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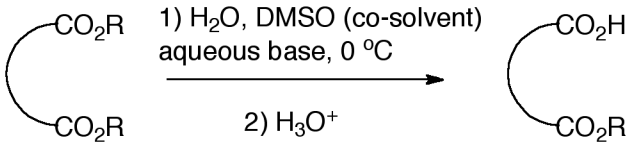

R= Me, Et, ^{i}Pr, ^{n}Pr, ^{i}Bu, ^{n}Bu

Practical Selective Monohydrolysis of Bulky Symmetric Diesters: Comparing with Sonochemistry

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Abstract: The conditions of the practical selective monohydrolysis of symmetric diesters we previously reported have been modified and applied to selective monohydrolysis of bulky symmetric diesters. While ultrasound is generally considered effective for two-phase reactions, its effect actually turned out to be rather marginal. Instead, use of a larger proportion of a polar aprotic co-solvent, DMSO, and aqueous KOH helped enhance the reaction rates and improve the yields of the half-esters. The reactions are simple, mild and practical without special devices.

Key Words: selective monohydrolysis; half-ester, symmetric diester; sonochemistry; practical synthesis

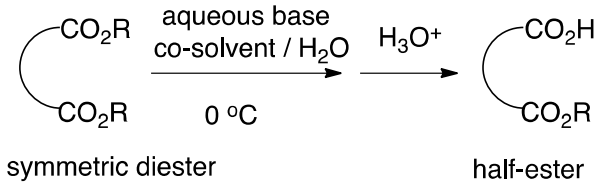
1. Introduction

Half-esters have been important building blocks for synthesis of various classes of compounds such as polymers, natural products, and pharmaceuticals.[1] Among the most typical methods for their preparation is monohydrolysis of one of the two identical ester groups in symmetric diesters. The challenge in this method, however, is to distinguish two identical groups. Consequently, classical

saponification typically leads to complex mixtures of the starting diester, the corresponding diacid, and a small amount of half-esters.[2]

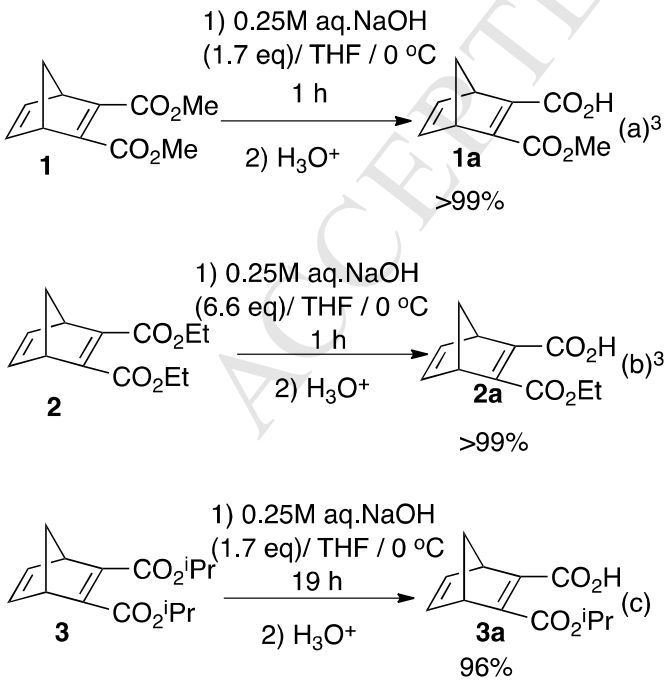
Previously we reported selective monohydrolysis of symmetric diesters. This reaction allows selective monohydrolysis of symmetric diesters in high yields under practical conditions (Scheme 1).[3]

Scheme 1 Selective monohydrolysis of symmetric diesters



However, in this reaction, monohydrolysis of relatively bulky symmetric diesters typically takes a long time, or needs greater amounts of a base in order to consume the starting diesters. Scheme 2 shows some examples for diesters with the same norbornadiene skeleton.[3] The monohydrolysis of dimethyl ester, needs approximately one hour with about 2 equivalents of the base. As the size of the ester groups increase, the reaction time and the amount of the base also increases.[4]

Scheme 2 Some examples of selective monohydrolysis



This trend is reflective of our previous observation that the monohydrolysis occurs at the interface between the aqueous phase and the diester, which means that bulky alkyl groups reduce the contact with the aqueous phase. The problem is that the extended reaction time tends to reduce the yields of the half-esters. Therefore, we attempted to improve the selectivity of the reactions by adjusting the reaction conditions.

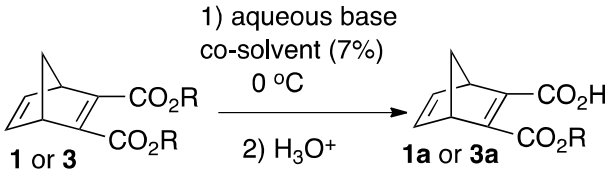
Regarding the mechanisms of this selectivity, we hypothesize that after one of the two identical ester groups is monohydrolyzed, the resultant intermediary carboxylates form micellar aggregates in which the remaining hydrophobic parts are directed inside with the hydrophilic carboxylate groups being outside. Such aggregates may potentially prohibit further hydrolysis with the remaining ester groups intact. In fact, in consonant with this hypothesis, we observed that a water-miscible polar aprotic co-solvent such as THF, CH_3CN, and DMSO increases the reaction rate and selectivity, while a protic co-solvent such as an alcohol decreases the selectivity.[5, 6] This decrease of the reaction rate is likely to be attributed to dissociation of the micellar aggregates. In addition, we reported that KOH often improves selectivities compared to NaOH, perhaps due to stronger affinity of the K^+ cation with carbonyl oxygen, leading to the enhanced electrophilicity of the starting ester group.[7] We demonstrated that improvement of the selectivities is possible for various symmetric diesters including dialkyl malonates.[8,9]

Therefore, based on this hypothesis and supporting observations, we tried to improve the selectivities of various bulky symmetric diesters.

2. Results and discussion

We first applied ultrasound to the monohydrolysis, as ultrasound-assisted reactions are known to increase reaction rates of heterogeneous reactions including two-phase reactions.[10] The results are summarized in Table 1.

Table 1. Effects of ultrasounds in selective monohydrolysis of dialkyl bicycle[2.2.1]hept-2,5-diene-2,3-dicarboxylates



Run	R	co-solvent	aqueous base	equivalent of base	ultrasound	reaction time	yield (%)[a]
1	**1**: Me	THF	NaOH	1.7	no	1 h	99
2		THF	NaOH	1.7	yes	15 min	98
3	**3**: iPr	THF	NaOH	1.7	no	19h	96 (3)
4		THF	NaOH	1.7	yes	1.5h	trace [b]
5		DMSO	KOH	1.7	yes	8h	19 (64)
6		DMSO	KOH	3.0	yes	7h	53 (24)
7		DMSO	KOH	4.5	yes	4h	57 (20)
8		DMSO	KOH	6.0	yes	3h	60 (12)

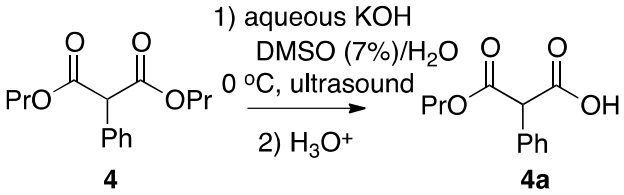
a: Isolated yields of the half-ester except for run 4. Yields of the recovered diester is shown in the parentheses.
b: Monitored by thin layer chromatography. Diester 3 remained mostly intact.

We first tried to monohydrolyze diester **1**. Indeed the acceleration of the reaction was observed with a comparable yield (Run 2), as the reaction time for the monohydrolysis was shortened from 1 hour to 15 minutes by sonication. The amount of co-solvent is 7% as we reported previously.[3] However, in the case of the corresponding diisopropyl ester, the situation was different. The monohydrolysis was completed in about 19 hours without ultrasound (Run 3). With the same equivalent of the base, KOH, using DMSO as a co-solvent, which was previously observed to enhance the reaction rates,[6] only 19% of the half-ester was obtained after 8 h sonication (Run 5). Runs 6-8 show that greater yields of the half-ester can be obtained with the increased base within shorter reaction times with DMSO. However, no significant improvement in the yields was achieved beyond the addition of 3.0 equivalents of the base. Therefore, it is questionable whether the reaction rate was accelerated by ultrasound or by increased amounts of the base.

Somewhat interesting results were selective monohydrolysis of dipropyl phenyl malonate, **4**. We had reported that this monohydrolysis reaction took 33 hours with 0.8 equivalents of aqueous

KOH, yielding about 77% of half-ester, **4a**.[8] We attempted to improve the results by applying ultrasound with DMSO and aqueous KOH. The results are shown in Table 2.

Table 2 Effects of ultrasounds in selective monohydrolysis of dipropyl phenyl malonate



4 **4a**

Run	ultrasound	equivalent of KOH	reaction time	yield (%)[a]
1	yes	0.8	10h	6 (76)
2	yes	1.5	3h	36 (52)
3	yes	3.0	2.5h	77 (1)
4	yes	3.0	2h	83 (4)
5	no	3.0	2.5h	10 (82)

a: Isolated yields of the half-ester. Yields of the recovered diester is shown in the parentheses.

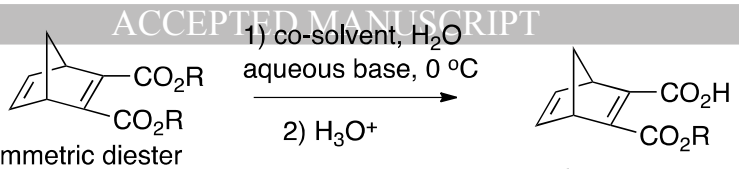
As can be seen from this table, when ultrasound was applied to the conditions we reported before,[8] only 6% of the half-ester was obtained even after 10 hours, which is the maximum amount of the processing time of the sonicator with recovery of 76% of the starting diester (Run 1), which means that ultrasound did not help accelerate the reaction. As the amount of the base increases, the yield of half-ester **4a** also increases with shorter sonication time. When 3 equivalents of the base were used with ultrasound, 83% of the half-ester was obtained with only 2 hours (Run 4). In order to confirm that this acceleration was due to ultrasound instead of the greater amount of the base, the same reaction condition was performed without ultrasound. The yield of the half-ester was only 10% with recovery of 81% diester after 2.5 hours (Run 5). Therefore, it appears that the ultrasound helped accelerate the selective monohydrolysis of dipropyl phenyl malonate.

From these results, we conclude that it may be possible by ultrasound to increase the reaction rate of some small-sized diesters such as a dimethyl ester without decreasing the selectivity. Some bulkier diesters may need additional amounts of base as a trigger of the ultrasonic effect in the

monohydrolysis. It is noteworthy that long duration processing by ultrasound tends to overheat the reaction vessel, requiring special precaution for cooling.

We next tried to modify the reaction conditions based on our proposed mechanistic hypothesis without relying on a special device.[11] We first screened the selective monohydrolysis of dialkyl bicycle[2.2.1]hept-2,5-diene-2,3-dicarboxylates, which were synthesized in high yields by simple Diels-Alder reactions of cyclopentadiene and the corresponding acetylene dicarboxylates.[12] The results are summarized in Table 3.

Table 3 Selective monohydrolysis of dialkyl bicycle[2.2.1]hept-2,5-diene-2,3-dicarboxylates



symmetric diester
R=Me, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu
1, **2**, **3**, **5**, **6**
(1.2 mmol)

half-ester
1a, **2a**, **3a**, **5a**, **6a**

Run	R	co-solvent	co-solvent (v/v): H_2O (mL)	aqueous base	reaction time	yield (%)[a]
1	**1**: Me	THF	2 mL (7%) : 20 mL	0.25 M NaOH 8 mL	45min	>99
2		DMSO	2 mL (7%) : 20 mL	0.25 M NaOH 8 mL	40min	>99
3		DMSO	2 mL (7%) : 20 mL	0.25 M KOH 8 mL	30min	>99
4	**2**: Et	THF	4 mL (13%) : 24 mL	0.5 M KOH 4 mL	5h 30min	95
5		THF	16 mL (44%) : 16 mL	0.5 M KOH 4 mL	3h	93
6		THF	24 mL (67%) : 8 mL	0.5 M KOH 4 mL	1h 50min	95
7		DMSO	4 mL (13%) : 24 mL	0.5 M KOH 4 mL	3h	84
8		DMSO	16 mL (44%) : 16 mL	0.5 M KOH 4 mL	2h	92
9		DMSO	24 mL (67%) : 8 mL	0.5 M KOH 4 mL	1h 30min	>99
10	**3**: ^{i}Pr	THF	22 mL (73%) : 4 mL	0.5 M KOH 4 mL	12h	71 (18)
11		DMSO	24 mL (67%) : 8 mL	0.5 M KOH 4 mL	4h 30min	87
12		DMSO	22 mL (73%): 4 mL	0.5 M KOH 4 mL	3h	93
13	**5**: ^{n}Pr	THF	22 mL (73%) : 4 mL	0.5 M KOH 4 mL	12h	78 (11)
14		DMSO	24 mL (67%) : 8 mL	0.5 M KOH 4 mL	4h	91
15		DMSO	22 mL (73%) : 4 mL	0.5 M KOH 4 mL	3h	96
16	**6**: ^{n}Bu	THF	32 mL (84%) : 2 mL	0.5 M KOH 4 mL	18h	63 (28)
17		DMSO	32 mL (84%) : 2 mL	0.5 M KOH 4 mL	6h	84

a: Isolated yields of the half-ester. Yields of the recovered diester is shown in the parentheses.

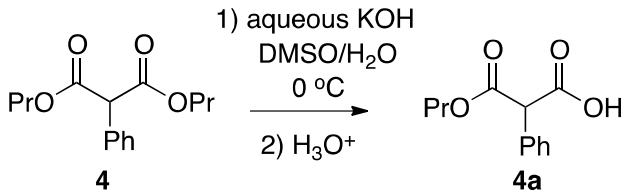
Again monohydrolysis of dimethyl ester, **1**, proceeded quite efficiently regardless of the type of the co-solvent or base, producing the half-ester in almost quantitative yields, although DMSO and KOH again appeared to have somewhat enhanced the reaction rate, consistently with our previous observations. The volume percentage of the co-solvent is the same as reported before (7%), which was found to be optimal for this diester.[3]

As we reported before, diethyl ester **2** needed about 3-4 times as much base.[3] KOH also worked better than NaOH. It became noticeable that the selectivities increased as the amount of THF increased even with the use of 1.7 equivalents of the base, and the optimal conditions existed when THF was between 13% and 67%. However, selectivity was rather significantly improved when DMSO was employed as a co-solvent, and the best and comparable results to the dimethyl ester, **1**, were obtained when 44-67% of DMSO was used in combination with aqueous KOH. These conditions were also effective for the diipropyl ester, **3**, and di-n-propyl ester, **5**, but the increased selectivities and reaction rates were achieved when a greater amount of DMSO was used. Therefore, it appears that use of a larger amount of DMSO helps improve the selectivity as the bulkiness of the diesters increases. A greater proportion of THF or DMSO was applied for monohydrolysis of di-n-butyl ester, **6**, and the effect of DMSO instead of THF became clearer for this monohydrolysis. The reaction times have also been shortened significantly even with the use of 1.7 equivalents of the base.

From these results, it appears that the optimal volume percentage of the co-solvent tends to increase with the increase of the size of the ester group. This greater proportion of polar aprotic co-solvent is likely to help increase the contact of the hydrophobic ester groups and the aqueous phase, which can increase the chance for hydrolysis of one of the two ester groups. The co-solvent is also likely to help protect the potential micellar aggregates formed from the intermediary carboxylates of bulky half-esters described above, and thereby prohibit further hydrolysis. The unsuccessful results with the ultrasound-assisted conditions described above may also be due to potential dissociation of the aggregates by sonication.

Gratifyingly, when monohydrolysis of diisopropyl phenyl malonate, **4**, was performed with the use of DMSO as a co-solvent, significant enhancement of the reaction rate was again observed, while we needed 33 hours with the conditions reported previously.[9] The starting diester was consumed in 6 hours under these conditions. Although this reaction time is slightly longer than with the ultrasound, when the same equivalent of the base (3.0 eq) was used, the yield has been improved to 86%, which is better than the ultrasound-assisted conditions described above.

Table 4 Selective monohydrolysis of propyl phenyl malonate



Run	DMSO: H_2O (v/v) : (mL)	0.5N KOH (mL)	reaction time	yield (%)a
1	2 mL (8%) : 20 mL	1.9 (0.8eq)	24h	74 (17)
2	22 mL (79%) : 4 mL	1.9 (0.8eq)	6h	72 (15)
3	22 mL (76%) : 4 mL	2.9 (1.2eq)	6h	79 (10)
4	22 mL (66%) : 4 mL	7.2 (3.0eq)	6h	86

a: Isolated yields of the half-ester. Yields of the recovered diester is shown in the parentheses.

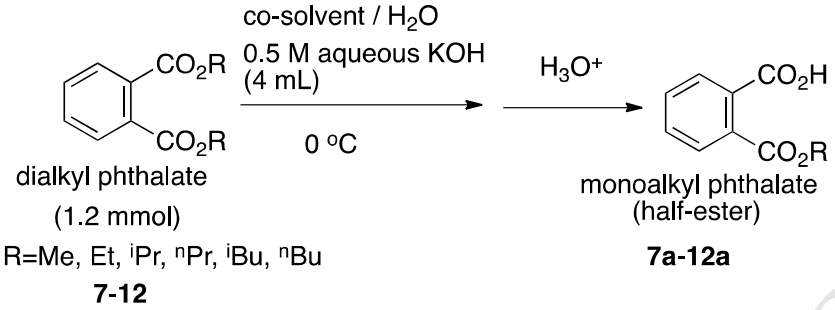
From a technical point of view, use of a larger proportion of THF at 0 °C also sometimes formed hydrates,[13] hampering the stirring of the reaction mixture, but this was not the case with DMSO. The product half-esters also all show high purities, despite the fact that DMSO is less volatile than THF or CH_3CN and may take a longer time to completely evaporate. As we reported before,[8,9] the corresponding diacids, if extant, remained in the aqueous phase and were not isolated or only a trace amount was isolated after the reaction mixture was worked up.

Based on the proportions that turned out to be the best in each reaction in Table 3, we next tried selective monohydrolysis of several bulky dialkyl phthalates, all of which are readily available inexpensively. The product half-esters, monoalkyl phthalates, exhibit a wide range of applications to various industrial products such as plasticizers and adhesives, as well as to synthesis of a variety of pharmaceuticals and polymers,[14] but they are rather expensive. Therefore, methods for their cost-effective production have been under close scrutiny.[15]

The results are summarized in Table 5. Here again, the effect of DMSO as a co-solvent is more remarkable. In all the cases, the yields of the corresponding half-esters are significantly higher with DMSO than with THF. The equivalent of the base applied in each run was only about 1.7

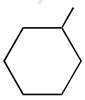
equivalent, but the reaction rate was significantly faster with DMSO than with THF. Again, the optimal percentage of the co-solvent tends to increase as the size of the ester groups increases.

Table 5 Selective monohydrolysis of dialkyl phthalates



dialkyl phthalate (1.2 mmol)
R=Me, Et, ^{i}Pr, ^{n}Pr, ^{i}Bu, ^{n}Bu
7-12

monoalkyl phthalate (half-ester)
7a-12a

Run	R	co-solvent	co-solvent (v/v): H_2O (mL)	reaction time	yield (%)a
1	**7**: Me	THF	2 mL (7%) : 20 mL	2h	88[b]
2		DMSO	2 mL (8%) : 20 mL	40min	94
3	**8**: Et	THF	24 mL (67%) : 8 mL	8h	66 (24)
4		DMSO	24 mL (67%) : 8 mL	2h	93
5	**9**: ^{i}Pr	THF	22 mL (73%) : 4 mL	14h	46 (45)
6		DMSO	22 mL (73%) : 4 mL	4h	81
7	**10**: ^{n}Pr	THF	22 mL (73%) : 4 mL	14h	55 (34)
8		DMSO	22 mL (73%) : 4 mL	3h 30min	85
9	**11**: ^{i}Bu	THF	32 mL (84%) : 2 mL	18h	34 (59)
10		DMSO	32 mL (84%) : 2 mL	10h	77 (11)
11	**12**: ^{n}Bu	THF	32 mL (84%) : 2 mL	18h	40 (47)
12		DMSO	32 mL (84%) : 2 mL	8h	81
13	**13:** 	DMSO	32 mL (84%) : 2 mL	8h	80 (13)
14		DMSO	40 mL (87%) : 2 mL	3.5h	90

a: Isolated yields of the half-ester. Yields of the recovered diester is shown in the parentheses.

b: The conditions we previously reported were applied with 0.25M NaOH (8 mL).[2,4]

3. Conclusions

In summary, we found that the use of a larger proportion of a water-miscible polar aprotic co-solvent, DMSO, and aqueous KOH can accelerate the selective monohydrolysis of a series of bulky symmetric diesters, leading to enhancement of the selectivity, producing the corresponding half-esters in high yields. This additional factor helps improve the results of the monohydrolysis reaction for bulky diesters in addition to a longer reaction time, use of other polar aprotic co-solvents such as THF or CH_3CN,[16] and/or greater amounts of an aqueous base when the reactivity is low. Although ultrasound-assisted conditions are generally perceived to enhance reaction rates of water-mediated reactions, these conditions turned out to have marginal effects for these monohydrolysis. Instead, conditions applying greater proportions of a polar aprotic solvent, DMSO, are practical and do not require a special device or expensive reagents. These conditions are also consistent with our mechanistic hypothesis and previous observations. All the half-esters synthesized by this method are stable and exhibit excellent purities.

4. Experimental section

General procedure for ultrasound-assisted selective monohydrolysis of symmetric diesters

A diester (0.60 mmol) was dissolved in 1 mL of DMSO or THF and 14-X (X:volume of the aqueous KOH) mL of water was added. The probe of the sonicator (VCX 750 sonicator, Sonics & Materials Inc., USA) was immersed in the reaction mixture. The reaction mixture was cooled to 0 ^{o}C, and the sonicator was turned on. To this mixture was added the indicated equivalent of a 0.5M aqueous KOH solution dropwise. The reaction mixture was irradiated under 20kHz ultrasound (750W, tip diameters of 13 mm) until the starting diester was consumed according to TLC or until the maximum amount of the processing time of the sonicator (10 hours) was elapsed, acidified with 1.0 M HCl, saturated with NaCl, extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The extract was concentrated in vacuo and purified by silica gel column chromatography with hexane:ethyl acetate and ethyl acetate to afford monopropyl ethyl malonate.

General procedure for selective monohydrolysis of norbornadiene without sonication

A diester (1.2 mmol) was dissolved in the specified amount of THF or DMSO, and the specified amount of water was added. The reaction mixture was immersed in an ice-water bath and cooled to 0 ^{o}C. To this reaction mixture was added the aqueous base in small portions with stirring until the starting diester was consumed according to TLC. The reaction mixture was acidified with 1.0 M HCl at the same temperature (0 ^{o}C), saturated with NaCl, extracted with ethyl acetate three to four times, and dried over Na_2SO_4. The extracts were evaporated *in vacuo* and purified by silica gel column chromatography to afford the desirable half-ester.

General procedure for selective monohydrolysis of diisopropyl phenyl malonate without sonication

Dipropyl phenyl malonate (316 mg, 1.2 mmol) was dissolved in the specified amount of DMSO and the specified amount of water was added, and the reaction mixture was cooled to 0 ^{o}C. To this mixture was added 0.5M KOH in small portions with stirring until the starting diester was consumed according to TLC. The reaction mixture was acidified with 1.0 M HCl at the same temperature (0 ^{o}C), saturated with NaCl, extracted with ethyl acetate three to four times, and dried over Na_2SO_4. The extract was concentrated *in vacuo* and purified by silica gel column chromatography with hexane:ethyl acetate and ethyl acetate to afford monopropyl ethyl malonate.

General procedure for selective monohydrolysis of dialkyl phthalate without sonication

A diester (1.2 mmol) was dissolved in the specified amount of THF or DMSO, and the specified amount of water was added. The reaction mixture was immersed in an ice-water bath and cooled to 0 □. To this reaction mixture, 4mL of 0.5 M KOH was added in small portions with stirring until the starting diester was consumed according to TLC. The reaction was stirred at the same temperature. It was then acidified with 1.0 M HCl at 0 □, saturated with NaCl, extracted with ethyl acetate three to four times, and dried over Na_2SO_4. The extracts were evaporated *in vacuo* and purified by silica gel column chromatography to afford the desirable half-ester.

The spectral data for all the half-esters reported here are as follows:

Half-ester **1a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 2.13 (1H, d, *J* = 7.0 Hz), 2.23 (1H, d, *J* = 7.0 Hz), 3.94 (3H, s), 4.10 (1H, br. s), 4.25 (1H, br. s), 6.90 (2H, m);^{13}C NMR (125 MHz, $CDCl_3$) δ= 53.52, 53.89, 54.88, 72.83, 141.87, 142.83, 151.14, 162.55, 162.66, 168.31; mp 107-108 °C (lit.108-109 °C).[17] HRMS Calcd for $C_{10}H_{11}O_4$ $(M+H)^+$: 195.0675. Found: 195.0651.

Half-ester **2a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.40 (3H, t, *J* = 7.5 Hz), 2.13 (1H, d, *J* = 7.0 Hz), 2.24 (1H, d, *J* = 7.0 Hz), 4.10 (1H, br.s), 4.28 (1H, br. s), 4.38 (2H, m), 6.91 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 14.08, 53.51, 54.88, 63.49, 72.83, 141.88, 142.90, 151.50, 162.34, 162.81, 167.91. HRMS Calcd for $C_{11}H_{13}O_4$ $(M+H)^+$: 209.0813. Found: 209.0818.

Half-ester **3a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.38 (6H, dd, *J* = 6.0 Hz, *J* = 6.5 Hz), 2.12 (1H, d, *J* = 7.0 Hz), 2.23 (1H, d, *J* = 7.0 Hz), 4.08 (1H, br. s), 4.25 (1H, br. s), 5.18 (1H, m), 6.91 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ=21.76, 53.51, 54.86, 71.87, 72.74, 141.86, 142.94, 151.96, 162.02, 162.96, 167.43. HRMS Calcd for $C_{12}H_{15}O_4$ $(M+H)^+$: 223.0970. Found: 223.0961.

Half-ester **4a:**

Oil. 1H NMR (500 MHz, $CDCl_3$) δ= 0.91 (3H, t, J = 7.5), 1.64 (2H, m, J = 7.5), 4.07 (2H, m), 4.64 (1H, s), 7.31 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 10.33, 21.92, 58.13, 67.39, 128.25, 128.64, 129.38, 132.98, 168.34, 171.76.HRMS Calcd for $C_{12}H_{15}O_4$ $(M+H)^+$: 223.0970. Found: 223.0962.

Half-ester **5a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.01 (3H, t, *J* = 7.5 Hz), 1.79 (2H, m), 2.13 (1H, d, *J* = 7.5 Hz), 2.24 (1H, d, *J* = 7.5 Hz), 4.10 (1H, br. s), 4.27 (2H, m), 4.32 (1H, br. s), 6.90 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.42, 21.80, 53.49, 54.84, 68.84, 72.76, 141.83, 142.93, 151.55, 162.28, 162.81, 167.93. HRMS Calcd for $C_{12}H_{15}O_4$ $(M+H)^+$: 223.0970. Found: 223.0979.

Half-ester **6a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 0.97 (3H, t, *J* = 7.5 Hz), 1.44 (2H, m), 1.74 (2H, m), 2.12 (1H, d, *J* = 7.0 Hz), 2.23 (1H, d, *J* = 7.0 Hz), 4.09 (1H, br. s), 4.24 (1H, br. s), 4.31 (2H, m), 6.90 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 13.78, 19.20, 30.36, 53.50, 54.84, 67.25, 72.76, 141.84, 142.92, 151.55, 162.25, 162.81, 167.94 HRMS Calcd for $C_{13}H_{17}O_4$ $(M+H)^+$: 237.1126. Found: 237.1136.

Half-ester **7a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 3.93 (3H, s), 7.59 (2H, m), 7.69 (1H, d, *J* = 7.8 Hz), 7.93(1H, d, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 53.03, 128.87, 130.00, 130.11,

131.04, 132.44 , 133.40 , 168.82, 172.23. mp 82–83 °C.(lit. 82-84 °C)[17] HRMS Calcd for $C_9H_9O_4$ $(M+H)^+$: 181.0500. Found: 181.0507.

Half-ester **8a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.37 (3H, t, *J* = 7.0 Hz), 4.39 (2H, q, *J* = 7.3 Hz), 7.59 (2H, m), 7.70 (1H, d, *J* = 7.0 Hz), 7.91 (1H, d, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 13.99, 62.07, 128.82, 129.88, 130.04, 130.88, 132.30, 133.64, 168.28, 172.71 HRMS Calcd for $C_{10}H_{11}O_4$ $(M+H)^+$: 195.0657. Found: 195.0649.

Half-ester **9a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.35 (6H, d, *J* = 6.5 Hz), 5.28 (1H, m), 7.57 (2H, m), 7.68 (1H, d, *J* = 7.5 Hz), 7.90 (1H, d, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 21.67, 69.83, 128.90, 129.94, 130.66, 130.78, 132.32, 134.05, 167.77, 172.73. mp 78-80 °C. (lit.79-81.5 °C)[18] HRMS Calcd for $C_{11}H_{13}O_4$ $(M+H)^+$: 209.0813. Found: 209.0805.

Half-ester **10a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.00 (3H, t, *J* = 7.5 Hz), 1.77 (2H, m), 4.29 (2H, t, *J* = 7.0 Hz), 7.59 (2H, m), 7.71 (1H, d, *J* = 7.0 Hz), 7.91 (1H, d, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 10.55, 21.87, 67.73, 128.87, 129.89, 130.08, 130.89, 132.31, 133.66, 168.35, 172.83. HRMS Calcd for $C_{11}H_{13}O_4$ $(M+H)^+$: 209.0813. Found: 209.0819.

Half-ester **11a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 0.99 (6H, d, *J* = 7.0 Hz), 2.05 (1H, m), 4.11 (2H, d, *J* = 7.0 Hz), 7.59 (2H, m), 7.72 (1H, d, *J* = 7.0 Hz), 7.91 (1H, d, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 19.26, 27.78, 72.59, 128.93, 129.95, 130.17, 130.95, 132.32, 133.64, 168.35, 172.54. mp 77.8-78.2 °C. (lit. 78-80 °C).[19] Anal calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.72; H, 6.36. HRMS Calcd for $C_{12}H_{15}O_4$ $(M+H)^+$: 223.0970. Found: 223.0977.

Half-ester **12a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 0.94 (3H, t, *J* = 7.5 Hz), 1.44 (2H, m), 1.73 (2H, m), 4.34 (2H, t, *J* = 6.5 Hz), 7.59 (2H, m), 7.70 (1H, d, *J* = 7.5 Hz), 7.91 (1H, d, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 13.81, 19.29, 30.54, 66.02, 128.90, 129.94, 130.11, 130.91, 132.32, 133.68, 168.37, 172.69. mp 73-74 °C. (lit. 73°C)[20] HRMS Calcd for $C_{12}H_{15}O_4$ $(M+H)^+$: 223.0970. Found: 223.0965.

Half-ester **13a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.27 (1H, m), 1.41 (2H, m), 1.54 (3H, m), 1.75 (2H, m), 1.98 (2H, m), 5.04 (1H, m), 7.56 (2H, m), 7.70 (1H, dd, *J*=1.5Hz, *J*=1.5Hz), 7.88 (1H, dd, *J*=1.5Hz, *J*=1.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 23.84, 25.44, 31.37, 74.61, 128.90, 129.73,

130.28, 130.77, 132.09, 133.81, 167.65, 172.48. HRMS Calcd for $C_{12}H_{15}O_4$ $(M+H)^+$: 249.1127. Found: 249.1126.

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Supplementary Data

Supplementary Data related to this article can be found online.

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References

1. For example, (a) Kumar, A.; Khan, S.; Ahmed, Q. N. *Org. Lett.* **2017**, *19*, 4730-4733.

(b) Lakic, M.; Sabo, L.; Ristic, S.; Savic, A.; Petricevic, S.; Nikolic, N.; Vukadinovic, A.; Jankovic, D.; Sabo, T. J.; Vranjes-Duric, S. *Appl. Organomet. Chem.* **2016**, *30*(2), 81-88.

(c) Chudasama, N. A.; Prasad, K.; Siddhanta, A. K. *Carbohydr. Polym*. **2016**, *151*, 735-742.

(d) Cavusoglu, J.; Cayli, G. J. *Appl. Polym. Sci*. **2015**, *132*, 41457/1-41457/6.

(e) Chudasama, N. A.; Siddhanta, A. K. *Carbohydr. Res*. **2015**, *417*, 57-65

(f) Yuan, H.-N.; Li, S.; Nie, J.; Zheng, Y.; Ma, J.-A. *Chem. Eur. J*. **2013**, *19*, 15856-15860.

(g) Singhal, R.; Mishra, A.; Nagpal, A. K.; Mathur, G. N. *J. Polym. Mater.* **2009**, *26*, 239-250.

(h) Yamada, S.; Mrozek, T.; Rager, T.; Owens, J.; Rangel, J.; Wilson, C. G.; Byers, J. *Macromolecules* **2004**, *37(2)*, 377-384.

(i) Gao, F.; Schricker, S. R.; Tong, Y.; Culbertson, B. M. *Polym. Mater. Sci. Eng.* **2002**, *86*, 247-248.

(j) Gao, F.; Schricker, S. R.; Tong, Y.; Culbertson, B. M. *J. Macromol. Sci. Pure Appl. Chem.* **2002**, *A39*, 267-286.

(k) Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu J.; Cacchio, T. *Tetrahedron Lett*. **2000**, *41*, 5647-5651.

(l) Sano, S.; Ushirogochi, H.; Morimoto, K.; Tamai, S.; Nagao, Y. *Chem. Commun*. **1996**, 1775-1776. and references cited therein.

2. Niwayama, S. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 983-994.
3. Niwayama, S. *J. Org. Chem*. **2000**, *65*, 5834-5836.
4. Niwayama, S. *Tetrahedron Lett*. **2000**, *41*, 10163-10166.
5. Niwayama, S.; Wang, H.; Hiraga, Y.; Clayton, J. C. *Tetrahedron Lett*. **2007**, *48*, 8508-8510.
6. Niwayama, S.; Cho, H.; Zabet-Moghaddam, M.; Whittlesey, B. R. *J. Org. Chem.* **2010**, *75*, 3775-3780.
7. Niwayama, S.; Rimkus, A. *Bull. Chem. Soc. Jpn*. **2005**, *78*, 498-500.
8. Niwayama, S.; Cho, H.; Lin, C. *Tetrahedron Lett*. **2008**, *49*, 4434-4436.
9. Niwayama, S.; Cho, H. *Chem. Pharm. Bull.* **2009**, *57*, 508-510.
10. For example, (a) Mason, T. J. *Chem. Soc. Rev*. **1997**, *26*, 443-451.

    (b)Yim, B.; Yoo, Y.; Nagata, Y.; Maeda, Y. *Chem. Lett.* **2001**, 938-939.

    (c) Vidal, M.; Garcia-Arriagada, M; Rezende, M. C.; Dominguez, M. *Synthesis*, **2016,** *48*, 4246-4252.

    (d) Qin, B.; Schneider, U. *J. Am. Chem. Soc*. **2016**, *138*, 13119-13122.

    (e) Jaita, S.; Phakhodee, W.; Pattarawarapam, M. *Synlett* **2015**, *26*, 2006-2008.

    (f) Soengas, R. G.; Silva, A. M. S. *Synlett* **2012**, *23*, 873-876.
11. Shi, J.; Niwayama, S. *Tetrahedron Lett*. **2018**, *59*, 799-802.

12. Huntress, E. H.; Lesslie, T. H.; Bornstein, J. *Org. Syn.* **1963**, *Coll. Vol. 4*, 329-330.

13. For example, (a) Iida, T.; Mori, H.; Mochizuki, T.; Mori, Y. H. *Chem. Eng. Sci.* **2001**, *56*, 4747-4758; (b) Makino, T.; Sugahara, T.; Ohgaki, K. *J. Chem. Eng. Data* **2005**, *50*, 2058-2060; (c) Gao, S.; Chapman, W. G.; House, W. *Ind. Eng. Chem. Res*. **2005**, *44*, 7373-7379.

14. For example, (a) Thum, S.; Kokornaczyk, A. K.; Seki, T.; Maria, M. D.; Zacarias, N. V. O.; de Vrues, H.; Weiss, C.; Koch, M; Schepmann, D.; Kitamura, M.; Tschammer, N.; Heitman, L. H.; Junker, A. Münsch, B. *Eur. J. Med. Chem*. **2017**, *135*, 401-413.

(b) Kuduk, S. D.; Skudlarek, J. W.; DiMarco, C. N.; Bruno, J. G.; Pausch, M. H.; O'Brien, J. A.; Cabalu, T. D.; Stevens, J.; Brunner, J.; Tannenbraum, P. L. Garson, S. L.; Savitz, A. T.; Harrell, C. M.; Cotter, A. L.; Winrow, C. J.; Renger, J. J.; Coleman, P. J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2488-2492.

(c) Aguilar, N.; Moyano, A.; Petricas, M. A.; Riera, A. *J. Org. Chem*. **1998**, *63*, 3560-3567.

(d) Shao, C.; Lu, A.; Wang, X.; Zhou, B.; Guan, X.; Zhang, Y. *Org. Biomol. Chem*. **2017**, *15*, 5033-5040.

(e) Raposo, M. M. M.; Sampaio, A. M. B. A.; Kirsch, G. *J. Heterocylic Chem*. **2005**, *42*, 1245-1251.

(f) Hradil, P.; Melnicky, R.; Grepl, M.; Koristek, K.; Hlavac, J.; Bertolasi, V. *Heterocycles*, **2006**, *68*, 1845-1859.

(g) Yang, D.; Ding, S.; Huang, J.; Zhao, K. *Chem. Commun*. **2013**, *49*, 1211-1213.

(h) Moy, T. M.; DePorter, C. D.; McGrath, J. E. *Polymer* **1993**, *34*, 819-24.

(i) Hu, L.; Wang, D.; Chen, X.; Yu, L.; Yu, Y.; Tan, Z.; Zhu, G. *Org. Biomol. Chem*. **2017**, *15*, 5674-5679.

(j) Del, B. M.; Ancillotti, C.; Checchini, L.; Fibbi, D.; Rossini, D.; Ciofi, L.; Rivoira, L.; Profeti, C.; Orlandini, S.; Furlanetto, S. *J. Pharm. Biomed. Anal*. **2018**, *148*, 6-16.

15. For example, (a) Meng, Q.-Y.; Wang, S.; König, B. *Angew. Chem. Int. Ed*. **2017**, *56*, 13426-13430.

(b) Ebert, G. W.; Juda, W. L.; Kosakowski, R. H.; Ma, B.; Dong, L.; Cummings, K. E.; Phelps, M. V. B.; Mostafa, A. E.; Luo, J. *J. Org. Chem*. **2005**, *70*, 4314-4317.

(c) Rekha, V. V.; Ramani, M. V.; Ratnamala, A.; Rupakalpana, V.; Subbaraju, G. V.; Satyanarayana, C.; Rao, C. S. *Org. Process. Rev. Dev*. **2009**, *13*, 769-773.

(d) Sabitha, G.; Srividya, R.; Yadav, J. S. *Tetrahedron*, **1999**, *55*, 4015-4018.

(e) Jiang, D.; Wang, Y. Y.; Xu, Y. N.; Dai, L. Y. *J. Chem. Res*. **2009**, *3*, 167-169.

(f) Udayakumar, S.; Pandurangan, A.; Sinha, P. K. *J. Mol. Catal. A: Chem*. **2005**, *240* 139-154.

(g) Yadav, G. D.; Rahuman, M. S. M. M. *Org. Process. Rev. Dev*. **2002**, *6*, 706-713.

(h) Dubey, P. K.; Mohiuddin, S. M. G.; Ramesh, D. *Asian J. Chem*. **1997**, *9*, 379-387.

(i) Ogawa, H.; Ichimura, Y.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 2481-2483.

(j) Kim, S. S.; Mah, Y. J.; Lee, H. J.; Park, S. K. *J. Photosci*. **2003**, *10*, 241-243.

16. We also tried other kinds of polar-aprotic solvents such as dioxane, DMF, pyridine, and DME as a co-solvent, but all these co-solvents turned out to be inferior to DMSO. For example, in the selective monohydrolysis of diisopropyl ester **3**, under the same conditions as run 12 in Table 3, yields of the half-ester, **3a**, were 39%(dioxane), 23%(DMF), 42%(pyridine), and 32%(DME) respectively after 3.5-hour reaction time.

17. Metz P. *Tetrahedron* **1989**, *45*, 7311-7316.

18. Mislow, K.; O'Brien, R. E.; Schaefer, H. *J. Am. Chem. Soc*. **1962**, *84*, 1940-1944.

19. https://www.chemicalbook.com/ChemicalProductProperty_US_CB1899322.aspx

20. Consden, R.; Duveen, D. I.; Kenyon, J. *J. Chem. Soc*. **1938**, 2104-2106.

- Practical selective monohydrolysis of symmetric diesters without a special device
- Highly efficient reactions starting from only readily available inexpensive reagents
- Production of costly half-esters under simple conditions from inexpensive starting diesters