Tetrahedron 67 (2011) 1960–1970

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Syntheses of all-methylated ellagitannin, isorugosin B and rugosin B

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ARTICLE INFO

Article history:
Received 13 November 2010
Received in revised form 24 December 2010
Accepted 4 January 2011
Available online 9 January 2011

Keywords:
Natural product
Ellagitannin
Axial chirality
Palladium
Regioisomer

ABSTRACT

Ellagitannins possess a wide range of biological activities and remarkable structural diversity, which commonly include an axially chiral biaryl unit. This paper describes syntheses of all-methylated versions of isorugosin B and rugosin B, which are regioisomeric, ellagitannin-related compounds. The key features of these syntheses involve the construction of an axially chiral biaryl function on a sugar moiety through a Pd-catalyzed intramolecular biaryl coupling reaction, Bringmann's atroposelective lactone opening reaction, and a two-step ester formation. This is the first synthetic approach for generating ellagitannins featuring a valoneoyl group.

1. Introduction

Ellagitannins are polyphenolic natural products with a wide range of biological activities, including antioxidant, antivirus, and antitumor activities. This class of compounds may therefore be useful in medicinal applications.[1] Additionally, several researchers have expressed an interest in the structural diversity within this class of compounds with particular emphasis on those structures exhibiting axially chiral biaryl components.[2] Effective methods for constructing axially chiral biaryl moieties have been developed[3] and syntheses of several ellagitannins involving biaryl units with C_2 symmetry, such as corilagin, sanguiin H-5, and coriariin A, have been demonstrated.[4] However, non-symmetric biaryl components have yet to be synthesized. The valoneoyl group (Fig. 1) is a significant structural component of ellagitannins[5] since the ellagitannins, which possess this structure indicates unique bioactivity. In particular, oenothein B[6] exhibits strong antitumor activity, based on potentiation of the host immune defense.[7] For this reason, the development of efficient strategies for constructing valoneoyl groups is important for syntheses involving this class of natural ellagitannins in new drug discovery.

The synthetic strategy described here is based on the initial construction of a valoneoyl group with subsequent attachment to a suitable glucose core. Trimethyl octa-*O*-methyl valonate (**1**), which has been frequently identified in structural determination of ellagitannins,[5] was chosen as the initial synthetic target. Despite being an important structural component of the ellagitannin family, an asymmetric synthesis of **1** has not previously been reported.[8] Axial chirality was generated using Bringmann's 'lactone concept,' which is an effective method for synthesizing axially chiral biaryl-type natural products.[9] It was thus expected that this technique would be applicable to the synthesis of hexadecamethyl derivatives of isorugosin B (**2**)[5d,5e] and rugosin B (**3**),[5f] which are the corresponding regioisomeric ellagitannins.

The current study demonstrates the first reported synthesis of valoneoyl-containing ellagitannins through the enantioselective construction of trimethyl octa-*O*-methyl valonate (**1**) and the syntheses of all-methylated versions of isorugosin B (**2**) and rugosin B (**3**).[10]

2. Results and discussion

2.1. Enantioselective synthesis of trimethyl octa-*O*-methyl valonate 1

The initial synthetic outline of **1** is depicted in Scheme 1. The target molecule **1** was synthesized from the six-membered ring lactone **4** using Bringmann's 'lactone concept' to forge the axially chiral biaryl components through a series of functional group manipulations. In this way, lactone **4** is a key intermediate in the synthesis. A Pd-catalyzed intramolecular biaryl coupling reaction[11] is presumably a useful method for the formation of **4**, which

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doi:10.1016/j.tet.2011.01.004

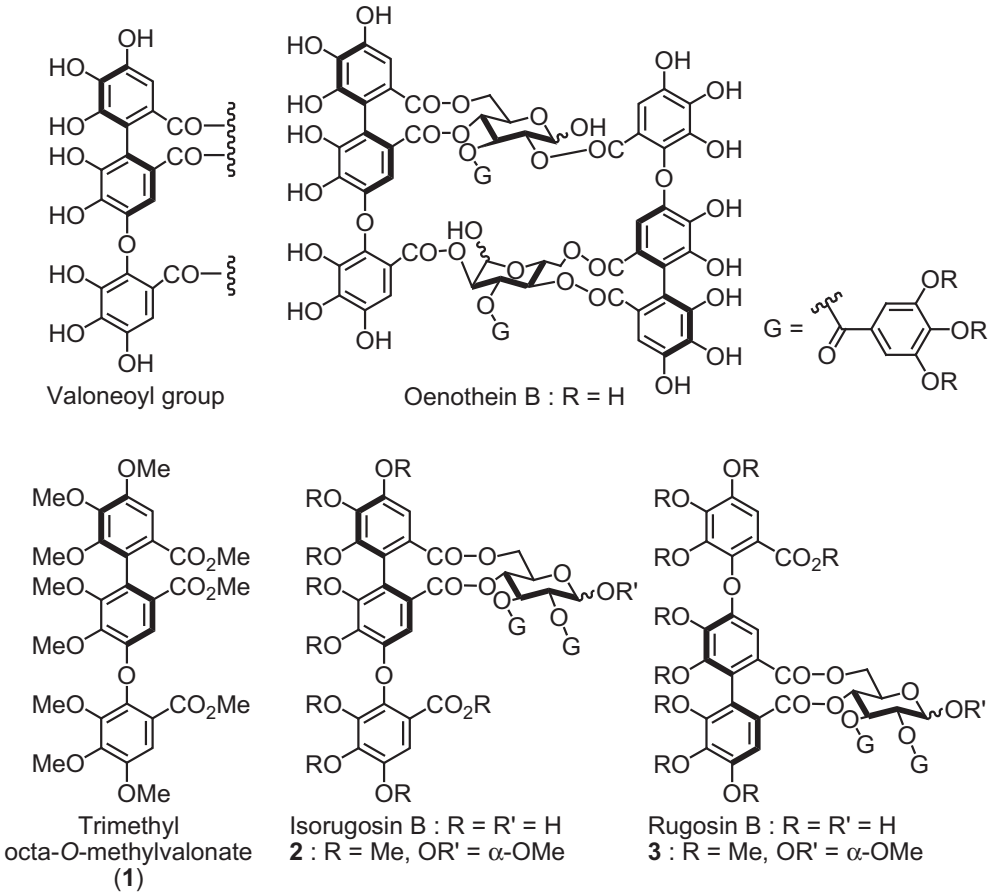
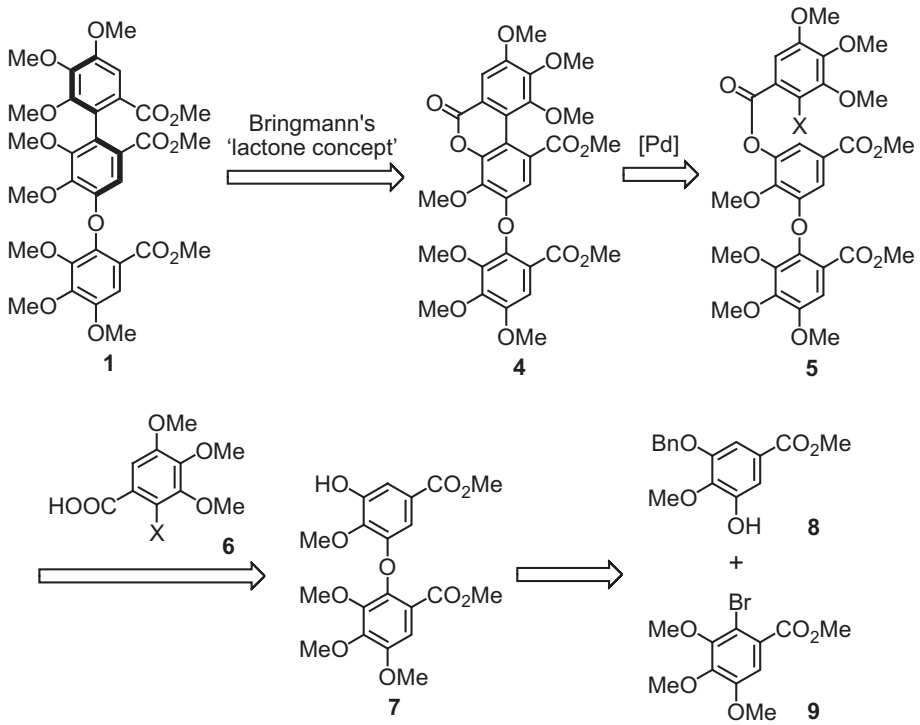


Fig. 1. Examples of valoneoyl-containing ellagitannins and its related compounds.



Scheme 1. Synthetic outline of **1**.

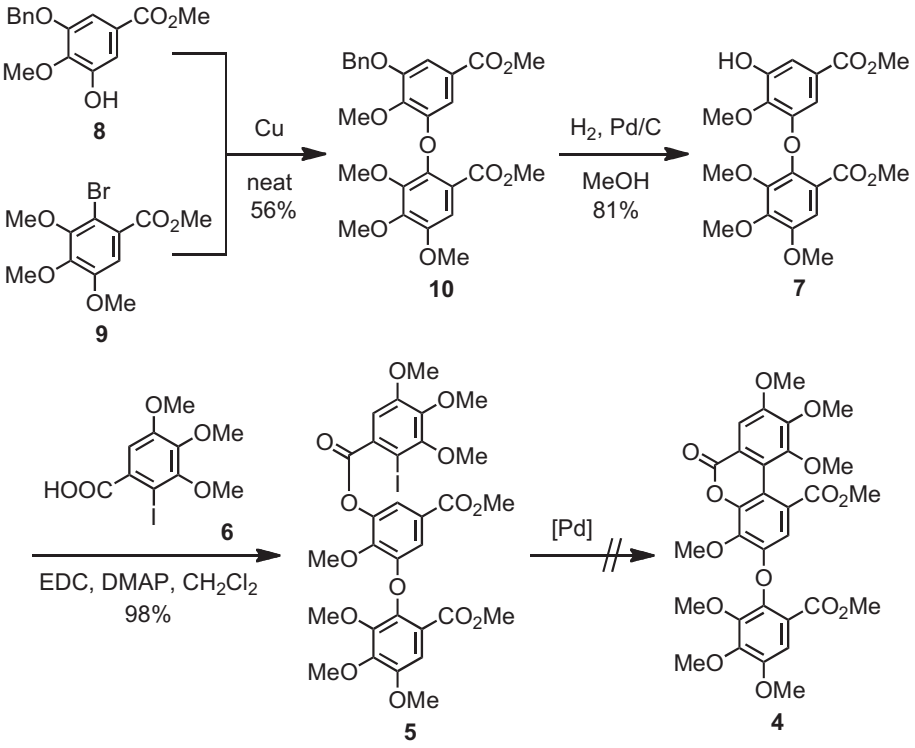
requires ester **5** as a precursor. Ester **5** can be obtained by a simple esterification between the corresponding carboxylic acid **6**[12] and phenol **7**. Phenol **7** can be prepared by an Ullmann-type coupling[13] of phenol **8**[14] and bromide **9**.[15]

The synthesis of **1** began with the preparation of the biaryl ether **10** through an Ullmann condensation of phenol **8**,[14] which was obtained from commercially available methyl gallate according to a previously reported method, and bromide **9**[15] (Scheme 2). Deprotection under hydrogenolysis conditions provided phenol **7**, which underwent esterification with carboxylic acid **6**[12] using EDC to afford ester **5** as a precursor of the intramolecular biaryl coupling reaction. However, all attempts to prepare the coupling product **4** were unsuccessful. This result is similar to previous results,[16] in which the electron-withdrawing properties of the ester group adjacent to the reacting position interfered with the Pd-mediated biaryl coupling reaction.

of the two acetoxy groups produced the triol **17**. A final two-step oxidation of three hydroxy groups and methylation of the resulting carboxylic acids gave compound **1**. The absolute configuration of the synthetic material was determined by comparing the sign of optical rotation with that in previously reported data.[18] The stereoselectivity of the asymmetric reduction could be explained by the Bringmann's model.[9] The above procedure was successful in producing (*S*)-**1**.

2.2. Syntheses of methylated ellagitannins

Given the success of the above synthesis, the strategy was expanded to produce the ellagitannin regioisomers, isorugosin B and rugosin B. As discussed above, this class of ellagitannins has not been previously synthesized because of difficulties inherent in the construction of the valoneoyl group on the sugar moiety. However,



Scheme 2. Attempt to construct the six-membered ring lactone **4**.

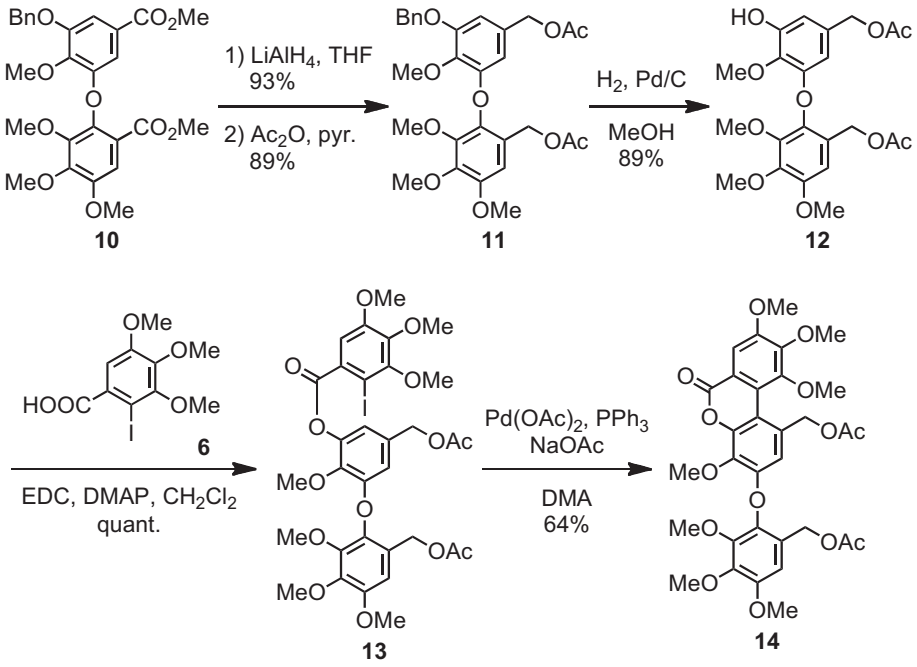
Accordingly, the ester group was converted to a carbinol or a protected carbinol, such as an acetoxymethyl or a siloxymethyl group. Converting the ester to an unprotected carbinol did not improve reactivity. In contrast, conversion to a protected carbinol provided the desired results; the best yields were obtained with the acetyl-protected carbinol. The synthesis of the six-membered lactone **14** is summarized in Scheme 3. Two ester groups in **10** were reduced with $LiAlH_4$ and acetylated to yield the bis-acetoxymethyl compound **11**, which was debenzylated to form phenol **12**. Phenol **12** was condensed with carboxylic acid **6** using the same conditions as those in Scheme 2 to yield the coupling precursor **13**. The intramolecular biaryl coupling reaction of **13** with $Pd(OAc)_2$, Ph_3P, and NaOAc produced the desired lactone **14** in good yield.

In the next stage, Bringmann's lactone opening reaction was applied to **14** to construct the axially chiral biaryl components (Scheme 4). The asymmetric reduction of **14** with a borane–CBS reagent system[17] succeeded in generating the optically active biaryl compound **15** in an enantiomerically pure form. The phenolic hydroxy group was subsequently methylated, and successive reduction

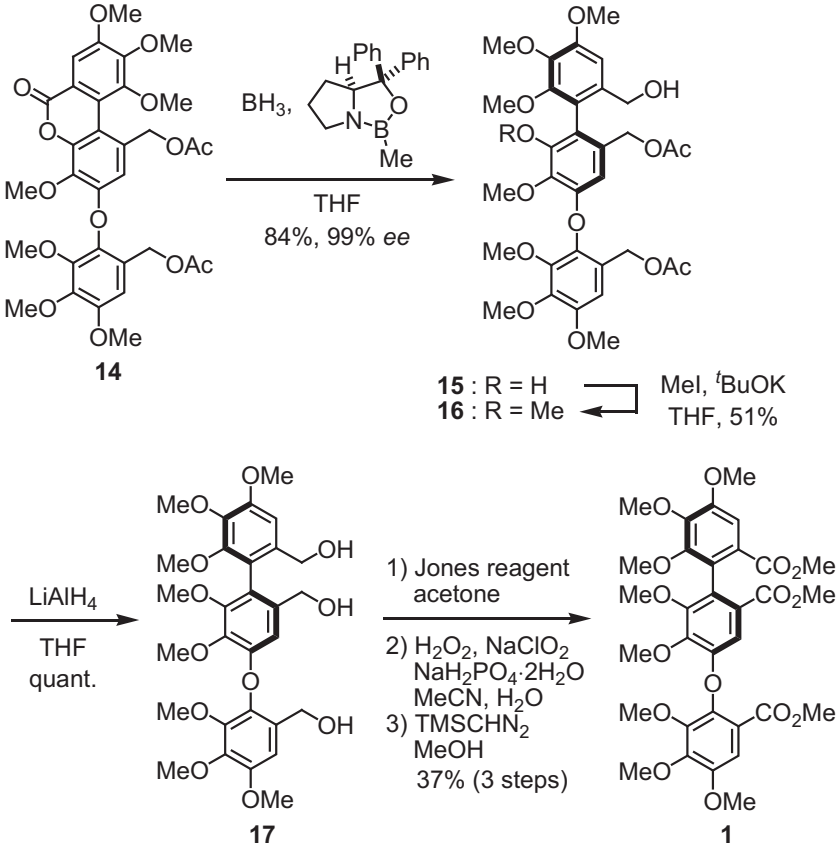
the above strategy enabled a smooth conversion of the axially chiral valoneoyl group into all-methylated versions of isorugosin B (**2**) and rugosin B (**3**).

The syntheses of **2** and **3** were relatively simple, as illustrated in Scheme 5. The most difficult step was the connection of the biaryl unit to the sugar moiety. This requires that two ester groups be formed in the final stage of the syntheses. In this context, the axially chiral biaryl compound **18** was the rational intermediate for regioselective esterification of glucose derivative **19**.[19] Although **18** can be obtained by a method analogous to that described above, the three ester groups in the valoneoyl group must be distinguishable from each other.

As depicted in Scheme 6, the synthesis started with the preparation of the biaryl ether by an Ullmann condensation between (siloxymethyl)phenol **20**, which was obtained by $LiAlH_4$ reduction and TBS protection of **8**, and the bromide **9**. Aldehyde **21** was isolated in 9% yield along with many other undesired by-products. It is likely that compound **20** underwent thermolysis of its silyl group, with subsequent auto-oxidation, to afford the formyl compound **22**

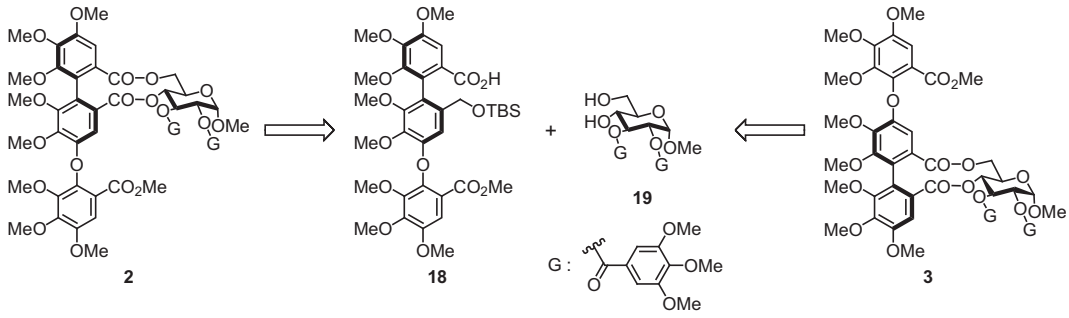


Scheme 3. Construction of six-membered ring lactone **14**.

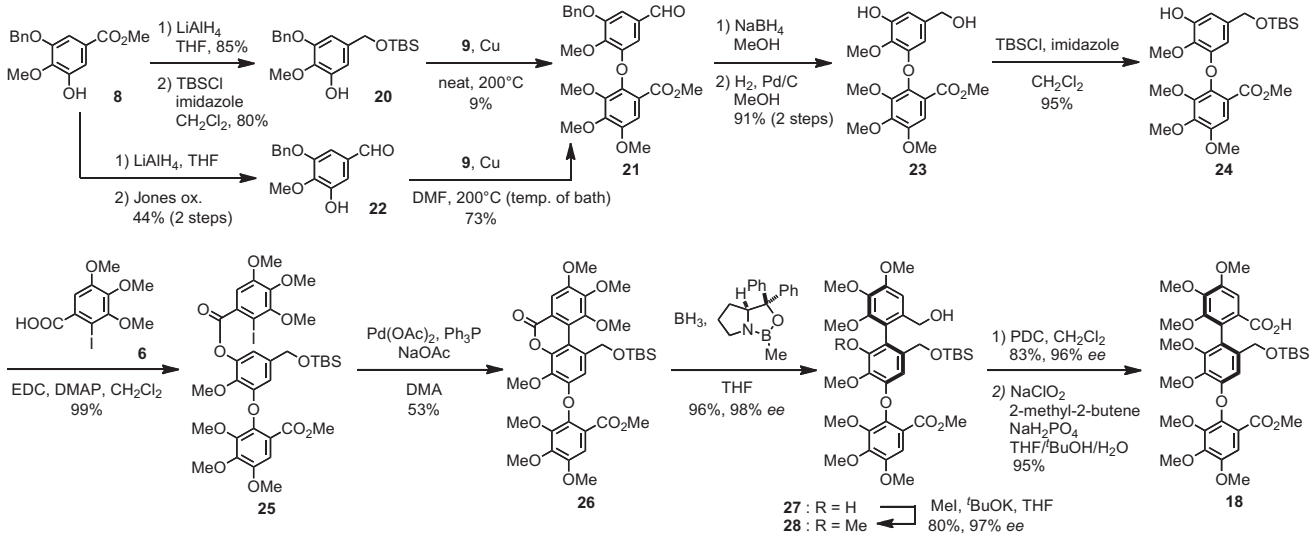


Scheme 4. Synthesis of (*S*)-**1**.

as a reactive species. Thus, it was considered that **22** would be a suitable synthetic precursor for the formation of the biaryl ether. Based on this, **22** was synthesized from **8** by $LiAlH_4$ reduction and Jones oxidation. The biaryl ether **21** was then obtained in good yield from the reaction of **22** and **9**. Reduction of the formyl group and deprotection of the benzyl group provided the benzyl alcohol **23**. Protection of the benzylic hydroxy group of **23** using a TBSCl–imidazole system succeeded in providing the desired phenol fragment **24**. Phenol **24** was then coupled with carboxylic acid **6** to afford the ester **25**. Ester **25** was then subjected to the



Scheme 5. Synthetic outline of **2** and **3**.

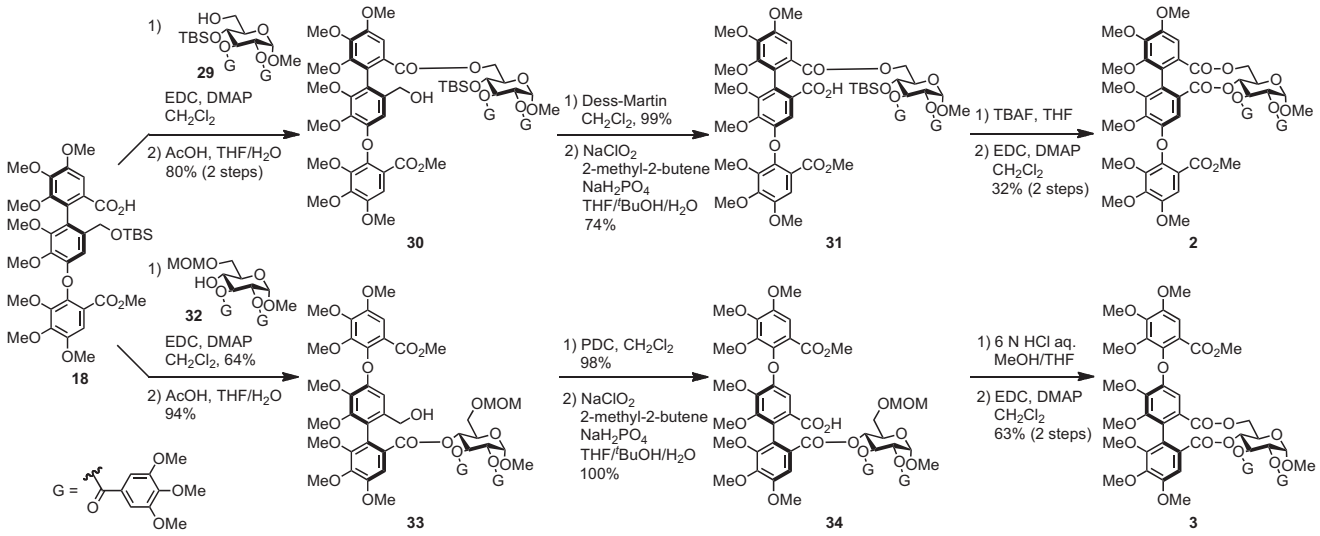


Scheme 6. Synthesis of key intermediate **18**.

intramolecular biaryl coupling reaction, using the same conditions as those in the previous scheme, to afford lactone **26**.

The lactone opening reaction of **26** proceeded smoothly under Bringmann's conditions to generate the axially chiral biaryl compound **27** in high enantiomeric excess, which was methylated to afford the benzyl alcohol **28**. The absolute configuration of the biaryl moiety was confirmed by a one-pot transformation of **28** to **17**, and measurement of the optical rotation.[20] Finally, a two-step oxidation (PDC oxidation and Pinnick oxidation[21]) of (*S*)-**28** resulted in the optically active carboxylic acid (*S*)-**18** as a key intermediate of the synthesis.

With the mono carboxylic acid (*S*)-**18** in hand, an 11-membered ring system was formed via a double esterification reaction between **18** and a glucose derivative (Scheme 7). Glucose derivatives



Scheme 7. Synthesis of **2** and **3**.

29 and **32** were prepared from compound **19**.[22] The first attachment of **18** to **29**, followed by selective desilylation of the primary alcohol, yielded the desired alcohol **30** as a single diastereoisomer, which was then oxidized to the ring-closing precursor, carboxylic acid **31**. The final manipulation of **31** consisted of removal of the TBS group with TBAF, and a subsequent intramolecular esterification under typical conditions to afford all-methylated isorugosin B (**2**). The moderate yield of this step may be due to the low reactivity of the secondary hydroxy group of the sugar. While the NMR spectrum of synthetic **2** was identical to that of the authentic chart, significant differences were observed regarding the sign of optical rotation.[23] This discrepancy was likely due to impurities in the natural sample, as evidenced by unidentified peaks in the authentic NMR chart.

The current investigation was concluded with the synthesis of **3**, which is a regioisomer of **2**. An esterification reaction between **18** and **32** with successive deprotection gave alcohol **33**, which was then subjected to a two-step oxidation to yield the carboxylic acid **34**. Finally, deprotection of the MOM group on the sugar moiety with aqueous HCl and successive esterification resulted in the synthesis of all-methylated rugosin B (**3**). The NMR spectrum and the optical rotation of synthetic **2** matched those of the reported data.[23]

3. Conclusions

An efficient strategy for the synthesis of valoneoyl-containing ellagitannins, which involved a Pd-catalyzed intramolecular biaryl coupling reaction, Bringmann's lactone opening reaction, and a two-step ester formation with the sugar core, was demonstrated. This process enabled syntheses of the valoneic acid derivative (**1**), and all-methylated versions of isorugosin B (**2**) and rugosin B (**3**). Based on these results, further syntheses of other natural ellagitannins, including isorugosin B, rugosin B, and oenothein B are underway.

4. Experimental section

4.1. General information

Melting points were measured using Yanagimoto micro melting point hot-plate and are uncorrected. Optical rotations were determined on a JASCO P-1020 or -1030 digital polarimeter. IR spectra were recoded on a Jasco FTIR-350 spectrophotometer. NMR spectra were taken with Varian Unity INOVA AS600 (600 MHz), Varian VXR-500 (500 MHz), Mercury 300 (300 MHz) or JEOL α-400 (400 MHz) instrument. Chemical shifts are given in δ parts per million with TMS as an internal standard. Elemental analyses were performed with Yanaco MT-5 or Elementar vario MICRO cube analyzer. FABMS was obtained with a VG-70SE or JEOL JMS-AX505HAD instrument using *m*-nitrobenzyl alcohol as the matrix. EIMS was obtained with JEOL JMS-700 or JMS-GCmate II instrument. HPLC was carried out using a Shimadzu LC-6A system, Shimadzu SPD-6A UV detector, Daicel CHIRALPACK® AD or CHIRALCEL® OD column. Silica gel column chromatography was carried out using wakogel® C-200 (Wako) or 9385 Kieselgel 60 (Merck). TLC analysis was performed on Kieselgel 60 F_{254} (Merck) plates. Solvents were dried using standard procedure.

*4.1.1. Methyl 2-(3-benzyloxy-5-formyl-2-methoxyphenoxy)-3,4,5-trimethoxybenzoate (**21**).* The mixture of **22** (7.50 g, 29.0 mmol), **9** (26.6 g, 87.2 mmol), and Cu (11.1 g, 175 mmol) in DMF (25 mL) was heated at 200 °C under Ar. After stirring for 1 h, the reaction mixture was cooled to ambient temperature, diluted with EtOAc, and filtrated. The filtrate was poured into H_2O (250 mL) and extracted with EtOAc (250 mL×3). The combined organic layer was washed with brine, dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the resulting residue (31.2 g) was purified by silica gel column chromatography (1:2; EtOAc/hexane) and recrystallization from EtOAc/hexane, providing **21** (10.3 g, 73%) as pale yellow prisms: mp 108–109.5 °C (EtOAc/hexane); IR (KBr) ν_{max} 2950, 2840, 1725, 1700, 1590, 1490, 1460, 1430, 1415, 1380, 1350, 1330, 1230, 1185, 1125, 1100, 1030, 990, 945, 840, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (3H, s, OMe), 3.77 (3H, s, OMe), 3.94 (3H, s, OMe), 3.97 (3H, s, OMe), 4.10 (3H, s, OMe), 5.22 (2H, s, C*H*$_2$), 6.65 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 7.20 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 7.31–7.51 (6H, m, C_6H_5, Ar-6-*H*) 9.67 (1H, s, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.3, 56.3, 61.3, 61.3, 61.5, 71.2, 108.3, 108.9, 109.6, 119.3, 127.5, 128.2, 128.7, 131.4, 136.4, 142.1, 143.9, 147.0, 147.3, 150.5, 153.1, 153.2, 165.0, 190.9. Anal. Calcd for $C_{26}H_{26}O_9$: C, 64.72; H, 5.43. Found: C, 64.78; H, 5.21; FAB-mass (positive ion mode) *m*/*z*: 482[M]$^+$, 483[M+H]$^+$.

*4.1.2. Methyl 2-(3-hydroxy-5-hydroxymethyl-2-methoxyphenoxy)-3,4,5-trimethoxybenzoate (**23**).* To a stirring solution of **21** (9.00 g, 18.7 mmol) in MeOH (200 mL), $NaBH_4$ (1.42 g, 37.5 mmol) was added and the resulting mixture was stirred at room temperature under Ar atmosphere. After 30 min, the reaction mixture was warmed to 40 °C and stirred. After check of TLC, the reaction mixture was quenched with 1 N HCl aq (100 mL) and evaporated to remove most of MeOH. The resulting residue was poured into H_2O (50 mL) and extracted with EtOAc (150 mL×3). The combined organic layer was washed with satd $NaHCO_3$ aq (150 mL) and brine (150 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated to afford alcohol (11.8 g) as colorless prisms, which was used in the next reaction without further purification: mp 118–120 °C (EtOAc/hexane); IR (KBr) ν_{max} 3500, 2960, 2360, 1700, 1600, 1430, 1350, 1240, 1220, 1130, 1100, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (3H, s, OMe), 3.78 (3H, s, OMe), 3.92 (3H, s, OMe), 3.96 (3H, s, OMe), 4.00 (3H, s, OMe), 4.44 (2H, s, *CH*$_2$OH), 5.16 (2H, s, PhC*H*$_2$O), 6.09 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 6.68 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 7.28–7.49 (6H, m, C_6H_5, Ar-6-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.3, 56.2, 61.1, 61.3, 61.5, 65.0, 71.0, 105.8, 106.3, 108.7, 119.4, 127.4, 128.0, 128.6, 136.5, 137.1, 137.6, 142.7, 147.1, 147.2, 150.1, 152.6, 152.9, 165.5. Anal. Calcd for $C_{26}H_{28}O_9$: C, 64.45; H, 5.83. Found: C, 64.37; H, 5.74. Found: C, 69.74; H, 5.42; FAB-mass (positive ion mode) *m*/*z*: 484[M]$^+$, 485[M+H]$^+$. The above alcohol was dissolved in MeOH (100 mL), 10% Pd/C (1.00 g) was added at room temperature. Under H_2 (1 atm) atmosphere, the mixture was stirred for 2 h, which was filtrated and evaporated. The obtained colorless solid (8.16 g) was recrystallized from EtOAc/hexane, providing **23** (6.72 g, 91%) as a colorless solid: mp 141–143 °C (EtOAc/hexane); IR (KBr) ν_{max} 3480, 3160, 3000, 2960, 1720, 1600, 1460, 1430, 1410, 1360, 1220, 1080, 1040, 995, 965, 800, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (3H, s, OMe), 3.75 (3H, s, OMe), 3.93 (3H, s, OMe), 3.96 (3H, s, OMe), 4.07 (3H, s, OMe), 4.41 (2H, s, C*H*$_2$OH), 5.95 (1H, s, ArO*H*, exchange with D_2O), 5.98 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 6.60 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 7.28 (1H, s, Ar-6-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 56.3, 61.3, 61.5, 64.9, 104.4, 107.5, 108.8, 119.5, 134.8, 137.0, 142.2, 147.1, 147.3, 149.7, 150.3, 151.9, 165.4. Anal. Calcd for $C_{19}H_{22}O_9$: C, 57.86; H, 5.62. Found: C, 57.81; H, 5.43; FAB-mass (positive ion mode) *m*/*z*: 394[M]$^+$.

*4.1.3. Methyl 2-(5-tert-butyldimethylsilyloxymethyl-3-hydroxy-2-methoxyphenoxy)-3,4,5-trimethoxybenzoate (**24**).* To a solution of **23** (4.50 g, 11.4 mmol) in CH_2Cl_2 (150 mL), TBSCl (3.10 g, 20.6 mmol) and imidazole (1.40 g, 20.6 mmol) were added at room temperature. After stirring for 10 min under Ar atmosphere, the mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (100 mL×3). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated, and the pale yellow residue (11.1 g) was purified by silica gel column chromatography (1:2; EtOAc/hexane), providing **24** (5.49 g, 95%) as a colorless oil: IR (neat) ν_{max} 3440, 2960, 2860, 2360, 1730,

1720, 1600, 1505, 1495, 1460, 1430, 1415, 1350, 1220, 1120, 1080, 1040, 990, 840, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.04 (6H, s, Si*Me*$_2$), 0.80 (9H, s, Si^t*Bu*), 3.72 (3H, s, OMe), 3.74 (3H, s, OMe), 3.92 (3H, s, OMe), 3.95 (3H, s, OMe), 4.07 (3H, s, OMe), 4.48 (2H, s, C*H*$_2$OTBS), 5.85 (1H, s, ArO*H*, exchange with D_2O), 5.96 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 6.54 (1H, d, *J*=1.8 Hz, Ar-4′ or 6′-*H*), 7.29 (1H, s, Ar-6-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.3, 25.9, 52.4, 56.4, 61.3, 61.4, 61.4, 64.4, 103.4, 106.0, 108.8, 119.6, 134.1, 137.5, 142.4, 147.3, 147.4, 149.5, 150.3, 151.8, 165.4. Anal. Calcd for $C_{25}H_{36}O_9Si$: C, 59.03; H, 7.13. Found: C, 58.73; H, 7.09; FAB-mass (positive ion mode) *m*/*z*: 508[M]$^+$, 509[M+H]$^+$.

*4.1.4. 5-tert-Butyldimethylsilyloxymethyl-2-methoxy-3-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-phenyl-2-iodo-3,4,5-trimethoxybenzoate (**25**).* To a solution of **6** (4.38 g, 13.0 mmol) and **24** (5.49 g, 10.8 mmol) in CH_2Cl_2 (100 mL), EDC (3.10 g, 16.2 mmol) and DMAP (0.396 g, 3.24 mmol) were added at room temperature. After stirring for 3 h under Ar atmosphere, the reaction mixture was poured into H_2O (200 mL) and then extracted with CH_2Cl_2 (100 mL×3). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated to give the pale yellow residue (11.3 g), which was purified by silica gel column chromatography (1:2; EtOAc/hexane), providing **25** (8.93 g, 100%) as a colorless amorphous foam: IR ($CHCl_3$) ν_{max} 3020, 2940, 2860, 1730, 1590, 1460, 1430, 1340, 1230, 1200, 1170, 1125, 1105, 1080, 1040, 1000, 840, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.02 (6H, s, Si*Me*$_2$), 0.81 (9H, s, Si^t*Bu*), 3.75 (3H, s, OMe), 3.78 (3H, s, OMe), 3.91 (3H, s, OMe), 3.93 (3H, s, OMe), 3.95 (3H, s, OMe), 3.96 (6H, s, OMe), 4.04 (3H, s, OMe), 4.57 (2H, s, C*H*$_2$OTBS), 6.39 (1H, d, *J*=2.0 Hz, phenyl-6-*H*), 6.80 (1H, d, *J*=2.5 Hz, phenyl-4-*H*), 7.31 (1H, s, phenyl-5′-*H*), 7.52 (1H, s, benzoate-6-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.2, 25.9, 52.5, 56.4, 56.5, 61.0, 61.2, 61.3, 61.3, 61.5, 63.9, 84.9, 108.9, 109.6, 111.4, 113.0, 119.5, 129.9, 137.1, 139.4, 142.3, 144.1, 145.6, 147.2, 147.3, 150.4, 153.0, 153.5, 154.2, 164.6, 165.4; HRMS (FAB, positive ion mode) calculated for $C_{35}H_{46}O_{13}SiI$ [M+H]$^+$: 829.1753; found: 829.1744 [M+H]$^+$.

*4.1.5. 1-tert-Butyldimethylsilyloxymethyl-3-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-4,8,9,10-tetramethoxydibenzo [b,d] pyran-6-one (**26**).* To a stirring solution of **25** (8.47 g, 10.2 mmol) in DMA (150 mL), NaOAc (1.68 g, 20.5 mmol), $Pd(OAc)_2$ (572 mg, 2.55 mmol), and PPh_3 (1.34 g, 5.11 mmol) were added at room temperature. The resulting mixture was heated at 120 °C and stirred under Ar atmosphere. After 80 min, the reaction mixture was cooled to room temperature, diluted with EtOAc (300 mL), and filtrated to remove solid material. The filtrate was poured into H_2O (500 mL) and extracted with EtOAc (300 mL×3). The combined organic layer was washed with brine (200 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the resulting residue (15.2 g) was purified by silica gel column chromatography (1:2; EtOAc/hexane) and recrystallization from EtOAc/hexane, providing **26** (3.77 g, 53%) as colorless needles: mp 171–173 °C (EtOAc/hexane); IR (KBr) ν_{max} 2950, 2850, 1735, 1595, 1480, 1460, 1430, 1340, 1220, 1120, 1080, 1000, 840, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.18 (6H, s, Si*Me*$_2$), 0.70 (9H, s, Si^t*Bu*), 3.49 (3H, s, OMe), 3.72 (3H, s, OMe), 3.80 (3H, s, OMe), 3.94 (3H, s, OMe), 3.98 (3H, s, OMe), 4.00 (3H, s, OMe), 4.05 (3H, s, OMe), 4.16 (3H, s, OMe), 4.60 (2H, s, C*H*$_2$OTBS), 6.77 (1H, s, Ar-2-*H*), 7.33 (1H, s, Ar-5′-*H*), 7.69 (1H, s, Ar-7-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, 18.2, 25.8, 52.3, 56.4, 56.5, 61.3, 61.4, 61.5, 61.5, 61.9, 64.0, 108.0, 109.0, 109.6, 110.2, 118.1, 119.4, 123.3, 134.7, 135.0, 142.3, 144.2, 147.2, 147.4, 148.4, 149.5, 150.5, 152.3, 153.1, 161.0, 165.2. Anal. Calcd for $C_{35}H_{44}O_{13}Si$: C, 59.98; H, 6.33. Found: C, 59.74; H, 6.31; FAB-mass (positive ion mode) *m*/*z*: 700[M]$^+$, 701[M+H]$^+$.

*4.1.6. (S)-6-tert-Butyldimethylsilyloxymethyl-2-hydroxy-6′-hydroxymethyl-2′,3,3′4′-tetramethoxy-4-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-1,1′-biphenyl (**27**).* To a solution of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (2.37 g, 8.55 mmol) in THF (50 mL), 1.06 M BH_3·THF in THF solution (10.8 mL, 11.4 mmol) was added at 0 °C and the mixture was warmed to room temperature. After stirring for 30 min under N_2 atmosphere, a solution of **26** (2.00 g, 2.85 mmol) in THF (120 mL) was dropwise added for 1 h at −40 °C and the resulting mixture was stirred for 15 h at the same temperature. The reaction mixture was then quenched with H_2O (50 mL), evaporated to remove most of THF, and poured into H_2O (50 mL). The aqueous solution was acidified with 10% HCl aq (0.5 mL) and extracted with Et_2O (120 mL×3). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the pale yellow residue (5.08 g) was purified by silica gel column chromatography (2:1; EtOAc/hexane), providing **27** (1.93 g, 96%, 98% ee) as a colorless solid: mp 77.9–80.9 °C (Et_2O/hexane); $[\alpha]_D^{18}$ −2.4 (*c* 0.54, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3680, 3000, 2940, 2860, 1710, 1595, 1485, 1460, 1435, 1420, 1340, 1235, 1120, 1090, 1000, 840, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.19 (3H, s, Si*Me*), −0.19 (3H, s, Si*Me*), 0.68 (9H, s, Si^t*Bu*), 3.56 (3H, s, OMe), 3.74 (3H, s, OMe), 3.76 (3H, s, OMe), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 3.96 (3H, s, OMe), 4.07 (1H, d, B of AB, *J*=13.2 Hz, CH$_A$*H*$_B$), 4.13 (3H, s, OMe), 4.21 (1H, d, A of AB, *J*=13.2 Hz, C*H*$_A$H$_B$), 4.24 (2H, s, C*H*$_2$), 6.26 (1H, s, 5-*H*), 6.91 (1H, s, 5′-*H*), 7.30 (1H, s, Phenoxy-5-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.5, 18.2, 25.8, 52.3, 56.0, 56.4, 60.9, 61.1, 61.3, 61.3, 61.5, 62.8, 63.8, 105.3, 108.6, 108.9, 114.1, 119.6, 120.6, 134.3, 135.9, 136.1, 142.0, 142.5, 146.7, 147.3, 147.4, 150.4, 151.3, 151.6, 153.4, 165.5. Anal. Calcd for $C_{35}H_{48}O_{13}Si$: C, 59.64; H, 6.86. Found: C, 59.64; H, 6.98; FAB-mass (positive ion mode) *m*/*z*: 704 [M]$^+$; HPLC conditions: Daicel CHIRALPACK® AD, ^{i}PrOH/hexane 1:15, 1.0 mL min^{-1}, 254 nm, $t_{R\ (minor)}$=24.7 min, $t_{R\ (major)}$=29.4 min.

*4.1.7. (S)-6-tert-Butyldimethylsilyloxymethyl-6′-hydroxymethyl-2,2′,3,3′4′-pentamethoxy-4-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-1,1′-biphenyl (**28**).* To a solution of **27** (1.86 g, 2.64 mmol) in THF (60 mL), MeI (0.2 mL, 3.21 mmol) and ^{t}BuOK (0.360 g, 3.21 mmol) were added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 48 h under N_2 atmosphere. The reaction mixture was poured into H_2O (100 mL) and extracted with Et_2O (150 mL×3). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the resulting residue (1.97 g) was purified by silica gel column chromatography (1:1; EtOAc/hexane), providing **28** (1.52 g, 80%, 97% ee) as a pale yellow amorphous: $[\alpha]_D^{18}$ +17.6 (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3020, 2940, 2860, 1710, 1595, 1480, 1460, 1430, 1415, 1395, 1350, 1320, 1235, 1120, 1090, 1000, 840, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.19 (3H, s, Si*Me*), −0.18 (3H, s, Si*Me*), 0.68 (9H, s, Si^t*Bu*), 3.66 (3H, s, OMe), 3.73 (3H, s, OMe), 3.74 (3H, s, OMe), 3.78 (3H, s, OMe), 3.86 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 3.96 (3H, s, OMe), 4.03 (1H, d, B of AB, *J*=13.5 Hz, CH$_A$*H*$_B$OTBS), 4.04 (3H, s, OMe), 4.15 (2H, s, ArC*H*$_2$OH), 4.24 (1H, d, A of AB, *J*=13.5 Hz, C*H*$_A$H$_B$OTBS), 6.48 (1H, s, Ar-5-*H*), 6.87 (1H, s, Ar-5′-*H*), 7.30 (1H, s, phenoxy-5-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.5, 18.2, 25.8, 52.3, 56.0, 56.4, 60.7, 60.9, 61.1, 61.3, 61.3, 62.6, 63.9, 108.4, 108.8, 108.9, 119.5, 121.0, 121.1, 135.7, 135.8, 140.7, 141.5, 143.0, 147.2, 147.4, 150.2, 151.0, 151.2, 152.7, 153.4, 165.6; HRMS (EI) calculated for $C_{36}H_{50}O_{13}Si$ [M]$^+$: 718.3021; found: 718.2998 [M]$^+$; HPLC conditions: Daicel CHIRALCEL® OD, ^{i}PrOH/hexane 1:15, 0.5 mL min^{-1}, 254 nm, $t_{R(minor)}$=35.6 min, $t_{R\ (major)}$=44.3 min.

*4.1.8. (S)-6′-tert-Butyldimethylsilyloxymethyl-2,2′,3,3′4-pentamethoxy-4′-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-1,1′-biphenyl-6-carboxylic acid (**18**).* To a stirring suspension of PDC (1.46 g, 3.88 mmol) in CH_2Cl_2 (10 mL), a solution of **28** (1.40 g, 1.95 mmol) in CH_2Cl_2 (30 mL) was added at 0 °C. After stirring for 25 h at room temperature, the reaction mixture was filtrated with

Celite and the filtrate was evaporated. The resulting residue (1.68 g) was purified by silica gel column chromatography (1:2; EtOAc/hexane), providing aldehyde (1.16 g, 83%, 96% ee) as a colorless amorphous: $[\alpha]_D^{15}$ +3.5 (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3010, 2940, 2860, 1710, 1680, 1590, 1480, 1460, 1430, 1415, 1350, 1320, 1230, 1120, 1090, 1000, 840, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.213 (3H, s, Si*Me*), −0.209 (3H, s, Si*Me*), 0.67 (9H, s, Si^t*Bu*), 3.62 (3H, s, OMe), 3.73 (3H, s, OMe), 3.75 (3H, s, OMe), 3.79 (3H, s, OMe), 3.92 (3H, s, OMe), 3.96 (3H, s, OMe), 3.97 (3H, s, OMe), 3.98 (3H, s, OMe), 4.04 (3H, s, OMe), 4.07 (1H, d, B of AB, *J*=14.0 Hz, CH_AH_BOTBS), 4.21 (1H, d, A of AB, *J*=14.0 Hz, CH_AH_BOTBS), 6.51 (1H, s, Ar-5-*H*), 7.30 (1H, s, Ar*H*), 7.35 (1H, s, Ar*H*), 9.55 (1H, s, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.6, 18.1, 25.8, 52.3, 56.2, 56.4, 60.8, 61.2, 61.3, 61.4, 62.5, 105.1, 107.8, 108.9, 117.2, 119.5, 128.2, 129.8, 136.2, 140.3, 142.8, 147.3, 147.4, 147.8, 150.3, 151.3, 151.7, 153.4, 153.4, 165.5, 191.3. Anal. Calcd for $C_{36}H_{48}O_{13}Si$: C, 60.32; H, 6.75. Found: C, 60.22; H, 7.05; FAB-mass (positive ion mode) *m*/*z*: 716 $[M]^+$, 717 $[M+H]^+$; HPLC conditions: Daicel CHIRALPACK® AD, ^{i}PrOH/hexane 1:30, 0.5 mL min^{-1}, 254 nm, $t_{R\ (minor)}$=18.6 min, $t_{R\ (major)}$=21.5 min. The above aldehyde (1.10 g, 1.50 mmol) was dissolved in THF (10 mL) and ^{t}BuOH (10 mL), and 2-methyl-2-butene (1.30 mL, 12.2 mmol) was added. The mixture was stirred at room temperature, and a solution of 80% $NaClO_2$ (0.520 g, 4.60 mmol) and $NaH_2PO_4\cdot 2H_2O$ (1.20 g, 7.69 mmol) in H_2O (10 mL) was dropwise added at room temperature. After stirring for 3 h, the reaction mixture was poured into H_2O (10 mL) and extracted with Et_2O (50 mL×3). The combined organic layer was washed with brine (30 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the resulting residue (1.54 g) was purified by silica gel column chromatography (1:1; EtOAc/hexane), providing **18** (1.07 g, 95%) as a colorless amorphous: $[\alpha]_D^{15}$ +16.0 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3010, 2940, 2860, 1720, 1595, 1480, 1460, 1430, 1420, 1400, 1350, 1320, 1230, 1120, 1085, 1035, 1000, 840, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.17 (3H, s, Si*Me*), −0.14 (3H, s, Si*Me*), 0.68 (9H, s, Si^t*Bu*), 3.59 (3H, s, OMe), 3.75 (3H, s, OMe), 3.75 (3H, s, OMe), 3.77 (3H, s, OMe), 3.93 (3H, s, OMe), 3.93 (3H, s, OMe), 3.94 (3H, s, OMe), 3.96 (3H, s, OMe), 4.00 (3H, s, OMe), 4.11 (1H, d, B of AB, *J*=11.5 Hz, CH_AH_BOTBS), 4.33 (1H, d, A of AB, *J*=11.5 Hz, CH_AH_BOTBS), 6.33 (1H, s, Ar-5′-*H*), 7.21 (1H, s, Ar*H*), 7.29 (1H, s, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.7, −5.6, 18.2, 25.8, 52.3, 56.2, 56.3, 60.7, 61.0, 61.0, 61.0, 61.2, 61.3, 63.8, 108.6, 108.8, 109.5, 119.6, 121.8, 124.2, 127.0, 134.0, 141.0, 143.0, 145.9, 147.3, 147.4, 150.2, 151.3, 151.4, 152.7, 152.8, 165.8, 170.6; HRMS (EI) calculated for $C_{36}H_{48}O_{14}Si$ $[M]^+$: 732.2813; found: 732.2839 $[M]^+$.

*4.1.9. Methyl 4-O-tert-butyldimethylsilyl-6-O-[(S)-2-{6-hydroxymethyl-2,3-dimethoxy-4-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-phenyl}-3,4,5-trimethoxybenzoyl]-2,3-di-O-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (**30**).* To a solution of **18** (742 mg, 1.01 mmol) and **29** (845 mg, 1.21 mmol) in CH_2Cl_2 (12 mL), EDC (350 mg, 1.83 mmol) and DMAP (50.0 mg, 0.410 mmol) were added at room temperature. After stirring for 24 h under N_2 atmosphere, the reaction mixture was poured into H_2O (25 mL) and then extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was washed with brine (25 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the colorless residue (1.67 g) was subjected to silica gel column chromatography (1:1; EtOAc/hexane), providing a mixture (1.47 g) of ester product and **29** as a colorless amorphous foam. The obtained mixture was directly dissolved in THF (7 mL) and H_2O (14 mL), and then AcOH (42 mL) was added to the solution which was stirred at room temperature. After 9 h, the reaction mixture was extracted with Et_2O (100 mL×3) and the combined organic layer was washed with satd $NaHCO_3$ aq (80 mL×3), H_2O (80 mL), and brine (80 mL). The organic solution was dried over $MgSO_4$, filtrated, and evaporated. The resulting residue (1.37 g) was purified by silica gel column chromatography (2:1; EtOAc/hexane), providing colorless amorphous **30** (1.05 g, 80%) as a single diastereoisomer: $[\alpha]_D^{17}$ +88.5 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2940, 2360, 1720, 1590, 1460, 1420, 1340, 1230, 1130, 1085, 840, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.09 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*), 0.77 (9H, s, Si^t*Bu*), 2.64 (1H, t, *J*=6.0 Hz, CH_2OH, exchange with D_2O), 3.39 (3H, s, OMe), 3.58 (3H, s, OMe), 3.754 (3H, s, OMe), 3.75 (3H, s, OMe), 3.76 (6H, s, OMe), 3.83 (9H, s, OMe), 3.85 (6H, s, OMe), 3.85 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 3.94 (3H, s, OMe), 3.95 (3H, s, OMe), 3.99−4.14 (3H, m), 4.00 (3H, s, OMe), 4.64 (1H, dd, A of ABX, *J*=1.2, 11.6 Hz, 6-*H*), 4.90 (1H, dd, *J*=3.6, 10.0 Hz, 2-H), 5.08 (1H, d, *J*=3.6 Hz, 1-*H*), 5.82 (1H, dd, *J*=8.4, 10.0 Hz, 3-*H*), 6.48 (1H, s, Valoneoyl-*H*), 7.17 (2H, s, Galloyl-*H*), 7.18 (2H, s, Galloyl-*H*), 7.264 (1H, s, Valoneoyl-*H*), 7.35 (1H, s, Valoneoyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.0, 17.9, 25.6, 52.2, 55.4, 56.1, 56.2, 56.3, 56.3, 60.8, 60.9, 60.9, 60.9, 61.0, 61.1, 61.2, 61.3, 63.5, 63.9, 69.9, 70.1, 72.9, 73.5, 96.7, 107.0, 107.2, 108.8, 109.3, 110.9, 119.5, 123.3, 124.1, 124.9, 125.9, 126.1, 134.9, 141.7, 142.6, 142.6, 143.1, 146.2, 147.3, 147.4, 150.2, 151.1, 152.0, 152.6, 152.9, 153.0, 153.1, 165.8, 165.8, 165.9, 166.6; HRMS (FAB, positive ion mode) calculated for $C_{63}H_{81}O_{27}Si$ $[M+H]^+$: 1297.4735; found: 1297.4753 $[M+H]^+$.

*4.1.10. Methyl 4-O-tert-butyldimethylsilyl-6-O-[(S)-2-{6-carboxy-2,3-dimethoxy-4-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-phenyl}-3,4,5-trimethoxybenzoyl]-2,3-di-O-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (**31**).* To a solution of **30** (873 mg, 0.673 mmol) in CH_2Cl_2 (25 mL), Dess−Martin periodinane (570 mg, 1.34 mmol) was added at room temperature. After the reaction mixture was stirred for 3 h, it was quenched with 10% $Na_2S_2O_3$ aq (10 mL), poured into H_2O (40 mL), and extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was washed with brine (25 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the colorless residue (978 mg) was purified by silica gel column chromatography (2:1; EtOAc/hexane), providing aldehyde (865 mg, 99%) as a colorless amorphous: $[\alpha]_D^{18}$ +52.9 (*c* 0.66, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3020, 2940, 1720, 1685, 1590, 1460, 1420, 1340, 1230, 1175, 1130, 1090, 1035, 1000, 840, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.11 (3H, s, Si*Me*), 0.02 (3H, s, Si*Me*), 0.75 (9H, s, Si^t*Bu*), 3.37 (3H, s, OMe), 3.58 (3H, s, OMe), 3.74 (6H, s, OMe), 3.75 (3H, s, OMe), 3.827 (6H, s, OMe), 3.833 (3H, s, OMe), 3.85 (9H, s, OMe), 3.93 (3H, s, OMe), 3.948 (3H, s, OMe), 3.954 (3H, s, OMe), 3.96 (3H, s, OMe), 4.12 (3H, s, OMe), 4.58 (1H, dd, A of ABX, *J*=1.6, 11.6 Hz, 6-*H*), 4.92 (1H, dd, *J*=3.6, 10.4 Hz, 2-*H*), 5.11 (1H, d, *J*=3.6 Hz, 1-*H*), 5.82 (1H, dd, *J*=8.4, 10.4 Hz, 3-*H*), 6.93 (1H, s, Valoneoyl-*H*), 7.17 (2H, s, Galloyl-*H*), 7.19 (2H, s, Galloyl-*H*), 7.29 (1H, s, Valoneoyl-*H*), 7.46 (1H, s, Valoneoyl-*H*), 9.46 (1H, s, C*H*O), glu-4-, 5-, and 6′-*H* overlapped with OMe signals; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.0, 17.9, 25.6, 52.3, 55.4, 56.2, 56.3, 56.3, 56.4, 60.7, 61.0, 61.0, 61.0, 61.2, 61.2, 61.2, 61.4, 63.6, 70.0, 70.1, 73.0, 73.6, 96.7, 107.0, 107.2, 108.5, 109.1, 109.5, 119.4, 123.4, 124.2, 124.9, 126.0, 129.4, 129.6, 142.6, 142.6, 146.1, 147.2, 147.5, 147.5, 150.6, 151.5, 152.4, 153.1, 165.3, 165.5, 165.8, 165.9, 190.5.; FAB-mass (positive ion mode) *m*/*z*: 1295 $[M+H]^+$. To a solution of the above aldehyde (256 mg, 0.198 mmol) in THF (4 mL) and ^{t}BuOH (4 mL), 2-methyl-2-butene (0.166 mL, 1.58 mmol) was added at room temperature. A solution of 80% $NaClO_2$ (67.2 mg, 0.594 mmol) and $NaH_2PO_4\cdot 2H_2O$ (155 mg, 0.994 mmol) in H_2O (2 mL) was dropwise added to the mixture. After stirring for 12 h, the reaction mixture was acidified with 10% HCl aq (1 mL) and extracted with Et_2O (20 mL×3). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the yellow residue (283 mg) was purified by silica gel column chromatography (1:14:28; EtOH/EtOAc/$CHCl_3$), providing **31** (193 mg, 74%) as a colorless amorphous: $[\alpha]_D^{19}$ +65.1 (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3020, 2940, 2360, 1720, 1590, 1460, 1420, 1340, 1230, 1130, 1085, 675, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.10 (3H, s, Si*Me*), 0.06

(3H, s, Si*Me*), 0.76 (9H, s, Si^t*Bu*), 3.38 (3H, s, OMe), 3.57 (3H, s, OMe), 3.68 (3H, s, OMe), 3.74 (3H, s, OMe), 3.76 (3H, s, OMe), 3.83 (6H, s, OMe), 3.84 (3H, s, OMe), 3.858 (6H, s, OMe), 3.862 (3H, s, OMe), 3.88 (3H, s, OMe), 3.93 (6H, s, OMe), 3.95 (3H, s, OMe), 4.06 (3H, s, OMe), 4.10 (1H, dd, B of ABX, *J*=5.2, 11.6 Hz, 6-*H*), 4.63 (1H, dd, A of ABX, *J*=1.2, 11.6 Hz, 6-*H*), 4.91 (1H, dd, *J*=3.6, 10.4 Hz, 2-*H*), 5.09 (1H, d, *J*=3.6 Hz, 1-*H*), 5.82 (1H, dd, *J*=8.4, 10.4 Hz, 3-*H*), 6.98 (1H, s, Valoneoyl-*H*), 7.17 (2H, s, Galloyl-*H*), 7.19 (2H, s, Galloyl-*H*), 7.27 (1H, s, Valoneoyl-*H*), 7.36 (1H, s, Valoneoyl-*H*), glu-4- and 5-*H* overlapped with OMe signals; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.0, 18.0, 25.6, 52.3, 55.3, 55.9, 56.2, 56.3, 56.3, 60.6, 60.8, 60.9, 61.0, 61.0, 61.0, 61.2, 61.3, 63.4, 70.0, 70.2, 73.0, 73.6, 96.7, 107.1, 107.2, 108.9, 108.9, 112.7, 119.4, 124.2, 124.5, 124.6, 125.0, 127.1, 127.1, 142.6, 142.6, 142.7, 146.0, 146.2, 147.2, 147.4, 150.4, 151.5, 151.7, 152.0, 152.3, 153.1, 165.7, 165.8, 165.9, 166.0, 170.1; HRMS (FAB, negative ion mode) calculated for $C_{63}H_{77}O_{28}Si$ $[M-H]^-$: 1309.4371; found: 1309.4405 $[M-H]^-$.

*4.1.11. All-methylated isorugosin B (hexadecamethyl derivative of isorugosin B) (**2**).* To a solution of **31** (55.6 mg, 42.4 μmol) in THF (4 mL), TBAF (85.0 μL, 85.0 μmol) was added at room temperature. After stirring for 30 min under N_2 atmosphere, the reaction mixture was poured into H_2O (10 mL), acidified with 10% HCl aq (1 mL), and extracted with Et_2O (15 mL×3). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated to afford desilylated product (41.1 mg) as a colorless amorphous, which was used in the next reaction without further purification. The obtained material was dissolved in CH_2Cl_2 (42 mL), and then EDC (81.3 mg, 424 μmol) and DMAP (25.9 mg, 212 μmol) were added to the solution at room temperature. The reaction mixture was stirred for 42 h under N_2 atmosphere, it was poured into H_2O (40 mL) and extracted with Et_2O (40 mL×3). The combined organic layer was washed with brine (40 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the resulting residue (87.3 mg) was purified by silica gel column chromatography (1:7; EtOAc/CH_2Cl_2), providing all-methylated isorugosin B (**2**) (15.8 mg, 32%) as a colorless amorphous: $[\alpha]_D^{25}$ +28.0 (*c* 1.52, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ 3.44 (3H, s, OMe), 3.64 (3H, s, OMe), 3.66 (3H, s, OMe), 3.69 (3H, s, OMe), 3.70 (3H, s, OMe), 3.74 (3H, s, OMe), 3.75 (6H, s, OMe), 3.76 (3H, s, OMe), 3.85 (6H, s, OMe), 3.89 (3H, s, OMe), 3.90 (3H, s, OMe), 3.94 (3H, s, OMe), 3.95 (1H, dd, B of ABX, *J*=1.2, 13.2 Hz, 6-*H*), 3.98 (3H, s, OMe), 4.00 (3H, s, OMe), 4.44 (1H, ddd, *J*=1.2, 6.4, 10.0 Hz, 5-*H*), 5.15 (1H, dd, *J*=4.0, 10.0 Hz, 2-*H*), 5.17 (1H, t, *J*=10.0 Hz, 4-*H*), 5.25 (1H, dd, A of ABX, *J*=6.4, 13.2 Hz, 6-*H*), 5.26 (1H, d, *J*=4.0 Hz, 1-*H*), 5.67 (1H, t, *J*=10.0 Hz, 3-*H*), 6.34 (1H, s, Valoneoyl-*H*), 6.98 (1H, s, Valoneoyl-*H*), 7.13 (2H, s, Galloyl-*H*), 7.23 (2H, s, Galloyl-*H*), 7.29 (1H, s, Valoneoyl-*H*); ^{13}C NMR (100 MHz, acetone-d_6) δ 52.4, 55.9, 56.4, 56.5, 56.5, 56.8, 60.6, 60.7, 60.9, 61.1, 61.1, 61.2, 61.3, 61.6, 64.0, 67.5, 71.0, 72.2, 73.6, 98.4, 107.0, 108.0, 108.1, 109.1, 109.7, 120.5, 123.0, 124.1, 125.0, 125.1, 128.9, 129.9, 142.6, 143.8, 144.0, 145.1, 145.2, 148.0, 148.2, 151.7, 153.5, 153.6, 153.9, 154.2, 154.3, 154.3, 165.8, 165.9, 166.3, 167.6, 168.2; HRMS (FAB, negative ion mode) calculated for $C_{56}H_{59}O_{27}$ $[M-CH_3]^-$: 1163.3244; found: 1163.3221 $[M-CH_3]^-$.

*4.1.12. Methyl 4-O-[(S)-2{6-hydroxymethyl-2,3-dimethoxy-4-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-phenyl}-3,4,5-trimethoxybenzoyl]-6-O-methoxymethyl-2,3-di-O-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (**33**).* To a solution of **18** (983 mg, 1.34 mmol) and **32** (1.01 g, 1.61 mmol) in CH_2Cl_2 (20 mL), EDC (462 mg, 2.41 mmol) and DMAP (65.5 mg, 0.536 mmol) were added at room temperature. After stirring for 24 h under N_2 atmosphere, the reaction mixture was poured into H_2O (100 mL) and then extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the pale yellow residue (2.01 g) was purified by silica gel column chromatography (1:1; EtOAc/hexane), providing ester (1.16 g, 64%) as a colorless amorphous: $[\alpha]_D^{25}$ −1.0 (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3030, 3010, 2940, 2840, 1725, 1590, 1505, 1460, 1420, 1340, 1235, 1175, 1130, 1085, 1035, 1000, 920, 860, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.19, (3H, s, Si*Me*), −0.10 (3H, s, Si*Me*), 0.68 (9H, s, Si^t*Bu*), 3.09 (1H, dd, B of ABX, *J*=3.2, 11.6 Hz, 6-*H*), 3.29 (3H, s, OMe), 3.39 (3H, s, OMe), 3.51 (3H, s, OMe), 3.564 (3H, s, OMe), 3.572 (1H, dd, A of ABX, *J*=2.0, 11.6 Hz, 6-*H*), 3.68 (3H, s, OMe), 3.73 (3H, s, OMe), 3.80 (3H, s, OMe), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 3.86 (12H, s, OMe), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 3.94 (3H, s, OMe), 4.01 (3H, s, OMe), 4.06 (1H, d, B of AB, *J*=14.0 Hz, CH_AH_B), 4.19 (1H, d, A of AB, *J*=14.0 Hz, CH_AH_B), 4.54 (1H, d, B of AB, *J*=6.8 Hz, CH_AH_B), 4.60 (1H, d, A of AB, *J*=6.8 Hz, CH_AH_B), 5.03 (1H, dd, *J*=3.6, 10.0 Hz, 2-*H*), 5.20 (1H, d, *J*=3.6 Hz, 1-*H*), 5.54 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 5.77 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 6.50 (1H, s, Valoneoyl-*H*), 6.97 (1H, s, Valoneoyl-*H*), 7.16 (2H, s, Galloyl-*H*), 7.23 (2H, s, Galloyl-*H*), 7.28 (1H, s, Valoneoyl-*H*), glu-5-*H* overlapped with OMe signals; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.7, 18.0, 25.7, 52.2, 55.4, 55.6, 55.7, 56.2, 56.3, 56.3, 60.5, 60.7, 60.9, 61.0, 61.0, 61.0, 61.2, 61.4, 62.1, 64.9, 68.4, 68.4, 71.5, 72.7, 97.0, 97.1, 107.0, 107.0, 107.2, 108.9, 109.3, 119.7, 121.1, 124.3, 124.5, 124.5, 125.6, 136.0, 140.1, 142.5, 142.6, 143.2, 146.0, 147.4, 147.5, 150.3, 151.0, 151.6, 152.5, 152.9, 153.1, 153.1, 165.4, 165.6, 165.7, 165.8; HRMS (FAB, positive ion mode) calculated for $C_{65}H_{85}O_{28}Si$ $[M+H]^+$: 1341.4997; found: 1341.5002 $[M+H]^+$. To a solution of the above ester (1.00 g, 0.745 mmol) in THF (10 mL) and H_2O (20 mL), AcOH (60 mL) was added and stirred at room temperature. After 8 h, the reaction mixture was quenched with satd $NaHCO_3$ aq (300 mL) and extracted with Et_2O (250 mL×3). The combined organic layer was washed with satd $NaHCO_3$ aq (150 mL×3), H_2O (200 mL), and brine (200 mL) and then the resulting organic solution was dried over $MgSO_4$, filtrated, and evaporated. The yellow residue (941 mg) was purified by silica gel column chromatography (2:1; EtOAc/hexane), providing colorless amorphous **33** (862 mg, 94%) as a single diastereoisomer: $[\alpha]_D^{25}$ +9.9 (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3520, 3030, 3010, 2940, 2840, 1720, 1590, 1505, 1460, 1420, 1340, 1230, 1175, 1130, 1085, 1035, 1000, 920, 865, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (1H, t, *J*=6.4 Hz, CH_2OH), 3.28 (3H, s, OMe), 3.45 (3H, s, OMe), 3.51 (1H, dd, B of ABX, *J*=4.0, 11.6 Hz, 6-*H*), 3.54 (3H, s, OMe), 3.55 (3H, s, OMe), 3.64 (1H, dd, A of ABX, *J*=2.4, 11.6 Hz, 6-*H*), 3.75 (3H, s, OMe), 3.82 (9H, s, OMe), 3.84 (3H, s, OMe), 3.847 (6H, s, OMe), 3.854 (6H, s, OMe), 3.89 (3H, s, OMe), 3.93 (3H, s, OMe), 3.96 (3H, s, OMe), 4.01 (3H, s, OMe), 4.55 (1H, d, B of AB, *J*=6.8 Hz, OCH_AH_BOMe), 4.61 (1H, d, A of AB, *J*=6.8 Hz, OCH_AH_BOMe), 5.07 (1H, dd, *J*=3.2, 10.0 Hz, 2-*H*), 5.24 (1H, d, *J*=3.2 Hz, 1-*H*), 5.44 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 5.79 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 6.49 (1H, s, Valoneoyl-*H*), 7.11 (2H, s, Galloyl-*H*), 7.19 (2H, s, Galloyl-*H*), 7.23 (1H, s, Valoneoyl-*H*), 7.27 (1H, s, Valoneoyl-*H*), glu-5-*H* and CH_2OH overlapped with OMe signals; ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 55.6, 55.6, 56.0, 56.2, 56.2, 56.3, 60.4, 60.6, 60.9, 60.9, 61.0, 61.2, 61.4, 63.0, 65.4, 68.5, 68.6, 71.1, 72.5, 96.8, 97.0, 107.0, 107.2, 108.8, 108.9, 109.9, 119.6, 123.0, 124.0, 124.0, 124.7, 125.3, 134.6, 141.0, 142.7, 142.8, 143.0, 146.2, 147.3, 147.5, 150.2, 151.3, 151.6, 152.5, 152.8, 153.1, 165.2, 165.6, 165.8, 166.1; HRMS (FAB, positive ion mode) calculated for $C_{59}H_{71}O_{28}$ $[M+H]^+$: 1227.4132; found: 1227.4144 $[M+H]^+$.

*4.1.13. Methyl 4-O-[(S)-2-{6-carboxy-2,3-dimethoxy-4-(2,3,4-trimethoxy-6-methoxycarbonylphenoxy)-phenyl}-3,4,5-trimethoxybenzoyl]-6-O-methoxymethyl-2,3-di-O-(3,4,5-trimethoxybenzoyl)-α-D-glucopyranoside (**34**).* To a stirring suspension of PDC (918 mg, 2.44 mmol) in CH_2Cl_2 (50 mL), a solution of **33** (749 mg, 0.610 mmol) in CH_2Cl_2 (100 mL) was added at 0 °C. After stirring for 21 h at room temperature, the reaction mixture was filtrated with Celite and the filtrate was evaporated. The resulting residue

(778 mg) was purified by silica gel column chromatography (2:1; EtOAc/hexane), providing aldehyde (731 mg, 98%) as a colorless amorphous: $[\alpha]_D^{25}$ +24.4 (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3030, 3010, 2940, 2840, 1730, 1690, 1590, 1505, 1460, 1420, 1340, 1230, 1175, 1130, 1090, 1035, 1000, 920, 860, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.21 (1H, dd, B of ABX, *J*=4.0, 11.6 Hz, 6-H), 3.27 (3H, s, OMe), 3.42 (3H, s, OMe), 3.50 (3H, s, OMe), 3.54 (3H, s, OMe), 3.56 (1H, dd, A of ABX, *J*=2.4, 11.6 Hz, 6-*H*), 3.75 (3H, s, OMe), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 3.83 (6H, s, OMe), 3.84 (3H, s, OMe), 3.85 (9H, s, OMe), 3.90 (3H, s, OMe), 3.94 (3H, s, OMe), 3.97(3H, s, OMe), 4.10 (3H, s, OMe), 4.48 (1H, d, B of AB, *J*=6.8 Hz, OCH_AH_BOMe), 4.56 (1H, d, A of AB, *J*=6.8 Hz, OCH_AH_BOMe), 5.07 (1H, dd, *J*=3.6, 10.0 Hz, 2-H), 5.20 (1H, d, *J*=3.6 Hz, 1-*H*), 5.44 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 5.81 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 6.89 (1H, s, Valoneoyl-*H*), 7.12 (2H, s, Galloyl-*H*), 7.13 (1H, s, Valoneoyl-*H*), 7.20 (2H, s, Galloyl-*H*), 7.30 (1H, s, Valoneoyl-*H*), 9.42 (1H, s, C*H*O), glu-5-*H* was hidden by OMe signals; ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 55.4, 55.5, 56.0, 56.2, 56.2, 56.3, 60.6, 60.6, 60.9, 61.0, 61.0, 61.1, 61.2, 61.4, 65.2, 68.4, 68.9, 71.1, 72.4, 96.9, 97.0, 107.0, 107.2, 108.4, 109.0, 109.4, 119.3, 122.5, 124.1, 124.2, 125.6, 129.3, 129.6, 142.4, 142.6, 142.7, 146.0, 147.3, 147.5, 150.6, 151.7, 152.1, 153.0, 153.1, 153.1, 165.0, 165.2, 165.5, 165.7, 190.4; HRMS (FAB, positive ion mode) calculated for $C_{59}H_{69}O_{28}$ $[M+H]^+$: 1225.3975; found: 1225.3989 $[M+H]^+$. To a solution of the above aldehyde (642 mg, 0.524 mmol) in THF (6 mL) and ^{t}BuOH (6 mL), 2-methyl-2-butene (0.557 mL, 5.24 mmol) was added at room temperature. To the mixture, a solution of 80% $NaClO_2$ (178 mg, 1.57 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (409 mg, 2.62 mmol) in H_2O (6 mL) was dropwise added. After stirring for 2 h, the reaction mixture was poured into H_2O (50 mL) and extracted with Et_2O (50 mL×3). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the colorless residue (711 mg) was purified by silica gel column chromatography (1:14:14; EtOH/EtOAc/$CHCl_3$), providing **34** (650 mg, quant) as a colorless amorphous: $[\alpha]_D^{25}$ +41.6 (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3030, 3010, 2940, 2840, 1730, 1590, 1505, 1490, 1460, 1430, 1420, 1390, 1340, 1230, 1175, 1130, 1085, 1030, 1000, 920, 860, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.31 (1H, dd, B of ABX, *J*=8.0, 10.8 Hz, 6-*H*), 3.38 (3H, s, OMe), 3.43 (3H, s, OMe), 3.47 (3H, s, OMe), 3.52 (3H, s, OMe), 3.66 (1H, dd, A of ABX, *J*=1.2, 10.8 Hz, 6-*H*), 3.77 (3H, s, OMe), 3.780 (3H, s, OMe), 3.782 (6H, s, OMe), 3.81 (3H, s, OMe), 3.856 (3H, s, OMe), 3.862 (6H, s, OMe), 3.90 (3H, s, OMe), 3.92 (3H, s, OMe), 3.94(3H, s, OMe), 3.97 (3H, s, OMe), 4.06 (3H, s, OMe), 4.63 (1H, d, B of AB, *J*=6.8 Hz, OCH_AH_BOMe), 4.69 (1H, d, A of AB, *J*=6.8 Hz, OCH_AH_BOMe), 5.08 (1H, dd, *J*=3.2, 10.0 Hz, 2-*H*), 5.17 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 5.24 (1H, d, *J*=3.2 Hz, 1-*H*), 6.02 (1H, t, *J*=10.0 Hz, 3 or 4-*H*), 7.05 (1H, s, Valoneoyl-*H*), 7.09 (2H, s, Galloyl-*H*), 7.15 (1H, s, Valoneoyl-*H*), 7.23 (2H, s, Galloyl-*H*), 7.28 (1H, s, Valoneoyl-*H*), glu-5-*H* overlapped with OMe signals; ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 55.3, 55.5, 55.9, 56.2, 56.2, 56.3, 60.4, 60.6, 60.9, 60.9, 61.0, 61.1, 61.2, 61.3, 66.5, 68.6, 69.0, 70.9, 72.5, 96.4, 97.0, 107.0, 107.2, 108.8, 109.0, 112.8, 119.4, 123.3, 123.7, 124.1, 124.2, 127.1, 127.8, 142.6, 142.7, 142.7, 146.1, 146.2, 147.2, 147.3, 150.4, 151.4, 151.8, 152.0, 152.1, 153.0, 153.1, 165.0, 165.7, 165.7, 165.9, 167.1; HRMS (FAB, positive ion mode) calculated for $C_{59}H_{69}O_{29}$ $[M+H]^+$: 1241.3924; found: 1241.3931 $[M+H]^+$.

*4.1.14. All-methylated rugosin B (hexadecamethyl derivative of rugosin B) (**3**).* To a solution of **34** (150 mg, 0.121 mmol) in THF (7.5 mL) and MeOH (7.5 mL), 6 N HCl aq (15 mL) was added at 0 °C. After stirring for 12 h at room temperature, the reaction mixture was extracted with Et_2O (50 mL×3) and the combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the obtained residue (159 mg) was used in the next reaction without further purification. To a solution of the prepared material in CH_2Cl_2 (121 mL), EDC (928 mg, 4.84 mmol) and DMAP (296 mg, 2.42 mmol) were added at room temperature. The reaction mixture was stirred for 2.5 day under N_2 atmosphere, it was poured into H_2O (80 mL) and extracted with CH_2Cl_2 (100 mL×3). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, and filtrated. The filtrate was evaporated and the resulting residue (441 mg) was purified by silica gel column chromatography (1:1; EtOAc/hexane), providing all-methylated rugosin B (**3**) (89.9 mg, 63%) as a colorless amorphous: $[\alpha]_D^{25}$ +68.0 (*c* 1.16, acetone); ^1H NMR (400 MHz, acetone-d_6) δ 3.44 (3H, s, OMe), 3.68 (3H, s, OMe), 3.71 (3H, s, OMe), 3.74 (3H, s, OMe), 3.77 (3H, s, OMe), 3.78 (6H, s, OMe), 3.79 (3H, s, OMe), 3.81 (3H, s, OMe), 3.84 (3H, s, OMe), 3.87 (9H, s, OMe), 3.96 (6H, s, OMe), 4.04 (3H, s, OMe), 4.48 (1H, ddd, *J*=1.2, 6.4, 10.0 Hz, 5-*H*), 5.12 (1H, dd, *J*=4.0, 10.0 Hz, 2-*H*), 5.169 (1H, dd, A of ABX, *J*=6.4, 13.2 Hz, 6-*H*), 5.170 (1H, t, *J*=10.0 Hz, 4-*H*), 5.26 (1H, d, *J*=4.0 Hz, 1-*H*), 5.85 (1H, t, *J*=10.0 Hz, 3-*H*), 6.52 (1H, s, Valoneoyl-*H*), 6.79 (1H, s, Valoneoyl-*H*), 7.27 (2H, s, Galloyl-*H*), 7.28 (2H, s, Galloyl-*H*), 7.32 (1H, s, Valoneoyl-*H*), glu-6′-*H* overlapped with OMe signals; ^{13}C NMR (100 MHz, acetone-d_6) δ 52.5, 55.9, 56.4, 56.5, 56.6, 60.6, 60.7, 61.0, 61.0, 61.1, 61.2, 61.3, 61.7, 64.1, 67.5, 71.3, 72.2, 73.8, 98.3, 106.7, 108.1, 108.1, 109.3, 109.5, 120.6, 123.5, 124.1, 125.0, 125.3, 129.2, 129.6, 142.9, 143.8, 144.0, 145.0, 145.5, 148.0, 148.3, 151.7, 153.5, 153.8, 153.9, 154.2, 154.3, 154.3, 165.9, 166.0, 166.5, 167.8, 167.9; HRMS (FAB, positive ion mode) calculated for $C_{57}H_{63}O_{27}$ $[M+H]^+$: 1179.3557; found: 1179.3579 $[M+H]^+$.

Acknowledgements

We acknowledge the gracious assistance of Prof. T. Hatano and Dr. H. Ito (Okayama University) in providing the natural sample of **1** and a copy of NMR data for **2**. The authors also thank the SC-NMR Laboratory of Okayama University for the use of their facilities.

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.01.004. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. *Chemistry and Biology of Ellagitannins. An Underestimated Class of Bioactive Plant Polyphenols*; Quideau, S., Ed.; World Scientific Publishing Pte. Ltd.: Singapore, 2009.
2. (a) Okuda, T. *Phytochemistry* **2005**, *66*, 2012–2031; (b) Khanbabaee, K.; van Ree, T. *Nat. Prod. Rep.* **2001**, *18*, 641–649; (c) Okuda, T.; Yoshida, T.; Hatano, T. *Phytochemistry* **1993**, *32*, 507–521.
3. (a) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475–503; (b) Khanbabaee, K.; van Ree, T. *Synthesis* **2001**, 1585–1610; (c) Feldman, K. S. *Phytochemistry* **2005**, *66*, 1984–2000.
4. (a) Yamada, H.; Nagao, K.; Dokei, K.; Kasai, Y.; Michihata, N. *J. Am. Chem. Soc.* **2008**, *130*, 7566–7567; (b) Su, X.; Surry, D. S.; Spandl, R. J.; Spring, D. R. *Org. Lett.* **2008**, *10*, 2593–2596; (c) Feldman, K. S.; Lawlor, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7396–7397; (d) Feldman, K. S.; Lawlor, M. D.; Sahasrabudhe, K. *J. Org. Chem.* **2000**, *65*, 8011–8019.
5. (a) Yoshida, T.; Ito, H.; Hipolito, L. J. *Phytochemistry* **2005**, *66*, 1972–1983; (b) Jin, Z.-X.; Ito, H.; Yoshida, T. *Phytochemistry* **1998**, *48*, 333–338; (c) Yoshida, T.; Chou, T.; Shingu, T.; Okuda, T. *Phytochemistry* **1995**, *40*, 556–561; (d) Hatano, T.; Kira, R.; Yasuhara, T.; Okuda, T. *Heterocycles* **1988**, *27*, 2081–2085; (e) Hatano, T.; Kira, R.; Yasuhara, T.; Okuda, T. *Chem. Pharm. Bull.* **1988**, *36*, 3920–3927; (f) Okuda, T.; Hatano, T.; Yazaki, K.; Ogawa, N. *Chem. Pharm. Bull.* **1982**, *30*, 4230–4233; (g) Okuda, T.; Hatano, T.; Ogawa, N. *Chem. Pharm. Bull.* **1982**, *30*, 4234–4237.
6. (a) Hatano, T.; Yasuhara, T.; Matsuda, M.; Yazaki, K.; Yoshida, T.; Okuda, T. *Chem. Pharm. Bull.* **1989**, *37*, 2269–2271; (b) Hatano, T.; Yasuhara, T.; Matsuda, M.; Yazaki, K.; Yoshida, T.; Okuda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2735–2743.
7. Miyamoto, K.; Nomura, M.; Murayama, T.; Furukawa, T.; Hatano, T.; Yoshida, T.; Koshiura, R.; Okuda, T. *Biol. Pharm. Bull.* **1993**, *16*, 379–387.
8. Racemic synthesis of 1 was already performed: Lin, J.-H.; Ishimatsu, M.; Tanaka, T.; Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1990**, *38*, 1844–1851.
9. (a) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525–558; (b) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615–624; (c) Bringmann, G.; Breuning, M.; Preifer, R.-M.; Schenk, W. A.; Kamikawa, K.; Uemura, M. *J. Organomet. Chem.* **2002**, *661*, 31–47; (d) Bringmann, G.; Tasler, S.; Preifer, R.-M.; Breuning, M. *J. Organomet. Chem.* **2002**, *661*, 49–65; (e) Bringmann, G.;

Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427.
10. A part of this work has been published as a preliminary communication, see: (a) Abe, H.; Sahara, Y.; Matsuzaki, Y.; Takeuchi, Y.; Harayama, T. *Tetrahedron Lett.* **2008**, *49*, 605–609; (b) Shioe, K.; Takeuchi, Y.; Harayama, T.; Abe, H. *Chem. Pharm. Bull.* **2010**, *58*, 435–437.
11. (a) Abe, H.; Harayama, T. *Heterocycles* **2008**, *75*, 1305–1320; (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238; (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469 references cited therein.
12. Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L. *J. Org. Chem.* **1985**, *50*, 4933–4938.
13. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
14. (a) Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron* **2005**, *61*, 1909–1918; (b) Tanaka, M.; Ikeya, Y.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron* **1995**, *51*, 11703–11724.
15. (a) Horning, E. C.; Parker, J. A. *J. Am. Chem. Soc.* **1952**, *74*, 2107–2108; (b) Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533–9540.
16. Takeda, S.; Abe, H.; Takeuchi, Y.; Harayama, T. *Tetrahedron* **2007**, *63*, 396–408.
17. Cho, B. T. *Tetrahedron* **2006**, *62*, 7621–7643.
18. Ishimaru, K.; Ishimatsu, M.; Nonaka, G.; Mihashi, K.; Iwase, Y.; Nishioka, I. *Chem. Pharm. Bull.* **1988**, *36*, 3319–3327.
19. Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577–2580.
20. Compound **28** was reduced with $LiAlH_4$ and then quenched with 10% HCl aq to afforded triol **17**. The sign of optical rotation of **17** matched with that of **17** in Scheme 4.
21. Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
22. See, Supplementary data.
23. Yoshida, T.; Chou, T.; Maruyama, Y.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 2681–2686.