Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2871–2879

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of a key intermediate aldehyde toward the polyene macrolide filipin III, based on a chiral oxazaborolidinone-promoted asymmetric aldol reaction

Syun-ichi Kiyooka,[a,*] Mostofa A. Hena [a] and Fumitaka Goto [b]

[a] *Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi, 780-8520, Japan*

[b] *Cellular Technology Institute, Otsuka Pharmaceutical Co., Ltd, Kagasuno, Kawauchi-cho, Tokushima, 771-0130, Japan*

Received 1 June 1999; accepted 1 July 1999

Abstract

A versatile preparation of an enantiopure aldehyde useful for the asymmetric total synthesis of filipin III was developed using a chiral oxazaborolidinone-promoted asymmetric aldol reaction with a dithiolane silyl nucleophile. The sign and magnitude of the specific rotation of the aldehyde, (4*R*,5*R*)-2,2-dimethyl-5-formyl-4-pentyl-1,3-dioxane, were reconfirmed. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

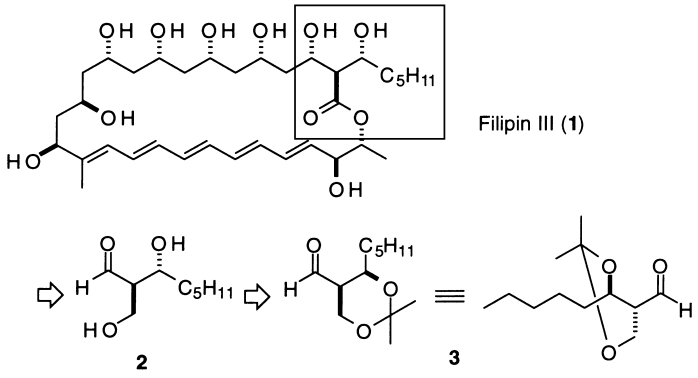
Filipin III **1**, a polyene macrolide antibiotic which is a membrane disrupter that selectively binds cholesterol, was isolated from cell culture filtrates of *Streptomyces filipinensis*.[1,2] The structure was determined[3] and the first total synthesis was reported by the same group.[4] The *syn*-1,3-polyol segment of **1** is a very challenging target for verifying the validity of our strategy[5] by repetition of the chiral oxazaborolidinone-promoted asymmetric aldol reaction with a dithiolane silyl nucleophile **7**, which is related to a synthetic equivalent of an acetate unit. Thus, we retrosynthetically chose aldehyde **3** as a synthetic equivalent of the right-hand upper fragment of filipin III, depicted in the box of Scheme 1.

Compound **3**, $[\alpha]_D^{23}$ +13.6 (*c* 0.94, $CHCl_3$),[3] has been prepared in seven steps involving a Sharpless asymmetric epoxidation during the structure elucidation study by Rychnovsky. We disclose herein a very simple enantioselective synthesis of essentially enantiopure **3** using a chiral oxazaborolidinone-promoted asymmetric aldol reaction starting from hexanal and a silyl nucleophile **7**.

* Corresponding author. E-mail: kiyo@cc.kochi-u.ac.jp

0957-4166/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.

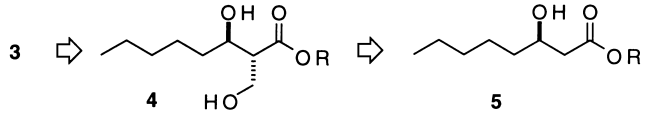
PII: S0957-4166(99)00278-5



Scheme 1.

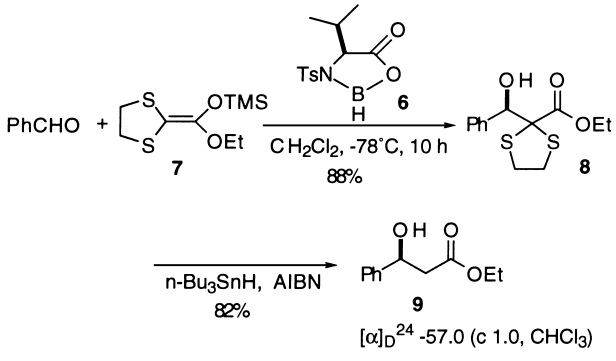
2. Results and discussion

A sequence of reactions to **3** was quite simply planned to involve two stereoselective aldol reactions, as shown in Scheme 2. The first is a *Si*-facial-selective aldol reaction of an acetate nucleophile with hexanal and the second is an *anti*-selective aldol reaction with formaldehyde. We have already reported a very highly enantioselective synthesis of acetate aldols by using the chiral oxazaborolidinone **6**-promoted asymmetric aldol reaction of dithiolane silyl nucleophile **7**.[5]



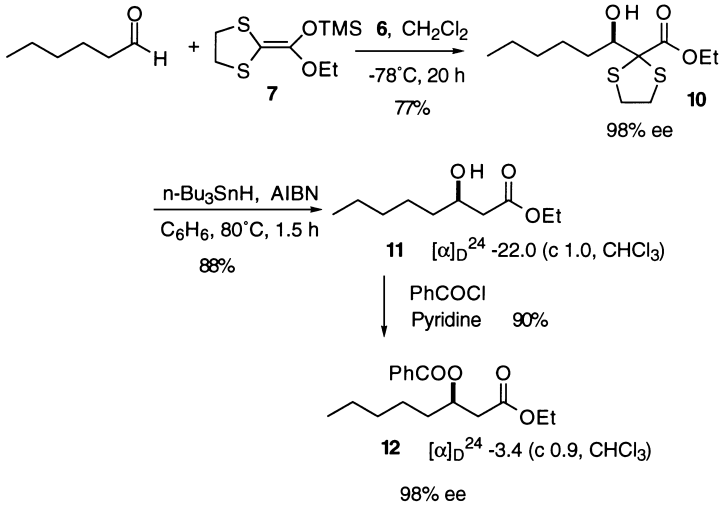
Scheme 2.

In order to ensure the stereochemical outcome in this aldol reaction, we reinvestigated the aldol reaction of benzaldehyde with **7** in the presence of a stoichiometric amount of **6**, coupled with the following desulfurization, to give ethyl (*S*)-3-hydroxy-3-phenylpropionate **9** (Scheme 3). During the desulfurization process of **8**, an improvement of the reaction conditions was achieved by replacing $Ni_2B–H_2$ with *n*-Bu_3SnH–AIBN such that the reaction proceeded more smoothly along with this simple manipulation. The sign and magnitude of the specific rotation, $[\alpha]_D^{24}$ −57.0 (*c* 1.0, $CHCl_3$), of the product **9** was in fair agreement with that, $[\alpha]_D^{20}$ −50.8 (*c* 1.07, $CHCl_3$), obtained from enzymatic reactions by Boaz.[6] The above transformation procedure, therefore, can reliably obtain the expected stereocenter at the β position with regard to reconfirmation of the *Si*-facial selectivity in the aldol reaction.



Scheme 3.

The starting aldol reaction directed to the enantioselective synthesis of **3** was carried out in the presence of the same promoter **6**. The dithiolane aldol **10** was obtained in good yield after a prolonged reaction at −78°C. The enantioselectivity of **10** was determined to be 98% ee by using a Chiralcel OD column. Compound **10** underwent the following radical desulfurization reaction to give the expected β-hydroxy ester **11** in high yield (Scheme 4). After benzoylation of **11**, the enantioselectivity of the sequence of reactions was rechecked by using a joint HPLC column of Chiralcel OD-H and Chiralpak AD to ascertain the absence of racemization during the process. Moreover, we have confirmed the absolute configuration (*R*) of **11** by comparing the ^{1}H and ^{19}F NMR chemical shift differences of the Mosher esters of **11** and the corresponding racemate.[7]



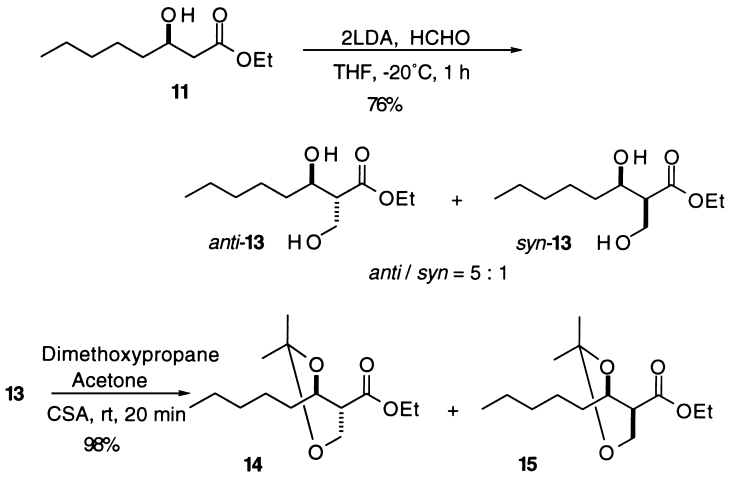
Scheme 4.

It was expected, from previous work on diastereoselective alkylation reactions with an enolate dianion, that the aldol reaction with the enolate dianion would lead to higher *anti* predominance.[8] The aldol reaction using the dianion derived from **11** proceeded at −20°C on introduction of gaseous formaldehyde to give a mixture of diastereomers of aldol **13** in good yield with good *anti* selectivity (5:1). But the mixture could not be separated by flash column chromatography. Under the standard conditions, **13** was directly converted to the corresponding acetonide derivatives **14** and **15**, respectively, which were shown to be the same isomeric ratio, in a quantitative yield (Scheme 5). The acetonides were easily separated by flash column chromatography and both the *syn* and *anti* structures were confirmed by NOE experiments, as shown in Fig. 1. As expected, we can propose the reaction course shown in Fig. 2 to be relevant.

The last step was accomplished by DIBAL-H reduction of **14** and **15** to give directly the corresponding aldehydes **3** and **16**, respectively, without the production of the corresponding alcohols (Scheme 6). The sign and magnitude of the specific rotation of the target aldehyde **3** was $[\alpha]_D^{24}$ −17.8 (*c* 1.4, $CHCl_3$).

3. Conclusion

Essentially enantiopure (4*R*,5*R*)-2,2-dimethyl-5-formyl-4-pentyl-1,3-dioxane **3** was prepared from hexanal via a short route in a practically acceptable overall yield by using a chiral oxazaborolidinone-promoted asymmetric aldol reaction followed by diastereoselective aldol reaction with an enolate dianion. Thus, the ready supply of aldehyde **3** in large quantities, available for the total synthesis of filipin III, is now possible.



Scheme 5.

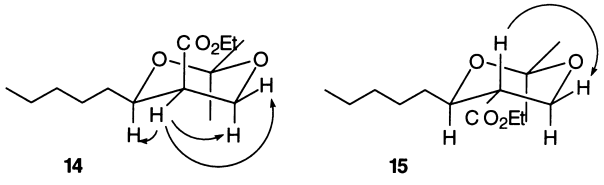


Figure 1. NOE correlations of acetonides

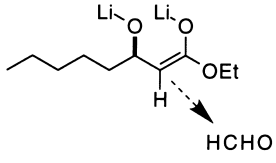
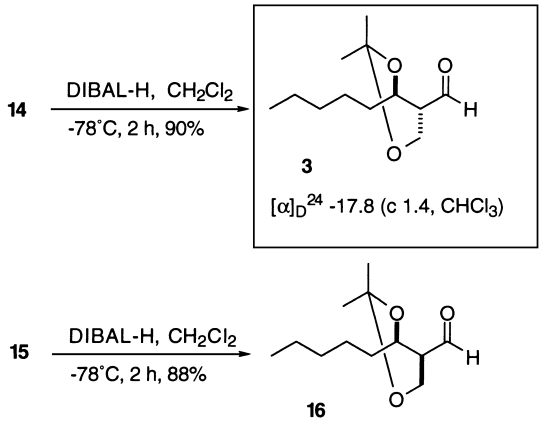


Figure 2. Reaction course to *anti* preference



Scheme 6.

4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All reactions involving organometallic reagents were conducted under an argon atmosphere. IR spectra were determined with a JASCO FT/IR-5300 fourier transform infrared recording spectrophotometer. ^{1}H NMR spectra were determined on a JEOL JNM-LA 400 (a superconducting, 400 MHz, FT instrument) spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) are in hertz, number of protons. ^{13}C NMR spectra were measured at 100 MHz with a JOEL JNM-LA 400 spectrometer. High-pressure liquid chromatography (HPLC) was done with a JASCO Model PU-980 liquid chromatograph.

4.2. 1-Ethoxy-2,2-(ethylenedithio)-1-trimethylsiloxyethene **7**

To a solution of diisopropylamine (17.5 mL, 0.13 mol) in dry THF (300 mL) at 0°C was added *n*-BuLi (78.1 mL, 0.13 mol, 1.6 M in hexane) dropwise. The solution was cooled to −78°C and ethyl dithiolanecarboxylate (14.3 mL, 0.1 mol) was added dropwise over 20 min. After 20 min, chlorotrimethylsilane (38 mL, 0.3 mol) was added. The solution was allowed to warm to rt and stirred overnight. After evaporation of the solvent in vacuo, the residue was diluted with dry hexane, filtered through Celite, and after removal of hexane in vacuo the residual oil was distilled (bp 108–109/0.1 mmHg) to provide the pure silyl nucleophile **7** as a yellow oil (20 g, 80%). IR (film) 1655 cm^{-1}. ^{1}H NMR ($CDCl_3$, 90 MHz) δ (ppm) 3.82 (q, *J*=7.0 Hz, 2H), 3.21 (br s, 4H), 1.20 (t, *J*=7.0 Hz, 3H), 0.19 (s, 9H).

4.3. Ethyl (3S)-2,2-(ethylenedithio)-3-hydroxy-3-phenylpropionate **8**

To a solution of *N*-(*p*-toluenesulfonyl)-*S*-valine (1.5 g, 5.5 mmol) in dry CH_2Cl_2 (25 mL) at 0°C was added BH_3·THF (5.0 mL, 5.0 mmol, 1 M in THF). The solution was stirred for 30 min at 0°C, then for an additional 30 min at rt. The solution was cooled to −78°C and benzaldehyde (0.5 mL, 5.0 mmol) in CH_2Cl_2 (1 mL) was added slowly over 5 min. After stirring for 5 min, **7** (1.4 g, 5.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 5 min, the reaction mixture was stirred for 3 h and a buffer solution (5 mL, pH 6.86) was added to quench the reaction. The reaction mixture was allowed to warm to rt and evaporated to a concentrated residue. The residue was diluted with ether and the phases were separated. The organic phase was washed with satd aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated in vacuo. Flash column chromatography (10% ethyl acetate/hexane) provided the pure aldol **8** (1.3 g, 88%). $[\alpha]_D^{24}$ −21.1 (*c* 0.9, $CHCl_3$). IR (film) 3422, 1720 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.30–7.51 (m, 5H), 5.31 (d, *J*=5.3 Hz, 1H), 4.23 (dq, *J*=7.0, 0.9 Hz, 2H), 3.49 (d, *J*=5.6 Hz, 1H), 3.23–3.32 (m, 2H), 3.00–3.10 (m, 2H), 1.28 (t, *J*=7.0, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.5, 138.5, 128.3, 128.0, 127.6, 77.1, 76.6, 62.6, 39.9, 39.8, 13.9. Anal. calcd for $C_{13}H_{16}O_3S_2$: C, 54.90; H, 5.67. Found: C, 54.77; H, 5.71.

4.4. Ethyl (3R)-3-hydroxy-3-phenylpropionate **9**

To a solution of **8** (1.1 g, 4.0 mmol) in benzene (10 mL) was added successively tributyltin hydride (4.3 mL, 16.0 mmol) and freshly recrystallized AIBN (26.4 mg). The mixture was refluxed at 80°C for 1.5 h with stirring. The reaction mixture was allowed to cool to rt and evaporated in vacuo to a crude material. The crude material was purified by flash column chromatography to give acetate aldol **9** (636.9 mg, 82%) as a colorless oil, which was determined to be 98% ee by using a Chiralcel OD column with 5% 2-propanol/hexane (1.0 mL/min, R_f 8.9 min, λ 254 nm). $[\alpha]_D^{24}$ −57.0 (*c* 1.0, $CHCl_3$). IR (film) 3456, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.26–7.41 (m, 5H), 5.14 (dt, *J*=7.5, 3.6 Hz), 4.19 (q, *J*=7.0 Hz, 2H), 3.28 (d, *J*=3.6 Hz, 1H), 2.77 (dd, *J*=16.3, 8.8 Hz, 1H), 2.39 (dd, *J*=16.3, 4.1 Hz, 1H), 1.26 (t, *J*=7.0, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.4, 142.4, 128.5, 127.8, 125.6, 70.3, 60.8, 43.3, 14.1. Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.56; H, 7.33.

4.5. Ethyl (3R)-2,2-(ethylenedithio)-3-hydroxyoctanoate **10**

To a solution of *N*-(*p*-toluenesulfonyl)-*S*-valine (25 g, 85.8 mmol) in dry CH_2Cl_2 (250 mL) at 0°C was added $BH_3 \cdot THF$ (78 mL, 78 mmol, 1 M in THF). The solution was stirred for 30 min at 0°C, then for an additional 30 min at rt. The solution was cooled to −78°C and hexanal (9.4 mL, 78 mmol) in CH_2Cl_2 (10 mL) was added slowly over 5 min. After stirring for 5 min, **7** (19.6 g, 78 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. The reaction mixture was stirred for 3 h and a buffer solution (50 mL, pH 6.86) was added to quench the reaction. The reaction mixture was allowed to warm to rt and evaporated to a concentrated residue. After the residue was diluted with ether, the organic phase was washed with satd aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated in vacuo. Flash column chromatography (10% ethyl acetate/hexane) provided the aldol **10** (16.7 g, 77%), which was determined to be 98% ee by using a Chiralcel OD column with 1.5% 2-propanolhexane (1.0 mL/min, R_f 20.5 min, λ 210 nm). $[\alpha]_D^{24}$ +10.0 (*c* 1.4, $CHCl_3$). IR (film) 3490, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.25 (q, *J*=7.0, 2H), 4.00–4.10 (m, 1H), 3.33–3.42 (m, 4H), 2.82 (d, *J*=7.0, 1H), 1.33–1.67 (m, 8H), 1.32 (t, *J*=7.0, 3H), 0.88 (t, *J*=6.8, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.8, 75.8, 75.5, 62.2, 39.9, 39.8, 34.0, 31.4, 26.1, 22.4, 13.9, 13.8. Anal. calcd for $C_{12}H_{22}O_3S_2$: C, 51.76; H, 7.96. Found: C, 51.60; H, 8.01.

4.6. Ethyl (3R)-3-hydroxyoctanoate **11**

To a solution of **10** (5.0 g, 18 mmol) in benzene (30 mL) was added successively tributyltin hydride (19.4 mL, 72.0 mmol) and freshly recrystallized AIBN (118.8 mg, 0.72 mmol). The resulting mixture was refluxed at 80°C for 1.5 h with stirring. The reaction mixture was then allowed to cool to rt and evaporated in vacuo to a crude material. The crude material was purified by flash column chromatography to give acetate aldol **11** (3.0 g, 88%) as a colorless oil. $[\alpha]_D^{24}$ −22.0 (*c* 1.0, $CHCl_3$). IR (film) 3484, 1726 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.17 (q, *J*=7.0 Hz, 2H), 3.97–4.12 (m, 1H), 3.05 (d, *J*=3.4 Hz, 1H), 2.49 (dd, *J*=16.3, 3.4 Hz, 1H), 2.39 (dd, *J*=16.3, 9.0 Hz, 1H), 1.27 (t, *J*=7.0, 3H), 1.25–1.54 (m, 8H), 0.89 (t, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.9, 67.9, 60.5, 41.3, 36.4, 31.6, 25.0, 22.5, 14.1, 13.9. Anal. calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.55; H, 10.85.

4.7. Ethyl (3R)-3-benzoyloxyoctanoate **12**

To a solution of **11** (161.9 mg, 0.86 mmol) in dry pyridine (1 mL) at 0°C benzoylchloride (0.1 mL, 0.86 mmol) was added. The mixture was allowed to warm to rt and stirred overnight. Pyridine was removed in vacuo, the residue was diluted with ether, washed with 10% HCl and satd aqueous $NaHCO_3$ solutions, dried over $MgSO_4$, and evaporated to a crude material. The crude material was purified by flash chromatography (3% ethyl acetate/hexane) to give the benzoyl derivative **12** (225.1 mg, 90%) as a colorless oil, which showed to be 98% ee by using a joint column of Chiralcel OD-H and Chiralpak AD with 3% 2-propanol/hexane (1.0 mL/min, R_f 16.8 min, λ 254 nm). $[\alpha]_D^{24}$ −3.4 (*c* 0.9, $CHCl_3$). IR (film) 1790, 1724 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.36–7.56 (m, 5H), 5.45–5.51 (m, 1H), 4.11 (q, *J*=7.0 Hz, 2H), 2.75 (dd, *J*=15.4, 7.5 Hz, 1H), 2.66 (dd, *J*=15.4, 5.4 Hz, 1H), 1.67–1.83 (m, 2H), 1.22–1.48 (m, 6H), 1.18 (t, *J*=7.0, 3H), 0.87 (t, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.3, 165.8, 162.2, 134.4, 130.4, 128.8, 71.2, 60.5, 39.4, 34.0, 31.4, 24.7, 22.3, 14.0, 13.8. Anal. calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 63.55; H, 10.85.

4.8. Ethyl (2R,3R)-3-hydroxy-2-(hydroxymethyl)octanoate anti-**13** and ethyl (2S,3R)-3-hydroxy-2-(hydroxymethyl)octanoate syn-**13**

To a solution of lithium diisopropylamide (8.0 mmol) in dry THF (30 mL) at −78°C was added **11** (753 mg, 4.0 mmol) in THF (5 mL) slowly over a period of 20 min, followed by stirring for 30 min. After the reaction mixture was warmed to −20°C, gaseous formaldehyde, which was generated by heating paraformaldehyde (760 mg, 24 mmol) along with phosphorus pentaoxide at 150°C, was introduced into the reaction mixture. After stirring the mixture for 1 h at the same temperature, it was quenched by the addition of satd aqueous NH_4Cl solution (5 mL). The mixture was extracted with ether, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude material was purified by flash column chromatography (15% ethyl acetate/hexane) to give a 5:1 mixture of *anti*-**13**: *syn*-**13** (664 mg, 76%). IR (film) 3489, 1724 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.15–4.28 (m, 2H), 3.86–4.08 (m, 3H), 3.06 (d, *J*=5.3 Hz, 1/6H), 2.99 (d, *J*=7.8 Hz, 5/6H), 2.88 (br s, 1H), 2.65 (dt, *J*=5.3, 9.1 Hz, 5/6H), 2.54 (dt, *J*=4.4, 4.3 Hz, 1/6H), 1.30 (t, *J*=7.0 Hz, 3H), 1.25–1.62 (m, 8H), 0.89 (t, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.6, 71.7, 62.6, 60.8 (60.9), 51.7 (51.4), 35.3 (34.9), 31.6, 25.4, 22.5, 14.1, 13.9 (numbers in parentheses stand for the minor isomer). Anal. calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.25; H, 10.23.

4.9. (4R,5R)-5-Ethoxycarbonyl-2,2-dimethyl-4-pentyl-1,3-dioxane **14** and (4R,5S)-5-ethoxycarbonyl-2,2-dimethyl-4-pentyl-1,3-dioxane **15**

To a solution of diol **13** (436.6 mg, 2.0 mmol) in dry acetone (10 mL) was added successively acetone dimethylacetal (0.49 mL, 4.0 mmol) and camphor-10-sulfonic acid (46.4 mg, 0.2 mmol) and the reaction mixture was stirred for 20 min at rt. The reaction was quenched by adding Et_3N (0.41 mL, 0.3 mmol). The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in ether, washed with water, and dried over $MgSO_4$. After evaporation of the solvent, the crude material was purified by flash column chromatography (4% ethyl acetate/hexane) to provide acetonide **14** (423.6 mg, 82%) and acetonide **15** (93.0 mg, 16%) as colorless oils. Acetonide **14**: $[\alpha]_D^{24}$ −10.0 (*c* 1.0, $CHCl_3$). IR (film) 1739, 1462 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.19 (ddq, *J*=10.7, 7.0, 4.1 Hz, 2H), 4.13 (dd, *J*=11.9, 2.9 Hz, 1H), 4.04 (dd, *J*=11.9, 4.4 Hz, 1H), 3.95–3.99 (m, 1H), 2.44 (br, dt, *J*=3.8, 3.4 Hz, 1H), 1.43 (s, 6H), 1.28 (t, *J*=7.0 Hz, 3H), 1.26–1.61 (m, 8H), 0.88 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100

MHz) δ (ppm) 171.0, 99.0, 69.3, 61.2, 60.5, 43.5, 32.9, 31.5, 28.3, 25.1, 22.4, 19.6, 14.1, 13.9. Anal. calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 65.12; H, 10.18. Acetonide **15**: $[\alpha]_D^{24}$ +51.6 (*c* 0.6, $CHCl_3$). IR (film) 1732, 1464 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.14 (ddq, *J*=10.7, 7.0, 2.9 Hz, 2H), 4.00 (dd, *J*=11.4, 10.4 Hz, 1H), 3.97–4.02 (m, 1H), 3.92 (dd, *J*=11.4, 5.4 Hz, 1H), 2.57 (dt, *J*=10.3, 5.4 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H), 1.26 (t, *J*=7.0 Hz, 3H), 1.22–1.52 (m, 8H), 0.88 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.5, 98.4, 69.9, 61.4, 60.5, 46.9, 34.4, 31.6, 29.2, 24.4, 22.5, 19.2, 14.1, 13.9. Anal. calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.98; H, 10.09.

*4.10. (4*R*,5*R*)-5-Formyl-2,2-dimethyl-4-pentyl-1,3-dioxane **3***

To a cooled (−78°C) solution of ester **14** (129.1 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added DIBAL (0.6 mL, 0.6 mmol, 1 M in toluene) over a period of 30 min. The reaction mixture was stirred at −78°C for 2 h, and then MeOH was added to quench the reaction. After 15 min water (1.0 mL) was added; the resulting mixture was then allowed to warm to rt and stirred vigorously to form a precipitate. After filtration of the precipitate, the mixture was diluted with ether and the phases were separated. The organic phase was washed with water and brine, dried over $MgSO_4$, and evaporated to a crude material. Purification of the crude material by flash column chromatography (2.5% ethyl acetate/hexane) provided aldehyde **3** (96.4 mg, 90%) as a colorless oil. $[\alpha]_D^{24}$ −17.8 (*c* 1.4, $CHCl_3$). IR (film) 1726 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 10.11 (d, *J*=4.1 Hz, 1H), 4.17 (dd, *J*=12.2, 2.9 Hz, 1H), 4.10 (dd, *J*=12.2, 1.5 Hz, 1H), 4.09–4.11 (m, 1H), 2.02–2.05 (m, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.23–1.65 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 204.8, 99.2, 70.1, 61.3, 49.6, 33.1, 31.4, 29.3, 24.8, 22.4, 18.6, 13.9. Anal. calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.50; H, 10.38.

*4.11. (4*R*,5*S*)-5-Formyl-2,2-dimethyl-4-pentyl-1,3-dioxane **16***

According to the reduction procedure described above, the reaction of aldehyde **3** with ester **15** (93.0 mg, 0.35 mmol) and DIBAL (0.45 mL, 0.45 mmol, 1 M in toluene) in CH_2Cl_2 (5 mL) afforded aldehyde **16** (66 mg, 88%) as a colorless oil. $[\alpha]_D^{24}$ +48.0 (*c* 0.5, $CHCl_3$). IR (film) 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.75 (d, *J*=2.2 Hz, 1H), 3.98–4.04 (m, 1H), 3.97 (d, *J*=6.1 Hz, 1H), 3.96 (dd, *J*=3.1 Hz, 1H), 2.64–2.70 (m, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.22–1.60 (m, 8H), 0.88 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.4, 98.7, 68.3, 58.5, 53.7, 34.7, 31.5, 28.4, 24.5, 22.5, 19.7, 13.9. Anal. calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.11; H, 10.30.

Acknowledgements

We thank the Ministry of Education, Science and Culture, Japan, for a Grant-in-Aid for Scientific Research (Nos. 9554046 and 10640525).

References

1. Whitfield, G. B.; Brock, T. D.; Ammann, A.; Gottlieb, D.; Carter, H. E. *J. Am. Chem. Soc*. **1955**, *77*, 4799–4801.
2. Gale, E. F. *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; p. 425.
3. Richardson, T. I.; Rychnovsky, S. D. *J. Org. Chem*. **1996**, *61*, 4219–4231. After our work was finished, we were informed by Prof. S. Rychnovsky that the measured rotation, α, was negative in the original notebook in his laboratory but in the calculation the sign of the rotation was inadvertently dropped.

4. Richardson, T. I.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **1997**, *119*, 12360–12361.
5. (a) Kiyooka, S.-i. *Rev. Heteroatom Chem*. **1997**, *17*, 245–270. (b) Kiyooka, S.-i.; Hena, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2181–2184. (c) Kiyooka, S.-i.; Maeda, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3371–3374. (d) Kiyooka, S.-i.; Maeda, H.; Hena, M. A.; Uchida, M.; Kim, C.-S.; Horiike, M. *Tetrahedron Lett*. **1998**, *39*, 8287–8290. (e) Hena, M. A.; Kim, C.-S.: Horiike, M.; Kiyooka, S.-i. *Tetrahedron Lett*. **1999**, *40*, 1161–1164.
6. Boaz, N. W. *J. Org. Chem*. **1992**, *57*, 4289–4292.
7. (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem*. **1973**, *38*, 2143–2147. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. *Tetrahedron* **1976**, *32*, 1363–1367.
8. (a) Ha, D.-C.; Kil, K.-E.; Choi, K.-S.; Park, H.-S. *Tetrahedron Lett*. **1996**, *37*, 5723–5726, and references cited therein. (b) Fráter, G. *Tetrahedron Lett*. **1981**, *22*, 425–428.