A Rapid Total Synthesis of an Ellagitannin†

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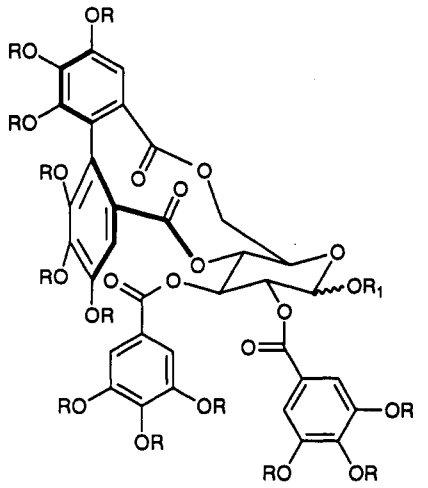
The ellagitannins are galloyl esters of glucose that contain at least one chiral biaryl (digalloyl) subunit. Included in this family are the tellimagrandins (1–3). The first asymmetric synthesis of (*S*)-4,4′,5,5′,6,6′-hexamethoxy-2,2′-diphenic acid, a ubiquitous subunit in ellagitannins, is reported by utilization of an intermolecular oxazoline-mediated asymmetric Ullmann coupling. Attachment of this acid to an appropriate glucose core resulted in the synthesis of an ellagitannin.

The ellagitannins are galloyl esters of glucose that contain at least one chiral biaryl (digalloyl) subunit. Included in this family are the tellimagrandins (1–3).[1] Ellagitannins have been shown to inhibit HIV reverse transcriptase[2] and DNA topoisomerase I mediated relaxation.[3] These compounds also display antioxidant activity[4] and play significant roles in the food and beverage industry, herbal medicines, leather tanning, and plant chemical defense systems.[1a,b] Although many ellagitannins have been isolated and well studied,[5,6] there is to date, only a single reported synthesis of these chiral biaryl glucose derivatives.[7a]

It has been suggested[1a,b] that the metabolic process for the synthesis of ellagitannins consists of the oxidative coupling of two galloyl appendages. With the glucose skeleton acting as a template, the aromatic units are juxtaposed facilitating a stereocontrolled oxidative coupling resulting in the formation of only the (*S*)-hexahydroxydiphenoate. Indeed, Feldman[7] has recently provided experimental support for this hypothesis by a diastereoselective oxidative biaryl coupling of two galloyl ester units attached to a chiral pyran template.

We envisioned that a rapid entry into this class of compounds could be achieved if the chiral biaryl unit was constructed initially, followed by attachment to an appropriately substituted glucose core. Toward this end, we report the first asymmetric synthesis of (*S*)-hexamethoxydiphenic acid (*S*)-**7** a ubiquitous subunit in ellagitannins. We have utilized this chiral atropisomer in the synthesis of an ellagitannin, O-permethyl tellimagrandin I (**3**).



1, Tellimagrandin I R = H, R_1 = H

2, Tellimagrandin II R = H, R_1 = (β)-galloyl

3, O - Permethyl Tellimagrandin I R = Me, R_1 =(α)-Me

We have recently described the oxazoline-mediated asymmetric Ullmann coupling of bromo oxazoline (*S*)-**4** to produce diastereomerically pure bis(oxazoline) (*S*)-**5** (Scheme 1).[8] To avoid endangering the stereochemical configuration about the chiral biaryl axis through rotation, mild conditions were required to hydrolyze the bis(oxazoline) (*S*)-**5** to the enantiomerically pure diacid (*S*)-**7**. Although standard protocol for such a transformation usually involves refluxing conditions,[9] a three-step process of room temperature reactions was devised for the hydrolysis of the oxazoline moiety.[10] Hence, ring opening of bis(oxazoline) (*S*)-**5** with TFA/H_2O followed by acetylation

† Dedicated to the memory of Professor Paul G. Gassman.

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(1) (a) Haslam, E. *Plant polyphenols: Vegetable tannins revisited*; Cambridge University Press: Cambridge, 1989. (b) *Plant Polyphenols: Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum: New York, 1992. (c) Tellimagrandin I was first isolated from *Tellima grandiflora*: Wilkins, C. K.; Bohm, B. A. *Phytochemistry* **1976**, *15*, 211. (d) ^1H and ^{13}C NMR data for tellimagrandin I (1) have been reported: Hatano, T.; Yoshida, T.; Shingu, T.; Okuda, T. *Chem. Pharm. Bull.* **1988**, *36*, 2925.

(2) Nonaka, G. I.; Nishioka, I.; Nishizawa, M.; Yamagishi, T.; Kashiwada, Y.; Dutschman, G. E.; Bodner, A. J.; Kilkuskie, R. E.; Cheng, Y.-C.; Lee, K.-H. *J. Nat. Prod.* **1990**, *53*, 587.

(3) (a) Bastow, K. F.; Bori, I. D.; Fukushima, Y.; Kashiwada, Y.; Tanaka, T.; Nonaka, G.; Nishioka, I.; Lee, K.-H. *Planta Med.* **1993**, *59*, 240. (b) Berry, D. E.; MacKenzie, L.; Shultis, E. A.; Chan, J. A.; Hecht, S. M. *J. Org. Chem.* **1992**, *57*, 420.

(4) For example, Okamura, H.; Mimura, A.; Yakou, Y.; Niwano, M.; Takahara, Y. *Phytochemistry* **1993**, *33*, 557.

(5) For a review on the specificity of these compounds in plants see: Okuda, T.; Yoshida, T.; Hatano, T. *Phytochemistry*, **1993**, *32*, 507.

(6) For some recent reports of ellagitannin isolations see: (a) Tanaka, T.; Orii, Y.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1993**, *41*, 1232. (b) Tanaka, T.; Tachibana, H.; Nonaka, G.-I.; Nishioka, I.; Hsu, F.-L.; Kohda, H.; Tanaka, O. *Chem. Pharm. Bull.* **1993**, *41*, 1214.. (c) Yoshida, T.; Ahmed, A. F.; Okuda, T. *Chem. Pharm. Bull.* **1993**, *41*, 672.. (d) Yoshida, T.; Tanei, S.; Liu, Y.-Z.; Yuan, K.; Ji, C.-R.; Okuda, T. *Phytochemistry* **1993**, *32*, 1287.. (e) For an example of a hydrolyzable tannin possessing a triterpenoid glycoside core containing a chiral biaryl subunit see: Chen, H.-F.; Tanaka, T.; Nonaka, G.-I.; Fujioka, T.; Mihashi, K. *Phytochemistry* **1993**, *32*, 1457.

(7) (a) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 1162. (b) A similar strategy (intramolecular stereocontrolled oxidative biaryl coupling) has been utilized in the synthesis of a vancomycin subunit: (i) Evans, D. A.; Dinsmore, C. J. *Tetrahedron Lett.* **1993**, *34*, 6029. (ii) Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426.

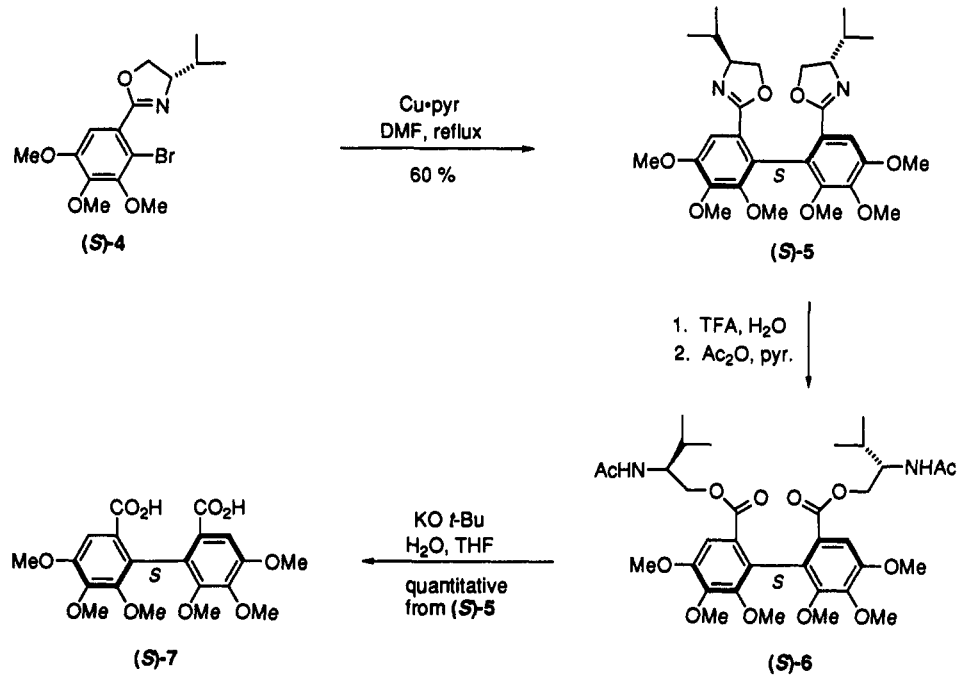
(8) Nelson, T. D.; Meyers, A. I. *Tetrahedron. Lett.* **1993**, *34*, 3061.

(9) For a review on recent advances in the chemistry of oxazolines see: Gant, T. G.; Meyers, A. I. *Tetrahedron Rep.* **1994**, *50*, 2297.

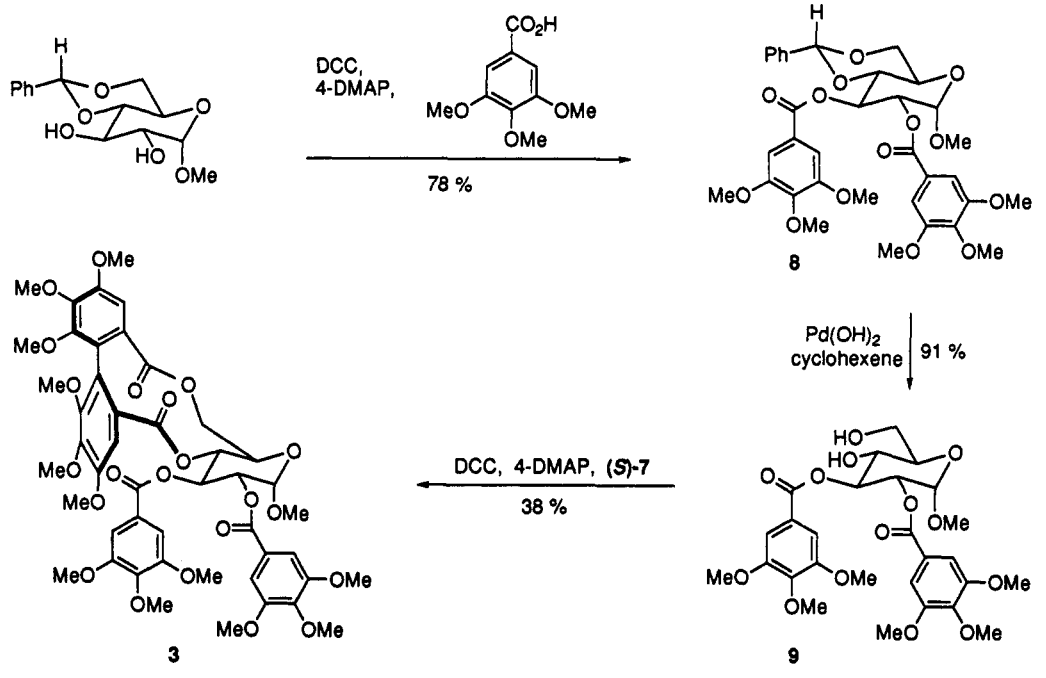
(10) For a similar transformation see: Phillion, D. P.; Pratt, J. K. *Synth. Commun.* **1992**, *22*, 13.

0022-3263/94/1959-2577$04.50/0

Scheme 1



Scheme 2



(to prevent recyclization) afforded diester (*S*)-**6**. Gassman saponification conditions,[11] using anhydrous potassium hydroxide (potassium *tert*-butoxide, H_2O, THF), gave a quantitative yield of the diacid (*S*)-**7**.

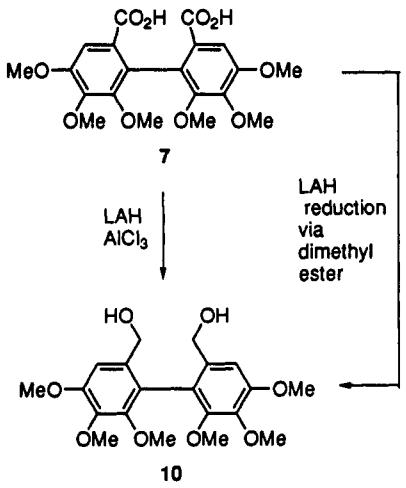
Comparison of the optical rotation of the resulting carboxylic acid (*S*)-**7** {$[\alpha]_D$ −20.0° (*c* 1.32, EtOH)} to that previously reported[12] {$[\alpha]_D$ −25.9° (*c* 0.9, EtOH)} suggested that partial racemization may have occurred during at least one of the three steps in the hydrolysis sequence. In order to clarify this, the stereochemical integrity of the biaryl was assessed by chiral HPLC analysis of the corresponding dicarbinol **10** formed by reduction of the diacid **7** with alane (LAH, $AlCl_3$).[13] As observed, the *S*/*R* ratio of the dicarbinol **10** was >99:<1; thus, indicating that the dicarboxylic acid **7** had not suffered any significant levels of rotation of the chiral biaryl axis. This is yet another example where care must be taken when using polarimetry for the determination of enantiomeric purity.

With the enantiomerically pure diacid **7** in hand, efforts were then directed toward the synthesis of the requisite glucose core (Scheme 2). Diesterification of the two free hydroxyl groups in commercially available[14] methyl 4,6-

(11) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

(12) The enantiomerically pure diacid (*S*)-**7** has been obtained by resolution of the racemate, c.f. (a) Schmidt, O. T.; Demmler, K. *Liebigs Ann. Chem.* **1952**, *576*, 85. (b) Insole, J. M. *J. Chem. Res.* (*M*) **1990**, 2831.

(13) Other reduction conditions were found to be inferior to the one described in this text, for example: (a) $LiBH_4$/TMSCl: Giannis, A.; Sandoff, K. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 218. (b) $NaBH_4/I_2$: Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5694.



O-benzylidene-α-D-glucopyranoside with 3,4,5-trimethoxybenzoic acid (gallic acid) using DCC and 4-(dimethylamino)pyridine (4-DMAP)[15] gave the diester **8** in a 78% yield. Hydrogenolysis of the benzylidene protecting group under catalytic transfer hydrogenation conditions [Pd(OH)$_2$, cyclohexene][16] released the diol **9** in a 91% yield. A DCC-mediated diesterification[15] between the (*S*)-hexamethoxydiphenic acid (***S***)-**7** with the diol glucose core **9** afforded the desired amorphous *O*-permethyl tellimagrandin I (**3**) in a 38% yield.[17] Verification of structure and stereochemistry for the latter was obtained by comparison with the *O*-permethylated product[18] derived from authentic tellimagrandin I (**1**) that was kindly supplied by Professor Okuda (Okayama University). The ^{1}H NMR spectra of products from both sources proved identical in every respect.[19]

Thus, the first asymmetric synthesis of (*S*)-hexamethoxydiphenic acid (*S*)-**7**,[20] a ubiquitous component in the ellagitannin family of hydrolyzable tannins, has been accomplished. Incorporation of this preconstructed, enantiomerically pure diacid into an appropriately substituted glucose core resulted in the asymmetric synthesis of an ellagitannin, *O*-permethyl tellimagrandin I (**3**), whose structure was verified by spectral comparison with an authentic sample.[19]

Experimental Section[21]

Bromo Oxazoline (*S*)-4. To 15.6 g (53.6 mmol) of 2-bromo-3,4,5-trimethoxybenzoic acid[22] and 20 mL of oxalyl chloride (2 M in CH_2Cl_2, 100 mmol, 1.9 equiv) in 125 mL of CH_2Cl_2 was added 4 drops of DMF, and the mixture was stirred at rt overnight. After the solvent was removed *in vacuo*, the residue was dissolved in 50 mL of CH_2Cl_2 and added via addition funnel to a solution of 5.65 g (54.9 mmol, 1.02 equiv) of (*S*)-valinol[23] and 17 mL of Et_3N in 200 mL of CH_2Cl_2 at 0 °C. (The addition funnel was rinsed with 25 mL of CH_2Cl_2 and this was also added to the valinol solution.) The reaction mixture was stirred at rt overnight, then washed with 3 N HCl, and dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in 250 mL of CH_2Cl_2 and cooled to 0 °C, and then a solution of 8.6 mL of $SOCl_2$ in 50 mL of CH_2Cl_2 was added dropwise. After stirring overnight at rt, the reaction mixture was cooled in an ice bath, quenched with water and aqueous $NaHCO_3$, separated, dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo*. To this residue was added 250 mL of CH_3CN, 30 mL of water, and 9.0 g of K_2CO_3 and this heated at reflux overnight. After cooling, the CH_3CN was evaporated and then diluted with CH_2Cl_2 and water. The layers were separated and the organic portion was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and filtered, and the solvent was evaporated. The residue was filtered through a plug of silica gel with EtOAc/hexane (1:1) and the solvent was removed *in vacuo* to afford 19.5 g of the bromo oxazoline (*S*)-**4** (100%) as a brown oil. This oil was suitable for subsequent use. If purified, yields on the order of 80% were typical: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 4.46–4.38 (m, 1H), 4.18–4.11 (m, 2H), 3.91 (s, 3H), 3.88 (S, 3H), 3.86 (s, 3H), 1.96–1.85 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.8 (s), 152.5 (s), 151.4 (s), 144.9 (s), 125.5 (s), 109.9 (d), 109.2 (s), 72.8 (d), 70.3 (t), 61.1 (q), 61.0 (q), 56.2 (q), 32.6 (d), 18.8 (q), 18.7 (q); FT-IR (film) 1658 cm^{-1}; a portion was purified to analytical purity by silica gel radial chromatography; $[\alpha]_D$ −35.3° (*c* 9.1, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_4NBr$: C, 50.29; H, 5.63; N, 3.91. Found: C, 50.16; H, 5.64; N, 3.90.

Bis(oxazoline) (*S*)-5. A flask containing 1.11 g (3.1 mmol) of the bromo oxazoline (*S*)-**4**, 1.04 g of activated copper powder,[24] and 1.5 mL of dry DMF was placed in a prewarmed (110 °C) sand bath for 3 h. An additional 8.5 mL of DMF was added and the mixture was heated to reflux for 24 h. After cooling, the mixture was diluted with CH_2Cl_2, washed with 4% aqueous ammonia (3 × 200 mL), and water (100 mL), and dried (Na_2SO_4), and the solvent was removed. The debrominated starting material (higher R_f) was removed from the bis(oxazoline) (*S*)-**5** by radial chromatography (98:2, hexane/Et_3N). Crystallization (ether/hexane) then afforded 500 mg (58% yield, two crops) of the diastereomerically pure bis(oxazoline) (*S*)-**5** as a colorless solid: mp 81.5–82.5 °C, $[\alpha]_D$ −31.8° (*c* = 3.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 2H), 4.02 (dd, J = 9.0, ≈ 7.65 Hz, 2H), 3.91 (s, 6H), 3.88 (s, 6H), 3.66–3.80 (m, 4H), 3.64 (s, 6H), 1.54–1.63 (m, 2H), 0.82 (d, J = 6.7 Hz, 6H), 0.74 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.4, 152.0, 151.6, 143.9, 125.4, 123.5, 108.1, 72.5, 70.0, 60.7, 60.4, 56.0, 32.7, 9.00. Anal. Calcd for $C_{30}H_{40}O_8N_2$: C, 64.73; H, 7.24; N, 5.03. Found: C, 64.89; H, 7.28; N, 5.06.

(*S*)-4,4′,5,5′,6,6′-Hexamethoxy-2,2′-diphenic Acid (7). A mixture of 983 mg (1.77 mmol) of bis(oxazoline) (*S*)-**5**, 100 mL of THF, 2 mL of water, 16 g of Na_2SO_4, and 3 mL of trifluoroacetic acid was stirred at rt overnight. Additional Na_2SO_4 was added to ensure anhydrous conditions. The mixture was filtered and the solvent was removed *in vacuo*. To the residue was added 40 mL of CH_2Cl_2, 4 mL of pyridine, and 4 mL of acetic anhydride. After stirring for 72 h at rt, the solution was diluted with CH_2Cl_2 and washed with water. The organic portion was dried ($MgSO_4$), and the solvent removed *in vacuo* to afford the crude diester diamide (*S*)-**6**. In a separate dry flask, 50 mL of ether, 600 mg (5.3 mmol) of potassium *tert*-butoxide, and 0.20 mL of water were stirred for 20 min.[11] An ether/THF solution of the crude diester diamide (*S*)-**6** was added via cannula and the mixture was stirred at rt for 36 h, diluted with ether, quenched with water, and then acidified with 3 N HCl. This mixture was diluted

(14) Sigma Chemical Co.
(15) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.
(16) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396.
(17) The diacid (*S*)-**7** did not racemize under the biaryl coupling conditions. This was determined from a control experiment by stirring the diacid (*S*)-**7**, DCC, and 4-DMAP in CH_2Cl_2 for 22 h. The resulting diacid (*S*)-**7** was converted to the dicarbinol **10** and assayed by chiral HPLC (*vide supra*).
(18) Contrary to this result, it was reported that all attempts at permethylation of tellimagrandin I (**1**) resulted in complex mixtures (see ref 1c).
(19) Copies of spectra for synthetic and authentic samples are included as supplementary material.
(20) (a)Recently, a variety of hexahydroxybiphenyl derivatives have been shown to inhibit protein kinase C. These analogs were obtained by functional group manipulation of the biphenyl obtained by degradation of naturally occurring ellagitannins. Kashiwada, Y.; Huang, L.; Ballas, L. M.; Jiang, J. B.; Janzen, W. P.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 195. (b) The enantiomerically pure chiral biphenyls described in ref 20a (and a wide range of other analogs) would by readily accessible by the asymmetric Ullmann coupling (described herein).
(21) For details concerning the "General Experimental Section" see: Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1011.
(22) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446.
(23) (a) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Organic Syntheses;* Wiley: New York, 1990; Collect. Vol. 7, p 531. (b) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.
(24) Fuson, R. C.; Cleveland, E. A. *Organic Syntheses;* Wiley: New York, 1955; Collect. Vol. 3, p 339.

with CH_2Cl_2 and water, and the layers were separated. The aqueous portion was saturated with NaCl and extracted again with CH_2Cl_2. The organic portions were combined, washed with brine, and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude acid was dissolved in 0.5 N NaOH and the solution was extracted three times with ether. The aqueous phase was acidified with 3 N HCl, extracted three times with ether, and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The diacid (*S*)-**7** (0.76 g, 102%) was obtained as an ether clathrate as a light tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.9–10.6 (bs, 2H), 7.42 (s, 2H), 3.93 (s, 6H), 3.91 (s, 6H), 3.54 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.1, 151.9, 151.0, 146.4, 128.0, 123.0, 110.1, 60.8, 60.5, 56.0. Crystallization from ether/petroleum ether gave diacid (*S*)-**7** (as an ether clathrate visible by ^{1}H NMR) as an off-white solid; mp 161–163 °C, resolidified upon racemization as the temperature approached 210 °C, remelted 240–244 °C; lit. mp[12a] 161 °C, resolidified upon racemization at 200–220 °C, remelted 240 °C; $[\alpha]_D$ −20.0° (*c* = 1.32, EtOH), lit.[12a] $[\alpha]_D$ −25.9° (*c* = 0.9, EtOH).

In order to confirm enantiomeric purity, the diacid **7** was converted to the dicarbinol **10**. To 178 mg of $AlCl_3$ in 8 mL of THF at 0 °C was added 2.0 mL of lithium aluminum hydride (1 M in THF). After stirring the mixture for 15 min, a solution of the diacid **7** (10 mg in 3 mL of THF) was added. The reaction mixture was allowed to warm to rt and stirred for 2.5 h. The mixture was recooled to 0 °C, quenched with 4 N NaOH, and diluted with water and CH_2Cl_2, and the layers were separated. The aqueous portion was again extracted with CH_2Cl_2, the organic portions were combined and dried ($MgSO_4$), and the solvent was removed. The residue was passed through a plug of silica gel to afford 10 mg of the crude dicarbinol **10** that was used for HPLC analysis directly to avoid inadvertant resolution. The physical data for dicarbinol (*S*)-**10** has been reported.[25]

Chiral HPLC analysis showed that the dicarbinol was enantiomerically pure (>99% ee). HPLC conditions were as follows: Chiralcel OD column, hexane/2-propanol (85:15), 1.0 mL/min, λ = 254 nm, (*R*)-**10** t_R 13 min, (*S*)-**10** t_R 18 min (see supplementary material). Racemic dicarbinol **10** was prepared by the procedure to reach (*S*)-**5** using methyl 2-bromo-3,4,5-trimethoxybenzoate (obtained from the methylation of 2-bromo-3,4,5-trimethoxybenzoic acid)[20] followed by LAH reduction to the dicarbinol. Alternatively, saponification of the dimethyl ester afforded racemic diacid **7**, which was reduced in accordance with the previously described protocol (LAH/$AlCl_3$).

Digalloyl Glucopyranoside 8. A mixture of 282 mg (1.58 mmol) of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, 676 mg (3.18 mmol, 2.0 equiv) of 3,4,5-trimethoxybenzoic acid, 676 mg (3.28 mmol, 2.1 equiv) of freshly distilled DCC, and 41 mg (0.3 mmol, 0.2 equiv) of 4-(dimethylamino)pyridine (4-DMAP) in 25 mL of CH_2Cl_2 was stirred at rt for 16 h. The resulting precipitate of dicyclohexylurea was filtered and the solvent was removed *in vacuo*. Ether was added to the residue to precipitate additional urea and this was also filtered. The filtrate was washed with water (4×) and dried ($MgSO_4$), and the solvent was evaporated. Purification by radial chromotagraphy (4-mm silica gel rotor, hexane to 40% ethyl acetate/hexane) afforded 825 mg (78%) of the digalloyl glucopyranoside **8** (R_f = 0.4, 50% ethyl acetate/hexane) as a colorless solid: mp 168.5–169.5 °C; $[\alpha]_D$ +50.9° (*c* 3.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.28 (m, 5H), 7.22 (s, 2H), 7.19 (s, 2H), 6.00 (t, *J* = 9.7 Hz, 1H), 5.56 (s, 1H), 5.21 (d, *J* = 3.7 Hz, 1H), 5.12 (dd, *J* = 9.8, 3.7 Hz, 1H), 4.35 (dd, *J* = 10.1, 4.7 Hz, 1H), 4.10–4.01 (m, 1H), 3.94–ca. 3.8 (m, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 3.83 (s, 6H), 3.82 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7 (s), 165.3 (s), 152.8 (s), 152.8 (s), 142.5 (s), 142.4 (s), 136.8 (s), 129.0 (d), 128.2 (d), 126.2 (d), 124.5 (s), 123.9 (s), 107.1 (d), 106.9 (d), 101.6 (d), 97.8 (d), 79.0 (d), 73.0 (d), 69.8 (d), 68.9 (t), 62.5 (d), 60.8, 56.1 (q), 56.1, 55.5 (q); FT-IR ($CHCl_3$) 1720 cm^{-1}. Anal. Calcd for $C_{34}H_{38}O_{14}$: C, 60.89; H, 5.71. Found: C, 60.95; H, 5.77.

***O*-Permethyl tellimagrandin (3).** A mixture of 186 mg (0.28 mmol) of digalloyl glucopyranoside **8**, 82 mg of palladium hydroxide on carbon (10%), 3 mL of freshly distilled cyclohexene, and 3 mL of absolute EtOH was heated to reflux for 2.5 h. After cooling, the mixture was passed through a plug of Celite, eluting with MeOH. Removal of the solvent *in vacuo* afforded 147 mg (91%) of the diol **9** as a colorless solid: mp 162–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 2H), 7.16 (s, 2H), 6.79 (s, 1H), 6.64 (s, 1H), 5.90 (t, *J* = 10.0 Hz, 1H), 5.29–5.22 (m, 3H), 5.07 (dd, *J* = 10.0, 3.8 Hz, 1H), 4.41 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.96 buried under methoxy region (m, 1H), 3.90 (s, 6H), 3.89 (s, 3H), 3.86 (s, 6H), 3.834 (s, 3H), 3.829 (s, 3H), 3.78 (s, 3H), 3.73 (s, 6H), 3.67 (s, 3H), 3.65 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.6 (s), 165.7 (s), 152.8 (s), 152.7 (s), 142.5 (s), 142.4 (s), 124.0 (s), 123.9 (s), 107.0 (d), 106.9 (d), 97.0 (d), 74.3 (d), 72.0 (d), 71.3 (d), 69.3 (d), 61.9 (t), 60.8 (q, degenerate, 2C), 56.1 (q, degenerate, 4C), 55.4 (q). *This compound was used in the following reaction without further purification.*

A mixture of 147 mg (0.25 mmol) of diol **9**, 110 mg (0.26 mmol, 1 equiv) of (*S*)-4,4′,5,5′,6,6′-hexamethoxy-2,2′-diphenic acid (**7**), 110 mg (0.53 mmol, 2.1 equiv) of freshly distilled DCC, 10 mg (0.08 mmol, 0.3 equiv) of 4-DMAP, and 25 mL of CH_2Cl_2 was stirred at rt for 17.5 h. The precipitate of urea was filtered and the solvent was removed *in vacuo*. Ether was added to the residue to precipitate additional urea and this was also filtered. The filtrate was washed with water (4×) and dried ($MgSO_4$), and the solvent was evaporated. Purification by radial chromatography (2-mm silica gel rotor) followed by preparative TLC afforded 91.6 mg (38%) of *O*-permethyl tellimagrandin I (**3**) as a colorless foam: EI$^+$ MS *m/z* (relative intensity) 195 (100%), 968 (0.54%); $[\alpha]_D$ +4.7° (*c* 0.1, CH_2Cl_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.6 (s), 166.9 (s), 165.7 (s), 165.4 (s), 153.0 (s), 152.83 (s), 152.76 (s), 152.2 (s), 144.5 (s), 144.0 (s), 142.5 (s), 142.3 (s), 128.3 (s), 127.7 (s), 123.9 (s), 123.8 (s), 122.5 (s), 122.1 (s), 107.1 (d, 2C), 107.0 (d, 2C), 105.6 (d), 105.5 (d), 97.4 (d), 72.8 (d), 71.0 (d), 70.1 (d), 66.7 (d), 63.2 (t), 61.0 (q), 60.8 (q), 60.7 (q), 60.6 (q), 56.1 (q), 56.0 (q), 55.9 (q), 55.7 (q); some of the methoxy resonances were degenerate.

For comparison purposes, a sample of authentic tellimagrandin I (**1**), provided by Professor Okuda (Okayama University), was permethylated as follows: A 5-mg sample of tellimagrandin I (**1**) in 3 mL of dry acetone was treated with 54 mg of K_2CO_3 and 6 drops of freshly distilled dimethyl sulfate for 36 h at rt. The solvent was removed *in vacuo* and the residue was purified by preparative TLC to afford 1 mg of *authentic* **3**. This material proved to be spectroscopically identical[19] with *synthetic* **3** from above.

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Supplementary Material Available: HPLC chromatograms for chiral dicarbinol **10** assay; copies of ^{1}H and ^{13}C NMR spectra of (*S*)-**7**, ^{13}C NMR spectrum of **9** and ^{1}H, ^{13}C, 2-D, and mass spectra of **3** (20 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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