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Divergent Synthesis of Four Monomeric Ellagitannins toward the Total Synthesis of an Oligomeric Ellagitannin, Nobotanin K

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Abstract: Oligomeric ellagitannins are challenging synthetic targets due to the need for an abundant supply of their composed monomeric ellagitannins and a synthetic methodology to connect them. This work focused on the divergent synthesis of the four monomeric ellagitannins from a common intermediate as a step toward the total synthesis of nobotanin K, a class of compounds that includes oligomeric ellagitannins and were isolated in plants belonging to the Melastomataceae family. Implementing our method, the four natural products could be easily supplied, suggesting that through this novel route, the total synthesis of nobotanin K could be achieved smoothly.

Keywords: ellagitannin; rugosin C; nobotanin D; casuarictin; pterocarinin C; divergent synthesis

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1. Introduction

Ellagitannins are a class of polyphenols, and more than a thousand such compounds have been isolated in nature (Figure 1) [1,2]. The basic structure of ellagitannins consists of esters of D-glucose with galloyl groups and hexahydroxydiphenoyl (HHDP, IUPAC named 4,4′,5,5′,6,6′-hexahydroxy-[1,1′-biphenyl]-2,2′-dicarbonyl) groups biosynthesized via the C–C coupling of two galloyl groups. Notably, approximately 40% of ellagitannins include C–O digallate structures, which are generated via the formation of a C–O bond between a galloyl group and a galloyl derivative such as the HHDP group. These major C–O digallate structures can lead to the oligomerization of monomeric ellagitannins, resulting in an increase in the structural diversity of ellagitannins.

Plants belonging to the Melastomataceae family produce a large of number of oligomeric ellagitannins. Currently, twenty-two compounds (nobotanins A–V) have been isolated, and all their structures have been determined. They comprise a monomeric ellagitannin (nobotanin D), eight dimeric ellagitannins (nobotanins A, B, F–I, O, and R), eight trimeric ellagitannins (nobotanins C, E, J, L–N, U, and V), and five tetrameric ellagitannins (nobotanins K, P, Q, S, and T) [3–13]. In bioactive studies conducted on these compounds, some of these oligomeric nobotanins exhibited remarkable activities, such as RNA tumor virus reverse transcriptase inhibition [14], antitumor activity [15], polyADP-ribose glycohydrolase inhibition [16], anti-HIV activity [17], and antiglycation activity [18]. These results indicate that nobotanins have the potential to become seed compounds for novel drug candidates.

The development of medicinal chemistry using bioactive nobotanins requires enough raw materials for preparing the desired compounds via chemical synthesis. However, examples of the total syntheses of oligomeric ellagitannins are limited to reports focusing on dimeric ellagitannins [19,20]. The reason appears to be that the divergent synthetic method of requisite monomeric ellagitannin fragments or their similar structure compounds for the synthesis of oligomeric ellagitannins has not been explored sufficiently. Herein, as part of the research effort dedicated to the total synthesis of oligomeric ellagitannins

among nobotanins, we report the divergent synthesis of four monomeric ellagitannins, which enables their production in satisfactory amounts.

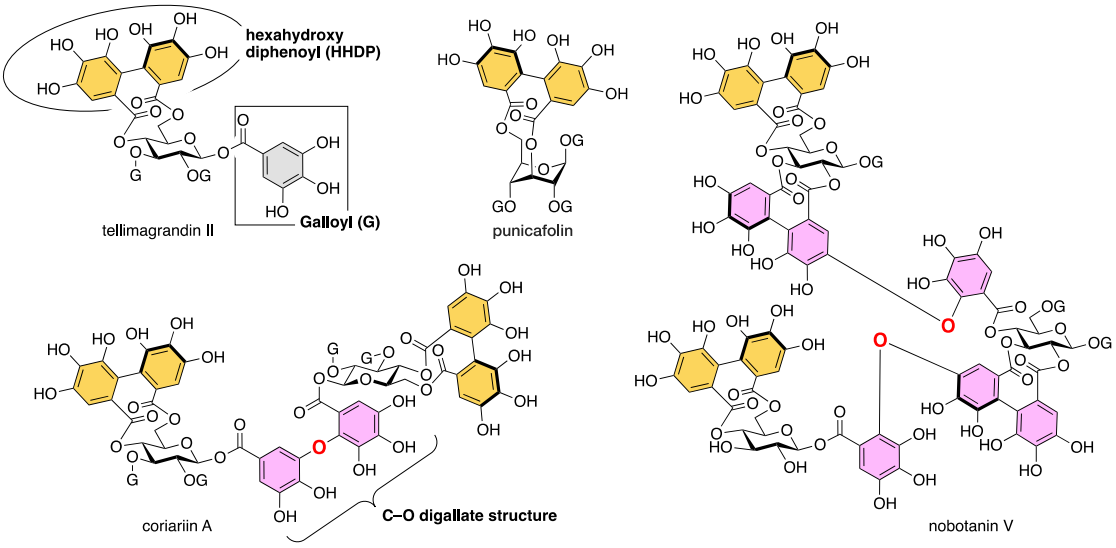


Figure 1. Representative structures of ellagitannins. G: galloyl; HHDP: hexahydroxydiphenoyl.

2. Results and Discussion

Among the nobotanins found in Melastomataceae, we selected nobotanin K (**1**) (Figure 2) as the target product because it is a tetrameric ellagitannin, wherein the component monomer structures are different, indicating that the establishment of the divergent synthesis of the four monomer fragments is essential for the total synthesis of **1**. The constituent four-component monomers commonly comprise an HHDP moiety, with (*S*)-axial chirality, which bridges between the second oxygen and third oxygen of glucose [7]. Therefore, the synthetic precursor of these four monomers should possess a 2,3-*O*-(*S*)-HHDP bridged glucose structure. The biosynthesis of **1** was assumed to involve the oligomerization of casuarictin (**2**) and pterocarinin C (**3**) [21]; thus, the analog sets of the two natural products as the precursors of the chemical synthesis of **1** would be appropriate. However, our goal was to divergently synthesize four monomeric ellagitannins; thus, we planned the synthetic strategy of **1** as illustrated in Figure 2. Nobotanin K (**1**) contained three C–O digallate structures, which were named the valoneoyl groups, where the hydroxy group at the 4-position of the HHDP group was connected to the C-2 carbon of the galloyl group. Although each connection pattern of the three valoneoyl groups was different, one of the HHDP moieties among them bridged between the 4-oxygen and 6-oxygen of glucose. Since we previously reported the synthesis of an ellagitannin comprising such a valoneoyl group [22], we decided to use a similar methodology for the construction of the same moiety in **1**. Thus, the upper dimeric unit in **1** was retro-synthesized to rugosin C (**4**) [23] (the compound colored in green in Figure 2—the relevant moiety in **1** was also highlighted in the same color) and nobotanin D (**5**) [24] (the structure colored in black in Figure 2), and we assumed that the connection between these two monomers would be achieved via esterification. Furthermore, we assumed that the dimeric unit in the lower half of the structure of **1** depicted in Figure 2 could be constructed via an approach similar to that implemented for the synthesis of C–O digallate structures; therefore, we envisioned casuarictin (**2**) [25] (the structure colored in fuchsia in Figure 2) and pterocarinin C (**3**) [26] (the structure colored in blue in Figure 2) to be the relevant synthetic precursors of **1**. This strategy would also be applied to the construction of the middle C–O bond. The four retro-synthesized monomeric ellagitannins (**2**–**5**) would be derived from thioglycoside **6**, which included the 2,3-*O*-(*S*)-HHDP bridge structure.

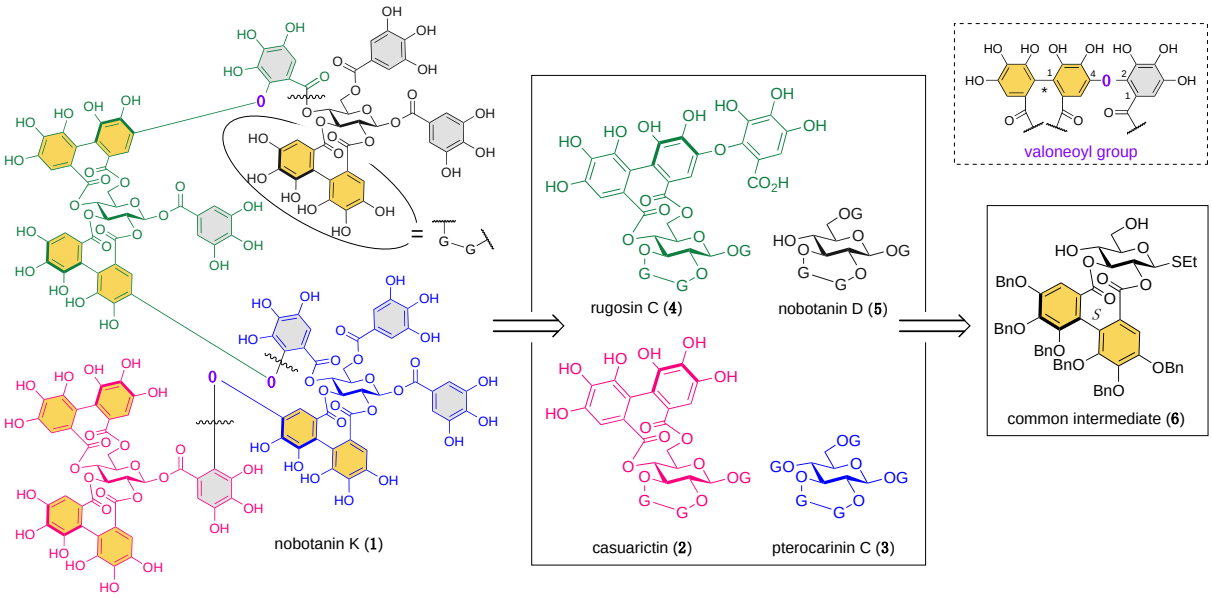
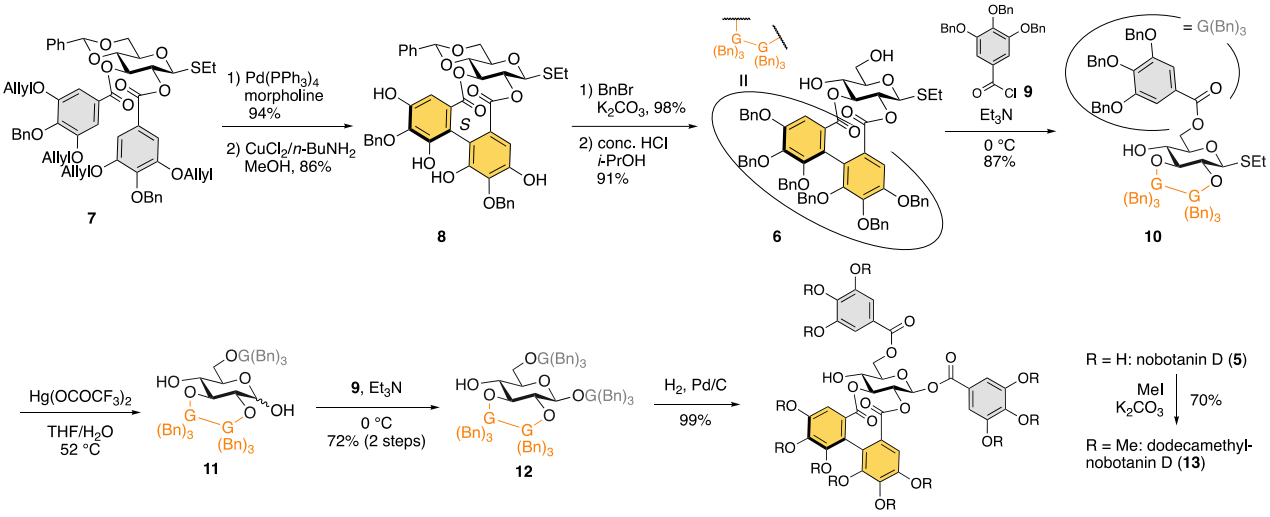


Figure 2. Structure of the tetrameric ellagitannin, nobotanin K (**1**), and this compound's retrosynthetic strategy. G–G: (*S*)-HHDP.

The common intermediate **6** in the synthesis of the four monomeric ellagitannins was prepared through the construction of the 2,3-*O*-(*S*)-HHDP bridge (Scheme 1). Thioglycoside **7**, which was easily prepared in five steps from D-glucose [27], was subjected to the removal of the four allyl groups, using tetrakis(triphenylphosphine)palladium(0) and morpholine, and to the $CuCl_2$/*n*-$BuNH_2$-mediated oxidative coupling [28] of the resulting tetraol, leading to the desired compound **8** being obtained in an 86% yield as a single isomer. This result was the same in our previous reports for the (*S*)-selective oxidative coupling of a 2,3-*O*-digalloylglucose derivative [20,27,29]. The (*S*)-axial chirality of **8** was confirmed via the transformation of **8** into the known compound (**S3**) [30] and comparison of the specific optical rotation value with the literature value (refer to Supplementary Materials for details). The two phenolic hydroxy groups of **8** were, subsequently, benzylated, and the removal of the benzylidene acetal under acidic conditions afforded diol **6**. Implementing the just-described four-step protocol, we succeeded in producing more than 7 g of compound **6**.

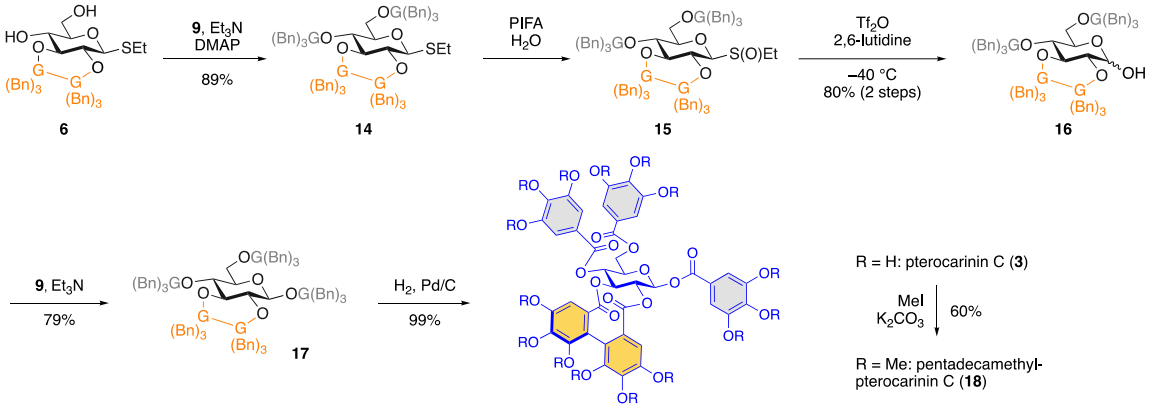


Scheme 1. Preparation of common synthetic intermediate **6** and total synthesis of nobotanin D (**5**).

With the common synthetic intermediate **6** in hand, the synthesis of nobotanin D (**5**) was first conducted (Scheme 1). The selective galloylation of the primary alcohol moiety of

diol **6** easily proceeded via the treatment of **6** with 4,5,6-*O*-tribenzylgalloyl chloride **9** [31] and triethylamine (Et_3N) at 0 °C to afford the monogallate **10** in an 87% yield. We then attempted to hydrolyze the *O*,*S*-acetal moiety at the anomeric position in **10**; however, under the typical reaction conditions using halogenating reagents [32–34], the desired reaction did not occur. By contrast, the use of mercury(II) trifluoroacetate [35] in aqueous tetrahydrofuran (THF) afforded hemiacetal **11**. The subsequent reaction of **11** with acyl chloride **9** and Et_3N at 0 °C induced the anomeric β-selective galloylation [36] of **11** to furnish **12** in a 72% yield over two steps. Finally, hydrogenolysis aimed at removing all benzyl (Bn) groups in **12,** producing nobotanin D (**5**). The ^{1}H-NMR spectrum and specific optical rotation value of the synthetic compound **5** were in good agreement with those of the natural product **5** (Table A1 in Appendix A). Permethylated compounds of ellagitannins were useful for the structural determination of the isolated/synthesized ellagitannin, because the NMR spectra of ellagitannins changed under the measurement conditions due to the presence of multiple phenolic hydroxy groups [22]. For the structure determination support of **5**, isolated or synthesized in the future, we prepared an unreported permethylated compound, dodecamethylnobotanin D (**13**).

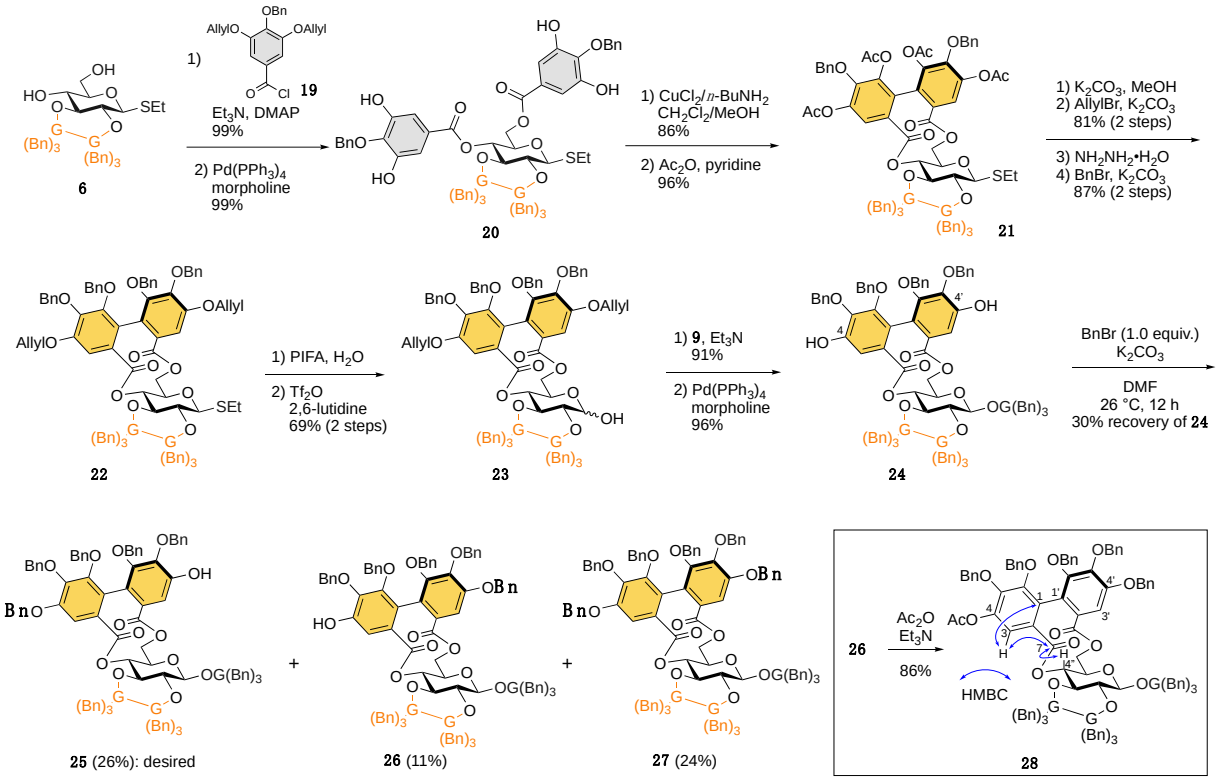
The synthetic strategy implemented to produce pterocarinin C (**3**) was described in Scheme 2. The reaction of diol **6** with **9** and Et_3N in the presence of *N*,*N*-dimethylaminopyridine (DMAP) afforded digallate **14** in an 89% yield. The subsequent hydrolysis of the anomer moiety in **14** proceeded smoothly via a two-step transformation procedure as follows [27,37]: After the oxidation of the sulfur atom of **14** using bis(trifluoroacetoxy)iodobenzene (PIFA) and water, the activation of the resulting sulfoxide **15** through trifluoromethanesulfonic anhydride (Tf_2O) and 2,6-lutidine at −40 °C induced an anomeric hydrolysis to produce hemiacetal **16** in an 80% yield over two steps. Finally, in a similar fashion to the synthesis of **5**, the implementation of a two-step protocol that included β-anomeric galloylation and hydrogenolysis ensured the completion of the total synthesis of **3**. The ^{1}H-NMR spectrum of the synthetic compound **3** was in good agreement with that reported for the natural product **3**. By contrast, the specific optical rotation value of the synthesized **3** differed from that of the natural product **3**. This inconsistency was attributed to the impurity of natural product **3**, because the ^{1}H NMR spectrum detected degradants that were perhaps generated during the preservation. Recently, the Kawabata group reported the total synthesis of **3** [38,39], and the specific optical value obtained for the synthesized compound was in good agreement with the value obtained in this study (Table A2 in Appendix A); therefore, we concluded that the structure of the herein-synthesized **3** was in no doubt correct. Since the fully methylated compound **3** was not reported, we exposed **3** to iodomethane and potassium carbonate to synthesize pentadecamethylpterocarinin C (**18**).



Scheme 2. Total synthesis of pterocarinin C (**3**).

We then turned our attention to the synthesis of two other natural products, casuarictin (**2**) and rugosin C (**4**) (Scheme 3). To construct a 4,6-*O*-(*S*)-HHDP bridge onto **6**, the introduction of two galloyl moieties using the treatment of **6** with acyl chloride **19** [40],

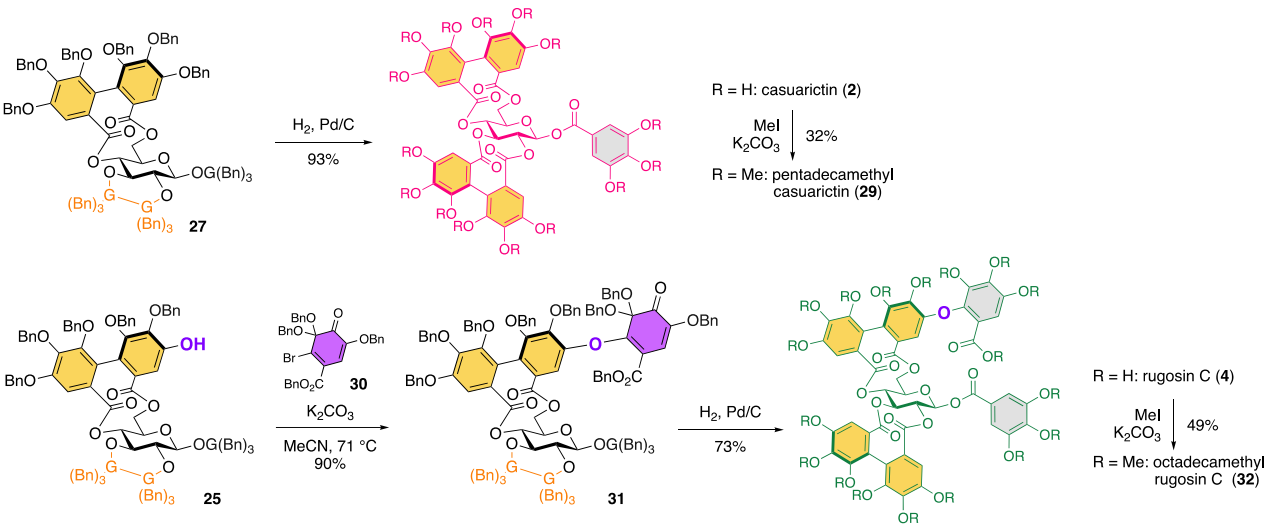
wherein the protection patterns of the two phenolic hydroxy groups differed from that of **9**, in the presence of Et_3N and DMAP, followed by the removal of the four allyl groups of the obtained digallate, afforded tetraol **20**. The subsequent oxidative coupling of **20** proceeded smoothly under our typical reaction protocol in dichloromethane/methanol [27], and the following acetylation provided tetraacetate **21**. To develop the synthesis of **4**, we next focused on the discrimination between the two phenolic hydroxy groups at the 4- and 4′-position in the 4,6-*O*-(*S*)-HHDP structure. Therefore, the two acetyl (Ac) groups in the 6-position and 6′-position of **21** were replaced by the Bn groups by implementing the following steps reported in [22]: the selective deprotection of two Ac groups at the 4-position and 4′-position under methanolysis conditions, the allylation of the resulting diol moieties, the removal of the remaining Ac groups using hydrazine, and the benzylation of the diol moieties generated, which afforded the diallyl-protected compound **22**. Similar to that implemented to transform **14** into **16** described in Scheme 2, hydrolysis of the *O*,*S*-acetal moiety in **22** delivered **23**, which was then subjected to the anomeric β-selective galloylation conditions followed by deallylation conditions, leading to the synthesis of diol **24**. The desired 4-Bn-protected compound **25** was then generated by controlling the number of equivalents of benzyl bromide added to the reaction mixture, similar to our previously reported reaction conditions [22]. Indeed, the addition of 1.0 equivalents of benzyl bromide afforded **25**, its isomer **26**, and the per-benzylated compound **27** in yields of 26%, 11%, and 24%, respectively, with the unreacted precursor **24** recovered in a 30% yield. The separation of these four compounds was achieved via silica gel chromatography purification using a mixture of *n*-hexane, ethyl acetate, and toluene as the eluent. The structure of **26** was determined with heteronuclear multiple-bond correlation spectroscopy (HMBC) analysis conducted on the acetylated compound **28** synthesized from isomer **26**, which indicated the correlations of H-3 to C-1 and of H-3 to C-7 on the HHDP structure, and that between C-7 and H-4″ in the glucose core.



Scheme 3. Preparation of phenol **25** toward the synthesis of rugosin C (**4**). DMF: dimethylformamide.

The syntheses of casuarictin (**2**) and rugosin C (**4**) are described in Scheme 4. The former was easily obtained from **27** via hydrogenolysis; notably, the ^{1}H NMR spectral

data and the specific optical rotation value recorded for the synthesized product **2** were in good agreement with the literature data (Table A3 in Appendix A) [25]. We also prepared pentadecamethyl casuarictin (**29**) via the treatment of **2** with iodomethane and potassium carbonate. On the other hand, the synthesis of **4** was realized by applying the method reported by our group for synthesizing C–O digallate structures [41–43]. Thus, the Michael addition of phenol **25** to orthoquinonemonoketal **30** [42,43], followed by the elimination of the bromide ion, produced **31** in a 90% yield. Hydrogenolytic conditions were adopted for the reductive aromatization of the orthoquinonemonoketal moiety, which occurred simultaneously with the removal of all the Bn groups to produce **4** in a 73% yield. Although the ^{1}H NMR spectral data recorded for the synthesized product **4** were not absolutely identified to those reported in the literature for the natural product [23], those of **32**, the permethylated derivative of the synthesized compound **4**, were also in good agreement with the literature data [3], confirming the structure of our synthetic compound **4** (Tables A4 and A5 in Appendix A).



Scheme 4. Total syntheses of casuarictin (**2**) and rugosin C (**4**).

3. Conclusions

We succeeded in performing the total synthesis of four monomeric ellagitannins via divergent synthesis. Among them, nobotanin D (**5**) and rugosin C (**4**) were the first example reports of the synthesis of these compounds. The bottom-up synthesis of the common intermediate **6** and discrimination of the two phenolic hydroxy groups in the 4,6-*O*-(*S*)-HHDP structure in **24** rendered this achievement possible. The synthetic methodology developed herein could contribute to the realization of the synthesis of various nobotanins, including nobotanin K (**1**), as well as the development of medicinal chemistry using the ellagitannin analog.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org3030022/s1.

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Data Availability Statement: Data are contained within Supplementary Materials.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Comparison of the spectral data between the synthetic and natural nobotanin D (**5**).

^{1}H NMR Data for Nobotanin D (5) in Acetone-d_6 + D_2O			
Assignment	**Natural Product**	**Synthetic Product**	**Δ(Natural–Syn.)**
	δ	**δ**	**δ**
galloyl	7.13	7.13	0.00
galloyl	7.12	7.12	0.00
HHDP	6.70	6.71	−0.01
HHDP	6.42	6.42	0.00
H-1	6.17	6.16	0.00
H-3	5.24	5.24	0.00
H-2	5.06	5.06	0.00
H-6	4.61	4.61	−0.01
H-6	4.46	4.46	0.00
H-5	4.08	4.08	0.00
H-4	4.00	4.00	−0.01
Specific optical rotation for nobotanin D (**5**) in MeOH (unit of *c*: mg/mL)			
natural product (*c* = 0.08, 25 °C)		synthetic product (*c* = 0.09, 25 °C)	
18		20	

Table A2. Comparison of the spectral data among the synthetic and natural pterocarinin C (**3**), and the literature data reported by the Kawabata group [38,39].

^{1}H NMR Data for Pterocarinin C (3) in Acetone-d_6					
	Natural Product	**Our Synthetic Product**	**Kawabata Group's Synthetic Product [38]**	**Δ(Natural–Ours)**	**Δ(Kawa.–Ours)**
Assignment	**δ**	**δ**	**δ**	**δ**	**δ**
galloyl	7.18	7.18	7.17	0.00	−0.01
galloyl	7.17	7.17	7.17	0.00	0
galloyl	7.14	7.14	7.15	0.00	0.01
HHDP	6.47	6.46	6.46	0.01	0
HHDP	6.44	6.43	6.44	0.01	0.01
H-1	6.36	6.36	6.35	0.00	−0.01
H-4	5.65–5.58	5.65–5.59	5.64–5.58	0–(−0.01)	(−0.01)–(−0.01)
H-3					
H-2	5.21	5.22	5.21	−0.01	−0.01
H-6	4.56	4.56	4.56	0.00	0
H-5	4.52	4.52	4.53–4.51	0.00	0
H-6	4.39	4.39	4.40	0.00	0.01
Specific optical rotation for pterocarinin C (**3**) in acetone (unit of *c*: mg/mL)					
natural product (*c* = 0.07, 25 °C)		Kawabata group [39] (*c* = 0.8, 20 °C)		ours (*c* = 1.0, 25 °C)	
18		59		56	

Table A3. Comparison of the spectral data between the synthetic casuarictin (**2**)and the literature data of **2** [25].

^{1}H NMR Data for Casuarictin (3) in Acetone-d_6			
Assignment	**Literature Data [25]**	**Synthetic Product**	**Δ(Lit.–Syn.)**
	δ	**δ**	**δ**
galloyl	7.18	7.18	0.00
HHDP	6.68	6.67	0.01
HHDP	6.55	6.54	0.01
HHDP	6.47	6.46	0.01
HHDP	6.38	6.37	0.01
H-1	6.22	6.22	0.00
H-3	5.45	5.45	0.00
H-6	5.37	5.37	0.00
H-4	5.18	5.19	−0.01
H-2	5.17	5.18	−0.01
H-5	4.50	4.51	−0.01
H-6	3.88	3.88	0.00
Specific optical rotation for casuarictin (**3**) in MeOH (unit of *c*: mg/mL)			
literature data [23] [a] (*c* = 0.2)		synthetic product (*c* = 0.12, 23 °C)	
35		26	

[a] Measured temperature was not recorded.

Table A4. Comparison of the ^{1}H NMR spectral data between the synthetic rugosin C (**4**) and the literature data of **4** [23].

^{1}H NMR Data for Rugosin C (3) in Acetone-d_6			
Assignment	**Literature Data [23]**	**Synthetic Product**	**Δ(Lit.–Syn.)**
	δ	**δ**	**δ**
galloyl	7.15	7.15	0.00
HHDP or valoneoyl	7.14	7.14	0.00
HHDP or valoneoyl	6.54	6.54	0.00
HHDP or valoneoyl	6.46	6.45	0.01
HHDP or valoneoyl	6.40	6.40	0.00
HHDP or valoneoyl	6.34	6.38	−0.04
H-1	6.18	6.19	−0.01
H-3	5.44	5.44	0.00
H-6	5.28	5.28	0.00
H-4	5.14	5.14	0.00
H-2	5.07	5.07	0.00
H-5	4.46	4.46	0.00
H-6	3.79	3.79	0.00

Table A5. Comparison of the ^{1}H NMR spectral data between the synthetic compound **32** and the literature data [3].

^{1}H NMR Data for Permethylated Rugosin C (32) in Acetone-d_6				
Assignment	**Number of Protons**	**Literature Data [3]**	**Synthetic Product**	**Δ(Lit.–Syn.)**
		δ	δ	δ
galloyl	2	7.31	7.32	−0.01
valoneoyl	1	7.25	7.25	0.00
HHDP and valoneoyl	1	6.85	6.83	0.02
	1	6.83	6.83	0.00
HHDP	1	6.69	6.69	0.00
valoneoyl	1	6.50	6.50	0.00
H-1	1	6.26	6.26	0.00
H-3	1	5.55	5.54	0.01
H-2	1	5.23	5.22	0.01
H-6	1	5.15	5.16	−0.01
H-4	1	5.06	5.07	−0.01
H-5	1	4.39	4.42	−0.03
O-Me	3	4.06	4.06	0.00
O-Me	3	3.90	3.90	0.00
O-Me	3	3.89	3.89	0.00
O-Me	3		3.89	0.00
O-Me	6	3.87	3.87	0.00
O-Me	3	3.86	3.86	0.00
O-Me	3	3.85	3.86	−0.01
O-Me	3	3.83	3.83	0.00
O-Me	3	3.80	3.82	−0.02
O-Me	3		3.80	0.00
O-Me	3	3.76	3.77	−0.01
O-Me	3		3.76	0.00
O-Me	3		3.76	0.00
O-Me	3	3.74	3.74	0.00
O-Me	3	3.70	3.70	0.00
O-Me	3	3.66	3.65	0.01
O-Me	3	3.58	3.60	−0.02

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