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Total synthesis of 3,3′,4-tri-*O*-methylellagic acid from gallic acid

Ashraful Alam[a] and Sadao Tsuboi[b,*]

[a]*Department of Chemistry, Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh*
[b]*Department of Material and Energy Science, Graduate School of Environmental Science, Okayama University, Tsushima, Okayama 700-8530, Japan*

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Abstract—Total synthesis of 3,3′,4-tri-*O*-methylellagic acid has been described from commercially available gallic acid. Construction of the crucial unsymmetric Ar–Ar bond has been carried out in various methods such as Heck coupling, Heck coupling followed by oxidation or anionic Fries rearrangement, Suzuki cross-coupling, etc., but all the attempts were unsuccessful. Then, finally it has been achieved by intramolecular Ullmann coupling reaction.

1. Introduction

Ellagic acid and its derivatives are very potent for their various biological activities such as anti-tumor,[1] anti-HIV,[2] anti-cancer,[3] anti-hepatitis,[4] anti-oxidant,[5] anti-microbial,[6] etc. Interestingly these compounds also exhibit free radical scavenging activity and thus are used in anti-aging supplement.[7] Takasaki et al.[8] reported the isolation of a variety of ellagic acid derivatives and their inhibitory effects on Epstein–Barr virus action. They found the enhanced inhibitory activity of some ellagic acid derivatives than the parent compound ellagic acid. For instance, 3,3′,4-tri-*O*-methylellagic acid and 3,3′,4-tri-*O*-methylellagic acid-4′-acetal are found to be 50 times more active than the parent ellagic acid. Besides the wide biological activities, these are used as important ingredients for anti-aging, skin lightening supplements, and other skin care cosmetics.[9] Earlier we have reported the isolation of 3,3′,4-tri-*O*-methylellagic acid from *Cassia alata* leaf extract,[10] and then we were interested in its total synthesis for the large supply as well as further study of it.

Unlike the symmetrically substituted 3,3′-di-*O*-methylellagic acid **1b**, syntheses of unsymmetrically substituted ellagic acids such as 3,3′,4-tri-*O*-methylellagic acid **1c** or 3,4,4′-tri-*O*-methylellagic acid **1d** are more challenging due to the construction of the required unsymmetric Ar–Ar bond. Syntheses and pharmaceutical study of a number of symmetric and several unsymmetric ellagic acid derivatives have been reported so far; but all of them were either isolated from natural species or derivatized from the ellagic acid **1a**. The process of derivatization of ellagic acid gives satisfactory result for the synthesis of symmetric derivatives, but not suitable at all for the synthesis of unsymmetric derivatives. For example, Ikeda et al.[11] and Takasaki et al.[8] have reported the syntheses of 3,3′,4-tri-*O*-methylellagic acid individually in 2.5% and 8% overall yields, respectively, by methylation of ellagic acid. Besides the very poor overall yields, the procedure of methylation is very cumbersome due to the formation of various methylated products and their separation is also difficult due to the extremely low solubility of all these methyl derivatives even in most of the commonly used polar solvents.

Herein, the total synthesis of 3,3′,4-tri-*O*-methylellagic acid is described via the construction of unsymmetric Ar–Ar bond, which has been achieved by the intramolecular Ullmann coupling of commercially available gallic acid. This strategy for the synthesis of 3,3′,4-tri-*O*-methylellagic acid can also provide a suitable route for the synthesis of other unsymmetric ellagic acid derivatives such as 3,4,4′-tri-*O*-methylellagic acid as well as many unsymmetric biaryls, particularly those highly hindered at *ortho*-positions. These biaryls are very important for the syntheses of various natural products containing the unsymmetric biaryl skeleton.

1.1. Formation of unsymmetric Ar–Ar bond by intermolecular cross-coupling

Among other methods, the 100-year old traditional Ullmann coupling is yet found to be very useful for the synthesis of many biaryls. But, most of them are symmetric biaryls and formation of the unsymmetric biaryls by the Ullmann cross-coupling is very rare. For the present case other commonly used cross-couplings such as reaction between aromatic Grignard reagents and aromatic halides mediated

* Corresponding author. Tel./fax: +81 86 251 8898; e-mail addresses: ashraf_sust@yahoo.com; stsuboi6@cc.okayama-u.ac.jp

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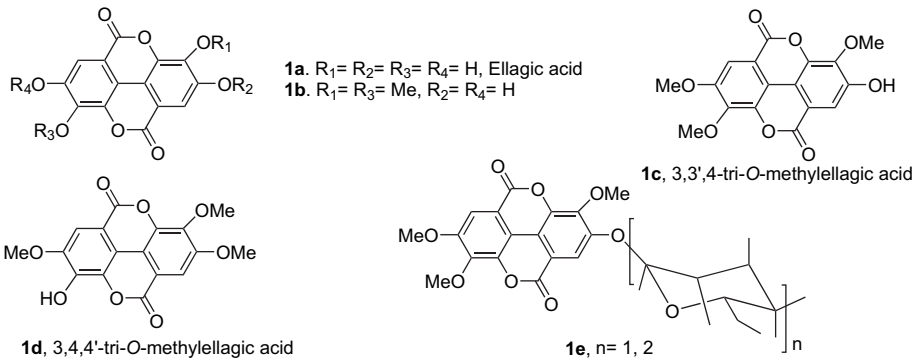


Figure 1. Ellagic acid and its derivatives.

by a variety of catalysts[12] are not suitable due to the presence of carbonyl group in both of the aromatics (Chart 1). Similarly, Suzuki cross-coupling between **5** and **6** (Chart 1) is also not suitable because it requires the use of organometallic reagent for the preparation of boronic acid component. Besides this, success of the cross-coupling reaction greatly depends on differences of the electronic environments of participating components; the higher the difference, the better the chance of getting the cross-coupling product. For the cross-coupling reaction the ratio of the symmetric and unsymmetric products is also highly dependent on the reaction conditions.[12,13]

1.2. Formation of unsymmetric Ar–Ar bond by intramolecular coupling

Unlike the symmetric Ullmann coupling, the intramolecular Ullmann coupling is rare and several methods for the intramolecular coupling have appeared so far. For example, Lipshutz et al.[14] developed a method for the synthesis of biaryls by intramolecular coupling of cyanocuprate intermediates. Intramolecular Ar–Ar bond formation via Heck type intramolecular coupling has been applied for the syntheses of a wide variety of natural products.[15] Intramolecular coupling reaction mediated by Grignard reagent[16] or Stille coupling[17] are also reported. Takahashi et al.[18] and Dai and Martin[19] have studied the formation of optically active biaryls by intramolecular coupling utilizing salicyl alcohol and glucoses, respectively, as template. Considering all the methods mentioned above, the unsymmetric Ar–Ar bond of 3,3′,4-tri-*O*-methylellagic acid has been planned to be constructed as depicted in Chart 1.

2. Results and discussion

In Chart 1 it has been shown that the ordinary cross-coupling between aryl bromides **3** and **4** is not suitable as both of them have the same structural and electronic environments. Thus, among other probable routes depicted, intramolecular Heck coupling was chosen first to carry out rather than other couplings.

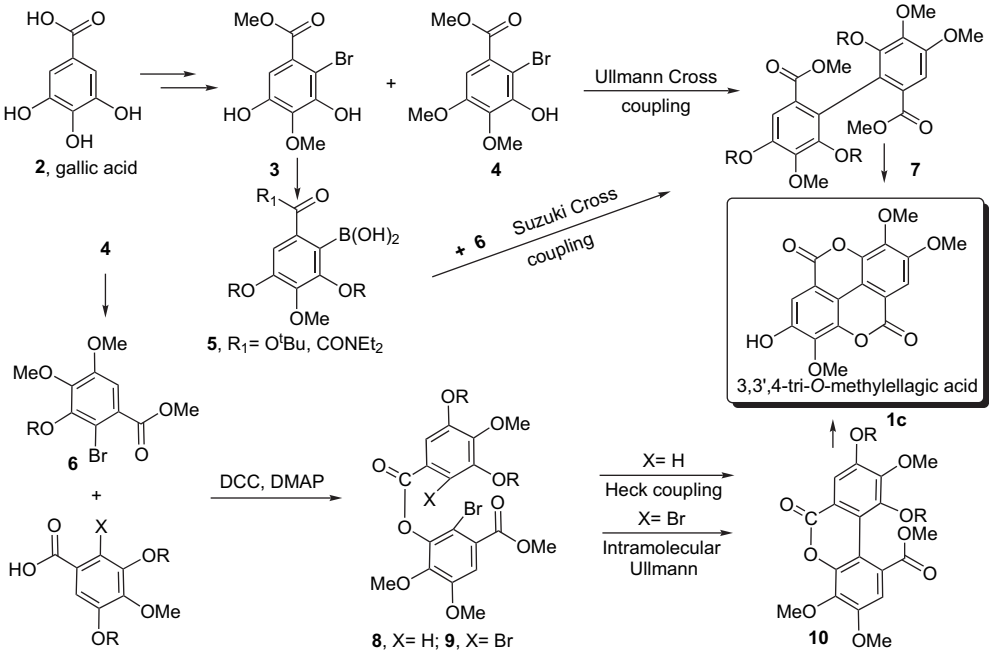
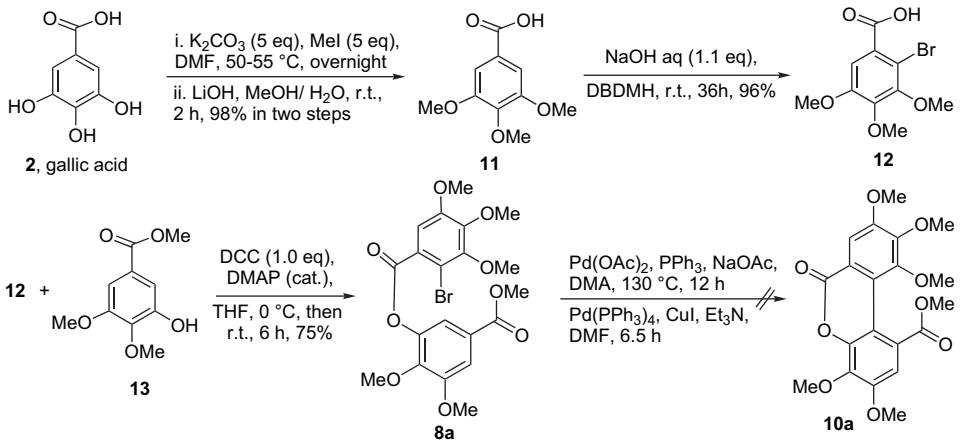


Chart 1. The probable routes for the synthesis of 3,3′,4-tri-*O*-methylellagic acid.



Scheme 1. Preparation and the Heck coupling of the model key intermediate **8a**.

2.1. Formation of unsymmetric Ar–Ar bond via intramolecular Heck type coupling

At first, the unsymmetric Ar–Ar bond of 3,3′,4-tri-*O*-methylellagic acid was planned to be synthesized from the intramolecular Heck coupling of compound **8** and thus a similar model key intermediate **8a** was prepared as shown in Scheme 1. Gallic acid **2** was treated with K_2CO_3 and MeI in DMF at 50–55 °C followed by hydrolysis of the methyl ester by treating with LiOH in MeOH/H_2O (1:1) at room temperature for 2 h to give the 3,4,5-trimethoxybenzoic acid **11** in 98% yield over two steps. Compound **11** was brominated with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in 1.1 equiv of aqueous NaOH to give the corresponding bromide **12** in 96% yield. Compound **12** was subjected to esterification with methyl 3-hydroxy-4,5-dimethoxybenzoate **13** in the presence of 1.0 equiv of DCC and catalytic amount of DMAP in THF at room temperature that resulted in the desired model key intermediate **8a** in 75% yield (Scheme 1).

After the easy access to the key intermediate **8a** in good overall yield from gallic acid **2** (71% overall yield from **2** over four steps), the next crucial step, intramolecular Heck coupling reaction was unsuccessful. Unfortunately, reaction of compound **8a** with Pd^{II} did not give the desired coupling product **10a** but recovered starting material or reduced debrominated product.

Not getting the desired coupling product **10a** with a variety of reagents was very much disappointing, though numerous examples of such coupling have been reported for the synthesis of a variety of natural products.[15] Then, literature survey revealed that among the reported examples of such coupling, none of them possesses a carbonyl group in one or both the aromatic rings. Similar disappointing result was also obtained by Bringmann et al.[20] Then, the problem with carbonyl functionality was planned to be overcome by any one of the following processes: (i) to convert another functional group (e.g., CH_3) to the carboxylic acid group after the coupling reaction, or (ii) to construct the required lactone by the remote anionic Fries rearrangement[20] (Chart 2). Between the two routes, the former one was tested first and for this purpose a model reaction was carried out with compound **8d** as shown in Scheme 2.

In Scheme 2, 2-bromo-3,4,5-trimethoxybenzoic acid **12** was esterified with the commercially available 3,5-dimethylphenol **16** in the presence of DCC to give the model intermediate **8d** in 98% yield. Treatment of compound **8d** with $Pd(OAc)_2$

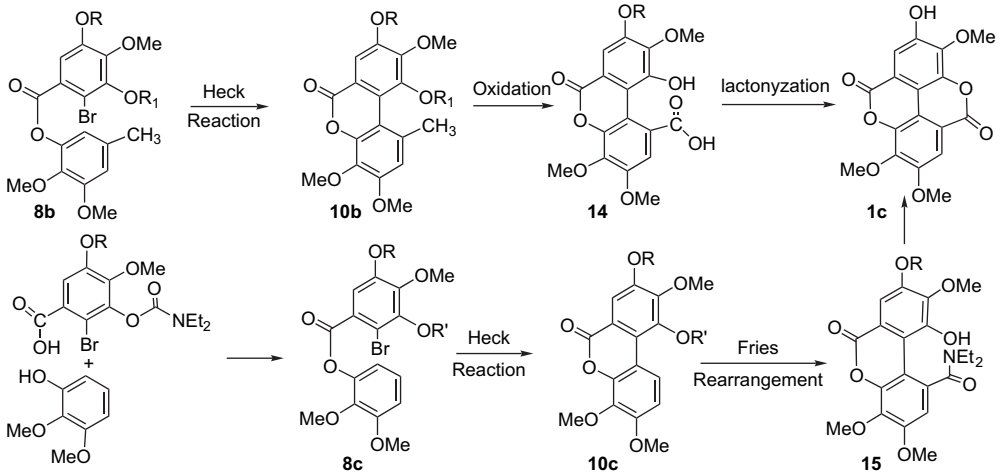
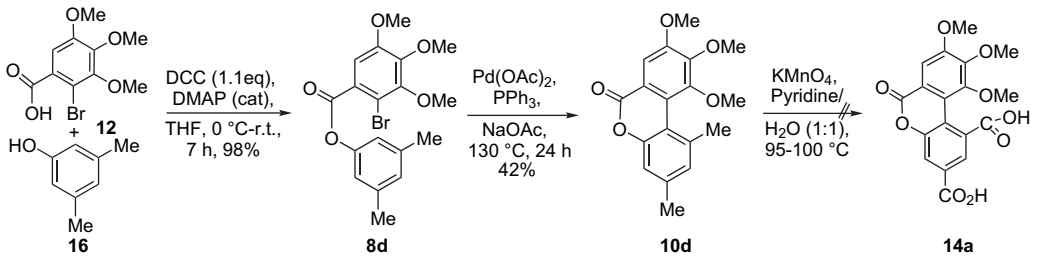


Chart 2. Heck coupling followed by oxidation or remote anionic Fries rearrangement.



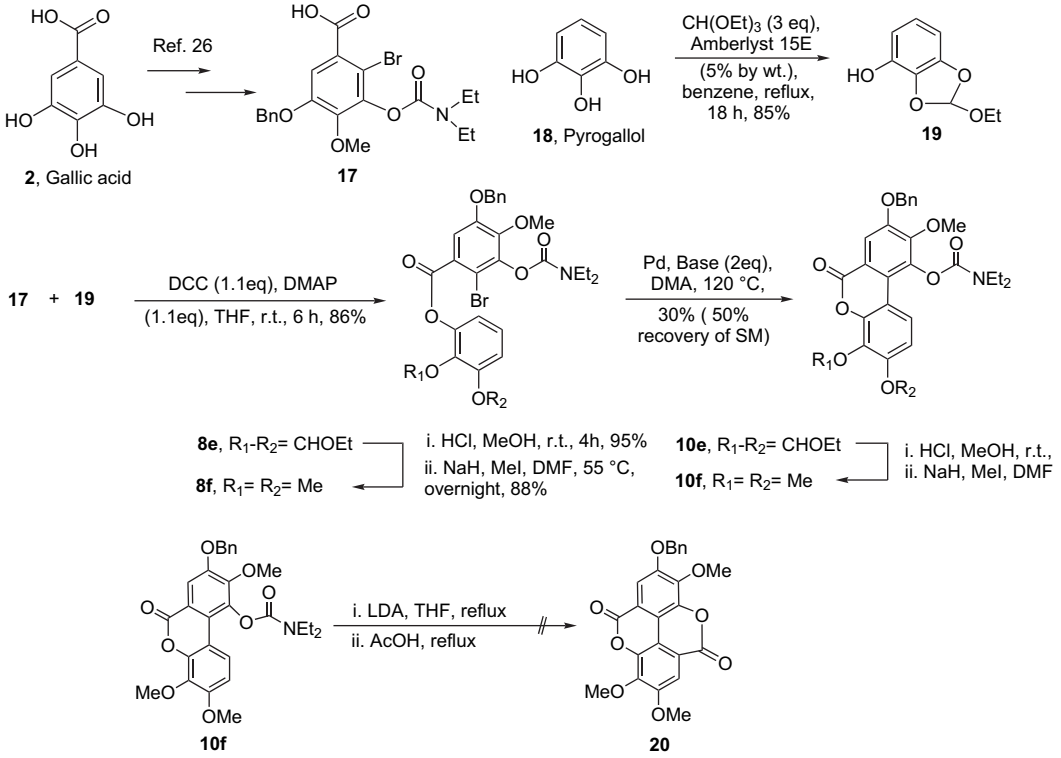
Scheme 2. Heck coupling followed by oxidation.

(10 mol %), PPh_3, and NaOAc at 130 °C for 24 h in the similar way as before gave the desired coupling product **10d** in 42% yield (based on 40% recovery of starting material). Changing of the reaction conditions was not successful to improve the yield of **10d**. Use of small quantity of Pd gave the same yield of **10d**, but higher amount of recovered starting material was found.

After replacing the carboxyl group in intermediate **8d** by alkyl group, the intramolecular Heck coupling was successful, giving coupling product **10d**. But unfortunately, oxidation of **10d** with $KMnO_4$ did not result in the desired oxidation of methyl group to carboxylic acid functionality (compound **14a**) but some unknown products. In addition to the low yield of **10d** and difficulty of its oxidation, the lower part (**16**) of the actually required intermediate **8b** (Chart 2) is not easily accessible from commercially available materials, whereas another intermediate **8e** (for the second path, Chart 2) could be prepared easily from pyrogallol as depicted in Scheme 3. Thus, we were shifted toward the second alternative route, the remote anionic Fries rearrangement approach.

2.2. Formation of unsymmetric Ar–Ar bond via intramolecular Heck coupling followed by Fries rearrangement

The key intermediate **8e** for the remote anionic Fries rearrangement approach was prepared by esterification of the functionalized methyl gallate **17** and pyrogallol derivative **19** (Scheme 3) in the presence of DCC and catalytic DMAP in THF (86% yield). Deprotection of the acetal group of pyrogallol part of **8e** followed by methyl etherification gave compound **8f** in 84% yield over two steps. Then, both **8e** and **8f** were subjected to the intramolecular Heck coupling reaction, but unfortunately the result of the coupling reaction was not satisfactory (Table 1). Reaction of compounds **8e**,**f** with catalytic amount of Pd^{II} in various reagents and reaction conditions was carried out, but the yields of **10e**,**f** were very low and they could not be improved more than 30% using sodium pivalate as base (entry 7). Herrmann's catalyst, which is known to be more efficient for the intramolecular coupling[21] than the commonly used palladium catalyst such as $Pd(OAc)_2$, $Pd(PPh_3)_4$, and



Scheme 3. Heck coupling followed by Fries rearrangement.

Table 1. Intramolecular Heck coupling of **8e**,**f**

Entry	8	Reagents and conditions	Result
1	**8e**, R_1–R_2=CHOEt	$Pd(OAc)_2$ (0.3 equiv), PPh_3 (0.6 equiv), NaOPiv (2.0 equiv), 110–120 °C, 1 h	**10e**, 4%
2	**8e**, R_1–R_2=CHOEt	$PdCl_2(PPh_3)_2$ (0.3 equiv), NaOAc (3.0 equiv), DMA, 100 °C, 3 h	Complex mixture
3	**8e**, R_1–R_2=CHOEt	Palladacycle (5 mol %), Cs_2CO_3 (2 equiv), DMA, 95 °C, 1 h	Many spots
4	**8f**, R_1=R_2=Me	$Pd(OAc)_2$ (0.3 equiv), PPh_3 (0.6 equiv), NaOAc (2.0 equiv), 110–120 °C, 3 h	**10f**, 8%[a]
5	**8f**, R_1=R_2=Me	Palladacycle (5 mol %), Cs_2CO_3 (2 equiv), DMA, 95 °C, 1 h	Complex mixture
6	**8f**, R_1=R_2=Me	$Pd(OAc)_2$ (0.15 equiv), PPh_3 (0.45 equiv), NaOPiv (2.0 equiv), 115–120 °C, 3 h	**10f**, 15%
7	**8f**, R_1=R_2=Me	$Pd(OAc)_2$ (0.15 equiv), PPh_3 (0.45 equiv), NaOPiv (2.0 equiv), 120–125 °C, 1 h	**10f**, 30%[b]
8	**8f**, R_1=R_2=Me	$Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.4 equiv), NaOPiv (2.0 equiv), 120 °C, 50 min	**10f**, 35%[c,d]

[a] Based on 27% recovered starting material.
[b] Based on 30% recovered starting material.
[c] Based on 58% recovered starting material.
[d] Product contained some unknown impurities that were not possible to separate.

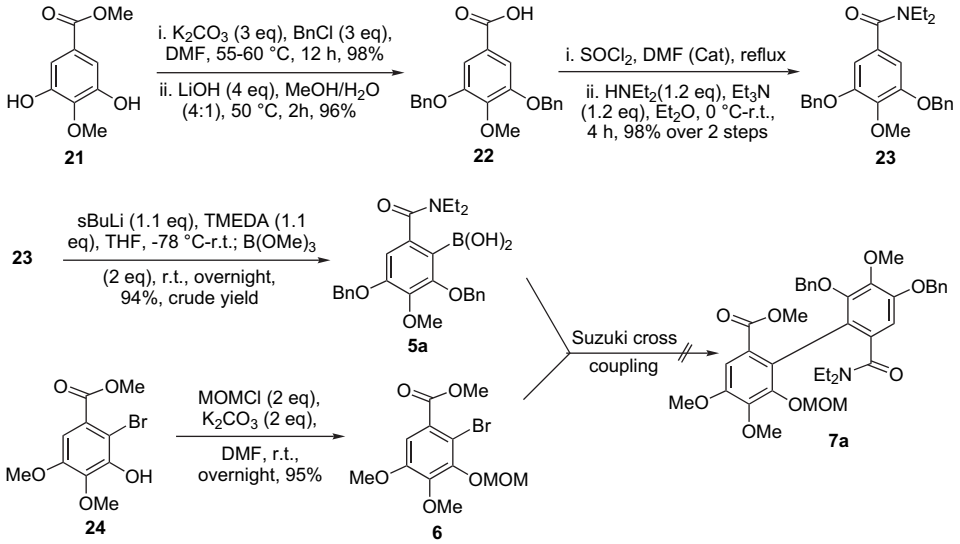
$Pd_2(dba)_3$, did not give better yield in the present case and the crude product showed many spots on TLC (entries 3 and 5). Use of less amount of Pd^{II} was found to increase the yield only a little (entry 8), and the product was found to contain an unknown substance that was not possible to separate by successive column chromatography or on preparative thin layer chromatography (PTLC).

The impure coupling product **10f** was then subjected to the next crucial step, the LDA mediated remote anionic Fries rearrangement. But, unfortunately after coming so long a way, the Fries rearrangement reaction was unsuccessful. Treatment of **10f** with LDA in THF resulted in many spots on TLC and refluxing of the crude product with AcOH resulted in no desired lactonized product **20** but a complex mixture (Scheme 3).

2.3. Formation of unsymmetric Ar–Ar bond via Suzuki cross-coupling

After getting the disappointing results for all the attempts taken so far, there were only two ways in hand, Suzuki cross-coupling and intramolecular Ullmann coupling. But both the methods are not much hopeful for the present case. The Suzuki cross-coupling is not suitable for the highly crowded aromatics and that of similar reactivities. Besides this, preparation of boronic acid component **5a** requires the special protection of the carbonyl group. As there was no other option at that moment, both the methods were applied for construction of the challenging unsymmetric Ar–Ar bond for the synthesis of 3,3′,4-tri-*O*-methylellagic acid.

In Scheme 4, methyl 3,5-dihydroxy-4-methoxybenzoate **21** was converted to the corresponding amide **23** in 92% overall yield from **21** via 3,5-dibenzyloxy-4-methoxybenzoic acid **22**. Lithiation of **23** followed by treatment with $B(OMe)_3$ resulted in the boronic acid **5a** in 94% crude yield. Protection of the remaining hydroxy group of methyl 2-bromo-3-hydroxy-4,5-dimethoxybenzoate **24**[25] as methoxymethyl ether (MOM) gave the bromide component **6** in 95% yield. But again unfortunately, after the preparation of boronic acid **5a** and the bromide **6** in good overall yields from the same starting material **21**, the Suzuki cross-coupling was unsuccessful and no coupling product **7a** was found to be formed. Actually the Suzuki cross-coupling of such highly *ortho*-substituted compounds has not appeared so far, though a few reports for the coupling of moderately crowded aromatics have been reported.[22]



Scheme 4. Preparation of boronic acid component and the Suzuki cross-coupling.

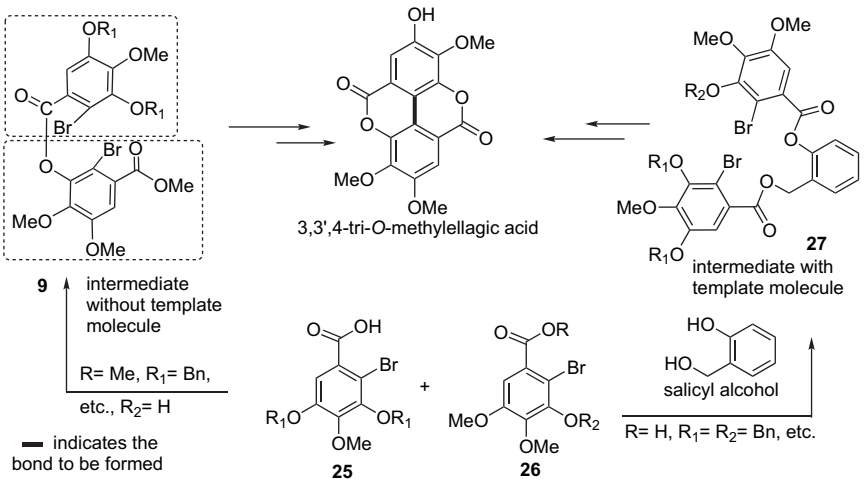


Chart 3. Plan for the preparation of intermediates for intramolecular Ullmann coupling.

2.4. Formation of unsymmetric Ar–Ar bond by intramolecular Ullmann coupling

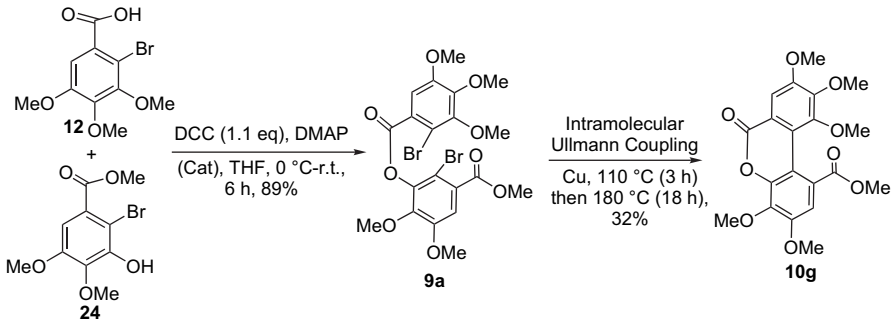
All the attempts to construct the required unsymmetric Ar–Ar bond taken so far become failed, and at this stage the intramolecular Ullmann coupling is the only remaining way to carry out. This intramolecular Ullmann coupling can be carried out in two ways: (i). from the key intermediate **9**, which can be obtained from esterification between **25** and **26**, or (ii) from the key compound **27**, which can be obtained by esterification of **25** and **26** with salicyl alcohol as a template molecule (Chart 3).

Between the intermediates **9** and **27**, the former one can be prepared easily in fewer steps compared to the latter one. So, at first the intermediate **9** was utilized for the intramolecular coupling reaction. Thus, a similar model compound **9a** was prepared in 89% yield from esterification of compounds **12** and **24** in the presence of DCC as shown in Scheme 5. Treatment of **9a** with Cu in the Ullmann coupling condition gave the corresponding desired coupling product **10g** in 32% yield. Other reagents used for the Ullmann coupling such as $NiCl_2$,[23] copper(II) thiophenecarboxylate (CuTC)[24] were also tested but did not give the desired coupling product.

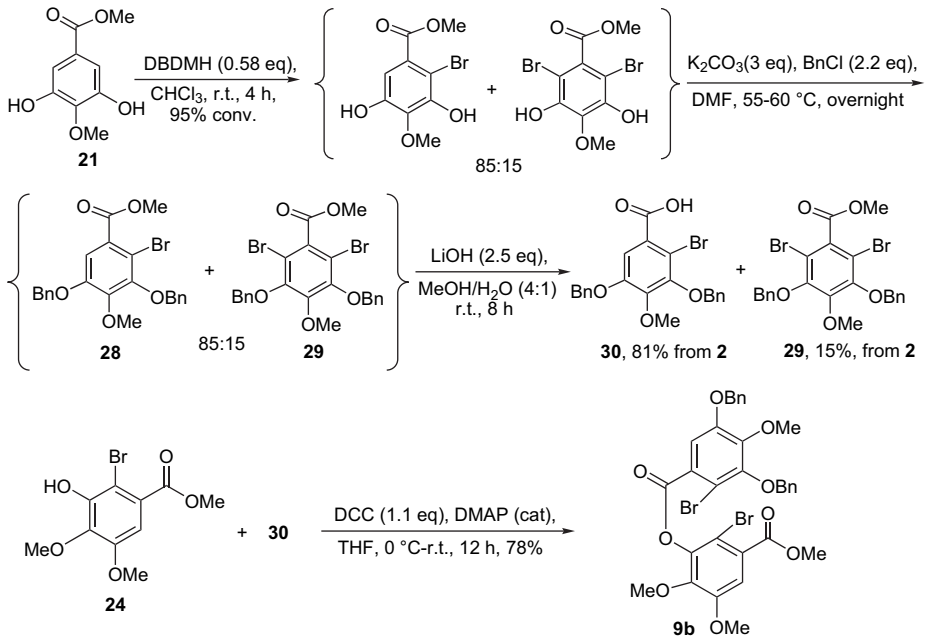
After the success in the intramolecular Ullmann coupling for the model compound **9a**, the actual precursor **9b** for the preparation of 3,3′,4-tri-*O*-methylellagic acid was prepared as shown in Scheme 6. The lower part (**24**) of **9b** has already been synthesized and the required bromide for the upper part (**30**) was prepared using our selective hydrolysis process.[25] Treatment of compound **21**[25] with DBDMH followed by benzylation and hydrolysis with LiOH in MeOH/H_2O at room temperature resulted in the mixture of bromo carboxylic acid **30** and unhydrolyzed dibromo ester **29** that was separated by simple column chromatography. The bromo acid **30** was esterified with the phenolic component **24** in the presence of DCC and DMAP in THF to give the desired key intermediate **9b** in 78% yield.

In Scheme 7, treatment of key intermediate **9b** with ordinary copper powder in DMF at 110 °C for 3 h and then at 180 °C for 18 h gave the corresponding coupling product **10h** in 59% yield. Benzyl deprotection of **10h** with Pd/C in EtOH gave 75% of the corresponding dihydroxy derivative **14b**. The benzyl deprotection was also carried out by treating **10h** with $TiCl_4$ in $CHCl_3$ at room temperature for 48 h, but it resulted in a mixture of the desired **14b** along with singly deprotected product and starting material **10h**. Finally, lactonization of **14b** by refluxing it with MeOH/H_2O (1:1) for 8 h resulted in the desired target molecule 3,3′,4-tri-*O*-methylellagic acid **1c** in almost quantitative yield.

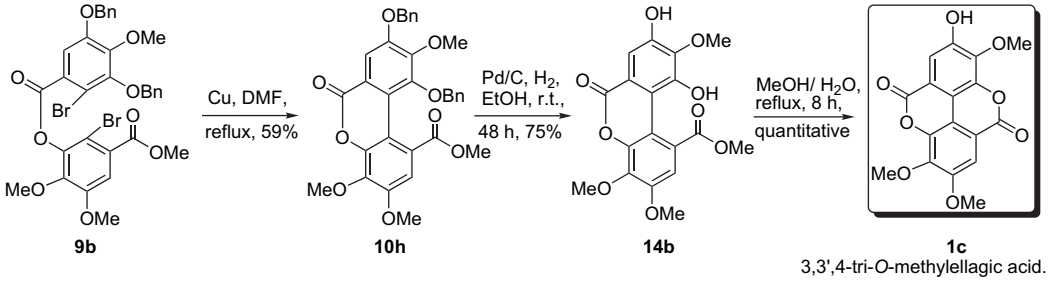
The 59% yield for the intramolecular Ullmann coupling reaction is noteworthy. Although intramolecular Ullmann coupling of compounds like **27** is rather common, that of compound **9** is rare. So far we know, the only such intramolecular Ullmann coupling has been reported by Gottesegen et al.[26] where the diiodocompound was utilized and only 17–20% of the desired coupling product was obtained.



Scheme 5. Model intramolecular Ullmann coupling.



Scheme 6. Preparation of intermediate **9b** for the intramolecular Ullmann coupling.



Scheme 7. Synthesis of 3,3′,4-tri-*O*-methylellagic acid by intramolecular Ullmann coupling.

3. Conclusion

The preparation of the challenging unsymmetric biaryl for the synthesis of 3,3′,4-tri-*O*-methylellagic acid has been achieved finally by the intramolecular Ullmann coupling reaction. This synthetic process will also be applicable for the synthesis of other unsymmetric ellagic acid derivatives such as 3,4,4′-tri-*O*-methylellagic acid and other 3,3′,4-tri-*O*-methylellagic acid-4′-glycoside derivatives (Fig. 1). So far we know, this is the first report of the total synthesis of 3,3′,4-tri-*O*-methylellagic acid from the simple building block gallic acid. This synthetic access to the unsymmetric ellagic acid derivatives will make it also possible to synthesize any other unsymmetrically substituted ellagic acid derivatives just by changing the functional groups in the gallic acid derivatives **25** and **26**. On the other hand, this would also be a useful route for the preparation of the unsymmetric biaryls; particularly those are from the highly *ortho*-substituted aryl halides and of similar structural and electronic environments. Reaction of **9b** with copper in the Ullmann coupling condition was almost clean and the purification on silica gel column chromatography was very simple. Cleavage of the lactone linkages of **10d–h**, with some chiral reagents give the axially chiral biaryls,[27] which are very important for their use as important fragments for many natural products as well as chiral reagents.[27,28]

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agents. Reactions were monitored on TLC on silica gel 60 F_{254} and visualized under UV light and/or 5% ethanolic solution of phosphomolybdic acid. Flash chromatography was performed on silica gel (Merck, 60N, spherical, neutral, 40–50 mesh). Melting points were determined with a Mel-Temp apparatus. IR was recorded on a Thermo Nicolet Avatar 360T2 instrument using either KBr or ATR. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded by Jeol AL 300 instrument. GC–MS was studied in a Shimadzu GCMS-QP5000 instrument (column length 30 m, Idm 0.25 mm, column temperature 50–250 °C). Elemental analysis of all the new compounds was carried out by Perkin Elmer 2400 series II CHNS/O analyzer, whereas the spectral data of the known compounds were matched with the references cited.

4.2. 3,4,5-Trimethoxybenzoic acid (11)

Gallic acid **2** (1.42 g) was treated with K_2CO_3 (5 equiv) and MeI (5 equiv) in DMF at 50–55 °C overnight to give methyl tri-*O*-methyl gallate, which was treated with LiOH (233 mg, 3.0 equiv) in MeOH/H_2O (1:1) at room temperature for 2 h. After completion of the reaction, the solvent (methanol) was removed in evaporator and the reaction mixture was acidified with 2 M HCl and extracted with EtOAc. The organic layer was washed with water and then brine, dried over $MgSO_4$, condensed in evaporator to give the corresponding acid **11** (1.74 g, 98%). The crude was very pure and was used in the next step without further purification. White needles; mp 166–167 °C; IR (ATR): 2947, 2833, 2643, 2574, 2514, 1684, 1586, 1507, 1466, 1415, 1324, 1268, 1224, 1182, 1122, 1001, 929, 858, 761, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 6H), 3.95 (s, 3H), 7.38 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 56.12, 60.82, 60.88, 107.30, 124.04, 124.86, 152.86, 171.89.

4.3. 2-Bromo-3,4,5-trimethoxybenzoic acid (12)

Trimethoxybenzoic acid **11** (1.15 g, 5.42 mmol) was dissolved in 1.4 M NaOH solution (1.1 equiv) and solid DBDMH (866 mg, 0.57 equiv) was added at room temperature and the reaction mixture was stirred for 36 h. After that time period, it was acidified with 2 M HCl and extracted with EtOAc. The organic layer was washed with water and then brine, dried over $MgSO_4$, condensed in evaporator to give the corresponding bromide **12** (1.51 g, 96%). The product was almost pure and was used in the next step without further purification. White crystal; mp 82–85 °C; IR (ATR): 2932, 1698, 1488, 1469, 1449, 1411, 1385, 1335, 1275, 1239, 1200, 1166, 1111, 1026, 1001, 922, 775, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.70, 22.73, 27.50, 27.52, 27.67, 27.70, 77.37, 77.68, 91.81, 113.47, 118.14, 118.65, 137.07. Spectral data were identical with the reported one.[28]

4.4. General procedure for the preparation of esters 8a,d–f, 9a,b

To a solution of carboxylic acid (**12**, **17**, **31**, 1.0 equiv) in dry THF was added the phenolic component (**16**, **19**, **24**, 1.0 equiv) followed by the addition of DCC (1.1 equiv) and 4-dimethylaminopyridine (DMAP) (10 mol %) at 0 °C. Then, the reaction mixture was stirred at room temperature for 6–24 h under N_2 atmosphere. After completion of the reaction, solvent was reduced and the solid material derived from DCC was separated by filtration and the thick crude product was placed directly on the chromatographic column, eluted with 20% EtOAc in hexane to give the pure coupling products (**8a**,**d–f**, **9a**,**b**) in good yields.

4.4.1. 5′,6′-Dimethoxy-3′-methoxycarbonylphenyl 2-bromo-3,4,5-trimethoxybenzoate (8a). Compounds **12** (1 equiv) and **13**[25] (1 equiv) were treated with DCC (1.1 equiv) and DMAP (cat) in THF for 6 h as described in the general procedure in Section 4.4 to give compound **8a** in 75% yield as a light yellow solid; IR (ATR): 2936, 1743, 1730, 1512, 1480, 1429, 1330, 1215, 1199, 1170, 1133, 1096, 1001, 738, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 3H), 3.96 (s, 9H), 3.97 (s, 3H), 3.98 (s, 3H), 7.42 (d, 1H, J=1.5 Hz), 7.52 (d, 1H, J=1.5 Hz), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.22, 56.12, 56.28, 60.34, 61.04, 61.14, 61.21, 108.90, 110.96, 111.18, 112.93, 125.16, 126.71, 142.62, 145.37, 147.01, 151.81, 152.00, 152.30, 162.28, 165.68. Anal. Calcd for $C_{20}H_{21}BrO_9$: C, 49.50; H, 4.36. Found: C, 49.52; H, 4.32.

4.4.2. 2′-Bromo-5′,6′-dimethoxy-3′-methoxycarbonylphenyl 2-bromo-3,4,5-trimethoxybenzoate (9a). Bromo acid component **12** (1 equiv) and the phenolic compound **24** (1 equiv) were treated with DCC (1.1 equiv) and DMAP (cat) in THF as described in the general procedure in Section 4.4 to give compound **9a** in 89% yield as yellow solid; mp 84–87 °C; IR (ATR): 2938, 1749, 1732, 1565, 1488, 1429, 1330, 1215, 1199, 1171, 1131, 1096, 1001, 738, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H), 3.94 (s, 9H), 3.95 (s, 3H), 3.98 (s, 3H), 7.42 (s, 1H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.22, 56.12, 56.28, 60.34, 61.04, 61.14, 61.21, 108.90, 110.96, 111.18, 112.93, 125.16, 126.71, 142.62, 145.37, 147.01, 151.81, 152.00, 152.30, 162.28, 165.68. Anal. Calcd for $C_{20}H_{20}Br_2O_9$: C, 42.58; H, 3.57. Found: C, 42.40; H, 3.50.

4.4.3. 2′-Bromo-5′,6′-dimethoxy-3′-methoxycarbonylphenyl 2-bromo-3,5-dibenzyloxy-4-methoxybenzoate (9b). A mixture of compound **24** (1.0 equiv) and compound **30** (1.0 equiv) was treated with DCC (1.1 equiv) and DMAP (cat) in THF for 12 h as described in the general procedure in Section 4.4 to give compound **9b** in 78% yield as gummy solid; IR (ATR): 2938, 1749, 1732, 1565, 1488, 1429, 1330, 1215, 1199, 1171, 1131, 1096, 1001, 929, 909, 846, 738, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 5.08 (s, 2H), 5.23 (2H), 7.33–7.44 (m, 9H), 7.56–7.65 (m, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.54, 56.28, 56.30, 61.21, 61.23, 61.37, 61.39, 71.19, 75.47, 109.01, 111.56, 112.92, 113.29, 125.27, 126.61, 127.39, 127.46, 128.26, 128.29, 128.45, 128.51, 128.71, 135.94, 136.68, 142.60, 145.41, 147.76, 150.98, 151.32, 151.98, 162.26, 165.68. Anal. Calcd for $C_{32}H_{28}Br_2O_9$: C, 53.65; H, 3.94. Found: C, 53.58; H, 3.90.

4.4.4. 3′,5′-Dimethylphenyl 2-bromo-3,4,5-trimethoxybenzoate (8d). Applying the general procedure in Section 4.4 (7 h), compound **8d** was prepared from compounds **12** (1 equiv) and **16** (1 equiv) in 98% yield as white needles; mp 84–85 °C; IR (ATR): 2932, 2831, 1732, 1613, 1571, 1486, 1339, 1290, 1217, 1164, 1145, 1109, 1028, 1001, 947, 914, 852, 852, 683 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 6H), 3.90 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 6.87 (s, 2H), 6.91(s, 1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.14, 56.22, 60.99, 61.14, 110.09, 110.48, 112.95, 119.00, 126.72, 127.77, 139.34, 146.40, 150.48, 151.55, 152.33, 155.63, 164.72. Anal. Calcd for $C_{18}H_{19}BrO_5$: C, 54.70; H, 4.85. Found: C, 54.68; H, 4.83.

4.4.5. 2′,3′-Dimethoxyphenyl 5-benzyloxy 2-bromo-3-(diethylcarbamoyloxy)-4-methoxybenzoate (8f). Compounds **17**[25] (1 equiv) and **19** (1 equiv) (preparation of **19** is described later in Section 4.6) were treated with DCC and DMAP in THF as described in the general procedure in Section 4.4 (6 h) to give compound **8e** in 86% yield, which was dissolved in MeOH/H_2O (2:1, 150 ml) and 2 M HCl was added dropwise at room temperature. During the addition of

HCl the reaction mixture became white instantly and after a while it disappeared. The addition of HCl was continued until the persistence of the white color. Then, the reaction mixture was stirred for additional 2 h at room temperature. The solvent (MeOH portion) was removed by evaporator and the crude product was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, and condensed in evaporator. Purification over silica gel chromatographic column gave the corresponding dihydroxy derivative. The dihydroxy derivative obtained was treated with NaH (1.5 equiv) and MeI (1.5 equiv) in DMF at 55 °C overnight to give 3.68 g of **8f** (84% over two steps) as yellow solid; mp 110–112 °C; IR (ATR): 2965, 2923, 1752, 1724, 1492, 1467, 1399, 1340, 1278, 1255, 1243, 1203, 1162, 1143, 1106, 1081, 1074, 1001, 968, 790, 748, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, J=7.2 Hz), 1.34 (t, 3H, J=7.2 Hz), 3.42 (q, 2H, J=7.2 Hz), 3.53 (q, 3H, J=7.2 Hz), 3.81 (s, 3H), 3.89 (s, 3H), 3.97 (s, 3H), 5.18 (s, 2H), 6.82 (q, 2H, J=8.2 Hz), 7.07 (t, 1H, J=8.2 Hz), 7.33–7.46 (m, 5H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.34, 14.17, 42.27, 42.56, 56.05, 56.08, 60.81, 60.85, 61.05, 61.09, 71.22, 110.32, 111.16, 114.60, 115.09, 123.46, 125.24, 127.48, 128.22, 128.63, 135.88, 141.13, 143.94, 144.08, 146.84, 150.92, 152.59, 153.79, 163.33. Anal. Calcd for $C_{28}H_{30}BrNO_8$: C, 57.15; H, 5.14; N, 2.38. Found: C, 57.19; H, 5.04; N, 2.29.

4.5. General procedure for the intramolecular Heck coupling (preparation of 10d–f)

A flame dried flask was charged with the ester (**8d–f**, 1.0 equiv), the specified catalyst $Pd(OAc)_2/PPh_3$ (ratio 1:2), $PdCl_2(PPh_3)_2$ or palladacycle, the specified base NaOAc, NaOPiv (2 equiv) and the content of flask was dried in vacuo for 1–2 h at 60 °C. Dry DMA was added to yield a suspension approximately 0.05 M of the starting material. The mixture was degassed under argon and heated at 120–130 °C for the specified time. Then, it was allowed to cool to room temperature. The reaction mixture was diluted with EtOAc, washed sequentially with 2 M HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel (10–15% EtOAc in hexane) gave the desired lactones **10d–f**.

4.5.1. 1,3-Dimethyl-8,9,10-trimethoxy-6*H*-dibenzo[*b*,*d*]-pyran-6-one (10d). Among the several runs, the best result was obtained by treating compound **8d** with $Pd(OAc)_2$ (10 mol %), PPh_3 (0.2 equiv), and NaOAc (2.0 equiv) at 130 °C for 24 h as described in the general procedure in Section 4.5. After purification by silica gel chromatography, the desired coupling product **10d** was obtained in 42% along with 40% of recovered starting material **8d**. Light yellow needles; mp 149–152 °C; IR (ATR): 2942, 2835, 1728, 1617, 1593, 1477, 1383, 1339, 1288, 1208, 1163, 1110, 1108, 1066, 1000, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 3H), 2.45 (s, 3H), 3.45 (s, 3H), 4.00 (s, 3H), 4.08 (s, 3H), 7.00 (m, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.06, 23.30, 61.04, 61.47, 107.60, 114.16, 114.19, 118.75, 119.05, 123.48, 128.68, 136.93, 138.95, 148.53, 149.94, 150.61, 153.09, 161.49. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 69.00; H, 5.68.

4.5.2. 8-Benzyloxy-3,4-ethoxymethylenedioxy-10-(diethylcarbamoyloxy)-9-methoxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (10e). Among the several runs, the best result was obtained as follows. The bromo ester **8e** (121 mg, 0.20 mmol) was treated with $Pd(OAc)_2$ (0.15 equiv), PPh_3 (0.45 equiv), and NaOPiv (2.0 equiv) at 120–125 °C for 1 h as described in the general procedure in Section 4.5 to give 7 mg of the desired coupling product **10e** (8%). Without further characterization of compound **10e** it was converted to compound **10f** by treating it with 2 N HCl in MeOH at room temperature for 4 h followed by methyl etherification by NaH and MeI in DMF at 50 °C overnight to give 80% of compound **10f**. Compound **10f** was also prepared directly from compound **8f** using the general procedure in Section 4.5 (Table 1). Combined **10f** was used for the next step without further purification.

4.5.3. 8-Benzyloxy-10-(diethylcarbamoyloxy)-3,4,9-trimethoxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (10f). The bromo ester **8f** (100 mg, 0.16 mmol) was treated with $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.3 equiv), and NaOPiv (2.0 equiv) at 120 °C for 55 min as described in the general procedure in Section 4.5 to give 31 mg of the desired coupling product **10f** (30% yield) as light yellow needles; mp 209–211 °C; IR (ATR): 1731, 1690, 1600, 1496, 1414, 1326, 1229, 1178, 1096, 997, 909, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, J=7.2 Hz), 1.34 (t, 3H, J=7.2 Hz), 3.42 (q, 2H, J=7.2 Hz), 3.53 (q, 2H, J=7.2 Hz), 3.95 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 5.24 (s, 2H), 6.79 (dd, 1H, J=1.5 Hz), 6.84 (dd, 1H, J=1.5 Hz), 7.07 (t, 1H, J=8.1 Hz), 7.32–7.47 (m, 5H), 7.69 (s, 1H). Anal. Calcd for $C_{28}H_{29}NO_8$: C, 66.26; H, 5.76; N, 2.76. Found: C, 66.00; H, 5.66; N, 2.60.

4.6. 2-Ethoxybenzo[1,3]dioxol-4-ol (19)

A mixture of pyrogallol **18** (4.50 g, 35.7 mmol), $CH(OEt)_3$ (17.8 ml, 3 equiv), and Amberlyst 15E (230 mg, 55% by weight) in benzene (100 ml) was refluxed for 18 h in a flask fitted with a Dean Stark trap for azeotropic removal of EtOH/benzene to give 5.50 g of compound **19** (85%) as light brown low melting solid, which turned dark red gradually after few days. IR (ATR): 3214, 1630, 1504, 1484, 1473, 1375, 1226, 1111, 1033, 972 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.1 Hz), 3.76 (q, 2H, J=7.2 Hz), 4.87 (br s, 1H), 6.48–6.53 (m, 2H), 6.72–6.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.77, 5944, 101.38, 110.81, 119.08, 122.00, 132.77, 138.92, 147.02.

4.7. 3,5-Dibenzyloxy-4-methoxybenzoic acid (22)

Compound **21** (1.00 g, 5.06 mmol) was treated with K_2CO_3 (2.09 g, 3.0 equiv), BnCl (2.23 g, 3.0 equiv), in DMF at 55–60 °C for 12 h. After completion of the reaction, the crude was extracted with diethyl ether, washed with water and brine, dried over $MgSO_4$, and concentrated to give 1.88 g (98%) of the corresponding dibenzyloxy derivative. The crude was then dissolved in $MeOH/H_2O$ (4:1) and LiOH (475 mg, 4.0 equiv) was added, the mixture was stirred at 50 °C for 5 h, and then it was acidified with HCl. Solvent (MeOH portion) was removed in evaporator and the organic part was extracted with EtOAc, washed with water and then brine, and dried over $MgSO_4$. Removal of solvent in evaporator gave 1.73 g of pure **22** (96%) as a white solid; mp 130–131 °C; ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 5.18 (s, 4H), 7.30–7.48 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 61.12, 71.19, 109.82,

123.92, 127.42, 128.05, 128.59, 136.56, 144.44, 152.23, 171.47.

4.8. 3,5-Dibenzyloxy-4-methoxydiethylbenzamide (23)

Compound **22** (500 mg, 1.37 mmol) was refluxed with freshly distilled $SOCl_2$ (5 ml) in the presence of few drops of DMF as catalyst for 2 h. After that, the excess $SOCl_2$ was removed using water aspirator via an alkali trap. Then, 2–3 ml of benzene was added for the azeotropic removal of the remaining $SOCl_2$ and then dried in a vacuum pump. $CHCl_3$ (5 ml) was added to dissolve the crude acid chloride, and Et_3N (1.2 equiv) and Et_2NH (1.2 equiv) were added successively to this solution at room temperature. The reaction mixture was stirred at room temperature for 4 h and then it was poured in ice crushed, extracted with EtOAc, washed with brine and water, and dried over $MgSO_4$. Removal of the solvent followed by chromatographic purification resulted in 546 mg of compound **23** (98% over two steps). IR (ATR): 2961, 2928, 1628, 1581, 1440, 1420, 1370, 1235, 1077, 1005, 737, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74 (t, 3H, J=7.1 Hz), 0.93 (t, 3H, J=7.1 Hz), 2.67 (q, 2H, J=7.1 Hz), 3.72 (q, 2H, J=7.1 Hz), 3.91 (s, 3H), 5.14 (s, 4H), 6.62 (s, 2H), 7.30–7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.15, 20.98, 6.33, 60.91, 71.14, 106.37, 106.40, 127.18, 127.88, 128.52, 132.28, 136.82, 140.23, 152.42, 170.64. Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.30; H, 6.85; N, 3.30.

4.9. 2,4-Dibenzyloxy-3-methoxy-6-diethylcarbamoylbenzeneboric acid (5a)

To a stirred solution of amide **23** (958 mg, 2.14 mmol) and TMEDA (0.36 ml, 2.35 mmol) in dry THF (12 ml) was added *s*-BuLi (2.14 ml, 1.1 M, 2.35 mmol, 1.1 equiv) dropwise over 15 min at −78 °C. The stirring was continued for 1 h at −78 °C and a solution of $B(OMe)_3$ (0.5 ml, 4.4 mmol) in 0.5 ml THF was added rapidly. The resultant mixture was allowed to reach room temperature overnight under stirring. After the completion of the reaction saturated aqueous NH_4Cl (4 ml) and water (3 ml) were added and the reaction mixture was acidified to approximately pH 6 with 2 M aqueous HCl (placing in a cooling bath). THF was removed in vacuo and the crude was extracted with CH_2Cl_2, dried in evaporator, and then in vacuum pump resulting in yellow floppy solid **5a** (994 mg crude, 94%). The crude **5a** was used in the next step without any purification and structural characterization.

4.10. Methyl 2-bromo-4,5-dimethoxy-3-methoxymethyloxybenzoic acid (6)

Compound **24**[25] (400 mg, 1.37 mmol) was treated with K_2CO_3 (380 mg, 2 equiv) and MOMCl (222 mg, 2.75 mmol, 2 equiv) in DMF (10 ml) under N_2 atmosphere at room temperature overnight. After the completion of reaction, water was added and the crude was extracted with EtOAc, washed with brine and water, and dried over $MgSO_4$. Removal of the solvent followed by chromatographic separation gave 437 mg of the pure compound **6** (95%) as light yellow oil; IR (ATR): 3000, 2938, 2834, 1733, 1553, 1482, 1426, 1378, 1335, 1256, 1213, 1158, 1111, 1072, 1002, 971, 924, 895, 816, 779, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 5.19 (s, 2H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.46, 56.17, 58.04, 60.97, 99.33, 109.30, 110.16, 127.89, 145.67, 148.54, 152.39, 166.48. Anal. Calcd for $C_{12}H_{15}BrO_6$: C, 43.00; H, 4.51. Found: C, 43.16; H, 4.35.

4.11. 2-Bromo-3,5-dibenzyloxy-4-methoxybenzoic acid (30)

The mono bromo derivative **30** was prepared from compound **21** using the selective hydrolysis process described in our earlier report.[25] Compound **21** in $CHCl_3$ was treated with 0.58 mol equiv of DBDMH at room temperature for 4 h that gave a mixture of the corresponding mono- and dibromide. This mixture was then converted to the corresponding benzyloxy derivatives (**28** and **29**) by treating the mixture with BnCl (2.2 equiv) and K_2CO_3 (3.0 equiv) in DMF at 55–60 °C overnight. The inseparable mixture of **28** and **29** was dissolved in $MeOH/H_2O$ (4:1) and treated with 2.5 equiv of LiOH at room temperature for 8 h, which resulted in the selective hydrolysis of **28** to the corresponding acid **30** and it was separated from the unhydrolyzed dibromo ester **29** (15% from **21**) by silica gel column chromatography (81% of **30** from **21**) as white powder; mp 133–135 °C; IR (ATR): 2932, 1698, 1576, 1566, 1413, 1366, 1328, 1269, 1239, 1096, 961, 907, 753, 733, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 5.06 (s, 2H), 5.16 (s, 2H), 7.32–7.47 (m, 8H), 7.49 (s, 1H), 7.56–7.59 (m, 2H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 60.95, 70.96, 75.17, 112.27, 127.175, 127.26, 127.95, 128.01, 128.11, 128.13, 128.16, 128.26, 128.30, 128.31, 128.34, 135.81, 136.39, 146.40, 151.10, 167.63. Anal. Calcd for $C_{22}H_{19}BrO_5$: C, 59.61; H, 4.32. Found: C, 59.40; H, 4.21. Compound **29** was obtained as side product as colorless oil (15%); IR (ATR): 2946, 2876, 1741, 1412, 1357, 1333, 1219, 1087, 1002, 906, 732, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H), 3.98 (s, 3H), 5.06 (s, 4H), 7.36–7.45 (m, 6H), 7.51–7.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 53.14, 61.62, 110.37, 128.49, 136.25, 149.99, 166.27.

4.12. General procedure for intramolecular Ullmann coupling

Compounds **9a**,**b** (1 equiv) were treated with 1 equiv (by weight) of ordinary copper powder (without any sort of activation) in DMF (10 ml/mmol) at 110 °C for 3 h and then at 180 °C for 16–18 h. Progress of the reaction was monitored by the highly fluorescent spot on TLC under UV light for the desired coupling product. After completion of the reaction, it was cooled at approximately 100 °C and poured into crushed ice. Then, the reaction mixture was diluted with chloroform and the organic layer was separated, washed three times with water and once with brine, dried over $MgSO_4$, and concentrated in evaporator. The crude product was purified by flash column chromatography with 80% chloroform in hexane and then 100% chloroform. During column chromatography the movement of the desired coupling product in the column can easily be monitored using UV lamp, which gave highly fluorescent color.

4.12.1. Methyl 3,4,8,9,10-pentamethoxy-6-oxo-6*H*-dibenzo[*b*,*d*]pyran-1-carboxylate (10g). Among the several runs, the best result was obtained by treating dibromo ester **9a** (100 mg, 0.18 mmol) with ordinary copper powder (100 mg) at 110 °C for 3 h and then at 175–180 °C for 18 h

according to the general procedure described in Section 4.12 to give 21 mg of the desired coupling product **10g** (32%) as fluorescent solid; IR (ATR): 2934, 1745, 1732, 1560, 1477, 1330, 1214, 1199, 1165, 1091, 1001, 738, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 3H), 3.77 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 7.25 (s, 1H), 7.67 (s, 1H).

4.12.2. Methyl 8,10-dibenzyloxy-3,4,9-trimethoxy-6-oxo-6*H*-dibenzo[*b*,*d*]pyran-1-carboxylate (10h). The key intermediate dibromo ester **9b** (560 mg, 0.78 mmol) was treated with ordinary copper powder (560 mg) in DMF according to the general procedure described in Section 4.12 for 16 h to give 436 mg of the desired coupling product **10h** in 59% yield as gummy solid; IR (ATR): 2940, 1735, 1734, 1565, 1422, 1335, 1201, 1168, 1171, 1130, 1096, 1001, 909, 738, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.95 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 5.06 (s, 2H), 5.24 (2H), 7.33–7.44 (m, 9H), 7.56–7.65 (m, 2H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.55, 56.29, 56.32, 61.23, 61.25, 61.39, 71.21, 75.50, 111.57, 112.93, 113.31, 125.25, 126.63, 127.40, 127.66, 128.27, 128.27, 128.52, 128.51, 128.72, 135.94, 136.69, 142.60, 145.43, 147.76, 150.98, 151.32, 151.98, 162.26, 165.68. Anal. Calcd for $C_{32}H_{28}O_9$: C, 69.06; H, 5.07. Found: C, 68.86; H, 5.13.

4.13. Methyl 8,10-dihydroxy-3,4,9-trimethoxy-6-oxo-6*H*-dibenzo[*b*,*d*]pyran-1-carboxylate (14b)

Compound **10h** (102 mg, 0.18 mmol) and Pd/C (36 mg, 10 mol %) in ethanol (5 ml) were stirred at room temperature under H_2 atmosphere for 48 h. During this time period, the reaction mixture was flushed occasionally with H_2 using the vacuum pump. After completion of the reaction, the solid materials were separated by filtration over Celite followed by washing with ethanol. After removal of the solvent, the crude product was placed directly on the silica gel column and eluted with chloroform to give 44 mg of compound **14b** (75%) as a gummy solid; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 4.24 (s, 3H), 5.57 (s, 1H), 6.05 (s, 1H), 7.19 (s, 1H), 7.68 (s, 1H). Anal. Calcd for $C_{18}H_{16}O_9$: C, 57.45; H, 4.29. Found: C, 57.38; H, 4.20.

4.14. 3,3′,4-Tri-*O*-methylellagic acid (1c)

Compound **14b** was refluxed with MeOH/H_2O (1:1) for 8 h to give the desired product **1c** almost in quantitative yield as a light yellow solid; mp 280–282 °C; IR (ATR): 3414, 1755, 1727, 1607, 1570, 1492, 1414, 1359, 1304, 1174, 1113, 1090, 1064, 986, 915, 755, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (s, 3H), 4.23 (s, 3H), 4.41 (s, 3H), 6.30 (s, 1H), 7.68 (s, 1H), 7.76 (s, 1H). Melting point and spectral data were identical with that of isolated[1] 3,3′,4-tri-*O*-methylellagic acid.

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References and notes

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