Synthesis of Trideca-*O*-methyl-α-pedunculagin. Diastereo-Favoritism Studies on Intramolecular Ester-Cyclization of Axially Chiral Diphenic Acids with Carbohydrate Core

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Total synthesis of trideca-*O*-methyl-α-pedunculagin was achieved by a simple sequence. The key step is the synthesis of methyl 4,6-*O*-benzylidene-2,3-*O*-[(*S*)-4,4′,5,5′,6,6′-hexamethoxydiphenoyl]-α-D-glucopyranoside through intramolecular ester-cyclization of racemic hexamethoxydiphenoyl chloride with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside at the 2,3-position. The diastereoselectivity results obtained in the intramolecular cyclization of hexamethoxydiphenic acid to the carbohydrate core raises a very interesting point in considering the pathway of (*R*)-diphenic acid biosynthesis.

Introduction

The ellagitannins,[1] the structures of which bear at least one axially chiral diphenic acid unit, are found in plants and are reported to have such important biological activities as anti-HIV,[2a] antitumor,[2b,c] and anti-topoisomerase[2d] activity. Although there has been increased interest in the synthesis of axially chiral biaryl compounds,[3,4] few syntheses of ellagitannin and the per-*O*-methylellagitannins have appeared.[5] The single reported example of ellagitannin synthesis was tellimagrandin I by Feldman et al. in 1994.[5a] Syntheses of per-*O*-methylellagitannins were accomplished by three groups that same year, Feldman's,[5a] Meyers',[5c] and Lipshutz's[5d] using different strategies.

Pedunculagin[6] and platycaryanin D[7] are naturally-occurring compounds of the ellagitannin family and each contains two chiral hexahydroxydiphenoyl (HHDP) units at the 2,3- and 4,6-positions with opposite stereochemistry. Pedunculagin has two (*S*)-HHDP groups, whereas platycaryanin D possesses the alternative (*R*)-HHDP moieties. How is the stereochemistry of these axially chiral diphenic acid moieties controlled during ellagitannin biosynthesis? This is one of the key points in any consideration of the biosynthetic mechanism of ellagitannins.[8,9] Haslam[8b] and Schmidt[8a] earlier proposed that the sugar core acts as a template in the oxidative coupling of two galloyl groups to form an (*S*)-HHDP acid moiety. This proposal is supported by the work of Feldman in the synthesis of tellimagrandin I, where only the (*S*)-diphenic acid unit is formed in the oxidative coupling step.[5a,b] A separate biosynthetic pathway might be operative in the (*R*)-HHDP series. We attempted to synthesize trideca-*O*-methyl-α-pedunculagin (**1**) and trideca-*O*-methyl-α-platycaryanin D (**2**) using a strategy that involves an optical resolution of axially chiral biaryls based on kinetic differences in ester-cyclization with a glucose template.[4] The total synthesis of trideca-*O*-methyl-α-pedunculagin (**1**) has thus been accomplished. Although that of trideca-*O*-methyl-α-platycaryanin D (**2**) was unsuccessful using this strategy, we obtained very interesting results that raised various suggestions about the pathway of (*R*)-HHDP acid biosynthesis.

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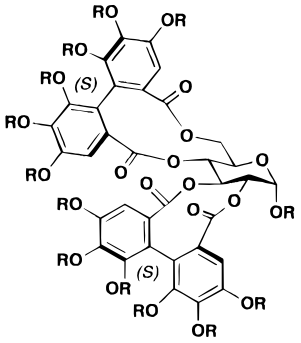
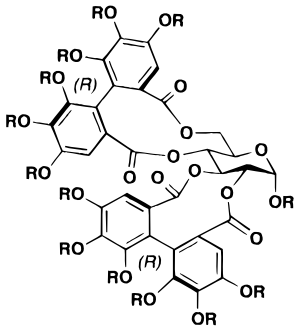


Trideca-O-methyl-α-Pedunculagin (1) (R=Me)

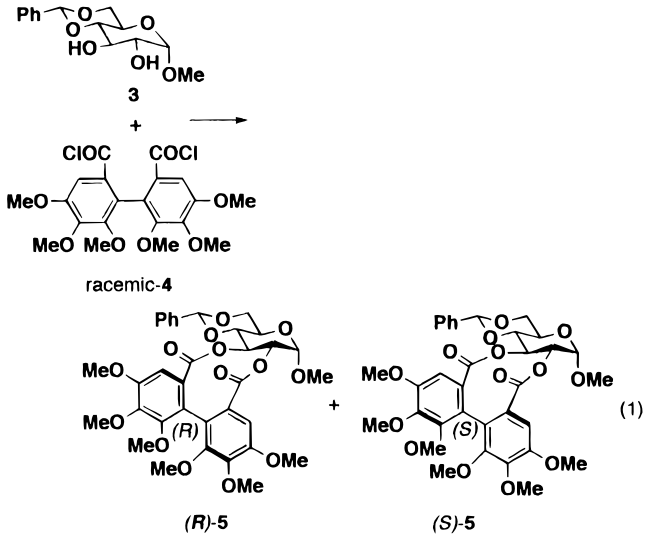


Trideca-O-methyl-α-Platycaryanin D (2) (R=Me)

Our strategy for the synthesis of trideca-*O*-methyl-α-pedunculagin (**1**) is a very simple one as illustrated in Scheme 1. Compound **1** contains two (*S*)-4,4′,5,5′,6,6′-hexamethoxydiphenoyl (HMDP) units, and therefore the first and key step is the diastereoselective ester-cyclization of racemic biaryl **4** with glucose template **3**. After deprotection of the 4,6-*O*-benzylidene group of (*S*)-**5**,[10] the resulting sugar can then be attached to the enantiomerically pure (*S*)-HMDP acid at the C4 and C6 positions, giving **1**. Thus, in just five steps the synthesis of an optically pure trideca-*O*-methyl-α-pedunculagin is accomplished.

Results and Discussion

1. Kinetic Resolution of 4,4′,5,5′,6,6′-Hexamethoxydiphenic Acid. Earlier study of ester-cyclization of racemic **4** with the glucose derivative **3** at the 2,3-position revealed that the proper combination of solvent system and base provide the cyclized ester (*R*)-**5**[10] diastereoselectively (eq 1).[4] The ratio of diastereoisomers strongly



(1)

depends on the reaction conditions as summarized in Table 1. Use of toluene as solvent (0.01 M) in the presence of sodium hydride as base gave (*R*)-**5** with extremely high diastereoselectivity (>1500:1)[11] in 37% isolated yield; this corresponded to 74% in theoretical yield. Although byproducts, mainly glycoside **7**, were

Scheme 1

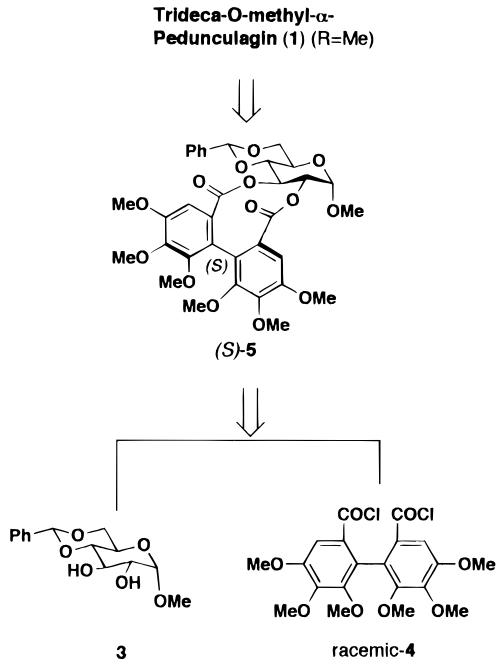


Table 1. Diastereoselectivity in the Preparation of 2,3-*O*-Hexamethoxydiphenoyl-α-D-glucopyranoside (5)

entry	conditions	% yield of (*R*)-**5**	% yield of (*S*)-**5**	ratio[a] (*R*)-**5**:(*S*)-**5**
1	NaH, toluene (0.01M), 0 °C−rt	37 (74%)	trace	>1500:1[b]
2	Et_3N, THF (0.01 M), rt	3 (6)	12 (24)	1:4.4
3	DMAP, toluene (0.01 M), rt	27 (54)	22 (44)	1.2:1

[a] The ratio was determined by HPLC analysis. [b] No isomer was detected. See experimental section.

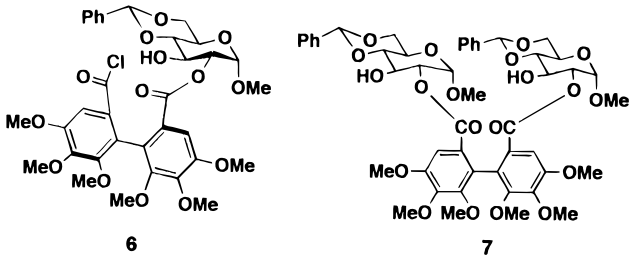


Figure 1.

formed in this reaction, the isolation of product **5** was accomplished very easily by silica gel glash column chromatography. HMDP acid (**8**) {38% ee (*S*)} was recovered from the byproducts through hydrolysis and then recycled after racemization in refluxing aqueous sodium hydroxide.[12]

Unfortunately, the system providing (*S*)-**5** was found to be inadequate compared to that providing (*R*)-**5**. The best selectivity obtained was 4.4:1 when a combination of THF (0.01M) and triethylamine (Et_3N) was employed for ester-cyclization, and many byproducts were produced in this system. Although these conditions provided (*S*)-**5** with the best diastereoselectivity, the chemical yield was

(10) The (*R*) and (*S*) nomenclature used prior to the compound refers to the absolute stereochemistry of the chiral axis of the biaryl unit.

(11) The ratio was determined by HPLC analysis. No isomer was detected in the reaction in which the best regioselectivity was recorded. Diastereoisomers of (*R*)-**5** and (*S*)-**5** can be isolated using silica gel TLC; we obtained (*R*)-**5** and (*S*)-**5** in a separate run under the same reaction conditions in which the ratio was calculated as 1520:1. Based on this result, the ratio was stated to be more tha 1500:1.

(12) The half-life for racemization of HMDP acid **5** was reported as 14.75 hr in refluxing aqueous alkali; Schmidt, O. T.; Demmler, K. *Liebigs Ann. Chem.* **1954**, *585*, 179.

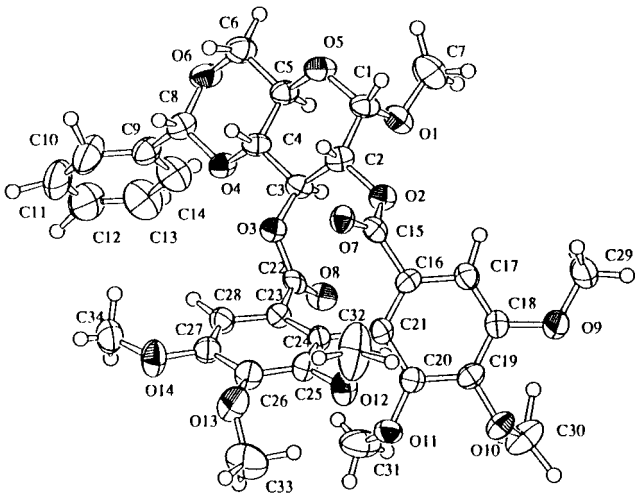


Figure 2. The ORTEP of (*S*)-**5**.

not sufficient. A combination of dichloromethane (CH_2Cl_2) and 4-(dimethylamino)pyridine (DMAP) was found to produce (*S*)-**5** in the highest yield, though no diastereoselectivity was observed under these reaction conditions. Reaction of racemic **4** with commercially available **3** in CH_2Cl_2 in the presence of DMAP at room temperature gave (*S*)-**5** in 22% yield, which corresponds to 44% theoretical yield, as a colorless prismatic crystal. We were able to confirm its absolute stereochemistry by X-ray crystallography. The axis angle of the two biphenyl groups in (*S*)-**5** was determined to be 63.7°, and the ORTEP drawing is shown in Figure 2.[13] To the best of our knowledge, this is the first example of an axis angle determination in HMDP groups which are bound to O-2/O-3 positions of a sugar core.

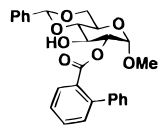
(*R*)-**5** was obtained with extraordinarily high selectivity, while diastereoselective preparation of (*S*)-**5** was unsuccessful. What caused this great difference in diastereoselectivity? The failure of the kinetic resolution of (*S*)-diphenic acid seems particularly instructive in the prediction of the biosynthetic pathway of the (*R*)-diphenic acids. Molecular mechanics calculations of (*S*)-**5**,[10] (*R*)-**5**,[10] (*S*)-**6**,[10] and (*R*)-**6**[10] were undertaken based on the results of X-ray crystallographic analysis of (*S*)-**5**. Because compound **7** was obtained as the major byproduct, we assumed that the reaction took place first at the C-2 position of **3** and that this was followed by an intramolecular esterification.[14] Compound **6** is, therefore, the intermediate of the ester-cyclization of glucose template **3** and acyl chloride **4**. The MacroModel program (version 4.5)[15] was employed to calculate the steric energy of (*R*)-**5** {278.8 kJ mol^{-1}}, (*S*)-**5** {257.2 kJ mol^{-1}}, (*R*)-**6** {143.3 kJ mol^{-1}}, and (*S*)-**6** {132.4 kJ mol^{-1}}.[10] Calculations suggested that both *S*-isomers, **5** and **6**, are sterically more stable than the corresponding *R*-isomers. The energy-minimized structures of (*R*)-**6** and (*S*)-**6** revealed the interesting fact that, between the two, a large difference in the distance between the hydroxyl group at the 3-position of the sugar core and the acyl carbon moiety of the biphenyl group exists (Figures 3, parts a and b). The distance in (*S*)-**6** was 5.640 Å (Figure 3a), whereas that of (*R*)-**6** was only 3.713 Å (Figure 3b). This distance in (*S*)-**6** is obviously too great to permit a cyclization reaction of these functional groups, though this isomer is more stable thermodynamically than the corresponding isomer, (*R*)-**6**. The results of calculation seem to explain well our observations of kinetically controlled diastereoselectivity.

Among the ellagitannins that have been isolated, the chirality of the HHDP group in the glucopyranose 2,3- and or 4,6-positions is entirely of the (*S*)-series, with rare exceptions.[16] The proposed mechanism for biosynthesis of the (*S*)-diphenic acids is oxidative coupling of two galloyl groups,[9] in which the sugar core acts as a template. Our esterification seems to suggest that a separate biosynthetic pathway for the (*R*)-diphenic acid series could be operative. An HHDP group may be esterified onto the sugar core first at the 2-position then cyclized kinetically at the 3-position in diastereoselective fashion. Results from both experiment and calculation lend credence to this second pathway for the biosynthesis of glucopyranoside-derived ellagitannins containing the (*R*)-HHDP moiety. Isomerization of HHDP acid was reported;[12] however, it seems difficult to invoke to explain the formation of the sterically unfavored (*R*)-HHDP acids. The present study seems to offer a more plausible explanation of the biosynthesis of the less favored (*R*)-diphenic acid.

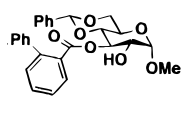
2. Synthesis of Trideca-*O*-methyl-α-Pedunculagin. On the basis of the conditions that provide the key intermediate (*R*)-**5** or (*S*)-**5**, we attempted to synthesize trideca-*O*-methyl-α-pedunculagin (**1**) and its atropisomer trideca-*O*-methyl-α-platycaryanin D (**2**). Because the (*S*)-diphenoyl moiety is found in many natural ellagitannins, the synthesis of trideca-*O*-methyl-α-pedunculagin (**1**) was first examined (Scheme 2). Hydrolysis of (*S*)-**5** with potassium *tert*-butoxide[5c] gave (*S*)-hexamethoxydiphenic acid (**8**) {$[\alpha]^{20}_D$ −26.2° (*c* 1.23, EtOH)} in quantitative yield. Removal of the benzylidene group of (*S*)-**5** under acidic conditions released diol (*S*)-**9**[10] in 83% yield. We initially attempted to combine (*R*)-**8** with diol (*R*)-**9**,[10] using DCC;[5d] none of the desired **1** was produced but a complex mixture was obtained. Esterification of (*S*)-**9** was found to proceed using acyl chloride (*S*)-**4**, instead of (*S*)-**8**. The reaction requires an elevated temperature, no desired compound being obtained when the reaction was carried out at room temperature. Synthesis of (+)-trideca-*O*-methyl-α-pedunculagin (**1**) was thus accomplished by a one-pot procedure in which (*S*)-**8** was first

(13) The authors have deposited coordinates for structure (*S*)-**5** with the Cambridge Data Centre. The coordinate can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

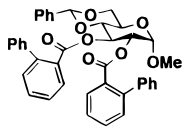
(14) Model reaction of 2-phenylbenzoyl chloride (**12**) with sugar **3** also seemed to support this idea. Glucose **3** was reacted with **12** (1 equiv) under the same reaction conditions in entry 1 in Table 1. The esters produced were 2-benzoate (84%), 3-benzoate (5%), and 2,3-dibenzoate (3%). On the other hand, the reaction was carried out under the conditions in entry 3 in Table 1 giving 2-benzoate (36%) and 2,3-dibenzoate (28%). In both reactions, the esterification seemed to take place at the 2-position, and 3-benzoate was derived from 2-benzoate through migration by silica gel TLC monitoring experiments. The mechanistic study of this regioselective esterification of glucose **3** is now in progress.



2-Benzoate



3-Benzoate



2,3-Dibenzoate

(15) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(16) Gupta, R. K.; Al-Shafi, S. M. K.; Layden, K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2525.

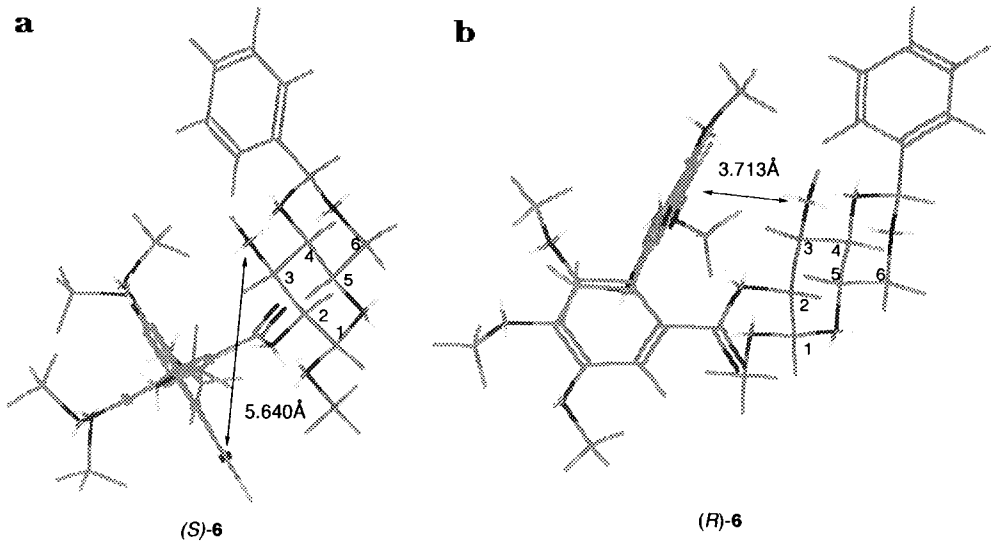
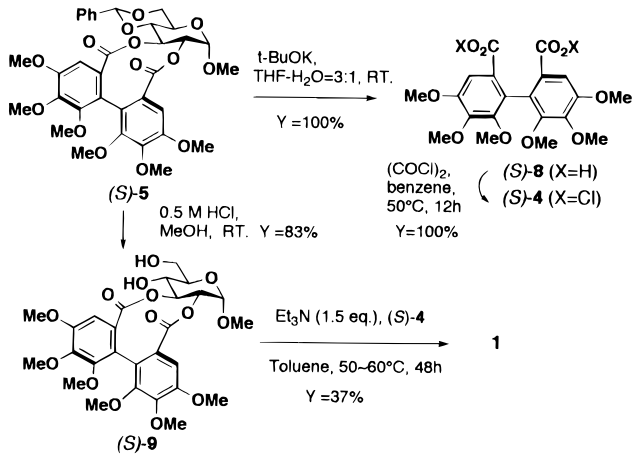
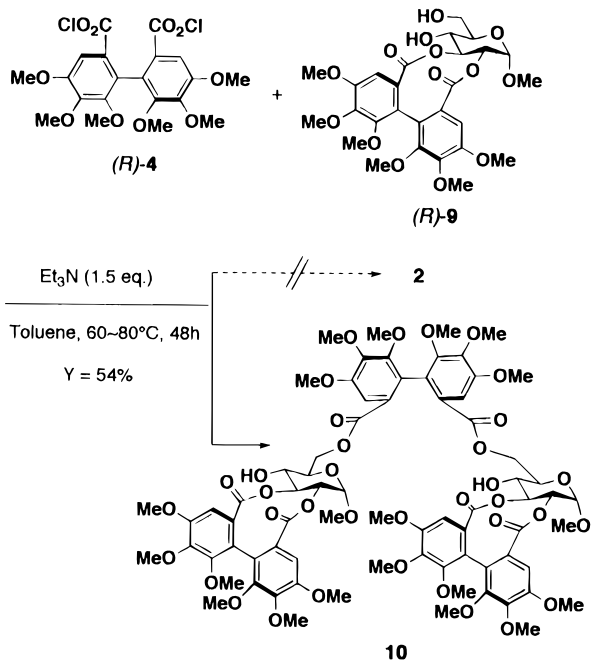


Figure 3.

Scheme 2



Scheme 3



converted to acyl chloride (*S*)-**4** and was then reacted with (*S*)-**9** in the presence of Et_3N in toluene at 50−60 °C for 48 h. This gave **1** {$[\alpha]^{22}_D$ +22.8° (*c* 0.73, acetone), lit.,[6b] +27.4°} in 37% yield after silica gel flash column chromatography.

In light of the highly diastereoselective esterification of axially chiral biaryl to give (*R*)-**5**, we expected that the synthesis of trideca-*O*-methyl-α-platycaryanin D (**2**) would be conveniently achieved. (*R*)-**5** was hydrolyzed to (*R*)-**9** {$[\alpha]^{20}_D$ +26.2° (*c* 1.23, EtOH)} in quantitative yield. With the completion of the lower portion of **2**, we next turned our attention to attaching the upper block. A coupling reaction was attempted with (*R*)-**4** and (*R*)-**9** under the same reaction conditions as described for the synthesis of trideca-*O*-methyl-α-pedunculagin (**1**). However, the final stage of the synthesis of **2** had the unexpected result that none of the desired product, **2**, and only dimeric compound **10**, was isolated as a characterizable compound (Scheme 3). Apparently, the C-6 position of **9** is more highly reactive than the C-4 position; hence intermolecular reaction proceeded preferentially through the intermediate **11** rather than intramolecular cyclization. Ironically, the preference of hexamethoxydiphenic acid unit for the sugar core's C-6 and C-4 positions worked unfavorably in the synthesis of **2**.

MacroModel (version 4.5) was again employed to calculate the steric energy of (*S*,*S*)-**11** {544.33 kJ mol^{-1}} and (*R*,*R*)-**11** {565.46 kJ mol^{-1}}.[10] Energy-minimized structures of (*S*,*S*)-**11** and (*R*,*R*)-**11** are shown in Figures 4, parts a and b. The findings seemed to explain the unexpected result. Like compound **6**, the (*S*,*S*)-isomer of **11** was found to be sterically more stable than the corresponding (*R*,*R*)-isomer. This time there was no marked difference in the distance between the hydroxyl group of the sugar and the acyl carbon moiety of the biphenyl group for the two isomers. A most remarkable difference is found in their geometry as shown in Figures 4, parts a and b. The biphenyl group of the right portion of (*R*,*R*)-**11** seems to prevent the hydroxyl and the acyl groups from coming close together, leading to dimeric compound **10** (Figure 4b). The results of the calculation explain why cyclized product **1** was obtained from (*S*,*S*)-**11**, and why increased temperature was essential to complete the cyclization. Thus a different strategy will be required to accomplish the synthesis of trideca-*O*-methyl-α-platycaryanin D.

The strategy we employed was found applicable to a simple synthesis of the (*S*)-series of the per-*O*-methylellagitannins. The present findings offer new and plausible

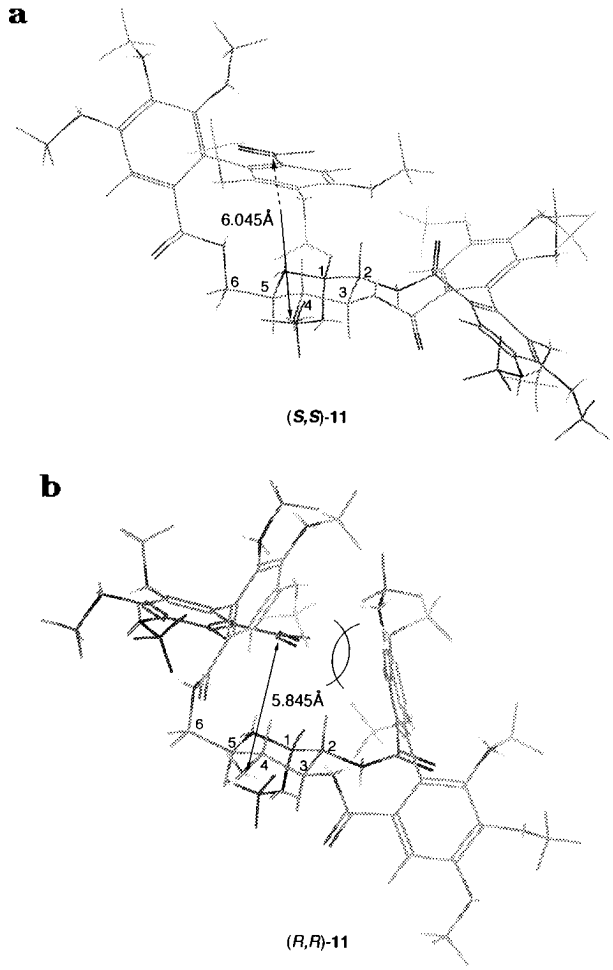


Figure 4.

ideas concerning the biosynthesis of the less favored ellagitannins having the (*R*)-HHDP moiety. Our methodology has also proven the importance of sugar as a resolving reagent of axially chiral biaryl compounds.

Experimental Section

General Procedures. Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Wako gel C-300 and Wako gel B5F were used for flash column chromatography and thin-layer chromatography (TLC), respectively. Melting points are uncorrected. Chemical shifts are expressed in δ value (ppm) downfield from tetramethylsilane (TMS) in $CDCl_3$ as an internal reference.

(±)-4,4′,5,5′,6,6′-Hexamethoxy-2,2′-diphenic Acid Chloride (4). To a suspension of ellagic acid (12.3 g, 40.7 mmol) in water (240 mL) were added tetrabutylammonium iodide (750 mg, 5 mol %) and dimethyl sulfate (40 mL, 431 mmol) at rt. To this suspension was slowly added KOH (40 g, 610 mmol) in water (80 mL) over 3 h under vigorous stirring, and the mixture was heated under reflux for 12 h. After being cooled to rt, the mixture was acidified with concd HCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated giving a crude solid (11.4 g). To a solution of the above crude solid in DMF (100 mL) was added NaH (6.7 g, 60% in mineral oil, 168 mmol) at 0 °C in several portions. After stirring the reaction mixture for 30 min, methyl iodide (14.0 mL, 224 mmol) was added and left stirring at rt overnight. The reaction was quenched by addition of 2 M HCl at 0 °C and the reaction mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$), evaporated, and chromatographed on a SiO_2 flash column using hexane and ethyl acetate (3:1) as an eluent, giving dimethyl hexamethoxydiphenoate in 43% yield (7.88 g): mp 80 °C; *Rf* 0.29, hexane/ethyl acetate (2:1); ^{1}H NMR (100 MHz, $CDCl_3$) δ 3.6 (s, 12 H), 4.1 (s, 12 H), 7.7 (s, 2 H); IR (KBr) 3600, 2950, 1720, 860, 730 cm^{-1}. To a solution of dimethyl hexamethoxydiphenoate (2.31 g, 5.1 mmol) in THF (15 mL) were added MeOH (5 mL), water (5 mL), and NaOH (841 mg, 20.4 mmol) at rt. The mixture was stirred under reflux for 16 h. After being cooled to rt, the mixture was acidified with 6 M HCl and extracted with CH_2Cl_2. The aqueous portion was saturated with NaCl and extracted again with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated, and the residue was recrystallized from ether to yield diacid **6** (2.06 g, 96%) as an off-white solid. A mixture of **6** (2.08 g, 4.9 mmol), oxalyl chloride (2.29 g, 19.6 mmol), and benzene (25 mL) was gradually heated to boiling, whereupon the acid chloride dissolved. After refluxing for 19 h, the solvent was removed *in vacuo* and the residue was recrystallized from a mixed solvent of ether and hexane to give **4** (1.85 g, 82%) as colorless plates: mp 81 °C (from ether/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.60 (s, 3 H), 3.97 (s, 6 H), 3.98 (s, 6 H), 7.60 (s, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.1, 60.7, 60.9, 112.4, 126.0, 127.2, 147.5, 150.9, 152.4, 166.0; IR (KBr) 2950, 1760, 1580, 930, 820 cm^{-1}. Anal. Calcd for $C_{20}H_{20}Cl_2O_8$: C, 52.30; H, 4.39. Found: C, 52.32; H, 4.38.

Methyl 4,6-*O*-Benzylidene-2,3-*O*-[(*R*)-4,4′,5,5′,6,6′-hexamethoxydiphenoyl]-α-D-glucopyranoside: (*R*)-**5**. To a suspension of NaH (49 mg, 1.2 mmol) in toluene (5 mL) was added **3** (170 mg, 0.6 mmol) at rt, and the mixture was stirred for 10 min and diluted with toluene (15 mL). To this was added dropwise a toluene (10 mL) solution of **4** (138 mg, 0.3 mmol) at 0 °C, and the mixture was warmed allowed to rt for 2.5 h with stirring. The reaction was quenched by addition of aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), evaporated, and chromatographed on a SiO_2 flash column using a mixed solvent of hexane and ethyl acetate (3:1) as an eluent, giving (*R*)-**5** as a colorless plate in 38% yield (76 mg, 0.114 mmol). No isomer was detected by HPLC analysis using Finepak SIL (JASCO, ∅4.6 mm × 250 mm, hexane: ethyl acetate = 2:1) under constant flow rate: 1 mL/min at 25 kg/cm^2. t_R of (*R*)-**5**: 18.4 min. (*S*)-**5**: 24.3 min. $k'_{((R)\text{-}5} = 5.1$, $k'_{((S)\text{-}5)} = 7.1$, $\alpha = 1.4$. Diasteroisomers of (*R*)-**5** and (*S*)-**5** can be isolated using silica gel TLC; we obtained (*R*)-**5** (836.00 mg) with (*S*)-**5** (0.55 mg) in a separate run under the same reaction conditions in which the ratio was calculated as 1520:1 in 31% chemical yield: mp 188−190 °C (from ether); *Rf* 0.47, hexane/ethyl acetate (1:1); $[\alpha]^{20}_D$ +116° (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29 (s, 3 H), 3.54 (s, 3 H), 3.63 (s, 3 H), 3.78−3.82 (m, 3 H, Glu H-4, H-5, H-6), 3.84 (s, 3 H), 3.94 (s, 6 H), 3.98 (s, 3 H), 4.28 (dd, 1 H, *J* = 3.4, 9.2 Hz, Glu H-6), 4.81 (dd, 1 H, *J* = 3.7, 9.2 Hz, Glu H-2), 4.86−4.92 (m, 1 H, Glu H-3), 4.92 (d, 1H, *J* = 3.7 Hz, Glu H-1), 5.56 (s, 1 H) 6.68 (brs, 1 H), 7.36−7.38 (m, 3 H), 7.48−7.49 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.5, 55.9, 60.8, 61.0, 62.7, 68.5, 74.9, 75.8, 78.0, 98.0, 101.4, 104.9, 109.9, 121.8, 124.0, 125.1, 125.7, 126.0, 128.1, 129.1, 136.9, 143.7, 152.3, 152.5, 152.7, 152.9, 166.3, 168.5; IR (KBr) 3450, 2950, 1740, 1390, 1140, 980, 860 cm^{-1}. Anal. Calcd for $C_{34}H_{36}O_{14}$: C, 61.07; H, 5.43. Found: C, 60.67; H, 5.49.

Methyl 4,6-*O*-Benzylidene-2,3-*O*-[(*S*)-4,4′,5,5′,6,6′-hexamethoxydiphenoyl]-α-D-glucopyranoside: (*S*)-**5**. To a solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **3** (1.23 g, 4.4 mmol) and DMAP (3.23 g, 26.4 mmol) in CH_2Cl_2 (340 mL) was slowly added a CH_2Cl_2 (100 mL) solution of **4** (2.0 mg, 4.4 mmol) (1 h) at 0 °C, and the mixture was stirred for 48 h at rt. The reaction mixture was quenched by addition of crushed ice, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to afford a crude solid which was purified by chromatography on a SiO_2 flash column using hexane/ethyl acetate (3:1), giving (*R*)-**5** (688 mg, 1.02 mmol, 23%) and (*S*)-**5** (648 mg, 0.968 mmol, 22%). Glycoside **7** was obtained as a major byproduct (314 mg, 0.325 mmol). (*S*)-**5**: mp 140 °C (recrystallized from methanol and ether); *Rf* 0.39, hexane/ethyl acetate (1:1); $[\alpha]^{20}_D$ +3.9° (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.61 (s, 3 H), 3.67 (s, 3 H), 3.84 (t, 1 H,

J = 10.4 Hz, Glu H-5), 3.88 (dd, 1 H, J = 9.9, 10.4 Hz, Glu H-4), 3.89 (s, 3 H), 3.93 (s, 6 H), 3.94 (s, 3 H), 3.98 (dd, 1 H, J = 4.6, 10.4 Hz, Glu H-6), 4.34 (dd, 1 H J = 4.6, 10.4 Hz, Glu H-6), 4.98 (d, 1 H, J = 3.4 Hz, Glu H-1), 5.21 (dd, 1 H, J = 3.4, 9.8 Hz, Glu H-2), 5.58 (s, 1H), 5.64 (t, 1H, J = 9.8 Hz, Glu H-3), 6.771 (s, 1H), 6.773 (s, 3 H), 7.39−7.40 (m, 3 H), 7.50−7.52 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.8, 56.1, 60.3, 60.6, 60.9, 61.6, 62.8, 68.2, 68.7, 74.3, 80.9, 97.1, 101.7, 104.7, 109.6, 124.6, 126.3, 128.1, 129.0, 129.2, 136.8, 137.0, 146.0, 151.1, 152.4, 153.0, 167.0, 167.9; IR (KBr) 3500, 2950, 1760, 1330, 920, 760 cm^{-1}.

Major byproduct 7: *Rf* 0.38 hexane/ethyl acetate (1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.65 (brs, 2 H, OH), 3.11 (s, 6 H), 3.32 (dt, 2 H, J = 4.6, 9.2 Hz, Glu H-3), 3.47 (s, 6 H) 3.56−3.80 (m, 6 H, Clu H-3, H-4, H-5), 3.79 (s, 6 H) 3.80 (s, 6 H), 4.07 (m, 2 H, Glu H-6) 4.64 (d, 2 H, J = 3.7 Hz, Glu H-1) 4.70 (dd, 2 H, J = 3.7, 9.2 Hz, Glu H-2), 5.32 (s, 2 H), 7.13−7.29 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.9, 56.2, 60.4, 60.7, 61.7, 68.2, 68.8, 74.4, 81.0, 97.2, 101.8, 109.6, 124.6, 126.2, 126.4, 128.2, 129.1, 137.0, 146.0, 151.2, 152.4, 167.1; IR (KBr) 3500, 2950, 1710, 1280, 920, 870, 750 cm^{-1}.

(*S*)-4,4′,5,5′,6,6′-Hexamethoxy-2,2′-diphenic acid: (*S*)-**8**.[5c,d] A potassium *tert*-butoxide (171 mg, 1.5 mmol) solution in a mixed solvent of THF (10 mL) and water (27 mg, 1.5 mmol) was stirred at rt for 5 min, and then (*S*)-**5** (170 mg, 0.25 mmol) was added and the mixture was stirred for 12 h at rt. The reaction mixture was diluted with CH_2Cl_2, 2 M HCl (10 mL) solution was added and left stirring for 30 min. The resulting aqueous portion was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated, and the residue was recrystallized from ether/hexane (1:1) and gave diacid (*S*)-**8** (104 mg) in quantitative yield: $[\alpha]^{18}_D$ −26.6° (*c* 0.23, EtOH), lit.,[6a] −25.9° (*S*); mp 162−163 °C, resolidified upon racemization at 220 °C; remelted at 240 °C; *Rf* 0.38, CH_2Cl_2/MeOH (5:1); IR (KBr) 3400, 2950, 1680, 1580, 1320, 890 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were identical to the reported spectral data.[5c] Using the same procedure, (*R*)-**8** was synthesized from (*R*)-**5** in a quantitative yield: $[\alpha]^{20}_D$ +26.2° (*c* 1.23, EtOH).

Methyl 2,3-*O*-[(*R*)-4,4′,5,5′,6,6′-Hexamethoxydiphenoyl]-α-D-glucopyranoside: (*R*)-**9**. A suspension of (*R*)-**5** (109 mg, 0.16 mmol) in methanol (2 mL) and 0.5 M HCl (0.7 mL) was heated under reflux for 2 h. After being cooled to rt, $NaHCO_3$ (300 mg) was added to the reaction mixture and evaporated *in vacuo* to dryness. The residue was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), evaporated, and chromatographed on a SiO_2 flash column using a mixed solvent of hexane and ethyl acetate (1:2) as an eluent, giving (*R*)-**9** (77 mg) in quantitative yield: mp 112 °C; *Rf* 0.38 hexane/ethyl acetate/MeOH (4:4:1); $[\alpha]^{22}_D$ +82.3° (*c* 1.26, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9 (brs, 2 H, OH), 3.32 (s, 3 H), 3.58 (s, 3 H), 3.61 (s, 3 H), 3.66 (dt, 1 H, J = 3.6, 9.8 Hz, Glu H-5), 3.79 (dd, 1 H, J = 8.7, 9.8 Hz, Glu H-4), 3.87 (d, 2 H, J = 3.6 Hz, Glu H-6) 3.92 (s, 3 H), 3.93 (s, 3 H), 3.95 (s, 3 H), 3.96 (s, 3 H) 4.66 (dd, 1 H, J = 3.6, 9.3 Hz, Glu H-2), 4.83 (dd, 1 H, J = 8.7, 9.3 Hz, Glu H-3), 4.92 (d, 1 H, J = 3.6 Hz, Glu H-1), 6.98 (brs, 1 H), 7.16 (brs, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.6, 56.1, 56.2, 61.0, 61.1, 61.7, 68.4, 71.2, 74.7, 79.8, 97.3, 124.3, 125.0, 152.5, 152.6, 152.9, 153.0, 167.0, 169.1; IR (KBr) 3450, 2950, 1720, 1330, 960, 850, 770 cm^{-1}. Anal. Calcd for $C_{27}H_{32}O_{14}$: C, 55.86; H, 5.56. Found: C, 55.88; H, 5.61.

Methyl 2,3-*O*-[(*S*)-4,4′,5,5′,6,6′-Hexamethoxydiphenoyl]-α-D-glucopyranoside: (*S*)-**9**. Using the same procedure, (*S*)-**9** was synthesized from (*S*)-**5** in 83% yield: mp 132 °C; *Rf* 0.32 hexane/ethyl acetate/MeOH (4:4:1); $[\alpha]^{19}_D$ +55.8° (*c* 0.86, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.6 (brs, 1 H, OH), 3.4 (s, 3 H), 3.55 (s, 3 H), 3.58 (s, 3 H), 3.4−3.7 (m, 4 H, Glu H-4, H-5, H-6), 3.78 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 6 H), 4.9 (d, 1 H, J = 3.4 Hz, Glu H-1), 5.0 (dd, 1 H, J = 3.4, 9.6 Hz, Glu H-2), 5.3 (t, 1 H, J = 9.6 Hz, Glu H-3), 6.7 (s, 1 H), 6.8 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.1, 56.0, 61.0, 61.8, 67.9, 71.4, 73.7, 97.3, 104.7, 120.4, 120.6, 128.3, 128.7, 143.8, 143.9, 152.4, 152.5, 153.1, 168.0, 168.6; IR (KBr) 3450, 2950, 2850, 1750, 1590, 1380, 1330, 920 cm^{-1}. Anal. Calcd for $C_{27}H_{32}O_{14}$: C, 55.86; H, 5.56. Found: C, 54.88; H, 5.71.

Trideca-*O*-methyl-α-Pedunculagin (1). A mixture of (*S*)-**8** (127 mg, 0.30 mmol), oxalyl chloride (381 mg, 3.0 mmol), and toluene (5 mL) was warmed to 50 °C. After stirring for 12 h at the same temperature, solvent was removed *in vacuo* to give the crude (*S*)-**4** which was used immediately without further purification. To a solution of (*S*)-**4** in toluene (50 mL) were added triethylamine (5 mL, excess) and a toluene (50 mL) solution of diol (*S*)-**9** (116 mg, 0.20 mmol) dropwise at 0 °C. After being stirred at 50−60 °C for 48 h, the reaction was quenched by addition of crushed ice and was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel TLC, using a mixed solvent of hexane, ethyl acetate, and methanol (8:8:1) as an eluent. This gave **1** in 37% yield as a white powder (63.8 mg): mp 152 °C (from ether/MeOH); *Rf* 0.7 hexane/ethyl acetate/MeOH (8:8:1); $[\alpha]^{22}_D$ +22.8° (*c* 0.73, acetone), lit.,[6b] +27.4°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.48 (s, 3 H), 3.62 (s, 3 H), 3.65 (s, 3 H), 3.67 (s, 3 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 3.8−3.9 (m, 1 H, Glu H-6), 3.89 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 6 H), 3.93 (s, 3 H), 3.96 (s, 6 H), 4.25−4.40 (m, 1 H, Glu H-5), 4.96 (d, 1 H, J = 3.4 Hz, Glu H-1), 5.14 (t, 1 H, J = 9.9 Hz, Glu H-4), 5.2−5.3 (m, 3H, Glu H-2, H-6), 5.56 (t, 1 H, J = 9.9 Hz, Glu H-3), 6.60 (s, 1 H), 6.76 (s, 1 H), 6.77 (s, 1 H), 6.82 (s, 1 H); ^{13}C NMR (50 MHz, C_6D_6) δ 54.87, 54.90, 55.20, 55.46, 55.52, 60.44, 60.60, 60.69, 60.78, 60.84, 60.98, 61.03, 63.39, 67.49, 70.72, 74.87, 75.22, 98.10, 105.95, 105.99, 106.05, 106.52, 121.08, 122.10, 123.63, 123.86, 126.74, 127.11, 127.23, 144.68, 144.89, 145.28, 145.36, 153.33, 153.47, 153.64, 153.90, 167.79, 167.89, 168.20, 168.66; IR spectrum was identical to that reported.[6b]

Dimer 10. Using the same procedure, (*R*)-**9** was reacted with (*R*)-**4** under the same reaction conditions described in the synthesis of **1**. Many products were produced in prolonged reaction under an elevated temperature, and trideca-*O*-methylplatycaryanin D (**2**) was not isolated. Dimer **10** was isolated as the only characterized compound in 54% yield based on (*R*)-**9** as a white powder: mp 176−178 °C (from ether/MeOH); *Rf* 0.5 hexane/ethyl acetate/MeOH (10:10:1), after twelve-fold development; $[\alpha]^{15}_D$ +123° (*c* 0.72, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.12 (s, 3 H), 3.43 (s, 3 H), 3.49 (d, OH, J = 14 Hz), 3.52 (s, 6 H), 3.60 (s, 6 H) 3.71 (t, 2H, J = 10.0 Hz, Glu H-4), 3.9−4.0 (m, 4H, Glu H-5, H-6) 3.80 (s, 6 H), 3.87 (s, 6 H), 3.92 (s, 6 H), 3.96 (s, 6 H), 3.99 (s, 6 H), 4.00 (s, 6 H), 4.17 (dd, 4 H, J = 3.4, 10.1 Hz, Glu H-6), 4.35 (d, 2 H, J = 3.7 Hz, Glu H-1), 4.58 (t, 2 H, J = 10.0 Hz), 4.74 (dd, 4 H, J = 3.7, 10.0 Hz), 6.61 (s, 2 H), 7.52 (s, 2 H), 7.58 (s, 2 H); ^{13}C NMR (50 MHz, C_6D_6) δ 55.1, 55.7, 55.8, 60.2, 60.3, 60.6, 60.7, 60.8, 63.0, 66.8, 69.5, 74.9, 81.5, 97.9, 105.2, 110.4, 111.8, 122.2, 124.6, 124.8, 125.9, 126.3, 126.7, 144.3, 146.0, 147.9, 152.2, 153.1, 153.2, 153.4, 153.6, 153.7, 167.1, 168.3, 171.6; IR (KBr) 2950, 1730, 1060, 1000, 960 cm^{-1}; MS (FAB) *m*/*z* 1547 (M + H)$^+$.

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Supporting Information Available: An HPLC profile of compound **5** and ^{1}H NMR and ^{13}C NMR spectra for (*S*)-**5**, (*R*)-**5**, (*S*)-**9**, (*R*)-**9**, **7**, **1**, and **10** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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