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Practical Selective Monohydrolysis of Bulky Symmetric Diesters

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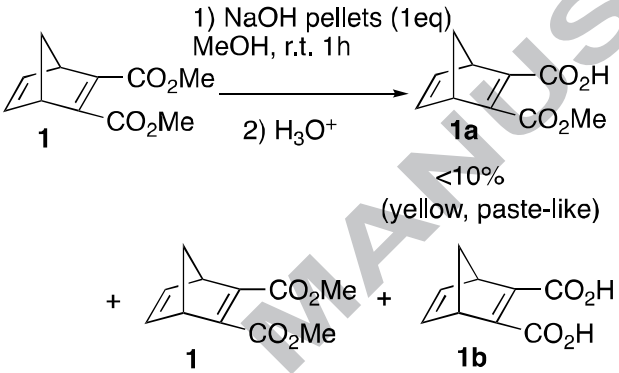
Abstract: The highly efficient selective monohydrolsis reaction we previously reported has been applied to monohydrolysis of several bulkyl symmetric diesters, including diethyl esters, dipropyl esters, and dibutyl esters. A greater proportion of a polar aprotic co-solvent, DMSO, and aqueous KOH appear to help improve the reactivity of bulky diesters compared to the corresponding dimethyl esters. The procedure is mild and practical, yielding the corresponding half-esters in high yields under simple conditions.

Key Words: hydrolysis, symmetric diester, half-ester, solvent effect, cost-effective synthesis

Half-esters are among the most important building blocks for organic synthesis of a variety of compounds including natural products, drugs, polymers, and dendrimers.[1] Most typically, they are prepared by monohydrolysis of symmetric diesters. However, the classical monosaponification of symmetric diesters tends to produce complex mixtures consisting of starting diesters, half-esters, and diacids in which both the ester groups are hydrolyzed, and a

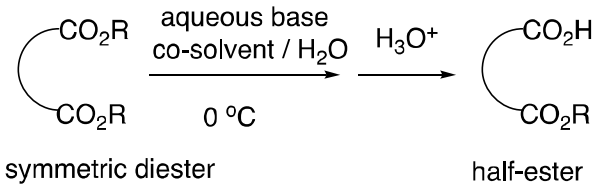
small percentage of the corresponding half-esters, typically as yellowish material. For example, in our experiments, monosaponification of dimethyl bicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylate, **1**, resulted in a complex mixture, and less than 10% of the half-ester was obtained as a yellowish paste-like solid (Scheme 1).[2] Enzymatic monohydrolysis of symmetric diesters requires random screening, as it provides no basis for prediction of the reactivity.

Scheme 1. Classical monosaponification of a symmetric diester



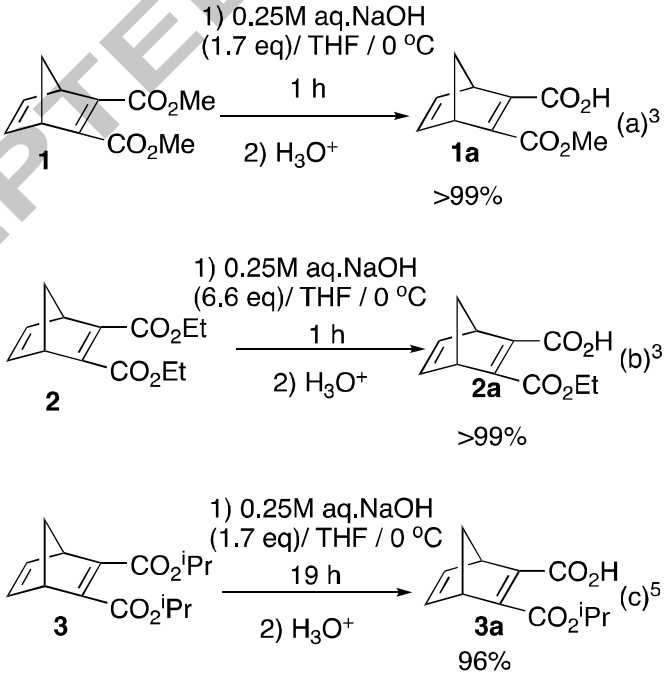
Earlier, we reported highly efficient selective monohydrolysis of symmetric diesters.[3] This reaction selectively monohydrolyzes a series of symmetric diesters under mild and practical conditions with high yields. The reaction mixtures are clean, and only the half-esters, and diacids as well as the starting diesters, if they exist, are observable, unlike the monosaponification reactions. In many cases, the yields are near quantitative (Scheme 2).

Scheme 2. Selective monohydrolysis of symmetric diesters



However, when the starting diesters have relatively bulky ester groups, the reactions sometimes require an extended period of time or greater amounts of a base for completion of the reactions within a shorter reaction time. The amount of base and the reaction time tend to increase as the bulkiness of the ester group increases depending on the starting diesters.[4] For example, while the dimethyl ester, **1**, is monohydrolyzed in about one hour with about 2 equivalents of a base, monohydrolysis of the corresponding diethyl ester, **2**, needs about three to four times the equivalent of the base or a longer reaction time,[3] and the same monohydrolysis of diisopropyl ester, **3**, requires about 19 hours (Scheme 3).[5]

Scheme 3. Examples of selective monohydrolysis



This trend is consistent with our observation reported before that the monohydrolysis occurs at the interface between the aqueous face and the diester, hence reflecting the reduced contact of the more hydrophobic ester groups with the aqueous phase. The drawback in this trend is occasional decrease of the yields of half-esters due to the prolonged reaction time. A long reaction time while maintaining 0 °C may also be difficult. Therefore, here we attempted to improve the selectivity of monohydrolysis of bulky symmetric diesters.

We initially applied ultrasound in order to accelerate the reaction rate,[6] because ultrasound-assisted reactions are known to enhance rates of many two-phase reactions.[7] However, ultrasound-assisted conditions did not improve the selectivity or reactivity of the diisopropyl ester, **3**. At the best result, the half-ester was obtained only in 60% yield with the use of 6 equivalents of aqueous KOH after 3 hours with recovery of 12% of the starting diester, **3**.[6]

We next tried to adjust reaction conditions without a special device. According to our hypothesis, once one of the two ester groups is monohydrolyzed, the intermediary monocarboxylates form micellar aggregates in which the remaining hydrophobic portions point inside and the hydrophilic carboxylate groups point outside, prohibiting further hydrolysis and keeping the remaining ester group intact. Consistent with this hypothesis, we observed that a water–miscible polar aprotic co-solvent such as THF and CH_3CN increases the reaction rate and selectivity while a protic co-solvent such as an alcohol decreases the selectivity, perhaps by dissociating the micellar aggregates.[8] We also previously reported that use of DMSO improved *exo*-selectivity of various dialkyl bicycle[2.2.1]heptane-2,3-carboxylates by accelerating the monohydrolysis of the sterically less hindered *exo*-ester groups.[9,10]

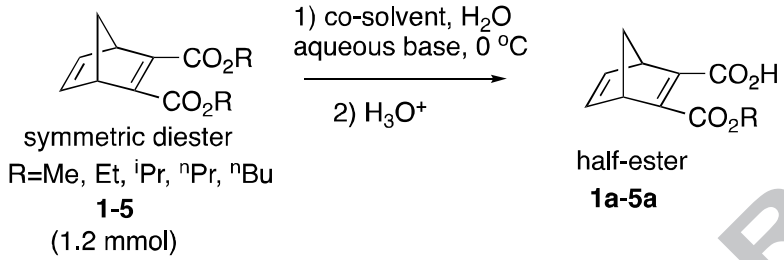
Furthermore, we found that KOH often improves selectivity and reactivity compared to NaOH, which is perhaps due to stronger affinity of K^+ with carbonyl oxygen, leading to the

enhanced electrophilic character of the starting ester group.[11] We reported that aqueous KOH improved selectivity in various diesters including dialkyl malonates.[11-13]

Here we report various selective monohydrolysis of symmetric bulky diesters by tuning the reaction conditions based on our previous findings and mechanistic hypothesis.

We first screened the selective monohydrolysis of dialkyl bicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylates.[14] All these diesters were synthesized in high yields by simple Diels-Alder reactions of cyclopentadiene and the corresponding dialkyl acetylenedicarboxylates.[15] The results are summarized in Table 1.

Table 1. Selective monohydrolysis of dialkyl bicycle[2.2.1]hept-2,5-diene-2,3-dicarboxylates



Run	R	co-solvent	co-solvent (v/v): H_2O (mL)	aqueous base	reaction time	yield (%)
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**: iPr	THF	22 mL (73%) : 4 mL	0.5 M KOH 4 mL	12h	71
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	**4**: nPr	THF	22 mL (73%) : 4 mL	0.5 M KOH 4 mL	12h	78
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	**5**: nBu	THF	32 mL (84%) : 2 mL	0.5 M KOH 4 mL	18h	63
17		DMSO	32 mL (84%) : 2 mL	0.5 M KOH 4 mL	6h	84

As for the dimethyl ester, **1**, the reaction is known to proceed quite efficiently regardless of the kinds of base or co-solvent.[3,8,11] Therefore, in all the cases, the reaction produced near-quantitative yields of the corresponding half-ester, **1a**, although we noticed, judging from the reaction time, that DMSO and KOH somewhat enhanced the reaction rate, which is consistent with our previous observation. The volume percentage of the co-solvent is the same as what we reported before (7%), which was found to be optimal for this dimethyl ester, **1**.

The diethyl ester, **2**, required about 3-4 times as much base in the conditions we reported before.[3] However, the selectivities increased as the amount of THF increased even with the use of 1.7 equivalents of the base. The maximal conditions appear to exist when the volume percentage of THF is between 13% and 67%. The aqueous KOH also appears to be better than aqueous NaOH, as reported previously. However, DMSO improved the selectivity rather significantly, and the best and comparable results to the dimethyl ester, **1**, were obtained when 44-67% of DMSO and aqueous KOH were used. These conditions worked out for the diipropyl ester, **3**, and di-n-propyl ester, **4**, but the better results were obtained when the greater amount of DMSO was used. Therefore, it appears that use of a larger amount of DMSO help improve the selectivity as the bulkiness increases. A greater proportion of THF or DMSO was applied for monohydrolysis of di-n-butyl ester, **5**, and the effect of DMSO became clearer for this monohydrolysis. The reaction times have also been shortened significantly even with the use of 1.7 equivalents of the base, while we sometimes needed more than a day for selective monohydrolysis of some dipropyl esters with the conditions reported previously.[3,12]

It appears that the maximal volume percentage of the co-solvent tends to increase as the size of the ester group increases, which is also consistent with the smaller optimal amount of co-solvents for the less bulky dimethyl ester, **1**, as mentioned above. This greater proportion of polar aprotic co-solvent is likely to help increase the contact of the hydrophobic ester groups and

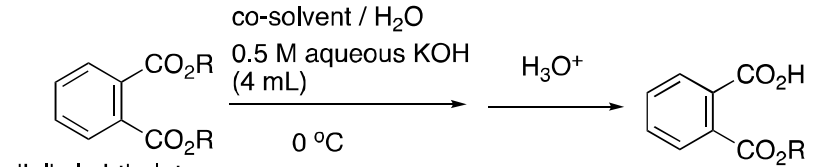
the aqueous face, increasing the chance for the hydrolysis of one of the two ester groups. The co-solvent may also help protect the potential micellar aggregates formed from the intermediary carboxylates of bulky half-esters described above, and thereby prohibiting further hydrolysis. The unsuccessful results with the ultrasound-assisted conditions mentioned above may also be attributed to potential dissociation of the aggregates by sonication.

From a technical point of view, use of a larger proportion of THF also sometimes formed hydrates, hampering the stirring of the reaction mixture, which was not the case with DMSO. Although DMSO is less volatile than THF or CH_3CN and may take a longer time to completely evaporate, the product half-esters all show high purities.

Applying the proportions that turned out to be the best in each reaction above, we next tried selective monohydrolysis of several bulky dialkyl phthalates. The starting symmetric diesters, dialkyl phthalates, are all readily available inexpensively. The product half-esters, monoalkyl phthalates, exhibit widespread applications to various industrial products such as plasticizers and adhesives, as well as to synthesis of a variety of pharmaceuticals and polymers,[16,17] but they are rather costly. Therefore, methods for their cost-effective production have been actively investigated.[18]

The results are summarized in Table 2. Again, the effect of DMSO is more prominent. The yields of the corresponding half-esters are significantly higher with DMSO than with THF. Although only about 1.7 equivalents of the base were used for each run, the reaction time was significantly shorter than with THF. Here again, the maximal percentages of the co-solvent tend to increase as the bulkiness of the ester groups increases. The increased volume percentages of the co-solvent also appear to help enhance the contact between the hydrophobic ester groups and the aqueous phase.

Table 2. Selective monohydrolysis of dialkyl phthalates



dialkyl phthalate
(1.2 mmol)
R=Me, Et, ^{i}Pr, ^{n}Pr, ^{i}Bu, ^{n}Bu
6-12

monoalkyl phthalate
(half-ester)
6a-12a

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

a: The conditions we previously reported were applied with 0.25M NaOH (8 mL).[2,5]

In summary, we found that a larger proportion of a water-miscible polar aprotic co-solvent, DMSO, and aqueous KOH helps accelerate the selective monohydrolysis reaction of several bulky symmetric diesters, and consequently enhances the selectivity, producing the

corresponding half-esters in high yields. We found that 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, and/or greater amounts of an aqueous base when the reactivity is low.[19] The conditions reported here are practical without requiring expensive reagents or equipment and consistent with our mechanistic hypothesis and previous observations. All the half-esters here show excellent purities and stability over a period of time.[20]

Acknowledgements:

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17. The experimental procedures are as follows: 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 is 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.

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19. It is recommended that the maximal amount of the co-solvent be adjusted depending on the starting diesters.

20. The structures of all the half-esters reported here were determined by ^{1}H NMR, ^{13}C NMR, and elemental analysis or HRMS. The spectral data are as follows:

Half-ester **1a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) = 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, $CDCl_3$) = 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). 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, 141.878, 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, $CDCl_3$) = 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, $CDCl_3$) =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. ^{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 **5a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) = 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, $CDCl_3$) = 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 **6a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) = 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, $CDCl_3$) = 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) HRMS Calcd for $C_9H_9O_4$ $(M+H)^+$: 181.0500. Found: 181.0507.

Half-ester **7a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) = 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, $CDCl_3$) = 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 **8a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) = 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, $CDCl_3$) = 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) HRMS Calcd for $C_{11}H_{13}O_4$ $(M+H)^+$: 209.0813. Found: 209.0805.

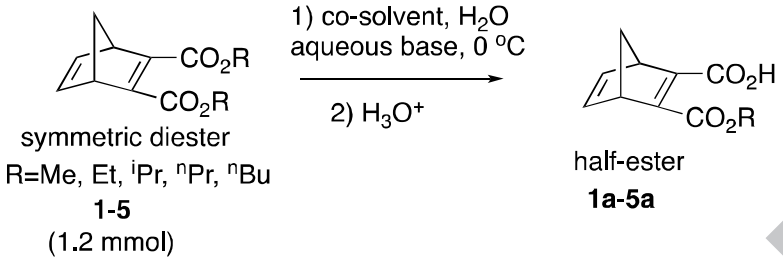
Half-ester **9a**. Oil. ^{1}H NMR (500 MHz, $CDCl_3$) = 1.00 (3H, t, *J* = 7.5 Hz), 1.77 (2H, m), 4.29 (2H, t, *J* = 7.0 Hz), 7.59 (2H, m), 7.71 (1H, d, *J* = 7.0 Hz), 7.91 (1H, d, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) = 10.55, 21.87, 67.73, 128.87, 129.89, 130.08, 130.89,

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 **10a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) = 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, $CDCl_3$) = 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). 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 **11a**. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) = 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, $CDCl_3$) = 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) HRMS Calcd for $C_{12}H_{15}O_4$ $(M+H)^+$: 223.0970. Found: 223.0965.

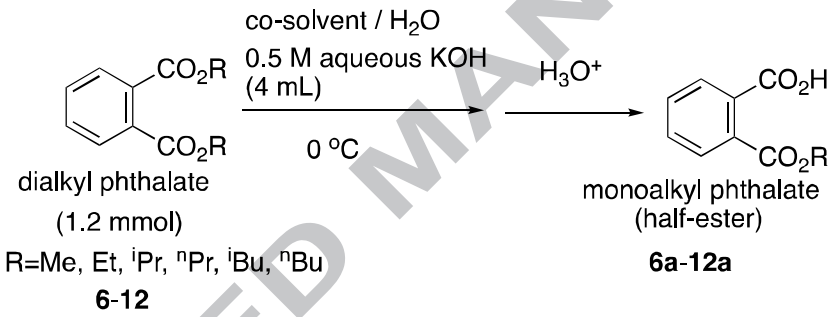
Table 1. Selective monohydrolysis of dialkyl bicycle[2.2.1]hept-2,5-diene-2,3-dicarboxylates



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

17	DMSO	32 mL (84%): 2mL	0.5 M KOH 4 mL	6h	84

Table 2. Selective monohydrolysis of dialkyl phthalates

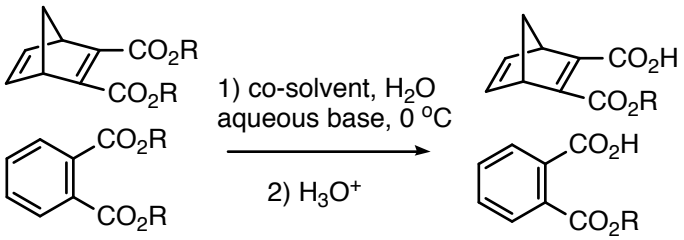


Run	R	co-solvent	co-solvent (v/v):H_2O (mL)	reaction time	yield (%)
1	**6**: Me	THF	2 mL (7%): 20 mL	2h	88 [a]
2		DMSO	2 mL (8%): 20 mL	40 min	94
3	**7**: Et	THF	24 mL (67%): 8mL	8h	66
4		DMSO	24 mL (67%): 8mL	2h	93
5	**8**: ^{i}Pr	THF	22 mL (73%): 4mL	14h	46
6		DMSO	22 mL (73%): 4mL	4h	81

7	**9**: ^{n}Pr	THF	22 mL (73%): 4mL	14h	55
8		DMSO	22 mL (73%): 4mL	3h 30min	85
9	**10**:^{i}Bu	THF	32 mL (84%): 2mL	18h	34
10		DMSO	32 mL (84%): 2mL	10h	77
11	**11**:^{n}Bu	THF	32 mL (84%): 2mL	18h	40
12		DMSO	32 mL (84%): 2mL	8h	81

a: The conditions we previously reported were applied with 0.25M NaOH (8 mL)[3,6]

- Practical reactions for selective monohydrolysis of symmetric diesters
- Highly versatile reactions requiring only readily accessible inexpensive reagents
- Efficient production of costly bulky half-esters without a special device



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