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Synthesis of (±)-Pterocarpin and Its Thia- and Aza-Analogues in a Modular Manner

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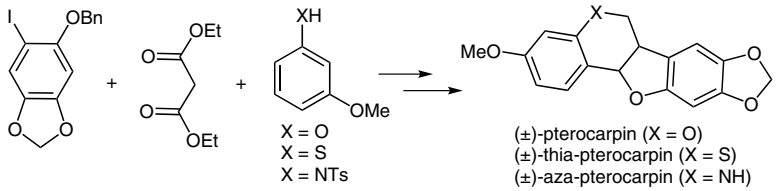

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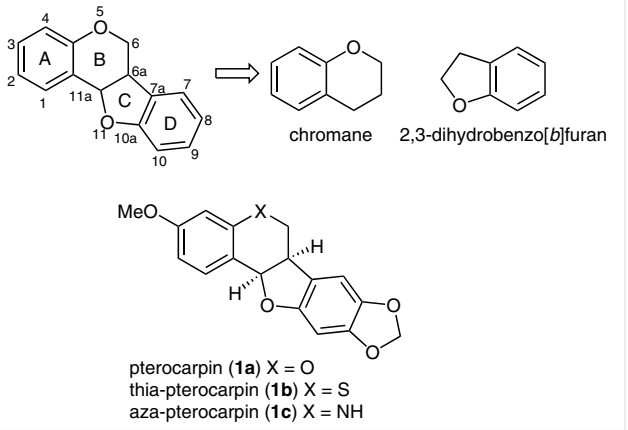
Abstract Syntheses of racemic pterocarpin, its thia- and aza-pterocarpin have been achieved in a modular manner using sesamol iodide, diethyl malonate and 3-methoxyphenol, 3-methoxythiophenol and *N*-tosyl-3-methoxyaniline as building blocks. Copper-mediated Hurtley coupling, Mitsunobu reaction, IBX-mediated oxidation, Pinnick oxidation, and intramolecular Friedel–Crafts acylation have been successfully exploited in the synthesis.

Key words pterocarpin synthesis, thia-pterocarpin synthesis, aza-pterocarpin synthesis, pterocarpan synthesis, isoflavanone synthesis

Pterocarpans make up the second-largest group of isoflavonoids. They contain a rearranged C_{15} skeleton wherein a chromane skeleton is structurally *cis*-fused with dihydrobenzofuran at positions 6a and 11a[1] (Scheme 1). Pterocarpin (**1a**, Scheme 1), a typical representative of pterocarpans, has been isolated from *Sophora tonkinensis*,[2a] *Euchresta formosana*,[2b] *Sophora flavescens*,[2c] *Sophora angustifolia*.[2d] It shows insect antifeedant[3] and heptoprotective activities[4] and has been identified as a potential inhibitor of neuraminidase with an IC_{50} of 1.4 μM.[5] A molecular docking experiment[5] revealed that pterocarpin, a noncompetitive inhibitor shown by the results of kinetic analysis, may bind to another binding pocket adjacent to the original active site of neuraminidase. This is highly significant for developing new drugs combat serious influenza virus.

The combination of its interesting structure and intriguing biological profile has made pterocarpin an attractive target for total synthesis. The synthesis of racemic pterocarpin has been achieved via palladium-catalyzed Heck

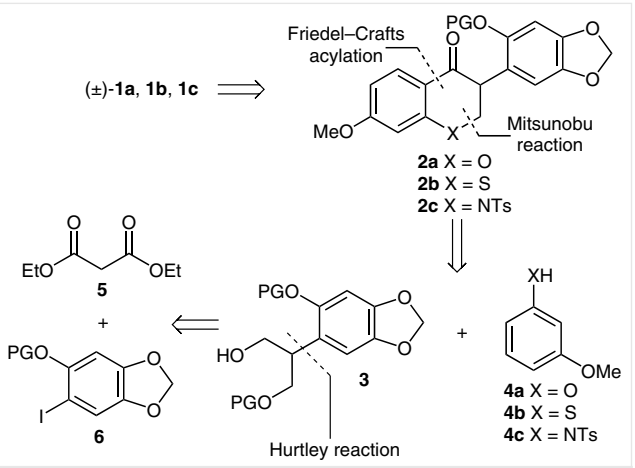


Scheme 1 The structure of pterocarpan and pterocarpin and its analogues

arylation of chromene with *o*-chloromercuriphenol,[6] phenyl iodonium(bis)trifluoroacetate (PIFA) mediated [3+2] cycloaddition of chromene with *p*-methoxyphenol,[7] and transformation from 2′-hydroxyisoflavone.[8] Recently, an elegant enantioselective synthesis of natural (–)-*cis*-pterocarpin and artificial (–)-*trans*-pterocarpin has been accomplished relying on silver-catalyzed condensation of 2,3-dihydrobenzoxasilepine with an aromatic aldehyde to result in the asymmetric construction of 2,3-dihydrobenzofuran.[9] Herein, we would like to describe a modular synthesis of (±)-pterocarpin (**1a**). In addition, since both thia and aza analogues usually serve as bioisosteres of naturally occurring flavonoids and exhibit diverse activities of importance,[10] thia- and aza-pterocarpin (**1b** and **1c**) also become our synthetic targets to facilitate in-depth study on structure–activity relationships of ptercocarpin (Scheme 1).

We envisaged that the construction of (±)-pterocarpin (**1a**) could be derived from isoflavanones **2**, which could be synthesized through Mitsunobu reaction between 3-methoxyphenol (**4a**) and 1,3-diol derivative **3** followed by intramolecular Friedel–Crafts acylation as key reactions.

1,3-Diol **3** could be obtained by means of Hurtley reaction of diethyl malonate **5** and iodide **6** derived from sesamol. Adopting the similar reaction sequences, replacement of **4a** with **4b** or **4c** would result in formation of thia- or aza-pterocarpin (**1b** or **1c**), respectively (Scheme 2).



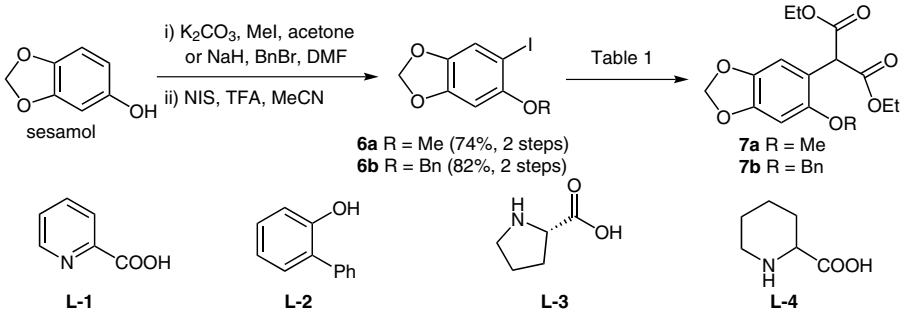
Scheme 2 Retrosynthetic analysis of (±)-pterocarpin (**1a**), thia-pterocarpin (**1b**), and aza-pterocarpin (**1c**)

The Hurtley reaction[11] refers to the copper-mediated α-arylation of activated methylene compounds and has been known for nearly a century. The scope and reaction conditions of this reaction have had significant improvements because of recent studies taking advantage of copper complexes with ancillary ligands including picolinic acid,[12] L-proline,[13a] 2-phenylphenol,[14] chelating Schiff bases,[15] and 1,10-phenanthroline.[16]

In our case, the presence of three electron-donating groups, with one of them being an *ortho* substituent, makes the Hurtley reaction of **6** very challenging. Thus, our synthesis commenced with the optimization of the coupling of iodide **6a**[17] with diethyl malonate under the promotion of copper(I) iodide in the presence of different ancillary ligands, the results are presented in Table 1. Reaction of **6a** with diethyl malonate under the promotion of 0.3 equivalents of copper(I) iodide with 0.6 equivalents of picolinic acid[12] (**L-1**) as ligand afforded α-arylated malonate **7a** in 25% yield (Table 1, entry 1), whereas the reaction using 2-phenylphenol[14] (**L-2**) as ligand led to trace of **7a** (Table 1, entry 2). Amino acids are a class of efficient ligands for the copper-catalyzed Hurtley reaction.[13] Thus the effects of L-proline[13a] (**L-3**) and racemic piperidine-2-carboxylic acid[18] (**L-4**) on the reaction proceeded smoothly and afforded **7a** in 56% yield (Table 1, entry 4).

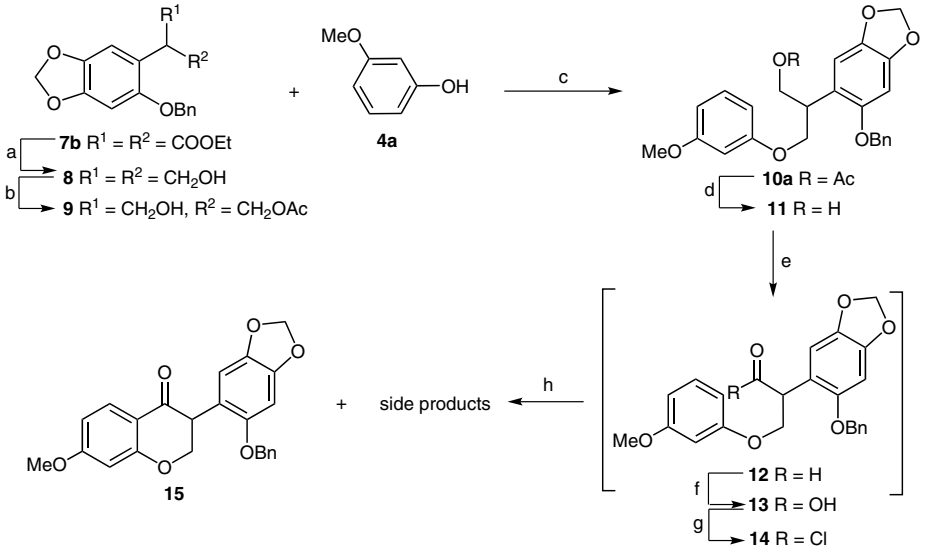
Addition of 4 Å molecular sieves to remove trace water in the reaction further improved the yield of **7a** to 71%[19] (Table 1, entry 5). Lowering the amounts of **L-4** and copper(I) iodide proved to be detrimental to the reaction, and

Table 1 Hurtley Reaction Between Iodide **6** and Diethyl Malonate[a]



Entry	Iodide	Ligand	Additive	Time (h)	Yield (%)
1	**6a**	**L-1**	none	24	25
2	**6a**	**L-2**	none	28	trace
3	**6a**	**L-3**	none	38	15
4	**6a**	**L-4**	none	24	56
5	**6a**	**L-4**	4 Å MS	12	71
6[b]	**6a**	**L-4**	4 Å MS	24	35
7	**6b**	**L-4**	4 Å MS	16	74

[a] Reaction conditions: **5** (2.2 mmol), **6a** or **6b** (1.1 mmol), CuI (0.33 mmol), ligand (0.66 mmol), Cs_2CO_3 (3.3 mmol) in 1,4-dioxane (1.3 mL) under Ar at 70 °C.
[b] Conditions: 0.1 mmol CuI and 0.2 mmol **L-4** were employed.

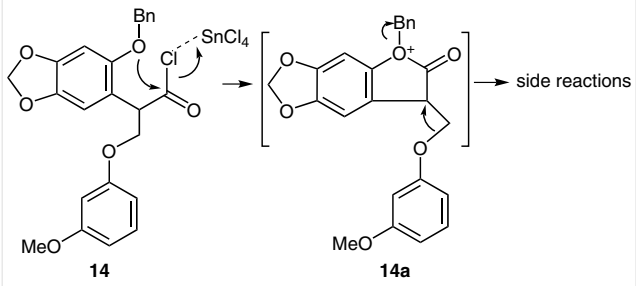


Scheme 3 Synthesis of isoflavanone **15**. *Reagents and conditions*: (a) $NaBH_4$, MeOH, 14 °C, 14 h, 89%; (b) *n*-Bu_4NOAc, Ac_2O, MeCN, 26 °C, 16 h, 70%; (c) ADDP, Bu_3P, THF, reflux, 12 h; (d) K_2CO_3, MeOH, 25 °C, overnight, 75% for two steps; (e) IBX, MeCN, 85 °C,0.5 h; (f) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-but-2-ene, *t*-BuOH, H_2O, 23 °C, 2 h; (g) $(COCl)_2$, DMF, CH_2Cl_2, 0–27 °C, 1 h; (h) $SnCl_4$, CH_2Cl_2, –20 °C, 14 h, 8% for **15** over four steps.

35% yield of **7a** was attained (Table 1, entry 6). Subjection of benzyl-protected iodide **6b**[20] and diethyl malonate to the optimized conditions resulted in the formation of arylated malonate **7b** in 74% yield (Table 1, entry 7).

With efficient access to α-arylated malonate established, we launched the synthesis of pterocarpin with **7b** because the benzyl group could be readily removed by hydrogenolysis (Scheme 3). Reduction of malonate **7b** with $NaBH_4$ in methanol gave 1,3-diol **8** in 89% yield (Scheme 3). Selective acetylation of polyols including carbohydrates has been achieved with Ac_2O in the presence of *n*-Bu_4NOAc in MeCN at 40 °C.[21] Therefore, treatment of **8** with Ac_2O/*n*-Bu_4NOAc in MeCN furnished monoacetylated alcohol **9** in 70% yield. Mitsunobu reaction has been widely used in the formation of aryl alkyl ether bonds,[22] however, our initial efforts failed to couple **9** with 3-methoxyphenol under classic Ph_3P/diethyl azodicarboxylate (DEAD) conditions. These results might be attributed to a pK_a >11 of 3-methoxyphenol (**4a**) because Mitsunobu reaction mediated by Ph_3P and DEAD requires the pK_a of nucleophiles <11.[23]

Bearing this in mind, 1,1′-(azodicarbonyl)dipiperidine (ADDP) was attempted since it is a suitable condensation reagent for nucleophile with a pK_a >11.[23] To our delight, treatment of phenol **4a** and **9** with ADDP and Bu_3P followed by deacetylation provided the desired alcohol **11** in 75% over two steps.[24] Due to the observations that intermediates aldehyde **12**, carboxylic acid, and acyl chloride were labile to flash SiO_2 chromatography, a four-step reaction sequence comprised of IBX oxidation,[25] $NaClO_2$-mediated Pinnick oxidation, acyl chloride formation, and final intramolecular Friedel–Crafts acylation[26] was carried out to convert alcohol **11** into isoflavanone **15** in 8% overall yield without purification of the intermediates. The low yield of **15** was ascribed to the attack of the benzyloxy group as competitive nucleophile to active acylium cation generated during the Friedel–Crafts reaction[27] to result in side reactions via intermediate **14a** (Scheme 4). As a consequence we replace the benzyl group with the electron-withdrawing mesyl group as protecting group of phenol to improve the efficiency of the synthesis (Scheme 5). Thus the crude mixture obtained from the condensation of **9** and **4a** was subjected to sequential debenzylation, mesylation, and deacetylation to furnish primary alcohol **18a**. Adopting the same four-step sequence as synthesis of **15**, conversion of **18a** into 7-methoxy-isoflavanone **21a** was achieved in 52% yield. In addition, a regioisomer, 5-methoxy-isoflavanone **22**, was isolated in 14% yield. It is derived from Friedel–Crafts acylation at the *ortho* position of the methoxy group of **18a**. Reduction of **21a** with $NaBH_4$ to alcohol **24a** followed by demesylation with NaOH[28] and final cyclization



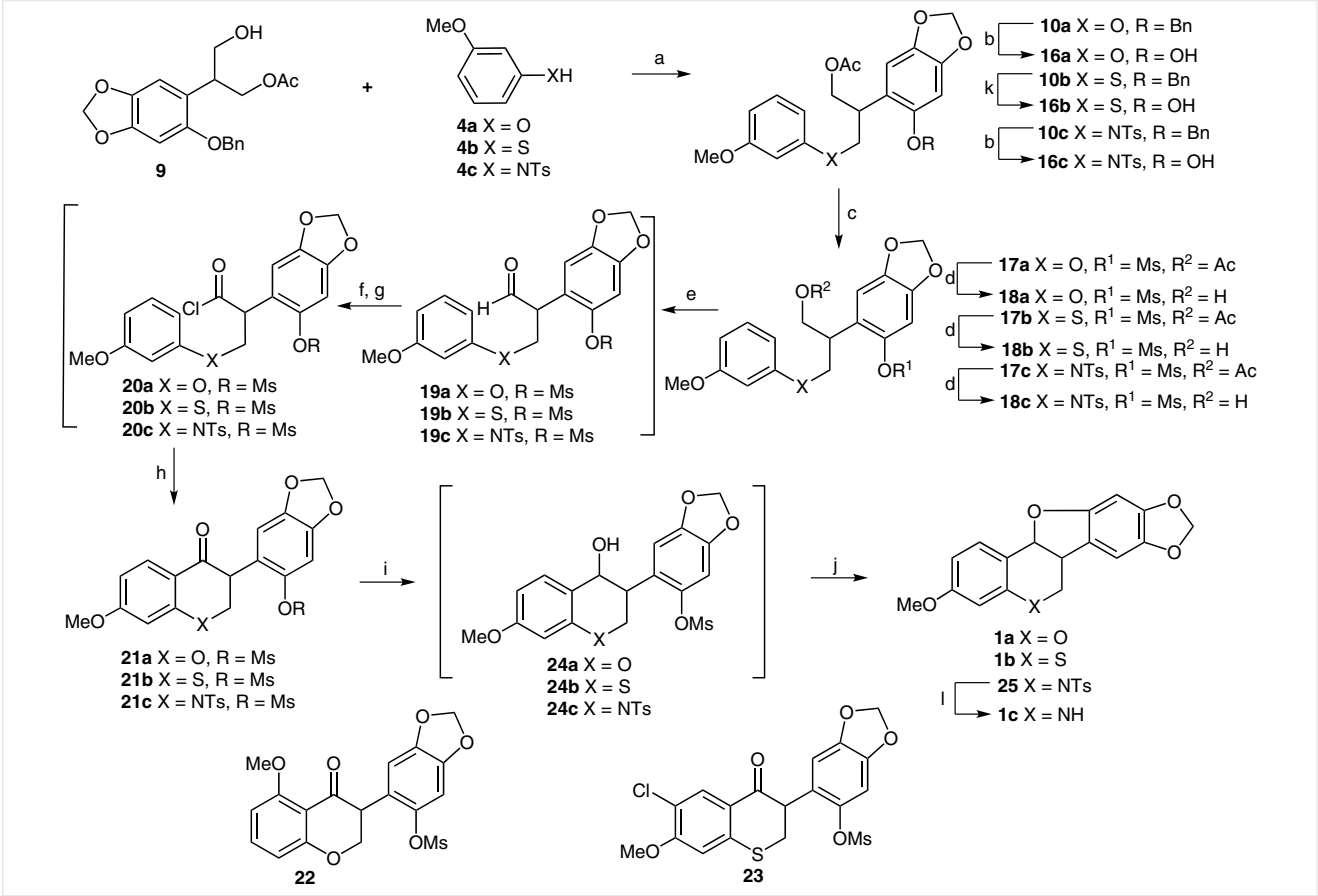
Scheme 4 Possible pathway for side reactions derived from **14**

with 1 M aqueous HCl furnished (±)-pterocarpin (**1a**) in 73% yield for three steps. Thus, the total synthesis of **1a** was accomplished in 16 steps in 11% yield from sesamol (Scheme 5).

Encouraged by the successful synthesis of (±)-pterocarpin and to demonstrate the diversity of our strategy, we turned our attention to the synthesis of racemic thia- and aza-pterocarpin (**1b** and **1c**).

As shown in Scheme 5, utilization of 3-methoxy-thiophenol (**4b**) and *N*-tosyl-3-methoxyaniline (**4c**)[29] in place of 3-methoxyphenol (**4a**), thia- and aza-pterocarpin (**1b** and **1c**) were achieved in overall yield of 3.4% (16 steps) and 4.4% (17 steps), respectively, with sesamol as starting material.

Some comments are pertinent to these syntheses. As expected, sulfide **10b** was readily obtained in 95% yield by Mitsunobu coupling of **4b** and **9** since thiol is well-known as a good nucleophile. Additionally, removal of the benzyl group on **10b** was performed with the cooperation of $BF_3{\cdot}OEt_2$ and Me_2S[30] to afford alcohol **16b** in 63% yield. While oxidation of alcohol **18b** to aldehyde **19b** with IBX in acetonitrile at 80 °C resulted in a complicated reaction, the reaction in DMSO at 35 °C proceeded cleanly. We attributed this observation to the formation of intermolecular hydrogen bond between the hydroxyl group and DMSO, which might lead to oxidation of the hydroxyl group in preference to that of the sulfide ether moiety.[31] Additionally, transformation of sulfide **10b** into the desired thiaisoflavanone **21b** (29%) was accompanied by unexpected chloride **23** in 11% yield. This could be rationalized by HOCl, in situ formed during the Pinnick oxidation, functioning as an electrophile to participate in electrophilic displacement of the electron-rich aromatic ring to provide chloride **23**.



Scheme 5 Synthesis of (±)-pterocarpin (**1a**), thia-pterocarpin (**1b**), and aza-pterocarpin (**1c**). *Reagents and conditions*: (a) ADDP, Bu_3P, THF for **10a** or toluene for **10b** and **10c**, reflux, 10 h, 95% for **10b**; (b) Pd/C, H_2, EtOH, 26 °C, 5 h, 84% for **16a** from **9**; 28% for **16c** from **9**; (c) MsCl, DIPEA, CH_2Cl_2, 26 °C, 4 h; (d) K_2CO_3, MeOH, 25 °C, 1 h, 91% for **18a** from **16a**, 93% for **18b** from **16b**, 90% for **18c** from **16c**; (e) IBX, MeCN, 85 °C, 0.5 h for **12**, **19a**, and **19b** or IBX, DMSO, 35 °C, 3 h for **19b**; (f) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methylbut-2-ene, *t*-BuOH, H_2O, 23 °C, 2 h; (g) $(COCl)_2$, DMF, CH_2Cl_2, 0–27 °C, 1 h; (h) $SnCl_4$, CH_2Cl_2, –20 °C, 14 h, 52% for **21a** and 14% for **22** from **19a**, 29% for **21b** and 11% for **23** from **18b**, 62% for **21c** from **18c**; (i) $NaBH_4$, MeOH, 25 °C, 4 h; (j) i) NaOH, MeOH, H_2O, 90 °C, 3 h; ii) 1 M HCl, 90 °C, 30 min, 73% for **1a** from **21a**; 55% for **1b** from **21b**; 87% for **26** from **21c**; (k) $BF_3{\cdot}OEt_2$, SMe_2, CH_2Cl_2, 30 °C, 50 h, 63%; (l) Mg, NH_4Cl, MeOH, 14 h, 25 °C, 85%.

For the synthesis of aza-pterocarpin **1c**, sulfonamide **16c** was obtained in 28% yield along with 69% recovery of **9** after Mitsunobu coupling followed by debenzylation. Efforts to improve the yield were unrewarded. Compared to the synthesis of (±)-pterocarpin (**1a**) and thia-pterocarpin (**1b**), one extra step to cleave the tosyl group on **25** was needed for the synthesis of **1c**. Reductive detosylation[32] with magnesium chips in methanol in the presence of ammonium chloride delivered the desired **1c** in 85% yield.

In summary, a modular strategy has been successfully applied in the total synthesis of (±)-pterocarpin, thia- and aza-pterocarpin relying on copper-mediated Hurtley reaction and Mitsunobu reaction as key operations. The main appeal of this work is the broad substrate scope of both the Hurtley reaction and Mitsunobu reaction, which provide a new approach to the synthesis of pterocarpans and the related natural products such as isoflavanones. With various protocols for enantioselective desymmetrization[33,34] of α-substituted 1,3-diols by chemical or enzymatic methods available, our method also opens up prospects for the enantioselective synthesis of pterocarpin and other pterocarpans, which are currently under way in our laboratory.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380520.

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(19) **Typical Procedure for the Hurtley Reaction**
An oven-dried vial equipped with a Teflon-coated magnetic stir bar was charged sequentially with freshly activated 4 Å MS (150 mg), CuI (65 mg, 0.33 mmol, 0.3 equiv), (±)-pipecolic acid (85 mg, 0.66 mmol, 0.6 equiv), Cs_2CO_3 (1.06 g, 3.3 mmol, 3.0 equiv), and **6a** (300 mg, 1.1 mmol, 1.0 equiv). After the vial was evacuated and backfilled with nitrogen (3×), anhydrous 1,4-dioxane (1.3 mL) was added followed by diethyl malonate **5** (350 μL, 2.2 mmol, 2.0 equiv). The vial was sealed and placed into a preheated oil bath at 70 °C. After stirring for 12 h, the reaction was cooled to r.t. The reaction mixtures were partitioned between EtOAc (3 × 20 mL) and sat. aq NH_4Cl (10 mL). The organic portions were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc–PE, 1:10) to afford pure **7a** (242 mg, 0.78 mmol, 71% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.88 (s, 1 H), 6.53 (s, 1 H), 5.92 (s, 2 H), 5.05 (s, 1 H), 4.27–4.16 (m, 4 H), 3.76 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 152.5, 148.2, 141.4, 113.8, 109.4, 101.4, 94.9, 61.7, 56.9, 50.8, 14.2. HRMS (ESI): *m/z* calcd for $C_{15}H_{19}O_7$ $[M + H]^+$: 311.1125; found: 311.1133.
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(24) **Typical Procedure for the Mitsunobu Reaction**
To a chilled (0 °C) and stirred solution of 1,1′-(azodicarbonyl)dipiperidine (ADDP, 241 mg, 0.96 mmol, 2.2 equiv) in anhydrous THF (5 mL) was added dropwise Bu_3P (271 μL, 1.09 mmol, 2.5 equiv) over 5 min. The resulting mixture was stirred for 0.5 h until the solution turned colorless. At this point, a solution of **9** (150 mg, 0.44 mmol, 1.0 equiv) in anhydrous THF (1.0 mL) followed by a solution 3-methoxyphenol **4a** (140 μL, 1.30

mmol, 3.0 equiv) in anhydrous THF (1.0 mL) were added dropwise. Then the reaction was warmed to 70 °C and stirred for another 12 h at this temperature. The solvent was removed in vacuo, and the residue was rapidly purified on a short silica gel column (EtOAc–PE, 1:5) to get rid of the Bu_3PO. The resultant residue, which contained 3-methoxyphenol and **10a**, was dissolved in MeOH (4 mL), and anhydrous K_2CO_3 (80 mg, 0.58 mmol, 1.3 equiv) was added. The suspension was stirred at r.t. overnight. The reaction was poured into H_2O and extracted with EtOAc (3 × 15 mL). The collected phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column (EtOAc–PE, 1:3) to afford **11** (135 mg, 0.33 mmol, 75%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.29 (m, 5 H), 7.13 (t, *J* = 8.2 Hz, 1 H), 6.84 (s, 1 H), 6.62 (s, 1 H), 6.53–6.48 (m, 2 H), 6.47 (t, *J* = 2.3 Hz, 1 H), 5.91 (s, 2 H), 5.02 (s, 2 H), 4.22–4.14 (m, 2 H), 4.04–4.00 (m, 1 H), 3.95–3.91 (m, 1 H), 3.83–3.75 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0, 160.0, 151.6, 147.0, 141.8, 136.9, 130.0, 128.8, 128.2, 127.6, 120.4, 108.3, 106.8, 101.3, 101.2, 96.8, 71.9, 69.3, 64.4, 55.4, 40.6. HRMS (ESI): *m/z* calcd for $C_{24}H_{25}O_6$ $[M + H]^+$: 409.1646; found: 409.1646.

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