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Synthesis of southern (C1′–C11′) fragment of pamamycin-635A

Ayako Miura, Hiromasa Kiyota* and Shigefumi Kuwahara

Department of Applied Bioorganic Chemistry, Division of Bioscience and Biotechnology for Future Bioindustry, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan

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Abstract—The synthesis of the southern (C1′–C11′) fragment of pamamycin-635A, isolated from *Streptomyces alboniger*, was achieved via an Evans aldol reaction, a *cis*-selective iodoetherification and a stereospecific deiodination as the key steps.
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1. Introduction

A series of antibiotic pamamycins have been isolated from various *Streptomyces* species (Fig. 1).[1] Among them, pamamycin-607 **1** was isolated from *Streptomyces alboniger*, and showed aerial mycelium-inducing activity in an aerial mycelium-less mutant of *S. alboniger*.[1b] Some total[2] and many partial syntheses[3] have been reported for **1**, but only two partial synthesis of a homologue pamamycin 635A **2**[1c] have been reported to date,[4] perhaps because of its structural complexity. We began the synthesis for **2** to supply a sample for further biological studies. Here we describe an enantioselective synthesis of the southern (C1′–C11′) hydroxy acid fragment **3**, also a constituent of pamamycins-621B[1e], 635C[1e] and 649B[1c] (*S. alboniger*) and 621A (*S. alboniger*[1e] and *S. aurantiacus* IMET 43917[1d]).

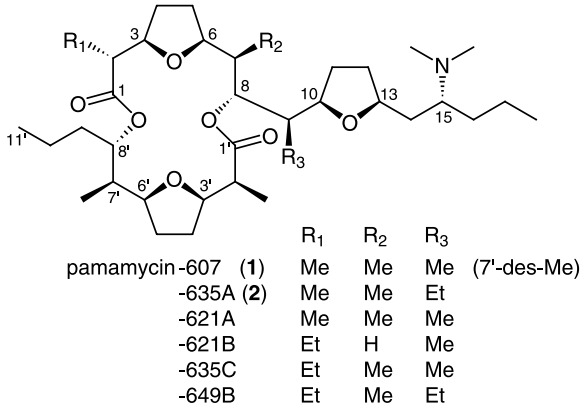
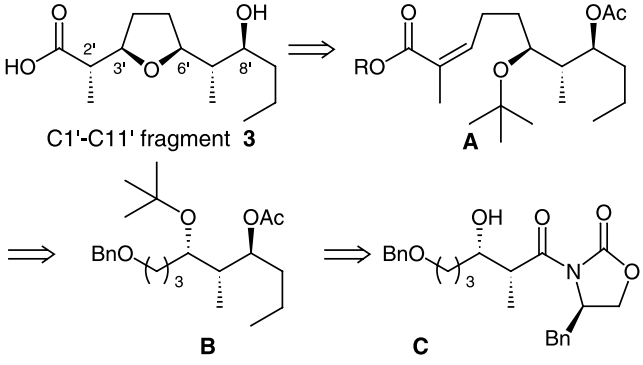


Figure 1. Structures of pamamycins.

2. Results and discussion

Scheme 1 depicts our synthetic plan.† The *cis*-tetrahydrofuran ring of **3** could be constructed by iodoetherification[5] of the corresponding (*Z*)-γ,δ-unsaturated *tert*-butoxy compound **A**, itself prepared from **B**. The *syn*-aldol moiety of **B** could be derived from the Evans aldol reaction[6] product **C**.[7,8]



Scheme 1. Retrosynthetic analysis of **3**.

As shown in Scheme 2, the known *syn*-aldol compound **5** (**C**)[8] was prepared by Evans reaction from **4**, which was then converted into its *tert*-butyl ether **6**.[3c,7] This compound was diastereomerically pure by ^{1}H NMR analysis. Then the Evans' oxazolizinone was replaced by ethanethiol to give **7**. This thioester was reduced with DIBAL and the resulting

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* Corresponding author. Tel.: +81 22 717 8785; fax: +81 22 717 8783; e-mail: kiyota@biochem.tohoku.ac.jp

† The carbon numbers will be described without primes for clarity.

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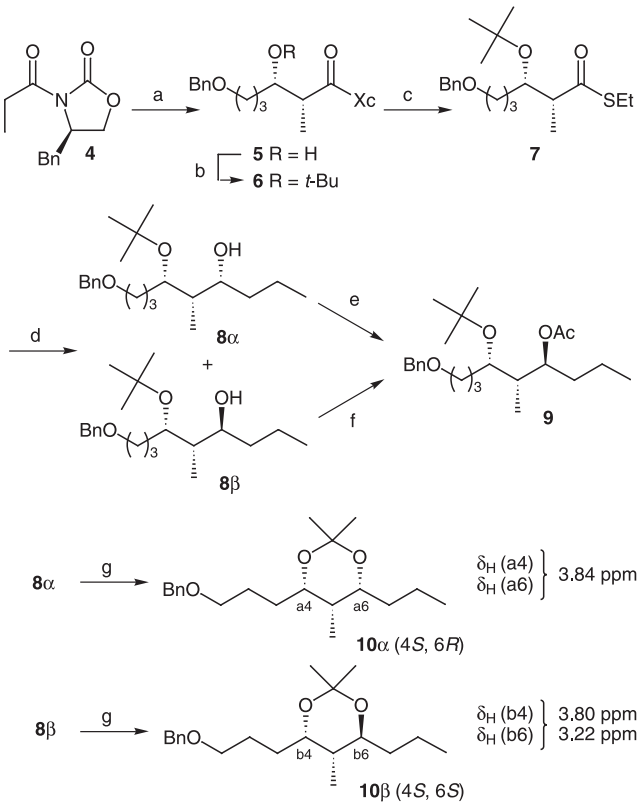
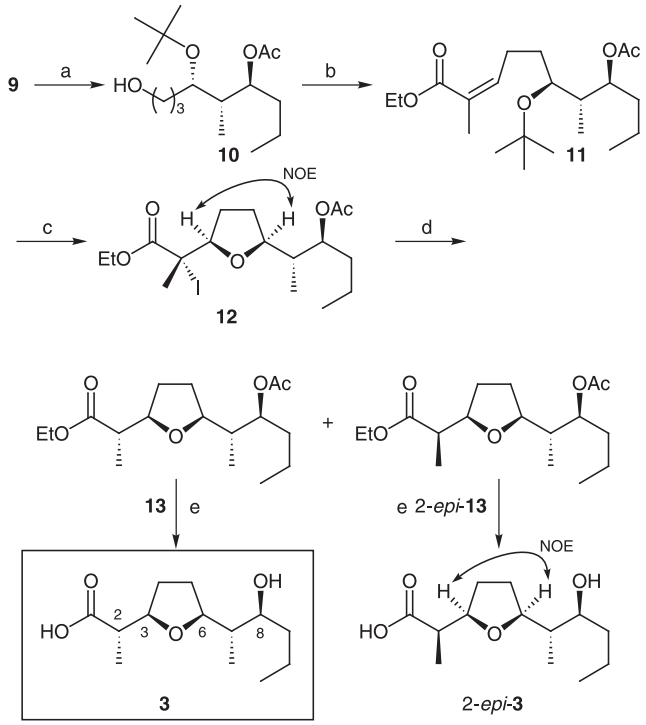


Scheme 2. Synthesis of the southern part of **2**. (a) *n*-Bu_2OTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C to rt (95%). (b) Amberlyst H-15, isobutene, hexane, −78 °C to rt (71%, and 20% of **5**). (c) *n*-BuLi, EtSH, THF, 0 °C. (d) (i) DIBAL, CH_2Cl_2, −78 °C (95%). (ii) *n*-PrMgBr, THF, −78 °C (70% of **8α** and 18% of **8β**). (e) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C. (ii) KOAc, 18-c-6, toluene, reflux (56%). (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (94%). (g) (i) TsOH, MeOH, 80 °C. (ii) 2,2-dimethoxypropane, TsOH, acetone, 0 °C (43% for **10α**, 23% for **10β**).

aldehyde treated with *n*-PrMgBr to afford alcohols **8α** and **8β** (80:20). These compounds were separated and converted to acetate **9**. To determine the relative stereochemistry, **8α** and **8β** were transformed to their corresponding acetonides **10α** and **10β**, respectively. The ^1H NMR chemical shift values in **10α**, $\delta_{a4}=\delta_{a6}=3.84$ ppm, showed that the 1,3-dioxane ring of **10α** had a *pseudo* mirror plane, therefore, the structure was determined as indicated. In addition, the selectivity of the reaction was consistent with Felkin–Anh model transition state.

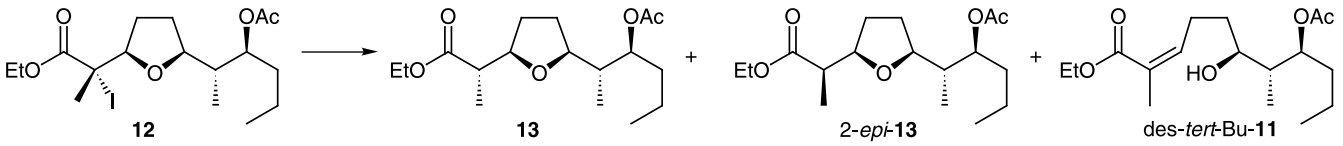
Removal of the benzyl protecting group of **9** gave alcohol



Scheme 3. Synthesis of **3** and its 2-epimer. (a) H_2, Pd-C, MeOH (97%). (b) (i) Dess–Martin periodinane, Et_2O, 0–20 °C. (ii) ethyl 2-(di-*o*-tolyl)phosphonopropanoate (77% in 2 steps). (c) ICl, $NaHCO_3$, CH_3CN, 20 °C (53% of **12** and 43% of recovered **11**). (d) $NaBH_4$, DMSO (60% of **13**, 23% of 2-*epi*-**13** and 17% of *des*-*tert*-butyl-**11**). (e) KOH, MeOH-H_2O (quant. yield for **3** and 78% for 2-*epi*-**3**).

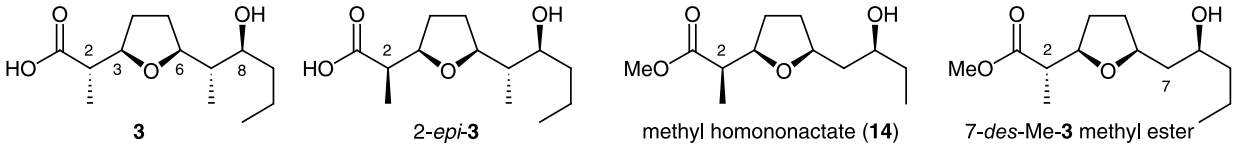
10 (Scheme 3). The alcohol **10** was converted to enone **11** (**A**) by Dess–Martin oxidation followed by Ando's modified Horner–Wadsworth–Emmons olefination (77%, *Z*/*E*=94:6).[9] Next, we tried the key iodoetherification. Treatment of compound **11** with iodine at 30 °C resulted in no reaction, but by screening other iodonium ion donors (IBr, NIS, iodonium dicollidine perchlorate: IDCP), we found ICl to be the reagent of choice. The yield of iodide **12** (*cis* only) was 53% but 43% of **11** was recovered. The *cis* stereochemistry of the tetrahydrofuran ring was confirmed by the observation of NOE between 3- and 6-protons of **12** and 2-*epi*-**3**. Reductive removal of the iodo group of **12** was done under various conditions (Table 1). The reaction proceeded with inversion of configuration using $NaBH_4$ in DMSO[10] at 10 °C to afford the desired **13** and 2-*epi*-**13** in 60 and 23%, respectively, along with 17% of *des*-*tert*-butyl-**11**. Radical

Table 1. Reductive deiodination of **12**



Entry	Conditions	**13** (%)	2-*epi*-**13**	des-*tert*-Bu-**11**	**12** (recovery)
1	$NaBH_4$, MeOH, 20 °C	52	40	4	4
2	$NaBH_4$, MeOH, −20 to 0 °C	53	29	10	8
3	$NaBH_4$, DMSO, −10 to 10 °C	60	23	17	—
4	$NaBH_4$, MeOH, 20 °C	52	40	4	4
5	$NaBH_3CN$, HMPA, 20–45 °C	19	18	—	63
6	*n*-Bu_3SnH, AIBN, CH_2Cl_2, −78 °C, *hv*	8	47	—	—

Table 2. Selected ^{1}H NMR data of **3** and the related compounds



3 2-*epi*-**3** methyl homononactate (**14**) 7-*des*-Me-**3** methyl ester

Position	Natural **3**[a]	**3**	2-*epi*-**3**	**3** Methyl ester[b]	**3** Methyl ester	2-*epi*-**3** Methyl ester	Methyl homononactate (**14**)[c]	7-*des*-Me-**3** methyl ester[d]
2	2.62	2.72	2.54	2.57	2.61	2.56	2.54	2.59
3	3.96	3.97	3.95	3.90[e]	3.94	3.95	3.94	3.99[e]
6	4.13	4.12	4.18	4.06[e]	4.10	4.12	4.14	4.13[e]
8	3.63	3.63	3.61	3.53[e]	3.58	3.57	(3.73)	3.84[e]
11	0.91	0.93	0.92	0.88,m	0.93	0.93	—	0.93
7-Me	0.88	0.90	0.91	0.88,m	0.88	0.89	—	—
2-Me	1.21	1.22	1.17	1.19	1.22	1.14	1.13	1.23

[a] Ref. 1d.
[b] Ref. 4a.
[c] Ref. 13.
[d] Ref. 2e.
[e] Not assigned.

reaction conditions resulted in the opposite selectivity.[11] In this case, the chirality of 2-position was lost through the radical intermediate, and the preferential formation of 2-*epi*-**13** is consistent with Guindon's results.[11] Finally, alkaline hydrolysis of **13** and 2-*epi*-**13** gave **3** and 2-*epi*-**3**, respectively, in an overall yield of 19% for **3**. Their methyl esters were prepared for spectral comparison.[4a] Selected ^{1}H NMR spectroscopic data are shown in Table 2. The chemical shift values of our synthetic compounds were slightly different from those reported, however, their structures are supported by Guindon's results[11] and the downfield chemical shifts of 2-methyl protons: comparison of (2*S**,3*R**)-configuration of pamamycin and (2*R**,3*R**)-configuration of nonactic acid derivatives (**14**).[4a,12,13]

3. Conclusion

Synthesis of the southern fragment of antibiotic pamamycin-635A, isolated from *Streptomyces alboniger*, was achieved in 19% overall yield using an Evans aldol reaction, a *cis*-selective iodoetherification and a stereospecific deiodination as the key steps. The structure of this hydroxy acid was confirmed by NMR data.

4. Experimental

4.1. General

Optical rotation values were measured by a Horiba Sepa-300 polarimeter. IR spectra were recorded as films by a Jasco IR Report-100 spectrometer, ^{1}H- and ^{13}C NMR spectra were recorded with a Varian Inova 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C), Inova 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) and Gemini 2000 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard, and mass spectra were recorded with a Jeol JMS-700 spectrometer. Elemental compositions were analyzed by Perkin–Elmer 2400II CHN analyzer. Merck silica gel 60 (70–230 mesh) was used for column chromatography.

4.1.1. (4*R*,2′*R*,3′*S*)-4-Benzyl-3-[(6′-benzyloxy-3′-*tert*-butoxy-2′-methyl)hexanoyl]-2-oxazolidinone (6). A 40 ml, pressure-bottle equipped with a magnetic stirrer bar was charged with **5** (1.2 g, 2.9 mmol) and dry hexane (3.5 ml) at room temperature, and the mixture was stirred for 12 h. To this was added isobutene (ca. 10 ml) at −78 °C and the bottle cap was closed tightly. The mixture was gradually warmed to room temperature and stirred for 2 d. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (6:1) gave **6** (0.93 g, 2.0 mmol, 71%) as a colorless oil and recovered **5** (0.23 g, 0.55 mmol, 20%) as a colorless oil. **6**; R_f: 0.54 (hexane/EtOAc=2:1), $[\alpha]_D^{24}$ −50° (c=0.78, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.15 (s, 9H, *t*-Bu), 1.21 (d, 3H, J=6.9 Hz, 2-Me), 1.49–1.73 (m, 4H, 4′-H and 5′-H), 2.75 (dd, 1H, J=9.3, 13.5 Hz, NCHCH_2Ph), 3.30 (dd, 1H, J=3.3, 13.5 Hz, NCHCH_2Ph), 3.44–3.50 (m, 2H, 6′-H), 3.81 (m, 1H, 4-H), 3.94–4.12 (m, 3H, 5-H_2 and 3′-H), 4.48 (s, 2H, OCH_2Ph), 4.53 (m, 1H, 4-H), 7.20–7.34 (m, 10H, Ph). FABMS (glycerol+NOBA): m/z=468 $(M+H)^+$, 412 $(M^+ + H\text{-}t\text{-}Bu)^+$. HR-FABMS: calcd for $C_{28}H_{38}NO_5$ $(M+H)^+$, 468.2750; found, 468.2754.

4.1.2. (2*R*,3*S*)-6-Benzyloxy-3-*tert*-butoxy-2-methyl-hexanoic acid *S*-ethyl ester (7). A 300 ml, three-necked round bottomed flask equipped with a magnetic stirrer bar, a 50 ml pressure-equalizing addition funnel, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with EtSH (2.5 ml, 34 mmol) in THF (50 ml) at 0 °C. 1.6 M *n*-BuLi in hexane (17.5 ml, 28 mmol) was added dropwise to the solution and stirred for 1 h. Then the mixture was cooled to −78 °C and was added **6** (5.20 g, 11.1 mmol) in THF (50 ml). The reaction mixture was gradually warmed to 0 °C and stirred for 2 h. This was quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was

chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **7** (mw: 352.53, 3.70 g, 10.5 mmol, 95%) as a colorless oil; R_f: 0.63 (hexane/EtOAc=4:1), $[\alpha]_D^{24}$ −35° (c=1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=1.16 (d, 3H, J=7.1 Hz, 2-Me), 1.18 (s, 9H, t-Bu), 1.23 (t, 3H, J=7.4 Hz, SCH_2CH_3), 1.39–1.76 (m, 4H, 4-H and 5-H), 2.77–2.91 (m, 3H, 2-H and SCH_2), 3.46 (t, 2H, J=6.3 Hz, 6-H), 3.74 (q, 1H, J=10.7, 5.2 Hz, 3-H), 4.50 (s, 2H, OCH_2Ph), 7.26–7.34 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.87, 14.59, 23.19, 25.27, 28.73 (Me_3C), 30.26, 52.78 (2-C), 70.51, 72.57, 72.72, 73.90, 127.41, 127.55, 128.29, 128.61, 202.48 (C=O). IR (film): ν=2980 (s) cm^{-1}, 2880 (m), 1680 (s, C=O), 1455 (m), 1365 (s), 1190 (s), 1100 (s), 1010 (s). FABMS (glycerol+NOBA): m/z=353 $(M+H)^+$, 297 $(M+H\text{-}t\text{-}Bu)^+$, 235 $(M+H\text{-}t\text{-}Bu\text{-}HSEt)^+$. HR-FABMS: calcd for $C_{20}H_{33}O_3S$ $(M+H)^+$, 353.2151; found, 353.2151. Found: C, 68.18%; H, 9.72%. Calcd for $C_{20}H_{32}O_3S$: C, 68.14%; H, 9.15%.

4.1.3. (4*R*,5*S*,6*S*)-9-Benzyloxy-6-*tert*-butoxy-5-methyl-4-nonanol (8α) and its (4*S*)-isomer (8β). A 200 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with **7** (3.70 g, 10.5 mmol) in dry CH_2Cl_2 (100 ml) at −78 °C. To the solution was added 0.95 M DIBAL-H in hexane (12 ml, 12 mmol). After 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with CH_2Cl_2. The combined extract was washed with sat. aq. $NaHCO_3$ soln. and brine, dried over $MgSO_4$ and concentrated in vacuo to give aldehyde as a pale yellow oil in an almost quantitative yield. ^1H NMR (300 MHz, $CDCl_3$): δ=1.04 (d, 3H, J=7.1 Hz, 2-Me), 1.19 (s, 9H, t-Bu), 1.40–1.75 (m, 4H, 4-, 5-H), 2.57 (ddq, 1H, J=3.7, 1.1, 6.8 Hz, 2-H), 3.45 (dd, J=2.5, 6.3 Hz, 6-H), 3.47 (dd, J=2.5, 6.3 Hz, 6-H), 3.84 (m, 1H, 3-H), 4.50 (s, 2H, OCH_2Ph), 7.26–7.36 (m, 5H, Ph), 9.82 (d, 1H, J=1.1 Hz, CHO). This aldehyde was used in the next step without further purification.

A 20 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with crude aldehyde (210 mg, 0.72 mmol) in THF (7 ml) at −78 °C. To the solution was added dropwise 2.2 M n-PrMgBr in THF (0.50 ml, 1.1 mmol). After 1 d, the reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave **8α** (mw: 336.51, 172 mg, 0.51 mmol, 70% from **7**) and **8**β (43 mg, 0.13 mmol, 18% from **7**) as colorless oils.

4.1.4. (4*R*,5*S*,6*S*)-6-[(3-Benzyloxy)propyl]-2,2,5-trimethyl-6-propyl-[1,3]dioxane (10α) and its (4*S*)-isomer (10β). A 20 ml, two-necked round-bottomed flask equipped with a magnetic stirrer bar, a Dimroth condenser and a septum was charged with **8α** (or **8**β) in MeOH at room temperature. To the solution was added a catalytic amount of p-TsOH and the mixture was stirred under reflux for 26 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave (4*S*,5*S*,6*R*)-1-benzyloxy-5-methyl-4,6-nonanediol (or (4*S*,5*S*,6*S*)-1-benzyloxy-5-methyl-4,6-nonanediol).

A 10 ml, two-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with the diol in acetone and 2,2-dimethoxypropane (2 equiv) at room temperature. To the solution was added a catalytic amount of p-TsOH at 0 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **10α** (mw: 320.47, or **10**β).

Compound **10α**. ^1H NMR (300 MHz, $CDCl_3$): δ=0.83 (d, 3H, J=6.9 Hz, 5-Me), 0.92 (t, 3H, J=6.9 Hz), 1.23–1.72 (m, 8H), 1.38 [s, 6H, $C(CH_3)_2$], 3.43–3.55 (m, 2H, CH_2OBn), 3.85–3.82 (m, 2H, 4-H and 6-H), 4.51 (s, 2H, OCH_2Ph), 7.27–7.35 (m, 5H, Ph).

Compound **10**β. ^1H NMR (300 MHz, $CDCl_3$): δ=3.22 (q, 1H, J=6.4, 13.3 Hz, 6-H), 3.45–3.52 (m, 2H, CH_2OBn), 3.80 (q, 1H, J=5.0, 13.4 Hz, 4-H).

4.1.5. (1*S*,2*R*,3*S*)-6-Benzyloxy-3-*tert*-butoxy-2-methylhexyl acetate (9). *From* **8**β. A 20 ml, one-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with **8**β (90 mg, 0.27 mmol) in dry CH_2Cl_2 (2 ml). To the solution was added Et_3N (0.34 ml, 3.36 mmol), Ac_2O (0.12 ml, 1.17 mmol) and DMAP (19 mg, 0.16 mmol) at room temperature and stirred for 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with CH_2Cl_2. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **9** (95 mg, 0.25 mmol, 94%) as a pale yellow oil.

From **8α**. A 100 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with **8α** (1.1 g, 3.3 mmol) in dry CH_2Cl_2 (20 ml) at room temperature. To the solution was added Et_3N (2.7 ml, 19.4 mmol), cooled to 0 °C and added MsCl (1.2 ml, 15.4 mmol). After 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$ soln. and brine, dried over $CaCl_2$ and concentrated in vacuo. The residue was used to next step without further purification.

A 300 ml, three-necked round bottomed flask equipped with a magnetic stirrer bar, a Dimroth condenser, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with crude mesylate in toluene (100 ml) at room temperature. To the solution was added KOAc (3.9 g, 40.0 mmol) and 18-crown-6 (1.7 g, 6.4 mmol), and stirred under reflux for 1 d. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was diluted with water and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave **9** (700 mg, 1.85 mmol, 56% from **10α**)

as a pale yellow oil; R_f: 0.52 (hexane/EtOAc=4:1), $[\alpha]_D^{26}$ +2.55° (c=1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.84–0.92 (m, 6H, 2-Me and 3′-H), 1.15 (s, 9H, *t*-Bu), 1.26–1.68 (m, 8H), 1.84 (m, 1H), 2.02 (s, 3H, Ac), 3.46–3.50 (m, 3H, 3-H and 6-H), 4.51 (s, 2H, CH_2Ph), 4.85 (dt, 1H, J=3.3, 7.4 Hz, 1-H), 7.29–7.35 (m, 5H, Ph). IR (film): ν=2960 (s), 2870 (m), 1730 (s, C=O), 1455 (w), 1365 (m), 1245 (s), 1195 (m), 1100 (m), 1020 (m). FABMS (glycerol+NOBA): m/z=379 $(M+H)^+$, 323 $(M+H\text{-}t\text{-}Bu)^+$. HR-FABMS: calcd for $C_{23}H_{39}O_4$ $(M+H)^+$, 379.2849; found, 379.2851.

4.1.6. (1*S*,2*R*,3*S*)-3-*tert*-Butoxy-6-hydroxy-2-methyl-1-propylhexyl acetate (10). A 20 ml, one-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with **9** (281 mg, 0.74 mmol) in dry MeOH (6 ml) at room temperature. To the solution was added 10% Pd-C (60 mg) and stirred for 18 h at 1 atm H_2. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **10** (207 mg, 0.72 mmol, 97%) as a pale yellow oil; R_f: 0.25 (hexane/EtOAc=2:1), $[\alpha]_D^{26}$ −8.40° (c=1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.89–0.93 (m, 6H, 2-Me and 3′-H), 1.19 (s, 9H, *t*-Bu), 1.24–1.77 (m, 8H), 1.89–2.00 (m, 1H), 2.04 (s, 3H, C(O)CH_3), 2.57 (bs, 1H, OH), 3.44–3.49 (m, 1H, 3-H), 3.64 (bs, 2H, 6-H), 4.86–4.92 (m, 1H, 1-H). IR (film): ν=3425 (m, OH), 2975 (s), 2875 (m), 1735 (s, C=O), 1460 (m), 1370 (m), 1250 (s), 1195 (m), 1060 (m), 1020 (m). FABMS (glycerol+NOBA): m/z=289 $(M+H)^+$. Found: C, 66.63%; H, 11.23%. Calcd for $C_{16}H_{32}O_4$: C, 66.63%; H, 11.18%.

4.1.7. Ethyl (6*S*,7*R*,8*S*)-8-acetoxy-6-*tert*-butoxy-2,7-dimethyl-2-undecenoate (11). A 20 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with Dess–Martin periodinane (310 mg, 0.73 mmol) in dry ether (4 ml) at 0 °C. To the mixture was added **10** (150 mg, 0.52 mmol) in dry ether (5 ml) at 0 °C and stirred for 8 h at room temperature. The reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was diluted with ether and washed with sat. aq. $NaHCO_3$ soln. and brine, dried over $MgSO_4$ and concentrated in vacuo to give aldehyde as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ=0.98 (d, 3H, J=7.1 Hz, 5-Me), 0.91 (t, 3H, J=7.3 Hz, 9-H), 1.16 (s, 9H, *t*-Bu), 118–1.60 (m, 4H), 1.73–1.92 (m, 3H), 2.56 (dt, 2H, J=1.4, 7.7 Hz, 2-H), 3.46 (q, 2H, J=5.2 Hz, 4-H), 4.84 (ddd, 1H, J=3.0, 5.7, 8.8 Hz, 6-H), 9.82 (m, 1H, CHO). The aldehyde was used to next step without further purification.

A 25 ml, three-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with 60% NaH (29 mg, 0.71 mmol) at room temperature. To this was added ethyl 2-(di-*o*-tolyl)phosphonopropanoate (185 mg, 0.51 mmol) in THF (2.5 ml) at 0 °C and stirred for 15 min. Then to the solution was added crude aldehyde (130 mg, 0.45 mmol) in THF (0.9 ml) at −78 °C and warmed gradually to 0 °C for over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc. The combined extract was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave *11* (148 mg, 0.40 mmol, 77% from **10**) as a pale yellow oil; R_f: 0.55 (hexane/EtOAc=4:1), $[\alpha]_D^{25}$ +5.3° (c=1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.85 (d, 3H, J=7.1 Hz, 7-Me), 0.90 (t, 3H, J=7.1 Hz, 11-H), 1.15 (s, 9H, *t*-Bu), 1.30 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.44–1.64 (m, 6H), 1.86 (m, 1H), 1.90 (dt, 3H, J=1.4, 1.7 Hz, 2-Me), 2.03 (s, 3H, OCH_3), 2.45 (pseudo q, 2H, J=7.4 Hz, 4-H), 3.49 (m, 1H, 6-H), 4.20 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.85 (dt, 1H, J=3.3 and 7.4 Hz, 8-H), 5.90–5.91 (tq, 1H, J=7.4, 1.7 Hz, 3-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=10.37, 14.21, 14.29, 18.00, 20.71, 21.39, 26.08, 29.00 (Me_3C), 33.05, 33.53, 39.19, 60.04, 71.39, 73.07, 75.70, 127.12, 142.65, 168.07, 170.70. IR (film): ν=2975 (s), 2875 (m), 1735 (s, C=O), 1720 (s, C=C), 1460 (m), 1370 (s), 1245 (s), 1200 (s), 1150 (s), 1020 (s). FABMS (glycerol+NOBA): m/z=371 $(M+H)^+$, 315 $(M+H\text{-}t\text{-}Bu)^+$. HR-FABMS: calcd for $C_{21}H_{39}O_5$ $(M+H)^+$, 371.2798; found, 371.2798.

4.1.8. Ethyl (2*R*,3*R*,6*S*,7*R*,8*S*)-8-acetoxy-3,6-epoxy-2-iodo-2,7-dimethylundecanoate (12). A 20 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with ICl (ca. 1 g, ca. 6 mmol) and $NaHCO_3$ (ca. 1 g, ca. 12 mmol) in dry CH_3CN (6 ml) at 0 °C, and stirred for 15 min. To the suspension was added **11** (146 mg, 0.394 mmol) and the mixture was stirred at 20 °C for 7.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ soln. and extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave **12** (92.0 mg, 0.209 mmol, 53%) as a pale yellow oil and recovered **11** (65 mg, 0.169 mmol, 43%).

Compound **12**. R_f: 0.48 (hexane/EtOAc=4:1), $[\alpha]_D^{26}$ −35.3° (c=1.00, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$): δ=0.91 (t, 3H, J=7.4 Hz, 11-H), 1.01 (d, 3H, J=7.0 Hz, 7-Me), 1.29 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.49–1.95 (m, 8H), 1.98 (s, 3H, 2-Me), 2.05 (s, 3H, C(O)CH_3), 3.73–3.80 (m, 1H, 6-H), 4.23 (q, 2H, J=7.1, 14.3 Hz, OCH_2CH_3), 4.28–4.33 (m, 1H, 3-H), 4.86–4.91 (m, 1H, 8-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=10.29, 13.75, 14.00, 18.95, 21.32, 25.89, 28.10, 30.39, 31.97, 41.21, 43.27, 61.92, 76.05, 80.87, 84.01, 170.84, 171.80. IR (film): ν=2960 (m), 2875 (m), 1730 (s, C=O), 1465 (w), 1380 (w), 1250 (s), 1060 (m), 1020 (m). FABMS (glycerol+NOBA): m/z=441 $(M+H)^+$, 381 $(M+H\text{-}AcOH)^+$. HR-FABMS: calcd for $C_{17}H_{30}O_5I$ $(M+H)^+$, 441.1138; found, 441.1138.

4.1.9. Ethyl (2*S*,3*R*,6*S*,7*R*,8*S*)-8-acetoxy-3,6-epoxy-2,7-dimethylundecanoate (13). A 5 ml round bottomed flask, equipped with a magnetic stirrer bar, was charged with **12** (16.2 mg, 0.0368 mmol) and $NaBH_4$ (3.8 mg, 0.1 mmol) in DMSO (0.5 ml) at −10 °C. The mixture was stirred for 2 h while the temperature of the solution was gradually raised to 10 °C. The reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated

in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) and toluene/EtOAc (20:1) gave **13** (6.9 mg, 0.022 mmol, 60%), 2-*epi*-**13** (2.7 mg, 0.0085 mmol, 23%) and des-*tert*-butyl-**11** (2.0 mg, 0.0063 mmol, 17%) as pale yellow oils.

Compound **13**. R_f: 0.57 (toluene/EtOAc=5:1), $[\alpha]_D^{25}$ +5.3° (c=0.14, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.896 (t, 3H, J=7.4 Hz, 11-H), 0.936 (d, 3H, J=7.4 Hz, 7-Me), 1.223 (d, 3H, J=7.1 Hz, 2-Me), 1.250 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.33 (pseudo dd, 1H, J=7.4, 10.5 Hz), 1.45–1.54 (m, 2H), 1.62–1.72 (m, 2H), 1.80 (m, 1H), 1.86–1.99 (m, 2H), 2.04 (s, 3H, $C(O)CH_3$), 2.45 (quint, 1H, J=7.1 Hz, 2-H), 3.71 (pseudo dt, 1H, J=7.7, 6.0 Hz, 6-H), 3.90 (pseudo dt, 1H, J=8.2, 6.3 Hz, 3-H), 4.12 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.88 (pseudo dt, 1H, J=8.2, 4.4 Hz, 8-H). IR (film): ν=2960 (s), 2875 (m), 1735 (s), 1730 (s), 1465 (m), 1375 (m), 1245 (s), 1180 (m), 1070 (m), 1015 (m). FABMS (glycerol+NOBA): m/z=315 $(M+H)^+$, 255 (M^++H-AcOH). HR-FABMS: calcd for $C_{17}H_{31}O_5$ $(M+H)^+$, 315.2172; found, 315.2172.

Compound 2-*Epi*-**13**. R_f: 0.50 (toluene/EtOAc=5:1), $[\alpha]_D^{26}$ −31° (c=0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.888 (t, 3H, J=7.1 Hz, 11-H), 0.934 (d, 3H, J=6.8 Hz, 7-Me), 1.094 (d, 3H, J=6.9 Hz, 2-Me), 1.256 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.30–1.73 (m, 5H), 1.86–1.95 (m, 2H), 1.82 (m, 1H), 2.04 (s, 3H, $C(O)CH_3$), 2.49 (dq, 1H, J=8.2, 6.9 Hz, 2-H), 3.70 (dt, 1H, J=7.4, 6.3 Hz, 3-H), 3.97 (dt, 1H, J=8.2, 6.3 Hz, 3-H), 4.09–4.20 (m, 2H, OCH_2CH_3), 4.84 (ddd, 1H, J=9.0, 5.0, 3.6 Hz, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.18, 13.28, 13.96, 14.23, 18.89, 21.29, 28.55, 29.38, 31.85, 41.58, 45.26, 60.24, 76.03, 80.24, 80.34, 170.80, 174.98. IR (film): ν=2960 (s), 2875 (m), 1735 (s), 1465 (m), 1380 (m), 1245 (s), 1070 (m), 1020 (m). FABMS (NOBA): m/z=315 $(M+H)^+$. FABMS (glycerol+NOBA): m/z=315 $(M+H)^+$, 255 $(M+H\text{-}AcOH)^+$. HR-FABMS: calcd for $C_{17}H_{31}O_5$ $(M+H)^+$, 315.2172; found, 315.2177.

4.1.10. (2*S*,3*R*,6*S*,7*R*,8*S*)-3,6-Epoxy-8-hydroxy-2,7-dimethylundecanoic acid (3). A solution of **13** (mw 314, 6.3 mg, 20 μmol) in 0.5 M KOH in MeOH-H_2O (1:1, 1 ml) was stirred at 20 °C for 12 h. The reaction mixture was concentrated in vacuo and the residue was diluted with H_2O. This was washed with ether and the aqueous layer was acidified with dil. HCl. This was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) and hexane/EtOAc/AcOH (2:1:0.1) gave **3** (5.0 mg, 20 μmol, quant.) as a colorless oil; $[\alpha]_D^{27}$ +8.0° (c=0.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.902 (d, 3H, J=7.1 Hz, 7-Me), 0.931 (t, 3H, J=7.0 Hz, H-11), 1.221 (d, 3H, J=7.0 Hz, 2-Me), 1.35 (m, 1H, H-10), 1.45–1.55 (m, 3H, 10-H), 1.68–1.8 (m, 2H), 1.8–1.92 (m, 2H), 2.00 (m, 1H, 4-H), 2.72 (quint, 1H, J=6.8 Hz, 2-H), 3.63 (pseudo q, 1H, J=5.9 Hz, 8-H), 3.97 (pseudo q, 1H, J=6.8 Hz, 3-H), 4.12 (m, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=12.05, 13.49, 14.18, 18.62, 26.74, 27.99, 37.23, 39.86, 43.25, 73.73, 80.20, 81.45, 177.06. IR (film): ν=3700–2200 (br, s), 1710 (s), 1260 (s), 1170 (s), 665 (m). FABMS (glycerol): m/z=245 $(M+H)^+$, 227 $(M+H\text{-}H_2O)^+$, 185, 93. HR-FABMS: calcd for $C_{13}H_{25}O_4$ $(M+H)^+$, 245.1753; found, 245.1759.

Compound **3** *methyl ester*. ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.884 (d, 3H, J=7.0 Hz, 7-Me), 0.934 (t, 3H, J=7.3 Hz, H-11), 1.225 (d, 3H, J=7.0 Hz, 2-Me), 1.36 (m, 1H), 1.45 (m, 2H), 1.54 (m, 1H), 1.65–1.75 (m, 2H), 1.83 (m, 2H), 1.97 (m, 1H), 2.61 (dq, 1H, J=7.3, 7.0 Hz, 2-H), 3.31 (br, 1H, OH), 3.58 (m, 1H, 8-H), 3.68 (s, 3H, OMe), 3.94 (pseudo q, 1H, J=7.0 Hz, 3-H), 4.10 (m, 1H, 6-H).

4.1.11. (2*R*,3*R*,6*S*,7*R*,8*S*)-3,6-Epoxy-8-hydroxy-2,7-dimethylundecanoic acid (2-*epi*-3). A solution of 2-*epi*-**13** (mw 314, 20.7 mg, 65.9 μmol) in 0.5 M KOH in MeOH-H_2O (1:1, 1 ml) was stirred at 20 °C for 12 h. The reaction mixture was concentrated in vacuo and the residue was diluted with H_2O. This was washed with ether and the aqueous layer was acidified with dil. HCl. This was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (2:1) and hexane/EtOAc/AcOH (2:1:0.1) gave 2-*epi*-**3** (12.6 mg, 51.6 μmol, 78%) as a colorless oil; $[\alpha]_D^{26}$ −17.3° (c=0.375, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.911 (t, 3H, J=7.1 Hz, 11-H), 0.923 (d, 3H, J=7.1 Hz, 7-Me), 1.168 (d, 3H, J=6.9 Hz, 2-Me), 1.35 (m, 1H, H-10), 1.4–1.6 (m, 3H, H-9, 10), 1.64 (m, 1H, H-4), 1.76 (m, 1H, H-5), 1.83 (m, 1H, H-7), 1.87 (m, 1H, H-5), 2.03 (m, 1H, H-4), 2.54 (d of quint, 1H, J=8.2, 6.9 Hz, H-2), 3.61 (pseudo dt, 1H, J=4.9, 6.6 Hz, H-8), 3.95 (dt, 1H, J=8.2, 7.1 Hz, H-3), 4.18 (ddd, J=7.7, 7.1, 3.3 Hz, 1H, H-6). ^{13}C NMR (150 MHz, $CDCl_3$): δ=12.03 (7-Me), 13.69 (2-Me), 14.18 (11), 18.72 (10), 26.75 (5), 29.01 (4), 37.20 (9), 39.85 (7), 44.57 (2), 73.98 (8), 80.86 (3), 81.42 (6), 177.08 (1). IR (film): ν=3700–2200 (br, s), 1710 (s), 1200 (s), 1170 (s), 665 (m). FABMS (glycerol): m/z=245 $(M+H)^+$, 227 $(M+H\text{-}H_2O)^+$, 154, 136. HR-FABMS: calcd for $C_{13}H_{25}O_4$ $(M+H)^+$, 245.1753; found, 245.1757.

2-*Epi*-**3** *methyl ester*. ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.891 (d, 3H, J=7.0 Hz, 7-Me), 0.927 (t, 3H, J=7.3 Hz, H-11), 1.135 (d, 3H, J=7.0 Hz, 2-Me), 1.36 (m, 1H), 1.44 (m, 2H), 1.48–1.64 (m, 2H), 1.75 (m, 1H), 1.8–1.9 (m, 2H), 1.99 (m, 1H), 2.56 (m, 1H, 2-H), 3.32 (d, 1H, J=4.7 Hz, OH), 3.57 (m, 1H, 8-H), 3.69 (s, 3H, OMe), 3.95 (pseudo q, 1H, J=7.0 Hz, 3-H), 4.12 (m, 1H, 6-H).

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