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AN IMPROVED, PRACTICAL SYNTHESIS OF THE DERIVATIVES OF 1-O-ACETYL-2-DEOXY-2-HYDROXYMETHYL-D-ERYTHROOXETANOSE, A KEY SUGAR MOIETY FOR THE SYNTHESIS OF OXETANOSYL-N-GLYCOSIDE+

Masashi Nagai,[1] Kuniki Kato,[1*] Tomohisa Takita,[1] Shigeru Nishiyama,[2] and Shousuke Yamamura[2]

1. Research Laboratories, Pharmaceuticals Group, Nippon Kayaku Co. Ltd.,3-31-12 Shimo, Kita-ku, Tokyo 115, Japan
2. Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223, Japan

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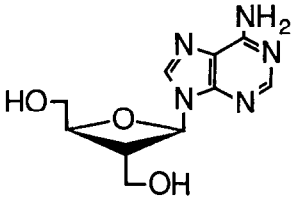
Abstract ---Intramolecular cyclization of the *cis*-epoxy-alcohol (**6**) with KOH in aq.DMSO provided predominantly the oxetane compound (**7**), which on oxidation followed by Baeyer-Villiger reaction gave 1-O-acetyl-D-erythrooxetanoses.

Interest has recently been growing in the synthesis of new nucleoside analogs with potential anti-retroviral activity, due to the emergence of the acquired immunodeficiency syndrome (AIDS) as a significant medical problem. In 1986 a remarkably unusual nucleoside, oxetanocin (**1**), was isolated from the fermentation broth of ***Baccillus megaterium*** , and the structural investigation and X-ray crystallographic analysis revealed that oxetanocin was the first natural nucleoside having an oxetanose as a sugar moiety.[1] More interestingly (**1**) and its analogues bearing other nucleic bases (i.e., guanine, 2,6-diaminopurine in place of adenine) showed potent antiviral activities against Herpes simplex virus I and II, Human cytomegalo virus, and HIV.[2]

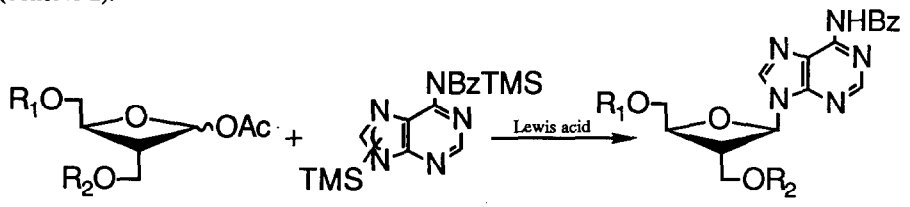


Oxetanocin (**1**)

From the biological and structural points of view, (**1**) has attracted a great deal of interest from synthetic organic chemists. Thus far, three syntheses of (**1**) have been reported. The success of the first synthesis was based on the formation of an oxetane ring by an intramolecular oxirane ring opening with allyloxycarbanion.[3] In a second synthesis, developed by the Abbott group, an oxetane was constructed via Wolff rearrangement of the α-diazoketo compound to give the ring contracted compound.[4] The third synthesis was developed in our laboratory.[5] Our strategy was conceptually different from other two routes, and involved construction of the

+ Oxetanosyl is taken to refer to the four membered sugar ring, analogous to furanosyl.

nucleoside analogue by N-glycosidation of a silylated purine with 1-O-acetyl-D-oxetanose (**2**) with the aid of Lewis acid (Scheme **1**).



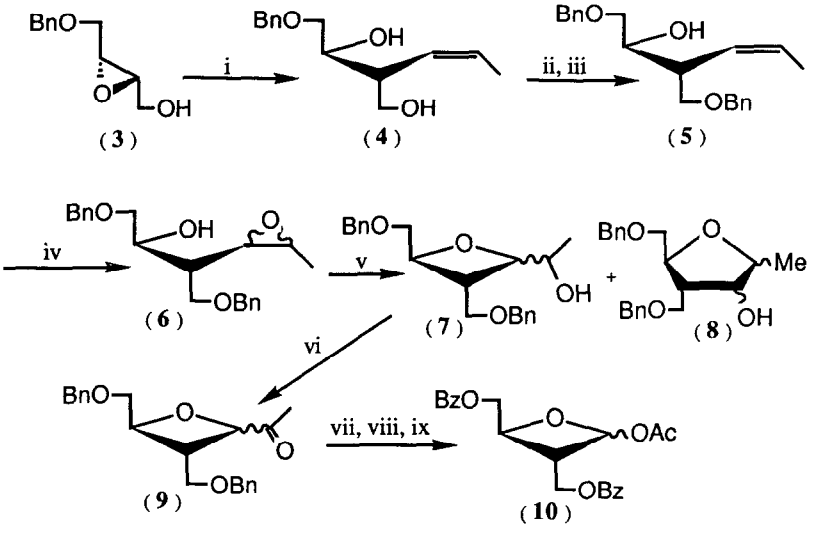
R_1,R_2 = acyl groups

(**2**)

Scheme **1**

This methodology has the advantage that it can be adapted to make oxetanocin analogues having various nucleic bases. In a large scale preparation of 1-O-acetyl-2-deoxy-2-hydroxymethyl-D-erythro-oxetanose derivatives (**2**), however, there are some disadvantages to the use of the reported method, i.e., the multi-step synthesis (17 steps from **3**), low overall yield (1.8%) and anhydrous C_1 unit homologation reaction.[5]

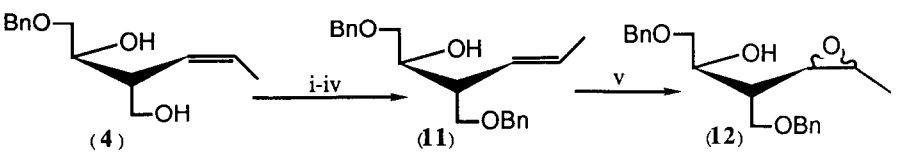
We now report an improved, practical synthesis of (**2**) starting from the same optically active epoxy-alcohol(**3**)[6], which can be made from (Z)-butene-1,4-diol monobenzyl ether by Sharpless oxidation in a large scale (Scheme **2**)



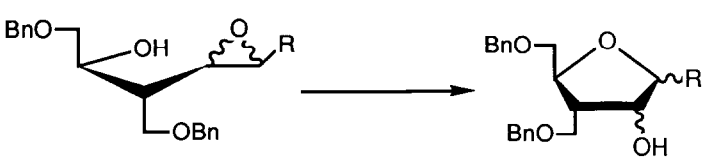
Scheme **2**. Reagents : i, MgBr, CuI; ii, $PhCH(OMe)_2$, pTsOH; iii, DIBAL-H; iv, mCPBA; v, KOH, aq.DMSO; vi, SO_3.py, Et_3N, DMSO; vii, mCPBA; viii, H_2/Pd-black; ix, BzCl, pyridine

Treatment of (**3**) with (Z)-1-propenylmagnesium bromide in the presence of CuI in THF-ether gave the desired (Z)-olefin-alcohol (**4**) in 74% yield.[7] **The geometry of the double bond in (4) was very**

significant to a cyclization mode. The primary hydroxyl group was then selectively protected with benzyl group by benzylidenation followed by reduction with DIBAL-H (diisobutylaluminum hydride) to afford the dibenzyl-olefin (**5**) in 92% overall yield. Epoxidation of (**5**) with *m*-chloroperbenzoic acid gave the *cis*-epoxide (**6**) as a 2:3 mixture of diastereomers in 86% yield, which was used in the next reaction without separation. The preparation of our key intermediate, the oxetane-alcohol (**7**), was achieved by utilizing Masamune's protocol.[8] Thus, reaction of (**6**) with KOH in 75% aq.DMSO gave the oxetane-alcohol (**7**) in 62% yield along with the oxolanol (**8**) in 9% yield. Compound (**7**) was then oxidized with SO_3-pyr complex- DMSO to give a 4:5 mixture of the acetyl-oxetane (**9**) in 87% yield. Finally, the mixture of each stereoisomer of (**9**) was converted to 1-O-acetyl-α and β-D-oxetanose dibenzoates (**10**) in 3 steps, i.e., Baeyer-Villiger reaction, hydrogenolysis, and benzoylation, in 78% overall yield. As both isomers could be available for the N-glycosidation, it was not necessary to separate each isomer.[5] Thus, 1-O-acetyl- α and β-D-oxetanoses could be synthesized in 9 steps from (**3**) in 27% overall yield. We believe that the route described herein can be of practical utility in the preparation of various oxetanocin analogues. The key feature of our methodology is the oxetane ring formation by intramolecular cyclization of 3,4-epoxy-alcohols. Masamune[8] and Moulines[9] investigated the direction of opening of oxirane ring of 3,4-epoxy alcohols to give 2-oxetanemethanols (4-exo opening) and/or 3-oxolanols (5-endo opening) using KOH-aqDMSO and Bu_3SnOMe, respectively. However, it is difficult to deduce a general principle of the direction of opening from their experimental results. So, we therefore studied the direction of opening of our compounds under the same reaction conditions. The following results were obtained; neither the *trans*-epoxide (**12**), derived from (**4**) (Scheme 3), nor the terminal-epoxide (**13**) afforded any oxetane compound, but oxolanols (**14**) and (**15**) were obtained in 79% and 55% yields, respectively.



Scheme 3. Reagents : i, $PhCH(OMe)_2$, pTsOH; ii, mCPBA; iii, K-tBuO, HMDS; iv, DIBAL-H; v, mCPBA.

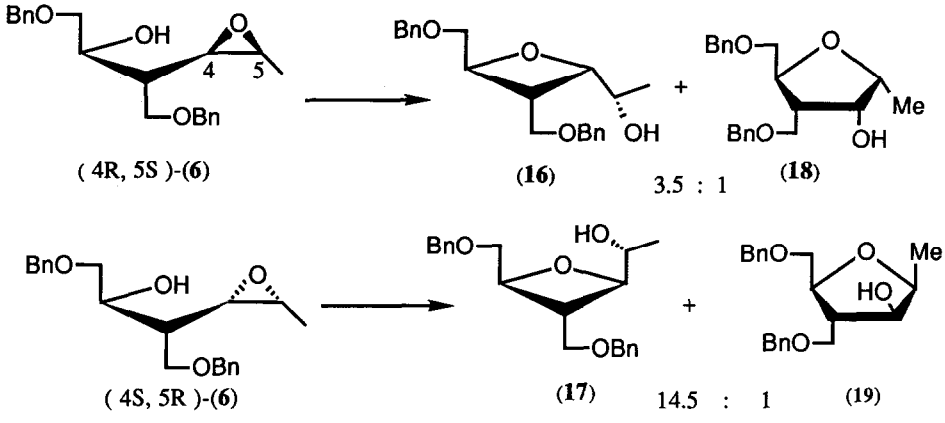


(**12**) R=Me (**14**) R=Me

(**13**) R=H (**15**) R=H

Then, to investigate an effect of the stereochemistry of an oxirane ring of the *cis*-epoxide (**6**) on a direction of opening, each stereoisomer of (**6**) was subjected to the reaction. Interestingly, (4R, 5S)-(**6**) provided (**16**) and

(**18**) in a ratio of 3.5:1 in 66% and on the other hand, from (4S, 5R)-(**6**), (**17**) and (**19**) were afforded in a ratio of 14.5:1 in 61% (Scheme 4).[10]



Scheme 4

Experimental

^{1}H N.m.r. spectra were recorded at 200 MHz with Gemini-200 (Varian) using $CDCl_3$ as a solvent and Me_4Si as an internal standard. Mass spectra were recorded in the *e.i.* mode with HITACHI M-80 Mass Spectrometer. I.r. spectra were recorded with HITACHI 260-10 Infrared Spectorophotometer. T.l.c. was performed on precoated plates of Silica Gel 60 F_{254} (E. Merck, Darmstadt). Detection was done by u.v. (254 nm) or spraying the plates with a solution of 10% phosphomolybdic acid-ethanol, followed in the latter case by heating on an electric plate. Flash chromatography on silica gel was effected using silica gel (200mesh) Fuji Devison Chem. Dichloromethane and toluene were distilled over calcium hydride. THF and diethyl ether were distilled over sodium benzophenone ketyl prior to use. Reactions were carried out under nitrogen atmosphere unless otherwise stated. Solvents were evaporated under reduced pressure.

(Z)-(2R,3S)-4-*Benzyloxy*-2-(*1-propenyl*)-1,3-*butanediol* (**4**).

To a stirred suspension of magnesium (7.7g, 315.8mmol) in THF (250ml) was added dropwise 1-bromo-1-propene (38.2g, 315.8mmol). The reaction mixture was heated at reflux until all magnesium was consumed. Then, to a stirred suspension of cuprous iodide (5.7g, 30.1mmol) in diethyl ether (700ml) was added dropwise the Grignard reagents prepared above at 0°C. After the reaction mixture was stirred at 0°C for 20min and then at -30°C for 20 min, (2S,3R)-2,3-epoxy-4-benzyloxy-1-butanol (**3**) (15.0g, 75.2mmol) was added. The black heterogeneous solution was stirred at -30°C for 4 h. The reaction mixture was partitioned between ether and sat. NH_4Cl that had been basified to pH8 by addition of concentrated NH_4OH. The aqueous layer was extracted with ether (2x200ml). The combined ethereal extract was washed with brine and the solvent was removed. The resulting residue was dissolved in MeOH (100ml) and treated with sodium metaperiodate (7.0g, 33.0mmol) in water (250ml) at 0°C for 1 h. The reaction mixture was diluted with AcOEt (500ml) and the organic solution was washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel

with $CHCl_3$-MeOH (30:1) to give (**4**) (13.16g, 74%); *m/z* 237 (M^++1) (Found 237.1473. $C_{14}H_{21}O_3$ requires 237.1489); γ_{max}(NaCl): 3400, 1655, 1610, 1100, 1030, and 910cm^{-1}; δ_H 1.64 (3H, dd, *J* 1.8 and 6.8Hz), 2.76 (1H, ddd, *J* 4.0, 6.0, and 11.0Hz), 3.47 (2H, d, *J* 6.0Hz), 3.68 (1H,dd, *J* 5.7 and 10.8Hz), 3.71 (1H, dd, *J* 5.7 and 10.8Hz), 4.06 (1H, td, *J* 5.7 and 4.0Hz), 4.54 (2H, s), 5.45 (1H, qdd, *J* 1.8, 11.0 and 11.0Hz), 5.73 (1H, qd, *J* 6.8 and 11.0Hz), and 7.33 (5H, complex).

(Z)-(2S,3R)-1-*Benzyloxy*-3-*benzyloxymethyl*-4-*hexen*-2-*ol* (**5**).

A mixture of (**4**) (13.2g, 55.7mmol), benzaldehyde dimethyl acetal (17.0g, 111.4mmol) and p-toluenesulfonic acid·H_2O (3.2g, 16.7mmol) in DMF (250ml) was stirred at room temperature for 16h. The reaction mixture was diluted with AcOEt (500ml) and the solution was washed with water, brine dried (Na_2SO_4), and evaporated. To the resulting residue in toluene (250ml) was added dropwise DIBAL-H (130ml, 1.5M solution in toluene, 195mmol) at -60°C and the reaction solution was stirred for 10h at -60 °C. After this excess of DIBAL-H was destroyed with MeOH (50ml) and 1N-NaOH (150ml), the reaction mixture was diluted with AcOEt (500ml). The organic solution was washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (8:1) to furnish (**5**) (16.8g, 92%); *m/z* 327 (M^++1) (Found 327.1962. $C_{21}H_{27}O_3$ requires 327.1958); γ_{max}(NaCl): 3450, 1660, 1610 and 1100cm^{-1}; δ_H 1.62 (3H, dd, *J* 1.6 and 6.6Hz), 2.67 (1H, d, *J* 3.0Hz), 2.86 (1H, dddd, *J* 3.3, 5.0, 7.1 and 11.0Hz), 3.45 (2H, d, *J* 5.6Hz), 3.50 (1H, dd, *J* 5.0 and 9.2Hz), 3.60 (1H, dd, *J* 7.1 and 9.2Hz), 4.12 (1H, tdd, *J* 5.6, 3.0 and 3.3Hz),.4.50 (2H, s), 4.52 (2H, s), 5.49 (1H, qdd, *J* 1.6, 11.0, and 11.0Hz), 5.67 (1H, qd, *J* 6.6 and 11.0Hz), and 7.33 (10H, complex).

(2S,3R)-1-*Benzyloxy*-3-*benzyloxymethyl*-4,5-cis-*epoxyhexan*-2-*ol* (**6**).

A mixture of (**5**) (16.8g, 51.2mmol), *m*-chloroperbenzoic acid (14.9g, 92.2mmol) and $NaHCO_3$ (10g) in dichloromethane (300ml) was stirred at room temperature for 17h. After the reaction mixture was stirred with 10% aq.$NaHSO_3$ (50ml) for 30min at 0 °C, the organic solution was washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (2.5:1) to provide (**6**) (15.1g, 86%); *m/z* 342 (M^+) (Found 342.1852. $C_{21}H_{26}O_4$ requires 342.1830); γ_{max}(NaCl): 3450, 1610, 1100, and 860cm^{-1}. (4R,5S)-(**6**) and (4S,5R)-(**6**) were separated on preparative silica gel TLC with hexane-AcOEt (2.5:1) in a ratio of 3:2. The absolute stereochemistry of oxirane ring of each isomer was determined by converting to the known optically active compound (**9**)[5] via (**16**) and (**17**), respectively.

(4R,5S)-(**6**); δ_H 1.23 (3H, d, *J* 5.6Hz), 1.65 (1H, m), 3.17 (2H, complex), 3.47 (2H, s), 3.64 (1H, dd, *J* 3.4 and 9.2Hz), 3.80 (1H, dd, *J* 5.8 and 9.2Hz), 4.16 (1H, td, *J* 5.1 and 6.8Hz), 4.53 (4H, s) and 7.32 (10H, complex).

(4S,5R)-(**6**); δ_H 1.25 (3H, d, *J* 5.5Hz), 1.74 (1H, m), 3.03 (1H, qd, *J* 5.6 and 4.5Hz), 3.14 (1H, dd, *J* 9.4 and 4.5Hz), 3.60 (4H, complex), 4.23 (1H, td, *J* 3.5 and 7.6Hz), 4.49 (2H, s), 4.56 (2H, s), and 7.33 (10H, complex).

General procedure for intramolecular cyclization of epoxy-alcohols..

A mixture of epoxy-alcohol (15mmol) and KOH (150mmol) in DMSO (100ml) and water (33ml) was heated under reflux for 1h. The reaction mixture was diluted with water and extracted with AcOEt. The organic solution was washed with water, brine, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed on silica gel with hexane-AcOEt (2:1).

(**7**); *m/z* 342(M^+) (Found 342.1857. $C_{21}H_{26}O_4$ requires 342.1830);. γ_{max}(NaCl) 3430, 1600, 1100, and 980 (oxetane ring)cm^{-1}.

(**8**); *m/z* 342(M^+) (Found 342.1841. $C_{21}H_{26}O_4$ requires 342.1830); γ_{max}(NaCl) 3420, 1610, and 1110cm^{-1}.

(**14**); *m/z* 342(M^+) (Found 342.1850. $C_{21}H_{26}O_4$ requires 342.1830); γ_{max}(NaCl) 3420, 1610, and 1110cm^{-1}.

(**15**); *m/z* 328(M^+) (Found 328.1577. $C_{20}H_{24}O_4$ requires 328.1562); γ_{max}(NaCl) 3420, 1605, and 1110cm^{-1}.

(**16**) prepared from (4R,5S)-(**6**); δ_H 1,14 (3H, d, *J* 6.5Hz), 3.21 (1H, dddd, *J* 7.0, 7.2, 7.8, and 8.5Hz), 3.67 (2H, d, *J* 5.0Hz), 3.70 (1H, dd, *J* 7.8 and 9.7Hz), 3.80 (1H, dd, *J* 7.2 and 9.7Hz), 4.04 (1H, qd, *J* 6.5 and 1.3Hz), 4.45 (1H, dd, *J* 5.0 and 8.5Hz), 4.49 (2H, s), 4.63 (2H, s), 4.64 (1H, dd, *J* 1.3 and 7.0Hz), and 7.34 (10H, complex).

(**17**) prepared from (4S,5R)-(**6**); δ_H 1.12 (3H, d, *J* 6.6Hz), 3.14 (1H, tdd, *J* 6.2, 6.4, and 6.6Hz), 3.54 (1H, dd, *J* 3.8 and 11.3Hz), 3.60 (2H, d, *J* 6.2Hz), 3.66 (1H, dd, *J* 2.9 and 11.3Hz), 3.80 (1H, qd, *J* 6.6 and 4.4Hz), 4.26 (1H, dd, *J* 6.6 and 4.4Hz), 4.52 (2H, s), 4.60 (1H, s), 4.62 (1H, s), 4.65 (1H, ddd, *J* 2.9, 3.8, and 6.4Hz), and 7.35 (10H, complex).

(**18**); δ_H 1.27 (3H, dd, *J* 1.8 and 6.3 Hz), 2.36 (1H, m), 3.5-3.7 (5H, complex), 3.8-4.1 (2H, complex), 4.52 (2H, s), 4.56 (1H, s), 4.58 (1H, s), and 7.32 (10H. complex).

(**19**); δ_H 1.26 (3H, d, *J* 6.2Hz), 2.50 (1H, m), 3.4-3.7 (5H, complex), 3.94 (2H, complex), 4.48 (1H, s), 4.52 (1H, s), 4.62 (2H, s), and 7.32 (10H, complex).

(3R,4S)-3,4-*Bis* (*benzyloxymethyl*)-2-*acetyloxetane* (**9**).

To a solution of (**8**) (3.0g, 8.7mmol) and triethylamine (18.5g, 183.0mmol) in DMSO (50ml) was added dropwise sulfurtrioxide pyridine complex (8.8g, 55.0mmol) in DMSO (50ml). The reaction mixture was stirred at room temperature for 2h. The dark brown solution was diluted with water (100ml) and extracted with AcOEt (2x100ml). The extract was washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (3:1) to afford (**9**) (2.6g, 87%); *m/z* 340(M^+) (Found 340.1694. $C_{21}H_{24}O_4$ requires 340.1673.); γ_{max}(NaCl): 1715 ($COCH_3$), 1605, 1130, 1100, 1030, and 990 (oxetane ring)cm^{-1}.

(2S,3R,4S)-(**9**) prepared from (**16**); δ_H 2.22 (3H, s), 3.27 (1H, tdd, *J* 3.7, 5.8, and 9.4Hz), 3.49 (2H, d, *J* 3.9Hz), 3.70 (2H, d, *J* 3.7Hz), 4.36 (1H, d, *J* 11.7Hz), 4.43 (1H, d, *J* 11.7Hz), 4.88 (1H, td, *J* 3.9 and 5.8Hz), 4.95 (1H, d, *J* 9.4Hz), and 7.26 (10H, complex). The physical properties of this product were identical with those reported.[5]

(2R,3R,4S)-(**9**) prepared from (**17**); δ_H 2.23 (3H, s), 3.12 (1H, tdd, *J* 5.5, 6.1, and 6.7Hz), 3.52 (1H. dd, *J* 3.3 and 15.2Hz), 3.68 (1H, dd, *J* 3.1 and 15.2Hz), 3.68 (2H, d, *J* 5.5Hz), 4.56 (2H, s), 4.57 (1H, s), 4.59 (1H, s), 4.60 (1H, ddd, *J* 3.1, 3.3, and 6.1Hz), 4.77 (1H, d, *J* 6.7Hz), and 7.32 (10H, complex). The physical properties of this product were identical with those reported.[5]

1-O-*Acetyl*-2-*deoxy*-2-*hydroxymethyl*-D-*erythrooxetanose dibenzoates* (**10**).

A mixture of (**9**) (5.6g, 16.3mmol), *m*-chloroperbenzoic acid (5.6g, 32.7mmol) and $NaHCO_3$ (6.8g) in dichloromethane (100ml) was stirred at room temperature for 24h. After this excess of m-chloroperbenzoic acid was destroyed with 10% aq.$NaHSO_3$ (200ml), the organic layer was washed with water, brine, dried (Na_2SO_4), and evaporated. The resulting residue in EtOH (100ml) was hydrogenolized in the presence of Pd-black (100mg) with H_2 for 5h. The reaction mixture was filtered through Celite bed and the filtrate was evaporated to dryness. To a solution of the residue in dichloromethane (200ml) and pyridine (48.9g, 620mmol) was added benzoyl chloride (38.8g,276mmol) at 0°C. The reaction mixture was stirred at room temperature for 8h and then diluted with ice-water (300ml). The organic solution was washed with water,brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (4:1) to yield (**10**) (4.9g, 78%); *m/z* 325 (M^+-59) (Found 325.1049. $C_{19}H_{17}O_5$ requires 325.1074.); γ_{max}(NaCl): 1750(sh), 1720, 1600, and 985 (oxetane ring)cm^{-1}..

(E)-(2S,3R)-1-*Benzyloxy*-3-*benzyloxymethyl*-4-*hexen*-2-*ol* (**11**).

A mixture of the benzylidene acetal of (**4**) (1.87g, 5.75mmol), *m*-chloroperbenzoic acid (1.59g, 9.20mmol), and $NaHCO_3$ (1.45g) in dichloromethane (65ml) was stirred at room temperature for 7h. After the reaction mixture was stirred with 10% aq.$NaHSO_3$ (20ml) for 30 min at 0°C, the organic solution was washed with water, brine, dried (Na_2SO_4), and evaporated to dryness. To a solution of the residue (1.56g) and 18-crown-6 (0.25g, 0.96mmol) in dry DMF (20ml) was added potassium tert-butoxide (1.65g, 14.70mmol) and hexamethyldisilane (2.15g, 14.69mmol) in one portion. The reaction mixture was stirred at 60°C for 2hr and then poured into ice-water(50ml) and extracted with AcOEt (2x50ml). The organic solution was washed with water, brine, dried (Na_2SO_4), and evaporated to dryness. To a solution of this residue in dry toluene (15ml) was added dropwise DIBAL-H (6.16ml,1.5Msolution in toluene, 9.24mmol) at -60°C and the reaction mixture was stirred for 4.5 hr at -50°C. After this excess of DIBAL-H was destroyed with MeOH (5ml) and 1N-NaOH (50ml), the reaction mixture was extracted with AcOEt (2x100ml). The organic extract was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (8:1) to give (**11**) (0.5g, 29%); *m/z* 327 (M^++1) (Found 327.1950. $C_{21}H_{27}O_3$ requires 327.1958.);.δ_H 1.68 (3H, d, *J* 4.6Hz), 2.43 (1H, m), 3.47 (2H, s), 3.56 (1H, dd, *J* 5.2 and 9.2Hz), 3.61 (1H, dd, *J* 6.8 and 9.2Hz), 4.04 (1H, m), 4.50 (2H, s), 4.51 (1H, d, *J* 11.9Hz), 4.56 (1H, d, *J* 11.9Hz), 5.47 (1H, dd, *J* 5.2 and 15.4Hz), 5.58 (1H, qd, *J* 4.6 and 15.4Hz), and 7.32 (10H, complex).

(2S,3R)-1-*Benzyloxy*-3-*benzyloxymethyl*-4,5-trans-*epoxyhexan*-2-*ol* (**12**).

A mixture of (**11**) (486.9mg, 1.49mmol), *m*-chloroperbenzoic acid and $NaHCO_3$ (380mg) in dichloromethane (15ml) was stirred at room temperature for 28hr. The reaction mixture was stirred with 10%aq.$NaHSO_3$ (2ml) for 30 min and extracted with dichloromethane (2x50ml). The extract was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (3:1) to give (**12**) (409.4mg, 80%); *m/z* 342 (M^+) (Found 342.1848. $C_{21}H_{26}O_4$ requires 342.1830.).

(2S,3R)-1-*Benzyloxy*-3-*benzyloxymethyl*-4,5-*epoxypentan*-2-*ol* (**13**).

Compound (**13**) was prepared from (**3**) in the same manner as for (**6**), using vinyl magnesium bromide instead of 1-propenyl magnesium bromide in 43% overall yield; *m/z* 328(M^+) (Found 328.1571. $C_{20}H_{24}O_4$ requires 328.1562); γ_{max}(NaCl) 3450, 1605, 1505, 1240, 1090 and 1025cm^{-1}.

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