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SYNTHESIS OF (-)-TALAROMYCINS A AND B†

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Abstract -- Highly enantiomerically pure (-)-talaromycins A and B [(3R,4S,6R,9R)- and (3S,4S,6R,9R)-9-ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane] were synthesized starting from chiral building blocks of microbial origin.

(-)-Talaromycins A **1a** and B **2a** were fungal toxins isolated by Lynn and co-workers in 1982 from Talaromyces stipitatus.[1,2] The toxicity of these spiroacetals may be due to their ability to block outward potassium fluxes, thus leading to muscle dysfunction.[1] Their unique spiroacetal structures **1a** and **2a** attracted much attention of synthetic chemists. Thus thermodynamically more stable (±)-talaromycin B **2a** with an eq CH_2OH group was synthesized by Schreiber et al.,[3] Kozikowski et al.,[4] Kocienski et al.[5] and Kay et al.[6] The less stable (±)-talaromycin A **1a** with an ax CH_2OH group was later synthesized by Schreiber et al.[7] As to the synthesis of the naturally occurring enantiomers of talaromycins, there exist only two reports.[8,9] Smith and Thompson was the first to synthesize (-)-talaromycins A and B in 1984.[8] The second synthesis of (-)-talaromycin A was reported by Midland and Gabriel in 1985.[9] As an extension of our continuing efforts to synthesize enantiomerically pure spiroacetals of insect origin,[10,11] we initiated a project to synthesize both (-)-talaromycins A and B in highly enantiomerically pure state.

Our synthetic plan is shown in Fig. 1. Chiral building blocks of microbial origin are employed as our starting materials. For the construction of the spiroacetal system, a Wittig reaction[12~14] between **A** and **B** is to be employed. The phosphorane **A** can be prepared from **C**, which in turn is the product of yeast reduction[15~17] of **D**. Dimethyl 3-oxopentanedioate **E** is the starting material for **D**. The aldehyde **B** is to be synthesized via **F** from ethyl (S)-3-hydroxybutanoate **G**, the product of yeast reduction of ethyl acetoacetate.[18] Execution of the above plan, which culminated to the synthesis of crystalline (-)-talaromycin A **1a**, will be detailed below.

The first phase of our work as shown in Fig. 2 was the synthesis of a phosphonium salt **14**, the precursor to the Wittig reagent **A**. Reduction of **3** (=**E**) with $NaBH_4$ gave **4a**. After protecting the OH group of **4a** as a THP ether, the resulting **4b** was reduced with LAH

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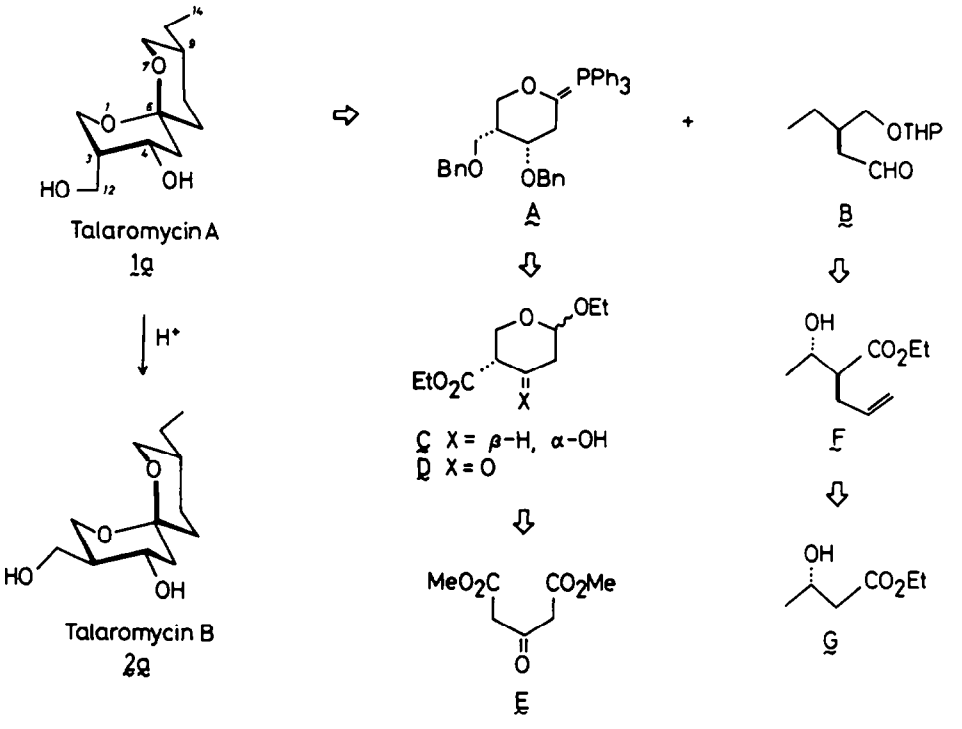

Fig. 1. Synthetic plan.

to give **5a**. This was treated with p-TsOH in MeOH to give a triol **5b**. Acetonide **6** was prepared from **5b** in the usual manner. Oxidation of **6** with pyridinium chlorochromate (PCC)[19] in the presence of MS 3Å[20] furnished aldehyde **7**. When a soln of **7** and p-TsOH in CH_2Cl_2-EtOH was heated, intramolecular acetalization took place to give a stereoisomeric mixture of **8** in 64 % yield from **7** or in 33 % overall yield from **3** in 7 steps. Although a synthesis of 4-hydroxy-2-methoxytetrahydropyran was known,[21] the present multi-step route furnished **8** in better overall yield. The alcohol **8** was oxidized with pyridinium dichromate (PDC)[22] in the presence of MS 3Å[20] to give **9** in 72 % yield. Ethoxycarbonylation of **9** could not be achieved under the conventional condition employing NaH and $CO(OEt)_2$. By the method of Mander and Sethi,[23] however, a CO_2Et group was successfuly introduced at C-5 of **9**. Thus **9** was treated with LDA and $NCCO_2Et$[24] to give a mixture of two regioisomeric β-keto esters **10** and **11** in a ratio of 10:1. This was purified by SiO_2 chromatography to give pure **10** in 55 % yield.

The next step was the crucial microbial reduction of **10**. Reduction of the β-keto ester **10** was tried with Saccharomyces bailii KI 0116, Pichia terricola KI 0117 and Saccharomyces cerevisiae (baker's yeast).[18] S. bailii and P. terricola were found to be unsuitable for this reduction giving almost no β-hydroxy ester, although S. bailii was an excellent organism to reduce a β-keto ester related to PGI_2.[25] Reduction of **10** was therefore carried out with baker's yeast. An emulsion of **10** in dilute Triton X-100 was added to a suspension of briskly fermenting baker's yeast at pH 8 (phosphate buffer) in the presence of sucrose. The product obtained in 81 % yield was a diastereomeric mixture at C-2 of hydroxy ester **12a**. The diastereomeric ratio was later determined as 63:37 by analyzing **13c** (vide infra). The diastereomers of **12a** were partially separated by SiO_2 chromatography to give the less polar isomer (major product), the more polar isomer (minor product) and their mixture. In the NMR spectrum of the less polar isomer of **12a**, a signal

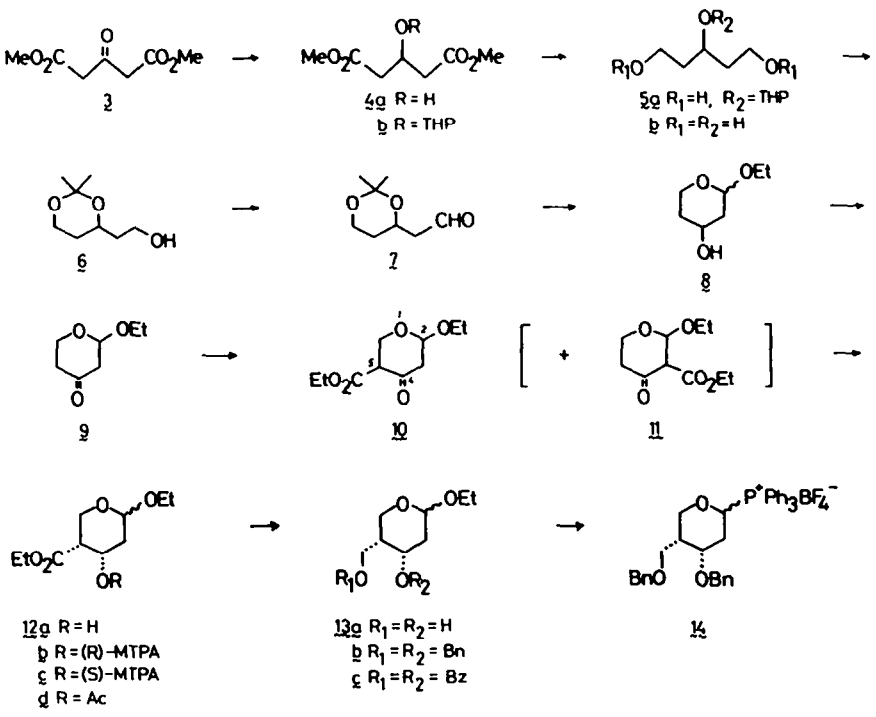

Fig. 2. Synthesis of the phosphonium salt 14.

due to an eq H at C-2 (δ 4.78, 1H, dd, J=3 and 3 Hz) and that due to an ax H at C-5 (δ 2.53, 1H, ddd, J=10, 4 and 2 Hz) were observed. In all of the published examples of the yeast reduction of cyclic β-keto esters, formation of cis-β-hydroxy esters were observed with (S)-configuration of the OH group.[15~17,25,26] The less polar isomer of **12a** was therefore assumed to be (2S,4S,5R)-**12a**, whose enantiomeric purity was estimated to be 43 % e.e. by the HPLC analysis of the corresponding (R)- and (S)-α-methoxy-α-trifluoromethylphenylacetates (MTPA esters[27]), (2S,4S,5R)-**12b** and **12c**. The more polar and minor isomer of **12a** exhibited in its NMR spectrum a signal due to an eq H at C-2 (δ 4.71, 1H, dd, J=4.4 and 3.6 Hz) and that due to an eq H at C-5 (δ 2.62, 1H, ddd, J=4.4, 4 and 3.2 Hz). Assuming the (S)-configuration for 4-OH, this isomer was thought to be (2R,4S,5R)-**12a**. Determination of the enantiomeric purity of (2R,4S,5R)-**12a** was rather troublesome, because its MTPA ester (2R,4S,5R)-**12b** showed no good separation of the diastereomers when analyzed by HPLC. The minor isomer (2R,4S,5R)-**12a** was therefore treated with p-TsOH in EtOH to effect equilibration at C-2 to generate (2S,4S,5R)-**12a**, whose MTPA ester (2S,4S,5R)-**12b** was known to exhibit good diastereomer separation by HPLC. The HPLC analysis of the MTPA esters derived from the above described equilibrated mixture showed the generated (2S,4S,5R)-**12a** to be of 100 % e.e. Accordingly the diastereomeric mixture of **12a** was of 64 % e.e. [(43 x 0.63) + (100 x 0.37) = 64] with regard to the chiral centers at C-4 and C-5.

To secure a supporting evidence for the assumed absolute configuration of the two isomers of **12a**, they were converted to the corresponding dibenzoates **13c** and their CD spectra were measured. To prepare **13c**, **12a** (diastereomeric mixture) was first acetylated with Ac_2O to **12d**. LAH reduction of **12d** gave **13a** in 97 % yield from **12a**. Direct reduction of **12a** with LAH afforded an inferior result. Benzoylation of **13a** yielded dibenzoates **13c** as a diastereomeric mixture at C-2 in a ratio of 63:37 as analyzed by HPLC. The dia-

stereomers of **13c** were separated by prep TLC to give the less polar isomer (21 % recovery) and the more polar isomer (52 % recovery). ^{1}H NMR spectra of these two isomers revealed that the former possessed an ax H at C-4 (δ 5.70, 1H, ddd, J=7.3, 4.4 and 4.1 Hz), while the latter had an eq H at C-4 (δ 5.47, 1H, ddd, J=5.8, 5.8 and 5.8 Hz). In both of them the C-2 H was in eq orientation (J=3.3~4.9 Hz) like in the starting β-hydroxy esters **12a**. Application of the exciton chirality method[28,29] to these dibenzoate isomers provided a supporting evidence concerning their absolute configuration. The exciton-split CD spectrum of the less polar isomer of **13c** in EtOH showed a positive first Cotton effect at 237 nm (Δε +11) and a negative second Cotton effect at 220 nm (Δε -2.8). The more polar isomer of **13c** also exhibited a positive first Cotton effect at 238 nm (Δε +5.8) and a negative second Coton effect at 220 nm (Δε -1.0). Comparison of these data with the CD spectra of some triterpene dibenzoates of similar structural feature[28] supported the assumed (4S)-configuration of the dibenzoates **13c** as depicted in Fig. 3. The less polar isomer was therefore (2R,4S,5S)-**13c** and the more polar one was (2S,4S,5S)-**13c**.

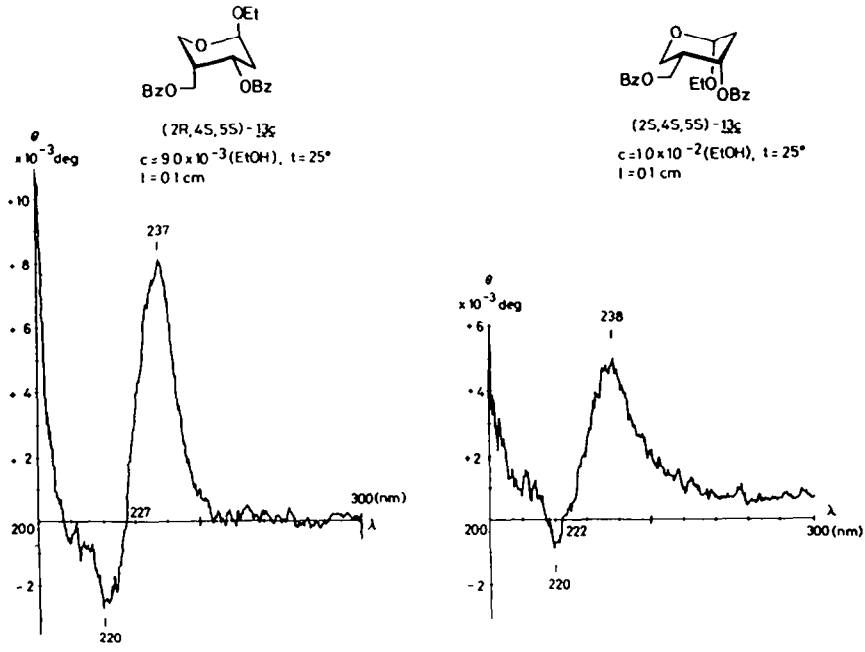

Fig. 3. CD spectra of (2R,4S,5S)-13c and (2S,4S,5S)-13c.

Having clarified the absolute configuration and enantiomeric purity of **13a**, the remaining task was its conversion to **14**. Treatment of a diastereomeric mixture of **13a** with $PhCH_2Br$ and NaH in the presence of $(n\text{-}Bu)_4NI$ in THF[cf.30] gave the corresponding dibenzyl ether **13b** in 80 % yield. The desired phosphonium salt **14** was prepared in quantitative yield from **13b** by heating it with $Ph_3PH^+BF_4^-$ in MeCN.[31,32] The overall yield of **14** from **3** was 8 % in 13 steps.

The second phase of our project as shown in Fig. 4 was the synthesis of the aldehyde **20** (=**B**), the other partner of the Wittig reaction. Reduction of ethyl acetoacetate **15** with a thermophilic yeast Saccharomyces bailii KI 0116 gave (S)-**16** (96~98 % e.e.) in 84 % yield.[18] The dianion derived from **16** was alkylated with allyl bromide according to Fráter to give **17a** contaminated with its syn-isomer (anti:syn=96:4) in 85 % yield.[33] The diastereomeric ratio was determined by capillary GLC using a diastereomeric mixture of ethyl

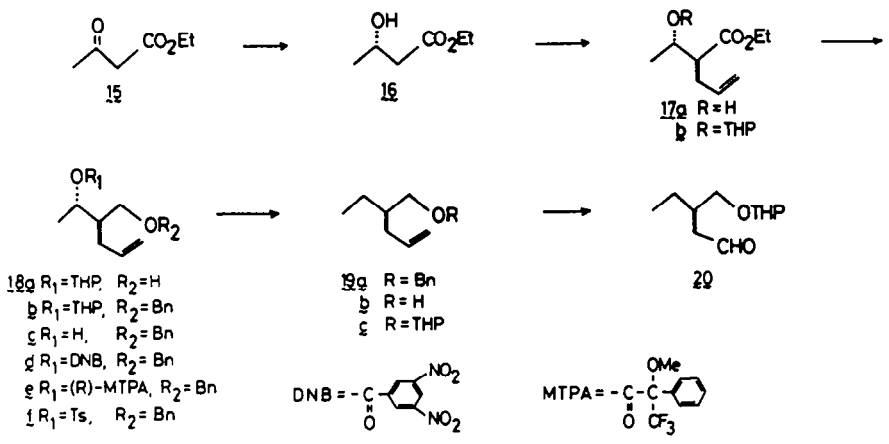

Fig. 4. Synthesis of the aldehyde 20.

(±)-2-(1'-hydroxyethyl)pent-4-enoate (anti:syn=51:49) as a reference sample. Conversion of **17a** to **20** was lengthy but straightforward. The OH group of **17a** was protected as THP ether. Reduction of the resulting **17b** with LAH gave an alcohol **18a**. This was benzylated to **18b**, and the THP protective group was removed from **18b** to give **18c**. The corresponding 3,5-dinitrobenzoate (DNB) **18d** was crystalline, and could be purified by recrystallization to give diastereomerically and enantiomerically pure **18d**. Treatment of **18d** with KOH gave pure **18c**, whose diastereomeric purity as 100 % was checked by capillary GLC. The corresponding (R)-MTPA ester **18e** exhibited a single peak upon HPLC analysis proving the high enantiomeric purity (100 % e.e.) of **18c**. As the task of the OH group to control the absolute configuration of the new chiral center was over, it was removed by tosylation to **18f** followed by its reduction with $LiBEt_3H$.[34] The benzyl (Bn) protective group of **19a** was then replaced by the THP group to give **19c** by reducing **19a** with Na/liq NH_3 and protecting the OH group of **19b**. Finally, the Lemieux-Johnson oxidation of **19c** with OsO_4-$NaIO_4$ gave (R)-**20** in 34 % overall yield from **15** in 13 steps. By switching the protective group from Bn to THP, the construction of the spiroacetal system became less complicated due to the more facile deprotection of the THP group compared with that of the Bn group.

The final stage of the synthesis as shown in Fig. 5 was the coupling of the two building blocks **14** and **20** by the Wittig reaction to give the desired 1,7-dioxaspiro[5.5]undecane system. Treatment of the phosphonium salt **14** with n-BuLi in THF-HMPA generated a deep red phosphorane **21**. This was condensed with the aldehyde **20** to give a cyclic enol ether **22**. Acid treatment (conc $HCl:H_2O:THF=1:5:20$) of crude **22** gave a mixture of spiroacetals. As one of the building blocks was optically impure (64 % e.e.), formation of four spiroacetal dibenzyl ethers (**1b**, **23b**, **25b** and **26b**) were expected. However, the products obtained after SiO_2 chromatography were a mixture of dibenzyl ethers **1b** and **23b** (46 % from **14**) and also a mixture of 12-monobenzyl ethers **1c**, **2c** and **24c** (35 % from **14**). The unexpected formation of 12-monobenzyl ethers could be rationalized as shown in Fig. 5 by the sequence **22** → **α** → **β** → **γ** → **1c** + **2c** + **24c** involving (i) olefin isomerization (ii) retro-Michael-like elimination of $PhCH_2OH$ (iii) addition of H_2O and (iv) spiroacetal formation. Under the acid condition employed, the above process competed to some extent with the desired hydrolysis of the THP group followed by spiroacetalization. The elimination-addition mechanism as above allowed the formation of **2c** and **24c**, where the OH group and the CH_2OBn group were in trans-relationship in contrast to the original cis-relation-

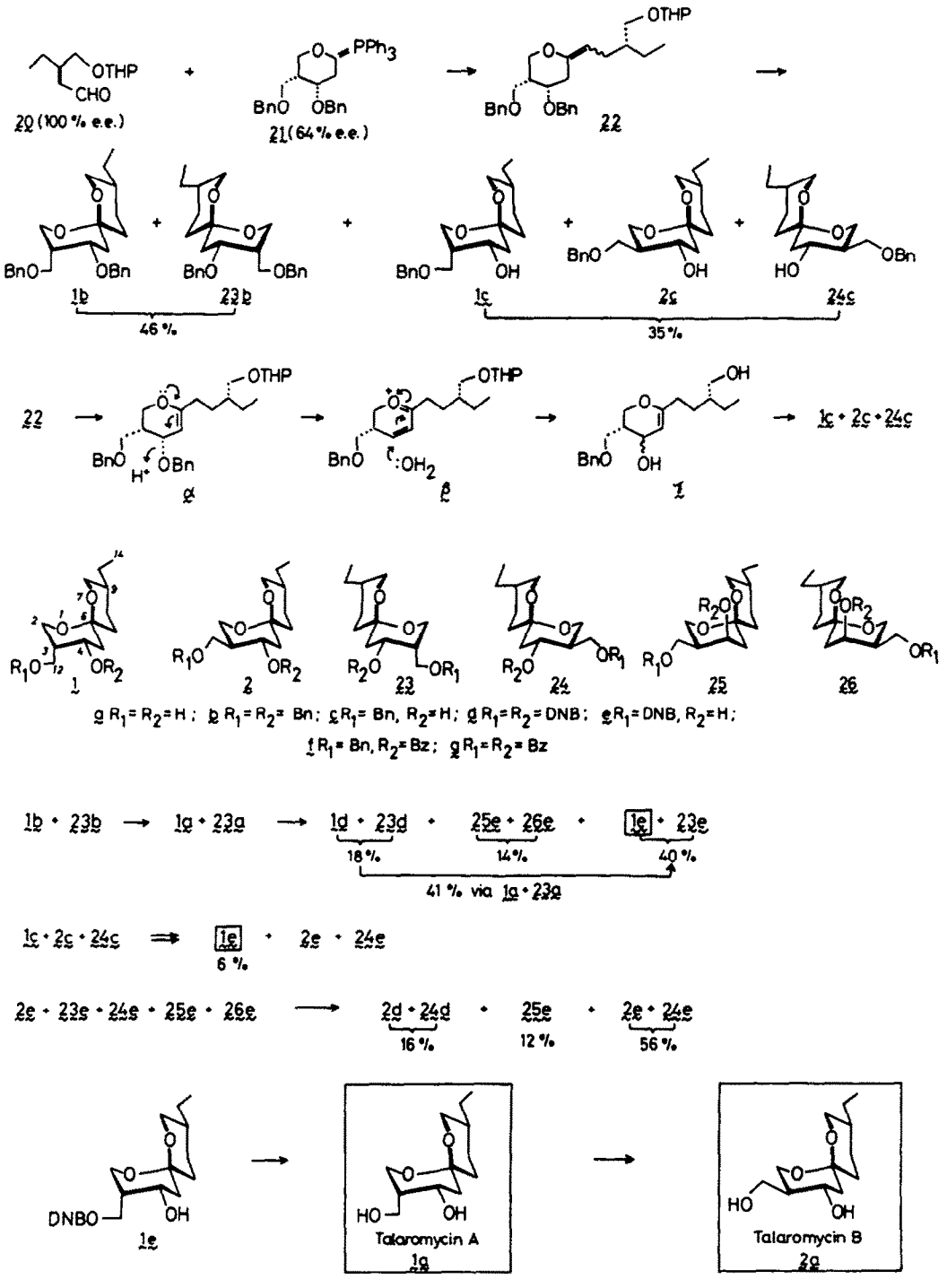

Fig. 5. Synthesis of Talaromycins A and B.

ship in **21**. The structures **1b**, **23b**, **1c**, **2c** and **24c** were deduced on the basis of the NMR analysis of thir 4-benzoates (**1f**, **2f** and **24f**) or that of their 12-mono DNB derivatives **1e**, **2e** and **23e** (see Experimental). Other two possible isomers could not be isolated from the reaction mixture.

Crystalline 12-mono DNB derivative **1e** of (3R,4S,6R,9R)-talaromycin A **1a** was derived from the mixture of the dibenzyl ethers **1b** and **23b** in the following manner. The mixture (2.35 g) of **1b** and **23b** was reduced with Na/liq NH_3 to give a mixture of **1a** and **23a** in 75 % yield. Treatment of the mixture of **1a** and **23a** with 3,5-dinitrobenzoyl chloride (DNBCl) in pyridine in the presence of 4-(N,N-dimethylamino)pyridine (DMAP) gave a complex mixture of products. This was chromatographed over SiO_2 to give, in the order of elution, a mixture of bis DNB esters (**1d** and **23d**; 18 % yield), a mixture of new mono DNB esters (**25e** and **26e**; 14 % yield), and a mixture of talaromycin A 12-mono DNB ester **1e** and its isomer **23e** (40 % yield). The new mono DNB esters **25e** and **26e** must have been generated by epimerization at the spiro-center in the course of the acylation reaction, because they could be detected by TLC monitoring of the acylation reaction. The epimerization was due to the preference of the CH_2ODNB group to adopt eq orientation. Pure talaromycin A 12-mono DNB ester **1e** (509 mg), m.p. 147~148°, $[\alpha]_D^{18}$ -113° ($CHCl_3$), was obtained by recrystallization of the mixture (730 mg) of **1e** and **23e**. Pure **23e** (123 mg), m.p. 171.5~173°, $[\alpha]_D^{18}$ +136° ($CHCl_3$), was also secured by purification with prep TLC and recrystallization. The mixture of bis DNB esters (**1d** and **23d**) was hydrolyzed with K_2CO_3 to a mixture of **1a** and **23a**, which was acylated again and recrystallized to give additional amounts of **1e** (62 mg) and **23e** (26 mg). A further amount of **1e** (93 mg) was obtained from a mixture (1.10 g) of monobenzyl ethers (**1c**, **2c** and **24c**) by reduction with Na/liq NH_3, acylation with DNBCl and recrystallization of the resulting mixture of mono DNB esters **1e**, **2e** and **24e**. In total, talaromycin A 12-mono DNB ester **1e** was obtained in 13 % overall yield from **13b** in 5 steps. From the combined mother liquor of the above-mentioned recrystallization experiments, small amounts of pure talaromycin B 12-mono DNB ester **2e**, m.p. 104~104.2°, $[\alpha]_D^{24}$ -29.8° ($CHCl_3$), and another mono DNB ester **25e**, m.p. 128.8~129.2°, $[\alpha]_D^{24}$ -77.7° ($CHCl_3$), were isolated. The amount of pure **2e** was so small that its hydrolysis to talaromycin B **2a** was not attempted. In Fig. 6 is shown the ratio of four 12-mono DNB esters (**1e**, **23e**, **25e** and **26e**) generated from the mixture of dibenzyl ethers (**1b** and **23b**) as expressed in percentages. As can be seen from Fig. 6, the ratio of the isomers reflected the enantiomeric purity of the phosphorane **21**.

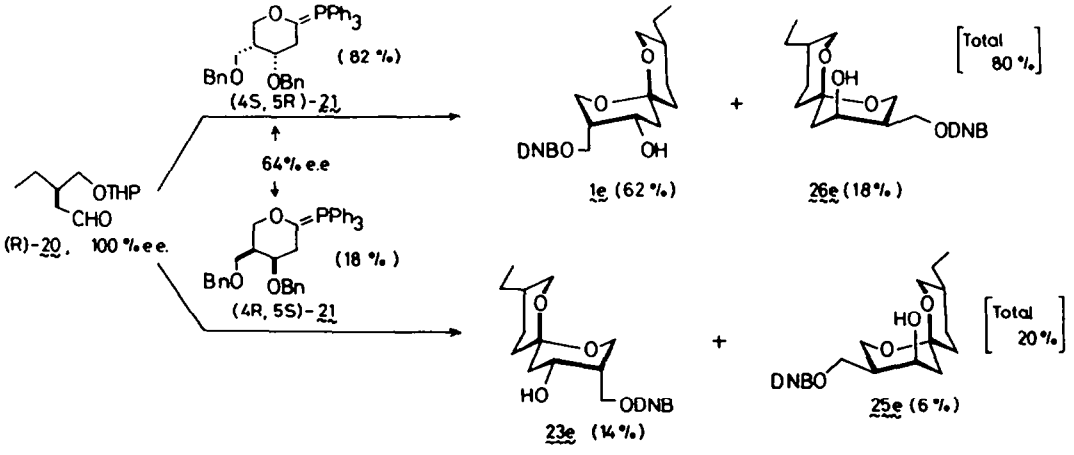

Fig. 6. Derivation of the 12- mono DNB esters of talaromycin stereoisomers.

To complete the synthesis, talaromycin A mono DNB ester **1e** was hydrolyzed with K_2CO_3 in MeOH-THF to give, in 89 % yield, the natural enantiomer of talaromycin A **1a** for the first time as crystals, m.p. 19~20°, $[\alpha]_D^{24}$ -146° ($CHCl_3$) [lit.[8] $[\alpha]_D^{20}$ -110.2° ($CHCl_3$);

lit.[9] $[\alpha]_D^{26}$ -124.9° ($CHCl_3$)]. Our success in synthesizing highly pure and crystalline (-)-talaromycin A **1a** may be due to the nicely crystalline nature of its 12-mono DNB ester **1e**. Because of that property we were able to purify it completely. (-)-Talaromycin B **2a**, $[\alpha]_D^{24}$ -89.1° ($CHCl_3$) [lit.[8] $[\alpha]_D^{20}$ -84.1° ($CHCl_3$)], was also prepared from **1e** by hydrolysis with K_2CO_3 followed by acid-catalyzed isomerization with Amberlyst®-15 (H^+-form) in MeOH in 78 % yield. The 400 MHz ^1H NMR spectra of our synthetic (-)-talaromycins A and B were in good accord with the authentic spectra of the natural products kindly provided by Prof. Lynn (360 MHz)[1] and Prof. Smith (250 and 500 MHz).[8] The ^{13}C NMR spectrum of (-)-talaromycin B was in accord with the data published for (±)-talaromycin B.[5] The CD spectra of the dibenzoates **1g** and **2g** of (-)-talaromycins A and B are shown in Fig. 6. They were also

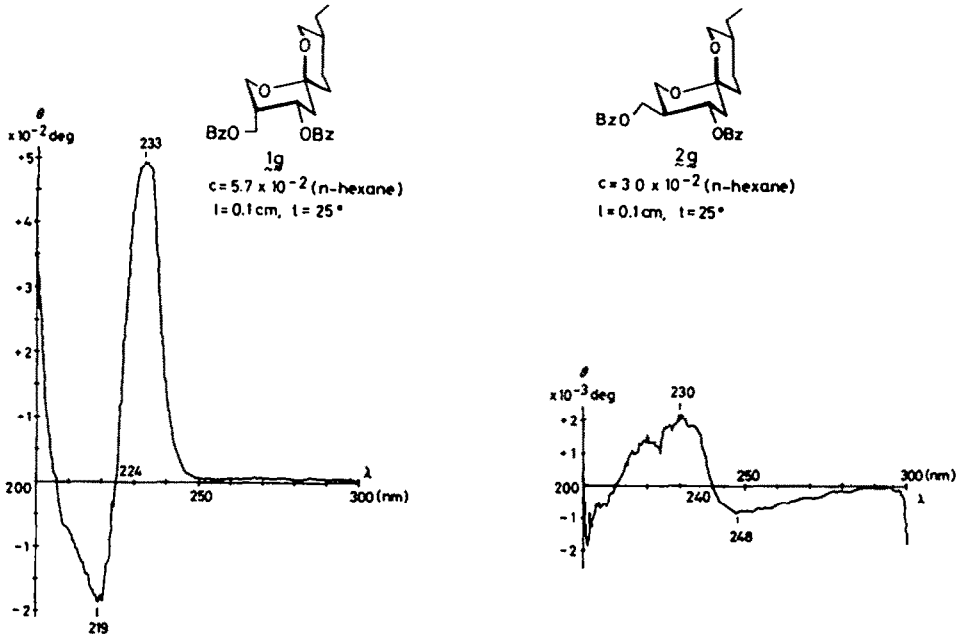

Fig. 7. CD spectra of the dibenzoates of talaromycins A and B.

identical to Prof. Lynn's authentic spectra of the dibenzoates derived from the natural products. The overall yield of **1a** was 4 % from ethyl acetoacetate **15** in 18 steps or 0.9 % from dimethyl 3-oxopentanedioate **3** in 19 steps. (-)-Talaromycin B **2a** was obtained in 3 % overall yield from **15** in 19 steps or in 0.8 % overall yield from **3** in 20 steps.

In summary, highly pure natural enantiomers of talaromycins A and B were synthesized in a convergent manner employing the chiral building blocks of microbial origin. The yeast reduction was again shown to be useful in organic synthesis. An enantiomerically impure intermediate such as **21** can satisfactorily be employed to afford enantiomerically pure target molecules after removing the unwanted diastereomers. Experimental importance of a crystalline intermediate in a chiral synthesis was also exemplified in the present case. The principle of 'optical enrichment'[9,11] in the case of a chiral synthesis was applicable to the present synthesis, too.

EXPERIMENTAL

All bps and mps were uncorrected. IR spectra were measured as films for oils or as nujol mulls or KBr discs for

solids on a Jasco IRA-102 or IRA-202 spectrometer unless otherwise stated. ^{1}H NMR spectra were recorded with TMS as an internal standard on a Hitachi R-24A (60 MHz) or on a JEOL JNM FX-100 (100 MHz, $CDCl_3$) or on a JEOL JNM GX-400 (400 MHz, $CDCl_3$) spectrometer. ^{13}C NMR spectra were measured with TMS as an internal standard as $CDCl_3$ soln at 25 MHz on a Jeol JNM FX-100 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter as $CHCl_3$ soln. ORD and CD spectra were measured on a Jasco J-20C spectropolarimeter. Mass spectra were recorded on a JEOL DX-303 or on a Hitachi RMU-6M spectrometer at 70 eV. Fuji-Davison BW-820 MH was used for SiO_2 column chromatography. Merck Kieselgel 60 Art 5717 or 5744 were used for prep TLC separation. HPLC analyses were performed on Nucleosil® 50-5 (25 cm x 4.6 mm) by the detection at 254 nm unless otherwise stated.

Dimethyl 3-tetrahydropyranyloxypentanedioate **4b**. Dimethyl 3-oxopentanedioate **3** (200 g, 1.15 mol) was reduced with $NaBH_4$ (16.7 g, 0.44 mol) in MeOH (700 ml) in a usual manner to give crude dimethyl 3-hydroxypentanedioate **4a** (213 g, quantitative), νmax 3550 (s), 1740 (s), 1200 (s) cm^{-1}. Crude **4a** (210.3 g, ~1.14 mol) was treated with dihydropyran (138 g, 1.64 mol) and p-TsOH·H_2O (0.4 g, 2.1 mmol) in Et_2O (1.2 l) in a usual manner to give crude **4b** (296.9 g, quantitative). Analytical sample: b.p. 105~121°/1.0 Torr; n_D^{18} 1.4521; νmax 1740 (s), 1200 (s), 1030 (s) cm^{-1}; δ (CCl_4) 1.10~1.95 (6H, m), 2.47, 2.54, 2.57 and 2.62 (total 4H, each d, J=6 Hz), 3.10~3.90 (2H, m), 3.64 (6H, s), 4.36 (1H, t, J=6 Hz), 4.72 (1H, br.s). (Found: C, 55.47; H, 7.68. Calc for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75 %).

Pentane-1,3,5-triol 3-THP ether **5a**. Crude **4b** (129 g, 0.50 mol) was reduced with $LiAlH_4$ (LAH, 30 g, 0.69 mol) in Et_2O (720 ml) in a usual manner to give crude **5a** (100 g, 98 % from **3**); νmax 3420 (s), 1140 (s), 1080 (s), 1030 (s) cm^{-1}; δ ($CDCl_3$) 1.00~2.40 (10H, m), 3.32 (2H, s, OHx2), 3.10~4.38 (7H, m), 4.4~4.8 (1H, br.s).

Pentane-1,3,5-triol **5b**. Crude **5a** (235.7 g, ~1.15 mol) was treated with p-TsOH·H_2O (2.6 g, 14 mmol) in MeOH (1.2 l) in a usual manner to give crude **5b** (146.9 g, quantitative). Analytical sample: b.p. 154~156°/1.3 Torr; n_D^{18} 1.4655; νmax 3400 (s), 1050 (s) cm^{-1}; δ (C_5D_5N-$CDCl_3$) 2.00 (4H, dt, J=6, 6 Hz), 4.09 (4H, t, J=6 Hz), 4.43 (1H, t, J=6 Hz), 5,86 (3H, s, OHx3). (Found: C, 50.35; H,10.15. Calc for $C_5H_{12}O_3$: C, 49.98; H, 10.07 %).

Pentane-1,3,5-triol 1,3-acetonide **6**. Crude **5b** (144 g, 1.13 mol) was treated with 2,2-dimethoxypropane (254 g, 2.4 mol) and p-TsOH·H_2O (6.5 g, 34 mmol) in acetone (1.2 l) in a usual manner to give **6** (98.3 g, b.p. 60~107°/15~16 Torr, 53 % from **3**). A portion was chromatographed over SiO_2 [n-hexane-Et_2O (15:1~2:1)] followed by distillation in the presence of K_2CO_3 to give an analytical sample: b.p. 113~115°/17 Torr; n_D^{18} 1.4495; νmax 3450 (s), 1200 (s), 1100 (s), 1060 (s) cm^{-1}; δ (CCl_4) 0.95~1.45 (2H, m), 1.32 (3H, s), 1.43 (3H, s), 1.63 (2H, dt, J=5, 5 Hz), 3.06 (1H, t, J=5 Hz, OH), 3.25~4.31 (4H, m). (Found: C, 60.40; H, 10.05. Calc for $C_8H_{16}O_3$: C, 59.98; H, 10.07 %).

3,5-Dihydroxypentanal acetonide **7**. According to the reported procedure,[19,20] **6** (20 g, 125 mmol) was oxidized with pyridinium chlorochromate (PCC, 45.4 g, 211 mmol) in CH_2Cl_2 (310 ml) in the presence of MS 3Å (40 g) to give crude **7** (19.3 g, 97 %). A portion of it was chromatographed over SiO_2 [n-pentane-Et_2O (20:1~3:1)] followed by distillation under Ar to give an analytical sample; b.p. 83~87°/45 Torr; n_D^{18} 1.4419; νmax 2750 (m), 1730 (s), 1200 (s), 1165 (s), 1100 (s) cm^{-1}; δ (CCl_4) 1.26 (3H, s), 1.41 (3H, s), 0.80~1.90 (2H, m), 2.45 (2H, ddd, J=2, 2, 6 Hz), 2.46 (1H, dd, J=2, 6 Hz), 3.40~4.00 (2H, m), 4.00~4.63 (1H, m), 9.86 (1H, dd, J=2, 2 Hz). (Found: C, 60.31; H, 8.87. Calc for $C_8H_{14}O_3$: C, 60.74; H, 8.92 %).

2-Ethoxytetrahydropyran-4-ol **8** A soln of crude **7** (18.2 g, ~115 mmol) and p-TsOH·H_2O (0.4 g, 2.1 mmol) in 99 % EtOH (80 ml) and CH_2Cl_2 (240 ml) was stirred and heated under reflux overnight with azeotropic removal of water by use of MS 4Å. After cooling, the mixture was neutralized by the addition of solid Na_2CO_3 (4.6 g, 43.4 mmol) and stirred further for 4 h at room temp. The solid was filtered off through a pad of Celite and washed with Et_2O. The combined filtrate and washings were concentrated in vacuo. The residue was diluted with Et_2O, filtered through a pad of Florisil, and the Florisil layer was washed with Et_2O. The combined filtrate and washings were concentrated in vacuo. The residue (15.8 g) was distilled in the presence of K_2CO_3 to give **8** (10.8 g, 64 %), b.p. 92~94°/9 Torr; n_D^{24} 1.4438; νmax 3430 (s), 1130, (s), 1060 (s) cm^{-1}; δ (CCl_4) 1.18 (~2.4H, t, J=7 Hz), 1.25 (~0.6H, t, J=7 Hz,), 1.35~2.40 (4H, m), 2.87~4.30 (6H, m), 4.52 (~0.2H, dd, J=3, 14 Hz), 4.78 (~0.8H, dd, J=3, 3 Hz). (Found: C, 57.41; H, 9.55. Calc for $C_7H_{14}O_3$: C, 57.51; H, 9.65 %).

2-Ethoxytetrahydropyran-4-one **9**. According to the reported procedure,[20,22] **8** (4.7 g, 32 mmol) was oxidized with pyridinium dichromate (PDC, 24.2 g, 64.3 mmol) in CH_2Cl_2 (90 ml) in the presence of MS 3Å (34 g) followed by chromatographic purification [SiO_2 (80 g), n-hexane-Et_2O (10:1)] then distillation to give **9** (3.3 g, 72 %), b.p. 104~107°/23 Torr; n_D^{25} 1.4395; νmax 1730 (s), 1120 (s), 1060 (s) cm^{-1}; δ (CCl_4) 1.21 (3H, t, J=7 Hz), 1.90~2.83 (4H, m), 3.10~4.35 (4H, m), 5.05 (1H, dd, J=3.6, 3.6 Hz). (Found: C, 58.11; H, 8.38. Calc for $C_7H_{12}O_3$: C, 58.31; H, 8.39 %).

Ethyl 2-Ethoxy-4-oxo-5-tetrahydropyrancarboxylate **10** and ethyl 2-ethoxy-4-oxo-3-tetrahydropyrancarboxylate **11**. A soln of LDA was prepared from n-BuLi (1.65 M in n-hexane, 12.4 ml, 20.5 mmol) and i-Pr_2NH (2.9 g, 20.5 mmol) in THF (45 ml) under Ar in a usual manner. To this soln was added dropwise a soln of **9** (2.5 g, 17.3 mmol) in THF (15 ml) over 13 min at -76°~-72° and then added HMPA (12 ml) over 2 min at -76°~-66°. The reaction temp was allowed to rise to -35° to give a homogeneous soln. To this was added a soln of ethyl cyanoformate[24] (2.2 g, 21.8 mmol) in HMPA (2 ml) all at once at -76°~-56°. After stirring for 15 min at -78°, the mixture was poured into ice-water, neutralized by the addition of dil HCl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (9.1 g) was chromatographed over SiO_2 [110 g, n-hexane-EtOAc (17:1)] followed by the purification of fractions contaminated with **11** by prep TLC [C_6H_6-EtOAc (5:1)] to give **10** (total 2.04 g, 55 %). Analytical sample: b.p. 98~99°/0.45 Torr; n_D^{20} 1.4656; νmax 1750 (s), 1730 (s), 1670 (s), 1635 (s), 1240 (s), 1060 (s) cm^{-1}; δ (CCl_4) 1.20 (3H, t, J=7 Hz), 1.29 and 1.36 (total 3H, each t, J=7 Hz), 1.90~2.80 (2H, m), 3.10~4.10 (2H, m), 4.17 (4H, q, J=7 Hz), 4.84 (1H, dd, J=2, 3 Hz), 5.12 (~0.27H, br.s), 11.77 (~0.53H, s), 12.12 (~0.2H, s). (Found: C, 55.18; H, 7.02. Calc for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46 %). Further elution with the same solvent gave **11** (total 0.20 g, 5.4 %); νmax 1745 (s), 1680 (s), 1640 (w), 1565 (s), 1265 (s), 1150 (s) cm^{-1}; δ (CCl_4) 1.25 (3H, t, J=7 Hz), 1.35 (3H, t, J=7 Hz), 1.90~2.70 (2H, m), 3.20~4.10 (3H, m), 4.02 (2H, q, J=7 Hz), 4.28 (2H, q, J=7 Hz), 5.07 (1H, br.d, J=5 Hz); MS m/z 216 (M^+), 215, 201, 171, 143, 73, 45, 43 (base peak).

Ethyl (2S,4S,5R)- and (2R,4S,5R)-2-ethoxy-4-hydroxy-5-tetrahydropyrancarboxylate **12a**. To a soln of sucrose (250 g, 730 mmol) in phosphate buffer (0.1 M, pH 8, 1.3 l) was added dry baker's yeast (110 g, Oriental Yeast Co., Ltd.) at 30°. After vigorous stirring for 10 min with aeration, to this fermenting mixture was added an emulsion of **10** (5.2 g, 24 mmol) in 0.2 % Triton X-100 aq soln (50 ml), and the stirring was continued for 1 h at 30°. After the addition of Et_2O, Celite and a small amount of Norit, the mixture was filtered. The filter-cake was washed thoroughly with EtOAc. The organic layer of the combined filtrate and washings was separated. The aq layer was saturated with NaCl and extracted with EtOAc. The combined EtOAc soln was dried ($MgSO_4$) and concentrated in vacuo. The residue (7.8 g) was chromatographed over SiO_2 (80 g). Firstly eluted fractions [n-hexane-EtOAc (15:1~12:1)] gave (2S,4S,5R)-**12a** (1.95 g, 37 %), n_D^{20} 1.4486; $[\alpha]_D^{18}$ +57.0° (c=0.51); νmax 3550 (s), 1730 (s), 1120 (s), 1100 (s), 1030 (s) cm^{-1}; δ (100 MHz +D_2O) 1.26 (3H, t, J=7.2 Hz), 1.29 (3H, t, J=7.2 Hz), 1.87 (1H, ddd, J=3.4, 3.5, 14.2 Hz), 2.04 (1H, ddd, J=2.0, 3.7, 14.2 Hz), 2.72 (1H, ddd, J=2.9, 5.0, 12.2 Hz), 3.46 (2H, dq, J=7.2, 9.6 Hz), 3.76 (1H, dd, J=5.0, 11.7 Hz), 3.67~3.98 (1H, m), 4.18 (1H, dd, J=11.7, 12.2 Hz), 4.20 (2H, q, J=7.2 Hz), 4.89 (1H, br.dd, J=2.0, 3.4 Hz); HR-MS m/z 217.1116 (M^+-H). Calc for $C_{10}H_{17}O_5$: 217.1076. Determination of the optical purity of (2S,4S,5R)-**12a** was as follows. (a) According to the reported procedure[27], (2S,4S,5R)-**12a** was con-

verted to its (R)- and (S)-MTPA ester, (2S,4S,5R)-**12b** and **12c**, respcetively. (b) HPLC analysis of (2S,4S,5R)-**12b**: [Column, Silica-125lN, 25 cm x 4.6 mm; n-hexane-THF (20:1), 1 ml/min] Rt 56.6 min (28.5 %), 57.9 min (71.5 %). HPLC analysis of the ~1:1 mixture of (2S,4S,5R)-**12b** and **12c** under the same condition as above showed Rt 58.7 min (48.4 %) and 60.0 min (51.6 %). Therefore the optical purity of (2S,4S,5R)-**12a** was determined to be 43 % e.e.

Secondly eluted fractions [n-hexane-EtOAc (10:1~8:1)] gave a mixture of (2S,4S,5R)- and (2R,4S,5R)-**12a** (1.60 g, 31 %).

Thirdly eluted fractions [n-hexane-EtOAc (8:1)] gave (2R,4S,5R)-**12a** (0.60 g, 11 %), n_D^{19} 1.4549; $[\alpha]_D^{18}$ -76.9° (c=0.54); νmax 3500 (s), 1735 (s), 1140 (s), 1065 (s) cm^{-1}; δ (CCl_4) 1.16 (3H, t, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.55~2.00 (2H, m), 2.62 (1H, ddd, J=3.2, 4.0, 4.4 Hz), 3.03 (1H, br.d, J=5.8 Hz, OH), 3.20~4.10 (5H, m), 4.16 (2H, q, J=7 Hz), 4.71 (1H, dd, J=3.6, 4.4 Hz); HR-MS m/z 217.1087 (M^+-H). Calc for $C_{10}H_{17}O_5$: 217.1076. Since the separation of the diastereomeric mixture of (2R,4S,5R)-**12b** and **12c** by HPLC was difficult, the optical purity of (2R,4S,5R)-**12a** was determined as follows. (a) Preparation of an equilibrium mixture of (2RS,4S,5R)-**12a**. A soln of (2R,4S,5R)-**12a** (9.5 mg, 0.043 mmol) and a catalytic amount of p-TsOH·H_2O in 99 % EtOH (0.5 ml) was stirred for a week at room temp and then diluted with Et_2O, washed with sat $NaHCO_3$ aq soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give (2RS,4S,5R)-**12a** (10.9 mg). (b) HPLC analysis of the MTPA ester, (2RS,4S,5R)-**12b**, prepared from (2RS,4S,5R)-**12a** and (S)-MTPA-Cl[27]: [under the same condition as described for that of (2S,4S,5R)-**12b**] Rt 37.3 min [70.8 %, (2R,4S,5R)-**12b**], 58.0 min [28.3 %, (2S,4S,5R)-**12b**]. (2S,4S,5R)-**12b** was shown to be a single diastereomer. Therefore the optical purity of (2R,4S,5R)-**12a** was determined to be 100 % e.e.

Ethyl (4S,5R)-4-Acetoxy-2-ethoxy-5-tetrahydropyrancarboxylate **12d**. (2RS,4S,5R)-**12a** (4.7 g, 22 mmol) was treated with Ac_2O (6.2 ml, 65.7 mmol) and 4-(N,N-dimethylamino)pyridine (DMAP, 0.25 g, 2.0 mmol) in C_5H_5N (20 ml) in a usual manner followed by chromatographic purification over SiO_2 [70 g, n-hexane-EtOAc (9:1)] to give **12d** (6.0 g, quantitative). A small amount of (2S,4S,5R)-**12d** was obtained from the later eluted fractions: n_D^{16} 1.4419; $[\alpha]_D^{17}$ +32.7° (c=1.07); νmax 1740 (s), 1240 (s), 1125 (s), 1025 (s) cm^{-1}; δ (CCl_4) 1.19 (3H, t, J=7 Hz), 1.23 (3H, t, J=7 Hz), 1.97 (3H, s), 1.70~2.20 (1H, m), 2.20~2.49 (1H, m), 2.66 (1H, ddd, J=3.2, 4.8, 11 Hz), 3.00~4.20 (4H, m), 4.12 (2H, q, J=7 Hz), 4.67 (1H, dd, J=2, 4 Hz), 5.21 (1H, ddd, J=3.2, 3.2, 3.2 Hz). (Found: C, 55.30; H, 7.73. Calc for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75 %).

(4S,5R)-2-Ethoxy-4-hydroxy-5-tetrahydropyranmethanol **13a**. **12d** (5.8 g, 22.3 mmol) was reduced with LAH (1.75 g, 46.1 mmol) in Et_2O (100 ml) in a usual manner to give crude **13a** (3.8 g, 97 %), νmax 3420 (s), 1120 (s), 1030 (s) cm^{-1}; δ (CCl_4) 1.25 (3H, t, J=7 Hz), 1.45 (2H, s, OHx2), 1.55~2.40 (3H, m), 2.80~4.60 (7H, m), 4.95 (1H, br.dd, J=3, 3 Hz); MS m/z 176 (M^+). This was employed in the next step without further purification.

(2R,4S,5S)- and (2S,4S,5S)-2-ethoxy-4-hydroxy-5-tetrahydropyranmethanol dibenzoate **13c**. **13a** (44 mg, 0.25 mmol) was treated with benzoyl chloride (0.12 ml, d 1.211, 1.0 mmol) in C_5H_5N (0.7 ml) in a usual manner followed by chromatographic purification over SiO_2 [2 g, n-hexane-EtOAc (40:1~30:1)] to give (2RS,4S,5S)-**13c** (91 mg, 95 %). HPLC [n-hexane-THF (20:1), 1.1 ml/min] Rt 31.9 min (37 %), 52.7 min (63 %). Further purification of this by prep TLC [n-hexane-Et_2O (5:1, x 8)] gave (2R,4S,5S)-**13c** (19 mg, 21 %) as a less polar isomer and (2S,4S,5S)-**13c** (47 mg, 52 %) as a more polar isomer. (2R,4S,5S)-**13c**; TLC [n-hexane-EtOAc (2:1)] Rf 0.66; CD (c=9.0 x 10^{-3}, EtOH, t=25°): [Δε (λ, nm)] +11 (237), 0 (227), -2.8 (220); νmax 3090 (w), 3040 (w), 1725 (vs), 1605 (m), 1590 (m), 1490 (m), 1270 (vs), 1110 (vs), 715 (vs), 690 (m) cm^{-1}; δ (100 MHz) 1.26 (3H, t, J=7.3 Hz), 1.97 (1H, ddd, J=4.4, 4.4, 13 Hz), 2.17 (1H, ddd, J=3.3, 7.3, 13.0), 2.40~2.77 (1H, m), 3.50 (1H, dq, J=7.3, 10 Hz), 3.84 (1H, dq, J=10, 7.3 Hz), 3.87 (1H, dd, J=5.8, 12 Hz), 4.11 (1H, dd, J=4.4, 12 Hz), 4.52 (2H, d, J=7.3 Hz), 4.91 (1H, dd, J=3.3, 4.4 Hz), 5.70 (1H, ddd, J=4.1, 4.4, 7.3 Hz), 7.20~7.70 (6H, m), 8.02 (4H, ddd, J=2.0, 7.3, 9.3 Hz); MS m/z 384 (M^+), 369, 339, 262, 217, 140, 123, 122, 105, 77. (2S,4S,5S)-**13c**: TLC [n-hexane-EtOAc (2:1)] Rf 0.60; CD (c=1.0 x 10^{-2}, EtOH, t=25°): [Δε (λ, nm)] +5.8 (238), 0 (222), -1.0 (220). νmax 3080 (w), 3050 (w), 1720 (vs), 1605 (s), 1585 (m), 1495 (w), 1270 (vs), 1110 (vs), 710 (s), 690 (m) cm^{-1}; δ (100 MHz) 1.21 (3H, t, J=7.3 Hz), 2.04 (1H, ddd, J=4.9, 5.8, 13 Hz), 2.17 (1H, ddd, J=4.9, 5.8, 13 Hz), 2.45~2.75 (1H, m), 3.45 (1H, dq, J=10, 7.3 Hz), 3.75 (1H, dd, J=8.7, 12 Hz), 3.86 (1H, dq, J=10, 7.3 Hz), 4.24 (1H, dd, J=8.4, 12 Hz), 4.43 (2H, d, J=7.3 Hz), 4.78 (1H, dd, J=4.9, 4.9 Hz), 5.47 (1H, ddd, J=5.8, 5.8, 5.8 Hz), 7.12~7.70 (6H, m), 8.04 (4H, ddd, J=2.0, 7.3, 9.3 Hz); MS m/z 384 (M^+), 369, 339, 262, 217, 140, 123, 122, 105, 77.

(4S,5R)-2-Ethoxy-4-hydroxy-5-tetrahydropyranmethanol dibenzyl ether **13b**. Under Ar **13a** (3.7 g, 21 mmol) was treated with NaH (3.5 g, 60 % in mineral oil, 87.5 mmol), $n\text{-}Bu_4N^+I^-$ (0.38 g, 1.0 mmol)[30] and $PhCH_2Br$ (10.9 g, 63.8 mmol) in THF (80 ml) with refluxing for 1 h followed by chromatographic purification over SiO_2 [70 g, n-hexane-EtOAc (50:1~10:1)] to give **13c** (6.0 g, 80 %), n_D^{27} 1.5267; $[\alpha]_D^{21}$ -16.3° (c=0.71); νmax 3110 (w), 3080 (m), 3050 (m), 1500 (m), 1100 (s), 740 (s), 700 (s) cm^{-1}; δ (CCl_4) 1.15 (3H, t, J=7 Hz), 1.50~1.87 (2H, m), 1.87~2.33 (1H, m), 3.00~4.21 (7H, m), 4.39 (4H, br.s), 4.49~4.82 (1H, m), 7.17 (10H, br.s); MS m/z 356 (M^+), 341, 310, 241, 219, 203, 202, 91.

(4S,5R)-4-Benzyloxy-5-benzyloxymethyl-2-tetrahydropyranyltriphenylphosphonium tetrafluoroborate **14**. A soln of **13b** (1.13 g, 3.17 mmol) and $Ph_3PH^+BF_4^-$ (1.26 g, 3.61 mmol)[31] in MeCN (20 ml) was stirred and heated under reflux for 1 h under Ar. The mixture was concentrated in vacuo, and the residue was washed with Et_2O (10 ml x 13). The residue was then suspended in C_6H_6 (20 ml), and the mixture was concentrated in vacuo to remove H_2O azeotropically. This process was repeated four times. The residue was heated at ~80° (bath temp) in vacuo overnight to dryness, giving crude **14** (2.20 g, quantitative). This was employed in the next step without further purification.

Ethyl (2S,1'S)-2-(1'-hydroxyethyl)pent-4-enoate (2S,1'S)-**17a** According to the reported procedure,[33] (S)-**16** [b.p. 70~75°/15 Torr; $[\alpha]_D^{21}$ +42.6° (c=1.04); 96~98 % e.e.; 26.4 g, 0.20 mol] gave (2S,1'S)-**17a** (29.3 g, 85.2 %), b.p. 95~103°/16 Torr; $[\alpha]_D^{22}$ +14.8° (c=1.55); [lit.[33] $[\alpha]_D^{22}$ +14.5° (c=0.37, $CHCl_3$); ca. 97 % e.e.].

Ethyl (2RS,1'RS)-2-(1'-hydroxyethyl)pent-4-enoate (2RS,1'RS)-**17a**. Ethyl 2-acetylpent-4-enoate [5.4 g, prepared from ethyl acetoacetate **15**, allyl bromide and K_2CO_3 in refluxing acetone-DMP (4:1); contaminated with dialkylated product (purity 60 %)] was reduced with $NaBH_4$ (0.49 g, 10.3 mmol) in 99 % EtOH (30 ml) in a usual manner. Chromatographic purification [SiO_2 (140 g), n-hexane-Et_2O (12:1~10:1)] gave ethyl 2-allyl-2-(1'-hydroxyethyl)pent-4-enoate (2.1 g, 26 % from **15**) and (±)-**17a** (2.1 g, b.p. 61~65°/3 Torr; 32 % from **15**).

Ethyl (2S,1'S)-2-(1'-tetrahydropyranyloxyethyl)pent-4-enoate **17b**. (2S,1'S)-**17a** (29.1 g, 169 mmol) was treated with dihydropyran (23.1 g, 274 mmol) and pyridinium p-toluenesulfonate (PPTS, 5.5 g, 21.9 mmol) in CH_2Cl_2 (150 ml) followed by a usual workup[cf.10,11] to give **17b** (43.7 g, quantitative), b.p. 92°/0.2 Torr; n_D^{24} 1.4476; $[\alpha]_D^{23}$ +25.3° (c=1.07); νmax 3110 (m), 1740 (s), 1650 (m), 1185 (s), 1125 (s), 1035 (s), 1025 (s), 990 (s), 915 (s) cm^{-1}; δ (CCl_4) 1.11 (3H, d, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1.35~2.00 (6H, m), 2.36 (2H, br.d, J=5 Hz), 1.97~2.65 (1H, m), 3.10~4.40 (3H, m), 4.08 and 4.10 (total 2H, each q, J=7 Hz), 4.45~4.78 (1H, br.d, J=8 Hz), 4.78~5.25 (2H, m), 5.25~6.30 (1H, m). (Found: C, 65.29; H, 9.44. Calc for $C_{14}H_{24}O_4$: C, 65.69; H, 9.44 %).

(2R,3S)-2-Allylbutane-1,3-diol 3-THP ether **18a**. **17b** (43.5 g, 169.7 mmol) was reduced with LAH (7.5 g, 198 mmol) in Et_2O (450 ml) in a usual manner[cf.10] to give **18a** (36.3 g, 99.7 %), b.p. 100~101°/0.2 Torr; n_D^{25} 1.4634; $[\alpha]_D^{24}$ +16.2° (c=1.10); νmax 3470 (s), 3100 (m), 1645 (m), 1025 (s), 995 (s), 910 (m) cm^{-1}; δ (CCl_4) 1.15 and 1.25 (total 3H, each d, J=7 Hz), 1.25~1.95 (7H, m), 2.12 (2H, dd, J=7, 7 Hz), 2.45 and 2.57 (total 1H, each dd, J=5, 5; 5, 7 Hz, OH), 3.12~4.30 (5H, m), 4.40~4.75 (1H, br.s), 4.75~5.35 (2H, m), 5.35~6.30 (1H, m). (Found: C, 66.84; H, 10.56. Calc for $C_{12}H_{22}O_3$: C, 67.25; H,

10.35 %).

(2R,3S)-2-Allylbutane-1,3-diol 1-benzyl 3-THP ether **18b**. **18a** (36.2 g, 169 mmol) was treated with NaH (11.8 g, 60 % in mineral oil, 295 mmol), n-$Bu_4N^+I^-$ (1.15 g, 3.1 mmol)[30] and $PhCH_2Br$ (39.5 g, 231 mmol) in THF (165 ml) with refluxing for 3 h under Ar followed by a usual workup to give crude **18b** (59.7 g). A portion (3 g) was chromatographed over SiO_2 [60 g, n-hexane-EtOAc (100:1~70:1~50:1)] followed by distillation in the presence of K_2CO_3 to give an analytical sample, b.p. 137°/0.3 Torr; n_D^{23} 1.4986; $[\alpha]_D^{22}$ +12.8° (c=1.01); νmax 3100 (w), 3060 (w), 1645 (m), 1505 (m), 1120 (s), 1080 (s), 1025 (s), 995 (s), 910 (m), 740 (m), 705 (s) cm^{-1}; δ (CCl_4) 1.05 and 1.15 (total 3H, each d, J=7 Hz), 1.25~1.75 (6H, br.m), 1.65~2.05 (1H, m), 2.11 (2H, br.dd, J=6, 7 Hz), 3.37 and 3.44 (total 2H, each d, J=5 Hz), 3.55~4.05 (2H, m), 3.87 (1H, m), 4.41 (2H, s), 4.45~4.73 (1H, br), 4.7~5.2 (2H, m), 5.3~6.2 (1H, m), 7.28 (5H, br.s). (Found: C, 74.90; H, 9.19. Calc for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27 %).

(2R,3S)-2-Allylbutane-1,3-diol 1-benzyl ether **18c**. (2R,3S)-**18b** (59.0 g, ~167 mmol) was treated with p-TsOH·H_2O (1.15 g, 6.0 mmol) in MeOH (500 ml). After a usual workup,[cf.11] chromatographic purification [SiO_2 (700 g), n-hexane-EtOAc (10:1~8:1)] gave **18c** (38.4 g, quantitative). Analytical sample: b.p. 108°/0.17 Torr; n_D^{24} 1.5056; $[\alpha]_D^{23}$ −1.50° (c=1.47); νmax 3520 (s), 3100 (m), 3060 (m), 3010 (s), 1645 (m), 1500 (m), 1010 (s), 1000 (s), 915 (s), 740 (s), 700 (s) cm^{-1}; δ (CCl_4) 1.12 (3H, d, J=7 Hz), 1.36~1.85 (1H, m), 2.12 (2H, br.dd, J=6, 7 Hz), 2.55~2.75 (1H, m, OH), 3.46 (2H, dd, J=3, 5 Hz), 3.71 (1H, dq, J=6, 6 Hz), 4.41 (2H, s), 4.72~5.20 (2H, m), 5.35~6.15 (1H, m), 7.27 (5H, br.s); Capillary GLC (Column, PEG 20M, 50 m x 0.25 mm at 170°; Carrier gas, N_2, 1.1 kg/cm^2) Rt 38.8 min (96.7 %), 39.9 min (3.3 %). (Found: C, 75.96; H, 9.01. Calc for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15 %).

(2R,3S)-2-Allylbutane-1,3-diol 1-benzyl ether 3-(3',5'-dinitro)benzoate **18d**. **18c** (36.9 g, ~159 mmol) was treated with 3,5-dinitrobenzoyl chloride (DNB-Cl, 40.4 g, 175 mmol) and DMAP (0.65 g, 5.3 mmol) in C_5H_5N (140 ml) in a usual manner[cf.11] to give crude **18d** (60.7 g, 92 %). This was recrystallized four times from n-hexane-Et_2O (3:1) followed by another recrystallization from n-hexane-Et_2O (100:1) to give pure **18d** (44.6 g, 73.5 % recovery) as yellowish needles, m.p. 61~62°; $[\alpha]_D^{24}$ +42.1° (c=2.50); νmax 3150 (w), 3120 (m), 1720 (s), 1655 (w), 1630 (m), 1600 (w), 1550 (s), 1500 (w), 1350(s), 1280 (s), 1180 (s), 925 (s), 880 (m), 760 (m), 735 (s), 730 (s), 720 (s), 705 (m) cm^{-1}; δ ($CDCl_3$) 1.44 (3H, d, J=6 Hz), 1.90~2.50 (1H, m), 2.20 (2H, dd, J=6, 6 Hz), 3.55 (2H, br.d, J=5 Hz), 4.45 (2H, s), 4.86~5.30 (2H, m), 5.30~6.20 (2H, m), 5.40~6.25 (1H, m), 5.55 (1H, dq, J=6, 6 Hz), 7.25 (5H, br.s), 9.10 (2H, d, J=2 Hz), 9.21 (1H, t, J=2 Hz). HPLC [n-hexane-THF (100:1), 1.3 ml/min] Rt 44.2 min (99.9 %). Its diastereomer eluted at Rt 42.3 min. (Found: C, 61.17; H, 5.39; N, 6.75. Calc for $C_{21}H_{22}O_7N_2$: C, 60.86; H, 5.35; N, 6.76 %).

Diastereomerically and enantiomerically pure (2R,3S)-2-Allylbutane-1,3-diol 1-benzyl ether **18c**. (2R,3S)-**18d** (44.6 g, 108 mmol) was hydrolyzed with N KOH aq soln (150 ml, 150 mmol) in THF-99 % EtOH (1:1, 360 ml)[cf.11] to give **18c** (23.5 g, 99 %), b.p. 108~109°/0.16 Torr; n_D^{26} 1.5045; $[\alpha]_D^{25}$ −1.96° (c=2.08); its IR and NMR spectra were almost identical with those described above. Capillary GLC (under the same condition as described above) Rt 18.4 min (100 %). Its diastereomer eluted at Rt 19.7 min. (Found: C, 76.28; H, 9.17. Calc for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15 %). According to the reported procedure,[27] (2R,3S)-**18e** was prepared from (2R,3S)-**18c** and (S)-MTPA chloride (MTPA-Cl). HPLC [n-hexane-THF (100:1), 1.3 ml/min] Rt 18.0 min [single peak, (2R,3S)-**18e**]. Its diastereomer (2S,3R)-**18e** prepared from (2RS,1'RS)-**17a** eluted at Rt 19.2 min.

(2R,3S)-2-Allylbutane-1,3-diol 1-benzyl ether 3-tosylate **18f**. (2R,3S)-**18c** (12 g, 54.5 mmol) was treated with p-TsCl (25 g, 130 mmol) and DMAP (1.46 g, 12 mmol) in C_5H_5N (30 ml) in a usual manner[cf.10,11] to give **18f** (20.5 g, quantitative). This was employed in the next step without further purification; νmax 3100 (w), 3060 (w), 3020 (m), 1645 (m), 1605 (m), 1500 (w), 1360 (m), 1180 (s), 1100 (s), 910 (s), 815 (m), 780 (m), 735 (m), 700 (m) cm^{-1}; δ (CCl_4) 1.21 (3H, d, J=7 Hz), 1.61~2.28 (3H, m), 2.38 (3H, s), 3.29 (2H, d, J=7 Hz), 4.30 (2H, s), 4.50~5.20 (3H, m), 5.25~6.10 (1H, m), 7.25 (2H, d, J=8 Hz), 7.26 (5H, br.s), 7.75 (2H, d, J=8 Hz).

(R)-5-Benzyloxy-4-ethyl-1-pentene **19a**. Super Hydride® ($LiBEt_3H$, 1 M in THF, 64 ml, 64 mmol) was added dropwise to a stirred soln of **18f** (12.1 g, 32 mmol) in THF (36 ml) below −5° under Ar. The mixture was stirred and heated under reflux for 20 min. After cooling, to the mixture were added H_2O (5 ml), 3 N NaOH aq soln (30 ml) and 35 % H_2O_2 aq soln (27 ml) successively below 50° with ice-cooling. The mixture was stirred for 30 min at room temp, then concentrated in vacuo to remove THF and EtOH. The residue was extracted with Et_2O (50 ml x 5). The extract was washed with H_2O and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (7.0 g) was chromatographed over SiO_2 [70 g n-pentane-Et_2O (20:1)] to give **19a** (6.5 g, quantitative). Analytical sample: b.p. 90°/0.3 Torr; n_D^{25} 1.4892; $[\alpha]_D^{24}$ +4.62° (c=1.36); νmax 3100 (w), 3050 (w), 3010 (w), 3000 (s), 1645 (m), 1500 (w), 1100 (s), 995 (m), 910 (s), 735 (s), 700 (s) cm^{-1}; δ (CCl_4) 0.86 (3H, t, J=6 Hz), 1.08~1.85 (3H, m), 2.11 (2H, dd, J=6, 6 Hz), 3.30 (2H, d, J=5 Hz), 4.41 (2H, s), 4.75~5.22 (2H, m), 5.40~6.20 (1H, m), 7.30 (5H, br.s). (Found: C, 82.34; H, 9.70. Calc for $C_{14}H_{20}O$: C, 82.30; H, 9.87 %).

(R)-2-Ethyl-4-penten-1-ol (R)-**19b**. To a soln of (R)-**19a** (6.5 g, 32 mmol) in THF (16 ml) and liq. NH_3 (~80 ml) was added finely cut Na (1.66 g, 72.2 mmol) portionwise with dry ice-acetone cooling and stirring. The mixture was refluxed for 10 min with stirring. To the dry ice-acetone cooled mixture was added solid NH_4Cl to discharge its deep blue color. NH_3 was evaporated from the mixture with stirring at room temp. The residue was diluted with Et_2O and filtered through a pad of Celite. The solid was washed with Et_2O. The combined filtrate and washings were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give crude (R)-**19b** (7.3 g, contaminated with PhMe). Analytical sample: b.p. 92~93°/53 Torr; n_D^{18} 1.4394; $[\alpha]_D^{19}$ −0.75° (c=1.56); νmax 3350 (s), 3070 (m), 1655 (s), 1040 (s), 990 (s), 910 (s) cm^{-1}; δ (CCl_4) 0.88 (3H, t, J=6 Hz), 1.05~1.60 (3H, m), 2.06 (2H, dd, J=6, 6 Hz), 2.86 (1H, br.t, J=5 Hz, OH), 2.43 (2H, br.dd, J=5, 5 Hz), 4.65~5.25 (2H, m), 5.30~6.20 (1H,m). (Found: C, 73.44; H, 12.21. Calc for $C_7H_{14}O$: C, 73.64; H, 12.36 %).

(R)-4-Ethyl-5-tetrahydropyranyloxy-1-pentene **19c**. Crude **19b** (7.3 g, ~32 mmol) was treated with dihydropyran (9.0 g, 107 mmol) and PPTS (4.0 g, 16 mmol) in CH_2Cl_2 (45 ml) as described above followed by chromatographic purification [SiO_2 (70 g), n-pentane-Et_2O (30:1)] then distillation in the presence of K_2CO_3 to give **19c** [6.1 g, quantitative from pure (2R,3S)-**18c**], b.p. 77°/3 Torr; n_D^{22} 1.4481; $[\alpha]_D^{21}$ +3.00° (c=1.07); νmax 3080 (m), 1640 (m), 1120 (s), 1030 (s), 990 (s), 910 (s) cm^{-1}; δ (CCl_4) 0.92 (3H, t, J=6 Hz), 1.15~2.00 (9H, m), 2.12 (2H, dd, J=6, 6 Hz), 2.98~4.10 (4H, m), 4.40~4.65 (1H, br.s), 4.75~5.30 (2H, m), 5.40~6.20 (1H, m). (Found: C, 72.62; H, 11.14. Calc for $C_{12}H_{22}O_2$: C, 72.62; H, 11.18 %).

(R)-3-(Tetrahydropyranyloxymethyl)pentanal **20**. To a stirred two-phase mixture of **19c** (1.5 g, 7.9 mmol) in Et_2O-H_2O (1:1, 40 ml) were added $NaIO_4$ (5.6 g, 26.2 mmol) and 5 % OsO_4 soln in THF (2.4 ml, 0.47 mmol) at room temp. After stirring vigorously for 2 h at room temp, an additional amount of $NaIO_4$ (3 g, 14 mmol) was added to the mixture. The vigorous stirring was further continued for 5.5 h at room temp. The precipitate was filtered off through a pad of Celite and washed with Et_2O. The organic layer was separated from the combined filtrate and washings, and the aq layer was extracted with Et_2O. The combined Et_2O soln was washed with $Na_2S_2O_3$ aq soln, sat $NaHCO_3$ aq soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled under Ar to give **20** (1.02 g, 65 %), b.p. 94°/2.0 Torr; n_D^{22} 1.4529; $[\alpha]_D^{22}$ +25.2° (c=1.07); νmax 2740 (m), 1725 (s), 1125 (s), 1035 (s) cm^{-1}; δ (CCl_4) 0.92 (3H, t, J=7 Hz), 1.15~2.15 (9H, m), 2.15~2.50 (2H, m), 2.80~3.96 (4H, m), 4.30~4.60 (1H, br.s), 9.74 and 9.79 (total 1H, each d, J=2 Hz). (Found: C, 66.07; H, 10.08. Calc for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07 %).

(3'R,4S,5R)-4-Benzyloxy-5-benzyloxymethyl-2-[(3'-tetrahydropyranyloxymethyl)pentylidene]tetrahydropyran **22.** To a stirred and cooled soln of crude **14** (2.20 g, ~3.17 mmol) and HMPA (5.5 ml) in THF (29 ml) was added dropwise n-BuLi (1.72 M in n-hexane, 2.1 ml, 3.61 mmol) at -67°~-63° under Ar. After stirring for 30 min at -67°, to this deep red ylide soln was added dropwise a soln of **20** (0.83 g, 4.12 mmol) in THF (6.5 ml) at -67°~-63° with stirring. The temp was raised gradually to room temp over 3 h 50 min and the stirring was continued for 6 h 15 min at room temp. To the mixture was added sat $NaHCO_3$ aq soln (18 ml) at -10°~0° with stirring. The mixture was concentrated in vacuo to remove THF. The residue was extracted with Et_2O (20 ml x 4). The extract was washed with sat $NaHCO_3$ aq soln and brine, dried (K_2CO_3) and concentrated in vacuo to give crude **22** (2.94 g). According to the procedure described above, 3.85 g (10.8 mmol) of **13b** was converted to 9.0 g of crude **22.** This was employed in the next step without further purification.

(3R,4S,6R,9R)- and (3S,4R,6S,9R)-4-Benzyloxy-3-benzyloxymethyl-9-ethyl-1,7-dioxaspiro[5.5]undecane **1b** + **23b** and (3R,4S,6R,9R)-, (3S,4S,6R,9R)- and (3R,4R,6S,9R)-3-benzyloxymethyl-9-ethyl-4-hydroxy-1,7-dioxaspiro[5.5]undecane **1c** + **2c** + **24c.** Crude **22** (9.0 g) was mixed with conc HCl-H_2O-THF (1:5:20, 90 ml) with ice-salt cooling. After stirring for 15 h at room temp, the mixture was neutralized by the addition of sat $NaHCO_3$ aq soln with stirring and ice-cooling, and concentrated in vacuo to remove THF. The residue was extracted with Et_2O. The extract was washed with sat $NaHCO_3$ aq soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (7.8 g) was chromatographed over SiO_2 [210 g, n-hexane-EtOAc (80:1~10:1)] to give a mixture (2.04 g, 46 % from **13b**) of **1b** and **23b**, n_D^{24} 1.5274; $[\alpha]_D^{22}$ -105° (c=0.51); νmax 3100 (w), 3080 (w), 3050 (m), 1500 (m), 1105 (vs), 1080 (vs), 1005 (s), 740 (s), 700 (s) cm^{-1}; δ (100 MHz) 0.88 and 0.90 (total 3H, each t, J=7.5 Hz), 1.00~1.80 (8H, m), 1.87 (1H, dd, J=5.2, 13.3 Hz), 2.10~2.43 (1H, m), 3.14 (~0.7H, dd, J=9.9, 9.9 Hz), 3.27~3.63 (~2.3H, m), 3.73 (2H, d, J=6.9 Hz), 4.95 and 4.97 (total 1H, each dd, J=3.7, 11.7; 4.0, 12.0 Hz), 4.06 (1H, ddd, J=5.1, 5.1, 11.0 Hz), 4.43 (1H, d, J=11.7 Hz), 4.47 (1H, d, J=11.7 Hz), 4.59 (1H, d, J=11 Hz), 4.62 (1H, d, J=11.7 Hz), 7.28 (~6H, br.s), 7.33 (~4H, br.s). (Found: C, 75.63; H, 8.38. Calc for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34 %). Further elution [n-hexane-EtOAc (10:1~3:1)] gave a mixture (1.21 g, 35 % from **13b**) of **1c**, **2c** and **24c**, νmax 3430 (s), 3100 (w), 3070 (w), 3040 (w), 1500 (w), 1075 (s), 1045 (s), 740 (m), 700 (m) cm^{-1}; δ (CCl_4) 0.88 (3H, t, J=6.4 Hz), 1.05~1.50 (10H, m), 2.90~4.30 (8H, m), 4.49 (2H, br.s), 7.32 (5H, br.s); MS m/z 320 (M^+), 302, 129, 127, 126, 125, 91 (base peak).

(3R,4S,6R,9R)-, (3S,4S,6R,9R)- and (3R,4R,6S,9R)-4-[3-Benzyloxymethyl-9-ethyl-1,7-dioxaspiro[5.5]undecyl] benzoate **1f**, **2f** and **24f.** A mixture of **1c**, **2c** and **24c** (25 mg, 0.078 mmol) was treated with benzoyl chloride (0.012 ml, d 1.211, 0.10 mmol) in C_5H_5N (0.5 ml) in a usual manner followed by purification with prep TLC [n-hexane-EtOAc (7:2)] to afford 28 mg (82 %) of **1f**, **2f** and **24f**, νmax 3110 (w), 3080 (w), 3050 (w), 1725 (s), 1605 (w), 1590 (w), 1495 (w), 1270 (s), 1100 (s), 740 (m), 715 (s) cm^{-1}; δ (100 MHz) 0.89, 0.91 and 0.96 (total 3H, each t, J=7.3 Hz), 1.00~2.00 (7H, m), 1.97 (1H, dd, J=5.1, 13.1 Hz), 2.10~2.53 (1H, m), 3.41 (~0.33H, dd, J=9.5, 9.5 Hz, **1f**), 3.52 (~0.33H, dd, J=13.1, 13.1 Hz, **2f**), 3.56 (~0.33H, dd, J=3.7, 13.1 Hz, **2f**), 3.61 (~0.33H, br.d, J=11.7 Hz, **24f**), 3.55~3.65 (~0.33H, m, **1f**), 3.60~3.80 (2H, m), 3.75 (~0.33H, dd, J=5.1, 11.7 Hz, **24f**), 3.73~3.82 (~0.66H, m, **1f**), 3.87 (~0.67H, dd, J=11.7, 11.7 Hz, **2f** + **24f**), 3.96 (~0.67H, dd, J=5.1, 11.7 Hz, **2f** + **24f**), 4.42 (~0.67H, s), 4.45 (~0.67H, s), 4.53 (~0.66H, s), 5.36 (~0.67H, ddd, J=5.1, 11, 11 Hz, **2f** + **24f**), 5.62 (~0.33H, ddd, J=5.5, 5.5, 11.7 Hz, **1f**), 7.26 and 7.29 (total 5H, each s), 7.36~7.75 (3H, m), 7.83~8.20 (2H, m); MS m/z 424 (M^+), 423, 321, 312, 302, 129, 127, 126, 123, 122, 105, 91, 77.

(3R,4S,6R,9R)- and (3S,4R,6S,9R)-9-Ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane **1a** and **23a.** A mixture of **1b** and **23b** (2.35 g, 5.72 mmol) was treated with Na (1.41 g, 61.3 mmol) in THF (6 ml) and liq. NH_3 (~80 ml) in the usual manner to give crude **1a** and **23a** (0.99 g, 75 %), νmax 3370 (s), 1070 (s) cm^{-1}; δ ($CDCl_3$) 0.88 (3H, distorted t, J=7 Hz), 2.35 (2H, s, OHx2), 1.1~2.4 (10H, m), 2.73~4.10 (6H, m), 4.10~4.65 (1H, m). This was employed in the next step without further purification.

(3S,4S,6R,9R)-, (3R,4R,6S,9R)-, (3R,4R,6R,9R)- and (3S,4S,6S,9R)-3-[9-Ethyl-4-hydroxy-1,7-dioxaspiro[5.5]undecyl]methyl (3',5'-dinitro)benzoate **1e** [talaromycin A 12-(3',5'-dinitro)benzoate], **23e**, **25e** and **26e.** A mixture of crude **1a** and **23a** (0.99 g, 4.3 mmol) was treated with DNB-Cl (1.10 g, 4.75 mmol) and DMAP (16 mg, 0.13 mmol) in C_5H_5N (18 ml) with ice-salt cooling. The stirring was continued for 3 days at room temp. After a usual workup,[11] the residue (1.8 g) was chromatographed over SiO_2 (40 g). Firstly eluted fractions [C_6H_6-EtOAc (80:1~60:1)] gave 487 mg (18 %) of **1d** and **23d** as crystals, TLC [n-hexane-EtOAc (3:1)] Rf 0.53; νmax 3120 (m), 1730 (s), 1630 (m), 1600 (w), 1550 (s), 1350 (s), 1280 (s), 1165 (s), 760 (s), 730 (s), 725 (s) cm^{-1}; δ ($CDCl_3$) 0.70~1.70 (3H, m), 1.10~2.15 (8H, m), 1.93~2.35 (1H, m), 2.35~2.90 (1H, m), 3.25~4.70 (4H, m), 4.77 (2H, br.d, J=6 Hz), 5.50~6.10 (1H, m), 9.00~9.37 (6H, m); MS m/z 406 (M^+-DNBOH).

Secondly eluted fractions (40:1~10:1) gave **25e** and **26e** (254 mg, 14 %), TLC [n-hexane-EtOAc (3:1)] Rf 0.36; νmax 3530 (s), 3120 (s), 1735 (s), 1630 (m), 1600 (w), 1550 (s), 1350 (s), 1280 (s), 1080 (s), 775 (m), 760 (m), 730 (s), 725 (s) cm^{-1}; δ ($CDCl_3$) 0.89 (3H, br.t, J=5 Hz), 1.10~2.20 (8H, m), 2.00~2.70 (2H, m), 3.10~4.37 (5H, m), 4.44 and 4.50 (total 2H, each br.d, J=7.0 Hz), 4.65~5.10 (1H, m), 9.23 (2H, d, J=2 Hz), 9.30 (1H, t, J=2 Hz); MS m/z 424 (M^+). 36 mg of this was further purified by prep TLC [n-hexane-EtOAc (3:1, x 2)] to afford **26e** (16 mg, 44 %) as a less polar isomer and **25e** (5 mg, 14 %) as a more polar isomer. **26e**: TLC [n-hexane-EtOAc (3:1 x 3)] Rf 0.62; νmax 3530 (s), 3120 (s), 1735 (s), 1630 (s), 1600 (m), 1550 (s), 1350 (s), 1280 (s), 1170 (s), 770 (s), 730 (s), 720 (s) cm^{-1}; δ (400 MHz) 0.93 (3H, t, J=7.3 Hz), 1.37~1.64 (5H, m), 1.68 (1H, dd, J=3, 14 Hz), 1.70 (1H, ddd, J=5.0, 13.5, 13.5 Hz), 2.00 (1H, dddd, J=4.5, 4.5, 13.5, 13.5 Hz), 2.03 (1H, dd, J=3, 14 Hz), 2.23~2.33 (1H, m), 3.52 (1H, br.d, J=11 Hz), 3.74 (1H, dd, J=5, 11 Hz), 3.81 (1H, dd, J=11, 11 Hz), 3.86 (1H, dd, J=2.8, 11 Hz), 3.92 (1H, d, J=10 Hz, OH), 4.07~4.13 (1H, m), 4.40 (1H, dd, J=7.5, 11 Hz), 4.55 (1H, dd, J=7.0, 11 Hz), 9.14 (2H, d, J=2 Hz), 9.23 (1H, t, J=2 Hz). **25e**: TLC [n-hexane-EtOAc (3:1, x3)] Rf 0.58; its physical and spectral data were described later.

Thirdly eluted fractions (10:1~5:1) gave **1e** and **23e** (730 mg, 40 %) as crystals, TLC [n-hexane-EtOAc (3:1)] Rf 0.13. This mixture was further purified by fractional recrystallization, and the mother liquor was also purified by prep TLC [n-hexane-EtOAc (3:1, x 5)] to afford **23e** (123 mg, 17 %) as a less polar isomer and **1e** (509 mg, 70 %) as a more polar isomer. **23e**: TLC [n-hexane-EtOAc (3:1, x4)] Rf 0.40; m.p. 171.5~173.0° (needles); $[\alpha]_D^{18}$ +136° (c=0.63); νmax 3460 (s), 3120 (w), 2990 (m), 1750 (s), 1630 (m), 1610 (w), 1550 (s), 1350 (vs), 1280 (s), 1170 (s), 735 (m), 730 (m), 725 (m) cm^{-1}; δ (400 MHz) 0.93 (3H, t, J=7.3 Hz), 1.19 (2H, dq, J=7.3, 5.3 Hz), 1.35~1.55 (3H, m), 1.54~1.64 (1H, m), 1.66 (1H, ddd, J=4.5, 13.0, 13.0, Hz), 1.74~1.87 (1H, br.s, OH), 1.94 (1H, dd, J=5.6, 13.0 Hz), 2.00 (1H, dddd, J=4.5, 4.5, 13.0, 13.0 Hz), 2.32~2.39 (1H, m), 3.44 (1H, ddd, J=11.5, 3.0, 3.0 Hz), 3.79 (1H, dd, J=3.0, 11.5 Hz), 3.84 (2H, seemingly d, J=2.0 Hz), 4.43 (1H, ddd, J=5.6, 5.6, 11.2 Hz), 4.62 (1H, dd, J=9.8, 11.0 Hz), 4.84 (1H, dd, J=4.0, 11.0 Hz), 9.16 (2H, d, J=2.0 Hz), 9.23 (1H, t, J=2.0 Hz). (Found: C, 54.16; H, 5.54; N, 6.50. Calc for $C_{19}H_{24}O_9N_2$: C, 53.77; H, 5.70; N, 6.60 %). **1e**: TLC [n-hexane-EtOAc (3:1, x 3)] Rf 0.34; m.p. 147~148° (fine needles); $[\alpha]_D^{18}$ -113° (c=2.13); νmax 3460 (s), 3130 (m), 3100 (m), 1730 (s), 1630 (m), 1600 (w), 1550 (s), 1350 (s), 1290 (s), 1170 (s), 1080 (s), 735 (s), 725 (s) cm^{-1}; δ (400 MHz) 0.89 (3H, t, J=7.5 Hz), 1.07~1.25 (2H, m), 1.41 (1H, dddd, J=3.5, 12.0, 12.0, 12.0 Hz), 1.42~1.61 (4H, m), 1.61~1.72 (1H, m), 1.75 (1H, ddd, J=3.5, 3.5, 13.0, Hz), 1.89 (1H, dd, J=5.6, 12.5 Hz), 2.31~2.39 (1H, m), 3.24 (1H, dd, J=11.0, 11.0 Hz), 3.56 (1H, ddd, J=2.0, 4.5, 11.0 Hz), 3.79 (1H, dd, J=2.0, 12.0 Hz), 3.83 (1H, dd, J=2.0, 12.0 Hz), 4.44 (1H, ddd, J=5.6, 5.6, 11.2 Hz), 4.62 (1H, dd, J=9.8, 11.0 Hz), 4.84 (1H, dd, J=4.0, 11.0 Hz), 9.16 (2H, d, J=2.0 Hz), 9.23 (1H, t, J=2.0

Hz). (Found: C, 54.11; H, 5.72; N, 6.50. Calc for $C_{19}H_{24}O_9N_2$: C, 53.77; H, 5.70; N, 6.60 %).

Conversion of (3S,4S,6R,9R)- and (3R,4R,6S,9R)-9-ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane bis (3',5'-dinitro)benzoate **1d** and **23d** to **1e** and **23e**. A mixture of **1d** and **23d** (487 mg, 0.79 mmol) was treated with solid K_2CO_3 (487 mg, 0.79 mmol) in MeOH (5 ml)–THF (2.5 ml) at room temp. The crude product was treated with DNB-Cl (194 mg, 0.84 mmol) in C_5H_5N (4 ml) and CH_2Cl_2 (1 ml) followed by chromatographic purification [SiO_4 (9 g), C_6H_6–EtOAc (25:1~6:1)] to give **1e** and **23e** [137 mg, 41 % from **1d** and **23d**]. This was further purified by fractional recrystallization and the mother liquor was also purified by prep TLC [n-hexane-EtOAc (3:1, x 3)] to afford **23e** (26 mg, 19 %) and **1e** (62 mg, 45 %).

Conversion of (**1c** + **2c** + **24c**) to **1e** and (**2e8** + **24e**). A mixture of **1c**, **2c** and **24c** (1.10 g, 3.44 mmol) was treated with Na (0.3 g, 13 mmol) in THF (3 ml) and liq. NH_3 (~30 ml) as usual. The crude product (0.86 g) was treated with DNB-Cl (796 mg, 3.5 mmol) in C_5H_5N (14 ml) followed by chromatographic purification over SiO_2 [20 g, C_6H_6-EtOAc (40:1~5:1)] to give a mixture [550 mg, 38 % from (**1c** + **2c** + **24c**)] of **1e**, **2e** and **24e**. This was fractionally recrystallized from n-hexane-EtOAc to give pure **1e** (93 mg, 17 %). A portion (21 mg) of the mother liquor was purified by prep TLC [n-hexane-EtOAc (4:1, x 20)] to give further amount of pure **1e** (3 mg) and a mixture (12 mg) of **2e** and **24e**; νmax 3470 (s), 3130 (s), 1730 (s), 1635 (s), 1600 (m), 1550 (s), 1345 (s), 1280 (s), 1170 (s), 775 (m), 735 (s), 725 (s) cm^{-1}; δ (100 MHz) 0.93 (3H, t, J=6.5 Hz), 1.05~2.20 (11H, m), 3.32~3.86 [total 2H; 3.50 (dd, J=12.0, 12.0, **2e**), 3.57 (d, J=10.0, **24e**), 3.77 (dd, J=3.0, 10.0 Hz, **24e**), 3.76~3.86 (m, **2e**)], 3.85 (1H, dd, J=10.0, 10.0 Hz), 3.93 (1H, dd, J=4.7, 10.0 Hz), 4.22 (1H, ddd, J=5.1, 13.0, 13.0 Hz), 4.55, 4.62, 4.63 and 4.84 (total 2H, each dd, J=5.1, 11.0; 5.1, 10.0; 4.7, 10.0; 4.4, 11.0 Hz), 9.15 and 9.18 (total 2H, each d, J=2.0 Hz), 9.26 (1H, t, J=2.0 Hz). MS: m/z 423 (M^+-1), 406, 341, 338, 213, 129, 126.

Conversion of (**2e** + **23e** + **24e** + **25e** + **26e**) to (**2d** + **24d**), **25e** and (**2e** + **24e**). A mixture of **2e**, **23e**, **24e**, **25e** and **26e** (507 mg, 1.19 mmol) was treated with K_2CO_3 (0.17 g, 1.2 mmol) in MeOH (3 ml)–$CHCl_3$ (0.5 ml) at room temp followed by chromatographic purification over SiO_2 [4 g, n-hexane-EtOAc (3:1~2:1)] to give 237 mg (86 %) of an oil. This was treated with conc HCl~H_2O-THF (1:5:20, 4 ml) for isomerization.cf.[8] The residue (227 mg) was treated with DNB-Cl (227 mg, 0.99 mmol) in C_5H_5N (5 ml) followed by chromatographic purification over SiO_2 (15 g). Firstly eluted fractions [C_6H_6-EtOAc (30:1~20:1)] gave a mixture (99 mg, 16 %) of **2d** and **24d**. Analytical sample [needles from n-hexane-EtOAc (3:1)]: m.p. 127~133°; $[\alpha]_D^{24}$ −2.9° (c=0.83); νmax 3120 (w), 1735 (s), 1550 (s), 1350(s), 1280 (s), 1165 (s), 735 (s), 725 (s) cm^{-1}; δ (100 MHz) 0.91 (~1.2H, t, J=6.1 Hz, **2d**), 0.95 (~1.8H, t, J=6.1 Hz, **24d**), 1.05~2.13 (8H, m), 2.31 (1H, dd, J=5.8, 10.2 Hz), 2.56 (1H, dddd, J=4.7, 5.8, 11.0, 11.0 Hz), 3.27 (~0.4H, dd, J=10.6, 10.6 Hz, **2d**), 3.54 (~0.6H, br.d, J=11.5 Hz, **24d**), 3.63 (~0.4H, br.d, J=10.6 Hz, **2d**), 3.83 (1H, dd, J=11.0, 11.0 Hz), 3.85 (~0.6H, br.d, J=11.5 Hz, **24d**), 4.03 (1H, dd, J=5.8, 11.0 Hz), 4.49 (2H, br.d, J=4.7 Hz), 5.65 (1H, ddd, J=5.1, 11.0 Hz), 9.12 and 9.14 (total 4H, each d, J=2.0 Hz), 9.25 (2H, t, J=2.0 Hz). (Found: C, 51.12; H, 4.23; N, 8.96. Calc for $C_{26}H_{26}O_{14}N_4$: C, 50.49; H, 4.24; N, 9.06 %).

Secondly eluted fractions (20:1~10:1) gave **25e** (50 mg, 12 %). Analytical sample (plates from n-hexane-EtOAc): m.p. 128.8~129.2°; $[\alpha]_D^{24}$ −77.7° (c=0.33); νmax 1730 (s), 1630 (w), 1545 (s), 1350 (s), 1290 (s), 1165 (m), 730(m), 725 (m) cm^{-1}; δ (400 MHz) 0.90 (3H, t, J=7.3 Hz), 1.09~1.29 (2H, m), 1.43 (1H, dddd, J=3.2, 12.5, 12.5, 12.5 Hz), 1.42~1.71 (4H, m), 1.74 (1H, dd, J=3.0, 14.5 Hz), 2.01 (1H, dd, J=3.0, 14.5 Hz), 2.23~2.33 (1H, m), 3.33 (1H, dd, J=11.0, 11.0 Hz), 3.66 (1H, ddd, J=2.0, 4.0, 11.0 Hz), 3.73 (1H, dd, J=5.0, 11.5 Hz), 3.79 (1H, dd, J=11.5, 11.5 Hz), 3.92 (1H, d, J=10.0 Hz, OH), 4.07~4.14 (1H, m), 4.39 (1H, dd, J=7.5, 11.0 Hz), 4.56 (1H, dd, J=7.0, 11.0 Hz), 9.14 (2H, d, J=2.0 Hz), 9.23 (1H, t, J=2.0 Hz). (Found: C, 54.19; H, 5.59; N, 6.56. Calc for $C_{19}H_{24}O_9N_2$: C, 53.77; H, 5.70; N, 6.62 %).

Thirdly eluted fractions (10:1~5:1) gave a mixture (210 mg, 50 %) of **2e** and **24e**. A small amount (100 mg) was further purified by SiO_2 chromatography [3 g, C_6H_6-EtOAc (20:1~8:1)] followed by prep TLC [n-hexane-EtOAc (3:1 x 3)] to give **24e** as a viscous oil (61 mg, 61 %) and **2e** (21 mg, 21 %) as crystals. **24e**: $[\alpha]_D^{24}$ +21.4° (c=0.51); νmax 3450 (m), 3120 (m), 1735 (s), 1635 (m), 1600 (s), 1550 (s), 1350 (s), 1280 (s), 1170 (m), 1080 (m), 735 (s), 725 (s) cm^{-1}; δ (400 MHz) 0.92 (3H, t, J=7.3 Hz), 1.36~1.44 (2H, m), 1.45 (1H, dd, J=10.5, 12.5 Hz), 1.45~1.54 (3H, m), 1.54~1.63 (1H, m), 1.69 (1H, ddd, J=4.5, 13.5, 13.5 Hz), 1.99 (1H, dddd, J=4.5, 4.5, 13.5, 13.5 Hz), 2.03~2.09 (1H, m), 2.12 (1H, dd, J=5.0, 12.5 Hz), 3.43 (1H, br.d, J=11.5 Hz), 3.62 (1H, dd, J=11.2, 11.2 Hz), 3.78 (1H, dd, J=3.0, 11.5 Hz), 3.86 (1H, dd, J=5.0, 11.2 Hz). 3.97 (1H, ddd, J=5.0, 10.5, 10.5 Hz), 4.60 (1H, dd, J=6.0, 11.5 Hz), 4.64 (1H, dd, J=4.0, 11.5 Hz), 9.14 (2H, d, J=2.0 Hz), 9.24 (1H, t, J=2.0 Hz). (Found: C, 53.76; H, 5.75; N, 6.42. Calc for $C_{19}H_{24}O_9N_2$: C, 53.77; H, 5.70; N, 6.60 %). **2e** (fine needles from n-hexane-EtOAc): m.p. 104~104.2°; $[\alpha]_D^{24}$ −29.8° (c=0.26); νmax 3460 (m), 3130 (w), 1730 (s), 1635 (m), 1550 (s), 1350 (s), 1280 (s), 1045 (s), 735 (m), 725 (m) cm^{-1}; δ (400 MHz) 0.89 (3H, t, J=7.5 Hz), 1.07~1.24 (2H, m), 1.41 (1H, dddd, J=3.0, 12.0, 12.0, 12.0 Hz), 1.42~1.49 (1H, m), 1.50 (1H, dd, J=11.0, 12.2 Hz), 1.55 (1H, ddd, J=4.0, 13.0, 13.0 Hz), 1.62~1.68 (1H, m), 1.74 (1H, ddd, J=3.0, 3.0, 13.0 Hz), 1.93 (1H, br.s, OH), 2.00~2.11 (1H, m), 2.07 (1H, dd, J=5.0, 12.2 Hz), 3.23 (1H, dd, J=11.0, 11.0 Hz), 3.55 (1H, ddd, J=2.0, 4.5, 11.0 Hz), 3.58 (1H, dd, J=11.5, 11.5 Hz), 3.84 (1H, dd, J=5.0, 11.5 Hz), 3.98 (1H, ddd, J=5.0, 11.0, 11.0 Hz), 4.58 (1H, dd, J=7.0, 11.0 Hz), 4.66 (1H, dd, J=3.5, 11.0 Hz), 9.14 (2H, d, J=2.0 Hz), 9.24 (1H, t, J=2.0 Hz). (Found: C, 53.82; H, 5.67; N, 6.63. Calc for $C_{19}H_{24}O_9N_2$: C, 53.77; H, 5.70; N, 6.60 %).

(3R,4S,6R,9R)-9-Ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane [(−)-talaromycin A] **1a** and (3S,4S,6R,9R)-9-Ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane [(−)-talaromycin B] **2a**. **1e** (100 mg, 0.24 mmol) was treated with K_2CO_3 (36 mg) in MeOH (1 ml)–THF (0.5 ml) at room temp followed by chromatographic purification [SiO_2 (0.8 g), n-hexane-EtOAc (4:1~2:1) followed by Et_2O] to give talaromycin A **1a** (57 mg, quantitative). Analytical sample [hygroscopic needles from n-pentane-Et_2O]: m.p. 19~20°; $[\alpha]_D^{24}$ −146° (c=0.46) [lit.[8] $[\alpha]_D^{20}$ −110.2° (c=0.83, $CHCl_3$), 91~93 % e.e.; lit.[9] $[\alpha]_D^{26}$ −124.9° (c=1.11, $CHCl_3$)]; ORD (c=8.9 x 10^{-2}, MeOH; t=25°) [[α] (λ, nm)] −129° (600), −200° (500), −365° (400), −516° (350), −786° (300), −1382° (250); νmax 3420 (s), 2970 (s), 2950 (s), 2920 (s), 2880 (s), 1470 (m), 1460 (m), 1450 (m), 1380 (m), 1340 (w), 1290 (w), 1260 (w), 1250 (w), 1240 (m), 1215 (m), 1185 (s), 1160 (s), 1150 (m), 1125 (w), 1105 (s), 1075 (vs), 1045 (s), 1020 (s), 995 (vs), 970 (m), 940 (w), 925 (w), 890 (w), 860 (s), 805 (m), 770 (m), 760 (m), 695 (w) cm^{-1}. νmax ($CHCl_3$) 3680 (w), 3620 (s), 3450 (s), 3020 (s), 2980 (s), 2950 (s), 2900 (s), 1465 (s), 1445 (s), 1385 (s), 1330 (m), 1290 (m), 1265 (s), 1180 (s), 1160 (s), 1130 (m), 1100 (vs), 1070 (vs), 1040 (vs), 995 (vs), 955 (m), 945 (m), 930 (w), 910 (w), 885 (w), 865 (s), 830 (w), 670 (s), 585 (m), 570 (m) cm^{-1}. Its IR spectrum as $CHCl_3$ soln was identical with that provided by Prof. A. B. Smith, III. δ (400 MHz) 0.88 (3H, t, J=7.5 Hz), 1.06~1.24 (2H, m), 1.38 (1H, dddd, J=4.0, 13.0, 13.0, 13.0 Hz), 1.36~1.48 (1H, m), 1.51 (1H, ddd, J=4.2, 13.0, 13.0 Hz), 1.59~1.66 (1H, m), 1.67~1.73 (1H, m), 1.72 (1H, dd, J=11.0, 13.0 Hz), 1.89 (1H, ddd, J=1.0, 5.0, 13.0 Hz), 2.11~2.18(1H, m), 2.25 (2H, br.s, OHx2), 3.19 (1H, dd, J=11.0, 11.0 Hz), 3.52 (1H, ddd, J=2.0, 4.5, 11.0 Hz), 3.58 (1H, dd, J=1.5, 12.0 Hz), 3.75 (1H, dd, J=2.8, 12.0 Hz), 3.80 (1H, dd, J=5.0, 11.0 Hz), 4.21 (1H, dd, J=9.0, 11.0 Hz), 4.41 (1H, ddd, J=5.0, 5.5, 11.0 Hz). Its ^1H NMR spectrum was identical with that reported.[1] ^{13}C NMR δ 11.1, 24.9, 25.2, 35.3, 37.0, 40.4, 41.3, 60.9, 61.7, 65.4, 67.1, 97.2. The δ value of the spiro center (97.2) was in good accord with that reported (97.2).[1] MS[cf.5b]: m/z 231 (M^++1), 230 (M^+), 212, 200, 157, 153, 147, 146, 145, 144, 143, 129, 127, 126, 125. HR-MS: m/z 230.1525 (M^+). Calc for $C_{12}H_{22}O_4$: 230.1518. (Found: C, 61.89; H, 9.65. Calc for $C_{12}H_{22}O_4{}^+(H_2O)$/9: C, 62.08; H, 9.66 %).

1a (54.4 mg) was treated with Amberlyst®-15 (10 mg) in MeOH (1 ml) followed by chromatographic purification [SiO_2 (1

g), n-hexane-EtOAc (3:1~2:1) followed by Et_2O] to give **2a** (42 mg, 78 % from **1e**) as a colorless viscous oil, n_D^{25} 1.4828; $[\alpha]_D^{24}$ -89.1° (c=0.48) [lit.[8] $[\alpha]_D^{20}$ -84.1° (c=0.46, $CHCl_3$), 91~93 % e.e.]; ORD (c=5.6 x 10^{-2}, MeOH; t=24°) [[α] (λ, nm)] -357° (600), -393° (500), -473° (400), -508° (350), -625° (300), -848° (250); νmax 3370 (s), 2980 (s), 2950 (s), 2900 (s), 1470 (s), 1450 (s), 1295 (w), 1265 (w), 1245 (w), 1215 (m), 1185 (s), 1160 (s), 1130 (s), 1090 (s), 1070 (s), 1040 (s), 1010 (s), 990 (s), 965 (w), 955 (w), 930 (w), 890 (s), 875 (s), 825 (w), 815 (w), 795 (s), 765 (s), 700 (w), 690 (w) cm^{-1}; νmax ($CHCl_3$) 3670 (w), 3620 (s), 3470 (s), 3010 (s), 2970 (s), 2950 (s), 2890 (s), 1470 (s), 1450 (s), 1440 (s), 1385 (s), 1340 (w), 1330 (w), 1295 (m), 1260 (s), 1240 (s), 1225 (s), 1180 (s), 1155 (s), 1140 (s), 1125 (s), 1085 (s), 1070 (s), 1040 (s), 1010 (vs), 990 (s), 970 (m), 955 (m), 930 (m), 890 (s), 870 (s), 665 (s), 615 (m), 575 (m), 565 (m). Its IR spectrum as $CHCl_3$ soln was virtually identical with that provided by Prof. A. B. Smith, III. δ (400 MHz) 0.88 (3H, t, J=7.5 Hz), 1.06~1.24 (2H, m), 1.40 (1H, dddd, J=3.6, 13.0, 13.0, 13.0 Hz), 1.45 (1H, dd, J=11.0, 12.5 Hz), 1.39~1.50 (1H, m), 1.54 (1H, ddd, J=4.0, 13.0, 13.0 Hz), 1.58~1.65 (1H, m), 1.71 (1H, ddd, J=2.5, 3.6, 13.0 Hz), 1.78~1.91 (1H, m), 1.99 (1H, dd, J=5.0, 12.0 Hz), 2.80 (2H, br.s, OHx2), 3.20 (1H, dd, J=11.0, 11.0 Hz), 3.32 (1H, dd, J=11.0, 11.0 Hz), 3.51 (1H, ddd, J=2.0, 4.5, 11.0 Hz), 3.59 (1H, dd, J=5.0, 11.0 Hz), 3.70 (2H, d, J=6.0 Hz), 4.05 (1H, ddd, J=5.0, 10.5, 11.0 Hz). Its ^1H NMR spectrum was identical with that reported.[1,2,5b] ^{13}C NMR δ 11.1, 24.8, 25.2, 35.2, 36.7, 44.1, 45.4, 60.4, 62.9, 65.3, 67.2, 97.2. Its ^{13}C NMR spectrum was identical with that of (±)-**2a** reported previously.[5b] MS[5b]: m/z 231 (M^++1), 230 (M^+), 212, 200, 157, 153, 147, 146, 145, 144, 143, 129, 127, 126, 125. HR-MS: m/z 230.1525 (M^+). Calc for $C_{12}H_{22}O_4$: 230.1518.

CD spectra of talaromycin A dibenzoate **1g**, talaromycin B dibenzoate **2g** and (3R,4S,6R,9R)-9-ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane dibenzoate **25g**. **1g**: (c=8.7 x 10^{-2}, EtOH, t=25°) [Δε (λ, nm)] +9.5 (238), 0 (227.5), -6.3 (221); (c=5.7 x 10^{-2}, n-hexane, t=25°) [Δε (λ, nm)] +11.5 (233), 0 (224), -4.3 (219). **2g**: (c=9.4 x 10^{-2}, EtOH, t=25°) [Δε (λ, nm)] +3.3 (232), +0.57 (223); (c=3.0 x 10^{-2}, n-hexane, t=25°) [Δε (λ, nm)] -0.4 (248), 0 (240), +1.0 (230). **25g**: (c=9.3 x 10^{-2}, EtOH, t=25°) [Δε (λ, nm) -7.3 (238), 0 (228), +3.1 (221). Its CD spectrum was antipodal to that of (2S,4S,5S)-**13c**.

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