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A FORMAL SYNTHESIS OF APLASMOMYCIN. ASSEMBLY OF THE C3-C17 SEGMENT BASED ON 1,3- AND 1,5-ASYMMETRIC REDUCTIONS

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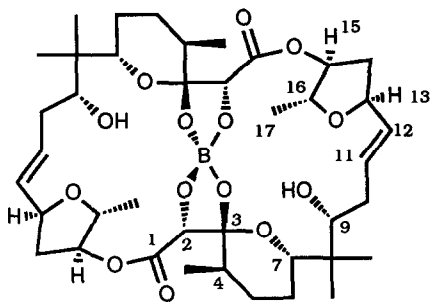
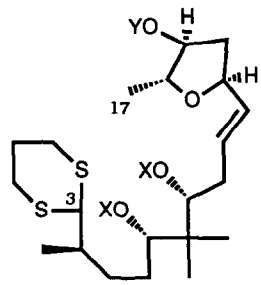
Abstract: The C3-C17 segment of a boron containing ionophoric antibiotic aplasmomycin (**1**), the key intermediate in Corey's total synthesis of **1**, was stereoselectively synthesized in an optically active form. This synthesis involved stereoselective construction of the two segments, (+)-dithiane **3** (C3-C11) and (+)-aldehyde **4** (C12-C17), based on remote controlled asymmetric reductions of the corresponding ketones as key steps and connection of **3** and **4** through the *trans*-double bond to elaborate the (+)-dithiane **2** (C3-C17), the key intermediate in Corey's total synthesis of **1**.

Aplasmomycin (**1**), a boron containing ionophoric antibiotic from *Streptomyces griseus*, inhibited Gram-positive bacteria *in vitro* and also *Plasmodium berghei in vivo*.[2] Stereostructure of **1** was determined by an X-ray crystallographic analysis as a C_2-symmetric diolide composed of two identical subunits with a borate bridge spanning the macrocycle.[3] The unique structure and biological activity of **1** distinguish this molecule as a very interesting target for synthesis and three independent total syntheses of **1** have been reported.[4] Recently, we have achieved a formal synthesis of **1**.[5] This synthesis featured stereocontrolled construction of the two segments, (+)-dithiane **3** (C3-C11) and (+)-aldehyde **4** (C12-C17), employing 1,3- and 1,5-asymmetric reduction of the corresponding ketones as key steps and connection of **3** and **4** through the *trans*-double bond to elaborate the (+)-dithiane **2** (C3-C17), the key intermediate in Corey's total synthesis of **1**. This paper concerns with full details of this formal synthesis of **1**.



1



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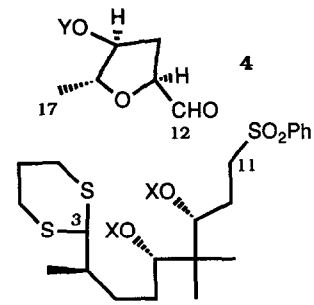


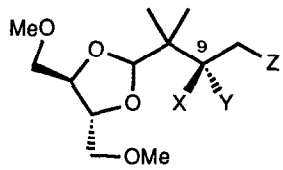
3

X=SitBuMe$_2$, Y=SitPr$_3$

Synthesis of C3-C11 Segment

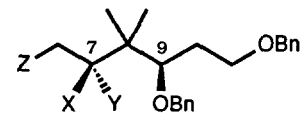
It had been found previously that high 1,5-asymmetric induction took place in reduction of the C_2-symmetric (+)-acetalketone **5** with lithium aluminumhydride in the presence of lithium bromide [ether-PhMe (1:1), -123 °C], giving the (+)-(*R*)-alcohol **6** in 98 % d.e. (in 100 mg scale with vigorous stirring).[6] Therefore, it was anticipated that for the chiral synthesis of the C3-C11 segment, the C-9 (aplasmomycin numbering) chiral center could be introduced by using this 1,5-asymmetric reduction and other chiral centers could be constructed diastereoselectively by the aid of the C-9 chiral center. Thus, for this purpose, the (+)-β,γ-unsaturated ketone **7** was employed. Reduction of **7** in 100 mg scale gave almost the same results as **5**. In contrast to small scale experiments, in carrying out the reduction in multigram scale, the d.e. value fell by lowering the reaction temperature below -100 °C, because effective vigorous stirring was difficult at this temperature. Furthermore, reproducibility of the d.e. value was poor. However, performing the reduction at -78 °C, the asymmetric reduction took place reproducibly in 86% d.e. even in multigram scale to give the (+)-(*R*)-alcohol **8** (**8**:**9**=13:1). The d.e. values were obtained by the ^{1}H NMR spectra at 90 MHz. By conversion of the resulting mixture of epimeric alcohols, **8** and **9** into a mixture of benzyl ethers, **10** and **11** [(1) H_2, Pd-C, AcOEt, rt, 1 h (2) $PhCH_2Cl$, NaO^{t}Am, DMSO, rt, 2 h, 87% (2 steps)], signals due to the acetal proton of **10** and **11** were observed as separated singlet peaks at δ 4.95 and δ 5.01, respectively. The (*R*)-configuration of **10** had already been determined.[6b]

The (+)-β-benzyloxyketone **12** was derived from **8** (86% d.e.) in 43% overall yield by (1) protection of the C-9 hydroxyl group as benzyl ether, (2) Lemieux-Johnson oxidation of the double bond, (3) reduction of the product aldehyde with borohydride, (4) conversion of the primary hydroxyl group into benzyl ether group, (5) removal of



a, b, c, d, e, f, g,

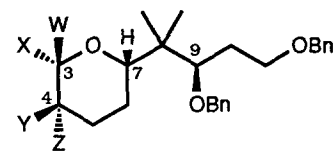
h, i, j, k, l, m, n



X=Y=O, Z=Et **5**
X=OH, Y=H, Z=Et **6**
X=Y=O, Z=CH=CH_2 **7**
X=OH, Y=H, Z=CH=CH_2 **8**
X=H, Y=OH, Z=CH=CH_2 **9**
X=OBn, Y=H, Z=Et **10**
X=H, Y=OBn, Z=Et **11**

X=Y=O, Z=CH=CH_2 **12**
X=OH, Y=H, Z=CH=CH_2 **13**
X=H, Y=OH, Z=CH=CH_2 **14**
X=OBn, Y=H, Z=CH_2OBn **15**
X=H, Y=OBn, Z=CH_2OBn **16**
X=OCOEt, Y=H, Z=CH_2I **17**

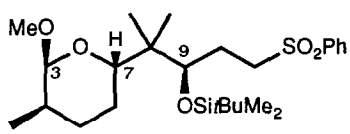
o, p, q, r



s, t, u, v, w

W=X=O, Y=Me, Z=H **18**
W=X=O, Y=H, Y=Me **19**
W=OMe, X=H, Y=Me, Z=H **20**
W=H, X=OMe, Y=Me, Z=H **21**

Bn=CH_2Ph



x, y

3

22

a) $LiAlH_4$, LiBr, ether-PhMe (1:1), -78 °C, 1 h, 97% b) $PhCH_2Cl$, NaO^{t}Am, DMSO, rt, 2 h, 91% c) OsO_4, $NaIO_4$, ether-H_2O, rt, 30 h d) $NaBH_4$, EtOH, 0 °C, 10 min, 82% (2 steps) e) $PhCH_2Cl$, NaO^{t}Am, DMSO, rt, 2 h, 87% f) 3N-HCl, acetone, reflux, 30 h, 78% g) CH_2=$CHCH_2MgBr$, ether, -78 °C, 1 h → rt, 2 h, 86% h) Jones reagent, acetone, 0 °C, 30 min, 98% i) $LiAlH_4$, ether-THF (9:1), -123 °C, 91% j) $(EtCO)_2O$, DMAP, Py, rt, 2 h, 96% k) OsO_4, $NaIO_4$, ether-H_2O, rt, 12 h l) $NaBH_4$, EtOH, 0 °C, 10 min, 87% (2 steps) m) *p*-TsCl, DMAP, Et_3N, rt, 12 h, 91% n) KI, DMSO, rt, 12 h, 94% o) LDA, THF, -78 °C, 2 h, 88% p) 1) KOMe, MeOH, rt, 7 days 2) *p*-TsOH•H_2O, CH_2Cl_2, rt, 30 min, 93% (2 steps) q) DIBAL, PhMe, -78 °C, 2 h r) CSA, MeOH, rt, 30 min, 57% (**20**), 30% (**21**) s) Na, liq. NH_3, -78 °C, 30 min t) *p*-TsCl, Et_3N, rt, 12 h, 89% (2 steps) u) LiSPh, THF, rt, 88% v) TBDMSOTf, 2,6-Lu, CH_2Cl_2, rt, 10 min w) *m*CPBA, CH_2Cl_2-sat. $NaHCO_3$ aq., rt, 1 h, 51% (optically pure **22**, 2 steps) x) $HS(CH_2)_3SH$, BF_3•OEt_2, CH_2Cl_2, 0 °C, 5 min, 87% y) TBDMSOTf, 2,6-Lu, CH_2Cl_2, rt, 3 h, 86%.

the chiral auxiliary by the treatment with hydrochloric acid, (6) Grignard reaction with allyl magnesium bromide, and (7) Jones oxidation.

As described previously,[6a] 1,3-asymmetric induction was anticipated to occur

selectively in hydride reduction of the β-alkoxyketones affording the corresponding *syn*-alcohols as the major epimers. 1,3-Asymmetric induction took place in the reduction of **12** with lithium aluminumhydride (ether, -123 °C) to give the desired (+)-*syn*-alcohol **13** predominantly (**13**:**14**=5:1, 400 MHz ^{1}H NMR) as expected. Employing ether-tetrahydrofuran solvent system, selectivity rose remarkably and the highest degree of 1,3-asymmetric reduction was obtained in 9:1 ether-tetrahydrofuran mixture to give **13** and **14** in a ratio of 16:1 (-123 °C) and 97% yield (Table 1, entry 1-6).

The stereochemistry at the C-7 position was determined as follows. These epimers, **13** and **14** could be separated by silica gel chromatography and each of them was converted into tetrabenzyl ethers, **15** and **16**, respectively [(1) $PhCH_2Cl$, NaO^tAm, DMSO, rt, 2 h (2) OsO_4, $NaIO_4$, ether-H_2O, rt, 12 h (3) $NaBH_4$, EtOH, 0 °C, 10 min (4) $PhCH_2Cl$, NaO^tAm, DMSO, rt, 2 h, 57% (**15**, 4 steps), 53% (**16**, 4 steps)]. Measurement of optical rotation revealed that **15** was optically inactive, whereas **16**, $[\alpha]_D^{20}$ +13.4° (c 2.00, $CHCl_3$, 86% e.e.), was active to confirmed the stereochemistry of **15** and **16**.

Alcohol **13** thus obtained was converted into a (+)-iodide **17** in 71% overall yield by the sequence of (1) protection of the C-7 hydroxyl group as propionate, which was used later for the introduction of C-3 unit, (2) Lemieux-Johnson oxidation of the double bond, (3) reduction of the product aldehyde with sodium borohydride, (4) tosylation of the primary hydroxyl group, and (5) displacement of tosylate by iodide.

In order to effect the ring closure reaction, treatment of **17** with various bases was examined. It turned out that among the bases examined, lithium diisopropylamide gave the best result and furthermore, over 2 equiv. of the base was required to achieved ring closure in good yield. After ring closure, kinetically controlled protonation with acetic acid of the lithium enolate gave a 1:1 epimeric mixture of lactones, **18** and **19**.

Stereocontrol at the C-4 chiral center was performed under equilibration conditions. Treatment of the epimeric mixture with potassium methoxide in methanol gave (+)-lactone **18** in high selectivity and 93% yield. The ratio of **18** to **19** was 17:1 (400 MHz ^{1}H NMR). The stereochemistry at the C-4 position was confirmed by considering thermodynamic stability of **18** over its epimer **19** and 400 MHz ^{1}H NMR spectrum of **18**. In ^{1}H NMR spectrum of **18**, the signals due to C-4 and C-7 protons appeared as double quintet (δ 2.37, J = 12.7 and 6.8 Hz) and double doublet (δ 4.28, J = 3.4 and 11.7 Hz) peaks, respectively. Analysis of coupling constants ($J_{4,5\beta}$ = 12.7 Hz, $J_{4,5\alpha}$ = 6.8 Hz, $J_{6\beta,7}$ = 3.4 Hz, and $J_{6\alpha,7}$ = 11.7 Hz) showed that the δ-lactone ring occupies a chair conformation with the equatorial oriented C-4 and C-7 alkyl substituents.

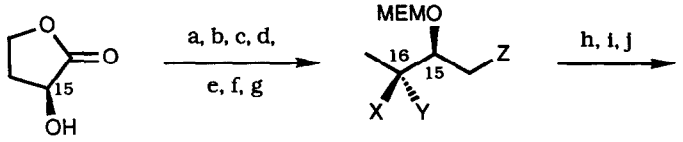
Reduction of **18** using diisobutylaluminumhydride followed by the treatment with camphorsulfonic acid in methanol (rt, 30 min) afforded a 2:1 mixture of the readily separable C-3 anomers, (+)-**20** and (-)-**21** in 57% and 30% yield (isolated yield by silica gel chromatography), respectively. Mainly from practical reasons, only the main anomer **20** was converted into the sulfone derivative by following the synthetic scheme described below. Another anomer **21** was treated with camphorsulfonic acid in methanol (rt, 12 h) to give an equilibrium mixture of **20** and **21** (**20**:**21**=1:1). Separation of anomers by silica gel chromatography afforded a 45% yield of **20** and a 46% yield of **21**, which was recycled. The stereochemistry of these anomers at the C-3 position was estimated as depicted in formula **20** and **21** by ^{1}H NMR spectral data. The 400 MHz spectra of **20** and **21** showed doublet peaks due to acetal protons at δ 4.45 (J = 3.2 Hz) and δ 3.79 (J = 8.2 Hz), respectively.

Conversion of the β-methoxy compound **20** into a (+)-sulfone **22** was performed in 61% overall yield by the sequence of (1) removal of the benzyl protecting groups by metallic sodium in liquid ammonia, (2) selective tosylation of the primary hydroxyl group, (3) treatment with lithium thiophenoxide, (4) protection of the C-9 hydroxyl group as *tert*-butyldimethylsilyl ether, and (5) oxidation with *m*-chloroperbenzoic acid. The hexane solution of **22** (86% e.e.) was seeded by the addition of a few crystals of racemic **22**, mp 88-89 °C (recrystallized from ether-hexane), prepared from 2-(2-hydroxy-1,1-dimethyl-4-pentenyl)-1,3-dioxolane according to the same procedure as that of optically active **22**, and the separated racemic crystals were removed. Optically pure **22**,[7] mp 90-91 °C and $[\alpha]_D^{20}$ +50.1° (c 2.00, $CHCl_3$), was obtained in 65% yield by further recrystallization of enriched **22** from ether-hexane solvent system. Dithiane formation followed by protection of the two hydroxyl groups as *tert*-butyldimethylsilyl ether gave rise to (+)-dithiane **3**, $[\alpha]_D^{20}$ +2.17° (c 2.40, MeOH), in 77% overall yield. 400 MHz ^{1}H NMR spectrum of synthetic **3** was identical with that provided by Drs. T. Nakata and T. Oishi.

Synthesis of C12-C17 Segment

As the starting material for the synthesis of the C12-C17 segment, (-)-(S)-2-hydroxy-4-butanolide (**23**) was selected, because it has the desired absolute configuration at the C-15 chiral center and furthermore, it can be prepared from (-)-L-malic acid readily and in high yield.[8] According to the Still's procedure,[8] sequential protection of the C-15 hydroxyl group as (2-methoxyethoxy)methyl ether, reaction with methyl lithium, and protection of the primary hydroxyl group as benzyloxymethyl ether converted **23** into a (-)-methylketone **24** in 77% overall yield.

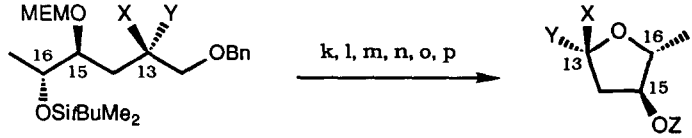
Next, selective introduction of the C-16 chiral center by 1,2-asymmetric



23

Bn=CH_2Ph

X=Y=O, Z=CH_2OCH_2OBn	**24**
X=H, Y=OH, Z=CH_2OCH_2OBn	**25**
X=OH, Y=H, Z=CH_2OCH_2OBn	**26**
X=H, Y=OH, Z=CH_2OH	**27**
X=H, Y=OMTPA, Z=CH_2OCH_2OBn	**28**
X=H, Y=OSi*t*BuMe$_2$, Z=CHO	**29**
X=OSi*t*BuMe$_2$, Y=H, Z=CHO	**30**



X=Y=O	**31**
X=OH, Y=H	**32**
X=H, Y=OH	**33**
X=OTs, Y=H	**34**
X=H, Y=OTs	**35**

X=CH_2OBn, Y=Z=H	**36**
X=H, Y=CH_2OBn, Z=H	**37**
X=CHO, Y=H, Z=Si*i*Pr$_3$	**4**

a) MEMCl, $^iPr_2NEt$, rt, 12 h, 88% b) MeLi, THF, -78 °C, 2 h, 98% c) $PhCH_2OCH_2Cl$, $^iPr_2NEt$, rt, 12 h, 89% d) $Zn(BH_4)_2$, ether, -78 °C, 3 h → rt, 12 h, 99% e) TBDMSCl, imidazole, DMF, 90 °C, 12 h, 89% f) Li, liq. NH_3, -78 °C, 30 min, 97% g) CrO_3•2Py, CH_2Cl_2, rt, 10 min, 84% h) $PhCH_2OCH_2Li$, THF, -78 °C, 4 h, 72% i) CrO_3•2Py, CH_2Cl_2, rt, 30 min, 99% j) $LiAlH(O^tBu)_3$, ether, -123 °C, 2 h, 98% k) 1) MeLi, THF, 0 °C, 5 min 2) *p*-TsCl, 0 °C → rt, 12 h, 83% l) $^nBu_4NF$, THF, rt, 12 h m) 3N-HCl, MeOH, reflux, 15 min, 77% (2 steps) n) TIPSCl, DMAP, CH_2Cl_2, rt, 12 h, 84% o) Na, liq. NH_3, -78 °C, 30 min, 86% p) 1) $(COCl)_2$-DMSO, CH_2Cl_2, -60 °C, 15 min 2) Et_3N, -60 °C, 5 min → 0 °C, 1.5 h, 94%.

reduction of **24** was attempted. It was expected that the desired (+)-*anti*-alcohol **25** could be obtained by chelation-controlled nucleophilic addition of hydride under the influence of the C-15 alkoxy group adjacent to carbonyl group. On the other hand, as shown in the 1,5-asymmetric reduction, it was anticipated that the interaction between metal cation and substrate could be increased by the addition of inorganic salts in reduction of ketones with lithium aluminumhydride. As expected, carrying out the reduction of **24** with lithium aluminumhydride in the presence of added 1 equiv. of magnesium bromide or zinc bromide (ether, -78 °C), selectivity of 1,2-asymmetric reduction was higher ($MgBr_2$; **25**:**26**=2:1, $ZnBr_2$; **25**:**26**=3:1, 400 MHz ^1H NMR) than that of simple reduction with lithium aluminumhydride (ether, -78 °C, **25**:**26**=1:1). However, the ratios of **25** to **26** were not satisfactory. Eventually, the desired **25** was

found to be obtained in a highly selective manner and in 99% yield by the use of zinc borohydride, which has been shown to give chelation-controlled products in the reduction of α-alkoxyketones.[9] By this method, the ratio of **25** to **26** was 15 to 1 according to 400 MHz ^{1}H NMR analysis.

The stereochemistry at the C-16 position was determined by leading **25** to a (+)-diol **27** (Li, liq. NH_3, -78 °C, 30 min, 91%) and its identification with an authentic sample derived from 2-deoxy-D-ribose.[10] Optical purity of **25** was ascertained by the 400 MHz ^{1}H NMR spectrum of its MTPA ester **28** (MTPACl, Py, rt, 12 h, 93%).

Since alcohols, **25** and **26** could not be separated by silica gel chromatography, the epimeric mixture (**25**:**26**=15:1) was employed for subsequent steps. After protection of the C-16 hydroxyl group as *tert*-butyldimethylsilyl ether, reductive cleavage of benzyloxymethyl group followed by Collins oxidation gave a (-)-*anti*-aldehyde **29** in 73% overall yield. At this stage, minor *syn*-aldehyde **30** could be separated from **29** by silica gel chromatography. Treatment of **29** with benzyloxymethyl lithium[11] and successive Collins oxidation afforded (-)-benzyloxymethylketone **31** in 71% overall yield.

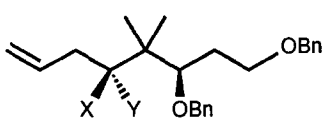
As expected, in the reduction of **31**, 1,3-asymmetric induction took place in fairly good selectivity with lithium tri-*tert*-butoxyaluminumhydride. Reduction of **31** in ether at -78 °C afforded the desired (-)-*syn*-alcohol **32** predominantly (**32**:**33**=5:1, 400 MHz ^{1}H NMR). Investigation on temperature dependence of this reduction revealed that lowering the reaction temperature raised selectivity remarkably. Ultimately, at -123 °C, the highest degree of 1,3-asymmetric induction was obtained giving **32** and **33** in a ratio of 10 to 1 and in 98% yield (Table 1, entry 19-24). The stereochemistry at C-13 chiral center was assumed on the basis of the fact that *syn*-alcohols were always obtained as major epimer in reduction of other β-alkoxyketones with lithium aluminumhydride or lithium tri-*tert*-butoxyaluminumhydride (*vide infra*). This assignment was obviously confirmed by successful conversion of **32** into the objective compound **4** (*vide infra*).

The epimers, **32** and **33** were not able to be separated by silica gel chromatography. Thus, the epimeric mixture (**32**:**33**=10:1) was used for the synthesis of **4**. After tosylation of the C-13 hydroxyl group of (-)-**32**, desilylation with tetrabutylammonium fluoride resulted in simultaneous tetrahydrofuran ring formation. Subsequent cleavage of the (2-methoxyethoxy)methyl ether gave the (+)-tetrahydrofuran **36** in 64% overall yield. At this stage, the minor tetrahydrofuran **37** could be readily separated from **36** by silica gel chromatography. Separation of the mixture of tosylate, **34** and **35** could be carried out with difficulty. Desilylation of each tosylates, **34** and **35** under the same conditions revealed that tetrahydrofuran ring closure reaction occurred in a stereospecific manner to give **36** (86%) and **37** (88%),

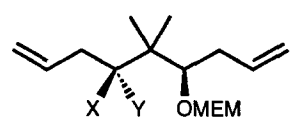
respectively, as a sole product. Successive protection of the C-15 hydroxyl group as triisopropylsilyl ether, cleavage of the benzyl ether by the treatment with metallic sodium in liquid ammonia, and Swern oxidation of the product alcohol produced (+)-aldehyde **4**, $[\alpha]_D^{20}$ +18.1° (c 1.00, $CHCl_3$), in 68% overall yield. Optical rotation and 400 MHz ^1H NMR spectrum of synthetic **4** were identical with those reported[4b] and provided, respectively, by Drs. T. Nakata and T. Oishi.

1,3-Asymmetric Reduction of β-Alkoxyketones

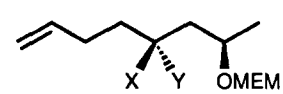
Recently, stereoselective construction of the 1,3-diols attracted much attention, since the 1,3-polyol system is frequently found in natural products such as polyene macrolide antibiotics.[12] As mentioned in this paper and previously,[6a] 1,3-asymmetric induction was found to take place in a highly stereoselective manner in reduction of β-alkoxyketones, **12**, **31**, and **44**[6a] employing lithium aluminumhydride or lithium tri-*tert*-butoxyaluminumhydride. Thus hydride reduction of other β-alkoxyketones, **38** and **41** were further attempted to examine the generality of this 1,3-asymmetric reduction of the β-alkoxyketones. Results of hydride reduction of β-alkoxyketones, **12**, **38**, **41**, **31**, and **44** are summarized in Table 1. The *syn*-alcohols were always obtained as major epimer. In cases of the alkoxymethylketones, **31** and **44**, high selectivity of 1,3-asymmetric reduction was obtained by employing lithium tri-*tert*-butoxyaluminumhydride as hydride reagent. On the other hand, in reduction of other ketones, **12**, **38**, and **41**, 1,3-asymmetric induction took place in fairly good selectivity with lithium aluminumhydride in ether-tetrahydrofuran solvent system. In contrast to 1,2-asymmetric reduction mentioned before, zinc borohydride gave only similar degree of selectivity as lithium aluminumhydride (entry 18, 25, and 33). In reduction



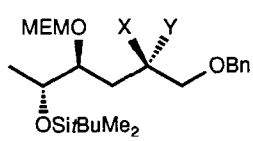
X=Y=O **12**
X=OH, Y=H **13**
X=H, Y=OH **14**



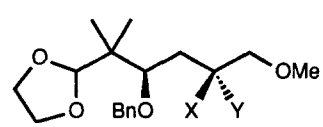
X=Y=O **38**
X=OH, Y=H **39**
X=H, Y=OH **40**



X=Y=O **41**
X=OH, Y=H **42**
X=H, Y=OH **43**



X=Y=O **31**
X=OH, Y=H **32**
X=H, Y=OH **33**



X=Y=O **44**
X=OH, Y=H **45**
X=H, Y=OH **46**

Bn=CH_2Ph

Table 1

Entry	Ketone	Hydride Reagent	Conditions	*Syn*:*Anti* [a]
1	**12**	$LiAlH_4$	ether, -78 °C	4:1 (**13**:**14**)
2		$LiAlH_4$	ether-THF (9:1), -78 °C	5:1
3		$LiAlH_4$	ether, -123 °C	5:1
4		$LiAlH_4$	ether-THF (19:1), -123 °C	12:1
5		$LiAlH_4$	ether-THF (9:1), -123 °C	16:1
6		$LiAlH_4$	ether-THF (4:1), -123 °C	9:1
7		$LiAlH_4$	LiBr, ether, -123 °C	5:1
8		$LiAlH_4$	$MgBr_2$, ether, -123°C	5:1
9		$LiAlH_4$	$ZnBr_2$, ether, -123 °C	5:1
10	**38**	$LiAlH_4$	ether, -78 °C	3:1 (**39**:**40**)[b]
11		$LiAlH_4$	ether, -123 °C	4:1
12		$LiAlH_4$	ether-THF (9:1), -123 °C	9:1
13		$NaBH_4$	EtOH, 0 °C	3:1
14	**41**	$LiAlH_4$	ether, -78 °C	4:1 (**42**:**43**)[c]
15		$LiAlH_4$	ether, -123 °C	5:1
16		$LiAlH_4$	ether-THF (9:1), -123 °C	7:1
17		$LiAlH(OtBu)_3$	ether, -78 °C	3:1
18		$Zn(BH_4)_2$	ether, -78 °C → rt	4:1
19	**31**	$LiAlH_4$	ether, -78 °C	1.3:1 (**32**:**33**)
20		$LiAlH_4$	ether, -123 °C	1.5:1
21		$LiAlH_4$	ether-THF (9:1),-123 °C	2:1
22		$LiAlH(OtBu)_3$	ether, -78 °C	5:1
23		$LiAlH(OtBu)_3$	ether, -100 °C	8:1
24		$LiAlH(OtBu)_3$	ether, -123 °C	10:1
25		$Zn(BH_4)_2$	ether, -78 °C → rt	1.5:1
26	**44**	$LiAlH_4$	ether, -78 °C	5:1 (**45**:**46**)[d]
27		$LiAlH_4$	ether, -123 °C	6:1
28		$LiAlH_4$	ether-THF (9:1), -123 °C	7:1
29		$LiAlH_4$	LiBr, ether, -123 °C	6:1
30		$LiAlH_4$	$MgBr_2$, ether, -123 °C	6:1
31		$LiAlH_4$	$ZnBr_2$, ether, -123 °C	5:1
32		$LiAlH(OtBu)_3$	ether, -78 °C	12:1
33		$Zn(BH_4)_2$	ether, -78 °C → rt	6:1
34		$NaBH_4$	EtOH, -78 °C	4:1

a) The ratios of the *syn*- and the *anti*-alcohols were obtained by 400 MHz ^1H NMR spectra.

b) The stereochemistry of the alcohols, **39** and **40** have already been established.[6a]

c) On the basis of the ^1H NMR spectral data (90 MHz) of phenylboronates, derived from the alcohols, **42** and **43** by successive cleavage of the (2-methoxyethoxy)methyl ether and treatment of the resulting 1,3-diols with phenylboric acid, the stereochemistry of **42** and **43** was determined unambiguously by deducing molecular symmetry: Tsuzuki, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1978**, 989.

d) By comparison of ^1H NMR spectral data (90 MHz) and TLC mobilities of the corresponding

1,3-diols, prepared from the alcohols, **45** and **46** by acidic hydrolysis, with those reported by Gerlach and Wetter, the stereochemistry of **45** and **46** were established cleanly: Gerlach, H.; Wetter, H. *Helv. Chim. Acta* **1974**, *57*, 2306.

with lithium aluminumhydride, the presence of 1 equiv. of added inorganic salt (entry 7, 8, 9, 29, 30, and 31) gave only a slight effect on selectivity[13] contrary to the 1,5-asymmetric reduction described previously.[6] Furthermore, similar selectivity as lithium aluminumhydride was obtained by employing sodium borohydride in ethanol (entry 13 and 34). On the basis of those observation it was suggested that steric bulkiness of the hydride reagent rather than interaction between metal cation and substrate plays an important role in this 1,3-asymmetric reduction.

Formal Synthesis of Aplasmomycin

Connection of (+)-**3** and (+)-**4** was carried out according to the Nakata-Oishi's procedure. Reaction of **3** with butyl lithium (THF, -78 °C, 10 min) produced the lithiated sulfone, which was coupled with 1.5 equiv. of **4** (HMPA-THF, -50 °C, 2 h). Direct treatment of the adduct with benzoyl chloride (DMAP, Et_3N, rt, 12 h) and reductive elimination of a isomeric mixture of the β-benzoyloxysulfones by sodium amalgam (THF-MeOH, -20 °C, 8 h) afforded (+)-**2**, $[\alpha]_D^{20}$ +6.92° (c 1.00, $CHCl_3$), in 40% overall yield from **3**. Optical rotation and 400 MHz ^1H NMR spectrum of synthetic **2** were identical with those reported[4b] and provided, respectively, by Drs. T. Nakata and T. Oishi. Since (+)-aplasmomycin (**1**) has already been derived from **2** by Corey *et al.*, our synthesis of **2** represents a formal synthesis of **1**.

Experimental

Optical rotations were determined on a JASCO DIP-SL instrument. IR spectra were recorded on a JASCO IR-S instrument and were calibrated with 1603 cm^{-1} absorption of polystyrene. ^1H NMR spectra were measured at 90 MHz on a Hitachi R-90H instrument and at 400 MHz on a JEOL JNM-FX 400 instrument. Chemical shifts are reported in δ units relative to tetramethylsilane as internal standard. Low resolution mass spectra were run on a JEOL JMS-D300 instrument (EI-MS) and JEOL-01SG-2 instrument (FI-MS). High resolution mass spectra were taken by a JEOL JMS-D300 instrument. Elemental analyses were performed at Laboratory for Instrumental Analysis of Hokkaido University.

2-(2-Hydroxy-1,1-dimethylethyl)-1,3-dioxolane

To a stirred mixture of isobutylaldehyde (100 g, 1.4 mol) and 37% formalin (150 g, 1.9 mol) was added 80 g (0.37 mol) of K_2CO_3 by portions under cooling in an ice bath. Stirring was continued for additional 30 min at rt. The mixture separated in two phases on standing. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in benzene (500 ml) containing ethylene glycol (160 g, 2.8 mol) and *p*-TsOH•H_2O (2.5 g, 13 mmol). The mixture was heated at reflux under a Dean-Stark

apparatus for 20 h. After cooling, the mixture was washed successively with 1N NaOH and brine, dried over Na_2SO_4, and evaporated *in vacuo*. Distillation of the crude product under reduced pressure gave 170 g (82%) of the hydroxyacetal: bp 100-110 °C (25 Torr); IR (neat) 3400 cm^{-1}: ^1H NMR ($CDCl_3$) δ 0.88 (6H, s), 3.30 (2H, s), 3.85 (4H, m), 4.35 (1H, s); EI-MS m/z 145 (M^+-H). *Anal.* Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65%. Found: C, 57.43; H, 9.76%.

2-Methyl-2-(1,3-dioxolan-2-yl)propanal

To a soln of the hydroxyacetal (40 g, 0.27 mol) in CH_2Cl_2 (400 ml) was added PCC (220 g, 1.2 mol) and NaOAc (4.0 g, 49 mmol) successively. The reaction mixture was stirred at rt for 3 h. To the mixture was added ether (400 ml) and the ethereal soln was removed by decantation. The precipitate was collected and extracted with two 100 ml portions of ether. The combined ethereal soln was washed successively with 2N NaOH and brine, dried over Na_2SO_4, and the solvent was distilled off at atmospheric pressure. Distillation of the residual oil under reduced pressure gave 29 g (75%) of the aldehyde: bp 80-85 °C (35 Torr); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (6H, s), 3.85 (4H, m), 4.70 (1H, s), 9.35 (1H, s); EI-MS 115 (M^+-CHO). *Anal.* Calcd. for $C_7H_{12}O_3$: C, 58.31; 8.39%. Found: C, 58.35; H, 8.78%.

2-(2-Hydroxy-1,1-dimethyl-4-pentenyl)-1,3-dioxolane

To a stirred soln of the aldehyde (40 g, 0.28 mol) in ether (200 ml) cooled to 0°C was added by portions a soln of CH_2=$CHCH_2MgBr$ [prepared from Mg (10 g, 0.41 mol) and CH_2=$CHCH_2Br$ (55 g, 0.45 mol) in ether (300 ml) under usual conditions]. After stirring was continued for 1.5 h at 0 °C, the reaction mixture was poured into ice-water and saturated NH_4Cl aq. was added to the mixture until all the solid materials dissolved. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal phases were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Distillation of the residual oil under reduced pressure gave 44 g (85%) of the homoallyl alcohol: bp 115-120 °C (25 Torr); IR (neat) 3400, 3020, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84, 0.89 (each 3H, s), 2.11 (2H, m), 3.48 (1H, m), 3.83 (4H, m), 4.58 (1H, s), 4.82, 5.10 (each 1H, m), 6.2-5.5 (1H, m); EI-MS m/z 145 (M^+-CH_2=$CHCH_2$). *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%. Found: C, 64.37; H, 9.63%.

A 1:1 Epimeric Mixture of (4*R*,5*R*)-4,5-Bis(methoxymethyl)-2-[(*R*)-2-hydroxy-1,1-dimethyl-4-pentenyl]-1,3-dioxolane (8) and (4*R*,5*R*)-4,5-Bis(methoxymethyl)-2-[(*S*)-2-hydroxy-1,1-dimethyl-4-pentenyl]-1,3-dioxolane (9)

To a stirred soln of the homoallyl alcohol (19 g, 0.10 mol) and NaO^{t}Am (23 g, 0.21 mol) in DMSO (150 ml) was added $PhCH_2Cl$ (15 g, 0.12 mol) at rt under Ar atmosphere. After stirring at rt for 2 h, brine (1.0 l) was added and the product was extracted with ether. The ethereal soln was washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave a crude product. Chromatography of the crude product on silica gel (hexane-AcOEt, 97:3) gave 25 g (88%) of 2-[2-(benzyloxy)-1,1-dimethyl-4-pentenyl]-1,3-dioxolane.

To a soln of the dioxolane (25 g, 89 mmol) in acetone (1.5 l) was added 3N HCl (320 ml) at rt. The reaction mixture was heated at reflux for 2 h. After cooling, the acetone was removed off *in vacuo* and the product was extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solv *in vacuo* afforded a crude product, which was purified by chromatography on silica gel (hexane-AcOEt, 97:3) to yield 19 g (92%) of 3-(benzyloxy)-2,2-dimethyl-5-hexenal.

The aldehyde (17 g, 75 mmol) was dissolved in PhH (640 ml) containing (+)-(2R,3R)-1,4-dimethoxy-2,3-butanediol[14] (12 g, 75 mmol) and *p*-TsOH•H_2O (6.6 g, 35 mmol) at rt. The mixture was heated at reflux under a Dean-Stark apparatus for 10 min. After cooling, solid Na_2CO_3 (2.4 g, 23 mmol) was added and the soln was

concentrated *in vacuo*. The residual oil was dissolved in ether and the ethereal soln was washed successively with saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 95:5) gave 22 g (79%) of a 1:1 epimeric mixture of the benzyl ethers of **8** and **9**.

Metallic Na (13 g, 0.55 mmol) was dissolved in liq. NH_3 (630 ml) at -78 °C under Ar atmosphere. To the resultant blue soln was added dropwise with stirring a soln of the mixture (24 g, 66 mmol) in ether (100 ml) at -78 °C. After stirring at -78 °C for 30 min, solid NH_4Cl was added in small portions until the blue color disappeared and then the NH_3 was left to evaporate. The residue was diluted with water and extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solv *in vacuo*, chromatography of the crude product on silica gel (hexane-AcOEt, 85:15) gave 16 g (85%) of a 1:1 epimeric mixture of **8** and **9**: IR (neat) 3560, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89, 0.97 (each 3H, s), 2.95 (1H, bs), 3.36 (6H, s), 4.85 (1H, s); FI-MS m/z 274 (M^+). *Anal.* Calcd. for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55%. Found: C, 61.20; H, 9.63%.

2-[(4*R*,5*R*)-4,5-Bis(methoxymethyl)-1,3-dioxolan-2-yl]-2-methyl-5-hexen-3-one (7)

A soln of the 1:1 epimeric mixture of **8** and **9** (1.0 g, 3.6 mmol) in acetone (20 ml) was cooled to 0 °C and Jones reagent was added dropwise until the faint red color persisted. After stirring at 0 °C for 30 min, the excess Jones reagent was destroyed by the addition of ^iPrOH. The precipitate was filtered off and washed with ether. The combined filtrates were concentrated *in vacuo* and the residue was extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 0.97 g (97%) of **7**: $[\alpha]_D^{20}$ +1.20° (c 2.00, $CHCl_3$); IR (neat) 1730, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (6H, s), 3.33 (2H, dt, 7 and 2 Hz), 3.36 (6H, s), 5.07 (1H, s); EI-MS m/z 272 (M^+), 271 (M^+-H), 275 (M^+-Me). Exact Mass. Calcd. for $C_{14}H_{24}O_5$: 272.1624. Found: 272.1656.

Alcohol 8 (86% d.e.)

To a stirred suspension of LiBr (0.63 g, 7.5 mmol) in a mixture of PhMe (30 ml) and ether (30 ml) cooled to -78 °C was added with vigorous stirring a soln of **7** (2.0 g, 7.5 mmol) in a mixture of PhMe (8.0 ml) and ether (8.0 ml) under Ar atmosphere. After stirring at -78 °C for 1 h, a suspension of $LiAlH_4$ (0.55 g, 15 mmol) in a mixture of PhMe (8.0 ml) and ether (8.0 ml) cooled to -78 °C was added at the same temp. After vigorous stirring at -78 °C for 2 h, the excess hydride was destroyed by the addition of water (0.50 ml). The mixture was neutralized with 1N HCl and extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 2.0 g (97%) of **8** in 86% d.e. (**8**:**9**=13:1, 90 MHz ^1H NMR of benzyl ethers, **10** and **11**), having $[\alpha]_D^{20}$ +14.2° (c 2.00, $CHCl_3$).

(*R*)-3,5-Bis(benzyloxy)-2,2-dimethylpentanal

To a stirred soln of **8** (86% d.e., 1.5 g, 5.5 mmol) and NaO^tAm (2.5 g, 2.3 mmol) in DMSO (15 ml) was added $PhCH_2Cl$ (2.2 g, 18 mmol) at rt under Ar atmosphere. After stirring at rt for 2 h, similar treatment as before gave a crude product, which was purified by chromatography on silica gel (hexane-AcOEt, 95:5) to give 1.8 g (91%) of a benzyl ether of **8**.

To a soln of the benzyl ether (1.8 g, 5.0 mmol) in a mixture of ether (75 ml) and water (40 ml) was added OsO_4 (40 mg, 0.16 mmol) at rt. After stirring at rt for 30 min, solid $NaIO_4$ (2.8 g, 13 mmol) was added in small portions at rt for 30 min. The stirring was continued at rt for 30 h and the product was extracted with ether. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. To the residual oil was added EtOH (35 ml) and the soln was cooled to 0 °C. Solid $NaBH_4$ (0.38 g, 10 mmol) was added and stirring was continued at 0 °C for 10 min. The reaction was quenched by the addition of AcOH. After

evaporation of the EtOH *in vacuo*, brine was added and the product was extracted with ether. The ethereal soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 60:40) gave 1.5 g (82%) of an alcohol.

To a stirred soln of the alcohol (1.1 g, 3.1 mmol) and NaO^{t}Am (1.4 g, 13 mmol) in DMSO (10 ml) was added $PhCH_2Cl$ (0.78 g, 6.1 mmol) at rt under Ar atmosphere. After stirring at rt for 2 h, the similar work-up as before gave a crude product, which was chromatographed on silica gel (hexane-AcOEt, 93:7) to yield 1.2 g (87%) of a dibenzyl ether.

To a soln of the dibenzyl ether (1.2 g, 2.7 mmol) in acetone (800 ml) was added 3N HCl (30 ml) at rt. The reaction mixture was heated at reflux for 30 h. Similar treatment as before gave a crude product. Chromatography of the crude product on silica gel (hexane-AcOEt, 97:3) gave 0.68 g (78%) of the aldehyde: $[\alpha]_D^{20}$ +22.2° (c 2.00, $CHCl_3$); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03, 1.10 (each 3H, s), 3.77 (1H, dd, 4 and 8 Hz), 4.46, 4.50 (each 2H, s), 7.23, 7.29 (each 5H, s), 9.58 (1H, s); EI-MS m/z 326 (M^+). Exact Mass. Calcd. for $C_{21}H_{26}O_3$: 326.1882. Found: 326.1879.

(*R*)-6,8-Bis(benzyloxy)-5,5-dimethyl-1-octen-4-one (12)

To a stirred soln of the aldehyde (0.91 g, 2.8 mmol) in ether (35 ml) cooled to -78 °C was added by portions a soln of CH_2=$CHCH_2MgBr$ [prepared from Mg (2.4 g, 0.10 mol) and CH_2=$CHCH_2Br$ (12 g, 0.10 mol) in ether (100 ml) under usual conditions] under Ar atmosphere. After stirring at -78 °C for 1 h, the temp allowed to rise to rt and the stirring was continued at rt for additional 2 h. The same treatment as mentioned before gave a crude product. Chromatography of the crude product on silica gel (hexane-AcOEt, 95:5) afforded 0.88 g (86%) of a 1.5:1 epimeric mixture of **13** and **14**.

A soln of the mixture (0.88 g, 2.4 mmol) in acetone (20 ml) was cooled to 0 °C and Jones reagent was added dropwise until the faint red color persisted. After stirring at 0 °C for 30 min, similar treatment as before gave 0.86 g (98%) of **12**: $[\alpha]_D^{20}$ +21.0° (c 2.00, $CHCl_3$); IR (neat) 1705, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11, 1.20 (each 3H, s), 3.28 (1H, dt, 7 and 2 Hz), 3.84 (1H, dd, 4 and 7 Hz), 4.43, 4.46 (each 2H, s), 7.19, 7.25 (each 5H, s); EI-MS m/z 366 (M^+). Exact Mass. Calcd. for $C_{24}H_{30}O_3$: 366.2195. Found: 366.2188.

(4*S*,6*R*)-6,8-Bis(benzyloxy)-5,5-dimethyl-1-octen-4-ol (13)

To a stirred suspension of $LiAlH_4$ (3.6 g, 9.5 mmol) in a mixture of ether (90 ml) and THF (10 ml) cooled to -123 °C was added dropwise a soln of **12** (1.3 g, 3.5 mmol) in a mixture of ether (9.0 ml) and THF (1.0 ml) under Ar atmosphere. After stirring at -123 °C for 2 h, the excess hydride was destroyed by the addition of water (90 ml) and working-up as before gave a crude product (1.3 g, 97%, **13**:**14**=16:1, 400 MHz, ^1H NMR), which was purified by chromatography on silica gel (hexane-AcOEt, 97:3) to yield 1.2 g (91%) of diastereomerically pure **13**: $[\alpha]_D^{20}$ +7.39° (c 2.00, $CHCl_3$); IR (neat) 3520, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85, 0.99 (each 3H, s), 4.49, 4.51 (each 1H, d, 11.7 Hz), 4.53, 4.55 (each 1H, d, 11.2 Hz); FI-MS m/z 369 (M^++H), 368 (M^+). *Anal.* Calcd. for $C_{24}H_{32}O_3$: C, 77.49; H, 9.05%. Found: C, 77.52; H, 8.99%.

(1*S*,3*R*)-3,5-Bis(benzyloxy)-1-(2-iodoethyl)-2,2-dimethylpentyl Propionate (17)

To a soln of **13** (0.76 g, 2.1 mmol) and DMAP (60 mg, 0.49 mmol) in pyridine (10 ml) was added $(EtCO)_2O$ (0.70 g, 5.4 mmol) at rt. After stirring at rt for 12 h, the solv was removed off *in vacuo*. To the resulting residue was added saturated $NaHCO_3$ aq. (10 ml) and the product was extracted with ether. The ethereal soln was washed successively with 1N HCl, saturated $NaHCO_3$ aq., and brine and dried over Na_2SO_4. Evaporation of the solv *in vacuo* afforded 0.87 g (96%) of a propionate.

To a soln of the propionate (0.87 g, 2.1 mmol) in a mixture of ether (40 ml) and water (40 ml) was added

OsO_4 (17 mg, 67 μmol) at rt. After stirring at rt for 30 min, solid $NaIO_4$ (1.1g, 5.1 mmol) was added in small portions at rt for 30 min. The stirring was continued at rt for 12 h, and the reaction mixture was processed as before to give a crude product, which was dissolved in EtOH (20 ml). The soln was cooled to 0 °C and solid $NaBH_4$ (0.16 g, 4.2 mmol) was added and the stirring was continued at 0 °C for 10 min. Similar treatment as before afforded a crude product. Chromatography of the crude product on silica gel (hexane-AcOEt, 80:20) yielded 0.76 g (87%) of an alcohol.

To a soln of the alcohol (0.70 g, 1.7 mmol) and DMAP (42 mg, 0.35 μmol) in Et_3N (15 ml) was added solid *p*-TsCl (1.9 g, 10 mmol) at rt. The stirring was continued at rt for 12 h. To the reaction mixture was added MeOH (5.0 ml) and the solv was removed off *in vacuo*. The residue was diluted with ether and the ethereal soln was washed successively with 1N HCl, saturated $NaHCO_3$ aq., and brine and dried over Na_2SO_4. After evaporation of the solv *in vacuo*, the crude product was chromatographed on silica gel (hexane-AcOEt, 92:8) to give 0.87 g (91%) of a tosylate.

To a soln of the tosylate (0.87 g, 0.50 mmol) in DMSO (8.0 ml) was added solid KI (7.6 g, 46 mmol) at rt. The stirring was continued at rt for 12 h. After the reaction was quenched by the addition of brine (30 ml), solid $Na_2S_2O_3$ was added in small portions until the yellow color disappeared. The product was extracted with ether and the ethereal soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 97:3) gave 0.76 g (94%) of **17**: $[\alpha]_D^{20}$ +2.61° (c 2.00, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89, 0.95 (each 3H, s), 1.11 (3H, t, 7 Hz), 2.32 (2H, q, 7 Hz), 4.44, 4.50 (each 2H, s), 4.98 (1H, dd, 4 and 8 Hz), 7.23, 7.26 (each 5H, s); EI-MS m/z 538 (M^+), 447 (M^+-$PhCH_2$). Exact Mass. Calcd. for $C_{26}H_{35}O_4I$: 538.1581. Found: 538.1542.

(2*R*,5*S*)-5-[(*R*)-2,4-Bis(benzyloxy)-1,1-dimethylbutyl]-2-methyl-5-pentanolide (18)

To a stirred soln of LDA [prepared from $^iPr_2NH$ (0.76 g, 7.5 mmol) and ^nBuLi (1.60M hexane soln, 3.9 ml, 6.2 mmol) in THF (15 ml) at 0 °C under Ar atmosphere for 20 min] cooled to -78 °C was added dropwise a soln of **17** (0.82 g, 1.5 mmol) in THF (5.0 ml). After stirring at -78 °C for 2 h, the reaction was quenched by the addition of AcOH (0.99 g, 16 mmol). The solv was removed off *in vacuo* and the residue was dissolved in ether. The ethereal soln was washed with brine and dried over Na_2SO_4. After evaporation of the solv *in vacuo*, chromatography of the residual oil on silica gel (hexane-AcOEt, 90:10) gave 0.55 g (88%) of a 1:1 epimeric mixture of **18** and **19**.

To a soln of KOMe [prepared from metallic K (0.79 g, 20 mmol) in MeOH (25 ml) at rt under Ar atmosphere for 30 min] was added a soln of the mixture (0.55 g, 1.3 mmol) in MeOH (4.0 ml) at rt. After stirring at rt for 7 days, the reaction was quenched by the addition of AcOH (1.2 g, 20 mmol) and the MeOH was evaporated *in vacuo*. The residue was diluted with AcOEt and the soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 ml) and the soln was treated with *p*-TsOH•H_2O (0.14 g, 0.74 mmol) at rt for 30 min, washed successively with saturated $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. After evaporation of the solv *in vacuo*, the crude product was chromatographed on silica gel (hexane-AcOEt, 90:10) to give 0.51 g (93%) of **18** (**18**:**19**=17:1, 400 MHz, ^1H NMR): $[\alpha]_D^{20}$ +10.8° (c 2.00, $CHCl_3$); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90, 1.07 (each 3H, s), 1.27 (3H, d, 6.8 Hz), 2.37 (1H, dquintet, 12.7 and 6.8 Hz), 3.59 (1H, dd, 3.4 and 9.0 Hz), 4.28 (1H, dd, 3.4 and 11.7 Hz), 4.47, 4.49, 4.52, 4.56 (each 1H, d, 11.7 Hz); EI-MS m/z 410 (M^+), 319 (M^+-$PhCH_2$). Exact Mass. Calcd. for $C_{26}H_{34}O_4$: 410.2457. Found: 410.2451.

(2*S*,3*R*,6*S*)-6-[(*R*)-2,4-Bis(benzyloxy)-1,1-dimethylbutyl]tetrahydro-2-methoxy-3-methyl-2*H*-pyran (20) and (2*R*,3*R*,6*S*)-6-[(*R*)-2,4-Bis(benzyloxy)-1,1-dimethylbutyl]tetrahydro-2-methoxy-3-methyl-2*H*-pyran (21)

To a stirred soln of **18** (**18**:**19**=17:1, 1.0 g, 2.4 mmol) in PhMe (20 ml) cooled to -78 °C was added dropwise DIBAL (1.76M hexane soln, 1.7 ml, 4.8 mmol) under Ar atmosphere. After stirring at -78 °C for 2 h, the excess hydride was destroyed by the addition of water (1.0 ml). The mixture was diluted with AcOEt, dried over Na_2SO_4, filtered through Celite, and concentrated *in vacuo*. The residual oil was dissolved in MeOH (20 ml) and the soln was treated with CSA (0.10 g, 0.44 mmol) at rt under Ar atmosphere for 30 min. The reaction was quenched by the addition of Et_3N (0.10 ml). After removal of the solv *in vacuo*, the residue was diluted with ether. The ethereal soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude oil on silica gel (hexane-AcOEt, 97:3) yielded 0.60 g (57%) of **20** (less polar epimer) and 0.32 g (30%) of **21** (more polar epimer).

β-Methoxy compound **20**: $[\alpha]_D^{20}$ +56.3° (c 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s), 0.85 (3H, d, 6.5 Hz), 1.02, 3.34 (each 3H, s), 3.66 (1H, dd, 1.8 and 11.3 Hz), 4.45 (1H, d, 3.2 Hz), 4.46, 4.50, 4.50, 4.55 (each 1H, d, 11.6 Hz); EI-MS m/z 426 (M^+), 395 (M^+-MeO), 394 (M^+-MeOH). Exact Mass. Calcd. for $C_{27}H_{38}O_4$: 426.2770. Found: 426.2727.

α-Methoxy compound **21**: $[\alpha]_D^{20}$ -2.97° (c 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s), 0.88 (3H, d, 6.4 Hz), 1.06 (3H, s), 3.23 (1H, dd, 2.0 and 11.1 Hz), 3.40 (3H, s), 3.67 (1H, dd, 2.4 and 9.8 Hz), 3.79 (1H, d, 8.2 Hz), 4.40, 4.48 (each 1H, d, 11.9 Hz), 4.52, 4.54 (each 1H, d, 11.4 Hz); EI-MS m/z 426 (M^+), 395 (M^+-MeO), 394 (M^+-MeOH). Exact Mass. Calcd. for $C_{27}H_{38}O_4$: 426.2770. Found: 426.2701.

Conversion of α-Methoxy Compound 21 into β-Methoxy Compound 20

A soln of **21** (0.16 g, 0.38 mmol) in MeOH (3.0 ml) was treated with CSA (16 mg, 69 μmol) at rt under Ar atmosphere for 12 h. The reaction mixture was worked up as above to give 72 mg (45%, isolated yield by silica gel chromatography) of **20** and 74 mg (46%) of **21**.

(2*S*,3*R*,6*S*)-6-[(*R*)-2-(*tert*-Butyldimethylsilyloxy)-1,1-dimethyl-4-(phenylsulfonyl)butyl]tetrahydro-2-methoxy-3-methyl-2*H*-pyran (22)

Metallic Na (0.37 g, 16 mmol) was dissolved in liquid NH_3 (20 ml) at -78 °C under Ar atmosphere. To the resultant blue soln was added dropwise with stirring a soln of **20** (0.19 g, 0.44 mmol) in ether (4.0 ml) at -78 °C. After stirring at -78 °C for 30 min, solid NH_4Cl was added in small portions until the blue color disappeared and then the NH_3 was left to evaporate. The residue was diluted with water and extracted with AcOEt. The extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crude product was dissolved in Et_3N (2.0 ml) and the soln was treated with *p*-TsCl (0.34 g, 1.8 mmol) at rt under Ar atmosphere for 12 h. The reaction mixture was processed as before and chromatography of the crude product on silica gel (hexane-AcOEt, 90:10) gave 0.16 g (89%) of a tosylate.

To a soln of LiSPh [prepared from PhSH (47 mg, 0.43 mmol) and ^{n}BuLi (1.60M hexane soln, 0.32 ml, 0.50 mmol) in THF (1.0 ml) at rt under Ar atmosphere for 5 min] was added a soln of the tosylate (0.16 g, 0.39 mmol) in THF (2.0 ml) at rt. After stirring at rt for 15 min, the reaction mixture was diluted with ether. The ethereal soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the residue on silica gel (hexane-AcOEt, 95:5) gave 0.12 g (88%) of a thioether.

To a soln of the thioether (0.12 g, 0.34 mmol) and 2,6-lutidine (0.44 g, 4.1 mmol) in CH_2Cl_2 (2.0 ml) was added TBDMSOTf (0.49 g, 1.9 mmol) at rt under Ar atmosphere. After stirring at rt for 10 min, the reaction was quenched by the addition of MeOH (1.0 ml). To the mixture was added saturated $NaHCO_3$ aq. and the

product was extracted with ether. The extracts were washed successively with saturated $CuSO_4$ aq., saturated $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (10 ml). To the stirred soln was added successively saturated $NaHCO_3$ aq. (15 ml) and solid *m*CPBA (85%, 0.29 g, 1.5 mmol) at rt. After stirring at rt for 1 h, the product was extracted with ether. The ethereal soln was washed with brine and dried over Na_2SO_4. After evaporation of the solv *in vacuo*, chromatography of the crude product on silica gel (hexane-AcOEt, 95:5) gave 0.13 g (79%) of **22**: $[\alpha]_D^{20}$ +43.0° (c 2.00, $CHCl_3$).

To a soln of **22** (0.13 g, 0.27 mmol) in hexane (2.0 ml) was added a few crystals of racemic **22**, mp 88-89 °C (recrystallized from ether-hexane), prepared from 2-(2-hydroxy-1,1-dimethyl-4-pentenyl)-1,3-dioxolane according to the same procedure as that of optically active **22**. After the suspension was set aside at 4 °C for 12 h, separated racemic crystals were removed and the mother liquor was concentrated *in vacuo* to afford optically purified **22**, which was recrystallized from ether-hexane giving 85 mg (65%) of optically pure **22**: mp 90-91 °C; $[\alpha]_D^{20}$ +50.1° (c 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ -0.05, 0.03, 0.75 (each 3H, s), 0.83 (3H, d, 6.7 Hz), 0.86 (12H, s), 3.10 (1H, ddd, 4.3, 12.2, and 13.7 Hz), 3.25 (3H, s), 3.30 (1H, ddd, 4.9, 12.2, and 13.7 Hz), 3.54 (1H, dd, 1.7 and 11.8 Hz), 3.65 (1H, dd, 3.8 and 6.3 Hz), 4.33 (1H, d, 3.4 Hz); EI-MS m/z 484 (M^+), 469 (M^+-Me), 453 (M^+-MeO), 452 (M^+-MeOH). Exact Mass. Calcd. for $C_{25}H_{44}O_5SSi$: 484.2679. Found: 484.2673.

2-[(1*R*,4*S*,6*R*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-1,5,5-trimethyl-8-(phenylsulfonyl)octyl]-1,3-dithiane (3)

To a soln of **22** (50 mg, 0.10 mmol) and $HS(CH_2)_3SH$ (20 mg, 0.18 mmol) in CH_2Cl_2 (1.0 ml) cooled to 0 °C was added BF_3•OEt_2 (5.0 mg, 35 μmol) under Ar atmosphere. After stirring at 0 °C for 5 min, to the reaction mixture was added saturated $NaHCO_3$ aq. (1.0 ml) and the product was extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (hexane-AcOEt, 80:20) to afford 40 mg (87%) of a diol.

To a soln of the diol (40 mg, 90 μmol) and 2,6-lutidine (0.19 g, 1.8 mmol) in CH_2Cl_2 (1.0 ml) was added TBDMSOTf (0.24 g, 0.91 mmol) at rt under Ar atmosphere. After stirring at rt for 3 h, similar treatment as before afforded a crude product, which was chromatographed on silica gel (hexane-AcOEt, 95:5) to yield 52 mg (86%) of **3**: $[\alpha]_D^{20}$ +2.17° (c 2.40, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ -0.05, -0.03, 0.02, 0.07, 0.71, 0.82 (each 3H, s), 0.86, 0.88 (each 9H, s), 1.07 (3H, d, 6.7 Hz), 3.10 (1H, ddd, 4.2, 12.5, and 13.8 Hz), 3.25 (1H, ddd, 4.8, 12.5, and 13.8 Hz), 3.36 (1H, dd, 3.7 and 5.3 Hz), 3.71 (1H, dd, 4.0 and 6.4 Hz), 4.04 (1H, d, 4.1 Hz). 400 MHz ^1H NMR spectrum of this sample was identical with that provided by Drs. T. Nakata and T. Oishi.

(*S*)-5-[(Benzyloxy)methoxy]-3-[(2-methoxyethoxy)methoxy]-2-pentanone (24)

To a soln of (-)-(*S*)-2-hydroxy-4-butanolide (**23**) (3.0 g, 29 mmol), prepared from (-)-L-malic acid according to Still's procedure,[8] in $^iPr_2NEt$ (30 ml) was added MEMCl (9.2 g, 74 mmol) at rt under Ar atmosphere. The stirring was continued at rt for 12 h and the reaction was quenched by the addition of MeOH (9.0 ml). After evaporation of the solv *in vacuo*, chromatography of the residue on silica gel (hexane-AcOEt, 40:60) gave 4.9 g (88%) of a MEM ether of **23**.

To a stirred soln of the MEM ether (4.9 g, 26 mmol) in THF (100 ml) cooled to -78 °C was added dropwise MeLi (1.25M ethereal soln, 23 ml, 28 mmol) under Ar atmosphere. After stirring at -78 °C for 2 h, the reaction was quenched by the addition of AcOH (1.9 g, 32 mmol). The solv was removed off *in vacuo* and the residual oil was diluted with AcOEt. The soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to yield 5.2 g (98%) of a hemiacetal.

To a soln of the hemiacetal (5.2 g, 25 mmol) in $^iPr_2NEt$ (100 ml) was added $PhCH_2OCH_2Cl$ (13 g, 81 mmol) at rt under Ar atmosphere. The stirring was continued at rt for 12 h and the reaction was quenched

by the addition of brine (1.0 ml). After evaporation of the $^{i}Pr_2NEt$ *in vacuo*, the product was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 70:30) gave 7.3 g (89%) of **24**: $[\alpha]_D^{20}$ -5.08° (c 2.00, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (2H, q, 6 Hz), 2.17, 3.35 (each 3H, s), 4.20 (1H, t, 6 Hz), 4.59, 4.71, 4.75 (each 2H, s), 7.32 (5H, s); FI-MS m/z 327 (M^++H). *Anal.* Calcd. for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03%. Found: C, 62.65; H, 8.04%.

(2*R*,3*S*)-5-[(Benzyloxy)methoxy]-3-[(2-methoxyethoxy)methoxy]-2-pentanol (25)

To a stirred soln of **24** (7.3 g, 22 mmol) in ether (150 ml) cooled to -78 °C was added dropwise $Zn(BH_4)_2$[9] (0.76M ethereal soln, 32 ml, 25 mmol) under Ar atmosphere. After stirring at -78 °C for 3 h, the temp allowed to rise to rt and the stirring was continued at rt for additional 12 h. The excess hydride was destroyed by the addition of water (5.0 ml). The mixture was diluted with AcOEt, dried over Na_2SO_4, and filtered through Celite. Concentration of the filtrates *in vacuo* afforded 7.3 g (99%) of **25** (**25**:**26**=15:1, 400 MHz ^1H NMR): $[\alpha]_D^{20}$ +16.3° (c 2.00, $CHCl_3$); IR (neat) 3520 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (3H, d, 6.7 Hz), 3.39 (3H, s), 4.75 (1H, d, 7.2 Hz), 4.75 (2H, s), 4.82 (1H, d, 7.2 Hz); FI-MS m/z 329 (M^++H). *Anal.* Calcd. for $C_{17}H_{28}O_6$: C, 63.74; H, 6.29%. Found: C, 63.68; H, 6.38%.

(3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-[(2-methoxyethoxy)methoxy]pentanal (29)

To a soln of **25** (**25**:**26**=15:1, 5.8 g, 17 mmol) and imidazole (17 g, 0.25 mol) in DMF (20 ml) was added a soln of TBDMSCl (19 g, 0.13 mol) in DMF (20 ml) at rt under At atmosphere. The reaction mixture was heated at 90 °C for 12 h. After cooling, brine (400 ml) was added and the product was extracted with ether. The ethereal soln was washed with brine and dried over Na_2SO_4. After evaporation of the solv *in vacuo*, chromatography of the residual oil on silica gel (hexane-AcOEt, 90:10) gave 7.0 g (89%) of a TBDMS ether of **25**.

Metallic Li (5.3 g, 0.76 mol) was dissolved in liquid NH_3 (500 ml) at -78 °C under Ar atmosphere. To the resultant blue soln was added dropwise with stirring a soln of the TBDMS ether (8.8 g, 20 mmol) in ether (180 ml) at -78 °C. After stirring at -78 °C for 30 min, solid NH_4Cl was added in small portions until the blue color disappeared and then the NH_3 was left to evaporate. The residue was diluted with water and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solv *in vacuo* gave 6.2 g (97%) of an alcohol.

To a stirred suspension of Collins reagent [prepared from CrO_3 (5.9 g, 60 mmol) and pyridine (9.4 g, 0.12 mol) in CH_2Cl_2 (90 ml) at rt under Ar atmosphere for 15 min] and Celite (18 g) was added a soln of the alcohol (3.1 g, 9.5 mmol) in CH_2Cl_2 (60 ml) at rt. The reaction mixture was stirred at rt for 10 min. The mixture was diluted with ether (500 ml) and filtered through Celite and the filtrates were washed successively with saturated $CuSO_4$ aq. and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (hexane-AcOEt, 95:5) to yield 2.6 g (84%) of diastereomerically pure **29**: $[\alpha]_D^{20}$ -39.1° (c 2.00, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (6H, s), 0.87 (9H, s), 1.13 (3H, d, 7 Hz), 2.59 (2H, dd, 3 and 6 Hz), 3.36 (3H, s), 4.78 (2H, s), 9.80 (1H, t, 3 Hz); FI-MS m/z 321 (M^++H). *Anal.* Calcd. for $C_{15}H_{32}O_5Si$: C, 56.22; H, 10.07%. Found: C, 56.33; H, 9.92%.

(4*S*,5*R*)-1-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4-[(2-methoxyethoxy)methoxy]-2-hexanone (31)

To a stirred soln of $PhCH_2OCH_2Li$ [prepared from $PhCH_2OCH_2Sn^nBu_3$ (5.5 g, 14 mmol) and ^nBuLi (1.60M hexane soln, 7.6 ml, 12 mmol) in THF (30 ml) at -78 °C under Ar atmosphere for 5 min][11] was added dropwise a soln of **29** (1.3 g, 4.0 mmol) in THF (30 ml) at -78 °C. After stirring at -78 °C for 4 h, the reaction

was quenched by the addition of AcOH (0.88 g, 15 mmol). The solv was removed off *in vacuo* and the residual oil was diluted with AcOEt. The soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 90:10) afforded 1.2 g (72%) of a 1.5:1 epimeric mixture of **32** and **33**.

To a suspension of Collins reagent [prepared from CrO_3 (2.3 g, 23 mmol) and pyridine (3.6 g, 46 mmol) in CH_2Cl_2 (35 ml) as before] and Celite (7.0 g) was added a soln of the mixture (1.0 g, 2.3 mmol) in CH_2Cl_2 (20 ml) at rt under Ar atmosphere. After stirring at rt for 30 min, the reaction mixture was processed as before to yield 0.98 g (99%) of **31**: $[\alpha]_D^{20}$ -41.5° (c 2.00, $CHCl_3$); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (6H, s), 0.87 (9H, s), 1.11 (3H, d, 7 Hz), 3.34 (3H, s), 4.19, 4.57, 4.73 (each 2H, s), 7.30 (5H, s); FI-MS m/z 441 (M^++H). *Anal.* Calcd. for $C_{23}H_{40}O_6Si$: C, 62.69; H, 9.15%. Found: C, 62.64; H, 9.25%.

(2*R*,4*S*,5*R*)-1-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4-[(2-methoxyethoxy)methoxy]-2-hexanol (32)

To a stirred suspension of $LiAlH(O^tBu)_3$ [prepared from $LiAlH_4$ (3.6 g, 95 mmol) and ^{t}BuOH (21 g, 0.27 mol) in ether (50 ml) at 0 °C under Ar atmosphere for 5 min] cooled to -123 °C was added dropwise a soln of **31** (0.51 g, 1.2 mmol) in ether (20 ml). After stirring at -123 °C for 2 h, the excess hydride was destroyed by the addition of water (2.5 ml). The mixture was dried over Na_2SO_4 and filtered through Celite. Concentration of the filtrates *in vacuo* gave 0.50 g (98%) of **32** (**32**:**33**=10:1, 400 MHz ^1H NMR): $[\alpha]_D^{20}$ -37.8° (c 2.00, $CHCl_3$); IR (neat) 3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (6H, s), 0.85 (9H, s), 1.06 (3H, d, 6.4 Hz), 1.64 (1H, ddd, 7.3, 8.5, and 14.7 Hz), 1.71 (1H, dt, 14.7 and 4.0 Hz), 3.31 (3H, s), 4.51 (2H, s), 4.72, 4.80 (each 1H, d, 6.7 Hz); FI-MS 443 (M^++H). *Anal.* Calcd. for $C_{23}H_{42}O_6Si$: C, 62.41; H, 9.56%. Found: C, 62.50; H, 9.48%.

(2*R*,3*S*,5*S*)-5-[(Benzyloxy)methyl]tetrahydro-2-methyl-3-furanol (36)

To a stirred soln of **32** (**32**:**33**=10:1, 0.45 g, 1.0 mmol) in ether (10 ml) cooled to 0 °C was added dropwise MeLi (1.25M ethereal soln, 0.98 ml, 1.3 mmol) under Ar atmosphere. After stirring at 0 °C for 5 min, solid *p*-TsCl (0.32 g, 1.6 mmol) was added at 0 °C. The stirring was continued at rt for 12 h. To the reaction mixture was added successively Et_3N (0.20 g, 2.0 mmol) and MeOH (0.70 ml). After evaporation of the solv *in vacuo*, the residue was diluted with ether. The ethereal soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 95:5) gave 0.50 g (83%) of a tosylate **34**.

To a soln of **34** (0.56 g, 3.8 mmol) in THF (10 ml) was added ^{n}Bu$_4$NF (1.00M THF soln, 3.8 ml, 3.8 mmol) at rt under Ar atmosphere. After stirring at rt for 12 h, the solv was removed off *in vacuo* and the residue was diluted with ether. The ethereal soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residual oil was dissolved in MeOH (25 ml). To the soln was added 3N HCl (15 ml) at rt. The reaction mixture was then heated at reflux for 15 min. After cooling, the solv was removed off *in vacuo* and chromatography of the residue on silica gel (hexane-AcOEt, 80:20) afforded 0.16 g (77%) of diastereomerically pure **36**: $[\alpha]_D^{20}$ +35.5° (c 2.00, $CHCl_3$); IR (neat) 3440 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (3H, d, 6.4 Hz), 1.85 (1H, dd, 3.1 and 13.9 Hz), 2.41 (1H, ddd, 5.4, 9.6, and 13.9 Hz), 3.45, 3.68 (each 1H, dd, 2.4 and 10.2 Hz), 3.90 (1H, d, 5.4 Hz), 4.16 (1H, q, 6.4 Hz), 4.32 (1H, ddt, 3.1, 9.6, and 2.4 Hz), 4.55, 4.68 (each 1H, 11.9 Hz); EI-MS m/z 222 (M^+). Exact Mass. Calcd., for $C_{12}H_{18}O_3$: 222.1256. Found: 222.1230.

(2*S*,4*S*,5*R*)-Tetrahydro-5-methyl-4-(triisopropylsilyloxy)-2-furancarbaldehyde (4)

To a soln of **36** (80 mg, 0.36 mmol) and DMAP (1.5 g, 12 mmol) in CH_2Cl_2 (3.0 ml) was added TIPSCl (1.1 g, 5.5 mmol) at rt under Ar atmosphere. After stirring at rt for 12 h, the reaction was quenched by the addition of MeOH (2.5 ml) and the solv was removed off *in vacuo*. The residue was diluted with ether and the

ethereal soln was washed successively with saturated $CuSO_4$ aq., saturated $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (hexane-AcOEt, 98:2) to give 0.12 g (84%) of a TIPS ether of **3**.

Metallic Na (0.35 g, 15 mmol) was dissolved in liquid NH_3 (20 ml) at -78 °C under Ar atmosphere. To the resultant blue soln was added dropwise with stirring a soln of the TIPS ether (0.12 g, 0.31 mmol) in ether (2.0 ml) at -78 °C. After stirring at -78 °C for 30 min, similar treatment as before gave a crude product, which was chromatographed on silica gel (hexane-AcOEt, 90:10) to afford 75 mg (86%) of an alcohol.

To a stirred soln of $(COCl)_2$-DMSO [prepared from $(COCl)_2$ (70 mg, 0.55 mmol) and DMSO (90 mg, 1.2 mmol) in CH_2Cl_2 (1.0 ml) at -60 °C under Ar atmosphere for 2 min] was added dropwise a soln of the alcohol (75 mg, 0.26 mmol) in CH_2Cl_2 (1.5 ml) at -60 °C. After stirring at -60 °C for 15 min, to the mixture was added Et_3N (0.29 g, 2.9 mmol) at -60 °C. The reaction mixture was stirred at -60 °C for 5 min and then allowed to warm to 0 °C for 1.5 h. Water (5.0 ml) was added and the product was extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 97:3) yielded 70 mg (94%) of **4**: $[\alpha]_D^{20}$ +18.1° (c 1.00, $CHCl_3$) [lit. $[\alpha]_D^{20}$ +17.0° (c 1.00, $CHCl_3$)][4b]; IR (neat) 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (3H, d, 6.5 Hz), 2.14 (1H, dt, 13.2 and 1.5 Hz), 2.38 (1H, ddd, 4.4, 9.3, and 13.2 Hz), 4.13 (1H, dt, 4.4 and 1.5 Hz), 4.25 (1H, dq, 1.5 and 6.5 Hz), 4.39 (1H, dt, 9.3 and 1.5 Hz), 9.78 (1H, d, 1.5 Hz). The optical rotation and 400 MHz ^1H NMR spectrum of this sample were identical with those reported[4b] and provided, respectively, by Drs. T. Nakata and T. Oishi.

2-[(*E*)-(4*S*,6*R*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-1,5,5-trimethyl-9-[(2*S*,4*S*,5*R*)-tetrahydro-5-methyl-4-(triisopropylsilyloxy)-2-furanyl]-8-nonenyl]-1,3-dithiane (2)

To a stirred soln of **3** (17 mg, 25 μmol) in THF (1.0 ml) cooled to -78 °C was added dropwise ^{n}BuLi (1.60M hexane soln, 0.017 ml, 27 μmol) under Ar atmosphere. The stirring was continued at -78 °C for 10 min and a soln of **4** (11 mg, 38 μmol) in THF (0.50 ml) was added at -78 °C. After the addition of HMPA (0.30 ml) at -78 °C, the temp was allowed to rise to -50 °C and the stirring was continued at -50 °C for 2 h. To the reaction mixture was added successively Et_3N (0.20 ml), BzCl (0.13 g, 0.92 mmol), and DMAP (3.0 mg, 25 μmol) at -50 °C and the temp was allowed to rise to rt. After stirring at rt for 12 h, the reaction was quenched by the addition of MeOH (1.0 ml). The resulting mixture was diluted with ether and the ethereal soln was washed successively with saturated $CuSO_4$ aq., saturated $NaHCO_3$ aq., and brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (hexane-AcOEt, 95:5) afforded 15 mg (56%, from **3**) of a diastereomeric mixture of β-benzoyloxysulfones.

To solid Na-Hg (5%, 0.70 g) was added a soln of the mixture (15 mg, 14 μmol) in a mixture of THF (0.20 ml) and MeOH (0.40 ml) at -20 °C under Ar atmosphere. After stirring at -20 °C for 8 h, the reaction was quenched by the addition of water (1.0 ml) and the product was extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solv *in vacuo*, the crude product was chromatographed on silica gel (hexane-AcOEt, 98:2) to give 8.1 mg (72%) of **2**: $[\alpha]_D^{20}$ +6.92° (c 1.00, $CHCl_3$) [lit. $[\alpha]_D^{20}$ +7.1° (c 0.96, $CHCl_3$)][4b];^1H NMR ($CDCl_3$, 400 MHz) δ 0.02, 0.03, 0.04, 0.09, 0.76, 0.85 (each 3H, s), 0.89, 0.91 (each 9H, s), 1.20 (3H, d, 6.4 Hz), 3.54 (1H, dd, 3.2 and 6.6 Hz), 3.68 (1H, dd, 3.9 and 6.5 Hz), 3.90 (1H, dq, 4.9 and 6.4 Hz), 4.03 (1H, dt, 4.9 and 6.3 Hz), 4.12 (1H, d, 4.2 Hz), 4.42 (1H, q, 7.0 Hz), 5.62 (1H, dd, 7.0 and 15.5 Hz), 5.69 (1H, ddd, 4.9, 7.6, and 15.5 Hz). The optical rotation and 400 MHz ^1H NMR spectrum of this sample were identical with those reported[4b] and provided, respectively, by Drs. T. Nakata and T. Oishi.

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