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STEREOSELECTIVE ACYCLIC KETONE REDUCTION

SYNTHESIS OF THE SYNTHONS HAVING THREE CONSECUTIVE CHIRAL CENTERS

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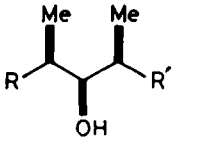
Abstract—Four possible diastereomers of a functionalized 1,3-dimethyl-2-hydroxy unit were synthesized based on the stereoselective reduction of various acyclic ketones (i.e. reduction of β-keto ester, β-hydroxy ketone, α-hydroxy ketone, and α-silyloxy ketone) and the regioselective ring opening of epoxide by 1,3-dithiane anion.

Chiral OH groups involved in naturally occuring polyketide antibiotics are known to be produced biogenetically by a stereoselective reduction of the ketone by means of NAD(P)H-enzyme system. We intended to mimic the enzymatic reduction in a laboratory by using a suitably designed substrate and a reducing reagent. As a substrate, a ketone having another oxygen function at a proper position of the same molecule was chosen and as a reducing reagent, metal hydride whose metal possess a strong ability to coordinate with two oxygen functions in the substrate was adopted. In these systems, it is strongly suggested that two O functions should come to the same plane mediated by the metal and the hydride anion should attack the carbonyl C from the less hindered side giving products stereoselectively. For this purpose, $Zn(BH_4)_2$ was found to be a reagent of choice among other metal hydrides. Thus, 2,3-*syn*(*erythro*)-2-methyl-3-hydroxy esters **1**,[1] 2,3-*syn*(*erythro*)-2-methyl-1,3-glycols **2**,[2] *anti*(*erythro*)-α,β-epoxy alcohols **3**,[3] and *anti*(*erythro*)-1,2-glycols **4**[4] have been obtained with high stereoselectivity by the reduction of the corresponding ketones using $Zn(BH_4)_2$. On the other hand, reduction of α-hydroxy ketone whose OH group is protected as a t-butyldiphenylsilyl ether with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) was found to afford the *syn*(*threo*)-1,2-glycol **5**.[4] The reduction is presumed to proceed through an open-chain model[5] in this case. Hereafter, reductions affording **1** ~ **5** should be designated as type 1 ~ 5 reduction, respectively. In every case, a relation between substitution pattern of the substrate and stereoselectivity of the products has been discussed in some detail.[1-4] Using these stereoselective reductions, synthesis of (±)-oudemansin[6] (type 1) and the intermediates for the construction of erythronolide A[7] (type 1), and the formal total synthesis of antimycin A_3[8] (type 1 and 4) have been achieved. In this report, syntheses of acyclic synthons having three consecutive chiral centers are described.[9]

A 1,3-dimethyl-2-hydroxy unit frequently appears in polyoxo, ansa, and polyether antibiotics and a stereoselective method for the synthesis of this structural unit has been extensively studied particularly in connection with the synthesis of monensin and rifamycins.[10] We also interested in the synthesis of these segments and applying the newly developed reductions (type 1, 2, 4 and 5) effectively, synthesis of four possible diastereomers (**6**, **7**, **8** and **9**) was achieved



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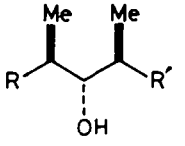

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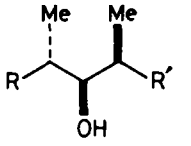

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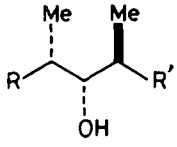

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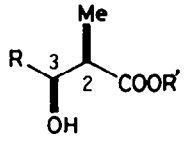
with remarkably high overall stereoselectivity. The starting 2,3-*syn*-2-methyl-1,3-glycol **10** was prepared by reduction of the β-keto ester **11** with $Zn(BH_4)_2$[1] (type 1, ratio 25:1; 73% combined yield) followed by $LiAlH_4$ reduction or by $Zn(BH_4)_2$ reduction of the β-hydroky ketone **12**[2] (type 2, ratio 25:1; 91% com-



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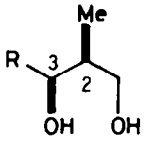

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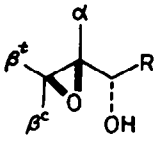

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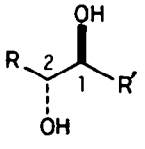

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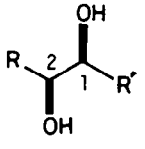

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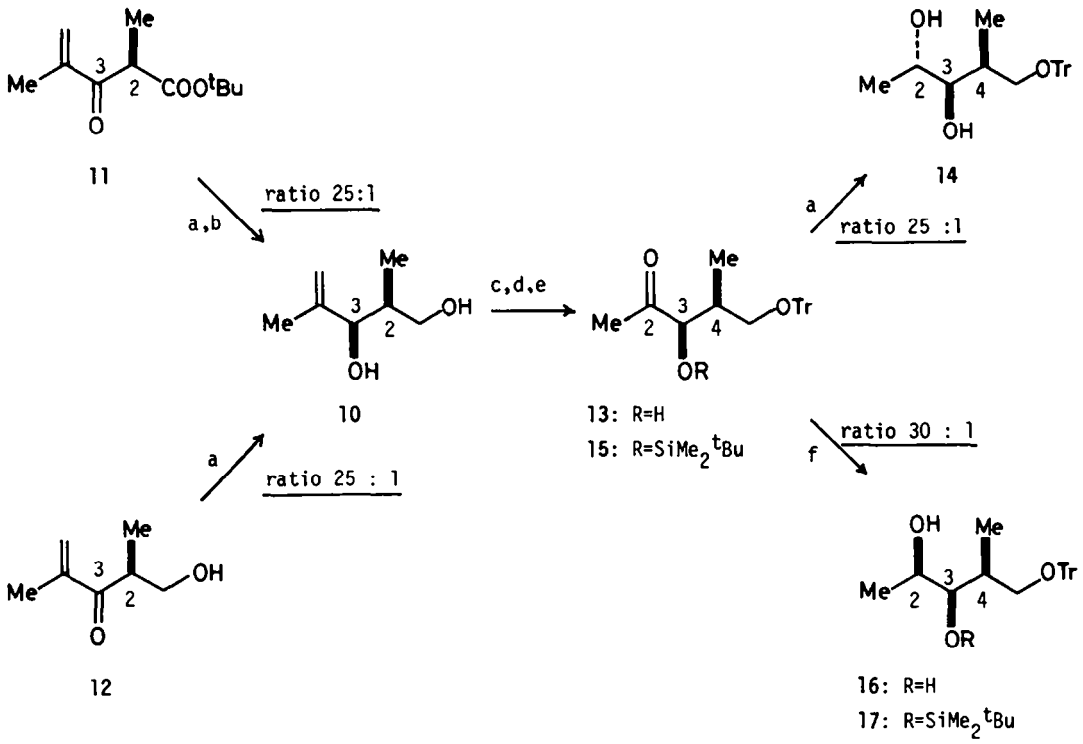
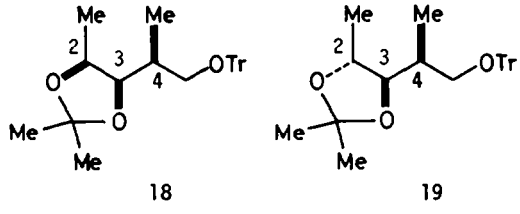


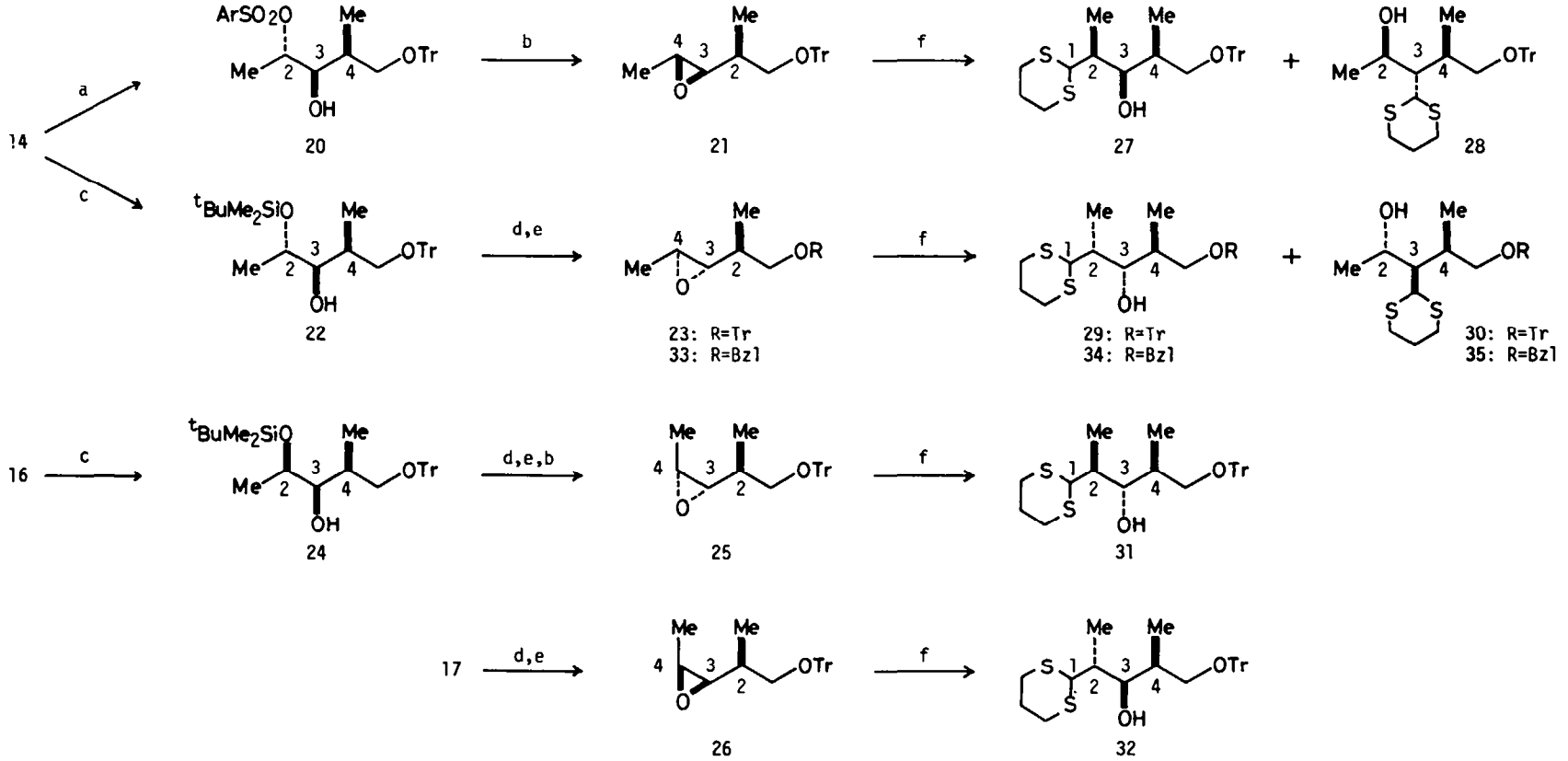
Scheme 1. (a) $Zn(BH_4)_2$/ether/0°, (b) $LiAlH_4$/ether/0°, (c) TrCl/py/rt, (d) O_3/MeOH/− 78°; Me_2S/− 78°→rt, (e) t-$BuMe_2SiCl$/imidazole/DMF/rt, (f) 10% Vitride/toluene/− 78°→rt (15 hr) or − 78° (15 min).

bined yield). The glycol **10** was tritylated and then subjected to ozonolysis to afford the α-keto alcohol **13** in 60% yield. Now, type 4 reduction can be applied to **13**. In fact, when **13** was treated with $Zn(BH_4)_2$ in ether at 0°, the 2,3-*anti*-glycol **14** was obtained with high selectivity (type 4, ratio 25:1; 99% combined yield). On the other hand, when type 5 reduction is applied to **13**, the isomeric 2,3-*syn*-glycol **16** is expected to be obtained. Thus, **13** was treated with t-$BuMe_2SiCl$[11] and the resulting 3-silyloxy ketone **15** was reduced with 10% Vitride[12] [$NaAlH_2(OCH_2CH_2OMe)_2$] in toluene at − 78° and then at room temp for 15 hr to yield **16** (type 5, ratio 30:1; 94% combined yield). Complete desilylation took place in this case. However, when the reduction was limited to 15 min at −78°, 2,3-*syn*-3-silyloxy-2-ol **17** was obtained as a sole product in 76% yield. Although desilylation did not take place, 22% of **15** was recovered unchanged. In these α-hydroxy ketone reductions, an extremely high selectivity was obtained in each case. These results hold quite well for the former prediction that both in type 4 and 5 reductions, when a branched alkyl group is present next to a hydroxyl or a silyloxy group, the reduction should proceed with high selectivity.[4] In another word, the present experiments provide strong supports for the validity of the above mentioned prediction. The stereochemistry of both **14** and **16** was confirmed by nuclear Overhauser effect (NOE). Namely, upon irradiation of C-2 Me in **19** prepared from **16**, 12.3% NOE was observed on C-3 H but no NOE was detected on C-3 H upon irradiation of C-2 Me in **18** prepared from **14**.[13] These results show that C-3 H and C-2 Me should be oriented in the same side of the 5-membered ring in **19**, but not in **18**.



Then, the 2,3-*anti*-alcohol **14** and the 2,3-*syn*-alcohols **16**, **17** were successfully converted to the (*E*)-epoxides **21**, **23** and the (*Z*)-epoxides **25**, **26**. Treatment of **14** with mesitylenesulfonyl chloride gave **20** (86%), regioselectively, which was treated with K_2CO_3 in MeOH to give the 2,3-*syn*-(*E*)-epoxide **21** in 89% yield. Regioselective protection of C-2 OH group in **14** by t-$BuMe_2SiCl$ afforded **22** in 94% yield. Mesylation followed by n-Bu_4NF treatment of **22** gave the 2,3-*anti*-(*E*)-epoxide **23** in 77% yield. On the other hand, the silyl ether **24** obtained from **16** in 94% yield, regioselectively, was converted to the 2,3-*anti*-(*Z*)-epoxide **25** (80%) by mesylation followed by treatment with n-Bu_4NF. Formation of epoxide was incomplete in this case, so the crude compound was treated with K_2CO_3 in MeOH for completion of the reaction. Epoxidation of **17** by the same procedure as used in the synthesis of **23** yielded the 2,3-*syn*-(*Z*)-epoxide **26** (98%). The coupling constants (Hz) between C-3 and C-4 protons of the four isomers (**21**, J = 2.2; **23**, J = 2.2; **25**, J = 4.4; **26**, J = 4.2) support the (*E*)-structure for **21** and **23**, and the (*Z*)-structure for **25** and **26**.[14]

Finally, ring opening of the four epoxides with 1,3-dithiane anion was undertaken. Reaction of **21** with 5 equiv of 2-lithio-1,3-dithiane in THF at 5° for



Scheme 2. (a) Mesitylenesulfonyl chloride/DMAP/py/benzene/rt, (b) K_2CO_3/MeOH/rt, (c) t-$BuMe_2SiCl$/imidazole/DMF/rt, (d) MsCl/py/rt, (e) n-$Bu_4NF \cdot 3H_2O$/THF/rt, (f) 1,3-dithiane/n-BuLi/THF/ $-20° \rightarrow 5°$.

one week produced the desired C-2 adduct **27** (68%) and the C-3 adduct **28** (15%) together with the recovered epoxide **21** (13%). Formation of C-3 adduct **30** (15%) was also observed in the ring opening of **23**. In this case, the yield of the desired **29** (44%) was unexpectedly less than that of **27**, but 38% of the starting epoxide **23** was recovered unchanged. However, much better selectivity was observed when the corresponding benzyl ether **33** was subjected to the same ring opening reaction (yields: **34**, 70%; **35**, 13%; **33**, 11%). In sharp contrast to these reactions, when the (*Z*)-epoxides **25** and **26** were subjected to the same reaction, the ring opening was almost finished within 64 hr at 5°, and only the desired C-2 adducts **31** and **32** were obtained in 96% and 82% (99% based on the reacted **26**) yields, respectively. The same tendency on the epoxide ring opening has been reported by Kinoshita *et al.*[15] in the related systems and the reason for this has also been reasonably explained by the same authors.[15] The discussion should be valid in the present case. The structure of the C-2 and C-3 adducts **27** ~ **35** was determined on the basis of the splitting patterns of the protons on the carbon bearing OH group in the 400 MHz NMR ($CDCl_3$ + D_2O: double doublets for **27**, **29**, **31**, **32** and **34** double quartet for **28**, **30** and **35**). The stereostructure of the products **27** ~ **35** was deduced from the well-established fact that ring opening of epoxide by nucleophiles proceeded with complete inversion of configuration at the attacked position.[16]

Facile and practical syntheses of the four possible diastereomers **27**, **29**, **31**, **32** and **34** were thus achieved. Synthesis of the corresponding optically active synthons is currently being undertaken.

EXPERIMENTAL

All m.ps were measured with a Yanagimoto micro m.p. apparatus and are uncorrected. IR spectra were recorded on a JASCO A-3 spectrometer. NMR spectra were obtained in $CDCl_3$ soln with TMS as an internal standard on a JEOL JNM-FX 400 or JNM-GX 400 spectrometer (400 MHz). Mass spectra (MS) were measured on a Hitachi M-80A double focussing instrument.

t-Butyl 2,4-*dimethyl*-3-*oxo*-4-*pentanoate* **11**.

To a soln of LDA in THF [prepared from i-Pr_2NH (12.8 g) in THF (150 ml) and a 1.56 M soln of n-BuLi in hexane (77 ml)] was added dropwise a soln of t-butyl propionate (15 g) in THF (15 ml) at − 78° under Ar and the mixture was stirred for 30 min. Then, a soln of methacrolein (8.9 g) in THF (10 ml) was added and the soln was stirred for 30 min. The reaction was quenched with sat $NaHCO_3$ aq and the mixture was extracted with ether. The extract was washed with sat NaCl aq, dried over Na_2SO_4, and evaporated to give a mixture of *syn*- and *anti*-β-hydroxy esters (21.28 g; 92%), which was used for the next step without purification. IR (neat) 3480, 1725, 1710 cm^{-1}; NMR δ 1.096 (d, J = 7.3 Hz; C-2 Me), 1.100 (d, J = 7.3 Hz; C-2 Me), 1.460, 1.463 (each s; t-Bu), 4.09 (dd, J = 7.6, 5.6 Hz; C-3 H), 4.34 (t like, J = 3.4 Hz; C-3 H).

To a soln of oxalyl chloride (11.8 ml) in CH_2Cl_2 (300 ml) was added a mixture of DMSO (19.6 ml) in CH_2Cl_2 (40 ml) at − 50° under Ar and then a soln of a mixture of β-hydroxy esters (21.28 g) in CH_2Cl_2 (50 ml) was added. After the mixture was stirred for 15 min at the same temp, Et_3N (88 ml) was added and the soln was allowed to warm to room temp. Water was added and CH_2Cl_2 layer was separated. Aqueous layer was extracted with ether. The combined organic layer was washed with sat NaCl aq, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel [hexane–ether (4:1)] to give 17.18 g (82%) of β-keto ester **11**. IR ($CHCl_3$) 1730, 1680 cm^{-1}; NMR δ 1.34 (d, J = 7.1 Hz; C-2 Me), 1.42 (s; t-Bu), 4.00 (q, J = 7.1 Hz; C-2 H). MS (FI) *m/z* 199 (MH^+).

2,3-syn-2,4-*Dimethyl*-4-*penten*-1,3-diol **10**

(*a*) To a soln of **11** (17.18 g) in ether (300 ml) was added to a soln of $Zn(BH_4)_2$ in ether (326 ml) [prepared from a sat soln (0.69 M) of $ZnCl_2$ in ether (80 ml) and $NaBH_4$ (4 g) in ether (300 ml)][2] under ice-cooling, and the mixture was stirred for 30 min at the same temp. After the addition of water (33 ml), the mixture was stirred for *ca* 30 min and then $MgSO_4$ was added for drying. The resulting suspension was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel [hexane–EtOAc (4:1)] to give 12.71 g (73%) of the *syn*-β-hydroxy ester which contained a small amount of the *anti*-isomer (*syn*–*anti* = 25:1; ratio determined by 400 MHz NMR). IR (neat) 3480, 1725, 1710 cm^{-1}; NMR δ 1.10 (d, J = 7.1 Hz; C-2 Me), 1.46 (s; t-Bu), 4.34 (broad s, $W_{1/2}$ = 8.9 Hz; C-3 H). MS (FI) *m/z* 201 (MH^+).

To a suspension of LAH (5.3 g) in ether (200 ml) was added under ice-cooling a soln of the above obtained *syn*-β-hydroxy ester (18.49 g) in ether (50 ml), and the mixture was stirred for 1 hr at the same temp. After the successive addition of water (5.3 ml), 15% NaOH aq (5.3 ml), and water (15.9 ml) under ice-cooling, the mixture was stirred for *ca* 15 min at room temp and then Na_2SO_4 was added. The resulting suspension was filtered and the filtrate was concentrated to give 12.19 g (100%) of **10**. IR (CCl_4) 3620, 3380 cm^{-1}; NMR δ 0.87 (d, J = 7.1 Hz; C-2 Me), 4.24 (d, J = 3.4 Hz; C-3 H). MS (Found: 130.1014. Calc for $C_7H_{14}O_2$: 130.0994).

(*b*) Formation of **10** from **12** by $Zn(BH_4)_2$ reduction will be described elsewhere (see Ref. 2).

The compound **10** obtained by method *a* was found to be identical with **10** obtained by method *b*.

3,4-syn-3-*Hydroxy*-5-*trityloxy*-2-*pentanone* **13**

Trityl chloride (1.135 g) was added to a soln of **10** (480 mg) in pyridine (5 ml), and the mixture was stirred for 24 hr at room temp. The mixture was diluted with ether, washed with 10% HCl aq, sat $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$, and evaporated to give the crude trityl ether (1.517 g) which was used for the next step without further purification. NMR δ 0.90 (d, J = 6.8 Hz; Me), 4.22 (broad s; C-3 H).

Ozone was introduced into a soln of the crude trityl ether (320 mg) in MeOH (15 ml) for 3 min at − 78°. After the addition of Me_2S (5 ml), the mixture was allowed to warm to room temp, stirred for 1 hr, and then evaporated. Preparative silica gel TLC [hexane–ether (2:1)] of the residue afforded 175 mg (60% from **10**) of **13**, which was recrystallized from hexane-ether to give colorless prisms, m.p. 111–112°. IR (Nujol) 3490, 1700, 1590 cm^{-1}; NMR δ 0.62 (d, J = 7.1 Hz; C-4 Me), 2.17 (s; COMe), 3.13 (dd, J = 9.3, 5.6 Hz; C-5 Ha), 3.30 (dd, J = 9.3, 8.5 Hz; C-5 Hb), 3.34 (d, J = 4.6 Hz; OH), 4.53 (dd, J = 4.6, 2.1 Hz; C-3 H). (Found: C, 80.17; H, 7.05. Calc for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00%).

2,3-anti-3,4-syn-4-*Methyl*-5-*trityloxypentan*-2,3-diol **14**

To a soln of **13** (500 mg) in ether (10 ml) was added a soln of $Zn(BH_4)_2$ in ether (6 ml) under ice-cooling, and the mixture was stirred for 30 min. After the addition of water (0.6 ml), the mixture was stirred for *ca* 30 min and then $MgSO_4$ was added. The resulting suspension was filtered and the filtrate was concentrated. Preparative silica gel TLC [hexane–EtOAc (1:1)] of the residue gave 490 mg (97%) of **14** which contained a small amount of *syn*-diol **16** (*anti*-**14**-*syn*-**16** = 25:1; ratio determined by 400 MHz NMR). IR ($CHCl_3$) 3480, 1595 cm^{-1}; NMR δ 1.13 (d, J = 7.1 Hz; Me), 1.19 (d, J = 6.7 Hz; Me), 3.12 (dd, J = 9.0, 3.9 Hz; C-5 Ha), 3.24 (dd, J = 9.0, 4.8 Hz; C-5 Hb), 3.50 (m; C-3 H), 3.73 (m; C-2 H). MS (Found: 299.1657 (M^+–C_6H_5). Calc for $C_{19}H_{23}O_3$: 299.1648).

3,4-syn-3-*t-Butyldimethylsilyloxy-4-methyl-5-trityloxy-2-pentanone* **15**

Imidazole (1.09 g) and t-butylchlorodimethylsilane (1.21 g) were added to a soln of **13** (2.0 g) in DMF (6 ml) at room temp and the mixture was stirred for 21 hr. Imidazole (364 mg) and t-butylchlorodimethylsilane (403 mg) were again added and the resulting mixture was stirred for additional 23 hr. Water was added and the soln was extracted with ether. The extract was washed with sat NaCl aq, dried over $MgSO_4$, and evaporated. The residue was subjected to flash silica gel chromatography [hexane–ether (4:1)] to give 2.422 g of **15** and 162 mg of crude **15** which was purified by preparative silica gel TLC [hexane–ether (4:1)] to give 150 mg of **15** (total amount of **15**, 2.572 g; 99%). Recrystallization from MeOH–H_2O gave a crystalline compound, m.p. 82–84°. IR ($CHCl_3$) 1725, 1700. 1600 cm^{-1} NMR δ −0.16, −0.03 (each s; $SiMe_2$), 0.79 (s; Si^tBu), 0.86 (d, J = 6.8 Hz; C-4 Me), 2.09 (s; COMe), 4.12 (d, J = 3.7 Hz; C-3 H). (Found: C, 76.23; H, 8.40. Calc for $C_{31}H_{40}O_3Si$: C, 76.19; H, 8.25%).

2,3-syn-3,4-syn-4-*Methyl-5-trityloxypentan*-2,3-diol **16**

To a soln of **15** (510 mg) in toluene (10 ml) was added a soln of 10% Vitride in toluene (10 ml) at −78° under Ar, and the mixture was stirred for 3 hr at the same temp and then for 15 hr at room temp. After the addition of water and 10% HCl aq, the mixture was extracted with ether. The extract was washed with 10% HCl aq, sat $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$, and then evaporated. Preparative silica gel TLC [hexane–EtOAc (1:1)] of the residue gave 370 mg (94%) of **16** which contained a small amount of *anti*-diol **14** (*syn*-**16**–*anti*-**14** = 30:1; ratio determined by 400 MHz, NMR). IR ($CHCl_3$) 3530, 1595 cm^{-1}; NMR δ 0.97 (d, J = 7.1 Hz; Me), 1.13 (d, J = 6.4 Hz; Me), 3.19 (d, J = 5.4 Hz; C-5 H_2), 3.47 (m, C-3 H), 3.74 (m; C-2 H). MS (Found: 299.1669 (M^+–C_6H_5). Calc for $C_{19}H_{23}O_3$: 299.1648).

2,3-syn-3,4-syn-3-t-*Butyldimethylsilyloxy-4-methyl-5-trityloxy-2-pentanol* **17**

To a soln of **15** (200 mg) in toluene (10 ml) was added a soln of 10% Vitride in toluene (5 ml) at −78° under Ar, and the mixture was stirred for 15 min at the same temp. After the same work-up as described above, preparative silica gel TLC [hexane–ether (3:1)] of the crude products gave 152 mg (76%; 97% based on the reacted **15**) of **17** and 44 mg (22%) of the recovered **15**. Recrystallization of **17** from MeOH–H_2O gave colorless plates, m.p. 91–94°. IR ($CHCl_3$) 3570, 3450, 1600 cm^{-1}; NMR δ −0.16, 0.02 (each s; $SiMe_2$), 0.79 (s; Si^tBu), 0.92 (d, J = 6.8 Hz; Me), 1.13 (d, J = 6.4 Hz; Me), 3.51 (dd, J = 5.4, 2.9 Hz; C-3 H), 3.64 (m; C-2 H). (Found: C, 76.01; H, 8.49. Calc for $C_{31}H_{42}O_3Si$: C, 75.87; H, 8.63%).

2,3-anti-3,4-syn-2,3-O-*Isopropylidene-4-methyl-5-trityloxypropan*-2,3-*diol* **18**

2,2-Dimethoxypropane (2 ml) and a trace of TsOH were added to a soln of **14** (118 mg) in ether (2 ml) and the mixture was allowed to stand at room temp. After 20 min, sat $NaHCO_3$ aq was added and the mixture was washed with sat NaCl aq, dried over $MgSO_4$, and then evaporated. Preparative silica gel TLC [hexane–ether (2:1)] of the residue gave 129 mg (98%) of **18**. NMR δ 1.01 (d, J = 6.6 Hz; C-2 Me), 1.13 (d, J = 6.6 Hz; C-4 Me), 3.90 (dd, J = 8.3, 5.4 Hz; C-3 H), 4.06 (quintet, J = ~6 Hz; C-2 H). MS (FD) *m/z* 416 (M^+).

2,3-syn-3,4-syn-2,3-O-*Isopropylidene-4-methyl-5-trityloxypropan*-2,3-*diol* **19**

Using the same procedure as described above, **19** was obtained from **16** in 95% yield. NMR δ 1.01 (d, J = 6.8 Hz; C-4 Me), 1.17 (d, J = 5.9 Hz; C-2 Me), 3.68 (dd, J = 8.3, 4.4 Hz; C-3 H), 3.88 (dq, J = 8.3, 5.9 Hz; C-2 H). MS (FD) *m/z* 416 (M^+).

2,3-syn-(E)-3,4-Epoxy-2-*methylpentyl trityl ether* **21**

Mesitylenesulfonyl chloride (542 mg) was added to a soln of **14** (465 mg) and 4-dimethylaminopyridine (35 mg) in benzene (2 ml)-pyridine (2 ml), and the mixture was stirred for 5 days at room temp. After the addition of water, the mixture was extracted with ether. The extract was washed with 10% HCl aq, sat $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$, and evaporated. Preparative silica gel TLC [hexane–ether (1:1)] of the residue gave 593 mg (86%) of **20** and 36 mg (8%) of the recovered **14**. The sulfonate **20** was immediately used for the next step without further purification. NMR δ 0.98 (d, J = 7.1 Hz; Me), 1.20 (d, J = 6.1 Hz; Me), 2.31 (s; 4′-Me), 2.59 (2′,6′-2 × Me), 4.64 (quintet, J = ~6 Hz; C-2 H).

A suspension of **20** (290 mg) and K_2CO_3 (1 g) in MeOH (10 ml) was stirred for 1 hr at room temp. After filtration and evaporation, the residue was dissolved in ether and the ether soln was washed with sat NaCl aq, dried over Na_2SO_4, and then evaporated. The residue was chromatographed on silica gel [hexane–ether (4:1)] to give 165 mg (89%) of **21**. IR ($CHCl_3$) 1595 cm^{-1}; NMR δ 0.97 (d, J = 6.8 Hz; C-2 Me), 1.34 (d, J = 5.4 Hz; C-4 Me), 2.56 (dd, J = 7.6, 2.2 Hz; C-3 H), 2.95 (dq, J = 5.4, 2.2 Hz; C-4 H). Ms (Found: 358.1940. Calc for $C_{25}H_{26}O_2$: 358.1934).

2,3-anti-3,4-syn-2-*t-Butyldimethylsilyloxy-4-methyl-5-trityloxy-3-pentanol* **22**

Imidazole (111 mg) and t-butylchlorodimethylsilane (118 mg) were added to a soln of **14** (246 mg) in DMF (1.5 ml) under ice-cooling, and the mixture was stirred for 30 min at the same temp and then for 20.5 hr at room temp. Imidazole (67 mg) and t-butylchlorodimethylsilane (78 mg) were again added and the resulting mixture was stirred for additional 2 hr. After the addition of water, the soln was extracted with ether. The extract was washed with sat NaCl aq, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel [hexane–ether (9:1)] to give 300 mg (94%) of **22**. IR ($CHCl_3$) 3500, 1595 cm^{-1}; NMR δ 0.01, 0.03 (each s; $SiMe_2$), 0.85 (s; Si^tBu), 1.10 (d, J = 6.8 Hz; Me), 1.11 (d, J = 6.1 Hz; Me), 3.05 (dd, J = 9.0, 3.9 Hz; C-5 Ha), 3.17 (dd, J = 9.0, 5.1 Hz; C-5 Hb), 3.49 (dt like, J = ~5.5, 2 Hz; C-3 H), 3.79 (quintet, J = ~6 Hz; C-2 H), MS (FD) *m/z* 490 (M^+).

2,3-anti-(E)-3,4-Epoxy-2-*methylpentyl trityl ether* **23**

MsCl (0.17 ml) was added to a soln of **22** (210 mg) in pyridine (1 ml), and the mixture was stirred for 12 hr at room temp. After the addition of water, the mixture was extracted with ether. The extract was washed with 10% HCl aq, sat $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$, and then evaporated to give the crude mesylate (392 mg), which was used for the next step without further purification. NMR δ 0.02, 0.03 (each s; $SiMe_2$), 0.87 (s; Si^tBu), 1.02 (d, J = 7.1 Hz; Me), 1.20 (d, J = 6.4 Hz; Me), 2.93 (s; SO_2Me), 4.67 (dd, J = 6.6, 3.2 Hz; C-3 H).

n-$Bu_4NF \cdot 3H_2O$ (680 mg) was added to a soln of the crude mesylate (392 mg) in THF (2 ml), and the mixture was stirred for 1.5 hr at room temp. n-$Bu_4NF \cdot 3H_2O$ (680 mg) was again added and the mixture was stirred for additional 4.5 hr. After the addition of water, the mixture was extracted with ether. The extract was washed with sat $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$, and evaporated. Preparative silica gel TLC [hexane–ether (2:1)] of the residue gave 118 mg (77% from **22**) of **23**. IR ($CHCl_3$) 1595 cm^{-1}; NMR δ 0.99 (d, J = 7.1 Hz; C-2 Me), 1.30 (d, J = 5.1 Hz; C-4 Me), 2.68 (dd, J = 7.0, 2.2 Hz; C-3 H), 2.81 (dq, J = 5.1, 2.2 Hz; C-4 H). MS (Found: 358.1931. Calc for $C_{25}H_{26}O_2$: 358.1934).

2,3-syn-3,4-syn-2-*t-Butyldimethylsilyloxy-4-methyl-5-trityloxy-3-pentanol* **24**

Imidazole (178 mg) and t-butylchlorodimethylsilane (197 mg) were added to a soln of **16** (328 mg) in DMF (1.5 ml)

under ice-cooling, and the mixture was stirred for 30 min at the same temp and then 2.5 hr at room temp. After the same work-up as described in the preparation of **22**, the residue was chromatographed on silica gel [hexane–ether (9:1)] to give 401 mg (94%) of **24**. IR ($CHCl_3$) 3650, 1595 cm^{-1}; NMR δ − 0.04, 0.03 (each s; $SiMe_2$), 0.86 (s; Si^{t}Bu), 0.99 (d, J = 7.1 Hz; Me), 1.10 (d, J = 6.1 Hz; Me), 3.63 (quintet, J = 6.1 Hz; C-2 H). MS (FD) *m/z* 490 (M^+).

2,3-anti-(Z)-3,4-*Epoxy*-2-*methylpentyl trityl ether* **25**

Using the same procedure as described in the preparation of **23**, **24** (307 mg) was mesylated with MsCl (0.29 ml) in pyridine (1 ml) to give the crude mesylate (655 mg), which was used for the next step without further purification. NMR δ − 0.005, 0.03 (each s; $SiMe_2$), 0.84 (each s; Si^{t}Bu), 1.04 (d, J = 6.8 Hz; Me), 1.17 (d, J = 6.4 Hz; Me), 2.79 (s; SO_2Me), 4.66 (t, J = 4.6 Hz; C-3 H).

n-$Bu_4NF \cdot 3H_2O$ (1.2 g) was added to a soln of the crude mesylate (655 mg) in THF (3 ml) and the mixture was stirred for 3 hr at room temp. n-$Bu_4NF \cdot 3H_2O$ (1.2 g) was again added and the soln was stirred overnight. Water was added and the mixture was extracted with ether. The extract was washed with sat NaCl aq, dried over $MgSO_4$, and evaporated. Epoxidation was not completed in this case. K_2CO_3 (300 mg) was added to the residue in MeOH (2 ml) and the mixture was stirred for 30 min at room temp. After filtration and evaporation, the residue was dissolved in ether and the ether soln was washed with sat NaCl aq, dried over $MgSO_4$, and then evaporated. Preparative silica gel TLC [hexane–ether (2:1)] of the residue gave 217 mg (80% from **24**) of **25**. IR ($CHCl_3$) 1595 cm^{-1}; NMR δ 1.04 (d, J = 6.8 Hz; C-2 Me), 1.28 (d, J = 5.6 Hz; C-4 Me), 2.84 (dd, J = 9.3, 4.4 Hz; C-3 H), 3.06 (dq, J = 5.6, 4.4 Hz; C-4 H). MS (Found: 358.1914. Calc for $C_{25}H_{26}O_2$: 358.1934).

2,3-syn-(Z)-3,4-*Epoxy*-2-*methylpentyl trityl ether* **26**

Using the same procedure as described in the preparation of **23**, **17** (585 mg) was mesylated with MsCl (0.46 ml) in pyridine (2 ml) to give the crude mesylate (813 mg), which was used for the next step without further purification. NMR δ − 0.19, 0.03 (each s; $SiMe_2$), 0.78 (s; Si^{t}Bu), 0.92 (d, J = 6.8 Hz; Me), 1.37 (d, J = 6.3 Hz; Me), 2.90 (s; SO_2Me), 3.83 (dd, J = 5.9, 2.7 Hz; C-3 H), 4.61 (quintet, J = 6.3 Hz; C-2 H).

A mixture of the crude mesylate (813 mg) and n-$Bu_4NF \cdot 3H_2O$ (1.9 g) in THF (4 ml) was stirred for 4 hr at room temp. After usual work-up, preparative silica gel TLC [hexane–ether (3:2)] gave 418 mg (98%) of **26**. IR ($CHCl_3$) 1595 cm^{-1}; NMR δ 1.09 (d, J = 6.8 Hz; C-2 Me), 1.30 (d, J = 5.6 Hz; C-4 Me), 2.69 (dd, J = 9.3, 4.2 Hz; C-3 H), 3.10 (dq, J = 5.6 Hz, 4.2 Hz; C-4 H). MS (Found: 358.1964. Calc for $C_{25}H_{26}O_2$: 358.1934).

2,3-syn-3,4-syn-2,4-*Dimethyl*-3-*hydroxy*-5-*trityloxypentanal trimethylenedithioacetal* **27** *and the positional isomer* **28**

To a soln of 1,3-dithiane (377 mg) in THF (10 ml) was added to a 1.51 M soln of n-BuLi in hexane (2.02 ml) at − 20° under Ar and the soln was stirred for 2 hr at the same temp. Then, a soln of **21** (220 mg) in THF (3 ml) was added and the mixture was stirred for 2 hr at − 20° and then for one week at 5°. Water was added and the mixture was extracted with ether. The extract was washed with sat NaCl aq, dried over $MgSO_4$, and evaporated. Preparative silica gel TLC [hexane–EtOAc (4:1); developed three times] of the residue gave 34 mg of crude **21**, 199 mg (68%) of **27**, and 53 mg of crude **28**. The crude **21** was again subjected to preparative TLC [hexane–EtOAc (6:1); developed three times] to give 28 mg (13%) of the recovered pure **21**. The crude **28** was also subjected to preparative TLC [hexane–EtOAc (2:1); developed two times] to give 44 mg (15%) of pure **28**. **27**: IR ($CHCl_3$) 3590, 3480, 1600 cm^{-1}; NMR δ 1.08 (d, J = 6.8 Hz; Me), 1.09 (d, J = 6.8 Hz; Me), 3.89 (dd, J = 9.4, 5.4 Hz; C-3 H: + D_2O, t, J = 5.4 Hz), 4.10 (d, J = 4.9 Hz; C-1 H). MS (FD) *m/z* 478 (M^+). **28**: IR ($CHCl_3$) 3580, 3420, 1595 cm^{-1}; NMR δ 1.20 (d, J = 6.8 Hz; Me), 1.26 (d, J = 6.4 Hz; Me), 4.08 (broad: C-2 H: + D_2O, quintet, J = 6.4 Hz), 4.12 (d, J = 3.7 Hz; –SCHS–). MS (FD) *m/z* 478 (M^+).

2,3-syn-3,4-anti-2,4-*Dimethyl*-3-*hydroxy*-5-*trityloxypentanal trimethylenedithioacetal* **29** *and the positional isomer* **30**

Ring opening of **23** (235 mg) in THF (3 ml) with 2-lithio-1,3-dithiane [prepared from 1,3-dithiane (408 mg) in THF (10 ml) and a 1.51 M soln of n-BuLi in hexane (2.19 ml)] was carried out by the same procedure as described in the preparation of **27**. The crude product was subjected to preparative silica gel TLC [hexane–EtOAc (3:1); developed two times] to give 300 mg of a mixture of sulfur-containing compound and **23**, 137 mg (44%) of **29**, and 36 mg (15%) of **30**. The crude **23** was purified by preparative TLC [hexane–EtOAc (6:1); developed three times] to give 89 mg (38%) of pure **23**. **29**: IR ($CHCl_3$) 3590, 3480, 1600 cm^{-1}; NMR δ 0.80 (d, J = 6.8 Hz; Me), 1.08 (d, J = 7.1 Hz; Me), 3.88 (broad d, J = 8.8 Hz; C-3 H: + D_2O, dd, J = 8.8, 2.4 Hz), 4.16 (d, J = 8.5 Hz; C-1 H). MS (FD) *m/z* 478 (M^+). **30**: IR ($CHCl_3$) 3580, 3420, 1595 cm^{-1}; NMR δ 1.20 (d, J = 6.6 Hz; Me), 1.25 (d, J = 7.1 Hz; Me), 4.02 (broad; C-2 H: + D_2O, dq, J = 6.6, 6.4 Hz), 4.25 (d, J = 3.7 Hz; –SCHS–). MS (FD) *m/z* 478 (M^+).

2,3-syn-3,4-anti-5-*Benzyloxy*-2,4-*dimethyl*-3-*hydroxypentanal trimethylenedithioacetal* **34** *and the positional isomer* **35**

Ring opening of **33** (240 mg) (prepared in the same way as described in the preparation of the trityl ether **23**) in THF (3 ml) with 2-lithio-1,3-dithiane [prepared from 1,3-dithiane (724 mg) in THF (10 ml) and a 1.45 M soln of n-BuLi in hexane (4.0 ml)] was carried out by the same procedure as described in the preparation of **27**. Reaction was completed within 68 hr at 5°. Preparative silica gel TLC [hexane–EtOAc (2:1)] of the products gave 264 mg (70%) of **34** and 49 mg (13%) of **35**. **34**: IR ($CHCl_3$) 3590, 3480, 1600 cm^{-1}; NMR δ 0.83 (d, J = 7.1 Hz; Me), 1.11 (d, J = 6.8 Hz; Me), 3.93 (dt, J = 8.8, 2.4 Hz; C-3 H: + D_2O, dd, J = 8.8, 2.4 Hz), 4.21 (d, J = 8.3 Hz; C-1 H). MS (Found: 326.1381. Calc for $C_{17}H_{26}O_2S_2$: 326.1376). **35**: IR ($CHCl_3$) 3580, 3420, 1600 cm^{-1}; NMR δ 1.20 (d, J = 7.3 Hz; Me), 1.30 (d, J = 6, 4 Hz; Me), 4.21 (quintet, J = 6.4 Hz; C-2 H: + D_2O, quintet, J = 6.4 Hz), 4.32 (d, J = 3.7 Hz; –SCHS–). MS (Found: 326.1381. Calc for $C_{17}H_{26}O_2S_2$: 326.1376).

2,3-anti-3,4-anti-2,4-*Dimethyl*-3-*hydroxy*-5-*trityloxypentanal trimethylenedithioacetal* **31**

Ring opening of **25** (197 mg) in THF (3 ml) with 2-lithio-1,3-dithane [prepared from 1,3-dithiane (340 mg) in THF (10 ml) and a 1.51 M soln of n-BuLi in hexane (1.82 ml)] was carried out by the same procedure as described in the preparation of **27**. Reaction was completed within 64 hr at 5° in this case. The crude **31** was subjected to preparative silica gel TLC [hexane–EtOAc (2:1)] to give 252 mg (96%) of **31**, which was recrystallized from hexane–ether to give colorless prisms, m.p. 134–136°. IR ($CHCl_3$) 3590, 3480, 1600 cm^{-1}; NMR δ 0.85 (d, J = 7.1 Hz; Me), 1.30 (d, J = 7.1 Hz; Me), 3.50 (dt, J = 9.0, 3.2 Hz; C-3 H: + D_2O, dd, J = 9.4, 3.3 Hz), 4.68 (d, J = 2.4 Hz; C-1 H). (Found: C, 72.75; H, 7.11. Calc for $C_{29}H_{34}O_2S_2$: C, 72.78; H, 7.16%).

2,3-anti-3,4-syn-2,4-*Dimethyl*-3-*hydroxy*-5-*trityloxypentanal trimethylenedithioacetal* **32**

Ring opening of **26** (226 mg) in THF (3 ml) with 2-lithio-1,3-dithiane [prepared from 1,3-dithiane (390 mg) in THF (10 ml) and a 1.51 M soln of n-BuLi in hexane (2.09 ml)] was carried out by the same procedure as described in the preparation of **27**. Reaction was almost finished within 64 hr at 5°. The crude product was subjected

to preparative silica gel TLC [hexane–EtOAc (2:1)] to give 298 mg of a mixture of sulfur-containing compound and **26** and 248 mg (82%; 99% based on the reacted **26**) of **32**. The crude **26** was purified by preparative TLC [hexane–EtOAc (6:1); developed three times] to give 39 mg (17%) of pure **26**. Recrystallization of **32** from hexane–ether gave colorless needles, m.p. 138–140°. IR ($CHCl_3$) 3590, 3475, 1595 cm^{-1}; NMR δ 0.97 (d, J = 7.1 Hz; Me), 0.98 (d, J = 7.1 Hz; Me), 3.84 (broad d, J = 10.0 Hz; C-3 H: + D_2O, dd, J = 10.0, 1.7 Hz), 4.65 (d, J = 2.4 Hz; C-1 H). (Found: C, 72.77; H, 7.19. Calc for $C_{29}H_{34}O_2S_2$: C, 72.78; H, 7.16%).

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