Stereoselective Synthesis of (±)-Ireland Alcohol Using Titanium-Mediated [2,3]Wittig Rearrangement Product as a Starting Material

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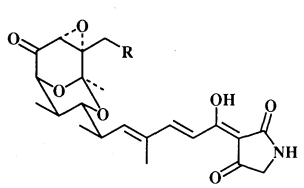
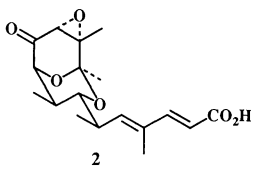
The synthesis of (±)-Ireland alcohol, a key intermediate for the synthesis of tirandamycin A, was achieved in a straightforward manner by using isopropyl (2*R**, 3*S**, 4*E*)-6-benzyloxy-2-hydroxy-3-methyl-4-hexenoate as a starting material, which was readily obtained by the [2,3]Wittig rearrangement of isopropyl [(*E*)-1-benzyloxymethyl-2-butenyloxy]acetate via its titanium enolate.

Since 1970's, some members of 3-acyltetramic acids, tirandamycin A (**1a**),[1] tirandamycin B (**1b**),[2] streptolydigin,[3] nocamycin,[4] Bu-2313 A,[5] and Bu-2313 B,[5] have aroused the interest of synthetic organic chemists because of their significant biological activities and unique structures, which are characterized by the presence of a 3-(2,4-alkadienoyl)tetramic acid moiety linked to a functionalized 2,9-dioxabicyclo[3.3.1]nonane ring system carrying four contiguous asymmetric centers. Tirandamycin A (**1a**)[6] isolated from the culture broth of *Streptomyces tirandis sp. n.*, has a fundamental structural feature of this class of compounds and shows potent inhibition for bacterial RNA polymerase in bacterial cell-free systems and interference with oxidative phosphorylation in rat liver mitochondria. Thus a number of synthetic efforts directed toward **1a** have been reported,[7] including some successful total syntheses.[7j,k,m,n] In 1981, Ireland et al. reported the synthesis of tirandamycic acid (**2**),[7b] the degradation product of **1a**, wherein multistep-transformation of D-glucose into an intermediary alcohol [Ireland alcohol (**3**)] was carried out. Since the compound **3** has four consecutive asymmetric centers and a bicyclic acetal structure common to 3-acyltetramic acids, development of an efficient synthetic method of **3** is considered to contribute the chemistry of this field.



1a: R = H Tirandamycin A
1b: R = OH Tirandamycin B



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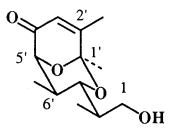
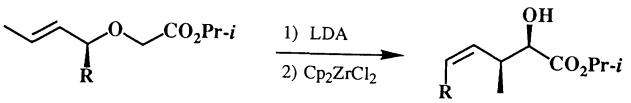


3: Ireland alcohol

Recently we reported that zirconium-mediated [2,3]-Wittig rearrangement of isopropyl [(2*E*)-2-alkenyloxy]acetates (**4**) proceeded with high *syn*, *Z*-selectivity,[8,9] and showed that the products **5** could serve as a useful starting material for the stereoselective construction of segments of the type R[CH(CH_3)CH(OH)]$_2$R′, biogenetically derived from propionic acid.[10] However it was further considered that, if both the terminal groups (R and R′) bore different type of oxygen functionalities, the potentiality of this segment as a building block for the synthesis of various kind of polyoxo compounds including tirandamycin family would increase. Thus we examined rearrangement of isopropyl [(*E*)-1-benzyloxymethyl-2-butenyloxy]acetate (**6**) bearing benzyloxyl group on the side chain of alkenyl moiety. Here we describe the stereoselectivity in the [2,3]Wittig rearrangement of **6**[11a] and synthesis of Ireland alcohol (**3**)[11b] by using the rearrangement product as a starting material in detail.



4: R = alkyl
6: R = $BnOCH_2$

5

Results and Discussion

[2.3]Wittig Rearrangement of Isopropyl [(*E*)-1-Benzyloxymethyl-2-butenyloxy]acetate (6). Compound **6** was prepared from crotonaldehyde as follows. Treatment of crotonaldehyde with benzyloxymethyllithium prepared in situ from benzyloxymethyltributyltin[12] and butyllithium, gave (*E*)-1-benzyloxy-3-penten-2-ol (**7**). Allylic alcohol **7** was converted into 2-allyloxyacetic acid **8** by treatment with 2-bromoacetic acid in the presence of sodium hydride.[13] Esterification of **8** with 2-iodopropane in HMPA gave **6** in good yield.

With **6** in hand, we first examined its rearrangement via zirconium enolate with expectation that high *syn*, *Z*-

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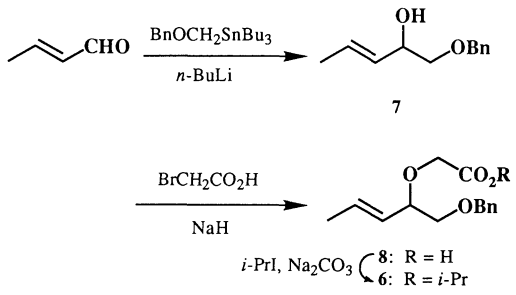
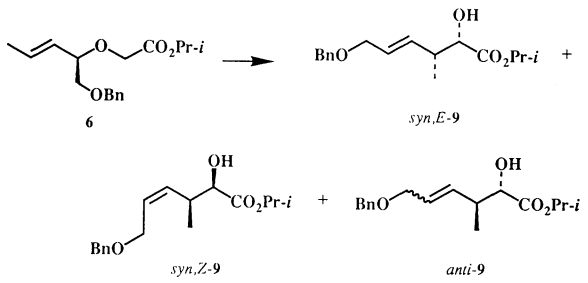


selectivity would be realized as in the case of **4**. However, the *E*: *Z* ratio of the newly formed double bond was quite poor and rather shifted to *E*-selective side, though high *syn*-selectivity was still observed [*syn*,*E*-**9**:*syn*,*Z*-**9**=1.5:1] (Table 1, Entry 1). This result suggested that the benzyloxyl oxygen atom partially coordinated to zirconium atom as visualized by Fig. 1, thus forcing the benzyloxymethyl substituent to take the otherwise disfavored *endo* orientation which led to *E*-double bond formation. Therefore, we assumed that the use of more Lewis acidic titanium ion would result in further enhancement of *E*-selectivity. Actually the addition of Cp_2TiCl_2 (Cp: cyclopentadienyl) to the lithium enolate derived from **6** remarkably improved *E*-selectivity (Entry 2). Moreover, almost perfect chirality transfer to the product was observed when the reaction was carried out with an optically active substrate. That is, the rearrangement of (*R*)-**6**[14] (79% ee) gave (2*S*, 3*R*)-

Table 1. [2,3]Wittig Rearrangement of **6**



Entry	Metal ion	*syn*,*E*-**9**	*syn*,*Z*-**9**	*anti*-**9**	Yield/%
1	$Zr(Cp_2ZrCl_2)$	1.5	1		72
2	$Ti(Cp_2TiCl_2)$	58	1	1	53
3	$Hf(Cp_2HfCl_2)$	29	2	1	37

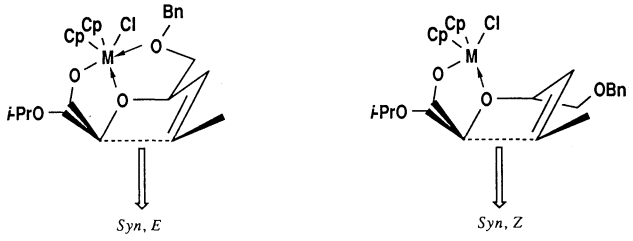
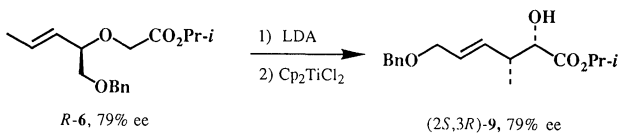


Fig. 1.

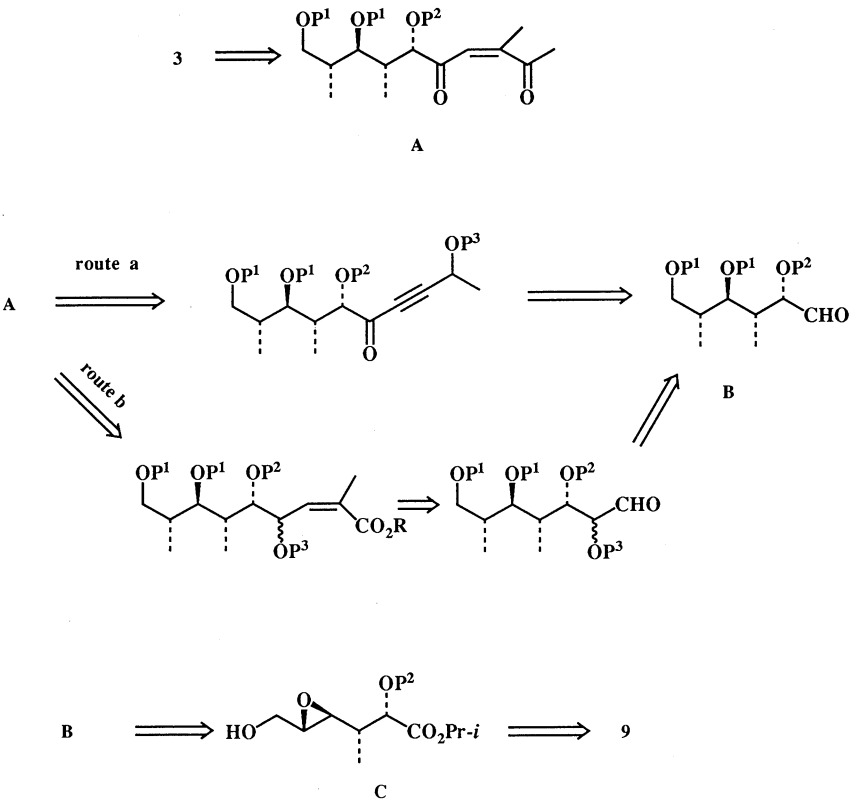


9 (79% ee). This sense of chirality transfer was opposite to that observed for the rearrangement of **4** via zirconium enolate,[9] as expected from the proposed transition states.

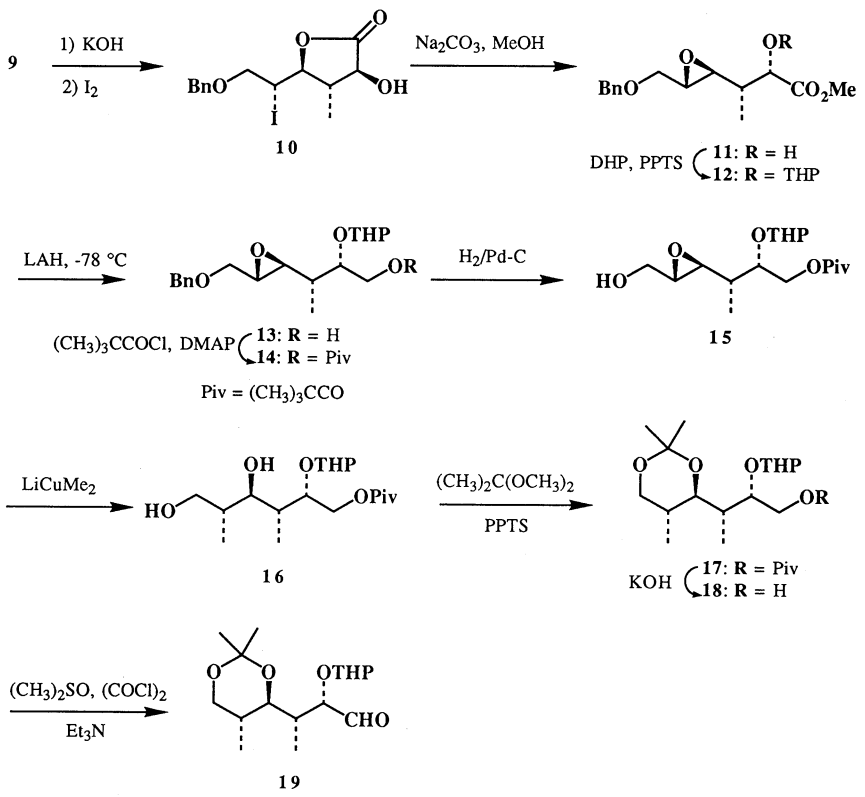
Although the rearrangement via hafnium enolate was expected to show increased *syn*, *Z*-selectivity from its less Lewis acidic nature, opposite *syn*,*E*-selectivity was observed (Entry 3). The reason of this unexpected stereoselectivity is not clear at present.

Synthesis of (±)-Ireland Alcohol. Next, we examined the transformation of the new rearrangement product **9** having different oxygen functionalities at each terminal carbons, to Ireland alcohol (**3**). Our approach is outlined in a retrosynthetic manner in Scheme 1. The bicyclic acetal structure of **3** was considered to be constructed by acid treatment of the acyclic diketone **A**, which could be in turn derived from appropriately protected aldehyde **B**. This five carbon extension seemed to be possible in two ways [**route a** (C4+C1) or **b** (C1+C3+C1)], wherein trisubstituted *Z*-enone unit could be introduced by Michael-type methylation of intermediary acetylenic ketone (**route a**) or by Wittig olefination of one carbon-elongated aldehyde (**route b**). The four consecutive asymmetric centers in **B** were expected to be established by the regioselective methylation of *anti*-epoxy alcohol **C** which could be obtained from **9** by using iodolactonization and alcoholysis sequence.

Thus the synthesis started with compound **9** which carried two chiral centers to be C-5′ and C-6′ asymmetric carbons (in the numbering of Ireland alcohol) of the target molecule (**3**) (Scheme 2). Compound **9** was hydrolyzed by aqueous potassium hydroxide and subjected to thermodynamically controlled iodolactonization to afford (2*R**,3*R**,4*R**,5*S**)-iodolactone **10** in 62% yield, which was further treated with methanolic Na_2CO_3 to give (2*R**,3*R**,4*R**,5*R**)-epoxy ester **11** stereoselectively in 90% yield.[15] Hydroxyl protection of **11** as a tetrahydropyranyl (THP) ether **12**[16] followed by LAH reduction afforded alcohol **13** in 85% yield. Under these conditions, the epoxide ring was remained intact. Hydroxyl protection of **13** as a pivalate **14** and subsequent debenzylation gave epoxy alcohol **15** in 99% yield. Treatment of **15** with lithium dimethylcuprate(I) gave the desired 1,3-diol **16** in 97% yield where no contamination of the regioisomeric 1,2-diol was detected.[17] The requisite four consecutive asymmetric centers being thus constructed, the functionality adjustment for the next carbon chain extension step was carried out. Protection of 1,3-diol **16** as an acetonide **17** followed by alkaline hydrolysis gave alcohol **18** in 88%



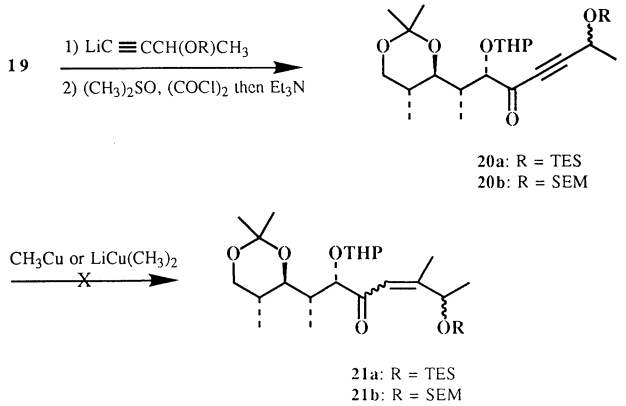
Scheme 1.



Scheme 2.

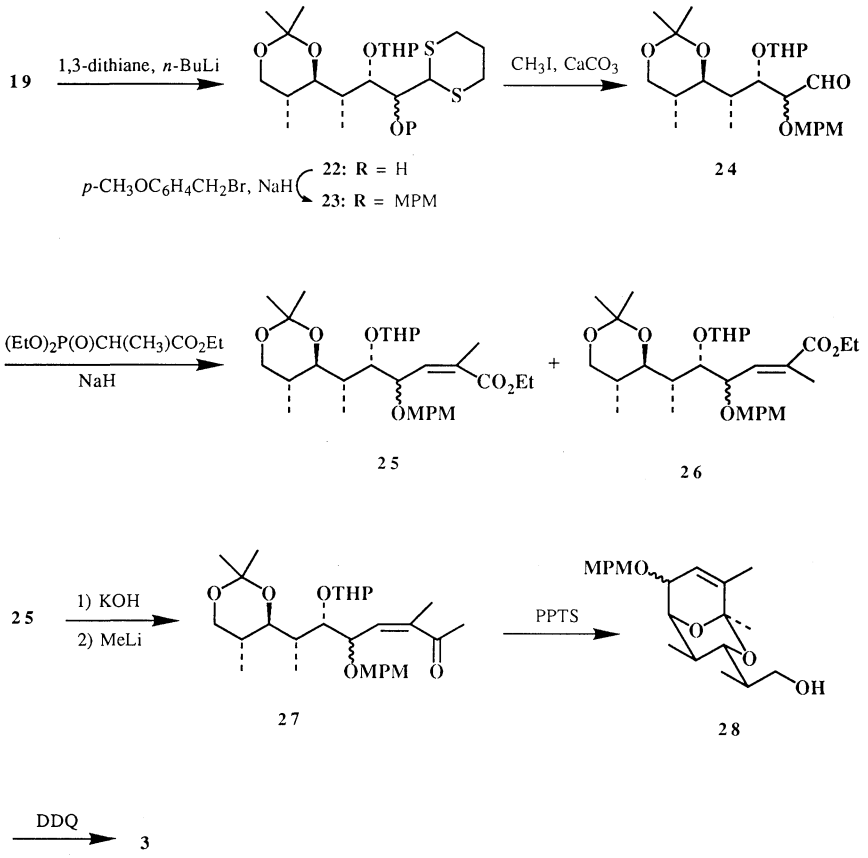
yield. Swern oxidation[18] of **18** gave the desired aldehyde **19** in 97% yield.

With **19** in hand, we first explored the possibility of **route a** for the introduction of the remaining *Z*-enone moiety (Scheme 3). Thus aldehyde **19** was treated with 3-(2-trimethylsilylethoxy)methoxy- or 3-triethylsilyloxy-1-lithiobutyne as the four carbon-unit and the resulting propargylic alcohols were oxidized to acetylenic ketones **20** by Swern oxidation. Treatment of **20** with MeCu gave a mixture of **21** and its *E*-isomer only in poor yield, and treatment with $LiCuMe_2$ did not give any desired product.



Scheme 3.

Then we examined **route b** (Scheme 4). Aldehyde **19** was treated with lithiated 1,3-dithiane to give a mixture of diastereomeric alcohols **22** in quantitative yield, which were used without separation in the following reaction. Compound **22** was protected as a *p*-methoxybenzyl (MPM) ether **23**,[19] and treated with methyl iodide in the presence of $CaCO_3$ to give the one carbon extended aldehyde **24** in 34% yield. Wittig–Horner reaction of **24** with triethyl 2-phosphonopropionate gave a 1 : 1 mixture of (*Z*)- and (*E*)-unsaturated esters. The mixture was separated into two fractions by silica-gel chromatography. The polar fraction contained a *Z*-isomer with a small amount of diastereomeric *Z*-isomers in 47% yield, while the less polar fraction contained a mixture of three diastereomeric *E*-isomers in 47% yield. The alkaline hydrolysis of *Z*-isomers **25** followed by treatment with methyllithium gave a single enone **27** in 79% yield after chromatographic purification, setting the stage for the construction of the bicyclic acetal structure. Treatment of the compound **27** with pyridinium *p*-toluenesulfonate[16] gave the desired bicyclic acetal **28** in 57% yield. Deprotection of **28** and the oxidation of the resulting allylic alcohol were effected at the same time by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) treatment[19] affording Ireland alcohol (**3**) in 99% yield. The identity of **3** was established by ^1H NMR and IR comparisons. All chemical shifts of ^1H NMR spectrum and fingerprint region of IR spectrum were identical with those of



Scheme 4.

authentic specimen.[7g] As compound **3** has been converted into tirandamycin A,[7b,o] this constitutes a formal total synthesis of tirandamycin A.

Experimental

^{1}H NMR spectra were measured at 400 MHz on a JEOL-400 GX or at the 90 MHz on a JEOL FX-90Q instrument. Chemical shifts were given by δ relative to that of internal Me_4Si. IR spectra were measured on a JASCO IR-700 instrument. Mass spectra were obtained on a JEOL SX-102 instrument. Column chromatography was conducted on Silica Gel 60, 70—230 mesh ASTM, available from E. Merck. Preparative thin-layer chromatography was performed on 0.5 mm×20 cm×20 cm E. Merck silica-gel plate (60 F-254). Solvents were dried and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen if necessary.

Isopropyl [(2*E*)-1-Benzyloxymethyl-2-butenyloxy]acetate (6). Butyllithium (1.6 mol dm^{-3} in hexane, 8.9 ml) was added at −78 °C to a solution of benzyloxymethyltributylstannane (5.30 ml) in THF (60 ml). After stirring for 5 min, crotonaldehyde (1.23 ml) was added to the mixture at the same temperature. After further stirring for 10 min, the reaction mixture was quenched with water and extracted with hexane. The organic layer was dried and concentrated in vacuo. Column chromatography of the residue (9 : 1 hexane–ethyl acetate) gave allylic alcohol **7** (2.65 g, 94%). ^{1}H NMR (90 MHz) δ=1.71 (d, J=5.4 Hz, 3H), 2.28—2.52 (m, 1H), 3.34—3.68 (m, 2H), 4.20—4.50 (m, 1H), 4.61 (s, 2H), 5.34—6.08 (m, 2H), 7.40 (s, 5H). IR (thin film) 3436, 2856, 1449, 1102, 965, 737, 697 cm^{-1}.

To a stirred mixture of **7** (1.05 g) and sodium hydride (60% in oil, 0.670 g) in THF (9 ml) was added dropwise a solution of bromoacetic acid (0.823 g) in THF (9 ml). The mixture was refluxed for 12 h, cooled to room temperature, poured into water, and extracted with ether. The aqueous layer was adjusted to pH 1 and extracted with dichloromethane. The organic layers were combined, dried, and concentrated. To the residue were added hexamethylphosphoric triamide (6 ml), sodium carbonate (0.360 g) and water (6 drops) successively. The whole mixture was stirred for 5 min. After isopropyl iodide (0.810 ml) was added, the mixture was further stirred for 12 h. The reaction mixture was then poured to water, extracted with hexane, dried, and concentrated in vacuo. Column chromatography of the residue (hexane–ethyl acetate 5 : 1) gave ester **6** (1.20 g, 76%). ^{1}H NMR (90 MHz) δ=1.23 (d, J=6.3 Hz, 6H), 1.54—1.69 (m, 1H), 1.71 (d, J=5.4 Hz, 3H), 3.34—3.64 (m, 2H), 4.02 (m, 1H), 4.05 (s, 2H), 4.58 (s, 2H), 4.86—6.00 (m, 2H), 7.30 (s, 5H). IR (thin film) 2974, 1748, 1449, 1374, 1280, 1206, 1104, 967, 736, 697 cm^{-1}. Found: C, 69.64; H, 8.32%. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%.

Isopropyl (2*R, 3*S**, 4*E*)-6-Benzyloxy-2-hydroxy-3-methyl-4-hexenoate (9).** A solution of **6** (2.14 g) in THF (5 ml) was added dropwise to a solution of LDA (0.815 mol dm^{-3}, 9.45 ml) in THF and hexane (1 : 1) at −100 °C. After 1 h, a solution of Cp_2TiCl_2 (2.37 g, 1.3 equiv) in THF (100 ml) was added to the mixture at the same temperature. After another 15 min, the reaction temperature was gradually raised to −20 °C and the mixture was left in refrigerator (−20 °C) for 19 h. The mixture was quenched with a saturated aqueous solution of KF (3.6 ml) and allowed to warm to room temperature. The mixture was then filtered through Celite and concentrated in vacuo. Column chromatogaphy of the residue (5 : 1 hexane–ethyl acetate) gave hydroxy ester **9** (1.54 g, 72%). ^{1}H NMR (400 MHz) δ=1.01 (d, J=6.8 Hz, 3H), 1.28 (d, J=5.9 Hz, 3H), 1.29 (d, J=5.4 Hz, 3H), 2.67 (m, 1H), 2.80 (m, 1H), 4.01 (d, J=5.4 Hz, 2H), 4.12 (br s, 1H), 5.11 (m, 1H), 5.70 (dt, J=15.6, 5.4 Hz, 1H), 5.77 (dd, J=15.6, 6.8 Hz, 1H), 7.26—7.38 (m, 5H). IR (thin film) 3508, 2974, 1721, 1450, 1372, 1259, 1104, 972, 738, 697 cm^{-1}. Found: C, 69.67; H, 8.25%. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%. Chemical correlation of **9** by acetylation and subsequent RuO_4 oxidation[21] to 1-isopropyl hydrogen (2*R**, 3*R**)-2-acetoxy-3-methylsuccinate which was derived from isopropyl (2*R**,3*S**,4*Z*)-2-hydroxy-3-methyl-4-pentenoate[9] in the same way, proved its stereochemistry to be 2*R**, 3*S**. Geometry of the double bond was determined to be *E* on the basis of the coupling constant (15.6 Hz) of olefinic protons.

(2*R,3*R**,4*R**,5*S**)-6-Benzyloxy-2-hydroxy-5-iodo-3-methyl-4-hexanolide (10).** Aqueous potassium hydroxide (1 mol dm^{-3}, 4.41 ml) was added at room temperature to a solution of hexenoate **9** (0.430 g) in methanol (14 ml). After 1 d, a bulk of methanol was removed under diminished pressure. The residual solution was diluted with water, adjusted to pH 4 by using 5% aqueous phosphoric acid, and extracted with dichloromethane. The organic layer was concentrated under vacuum and diluted with acetonitrile (20 ml). To this solution was added iodine (1.12 g) and the mixture was stirred at 0 °C for 18 h. The mixture was decolorized with aqueous $Na_2S_2O_3$, extracted with ether, dried over Na_2SO_4, and concentrated. Column chromatography of the residue (7 : 3 hexane–ethyl acetate) gave iodolactone **10** (0.345 g, 62%). ^{1}H NMR (90 MHz) δ=1.33 (d, J=6.8 Hz, 3H), 2.23—2.71 (m, 1H), 3.06—3.35 (m, 1H), 3.70—3.94 (m, 2H), 3.95—4.32 (m, 2H), 4.35—4.51 (m, 1H), 4.54 (s, 2H), 7.32 (s, 5H). IR (thin film) 3442, 2862, 1783, 1450, 1366, 1310, 1185, 698 cm^{-1}. Found: C, 44.67; H, 4.54%. Calcd for $C_{14}H_{17}O_4I$: C, 44.70; H, 4.55%.

Methyl (2*R, 3*R**, 4*R**, 5*R**)-6-Benzyloxy-4,5-epoxy-2-hydroxy-3-methylhexanoate (11).** A mixture of iodolactone **10** (0.345 g) and powdered anhydrous Na_2CO_3 (2 equiv, 0.194 g) in methanol (18 ml) was stirred at room temperature for 2 d in the dark. The mixture was then concentrated under reduced pressure and partitioned between water and ether. The ethereal layer was washed with water and brine successively, dried over Na_2SO_4, and concentrated. Column chromatography of the residue (7 : 3 hexane–ethyl acetate) gave epoxy ester **11** (0.231 g, 90%). ^{1}H NMR (90 MHz) δ=0.90 (d, J=6.8 Hz, 3H), 1.54—2.00 (m, 1H), 2.66—3.14 (m, 3H), 3.30—3.72 (m, 2H), 3.88 (s, 3H), 4.32—4.48 (m, 1H), 4.56 (s, 2H), 7.35 (s, 5H). IR (thin film) 3504, 2952, 1741, 1450, 1236, 1135, 985, 898, 742, 698 cm^{-1}. Found: C, 64.00; H, 7.12%. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19%.

Methyl (2*R,3*S**,4*R**,5*R**)-6-Benzyloxy-4,5-epoxy-3-methyl-2-(2-tetrahydropyranyloxy)hexanoate (12).** A solution of epoxy ester **11** (0.599 g) and dihydropyran (1.2 equiv, 0.234 ml) in dry dichloromethane (22 ml) containing pyridinium *p*-toluenesulfonate (0.1 equiv, 55.0 mg) was stirred for 6 h at room temperature, and the solvent was evaporated. Column chromatography of the residue (5 : 1 hexane–ethyl acetate) gave the tetrahydropyranyl ether **12** (0.755 g, 99%) as a diastereomeric mixture. [Hereafter, compounds (**12**—**27**) were dealt with as diastereomeric mixtures]. ^{1}H NMR (90 MHz) δ=1.00 (d, J=6.8 Hz, 3H), 1.34—2.09 (m, 7H), 2.82

(dd, J=8.1, 1.8 Hz, 1H), 2.92—3.20 (m, 1H), 3.28—4.04 (m, 4H), 3.72 (s, 3H), 4.15 (d, J=4.5 Hz, 1H), 4.48—4.84 (m, 1H), 4.55 (s, 2H), 7.32 (s, 5H). IR (thin film) 2940, 1748, 1450, 1200, 1123, 1022, 904, 739, 698 cm^{-1}. Found: C, 65.76; H, 7.74%. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74%.

(2*R,3*S**,4*R**,5*R**)-6-Benzyloxy-4,5-epoxy-3-methyl-2-(2-tetrahydropyranyloxy)-1-hexanol (13).** Lithium aluminum hydride (1.0 mol dm^{-3} solution in THF, 2.8 ml) was added at −78 °C to a solution of the tetrahydropyranyl ether **12** (1.02 g) in THF (28 ml). After stirring for 1 h, the mixture was quenched with a saturated aqueous solution of KF (2.8 ml), extracted with ether, dried over Na_2SO_4, and concentrated. Column chromatography of the residue (7:3 hexane–ethyl acetate) gave alcohol **13** (0.803 g, 85%). ^{1}H NMR (400 MHz) δ=0.85 (d, J=7.08 Hz) and 1.03 (d, J=7.08 Hz) (3H), 1.04—1.70 (m, 7H), 2.71—2.84 (2H), 3.14—4.01 (8H), 4.39—4.77 (3H), 7.20 (s, 5H). IR (thin film) 3440, 2934, 1450, 1372, 1201, 1073, 1027, 900, 739, 697 cm^{-1}. Found: C, 67.74; H, 8.36%. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39%.

(2*R,3*S**,4*R**,5*R**)-6-Benzyloxy-4,5-epoxy-3-methyl-2-(2-tetrahydropyranyloxy)hexyl Pivalate (14).** 4-Dimethylaminopyridine (1.3 equiv, 0.284 g) and pivaloyl chloride (1.2 equiv, 0.265 ml) were added at room temperature to a solution of alcohol **13** (0.603 g) in dry dichloromethane (18 ml). After stirring for 12 h, the solvent was evaporated. Column chromatography of the residue (5:1 hexane–ethyl acetate) gave pivalate **14** (0.752 g, 99%). ^{1}H NMR (400 MHz) δ=0.97 (d, J=6.83 Hz) and 1.02 (d, J=7.33 Hz) (3H), 1.19 (s, 9H), 1.52—1.80 (m, 7H), 2.82 (dd, J=7.57, 2.20 Hz), and 2.95 (dd, J=7.32, 2.44 Hz) (1H), 3.01 (m, 1H), 3.44—4.28 (7H), 4.56 (m, 2H), 4.71 (m) and 4.78 (m) (1H), 7.34 (s, 5H). IR (thin film) 2950, 1728, 1453, 1363, 1280, 1157, 1031, 900, 736, 697 cm^{-1}. Found: C, 68.42; H, 8.51%. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63%.

(2*R,3*S**,4*R**,5*R**)-4,5-Epoxy-6-hydroxy-3-methyl-2-(2-tetrahydropyranyloxy)hexyl Pivalate (15).** A mixture of pivalate **14** (0.974 g) and 10% Pd/C (1.92 g) in ethanol (23 ml) was placed under hydrogen and stirred for 8 h. The mixture was then filtered through Celite and concentrated to give epoxy alcohol **15** (0.760 g, 99%). ^{1}H NMR (90 MHz) δ=0.90 (d, J=7.2 Hz) and 0.98 (d, J=7.2 Hz) (3H), 1.19 (s, 9H), 1.41—2.01 (m, 8H), 2.85—3.08 (m, 2H), 3.31—4.33 (m, 7H), 4.61—4.79 (m, 1H). IR (thin film) 3440, 2950, 1728, 1477, 1395, 1281, 1154, 1031, 897 cm^{-1}. Found: C, 61.63; H, 9.07%. Calcd for $C_{17}H_{30}O_6$: C, 61.80; H, 9.15%.

(2*R,3*S**,4*S**,5*S**)-4,6-Dihydroxy-3,5-dimethyl-2-(2-tetrahydropyranyloxy)hexyl Pivalate (16).** To a slurry of Me_2S complex of copper(I) iodide (3 equiv, 1.35 g) in anhydrous ether (15 ml) was added methyllithium (6 equiv, 0.84 mol dm^{-3} in ether, 12.7 ml) at −30 °C and the mixture was stirred for a few minutes. The mixture was then treated with epoxy alcohol **15** (0.587 g in ether, 15 ml) at −30 °C. The reaction temperature was gradually raised to 5 °C and the mixture was kept standing in refrigerator (5 °C) for 13 h. The solution was quenched with aqueous ammonium sulfate, extracted with ether, dried over Na_2SO_4, and concentrated. Column chromatography of the residue (3:2 hexane–ethyl acetate) gave diol **16** (0.595 g, 97%). ^{1}H NMR (400 MHz) δ=0.92 (d, J=6.84 Hz) and 0.96 (d, J=6.84 Hz) (3H), 1.04 (d, J=6.83 Hz) and 1.09 (d, J=6.83 Hz) (3H), 1.21 (s) and 1.22 (s) (9H), 1.47—2.05 (m, 8H), 3.31—4.82 (11H). Found: C, 62.18; H, 10.02%. Calcd for $C_{18}H_{34}O_6$: C, 62.40; H, 9.89%.

(2*R, 3*S**, 4*S**, 5*S**)-4,6-Isopropylidenedioxy-3,5-dimethyl-2-(2-tetrahydropyranyloxy)hexyl Pivalate (17).** A solution of diol **16** (0.706 g) and 2,2-dimethoxypropane (10 equiv, 2.5 ml) in dry benzene (40 ml) containing pyridinium p-toluenesulfonate (0.1 equiv, 52.0 mg) was stirred for 12 h at room temperature and concentrated. Column chromatography of the residue (5:1 hexane–ethyl acetate) gave acetonide **17** (0.698 g, 89%). ^{1}H NMR (400 MHz) δ=0.77 (d, J=6.84 Hz) and 0.85 (d, J=6.84 Hz) (3H), 1.00 (d, J=7.32 Hz) and 1.05 (d, J=7.32 Hz) (3H), 1.20 (s, 9H), 1.38 (s, 3H), 1.51—2.14 (m, 8H), 1.60 (s, 3H), 3.38—4.82 (m, 9H). IR (thin film) 2930, 1726, 1453, 1380, 1280, 1154, 1031, 868 cm^{-1}. Found: C, 65.15; H, 10.03%. Calcd for $C_{21}H_{38}O_6$: C, 65.26; H, 9.91%.

(2*R, 3*S**, 4*S**, 5*S**)-4,6-Isopropylidenedioxy-3,5-dimethyl-2-(2-tetrahydropyranyloxy)-1-hexanol (18).** Aqueous potassium hydroxide (1 mol dm^{-3}, 9.02 ml) was added at room temperature to a solution of acetonide **17** (0.698 g) in methanol (18 ml). After 20 h, a bulk of methanol was removed under diminished pressure. The residual solution was extracted with ether. The organic layer was washed with water, dried, and concentrated. Column chromatography of the residue (7:3 hexane–ethyl acetate) gave alcohol **18** (0.545 g, 99%). ^{1}H NMR (400 MHz) δ=0.78 (d, J=6.84 Hz) and 0.86 (d, J=6.84 Hz) (3H), 0.98 (d, J=7.33 Hz) and 1.03 (d, J=7.32 Hz) (3H), 1.37 (s) and 1.41 (s), (3H), 1.39 (s) and 1.43 (s) (3H), 1.49—2.05 (m, 9H), 3.34—4.00 (m, 8H), 4.51 (m) and 4.77 (m) (1H). IR (thin film) 3454, 2934, 1456, 1378, 1263, 1198, 1025, 867 cm^{-1}. Found: C, 63.17; H, 10.09%. Calcd for $C_{16}H_{30}O_5$: C, 63.55; H, 10.00%.

(2*R, 3*S**, 4*S**, 5S*)-4,6-Isopropylidenedioxy-3,5-dimethyl-2-(2-tetrahydropyranyloxy)hexanal (19).** Dimethyl sulfoxide (2.2 equiv, 226 μl) was added to a stirred solution of oxalyl chloride (1.1 equiv, 136 μl) in dichloromethane (8 ml) at −50 to −60 °C. After 2 min, a solution of **18** (0.427 g) in dichloromethane (7 ml) was added to the mixture within 5 min. After another 10 min, triethylamine (5 equiv, 994 μl) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. The mixture was then filtered through Celite and concentrated in vacuo. Column chromatography of the residue (5:1 hexane–ethyl acetate) gave aldehyde **19** (0.412 g, 97%) which was immediately used for the next reaction.

(1*RS,2*R**,3*S**,4*S**,5*S**)-1-(1,3-Dithian-2-yl)-4,6-isopropylidenedioxy-3,5-dimethyl-2-(2-tetrahydropyranyloxy)-1-hexanol (22).** A solution of 1,3-dithiane (0.958 g) in dry THF (9.6 ml) was cooled to −40 °C, and a solution of butyllithium in hexane (1.63 mol dm^{-3}, 4.89 ml) was added dropwise. After being stirred for 2 h at −20 °C, the mixture was recooled to −40 °C. A solution of aldehyde **19** (0.448 g) in dry THF (2 ml) was added dropwise to this stirred solution, and stirring was continued at −20 °C for 2 h and at 5 °C for 40 h. The mixture was poured into cold water, and extracted with chloroform. The extract was dried and concentrated to give a residue which was chromatographed on silica gel (4:1 hexane–ethyl acetate) to give dithiane **22** (0.621 g, 99%). ^{1}H NMR (400 MHz) δ=0.76—1.11 (6H), 1.39—1.42 (6H), 1.42—2.20 (m, 11H), 2.72—2.97 (m, 4H), 3.34—4.66 (m, 9H). Found: C, 56.98; H, 8.88%. Calcd for $C_{20}H_{36}O_5S_2$: C, 57.11; H, 8.63%.

(1*RS, 2*R**, 3*S**, 4*S**, 5*S**)-1-(1,3-Dithian-2-yl)-4,6-isopropylidenedioxy-1-(*p*-methoxybenzyloxy)-3,5-dimethyl-2-(2-tetrahydropyranyloxy)hexane (23).** To a mixture of dithiane **22** (0.171 g) and sodium hydride (1.1 equiv, 60% in oil, 18.0 mg) in THF (4 ml) and DMF (1 ml) was added p-methoxybenzyl

(MPM) chloride (1.1 equiv, 65.0 μl). The mixture was stirred at room temperature for 16 h and concentrated under reduced pressure. Column chromatography of the residue (5:1 hexane–ethyl acetate) gave MPM ether **23** (0.139 g, 63%). ^{1}H NMR (400 MHz) δ=0.47—1.02 (6H), 1.03—1.40 (6H), 1.50—2.20 (m, 10H), 2.77—2.96 (m, 4H), 3.22—4.91 (m, 11H), 3.79 (s, 3H), 6.83—6.89 (m, 2H), 7.26—7.42 (m, 2H). Found: C, 61.87; H, 8.14%. Calcd for $C_{28}H_{44}O_6S_2$: C, 62.19; H, 8.20%.

(2*RS,3*R**,4*S**,5*S**,6*S**)-5,7-Isopropylidenedioxy-2-(*p*-methoxybenzyloxy)-4,6-dimethyl-3-(2-tetrahydropyranyloxy)-heptanal (24).** Methyl iodide (4 equiv, 65.0 μl) was added to a mixture of MPM ether **23** (0.139 g), calcium carbonate (7 equiv, 0.181 mg), acetonitrile (0.97 ml), and water (0.2 ml). After stirring for 40 h at room temperature, the mixture was extracted with ether, dried, and evaporated. Column chromatography of the residue (5:1 hexane–ethyl acetate) gave aldehyde **24** (64.1 mg, 55%) which was immediately used for the next reaction.

Ethyl (4*RS, 5*R**, 6*S**, 7*S**, 2*Z*)-7,9-Isopropylidenedioxy-4-(*p*-methoxybenzyloxy)-2,6,8-trimethyl-5-(2-tetrahydropyranyloxy)-2-nonenoate (25).** To a suspension of sodium hydride (60% in oil, 33.7 mg) in ether (1 ml) was added triethyl 2-phosphonopropionate (181 μl) at room temperature. After 1 h, a solution of aldehyde **24** (64.1 mg) in ether (0.5 ml) was added to the mixture at −78°C. The reaction temperature was gradually raised to −20°C and the mixture was kept standing in refrigerator (−20°C) for 12 h. The mixture was quenched with water, extracted with ether, dried, and evaporated. Column chromatography of the residue (5:1 hexane–ethyl acetate) gave a mixture of *Z*-olefins **25** (36.2 mg, 47%) and a mixture of *E*-olefins **26** (36.2 mg, 47%), respectively. **25**: ^{1}H NMR data are described for the major isomer in a mixture of *Z*-olefines (400 MHz): δ=0.53 (d, *J*=6.83 Hz, 3H), 0.95 (d, *J*=7.33 Hz, 3H), 1.25 (t, *J*=7.08 Hz, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.37—1.95 (8H), 1.97 (d, *J*=1.47 Hz, 3H), 3.24—4.88 (m, 12H), 3.78 (s, 3H), 5.92 (dd, *J*=9.27, 1.47 Hz, 1H), 6.83 (d, *J*=8.79 Hz, 2H), 7.25 (d, *J*=9.76 Hz, 2H). IR (KBr) 2932, 1710, 1511, 1451, 1369, 1245, 1029 cm^{-1}. Found: C, 67.24; H, 8.68%. Calcd for $C_{30}H_{46}O_8$: C, 67.39; H, 8.67%.

(5*RS, 6*R**, 7*S**, 8*S**, 9*S**, 3*Z*)-8,10-Isopropylidenedioxy-5-(*p*-methoxybenzyloxy)-3,7,9-trimethyl-6-(2-tetrahydropyranyloxy)-3-decen-2-one (27).** Aqueous potassium hydroxide (1 mol dm^{-3} solution, 177 μl) was added at room temperature to a solution of a mixture of *Z*-olefins **25** (15.8 mg) in methanol (0.3 ml). After 2 d, a bulk of methanol was removed under reduced pressure. The residual solution was adjusted to pH 4 by using 5% aqueous phosphoric acid and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered through a pad of silica gel, and concentrated to give the corresponding acid (13.0 mg, 87%). The acid was dissolved in ether (0.26 ml) and to this solution was added methyllithium (1.0 mol dm^{-3} solution in ether, 64.0 μl) at room temperature. After 1 h, the mixture was quenched with water, extracted with ether, dried, and concentrated. Thin-layer chromatography of the residue (7:3 hexane–ethyl acetate) gave enone **27** (10.2 mg, 79%). ^{1}H NMR (400 MHz) δ=0.47 (d, *J*=6.35 Hz, 3H), 0.88 (d, *J*=7.33 Hz, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.38—1.74 (m, 8H), 1.90 (s, 3H), 2.17 (s, 3H), 3.18—4.74 (m, 10H), 3.72 (s, 3H), 5.62 (dd, *J*=8.30, 1.47 Hz, 1H), 6.76 (d, *J*=8.79 Hz, 2H), 7.15 (d, *J*=8.79 Hz, 2H). IR (KBr) 2934, 1691, 1610, 1511, 1451, 1369, 1246, 1030 cm^{-1}. Found: C, 68.88; H, 8.77%. Calcd for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79%.

(2*R)-2-[(1*S**, 4*RS**, 5*S**, 6*R**, 7*R**)-4-(*p*-Methoxybenzyloxy)-1,2,6-trimethyl-8,9-dioxabicyclo[3.3.1]non-2-en-7-yl]-1-propanol (28).** A solution of enone **27** (4.9 mg) and pyridnium *p*-toluenesulfonate (0.7 mg) in methanol (0.275 ml) was stirred at room temperature for 20 h. The solvent was evaporated in vacuo, and thin-layer chromatography of the residue (7:3 hexane–ethyl acetate) gave the bicyclic acetal **28** (2.0 mg, 57%). ^{1}H NMR (400 MHz) δ=1.03 (d, *J*=7.32 Hz, 3H), 1.10 (d, *J*=6.83 Hz, 3H), 1.39 (s, 3H), 1.61 (d, *J*=1.54 Hz, 3H), 1.86 (m, 1H), 2.40 (m, 1H), 2.80 (m, 1H), 3.50 (m, 1H), 3.80 (s, 3H), 3.88 (dd, *J*=11.23, 1.95 Hz, 1H), 3.98 (dd, *J*=11.23, 2.93 Hz, 1H), 4.11 (dd, *J*=5.86, 5.86 Hz, 1H), 4.46 (m, 1H), 4.51 (s, 2H), 5.83 (s, 1H), 6.88 (d, *J*=8.79 Hz, 2H), 7.25 (d, *J*=8.79 Hz, 2H). HRMS Calcd for $C_{21}H_{30}O_5$: M, 362.20915. Found: *m*/*z* 362.20937.

(2*R)-2-[(1*S**,5*S**,6*R**,7*R**)-1,2,6-Trimethyl-4-oxo-8,9-dioxabicyclo[3.3.1]non-2-en-7-yl]-1-propanol (3).** To a solution of the bicyclic acetal **28** (3.0 mg) in dichloromethane–water (18:1, 80 μl) was added 2,3-dichloro-5,6-dicyanobenzoquinone (2.2 equiv, 4.0 mg) at room temperature. After 1 h, the mixture was filtered through Celite and concentrated in vacuo. Thin-layer chromatography of the residue (7:3 hexane–ethylacetate) gave Ireland alcohol **3** (2.0 mg, 99%) as a crystalline solid, which was recrystallized from pentane–ether; mp 52—53°C. ^{1}H NMR (400 MHz) δ=0.78 (d, *J*=6.83 Hz, 3H), 1.09 (d, *J*=6.83 Hz, 3H), 1.55 (s, 3H), 1.89 (m, 1H), 1.93 (d, *J*=1.46 Hz, 3H), 2.34 (m, 1H, OH), 2.41 (m, 1H), 3.52 (dd, *J*=11.48, 2.20 Hz, 1H), 3.62 (m, 1H), 3.94 (dd, *J*=11.48, 3.17 Hz, 1H), 4.10 (d, *J*=6.34 Hz, 1H), 6.15 (s, 1H). IR (CCl_4) 2970, 1683, 1377, 1115, 1063, 997, 887 cm^{-1}. HRMS Calcd for $C_{13}H_{20}O_4$: M, 240.13604. Found: *m*/*z* 240.13648.

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