This article was downloaded by: [University of Texas Libraries]
On: 26 November 2014, At: 22:31
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Agricultural and Biological Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbbb19

Synthesis of Both Enantiomers of 9-Ethyl-1,7-dioxaspiro[5.5]-undecan-4-one, the Key Intermediate in the Synthesis of Talaromycins A and B

Masaya Ikunaka[a] & Kenji Mori[a]

[a] Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

Published online: 09 Sep 2014.

To cite this article: Masaya Ikunaka & Kenji Mori (1987) Synthesis of Both Enantiomers of 9-Ethyl-1,7-dioxaspiro[5.5]-undecan-4-one, the Key Intermediate in the Synthesis of Talaromycins A and B, Agricultural and Biological Chemistry, 51:2, 565-571

To link to this article: http://dx.doi.org/10.1080/00021369.1987.10868025

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Synthesis of Both Enantiomers of 9-Ethyl-1,7-dioxaspiro[5.5]-undecan-4-one, the Key Intermediate in the Synthesis of Talaromycins A and B†

Masaya IKUNAKA and Kenji MORI*

Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

Received September 24, 1986

The title compounds were synthesized from starting materials of microbial origin by employing a Wittig reaction as the key step.

Downloaded by [University of Texas Libraries] at 22:31 26 November 2014

Talaromycins A (**1a**) and B (**1b**) were isolated by Lynn *et al.* from the toxic fungus, *Talaromyces stipitatus*.[1] They are the first spiroacetals of fungal origin, although those of insect and bacterial origin are common. Because of the unique spiroacetal structures of **1a** and **1b**, many synthetic approaches have been developed.[2] As an extension of the synthesis of enantiomerically pure spiroacetals of insect pheromones,[3] we also synthesized **1a** and **1b** in a highly stereoselective way.[2] In our chiral synthesis of **1a** and **1b**, the spiroacetal system was constructed *via* a cyclic enol ether by employing a Wittig reaction,[4] both chiral partners of which were derived by microbial processes. To verify the feasibility of this synthetic plan, synthesis of the enantiomers of 9-ethyl-1,7-dioxaspiro[5.5]undecan-4-one (**2**) was attempted at the preliminary stage of our talaromycin synthesis. Smith and Thompson employed (6*R*,9*R*)-**2** as the key intermediate in their first chiral synthesis of **1a** and **1b**.[5] An

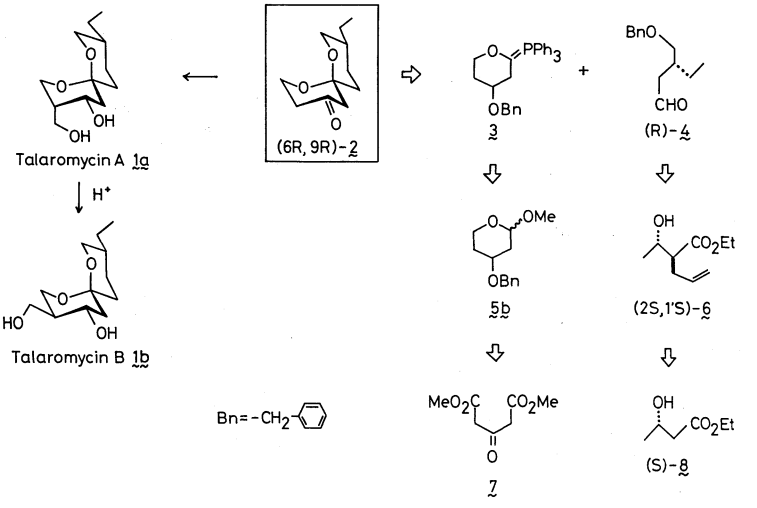

FIG. 1. Synthetic Plan.

† Synthetic Microbial Chemistry, Part XIV. For Part XIII, see ref. 2. The experimental part of this work was taken from the forthcoming doctoral dissertation of M. I. (March, 1987).

* Address correspondence to this author.

Downloaded by [University of Texas Libraries] at 22:31 26 November 2014

alternative synthesis of (6*R*,9*R*)-**2** therefore constitutes a formal total synthesis of both **1a** and **1b**. Herein, we report the synthesis of both the enantiomers of **2**.

Our synthetic plan is shown in Fig. 1. A Wittig reaction between **3** and **4** was employed to construct the spiroacetal system.[4] The phosphorane (**3**) could be prepared from dimethyl 3-oxopentanedioate (**7**) *via* the cyclic acetal (**5b**). Both the enantiomers of the aldehyde (**4**) were to be synthesized *via* **6** from ethyl (*R*)- and (*S*)-3-hydroxybutanoate (**8**), both of which were of microbial origin.[6]

A phosphonium salt (**10**), the precursor to the Wittig reagent (**3**), was synthesized from **9**, which was in turn prepared from **7** in a 51% yield in 6 steps by the reported method[2] (Fig. 2). Intramolecular acetalization of **9** took place by acid catalysis with *p*-toluenesulfonic acid monohydrate in methanol to give **5a** in a 56% yield. Although a synthesis of **5a** was known,[7] a multi-gram quantity of **5a** was obtained in a better overall yield according to the present route. Benzylation[cf.8] of **5a** gave **5b** in an 82% yield. Then, the phosphonium salt (**10**) was prepared from **5b** and hydrogentriphenylphosphonium tetrafluoroborate[9] in a quantitative yield.[2,10] The overall yield of **10** from **7** was 23% in 9 steps.

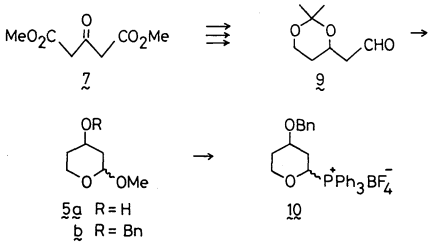

FIG. 2. Synthesis of the Phosphonium Salt (**10**).

Both the enantiomers of **4**, the electrophilic partner of the Wittig reaction, were synthesized in the following manner (Fig. 3). (*R*)-Aldehyde (**4**) was synthesized *via* (*R*)-**11**[2] from (*S*)-**8**, which was the reduction product of ethyl acetoacetate with a thermophilic yeast, *Saccharomyces bailii* KI 0116.[6] According to the reported method,[2] (*S*)-**8** of about 97% enantiomeric excess (*e.e.*) was transformed *via* crystalline (2*R*,3*S*)-**12** of 100% diastereomeric and enantiomeric purity to (*R*)-**11**. The Lemieux-Johnson oxidation of (*R*)-**11** with osmium tetroxide-sodium periodate gave (*R*)-**4** in a 75% yield. The overall yield of (*R*)-**4** from (*S*)-**8** was 43% in 10 steps. The starting material for (*S*)-**4** was (*R*)-**8** of 100% *e.e.*, which was the ethanolysis product of poly[(*R*)-3-hydroxybutanoic acid] produced by *Zoogloea ramigera* I-16-M (ATCC 19623)[6] (Fig. 3). In the same manner as that reported,[2] (*R*)-**8** was converted *via* crystalline (2*S*,3*R*)-**12** in a diastereomerically and enantiomerically pure state to (*S*)-**11**. Confirmation of the optical purity of (2*S*,3*R*)-**12** was carried out by the reported method.[2] Oxidation of (*S*)-**11** in the manner already described gave (*S*)-**4** in a 76% yield. The overall yield of (*S*)-**4** from (*R*)-**8** was 44% in 10 steps.

Having secured the partners for the Wittig reaction, their coupling was executed (Fig. 4). Treatment of (**10**) with *n*-butyllithium in tetrahydrofuran-hexamethylphosphoric triamide generated a deep red phosphorane (**3**),

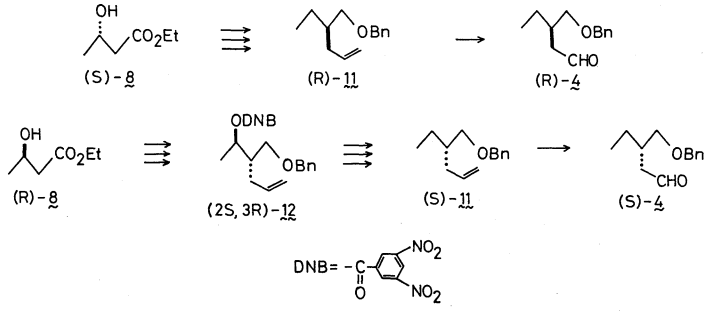

FIG. 3. Synthesis of the Enantiomers of **4**.

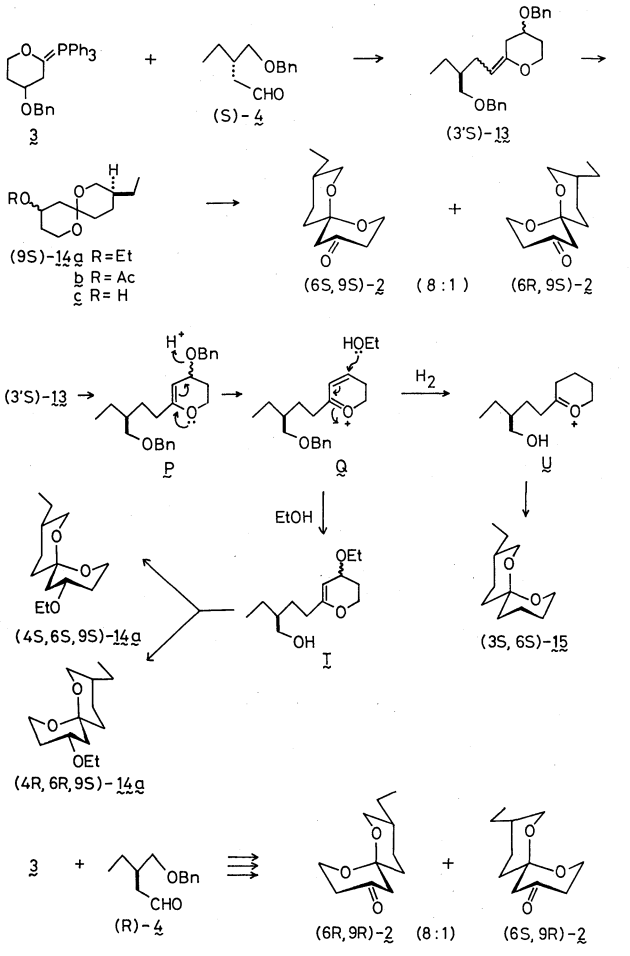

FIG. 4. Synthesis of the Enantiomers of **2**.

which was then condensed with (*S*)-**4** to give (3′*S*)-**13** in a 58% yield. Hydrogenolysis of (3′*S*)-**13** with hydrogen and palladium on charcoal in an acidic medium (*p*-toluenesulfonic acid in ethanol) yielded a complex mixture of spiroacetals, which was analyzed by GC-MS. The peak with a shorter retention time (M^+ 184, 26%) was assumed to be due to (3*S*,6*S*)-3-ethyl-1,7-dioxaspiro[5.5]undecane (**15**), and that with a longer retention time (M^+ 228, 60%) was assumed to be due to a stereoisomeric mixture of (9*S*)-4-ethoxy-9-ethyl-1,7-dioxaspiro[5.5]undecane (**14a**). The absolute configuration of the former was deduced on the basis of the oxygen-anomeric effect[3] and the reasonable reaction pathway explaining its formation (see below). The ethyl ether (9*S*)-**14a** was oxidized with ruthenium dioxide[11]-sodium periodate to give (9*S*)-**14b** in a 44% yield.[12] This oxidation process also produced (9*S*)-9-ethyl-1,7-dioxaspiro[5.5]undecan-4-one (**2**) in a 26% yield.[13] In the NMR spectrum of the mixture of these oxidation products, only a signal due to an axial proton at C-4 (δ 5.01 ppm, dddd, $J = 11, 11, 6, 6$ Hz) was observed. Thus, (9*S*)-**14b** was assumed to be a stereoisomeric mixture of (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14b** on the basis of the oxygen-anomeric effect. Similarly, (9*S*)-**14a** was assumed to be a mixture of (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14a**.

Downloaded by [University of Texas Libraries] at 22:31 26 November 2014

Downloaded by [University of Texas Libraries] at 22:31 26 November 2014

The unexpected formation of (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14a** could be rationalized by the sequence (3′*S*)-(**13**)→ **P**→ **Q**→**T**→ (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14a** involving (i) olefin isomerization (ii) retro-Michael-like elimination of benzyl alcohol (iii) addition of ethanol and (iv) spiroacetalization. The equatorial orientation of an oxygen substituent newly added at C-4 was the case not only with another of our experimental results[2] but also with that reported by Smith and Thompson.[5] The formation of (3*S*,6*S*)-**15** could also be rationalized in a similar way, where hydrogenation of **Q** to **U** followed by spiroacetalization gave (3*S*,6*S*)-**15**.

Treatment of a mixture of (9*S*)-**14b** and (9*S*)-**2** with potassium carbonate in methanol followed by chromatographic purification over silica gel gave (9*S*)-**2** in a 15% yield from (9*S*)-**14a**, and (9*S*)-**14c** in a 40% yield from (9*S*)-**14a**. As (9*S*)-**14c** was shown to possess an axial proton at C-4 (δ 4.08 ppm, dddd, J=12, 12, 6, 6 Hz) from its NMR spectrum, it was assumed to be a stereosiomeric mixture of (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14c**. Jones oxidation of (9*S*)-**14c** followed by the equilibration under an acidic condition [concentrated hydrochloric acid–water–tetrahydrofuran (1 : 5 : 20)] gave a mixture of (6*S*,9*S*)- and (6*R*,9*S*)-**2** in a 63% yield, the ratio of which was determined to be 8 : 1 by capillary GLC analysis. Its IR and NMR spectra were virtually identical with those of (6*R*,9*R*)-**2** reported by Smith and Thompson.[5] From its ^{13}C-NMR spectrum, the assigned structure and the ratio of the stereoisomers were confirmed. The overall yield of the equilibrium mixture of (6*S*,9*S*)- and (6*R*,9*S*)-**2** [$[\alpha]_D^{23}$ +111° (chloroform)] was 4% from **7** in 15 steps and 7% from (*R*)-**8** in 16 steps.

In the same manner as that described above, the equilibrium mixture of (6*R*,9*R*)- and (6*S*,9*S*)-**2** [$[\alpha]_D^{23}$ −110° (chloroform)] in the ratio of 8 : 1 was synthesized from **10** and (*R*)-**4** in a 7.8% yield in 6 steps (Fig. 4). The overall yield of the equilibrium mixture of (6*R*,9*R*)- and (6*S*,9*R*)-**2** was 2% from **7** in 15 steps and 3.6% from (*S*)-**8** in 16 steps.

In conclusion, both the enantiomers of **2** were synthesized in a convergent manner. This model study on taloromycin synthesis confirmed the versatility of chiral starting materials of a microbial origin.

EXPERIMENTAL

All boiling points (bp) and melting points (mp) were uncorrected. IR spectra were measured as films for oils and as Nujol mulls for solids on a Jasco A-102 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-24A (60 MHz) or on a Jeol JNM FX-100 (100 MHz) spectrometer with TMS as an internal standard. ^{13}C-NMR spectra were recorded on a Jeol JNM FX-100 spectrometer at 25 MHz with TMS as an internal standard. Optical rotations were measured on a Jasco DIP-140 polarimeter. ORD and CD spectra were measured on a Jasco J-20C spectropolarimeter. Mass spectra were recorded at 70 eV on a Hitachi RMU-6M or a Jeol DX-300 spectrometer. GC-MS analyses were performed on a Jeol DX-300 spectrometer (column, OV-1, 1 m × 3 mm; carrier gas, helium at 15 ml/min) and the product ratios were calculated from the peak heights in a total ion monitor. GLC analyses were performed on a Jeol JGC-20 K or on a Yanaco G 180 gas chromatograph (carrier gas, nitrogen). A Fuji-Davison BW-820 MH was used for silica gel chromatography.

4-Hydroxy-2-methoxytetrahydropyran (**5a**).[7] A mixture of crude 3,5-dihydroxypentanal acetonide (**9**) (19.3 g, about 122 mmol),[2] *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 0.64 g, 3.4 mmol) and magnesium sulfate ($MgSO_4$, 8 g, 6.6 mmol) in methanol (MeOH, 400 ml) was stirred for 43 hr at room temperature. Sodium bicarbonate ($NaHCO_3$, 12 g, 143 mmol) was added to the mixture. After stirring for 1.5 hr at room temperature, the mixture was diluted with ether (Et_2O) and filtered. The mixture was concentrated *in vacuo* below 30°C to give a yellow oil (11.7 g). This was distilled in the presence of potassium carbonate (K_2CO_3) to give **5a** (9.03 g, 56%; bp 79 ~ 93°C/12 mmHg). A portion (1.5 g) was further purified by chromatography over silica gel [SiO_2, 15 g; *n*-pentane–Et_2O (5 : 1–3 : 1)] followed by distillation in the presence of K_2CO_3 to give an analytical sample (1.04 g), bp 95°C/11 mmHg; n_D^{20} 1.4512; IR ν_{max} cm^{-1} 3430 (s), 1125 (s), 1055 (s); NMR δ [carbon tetrachloride (CCl_4)] 1.10 ~ 2.12 (4H, m), 3.27 (about 2.4H, s), 3.37 (about 0.6H, s), 3.00 ~ 4.35 (4H, m), 4.55 (about 0.2H, dd, J=8, 3 Hz), 4.67 (about 0.8H, dd, J=3, 3 Hz); GLC [column, 3% OV-17, 1.5 m × 3 mm at 70°C + 2°C/min; carrier gas, 0.9 kg/cm^2): t_R 2.8 min (18.7%), 3.7 min (81.3%); MS (*m*/*z*) 132 (M^+).

Downloaded by [University of Texas Libraries] at 22:31 26 November 2014

4-Benzyloxy-2-methoxytetrahydropyran (**5b**). To a stirred and ice-cooled suspension of sodium hydride (60% in mineral oil, 3.8 g, 95 mmol; washed 3 times with dry *n*-pentane) in dry tetrahydrofuran (THF, 50 ml) was added dropwise a solution of **5a** (8.3 g, 63 mmol) in dry THF (18 ml) at between 0 and 5°C under argon (Ar). After stirring for 1 hr at room temperature, to the mixture were added tetra(*n*-butyl)ammonium iodide (350 mg, 0.95 mmol)[8] at room temperature, and benzyl bromide (9.8 ml, d 1.438, 82.3 mmol) dropwise below 25°C with ice-cooling. The mixture was stirred for 1.5 hr at room temperature and for a further 1.5 hr with heating under reflux. Ice-cooled water (H_2O, 40 ml) was added to the mixture with ice-cooling. The mixture was concentrated *in vacuo* to remove THF. The residue was extracted with Et_2O. The Et_2O extract was washed with H_2O, $NaHCO_3$ solution and brine, dried over K_2CO_3–$MgSO_4$ and concentrated *in vacuo* to give a red residue (18.6 g). This was purified by chromatography over SiO_2 [150 g; *n*-pentane–Et_2O (80 : 1–40 : 1–20 : 1)] followed by distillation in the presence of K_2CO_3 to give a mixture (11.5 g, 82%) of *trans*- and *cis*-**5b**, bp 114 ~ 122°C/1.5 mmHg; n_D^{19} 1.5061; IR ν_{max} cm^{-1} 3120 (w), 3100 (w), 3060 (m), 1505 (m), 1100 (vs), 1060 (vs), 740 (s), 705 (s); NMR δ (CCl_4) 1.05 ~ 2.21 (4H, m), 3.22 (about 2.1H, s), 3.31 (about 0.9H, s), 3.58 (1H, dd, J=8, 3 Hz), 3.60 ~ 3.98 (2H, m), 4.14 (about 0.3H, dd, J=8, 3 Hz), 4.44 (2H, s), 4.65 (about 0.7H, dd, J=3, 3 Hz), 7.22 (5H, br.s); GLC (column, 3% OV-17, 1.5 m × 3 mm at 110°C + 2°C/min; carrier gas, 0.9 kg/cm^2): t_R 18.3 min (76.7%), 20.1 min (23.3%); *Anal.* Found: C, 70.03; H, 8.21. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

4-Benzyloxy-2-tetrahydropyranyltriphenylphosphonium tetrafluoroborate (**10**). A solution of hydrogentriphenylphosphonium tetrafluoroborate (9.29 g, 26.5 mmol)[9,10] and **5b** (5.2 g, 23.4 mmol) in dry acetonitrile (MeCN, 40 ml) was stirred and heated under reflux overnight. The mixture was concentrated *in vacuo* and heated at 70°C (bath temperature) *in vacuo* at 3 mmHg overnight to dryness to give crude **10** (about 14 g, quantitative). This was employed in the next step without further purification.

(*R*)-*3-(Benzyloxymethyl)pentanal* (**4**). To a stirred two-phase mixture of (*R*)-5-benzyloxy-4-ethyl-1-pentene (**11**, 4.0 g, 19.6 mmol)[2] in Et_2O–H_2O (1 : 1, 220 ml) were added a 2.5% solution of osmium tetroxide in THF (10 ml, 0.98 mmol) and sodium periodate ($NaIO_4$, 27.0 g, 126 mmol) at room temperature. After stirring overnight, the precipitate was filtered off through a pad of Celite and washed with Et_2O. From the combined filtrate and washings was separated the organic layer, and the aqueous layer was extracted with Et_2O. The combined Et_2O solution was washed with sodium thiosulfate solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a black residue (4.5 g). This was distilled *in vacuo* under Ar to give (*R*)-**4** (3.0 g, 75%), bp 102 ~ 104°C/0.15 mmHg; n_D^{25} 1.4969; $[\alpha]_D^{24}$ +17.6° [c=1.18, chloroform ($CHCl_3$)]; IR ν_{max} cm^{-1} 3120 (w), 3100 (w), 3070 (w), 2750 (w), 1730 (s), 1105 (s), 1035 (m), 740 (s), 705 (s); NMR δ (CCl_4) 0.87 (3H, deformed t, J=6 Hz), 1.35 (2H, dq, J=6, 6 Hz), 1.85 ~ 2.35 (1H, m), 2.29 (2H, dd, J=4, 2 Hz), 3.25 and 3.30 (total 2H, each d, J=8, 2; 8, 4 Hz), 4.39 (2H, s), 7.23 (5H, br.s), 9.73 (1H, t, J=2 Hz); *Anal.* Found: C, 75.34; H, 8.79. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

(*2S,3R*)-*2-Allylbutane-1,3-diol 1-benzyl ether 3-(3′,5′-dinitro)-benzoate* (**12**). In the same manner as that reported,[2] acylation of (2*S*,3*R*)-2-allylbutane-1,3-diol 1-benzyl ether [28.9 g, 131 mmol; prepared from (*R*)-**8** in a 69% yield by the reported method[2]] gave (2*S*,3*R*)-**12** (55.2 g, quantitative) as crude yellowish crystals. These were recrystallized twice from *n*-hexane–Et_2O (3 : 1) to give pure (2*S*,3*R*)-**12** (48.0 g, 88% recovery) as pale yellow rods, mp 58.0 ~ 58.5°C; $[\alpha]_D^{21}$ −42.8° (c=2.55, $CHCl_3$). Its IR and NMR spectra were almost identical with those of (2*R*,3*S*)-**12**.[2] HPLC analysis of (2*S*,3*R*)-**12** under the same conditions as those reported[2] showed it to be diastereomerically pure. *Anal.* Found: C, 60.54; H, 5.46; N, 6.81. Calcd. for $C_{21}H_{22}O_7N_2$: C, 60.86; H, 5.35; N, 6.76%. According to the reported procedure,[2] its optical purity was also confirmed to be of 100% *e.e.*

(*S*)-*3-(Benzyloxymethyl)pentanal* (**4**). In the same manner as with the preparation of (*R*)-**4**, (*S*)-**11** [4.48 g, 21.9 mmol; prepared from (2*S*,3*R*)-**12** by the reported method[2]] gave (*S*)-**4** (3.87 g, 76%), bp 117°C/0.8 mmHg; n_D^{19} 1.4969; $[\alpha]_D^{21}$ −17.1 (c=1.17, $CHCl_3$). Its IR and NMR spectra were almost identical with those of (*R*)-**4**. *Anal.* Found: C, 75.34; H, 8.79. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

(*3′S*)-*4-Benzyloxy-2-[(3′-benzyloxymethyl)-pentylidene]tetrahydropyran* (**13**). To a stirred and cooled solution of crude **10** (about 14 g, about 23.4 mmol) and dry hexamethylphosphoric triamide (12.5 ml) in dry THF (100 ml) was added a solution of *n*-butyllithium in *n*-hexane (1.20 N, 17 ml, 20.4 mmol) at between −65 and −58°C under Ar. After stirring for 15 min at −65°C, to this deep red ylide solution was added dropwise a solution of (*S*)-**4** (3.43 g, 16.6 mmol) in dry THF (12.5 ml) with stirring at between −68 and −65°C. The reaction temperature was gradually raised to room temperature and the stirring was continued overnight. The usual workup[2] gave a crude red oil (11.9 g). This was chromatographed over SiO_2 (200 g). Elution with *n*-hexane–ethyl acetate (60 : 1–20 : 1–10 : 1) gave (3′*S*)-**13** (3.68 g, 58%). Spectral data were recorded on the later-eluting fractions, IR ν_{max} cm^{-1} 3120 (w), 3100 (w), 3060 (w), 1680 (m), 1505 (m), 1255 (m), 1100 (s), 1030 (m), 735 (s), 700 (s); NMR δ (CCl_4) 0.85 (3H, t, J=6 Hz), 1.05 ~ 1.55 (3H, m), 1.55 ~ 2.30 (5H, m), 2.64 (1H, dm, J= 12 Hz), 3.37 (2H, d, J=5 Hz), 3.30 ~ 3.70 (2H, m), 3.94 (1H, dd, J=12, 6 Hz), 4.38 (2H, s), 4.43 (2H, s), 4.86 (1H, t, J=8 Hz), 7.22 (10H, br.s). In contrast, the earlier-eluting fractions showed an olefinic proton at δ 4.90 ~ 5.40 ppm in

Downloaded by [University of Texas Libraries] at 22:31 26 November 2014

their NMR spectrum and *m/z* 380 (M^+) in their MS.

(9S)-4-Ethoxy-9-ethyl-1,7-dioxaspiro[5.5]undecane (**14a**). After a mixture of (3'*S*)-**13** (0.67 g, 1.76 mmol), *p*-TsOH·H_2O (75 mg, 0.35 mmol) and 10% palladium on charcoal (0.13 g) in ethanol (7 ml) had been stirred for 4 hr 35 min, hydrogen (H_2) was introduced into the reaction flask. Stirring was continued overnight at room temperature under H_2. The mixture was neutralized by the addition of sodium carbonate (0.3 g, 2.8 mmol) and then filtered. The filtrate was concentrated *in vacuo*. The residue (about 0.5 g) was chromatographed over SiO_2 (6.0 g). Elution with *n*-hexane–Et_2O (5:1) gave a crude mixture (0.36 g, 90%) of (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14a**, IR ν_{max} cm^{-1} 1095 (s), 1065 (s); NMR δ (CCl_4) 0.87 (3H, t, J=6 Hz), 1.09 (3H, t, J=7 Hz), 1.20~2.30 (11H, m), 3.40 (2H, q, J=7 Hz), 2.80~4.00 (5H, m); GC-MS (column at 100°C+2°C/min): t_R 7.8 min [26%, (3*S*,6*S*)-3-ethyl-1,7-dioxaspiro[5.5]undecane (**15**); 184 (M^+, 21%), 156 (1%), 155 (2%), 154 (5%), 139 (6%), 129 (27%), 128 (11%), 127 (3%), 126 (25%), 125 (2%), 111 (24%), 101 (98%), 100 (34%), 99 (10%), 98 (100%), 97 (8%)],[14] 14.3 min [60%, (9*S*)-**14a**; 229 (M^++1, 1%), 228 (M^+, 2%), 199 (4%), 183 (33%), 145 (100%), 144 (2%), 143 (2%), 139 (3%), 129 (72%), 128 (1%), 127 (38%)].[14]

(9S)-4-Acetoxy-9-ethyl-1,7-dioxaspiro[5.5]undecane (**14b**). To a stirred two-phase mixture of (9*S*)-**14a** (558 mg, 2.4 mmol) in CCl_4–MeCN–H_2O (2:2:3, 14 ml) were added $NaIO_4$ (2.4 g, 11.2 mmol) and ruthenium dioxide (20 mg, 0.15 mmol; activated according to the reported procedure[11])[12] at room temperature. The usual work-up[12] gave a green residue. This was diluted with methylene chloride and filtered through a pad of Florisil. The filtrate was concentrated *in vacuo* to give a crude mixture (475 mg, 82%) of (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14b**, IR ν_{max} cm^{-1} 1750 (s), 1250 (s), 1100 (s), 1060 (s); NMR δ (CCl_4) 0.90 and 0.95 (total 3H, each t, J=6 Hz), 1.10~2.15 (11H, m), 1.93 (3H, s), 2.90~4.03 (4H, m), 5.01 (1H, dddd, J=11, 11, 6, 6 Hz); GC-MS (column at 100°C+8°C/min): t_R 5.7 min [26%, (9*S*)-**2**; 199 (M^++1, 6%), 198 (M^+, 45%), 168 (7%), 129 (13%), 127 (4%), 126 (30%), 125 (9%), 115 (100%), 114 (6%), 113 (9%), 112 (90%), 111 (12%)],[14] 7.2 min [5%, (4*R*,6*R*,9*S*)-**14b**; 243 (M^++1, 1%), 183 (10%), 182 (2%), 159 (3%), 158 (2%), 129 (5%), 127 (1%), 99 (100%), 98 (3%), 97 (7%)],[14] 7.7 min [39%, (4*S*,6*S*,9*S*)-**14b**; 243 (M^++1, 1%), 183 (18%), 182 (5%), 159 (4%), 158 (3.5%), 129 (10%), 127 (2%), 99 (100%), 98 (5%), 97 (13%)].[14] This was employed in the next step without further purification.

(9S)-9-Ethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**14c**). (9*S*)-**14b** (455 mg, about 1.88 mmol) was treated with K_2CO_3 (0.36 g, 26 mmol) in MeOH (5 ml) at room temperature in the usual manner to give an orange residue (0.4 g). This was chromatographed over SiO_2 (8 g). Elution with *n*-hexane–Et_2O (8:1–6:1) gave (9*S*)-**2** [70 mg, 15% from (9*S*)-**14a**], IR ν_{max} cm^{-1} 1730 (s), 1090 (s), 1055 (s); NMR δ [chloroform-d_1 ($CDCl_3$)] 0.88 (3H, br.t, J=5 Hz), 0.95~2.08 (7H, m), 2.43 (2H, br.s), 2.11~2.91 (2H, m), 3.15~3.79 (2H, m), 3.79~4.15 (2H, m). Further elution with *n*-hexane–Et_2O (6:1) followed by Et_2O gave a mixture [184 mg, 40% from (9*S*)-**14a**] of (4*S*,6*S*,9*S*)- and (4*R*,6*R*,9*S*)-**14c**, IR ν_{max} cm^{-1} 3400 (s), 1090 (s), 1065 (s); NMR δ ($CDCl_3$) 0.85 and 0.89 (total 3H, each t, J=6 Hz), 1.00~1.75 (8H, m), 1.65~2.30 (4H, m), 3.05~3.83 (4H, m), 4.08 (1H, dddd, J=12, 12, 6, 6 Hz); GC-MS (column at 100°C+8°C/min); t_R 5.7 min [single peak; 201 (M^++1, 2%), 183 (4%), 182 (0.5%), 129 (53%), 128 (5%), 127 (7%), 126 (22%), 125 (1%), 117 (100%)].[14]

(6S,9S)- and (6R,9S)-9-Ethyl-1,7-dioxaspiro[5.5]undecan-4-one (**2**). (9*S*)-**14c** (184 mg, 0.92 mmol) was oxidized with Jones reagent in acetone (4 ml) in the usual manner to give crude (9*S*)-**2** (162 mg, 89%), IR ν_{max} cm^{-1} 1730 (s), 1090 (s), 1035 (s). This was mixed with concentrated hydrochloric acid–H_2O–THF (1:5:20, 3 ml) and stirred overnight at room temperature. Neutralization with $NaHCO_3$ followed by the usual workup gave a crude oil (157 mg). This was chromatographed over SiO_2 (3 g). Elution with *n*-pentane–Et_2O (5:1) gave a mixture [115 mg, 63% from (9*S*)-**14c**] of (6*S*,9*S*)- and (6*R*,9*S*)-**2** in an 8:1 ratio, n_D^{26} 1.4686; $[\alpha]_D^{23}$ +111° (c=0.45, $CHCl_3$); CD ($c=3.3\times10^{-2}$, 24°C): $\Delta\varepsilon$ +0.59 (286 nm); ORD ($c=3.3\times10^{-2}$, 24°C): [α] (λ, nm) +1333 (304), +227 (267), +833 (220); IR ν_{max} cm^{-1} 3100 (s), 2960 (s), 2900 (s), 1730 (s), 1470 (m), 1455 (m), 1435 (w), 1410 (w), 1385 (s), 1370 (m), 1335 (m), 1315 (s), 1290 (w), 1255 (s), 1240 (s), 1210 (s), 1205 (m), 1175 (s), 1155 (s), 1090 (s), 1070 (s), 1055 (s), 1040 (s), 1005 (s), 990 (s), 970 (m), 945 (w), 930 (s), 890 (m), 865 (s), 840 (w), 810 (w), 765 (m), 695 (w); NMR (100 MHz) δ ($CDCl_3$) 0.88 (3H, t, J=6 Hz), 1.00~1.30 (2H, m), 1.30~1.80 (4H, m), 1.80~2.06 (1H, m), 2.30 (1H, br.d, J=11.6 Hz), 2.44 (2H, br.s), 2.58 (1H, ddd, J=14.5, 11.6, 8.3 Hz), 3.22 (about 0.88H, dd, J=11.6, 11.6 Hz), 3.41 (about 0.12H, br.d, J=10 Hz), 3.58 (about 0.88H, dd, J=11.6, 3.2 Hz), 3.65 (about 0.12H, dd, J=11.6, 2.9 Hz), 3.76~4.16 (2H, m); ^{13}C-NMR δ ($CDCl_3$) for (6*S*,9*S*)-**2** 11.1, 25.0, 25.1, 35.0, 36.1, 41.0, 52.3, 59.0, 65.7, 99.3, 205.5; for (6*R*,9*R*)-**2** 12.1, 22.4, 30.4, 34.0, 52.1, 59.2, 63.5, 99.6; GLC (column, OV-101, 50 m×0.25 mm at 160°C; carrier gas, 1.1 kg/cm^2): t_R 39.5 min (11.0%), 40.4 min (88.1%); MS (*m/z*) 200 (M^++2, 1%), 199 (M^++1, 7%), 198 (M^+, 50%), 168 (7%), 129 (11%), 127 (3%), 126 (28%), 125 (8%), 115 (100%), 114 (4%), 113 (8%), 112 (86%), 111 (12%)[14]; *Anal.* Found: C, 66.60; H, 8.93. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%.

(3'R)-4-Benzyloxy-2-[(3'-benzyloxymethyl)-pentylidene]tetrahydropyran (**13**). In the same manner as with the preparation of (3'*S*)-**13**, **5b** (5.74 g, 25.8 mmol) and (*R*)-**4** (3.0 g, 14.5 mmol) gave (3'*R*)-**13** (3.6 g, 65%). Its IR and NMR spectra were almost identical with those of (3'*S*)-**13**.

(9R)-4-Ethoxy-9-ethyl-1,7-dioxaspiro[5.5]undecane (**14a**). In the same manner as with the preparation of (9*S*)-**14a**, (3′*R*)-**13** (2.3 g, 5.8 mmol) gave a crude mixture (0.54 g, 41%) of (4*R*,6*R*,9*R*)- and (4*S*,6*S*,9*R*)-**14a**. Its IR and NMR spectra were almost identical with those of (9*S*)-**14a**. GC-MS (column at 80°C + 4°C/min): t_R 7.9 min [16%, (3*R*,6*R*)-**15**; 184 (M^+, 12%), 101 (82%), 98 (100%)], 14.4 min [31%, (9*R*)-**14a**; 228 (M^+, 3%), 145 (100%)]. This was employed in the next step without further purification.

(9R)-4-Acetoxy-9-ethyl-1,7-dioxaspiro[5.5]undecane (**14b**). In the same manner as with the preparation of (9*S*)-**14b**, (9*R*)-**14a** (0.5 g, 2.2 mmol) gave a crude mixture (0.36 g, 68%) of (4*R*,6*R*,9*R*)- and (4*S*,6*S*,9*R*)-**14b**. Its IR and NMR spectra were almost identical with those of (9*S*)-**14b**. GC-MS (column at 100°C + 8°C/min): t_R 3.9 min [23%, (3*R*,6*R*)-**15**; 184 (M^+, 22%), 101 (93%), 98 (100%)], 6.4 min [15%, (9*R*)-**2**; 198 (M^+, 55%), 115 (100%), 112 (89%)], 8.4 min [31%, (9*R*)-**14b**; 243 ($M^+ + 1$, 0.2%), 242 (M^+, 1.5%), 99 (100%)]. This was employed in the next step without further purification.

(9R)-9-Ethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**14c**). In the same manner as with the preparation of (9*S*)-**14c**, (9*R*)-**14b** (0.36 g, about 1.5 mmol) gave a crude mixture (0.16 g, 54%) of (4*R*,6*R*,9*R*)- and (4*S*,6*S*,9*R*)-**14c**. Its IR and NMR spectra were almost identical with those of (9*S*)-**14c**. GC-MS (column at 100°C + 4°C/min): t_R 3.8 min [29%, (3*R*,6*R*)-**15**; 184 (M^+, 22%), 101 (93%), 98 (100%)], 6.4 min [48%, (9*R*)-**2** and (9*R*)-**14c**; 200 (M^+, 22%), 198 (M^+, 5%), 117 (100%), 115 (16%)]. This was employed in the next step without further purification.

(6R,9R)- and (6S,9R)-9-Ethyl-1,7-dioxaspiro[5.5]-undecan-4-one (**2**). In the same manner as with the preparation of (9*S*)-**2**, Jones oxidation of (9*R*)-**14c** (0.16 g, about 0.8 mmol) followed by acid-catalyzed equilibration gave a mixture [47 mg, 12% from (3′*R*)-**13**] of (6*R*,9*R*)- and (6*S*,9*R*)-**2** in an 8:1 ratio, n_D^{24} 1.4694; $[\alpha]_D^{23}$ −110° (c = 0.49, $CHCl_3$). CD ($c = 3.2 \times 10^{-2}$, 24°): $\Delta\varepsilon$ −0.61 (286 nm); ORD ($c = 3.2 \times 10^{-2}$, 24°C): [α] (λ, nm) −1219 (304), 0 (267), −664 (220). Its IR, NMR and MS spectra were identical with those of (9*R*)-**2**. GLC (column, OV-101, 50 m × 0.25 mm at 164°C; carrier gas, 1.0 kg/cm²): t_R 95.3 min (11.8%), 97.7 min (88.2%).

Acknowledgments. This work was supported in part by a Grant-in-Aid for Scientific Research (No. 60430023) from the Ministry of Education, Science and Culture of Japan. K. M. thanks Professor S. V. Ley (Imperial College, London) for discussion.

REFERENCES

1) a) D. G. Lynn, N. J. Phillips, W. C. Hutton, J. Shabanowitz, D. I. Fennel and R. J. Cole, *J. Am. Chem. Soc.*, **104**, 7319 (1982).
b) W. C. Hutton, N. J. Phillips, D. W. Graden and D. G. Lynn, *J. Chem. Soc., Chem. Commun.*, **1983**, 864.
2) K. Mori and M. Ikunaka, *Tetrahedron*, **43**, 45 (1987) and references cited therein.
3) K. Mori, H. Soga and M. Ikunaka, *Liebigs Ann. Chem.*, **1985**, 2194 and references cited therein.
4) a) S. V. Ley and B. Lygo, *Tetrahedron Lett.*, **25**, 113 (1984).
b) D. Culshaw, P. Grice, S. V. Ley and G. A. Strange, *Tetrahedron Lett.*, **26**, 5837 (1985).
5) A. B. Smith, III and A. S. Thompson, *J. Org. Chem.*, **49**, 1469 (1984).
6) T. Sugai, M. Fujita and K. Mori, *Nippon Kagaku Kaishi* (*J. Chem. Soc. Jpn.*), **1983**, 1315.
7) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 1543 (1968).
8) S. Czernecki, C. Gergoulis and C. Provelenghiou, *Tetrahedron Lett.*, **1976**, 3535.
9) D. A. Clark and P. L. Fuchs, *Synthesis*, **1977**, 628.
10) C. G. Kruse, E. K. Poels and A. ver der Gen, *J. Org. Chem.*, **44**, 2911 (1979).
11) C. L. Stevens and C. P. Bryant, *Methods Carbohydr. Chem.*, **6**, 337 (1972).
12) P. H. J. Carsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
13) A. B. Smith, III and R. M. Scarborough, Jr., *Synth. Commun.*, **10**, 205 (1980).
14) W. Francke, G. Hindorf and W. Reith, *Naturwissenschaften*, **66**, 619 (1979).

Downloaded by [University of Texas Libraries] at 22:31 26 November 2014