# An Inverse Electron-Demand Diels–Alder-Based Total Synthesis of Urolithin M7

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**Abstract:** Urolithin M7 was synthesized from 2-hydroxy-4-methoxybenzaldehyde in 8 steps and 48% overall yield. The key step was an inverse electron demand Diels–Alder (IEDDA) reaction between diene **10** and the enamine (**7**) derived from dimethoxyacetaldehyde and pyrrolidine, which generated the 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton.

**Key words:** inverse electron demand Diels–Alder, domino reaction, dibenzopyranone, urolithin M7

Ellagitannins are present in a variety of foods, such as berries, pomegranates, walnuts, and almonds.[2] They exhibit a range of biological properties including antimicrobial,[3a,b] antiviral,[3c] antioxidant,[3d] antimutagenic,[3e] and antitumor[3f,g] activity. The urolithins, which are metabolites of ellagitanins, for example, ellagic acid (**1**, Figure 1),[4] have a common tricyclic aromatic core {6*H*-dibenzo[*b*,*d*]pyran-6-one} and differ in the number and position of hydroxyl substituents. Kim and co-workers reported the isolation of urolithin M7[4d] {**2**, 3,8,10-trihydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one} from the dried feces of a squirrel, *Trogopterus xanthipes*.[5] These feces (excrementum pteropi) have been used in Chinese traditional medicine for the treatment of angiostasis and dysmenorrhea.[6]

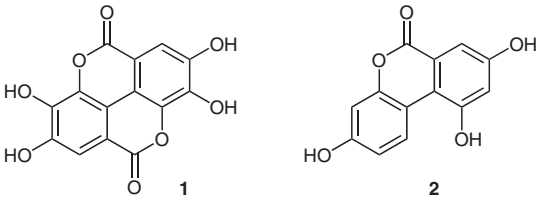
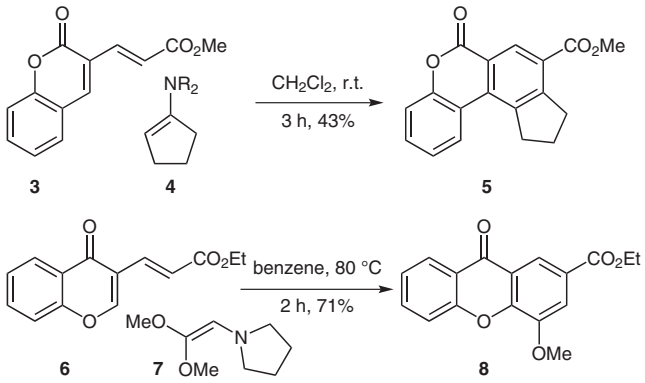


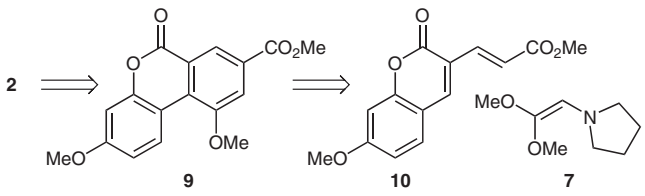

**Figure 1** Structures of ellagic acid (**1**) and urolithin M7 (**2**)

Previously, we reported that coumarin-fused electron-deficient diene **3** reacts with enamines (electron-rich dienophilies) such as **4** to afford dibenzo[*b*,*d*]pyran-6-ones.[7] This occurs by a domino sequence involving a formal inverse electron-demand Diels–Alder reaction followed by a 1,2-elimination of pyrrolidine and a dehydrogenation (presumably a transfer hydrogenation). More recently, chromone-fused diene **6** was found to react with enamine **7**, which is derived from pyrrolidine and dimethoxyacetaldehyde, to afford xanthone **8** (Scheme 1).[8] In this case, the new aromatic ring is generated by a formal IEDDA reaction followed by two successive 1,2-elimination reactions. With both a concise approach to the 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton and means to generate a 1,3-disubstituted aromatic ring, an opportunity to synthesize urolithin M7 (**2**) using this methodology was identified.




**Scheme 1** Examples of IEDDA-driven domino reactions of coumarin-fused diene **3** and chromone-fused diene **6**

A retrosynthetic analysis of **2** (Scheme 2) began with functional-group interconversions to provide trisubstituted dibenzo[*b*,*d*]pyran-6-one **9**, which is the anticipated product of an IEDDA-driven domino reaction between coumarin-fused diene **10** and enamine **7**.




**Scheme 2** Retrosynthetic analysis of urolithin M7

The synthesis commenced with reaction between commercially available salicylaldehyde **11** and dimethyl glutaconate **12** (*E*/*Z* = ca. 4:1) to produce coumarin-fused diene **10** (78%) and chromene **13** (22%, Scheme 3). Diene **10** precipitated from the reaction mixture upon cooling, which rendered separation of the two products trivial. The *E* configuration of the double bond in the side chain was

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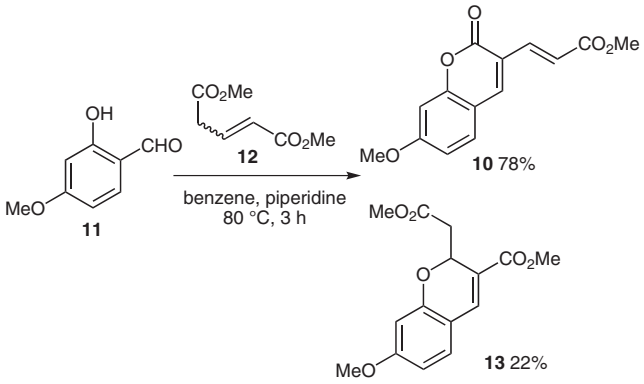


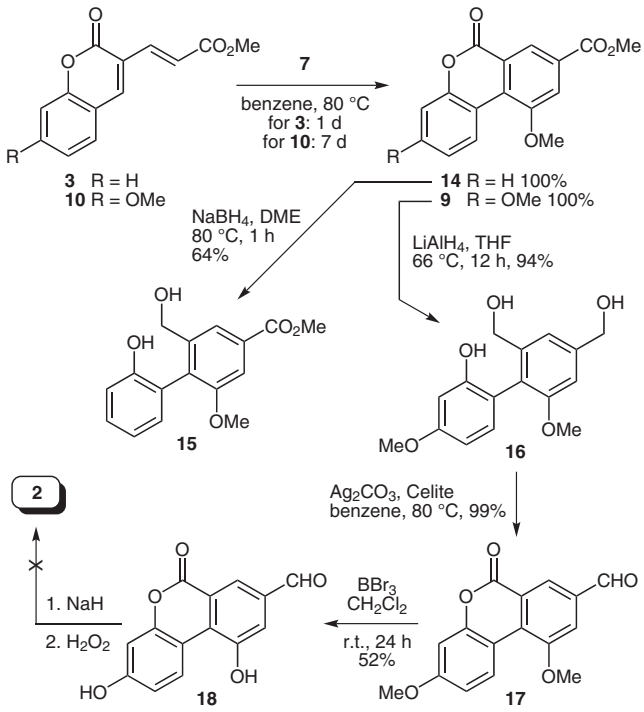

**Scheme 3** Synthesis of diene **10**

indicated by the magnitude of the coupling constant between the attached protons ($J$ = 15.9 Hz).

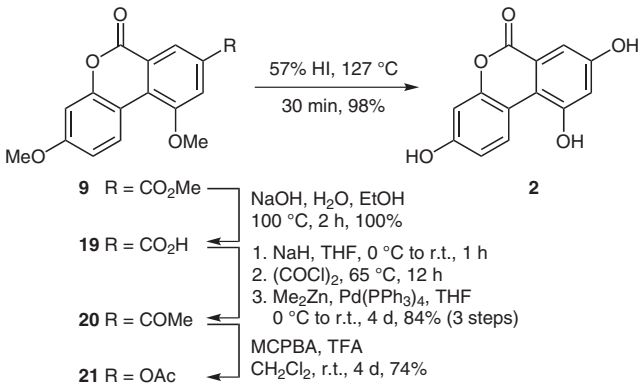
Before proceeding with diene **10**, the IEDDA-driven domino reaction with enamine **7** was first performed with the parent coumarin-fused diene **3**. 6*H*-Dibenzo[*b*,*d*]pyran-6-one **14** was obtained quantitatively after 1 day of reaction (Scheme 4). The electron-donating methoxy group in **10** is directly conjugated with the diene unit, which renders it less electron deficient than the one in **3**. Consequently, the reaction of **10** with enamine **7** was considerably slower. Nevertheless, it also proceeded quantitatively, affording **9** after 7 days of reaction.[9] The 1,3 relationship between the methyl ester and the new methoxy group in **14** and **9** is consistent with a completely regioselective addition of the dienophile **7** to the dienes **3** and **10**. Equally high regioselectivity was observed in the reaction of **7** with chromone-fused diene **6**. This seems to indicate that the 1-pyrrolidinyl group is a more effective π-donor than the two methoxy groups combined.

Having generated the core 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton with functionality at all of the required positions, it only remained to adjust the nature of the functional groups. The main challenge here was the conversion of the methyl ester into a hydroxyl group without affecting the 2-pyranone system. Dibenzopyranone **14** was used to ascertain whether the methyl ester could be reduced chemoselectively. Unfortunately, reaction of **14** with DIBAL at –50 °C gave multiple products (TLC analysis) and the use of $NaBH_4$ in DME[10] resulted in the selective reduction of the lactone to afford diol **15** in 64% yield. Since the wrong carbonyl group was selectively reduced, an alternative approach was investigated.

Both the methyl ester and the lactone in **9** were reduced with $LiAlH_4$ to afford triol **16** in 94% yield (Scheme 4). An attempt to simultaneously regenerate the lactone (via a hemiacetal) and produce an aldehyde (i.e., **17**) using $MnO_2$ resulted in the formation of a complex mixture of products (TLC analysis), but changing the oxidant to PCC afforded aldehyde **17** in 81% yield. Subsequently, it was discovered that Fétizon's reagent[11] ($Ag_2CO_3$ on Celite) afforded **17** in 99% yield. Demethylation of **17** with $BBr_3$ to afford diol **18** (52%) was then performed in preparation for a Dakin oxidation,[12] which would convert the formyl group into a hydroxyl group and thus complete the synthesis of **2**. The Dakin oxidation normally requires the presence of a hydroxyl group *ortho* or *para* to the formyl group slated for oxidation.[12] In the case of **18**, it was envisaged that the OH substituent in extended conjugation with the aldehyde would enable the Dakin oxidation to proceed. However, all attempts to achieve this transformation failed.




**Scheme 4** Unsuccessful approach to urolithin M7 (**2**)




**Scheme 5** Completion of the synthesis of urolithin M7

The ultimately successful pathway proceeded from **9** through a hydrolysis reaction, the acidic workup of which presumably reformed the lactone to give carboxylic acid **19** (Scheme 5). Treatment of **19** with NaH generated the corresponding carboxylate salt, which was reacted in crude form with oxalyl chloride at reflux. The resulting crude acid chloride was reacted with dimethylzinc in the presence of $Pd(PPh_3)_4$ to afford methyl ketone **20** in good

yield (84%).[13] Baeyer–Villiger oxidation[14] of **20** using MCPBA/trifluroroacetic acid at room temperature now proceeded smoothly to afford acetate **21** in 74% yield. Global deprotection of all three phenolic OH groups was achieved upon heating **21** in aqueous concentrated HI solution for 30 minutes to afford the natural product **2** in 98% yield. The overall yield of urolithin M7 from the commercially available salicylaldehyde **11** was 48% over eight steps. The $^1$H NMR and $^{13}$C NMR spectra of **2** matched the reported data from the original isolation paper.[5]

In summary, a concise, high-yielding total synthesis of urolithin M7 has been completed. The key step was an IEDDA-driven domino reaction of coumarin-fused diene **10**.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **Experimental Procedure for 9**
A solution of dimethoxyacetaldehyde (60 wt% solution in $H_2O$, 19.6 mL, 0.130 mol) and pyrrolidine (9.76 mL, 0.117 mol) in benzene (150 mL) was heated at reflux with azeotropic removal of $H_2O$ for 1 h. The resulting mixture was allowed to cool for 10 min, and solid **10** (3.38 g, 13.0 mmol) was added in one portion. The resulting mixture was heated at reflux for 7 d. The reaction mixture was cooled to r.t. and then concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$ (150 mL) and washed with aq 1 M HCl solution (5 × 50 mL), dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure to afford **9** (4.08 g, 100%) as a tan solid: mp 195–196 °C. IR (Nujol): ν = 1735 (s), 1715 (s), 1607 (m), 1121 (s) cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.76 (d, *J* = 9.3 Hz, 1 H), 8.57 (d, *J* = 1.1 Hz, 1 H), 7.80 (d, *J* = 1.0 Hz, 1 H), 6.81 (dd, *J* = 9.6, 3.0 Hz, 1 H), 6.76 (d, *J* = 2.6 Hz, 1 H), 4.08 (s, 3 H), 3.96 (s, 3 H), 3.87 (s, 3 H). $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ = 165.6, 161.3, 160.7, 156.4, 152.7, 130.0, 129.1, 128.0, 124.0, 121.3, 116.1, 111.7, 110.0, 101.3, 56.1, 55.3, 52.4. MS (EI): *m/z* (%) = 314 (100) [M$^+$], 299 (53), 283 (13), 212 (4), 157 (4). Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49. Found C, 65.03; H, 4.61.
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