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δ-Lactone formation from δ-hydroxy-*trans*-α,β-unsaturated carboxylic acids accompanied by trans–cis isomerization: synthesis of (−)-tetra-*O*-acetylosmundalin

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Abstract—(±)-(4,5-*anti*)-4-Benzyloxy-5-hydroxy-(2*E*)-hexenoic acid **6** was subjected to δ-lactonization in the presence of 2,4,6-trichlorobenzoyl chloride and pyridine to give the α,β-unsaturated-δ-lactone congener (±)-**7** (87% yield) accompanied by trans–cis isomerization. This δ-lactonization procedure was applied to the chiral synthesis of (+)-(4*S*,5*R*)-**7** or (−)-(4*R*,5*S*)-**7** from the chiral starting material (+)-(4*S*,5*R*)-**6** or (−)-(4*R*,5*S*)-**6**. Deprotection of the benzyl group in (+)-(4*S*,5*R*)-**7** or (−)-(4*R*,5*S*)-**7** by the $AlCl_3$/*m*-xylene system gave the natural osmundalactone (+)-(4*S*,5*R*)-**5** or (−)-(4*R*,5*S*)-**5** in good yield, respectively. Condensation of (−)-(4*R*,5*S*)-**5** and tetraacetyl-β-D-glucosyltrichloroimidate **22** in the presence of $BF_3 \cdot Et_2O$ afforded the condensation product (−)-**8** (97% yield), which was identical to tetra-*O*-acetylosmundalin (−)-**8** derived from natural osmundalin **9**.
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1. Introduction

α,β-Unsaturated-δ-lactones are found as structural subunits in a wide variety of natural products possessing diverse biological activities. Furthermore, simple lactones have been used as intermediates for the synthesis of biologically active compounds. We previously reported the enantioselective hydrolysis of (±)-(4,5-*anti*)-5-acetoxy-4-benzyloxy-(2*E*)-hexenoate **1** using the lipase 'Amano P' from *Pseudomonas* sp. in phosphate buffer solution to give the (4*R*,5*S*)-5-acetoxy ester **1** (>99% ee, 48% yield) and the (4*S*,5*R*)-5-hydroxy ester **2** (>99% ee, 44% yield). The subsequent methanolysis of (4*R*,5*S*)-**1** provided (4*R*,5*S*)-**2** in 84% yield.[1] The *E*-value[2] of this enzymatic reaction was estimated to be 1060. The syntheses of biologically active natural products such as (+)-asperlin **3**[3] or (+)-anamarine **4**[4] from (4*S*,5*R*)-**2** or (4*R*,5*S*)-**2** required practical routes to the chiral oxygen-substituted α,β-unsaturated-δ-lactone. The synthesis of (4*S*,5*R*)-osmundalactone **5**[5] or (4*R*,5*S*)-osmundalactone **5**[6] from (4*S*,5*R*)-**2** or (4*R*,5*S*)-**2**, respectively, would serve as an excellent model experiment. In general, the syntheses of α,β-unsaturated lactones **A** are achieved based on the direct lactonization of the corresponding γ- or δ-hydroxy-α,β-unsaturated esters **B**. To achieve efficient syntheses of molecules **A**, it is necessary to obtain the *Z*-isomer of the α,β-unsaturated esters **B** in a stereoselective manner. This problem could be overcome by applying the modified Horner–Emmons reaction of α- or β-*O*-protected aldehyde **C** and methoxycarbonylmethylentrialkoxyphosphorane **D**.[7] Ring-closing metatheses using Grubbs reagent have recently been reported to be a useful method to construct α,β-unsaturated lactone structures[8] (Scheme 1).

We now report the efficient synthesis of α,β-unsaturated-δ-lactone (±)-**7** from (±)-(4,5-*anti*)-5-hydroxy-4-benzyloxy-(2*E*)-hexenoic acid **6** accompanied by trans–cis isomerization. Moreover, the syntheses of (4*S*,5*R*)- or (4*R*,5*S*)-osumundalactone **5** from (4*S*,5*R*)- or (4*R*,5*S*)-**2**, respectively, and application to the first synthesis of tetra-*O*-acetylosmundalin **8**[6] (Scheme 1) derived from natural osmundalin **9**[6] will be described.

2. Results and discussion

When the reported methyl ester (±)-**2**[1] was individually subjected to heating in the presence of 10-camphorsulfonic acid (CSA) or 4-dimethylaminopyridine (DMAP), the starting (±)-**2** was recovered. The reaction of carboxylic acid (±)-**6** with CSA and DMAP gave α,β-unsaturated δ-lactone (±)-**7** in 46% yield, while (±)-**6** in the presence of CSA alone afforded the starting (±)-**6**. Surprisingly, the reaction of (±)-**6** with DMAP gave (±)-**7** in 30% yield (Scheme 2). These results indicate that CSA did not serve any purpose

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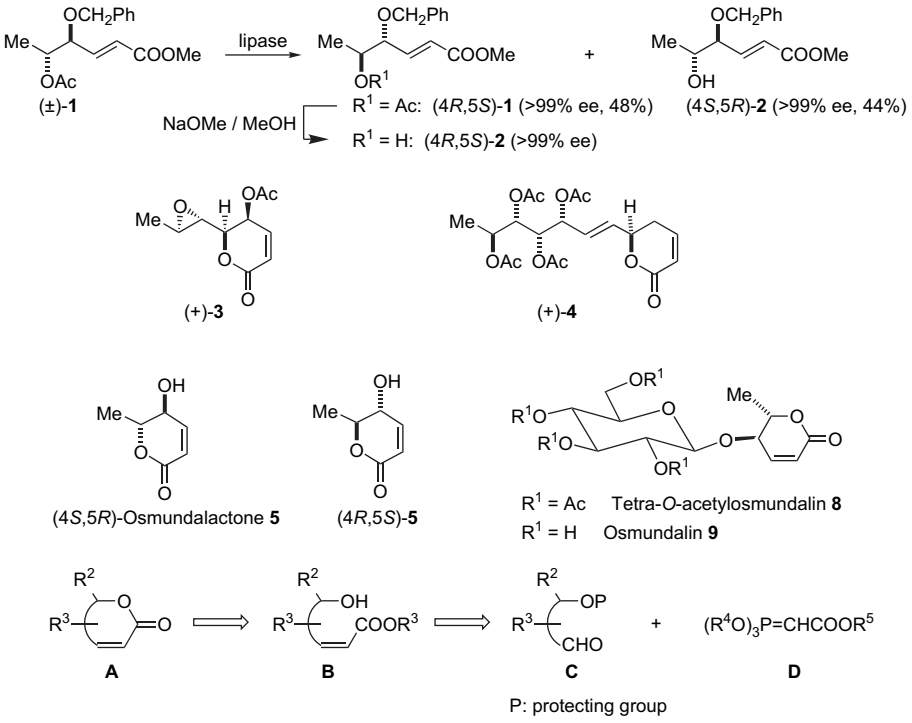
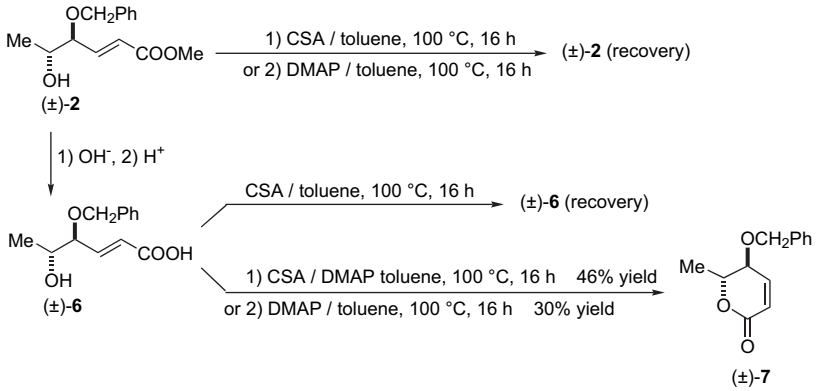


Scheme 1.

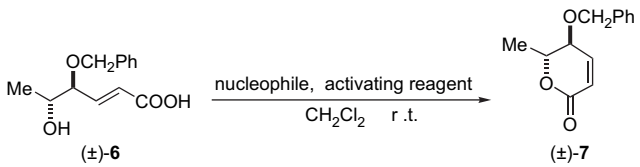
in the reaction, while DMAP worked against the isomerization of the double bond. The formation of (±)-**7** could be explained by thermal δ-lactonization after DMAP-assisted double bond isomerization. DMAP is reported to function as a nucleophilic catalyst as well as a Brønsted base.[9] Morita–Baylis–Hillman reactions[10] and isomerization of nitroalkenes[11] are typical examples of nucleophile-assisted reactions, where nucleophiles function as nucleophilic catalyst in the reactions of α,β-unsaturated esters or nitroalkenes. In order to promote smooth δ-lactonization in this reaction, the carboxylic acid group in (±)-**6** must be activated. To investigate conditions for effective α,β-unsaturated δ-lactonization from (±)-**6** in conjunction with double bond isomerization, the reaction of (±)-**6** using various kinds of nucleophiles and activating reagents was examined, and the results are shown in Table 1.

The reaction of (±)-**6** with 2,4,6-trichlorobenzoyl chloride[12]/DMAP (entry 1) or 2,4,6-trichlorobenzoyl chloride/DMAP and triphenylphosphine (Ph_3P) as an additional nucleophile (entry 2) gave 59% and 69% of (±)-**7**, respectively. For the purpose of finding a more effective additive, other nucleophiles were examined. Addition of morpholine instead of Ph_3P afforded the corresponding morpholine-amide **10** in 62% yield (entry 3). The reaction of (±)-**6** with 2,4,6-trichlorobenzoyl chloride and 1,4-diazabicyclo[2,2,2]octane (DABCO) (entry 4) gave the unexpected 12-membered diolide **11**[13] in 4.4% yield, though the major product recovered was (±)-**6**. When pyridine was used as the nucleophile, the usage of 2,4,6-trichlorobenzoyl chloride (entry 5), 2-chlorobenzoyl chloride (entry 6), methyl chloroformate (entry 7), isobutyl chloroformate (entry 9), methanesulfonyl chloride (MsCl) (entry 10) provided yields of (±)-**7** of 87%, 65%, 50%, 77% and 41%, respectively. The combination of methyl chloroformate and DMAP (entry 8) gave (±)-**7** (38%) and methyl ester **2** (18%). The combination of 2,2′-dipyridyl disulfide and Ph_3P[14] (entry 11) yielded (±)-**7** (12%) and the thiopyridine adduct **12** (31%). The combination of

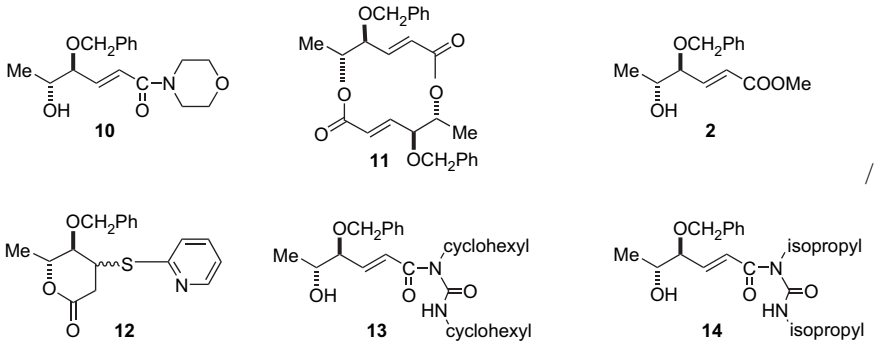


Scheme 2.

Table 1

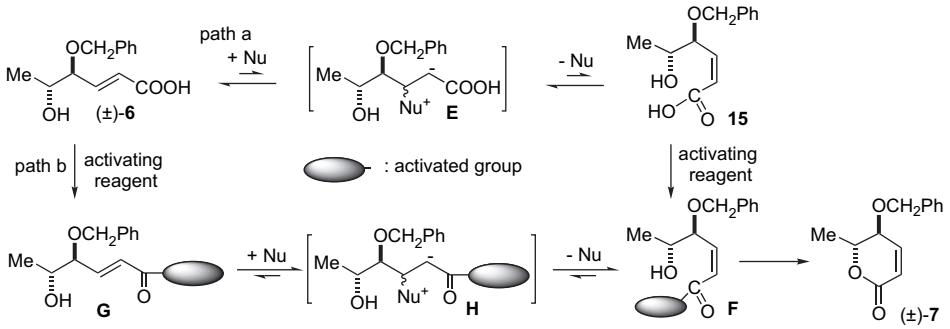


Entry	Activating reagent (1.1 equiv)	Nucleophile	Reaction time (h)	Yield of (±)-**7** (%)
1	2,4,6-Trichlorobenzoyl chloride/DMAP	DMAP	6	59
2	2,4,6-Trichlorobenzoyl chloride/DMAP	Ph_3P	6	69
3	2,4,6-Trichlorobenzoyl chloride/DMAP	Morpholine	4	0, Morpholine-amide **10** (62%)
4	2,4,6-Trichlorobenzoyl chloride/ 1,4-diazabicyclo[2,2,2]octane	1,4-Diazabicyclo[2,2,2]octane	3	0, 12-Membered diolide **11** (2.2%)
5	2,4,6-Trichlorobenzoyl chloride/pyridine[a]	Pyridine	1	87
6	2-Chlorobenzoyl chloride/pyridine[a]	Pyridine	3	65
7	Methyl chloroformate/pyridine[a]	Pyridine	3	50
8	Methyl chloroformate/DMAP	DMAP	1	38, Methyl ester **2** (18%)
9	Isobutyl chloroformate/pyridine[a]	Pyridine	3	77
10	Methanesulfonyl chloride/pyridine[a]	Pyridine	3	41
11	2,2′-Dipyridyl disulfide/Ph_3P[b]	Ph_3P	1	12, Thiopyridine adduct **12** (31%)
12	Dicyclohexylcarbodiimide	Ph_3P	2	34, DCC-adduct **13** (44%)
13	Dicyclohexylcarbodiimide	DMAP	12	60, DCC-adduct **13** (11%)
14	Dicyclohexylcarbodiimide	2,4,6-Collidine	9	0, DCC-adduct **13** (40%)
15	Diisopropylcarbodiimide	Pyridine	24	45, DIPC-adduct **14** (14%)



[a] Reaction solvent: pyridine.
[b] Reaction solvent: MeCN, CF_3SO_3Ag was added.

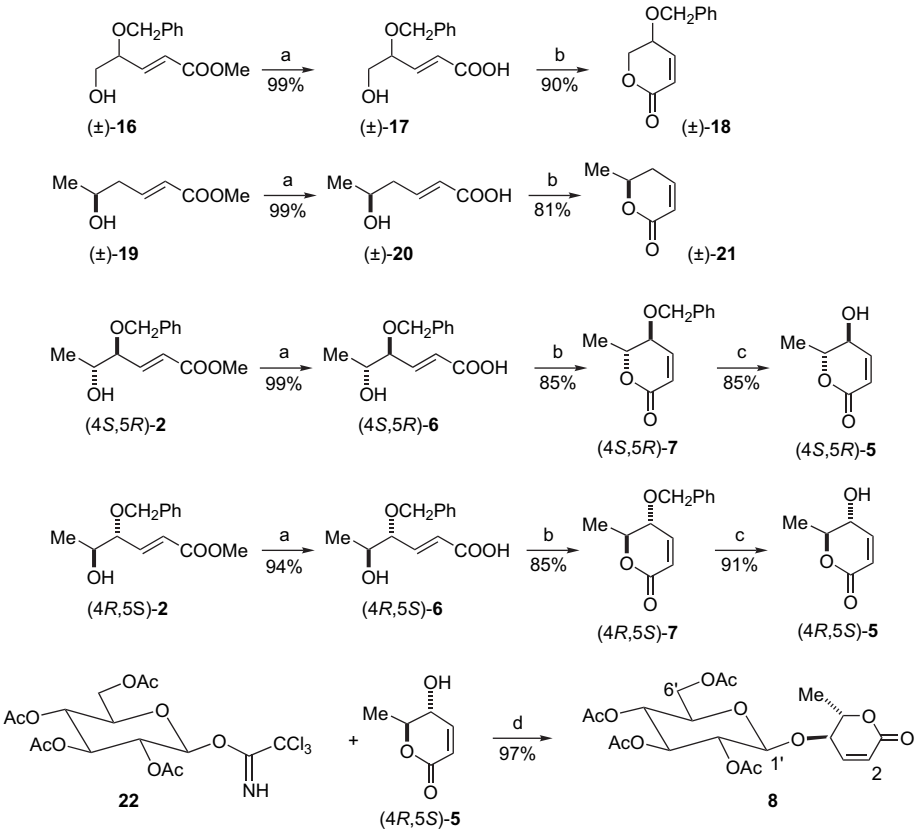
dicyclohexylcarbodiimide (DCC) and Ph_3P (entry 12) or DCC and DMAP (entry 13) gave (±)-**7** (34% or 60%) along with DCC-adduct **13** (44% or 11%), respectively. In the case of DCC and 2,4,6-collidine (entry 14), only the DCC-adduct **13** (40%) was obtained. The combination of diisopropylcarbodiimide (DIPC) and pyridine (entry 15) afforded (±)-**7** (45%) and the DIPC-adduct **14** (14%). From a synthetic point of view, the combination of 2,4,6-trichlorobenzoyl chloride and pyridine (entry 5) was found to be the most practical procedure for the preparation of α,β-unsaturated δ-lactone (±)-**7** from (±)-**6** accompanied by trans–cis isomerization. The use of isobutyl chloroformate (entry 9), however, is more practical due to the lower price of isobutyl chloroformate compared to that of 2,4,6-trichlorobenzoyl chloride.



Scheme 3.

There are two plausible mechanistic routes for α,β-unsaturated δ-lactonization accompanied by trans–cis isomerization [(±)-**6** to (±)-**7**] as shown in Scheme 3. One is the Michael addition (intermediate **E**) of the nucleophile to the α,β-unsaturated double bond in (±)-**6** followed by consecutive cis isomerization (intermediate **15**) along with the elimination of nucleophile, followed by activation (intermediate **F**) of the carboxylic acid group in **15** and δ-lactonization (path a). The other possible route is the activation (intermediate **G**) of the carboxylic acid group followed by consecutive Michael addition (intermediate **H**) of the nucleophile, formation of the cis-isomer (intermediate **F**) along with the elimination of the nucleophile and δ-lactonization (path b). Pyridine-assisted addition–elimination reaction on **6** did not occur because carboxylic acid (±)-**6** exists as a pyridinium carboxylate in pyridine. When (±)-**6** and (±)-**7** were subjected to exchange reaction using a 4:1 mixture of deuterated pyridine and deuterated methanol (C_5D_5N/CD_3OD=4:1) in an NMR tube for 25 h at 25 °C, formation of C(2)-deuterium exchange products [(±)-**6** and (±)-**7**] was not observed in either case. This result indicates that pyridine-assisted addition–elimination reaction does not occur via path a. No observation of C(2)-deuterium exchange reaction in the course of path b might be explained from the fact that conversion rates from **G** to **H**, from **H** to **F**, and from **F** to (±)-**7** are extremely high. Therefore, the formation of (±)-**7** from (±)-**6** might occur via path b. The present reaction was completed within several hours in comparison to Morita–Baylis–Hillman reactions' case. The faster rate of δ-lactonization from intermediate **G** might be due to the pyridine-assisted addition–elimination reaction. The scope and limitation of this reaction should be examined and two examples are shown in Scheme 4. Alkaline hydrolysis of (±)-**16**[15] or (±)-**19**[16] gave quantitatively carboxylic acid (±)-**17** (99%) or (±)-**20** (99%), respectively, which was separately subjected to δ-lactonization using 2,4,6-trichlorobenzoyl chloride and pyridine to afford (±)-**18** (90% yield) or (±)-**21** (81% yield), respectively.

Application of this reaction to natural product synthesis was examined. The syntheses of (+)-(4*S*,5*R*)-osmundalactone **5** and (−)-(4*R*,5*S*)-osmundalactone **5**, and tetra-*O*-acetylosmundalin **8** are shown in Scheme 4. (+)-Osmundalactone **5** was isolated from the fungus *Paxillus atrotomentosus*. The structure was established by spectroscopic methods and X-ray analysis.[5] From the Japanese foodstuff *Akaboshi zenmai*, consisting of dried leaves of *Osmunda japonica* Thunberg and from the Vermont royal fern *Osmunda regalis* var. *spectabilis* (Wilid.) Gray a new hydroxypentenolide glucoside, osmundalin **9**, was isolated.[6] Osmundalin **9** was characterized as its crystalline tetra-*O*-acetylosmundalin **8** and the structure and absolute stereochemistry of **9** were established by spectroscopic and degradation methods and its aglycone, (−)-osmundalactone **5**, was synthesized.[6] Alkaline hydrolysis of the reported (4*S*,5*R*)-**2**[1] with 2 M NaOH solution in *i*-PrOH gave carboxylic acid (+)-(4*S*,5*R*)-**6** (99%), which was subjected to δ-lactonization using 2,4,6-trichlorobenzoyl chloride and pyridine to afford (+)-(4*S*,5*R*)-**7** in 85% yield. Benzyl ether (+)-(4*S*,5*R*)-**7** was deprotected using the reported $AlCl_3$/*m*-xylene system[1] to provide alcohol (+)-



Scheme 4. Reagents and conditions: (a) (1) 2 M NaOH/*i*-PrOH, rt; (2) 2 M HCl; (b) 2,4,6-trichlorobenzoyl chloride/pyridine, rt; (c) $AlCl_3$/*m*-xylene, CH_2Cl_2, 0 °C; (d) $BF_3 \cdot Et_2O$, CH_2Cl_2, rt.

(4*S*,5*R*)-**5** {$[\alpha]_D^{26}$ +69.1 (*c* 0.53, H_2O)} in 85% yield. NMR data of (+)-(4*S*,5*R*)-**5** were identical to those of the natural osmundalactone (+)-(4*S*,5*R*)-**5**[5] as was the specific rotation {$[\alpha]_D^{22}$ +70.9 (*c* 1.27, H_2O)}. The synthesis of (−)-osmundalactone (4*R*,5*S*)-**5** was achieved in the same way as the synthesis of (+)-(4*S*,5*R*)-**5** from (4*S*,5*R*)-**2**. Alkaline hydrolysis of the reported (4*R*,5*S*)-**2**[1] gave carboxylic acid (−)-(4*R*,5*S*)-**6** (94%), which was subjected to δ-lactonization to afford (−)-(4*R*,5*S*)-**7** in 85% yield. Deprotection of the benzyl group in (−)-(4*R*,5*S*)-**7** provided alcohol (−)-(4*R*,5*S*)-**5** {$[\alpha]_D^{28}$ −68.4 (*c* 0.41, H_2O)}. NMR data of (−)-(4*R*,5*S*)-**5** were identical to those of the natural osmundalactone (−)-(4*R*,5*S*)-**5**[6] as was the specific rotation {$[\alpha]_D^{22}$ −70.6 (*c* 2.0, H_2O)}. The reaction of (−)-(4*R*,5*S*)-**5** and tetraacetyl-β-D-glucosyltrichloroimidate **22**[17] in the presence of $BF_3 \cdot Et_2O$ afforded the condensation product (−)-**8** {$[\alpha]_D^{25}$ −40.4 (*c* 1.0, $CHCl_3$)} in 97% yield. NMR data of (−)-**8** were identical to those of the reported tetra-*O*-acetylosmundalin **8**[6,18] derived from natural osmundalin **9** as was the specific rotation {$[\alpha]_D^{20}$ −40.9 (*c* 1.0, $CHCl_3$)}.

3. Conclusion

(±)-(4,5-*anti*)-4-benzyloxy-5-hydroxy-(2*E*)-hexenoic acid **6** was subjected to δ-lactonization in the presence of 2,4,6-trichlorobenzoyl chloride and pyridine to give the α,β-unsaturated-δ-lactone congener (±)-**7** (87% yield) accompanied by trans–cis isomerization. The mechanism of this δ-lactonization was discussed. This δ-lactonization procedure was applied to the chiral synthesis of (+)-(4*S*,5*R*)-**7** or (−)-(4*R*,5*S*)-**7** from the chiral starting (+)-(4*S*,5*R*)-**2** or (−)-(4*R*,5*S*)-**2**, respectively. Deprotection of the benzyl group in (+)-(4*S*,5*R*)-**7** or (−)-(4*R*,5*S*)-**7** by the $AlCl_3$/*m*-xylene system gave natural osmundalactone (+)-(4*S*,5*R*)-**5** or (−)-(4*R*,5*S*)-**5** in good yield, respectively. Condensation of (−)-(4*R*,5*S*)-**5** and tetraacetyl-β-D-glucosyltrichloroimidate **22** in the presence of $BF_3 \cdot Et_2O$ afforded the condensation product (−)-**8** in 97% yield, which was identical to tetra-*O*-acetylosmundalin **8** derived from natural osmundalin **9**.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded on Jeol AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. High-resolution mass spectra (HRMS) and fast atom bombardment mass spectra (FABMS) were obtained with a Jeol JMS 600H spectrometer. IR spectra were recorded with a Jasco FT/IR-300 spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4.2. (±)-(4,5-*anti*)-4-Benzyloxy-5-hydroxy-(2*E*)-hexenoic acid (6)

A mixture of the reported (±)-**2**[1] (13.68 g, 54.5 mmol) and 2 M NaOH solution (55 mL) in *i*-PrOH (110 mL) was stirred for 1 h at rt and the reaction mixture was evaporated to give a residue. Then it was acidified with 2 M HCl solution and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (300 g, $CHCl_3$/MeOH=10:1) to afford (±)-**6** (12.34 g, 95%) as a colorless oil. (±)-**6**: IR ($CHCl_3$): 3450, 1702 cm^{-1}; ^1H NMR: δ 1.15 (3H, d, *J*=6.0 Hz), 2.38 (1H, d, *J*=4.4 Hz, OH), 3.94 (1H, ddd, *J*=6.0, 4.0, 1.2 Hz), 3.97 (1H, qd, *J*=6.0, 4.0 Hz), 4.42, 4.64 (each 1H, d, *J*=12.0 Hz), 6.07 (1H, dd, *J*=16.0, 1.2 Hz), 7.02 (1H, dd, *J*=16.0, 6.0 Hz), 7.10–7.40 (5H, m). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%. Found: C, 65.94; H, 6.84. FABMS *m*/*z*: 237 (M^++1).

4.3. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Scheme 2)

A mixture of (±)-**6** (0.085 g, 0.36 mmol), CSA (0.10 g, 0.43 mmol), and DMAP (0.053 g, 0.43 mmol) in toluene (5 mL) was stirred for 16 h at 100 °C, and the reaction mixture was diluted with Et_2O. The organic layer was washed with 2 M NaOH solution and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt=8:1) to afford (±)-**7** (0.037 g, 46%) as a colorless oil. The alkaline layer was acidified with 2 M HCl solution and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave crude (±)-**6** (0.029 g, 34%) as a colorless oil. Compound (±)-**7**: IR (neat): 1732 cm^{-1}; ^1H NMR: δ 1.42 (3H, d, *J*=6.0 Hz), 3.97 (1H, ddd, *J*=8.0, 2.0, 2.0 Hz), 4.45 (1H, qd, *J*=8.0, 2.0 Hz), 4.60, 4.69 (each 1H, d, *J*=12.0 Hz), 5.98 (1H, dd, *J*=10.0, 0.2 Hz), 6.85 (1H, dd, *J*=10.0, 4.0 Hz), 7.28–7.39 (5H, m). ^{13}C NMR: δ 18.5 (q), 70.0 (t), 73.9 (d), 77.2 (d), 120.8 (d), 127.9 (2C, d), 128.3 (d), 128.5 (2C, d), 136.7 (s), 145.8 (d), 162.7 (s). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%. Found: C, 71.24; H, 6.64. FABMS *m*/*z*: 219 (M^++1).

4.4. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Scheme 2)

A mixture of (±)-**6** (0.130 g, 0.55 mmol) and DMAP (0.08 g, 0.66 mmol) in toluene (5 mL) was stirred for 16 h at 100 °C. The reaction mixture was worked up in the same way as described in Section 2.3 to afford (±)-**6** (0.037 g, 30%) as a colorless oil. ^1H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**.

4.5. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 1)

To a solution of (±)-**6** (0.688 g, 2.9 mmol) in CH_2Cl_2 (15 mL) were added 2,4,6-trichlorobenzoyl chloride (0.78 g, 3.19 mmol) and DMAP (0.71 g, 5.8 mmol) and the reaction mixture was stirred for 6 h at rt. The reaction mixture was diluted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt=8:1) to afford (±)-**7** (0.374 g, 59%) as a colorless oil. ^1H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**.

4.6. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 2)

To a solution of (±)-**6** (0.512 g, 2.2 mmol) and DMAP (0.32 g, 2.6 mmol) in CH_2Cl_2 (15 mL) was added 2,4,6-trichlorobenzoyl chloride (0.59 g, 2.4 mmol) at 0 °C and then Ph_3P (1.15 g, 4.4 mmol) was added. The whole reaction mixture was stirred for 6 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (0.326 g, 69%) as a colorless oil. ^{1}H NMR data of the present (±)-**6** were identical to those of the previous (±)-**7**.

4.7. δ-Lactonization from (±)-6 (synthesis of (±)-10) (Table 1, entry 3)

To a solution of (±)-**7** (0.503 g, 2.1 mmol) and DMAP (0.31 g, 2.5 mmol) in CH_2Cl_2 (15 mL) was added 2,4,6-trichlorobenzoyl chloride (0.59 g, 2.4 mmol) at 0 °C and then morpholine (0.37 g, 4.2 mmol) was added. The whole reaction mixture was stirred for 4 h at rt. The reaction mixture was diluted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=1:1) to afford (±)-**10** (0.403 g, 62%). Compound (±)-**10**: ^{1}H NMR: δ 1.16 (3H, d, J=6.0 Hz), 2.20–3.68 (8H, m), 3.94 (2H, m), 4.45, 4.62 (each 1H, d, J=12.0 Hz), 6.43 (1H, dd, J=10.0, 0.2 Hz), 6.82 (1H, dd, J=10.0, 4.0 Hz), 7.20–7.40 (5H, m). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59%. Found: C, 66.33; H, 7.43; N, 4.35. FABMS *m*/*z*: 306 (M^++1).

4.8. δ-Lactonization from (±)-6 (synthesis of (±)-11) (Table 1, entry 4)

To a solution of (±)-**6** (0.500 g, 2.1 mmol) in CH_2Cl_2 (15 mL) was added 2,4,6-trichlorobenzoyl chloride (0.56 g, 2.3 mmol) at 0 °C and then 1,4-diazabicyclo[2.2.2]-octane (DABCO, 0.75 g, 6.7 mmol) was added. The whole reaction mixture was stirred for 3 h at rt. The reaction mixture was diluted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=12:1) to afford (±)-**11** (0.02 g, 2.2%). ^{1}H NMR data of the present (±)-**11** were identical to those of the reported (±)-**11**.[3] FABMS *m*/*z*: 437 (M^++1).

4.9. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 5)

To a solution of (±)-**6** (1.79 g, 7.6 mmol) in pyridine (15 mL) was added 2,4,6-trichlorobenzoyl chloride (2.04 g, 8.3 mmol) at 0 °C and the reaction mixture was stirred for 1 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (1.437 g, 87%) as a colorless oil. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**.

4.10. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 6)

To a solution of (±)-**6** (0.537 g, 2.2 mmol) in pyridine (4 mL) was added a solution of 2-chlorobenzoyl chloride (0.44 g, 2.59 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the reaction mixture was stirred for 3 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (0.325 g, 65%) as a colorless oil. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**.

4.11. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 7)

To a solution of (±)-**6** (0.20 g, 0.85 mmol) in pyridine (2 mL) was added a solution of methyl chloroformate (0.09 g, 0.95 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the reaction mixture was stirred for 3 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (0.092 g, 50%) as a colorless oil. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**.

4.12. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 8)

To a solution of (±)-**6** (0.20 g, 0.85 mmol) in CH_2Cl_2 (2 mL) was added DMAP (0.31 g, 2.5 mmol) and then a solution of methyl chloroformate (0.09 g, 0.95 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added. The reaction mixture was stirred for 1 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (0.070 g, 38%) as a colorless oil and (±)-**2** (0.037 g, 18%) as a colorless oil. ^{1}H NMR data of the present (±)-**7** and (±)-**2** were identical to those of the previous (±)-**7** and (±)-**2**, respectively.

4.13. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 9)

To a solution of (±)-**6** (0.504 g, 2.1 mmol) in pyridine (4 mL) was added a solution of isobutyl chloroformate (0.32 g, 2.3 mmol) in $CHCl_3$ (1 mL) at 0 °C and the reaction mixture was stirred for 3 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (0.358 g, 77%) as a colorless oil. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**.

4.14. δ-Lactonization from (±)-6 (synthesis of (±)-7) (Table 1, entry 10)

To a solution of (±)-**6** (0.457 g, 1.9 mmol) in pyridine (4 mL) was added a solution of methanesulfonyl chloride (MsCl, 0.24 g, 2.1 mmol) in $CHCl_3$ (1 mL) at 0 °C and the reaction mixture was stirred for 3 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (0.172 g, 41%) as a colorless oil. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**.

4.15. δ-Lactonization from (±)-6 (syntheses of (±)-7 and 12a,b) (Table 1, entry 11)

To a mixture of (±)-**6** (0.506 g, 2.4 mmol), 2,2′-dipyridyl disulfide (0.47 g, 2.1 mmol), and Ph_3P (0.56 g, 2.1 mmol) in benzene (2 mL) was added a solution of 0.4 M silver trifluoromethanesulfonate (CF_3SO_3Ag)/toluene solution (15 mL) in MeCN (10 mL) and the reaction mixture was allowed to

stand for 1 h at rt. The reaction mixture was filtered off and the filtrate was evaporated to give a residue. It was diluted with benzene and the organic layer was washed with 0.5 M NaOH, brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt=5:1) to afford (±)-**7** (0.058 g, 12%) and **12a** (0.11 g) and **12b** (0.112 g), total (0.222 g, 31%) in elution order. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**. Compound **12a**: IR ($CHCl_3$): 1749 cm^{-1}; ^{1}H NMR: δ 1.40 (3H, d, *J*=6.0 Hz), 2.91 (1H, s), 2.93 (1H, d, *J*=1.0 Hz), 3.70 (1H, t, *J*=3.0 Hz), 4.60 (2H, s), 4.67 (2H, m), 6.91 (1H, ddd, *J*=8.0, 5.0, 1.0 Hz), 7.09 (1H, dt, *J*=8.0, 1.0 Hz), 7.19–7.31 (5H, m), 7.40 (1H, ddd, *J*=10.0, 7.0, 2.0 Hz), 8.30 (1H, ddd, *J*=5.0, 2.0, 1.0 Hz). Anal. Calcd for $C_{18}H_{19}O_3NS$: C, 65.63; H, 5.81; N, 4.25%. Found: C, 65.64; H, 5.86; N, 4.25. FABMS *m*/*z*: 330 (M^++1). Compound **12b**: IR (neat): 1733 cm^{-1}; ^{1}H NMR: δ 1.43 (3H, d, *J*=6.0 Hz), 2.84 (1H, dd, *J*=16.0, 4.0 Hz), 3.21 (1H, dd, *J*=16.0, 6.0 Hz), 3.63 (1H, dd, *J*=8.0, 5.0 Hz), 4.30 (1H, qd, *J*=6.0, 6.0 Hz), 4.47 (1H, dt, *J*=6.0, 5.0 Hz), 4.60, 4.85 (each 1H, *J*=12.0 Hz), 7.16 (1H, dt, *J*=8.0, 1.0 Hz), 7.20 (1H, ddd, *J*=8.0, 5.0, 1.0 Hz), 7.23–7.39 (5H, m), 7.49 (1H, ddd, *J*=9.0, 7.0, 2.0 Hz), 8.42 (1H, d, *J*=5.0 Hz). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25%. Found: C, 65.49; H, 5.95; N, 4.23. FABMS *m*/*z*: 330 (M^++1).

4.16. δ-Lactonization from (±)-6 (syntheses of (±)-7 and 13) (Table 1, entry 12)

To a solution of (±)-**6** (0.455 g, 1.9 mmol) in CH_2Cl_2 (8 mL) were added DMAP (0.24 g, 1.9 mmol) and 1,3-dicyclohexylcarbodiimide (DCC, 0.40 g, 1.9 mmol) at 0 °C and then Ph_3P (1.01 g, 3.86 mmol) was added. The whole reaction mixture was stirred for 2 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**7** (0.143 g, 34%) and **13** (0.375 g, 44%) in elution order. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**. Compound **13**: ^{1}H NMR: δ 1.15 (3H, d, *J*=6.0 Hz), 1.09–1.95 (10H, m), 2.31 (1H, br s), 3.60–3.70 (1H, m), 3.98–4.07 (1H, m), 3.90–3.96 (2H, m), 4.42, 4.62 (each 1H, d, *J*=12.0 Hz), 6.41 (1H, d, *J*=16.0 Hz), 6.85 (1H, d, *J*=16.0, 6.0 Hz), 7.02 (1H, br s), 7.26–7.36 (5H, m). FABMS *m*/*z*: 443 (M^++1).

4.17. δ-Lactonization from (±)-6 (syntheses of (±)-7 and 13) (Table 1, entry 13)

To a solution of (±)-**6** (1.718 g, 7.3 mmol) in CH_2Cl_2 (20 mL) was added DMAP (1.78 g, 14.6 mmol) and the reaction mixture was stirred for 1 h at rt. 1,3-Dicyclohexylcarbodiimide (DCC, 1.81 g, 8.7 mmol) was added to the above reaction mixture and the whole mixture was stirred for 12 h at rt. The reaction mixture was filtered off and filtrate was washed with 2 M NaOH solution and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt=5:1) to afford (±)-**7** (0.961 g, 60%) and **13** (0.35 g, 11%) in elution order. ^{1}H NMR data of the present (±)-**7** and **13** were identical to those of the previous (±)-**7** and **13**.

4.18. δ-Lactonization from (±)-6 (synthesis of 13) (Table 1, entry 14)

To a solution of (±)-**6** (1.02 g, 4.3 mmol) and 2,4,6-collidine (1.05 g, 8.6 mmol) in CH_2Cl_2 (10 mL) was added DCC (0.89 g, 4.3 mmol) and the mixture was stirred for 9 h at rt. The reaction mixture was worked up in the same way as described in Section 2.17 to afford **13** (0.722 g, 38%). ^{1}H NMR data of the present **13** were identical to those of the previous **13**.

4.19. δ-Lactonization from (±)-6 (syntheses of (±)-7 and 14) (Table 1, entry 15)

To a solution of (±)-**6** (0.289 g, 1.2 mmol) in CH_2Cl_2 (18 mL) was added pyridine (0.97 g, 12.3 mmol) and a solution of 1,3-diisopropylcarbodiimide (DIPC, 0.17 g, 1.3 mmol) in CH_2Cl_2 (2 mL) was added to the above reaction mixture at 0 °C. The whole reaction mixture was stirred for 24 h at rt. The reaction mixture was worked up in the same way as described in Section 2.17 to afford (±)-**7** (0.120 g, 45%) and **14** (0.063 g, 14%) in elution order. ^{1}H NMR data of the present (±)-**7** were identical to those of the previous (±)-**7**. Compound **14**: ^{1}H NMR: δ 1.16 (3H, d, *J*=7.0 Hz), 1.17 (6H, d, *J*=7.0 Hz), 1.39 (6H, d, *J*=7.0 Hz), 2.27–2.40 (1H, br s), 3.94 (1H, dd, *J*=6.0, 7.0 Hz), 3.96 (2H, sextet, *J*=7.0 Hz), 4.42 (1H, dq, *J*=7.0, 7.0 Hz), 4.40, 4.62 (each 1H, d, *J*=12.0 Hz), 6.44 (1H, d, *J*=16.0 Hz), 6.86 (1H, dd, *J*=16.0, 6.0 Hz), 7.28–7.35 (5H, m), 7.42 (1H, br s). Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73%. Found: C, 66.40; H, 8.58; N, 7.40. FABMS *m*/*z*: 363 (M^++1).

4.20. δ-Lactonization from (±)-3-benzyloxy-4-hydroxy-(2*E*)-pentenoate 16 (synthesis of (±)-18)

(1) A mixture of (±)-**16**[15] (0.186 g, 0.79 mmol) and 2 M NaOH solution (2 mL) in *i*-PrOH (3 mL) was stirred for 12 h at rt. The reaction mixture was worked up in the same way as for (±)-**6** to give (±)-**17** (0.175 g, 99%). Compound (±)-**17**: ^{1}H NMR: δ 3.62 (1H, dd, *J*=12.0, 6.0 Hz), 3.71 (1H, dd, *J*=12.0, 4.0 Hz, OH), 4.17 (1H, dddd, *J*=6.0, 6.0, 4.0, 2.0 Hz), 4.45 (1H, d, *J*=12.0 Hz), 4.66 (1H, d, *J*=12.0 Hz), 6.13 (1H, dd, *J*=16.0, 10.0 Hz), 6.97 (1H, d, *J*=16.0, 6.0 Hz), 7.27–7.40 (5H, m). The crude (±)-**17** was used for the next reaction without further purification. (2) To a solution of (±)-**17** (0.175 g, 0.79 mmol) in pyridine (2 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (0.21 g, 0.87 mmol) in CH_2Cl_2 (0.2 mL) at 0 °C and the reaction mixture was stirred for 2 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**18** (0.145 g, 90%) as a colorless oil. Compound (±)-**18**: IR (neat): 1730, 1629 cm^{-1}; ^{1}H NMR: δ 4.17 (1H, dddd, *J*=5.0, 5.0, 4.0, 1.0 Hz), 4.39 (1H, dd, *J*=10.0, 5.0 Hz), 4.41 (1H, dd, *J*=10.0, 5.0 Hz), 4.61 (2H, s), 6.05 (1H, dd, *J*=10.0, 1.0 Hz), 6.89 (1H, dd, *J*=10.0, 4.0 Hz). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. Found: C, 70.74; H, 6.00. FABMS *m*/*z*: 205 (M^++1).

4.21. δ-Lactonization from (±)-5-hydroxy-(2*E*)-hexenoate 19 (synthesis of (±)-21)

(1) To a solution of (±)-**19**[16] (0.163 g, 1.13 mmol) in THF (2 mL) was added 2 M NaOH solution (1.5 mL) and the

reaction mixture was stirred for 2.5 h at rt. The reaction mixture was worked up in the same way as for (±)-**6** to give (±)-**20** (0.147 g, 99%). Compound (±)-**20**: ^{1}H NMR: δ 1.20 (3H, d, J=6.0 Hz), 2.35 (2H, dd, J=7.0, 7.0 Hz), 3.96 (1H, ddq, J=7.0, 7.0, 6.0 Hz), 5.85 (1H, d, J=16.0 Hz), 6.43–6.70 (1H, m), 7.02 (1H, dt, J=16.0, 7.0 Hz). The crude (±)-**20** was used for the next reaction without further purification. (2) To a solution of (±)-**20** (0.147 g, 1.13 mmol) in CH_2Cl_2 (3 mL) were added pyridine (0.159 g, 2.26 mmol) and pyridinium chloride (0.232 g, 2.26 mmol). To the above reaction mixture was added a solution of 2,4,6-trichlorobenzoyl chloride (0.268 g, 2.26 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C and the reaction mixture was stirred for 1 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (±)-**21** (0.193 g, 81%) as a colorless oil. Compound (±)-**21**: IR (neat): 1724, 1390 cm^{-1}; ^{1}H NMR: δ 1.39 (3H, d, J=7.0 Hz), 2.25 (1H, dddd, J=18.0, 11.0, 2.0, 2.0 Hz), 2.32 (1H, dddd, J=18.0, 6.0, 3.0, 1.0 Hz), 4.52 (1H, ddq, J=11.0, 7.0, 3.0 Hz), 5.96 (1H, ddd, J=10.0, 2.0, 1.0 Hz), 6.83 (1H, ddd, J=10.0, 6.0, 1.0 Hz). Anal. Calcd for $C_6H_8O_2$: C, 62.27; H, 7.19%. Found: C, 61.99; H, 7.35. FABMS m/z: 113 (M^++1).

4.22. δ-Lactonization from (+)-(4*S*,5*R*)-6 (synthesis of (4*S*,5*R*)-osmundalactone 5)

(1) A mixture of the reported (4*S*,5*R*)-**2**[1] (6.30 g, 25 mmol) and 2 M NaOH solution (25 mL) in *i*-PrOH (50 mL) was stirred for 90 min at rt. The reaction mixture was worked up in the same way as for (±)-**6** to give (+)-(4*S*,5*R*)-**6** (5.90 g, 99%). Compound (+)-(4*S*,5*R*)-**6**: $[\alpha]_D^{25}$ +69.51 (c 0.33, $CHCl_3$). ^{1}H NMR data of (+)-(4*S*,5*R*)-**6** were identical to those of (±)-**6**. (2) To a solution of (+)-(4*S*,5*R*)-**6** (0.225 g, 0.95 mmol) in pyridine (2 mL) was added 2,4,6-trichlorobenzoyl chloride (0.26 g, 1.05 mmol) at 0 °C and the reaction mixture was stirred for 1 h at rt. The reaction mixture was worked up in the same way as described in Section 2.5 to afford (4*S*,5*R*)-**7** (0.177 g, 85%) as a colorless oil. ^{1}H NMR data of (4*S*,5*R*)-**7** were identical to those of (±)-**7**. Compound (+)-(4*S*,5*R*)-**7**: $[\alpha]_D^{25}$ +97.4 (c 0.35, $CHCl_3$). (3) To a suspension of $AlCl_3$ (5.06 g, 38.0 mmol) in CH_2Cl_2 (75 mL) was added a solution of (+)-(4*S*,5*R*)-**7** (3.310 g,1.6 mmol) in *m*-xylene (12 mL) at 0 °C and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was poured into ice-water and extracted with Et_2O. The Et_2O layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (300 g, *n*-hexane/AcOEt=1:1) to afford (+)-(4*S*,5*R*)-**5** (1.654 g, 85%). Compound (+)-(4*S*,5*R*)-**5**: $[\alpha]_D^{26}$ +69.1 (c 0.53, H_2O). IR ($CHCl_3$): 3422, 1727 cm^{-1}; ^{1}H NMR: δ 1.44 (3H, d, J=6.0 Hz), 2.85 (1H, d, J=7.0 Hz, OH), 4.20 (1H, ddd, J=8.0, 2.0, 2.0 Hz), 4.34 (1H, qd, J=8.0, 6.0 Hz), 5.91 (1H, dd, J=8.0, 2.0 Hz), 6.83 (1H, dd, J=8.0, 2.0 Hz). ^{13}C NMR: δ 18.2 (q), 67.5 (d), 79.2 (d), 120.0 (d), 149.0 (d), 163.5 (s). Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29%. Found: C, 56.07; H, 6.37. FABMS m/z: 129 (M^++1).

4.23. δ-Lactonization from (−)-(4*R*,5*S*)-6 (synthesis of (4*R*,5*S*)-osmundalactone 5)

(1)The reported (4*R*,5*S*)-**2**[1] (1.449 g, 58 mmol) was converted to (−)-(4*R*,5*S*)-**6** {1.288 g, 94%, $[\alpha]_D^{25}$ −69.97 (c 0.37, $CHCl_3$)} in the same way as for (+)-(4*S*,5*R*)-**6**. (2) δ-Lactonization from (−)-(4*R*,5*S*)-**6** (3.00 g, 12.7 mmol) in the same way as for (+)-(4*S*,5*R*)-**6** afforded (4*R*,5*S*)-**7** {2.342 g, 85%, $[\alpha]_D^{25}$ −97.8 (c 0.32, $CHCl_3$)}. (3) Deprotection of benzyl group of (−)-(4*R*,5*S*)-**7** (0.352 g, 1.6 mmol) in the same way as for (+)-(4*S*,5*R*)-**7** gave (−)-(4*R*,5*S*)-**5** {0.189 g, 91%, $[\alpha]_D^{28}$ −68.4 (c 0.41, H_2O)}.

4.24. Tetra-*O*-acetylosmundalin 8

To a solution of (−)-(4*R*,5*S*)-**5** (0.028 g, 0.22 mmol) and tetraacetyl-β-D-glucosyltrichloroimidate **22**[15] (0.218 g, 0.44 mmol) in CH_2Cl_2 (6 mL) was added $BF_3\cdot Et_2O$ (0.013 g, 0.09 mmol) at 0 °C and the reaction mixture was stirred for 3.5 h at rt. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=1:1) to afford (−)-**8** (0.099 g, 97%) as a colorless oil. Compound (−)-**8**: $[\alpha]_D^{25}$ −40.4 (c 1.0, $CHCl_3$). IR ($CHCl_3$): 1756 cm^{-1}; ^{1}H NMR: δ 1.42 (3H, d, J=6.0 Hz, 5-Me), 4.27 (1H, ddd, J=8.0, 2.4, 2.0 Hz, 4-H), 4.42 (1H, qd, J=8.0, 6.0 Hz, 5-H), 6.02 (1H, dd, J=10.0, 1.8 Hz, 2-H), 6.71 (1H, dd, J=10.0, 2.4 Hz, 3-H), 1.98, 2.00, 2.02, 2.06 (each 3H, s, OAc), 3.69 (1H, ddd, J=10.0, 4.4, 2.4 Hz, 5′-H), 4.14 (1H, dd, J=12.0, 2.4 Hz, 6′a-H), 4.20 (1H, dd, J=12.0, 4.4 Hz, 6′b-H), 4.67 (1H, d, J=8.0 Hz, 1′-H), 4.95 (1H, dd, J=10.0, 8.0 Hz, 2′-H), 5.05 (1H, dd, J=10.0, 10.0 Hz, 4′-H), 5.18 (1H, dd, J=10.0, 10.0 Hz, 3′-H). ^{13}C NMR: δ 18.27 (q, 6), 77.10 (d, 5), 73.00 (d, 4), 121.80 (d, 2), 144.20 (d, 3), 162.07 (s, 1), 20.67, 20.67, 20.73, 20.79 (each q, *Me*COO–), 61.84 (t, 6′), 68.25 (d, 4′), 71.13 (d, 2′), 72.15 (d, 5′), 72.57 (d, 3′), 98.84 (d, 1′), 168.86, 169.06, 169.92, 170.19 (each s, Me*CO*O–). Anal. Calcd for $C_{20}H_{26}O_{12}$: C, 52.40; H, 5.72%. Found: C, 52.11; H, 5.89. FABMS m/z: 459 (M^++1).

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