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FULL PAPER

First Total Synthesis of Neostrictinin

Kazutada Ikeuchi,*[a][†] Tatsuya Ueji,[a] Shintaro Matsumoto,[a] Shinnosuke Wakamori[a] and Hidetoshi Yamada*[a]

This paper is dedicated to the memory of Professor Hidetoshi Yamada, who sadly passed away on November 23, 2019.

Abstract: Herein, we describe the first total synthesis of neostrictinin, a natural ellagitannin bearing a (*R*)-hexahydroxydiphenoyl (HHDP) bridge between the 4- and 6-oxygens of D-glucose. Among the multitude of 4,6-*O*-HHDP bridged ellagitannins, (*R*)-axial chirality of the HHDP bridge is quite rare as it is less stable than the corresponding (*S*)-isomer. The labile bridge was constructed using a two-step bislactonization that involved: (1) mono-acylation of the primary alcohol of ethyl 2,3-*O*-benzyl-1-thio-β-D-glucopyranoside using protected (*R*)-hexahydroxydiphenic anhydride and (2) intramolecular lactonization of the obtained seco acid by treatment with a Mukaiyama condensation reagent (2-chloro-*N*-methylpyridinium iodide) and 2,6-lutidine. Structural confirmation of the synthesized neostrictinin and the preparation of its anomer are also reported.

Introduction

Ellagitannins are structurally diverse hydrolyzable tannins.[1] A large majority of the several hundred natural ellagitannins that have been isolated and characterized to date contain one or more hexahydroxydiphenoyl (HHDP) groups (Figure 1, a). Hydrolysis of ellagitannins releases ellagic acid derived from the HHDP group, which is the origin of the name 'ellagitannin'. Biosynthesis of the HHDP moiety is realized via oxidative aryl–aryl coupling of the two galloyl groups of 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (β-PGG; **1**).[2] The HHDP group is axially chiral due to the restricted rotation of the tetra-*ortho*-substituted aryl–aryl bond. Induction of axial chirality has been rationalized by the Haslam-Schmidt hypothesis, which claims that axial chirality originates from diastereoselective coupling, induced by conformational constraints within **1**.[1a,3] Therefore, the axial chirality of the HHDP group tends to be governed by the location of the biarylic bridge. For example, the axial chirality of the HHDP group bridging between the oxygenated 4- and 6-positions (4-O and 6-O) of D-glucose is generally *S*.[4] This tendency is reflected in the chemical synthesis of most HHDP groups, as (*S*)-selective coupling is dominant in the synthesis of the 4,6-*O*-HHDP moiety.[5]

However, natural ellagitannins occasionally contain an HHDP group with exceptional axial chirality. The 4,6-*O*-(*R*)-HHDP group is a representative example as it is present in only four of all the isolated natural ellagitannins.[6] Among these four, neostrictinin (**2**) was recently discovered by Era, Tanaka, and co-workers from the dried stem of *Penthorum chinense* (Penthoraceae) along with its (a*S*)-isomer, strictinin (**3**) (Figure 1, b).[6c] The structure of **2** was determined via spectroscopic techniques including NMR, high-resolution FABMS, and electronic circular dichroism. Its structure was additionally supported by comparison of the ^{1}H and ^{13}C NMR data obtained experimentally with those calculated via computational methods. Herein, we report the first total synthesis of **2** and confirmation of the proposed structure.

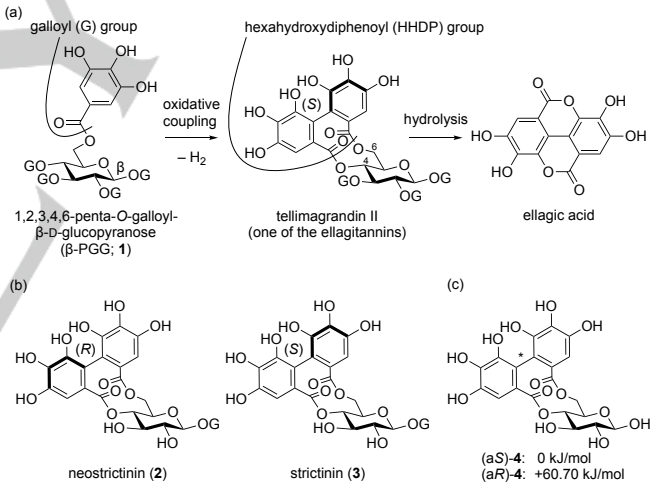

Figure 1. (a) Biosynthesis and hydrolysis of a HHDP group. (b) Structures of neostrictinin (**2**) and strictinin (**3**). (c) Difference in the calculated potential energy between the 4,6-O-(*R*)- and (*S*)-HHDP compounds (DFT, B3LYP/6-31G* level *in vacuo*).

Results and Discussion

The factors that drive the formation of 4,6-*O*-(*S*)-HHDP-D-glucose exclude the use of common procedures for synthesizing 4,6-*O*-HHDP bridges. According to chemical calculations, 4,6-*O*-(*S*)-HHDP-β-D-glucose (**4**) is 60.70 kJ/mol more stable than its diastereomer (a*R*)-**4** (Figure 1, c).[7] This difference in stability strongly affects axial chirality in the chemical construction of the 4,6-*O*-HHDP bridge. Thus, (*S*)-HHDP compounds are exclusively formed in aryl–aryl couplings of 4,6-*O*-digallates (Scheme 1, a).[6] Furthermore, double esterification of the 4,6-diol moiety of

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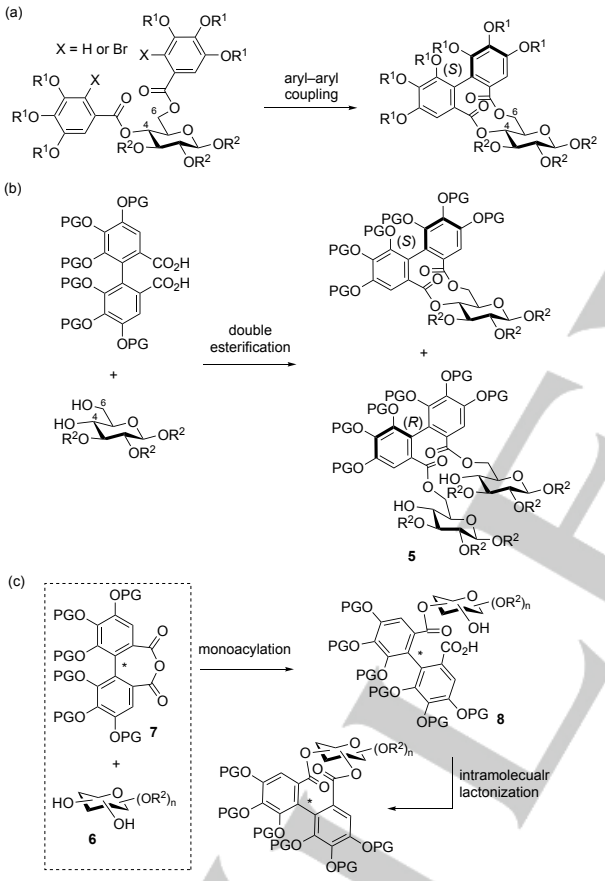
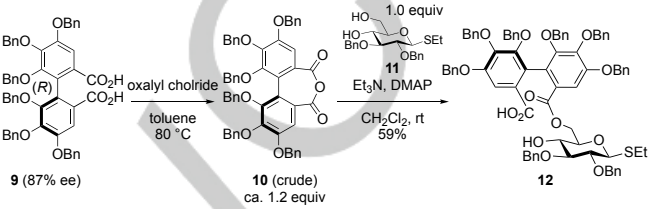
glucose derivatives with racemic protected-hexahydroxydiphenic acids produces only a single diastereomer bearing the (*S*)-HHDP bridge due to kinetic resolution (Scheme 1, b).[8] The mismatched enantiomer of hexahydroxydiphenic acid, the (*R*)-isomer in this case, favors the diesterified derivative **5**, bearing one HHDP group tethered to two glucose units.[8b,9] Therefore, these two methods cannot be applied for the synthesis of the 4,6-*O*-(*R*)-HHDP bridge. To construct such unfavorable bridge, the use of two-step bislactonization via mono-acylation of diol **6** with acid anhydride **7**, followed by intramolecular lactonization of seco acid **8** is preformed (Scheme 1, c).[10] This method has the potential to form an HHDP bridge, the construction of which is difficult via aryl–aryl coupling and double esterification.[11] Therefore, the formation of the 4,6-(*R*)-HHDP bridge is feasible using the two-step bislactonization.



Scheme 1. (a) The (*S*)-selective aryl–aryl coupling of galloyl groups on O-4 and O-6. (b) The (*S*)-selective double esterification via kinetic resolution. (c) The concept of two-step lactonization. R^1 = H or protecting group (PG); R^2 = components of ellagitannins or PG.

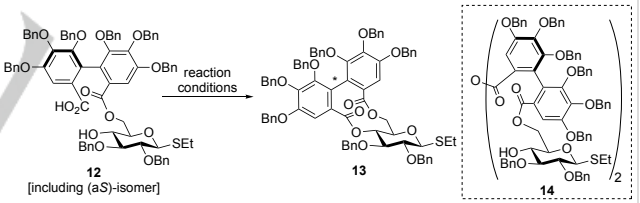
To examine this synthetic strategy, seco acid **12** derived from benzyl-protected (*R*)-hexahydroxydiphenic acid **9**[12] was prepared (Scheme 2). To elucidate the difference in reactivity between the rotational isomers, 87% *ee* of **9** was used. Treatment of **9** with oxalyl chloride at 80 °C provided the corresponding acid anhydride **10**, which was then subjected to monoacylation with diol **11**[5f] in the presence of triethylamine and 4-dimethylaminopyridine (DMAP). The reaction selectively proceeded at the less hindered 6-O of **11** to afford seco acid **12** in 59% yield with the (a*S*)-isomer of **12** as a minor component. Separation of the diastereomers and distinction of diastereomeric signals in the ^{1}H NMR spectrum was complicated and their ratio could not be determined using the method.



Scheme 2. Preparation of seco acid **12**. Bn = benzyl

The intramolecular lactonization of the diastereomeric mixture **12** was examined under various conditions and the obtained results are summarized in Table 1. Applying the previously successful reaction conditions for the HHDP bridge construction by intramolecular lactonization [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) and DMAP],[11] did not provide **13** (entry 1). Neither the Yamaguchi reagent (2,4,6-

Table 1. Investigations of intramolecular lactonization using seco acid **12**.



Entry	Reaction conditions[a]	Isolated yield (%)	a*R*/a*S*[b]
1	EDCI·HCl, DMAP, $(CH_2Cl)_2$	not detected	–
2	1) TCBCl, Et_3N, THF[c] 2) DMAP, toluene	not detected	–
3	MNBA, DMAP, toluene	not detected	–
4	oxalyl chloride, DMAP, toluene	10	2.2/1
5	CMPI, 2,6-lutidine, toluene	29 (35)[d]	3.5/1
6	CMPI, *i*-Pr_2NEt, toluene	14 (18)[d]	4.3/1
7[e]	CMPI, 2,6-lutidine, toluene	55	7.5/1

[a]General reaction conditions: reagent (2.0 equiv), base/additive (1.2–2.3 equiv), solvent (3 mM), 100 °C. See supporting Information (SI)-S-3 for further details. [b]Determined by ^{1}H NMR. [c]The reaction was conducted at 60 °C. [d]Isolated yield of the dimeric acid anhydride **14**. [e]5.0 equiv of CMPI and 10 equiv of 2,6-lutidine were used. THF = tetrahydrofuran.

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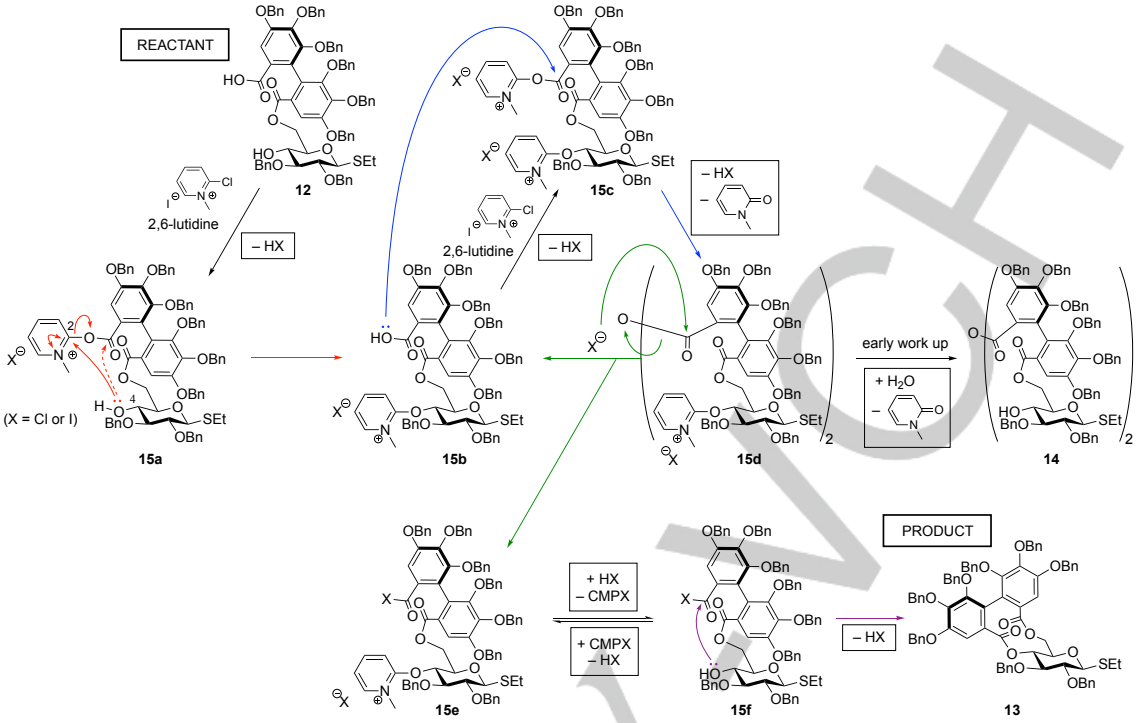

Scheme 3. Proposed reaction mechanism of the intramolecular lactonization of seco acid **12**.

trichlorobenzoyl chloride; TCBCl)[13] nor Shiina reagent (2-methyl-6-nitrobenzoic anhydride; MNBA)[14] afforded the 4,6-*O*-(*R*)-HHDP bridge (entries 2 and 3). Although the treatment of **12** with oxalyl chloride in the presence of DMAP afforded the desired (a*R*)-**13** along with (a*S*)-**13** derived from the minor reactant (a*S*)-**12**, their total yield was poor (entry 4). A breakthrough occurred under Mukaiyama esterification conditions.[15] Thus, reaction of **12** with 2-chloro-*N*-methylpyridinium iodide (CMPI) and 2,6-lutidine in toluene at 100 °C afforded **13** in 29% isolated yield and a 3.5:1 diastereomeric mixture, with *R* axial chirality in the major isomer (entry 5). The substitution of 2,6-lutidine with *N*,*N*-diisopropylethylamine decreased the yield of **13** (entry 6). Optimization of the CMPI/2,6-lutidine system for intramolecular lactonization (see SI-S-4) showed that 5 equiv of CMPI and 10 equiv of 2,6-lutidine gave optimal results, affording **13** in 55% isolated yield in a 7.5:1 diastereomeric ratio (entry 7).

Isolation of dimeric acid anhydride **14** and reaction monitoring via NMR spectroscopy during the transformation of **12** into **13** (see SI-S-5) showed that the CMPI-mediated intramolecular lactonization follows an unusual reaction pathway. Anhydride **14** was isolated for entries 5 and 6 of Table 1 in 35% and 18% yields, respectively, and the structure was characterized using NMR and HRMS analyses. The ^{1}H NMR spectrum of reaction monitoring after elapse of 20 min showed the disappearance of signals corresponding to **12**, along with the generation of the acylated pyridinium salt **15a**. Over the following 5 h, **15a** was transformed into a major compound, showing signals akin to those of **14** (Figure S1). Integration of these signals then decreased while the signals corresponding to **13** emerged (Figure S2). An additional 12 h of reaction time resulted in **13** as a major product. The NMR experiments also detected the continuous production of *N*-methyl-2-pyridone derived from CMPI (Figure S3). Based on these results, a reaction mechanism is proposed for the intramolecular lactonization, as shown in Scheme 3. The first step involves the facile generation of acyl pyridinium salt **15a** via reaction of seco acid **12** with CMPI. Formation of the 4,6-(*R*)-HHDP bridge via intramolecular lactonization of **15a** (red dash curved arrow) was disfavored due to bridge strain, hence a different reaction pathway was followed in the next step. Thus, an attack by the hydroxy group at the 2-position carbon in the pyridinium ring of **15a**, followed by intramolecular migration[16] (red plain curved arrow) delivers carboxylic acid **15b**. Further reaction of **15b** with CMPI provides the acyl pyridinium salt **15c**, which becomes trapped with unreacted **15b** (blue curved arrow) to afford the dimer **15d**. NMR experiments suggested that the major product after 5 h was **15d**, and that **14** was the hydrolysis product, generated in the work-up process.[17] Subsequent transformation was initiated upon the degradation of **15d** by a chloride/iodide ion (X^-). Thus, the *in situ* accumulated X^- attacks the acyl group of **15d** (green curved arrow), which then fragments into carboxylic acid **15b** and acyl halide **15e**. Performing the reaction at 100 °C was key for the degradation, because the yield of **13** dramatically decreased to 7% and that of **14** increased to 53% when the reaction was performed at 80 °C (entry 6 of SI-S-4). Although the fragmentation reaction that releases **15b** and **15e** is reversible, excess CMPI ensures a high reaction rate between **15b** with CMPI, driving the equilibrium towards the degradation side. The presence of excess CMPI and X^- causes **15e** to be in equilibrium with alcohol **15f**, arising from elimination of the pyridinium moiety at the 4-O. At this stage, the acyl halide is the only functional group permitting the

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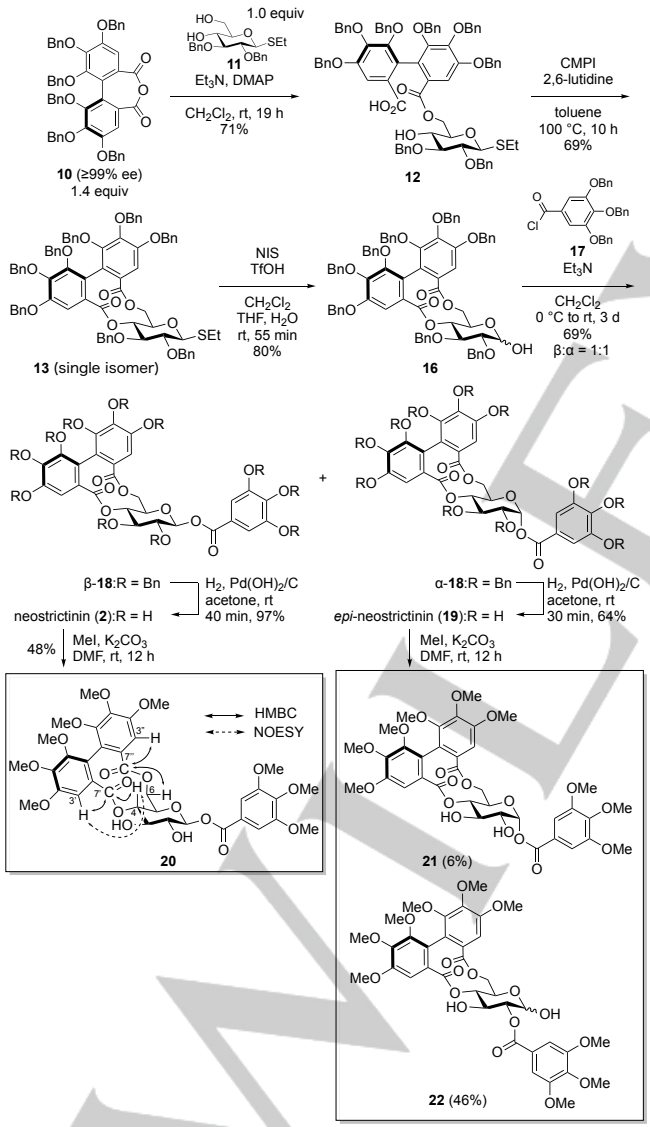
intramolecular attack by the hydroxy group of **15f**. Thus, the intramolecular lactonization finally proceeds (purple curved arrow) to afford the 4,6-(*R*)-HHDP bridged compound **13**. A significant yield decrease was observed when the reaction was conducted at a concentration of 10 mM (entry 4 of SI-S-4), indicating that the concentration of **15f** affects intramolecular lactonization. The newly developed reaction system enables the generation of **15f** at low concentrations, allowing the construction of the unfavored bridge.

After optimizing the method for constructing the 4,6-*O*-(*R*)-HHDP structure, the total synthesis of neostrictinin (**2**) was performed using enantiomerically pure **10** (Scheme 4). After preparing seco acid **12** using (*R*)-**10** and diol **11**, the treatment of **12** under optimized reaction conditions (Table 1, entry 7) produced (*R*)-**13** as a single isomer in 69% isolated yield. The remaining synthetic steps needed to produce **2** followed the synthesis of strictinin (**3**).[5f] Thus, hydrolysis of the anomeric ethylthio group using *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) in the presence of water afforded pyranose **16**. Subsequent acylation of the 1-O of **16** with tri-*O*-benzyl galloyl chloride (**17**) provided an unexpected result. While the 2/98 α/β-selectivity was observed in the acylation of (a*S*)-**16** using **17** and triethylamine,[18] a similar selectivity was not achieved when applying the same reaction conditions to (*a*R)-**16**, affording a 1:1 anomeric mixture of **18** in 69% yield. Further attempts to achieve the desired β-selectivity were unsuccessful (see SI-S-6). Following anomeric mixture separation by silica gel chromatography, debenzylation of β-**18** via hydrogenolysis produced neostrictinin (**2**). Similarly, the debenzylation of α-**18** provided *epi*-neostrictinin (**19**), which has not been isolated from natural sources to date. The ^{1}H- and ^{13}C NMR spectral data for synthetic **2** agreed with literature data for the corresponding natural product **2**, but was not identical (see SI-S-7). The slight variance was attributed to differences in the aggregation states caused by the phenolic hydroxyl groups.



Scheme 4. The synthesis of neostrictinin (**2**) and *epi*-neostrictinin (**19**). DMF = *N*,*N*-dimethylformamide

The HMBC and NOESY spectra of the nonamethylated compound **20**, derived from synthetic **2**, displayed diagnostic correlation signals confirming that synthetic **2** contained the 4,6-(*R*)-*O*-HHDP bridge (Scheme 4). A distinct signal in the NOESY spectrum of natural **2** arising from the correlation between hydrogens on C-4 and C-3" (H-4/H-3"), is not detected in the (a*S*)-isomer, strictinin (**3**). In the NOESY spectrum of **20**, this correlation was clearly visible (see SI-S-8). In addition, the HMBC spectrum of **20** exhibited correlations between H-3'/C-7', C-7'/H-4, H-3"/C-7", and C-7"/H-6 (see SI-S-9), confirming that the (*R*)-HHDP group was correctly situated. Therefore, the structure of **20** was consistent with a derivative of **2**, indicating that the structures of natural and synthesized neostrictinin were identical. Additionally, we synthesized nonamethylated *epi*-neostrictinin (**21**). The methylation reaction induced acyl migration to afford the 2-O acylated derivative **22** and the desired **21** in 46% and 6% yields, respectively. The NMR chemical shifts of unprotected ellagitannins tend to differ due to aggregation. Because this complication has been solved by comparison of data for the methylated analogues, the spectral data of **21** and **22** is useful for their structural determination in conjunction with isolation of the corresponding natural products.

Conclusions

Neostrictinin (**2**) and *epi*-neostrictinin (**19**) were synthesized in five steps from acid anhydride **10** in 13% and 8.7% overall yields, respectively. This is the first report of the synthesis of an ellagitannin bearing the rare 4,6-*O*-(*R*)-HHDP bridge. Chemical construction of the uncommon bridge was achieved via two-step bislactonization, which entailed monoacylation of diol **11** using **10**, followed by intramolecular lactonization of the obtained seco acid **12**. The latter reaction proceeded efficiently via a dimeric reaction pathway of **12** when CMPI and 2,6-lutidine were in excess at 100 °C. In addition, the HMBC and NOESY spectra of nonamethylated derivative **20**, prepared from synthetic **2**, exhibited requisite correlations that verified the presence of the

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4,6-*O*-(*R*)-HHDP bridge, confirming that the structure of the synthesized **2** was identical to that of natural **2**. Structural identification of synthetic/natural ellagitannins is often problematic, as in our case. Thus, methylation of synthetic/natural ellagitannins is beneficial for the elucidation of ellagitannin chemistry.

Experimental Section

General information

All commercially available reagents were used as received. All moisture and air sensitive reactions were carried out in glassware equipped with rubber septa (or a septum) under the positive pressure of argon or nitrogen. When necessary, the glassware was dried under reduced pressure by heating with a heat-gun and solvents were distilled prior to use. The substrates were azeotropically dried if needed by evaporation of their acetonitrile or toluene solution several times to remove trace water that may be contained to the substrates. Concentration was performed under reduced pressure. The reactions were monitored by TLC and MS. Anhydrous $MgSO_4$ or Na_2SO_4 was used to dry organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was concentrated and subjected to further purification protocols if necessary. This sequence was represented as "the general drying procedure" in the following experimental methods. TLC was performed on Merck pre-coated silica gel 60 F-254 plates or Merck RP-19 F-254 plates. Spots were visualized by exposure to UV light, or by immersion into a solution of 2% anisaldehyde, 5% H_2SO_4 in ethanol or a solution of 10% phosphomolybdic acid in ethanol, followed by heating at ca. 200 °C. Column chromatography was performed on Merck silica gel 60 (63–200 or 40–63 μm) and Kanto Chemical silica gel 60 N (Spherical, neutral, 40–50 or 63–210 μm). The other carrier materials were noted in each case. The melting points were determined using a Yanagimoto micro-melting point apparatus and uncorrected. Optical rotations were determined using a JASCO DIP-370 polarimeter with a 100 mm cell at 589 nm. IR spectra were recorded on Shimazu IRAffinity-1S, and the major absorbance bands are all reported in wavenumbers (cm^{-1}). HRMS were obtained on a JEOL JMS-T100LC spectrometer for ESI. NMR spectra were recorded on JEOL JNM-ECX-400 (400 MHz for ^1H and 101 MHz for ^{13}C) or JNM-ECX-500 (500 MHz for ^1H and 126 MHz for ^{13}C) with either TMS or residual proton of deuterated solvent as internal reference in the indicated solvent in each parenthesis. The ^1H NMR spectroscopic data are indicated by a chemical shift (δ), with the multiplicity, the coupling constants, the integration in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The ^{13}C NMR spectroscopic data are reported as the chemical shift (δ), with the hydrogen multiplicity obtained from the DEPT spectra in parentheses. The multiplicities are abbreviated as s: C, d: CH, t: CH_2, and q: CH_3. When the number of the carbon was more than one, the number was added in the parentheses.

Synthesis of seco acid 12

To a stirred solution of **11** (444 mg, 1.10 mmol), Et_3N (545 mg, 5.41 mmol) and DMAP (53.0 mg, 433 μmol) in CH_2Cl_2 (10 mL) was added a solution of prepared 99% ee of **10**[11a] (ca. 1.54 mmol) in CH_2Cl_2 (20 mL) by cannula at rt. After the reaction mixture was stirred for 19 h at rt, saturated NH_4Cl aq was added to the reaction mixture. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H_2O and brine. After the general drying procedure, the crude product was purified by column chromatography (30 g of SiO_2, hexane/EtOAc = 2/1 to 0/1, followed by 5 g of SiO_2, hexane/EtOAc = 2/1) to give **12** (982 mg, 776 μmol, 71%) as a colorless needless.

Data for **12**: mp 144.5–148.0 °C. $[\alpha]_D^{22}$ –38.7 (*c* 0.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 23 °C) δ 7.56 (s, 1H), 7.56 (s, 1H), 7.46 (d, *J* = 7.1 Hz, 2H), 7.43–7.17 (m, 27H), 7.11–7.02 (m, 7H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 6.6 Hz, 2H), 5.11 (d, *J* = 11.2 Hz, 1H), 5.10 (s, 2H), 5.00 (d, *J* = 11.2 Hz, 1H), 4.99 (s, 2H), 4.95 (s, 2H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.80 (d, *J* = 11,7 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.60 (d, *J* = 10.5 Hz, 1H), 4.35 (dd, *J* = 12.3, 4.4 Hz, 1H), 4.34 (d, *J* = 9.9 Hz, 1H), 4.23 (dd, *J* = 12.3, 1.6 Hz, 1H), 3.36 (dd, *J* = 9.2, 8.8 Hz, 1H), 3.21 (dd, *J* = 9.9, 8.8 Hz, 1H), 3.21 (ddd, *J* = 9.2, 4.4, 1.6 Hz, 1H), 3.07 (dd, *J* = 9.2, 9.2 Hz, 1H), 2.68–2.53 (m, 2H), 1.15 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, 24 °C) δ 170.8 (s), 167.1 (s), 151.9 (s), 151.9 (s), 151.3 (s), 151.2 (s), 146.2 (s), 145.8 (s), 138.7 (s), 138.2 (s), 138.0 (s), 137.8 (s), 137.5 (s), 137.3 (s), 136.7 (s), 136.7 (s), 128.8–127.4 (overlapping 40 doublets and 1 singlet, 41C), 127.2 (s), 125.1 (s), 124.6 (s), 111.8 (d), 111.5 (d), 86.0 (d), 85.4 (d), 81.3 (d), 77.4 (d), 75.7 (t), 75.5 (t), 75.5 (t), 75.3 (t), 75.0 (t), 74.7 (t), 71.2 (t), 70.7 (t), 70.0 (d), 64.3 (t), 25.0 (t), 15.1 (q). IR (ATR) 3063, 3030, 2930, 2874, 1699, 1589, 1454, 1364, 1213, 1096, 908, 845, 735, 696 cm^{-1}. HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_{78}H_{71}O_{14}S_1$ 1263.4565, found 1263.4566.

Synthesis of 4,6-*O*-(*R*)-HHDP bridged compound 13

To a stirred solution of **12** (17.0 mg, 13.4 μmol) and 2,6-lutidine (14.0 mg, 134 μmol) in toluene (4.5 mL) was added 2-chloro-*N*-methylpyridinium iodide (CMPI) (17.5 mg, 67.2 μmol) at rt. After the reaction mixture was stirred for 10 h at 100 °C, saturated NH_4Cl aq was added to the reaction mixture. The separated organic layer was successively washed with saturated NH_4Cl aq, 10% $Na_2S_2O_3$ aq, and brine. After the general drying procedure, the crude product was purified by column chromatography (SiO_2 1 g, hexane/EtOAc = 5/1) to give **13** (11.6 mg, 9.39 μmol, 69%) as a yellow amorphous solid.

Data for **13**: $[\alpha]_D^{23}$ +14.3 (*c* 0.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 22 °C) δ 7.48–7.20 (m, 30H), 7.15–7.05 (m, 8H), 6.87 (d, *J* = 6.9 Hz, 2H), 6.83 (d, *J* = 6.9 Hz, 2H), 5.17 (s, 2H), 5.08 (d, *J* = 11.0 Hz, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.94 (d, *J* = 11.0 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 10.1 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.78 (dd, *J* = 11.1, 6.0 Hz, 1H), 4.77 (d, *J* = 10.8 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.71 (dd, *J* = 9.4, 9.2 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 4.10 (d, *J* = 11.7 Hz, 1H), 3.94 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.91 (ddd, *J* = 10.1, 9.4, 6.0 Hz, 1H), 3.54 (dd, *J* = 11.1, 10.1 Hz, 1H), 3.39 (dd, *J* = 9.6, 9.2 Hz, 1H), 2.80–2.66 (m, 2H), 1.32 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, 24 °C) δ 168.1 (s), 166.7 (s), 152.8 (s), 152.5 (s), 152.5 (s), 151.6 (s), 145.8 (s), 143.7 (s), 138.3 (s), 137.8 (s), 137.7 (s), 137.6 (s), 137.4 (s), 136.6 (s), 136.5 (s), 129.4 (d, 2C), 128.8–127.4 (overlapping 38 doublets, 38C), 126.0 (s), 125.5 (s), 124.9 (s), 124.8 (s), 110.6 (d), 108.3 (d), 85.0 (d), 84.7 (d), 80.9 (d), 80.6 (d), 77.4 (t), 75.5 (t), 75.4 (t), 75.3 (t), 75.0 (t), 74.7 (t), 72.6 (d), 71.2 (t), 70.6 (t), 65.5 (t), 25.3 (t), 15.3 (q). IR (ATR) 3063, 3030, 2930, 2876, 1728, 1591, 1497, 1366, 1198, 1096, 910, 849, 737, 696 cm^{-1}. HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{78}H_{70}O_{13}S_1Na$ 1269.4435, found 1269.4419.

Synthesis of hemiacetal 16

To a stirred solution of **13** (124 mg, 99.4 μmol) in CH_2Cl_2 (5.0 mL) and H_2O (0.5 mL) was added a solution of NIS (113 mg, 498 μmol) and TfOH (8.7 mg, 58 μmol) in THF (10.0 mL) and CH_2Cl_2 (0.2 mL) at rt. After the reaction mixture was stirred for 55 min at rt, 10% $Na_2S_2O_3$ aq was added to the reaction mixture. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with water and brine. After the general drying procedure, the crude product was purified by column chromatography (SiO_2 5 g, hexane/EtOAc = 4/1 to 1/1) to give **16** (95.7 mg, 79.5 μmol, 80%, d.r. = ca. 2/1) as a colorless syrup.

Data for **16**: H NMR of major isomer (400 MHz, $CDCl_3$, 22 °C) δ 7.48–7.05 (m, 38H), 6.88–6.82 (m, 4H), 5.21 (br s, 1H), 5.14 (s, 2H), 5.10–4.63 (m, 14H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.37 (ddd, *J* = 9.5, 9.5, 5.7 Hz, 1H), 4.28 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.00 (d, *J* = 11.5 Hz, 1H), 3.48 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.43 (dd, *J* = 10.5, 10.5 Hz, 1H), 3.10 (br s, 1H). ^{13}C NMR of major isomer (101 MHz, $CDCl_3$, 21 °C) δ 168.3 (s), 166.9 (s), 152.8 (s), 152.5 (s), 152.5 (s), 151.6 (s), 145.7 (s), 143.5 (s), 138.3 (s), 138.0 (s), 137.5 (s, 3C),

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137.3 (s), 136.6 (s), 136.5 (s), 129.6 (d, 2C), 128.9–127.4 (d, overlapping 38 doublets: 19 peaks were observed, 38C), 126.1 (s), 125.7 (s), 124.9 (s), 124.6 (s), 110.4 (d), 108.4 (d), 90.5 (d), 80.9 (d), 79.7 (d), 78.8 (d), 77.6 (t), 75.3 (t, 2C), 75.0 (t), 74.7 (t), 72.8 (t), 71.2 (t), 70.5 (t), 66.1 (t), 65.2 (d). IR (ATR) 3600–3100, 3063, 3030, 2941, 2874, 1728, 1591, 1497, 1366, 1200, 1096, 910, 748, 696 cm^{-1}. ^{1}HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{76}H_{66}O_{14}Na$ 1225.4350, found 1225.4326.

Synthesis of galloyl ester β-18 and α-18

To a stirred solution of **16** (39.0 mg, 32.4 μmol) and Et_3N (13.8 mg, 136 μmol) in CH_2Cl_2 (5.0 mL) was added dropwise a solution of prepared **17**[19] (ca. 121 μmol) in CH_2Cl_2 (5.0 mL) at 0 °C. After the reaction mixture was stirred at rt for 3 d, 1 M HCl aq was added to the reaction mixture. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H_2O and brine. After the general drying procedure, the crude product was purified by column chromatography (SiO_2 5 g, hexane/EtOAc = 5/1 to 4/1, followed by SiO_2 5 g, hexane/EtOAc = 5:1) to give α-**18** (17.9 mg, 11.0 μmol, 34%) as a colorless syrup and β-**18** (18.6 mg, 11.4 μmol, 35%) as a colorless syrup.

Data for β-**18**: $[\alpha]_D^{21}$ +7.69 (*c* 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.47 (d, *J* = 6.9 Hz, 2H), 7.44–7.31 (m, 28H), 7.31–7.05 (m, 25H), 6.88 (d, *J* = 7.5 Hz, 2H), 6.83 (d, *J* = 7.5 Hz, 2H), 5.89 (d, *J* = 8.0 Hz, 1H), 5.19 (d, *J* = 11.5 Hz, 1H), 5.16 (d, *J* = 11.5 Hz, 1H), 5.14 (s, 2H), 5.12 (d, *J* = 11.5 Hz, 2H), 5.09 (d, *J* = 11.5 Hz, 2H), 5.08 (d, *J* = 10.9 Hz, 1H), 4.99 (d, *J* = 10.3 Hz, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 4.92 (d, *J* = 10.9 Hz, 2H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.81 (d, *J* = 10.3 Hz, 1H), 4.81–4.77 (m, 4H), 4.77 (d, *J* = 10.9 Hz, 1H), 4.73 (d, *J* = 10.9 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.12 (ddd, *J* = 9.7, 8.6, 4.6 Hz, 1H), 4.08 (d, *J* = 11.5 Hz, 1H), 4.06 (dd, *J* = 9.7, 9.2 Hz, 1H), 3.69 (dd, *J* = 9.2, 8.0 Hz, 1H), 3.54 (dd, *J* = 10.9, 9.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C) δ 167.9 (s), 166.6 (s), 164.2 (s), 152.8 (s, 2C), 152.7 (s), 152.6 (s), 152.6 (s), 151.6 (s), 145.8 (s), 143.7 (s), 143.5 (s), 138.3 (s), 137.6 (s), 137.6 (s), 137.5 (s, 2C), 137.4 (s), 136.7 (s), 136.6 (s), 136.6 (s, 2C), 136.5 (s), 129.5 (d, 2C), 128.9 (d, 2C), 128.7–127.4 (overlapping 29 doublets: 20 peaks were observed, 29C), 125.9 (s), 125.6 (s), 125.1 (s), 124.5 (s), 123.9 (s), 110.5 (d), 109.8 (d, 2C), 108.3 (d), 93.9 (d), 83.6 (d), 80.1 (d), 80.0 (d), 75.4 (t), 75.3 (t), 75.3 (t), 75.0 (t), 74.9 (t), 74.7 (t), 71.5 (t, 2C), 71.4 (t), 71.2 (t), 70.6 (t), 70.0 (d), 65.3 (t). IR (ATR) 3063, 3030, 2938, 2878, 1732, 1589, 1429, 1331, 1196, 1098, 737, 696 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{104}H_{88}O_{18}Na$ 1647.5868, found 1647.5873.

Data for α-**18**: $[\alpha]_D^{24}$ +25.7 (*c* 0.18, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 22 °C) δ 7.47–7.06 (m, 51H), 7.37 (s, 2H), 7.32 (s, 1H), 7.25 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.46 (d, *J* = 3.4 Hz, 1H), 5.20 (s, 4H), 5.19 (s, 2H), 5.16 (s, 2H), 5.10 (d, *J* = 11.5 Hz, 1H), 5.01 (d, *J* = 9.7 Hz, 1H), 4.96 (d, *J* = 10.9 Hz, 1H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.81 (d, *J* = 11.5 Hz, 1H), 4.78 (d, *J* = 9.7 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.74 (dd, *J* = 9.2, 8.6 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.67 (dd, *J* = 11.5, 5.2 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.18 (dd, *J* = 9.7, 9.2 Hz, 1H), 4.18 (ddd, *J* = 9.7, 8.6, 5.2 Hz, 1H), 4.03 (d, *J* = 11.5 Hz, 1H), 3.66 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.41 (dd, *J* = 11.5, 9.7 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$, 22 °C) δ 168.0 (s), 166.6 (s), 164.5 (s), 152.8 (s), 152.7 (s, 2C), 152.6 (s), 152.6 (s), 151.6 (s), 145.8 (s), 143.6 (s), 143.3 (s), 138.3 (s), 137.8 (s), 137.5 (s), 137.5 (s), 137.4 (s), 137.4 (s), 137.3 (s), 136.7 (s, 2C), 136.6 (s), 136.5 (s), 129.6 (d, 2C), 128.9–127.4 (overlapping 53 doublets: 26 peaks were observed, 53C), 126.0 (s), 125.5 (s), 125.0 (s), 124.7 (s), 124.2 (s), 110.4 (d), 109.7 (d, 2C), 108.3 (d), 89.3 (d), 80.1 (d), 79.8 (d), 77.6 (d), 75.3 (t, 2C), 75.0 (t), 74.7 (t), 72.6 (t), 71.4 (t, 2C), 71.3 (t, 2C), 71.2 (t), 70.5 (t), 67.5 (d), 65.6 (t). IR (ATR) 3065, 3032, 2883, 1730, 1589, 1429, 1331, 1198, 1098, 735, 696 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{108}H_{88}O_{18}Na$ 1647.5868, found 1647.5857.

Synthesis of neostrictinin (2)

A mixture of β-**18** (10.0 mg, 6.15 μmol) and $Pd(OH)_2$/C (20 wt %, 19.8 mg, 28.4 mmol) in acetone (2.5 mL) was stirred for 40 min at rt under H_2 atmosphere. The mixture was filtered through a cotton-Celite® pad to remove $Pd(OH)_2$/C. The concentrated filtrate was purified by Sephadex™ LH-20 (1.0 g, acetone/MeOH = 1/0 to 1/1) to give neostrictinin (**2**) (3.7 mg, 5.8 μmol, 97%) as a brown amorphous solid.

Data for **2**: $[\alpha]_D^{23}$ +17.2 (*c* 0.48, MeOH). ^{1}H NMR (500 MHz, acetone-d_6, 23 °C) δ 7.15 (s, 2H), 7.06 (s, 1H), 6.83 (s, 1H), 5.73 (d, *J* = 8.6 Hz, 1H), 4.83 (dd, *J* = 9.7, 9.2 Hz, 1H), 4.58 (dd, *J* = 10.9, 5.2 Hz, 1H), 4.04 (ddd, *J* = 10.3, 9.7, 5.2 Hz, 1H), 3.94 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.71 (dd, *J* = 9.2, 8.6 Hz, 1H), 3.54 (dd, *J* = 10.9, 10.3 Hz, 1H). ^{13}C NMR (126 MHz, acetone-d_6, 23 °C) δ 168.5 (s), 167.9 (s), 165.4 (s), 146.2 (s, 2C), 145.9 (s), 145.4 (s), 145.2 (s), 144.3 (s), 139.5 (s), 137.2 (s), 135.7 (s), 124.2 (s), 123.3 (s), 120.7 (s), 115.9 (s), 115.8 (s), 110.4 (d, 2C), 109.6 (d), 108.8 (d), 94.7 (d), 81.3 (d), 76.2 (d), 73.2 (d), 71.1 (d), 65.7 (t). IR (ATR) 3500–3000, 2959, 1699, 1616, 1466, 1362, 1200, 1045, 829, 768 cm^{-1}. HRMS (ESI) *m*/*z* [M – H]$^-$ calcd for $C_{27}H_{21}O_{18}$ 633.0728, found 633.0732.

Synthesis of *epi*-neostrictinin (19)

A mixture of α-**18** (16.0 mg, 9.84 μmol) and $Pd(OH)_2$/C (10 wt %, 38.3 mg, 36.0 mmol) in acetone (2.0 mL) was stirred for 30 min at rt under H_2 atmosphere. The mixture was filtered through a cotton-Celite® pad to remove $Pd(OH)_2$/C. The concentrated filtrate was purified by Sephadex™ LH-20 (300 mg, acetone) to give *epi*-neostrictinin (**19**) (4.0 mg, 6.3 μmol, 64%) as a colorless amorphous solid.

Data for **19**: $[\alpha]_D^{19}$ +35.0 (*c* 0.04, acetone). ^{1}H NMR (500 MHz, acetone-d_6, 21 °C) δ 7.17 (s, 2H), 7.10 (s, 1H), 6.80 (s, 1H), 6.29 (d, *J* = 3.4 Hz, 1H), 4.89 (dd, *J* = 9.2, 8.6 Hz, 1H), 4.54 (dd, *J* = 10.6, 5.2 Hz, 1H), 4.23 (dd, *J* = 9.7, 8.6 Hz, 1H), 4.14 (ddd, *J* = 9.7, 9.2, 5.2 Hz, 1H), 3.84 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.52 (dd, *J* = 10.6, 9.7 Hz, 1H). ^{13}C NMR (126 MHz, acetone-d_6, 18 °C) δ 168.5 (s), 167.9 (s), 165.2 (s), 146.2 (s, 2C), 145.8 (s), 145.5 (s), 145.2 (s), 144.3 (s), 139.4 (s), 137.1 (s), 135.7 (s), 124.1 (s), 123.3 (s), 120.9 (s), 115.8 (s), 115.7 (s), 110.1 (d, 2C), 109.4 (d), 108.7 (d), 92.0 (d), 81.5 (d), 72.9 (d), 71.5 (d), 68.7 (d), 66.0 (t). IR (ATR) 3674–3010, 2959, 1699, 1616, 1447, 1360, 1198, 1040, 962, 764 cm^{-1}. HRMS (ESI) *m*/*z* [M – H]$^-$ calcd for $C_{27}H_{21}O_{18}$ 633.0728, found 633.0741.

Synthesis of nonamethylated neostrictinin (20)

To a stirred solution of **2** (5.4 mg, 8.5 μmol) and MeI (29.6 mg, 212 μmol) in DMF (1.0 mL) was added K_2CO_3 (10.6 mg, 76.6 μmol) at rt. After the reaction mixture was stirred at rt for 12 h, saturated NH_4Cl aq was added to the reaction mixture. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H_2O and brine. After the general drying procedure, the crude product was purified by preparative TLC (hexane/EtOAc = 1/1) to give **20** (3.1 mg, 4.1 μmol, 48%) as a colorless amorphous solid.

Data for **20**: $[\alpha]_D^{20}$ +44.2 (*c* 0.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 22 °C) δ 7.33 (s, 1H), 7.29 (s, 2H), 7.04 (s, 1H), 5.83 (d, *J* = 8.6 Hz, 1H), 4.81 (dd, *J* = 9.7, 8.6 Hz, 1H), 4.66 (dd, *J* = 10.9, 5.7 Hz, 1H), 4.16–4.11 (m, 2H), 3.94 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 6H), 3.90 (s, 6H), 3.81 (dd, *J* = 9.7, 8.6 Hz, 1H), 3.75 (dd, *J* = 10.9, 9.7 Hz, 1H), 3.69 (s, 3H), 3.58 (s, 3H), 3.30 (br s, 1H), 2.63 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, 22 °C) δ 168.1 (s), 167.2 (s), 164.6 (s), 153.4 (s), 153.2 (s, 2C), 153.1 (s), 152.6 (s), 152.2 (s), 145.3 (s), 144.0 (s), 143.3 (s), 125.7 (s), 125.4 (s), 124.2 (s), 123.6 (s), 122.8 (s), 107.8 (d), 107.5 (d, 2C), 107.3 (d), 93.5 (d), 79.8 (d), 75.3 (d), 72.7 (d), 70.6 (d), 65.5 (t), 61.3 (q), 61.2 (q), 61.1 (q), 61.1 (q), 60.8 (q), 56.5 (q), 56.3 (q), 56.1 (q). IR (ATR) 3690–3211, 2940, 2849, 1734, 1591, 1395, 1339, 1218, 1103, 771 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{40}O_{18}Na$ 783.2112, found 783.2108.

Synthesis of nonamethylated *epi*-neostrictinin (21) and the acyl migrated compound 22

To a stirred solution of **19** (4.0 mg, 6.3 μmol) and MeI (22.8 mg, 160 μmol) in DMF (1.0 mL) was added K_2CO_3 (8.7 mg, 63 μmol) at rt. After the reaction mixture was stirred at rt for 12 h, saturated NH_4Cl aq was added to the reaction mixture. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H_2O and brine. After the general drying procedure, the crude product was purified by

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preparative TLC (hexane/EtOAc = 1/1) to give **21** (0.3 mg, 0.4 μmol, 6%) as a colorless amorphous solid and **22** (2.2 mg, 2.9 μmol, 46%, d.r. = ca. 3/1) as a colorless amorphous solid.

Data for **21**: $[\alpha]_D^{21}$ +104 (*c* 0.009, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 22 °C) δ 7.35 (s, 1H), 7.29 (s, 2H), 7.01 (s, 1H), 6.42 (d, *J* = 3.4 Hz, 1H), 4.83 (dd, *J* = 9.2, 8.6 Hz, 1H), 4.63 (dd, *J* = 11.2, 5.2 Hz, 1H), 4.38 (ddd, *J* = 9.5, 9.2, 2.9 Hz, 1H), 4.30 (ddd, *J* = 9.5, 8.6, 5.2 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 6H), 3.91 (m, 1H), 3.89 (s, 3H), 3.71 (dd, *J* = 11.2, 9.5 Hz, 1H), 3.69 (s, 3H), 3.58 (s, 3H), 3.07 (d, *J* = 2.9 Hz, 1H), 2.38 (d, *J* = 5.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, 22 °C) δ 168.1 (s), 167.1 (s), 164.8 (s), 153.5 (s), 153.3 (s, 2C), 153.1 (s), 152.6 (s), 152.3 (s), 145.3 (s), 144.1 (s), 143.5 (s), 125.6 (s), 125.5 (s), 124.3 (s), 123.7 (s), 122.9 (s), 107.8 (d), 107.5 (d, 2C), 107.3 (d), 91.4 (d), 80.2 (d), 72.6 (d), 71.2 (d), 68.2 (d), 65.8 (t), 61.3 (q), 61.2 (q), 61.1 (q), 61.1 (q), 60.8 (q), 56.6 (q), 56.4 (q, 2C), 56.1 (q). IR (ATR) 3647–3170, 2943, 2845, 1717, 1591, 1395, 1340, 1219, 1103, 769 cm^{-1}. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{40}O_{18}Na$ 783.2112, found 783.2109.

Data for **22**: ^1H NMR of major isomer (500 MHz, $CDCl_3$, 21 °C) δ 7.33 (s, 1H), 7.33 (s, 2H), 7.06 (s, 1H), 5.49 (dd, *J* = 3.4, 2.9 Hz, 1H), 4.97 (dd, *J* = 10.3, 3.4 Hz, 1H), 4.85 (dd, *J* = 8.6, 8.3 Hz, 1H), 4.69 (ddd, *J* = 10.3, 8.3, 4.0 Hz, 1H), 4.63 (dd, *J* = 10.9, 5.7 Hz, 1H), 4.42 (ddd, *J* = 10.3, 8.6, 5.7 Hz, 1H), 3.94 (s, 3H), 3.94 (s, 3H), 3.92 (s, 9H), 3.91 (s, 3H), 3.91 (s, 3H), 3.69 (s, 3H), 3.69 (dd, *J* = 10.9, 10.3 Hz, 1H), 3.59 (s, 3H), 3.00 (d, *J* = 2.9 Hz, 1H), 2.86 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR of major isomer (126 MHz, $CDCl_3$, 20 °C) δ 168.2 (s), 167.4 (s), 166.0 (s), 153.4 (s), 153.2 (s, 2C), 153.0 (s), 152.6 (s), 152.2 (s), 145.3 (s), 143.9 (s), 143.0 (s), 125.7 (s), 125.6 (s), 124.1 (s, 2C), 123.1 (s), 107.8 (d), 107.4 (d), 107.2 (d, 2C), 89.9 (d), 81.1 (d), 73.7 (d), 69.6 (d), 66.1 (t), 65.4 (d), 61.3 (q), 61.1 (q), 61.1 (q), 60.9 (q), 60.8 (q), 56.5 (q, 2C), 56.4 (q), 56.1 (q). IR (ATR) 3647–3170, 2943, 2845, 1717, 1591, 1395, 1340, 1219, 1103, 769 cm^{-1}. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{40}O_{18}Na$ 783.2112, found 783.2103.

Isolation of dimeric acid anhydride (14): the experiment procedure of entry 5 in Table 1

To a stirred solution of (a*R*)-**12** including (a*S*)-**12** (38.8 mg, 30.7 μmol) and 2,6-lutidine (14.0 mg, 61.4 μmol) in toluene (10.2 mL) was added CMPI (15.7 mg, 61.4 μmol) at 100 °C. After the reaction mixture was stirred for 12 h at 100 °C, sat. NH_4Cl aq was added to the reaction mixture. The separated organic layer was successively washed with sat. NH_4Cl aq and brine. After the general drying procedure, the crude product was purified by preparative TLC (hexane/EtOAc = 8/1 to 5/1) to afford **13** (11.2 mg, 89.0 μmol, 29%, a*R*/a*S* = 3/1) as a colorless syrup and and **14** (13.6 mg, 5.4 μmol, 35%) as a pale yellow syrup.

Data for **14**: $[\alpha]_D^{25}$ –26.5 (*c* 0.24, $CHCl_3$).^1H NMR (500 MHz, $CDCl_3$, 20 °C) δ 7.53 (s, 2H), 7.52 (s, 2H), 7.40–7.03 (m, 72H), 6.79 (d, *J* = 6.9 Hz, 4H), 6.77 (d, *J* = 6.9 Hz, 4H), 5.02–4.70 (m, 30H), 4.54 (d, *J* = 10.3 Hz, 2H), 4.34 (d, *J* = 9.7 Hz, 2H), 4.33 (dd, *J* = 12.0, 4.0 Hz, 2H), 4.25 (dd, *J* = 12.0, 2.3 Hz, 2H), 3.35 (dd, *J* = 9.2, 8.6 Hz, 2H), 3.25 (ddd, *J* = 9.7, 4.0, 2.3 Hz, 2H), 3.13 (dd, *J* = 9.7, 8.6 Hz, 2H), 3.05 (ddd, *J* = 9.7, 9.2, 4.6 Hz, 2H), 2.85 (d, *J* = 4.6 Hz, 2H), 2.63–2.52 (m, 4H), 1.13 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 22 °C) δ 166.7 (s, 2C), 162.7 (s, 2C), 152.0 (s, 4C), 151.4 (s, 2C), 150.9 (s, 2C), 147.5 (s, 2C), 146.1 (s, 2C), 138.8 (s, 2C), 138.3 (s, 2C), 137.9 (s, 2C), 137.8 (s, 2C), 137.4 (s, 2C), 137.3 (s, 2C), 136.7 (s, 2C), 136.5 (s, 2C), 129.6 (s, 2C), 128.8–127.3 (overlapping 40 doublets: 16 peaks were observed, 80C), 126.7 (s, 2C), 125.0 (s, 2C), 123.4 (s, 2C), 112.3 (d, 2C), 112.1 (d, 2C), 86.1 (d, 2C), 85.4 (d, 2C), 81.3 (d, 2C), 77.5 (d, 2C), 75.7 (t, 2C), 75.5 (t, 4C), 75.2 (t, 2C), 75.1 (t, 2C), 74.6 (t, 2C), 71.1 (t, 2C), 70.8 (t, 2C), 70.2 (d, 2C), 64.2 (t, 2C), 25.0 (t, 2C), 15.1 (q, 2C). IR (ATR) 3628–3156, 3063, 3032, 2920, 2851, 1778, 1705, 1589, 1454, 1327, 1094, 735, 696 cm^{-1}. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{156}H_{142}O_{27}S_2Na$ 2533.9078, found 2533.9056.

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Keywords: neostrictinin • ellagitannins • 4,6-*O*-(*R*)-hexahydroxydiphenoyl bridge • two-step bislactonization • 2-chloro-*N*-methylpyridinium iodide

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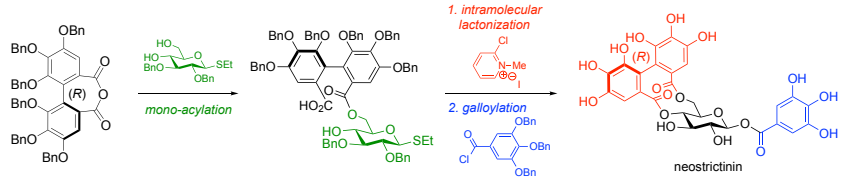

We achieved the first total synthesis of neostrictinin, a rare ellagitannin bearing a 4,6-*O*-(*R*)-hexahydroxydiphenoyl bridge, via two-step bislactonization. The latter intramolecular lactonization proceeded under Mukaiyama reaction conditions to form the uncommon bridge efficiently. Subsequent three-step reaction including anomeric galloylation completed the synthesis.

Total synthesis

Kazutada Ikeuchi, Tatsuya Ueji, Shintaro Matsumoto, Shinnosuke Wakamori, Hidetoshi Yamada**

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