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通过(*E*)-7-甲基-2,6-辛二烯酸的立体选择性 Mizoroki-Heck 芳基化反应合成(*E*)-3-芳基-7-甲基-2,6-辛二烯酸

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摘要 对 $Pd(OAc)_2$ 和 $P(o\text{-}MeC_6H_4)_3$ 催化的(*E*)-7-甲基-2,6-辛二烯酸与碘代芳烃的立体选择性 Mizoroki-Heck 芳基化反应进行了优化, 在减少催化剂的用量以及过量的三乙胺同时作碱和溶剂的条件下, 产物的收率得到了显著的改善. 在回流温度下通过 Mizoroki-Heck 芳基化反应, 以 37%～68%的分离收率合成了 20 个(*E*)-3-芳基-7-甲基-2,6-辛二烯酸, 它们的结构经过 IR, ^{1}H NMR, ^{13}C NMR, HR-ESI-MS 和 X 射线衍射的表征.
关键词 (*E*)-3-芳基-7-甲基-2,6-辛二烯酸; Mizoroki-Heck 芳基化反应; 构型; 合成

Synthesis of (*E*)-3-Aryl-7-methylocta-2,6-dienoic Acid via Stereoselective Mizoroki-Heck Arylation of (*E*)-7-Methylocta-2,6-dienoic Acid

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Abstract Stereoselective Mizoroki-Heck arylation of (*E*)-7-methylocta-2,6-dienoic acid with aryl iodide catalyzed by $Pd(OAc)_2$ and $P(o\text{-}MeC_6H_4)_3$ was optimized, and the yields were improved under the condition of excess Et_3N both as the base and solvent with reduced amount of catalysts. Twenty (*E*)-3-aryl-7-methylocta-2,6-dienoic acids were directly synthesized via Mizoroki-Heck arylation in 37%～68% isolated yields at reflux temperature. Their structures were characterized by IR, ^{1}H, ^{13}C NMR, HR-ESI-MS data and X-ray diffraction.
Keywords (*E*)-3-aryl-7-methylocta-2,6-dienoic acid; Mizoroki-Heck arylation; configuration; synthesis

1 Introduction

Cinnamide and cinnamate derivatives are one important class of compounds, which exhibited various biological activities such as nervous central system depressant, anticonvulsant, anti-allergic, antineoplastic, anti-infective, fungicidal and herbicidal activities.[1] Several excellent fungicides, such as dimethomorphy, fluormorphy and pyrimorphy (Figure 1), have been successfully developed and widely used in agricultural fields.[2] A lot of attention was still paid to the synthesis and bioassay of the novel cinnamide and cinnamate derivatives in the medicinal, agricultural, and natural product chemistry in recent years.[3a~3d] The 3,7-dimethylocta-2,6-dienamides and its 6,7-epoxy analogues were synthesized, and showed that they exhibited good fungicidal activities against several phytopathagens in our previous report.[3e] Therefore, the new amides are designed by replacement of C_3-methyl with various aryl groups (Figure 1) and we hope to improve their fungicidal activities. However, the new cinnamic acids for synthesizing these novel amide derivatives were not commercially available and highly desired.

In the other aspect, (6*R*)-3,7-dimethyl-7-hydroxy-2-octen-6-olide (*R*-**1**), which has an unique seven-membered lactone, and (2*Z*,6*R*)-6,7-dihydroxy-3,7-dimethylocta-2-enoic acid (*Z*,*R*-**2**) were first isolated from the honey bee fungal entomopathogen *Ascosphaera apis*, as well as the fruit of plant *Litsea cubeba* in Tibet, and exhibited good antifungal and antioxidant activities (Figure 2).[4,5] This type of seven-membered lactone with *α*-hydroxy side chain was seldom found in nature and synthesized in literatures. 6,7-Dihydroxy-3,7-dimethyloct-2-enoic acid was isolated from the root of *Amomum tsao-ko*, and reported to be used in the treatment of skin lesion in a patent, but the olefin configuration, absolute configuration of chiral center

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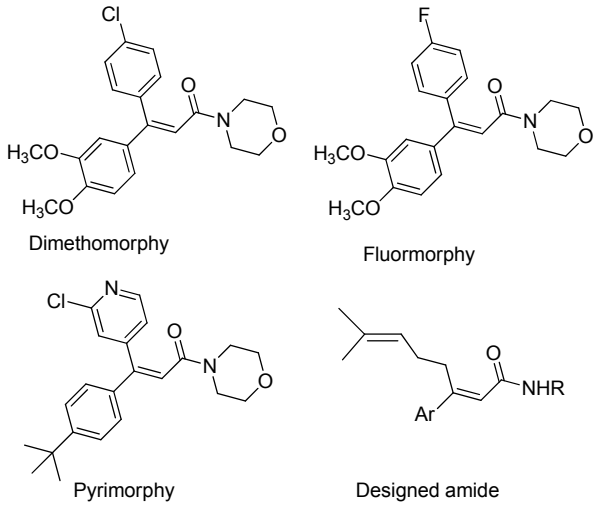


Figure 1 The structures of typical cinnamide fungicides and designed amides

and its source were unknown.[6~8] In the previous paper, the racemic 3,7-dimethyl-7-hydroxy-2-octen-6-olide (**1**), (2*E*)-6,7-dihydroxy- 3,7-dimethyl-octa-2-enoic acid (*E*-**2**), and 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide (**3**) were totally synthesized via epoxidation-lactonization approaches of olefin acid.[9~11] The (6*R*) and (6*S*) isomers (*R*-**1** and *S*-**1**), four isomers of 6,7-dihydroxy-3,7-dimethyl-octa-2-enoic acid **2** and their esters were also synthesized with high *ee* values via Sharpless asymmetry dihydroxylation as the key steps due to its ability of construction chiral alcohol.[12~14] The *in vivo* bioassay results showed that the antifungal activities of acids **2** are much better than that of their esters against five phytopathagens.[15] In order to further compare the antifungal activity differences against phytopathagens and get insights into the structure-antifungal activity relationship among the seven-membered lactone, ring-opening olefin acid and its derivatives, the new seven-membered lactones (Figure 2) were designed by replacement of C_3-methyl in **1** with various aryl groups. However, the key intermediates (*E*)-3-aryl-7-methylocta-2,6-dienoic acid **4** (novel cinnamic acid derivatives) for synthesizing these lactones and derivatives are not commercially available (Scheme 1). The main products with the undesired *Z*-configuration of double bond (*Z*-**4**) were afforded when utilizing the Witting-Horner reaction to prepare them under various conditions (Scheme 1, Eq. 1), the raw materials ketone **5** also needs to be synthesized in 3～5 steps,[16] which even made this approach more impractical.

Mizoroki-Heck arylation is an efficient protocol of preparing various *α*,*β*-unsaturated compounds with the *β*-aryl group. Mizoroki-Heck arylation of *α*,*β*-unsaturated acid esters, carboxamide, and acrylonitrile was reported and reviewed.[17] The direct Mizoroki-Heck arylation of acrylic acid, (*E*)-but-2-enoic acid, (*E*,*E*)-2,4-pentadienoic acid, and (*E*)-cinnamic acid were also sparsely reported (Scheme 1), but yields decreased greatly with the bulky groups at the *β*-position.[17c~17e,18] Therefore, an efficient approach for the preparation of *α*,*β*-unsaturated acid with an aromatic substituent group at the *β*-position via the direct Mizoroki-Heck arylation of simple *α*,*β*-unsaturated acid is highly required. Large scale synthesis of (*E*)-7-methylocta-2,6-dienoic acid (**6a**) and its ester (**6b**) were successfully carried out according to the procedure in the literature,[19] then the direct synthetic strategy of (*E*)-3-aryl-7-methylocta-2,6-dienoic acid (**4**) via Mizoroki-Heck arylation of (*E*)-7-methyl-octa-2,6-dienoic acid **6a** or its ester **6b** with aryl iodide was explored and the results were presented in this paper (Scheme 1).

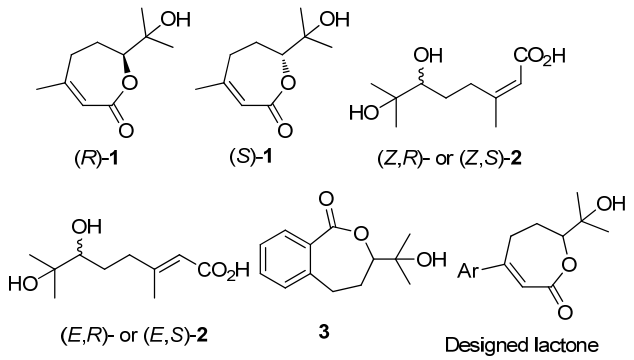
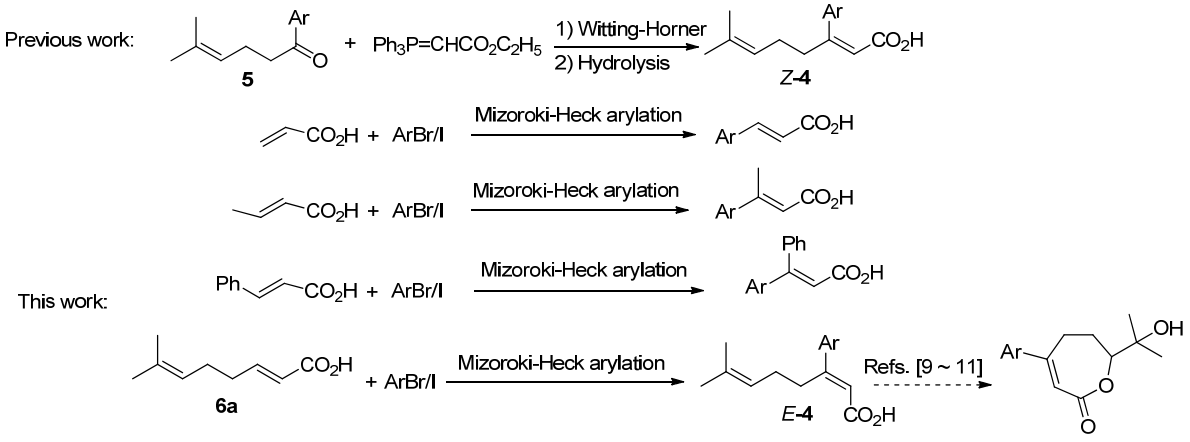


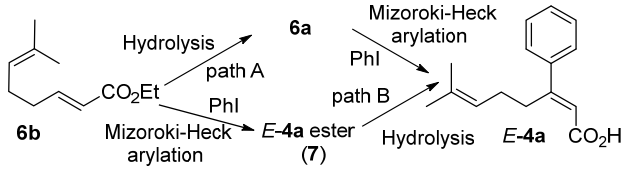
Figure 2 Structures of lactones (**1**, **3**), 6,7-dihydroxy-3,7-dimethylocta-2-enoic acid (**2**) and designed lactone



Scheme 1 Synthetic routes of 3-aryl-7-methylocta-2,6-dienoic acid **4** and the other acids

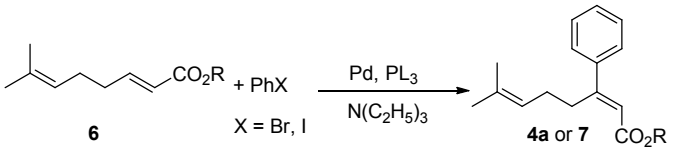
2 Results and discussion

(*E*)-7-Methylocta-2,6-dienoic acid (**6a**) and its ester (**6b**) were obtained following the procedure in the literature,[19] then the synthesis of (*E*)-3-aryl-7-methylocta-2,6-dienoic acid **4** could be carried out in two pathways (paths A and B) as indicated in Scheme 2 (took **4a** as an example), and the only difference was the order of Mizoroki-Heck arylation and hydrolysis. The Mizoroki-Heck arylation synthetic route (Scheme 2, path A) was initially investigated according to the standard procedures in the literatures[18] and the results were showed in Table 1 (Table 1, Entries 1～6). When Et_3N in *N*,*N*-dimethylformamide (DMF) was used as a base, Et_3N increased from 5 equiv. to 30 equiv., the isolated yields increased from less than 10% to 47% (Table 1, Entries 1～4). When PhI decreased from 2 equiv. to 1.5 equiv., the yield decreased from 47% to less than 10% (Table 1, Entry 5), while PhI increased from 2 equiv. to 3 equiv., the yield decreased from 47% to 44% (Table 1, Entry 6). So we decided to perform this reaction without solvent. When the quantity of Et_3N remained 20 equiv. of material **6a** and the solvent DMF was not utilized, the reaction still had 47% yield (Table 1, Entry 7). In this case, the following reaction was carried out under the condition of only excess Et_3N both as base and solvent. When PhI was replaced with PhBr, the yield significantly decreased due to the weak reaction activity of PhBr (Table 1, Entry 8). The reaction was not completed with only 39% yield when it stopped at 10 h (Table 1, Entry 9), but the yield significantly decreased to 41% when the reaction time was extended to 30 h because byproduct appeared (Table 1, Entry 10). The yields only reached 49% and 40% when $Pd_2(DBA)_3$ and $PdCl_2$ were in replacement of $Pd(OAc)_2$ as catalysts (Table 1, Entries 11 and 12). When ester **6b** was utilized to perform the Mizoroki-Heck arylation in the same protocol as in Entries 11 and 12 (Scheme 2, path B), the yields of **7** were only 22% and 25% (Table 1, Entries 13 and 14), much less than that of **4a** (47% and 49%) in Entries 11 and 12, so only acid **6a** would be used as the starting material for the following



Scheme 2 Two routes of (*E*)-3-aryl-7-methylocta-2,6-dienoic acid (**4a**) by Mizoroki-Heck arylation

Table 1 Preparation condition optimization of (*E*)-3-phenyl-7-dimethylocta-2,6-dienoic acid **4a**[a]



4a and **6a** R = H; **7** and **6b** R = Et

Entry	6a/6b	Pd (mol%)	PL_3 (mol%)	PhX/equiv.	NEt_3/equiv.	*T*/h	Yield[b]/% of 4a/7
1	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	5	20	＜10
2	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	10	20	＜10
3	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	48
4	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	30	20	47
5	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	1.5	20	20	＜10
6	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	3	20	20	44
7	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	47
8	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	＜10[c]
9	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	10	39
10	**6a**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	30	41
11	**6a**	$Pd_2(DBA)_3$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	49
12	**6a**	$PdCl_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	40
13	**6b**	$Pd(OAc)_2$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	22[d]
14	**6b**	$Pd_2(DBA)_3$ (10)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	25[d]
15	**6a**	$Pd(OAc)_2$ (10)	P(*m*-$MeC_6H_4)_3$ (20)	2	20	20	＜10
16	**6a**	$Pd(OAc)_2$ (10)	P(*p*-$MeC_6H_4)_3$ (20)	2	20	20	＜10
17	**6a**	$Pd(OAc)_2$ (10)	PPh_3 (20)	2	20	20	＜10
18	**6a**	$Pd(OAc)_2$ (10)	P(*t*-But)$_3$ (20)	2	20	20	28
19	**6a**	$Pd_2(DBA)_3$ (10)	P(*t*-But)$_3$ (20)	2	20	20	27
20	**6a**	$Pd(OAc)_2$ (5)	P(*o*-$MeC_6H_4)_3$ (10)	2	20	20	54
21	**6a**	$Pd(OAc)_2$ (5)	P(*o*-$MeC_6H_4)_3$ (15)	2	20	20	51
22	**6a**	$Pd(OAc)_2$ (5)	P(*o*-$MeC_6H_4)_3$ (20)	2	20	20	N.R.

[a] Reaction conditions: **6a**/**6b** (0.3 mmol) in dry DMF (1 mL) or no DMF, reflux; [b] Isolated yield of **4a**; [c] PhBr was used; [d] isolated yield of **7**.

experiment (Scheme 2, path A). However the phosphorus catalyst P(*o*-$MeC_6H_4)_3$ was changed to P(*m*-$MeC_6H_4)_3$, P(*p*-$MeC_6H_4)_3$, PPh_3 and P(*t*-But)$_3$, the yield significantly decreased to less than 10% (Table 1, Entries 15～17), 28% and 27% (Table 1, Entries 18, 19). Finally, 5 mol% $Pd(OAc)_2$ was used. When 10 and 15 mol% P(*o*-$MeC_6H_4)_3$ were used, the yields were improved to 54% and 51%, respectively, while 20 mol% P(*o*-$MeC_6H_4)_3$ was used, the reaction was not detected (Table 1, Entries 20～22). So, the following large-scale reaction was performed under the condition: **6a**∶ArI (*n*∶*n*＝1∶2), $Pd(OAc)_2$ (5 mol%) and P(*o*-$MeC_6H_4)_3$ (10 mol%) as catalysts, excess Et_3N (20 equiv. acid **6a**) both as the base and solvent, and 20 h at reflux temperature.

Then the large-scale (2 mmol) reactions were performed under the conditions outlined above and the results were given in Table 2. In comparison with the result of entry 16 in Table 1, the yield of **4a** was further improved to be 60% when 2 mmol of **6a** was used (Table 2, Entry 1). Also the isolated yields of the other products **4b**～**4t** approached 37%～68% on this scale (The NMR yields in 54%～85%) (Table 2, Entries 2～20). The reason probably was that the side-reaction and the product loss during the isolation process were decreased. Compared with the conventional Mizoroki-Heck arylation in organic solvents, the yields were significantly improved after the modification of reaction conditons, although the yields were relatively lower than that of acrylic acid, (*E*)-but-2-enoic acid, and (*E*,*E*)-2,4-pentadienoic acid due to the bulky group at the *β*-position.[17,18] The results in Table 2 indicated that this method was compatiable to both the electron-donating and electron-withdrawing groups on the benzene ring, its advantage was to reduce the quantity of catalyst and avoid the usage of organic solvents. The products were characterized by ^{1}H NMR, ^{13}C NMR, HR-ESI-MS, and X-ray diffraction of compound **4i** (Figure 3). The olefin configuration of the product 3-aryl-7-methylocta-2,6-dienoic acid was deduced as *E*-configuration based on the crystal structure of **4i**, which was the desired isomer for synthesizing these seven-membered lactones. These transformations from **4** to their correspondent seven-membered lactones are in progress.

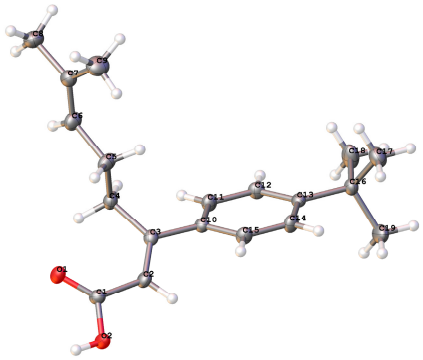
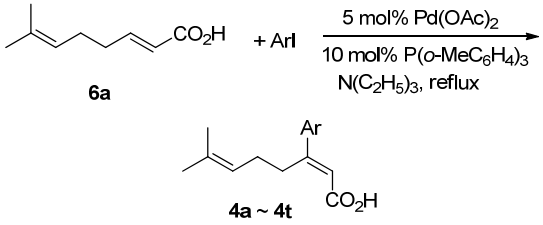


Figure 3 X-ray crystal structure of compound **4i**

Table 2 Preparation of (*Z*)-3-aryl-7-methylocta-2,6-dienoic acid **4**[a]



Entry	Ar	Product	Yield/%
1	C_6H_5	**4a**	60[b] (78)[c]
2	*o*-ClC_6H_4	**4b**	64 (84)
3	*m*-ClC_6H_4	**4c**	62 (81)
4	*p*-ClC_6H_4	**4d**	51 (74)
5	*p*-$CH_3C_6H_4$	**4e**	52 (72)
6	*p*-FC_6H_4	**4f**	38 (61)
7	*p*-$CF_3C_6H_4$	**4g**	55 (74)
8	*p*-$CH_3OC_6H_4$	**4h**	59 (78)
9	*p*-$(CH_3)_3CC_6H_4$	**4i**	47 (66)
10	*p*-$CH_3COC_6H_4$	**4j**	55 (80)
11	*p*-$CH_3OCOC_6H_4$	**4k**	54 (84)
12	*p*-NCC_6H_4	**4l**	64 (82)
13	*o*-$CH_3C_6H_4$	**4m**	56 (84)
14	*o*-$CH_3OC_6H_4$	**4n**	37 (54)
15	*o*,*p*-$(CH_3)_2C_6H_3$	**4o**	62 (79)
16	*m*,*m*-$(CH_3)_2C_6H_3$	**4p**	68 (85)
17	*α*-$C_{10}H_7$	**4q**	46 (64)
18	*β*-$C_{10}H_7$	**4r**	57 (74)
19	*p*-$C_6H_5C_6H_4$	**4s**	49 (68)
20	1-Methyl-1*H*-indol-4-yl	**4t**	50 (66)

[a] Reaction conditions: **6a** (2 mmol), 20 equiv. Et_3N, reflux, reaction time 20 h; [b] isolated yield; [c] NMR yield.

3 Conclusion

The reaction conditions of Mizoroki-Heck arylation of (*E*)-7-methylocta-2,6-dienoic acid with aryl iodide catalyzed by $Pd(OAc)_2$ and P(*o*-$MeC_6H_4)_3$ were optimized, and the yields were improved under the condition of excess Et_3N both as the base and solvent with reduced amount of catalysts. Twenty (*E*)-3-aryl-7-methylocta-2,6-dienoic acids were directly synthesized via Mizoroki-Heck arylation of (*E*)-7-methylocta-2,6-dienoic acid as the key step in 37%～68% isolated yields. Their structures were characterized by ^{1}H NMR, ^{13}C NMR, HR-ESI-MS data and X-ray diffraction study.

4 Experimental section

4.1 General information

All reactions were performed under a N_2 atmosphere with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Flash column chromatography was performed using Qingdao Haiyang silica gel (200～300 mesh). Melting

points were measured on a Yanagimoto apparatus (Yanagimoto MFG Co., Kyoto, Japan) and are uncorrected. IR spectra were recorded on a Thermo Nicolet IS10 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DPX 300 spectrometer with $CDCl_3$ as a solvent and TMS as an internal standard. HR-ESI-MS spectra were analyzed on a Bruker Apex II mass spectrometer. The crystal structure was analyzed with a Thermo Fisher ESCALAB 250 four-circle X-ray diffractometry.

4.2 Synthesis of (*E*)-7-methylocta-2,6-dienoic acid and its ester 6a and 6b

The synthesis of (*E*)-7-methylocta-2,6-dienoic acid ester **6b** was following the protocol as decribed in the literature and the spectral data were identical with that reported.[19a] Then, 620 mg (3.4 mmol) of **6b**, 600 mg (14.3 mmol) of LiOH•H_2O, 10 mL of water, and 10 mL of methanol were added into a 50 mL flask. The solution was stirred and heated to 40 ℃ for 12 h, the methanol was removed, and the aqueous layer was adjusted to pH 1～2 with HCl solution, then diluted with H_2O (20 mL) and extracted with AcOEt (30 mL×3). The organic phase was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on a silica gel column [*V*(petroleum)/*V*(ethyl acetate)=20/1] to afford a light yellow oil **6a** (506 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.04 (brs, 1H), 7.10 (dt, J=15.6, 6.7 Hz, 1H), 5.85 (dd, J=15.6, 1.3 Hz, 1H), 5.14～5.09 (m, 1H), 2.32～2.13 (m, 4H), 1.71 (s, 3H), 1.62 (s, 3H). The spectral data were consistent with that reported in the literature.[19b]

4.3 Synthesis of (*E*)-3-aryl-7-methylocta-2,6-dienoic acid (4)

$Pd(OAc)_2$ (0.05 equiv.), P(*o*-MeC_6H_4)$_3$ (0.10 equiv.), ArI (2.0 equiv.), acid **6a** (300 mg, 2.0 mmol) and $N(C_2H_5)_3$ (20.0 equiv.) were added, and the reaction mixture was stirred under a N_2 atmosphere and heated at 110 ℃ for 20 h. The reaction was then cooled to room temperature, quenched with 1 mol/L HCl, diluted with H_2O, and extracted with ethyl acetate (30 mL×3). The organic phase was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to afford compounds **4**.

(*E*)-3-Phenyl-7-methylocta-2,6-dienoic acid (**4a**): A colorless liquid, 269 mg, yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.80 (br, 1H), 7.50～7.39 (m, 5H), 6.09 (s, 1H), 5.16 (t, J=6.9 Hz, 1H), 3.16 (t, J=7.8 Hz, 2H), 2.19～2.11 (m, 2H), 1.68 (s, 3H), 1.54 (s, 3H). HR-ESI-MS calcd for $C_{15}H_{19}O_2$ $[M+H]^+$ 231.1380, found 231.1384.

(*E*)-3-*o*-Chlorophenyl-7-methylocta-2,6-dienoic acid (**4b**): A colorless liquid, 330 mg, yield 64%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.50 (br, 1H), 7.35～7.19 (m, 4H), 5.89 (s, 1H), 5.15 (t, J=6.9 Hz, 1H), 3.16 (t, J=7.8 Hz, 2H), 2.15～2.08 (m, 2H), 1.66 (s, 3H), 1.52 (s, 3H). HR-ESI-MS calcd $C_{15}H_{18}ClO_2$ $[M+H]^+$ 265.0990, found 265.0987.

(*E*)-3-*m*-Chlorophenyl-7-methylocta-2,6-dienoic acid (**4c**): A colorless liquid, 320 mg, yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46～7.28 (m, 4H), 6.08 (s, 1H), 5.14 (t, J=6.9 Hz, 1H), 3.15 (t, J=7.8 Hz, 2H), 2.18～2.09 (m, 2H), 1.68 (s, 3H), 1.53 (s, 3H). HR-ESI-MS calcd for $C_{15}H_{18}ClO_2$ $[M+H]^+$ 265.0990, found 265.0988.

(*E*-3-*p*-Chlorophenyl-7-methylocta-2,6-dienoic acid (**4d**): A colorless liquid, 260 mg, yield 51%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42～7.36 (m, 4H), 6.07 (s, 1H), 5.14 (t, J=7.2 Hz, 1H), 3.13 (t, J=7.5 Hz, 2H), 2.17～2.09 (m, 2H), 1.67 (s, 3H), 1.54 (s, 3H). HR-ESI-MS calcd for $C_{15}H_{18}ClO_2$ $[M+H]^+$ 265.0990, found 265.0991.

(*E*)-3-*p*-Methylphenyl-7-methylocta-2,6-dienoic acid (**4e**): A colorless liquid, 248 mg, yield 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.83 (br, 1H), 7.39 (d, J=7.8 Hz, 2H), 7.21 (d, J=7.8 Hz, 2H), 6.10 (s, 1H), 5.18 (t, J=7.2 Hz, 1H), 3.14 (t, J=7.8 Hz, 2H), 2.40 (s, 3H), 2.19～2.13 (m, 2H), 1.68 (s, 3H), 1.56 (s, 3H). HR-ESI-MS calcd for $C_{16}H_{21}O_2$ $[M+H]^+$ 245.1536, found 245.1538.

(*E*)-3-*p*-Flurophenyl-7-methylocta-2,6-dienoic acid (**4f**): A colorless liquid, 183 mg, yield 38%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50～7.45 (m, 2H), 7.15～7.08 (m, 2H), 6.05 (s, 1H), 5.14 (t, J=7.2 Hz, 1H), 3.15 (t, J=7.5 Hz, 2H), 2.17～2.06 (m, 2H), 1.67 (s, 3H), 1.53 (s, 3H). HR-ESI-MS calcd for $C_{15}H_{18}FO_2$ $[M+H]^+$ 249.1285, found 249.1282.

(*E*)-3-*p*-Triflurometh ylphenyl-7-methylocta-2,6-dieno-ic acid (**4g**): A colorless liquid, 320 mg, yield 55%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65～7.54 (m, 4H), 6.06 (s, 1H), 5.16 (t, J=7.2 Hz, 1H), 3.15 (t, J=7.5 Hz, 2H), 2.25～2.16 (m, 2H), 1.68 (s, 3H), 1.54 (s, 3H). HR-ESI-MS calcd for $C_{16}H_{18}F_3O_2$ $[M+H]^+$ 299.1253, found 299.1256.

(*E*)-3-*p*-Methoxylphenyl-7-methylocta-2,6-dienoic acid (**4h**): A colorless liquid, 301 mg, yield 59%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.85 (br, 1H), 7.46 (d, J=9.0 Hz, 2H), 6.93 (d, J=9.0 Hz, 2H), 6.08 (s, 1H), 5.18 (t, J=7.8 Hz, 1H), 3.86 (s, 3H), 3.14 (t, J=8.1 Hz, 2H), 2.20～2.12 (m, 2H), 1.69 (s, 3H), 1.56 (s, 3H). HR-ESI-MS calcd for $C_{16}H_{21}O_3$ $[M+H]^+$ 261.1485, found 261.1488.

(*E*)-3-*p*-*tert*-Butylphenyl-7-methylocta-2,6-dienoic acid (**4i**): A colorless solid, 264 mg, yield 47%. m.p. 136～137 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47～7.40 (m, 4H), 6.13 (s, 1H), 5.18 (t, J=7.2 Hz, 1H), 3.15 (t, J=8.1 Hz, 2H), 2.22～2.13 (m, 2H), 1.69 (s, 3H), 1.57 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.83, 162.45, 152.24, 137.69, 132.04, 126.19, 125.16, 123.21, 115.58, 34.35, 30.90, 27.57, 25.32, 17.23; IR ν: 3420～2500 (br), 3035, 2963, 2930, 2908, 1685, 1615, 1601, 1488, 1450, 1416, 1294, 1269, 1213, 834. HR-ESI-MS calcd for $C_{19}H_{27}O_2$ $[M+H]^+$ 287.2006, found 287.2008.

(*E*)-3-*p*-Acetylphenyl-7-methylocta-2,6-dienoic acid (**4j**): A colorless liquid, 293 mg, yield 55%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 6.10 (s, 1H), 5.09 (t, J=6.9 Hz, 1H), 3.15 (t, J=7.5 Hz, 2H), 2.63 (s, 3H), 2.16～2.08 (m, 2H), 1.64 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.14, 170.32, 161.29, 145.51, 137.01, 132.44, 128.24, 126.71, 122.67, 117.78, 30.92, 27.11, 26.30, 25.27, 17.21; IR ν: 3400～2600 (br), 3025, 2962, 2924, 2854, 1716, 1684, 1621, 1603, 1359, 1265, 1214, 838 cm^{-1}. HR-ESI-MS calcd for $C_{17}H_{21}O_3$ $[M+H]^+$ 273.1485, found 273.1488.

(*E*)-3-*p*-Methoxycarbonylphenyl-7-methylocta-2,6-dienoic acid (**4k**): A colorless liquid, 300 mg, yield 54%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H), 6.09 (s, 1H), 5.11 (t, J=6.9 Hz, 1H), 3.94 (s, 3H), 3.15 (t, J=7.5 Hz, 2H), 2.16～2.07 (m, 2H), 1.64 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.91, 166.26, 161.44, 145.40, 132.40, 130.24, 129.48, 126.48, 122.70, 117.84, 51.88, 30.95, 27.11, 25.26, 17.19; IR v: 3430～2600 (br), 3032, 2952, 2925, 2855, 1723, 1688, 1617, 1609, 1456, 1436, 1418, 1277, 1214, 1111, 855, 775, 707 cm^{-1}. HR-ESI-MS calcd for $C_{16}H_{21}O_4$ $[M+H]^+$ 289.1434, found 289.1432.

(*E*)-3-*p*-Cyanophenyl-7-methylocta-2,6-dienoic acid (**4l**): A colorless liquid, 320 mg, yield 64%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.58 (br, 1H), 7.60 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H), 6.10 (s, 1H), 5.18 (t, J=7.8 Hz, 1H), 3.16 (t, J=8.1 Hz, 2H), 2.21～2.14 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H). HR-ESI-MS calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332, found 256.1335.

(*E*)-3-*o*-Methylphenyl-7-methylocta-2,6-dienoic acid (**4m**): A colorless liquid, 266 mg, yield 56%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25～7.17 (m, 3H), 7.08 (d, J=7.0 Hz, 1H), 5.78 (s, 1H), 5.11 (t, J=7.0 Hz, 1H), 3.01 (m, J=7.8 Hz, 2H), 2.31 (s, 3H), 2.14～2.07 (m, 2H), 1.67 (s, 3H), 1.54 (s, 3H). HR-ESI-MS calcd for $C_{16}H_{21}O_2$ $[M+H]^+$ 245.1536, found 245.1539.

(*E*)-3-*o*-Methoxylphenyl-7-methylocta-2,6-dienoic acid (**4n**): A colorless liquid, 185 mg, yield 37%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36～7.30 (m, 1H), 7.13～7.10 (m, 1H), 6.99～6.90 (m, 2H), 5.88 (s, 1H), 5.10 (t, J=7.2 Hz, 1H), 3.84 (s, 3H), 3.10 (t, J=7.8 Hz, 2H), 2.10～2.02 (m, 2H), 1.66 (s, 3H), 1.52 (s, 3H). HR-ESI-MS calcd for $C_{16}H_{21}O_3$ $[M+H]^+$ 261.1485, found 261.1489.

(*E*)-3-*o*,*p*-Dimethylphenyl-7-methylocta-2,6-dienoic acid (**4o**): A colorless liquid, 320 mg, yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28～7.07 (m, 3H), 5.78 (s, 1H), 5.11 (t, J=7.2 Hz, 1H), 3.01 (t, J=7.8 Hz, 2H), 2.31 (s, 6H), 2.14～2.07 (m, 2H), 1.67 (s, 3H), 1.53 (s, 3H). HR-ESI-MS calcd for $C_{17}H_{23}O_2$ $[M+H]^+$ 259.1693, found 259.1698.

(*E*)-3-*m*,*m*-Dimethylphenyl-7-methylocta-2,6-dienoic acid (**4p**): A colorless liquid, 343 mg, yield 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09～7.04 (m, 3H), 6.07 (s, 1H), 5.18 (t, J=7.2 Hz, 1H), 3.13 (t, J=8.1 Hz, 2H), 2.37 (s, 6H), 2.18～2.10 (m, 2H), 1.69 (s, 3H), 1.57 (s, 3H). HR-ESI-MS calcd for $C_{17}H_{23}O_2$ $[M+H]^+$ 259.1693, found 259.1696.

(*E*)-3-*α*-Naphthyl-7-methylocta-2,6-dienoic acid (**4q**): A colorless liquid, 250 mg, yield 46%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92～7.83 (m, 3H), 7.53～7.45 (m, 3H), 7.30 (d, J=7.2 Hz, 1H), 6.02 (s, 1H), 5.09 (t, J=7.2 Hz, 1H), 3.21 (t, J=7.8 Hz, 2H), 2.17～2.09 (m, 2H), 1.63 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.21, 163.67, 140.05, 133.37, 132.18, 130.18, 128.08, 128.01, 125.93, 125.64, 125.10, 124.67, 124.32, 123.06, 119.72, 34.19, 26.73, 25.28, 17.18; IR v: 3410～2500 (br), 3044, 2965, 2923, 2854, 1684, 1627, 1590, 1501, 1437, 1409, 1290, 1252, 1221, 800, 776 cm^{-1}. HR-ESI-MS calcd for $C_{19}H_{21}O_2$ $[M+H]^+$ 281.1536, found 281.1532.

(*E*)-3-*β*-Naphthyl-7-methylocta-2,6-dienoic acid (**4r**): A colorless liquid, 320 mg, yield 57%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.95～7.80 (m, 3H), 7.65～7.50 (m, 3H), 6.25 (s, 1H), 5.20 (t, J=7.2 Hz, 1H), 3.25 (t, J=7.8 Hz, 2H), 2.24～2.15 (m, 2H), 1.68 (s, 3H), 1.54 (s, 3H). HR-ESI-MS calcd for $C_{19}H_{21}O_2$ $[M+H]^+$ 281.1536, found 281.1539.

(*E*)-3-(1,1-Biphenyl-4-yl)-7-methylocta-2,6-dienoic acid (**4s**): A colorless solid, 290 mg, yield 49%. m.p. 125～126 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65～7.36 (m, 9H), 6.17 (s, 1H), 5.19 (t, J=7.2 Hz, 1H), 3.20 (t, J=7.8 Hz, 2H), 2.24～2.18 (m, 2H), 1.69 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.34, 162.13, 141.73, 139.93, 139.57, 132.21, 128.54, 127.35, 126.94, 126.89, 126.71, 123.06, 116.10, 30.90, 27.47, 25.33, 17.26; IR v: 3400～2500 (br), 3028, 2969, 2920, 1686, 1614, 1602, 1487, 1448, 1413, 1296, 1270, 1215, 1204, 838, 768, 693 cm^{-1}. HR-ESI-MS calcd for $C_{21}H_{23}O_2$ $[M+H]^+$ 307.1693, found 307.1695.

(*E*)-3-(1-Methyl-1*H*-indol-4-yl)-7-methylocta-2,6-dienoic acid (**4t**): A colorless liquid, 275 mg, yield 50%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (d, J=8.1 Hz, 1H), 7.24 (d, J=8.1 Hz, 1H), 7.13～7.11 (m, 2H), 6.61 (d, J=3.0 Hz, 1H), 6.22 (s, 1H), 5.15 (t, J=7.5 Hz, 1H), 3.84 (s, 3H), 3.28 (t, J=7.8 Hz, 2H), 2.18～2.10 (m, 2H), 1.65 (s, 3H), 1.49 (s, 3H). HR-ESI-MS calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.1645, found 284.1641.

4.4 X-ray diffraction analysis of (*E*)-3-*p*-*tert*-butylphenyl-7-methylocta-2,6-dienoic acid (4i)

The crystals of (*E*)-3-*p*-*tert*-butylphenyl-7-methylocta-2,6-dienoic acid (**4i**) were obtained from CH_2Cl_2 in a very slow evaporation as colorless plate crystal. The 0.25 mm×0.23 mm×0.15 mm crystal was selected for analysis. All of parameters and structure information for compound **4i** have been deposited at the Cambridge Crystallographic Data Centre. CCDC ID 1860432 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information NMR spectra of target compounds and crystal structure data of compound **4I**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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