m), 1.39 (3H, s), 1.31-1.50 (2H, m), and 1.27 (3H, s); IR (neat),

ν_{max} 2940, 1782, 1756, 1728, 1592, 1400, 1374, 1266, 1198, 1102, 1012, and 848 cm^{-1}; EI-LR-MS, m/z 490 (M^+, 0.1%), 492 (M^+, 0.1), 477 (4.1), 475 (4.1), 404 (21.0), 402 (21.4), 183 (100), 185 (97.9), 91 (34.1), and 43 (35.2); EI-HR-MS, calcd. for $C_{24}H_{27}O_6Br$ 490.0991, found 490.0998; TLC (hexane/EtOAc, 1:1), R_f 0.83.

(3a*S,6a*S**,10*R**,10a*S**)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-hydroxy-3,3a,4,6a,7,8,9,10-octahydro-1*H*-naphto[1,8a-c]furan-2-one] (27a), its (3a*R**,6a*R**,10*R**,10a*R**)-isomer (27b), and its (3a*S**,6a*R**,10*R**,10a*S**)-isomer (27c)**

To a thick wall glass tube (ϕ 10×90 mm, 2 mm in thickness) was added a solution of **22** (33.2 mg, 0.108 mmol) in toluene (2 mL) along with toluene rinse (0.5 mL). The tube was sealed, heated at 200 °C for 12 h, and then allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to afford the mixture of adducts. The mixture was separated by HPLC (Develosil 60-3, hexane/EtOAc 1:3, 3 mL/min, RI) to afford **27b** (t_R = 11.7 min, 4.8 mg, 14.5%, contaminated with 13% of **27c**) as white crystals followed by **27c** (t_R = 12.2 min, 6.8 mg, 20.5%, contaminated with 26% of **27b**) as a colorless oil and **27a** (t_R = 14.4 min, 12.2 mg, 37%, contaminated with 5% of **22**). These adducts were led to its TBS derivatives (excess TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C-r.t.) and identified by its ^{1}H-NMR spectra.

(3a*S*,6a*S*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-hydroxy-3,3a,4,6a,7,8,9,10-octahydro-1*H*-naphto[1,8a-c]furan-2-one] (-)-(27a)

A tighten 300 mL autoclave (SUS 316) containing **22** (4.69 g, 15.2 mmol), toluene (200 mL), and BHT (41.4 mg, 0.19 mmol) was heated at 210 °C for 2 days. The reaction mixture was allowed to cool to room temperature, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 200 g, hexane/EtOAc 2:1-1:2) afforded a mixture of **27b** and **27c** (1.77 g, 38%) as white crystals, followed by **27a** (1.97 g, 42%) as white crystals. This material (**27a**) was purified further by recrystallization from benzene to

afford a colorless prism. **27a**: m.p., 185-188 °C; $[\alpha]_D^{22}$ -14.8 ° (c 1.02, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ6.18 (1H, dt, *J* = 9.4, 3.2 Hz, C_6-*H*), 6.11 (1H, m, C_5-*H*), 4.30 (1H, d, *J* = 8.6 Hz, one of C_1-*H*), 3.92 (1H, d, *J* = 11.6 Hz, one of $C_{6'}$-*H*), 3.87 (1H, dd, *J* = 1.6, 12.0 Hz, one of $C_{4'}$-*H*), 3.66 (1H, m, C_{10}-*H*), 3.64 (1H, d, *J* = 8.6 Hz, one of C_1-*H*), 3.38 (1H, dd, *J* = 1.6, 11.6 Hz, one of $C_{6'}$-*H*), 3.21 (1H, dd, *J* = 1.6, 12.0 Hz, one of $C_{4'}$-*H*), 2.83 (1H, dd, *J* = 0.8, 9.2 Hz, C_{3a}-*H*), 2.57 (1H, dd, *J* = 6.8, 19.0 Hz, one of C_4-*H*), 2.51 (1H, dt, *J* = 14.4, 3.2 Hz, C_8-$H_{eq.}$), 2.43 (1H, br, O*H*), 2.25 (1H, m, one of C_4-*H*), 1.79-1.89 (2H, m, C_{6a}-*H* and C_9-$H_{eq.}$), 1.66 (1H, m, C_9-$H_{ax.}$), 1.45, 1.38 (each 3H, s, acetonide CH_3), and 1.12 (1H, ddt, *J* = 2.0, 3.6, 14.0 Hz, C_8-$H_{ax.}$); IR (KBr), ν_{max} 3456, 2948, 2880, 1766, 1458, 1374, 1202, 1160, 1036, 832, and 734 cm^{-1}; EI-LR-MS, m/z 308 (M^+, 7.7%), 293 (100), 157 (32), 129 (31), 91 (49), and 43 (64); EI-HR-MS, calcd. for $C_{17}H_{24}O_5$ 308.1623, found 308.1643; TLC (hexane/EtOAc, 1:3), R_f 0.23.

(3a*S,6a*S**,10*R**,10a*S**)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-(*tert*-butyldimethylsilyl)oxy-3,3a,4,6a,7,8,9,10-octahydro-1*H*-naphto[1,8a-c]furan-2-one] (28a), its (3a*R**,6a*R**,10*R**,10a*R**)-isomer (28b), its (3a*S**,6a*R**,10*R**,10a*S**)-isomer (28c), and (3a*R**,6a*S**,10*R**,10a*R**)-isomer (28d)**

Thermolysis of **21** (56.4 mg, 0.134 mmol) in toluene (3 mL) was performed as described above. The resulting mixture of adducts was separated by HPLC (Develosil 60-3, hexane/EtOAc 5:1, 3 mL/min, RI) to afford a mixture of **28b** and **28c** (3:1 mixture, t_R = 10.2 min, 27.7 mg, 49%) as white crystals followed by **28a** (t_R = 11.7 min, 15.9 mg, 28%) as white crystals, (*Z*)-**21** (t_R = 13.5 min, 1.0 mg, 2%) as an oil, and **28d** (t_R = 14.2 min, 2.5 mg, 4%) as an oil. The adducts (**28a-c**) were led to its *p*-bromobenzoyl derivatives(**32a-c**), and these structures were identified by respective ^{1}H-NMR spectra.

28d: white crystals; m.p., 113-115 °C; ^{1}H-NMR (400MHz, C_6D_6), δ5.51 (1H, ddd, J = 3.4, 6.2, 10.2 Hz, C_5-*H*), 5.28 (1H, ddd, *J* = 3.4, 7.4, 10.2 Hz, C_6-*H*), 3.71 (1H, d, *J* = 11.4 Hz, one of $C_{6'}$-*H*), 3.65 (1H, d, *J* = 8.6 Hz, one of C_1-*H*), 3.62 (1H, dd, *J* = 11.4, 2.0 Hz, one of $C_{4'}$-*H*), 3.61 (1H, d, *J* = 8.6 Hz, one of

C_1-*H*), 3.39 (1H, dd, *J* = 2.4, 11.4 Hz, one of $C_{4'}$-*H*), 3.18 (1H, dd, *J* = 4.8, 11.2 Hz, C_{10}-*H*), 2.96 (1H, dd, *J* = 2.4, 11.4 Hz, one of $C_{6'}$-*H*), 2.63 (1H, dt, *J* = 14.0, 3.2 Hz, C_8-$H_{eq.}$), 2.51 (1H, dd, *J* = 11.4, 2.0 Hz, C_{3a}-*H*), 2.17 (1H, ddd, *J* = 2.0, 6.2, 17.4 Hz, one of C_4-*H*), 1.82 (1H, ddt, *J* = 11.4, 17.4, 3.4 Hz, one of C_4-*H*), 1.52 (3H, s, acetonide CH_3), 1.43 (1H, m, one of C_9-*H*), 1.35 (1H, m, one of C_9-*H*), 1.29 (3H, s, acetonide CH_3), 1.07 (9H, s, (CH_3)$_3$CSi), 0.87 (1H, d, *J* = 7.4 Hz, C_{6a}-*H*), 0.70 (1H, brdt, *J* = 14.0, 2.0 Hz, C_8-$H_{ax.}$), 0.14 (3H, s, CH_3Si), and 0.06 (3H, s, CH_3Si); IR (KBr), ν_{max} 2932, 2856, 1772, 1258, 1198, 1156, 1086, 1040, 996, 968, 836, and 772 cm^{-1}; EI-LR-MS, m/z 422 (M^+, 0.13%), 365 (26.5), 307 (19.7), 277 (41.0), 247 (52.1), 157 (37.7), and 75 (100); EI- HR-MS, calcd. for $C_{23}H_{38}O_5Si$ 422.2488, found 422.2497.

(*Z*)-**21:** ^{1}H-NMR (400MHz, C_6D_6), δ6.43 (1H, brdt, *J* = 16.6, 10.8 Hz), 5.95 (1H, t, *J* = 10.8 Hz), 5.77 (1H, m), 5.07 (1H, brd, *J* = 16.6 Hz), 5.06 (1H, brd, *J* = 10.8 Hz), 4.73 (1H, d, *J* = 10.8 Hz), 4.37 (1H, dd, *J* = 2.0, 17.6 Hz), 4.21 (1H, dd, *J* = 16.4, 1.2 Hz), 4.15 (1H, brt, *J* = 5.6 Hz), 3.71 (2H, d, *J* = 11.2 Hz), 3.59 (2H, d, *J* = 11.2 Hz), 1.73-1.92 (2H, m), 1.25-1.45 (2H, m), 1.46, 1.29 (each 3H, s), 0.90 (9H, s), 0.00, and -0.14 (each 3H, s).

(3a*S*,6a*S*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-(*tert*-butyldimethylsilyl)oxy-3,3a,4,6a,7,8,9,10-octahydro-1*H*-naphto[1,8a-c]furan-2-one] (-)-(28a)

A solution of (-)-**27a** (113.8 mg, 0.369 mmol), 2,6-lutidine (90 μL, 0.828 mmol) and TBSOTf (130 μL, 0.566 mmol) in CH_2Cl_2 (2 mL) was stirred for 2.5 h. To the solution was added water (2 mL), then the mixture was diluted with Et_2O (20 mL). The organic layer was washed successively with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, water and brine (each 5 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (230/70W, 10 g, hexane/EtOAc 10:1-3:1) afforded (-)-**28a** (144.7 mg, 0.343 mmol, 93%) as white crystals; mp, 127-130 °C ;$[\alpha]_D^{24}$ -27.8 ° (c 1.42, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ5.82 (1H, dt, *J* = 9.6, 3.0 Hz, C_6-*H*), 5.74 (1H, ddt, *J* = 7.0, 9.6, 3.0 Hz, C_5-*H*), 4.01 (1H, d, *J* = 8.6 Hz, one of C_1-*H*), 3.69 (1H, d, *J* = 11.6 Hz, one of $C_{4'}$-*H* or one

of $C_{6'}$-*H*), 3.50 (1H, dd, *J* = 1.8, 11.6 Hz, one of $C_{4'}$-*H* or one of $C_{6'}$-*H*), 3.28 (1H, d, *J* = 8.6 Hz, one of C_1-*H*), 3.17 (1H, dd, *J* = 4.8, 11.2 Hz, C_{10}-*H*), 3.11 (1H, dd, *J* = 2.0, 11.6 Hz, one of $C_{4'}$-*H* or one of $C_{6'}$-*H*), 2.99 (1H, dd, *J* = 2.6, 11.6 Hz, one of $C_{4'}$-*H* or one of $C_{6'}$-*H*), 2.59 (1H, dd, *J* = 7.0, 16.0 Hz, one of C_4-*H*), 2.49 (1H, d, *J* = 9.2 Hz, C_{3a}-*H*), 2.40 (1H, dt, *J* = 13.8, 3.8 Hz, C_8-$H_{eq.}$), 1.83 (1H, m, one of C_4-*H*), 1.48 (3H, s, acetonide CH_3), 1.44 (1H, ddt, *J* = 14.0, 4.8, 3.8 Hz, one of C_9-*H*), 1.29 (3H, s, acetonide CH_3), 1.29 (1H, m, one of C_9-*H*), 1.20 (1H, q, *J* = 3.0 Hz, C_{6a}-*H*), 1.01 (9H, s, (CH_3)$_3$CSi), 0.65 (1H, ddt, *J* = 1.8, 3.8, 13.8 Hz, C_8-$H_{ax.}$), 0.08 (3H, s, CH_3Si), and 0.02 (3H, s, CH_3Si); IR (KBr), ν_{max} 2952, 2856, 1770, 1466, 1374, 1260, 1206, 1160, 1106, 1050, 836, and 776 cm^{-1}; EI-LR-MS, m/z 422 (0.1%), 407 (5.7), 365 (44.4), 307 (28.2), 277 (35.9), 157 (31.1), 75 (100); EI-HR-MS, calcd. for $C_{23}H_{38}O_5Si$ 422.2489, found 422.2515.

(3a*S,6a*S**,10*R**,10a*S**)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-(*tert*-butyldiphenylsilyl)oxy-3,3a,4,6a,7,8,9,10-octahydro-1*H*-naphto[1,8a-c]furan-2-one] (29a), its (3a*R**,6a*R**,10*R**,10a*R**)-isomer (29b), its (3a*S**,6a*R**,10*R**,10a*S**)-isomer (29c), and (3a*R**,6a*S**,10*R**,10a*R**)-isomer (29d)**

Thermolysis of **23** (46.0 mg, 0.089 mmol) in toluene (3 mL) was performed as described above. Ratio of the resulting crude mixture of adducts was estimated to be 49:27:23:2 (corresponding to **29a**, **29b**, **29c**, and **29d**, respectively) by integration of olefinic protons (*vide infra*) by using 400 MHz NMR. The mixture was partially separated by HPLC (Develosil 60-3, hexane/CH_2Cl_2/CH_3CN 8:2:1, RI), and it gave the mixture of **29a**, **29b**, and **29c** (ca. 2:1:1, respectively., 34.9 mg,. 76%) and almost pure **29d** (5.5 mg). The former mixture was treated with TBAF and the resulting mixture was identified by its ^{1}H-NMR spectra with those of **27a-c**. ^{1}H-NMR data of olefinic protons for adducts **29a-d** (400 MHz, C_6D_6): **29a**, δ5.74 (2H, m); **29b**, δ5.92 and 5.76 (each 1H, m); **29c**, δ5.42 and 5.10 (each 1H, m); **29d**, δ5.51 and 5.18 (each 1H, m).

(3a*S*,6a*S***,10*R***,10a*S***)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[3,3a,4,6a,7,8,9,10-octahydro-10-(triisopropylsilyl)oxy-1*H*-naphto[1,8a-c]furan-2-one] (30a), its (3a*R***,6a*R***,10*R***,10a*R***)-isomer (30b), its (3a*S***,6a*R***,10*R***,10a*S***)-isomer (30c), and (3a*R***,6a*S***,10*R***,10a*R***)-isomer (30d)**

Thermolysis of **24** (46.0 mg, 0.089 mmol) in toluene (3 mL) was performed as described above. Ratio of the resulting crude mixture (11.4 mg) of adducts was estimated to be 42:30:22:5 (corresponding to **30a**, **30b**, **30c**, and **30d**, respectively) by integration of olefinic protons (*vide infra*) by using 400 MHz NMR. ^{1}H-NMR data of olefinic protons for adducts **30a-d** (400 MHz, C_6D_6): **30a**, δ5.78 (2H, m); **30b**, δ5.93 and 5.83 (each 1H, m); **30c**, δ5.61 and 5.31 (each 1H, m); **30d**, δ5.53 (1H, m) and the other signal of olefinic proton for **30d** was obscured by signals from other isomers.

(3a*S*,6a*S***,10*R***,10a*S***)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-acetoxy-3,3a,4,6a,7,8,9,10-octahydro-1*H*-naphto[1,8a-c]furan-2-one] (31a), its (3a*R***,6a*R***,10*R***,10a*R***)-isomer (31b), its (3a*S***,6a*R***,10*R***,10a*S***)-isomer (31c), and (3a*R***,6a*S***,10*R***,10a*R***)-isomer (31d)**

Thermolysis of **25** (12.3 mg, 35.1 μmol) in toluene (1.5 mL) was performed as described above, and the resulting crude mixture was purified by silica gel chromatography (230/70W, 1 g, hexane/EtOAc 2:1) to afford a mixture of adducts **31a-d** (10.2 mg, 83%) as white crystals: R_f 0.43 (hexane/EtOAc, 1:1). The ratio of the mixture was estimated to be 58:14:25:2 (corresponding to **31a**, **31b**, **31c**, and **31d**, respectively) by integration of olefinic protons and C_{10} protons using 400 MHz NMR. ^{1}H-NMR data of olefinic and C_{10} protons for adducts **31a-d** (400 MHz, C_6D_6), **31a**, δ5.75 and 5.66 (each 1H, m), 4.62 (1H, dd, J = 4.4, 11.7 Hz); **31b**, δ5.81 and 5.70 (each 1H, m), 4.76 (1H, brs); **31c**, δ5.53 (1H, m), 5.22 (1H, brd, J = 9.9 Hz), 4.74 (1H, dd, J = 4.8, 11.0 Hz); **31d**, δ4.84 (1H, dd, J = 3.8, 12.1 Hz), The olefinic protons of this adduct were obscured.

(3a*S*,6a*S***,10*R***,10a*S***)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-(*p*-bromobenzoyl)oxy-3,3a,4,6a,7,8,9,10-octahydro-1*H*-naphto[1,8a-c]furan-2-one] (32a), its (3a*R***,6a*R***,10*R***,10a*R***)-isomer (32b), its (3a*S***,6a*R***,10*R***,10a*S***)-isomer (32c), and its (3a*R***,6a*S***,10*R***,10a*R***)-isomer (32d)**

Thermolysis of **26** (16.9 mg, 34.4 μmol) in toluene (1.5 mL) was performed as described above, and the resulting crude mixture was purified by silica gel chromatography (230/70W, 2 g, hexane/EtOAc 5:1-3:1) to afford a mixture of adducts **32a-d** (14.1 mg, 83%) as white crystals. The ratio of the mixture was estimated to be 58:14:25:2 (corresponding to **32a**, **32b**, **32c**, and **32d**, respectively) by integration of olefinic protons and C_{10} proton using 400 MHz NMR. The ^{1}H-NMR data of the olefinic and C_{10} protons for the adduct **32d**: (400 MHz, C_6D_6), δ5.46 ,5.20 (each 1H, m), and 4.90 (1H, dd, J = 4.9, 11.7 Hz). The adducts (**32a-c**) could be separated as single isomers by HPLC (Develosil 60-3, hexane/EtOAc 3:1, 3 mL/min, RI).

32a: t_R = 12.8 min; white crystals; m.p., 235-237 °C; ^{1}H-NMR (400MHz, C_6D_6), δ7.90 (2H, brd, J = 8.8 Hz, *p*-BrBz), 7.17 (2H, brd, J = 8.8 Hz, *p*-BrBz), 5.80 (1H, dt, J = 9.5, 2.9 Hz, C_6-*H*), 5.68 (1H, ddt, J = 9.5, 6.9, 2.9 Hz, C_5-*H*), 4.67 (1H, dd, J = 11.4, 3.7 Hz, C_{10}-*H*), 3.96 (1H, d, J = 9.2 Hz, one of C_1-*H*), 3.55 (1H, d, J = 11.7 Hz, one of $C_{4'}$-*H*), 3.46 (1H, dd, J = 1.8, 11.7 Hz, one of $C_{6'}$-*H*), 3.37 (1H, d, J = 9.2 Hz, one of C_1-*H*), 3.06 (1H, dd, J = 1.5, 11.7 Hz, $C_{6'}$-$H_{eq.}$), 2.93 (1H, dd, J = 1.5, 11.7 Hz, one of $C_{4'}$-*H*), 2.40 (1H, ddd, J = 16.2, 6.9, 1.1 Hz, one of C_4-*H*), 2.33 (1H, dt, J = 13.9, 3.7 Hz, C_8-$H_{eq.}$), 2.29 (1H, dd, J = 9.5, 1.1 Hz, C_{3a}-*H*), 1.92 (1H, dq, J = 13.6, 3.7 Hz, C_9-H_{eq}), 1.72 (1H, ddq, J = 16.2, 9.5, 2.9 Hz, one of C_4-*H*), 1.42 (3H, s, acetonide CH_3), 1.27 (3H, s, acetonide CH_3), 1.25 (1H, m, C_9-$H_{ax.}$), 1.20 (1H, q, J = 2.9 Hz, C_{6a}-*H*), and 0.74 (1H, brt, J = 13.9 Hz, C_8-$H_{ax.}$); IR (KBr), ν_{max} 2988, 2952, 1774, 1720, 1590, 1486, 1400, 1578, 1270, 1202, 1176, 1156, 1102, 1072, 1062, 1038, 1026, 1010, 990, 854, 832, and 756 cm^{-1}; EI-LR-MS, m/z 492 (M^+, 3.1%), 490 (M^+, 2.9), 475 (33.0), 477 (32.1), 183 (100), 185 (97.3), and 43 (35.7); EI-HR-MS calcd. for $C_{24}H_{27}O_6Br$ 490.0991, found 490.0971; TLC (hexane/EtOAc, 2:3).

32b: t_R = 11.1 min; white crystals; m.p., 217-218.5 °C; ^{1}H-NMR (400MHz,

C_6D_6), δ7.65 (2H, brd, J = 8.4 Hz, p-BrBz), 7.21 (2H, brd, J = 8.4 Hz, p-BrBz), 5.87 (1H, ddd, J = 9.5, 3.3, 2.9 Hz, C_6-*H*), 5.71 (1H, ddt, J = 9.5, 6.6, 2.9 Hz, C_5-*H*), 4.96 (1H, brs, C_{10}-*H*), 3.72 (1H, d, J = 11.7 Hz, one of $C_{4'}$-*H*), 3.48 (1H, brd, J = 11.7 Hz, one of $C_{6'}$-*H*), 3.31 (1H, d, J = 9.5 Hz, one of C_1-*H*), 3.29 (1H, brd, J = 9.5 Hz, one of C_1-*H*), 3.11 (1H, dd, J = 1.5, 11.7 Hz, one of $C_{4'}$-*H*), 3.05 (1H, dd, J = 1.5, 11.7 Hz, one of $C_{6'}$-*H*), 2.61 (1H, dd, J = 8.3, 1.3 Hz, C_{3a}-*H*), 2.53 (1H, ddd, J = 15.7, 6.6, 1.3 Hz, one of C_4-*H*), 2.17 (1H, ddd, J = 13.6, 3.3, 3.0 Hz, C_8-$H_{eq.}$), 2.07 (1H, dt, J = 3.3, 2.9 Hz, C_{6a}-*H*), 1.82 (1H, ddq, J = 15.7, 8.3, 2.9 Hz, one of C_4-*H*), 1.75 (1H, dq, J = 15.7, 3.3 Hz, C_9-$H_{eq.}$), 1.43, 1.30 (each 3H, s, acetonide CH_3), 1.28 (1H, m, C_9-$H_{ax.}$), and 1.09 (1H, brt, J = 13.6 Hz, C_8-$H_{ax.}$); IR (KBr), ν_{max} 2988, 2936, 1762, 1724, 1590, 1398, 1374, 1272, 1202, 1174, 1158, 1114, 1094, 1068, 1032, 1012, 998, 848, 838, and 754 cm^{-1}; EI-LR-MS, m/z 492 (M^+, 1.7%), 490 (M^+, 1.6), 477 (25.5), 475 (25.2), 202 (36.6), 185 (96.9), 183 (100), 129 (41.4), and 43 (42.3); EI-HR-MS, calcd. for $C_{24}H_{27}O_6Br$ 490.0991, found 490.0979.

32c: t_R = 11.6 min; white crystals; m.p., 217-219 °C; ^{1}H-NMR (400MHz, C_6D_6), δ7.76 (2H, brd, J = 8.8 Hz, p-BrBz), 7.20 (2H, brd, J = 8.8 Hz, p-BrBz), 5.56 (1H, m, C_5-*H*), 5.27 (1H, dt, J = 9.6, 2.8 Hz, C_6-*H*), 4.81 (1H, dd, J = 4.8, 11.2 Hz, C_{10}-*H*), 4.17 (1H, d, J = 9.4 Hz, one of C_1-*H*), 3.76 (1H, d, J = 9.4 Hz, one of C_1-*H*), 3.44 (1H, d, J = 11.6 Hz, one of $C_{4'}$-*H* or $C_{6'}$-*H*), 3.42 (1H, dd, J = 1.6, 11.6 Hz, one of $C_{4'}$-*H* or $C_{6'}$-*H*), 3.29 (1H, d, J = 11.6 Hz, one of $C_{4'}$-*H* or $C_{6'}$-*H*), 3.28 (1H, dd, J = 11.6, 1.6 Hz, one of $C_{4'}$-*H* or $C_{6'}$-*H*), 2.24 (1H, brdt, J = 15.6, 6.4 Hz, C_4-*H*), 2.14 (1H, t, J = 6.8 Hz, C_{3a}-*H*), 2.07 (1H, brs, C_{6a}-*H*), 2.04 (1H, m, one of C_4-*H*), 1.78 (1H, m, C_8-$H_{eq.}$), 1.74 (1H, m, C_9-$H_{eq.}$), 1.40, 1.28 (each 3H, s, acetonide CH_3), 1.17 (1H, m, C_9-$H_{ax.}$), and 1.06 (1H, m, C_8-$H_{ax.}$); IR (KBr), ν_{max} 2996, 2928, 1776, 1724, 1592, 1380, 1316, 1270, 1252, 1230, 1202, 1186, 1140, 1124, 1102, 1076, 1060, 1038, 1012, 824, and 754 cm^{-1}; EI-LR-MS, m/z 492 (M^+, 2.7%), 490 (M^+, 2.6), 477 (10.2), 475 (9.9), 232 (47.3), 185 (98.4), and 183 (100), EI-HR-MS, calcd. for $C_{24}H_{27}O_6Br$ 490.0991, found 490.1003.

4-[3'-(5''-Allyl-2'',2''-dimethyl-1'',3''-dioxan-5''-yl)-1'-oxopropyl]-2,5-dihydro-2-furanone (38)

The solution of **16** (376.1 mg, 1.27 mmol) and PDC (715.3 mg, 1.90 mmol) in CH_2Cl_2 (5 mL) was stirred for 17 h, then diluted with Et_2O (30 mL), filtrated through Florisil-Celite pad along with Et_2O wash (100 mL). The filtrate was concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 10 g, hexane/EtOAc 2:1-1:2) afforded **38** (266.3 mg, 0.91 mmol, 71 %) as a pale yellow oil which was crystallized on standing in freezer to give white crystals: ^{1}H-NMR (270 MHz, C_6D_6), δ5.71 (1H, brs), 5.51 (1H, ddt, J = 10.8, 16.2, 7.5 Hz), 4.99 (1H, brd, J = 10.8 Hz), 4.98 (1H, brd, J = 16.2 Hz), 4.27 (2H, d, J = 2.0 Hz), 3.45, 3.36 (each 2H, d, J = 11.9 Hz), 2.20 (2H, m), 1.82 (2H, brd, J = 7.5 Hz), 1.67 (2H, m), 1.39, and 1.36 (each 3H, s); IR (neat), ν_{max} 3080, 2940, 1784, 1690, 1456, 1374, 1258, 1198, 1038, 920, and 832 cm^{-1}; FAB-LR-MS, m/z 295 (M^++1, 11.4%), 289 (27.8), and 154 (100); FAB-HR-MS, calcd. for $C_{16}H_{23}O_5$ (M^++1) 295.1545, found 295.1549; TLC (hexane/EtOAc, 1:2), R_f 0.71.

3-(5''-Allyl-2'',2''-dimethyl-1'',3''-dioxan-5''-yl)-1-[2-(triisopropylsilyl)oxy-4-furyl]-1-propanone (41)

Method A (from **38**).

To a cooled (0 °C) solution of **38** (204.1 mg, 0.694 mmol) and 2,6-lutidine (0.21 mL, 1.80 mmol) was added TIPSOTf (0.33 mL, 1.23 mmol) *via* syringe. The resulting solution was stirred at the same temperature for 1 h, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 10 g, hexane/EtOAc 20:1) afforded **41** (274.0 mg, 0.609 mmol, 88 %) as a pale yellow oil; ^{1}H-NMR (400 MHz, C_6D_6), δ7.47 (1H, d, J = 1.6 Hz), 5.77 (1H, ddt, J = 9.6, 17.6, 7.6 Hz), 5.50 (1H, d, J = 1.6 Hz), 5.13 (1H, brd, J = 17.6 Hz), 5.12 (1H, brd, J = 9.6 Hz), 3.62 (2H, d, J = 11.6 Hz), 3.59 (2H, d, J = 11.6 Hz), 2.66 (2H, m), 2.18 (2H, d, J = 8.0 Hz), 1.75 (2H, m), 1.42, 1.40 (each 3H, s), 1.21-1.33 (3H, m), and 1.09 (18H, d, J = 8.0 Hz); IR (neat), ν_{max} 2948, 2868, 1678, 1628, 1550, 1466, 1308, 1198, 1038, 950, and 834 cm^{-1}; FAB-LR-MS, m/z 451 (M^++1, 55.2%), 393 (100), 307 (18.6), and 289 (11.2); FAB-HR-MS,

calcd. for $C_{25}H_{43}O_5Si$ (M^++1) 451.2880, found 451.2859; TLC (hexane/EtOAc, 1:1), R_f 0.77.

Method B (from **46**).

To a cooled (-78 °C) and vigorously stirred Et_2O (200 mL) was added *t*-BuLi (1.62 M solution in pentane, 92.0 mL, 149.0 mmol) by using an addition funnel over 10 min. To the solution was added a solution of **13** (23.69 g, 74.3 mmol) in Et_2O (50 mL) over 20 min, and the resulting orange solution was stirred for 20 min. To a cooled (-78 °C) and vigorously stirred solution of **46** (18.28 g, 67.4 mmol) in Et_2O (250 mL) was transferred the lithiofuran solution prepared above *via* thick cannula (ϕ 2 mm) over 10 min, and the resulting solution was stirred for 30 min. The reaction mixture was quenched by an addition of sat. aq. NH_4Cl (100 mL), and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with water and brine (each 100 mL). The combined aqueous layers were extracted again with EtOAc (100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 400 g, hexane/EtOAc 40:1-1:3) afforded **41** (19.62 g, 43.5 mmol, 65%), followed by the recovered **46** (contaminated with 9% of 2,5-dihydro-2-furanone, 6.07 g, 20.35 mmol, 30%).

S-2-Pyridyl 3-(5'-allyl-2',2'-dimethyl-1',3'-dioxan-5'-yl)-1-propanethioate (45)

To the cooled (-8 °C) and stirred cloudy solution of **9** (9.65 g, 45.5 mmol), 2-methyl-2-butene (48.0 mL, 453 mmol), and $NaH_2PO_4 \cdot 2H_2O$ (10.17 g, 65.2 mmol) in *t*-BuOH (120 mL) and H_2O (40 mL) was added $NaClO_2$ (>86% purity, 7.21 g, >68.6 mmol) in several sequential portions and the resulting orange solution was stirred at the same temperature for 1 h. An white precipitate was formed during this period. The resulting pale yellow reaction mixture was quenched by an addition of 10% aq. $NaHSO_3$ (20 mL), then concentrated *in vacuo*. The aqueous residue was extracted with Et_2O (4×100 mL). The combined Et_2O layers were washed with brine (30 mL). The combined aqueous layers

were extracted further with CH_2Cl_2 (2×30 mL). The combined CH_2Cl_2 layers were washed with brine (6 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Benzene (20 mL) was added to the residue, and the mixture was concentrated *in vacuo*. The benzene addition followed by concentration was repeated again to insure complete removal of water and *t*-BuOH to afford crude **44** (12.11 g) as white crystals. This material was dissolved in CH_2Cl_2 (300 mL). To the stirred solution were added 2,2'-dipyridyl disulfide (11.08 g, 50.3 mmol) and triphenylphosphine (13.89 g, 53.0 mmol), and the resulting pale yellow solution was stirred at room temperature for 80 min. Then, water (40 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined CH_2Cl_2 layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 200 g, hexane/EtOAc 7:1-2:1) afforded **45** (14.06 g, 43.8 mmol, 96% for 2 steps) as a yellow oil; ^{1}H-NMR (270 MHz, C_6D_6), δ8.37 (1H, brdd, J = 1.7, 6.6 Hz), 7.58 (1H, brd, J = 7.9 Hz), 7.00 (1H, dt, J = 1.7, 7.9 Hz), 6.52 (1H, brdd, J = 4.6, 6.6 Hz), 5.53 (1H, ddt, J = 17.8, 10.6, 7.6 Hz), 4.99 (1H, brd, J = 17.8 Hz), 4.98 (1H, brd, J = 10.6 Hz), 3.32, 3.29 (each 2H, d, J = 11.5 Hz), 2.43 (2H, m), 1.92 (2H, brd, J = 7.6 Hz), 1.69 (2H, m), 1.37, and 1.34 (each 3H, s); IR (neat), ν_{max} 3072, 2988, 2872, 1818, 1716, 1642, 1574, 1454, 1372, 1258, 1198, and 1040 cm^{-1}; FAB-LR-MS, m/z 322 (M^++1, 21.2%), 307 (39.2), 289 (24.6), and 154 (100); FAB-HR-MS, calcd. for $C_{17}H_{24}O_3NS$ (M^++1) 322.1477, found 322.1449; TLC (hexane/EtOAc, 1:1), R_f 0.57.

***N*-Methoxy-*N*-methyl-3-(5'-allyl-2',2'-dimethyl-1',3'-dioxan-5'-yl)-1-propaneamide (46)**

The solution of **45** (5.83 g, 18.1 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (1.96 g, 20.1 mmol), and Et_3N (2.8 mL, 20.1 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 70 min. The reaction mixture was washed successively with 1 M aq. NaOH (3×10 mL), water (10 mL), and brine (10 mL). The combined aqueous layers were extracted with Et_2O (10 mL). The

combined organic layers were dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 100 g, hexane/EtOAc 2:1-1:1) afforded **46** (4.81 g, 17.7 mmol, 98%) as a pale yellow oil; ^{1}H-NMR (270 MHz, C_6D_6), δ5.79 (1H, ddt, J = 17.8, 9.2, 7.9 Hz), 5.12 (1H, brd, J = 17.8 Hz), 5.11 (1H, brd, J = 9.2 Hz), 3.70 (3H, s), 3.60 (4H, s), 3.18 (3H, s), 2.42 (2H, m), 2.21 (2H, brd, J = 7.9 Hz), 1.67 (2H. m), 1.41, and 1.40 (each 3H, s); IR (neat), ν_{max} 2992, 2940, 2868, 1668, 1456, 1418, 1388, 1260, 1198, 1090, 998, and 832 cm^{-1}; EI-LR-MS, m/z 271 (M^+, 0.04%), 256 (46.4), 211 (85.7), 153 (50.2), 93 (100), 55 (94.8), and 43 (77.1); EI-HR-MS, calcd. for $C_{14}H_{25}O_4N$ 271.1784, found 271.1803; TLC (hexane/EtOAc, 1:1), R_f 0.20.

(3a*S*,5*S*,6*R*,6*aS*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-(*tert*-butyldimethylsilyl)oxy-5,6-di(hydroxy)perhydro-1*H*-naphto[1,8a-c]furan-2-one] (48) and (3a*S*,5*R*,6*S*,6*aS*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[10-(*tert*-butyldimethylsilyl)oxy-5,6-di(hydroxy)perhydro-1*H*-naphto[1,8a-c]furan-2-one] (49)

A solution of (-)-**28a** (1.16 g, 2.74 mmol), OsO_4 (19.7 mM solution in *t*-BuOH, 12 mL, 0.393 mmol), and NMO (370.8 mg, 3.17 mmol) in THF (12 mL) and H_2O (6 mL) was stirred at room temperature for 2 days. To the solution was added $NaHSO_3$ (1.07 g), and the resulting mixture was stirred at the same temperature for 1 h, then filtrated through Celite pad along with THF wash (100 mL). The filtrate was concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 40 g, hexane/EtOAc 2:1-1:3) afforded **48** (915.2 mg, 2.00 mmol, 73%) as white crystals followed by **49** (248.2 mg, 0.54 mmol, 20%) as a colorless oil. **48**: m.p., 121-124 °C; $[\alpha]_D^{22}$ -13.2 ° (c 0.65, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ5.30 (1H, brs, O*H*), 4.43 (1H, dd, J = 9.4, 4.4 Hz, C_6-*H*), 4.38 (1H, d, J = 9.2 Hz, one of C_1-*H*), 4.09 (1H, d, J = 9.2 Hz, one of C_1-*H*), 3.92 (1H, ddd, J = 4.4, 3.2, 8.3 Hz, C_5-*H*), 3.77 (1H, d, J = 12.4 Hz, one of $C_{4'}$-*H*), 3.70 (1H, d, J = 12.4 Hz, one of $C_{6'}$-*H*), 3.56 (1H, d, J = 12.4 Hz, one of $C_{6'}$-*H*), 3.53 (1H, d, J = 12.4 Hz, one of $C_{4'}$-*H*), 3.45 (1H, dd, J = 4.4, 11.6 Hz, C_{10}-*H*), 3.12 (1H, br, O*H*), 2.46 (1H, t, J = 7.2 Hz, C_{3a}-*H*),

2.20 (1H, ddd, J = 7.2, 8.3, 15.6 Hz, one of C_4-*H*), 1.80 (1H, ddd, J = 3.2, 7.2, 15.6 Hz, one of C_4-*H*), 1.79 (1H, d, J = 9.4 Hz, C_{6a}-*H*), 1.50-1.75 (3H, m, C_8-$H_{eq.}$ and C_9-*H*), 1.42 (6H, s, acetonide CH_3), 1.09 (1H, dt, J = 4.0, 13.6 Hz, C_8-$H_{ax.}$), 0.36 (9H, s, SiC(CH_3)$_3$), and 0.06 (6H, s, Si(CH_3)$_2$); IR (KBr), ν_{max} 3448, 2936, 1772, 1636, 1466, 1378, 1256, 1104, 972, and 838 cm^{-1}; FAB-LR-MS, m/z 457 (M^++1, 4.3%), 341 (10.3), and 154 (100); FAB-HR-MS, calcd. for $C_{23}H_{41}O_7Si$ (M^++1) 457.2622, found 457.2652; TLC (hexane/EtOAc, 1:3), R_f 0.34. **49**: $[\alpha]_D^{22}$ 2.3 ° (c 0.70, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ5.20 (1H, d, J = 8.4 Hz, C_1-*H*), 4.65 (1H, brs, C_6-*H*), 4.64 (1H, brs, O*H*), 4.39 (1H, d, J = 8.4 Hz, C_1-*H*), 3.76 (2H, s, $C_{4'}$-*H*), 3.66 (1H, d, J = 12.6 Hz, one of $C_{6'}$-*H*), 3.62 (1H, brd, J = 12.0 Hz, C_5-*H*), 3.52 (1H, d, J = 12.6 Hz, one of $C_{6'}$-*H*), 3.32 (1H, dd, J = 4.0, 10.8 Hz, C_{10}-*H*), 2.46 (1H, br, O*H*), 2.13-2.23 (3H, m, C_4-*H* and C_{3a}-*H*), 1.38-1.78 (3H, m, C_9-*H* and C_8-$H_{eq.}$), 1.46, 1.44 (each 3H, s, acetonide CH_3), 1.34 (1H, brs, C_{6a}-*H*), 1.06 (1H, dt, J = 4.0, 13.6 Hz, C_8-$H_{ax.}$), 0.87 (9H, s, SiC(CH_3)$_3$), 0.06, and 0.05 (each 3H, s, SiCH_3); IR (neat), ν_{max} 3420, 2936, 2856, 1774, 1474, 1376, 1254, 1108, 1062, 944, and 836 cm^{-1}; FAB-LR-MS, m/z 457 (M^++1, 13.5%), and 136 (100); FAB-HR-MS, calcd. for $C_{23}H_{41}O_7Si$ (M^++1) 457.2622, found 457.2592; TLC (hexane/EtOAc, 1:3), R_f 0.16.

(3a*S*,5*S*,6*R*,6a*S*,10*R*,10a*S*)-2'-(*p*-methoxyphenyl)-1',3'-dioxane-5'-spiro-7-[5,6-[isopropylidenedioxy]-10-(*tert*-butyldimethylsilyl)oxyperhydro-1*H*-naphto[1,8a-c]furan-2-one] (50)

To a refluxed solution of **48** (795.1 mg, 1.74 mmol) was added PPTS (19.6 mg, 78.0 μmol), and the solution was stirred at the same temperature for 15 min with azeotropic removal of water (Dean-Stark). To the solution was added *p*-anisaldehyde (0.3 mL, 2.47 mmol), and the resulting mixture was stirred under the same condition for further 30 min. Then, the solution was allowed to cool to room temperature, diluted with Et_2O (20 mL), washed successively with sat. aq. $NaHCO_3$, water, and brine (each 2 mL), dried over anhydrous $MgSO_4$, and then concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 30 g, hexane/EtOAc 8:1-6:1) afforded **50** (792.5 mg, 1.38 mmol, 79%) as a colorless amorphous solid: m.p., 141-143 °; $[\alpha]_D^{27}$

-28.5 ° (c 1.07, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.40 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6H_4$CH), 6.90 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6H_4$CH), 5.38 (1H, s, $C_{2'}$-*H*), 4.39-4.45 (3H, m, one of $C_{4'}$-*H*, one of C_1-*H*, and C_6-*H*), 4.05 (H, brd, *J* = 11.6 Hz, $C_{6'}$-*H*), 4.00 (1H, m, C_5-*H*), 3.85 (1H, dd, *J* = 10.8, 2.8 Hz, one of $C_{4'}$-*H*), 3.81 (3H, s, ArOC*H*$_3$), 3.67 (1H, d, *J* = 9.2 Hz, one of C_1-*H*), 3.58 (1H, dd, *J* = 11.6, 2.8 Hz, one of $C_{6'}$-*H*), 3.50 (1H, dd, *J* = 4.4, 11.2 Hz, C_{10}-*H*), 2.84 (1H, dt, *J* = 14.6, 3.2 Hz, C_8-$H_{eq.}$), 2.58 (1H, brd, *J* = 7.2 Hz, C_{3a}-*H*), 2.17 (1H, brdd, *J* = 4.4, 13.0 Hz, one of C_4-*H*), 1.83 (1H, m, one of C_9-*H*), 1.74 (1H, dt, *J* = 7.2, 13.0 Hz, one of C_4-*H*), 1.66 (1H, m, one of C_9-*H*), 1.61 (1H, d, *J* = 8.8 Hz, C_{6a}-*H*), 1.45, 1.38 (each 3H, s, acetonide C*H*$_3$), 1.18 (1H, brt, *J* = 14.6 Hz, C_8-$H_{ax.}$), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), 0.10, and 0.07 (each 3H, s, SiC*H*$_3$); IR (neat), ν_{max} 2936, 2856, 1772, 1616, 1464, 1384, 1252, 1164, 1076, 1034, 978, 894, and 834 cm^{-1}; FAB-LR-MS, m/z 575 (M^++1, 11.9%), 460 (8.2), 341 (18.3), and 307 (100); FAB-HR-MS, calcd. for $C_{31}H_{47}O_8Si$ (M^++1) 575.3040, found 575.3070; TLC (hexane/EtOAc, 1:1), R_f 0.77.

(3a*S*,5*S*,6*R*,6a*S*,7*R*,10*R*,10a*S*)-10-(*tert*-butyldimethylsilyl)oxy-7-hydroxy-methyl-5,6-[isopropylidenedioxy]-7-(*p*-methoxybenzyloxymethyl)perhydro-1*H*-naphto[1,8a-c]furan-2-one (51)

To a mixture of **50** (792.5 mg, 1.38 mmol), MS3Å (activated by heating at 200 °C for 4 h, 1.54 g) and $NaBH_3CN$ (1.73 g, 27.5 mmol) in DMF (30 mL) was added TfOH (2.1 mL, 27.3 mmol) over 5 min, maintaining the temperature below 25 °C . The mixture was stirred at the same temperature for 90 min, then cooled to 0 °C, and quenched by slow addition of sat. aq. $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (4×50 mL). The combined organic layers were washed with brine (30 mL), filtrated through Celite pad, and concentrated *in vacuo*. Residual DMF was removed under high vacuum (below 1 mmHg) at ca. 35 °C by using dry ice-EtOH trap. Purification of the residue by silica gel chromatography (230/70W, 20 g, hexane/EtOAc 5:1-3:1) afforded **51** (contaminated with 14% of (7*S*)-isomer (**52**), 640.0 mg, 1.10 mmol, 80%) as white crystals: m.p., 59 °; $[\alpha]_D^{23}$ -25.6 ° (c 1.10, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) for **51**, δ7.23 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6H_4$CH$_2$), 6.88 (2H,

m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6$*H*$_4$CH$_2$), 4.53 (1H, dd, *J* = 6.4, 8.8 Hz, C$_6$-*H*), 4.47 (1H, d, *J* = 9.6 Hz, one of C$_1$-*H*), 4.44 (1H, d, *J* = 11.2 Hz, one of C*H*$_2$Ar), 4.43 (1H, d *J* = 11.2 Hz, one of C*H*$_2$Ar), 3.96 (1H, m, C$_5$-*H*), 3.92 (1H, d, *J* = 9.2 Hz, one of C*H*$_2$OMPM), 3.91 (1H, d, *J* = 9.2 Hz, one of C$_1$-*H*), 3.81 (3H, s, C*H*$_3$OAr), 3.74 (1H, brd, *J* = 11.6 Hz, one of C*H*$_2$OH), 3.49 (1H, brd, *J* = 11.6 Hz, one of C*H*$_2$OH), 3.43 (1H, dd, *J* = 5.2 Hz, C$_{10}$-*H*), 3.25 (1H, d, *J* = 8.8 Hz, one of C*H*$_2$OMPM), 2.67 (1H, br, O*H*), 2.52 (1H, d, *J* = 6.8 Hz, C$_{3a}$-*H*), 2.16 (1H, dt, *J* = 14.4, 2.8 Hz, C$_8$-*H*$_{eq.}$), 2.12 (1H, dd, *J* = 15.6, 6.0 Hz, one of C$_4$-*H*), 1.74 (1H, d, *J* = 8.8 Hz, C$_{6a}$-*H*), 1.40-1.80 (3H, m, C$_9$-*H* and one of C$_4$-*H*), 1.43, 1.26 (each 3H, s, acetonide C*H*$_3$), 1.17 (1H, dt, *J* = 4.0, 14.4 Hz, C$_8$-*H*$_{aq.}$), 0.84 (9H, s, SiC(C*H*$_3$)$_3$), 0.07, and 0.04 (each 3H, s, SiC*H*$_3$); IR (KBr), ν_{max} 3472, 2940, 1772, 1616, 1516, 1472, 1372, 1252, 1172, 1032, 972, and 840 cm^{-1}; EI-LR-MS, m/z 576 (M$^+$, 0.5%), 383 (1.4), 323 (5.0), 121 (100), and 75 (9.4); EI-HR-MS, calcd. for $C_{31}H_{48}O_8Si$ 576.3118, found 576.3143; TLC (hexane/EtOAc, 1:1), R_f 0.60.

(3a*S*,5*S*,6*R*,6a*S*,7*R*,10*R*,10a*S*)-7-benzyloxymethyl-10-(*tert*-butyldimethyl-silyl)oxy-5,6-isopropylidenedioxy-7-(*p*-methoxybenzyloxymethyl)perhydro-1*H*-naphto[1,8a-c]furan-2-one (53)

To a stirred solution of a 6.2:1 mixture of **51** and **52** (640.8 mg, 1.11 mmol) in THF (20 mL) were added successively NaH (60% in oil, 91.3 mg, 2.05 mmol), TBAI (24.8 mg, 67.1μmol), and BnBr (0.26 mL, 2.19 mmol). The mixture was stirred for 1 d, followed by addition of NaH (95.0 mg, 2.37 mmol), TBAI (34.9 mg, 94.5 mmol), BnBr (0.26 mL, 2.19 mmol). The mixture was stirred for further 1 d, then cooled to 0 °C, quenched with sat. aq. NH_4Cl (2 mL), and then concentrated *in vacuo*. The aqueous residue was added by water (5 mL), extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 15 g, hexane/EtOAc 20:1-1:1) afforded **53** (contaminated with 14% of (7*S*)-isomer , 690.3 mg, 1.04 mmol, 93%) as a colorless viscous oil: $[\alpha]_D^{23}$ -8.3 ° (c 1.18, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$),

δ7.23-7.35 (7H, m, $C_6H_5CH_2$ and two of *p*-$MeOC_6H_4CH_2$), 6.86 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-$MeOC_6H_4CH_2$), 4.84 (1H, dd, *J* = 7.2, 9.0 Hz, C_6-*H*), 4.33-4.48 (5H, m, $PhCH_2$, p-$MeOPhCH_2$, and one of C_1-*H*), 3.90 (1H, d, *J* = 9.6 Hz, one of C_1-*H*), 3.88 (1H, m, C_5-*H*), 3.79 (3H, s, CH_3OAr), 3.60 (1H, d, *J* = 9.2 Hz, one of $BnOCH_2$ or one of $MPMOCH_2$), 3.48 (1H, d, *J* = 9.2 Hz, one of $BnOCH_2$ or one of $MPMOCH_2$), 3.41 (1H, dd, *J* = 4.8, 11.2 Hz, C_{10}-*H*), 3.38, 3.36 (each 1H, d, *J* = 10.2 Hz, one of $BnOCH_2$ or one of $MPMOCH_2$), 2.51 (1H, d, *J* = 6.8 Hz, C_{3a}-*H*), 2.10 (1H, dd, *J* = 4.0, 12.4 Hz, C_4-*H*), 2.00 (1H, d, *J* = 9.0 Hz, C_{6a}-*H*), 1.39-1.77 (5H, m, C_9-*H* and one of C_4-*H*), 1.43, 1.22 (each 3H, s, acetonide CH_3), 0.84 (9H, s, $SiC(CH_3)_3$), 0.04, and 0.03 (each 3H, s, $SiCH_3$); IR (neat), ν_{max} 2936, 2856, 1772, 1358, 1260, 1176, 1074, 968, and 840 cm^{-1}; FAB-LR-MS, m/z 667 (M^++1, 15.4), 609 (4.9), 307 (13.7), 211 (35.9), 154 (58.9), and 121 (100); FAB-HR-MS, calcd. for $C_{38}H_{55}O_8Si$ (M^++1) 667.3666, found 667.3635; TLC (hexane/EtOAc, 1:1), R_f 0.77.

(3a*S*,5*S*,6*R*,6a*S*,7*S*,10*R*,10a*S*)-7-benzyloxymethyl-10-(*tert*-butyldimethylsilyl)oxy-5,6-isopropylidenedioxy-7-hydroxymethylperhydro-1*H*-naphto[1,8a-c]furan-2-one (54)

To a solution of a mixture of **53** and its (7*S*)-epimer (690.3 mg, 1.04 mmol) in CH_2Cl_2 (20 mL) and H_2O (1 mL) was added DDQ (352.4 mg, 1.55 mmol), and the resulting dark green mixture was stirred for 1.5 h. The reaction mixture was diluted with Et_2O (30 mL), washed with sat. aq. $NaHCO_3$, water, and brine (each 6 mL), filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 30 g, hexane/EtOAc 8:1-2:1) afforded **54** (488.5 mg, 0.893 mmol, 86%) as a colorless viscous oil followed by (7*S*)-epimer of **54** (92.3 mg, 0.169 mmol, 16%) as a colorless oil. **54**: $[\alpha]_D^{23}$ -17.0 ° (c 0.71, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.28-7.38 (5H, m, $C_6H_5CH_2$), 4.81 (1H, dd, *J* = 6.4, 9.0 Hz, C_6-*H*), 4.53 (1H, d, *J* = 11.6 Hz, one of $PhCH_2$), 4.41 (1H, d, *J* = 11.6 Hz, one of $PhCH_2$), 4.38 (1H, d, *J* = 13.6 Hz, one of C_1-*H*), 3.99 (1H, d, *J* = 12.2 Hz, one of CH_2OH), 3.95 (1H, m, C_5-*H*), 3.89 (1H, d, *J* = 13.6 Hz, one of C_1-*H*), 3.48 (1H, d, *J* = 9.8 Hz, one of $BnOCH_2$), 3.43 (1H, dd, *J* = 4.8, 11.2 Hz, C_{10}-*H*), 3.26 (1H, brd, *J* = 12.2

Hz, one of CH_2OH), 3.15 (1H, d, J = 9.8 Hz, one of BnOCH_2), 2.97 (1H, br, OH),. 2.17 (1H, dd, J = 4.0, 13.6 Hz, one of C_4-H), 1.94 (1H, d, J = 9.0 Hz, C_{6a}-H), 1.75 (1H, dd, J = 7.2, 13.4 Hz, one of C_4-H), 1.68 (1H, m, one of C_9-H), 1.36-1.64 (3H, m, C_8-H and one of C_9-H), 1.46, 1.28 (each 3H, s, acetonide CH_3), 0.84 (9H, s, SiC(CH_3)$_3$), 0.06, and 0.04 (each 3H, s, SiCH_3); IR (neat), ν_{max} 3544, 2936, 1776, 1458, 1384, 1256, 1106, 1072, 976, and 838 cm^{-1}; FAB-LR-MS, m/z 547 (M^++1, 32.6), 341 (11.8), and 154 (100); FAB-HR-MS, calcd. for $C_{30}H_{47}O_7Si$ (M^++1) 547.3091, found 547.3081; TLC (hexane/EtOAc, 2:1), R_f 0.40.

(3a*S*,5*S*,6*R*,6a*S*,7*R*,10*R*,10a*S*)-7-benzyloxymethyl-10-(*tert*-butyldimethyl-silyl)oxy-5,6-isopropylidenedioxy-7-methanesulfonyloxymethylperhydro-1*H*-naphto[1,8a-c]furan-2-one (55)

To a cooled (0 °C) and stirred solution of **54** (488.5 mg, 0.893 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (0.30 mL, 2.15 mmol) and MsCl (0.14 mL, 1.81 mmol), and the resulting solution was stirred for 1.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with sat. aq. NH_4Cl, water, and brine (each 8 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 2 g, hexane/EtOAc 5:1-3:1) afforded **55** (634.0 mg) as a pale yellow viscous oil. This material was used for the next step while it contains ca. 76 mg of EtOAc. Analytical sample was completely dried *in vacuo*: $[\alpha]_D^{23}$ -11.3 ° (c 1.85, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.29-7.39 (5H, m, $C_6H_5CH_2$), 4.84 (1H, dd, J = 6.8, 9.2 Hz, C_6-H), 4.48, 4.47 (each 1H, d, J = 11.7 Hz, one of $C_6H_5CH_2$), 4.44 (1H, d, J = 9.5 Hz, one of MsOCH_2), 4.34 (1H, d, J = 9.3 Hz, one of C_1-H), 4.29 (1H, d, J = 9.5 Hz, one of MsOCH_2), 3.93 (1H, ddd, J = 11.7, 6.8, 4.6 Hz, C_5-H), 3.84 (1H, d, J = 9.3 Hz, one of C_1-H), 3.43 (1H, d, J = 10.3 Hz, one of BnOCH_2), 3.42 (1H, m, C_{10}-H), 3.35 (1H, d, J = 10.3 Hz, one of BnOCH_2), 2.97 (3H, s, CH_3SO_3), 2.54 (1H, brd, J = 6.2 Hz, C_{3a}-H), 2.16 (1H, brdd, J = 13.6, 4.6 Hz, one of C_4-H), 1.87 (1H, d, J = 9.2 Hz, C_{6a}-H), 1.37-1.76 (5H, m, C_8-H, C_9-H, and one of C_4-H), 1.41, 1.22

(each 3H, s, acetonide CH_3), 0.84 (9H, s, SiC(CH_3)$_3$), 0.06, and 0.04 (each 3H, s, SiCH_3); IR (neat), ν_{max} 2936, 1772, 1358, 1260, 1176, 1074, 968, and 840 cm^{-1}; EI-LR-MS, m/z 624 (M^+, 0.06%), 417 (4.6), 323 (11.5), 91 (100), and 75 (10.7); EI-HR-MS, calcd. for $C_{31}H_{48}O_9SSi$ 624.2788, found 624.2798; TLC (hexane/EtOAc, 3:2), R_f 0.41.

(2a*R*,3*S*,4a*S*,7a*S*,8*R*,10a*R*,10b*S*)-10a-benzyloxymethyl-8-(*tert*-butyldimethylsilyl)oxy-3-hydroxyperhydronaphtho[1,8-bc:4,4a-c']difuran-5-one (56) and (2a*R*,3*S*,4a*S*,7a*S*,8*R*,10a*R*,10b*S*)-10a-benzyloxymethyl-3,8-dihydroxyperhydronaphtho[1,8-bc:4,4a-c']difuran-5-one (57)

A solution of **55** (634.0 mg, in this material was contained ca. 76 mg of EtOAc, 0.893 mmol), PTS·H_2O (50.0 mg, 0.263 mmol) in ethylene glycol (1 mL) and THF (20 mL) was stirred and heated at reflux for 31 h. Then, the solution was allowed to cool to room temperature and sat. aq. $NaHCO_3$ (5 mL) was added. The mixture was concentrated *in vacuo* and the resulting aqueous layer was extracted with EtOAc (4×20 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 20 g, hexane/EtOAc 2:1-EtOAc) afforded recovered **55** (52.7 mg, 84.3 μmol, 9% for 2 steps) followed by **56** (360 3 mg, 0.737 mmol, 83% for 2 steps) as white crystals and almost pure **57** (39.0 mg, ~0.104 mmol, ~12% for 2 steps) as white crystals. **56**: m.p., 188-190 °; $[\alpha]_D^{24}$ -2.5 ° (c 0.12, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.30-7.39 (5H, s, $C_6H_5CH_2$), 4.55, 4.49 (each 1H, d, J = 11.9 Hz, one of PhCH_2), 4.29 (1H, d, J = 9.2 Hz, one of C_1-H), 4.27 (1H, m, C_3-H), 4.20 (1H, d, J = 8.1 Hz, one of C_1-H), 4.02 (1H, d, J = 9.2 Hz, one of C_7-H), 3.84 (1H, dd, J = 2.6, 12.1 Hz, one of C_{2a}-H), 3.61 (1H, dd, J = 4.8, 11.0 Hz, C_8-H), 3.38 (1H, brd, J = 8.1 Hz, one of C_1-H), 3.33 (1H, brd, J = 8.8 Hz, one of BnOCH_2), 3.24 (1H, dd, J = 8.8, 1.1 Hz, one of BnOCH_2), 2.42 (1H, ddd, J = 3.7, 6.6, 14.7 Hz, one of C_4-H), 2.37 (1H, dd, J = 6.6, 11.7 Hz, C_{4a}-H), 2.17 (1H, d, J = 12.1 Hz, C_{10b}-H), 2.08 (1H, dt, J = 13.4, 2.9 Hz, C_{10}-$H_{eq.}$), 2.01 (1H, br, OH), 1.72 (1H, dq, J = 14.3, 4.4 Hz, one of C_9-H), 1.56 (1H, m, one of C_9-H), 1.47 (1H, m, one of C_4-H), 1.29 (1H, dt, J =

4.4, 13.4 Hz, C_{10}-$H_{ax.}$), 0.86 (9H, s, SiC(CH_3)$_3$), 0.06, and 0.05 (each 3H, s, SiCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$), δ-4.9 (SiCH_3), 4.2 (SiCH_3), 17.8 (SiC(CH$_3$)$_3$), 25.6 (SiC(CH_3)$_3$), 29.2 (C_9), 30.2 (C_{10}), 31.5 (C4), 42.3 (C_{4a}), 43.2 (C_{10a}), 44.1 (C_{10b}), 47.7 (C_{7a}), 65.4 (C_3), 66.7 (C_7), 69.0 (BnOCH_2), 73.7 ($C_6H_4CH_2$), 75.3 (C_{2a}), 78.37 (C_1), 78.46 (C_8), 127.7 (one of $C_6H_5CH_2$), 127.9 (two of $C_6H_5CH_2$), 128.5 (two of $C_6H_5CH_2$), 137.7 (one of $C_6H_5CH_2$), and 177.8 (C_5); IR (KBr), ν_{max} 3540, 2952, 1774, 1160, 1096, 1050, 866, and 834 cm^{-1}; FAB-LR-MS, m/z 489 (M^++1, 22.6%), 307 (100). 154 (100); FAB-HR-MS, calcd. for $C_{24}H_{41}O_6Si$ (M^++1) 489.2672, found 489.2694; TLC (hexane/EtOAc, 1:2), R_f 0.34. **57**: m.p., 195-198 °; $[\alpha]_D^{24}$ +9.2 ° (c 1.04, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.30-7.40 (5H, m, $C_6H_5CH_2$), 4.56, 4.49 (each 1H, d, J = 11.9 Hz, PhCH_2), 4.29 (1H, m, C_3-H), 4.27 (1H, d, J = 9.5 Hz, one of C_7-H), 4.19 (1H, d, J = 7.9 Hz, C_1-H), 4.07 (1H, d, J = 9.5 Hz, C_7-H), 3.85 (1H, dd, J = 2.6, 12.5 Hz, C_{2a}-H), 3.71 (1H, m, C_8-H), 3.40 (1H, brd, J = 7.9 Hz, one of C_1-H), 3.33 (1H, d, J = 9.7 Hz, one of BnOCH_2), 3.25 (1H, brd, J = 9.7 Hz, one of BnOCH_2), 2.51 (1H, dd, J = 6.4, 12.1 Hz, one of C_4-H), 2.44 (1H, ddd, J = 3.7, 6.4, 15.0 Hz, C_{4a}-H), 2.19 (1H, d, J = 12.5 Hz, C_{10b}-H), 2.11 (1H, m, C_{10}-$H_{eq.}$), and 1.27-1.83 (4H, m, C_9-H, C_{10}-$H_{ax.}$, and one of C_4-H); IR (KBr), ν_{max} 3448, 2880, 1750, 1456, 1254, 1198, 1090, 954, 730 cm^{-1}; EI-LR-MS, m/z 374 (M^+, 14.7%), 253 (68.5), 235 (33.6), 217 (20.6), 171 (25.2), 91 (100); EI-HR-MS; calcd. for $C_{21}H_{26}O_6$ 374.1730, found 374.1738; TLC (hexane/EtOAc, 1:4), R_f 0.11.

(3a*S*,5*S*,6*R*,6a*S*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[5,6-[(*S*)-benzylidenedioxy]-10-(*tert*-butyldimethylsilyl)oxyperhydro-1*H*-naphto[1,8a-c]furan-2-one] (58) and (3a*S*,5*S*,6*R*,6a*S*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[5,6-[(*R*)-benzylidenedioxy]-10-(*tert*-butyldimethylsilyl)oxyperhydro-1*H*-naphto[1,8a-c]furan-2-one] (59)

To the stirred solution of **48** (65.3 mg, 0.143 mmol) in CH_2Cl_2 (3 mL) were added in order PPTS (10.9 mg, 43.4 μmol), *p*-anisaldehyde dimethylacetal (0.4 mL, 2.35 mmol), and activated MS4Å (132 mg) at the room temperature. The mixture was stirred for 15 min, then quenched by adding sat. aq. $NaHCO_3$ (2 mL). The aqueous layer was extracted with Et_2O (3×3mL). The combined

organic layers were washed with water and brine (each 2 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated in vacuo. Purification of the residue by silica gel chromatography (400/230W, 5 g, hexane/EtOAc 10:1-1:2) afforded **59** (6.4 mg, 11.1 μmol, 8%) as white crystals followed by **58** (64.9 mg, 0.112 mmol, 79%) as white crystals. **58**: m.p., 190-192 °C; $[\alpha]_D^{24}$ -20.8 ° (c 0.65, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.32 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6H_4$CH), 6.84 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6H_4$CH), 5.70 (1H, s, ArC*H*(OR)$_2$), 4.43 (1H, d, *J* = 12.2 Hz, one of $C_{4'}$-*H*), 4.42 (1H, dd, *J* = 6.8, 9.2 Hz, C_6-*H*), 4.34 (1H, d, *J* = 9.4 Hz, one of C_1-*H*), 4.03 (1H, m, C_5-*H*), 3.99 (1H, d, *J* = 12.0 Hz, $C_{6'}$-*H*), 3.75 (3H, s, ArOC*H*$_3$), 3.67 (1H, d, *J* = 9.4 Hz, C_1-*H*), 3.74-3.45 (2H, m, C_{10}-*H* and $C_{6'}$-*H*), 3.07 (1H, dd, *J* = 2.4, 12.2 Hz, one of $C_{4'}$-*H*), 2.60 (1H, dt, *J* = 13.8, 3.2 Hz, C_8-$H_{eq.}$), 2.54 (1H, brd, *J* = 8.0 Hz, C_{3a}-*H*), 2.23 (1H, brdd, *J* = 3.6, 13.2 Hz, one of C_4-*H*), 1.80 (1H, dd, *J* = 8.0, 13.2 Hz, one of C_4-*H*), 1.74 (1H, m, one of C_9-*H*), 1.62 (1H, d, *J* = 9.2 Hz, C_{6a}-*H*), 1.52 (1H, m, one of C_9-*H*), 1.36, 1.31 (each 3H, s, acetonide C*H*$_3$), 1.00 (1H, dt, *J* = 2.4, 13.8 Hz, C_8-$H_{ax.}$), 0.79 (9H, s, SiC(C*H*$_3$)$_3$), 0.10, and 0.07 (each 3H, s, SiC*H*$_3$); IR (KBr), ν_{max} 2956, 2860, 1766, 1616, 1520, 1472, 1374, 1254, 1110, 1086, 976, and 834 cm^{-1}; FAB-LR-MS, m/z 575 (M^++1, 31.2%), 154 (100); FAB-HR-MS, calcd. for $C_{31}H_{47}O_8Si$ (M^++1) 575.3040, found 575.3013; TLC (hexane/EtOAc, 2:1), R_f 0.29. **59**: m.p., 217-219 °C; $[\alpha]_D^{25}$ -17.2 ° (c 0.32, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.37 (2H, m, J_{ortho} = 8.6 Hz, two of *p*-MeOC$_6H_4$CH), 6.90 (2H, m, J_{ortho} = 8.6 Hz, two of *p*-MeOC$_6H_4$CH), 6.18 (1H, s, ArC*H*(OR)$_2$), 4.53 (1H, d, *J* = 12.4 Hz, one of $C_{4'}$-*H*), 4.33 (1H, d, *J* = 9.4 Hz, one of C_1-*H*), 4.24 (1H, dd, *J* = 6.8, 8.6 Hz, C_6-*H*), 4.11 (1H, m, C_5-*H*), 3.87 (1H, brd, *J* = 10.8 Hz, one of $C_{6'}$-*H*), 3.82 (3H, s. ArOC*H*$_3$), 3.59 (1H, d, *J* = 9.4 Hz, one of C_1-*H*), 3.48 (1H, dd, *J* = 4.4, 11.2 Hz, C_{10}-*H*), 3.33 (1H, dd, *J* = 2.2, 10.8 Hz, one of $C_{6'}$-*H*), 3.21 (1H, dd, *J* = 2.2, 12.4 Hz, one of $C_{4'}$-*H*), 2.65 (1H, dt, *J* = 14.4, 3.6 Hz, C_8-$H_{eq.}$), 2.61 (1H, brd, *J* = 6.8 Hz, C_{3a}-*H*), 2.25 (1H, brdd, *J* = 4.8, 13.4 Hz, one of C_4-*H*), 1.90 (1H, dt, *J* = 6.8, 13.4 Hz, one of C_4-*H*), 1.79 (1H, dq, *J* = 14.0, 4.4 Hz, C_9-$H_{eq.}$), 1.64 (1H, d, *J* = 8.6 Hz, C_{6a}-*H*), 1.58 (1H, m, C_9-$H_{ax.}$), 1.37, 1.35 (each 3H, s, acetonide C*H*$_3$), 1.07 (1H, m, C_8-$H_{ax.}$), 0.85 (9H, s, SiC(C*H*$_3$)$_3$), 0.09, and 0.07 (each 3H, s,

SiCH_3); IR (KBr), ν_{max} 2952, 2856, 1770, 1616, 1516, 1466, 1374, 1254, 1154, 1094, 1032, 976, and 836 cm^{-1}; FAB-LR-MS, m/z 575 (M^++1, 5.2%), and 136 (100); FAB-HR-MS, calcd. for $C_{31}H_{47}O_8Si$ (M^++1) 575.3040, found 575.3052; TLC (hexane/EtOAc, 2:1), R_f 0.43.

(2a*R*,3*S*,4a*S*,7a*S*,8*R*,10a*R*,10b*S*)-10a-benzyloxymethyl-8-(*tert*-butyldimethylsilyl)oxy-3-(*p*-methoxybenzyl)oxyperhydronaphtho[1,8-bc:4,4a-c']difuran-5-one (60)

To a cooled (0 °C) suspension of **56** (317.5 mg, 0.650 mmol) and *p*-methoxybenzyltrichloroacetimidate (0.2 mL, 0.963 mmol) in Et_2O (20 mL) was added TfOH (32.5 mM solution in Et_2O, 50 μL, 1.63 μmol, 0.25 mol%), and the resulting mixture was allowed to warm to room temperature over 1 h. The white suspension was turned to a colorless solution during this period. To the solution was added an additional *p*-methoxybenzyltrichloroacetimidate (0.1 mL, 0.482 mmol), and the mixture was stirred for further 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (2×20 mL). The combined organic layers were washed with brine (8 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by twice silica gel chromatography (400/230W, 20 g, hexane/EtOAc 6:1-3:1) afforded **60** (278.0 mg, 0.457 mmol, 70%) as a colorless oil: $[\alpha]_D^{20}$ -18.9 ° (c 0.49, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.26-7.39 (7H, m, $C_6H_5CH_2$ and two of $MeOC_6H_4CH_2$), 6.89 (2H, m, J_{ortho} = 8.4 Hz, two of $MeOC_6H_4CH_2$), 4.72, 4.59 (each 1H, d, J = 12.0 Hz, $MeOC_6H_4CH_2$), 4.56, 4.49 (each 1H, d, J = 11.4 Hz, $C_6H_5CH_2$), 4.28 (1H, d, J = 9.0 Hz, one of C_7-*H*), 4.19 (1H, d, J = 7.8 Hz, one of C_1-*H*), 4.03 (1H, m, C_3-*H*), 4.01 (1H, d, J = 9.0 Hz, one of C_7-*H*), 3.85 (1H, dd, J = 2.4, 12.2 Hz, C_{2a}-*H*), 3.81 (3H, s, CH_3OAr), 3.60 (1H, dd, J = 4.4, 10.8 Hz, C_8-*H*), 3.37 (1H, d, J = 7.8 Hz, one of C_1-*H*), 3.31, 3.20 (each 1H, d, J = 9.0 Hz, $BnOCH_2$), 2.26-2.39 (2H, m, C_{4a}-*H* and one of C_4-*H*), 2.28 (1H, d, J = 12.2 Hz, C_{10b}-*H*), 2.08 (1H, dt, J = 13.2, 2.4 Hz, C_{10}-$H_{eq.}$), 1.70, 1.58 (each 1H, m, C_9-*H*), 1.37 (1H, ddd, J = 2.4, 12.4, 14.4 Hz, one of C_4-*H*), 1.26 (1H, dt, J = 4.4, 13.2 Hz, C_{10}-$H_{ax.}$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.06, and 0.04 (each 3H, s, $SiCH_3$); IR (neat), ν_{max} 2932, 1776, 1614, 1516,

1472, 1366, 1252, 1178, 1102, 1032, and 838 cm^{-1}; FAB-LR-MS, m/z 609 (M^++1, 37.6%), 551 (7.1), 471 (5.0), 307 (26.1), 211 (58.9), and 91 (100); FAB-HR-MS, calcd. for $C_{35}H_{49}O_7Si$ (M^++1) 609.3247, found 609.3278; TLC (hexane/EtOAc, 1:1), R_f 0.60.

(2a*R*,3*S*,4a*S*,7a*S*,8*R*,10a*R*,10b*S*)-10a-benzyloxymethyl-8-hydroxy-3-(*p*-methoxybenzyl)oxyperhydronaphtho[1,8-bc:4,4a-c']difuran-5-one (61)

To a cooled (0 °C) solution of **60** (275 mg, 0.452 mmol) in THF (8 mL) was added TBAF (1.0 M solution in THF, 0.90 mL, 0.90 mmol). The solution was stirred at the same temperature for 13 min, and then allowed to warm to room temperature over 1 h. To the resulting pale brown solution was added sat. aq. NH_4Cl (5 mL), and the mixture was concentrated *in vacuo*. The aqueous residue was extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 6 g, hexane/EtOAc 5:1-1:2) afforded the recovered **60** (9.3 mg, 15.3 μmol, 3%) followed by **61** (211.8 mg, 0.428 mmol, 95%) as a colorless oil: $[\alpha]_D^{22}$ -4.6 ° (c 0.82, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.24-7.39 (7H, m, $C_6H_5CH_2$ and two of $MeOC_6H_4CH_2$), 6.88 (2H, m, J_{ortho} = 8.4 Hz, two of $MeOC_6H_4CH_2$), 4.71, 4.58 (each 1H, d, J = 11.6 Hz, $MeOC_6H_4CH_2$), 4.56, 4.49 (each 1H, d, J = 12.4 Hz, $C_6H_5CH_2$), 4.27 (1H, d, J = 9.2 Hz, one of C_7-*H*), 4.17 (1H, d, J = 8.4 Hz, one of C_1-*H*), 4.06 (1H, d, J = 9.2 Hz, one of C_7-*H*), 4.05 (1H, brs, C_3-*H*), 3.87 (1H, dd, J = 2.8, 13.0 Hz, C_{2a}-*H*), 3.81 (3H, s, CH_3OAr), 3.70 (1H, dd, J = 4.8, 11.2 Hz, C_8-*H*), 3.37 (1H, d, J = 8.4 Hz, one of C_1-*H*), 3.31, 3.21 (1H, d, J = 8.8 Hz, $BnOCH_2$), 2.47 (1H, dd, J = 5.4, 12.0 Hz, one of C_4-*H*), 2.36 (1H, ddd, J = 14.2, 5.4, 3.5 Hz, C_{4a}-*H*), 2.30 (1H, d, J = 13.0 Hz, C_{10b}-*H*), 2.10 (1H, dt, J = 13.6, 2.3 Hz, C_{10}-$H_{eq.}$), 1.62-1.77 (2H, m, C_9-*H*), and 1.24-1.44 (2H, m, C_{10}-$H_{ax.}$ and one of C_4-*H*); IR (neat), ν_{max} 3448, 2932, 1774, 1616, 1516, 1456, 1302, 1248, 1180, 1096, 954, and 822 cm^{-1}; EI-LR-MS, m/z 494 (M+, 3.8%), 373 (5.3), 267 (13.6), 121 (87.8), and 91 (100); EI-HR-MS, calcd. for $C_{29}H_{34}O_7$ 494.2304, found 494.2288; TLC (hexane/EtOAc, 1:1), R_f

0.29.

(2a*R*,3*S*,4a*S*,7a*S*,10a*R*,10b*S*)-10a-benzyloxymethyl-3-(*p*-methoxybenzyl)oxyperhydronaphtho[1,8-bc:4,4a-c']difuran-5,8-dione (62)

To a suspension of **61** (82.2 mg, 0.166 mmol) and MS3Å (not activated particularly, three spatura-full) in CH_2Cl_2 (3 mL) was added PDC (94.4 mg, 0.251 mmol), and the resulting dark brown suspension was stirred at room temperature for 140 min. The mixture was diluted with Et_2O (15 mL), filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 2 g, hexane/EtOAc 2:1) afforded **62** (67.3 mg, 0.137 mmol, 82%) as a colorless oil: $[\alpha]_D^{23}$ -23.2 ° (c 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ7.31-7.41 (5H, m, $C_6H_5CH_2$), 7.23 (1H, m, J_{ortho} = 8.6 Hz, two of $MeOC_6H_4CH_2$), 6.87 (2H, m, J_{ortho} = 8.6 Hz, two of $MeOC_6H_4CH_2$), 4.66 (1H, d, J = 11.7 Hz, one of $MeOC_6H_4CH_2$), 4.59 (1H, d, J = 11.9 Hz, one of $C_6H_5CH_2$), 4.56 (1H, d, J = 11.7 Hz, one of $MeOC_6H_4CH_2$), 4.54 (1H, d, J = 11.9 Hz, $C_6H_5CH_2$), 4.24, 4.15 (each 1H, d, J = 10.3 Hz, C_7-*H*), 4.07 (1H, d, J = 8.2 Hz, one of C_1-*H*), 4.03 (1H, m, C_3-*H*), 3.98 (1H, d, J = 2.9, 12.1 Hz, C_{2a}-*H*), 3.81 (3H, s, CH_3OAr), 3.55 (2H, s, $BnOCH_2$), 3.46 (1H, d, J = 8.2 Hz, one of C_1-*H*), 2.79-2.88 (2H, m, C_{4a}-*H* and one of C_4-*H*), 2.74 (1H, d, J = 12.1 Hz, C_{10b}-*H*), 2.28-2.41 (3H, m, one of C_{10}-*H*, one of C_4-*H*, and one of C_9-*H*), 1.78 (1H, dt, J = 5.5, 13.6 Hz, one of C_{10}-*H*), and 1.41 (1H, ddd, J = 2.2, 13.2, 15.0 Hz, one of C_4-*H*); IR (neat), ν_{max} 2876, 1786, 1716, 1616, 1516, 1458, 1368, 1302, 1252, 1174, 1098, 920, and 822 cm^{-1}; EI-LR-MS, m/z 492 (M^+, 5.9%), 263 (18.3), 137 (11.7), 91 (100); EI-HR-MS, calcd. for $C_{29}H_{32}O_7$ 498.2148, found 492.2184; TLC (hexane/EtOAc, 1:1), R_f 3.70.

(2a*R*,3*S*,4a*S*,7a*S*,10a*R*,10b*S*)-10a-benzyloxymethyl-8-(trimethylsilyl)oxy-3-(*p*-methoxybenzyl)oxy-2a,3,4,4a,5,10,10a,10b-octahydro-1*H*-naphtho[1,8-bc:4,4a-c']difuran-5-one (63)

To a cooled (-78 °C) solution of LDA, which was prepared by mixing diisopropylamine (100 μL, 0.714 mmol) and *n*-BuLi (1.63 M solution in hexane, 0.34 mL, 0.554 mmol) in THF (2 mL) at 0 °C for 30 min, was added a solution

of **62** (90.7 mg, 0.184 mmol) in THF (1 mL) along with THF wash (1 mL). The pale yellow solution was sirred at the same temperature for 1 h. TMSOTf (140 μL, 0.724 mmol) was added dropwise to the solution, and the resulting solution was stirred for 20 min. The reaction was quenched with sat. aq. NH_4Cl (3 mL), and the mixture was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc (4×4 mL). The combined organic extracts were washed with brine (2 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 2 g, hexane/EtOAc 2:1-1:2) afforded **63** (68.8 mg, 0.122 mmol, 66%) as a pale yellow oil followed by the recovered **62** (13.9 mg, 0.028 mmol, 15%). **63**: $[\alpha]_D^{17}$ -33.3 ° (c 1.70, $CHCl_3$); ^{1}H-NMR (270 MHz, C_6D_6), δ7.18-7.30 (7H, m, $C_6H_5CH_2$ and two of $MeOC_6H_4CH_2$), 6.85 (2H, d, J = 8.9 Hz, two of $MeOC_6H_4CH_2$), 4.73, 4.57 (each 1H, d, J = 11.9 Hz, one of $MeOC_6H_5CH_2$), 4.50 (1H, dd, J = 2.3, 5.0 Hz, C_9-*H*), 4.34 (1H, d, J = 7.6 Hz, one of C_1-*H*), 4.24, 4.20 (each 1H, d, J = 12.2 Hz, $C_6H_5CH_2$), 4.07 (2H, s, C_7-*H*), 3.74-3.80 (2H, m, C_{2a}-*H* and C_3-*H*), 3.62 (1H, d, J = 7.6 Hz, one of C_1-*H*), 3.34 (3H, s, CH_3OAr), 3.11 (1H, d, J = 8.8 Hz, one of $BnOCH_2$), 3.03 (1H, d, J = 12.9 Hz, C_{10b}-*H*), 3.01 (1H, d, J = 8.8 Hz, $BnOCH_2$), 2.76 (1H, dd, J = 5.9, 12.2 Hz, C_{4a}-*H*), 2.26 (1H, m, one of C_4-*H*), 2.05 (1H, dd, J = 5.0, 16.8 Hz, one of C_{10}-*H*), 1.81 (1H, dd, J = 2.3, 16.8 Hz, C_{10}-*H*), 1.07 (1H, m, one of C_4-*H*), and 0.21 (9H, m, $Si(CH_3)_3$); IR (neat), ν_{max} 2956, 2868, 1780, 1636, 1614, 1516, 1458, 1302, 1214, 1174, 1114, 1094, 1024, 962, 920, 874, and 750 cm^{-1}; EI-LR-MS, m/z 564 (M^+, 5.7%), 443 (8.8),, 353 (9.9), 309 (17.6), 121 (100), 91 (73.2), 73 (23.4); EI-HR-MS, calcd. for $C_{32}H_{40}O_7Si$ 564.2543, found 564.2568, TLC (hexane/EtOAc, 1:1), R_f 0.59.

(2a*R*,3*S*,4a*S*,7a*S*,9*RS*,10a*R*,10b*S*)-10a-benzyloxymethyl-3-(*p*-methoxybenzyl)oxy-9-(phenylseleno)perhydronaphtho[1,8-bc:4,4a-c']difuran-5,8-dione (64)

To a cooled (0 °C) solution of **63** (12.9 mg, 22.8 μmol) and *N*-PSP (10.7 mg, 35.4 μmol) in THF (2 mL) was added TMSOTf (1 μL, 5.17 μmol) *via* microsyringe. The reaction mixture was stirred at the same temperature for 30

min, then allowed to warm to room temperature over 35 min. Further amount of TMSOTf (4 μL, 20.7 μmol) was added to the reaction mixture, and the pale yellow solution was stirred for another 35 min. The reaction was quenched with water (2 mL), and then the mixture was concentrated *in vacuo*. The residue was extracted with EtOAc (4×3 mL). The combined organic extracts were washed with brine (1 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 400 mg, hexane/EtOAc 2:1-1:1) afforded the crude mixture of **62**, **64**, and **65**. Further purification of the mixture by HPLC (Develosil 60-3, hexane/EtOAc 1:2, 3 mL/min, UV, 254 nm) afforded **64** (conterminated with 13% of **65**, 2.9 mg, total 21%) as a colorless oil, and pure **65** (2.6 mg, 6.33 μmol, 28%) as a colorless oil. **64**: t_R = 8.4 min; $[\alpha]_D^{21}$ -7.9 ° (c 0.14, $CHCl_3$) (this sample was contaminated with 13% of **65**); ^{1}H-NMR (400 MHz, $CDCl_3$) δ7.54 (2H, m, J_{ortho} = 8.1 Hz, two of C_6H_5Se), 7.16-7.38 (10H, m, $C_6H_5CH_2$, two of $MeOC_6H_4CH_2$, and three of C_6H_5Se), 6.88 (2H, m, J_{ortho} = 8.4 Hz, two of $MeOC_6H_4CH_2$), 4.87 (1H, dd, *J* = 6.6, 12.8 Hz, C_9-*H*), 4.64, 4.56 (each 1H, d, *J* = 11.8 Hz, $MeOPhCH_2$), 4.48, 4.46 (each 1H, d, *J* = 11.6 Hz, $PhCH_2$), 4.26, 4.25 (each 1H, d, *J* = 10.6 Hz, C_7-*H*), 4.03 (1H, m, C_2-*H*), 3.95 (1H, dd, *J* = 2.6, 11.7 Hz, C_{2a}-*H*), 3.82 (3H, s, CH_3OPhCH_2), 3.80 (1H, m, one of C_1-*H*), 3.56, 3.54 (each 1H, d, *J* = 9.6 Hz, $BnOCH_2$), 3.39 (1H, d, *J* = 8.4 Hz, one of C_1-*H*), 2.95 (1H, dd, *J* = 5.8, 12.8 Hz, C_{4a}-*H*), 2.80 (1H, d, *J* = 11.7 Hz, C_{10b}-*H*), 2.49 (1H, dd, *J* = 6.6, 12.8 Hz, one of C_{10}-*H*), 2.38 (1H, ddd, *J* = 3.6, 5.8, 14.8 Hz, one of C_4-*H*), 2.04 (1H, t, *J* = 12.8 Hz, one of C_{10}-*H*), and 1.43 (1H, ddd, J = 2.2, 12.8, 14.8 Hz, one of C_4-*H*); IR (neat), ν_{max} 2932, 1782, 1714, 1614, 1516, 1458, 1368, 1250, and 1176 cm^{-1}; FAB-LR-MS, m/z 491 (1.0%, M^+-PhSe), 91 (12.7, Bn), 93 (100); TLC (toluene/EtOAc, 3:1), R_f 0.40. **65**: t_R = 10.2 min; $[\alpha]_D^{21}$ +27.9 ° (c 0.38, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ7.28-7.39 (3H, m, three of $C_6H_5CH_2$), 7.23-7.27 (2H, m, two of $C_6H_5CH_2$), 7.23 (2H, m, J_{ortho} = 8.6 Hz, two of $MeOC_6H_4CH_2$), 7.12 (1H, d, *J* = 9.9 Hz, C_{10}-*H*), 6.87 (2H, m, J_{ortho} = 8.6 Hz, two of $MeOC_6H_4CH_2$), 6.13 (1H, d, *J* = 9.9 Hz, C_9-*H*), 4.68, 4.57 (each 1H, d, *J* = 11.6 Hz, $MeOC_6H_4CH_2$), 4.51, 4.49 (each 1H, d, *J* = 11.9 Hz, $C_6H_5CH_2$), 4.18, 4.11 (each 1H, d, *J* = 10.3 Hz, C_7-*H*), 4.09 (1H, m, C_3-*H*), 4.09

(1H, d, J = 7.9 Hz, one of C_1-*H*), 3.97 (1H, dd, *J* = 2.6, 12.5 Hz, C_{2a}-*H*), 3.80 (3H, s, C*H*$_3$OC$_6$H$_4$CH$_2$), 3.66 (1H, d, J = 7.9 Hz, one of C_1-*H*), 3.48, 3.40 (each 1H, d, *J* = 9.0 Hz, BnOC*H*$_2$), 3.12 (1H, d, *J* = 12.5 Hz, C_{10b}-*H*), 2.75 (1H, dd, *J* = 5.9, 12.8 Hz, C_{4a}-*H*), 2.41 (1H, ddd, *J* = 4.0, 5.9, 15.0 Hz, one of C_4-*H*), and 1.48 (1H, ddd, *J* = 2.2, 12.8, 15.0 Hz, one of C_4-*H*); IR (neat), ν_{max} 2876, 1782, 1686, 1616, 1516, 1248, 1174, 1102, 1078, 1022, and 840 cm^{-1}; EI-LR-MS, m/z 490 (13.7%), 369 (7.6), 263 (8.0), 121 (96.3), 91 (100); EI-HR-MS, calcd. for $C_{29}H_{30}O_7$ 490.1992, found 490.1982; TLC (toluene/EtOAc, 3:1), R_f 0.37.

(2a*R*,3*S*,4a*S*,7a*S*,10a*R*,10b*S*)-10a-benzyloxymethyl-3-(*p*-methoxybenzyl)oxy-2a,3,4,4a,5,8,10a,10b-octahydronaphtho[1,8-bc:4,4a-c']difuran-5,8-dione (65)

To a stirred solution of **64** (contaminated with 13% of **65**, 9.4 mg, 12.6 μmol for **64**, 2.7 μmol for **65**) in MeOH (2 mL) and H_2O (0.5 mL) was added $NaIO_4$ (26 mg, 121.6 μmol) at room temperature, and the solution was stirred 8 h. During this period, white precipitate was formed. The mixture was filtrated through Celite pad, and the filtrate was concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 2 g, hexane/EtOAc 3:2) afforded **65** (6.5 mg, 13.2 μmol, total 87%) as a colorless oil.

(2a*R*,3*S*,4a*S*,7a*S*,9*S*,10*S*,10a*S*,10b*S*)-10a-benzyloxymethyl-9,10-epoxy-3-(*p*-methoxybenzyl)oxyperhydronaphtho[1,8-bc:4,4a-c']difuran-5,8-dione (66)

To a stirred solution of **65** (2.6 mg, 5.30 μmol) in DMSO (0.5 mL) were added successively TBHP (70%, 2.5 μL, 18.3 μmol) and TBAF (1.0 M solution in THF, 10 μL, 10 μmol). The resulting pale yellow solution was stirred at room temperature for 30 min. To the solution was added water (1.5 mL), and the mixture was extracted with EtOAc (4×4 mL). The combined organic extracts were washed with brine (1.5 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 400 mg, hexane/EtOAc 2:1-1:1) afforded the 5:1 mixture of **66** and **65** (1.6 mg, total 3.18 μmol, 50% for **66**, 10% for **65**) as a

colorless oil. This material was used the next step without further purification. **66:** TLC (toluene/EtOAc, 3:1), R_f 0.46.

(2a*R*,3*S*,4a*S*,7a*S*,10*R*,10a*S*,10b*S*)-10a-benzyloxymethyl-10-hydroxy-3-(*p*-methoxybenzyl)oxyperhydronaphtho[1,8-bc:4,4a-c']difuran-5,8-dione (67)

A solution of $Na^+[PhSeB(OEt)_3]^-$ (0.25 M solution in EtOH) was prepared as follows: To a cooled (0 °C) and stirred soluiton of diphenyldiselenide (233.9mg, 0.75 mmol) in EtOH (3 mL) was added $NaBH_4$ (59.2 mg, 1.56 mmol) in one portion (the reaction was exothermic and vigorous hydrogen evoluiton was occurred). The mixture was stirred at the same temperature for 3 min, and allowed to warm to room temperature over 1 h. To the resulting pale yellow suspension was added AcOH (15 μL, 0.26 mmol) *via* microsyringe.

To a stirred solution of **66** and **65** (5:1 mixture, 2.65 mmol for **66**) in EtOH (0.5 mL) was added the $Na^+[PhSeB(OEt)_3]^-$ solution (65 μL, 16.3 μmol) *via* microsyringe at room temperature. The resulting pale yellow mixture was stirred at the same temperature for 20 min, and further $Na^+[PhSeB(OEt)_3]^-$ solution (30 μL, 7.52 μmol) was added. After 10 min, the reaction mixture was diluted with EtOAc (8 mL), and washed with brine (1 mL). The brine layer was further extracted with EtOAc (1 mL). The combined organic extracts were filterated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatograhy (400/230W, 400 mg, hexane/EtOAc 2:1-1:1) afforded **65** (0.7 mg, 1.42 μmol, 45%) as a colorless oil followed by **67** (0.8 mg, 1.57 μmol, 50%) as a colorless oil. **67**: $[\alpha]_D^{20}$ -14.0 ° (c 0.10, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ7.20-7.43 (7H, m, $C_6H_5CH_2$, and two of $MeOC_6H_4CH_2$), 6.86 (2H, m, J_{ortho} = 8.8 Hz, two of $MeOC_6H_4CH_2$), 4.73 (1H, d, J = 11.8 Hz, one of $MeOC_6H_4CH_2$), 4.59 (1H, d, J = 11.8 Hz, one of $C_6H_5CH_2$), 4.56 (1H, d, J = 11.8 Hz, one of $MeOC_6H_4CH_2$), 4.51 (1H, d, J = 11.8 Hz, one of $C_6H_5CH_2$), 4.46 (1H, m, C_{10}-*H*), 4.23, 4.14 (each 1H, d, J = 10.4 Hz, C_7-*H*), 4.04 (1H, m, C_3-*H*), 4.02 (1H, d, J = 8.4 Hz, C_1-*H*), 3.95 (1H, dd, J = 2.8, 12.4 Hz, C_{2a}-*H*), 3.90 (1H, d, J = 8.4 Hz, C_1-*H*), 3.80 (3H, s, $CH_3OC_6H_4CH_2$), 3.56, 3.52 (each 1H, d, J = 9.4 Hz, $BnOCH_2$), 3.37 (1H, d, J = 12.4 Hz, C_{10b}-*H*), 3.15 (1H, dd, J = 4.0, 16.4

Hz, one of C_9-*H*), 2.90 (1H, dd, *J* = 5.8, 12.8 Hz, C_{4a}-*H*), 2.51 (1H, dd, *J* = 2.8, 16.4 Hz, one of C_9-*H*), 2.35 (1H, ddd, *J* = 4.0, 5.8, 14.8 Hz, one of C_4-*H*), and 1.42 (1H, ddd, *J* = 2.4, 12.8, 14.8 Hz, one of C_4-*H*); IR (neat), ν_{max} 3416, 2928, 1780, 1718, 1614, 1516, 1458, 1248, 1176, 1082, 1028, and 832 cm^{-1}; FAB-LR-MS, m/z 508 (5.4%), 507 (14.7), 183 (100); FAB-HR-MS, calcd. for $C_{29}H_{31}O_8$ (M^+-1) 507.2019, found 507.2064; TLC (hexane/EtOAc, 2:3), R_f 0.37.

(*3R,4S,5R*)-5-*tert*-(Butyldimethylsilyl)oxymethyl-3,4-isopropylidenedioxy-furan-2-one (72)

A solution of **71** (1.00 g, 5.31 mmol), TBSCl (1.21 g, 8.03 mmol), and imidazole (755.0 mg, 11.1 mmol) in DMF (5 mL) was stirred at room temperature for 1 d. The reaction mixture was poured into sat. aq. NH_4Cl (50 mL), and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were washed successively with water and brine (each 10 mL), dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 10 g, hexane/EtOAc 20:1-3:1) afforded **72** (1.55 g, 5.12 mmol, 97%) as white crystals: ^{1}H-NMR (270 MHz, $CDCl_3$), δ4.73, 4.71 (each 1H, d, *J* = 5.6 Hz), 4.60 (1H, dd, *J* = 1.3, 2.0 Hz), 3.88 (1H, dd, *J* = 2.0, 11.2 Hz), 3.81 (1H, dd, *J* = 1.3, 11.2 Hz), 1.48, 1.39 (each 3H, s), 0.88 (9H, s), 0.07, and 0.06 (each 3H, s); IR (KBr), ν_{max} 2956, 1776, 1474, 1362, 1260, 1222, 1176, 1112, 1082, 988, 842, and 774 cm^{-1}; TLC (hexane/EtOAc, 2:1), R_f 0.54.

(*3R,4S,5R*)-5-*tert*-(Butyldimethylsilyl)oxymethyl-3,4-isopropylidenedioxy-2-methylenefuran (73)

To a cooled (-45 °C) and stirred solution of **72** (101.6 mg, 0.336 mmol) and pyridine (60 μL, 0.742 mmol) in THF (2 mL) was added Tebbe reagent (ca. 0.4 M solution in toluene, 1.7 mL, 0.68 mmol). The dark red solution was allowed to warm to -10 °C over 40 min. To the reaction mixture was added 4 M aq. NaOH (0.3 mL), then the resulting orange mixture was allowed to warm to room temperature. The mixture was diluted with Et_2O (5 mL), dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*.

Purification of the residue by neutral alumina (grade III, 5 g, hexane/Et_2O 30:1) afforded **73** (77.1 mg, 0.257 mmol, 76%) as a yellow oil: ^{1}H-NMR (270 MHz, C_6D_6), δ5.09 (1H, d, *J* = 6.0 Hz), 4.64 (1H, brs), 4.61 (1H, d, *J* = 6.0 Hz), 4.38 (1H, dd, *J* = 2.2, 3.0 Hz), 4.34 (1H, brs), 3.44 (1H, dd, *J* = 3.0, 11.1 Hz), 3.27 (1H, dd, *J* = 2.2, 11.1 Hz), 1.58, 1.33 (each 3H, s), 0.91 (9H, s), 0.01, and -0.02 (each 3H, s); IR (neat), ν_{max} 2932, 2856, 1732, 1464, 1384, 1258, 1084, and 836 cm^{-1}; TLC (hexane/EtOAc, 5:1), R_f 0.63.

(2*S*,3*R*,4*S*,5*R*)-5-*tert*-(Butyldimethylsilyl)oxymethyl-2-hydroky-2-hydroxymethyl-3,4-isopropylidenedioxyfuran (75a) and its (2*R*,3*R*,4*S*,5*R*)-isomer (75b)

A solution of **73** (86.6 mg, 0.288 mmol), OsO_4 (19.6 mM solution in *t*-BuOH, 1.4 mL, 27.5 μmol), NMO (40.0 mg, 0.341 mmol) in THF (1.4 mL) and water (0.7 mL) was stirred at room temperature for 70 min. To the reaction mixture was added $NaHSO_3$ (213 mg), and the resulting mixture was stirred at the same temperature for 2 h. The mixture was filtrated through Celite, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 2.5 g, hexane/EtOAc 1:1) afforded a mixture of **75a** and **75b** (3:1 mixture, 88.6 mg, 92%) as a colorless oil: ^{1}H-NMR (270 MHz, $CDCl_3$), δ5.23 ($1H_{maj}$, br), 4.83 ($1H_{min}$, dd, *J* = 4.0, 6.8 Hz), 4.80 ($1H_{maj}$, dd, *J* = 1.3, 6.1 Hz), 4.73 ($1H_{min}$, d, *J* = 6.8 Hz), 4.58 ($1H_{maj}$, *J* = 6.1 Hz), 4.34 ($1H_{maj}$, m), 4.21 ($1H_{min}$, m), 1.61 ($3H_{min}$, s), 1.51 ($3H_{maj}$, s), 1.41 ($3H_{min}$, s), 1.34 ($3H_{maj}$, s), 0.93 ($9H_{maj}$, s), 0.91 ($9H_{min}$, s), 0.16, 0.15 (each $3H_{maj}$, s), 0.10, and 0.09 (each $3H_{min}$, s); IR (neat), ν_{max} 3392, 2940, 2860, 1455, 1376, 1258, 1164, 1074, 940, and 838 cm^{-1}; TLC (hexane/EtOAc, 1:1). R_f 0.51.

(3a*S*,5*S*,6*R*,6a*S*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[5,6-[(*S*)-benzylidenedioxy]-10-(*tert*-butyldimethylsilyl)oxy-2-(methylene)perhydro-1*H*-naphto[1,8a-c]furan] (76)

To a cooled (-40 °C) and stirred solution of **58** (43.3 mg, 75.3 μmol) and pyridine (10 μL, 0.123 mmol) in THF (1 mL) was added Tebbe reagent (ca. 0.4 M solution in toluene, 0.4 mL, 0.16 mmol), and the resulting dark red mixture

was warmed to -20 °C over 1 h. An additional amount of Tebbe reagent (total 1.6 mL, 0.64 mL) was added in two portions and the mixture was warmed to 0 °C over 2 h. With continued stirring, the reaction was quenched by adding 4 M aq. NaOH (0.2 mL), and diluted with Et_2O (10 mL). During this time, the white precipitate was formed. (The color of the precipitate was varied to bluish to yellowish white on different occasions.) The mixture was dried over anhydrous Na_2SO_4, filtrated through Celite pad, and concentrated *in vacuo*. The residue was purified by chromatography on alumina (Merck Art. 1097, 15 g, hexane/EtOAc 10:1-2:1) to afford almost pure **76** (43.1 mg) as a yellow oil. This material was used in the next reaction without further purification: TLC (hexane/EtOAc, 2:1), R_f 0.57.

(3*S*,3a*S*,*5S*,*6R*,*6aS*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[5,6-[(*S*)-benzylidenedioxy]-10-(*tert*-butyldimethylsilyl)oxy-2-hydroxy-2-hydroxymethylperhydro-1*H*-naphto[1,8a-c]furan] (77a) and its (3*R*,3a*S*,*5S*,*6R*,*6aS*,10*R*,10a*S*)-isomer (77b)

The almost pure **76** (43.1 mg) was dissolved in pyridine (1 mL) and stirred at room temperature. To the solution was added OsO_4 (0.49 M solution in benzene, 0.23 mL, 112.7 μmol) and the resulting mixture was stirred for 20 h. An additional amount of OsO_4 (0.1 mL, 49.0 μmol) was added to the solution, and the mixture was stirred further 5 h. Then, the remaining oxidant was quenched by adding $NaHSO_3$ (408 mg) and water (2 mL), and the resulting mixture was stirred for 3 h. The aqueous layer was extracted with Et_2O (3×3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated through Celite pad, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (230/70W, 2.5 g, hexane/EtOAc 7:1-1:1) afforded a mixture of **77a** and **77b** (10:3 mixture of diastereomers, 35.2 mg, 58.0 μmol, 77% over 2 steps) as a pale yellow oil. The obtained major isomer was slowly transferred to the minor isomer in C_6D_6: ^{1}H-NMR (400 MHz, C_6D_6, 45 °C) for the major isomer, δ7.59 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC_6H_4CH), 6.89 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC_6H_4CH), 5.74 (1H, s, ArCH(OR)$_2$), 4.98 (1H, d, J = 12.0 Hz, one of C_4-H), 4.90 (1H, q, J = 7.2 Hz, C_5-H), 4.38 (1H, dd,

J = 7.2, 11.6 Hz, C_6-*H*), 4.28 (1H, d, J = 11.2 Hz, one of $C_{6'}$-*H*), 3.99 (1H, d, J = 9.0 Hz, one of C_1-*H* or one of CH_2OH), 3.67 (1H, d, J = 9.0 Hz, one of C_1-*H* or one of CH_2OH), 3.64 (1H, d, J = 11.2 Hz, one of C_1-*H* or one of CH_2OH), 3.56 (1H, dd, J = 2.6, 11.2 Hz, one of $C_{6'}$-*H*), 3.34 (1H, m, one of C_1-*H* or one of CH_2OH), 3.33 (3H, s, $ArOCH_3$), 3.24 (1H, dd, J = 5.2, 8.4 Hz, C_{10a}-H), 3.15 (1H, dd, J = 2.6, 12.0 Hz, one of $C_{4'}$-*H*), 2.95 (1H, br, O*H*), 2.51 (1H, ddd, J = 4.0, 6.0, 14.4 Hz, C_8-$H_{eq.}$), 2.15-2.23 (2H, m, one of C_{3a}-*H* and C_4-*H*), 1.42-1.77 (3H, m, C_9-*H* and one of C_4-*H*), 1.53, 1.46 (each 3H, s, acetonide CH_3), 1.34 (1H, m, C_8-$H_{ax.}$), 1.19 (1H, d, J = 11.6 Hz, C_{6a}-*H*), 0.99 (9H, s, $SiC(CH_3)_3$), 0.06, and 0.04 (each 3H, s, $SiCH_3$); for the minor isomer, δ7.55, 6.89 (each 2H, m, J_{ortho} = 8.6 Hz. *p*-$MeOC_6H_4CH$), 6.18 (1H, d, J = 2.0 Hz, hemiacetal O*H*), 5.61 (1H, s, $ArCH(OR)_2$), 4.95 (1H, d, J = 11.2 Hz, one of $C_{4'}$-*H*), 4.32 (1H, m, C_5-*H*), 3.98-4.09 (3H, m, C_6-*H*, one of $C_{6'}$-*H*, and one of CH_2OH), 3.85-3.89 (2H, m, one of C_1-*H* and one of CH_2OH), 3.54 (1H, brd, J = 10.0 Hz, one of $C_{6'}$-*H*), 3.46 (1H, d, J = 9.6 Hz, one of C_1-*H*), 3.36 (3H, s, $ArOCH_3$), 3.33 (1H, m, C_{10}-*H*), 3.04 (1H, d, J = 11.6 Hz, one of $C_{4'}$-*H*), 2.86 (1H, m, one of C_8-*H*), 2.59 (1H, dd, J = 5.2, 14.4 Hz, one of C_4-*H*), 2.24 (1H, brd, J = 6.0 Hz, C_{3a}-*H*), 2.10 (1H, dd, J = 3.6, 9.6 Hz, CH_2OH), 1.65 (1H, m, one of C_4-*H*), 1.53, 1.45 (each 3H, s, acetonide CH_3), 1.26 (1H, d, J = 10.4 Hz, C_{6a}-*H*), 1.24 (1H, m, one of C_9-*H*), 0.95 (9H, s, $SiC(CH_3)_3$), 0.90 (1H, m, one of C_8-*H*), 0.09, and 0.05 (each 3H, s, $SiCH_3$); IR (neat), ν_{max} 3416, 2940, 1618, 1520, 1464, 1376, 1254, 1172, 1078, 976, and 832 cm^{-1}; FAB-LR-MS, m/z 607 (M^++1, 9.5%), 589 (13.4), 549 (7.6), 460 (8.6), 391 (12.9), and 307 (100); FAB-HR-MS, calcd. for $C_{32}H_{51}O_9Si$ (M^++1) 607.3303, found 607.3282; TLC (hexane/EtOAc, 1:2), R_f 0.66 for the major isomer, 0.60 for the minor isomer.

(3*SR*,3a*S*,5*S*,6*R*,6*aS*,10*R*,10a*S*)-2',2'-Dimethyl-1',3'-dioxane-5'-spiro-7-[5,6-[(*S*)-benzylidenedioxy]-3-benzyloxy--3-benzyloxymethyl-10-(*tert*-butyldimethylsilyl)oxyperhydro-1*H*-naphto[1,8a-c]furan] (78)

To a cooled (0 °C) round-bottom flask containing NaH (60% in oil, 13.5 mg, 0.338 mmol) was added a solution of **77** (29.5 mg, 48.6 μmol) in THF (1 mL) along with THF wash (1 mL), and the suspension was stirred at the same

temperature. TBAI (7.7 mg, 20.8 μmol) and BnBr (60 μL, 0.504 mmol) were added, and the resulting reaction mixture was allowed to warm to room temperature over 31 h. The reaction was quenched with sat. aq. NH_4Cl (1 mL), and concentrated *in vacuo*. The aqueous residue was extracted with Et_2O (4×2 mL). The combined Et_2O layers were dried over anhydrous $MgSO_4$, filtrated through cotton, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 2.5 g, hexane/EtOAc 30:1-5:1) afforded **78** (as a single isomer, 30.7 mg, 39.0 μmol, 80%) as a colorless oil: ^{1}H-NMR (400 MHz, C_6D_6), δ7.51 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6H_4$CH), 7.42 (2H, m, J_{ortho} = 7.0 Hz, two of $C_6H_5CH_2$), 7.32 (2H, m, J_{ortho} = 7.3 Hz, two of $C_6H_5CH_2$), 7.10-7.24 (6H, m, six of $C_6H_5CH_2$), 6.83 (2H, m, J_{ortho} = 8.8 Hz, two of *p*-MeOC$_6H_4$CH), 5.63 (1H, s, ArC*H*(OR)$_2$), 4.95-5.01 (2H, m, C_5-*H* and one of $C_{4'}$-*H*), 4.56 (2H, s, PhCH_2O), 4.41, 4.37 (each 1H, d, *J* = 12.1 Hz, PhCH_2O), 4.23-4.28 (2H, m, C_6-*H* and one of $C_{6'}$-*H*), 4.10 (1H, d, *J* = 8.6 Hz, one of BnOCH_2), 3.85 (1H, d, *J* = 10.1 Hz, one of BnOCH_2), 3.63 (1H, d, *J* = 10.1 Hz, one of BnOCH_2), 3.62 (1H, d, *J* = 8.6 Hz, one of BnOCH_2), 3.55 (1H, dd, *J* = 1.8, 11.0 Hz, one of $C_{6'}$-*H*), 3.27 (3H, s, ArOCH_3), 3.25 (1H, dd, *J* = 5.5, 8.4 Hz, one of $C_{4'}$-*H*), 3.16 (1H, dd, *J* = 2.6, 11.7 Hz, one of $C_{4'}$-*H*), 3.03 (1H, ddd, *J* = 1.5, 7.3, 14.5 Hz, one of C_4-*H*), 2.64 (1H, brd, *J* = 5.8 Hz, C_{3a}-*H*), 2.48 (1H, ddd, *J* = 4.0, 6.2, 13.9 Hz, C_8-$H_{eq.}$), 1.92 (1H, ddd, *J* = 5.8, 8.8, 14.5 Hz, one of C_4-*H*), 1.30-1.72 (3H, m, C_9-*H* and C_8-$H_{ax.}$), 1.52, 1.42 (each 3H, s, acetonide CH_3), 1.20 (1H, d, *J* = 11.2 Hz, C_{6a}-*H*), 1.03 (9H, s, SiC(CH_3)$_3$), 0.08, and 0.04 (each 3H, s, SiCH_3); TLC (hexane/EtOAc, 3:1), R_f 0.60.

(3*S*,3a*S*,5*S*,6*R*,6a*S*,10*R*,10a*S*)-5,6-[(*S*)-benzylidenedioxy]-3-benzyloxy-methyl-10-(*tert*-butyldimethylsilyl)oxy-3-methoxy-7,7-bis(hydroxymethyl)-perhydro-1*H*-naphto[1,8a-c]furan (79)

To a solution of **78** (29.0 mg, 36.8 μmol) in MeOH (2 mL) was added PPTS (3 mg, 11.9 μmol) at 0 °C, and the solution was stirred at the same temperature for 1 h, then allowed to warm to room temperature over 2 h. To the solution was added sat. aq. $NaHCO_3$ (1 mL), and the resulting mixture was concentrated *in vacuo*. Further water (1 mL) was added to the remaining

aqueous layer, and extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous $MgSO_4$, filtrated through Celite, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (400/230W, 0.4 g, hexane/EtOAc 5:1-2:1) afforded **79** (contaminated with 12% of (3*R*)-epimer, 15.0 mg, 22.4 μmol, 61%) as white crystals: m.p., 131-134 °C; $[\alpha]_D^{23}$ -41.9 ° (c 0.18, benzene); ^{1}H-NMR (400 MHz, C_6D_6), δ7.54 (2H, m, J_{ortho} = 8.6 Hz, two of *p*-MeOC_6H_4CH), 7.11-7.32 (5H, m, $C_6H_5CH_2$), 6.86 (2H, m, J_{ortho} = 8.6 Hz, two of *p*-MeOC_6H_4CH), 5.60 (1H, s, ArC*H*$(OR)_2$), 4.98 (1H, q, *J* = 8.1 Hz, C_5-*H*), 4.72-4.79 (2H, m, CH_2OH and C_6-*H*), 4.46, 4.39 (each 1H, d, *J* = 12.1 Hz, OCH_2Ph), 4.08, 4.00 (each 1H, d, *J* = 8.8 Hz, C_1-*H*), 3.85 (1H, d, *J* = 10.3 Hz, CH_2OBn), 3.70 (1H, m, one of CH_2OH), 3.55 (1H, d, *J* = 10.3 Hz, CH_2OBn), 3.37-3.51 (3H, m, three of CH_2OH), 3.28 (3H, s, ArOCH_3), 3.24 (1H, m, one of CH_2OH), 3.17 (3H, s, OCH_3), 3.16 (1H, dd, *J* = 4.8, 11.0 Hz, C_{10}-*H*), 3.02 (1H, brdd, *J* = 8.1, 14.0 Hz, C_4-*H*), 2.67 (1H, brd, *J* = 5.6 Hz, C_{3a}-*H*), 1.94 (1H, ddd, *J* = 5.6, 8.1, 14.0 Hz, C_4-*H*), 1.30-1.49 (2H, m, C_9-*H*), 1.42 (1H, d, *J* = 11.7 Hz, C_{6a}-*H*), 1.17 (1H, m, one of C_8-$H_{eq.}$), 1.01 (9H, s, SiC$(CH_3)_3$), 0.68 (1H, dt, *J* = 5.6, 14.1 Hz, C_8-$H_{ax.}$), 0.04, and 0.03 (each 3H, s, SiCH_3); IR (neat), ν_{max} 3452, 2936, 1616, 1520, 1472, 1308, 1252, 1110, 1084, and 836 cm^{-1}; EI-LR-MS, m/z 670 (0.8%, M^+), 549 (5.4), 337 (7.2), 281 (17.0), 137 (36.5), 91 (100), and 73 (30.2); EI-HR-MS, calcd. for $C_{37}H_{54}O_9Si$ 670.3579, found 670.3558; TLC (hexane/EtOAc, 1:1), R_f 0.40.

Acknowledgments

All the studies described in this thesis were carried out under the supervision of Professor Dr. Akio MURAI, Division of Chemistry, Graduate School of Science, Hokkaido University. The author would like to express deeply my sincere appreciation to Professor MURAI for his guidance and constant encouragement throughout the course of this work, in the preparation of this thesis, and for helpful discussions. He has also widen the author's knowledge and experience in the synthetic organic chemistry area.

The author wishes to thank sincerely Professor Dr. Takashi TSUJI, Professor Dr. Masaaki MIYASHITA, and Professor Dr. Keiji MARUOKA, Division of Chemistry, Graduate School of Science, Hokkaido University, for their reading this thesis and their helpful discussions. Especially for Professor MIYASHITA, the author would like to express special thanks for his fruitful discussions at the last stage of the work described in chapter 3, and heartfelt encouragement.

The author is deeply thankful to Professor Dr. Hideshi NAKAMURA for his helpful discussion. His knowledge that has been spread over the life science area gave the author very deep expression.

On the occasion of expressing the acknowledgments, the author would like to express my gratitude to Professor Dr. Akio FUKUZAWA, Faculty of engineering, Hokkaido Tokai University, for his tenderhearted encouragement. In the early stage of the author's research, Professor FUKUZAWA had provided various experiments (such as collection of research material from the field, and isolation, purification, and modification of some complex natural organic compounds) to the author.

The author is thankful to Dr. Kensyu FUJIWARA and Dr. Jun ISHIHARA for their helpful discussions and encouragement.

The author's special thanks are given to my colleagues, especially for Mr. Nobuyuki HAYASHI and Mr. Shinji NARA for their kindness and helpful discussion. They are not only the author's dear friends, but also friendly rivals in research area.

The author is also thankful to past and present members in the Murai's

laboratory. Especially, the author expresses thanks to Mr. Satoshi KOBAYASHI for his kindness, and his help and effort toward the synthetic study of azadirachtin.

The author also expresses his heartfelt thanks to the nature of Hokkaido Island.

In conclusion, the author expresses the largest and sincere gratitude to his mother, brother, and especially to his late father for financial help and heartfelt encouragement.

January, 1997

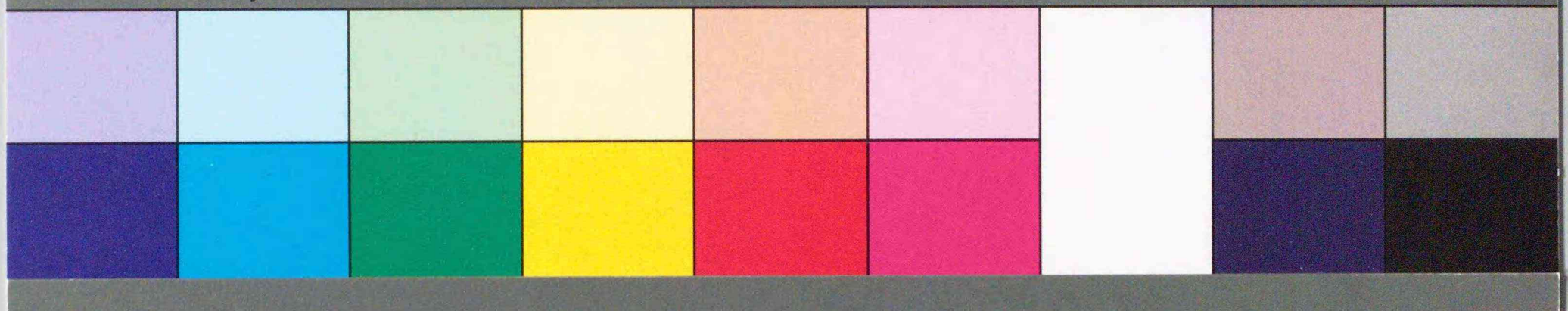
Naoki Kanoh

inches 1 2 3 4 5 6 7 8

cm 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

Kodak Color Control Patches

Blue Cyan Green Yellow Red Magenta White 3/Color Black



Kodak Gray Scale

C Y M

A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19