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Regioselective Hydrolysis and Transesterification of Dimethyl 3-Benzamidophthalates Assisted by a Neighboring Amide Group

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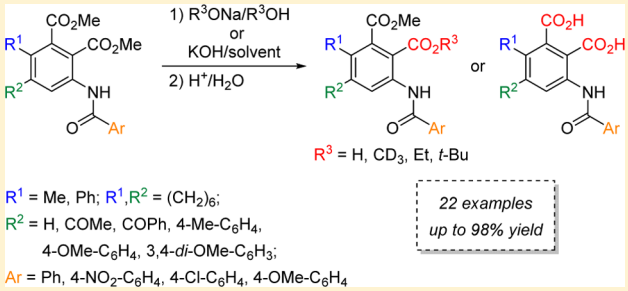
Supporting Information

ABSTRACT: An efficient, highly regioselective hydrolysis and transesterification of dimethyl 3-benzamidophthalates into the corresponding carboxylic acid monoesters and mixed esters (including *tert*-butyl esters) under basic conditions is presented. The selectivity is governed by the neighboring 3-benzamido moiety's participation and by the nature of the solvent. In alcohols the reaction occurred exclusively at the *ortho*-position to the benzamido functionality, in pyridine or acetonitrile at both ester groups. An insight into the mechanistic pathway was obtained from a ^{1}H NMR study in perdeuteromethanol.

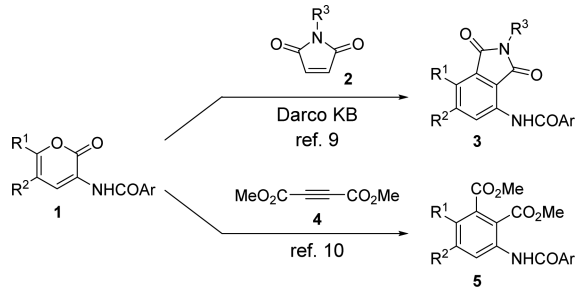


Ester hydrolysis represents a fundamental reaction in the toolbox of the synthetic organic chemist. It is normally promoted by either acid or base catalysis. With hydroxide ions (OH^-), the reaction is shifted toward the carboxylates.[1] The methodologies that enable the high regio- and stereoselective partial hydrolysis of di- or polyester substrates into the corresponding monoesters—versatile and highly attractive building blocks in organic chemistry[2]—are of the greatest importance. The use of enzymes[3] in the presence of various additives, like ionic liquids[3b] and cosolvents,[3c] has been shown to provide a substantial increase in the reaction rate, and especially a higher selectivity in asymmetric hydrolysis. Base-catalyzed hydrolysis is usually less controllable and selective, and generally proceeds rapidly into completely hydrolyzed products.[4] A few examples of the monohydrolysis of diesters are precedential. These are related to specific imidazole-functionalized starting substrates[5] or the use of an appropriate cosolvent in the basic aqueous reaction medium.[6] Therefore, the monohydrolysis of diesters remains a very challenging task.

Here, we present a simple and highly efficient regioselective hydrolysis and transesterification of substituted dimethyl 3-benzamidophthalates into the corresponding monoesters and mixed esters that might serve as versatile building blocks in organic chemistry. Of note is the potential applicability of the aminophthalic acid derivatives as fungicides for the treatment of various plant diseases.[7] The standard preparation of this type of monoesters still relies on a selective ring-opening alcoholysis of cyclic anhydrides or a selective esterification of substituted aminophthalic acids in the presence of strong acids.[2a,7,8]

The Diels–Alder reaction between 2*H*-pyran-2-ones **1** and *N*-substituted maleimides **2** in the presence of activated carbon Darco KB provides phthalimides **3** (Scheme 1).[9] As an alternative, we envisaged that the application of dimethyl acetylenedicarboxylate **4** as a dienophile resulting in the formation of phthalate derivatives **5**[10] should open new pathways toward densely functionalized phthalic acid derivatives.

Scheme 1. Synthesis of Phthalic Acid Derivatives



To identify the reaction conditions suitable for a selective hydrolysis of the ester groups in dimethyl 3-benzamidophthalates, we performed a screening with compound **5a** as a model substrate (Table 1). We initially selected methanol as the reaction solvent and tested the hydrolytic activity of various simple alkali-metal hydroxides; a modification of the method that was previously used for the complete hydrolysis of a large variety of mono- and diesters was applied.[4]

Stirring the suspension of dimethyl phthalate **5a** (0.5 mmol) in 1 M KOH methanolic solution for 6 h at ambient temperature did not afford any observable product of hydrolysis (Table 1, Run 1). This could be due to the sparing solubility of the starting substrate in methanol at room temperature. Heating the same reaction mixture under reflux for only 15 min, however, resulted in a complete conversion of **5a** into the monoacid derivative **6a** as the sole product (Run 2). The results of the hydrolysis mediated by other alkali-metal hydroxides are also shown in Table 1. KOH and LiOH

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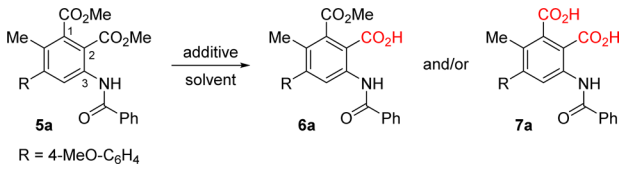
Table 1. Solvent (5 mL) and Additive (10−30 equiv) Screening in the Hydrolysis of the Phthalate 5a (0.5 mmol)



run	solvent[a]	additive	t (min)	5a:6a:7a (%)[b]
1	MeOH	KOH	360[c]	100:0:0
2	MeOH	KOH	15 or 180	0:100:0
3	MeOH	LiOH	15 or 180	0:100:0
4	MeOH	NaOH	180	6:94:0
5	MeOH	CsOH[d]	180	0:95:5
6	MeOH	$NaHCO_3$	180	100:0:0
7	MeOH	H_2O	15	100:0:0
8	MeOH	KOH[e]	180	0:38:62
9	*n*-heptane	KOH	15	69:23:8
10	PhMe	KOH	15	5:76:19
11	2-MeTHF	KOH	15	4:73:23
12	Pyridine	KOH	15	0:0:100
13	MeCN	KOH	15	0:48:52
14	MeCN	KOH	60	0:0:100
15	H_2O	KOH	15	4:92:4
16	H_2O	KOH	180	0:0:37[f]
17	H_2O/MeOH[g]	KOH	15	84:12:4
18	H_2O	HCl[h]	15	100:0:0
19	EtOH	KOH	15	0:62[i]:10

[a]Reflux (Heating-block temperature was set to 20 °C above the boiling point of the solvent) of a mixture of **5a** (216 mg, 0.5 mmol) and additive (5 mmol, 10 equiv) in 5 mL of solvent (yielding 1 M solution of additive; for exceptions see below). [b]Determined by ^{1}H NMR spectroscopic analyses of the isolated crude products. [c]At room temperature. [d]CsOH·H_2O was used. [e]5 mL of 3 M KOH methanolic solution. [f]Accompanied by debenzoylated dihydrolyzed product (63%). [g]H_2O/MeOH in the ratio 1:1 (5 mL). [h]1 M aqueous HCl solution (5 mL). [i]Accompanied by the product of transesterification at the position 1, ethyl monoester in 28% yield.

enabled a complete conversion of **5a** within 15 min of heating (Runs 2 and 3); the less MeOH-soluble NaOH was not completely effective even after 180 min of reflux (Run 4), whereas with CsOH, besides the monohydrolyzed product **6a** the diacid **7a** was formed in a small quantity (Run 5). As expected, higher concentrations of KOH (Run 8) resulted in a loss of selectivity, yielding both mono- and dihydrolyzed products **6a** and **7a**.

Next, we examined the effect of different solvents on the hydrolysis of **5a**. A series of experiments was performed in mixtures containing KOH (280 mg, 5 mmol) and 5 mL of solvents (1 M KOH solutions, providing that the entire amount of additive is dissolved) that have comparable boiling points (Runs 9−19). In *n*-heptane, the least-polar solvent tested, the hydrolysis of **5a** was slow and rather unselective, compared to the reaction in methanol (see Runs 2 and 9). Higher conversions of **5a** with a similarly poor selectivity were observed in toluene and 2-methyltetrahydrofuran as the reaction media (Runs 10 and 11). The use of polar aprotic pyridine as a solvent, not surprisingly, gave exclusively the dihydrolyzed product **7a**, since pyridine is an effective nucleophilic hydrolysis catalyst (Run 12). Acetonitrile worked in a similar way, but was considerably slower (Runs 13 and 14).

By comparing the results from Table 1, Runs 1−14, it appears that the protic nature of the reaction solvent is essential for maintaining the selectivity in the monohydrolysis of **5a**. To test this hypothesis, the reaction was conducted in 1 M KOH aqueous solution. For a short reaction time, the results were comparable to those from methanol (compare Runs 2 and 15), with **6a** being the main product and the dihydrolyzed compound **7a** as a byproduct (4%). After prolonged heating of the reaction mixture for 3 h, a complete hydrolysis of both ester groups, accompanied by the hydrolysis of the benzamido moiety, took place (Run 16). The use of a mixture H_2O/MeOH or performing the reaction under acidic conditions gave only a disappointing 0−16% conversion of **5a** (Runs 17, 18). Surprisingly, the reaction of the dimethyl ester **5a** in a boiling 1 M KOH ethanolic solution resulted in mono- and dihydrolysis into **6a** and **7a**, accompanied by the formation of ethyl monoester—the product of the simultaneous hydrolysis of the C-2 ester function and transesterification at the C-1 ester group, as determined by ^{1}H NMR spectroscopy (Run 19).

The best reaction conditions from Table 1 (Runs 2, 12 and 14) were used for the substrate scope screening with different dimethyl 3-benzamidophthalates **5a−l**. The heating of **5a−l** with KOH in MeOH[11] for 15−30 min afforded the desired monoesters **6a−l** in good-to-excellent yields (Table 2, Runs 1−12). Complete hydrolysis into products **7a,c,h** was achieved by treating **5a,c,h** with KOH in MeCN or pyridine (Runs 13−15). The transformations proved to be clean, as determined by ^{1}H NMR analyses of the crude reaction mixtures.

We extended our study to the transesterification.[1b,12] The heating of **5a,b,c,f,h** in EtOH or *t*-BuOH in the presence of catalytic amounts of the corresponding sodium alkoxide led to the exclusive formation of the monotransesterified products **8a,c,f,h** or **9a,b** in high (89−97%) yields (Table 2, Runs 16−21). The addition of 4 Å molecular sieves in Runs 20 and 21 to capture the liberated methanol from **5a,b** proved beneficial to achieving a complete conversion to **9a,b**.

The regiochemistry of the partial hydrolysis of **5a** could not be unequivocally elucidated by NMR spectroscopy. Instead, the structure of the monoester **6a** was determined by the single-crystal X-ray analysis of its potassium salt (Figure S1), indicating that the C-2 ester moiety underwent hydrolysis. The place of the transesterification, i.e., the structures of the mixed esters **8a** and **9a**, were determined from their hydrolysis in a methanolic solution of KOH, which gave monomethyl ester **6a**.

The regioselectivity of the C-2 over the C-1 ester group hydrolysis in **5** could be explained by the anchimeric assistance of the neighboring 3-benzamido group. An effective intramolecular hydrogen bonding between the N−H proton and the C-2 carbonyl group to form a 6-membered ring renders the latter more electrophilic and consequently more reactive toward the nucleophiles (Figure 1). This has been supported by an independent experiment with the *N*-methyl derivative **10a**, prepared by the methylation of **5a** with dimethyl sulfate under basic conditions[13] and shown in Scheme 2. Under the same hydrolytic reaction conditions as for **5a**, the *N*-methyl derivative **10a** afforded a complex mixture of products. Additionally, due to steric effects the remaining C-1 methoxycarbonyl group is forced to be perpendicular to the aromatic skeleton[6a,14] (see also Figure S1), consequently it is not being exposed enough to the nucleophilic attack. The possibility of a purely electronic effect on the regioselectivity of the hydrolysis was not considered because of a previous

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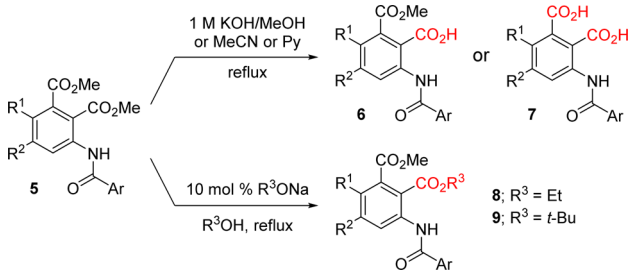
Table 2. Substrate Scope in the Preparation of Compounds 6–9



run	5	R^1	R^2	Ar	6–9	t (min)[a]	yield (%)[b]
1	**5a**	Me	4-OMe-C_6H_4	Ph	**6a**	15	85
2	**5b**	Me	H	Ph	**6b**	15	84
3	**5c**	Ph	H	Ph	**6c**	15	84
4	**5d**	Me	COMe	Ph	**6d**	15	88
5	**5e**	Me	COPh	Ph	**6e**	15	84
6	**5f**	Me	4-Me-C_6H_4	Ph	**6f**	30	81
7	**5g**	Me	3,4-*di*-OMe-C_6H_3	Ph	**6g**	30	83
8	**5h**		$-(CH_2)_6-$	Ph	**6h**	30	79
9	**5i**	Me	H	4-NO_2-C_6H_4	**6i**	15	86
10	**5j**	Me	COMe	4-NO_2-C_6H_4	**6j**	15	82
11	**5k**	Me	COMe	4-Cl-C_6H_4	**6k**	15	85
12	**5l**	Me	COMe	4-OMe-C_6H_4	**6l**	15	84
13	**5a**	Me	4-OMe-C_6H_4	Ph	**7a**	60[c]	92
14	**5c**	Ph	H	Ph	**7c**	30[d]	89
15	**5h**		$-(CH_2)_6-$	Ph	**7h**	30[d]	91
16	**5a**	Me	4-OMe-C_6H_4	Ph	**8a**	30[e]	93
17	**5c**	Ph	H	Ph	**8c**	30[e]	95
18	**5f**	Me	4-Me-C_6H_4	Ph	**8f**	30[e]	91
19	**5h**		$-(CH_2)_6-$	Ph	**8h**	30[e]	97
20	**5a**	Me	4-OMe-C_6H_4	Ph	**9a**	360[f]	89
21	**5b**	Me	H	Ph	**9b**	180[f]	93

[a]Reaction conditions: Starting phthalate **5** (0.5 mmol), 1 M KOH methanolic solution (5 mL),[11] reflux (Heating-block temperature was set to 20 °C above the boiling point of the solvent). [b]Yield of the isolated pure product. [c]KOH (280 mg, 5 mmol; 10 equiv) in MeCN (5 mL). [d]KOH (280 mg, 5 mmol; 10 equiv) in pyridine (5 mL). [e]10 mol % of EtONa (3.4 mg, 0.05 mmol) in EtOH (5 mL). [f]10 mol % of *t*-BuONa (4.8 mg, 0.05 mmol) in *t*-BuOH (5 mL), 4 Å MS.

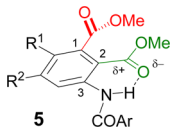
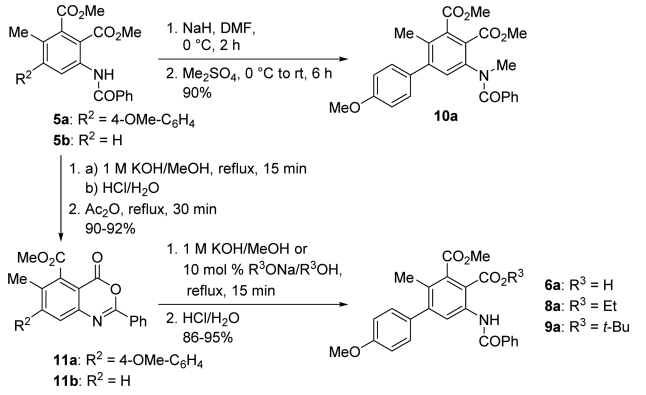


Figure 1. Molecular structure of **5**.

observation,[15] where the structurally related 3-methoxyphthalic acid diethyl ester was monohydrolyzed at the remote ester function on heating with 1 equiv of $KHCO_3$ in ethanol.

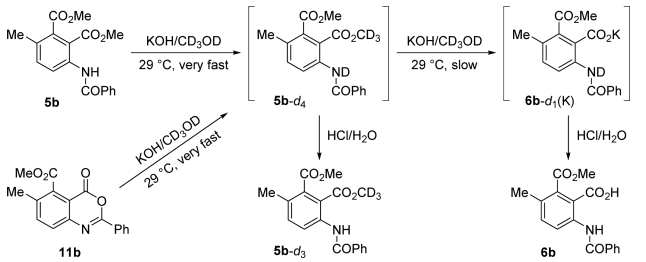
Another rationale for the above-mentioned selectivity of the hydrolysis and transesterification of **5** could be through the reaction proceeding via the intermediary-formed 3,1-benzoxazin-4-one derivative **11**. We were able to detect **11a** and **11b** in situ by NMR spectroscopy in the transesterification reaction of **5a** and **5b** with 10 mol % of *t*-BuONa in *t*-BuOH into the mixed esters **9a** and **9b** (Table 2, Runs 20 and 21). The

Scheme 2. Synthesis of 3-Benzamidophthalates 6a, 8a, 9a and 10a, and 3,1-Benzoxazin-4-ones 11a,b



intermediates **11a,b** remained present in the reaction mixture at a low (ca. 5%) level throughout the course of the reaction. The general lack of detecting 3,1-benzoxazin-4-one intermediates in other experiments from Tables 1 and 2 is reasonable owing to their highly reactive nature.[16] 3,1-Benzoxazin-4-ones **11a,b** were also prepared independently and **11a** was exposed to the above-described reaction conditions, affording the expected products, i.e., monoester **6a** and mixed esters **8a** and **9a**, respectively (Scheme 2). To get an insight into the reaction pathway we monitored the hydrolysis of the sufficiently soluble **5b** and **11b** by ^{1}H NMR spectroscopy in CD_3OD at ambient temperature (Scheme 3; Supporting Information, Figures S2–

Scheme 3. Reaction Sequence from 5b toward 6b as Determined by an NMR Study



S4). The starting compound **5b** transforms in an NMR tube with KOH in CD_3OD at room temperature within l min into the deuterated derivative **5b**-d_4 and no **11b** could be detected (Figure S2). Derivative **5b**-d_4 then slowly transforms (within 2–3 h) solely into **6b**-d_1(K). A similar experiment with **11b**, as well as with an equimolar mixture of compounds **5b** and **11b**, gave exactly the same reaction profile as in the case of **5b**. This led us to the conclusion that the compound **11b** is not an intermediate in the **5b** → **6b** transformation; if **11b** had appeared as an intermediate, it should have been transformed with CD_3OD immediately into the diester **5b**-d_4.

The 3,1-benzoxazin-4-one intermediate **11** could be rationalized by a base-mediated amide-iminol tautomerism and further cyclization with the neighboring ester moiety. In this particular case, *t*-BuONa in *t*-BuOH was employed, which is the strongest base but the weakest nucleophile among the reagents applied. Hence, it is likely that **5a,b** reacted with the *t*-BuONa nucleophile toward **9a,b** in a comparable reaction rate as toward **11a,b**.

The chemoselectivity of the monohydrolysis of **5** in protic solvents could be explained by an effective H-bond-driven

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solvation of the C-2 carboxylate group in **6**, accompanied by the steric hindrance with vicinal substituents, rendering the attack of the solvated nucleophile at the C-1 ester moiety less favorable. This is in line with the observation that in aprotic solvents, where no effective solvation occurs, the hydrolysis of **5** is accompanied by substantial amounts of phthalic acid **7**. To avoid an eventual transesterification at position 1, similar to that of the substrate **5a** with KOH/EtOH into ethyl monoester (in 28% yield; Table 1, Run 19), it is essential for the monohydrolysis to use the same alcohol for the solvent as is the alkyl moiety of the C-1 ester function in **5**. Namely, the nucleophilicities for substitution at a carbonyl carbon follow the order ethoxide ion > methoxide ion > hydroxide ion > *tert*-butoxide ion.[17]

In summary, we have developed a synthetic protocol for the highly regioselective cleavage of the ester function of 3-benzamidophthalic acid diesters into the corresponding monoesters as well as transesterification into the mixed esters, including relatively hindered *tert*-butyl esters. The hydrolysis was performed with an excess of KOH and the transesterification with catalytic amounts of various alkoxides. The regioselectivity is controlled by the participation of the neighboring 3-benzamido moiety. The hydrolysis takes place by the direct attack of the nucleophile onto the ester moiety at position 2, as determined by the NMR study. The transesterification could occur via the same reaction course or, alternatively, via the intermediary-formed 3,1-benzoxazin-4-one derivative **11**. The latter takes place in those cases where the nucleophile possesses weak nucleophilic and strong basic features (*t*-BuONa in *t*-BuOH). In polar aprotic solvents (MeCN, pyridine) a complete hydrolysis of both ester moieties could be achieved, whereas for the regioselective partial transformations the use of protic solvents is crucial.

EXPERIMENTAL SECTION

General Experimental Methods. Melting points were determined on a microhot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded with 500 or 300 MHz spectrometers at 29 °C (unless stated otherwise) and are reported in ppm using TMS as an internal standard. ^{13}C NMR spectra were recorded at 125 MHz and are referenced against the central line of the solvent signal (DMSO-d_6 septet at δ = 39.5 ppm, CD_3OD septet at 49.1 ppm). The coupling constants (J) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet) or br (broadened). ^{1}H NMR peak assignments are based on the analyses of ^{1}H−^{1}H *gs*-COSY, ^{1}H−^{13}C *gs*-HSQC and ^{1}H−^{13}C *gs*-HMBC 2D NMR spectra. ^{1}H NMR studies of the reaction pathway from **5b** and **11b** into **6b** were performed in perdeuterated methanol with 99.80 atom % D isotopic purity at 29 °C with a 300 MHz NMR instrument. IR spectra were recorded on a FT-IR spectrometer using ATR. High-resolution mass spectra (HRMS) were obtained with a time-of-flight (TOF) mass spectrometer equipped with an electrospray source at atmospheric pressure ionization (ESI). Elemental analyses (C, H, N) were performed with a CHNS/O Analyzer. TLC was carried out on silica-gel TLC-cards with a fluorescent indicator, visualization was accomplished with UV light (254 nm). Solvents (EtOH, *t*-BuOH) were dried according to published methods. Reactions not involving aqueous reagents were carried out under an argon atmosphere and in oven-dried glassware. One M KOH/MeOH was used as a commercially available solution or laboratory made from KOH (85%) and MeOH (99.9%). EtONa (95%), *t*-BuONa (99.9%) and all the other reagents were purchased from commercial sources.

Synthesis of Starting Phthalates 5. The starting compounds **5a−l** were prepared via a Diels−Alder reaction between appropriate 2*H*-pyran-2-ones **1a−l** and dimethyl acetylenedicarboxylate (**4**) under thermal conditions.[10] The new phthalates **5c,f,h−l** were also synthesized using a modified method as follows. A mixture of compounds **1** (4 mmol), **4** (1136 mg, 8 mmol) and *n*-butanol (400 mg, 5.4 mmol) was placed in a glass ACE pressure tube (15 mL), closed with a Teflon-screwed stopper, and heated in an oil bath at 180 °C for 3 h. The reaction mixture was cooled and the oily residue was treated with methanol (2 mL). The precipitated material was filtered off, washed with methanol (4 mL) and dried.

Analytical data of dimethyl 5-benzamido-4′-methoxy-2-methyl-[1,1′-biphenyl]-3,4-dicarboxylate (**5a**),[10b] dimethyl 3-benzamido-6-methylphthalate (**5b**),[10b] dimethyl 4-acetyl-6-benzamido-3-methylphthalate (**5d**),[10c] dimethyl 6-benzamido-4-benzoyl-3-methylphthalate (**5e**),[10c] and dimethyl 5-benzamido-3′,4′-dimethoxy-2-methyl-[1,1′-biphenyl]-3,4-dicarboxylate (**5g**)[10b] are identical to those reported in the literature.

*Dimethyl 4-benzamido-[1,1′-biphenyl]-2,3-dicarboxylate (**5c**).* White solid (1198 mg, 77%); mp 153−155 °C (MeOH); IR (ATR) 3324, 2947, 1715, 1695, 1679, 1583, 1525, 1490, 1439, 1425, 1319, 1295, 1231 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.57 (s, 3H), 3.73 (s, 3H), 7.32 (m, 2H), 7.41 (m, 1H), 7.46 (m, 2H), 7.57 (m, 2H), 7.64 (m, 2H), 7.95 (m, 3H), 10.57 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 52.3, 52.6, 123.7, 126.0, 127.6, 127.8, 128.0, 128.5, 128.6, 132.1, 133.2, 134.0, 136.0, 136.1, 138.9, 165.6, 166.1, 168.0 (1 aromatic signal hidden); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{20}NO_5$ 390.1336, found 390.1337. Anal. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 71.08; H, 4.84; N, 3.64.

*Dimethyl 5-benzamido-2,4′-dimethyl-[1,1′-biphenyl]-3,4-dicarboxylate (**5f**).* White solid (1184 mg, 71%); mp 170−171 °C (MeOH); IR (ATR) 3328, 2953, 1724, 1693, 1678, 1577, 1505, 1487, 1443, 1399, 1328, 1318, 1263, 1242, 1217 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.10 (s, 3H), 2.36 (s, 3H), 3.42 (s, 3H), 3.71 (s, 3H), 7.06 and 7.24 (AA′XX′, J = 8.0 Hz, 2H each), 7.58 (m, 2H), 7.64 (m, 1H), 7.92 (s, 1H), 7.97 (m, 2H), 10.69 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.7, 20.8, 51.9, 52.5, 119.5, 126.1, 127.5, 128.68, 128.72, 128.9, 132.0, 134.1, 134.4, 135.0, 135.6, 136.3, 136.8, 141.0, 165.4, 166.3, 167.8; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{25}H_{24}NO_5$ 418.1649, found 418.1653. Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 72.14; H, 5.66; N, 3.42.

*Dimethyl 3-benzamido-5,6,7,8,9,10-hexahydrobenzo[8]-annulene-1,2-dicarboxylate (**5h**).* White solid (853 mg, 54%); mp 128−129 °C (MeOH); IR (ATR) 3303, 3263, 2925, 2847, 1710, 1692, 1671, 1581, 1519, 1492, 1442, 1408, 1311, 1275, 1261, 1224 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 (m, 4H), 1.65 (m, 4H), 2.72 (m, 2H), 2.82 (m, 2H), 3.71 (s, 3H), 3.80 (s, 3H), 7.55 (m, 2H), 7.62 (m, 1H), 7.76 (s, 1H), 7.93 (m, 2H), 10.56 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.2, 25.7, 27.5, 30.7, 31.7, 32.2, 52.3, 52.5, 120.2, 125.6, 127.4, 128.6, 131.9, 133.8, 134.2, 134.4, 135.4, 146.8, 165.2, 166.4, 168.6; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{26}NO_5$ 396.1805, found 396.1806. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.80; H, 6.43; N, 3.59.

*Dimethyl 3-methyl-6-(4-nitrobenzamido)phthalate (**5i**).* Yellow solid (1101 mg, 74%); mp 173−175 °C (MeOH); IR (ATR) 3255, 3113, 3087, 2947, 1731, 1677, 1603, 1526, 1440, 1346, 1309, 1291, 1260, 1245, 1221 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.31 (s, 3H), 3.72 (s, 3H), 3.83 (s, 3H), 7.52 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 8.15 and 8.39 (AA′XX′, J = 8.8 Hz, 2H each), 10.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.7, 52.5, 52.6, 123.8, 124.5, 126.5, 129.0, 132.4, 133.6, 134.0, 139.7, 149.4, 164.0, 166.1, 168.0 (1 aromatic signal hidden); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{17}N_2O_7$ 373.1030, found 373.1027. Anal. Calcd for $C_{18}H_{16}N_2O_7$: C, 58.07; H, 4.33; N, 7.52. Found: C, 58.17; H, 4.29; N, 7.39.

*Dimethyl 4-acetyl-3-methyl-6-(4-nitrobenzamido)phthalate (**5j**).* Off-white solid (1175 mg, 71%); mp 209−211 °C (MeOH); IR (ATR) 3295, 3264, 3109, 3082, 2947, 1740, 1696, 1687, 1577, 1519, 1434, 1346, 1324, 1303, 1267, 1229, 1215, 1204 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.60 (s, 3H), 3.72 (s, 3H), 3.85 (s, 3H), 7.98 (s, 1H), 8.17 and 8.41 (AA′XX′, J = 8.5 Hz, 2H each), 10.87 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.5, 30.3, 52.72, 52.74, 123.8, 126.0, 126.4, 129.1, 130.0, 133.9, 135.7, 139.4, 142.4, 149.5, 164.1, 165.4, 167.7, 201.7; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{20}H_{19}N_2O_8$ 415.1136, found 415.1139. Anal. Calcd for

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$C_{20}H_{18}N_2O_8$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.57; H, 4.28; N, 6.69.

*Dimethyl 4-acetyl-6-(4-chlorobenzamido)-3-methylphthalate (**5k**).* Pale yellow solid (1160 mg, 72%); mp 165−167 °C (MeOH); IR (ATR) 3339, 2952, 1736, 1680, 1578, 1518, 1486, 1433, 1395, 1299, 1269, 1247, 1216, 1200 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.59 (s, 3H), 3.70 (s, 3H), 3.83 (s, 3H), 7.64 and 7.96 (AA′XX′, J = 8.8 Hz, 2H each), 8.00 (s, 1H), 10.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.5, 30.3, 52.66, 52.70, 125.6, 125.9, 128.7, 129.4, 129.5, 132.5, 134.3, 135.7, 136.9, 142.3, 164.6, 165.5, 167.8, 201.7; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{20}H_{19}ClNO_6$ 404.0895, found 404.0895. Anal. Calcd for $C_{20}H_{18}ClNO_6$: C, 59.49; H, 4.49; N, 3.47. Found: C, 59.40; H, 4.29; N, 3.49.

*Dimethyl 4-acetyl-6-(4-methoxybenzamido)-3-methylphthalate (**5l**).* Pale yellow solid (1213 mg, 76%); mp 139−141 °C (MeOH); IR (ATR) 3325, 2952, 2838, 1727, 1674, 1581, 1505, 1436, 1397, 1298, 1248, 1224 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.59 (s, 3H), 3.72 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 7.10 and 7.94 (AA′XX′, J = 9.0 Hz, 2H each), 8.09 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.4, 30.3, 52.6, 52.7, 55.5, 113.9, 124.9, 125.1, 125.8, 128.7, 129.5, 135.0, 135.8, 142.3, 162.3, 164.9, 165.7, 167.9, 201.8; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{21}H_{22}NO_7$ 400.1391, found 400.1387. Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.02; H, 5.44; N, 3.53.

General Synthetic Route (A) to Monoester Carboxylic Acid Derivatives 6. A suspension of the starting phthalate **5** (0.5 mmol) in 1 M KOH methanolic solution (5 mL) was refluxed for the time indicated in Table 2. The reaction was monitored by TLC analysis (petroleum ether/EtOAc, 3:1). After completion, the reaction mixture was cooled and acidified to pH 1−2 with 6 M aqueous solution of HCl (~3 mL), resulting in the precipitation of a pure monoester-monoacid product (see Table 2, Runs 1−12). The precipitate was collected by filtration, washed with a mixture of H_2O/MeOH (3:1, 3 mL) and dried.

*5-Benzamido-4′-methoxy-3-(methoxycarbonyl)-2-methyl-[1,1′-biphenyl]-4-carboxylic acid (**6a**).* White solid (178 mg, 85% yield); mp 230−232 °C (MeOH/H_2O); IR (ATR) 2955, 2845, 1716, 1687, 1637, 1602, 1573, 1510, 1441, 1391, 1335, 1288, 1231 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.12 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 7.06 and 7.33 (AA′XX′, J = 8.5 Hz, 2H each), 7.57 (m, 2H), 7.63 (m, 1H), 7.93 (m, 2H), 8.21 (s, 1H), 11.22 (s, 1H), 14.05 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.9, 52.4, 55.2, 113.9, 118.3, 124.3, 127.2, 127.4, 128.8, 130.1, 131.9, 132.1, 134.3, 136.3, 136.4, 145.8, 158.9, 164.9, 168.0, 168.8; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{24}H_{22}NO_6$ 420.1442, found 420.1437. Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.49; H, 4.97; N, 3.27.

*Potassium Salt of **6a** Was Obtained on Cooling the Reaction Mixture, Before Acidification.* Off-white crystals (114 mg, 50%); mp 234−235 °C (MeOH); IR (ATR) 2948, 2838, 1720, 1661, 1607, 1568, 1509, 1488, 1448, 1417, 1403, 1350, 1331, 1284, 1227 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.01 (s, 3H), 3.73 (s, 3H), 3.81 (s, 3H), 7.03 and 7.28 (AA′XX′, J = 8.8 Hz, 2H each), 7.57 (m, 3H), 8.02 (m, 2H), 8.64 (s, 1H), 15.46 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.4, 51.5, 55.2, 113.7, 120.3, 122.3, 124.4, 127.2, 128.7, 130.2, 131.5, 133.3, 135.4, 137.9, 138.2, 142.8, 158.5, 164.2, 168.2, 170.9; HRMS (ESI-TOF) m/z $[M - K + 2H]^+$ Calcd for $C_{24}H_{22}NO_6$ 420.1442, found 420.1439.

*6-Benzamido-2-(methoxycarbonyl)-3-methylbenzoic acid (**6b**).* White solid (131 mg, 84%); mp 210−212 °C (MeOH/H_2O); IR (ATR) 2995, 2953, 1725, 1710, 1650, 1604, 1576, 1537, 1495, 1449, 1292, 1186 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.26 (s, 3H), 3.80 (s, 3H), 7.51 (d, J = 8.5 Hz, 1H), 7.57 (m, 2H), 7.63 (m, 1H), 7.94 (m, 2H), 8.15 (d, J = 8.5 Hz, 1H), 11.01 (s, 1H), 13.93 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.5, 52.3, 120.7, 123.9, 127.3, 128.8, 130.5, 132.0, 133.9, 134.3, 134.8, 136.2, 164.9, 168.1, 168.5; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{16}NO_5$ 314.1023, found 314.1024. Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.11; H, 4.67; N, 4.47.

*4-Benzamido-2-(methoxycarbonyl)-[1,1′-biphenyl]-3-carboxylic acid (**6c**).* White solid (158 mg, 84%); mp 211−213 °C (MeOH/H_2O); IR (ATR) 2944, 1726, 1686, 1639, 1589, 1573, 1514, 1487, 1435, 1411, 1379, 1294, 1218 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.55 (s, 3H), 7.33 (m, 2H), 7.43 (m, 3H), 7.62 (m, 4H), 7.96 (m, 2H), 8.27 (d, J = 8.5 Hz, 1H), 11.01 (s, 1H), 14.00 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 52.1, 121.8, 124.2, 127.3, 127.7, 128.1, 128.5, 128.8, 132.1, 133.4, 134.0, 134.2, 135.3, 137.1, 139.0, 165.1, 167.9, 168.2; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{18}NO_5$ 376.1179, found 376.1178. Anal. Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.56; N, 3.73. Found: C, 70.42; H, 4.41; N, 3.76.

*4-Acetyl-6-benzamido-2-(methoxycarbonyl)-3-methylbenzoic acid (**6d**).* White solid (156 mg, 88%); mp 159−161 °C (MeOH/H_2O); IR (ATR) 2950, 1740, 1701, 1683, 1644, 1604, 1581, 1522, 1495, 1433, 1286, 1203 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.24 (s, 3H), 2.59 (s, 3H), 3.81 (s, 3H), 7.57 (m, 2H), 7.64 (m, 1H), 7.95 (m, 2H), 8.37 (s, 1H), 11.02 (s, 1H), 13.95 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.3, 30.3, 52.5, 123.6, 123.8, 127.4, 128.1, 128.7, 132.1, 134.0, 135.8, 136.6, 142.4, 165.2, 167.2, 168.2, 202.0; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{18}NO_6$ 356.1129, found 356.1129. Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 63.93; H, 4.80; N, 3.90.

*6-Benzamido-4-benzoyl-2-(methoxycarbonyl)-3-methylbenzoic acid (**6e**).* White solid (175 mg, 84%); mp 258−260 °C (MeOH/H_2O); IR (ATR) 3305, 2956, 1721, 1698, 1673, 1638, 1574, 1517, 1221 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.09 (s, 3H), 3.83 (s, 3H), 7.59 (m, 5H), 7.75 (m, 1H), 7.80 (m, 2H), 7.92 (m, 2H), 8.16 (s, 1H), 11.12 (s, 1H), 14.01 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.1, 52.6, 122.3, 127.3, 127.5, 128.8, 129.2, 129.8, 132.2, 134.0, 134.4, 135.8, 136.0, 136.5, 142.5, 165.1, 167.4, 168.0, 196.2 (1 aromatic signal hidden); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{24}H_{20}NO_6$ 418.1285, found 418.1283. Anal. Calcd for $C_{24}H_{19}NO_6$: C, 69.06; H, 4.59; N, 3.36. Found: C, 69.08; H, 4.40; N, 3.41.

*5-Benzamido-3-(methoxycarbonyl)-2,4′-dimethyl-[1,1′-biphenyl]-4-carboxylic acid (**6f**).* White solid (163 mg, 81%); mp 251−253 °C (MeOH/H_2O); IR (ATR) 3235, 2955, 2919, 1681, 1581, 1507, 1492, 1434, 1393, 1329, 1228 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.09 (s, 3H), 2.35 (s, 3H), 3.37 (s, 3H), 7.05 and 7.23 (AA′XX′, J = 7.8 Hz, 2H each), 7.62 (m, 3H), 7.96 (m, 2H), 8.27 (s, 1H), 11.27 (s, 1H), 13.94 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.8, 20.9, 51.7, 117.1, 124.3, 127.2, 128.7, 128.8, 129.0, 132.1, 134.3, 134.4, 134.9, 135.8, 136.7, 137.6, 141.4, 165.0, 168.0, 168.1; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{24}H_{22}NO_5$ 404.1492, found 404.1496. Anal. Calcd for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47. Found: C, 71.06; H, 5.13; N, 3.47.

*5-Benzamido-3′,4′-dimethoxy-3-(methoxycarbonyl)-2-methyl-[1,1′-biphenyl]-4-carboxylic acid (**6g**).* White solid (186 mg, 83%); mp 187−189 °C (MeOH/H_2O); IR (ATR) 3348, 2957, 1711, 1632, 1603, 1567, 1531, 1517, 1421, 1337, 1311, 1238, 1217 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.13 (s, 3H), 3.79 (s, 3H), 3.82 (s, 6H), 6.90 (m, 1H), 6.96 (s, 1H), 7.07 (m, 1H), 7.57 (m, 2H), 7.63 (m, 1H), 7.94 (m, 2H), 8.21 (m, 1H), 11.20 (s, 1H), 14.02 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 17.0, 52.4, 55.5, 55.6, 111.7, 112.5, 118.4, 121.1, 124.4, 127.2, 127.6, 128.8, 132.1, 132.2, 134.3, 136.3, 146.1, 148.4, 148.5, 165.0, 168.1, 168.9 (1 aromatic signal hidden); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{25}H_{24}NO_7$ 450.1547, found 450.1545. Anal. Calcd for $C_{25}H_{23}NO_7$: C, 66.81; H, 5.16; N, 3.12. Found: C, 66.68; H 4.97, N, 3.15.

*3-Benzamido-1-(methoxycarbonyl)-5,6,7,8,9,10-hexahydrobenzo[8]annulene-2-carboxylic acid (**6h**).* White solid (150 mg, 79%); mp 211−213 °C (MeOH/H_2O); IR (ATR) 2923, 2847, 1727, 1682, 1654, 1579, 1516, 1494, 1304, 1223 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 1.33 (m, 4H), 1.65 (m, 4H), 2.69 (m, 2H), 2.82 (m, 2H), 3.77 (s, 3H), 7.57 (m, 2H), 7.63 (m, 1H), 7.93 (m, 2H), 8.16 (s, 1H), 11.17 (s, 1H), 13.91 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.3, 25.7, 27.5, 30.7, 31.7, 32.4, 52.2, 117.7, 123.7, 127.2, 128.8, 132.0, 132.9, 134.5, 135.4, 136.9, 147.2, 164.8, 168.2, 169.0; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{24}NO_5$ 382.1649, found 382.1645. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 68.98; H, 5.84; N, 3.70.

*2-(Methoxycarbonyl)-3-methyl-6-(4-nitrobenzamido)benzoic acid (**6i**).* Pale yellow solid (154 mg, 86%); mp 232−234 °C (MeOH/

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H_2O); IR (ATR) 3109, 2954, 1737, 1679, 1600, 1524, 1343, 1289, 1210 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.28 (s, 3H), 3.80 (s, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 8.16 and 8.40 (AA′XX′, J = 8.3 Hz, 2H each), 11.10 (s, 1H), 13.81 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.6, 52.4, 122.7, 123.9, 125.0, 128.9, 131.4, 133.7, 134.6, 135.1, 139.9, 149.4, 163.6, 167.8, 168.4; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_7$ 359.0874, found 359.0871. Anal. Calcd for $C_{17}H_{14}N_2O_7$: C, 56.99; H, 3.94; N, 7.82. Found: C, 56.63; H, 3.92; N, 7.64.

*4-Acetyl-2-(methoxycarbonyl)-3-methyl-6-(4-nitrobenzamido)-benzoic acid (**6j**).* Off-white solid (164 mg, 82%); mp 208−210 °C (MeOH/H_2O); IR (ATR) 3185, 1731, 1687, 1604, 1581, 1524, 1492, 1345, 1330, 1250, 1220 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.26 (s, 3H), 2.59 (s, 3H), 3.81 (s, 3H), 8.18 and 8.41 (AA′XX′, J = 9.0 Hz, 2H each), 8.18 (s, 1H), 11.11 (s, 1H), 13.75 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.4, 30.3, 52.6, 123.9, 124.8, 125.6, 129.0, 129.2, 134.7, 136.5, 139.6, 142.3, 149.4, 163.8, 166.9, 168.1, 201.8; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_8$ 401.0979, found 401.0976. Anal. Calcd for $C_{19}H_{16}N_2O_8$: C, 57.00; H, 4.03; N, 7.00. Found: C, 56.73; H, 3.69; N, 6.95.

*4-Acetyl-6-(4-chlorobenzamido)-2-(methoxycarbonyl)-3-methylbenzoic acid (**6k**).* White solid (165 mg, 85%); mp 204−206 °C (MeOH/H_2O); IR (ATR) 3406, 2948, 2740, 2563, 1737, 1721, 1689, 1646, 1577, 1522, 1489, 1412, 1258, 1206 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.59 (s, 3H), 3.80 (s, 3H), 7.65 and 7.97 (AA′XX′, J = 8.5 Hz, 2H each), 8.25 (s, 1H), 10.96 (s, 1H), 13.77 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.3, 30.3, 52.5, 124.3, 124.7, 128.6, 128.8, 129.4, 132.8, 135.2, 136.5, 136.9, 142.3, 164.3, 167.1, 168.2, 201.9; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{17}ClNO_6$ 390.0739, found 390.0734. Anal. Calcd for $C_{19}H_{16}ClNO_6$: C, 58.55; H, 4.14; N, 3.59. Found: C, 58.47; H, 3.88; N, 3.57.

*4-Acetyl-6-(4-methoxybenzamido)-2-(methoxycarbonyl)-3-methylbenzoic acid (**6l**).* White solid (162 mg, 84%); mp 211−213 °C (MeOH/H_2O); IR (ATR) 2939, 1741, 1679, 1598, 1585, 1505, 1439, 1307, 1216, 1178 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.24 (s, 3H), 2.59 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 7.10 and 7.93 (AA′XX′, J = 9.0 Hz, 2H each), 8.40 (s, 1H), 10.89 (s, 1H), 13.99 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.3, 30.3, 52.5, 55.5, 114.0, 123.1, 123.4, 126.1, 127.8, 129.3, 136.1, 136.7, 142.5, 162.3, 164.6, 167.4, 168.2, 202.0; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{20}H_{20}NO_7$ 386.1234, found 386.1229. Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.03; H, 4.96; N, 3.66.

General Synthetic Route (B) to Phthalic Acid Derivatives 7. A suspension of the starting phthalate **5** (0.5 mmol) and KOH (280 mg, 5 mmol) in 5 mL of MeCN or pyridine was refluxed for 30−60 min (see Table 2, Runs 13−15). The reaction was followed by TLC (petroleum ether/EtOAc, 3:1), and after completion the solvent was removed under reduced pressure. The remaining residue was dissolved in MeOH (5 mL) and acidified to pH 1−2 with 6 M aqueous solution of HCl (~5 mL), resulting in the precipitation of pure diacid **7**. The precipitate was collected on a filter, washed with a small portion of a mixture of H_2O/MeOH (3:1, 3 mL) and dried.

*5-Benzamido-4′-methoxy-2-methyl-[1,1′-biphenyl]-3,4-dicarboxylic acid (**7a**).* White solid (187 mg, 92%); mp the compound spontaneously eliminates H_2O while heating (from MeOH/H_2O); IR (ATR) 3358, 2966, 2539, 1687, 1655, 1609, 1567, 1522, 1508, 1492, 1444, 1393, 1330, 1278, 1246 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.18 (s, 3H), 3.82 (s, 3H), 7.07 and 7.33 (AA′XX′, J = 8.8 Hz, 2H each), 7.60 (m, 3H), 7.94 (m, 2H), 8.14 (s, 1H), 11.16 (s, 1H), 13.25 (br s, 1H), 13.93 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 17.1, 55.2, 113.9, 118.2, 123.8, 126.9, 127.2, 128.8, 130.1, 132.1, 132.2, 134.4, 136.0, 138.0, 145.6, 158.9, 164.9, 168.4, 169.9; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{23}H_{20}NO_6$ 406.1285, found 406.1283.

*4-Benzamido-[1,1′-biphenyl]-2,3-dicarboxylic acid (**7c**).* Pale yellow solid (161 mg, 89%); mp the compound spontaneously eliminates H_2O while heating (from MeOH/H_2O); IR (ATR) 3095, 1705, 1692, 1644, 1592, 1530, 1492, 1420, 1377, 1305, 1207 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.42 (m, 5H), 7.57 (m, 3H), 7.65 (m, 1H), 7.96 (m, 2H), 8.18 (d, J = 8.5 Hz, 1H), 10.91 (s, 1H), 13.00 (br s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 121.9, 123.8, 127.4, 127.6, 128.4, 128.5, 128.9, 132.2, 133.4, 134.3, 135.1, 135.6, 136.8, 139.6, 165.2, 168.4, 169.3; HRMS (ESI-TOF) m/z $[M - H]^-$ Calcd for $C_{21}H_{14}NO_5$ 360.0877, found 360.0883.

*3-Benzamido-5,6,7,8,9,10-hexahydrobenzo[8]annulene-1,2-dicarboxylic acid (**7h**).* White solid (167 mg, 91%); mp the compound spontaneously eliminates H_2O while heating (from MeOH/H_2O); IR (ATR) 3389, 2922, 2852, 1745, 1690, 1663, 1603, 1579, 1524, 1492, 1445, 1406, 1264, 1226 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 1.33 (m, 4H), 1.67 (m, 4H), 2.79 (m, 4H), 7.60 (m, 3H), 7.93 (m, 2H), 8.09 (s, 1H), 11.14 (s, 1H), 13.05 (br s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.4, 25.7, 27.6, 30.7, 31.8, 32.5, 117.5, 123.2, 127.2, 128.8, 132.0, 132.4, 134.5, 136.6, 137.1, 146.9, 164.9, 168.6, 170.1; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{21}H_{22}NO_5$ 368.1492, found 368.1490.

General Synthetic Route (C) to Mixed Ester Derivatives 8 and 9. The phthalate substrate **5** (0.5 mmol) and sodium alkoxide (10 mol %, based on **5**) were dissolved in the corresponding dry alcohol (5 mL). In the case of **9**, 4 Å molecular sieves (150 mg) were added to the solution. The resulting mixture was heated under reflux for the time indicated in Table 2. The course of the reaction was followed by TLC (petroleum ether/EtOAc, 3:1) and after completion, the reaction mixture was cooled and acidified to pH 1−2 with 6 M aqueous solution of HCl (~3 mL), resulting in the precipitation of the mixed esters **8** or **9** (see Table 2, Runs 16−20). The precipitate was collected by filtration, washed with methanol (2 mL) and dried.

*4-Ethyl 3-methyl 5-benzamido-4′-methoxy-2-methyl-[1,1′-biphenyl]-3,4-dicarboxylate (**8a**).* Off-white solid (208 mg, 93%); mp 149−150 °C (EtOH); IR (ATR) 3302, 3254, 2949, 1709, 1689, 1668, 1579, 1506, 1492, 1442, 1336, 1274, 1228 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 1.17 (t, J = 7.1 Hz, 3H), 2.15 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 7.06 and 7.33 (AA′XX′, J = 8.8 Hz, 2H each), 7.56 (m, 2H), 7.62 (m, 1H), 7.79 (s, 1H), 7.95 (m, 2H), 10.66 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.7, 17.0, 52.4, 55.2, 61.5, 113.9, 121.0, 126.2, 127.5, 128.4, 128.7, 130.2, 131.7, 132.0, 134.1, 135.0, 135.4, 145.4, 158.9, 165.3, 165.9, 168.5; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{26}H_{26}NO_6$ 448.1755, found 448.1750. Anal. Calcd for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13. Found: C, 69.91; H, 5.72; N, 3.22.

*3-Ethyl 2-methyl 4-benzamido-[1,1′-biphenyl]-2,3-dicarboxylate (**8c**).* Off-white solid (191 mg, 95%); mp 121−122 °C (EtOH); IR (ATR) 3295, 2996, 2952, 1715, 1686, 1670, 1594, 1575, 1515, 1488, 1433, 1276, 1230 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 1.14 (t, J = 7.2 Hz, 3H), 3.55 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 7.32 (m, 2H), 7.41 (m, 1H), 7.46 (m, 2H), 7.58 (m, 2H), 7.64 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H) 7.97 (m, 2H), 10.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.6, 52.1, 61.5, 123.8, 126.0, 127.6, 127.8, 128.0, 128.5, 128.6, 132.1, 133.1, 133.3, 134.0, 136.0, 136.1, 138.9, 165.5, 165.7, 168.0; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{24}H_{22}NO_5$ 404.1492, found 404.1488. Anal. Calcd for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47. Found: C, 71.42; H, 4.99; N, 3.47.

*4-Ethyl 3-methyl 5-benzamido-2,4′-dimethyl-[1,1′-biphenyl]-3,4-dicarboxylate (**8f**).* White solid (196 mg, 91%); mp 171−173 °C (MeOH); IR (ATR) 3238, 2990, 2955, 1728, 1685, 1670, 1583, 1508, 1493, 1436, 1408, 1367, 1330, 1303, 1264, 1240 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 1.12 (t, J = 7.1 Hz, 3H), 2.10 (s, 3H), 2.36 (s, 3H), 3.39 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 7.05 and 7.24 (AA′XX′, J = 8.0 Hz, 2H each), 7.58 (m, 2H), 7.64 (m, 1H), 7.89 (s, 1H), 7.96 (m, 2H), 10.68 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.6, 20.6, 20.8, 51.7, 61.3, 119.6, 126.1, 127.4, 128.65, 128.68, 128.9, 132.0, 134.1, 134.4, 135.1, 135.6, 136.3, 136.7, 140.9, 165.3, 165.8, 167.7; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{26}H_{26}NO_5$ 432.1805, found 432.1809. Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.18; H, 5.75; N, 3.24.

*2-Ethyl 1-methyl 3-benzamido-5,6,7,8,9,10-hexahydrobenzo[8]-annulene-1,2-dicarboxylate (**8h**).* White solid (198 mg, 97%); mp 96−97 °C (EtOH); IR (ATR) 3233, 2926, 2848, 1716, 1675, 1579, 1514, 1411, 1329, 1308, 1224 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6)

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δ 1.14 (t, J = 7.1 Hz, 3H), 1.33 (m, 4H), 1.65 (m, 4H), 2.71 (m, 2H), 2.81 (m, 2H), 3.80 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 7.56 (m, 2H), 7.62 (m, 1H), 7.74 (s, 1H), 7.94 (m, 2H), 10.60 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.7, 25.2, 25.7, 27.5, 30.6, 31.7, 32.2, 52.2, 61.3, 120.4, 125.7, 127.4, 128.6, 131.9, 133.8, 134.2, 134.5, 135.4, 146.7, 165.2, 166.0, 168.6; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{28}NO_5$ 410.1962, found 410.1957. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.36; H, 6.35; N, 3.43.

*4-(tert-Butyl) 3-methyl 5-benzamido-4′-methoxy-2-methyl-[1,1′-biphenyl]-3,4-dicarboxylate (**9a**).* White solid (211 mg, 89%); mp 165−167 °C (MeOH); IR (ATR) 3291, 2955, 1732, 1712, 1668, 1578, 1507, 1491, 1402, 1305, 1278, 1231 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.38 (s, 9H), 2.13 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 7.06 and 7.31 (AA′XX′, J = 8.8 Hz, 2H each), 7.56 (m, 3H), 7.62 (m, 1H), 7.97 (m, 2H), 10.52 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 17.0, 27.5, 52.4, 55.2, 82.0, 113.9, 124.2, 127.0, 127.5, 128.6, 128.8, 130.1, 131.7, 132.0, 133.9, 134.1, 135.0, 144.7, 158.9, 165.0, 165.2, 168.4; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{28}H_{30}NO_6$ 476.2068, found 476.2063. Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.46; H, 6.27; N, 3.03.

*2-(tert-Butyl) 1-methyl 3-benzamido-6-methylphthalate (**9b**).* Yellow solid (172 mg, 93%); mp 100−101 °C (MeOH); IR (ATR) 3316, 2981, 2929, 1736, 1690, 1674, 1600, 1585, 1529, 1490, 1393, 1368, 1316, 1281, 1244, 1218 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.37 (s, 9H), 2.29 (s, 3H), 3.82 (s, 3H), 7.46 (d, J = 8.0 Hz, 1H), 7.55 (m, 2H), 7.61 (m, 2H), 7.97 (m, 2H), 10.40 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.7, 27.4, 52.2, 81.9, 126.1, 126.6, 127.4, 128.5, 131.87, 131.92, 132.9, 133.4, 133.9, 134.2, 165.09, 165.12, 168.0; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{21}H_{22}NO_5$ 368.1503, found 368.1499. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.16; H, 6.22; N, 3.80.

Procedure for the Synthesis of the *N*-Methyl Derivative 10a. NaH (60% in mineral oil; 40 mg, 1 mmol) was added to a cooled solution (0 °C) of **5a** (433 mg, 1 mmol) in dry DMF (10 mL). The solution was stirred for 2 h at 0 °C. Afterward, Me_2SO_4 (237 μL, 2.5 mmol) was added and the reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction was quenched with Me_2NH (≈60% in H_2O, 0.8 mL) and stirred for an additional 6 h. Then water (15 mL) was added and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with diluted HCl (5%, 20 mL), water (20 mL), and brine (20 mL), and dried over anhydrous Na_2SO_4. Upon filtration, evaporation of the solvent under reduced pressure and recrystallization from MeOH, **10a** was obtained as a white solid.

*Dimethyl 4′-methoxy-2-methyl-5-(N-methylbenzamido)-[1,1′-biphenyl]-3,4-dicarboxylate (**10a**).* White solid (402 mg, 90%); mp 108−109 °C (MeOH); IR (ATR) 2956, 2839, 1731, 1639, 1608, 1518, 1430, 1370, 1340, 1272, 1251, 1223 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ 2.11 (s, 3H), 3.26 (s, 3H), 3.80 (m, 9H), 6.99 and 7.11 (AA′XX′, J = 14.5 Hz, 2H each), 7.28 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 17.4, 37.8, 52.6, 52.9, 55.2, 113.8, 127.0, 127.8, 127.9, 129.6, 130.3, 130.9, 132.0, 132.5, 134.6, 135.8, 140.5, 145.6, 159.0, 165.6, 167.6, 169.2; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{26}H_{26}NO_6$ 448.1755, found 448.1750. Anal. Calcd for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13. Found: C, 70.02; H, 5.74; N, 3.14.

Procedure for the Synthesis of 3,1-Benzoxazin-4-ones 11. Benzamidobenzoic acid **6** (1 mmol) in acetic anhydride (5 mL) was heated under reflux for 30 min. The reaction mixture was transferred into ice-cold water (10 mL) and the precipitated solid was collected by filtration, washed with methanol and dried.

*Methyl 7-(4-methoxyphenyl)-6-methyl-4-oxo-2-phenyl-4H-benzo[d][1,3]oxazine-5-carboxylate (**11a**).* White solid (361 mg, 90%); mp 238−239 °C (MeOH/$CHCl_3$); IR (ATR) 2957, 1752, 1728, 1607, 1597, 1574, 1515, 1447, 1435, 1351, 1291, 1247 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.12 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 7.08 and 7.41 (AA′XX′, J = 8.5 Hz, 2H each), 7.63 (m, 4H), 8.18 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 17.1, 52.8, 55.2, 111.9, 114.0, 127.8, 128.2, 129.1, 129.7, 130.3, 130.9, 132.5, 132.9, 134.8, 144.5, 150.4, 156.7, 157.4, 159.3, 167.9; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{20}NO_5$ 402.1336, found 402.1330. Anal. Calcd for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 71.57; H, 4.52; N, 3.45.

*Methyl 6-methyl-4-oxo-2-phenyl-4H-benzo[d][1,3]oxazine-5-carboxylate (**11b**).* Pale yellow solid (271 mg, 92%); mp 146−148 °C (MeOH/$CHCl_3$); IR (ATR) 2948, 1769, 1725, 1621, 1593, 1576, 1494, 1476, 1447, 1436, 1327, 1309, 1276, 1252 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.35 (s, 3H), 3.91 (s, 3H), 7.60 (m, 2H), 7.67 (m, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 8.17 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.2, 52.6, 113.2, 127.7, 127.8, 129.0, 129.7, 132.8, 133.5, 134.8, 138.6, 144.6, 156.3, 157.5, 167.7; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{14}NO_4$ 296.0917, found 296.0921. Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.04; H, 4.24; N, 4.72.

Transformation of the Intermediate 11a into Benzamidobenzoic Acid 6a. A suspension of the compound **11a** (200 mg, 0.5 mmol) in 1 M KOH methanolic solution (5 mL) was refluxed for 15 min. Following general synthetic route A, **6a** (181 mg, 86%) was obtained.

Transformation of the Intermediate 11a into Mixed Ester Derivatives 8a and 9a. A suspension of the compound **11a** (200 mg, 0.5 mmol) and sodium alkoxide (10 mol %; EtONa for **8a** and *t*-BuONa for **9a**) in the corresponding dry alcohol (5 mL; EtOH for **8a** and *t*-BuOH for **9a**) was heated under reflux for 15 min. Following general synthetic route C, products **8a** (212 mg, 95%) and **9a** (216 mg, 91%) were obtained.

^{1}H NMR Studies of the Reaction Pathway from 5b and 11b into Monohydrolyzed Product 6b. To the starting compound **5b** or **11b** (0.06 mmol) in an NMR tube, KOH solution in perdeuterated methanol (16.8 mg, 0.3 mmol of KOH; 0.7 mL of CD_3OD) was added. The course of the reaction was monitored by ^{1}H NMR spectroscopy (see Supporting Information, Figures S2−S4).

Procedure for the Synthesis of Phthalate 5b-d_3. A solution of the starting phthalate **5b** (98 mg, 0.3 mmol) and KOH (8.4 mg, 0.15 mmol) in perdeuterated methanol (3 mL) was stirred at room temperature for 5 min. The reaction mixture was cooled to 0 °C and acidified to pH 1−2 with 1 M aqueous solution of HCl (∼3 mL). The precipitate was collected by filtration, washed with water (2 mL) and dried. Upon recrystallization from MeOH, **5b**-d_3 was obtained as an off-white solid.

*1-Methyl 2-(methyl-d_3) 3-benzamido-6-methylphthalate (**5b**-d_3).* Off-white solid (97 mg, 98%); mp 116−117 °C (MeOH); IR (ATR) 3256, 2954, 1730, 1681, 1670, 1597, 1520, 1491, 1436, 1399, 1325, 1284, 1263, 1251, 1222 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 2.32 (s, 3H, 6-Me), 3.89 (s, 3H, CO_2Me), 7.48 (d, J = 8.5 Hz, 1H, 5-H), 7.54 (m, 2H, 3′-H, 5′-H), 7.61 (m, 1H, 4′-H), 7.94 (m, 2H, 2′-H, 6′-H), 8.25 (d, J = 8.5 Hz, 1H, 4-H) (exchangeable NH signal is hidden); ^{13}C NMR (125 MHz, CD_3OD) δ 19.3, 52.9 (sep, J = 22.3 Hz), 53.1, 120.8, 125.3, 128.5, 130.0, 133.1, 133.5, 135.7, 135.9, 136.2, 137.8, 168.1, 169.0, 170.6; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{15}D_3NO_5$ 331.1368, found 331.1367.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00765.

^{1}H NMR studies of hydrolysis of **5b** and **11b**; copies of ^{1}H and ^{13}C NMR spectra for all new products; X-ray single crystal structure analysis data of potassium salt of **6a** (PDF)

Crystal data of potassium salt of **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

We dedicate this work with deep respect to Professor Miha Tišler on the occasion of his 90th birthday.

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