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FURTHER SYNTHETIC STUDIES ON RIFAMYCIN S[1]

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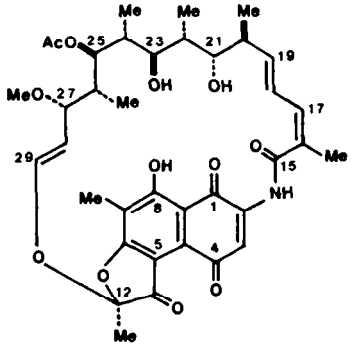
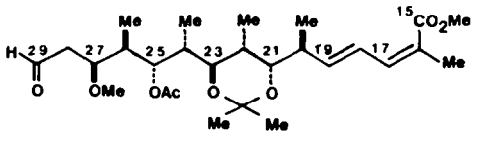
Abstract—Two new highly stereocontrolled syntheses of the optically active form of the aliphatic segment **2** of rifamycin S are described.

Rifamycins (originally spelled rifomycins),[2] isolated from the fermentation medium of *Norcardia mediterranei* by Senti, Greco and Ballotta in 1959, were the first examples of a novel class of antibiotics, ansamycins, characterized by an aliphatic bridge linking two non-adjacent positions of an aromatic nucleus. The great number of antibiotics belonging to this class can be divided into two subclasses: those the ansa bridge of which is attached to a naphthoquinone or naphthalene nucleus, represented by rifamycin S, and those the ansa bridge of which is attached to a benzoquinone or benzene nucleus, represented by maytansine. Rifampicin (U.S.: rifampin), a derivative of rifamycins, is a widely-used, orally-active tuberculostatic agent. The structure of rifamycins was elucidated chemically by Prelog and Oppolzer, and X-ray crystallographically by Brufani, Fedeli, Gliacomello and Vaciago. We undertook an active research program of a chemical synthesis of rifamycin S (**1**) some time ago, which has recently resulted in the first successful total synthesis of the antibiotic.[3,4] In this paper, we would like to discuss our further efforts on the synthesis of the aliphatic segment **2** of rifamycin S.



1 : Rifamycin S



2

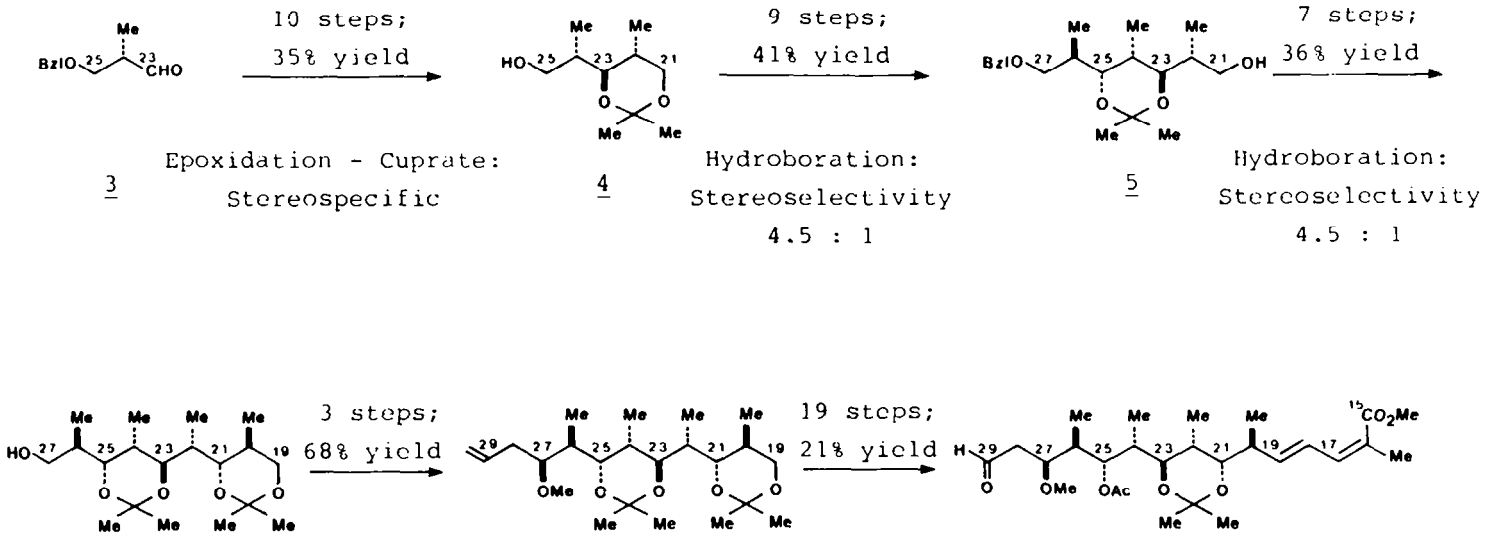
Our previous synthesis of this segment in a racemic form is summarized in Scheme 1 with indications of the degree of stereoselectivity for each key reaction.[3a,e] There remained several unsolved problems in this sequence. Our first concern was the synthesis of the aliphatic segment **2** in an optically active form with the natural absolute configuration. We planned to repeat the previous sequence with the optically active aldehyde **3**, which was expected to be available from the optically active alcohol **8**.[5] Because of the presence of the aldehyde group adjacent to the asymmetric center, it became necessary to establish a method to verify the optical purity of **3**. After several unsuccessful attempts,[6] the sequence of reactions in Scheme 3 was found satisfactory for the present purposes. Namely, the aldehyde **3** was converted to the *trans*-allylic alcohol **11** by Wittig reaction,[7] followed by diisobutylaluminum hydride (DIBAL) reduction. Sharpless asymmetric epoxidation[8] of **11** using L-(+)-diethyl tartrate yielded a mixture of the epoxide **12** and its diastereomeric epoxide.[9] The ratio of the two epoxides was determined from the NMR spectrum in deuterated benzene.[10] Since this asymmetric epoxidation is known to work with 95% or higher enantiomeric excess for this type of *trans*-allylic alcohol,[8] this method provides the minimum value of optical purity for the allylic alcohol **11**, and consequently of the aldehyde **3**. Thus, it was shown that less than 2%, if any, of the optical purity of **10** was lost during the oxidation under Swern conditions[11] and the subsequent transformation.[12] A considerable amount of the optical purity of **10** was lost under pyridinium chlorochromate (PCC) oxidation conditions and also under classical Wittig conditions.

After having confirmed the high optical purity, optically active aldehyde **3** was successfully transformed into optically active aliphatic segment **2** with the natural absolute configuration by following the previously established route.[3a,e,13]

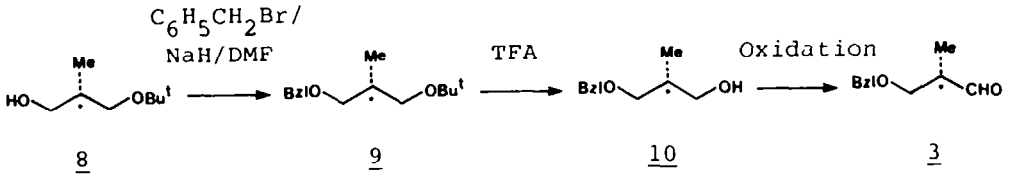
Our second concern was improvement of the stereoselectivity of some steps in Scheme 1. In connection with this, the Sharpless asymmetric epoxidation seemed to have attractive potential to control the asymmetric centers at the C.20–22 and C.24–26 positions.

As summarized in Scheme 4, the asymmetric epoxidation of the optically active *trans*-allylic alcohol **11** yielded the epoxide **12** or **14** with 95 : 5 stereoselectivity, depending on the chiral ligand used. Thus, this is a case in which the asymmetric epoxidation outweighs the effect from the adjacent asymmetric center existing in **11**.

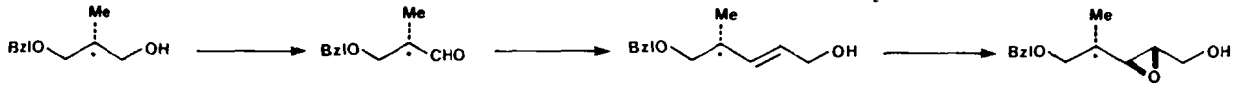
Contrary to the case of the *trans*-allylic alcohol **11**, the asymmetric epoxidation of the corresponding *cis*-allylic alcohol **16** presented an interesting case in which the adjacent chiral center played an important role. The *cis*-allylic alcohol **16** was prepared from the aldehyde **3**



Scheme 1



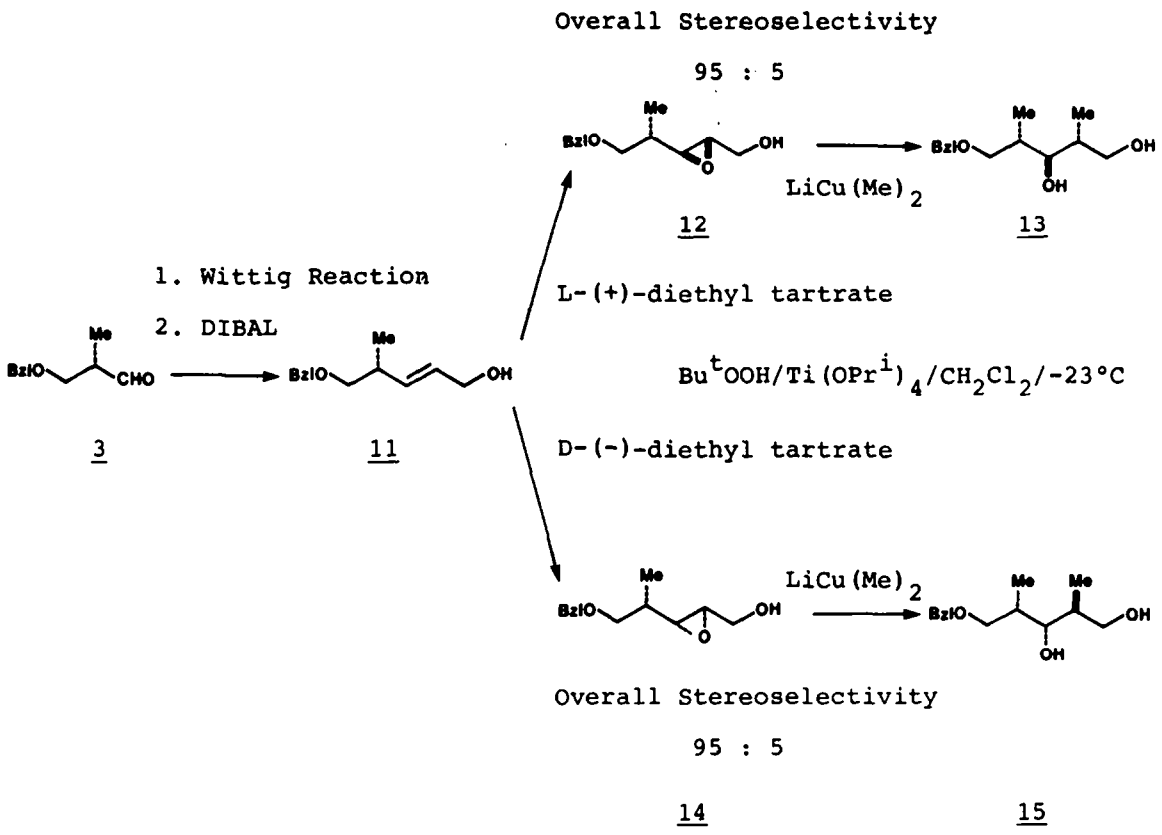
Scheme 2



10 3 11 12

*Oxidation	**Wittig Reaction	Overall Stereoselectivity
DMSO/$(COCl)_2$, then Et_3N	$(Pr^iO)_2P(O)CH_2CO_2Et/KOBu^t/THF/-78°C$	95 : 5
DMSO/$(COCl)_2$, then Et_3N	$(C_6H_5)_3P=CHCO_2Et/CH_2Cl_2/0°C$	7 : 1
$PCC/CH_2Cl_2/RT$	$(C_6H_5)_3P=CHCO_2Et/CH_2Cl_2/0°C$	3 : 1

Scheme 3



Scheme 4

by the two methods shown in Scheme 5. Although there was no direct evidence available, the *cis*-allylic alcohol **16**, synthesized by using the phosphonate reagent,[7] was figured to be virtually optically pure, based on results of the *trans*-allylic alcohol experimental series (*cf* Scheme 3). The optical purity of **16**, prepared stereospecifically by the first route, was found to be as good as that of **16**, prepared by the second route. The asymmetric epoxidation of **16** using L-(+)-diethyl tartrate yielded the expected[8] epoxide **19** as the major product, but the stereoselectivity was only about 5 : 1.[14] It is worth mentioning that the epoxidation rate of the *cis*-allylic alcohol **16** was much slower than that of the *trans*-allylic alcohol **11**. The epoxidation of **16**, using D-(−)-diethyl tartrate, did proceed at a rate comparable to the L-(+)-diethyl tartrate series, but yielded an about 1 : 1 mixture of the epoxides **17** and **19**.[9a,15]

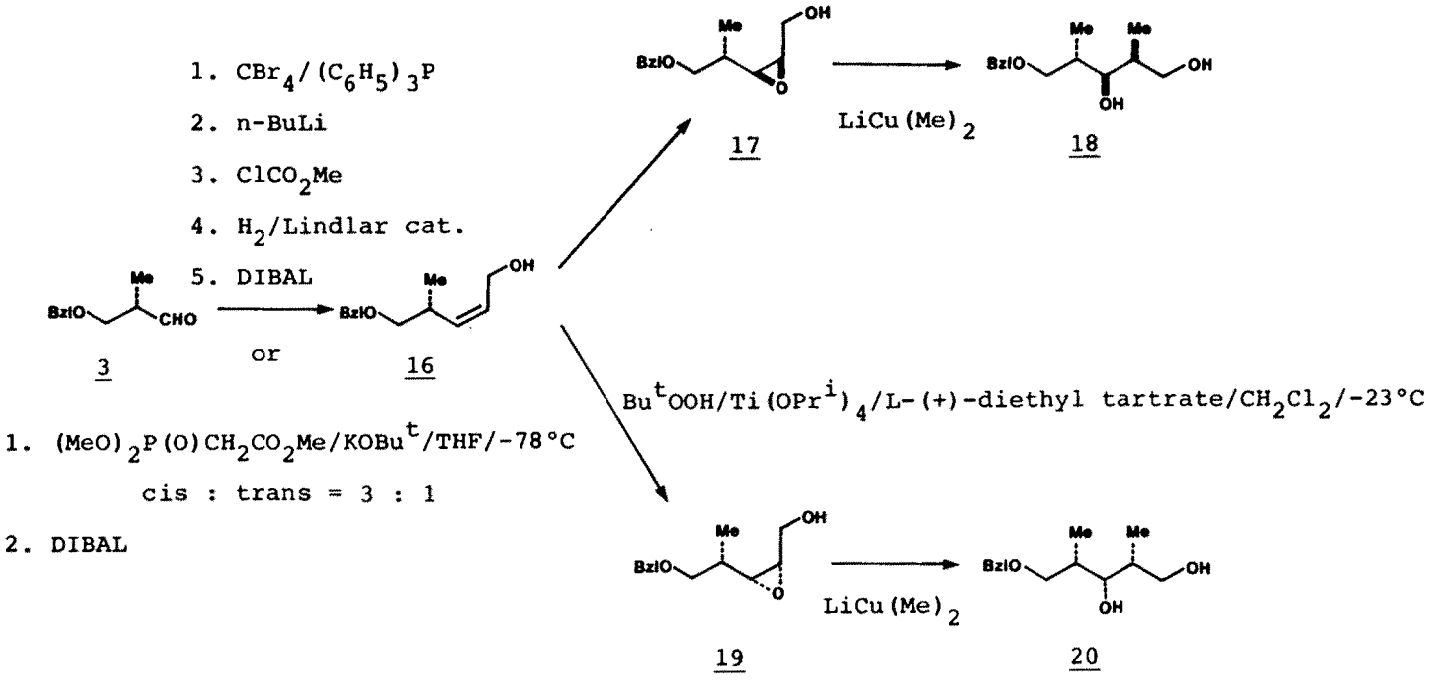
The poor stereoselectivity observed for the asymmetric epoxidation of the *cis*-allylic alcohol **16** was not necessarily surprising when one takes into account the following observations. Namely, the *meta*-chloroperbenzoic acid (MCPBA) epoxidation of the *cis*-allylic alcohol **16** yielded almost exclusively the epoxide **17**, while that of the *trans*-allylic alcohol **11** yielded a 3 : 2 mixture of **12** and **14**.[9a] These results can be explained in terms of the cooperative effect of the two polar groups and the difference of the steric crowding between **16** and **11**.[9] The asymmetric induction in the Sharpless asymmetric epoxidation reaction seems to be realized via complexation of titanium with diethyl tartrate, t-butyl hydroperoxide, and allylic alcohols. This may imply that sterically crowded allylic alcohols such as **16** would not necessarily follow the usual course of the reaction. From a practical point of view, these two methods—asymmetric epoxidation and MCPBA epoxidation—fortunately compensate for each other.

As observed previously,[9a] dimethyl cuprate reaction of the epoxides **12**, **14**, **17** and **19** in ether at −40°[16] proceeded regio- and stereospecifically to yield the monoprotected triols **13**, **15**, **18** and **20**, respectively, in high yield.

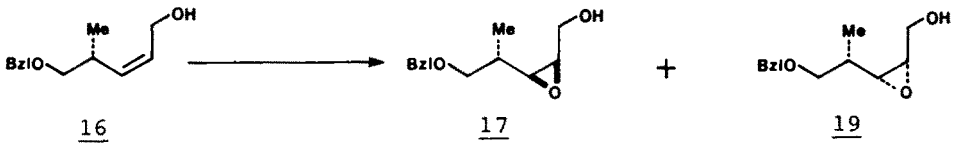
Control of the stereochemistry at the C.20–C.21 and the C.25–C.26 positions of the aliphatic segment **2** was expected, and indeed realized, straightforwardly by repeating this method. Namely, the acetonide **4**, prepared from **13** in two routine steps, was subjected to the same sequences of reactions as the one described before, to give the tetrol monoacetonide **23** with about **95 : 5** overall stereoselectivity.

After adjustment of the protecting group of **23**, i.e. **23**→**24**→**25**,[3a,e,17] the same sequence of reactions was once again applied to **25** to yield the monoacetonide **27** with about 95 : 5 overall stereoselectivity. The monoacetonide **27** was then converted to the pentol diacetonide **6**, which was one of the intermediates of our previous synthesis summarized in Scheme 1.[3a,e]

The C.27 stereochemistry of the aliphatic segment was previously controlled by a diallylzinc reaction of the aldehyde **28**.[3a,e] The observed stereoselectivity with this reagent was 4.6 : 1, favoring the desired alcohol **29**.[18] After many unsuccessful attempts, the tin reagent prepared according to Mukaiyama's procedure[19] was found to react smoothly with the aldehyde **28** and yielded the desired alcohol **29** with a 20 : 1 stereoselectivity.

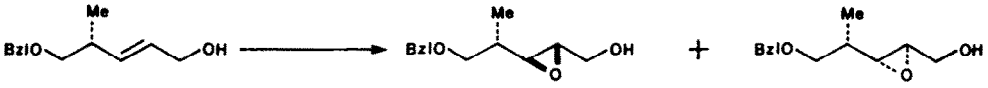

Overall Stereoselectivity
MCPBA Epoxidation : >25 : 1
Asym. Epoxidation : ca. 1 : 1
1. $CBr_4/(C_6H_5)_3P$
2. n-BuLi
3. $ClCO_2Me$
4. H_2/Lindlar cat.
5. DIBAL
BzlO
Me
CHO
OH
3
or
16
17
18
$LiCu(Me)_2$
1. $(MeO)_2P(O)CH_2CO_2Me/KOBu^t/THF/-78°C$
cis : trans = 3 : 1
2. DIBAL
$Bu^tOOH/Ti(OPr^i)_4$/L-(+)-diethyl tartrate/CH_2Cl_2/-23°C
19
20
Overall Stereoselectivity
ca. 5 : 1

Scheme 5



16 17 19

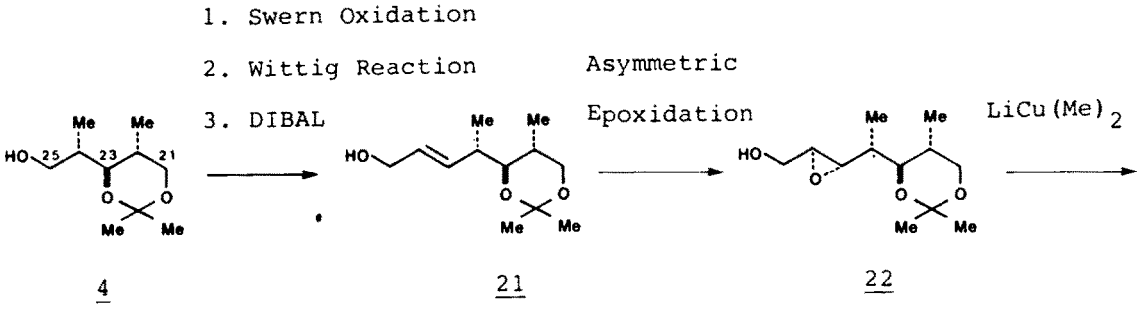
MCPBA/CH_2Cl_2/0°C >25 : 1



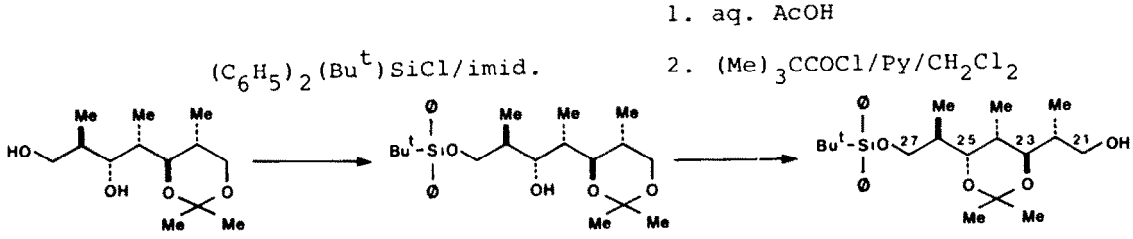
11 12 14

MCPBA/CH_2Cl_2/0°C 3 : 2

Scheme 6



4 21 22



23 24 25

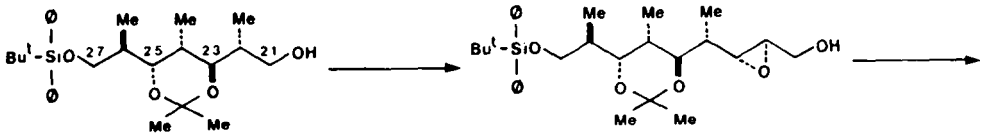
Scheme 7

This was exciting for two specific reasons. First, the stereoselectivity of this step was now greatly improved. Second, the observed degree of this stereoselectivity was exceptionally high for this type of reaction,[20] which led us to propose a cyclic transition state; namely, this reaction may involve complexation of the organometallic reagent with the two oxygen atoms, i.e. one aldehyde oxygen and one acetonide oxygen, and then proceed via a 6-centered, 6-electron transition state. *cis*- or *trans*-Decalin-type complexation could be considered, but the reaction would unlikely proceed via the *cis*-decalin-type transition state because of the steric crowding. Between the two *trans*-decalin-type transition states, **A** and **B**, transition state **B** would be considered less preferred because of the existence of a boat-like 6-membered ring. Thus, transition state **A** accounts for the stereochemical outcome of this reaction. This proposed explanation, combined with application of the reaction reported by Hiyama and Nozaki *et al.*,[21] encouraged us to study one additional approach to the aliphatic segment **2** of rifamycin S.

Hiyama and Nozaki *et al.* discovered a reaction of aldehydes with chromous salt, prepared from *trans*- or *cis*-crotyl bromide, to yield alcohols with exceptionally high erythro selectivity. For example, benzaldehyde gave exclusively the alcohol **32**. An aldehyde with an asym-

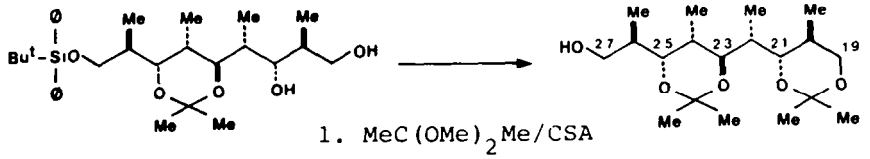
1. Swern Oxidation
2. Wittig Rxn/-40°C

$LiCu(Me)_2$



25 3. DIBAL 26

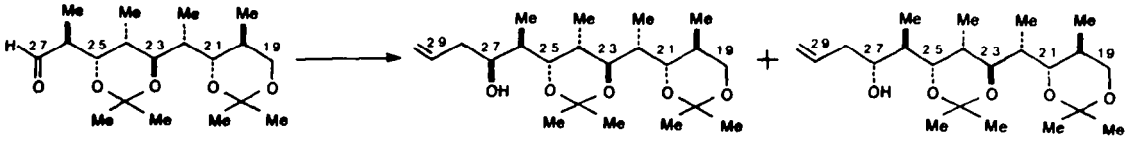
4. Asym. Epoxidation



1. $MeC(OMe)_2Me$/CSA
2. $(n\text{-}Bu)_4NF$/THF

27 6

Scheme 8



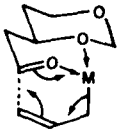
28 29 30

$CH_2=CHCH_2I/SnCl_2/DMI/C_6H_6/RT$ Stereoselectivity 20 : 1

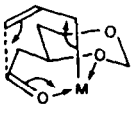
Scheme 9

To the observed major product

trans-Decalin-like:

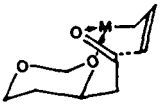


A

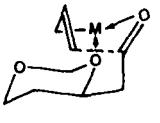


B

cis-Decalin-like:



C



D

Scheme 10

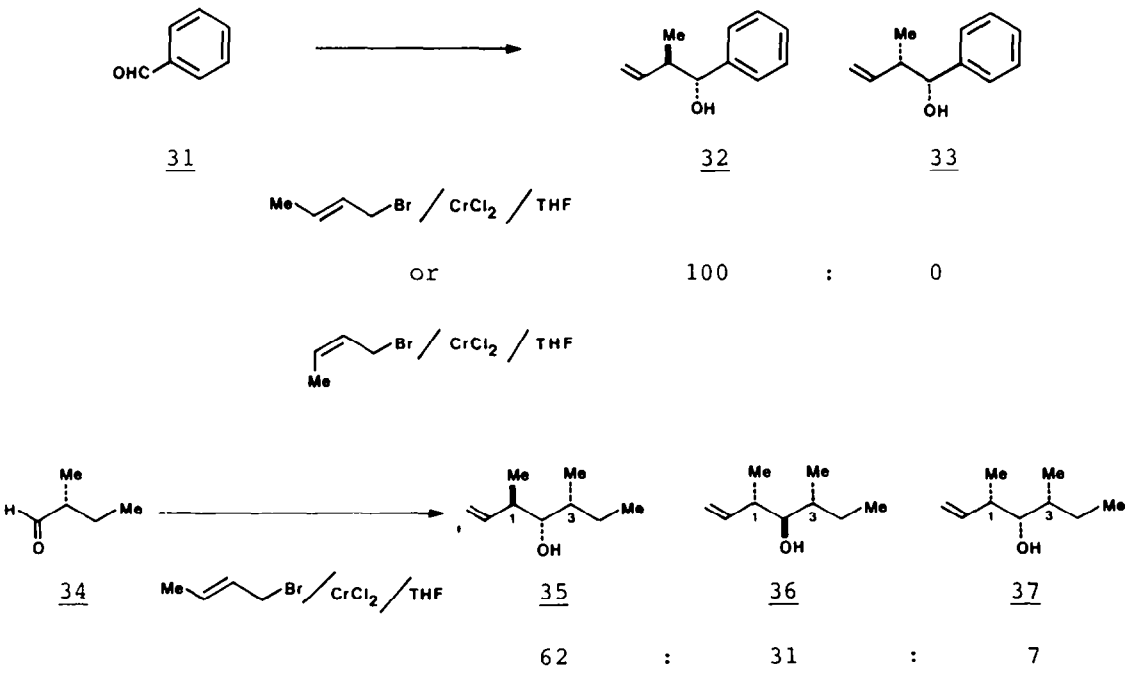
metric center at the α-position such as **34** was also studied; the excellent erythro selectivity was still observed with respect to the 1,2-positions,[22] but the stereoselectivity with respect to the 2,3-positions was poor, making the reaction less attractive for control of the stereochemistry at the 1,2,3-positions simultaneously. However, the proposed explanation for the reaction described before suggests the possibility of enhancing the 2,3-stereoselectivity. This possibility, depicted in Scheme 12, illuminates the importance of this reaction for the synthesis of aliphatic segment **2**.

Encouraged by this consideration, the reaction of the aldehyde **38** with the chromous salt, was investigated. The reagent, prepared from *trans*- or *cis*-crotyl iodide,[23] reacted smoothly with the aldehyde **38** to yield the expected product(s). The product ratio was studied by analytical hlc after transformation of the crude product to the corresponding silyl ether(s). The stereoselectivity of this reaction was thus found to be better than 20 : 1. The major product was found to be identical with compound **24**, one of the intermediates of the previous synthesis (Scheme 7). Judging from the spectroscopic data, the second major product was a stereoisomer of **24**, but the stereochemistry assignment was not yet established at this time. Although two additional products were detected in the hlc analysis, it still remains unknown whether these are stereoisomers of **24** or not.

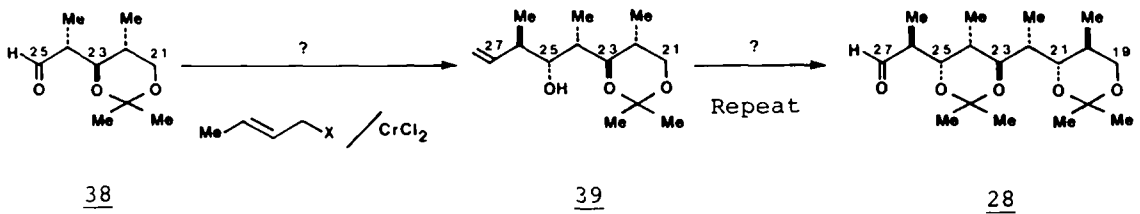
Clearly this reaction achieves a transformation equivalent to a crossed aldol reaction. In general, threo stereochemistry can effectively be controlled by a crossed aldol reaction,[24] and consequently 1,2,3-stereochemistry[22] belonging to **44** and **45** in Scheme 16 can be controlled by using a chiral starting substance.[24] However, controlling erythro stereochemistry by a crossed aldol reaction is not a routine matter,[25] primarily because of the lack of effective synthesis of an enolate or masked enolate with the double bond geometry required for the erythro stereocontrol. This problem is now quite simply and effectively overcome by the chromous method.

Using this method, the aliphatic segment **2** was straightforwardly synthesized. After the adjustment of the functional groups of **24**, the reaction of the chromous salt was again applied to **40** to yield the desired product with stereoselectivity of better than 20 : 1. As described before, the allyltin reaction of **28** yielded the desired alcohol **29** with stereoselectivity of 20 : 1, which was converted to the aliphatic segment **2** by using our previous procedure.[3a,e]

Scheme 15 summarizes the current status of the syn-

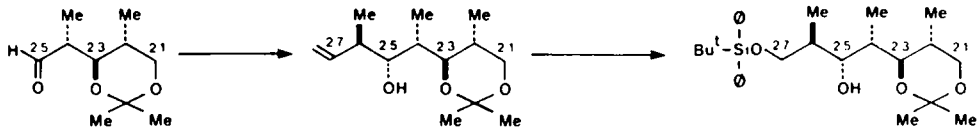


Scheme 11

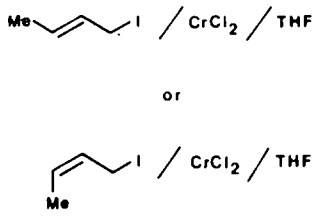


Scheme 12

1. O_3
2. $NaBH_4$
3. $(C_6H_5)_2(Bu^t)SiCl$



38 39 24

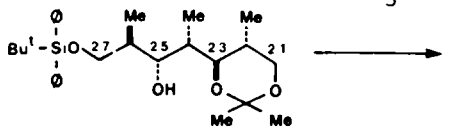


Stereoselectivity

>20 : 1 : 0.5(?) : 0.5(?)

Scheme 13

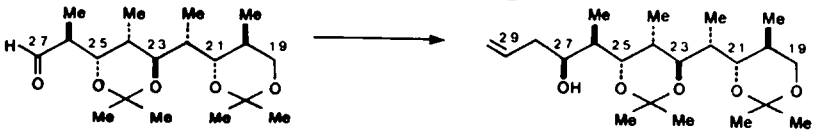
1. aq. AcOH
2. $(Me)_3CCOCl/Py$
3. LAH
4. Swern Oxidation



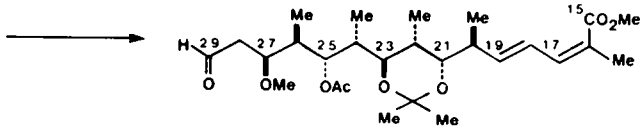
24 40

1. $MeCH=CHCH_2I/CrCl_2$
2. O_3
3. $NaBH_4$
4. $MeC(OMe)_2Me/CSA$
5. $(n\text{-}Bu)_4NF/THF$
6. Swern Oxidation

$CH_2=CHCH_2I/SnCl_2$



28 29



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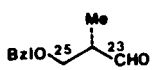
Scheme 14



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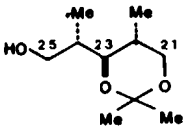

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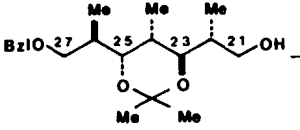
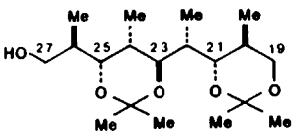


5

MCPBA Epoxid./Cuprate: Stereospecific

Asym. Epoxid./Cuprate: 20 : 1

Hydroboration:	4.5 : 1	4.5 : 1
Asym. Epoxid./Cuprate:	20 : 1	20 : 1
Chromous Salt:	>20 : 1	>20 : 1



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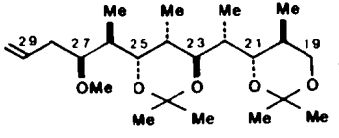

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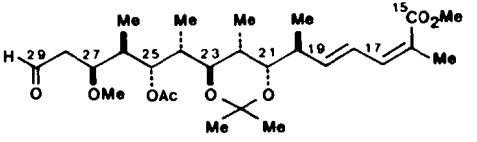


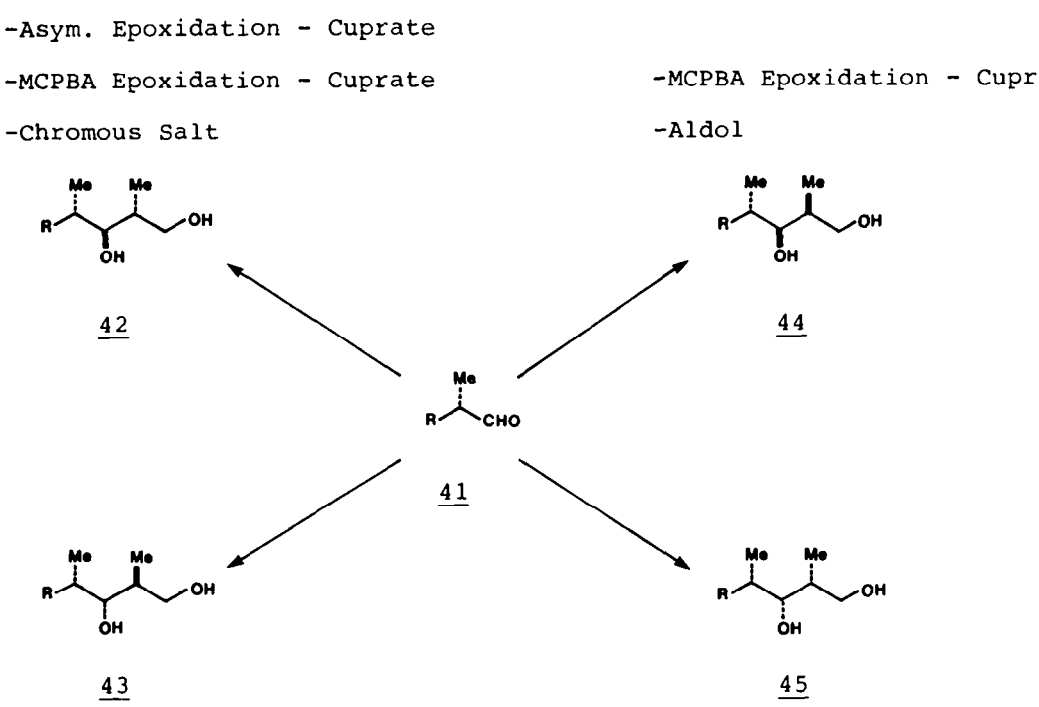
2

Diallylzinc: 15 : 1[18]

Allytin: 20 : 1

Wittig: 10 : 1

Scheme 15



Scheme 16

thesis of the aliphatic segment **2** of rifamycin S, with indications of the degree of stereoselectivity for each key step.

In addition, Scheme 16 summarizes the current status of the chain-extension methods.[9] A synthesis of a wide variety of natural products, particularly those derived from polyketide precursors in their biogenesis, is envisioned by the straightforward use of these methods.

EXPERIMENTAL

NMR spectra were recorded on a Varian HFT-80 instrument in the Fourier Transform mode. Chemical shifts are reported in ppm downfield from TMS (δ) as internal standard. Following abbreviations are used for spin multiplicity; s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. MS and high resolution mass spectra (Exact Mass) were determined on a Kratos MS-50 double focusing instrument in the chemical ionization mode. Optical rotations were measured on a Perkin–Elmer Model 241 polarimeter at ambient temp. IR spectra were recorded on a Perkin–Elmer Model 727 spectrophotometer and are reported in wave numbers (cm^{-1}).

Analytical tlc was performed on 0.25 mm pre-coated silica gel plates purchased from E. Merck. Preparative tlc separations were made on plates (20 × 20 cm) prepared with a 2 mm layer of silica gel PF_{254} from E. Merck.

Reagents and solvents were commercial grades and were used as supplied with the following exceptions: methylene chloride: distilled; ether and tetrahydrofuran (THF): distilled from sodium benzophenone ketyl; pyridine and triethylamine: dried over potassium hydroxide.

All alkylating and acylating agents were passed through a short aluminium oxide column prior to use. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Diol monobenzyl alcohol **10** *from diol mono-t-butyl ether* **8**[26]

To a cold (0°) suspension of NaH (6.23 g; 0.260 mol) prepared from 60% NaH (10.4 g), in a mixture of THF (450 ml) and DMF, (150 ml) **8** (29.5 g; 0.202 mol) was added.[5,26] The mixture was allowed to warm to room temp., stirred for 3 hr at this temp., cooled to 0°, and then benzyl bromide (25.2 ml); 36.7 g, 0.212 mol) was added. After being stirred for 14 hr at room temp., the mixture was cooled to 0°, and 25 ml of MeOH was added dropwise. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with ether, washed with water and sat NaCl aq and dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 45.5 g of the crude **9** pure enough for the next step without further purification.

To cold (0°) trifluoroacetic acid (85 ml), **9** (38.0 g) was added dropwise as the crude product prepared from 24.6 g of **8**. After being stirred for 4 hr at 0° and 1 hr at 25°, the mixture was concentrated under reduced pressure until it became about half its original volume. To the cold (0°) mixture, 15% NaOH (400 ml) was added dropwise over a period of 1 hr. The resulting mixture was stirred for 1 hr at 25°, and thoroughly extracted with ether. The combined extracts were washed with water, cold 1N HCl, water, and sat NaCl aq, dried over $MgSO_4$, filtered, concentrated, and chromatographed by silica gel column [eluted with hexane–ether (3 : 1)] to give 28.2 g of **10** (94% overall from **8**) as a slightly yellow oil. NMR ($CDCl_3$): 0.89 (3H, d, J = 6.9 Hz), 4.51 (2H, s). Exact Mass; Found: 181.1229; Calcd. for $C_{11}H_{17}O_2$ ($M+H^+$): 181.1228. α_D: +17.2° (*c* 3.24, $CHCl_3$). IR (neat): 3380 cm^{-1}.

trans-*Allylic alcohol* **11** *from diol monobenzyl alcohol* **10**

To a cold (−78°) soln of oxalyl chloride (368 μl;

533 mg, 4.21 mmol) in CH_2Cl_2 (10 ml) was added dropwise a soln of dimethyl sulfoxide (397 μl; 439 mg, 5.62 mmol) in 1 ml of CH_2Cl_2.[11] The mixture was stirred for 3 min at −78°, and then a soln of **10** (500 mg; 2.81 mmol) in CH_2Cl_2 (3 ml) was added dropwise with stirring. After 15 min at −78°, Et_3N (1.96 ml; 1.42 g, 14.0 mmol) was added dropwise and stirring was continued for 15 min at this temp. The mixture was allowed to warm to 0° for *ca.* 20 min with stirring, and partitioned between a mixture of benzene–ether (4 : 1) and water. The organic layer was washed with sat NaCl aq, dried over $MgSO_4$, concentrated under reduced pressure to give 475 mg (96%) of the practically pure aldehyde **3**. This product was *immediately* used for the next step without further purification. NMR ($CDCl_3$): 1.10 (3H, d, J = 7.2 Hz), 4.52 (2H, s), 9.72 (1H, d, J = 1.5).

To an ice-cold soln of diisopropyl ethoxycarbonylmethylphosphonate (2.45 g; 8.99 mmol) in THF (20 ml), t-BuOK (909 mg; 8.09 mmol) was added. After being stirred for 1 hr at 25°, the mixture was cooled in a dry-ice acetone bath. To the stirring soln, the crude aldehyde **3** (400 mg; 2.25 mmol) in 5 ml of THF was added dropwise. The mixture was stirred for 20 min at −78°, poured into ether and sat NH_4Cl aq, and the water layer was thoroughly extracted with CH_2Cl_2. The combined organic layer was washed with sat NaCl aq, dried over $MgSO_4$, concentrated, and chromatographed by silica gel column [eluted with hexane-ether (2 : 1)] to give 480 mg of the crude α,β-unsaturated ester. Preparative layer chromatography [silica gel, hexane-ether (2 : 1)] gave 9.7 mg (1.4%) of the *cis*-α,β-unsaturated ester and 578 mg (83%) of the *trans*-α,β-unsaturated ester as colorless oils.

cis-α,β-*Unsaturated ester.* NMR ($CDCl_3$): 1.06 (3H, d, J = 6.4 Hz), 1.27 (3H, t, J = 7.2), 4.50 (2H, s), 5.76 (1H, d, J = 11.5), 6.20 (1H, dd, J = 11.5, 9.0).

trans-α,β-*Unsaturated ester.* NMR ($CDCl_3$): 1.07 (3H, d, J = 6.8 Hz), 1.26 (3H, t, J = 7.2), 4.48 (2H, s), 5.33 (1H, dd, J = 15.5, 1.9), 6.91 (1H, dd, J = 15.5, 6.8). α_D: +15.0° (*c* 3.02, $CHCl_3$). IR (neat): 1720, 1650 cm^{-1}.

A soln of the *trans*-α,β-unsaturated ester (400 mg; 1.55 mmol) in a mixture of CH_2Cl_2 (10 ml) and hexane (20 ml) was cooled in a dry-ice acetone bath. To the soln, 1.0 M DIBAL (6.2 ml; 6.2 mmol) in hexane was added dropwise. The mixture was stirred for 40 min at this temp., and then 1 ml of MeOH was added dropwise and the mixture was allowed to warm to room temp. To the soln was added 2 ml of sat NaCl aq, 300 ml of ether and *ca.* 5 g of anhydrous $MgSO_4$. The resulting mixture was stirred for 1 hr at room temp., filtered, and concentrated under reduced pressure to give 318 mg (100%) of the practically pure **11** as colorless oil. A sample of **11** for spectroscopic analysis was prepared by preparative silica gel tlc [eluted with hexane-CH_2Cl_2-acetone (20 : 20 : 3)]. NMR ($CDCl_3$): 1.04 (3H, d, J = 6.4 Hz), 4.51 (2H, s), 5.67 (2H, m). Exact Mass: Found: 207.1387; Calcd. for $C_{13}H_{19}O_2$ ($M+H^+$): 207.1385. α_D: +9.90° (*c* 3.12, $CHCl_3$). IR (neat): 3375 cm^{-1}.

Epoxide **12** *from allylic alcohol* **11**

Asymmetric epoxidation of **11**. To a cold (−23°) soln of titanium tetraisopropoxide (149 μl; 142 mg, 0.500 mmol) in CH_2Cl_2 (4 ml) was added via syringe a soln of L(+)-diethyl tartrate (85.8 μl; 103 mg, 0.500 mmol) in 0.35 ml of CH_2Cl_2. After 10 min at −23°, **11** (92.7 mg; 0.450 mmol) in 0.5 ml of CH_2Cl_2 and 2 M anhyd t-butyl hydroperoxide (500 μl; 1.0 mmol) in CH_2Cl_2, was added to the soln dropwise. The mixture was stirred for 40 min at −23°, and 1.25 ml of 10% aqueous tartaric acid soln was added. The resulting mixture was stirred for 30 min at −23° and for 1 hr at 25°. The organic layer was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a colorless oil. To a cold (0°) soln of this residue in 3.8 ml of ether 1 N NaOH (1.5 ml) was added. After being stirred for 30 min at 0°, the organic layer was diluted with ether, washed with water and sat NaCl aq, dried over $MgSO_4$, filtered, concentrated, and separated by preparative silica gel tlc [eluted with hexane–ether (1 : 2)] to give 88.1 mg (88%) of the product consisting of 95% of the β-epoxide **12** and 5% of the α-epoxide **14** (analysed by NMR in C_6D_6) as colorless oil. As all attempts to separate **12** and **14** were fruitless, the following spectroscopic data of **12** were recorded in the substance contaminated with 5% of **14**. NMR (C_6D_6): 0.88 (3H, d, J = 6.9 Hz), 4.28 (2H, s). Exact Mass: Found: 233.1333: Calcd. for $C_{13}H_{19}O_3$ ($M+H^+$): 233.1334. α_D: −27.7° (*c* 1.19, $CHCl_3$). IR (neat): 3400 cm^{-1}.

Epoxide **14** *from allylic alcohol* **11**

Asymmetric epoxidation of **11**. This epoxidation was carried out by the same procedure as the one given for preparation of **12** from **11**, except for using D-(−)-diethyl tartrate instead of L-(+)-diethyl tartrate. The following spectroscopic data were recorded on **14**, contaminated with about 5% of **12**. NMR (C_6D_6): 0.90 (3H, d, J = 6.8 Hz), 4.24 (2H, s). Exact Mass: Found: 233.1334; Calcd. for $C_{13}H_{19}O_3$ ($M+H^+$): 223.1334. α_D: +32.4° (*c* 1.57, $CHCl_3$). IR (neat): 3300 cm^{-1}.

cis-*Allylic alcohol* **16** *from aldehyde* **3**

Method 1. To a cold (0°) soln of CBr_4 (2.10 g; 6.33 mmol) in CH_2Cl_2 (25 ml), triphenylphosphine (3.33 g; 12.7 mmol) was added portionwise. After 1 hr at 0°, a soln of aldehyde, the crude product prepared from **10** (500 mg; 2.81 mmol) in CH_2Cl_2 (5 ml) was added dropwise over 30 min. After addition was complete, the mixture was stirred for 5 min at 0°, poured into a stirring hexane (250 ml), filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with 50 ml of hexane, triphenylphosphine oxide was removed by filtration and washed with hexane. The filtrate and the washings were combined, concentrated, and separated by preparative silica gel tlc [eluted with hexane–ether (20 : 1] to give 838 mg (84% overall yield from **10**) of the dibromolefin as colorless oil. NMR ($CDCl_3$): 1.07 (3H, d, J = 6.9 Hz), 4.51 (2H, s), 6.30 (1H, d, J = 9.0). α_D: −21.0° (*c* 2.23, $CHCl_3$).

To a cold (−78°) soln of dibromoolefin (800 mg; 2.26 mmol) in THF (30 ml), 2.4 M n-BuLi (1.98 ml; 4.75 mmol) in hexane was added dropwise. After 20 min at −78°, methyl chloroformate (873 μl; 1.07 g, 11.3 mmol) was added dropwise. The mixture was stirred for 10 min at −78°, warmed to room temp. for 30 min, poured into ether and sat NaCl aq. The organic layer was washed with sat $NaHCO_3$ aq, NaCl aq, dried over $MgSO_4$, concentrated, and chromatographed by silica gel column [eluted with hexane–ether (15 : 1)] to give 450 mg (81%) of the acetylene as colorless oil. NMR ($CDCl_3$): 1.26 (3H, d, J = 6.9 Hz), 3.75 (3H, s), 4.55 (2H, s). α_D: +17.1° (*c* 3.35, $CHCl_3$). IR (neat): 2220, 1710 cm^{-1}.

A mixture of the acetylene (200 mg; 0.813 mmol), quinoline (300 μl) and Lindlar catalyst (150 mg) in 25 ml of hexane was stirred under balloon pressure of H_2 at room temp. until the acetylene completely disappeared [*ca.* 15 min, monitored by silica gel tlc by using hexane–ether (1 : 1) as the eluent], filtered through 5 g of silica gel, and the silica gel was washed with 50 ml of a mixture of hexane and ether (5 : 1). The filtrate and washings were combined, concentrated, and chromatographed by silica gel column [eluted with hexane–ether (15 : 1) to give 180 mg (89%) of the *cis*-α,β-unsaturated ester as colorless oil. NMR ($CDCl_3$): 1.06 (3H, d, J = 6.7 Hz), 3.69 (3H, s), 4.50 (2H, s), 5.79 (1H, d, J = 11.7), 6.12 (1H, dd, J = 11.7, 9.2). Exact Mass: Found: 235.1334; Calcd. for $C_{14}H_{19}O_3$ ($M+H^+$): 235.1334. α_D: −62.8° (*c* 3.16, $CHCl_3$). IR (neat): 1720, 1640 cm^{-1}.

To a cold (−78°) soln of the *cis*-α,β-unsaturated ester (170 mg; 0.685 mmol) in a mixture of CH_2Cl_2 (10 ml) and hexane (10 ml), 1.0 M DIBAL (2.4 ml; 2.4 mmol) in hexane was added dropwise. After 40 min at this temp., 0.5 ml of MeOH, 1 ml of sat NaCl aq, and 50 ml of ether was added dropwise. The mixture was stirred for 20 min at room temp., the ether layer was dried over $MgSO_4$, concentrated under reduced pressure, and separated by preparative silica gel tlc [eluted with hexane–ether (1 : 2)] to give 138 mg (98%) of allylic alcohol **16** as colorless oil. NMR ($CDCl_3$): 0.96 (3H, d, J = 6.5 Hz), 4.51 (2H, s), 5.34 (1H, m), 5.75 (1H, m). Exact Mass: Found: 207.1386; Calcd. for $C_{13}H_{19}O_2$ ($M+H^+$): 207.1385. α_D: −1.31° (*c* 3.36, $CHCl_3$). IR (neat) 3275 cm^{-1}.

cis-*Allylic alcohol* **16** *from aldehyde* **3**

Method 2. To an ice-cold soln of dimethyl methoxycarbonylmethylphosphonate (413 mg; 2.27 mmol) in THF (15 ml), t-BuOK (229 mg; 2.05 mmol) was added. After being stirred for 1 hr at 25°,

the mixture was cooled in a dry-ice acetone bath. To the stirring soln was added dropwise 70 mg of the crude aldehyde in 1 ml of THF. The mixture was stirred for 40 min at this temp., poured into ether and sat NH_4Cl aq, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined organic layers were washed with sat NaCl aq, dried over $MgSO_4$, filtered, concentrated and chromographed by silica gel column [eluted with hexane–ether (3 : 1)] to give 81 mg (82% overall yield from **10**) of a mixture of the *cis*- and *trans*-α,β-unsaturated esters as colorless oil. This mixture was separated by preparative tlc [eluted with hexane–ether (5 : 1)] to give 55 mg of the *cis*-α,β-unsaturated ester and 18 mg of the *trans*-α,β-unsaturated ester.

The α_D of the *cis*-α,β-unsaturated ester was $-63.2°$ (*c* 3.13, $CHCl_3$), which agreed with the value observed for the *cis*-α,β-unsaturated ester prepared by Method 1.

The reduction of the *cis*-α,β-unsaturated ester was carried out under the same conditions as those given under Method 1.

Epoxide **17** *from* cis-*allylic alcohol* **16**

MCPBA method. A soln of **16** (20.6 mg; 1.00 mmol) in CH_2Cl_2 (6 ml) was cooled in an ice-acetone bath (*ca.* $-10°$). To the soln, MCPBA (51.6 mg; 0.300 mmol) was added. After being stirred for 1 hr at this temp. and for 1.5 hr at 0°, the mixture was diluted with ether, washed with 1N NaOH, water, sat NaCl aq, dried over $MgSO_4$, filtered, and concentrated to give 20.5 mg (93%) of a mixture of the epoxides. Preparative silica gel tlc [eluted with hexane–ether (1 : 2) gave 18.2 mg of **17** and 0.7 mg of **19**. Spectroscopic data of **17**: NMR (C_6D_6): 0.88 (3H, d, J = 6.8 Hz), 4.32 (2H, s). Exact Mass: Found: 223.1338: Calcd. for $C_{13}H_{19}O_3$ ($M+H^+$); 233.1334. α_D: $-16.4°$ (*c* 1.76, $CHCl_3$). IR (neat): 3400 cm^{-1}.

Epoxide **17** *from* cis-*allylic alcohol* **16**

Asymmetric epoxidation method. The epoxidation was carried out by the same procedure as the one given for preparation of **12** from **11**, except for the mixture being kept for 24 hr at $-23°$ instead of 40 min at $-23°$. The ratio of the epoxides **17** and **19** in the crude product was estimated at about 1:1 by an NMR spectrum in C_6D_6, which agreed with the ratio based on the amounts of isolated epoxides **17** and **19** by preparative silica gel tlc [eluted with hexane–ether (1 : 2)].

Epoxide **19** *from* cis-*allylic alcohol* **16**

Asymmetric epoxidation of **16**. This epoxidation was carried out by the same procedure as the one given for preparation of **12** from **11**, except for the mixture being kept for 24 hr at $-23°$ instead of 40 min at $-23°$. The crude product was separated by preparative silica gel tlc [eluted with hexane–ether (1 : 2)], to give **19** (66%) and **17** (13%). Spectroscopic data of **19**: NMR (C_6D_6): 0.79 (3H, d, J = 6.7 Hz), 4.10 (2H, s). Exact Mass: Found: 223.1337; Calcd. for $C_{13}H_{19}O_3$ ($M+H^+$): 223.1334. α_D: $+36.3°$ (*c* 1.11, $CHCl_3$). IR (neat): 3425 cm^{-1}.

Triol monobenzyl ether **13** *from epoxide* **12**

To a cold ($-23°$) suspension copper (I) iodide (1.3 g; 6.8 mmol) in ether (20 ml), 1.6 M MeLi (8.0 ml; 12.8 mmol) in ether was added dropwise until it became a colorless soln. After 30 min at this temp., the soln was cooled to $-40°$, and then **12** (100 mg; 0.450 mmol) in 2 ml of ether was added dropwise. After being stirred for 5 hr at $-40°$ and then for 30 min at $-23°$, the mixture was poured into a mixture of sat NH_4Cl aq and 28% NH_4OH aq (2 : 1), and the blue aqueous layer was thoroughly extracted with CH_2Cl_2. The combined organic layers were washed with sat NaCl aq, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and separated by preparative silica gel tlc [eluted with hexane–ether (2 : 1); two developments] to give 96 mg (89%) of **13** and 5 mg (4%) of **15**. Spectroscopic data of **13**: NMR (C_6D_6): 0.84 (3H, d, J = 6.9 Hz), 0.86 (3H, d, J = 6.9), 4.16 (2H, s). Exact Mass: Found: 239.1646; Calcd. for $C_{14}H_{23}O_3$ ($M+H^+$): 239.1647. α_D: $+3.63°$ (*c* 2.67, $CHCl_3$). IR (neat: 3375 cm^{-1}.

Triol monobenzyl ethers **15**, **18** *and* **20**

Using the same procedure as the one given for preparation of **13** from **12**, triol monobenzyl ethers **15**, **18** and **20** were prepared from the corresponding epoxides, respectively. The following spectroscopic data were recorded on **15**, **18** and **20**:

Triol monobenzyl ether **15**. NMR (C_6D_6): 0.57 (3H, d, J = 6.9 Hz), 0.97 (3H, d, J = 6.9), 4.20 (2H, s). Exact Mass: Found: 239.1647; Calcd. for $C_{14}H_{23}O_3$ ($M+H^+$): 239.1647. α_D: $+44.5°$ (*c* 1.16, $CHCl_3$). IR (neat): 3375 cm^{-1}.

Triol monobenzyl ether **18**. NMR (C_6D_6): 0.55 (3H, d, J = 6.9 Hz), 0.98 (3H, d, J = 6.8), 4.18 (2H, s). Exact Mass: Found: 239.1652; Calc. for $C_{14}H_{23}O_3$($M+H^+$): 239.1647. α_D: $+38.4°$ (*c* 0.94, $CHCl_3$). IR (neat): 3375 cm^{-1}.

Triol monobenzyl ether **20**. NMR (C_6D_6): 0.55 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.9), 4.22 (2H, s). Exact Mass: Found: 239.1654; Calcd. for $C_{14}H_{23}O_3$ ($M+H^+$): 239.1647. α_D: $+7.10°$ (*c* 2.72, $CHCl_3$). IR (neat): 3375 cm^{-1}.

Triol monoacetonide **4** *from triol monobenzyl ether* **13**

To a soln of **13** (2.22 g; 9.33 mmol) and 2,2-dimethoxyproprane (7 ml) in 140 ml of acetone, camphorsulfonic acid (200 mg) was added. After being stirred for 30 min at 25°, Et_3N (400 μl) was added. The resulting mixture was diluted with a mixture of hexane and ether (2 : 1), filtered through 20 g of silica gel, and the silica gel was washed with a mixture of hexane and ether (2 : 1). The combined filtrate was concentrated under reduced pressure and chromatographed by medium pressure silica gel column chromatography [eluted with hexane–ether (15:1)] to give 2.38 g (92%) of the triol monoacetonide benzyl ether. NMR (C_6D_6): 0.51 (3H, d, J = 6.6 Hz), 1.11 (3H, d, J = 7.0), 1.27 (3H, s), 1.48 (3H, s), 4.34 (2H, s). α_D: $-22.0°$ (*c* 2.60, $CHCl_3$).

To 50 ml of liquid ammonia, Li (388 mg; 55.4 mmol) was added, and the mixture was stirred until the metal was dissolved. To the soln, the triol monoacetonide benzyl ether (2.20 g; 7.91 mmol) in 10 ml of THF was added and the cooling bath was removed. After being stirred for 20 min at reflux temp., the reaction was quenched with *ca.* 2 g of solid NH_4Cl, and ammonia was evaporated at room temp. The resulting white residue was partitioned between ether and sat NaCl aq, and the water layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed by silica gel column [eluted with hexane–ether (1 : 1)] to give 1.43 g (96%) of **4** as a colorless oil. NMR ($CDCl_3$): 0.76 (3H, d, J = 6.6 Hz), 1.12 (3H, d, J = 7.1), 1.38 (3H, s), 1.40 (3H, s). Exact Mass: Found: 189.1495; Calcd. for $C_{10}H_{21}O_3$ ($M+H^+$): 189.1491. α_D: $-22.8°$ (*c* 3.73, $CHCl_3$). IR (neat): 3450 cm^{-1}.

Allylic alcohol **21** *from triol monoacetonide* **4**

The allylic alcohol **21** was obtained from the triol monoacetonide **4** in 94% overall yield by using the same procedures as the ones given for transformation of **10** to **11**. The following spectroscopic data were recorded for the intermediates, and the allylic alcohol **21**:

Aldehyde. NMR ($CDCl_3$): 0.77 (3H, d, J = 6.6 Hz), 1.18 (3H, d, J = 7.0), 1.36 (3H, s), 1.42 (3H, s), 9.76 (1H, d, J = 2.5) IR (neat): 1720 cm^{-1}.

trans-α,β-*Unsaturated ester.* NMR ($CDCl_3$): 0.69 (3H, d, J = 6.6 Hz), 1.10 (3H, dd, J = 7.0), 1.27 (3H, t, J = 7.1), 1.36 (3H, s), 1.38 (3H, s), 5.78 (1H, dd, J = 15.9, 0.7), 7.00 (1H, dd, J = 15.9, 9.0). IR (neat): 1720, 1650 cm^{-1}.

Allylic alcohol **21**. NMR ($CDCl_3$): 0.70 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.9), 1.36 (3H, s), 1.38 (3H, s), 5.70 (2H, m). Exact Mass: Found: 215.1651; Calcd. for $C_{12}H_{23}O_3$ ($M+H^+$); 215.1647. α_D: $+7.31°$ (*c* 1.60, $CHCl_3$). IR (neat): 3400, 1670 cm^{-1}.

Epoxide **22** *from allylic alcohol* **21**

The epoxide **22** was obtained from **21** in 78% yield by using the same procedure as the one given for the asymmetric epoxidation of **11** to **12**. The major epoxide **22** was sepatated from the minor epoxide by preparative silica gel tlc [eluted with hexane–ether–acetone (5 : 5 : 1)]. The ratio of the two epoxides was 95 : 5. The following spectroscopic data were recorded on the major epoxide **22**. NMR ($CDCl_3$): 0.75 (3H, d, J = 6.6 Hz), 1.13 (3H, d, J = 6.5), 1.37 (3H, s), 1.39 (3H, s). Exact Mass: Found: 231.1592; Calcd. for $C_{12}H_{23}O_4$ ($M+H^+$): 231.1596. α_D: $-44.0°$ (*c* 0.74, $CHCl_3$). IR (neat): 3420 cm^{-1}.

Tetrol monoacetonide **23** *from epoxide* **22**

The tetrol monoacetonide **23** was obtained from **22** in 95% yield by using the same procedure as the one given for transformation of **12** to **13**. The following spectroscopic data were recorded. NMR ($CDCl_3$): 0.72 (3H, d, J = 6.6 Hz), 0.74 (3H, d, J = 6.9), 1.04 (3H, d, J = 7.1), 1.40 (6H, s). Exact Mass: Found: 247.1907; Calc. for $C_{13}H_{27}O_4$ ($M+H^+$): 247.1909. α_D: −40.4° (*c* 6.29, $CHCl_3$). IR (neat): 3460 cm^{-1}.

Tetrol monoacetonide monosilyl ether **24** *from tetrol monoacetonide* **23**

A soln of **23** (286 mg; 1.16 mmol), imidazol (118 mg; 1.74 mmol), and t-butylchlorodiphenylsilane (391 mg; 1.40 mmol) in 1 ml of DMF was stirred for 30 min at room temp. The mixture was partitioned between ether and water. The water layer was thoroughly extracted with CH_2Cl_2. The combined organic layers were washed with NaCl aq, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and separated on preparative silica gel tlc [eluted with hexane-CH_2Cl_2-acetone (40 : 40 : 1)] to give 561 mg (99.6%) of **24** as a colorless oil. NMR ($CDCl_3$): 0.72 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.7), 0.98 (3H, d, J = 7.2), 1.06 (9H, s), 1.37 (3H, s), 1.39 (3H, s). Exact Mass: Found: 485.3082; Calcd. for $C_{29}H_{45}O_4Si$ ($M+H^+$): 485.3087. α_D: −9.29° (*c* 3.22, $CHCl_3$). IR (neat): 3500 cm^{-1}.

Tetrol monoacetonide monosilyl ether **25** *from tetrol monoacetonide monosilyl ether* **24**

A mixture of **24** (450 mg; 0.930 mmol), AcOH (8 ml) and water (2 ml) was stirred for 10 min at 40°, and the volatile material was removed *in vacuo* to give 413 mg (100%) of the tetrol monosilyl ether as a slightly yellow oil. This material was used for the next step without further purification. A sample for spectroscopic analysis was prepared by preparative silica gel tlc [eluted with hexane–CH_2Cl_2–acetone (5:5:1)]. NMR ($CDCl_3$): 0.65 (3H, d, J = 6.9 Hz), 0.77 (3H, d, J = 6.9), 1.06 (9H, s), 1.10 (3H, d, J = 7.0). α_D: −26.3° (*c* 2.51, $CHCl_3$).

To an ice-cold soln of the crude tetrol monosilyl ether (400 mg; 0.901 mmol) and pyridine (450 μl; 5.82 mmol) in 10 ml CH_2Cl_2, trimethylacetyl chloride (300 μl; 306 mg, 2.54 mmol) was added dropwise. After being stirred for 1.5 hr at 0° and for 2 hr at room temp., the mixture was partitioned between ether and sat NaCl aq. The aqueous layer was thoroughly extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and separated by preparative silica gel tlc [eluted with hexane–CH_2Cl_2–acetone (10 : 10 : 1)] to give 437 mg (92%) of the tetrol monosilyl ether monopyvaloyl ester. NMR ($CDCl_3$): 0.67 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 6.8), 1.05 (9H, s), 1.08 (3H, d, J = 7.1), 1.22 (9H, s). α_D: −4.40° (*c* 4.57, $CHCl_3$). IR (neat): 3430, 1720 cm^{-1}.

To a soln of the tetrol monosilyl ether monopyvaloyl ester (390 mg; 0.739 mmol) in 2,2-dimethoxypropane (8 ml), camphorsulfonic acid (6 mg) was added. After 2 hr at room temp., Et_3N (10 μl) was added. The resulting mixture was concentrated under reduced pressure and chromatographed by silica gel column [eluted with hexane–ether (5 : 1)] to give 405 mg (99%) of the tetrol monosilyl ether monopyvaloyl ester monoacetonide as a colorless oil. NMR ($CDCl_3$): 0.86 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.4), 1.00 (3H, d, J = 7.1), 1.06 (9H, s), 1.20 (12H, s), 1.23 (3H, s). α_D: −18.6° (*c* 4.25, $CHCl_3$). IR (neat): 1730 cm^{-1}.

To a soln of the tetrol monosilyl ether monopyvaloyl ester monoacetonide (395 mg; 0.708 mmol) in ether (15 ml), LAH (27 mg; 0.708 mmol) was added portionwise. After addition was complete, the mixture was stirred for 15 min at 25°. It was then cooled to 0°, and 50 ml of ether and 10 drops of sat NaCl aq were added. The resulting mixture was stirred for 20 min at 25°. The ether layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 341 mg (100%) of practically pure **25**. A sample for spectroscopic analysis was prepared by preparative silica gel tlc [eluted with hexane–ether (1 : 1)] as a colorless oil. NMR ($CDCl_3$): 0.88 (3h, d, J = 6.7 Hz), 0.93 (3H, d, J = 6.6), 0.98 (3H, d, J = 7.2), 1.06 (9H, s), 1.21 (3H, s), 1.29 (3H, s). Exact Mass: Found: 485.3092; Calcd. for $C_{29}H_{45}O_4Si$ ($M+H^+$): 485.3087. α_D: −30.8° (*c* 3.00, $CHCl_3$). IR (neat): 3450 cm^{-1}.

Epoxide **26** *from tetrol monosilyl ether monoacetonide* **25**

The epoxide **26** was obtained from **25** in 76% overall yield by using the same procedures as the ones described for transformation of **10** into **12**. The stereoselectivity of the asymmetric epoxidation was 95 : 5, which was determined based on the amounts of the two epoxides isolated by silica gel tlc [eluted with hexane–ether (2 : 3)]. The following spectroscopic data were recorded for the intermediates and the epoxide **26**.

Aldehyde. NMR ($CDCl_3$): 0.90 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.6), 1.07 (9H, s), 1.13 (3H, d, J = 7.5), 1.20 (3H, s), 1.27 (3H, s), 9.73 (1H, d, J = 2.6). α_D: −12.8° (*c* 1.82, $CHCl_3$). IR (neat: 1725 cm^{-1}.

trans-*α,β-Unsaturated ester.* NMR ($CDCl_3$): 0.84 (3H, d, J = 6.6 Hz), 0.90 (3H, d, J = 6.6), 1.06 (9H, s), 1.11 (3H, d, J = 7.0), 1.19 (3H, s), 1.25 (3H, s), 1.29 (3H, t, J = 7.2), 5.83 (1H, dd, J = 15.8, 1.0), 7.02 (1H, dd, J = 15.8, 8.0). α_D: −32.7° (*c* 2.33, $CHCl_3$). IR (neat): 1720, 1650 cm^{-1}.

trans-*Allylic alcohol.* NMR ($CDCl_3$): 0.87 (3H, d, J = 6.5 Hz), 0.90 (3H, d, J = 6.4), 1.06 (9H, s), 1.06 (3H, d, J = 6.7), 1.19 (3H, s), 1.25 (3H, s), 5.70 (2H, m). α_D: −37.7° (*c* 2.50, $CHCl_3$).

Epoxide **26**. NMR ($CDCl_3$): 0.88 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6), 1.06 (3H, d, J = 6.2), 1.18 (3H, s), 1.26 (3H, s). Exact Mass: Found: 527.3189; Calcd. for $C_{31}H_{47}O_5Si$ ($M+H^+$): 527.3193. α_D: −21.0° (*c* 1.65, $CHCl_3$). IR (neat): 3450 cm^{-1}.

Pentol monosilyl ether monoacetonide **27** *from epoxide* **26**

The monoacetonide **27** was obtained from **26** in 96% yield using the same procedure as the one given for transformation of **12** to **13**. The following spectroscopic data were recorded. NMR ($CDCl_3$): 0.75 (3H, d, J = 7.1 Hz), 0.84 (3H, d, J = 7.1), 0.87 (3H, d, J = 6.6), 0.96 (3H, d, J = 6.7), 1.07 (9H, s), 1.21 (3H, s), 1.25 (3H, s). Exact Mass: Found: 543.3512; Calcd. for $C_{32}H_{51}O_5Si$ ($M+H^+$): 543.3506. α_D: −15.8° (*c* 1.73, $CHCl_3$). IR (neat): 3400 cm^{-1}.

Pentol diacetonide **6** *from pentol monosilyl ether monoacetonide* **27**

To a soln of **27** (220 mg; 0.406 mmol) in 2,2-dimethoxypropane (3 ml) was added a trace amount (*ca.* 2 mg) of camphorsulfonic acid. After 15 min at room temp., Et_3N (10 μl) was added. The resulting mixture was concentrated under reduced pressure, and chromatographed by silica gel column [eluted with hexane–ether (2 : 1)] to give 224 mg (95%) of the pentol monosilyl ether diacetonide as a colorless oil. The following spectroscopic data were recorded. NMR ($CDCl_3$): 0.69 (3H, d, J = 6.7 Hz), 0.88 (3H, d, J = 6.2), 0.88 (d, J = 6.4), 0.92 (3H, d, J = 6.6), 1.06 (9H, s), 1.19 (3H, s), 1.24 (3H, s), 1.33 (3H, s), 1.37 (3H, s). α_D: −3.49° (*c* 1.52, $CHCl_3$).

To a soln of pentol monosilyl ether diacetonide (180 mg; 0.309 mmol) in THF (3 ml), 1M tetrabutylammonium fluoride (118 μl; 0.618 mmol) in THF was added. After being stirred for 4 hr at 25°, the mixture was partitioned between ether and sat NaCl aq, and the aqueous layer was extracted with three portions of ether. The combined ether extracts were dried over $MgSO_4$, concentrated under reduced pressure and chromatographed by silica gel tlc [eluted with hexane–ether (1 : 1)] to give 74 mg (98%) of **6**. NMR ($CDCl_3$): 0.68 (3H, d, J = 6.3 Hz), 0.86 (3H, d, J = 6.3), 0.87 (3H, d, J = 7.0), 0.93 (3H, d, J = 6.6), 1.30 (3H, s), 1.34 (3H, s), 1.36 (6H, s). Exact Mass: Found: 345.2650; Calcd. for $C_{19}H_{37}O_5$ ($M+H^+$): 345.2641. α_D: −7.60° (*c* 0.90, $CHCl_3$). IR (neat): 3500 cm^{-1}.

Pentol diacetonide **29** *from diacetonide aldehyde* **28**

Diallylzinc procedure. The aldehyde **28** was prepared from **6** by using the same procedure as the one given for oxidation of **10**. The crude **28** was *immediately* used for the next step without further purification. NMR ($CDCl_3$): 0.69 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6), 0.94 (3H, d, J = 6.4), 0.96 (3H, d, J = 6.7), 1.29 (6H, s), 1.34 (3H, s), 1.37 (3H, s), 9.71 (1H, d, J = 2.5 Hz).

To cold (0°) ether (6 ml), 1.4 M allylmagnesium bromide (0.53 ml; 0.74 mmol) in ether and 0.50M $ZnCl_2$ (2.0 ml; 1.0 mmol) in ether was added dropwise. The mixture was warmed to room temp., stirred for 5 min at this temp., and cooled in a dry-ice

ether bath, and then a soln of crude **28**, prepared from 60 mg of **6**, in 0.5 ml of ether was added over 20 min. After being stirred for 10 min, the mixture was poured into ether and sat NH_4Cl aq and the aqueous layer was extracted with three portions of CH_2Cl_2. The combined extracts were washed with sat NaCl aq, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and separated by preparative silica gel tlc [developed three times with hexane–ether (2:1)] to give 61 mg (86%) of **29** and 4.2 mg (5%) of **30**.

Pentol diacetonide **29**. NMR ($CDCl_3$): 0.69 (3H, d, J = 6.7 Hz), 0.80 (3H, d, J = 6.8), 0.87 (3H, d, J = 6.4), 0.89 (3H, d, J = 6.7), 1.30 (3H, s), 1.34 (6H, s), 1.37 (3H, s), 5.08 (1H, br d, J = 11.9), 5.10 (1H, br d, J = 15.4), 5.85 (1H, m). Exact Mass: Found: 385.2948; Calcd. for $C_{22}H_{41}O_5$ $(M+H^+)$: 385.2954. α_D: −2.33° (*c* 1.20, $CHCl_3$). IR (neat): 3375, 1640 cm^{-1}.

Pentol diacetonide **30**. NMR ($CDCl_3$): 0.69 (3H, d, J = 6.6 Hz), 0.76 (3H, d, J = 6.0), 0.87 (3H, d, J = 7.0), 0.92 (3H, d, J = 6.7), 1.30 (3H, s), 1.36 (9H, br s), 5.08 (1H, br d, J = 11.9), 5.10 (1H, br d, J = 15.4), 5.85 (1H, m).

Pentol diacetonide **29** *from diacetonide aldehyde* **28**

Allyltin procedure. To a soln of crude **28** (20 mg; 0.083 mmol) and 1,2-dimethyl-2-imidazolidinone (80 μl) in 2 ml benzene, anhyd stannous chloride (344 mg; 1.67 mmol) and allyliodide (60 μl; 112 mg, 0.664 mmol) was added. The resulting suspension was vigorously stirred for 60 sec at 25°, partitioned between ether and sat $NaHCO_3$ aq, and the aqueous layer was extracted with ether. The combined extracts were washed with sat NaCl aq, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and separated by preparative silica gel tlc [developed three times with hexane–ether (2 : 1)] to give 16.1 mg (68%) of **29** and 0.7 mg (3%) of **30**.

Triol monoacetonide **39** *from aldehyde* **38**

To a cold (0°) suspension of anhyd chromic chloride (298 mg; 1.88 mmol) in THF (4 ml), LAH (36.8 mg; 0.94 mmol) was added portionwise. The mixture was stirred for 5 min at 0° and for 20 min at room temp. and cooled in an ice bath, then 50 mg (the crude oxidation product; 0.269 mmol) of **38** in 1 ml of THF was added. After 10 min, *trans*-crotyl iodide (136 mg; 0.807 mmol) in 1.5 ml of THF was added dropwise over a period of 15 min and stirring was continued for 30 min at this temp. The mixture was poured into sat $NaHCO_3$ aq and ether, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined extracts were washed with sat NaCl aq., dried over $MgSO_4$, filtered, concentrated under reduced pressure to give 57 mg (86%) of colorless oil. This crude material was used directly for preparation of the tetrol monosilyl ether monoacetonide **24** without further purification. A sample of **39** for spectroscopic analysis was prepared by preparative silica gel tlc [eluted with hexane–CH_2Cl_2–ether (3:1:1)]. NMR ($CDCl_3$): 0.63 (3H, d, J = 6.7 Hz), 0.82 (3H, d, J = 6.9), 0.92 (3H, d, J = 7.0), 1.27 (3H, s), 1.29 (3H, s), 4.95 (1H, br d, J = 9.5), 4.96 (1H, br d, J = 17.0), 5.75 (1H, ddd, 17.0, 9.5, 7.5).

Tetrol monosilyl ether monoacetonide **24** *from* **39**

O_3 was introduced into a soln of **39** (57 mg), the product obtained from 50 mg of **38**, in 5 ml of MeOH at −78° until the blue color persisted for more than 2 min. The excess O_3 was removed by allowing O_2 to bubble through the soln at −78°. Then 1.2 ml of dimethyl sulfide was added dropwise, the mixture was allowed to warm to 25° over 30 min, stirred for 30 min at 25°, then cooled to 0°. To the soln was added portionwise excess (90 mg) of sodium borohydride; stirring was continued for 30 min at 0°. The mixture was concentrated, partitioned between sat NaCl aq and ether, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, and concentrated under reduced pressure to give 58 mg of the crude tetrol monoacetonide as a colorless oil. To a soln of this material and imidazol (42 mg; 0.62 mmol) in 0.6 ml of DMF, t-butylchlorodiphenylsilane (84 μl; 89 mg, 0.32 mmol) was added dropwise. After being stirred for 20 min at 25°, the mixture was poured into ether and water, and the aqueous layer was extracted with three portions of ether. The combined extracts were washed with water, sat NaCl aq, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, consisting of a diastereomeric mixture (>20 : 1 : ~0.5 : ~0.5) as a colorless oil. This ratio was analyzed by the use of high pressure liquid chromatography [Waters M-6000A; porasil, hexane–ether (15 : 1)]. Preparative silica gel tlc [eluted with hexane–ether (20 : 3)] gave 65.5 mg (72% overall yield from **38**) of a colorless oil as the major product. This material was identical with the ether **24**, prepared from the previous route, in every respect (IR, NMR, MS, α_D).

Almost identical results were obtained in the experiment using *cis*-crotyl iodide instead of *trans*-crotyl iodide.

Diacetonide aldehyde **28** *from aldehyde* **41**

The aldehyde **28** was obtained in 77% overall yield by using the same procedures as the ones given previously (i.e., see the procedure for **38**→**24**, **27**→**6**, and **10**→**3**). The following spectroscopic data were recorded for the vinyl intermediate. All other intermediates were described under the previous route.

Vinyl compound. NMR ($CDCl_3$): 0.84 (3h, d, J = 7.0 Hz), 0.93 (9H, d, J = 6.8), 1.06 (9H, s), 1.20 (3H, s), 1.26 (3H, s), 5.06 (1H, br d, J = 9.5), 5.07 (1H, br d, J = 17.0), 5.85 (1H, ddd, 17.0, 9.5, 7.5).

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[6]Unsuccessful attempts include NMR studies using optically active shift reagents on the *trans*-α,β-unsaturated ester and the *trans*-allylic alcohol (**11**), and NMR and hlc studies on the MTPA ester of **11**.

[7]In the studies on the synthesis of monensin, we recognized that the ratio of *cis* and *trans* esters in the Horner–Emmons modification of Wittig reaction is sensitive to the structure of phosphonate reagents. In general, a phosphonate reagent with a large phosphonate ester group yields predominantly a *trans*-α,β-unsaturated ester, while a phosphonate reagent with a small phosphonate ester group yields predominantly a *cis*-α,β-unsaturated ester. An example is shown below; G. Schmid, Y. Oikawa and Y. Kishi, unpublished results.

[8a]T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.* **102**, 5974 (1980); [b]B. E. Rossiter, T. Katsuki and K. B. Sharpless, *Ibid.* **103**, 464 (1981).

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	Conditions	Cis		Trans
$(C_6H_5)_3P{=}C(Me)CO_2Et$	CH_2Cl_2/RT	5	:	95
	MeOH/RT	15	:	85
$(EtO)_2P(O)CH(Me)CO_2Et$	$KOBu^t$/THF/−78 °C	60	:	40
$(Pr^iO)_2P(O)CH(Me)CO_2Pr^i$	"	5	:	95
$(Pr^iO)_2P(O)CH(Me)CO_2Et$	"	10	:	90
$(MeO)_2P(O)CH(Me)CO_2Et$	"	90	:	10
$(MeO)_2P(O)CH(Me)CO_2Me$	"	95	:	5

[10]The signals due to the methyl and benzyl groups of **12** and **14** were used for this purpose.

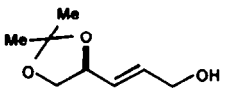
[11]A. J. Mancuso, S. -L. Juang and D. Swern, *J. Org. Chem.* **41**, 2480 (1978).

[12]The same conclusion was drawn from the asymmetric epoxidation experiments using D-(−)-diethyl tartrate (Scheme 4).

[13]The details of the transformation will be included in the full paper of the previous synthesis.

[14]This ratio was determined from the NMR spectrum as well as from the amounts of the products isolated by preparative tlc.

[15]Similar results were obtained on the asymmetric epoxide of the *trans*- and *cis*-allylic alcohols **48** and **49**. Namely, the *trans*-allylic alcohol **48** yielded the α- and β-epoxides, depending on the chiral ligand used, with high stereoselectivity (96:4). The *cis*-allylic alcohol **49** yielded the expected epoxide as the major product (the ratio = 12:1) on the asymmetric epoxidation with L-(+)-diethyl tartrate, while **49** yielded the *un*expected epoxide as the major product (the ratio = 1.6 : 1) with D-(−)-diethyl tartrate: N. Minami, S. Ko and Y. Kishi, unpublished results.



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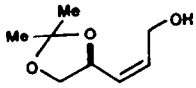

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[16]The regioselectivity was found to be rather sensitive to the reaction temperature. At −40°, the epoxide **12** gave exclusively **13**, whereas at 0°, **12** gave an about 3 : 1 mixture of **13** and its regioisomer.

[17]On treatment with 2,2-dimethoxypropane and camphorsulfonic acid in acetone at room temperature, the acetonide **24** yielded an about 1 : 1 mixture of **24** and **25**.

[18]We have recently realized that the stereoselectivity of the diallylzinc reaction depends greatly upon the purity of the reagent and less upon the rate of addition of the reagent. Thus, the best stereoselectivity observed is about 15 : 1.

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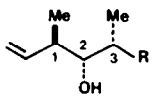
[22]The numbering was used as indicated below.



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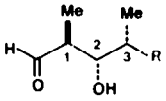

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[23]Chromous salt prepared from $CrCl_3$ and LAH_4 in THF gave better results than commercial $CrCl_2$.

[24]Numerous papers on crossed aldol reactions have recently been published. For some of them, see S. Masamune, W. Choy, F. A. J. Kerdesky and B. Imperiali, *J. Am. Chem. Soc.* **103**, 1566 (1981), and refs. cited.

[25]In some cases, the erythro stereochemistry can be controlled by a crossed aldol reaction. For example, see T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer and Y. Kishi, *J. Am. Chem. Soc.* **100**, 2933 (1978).

[26]We are indebted to Dr. Noal Cohen, Hoffmann-La Roche Inc., for a sample of (*S*)-(+)-3-hydroxy-2-methylpropionic acid.