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Remote Exo/Endo Selectivity in Selective Monohydrolysis of Dialkyl Bicyclo[2.2.1]heptane-2,3-dicarboxylate Derivatives

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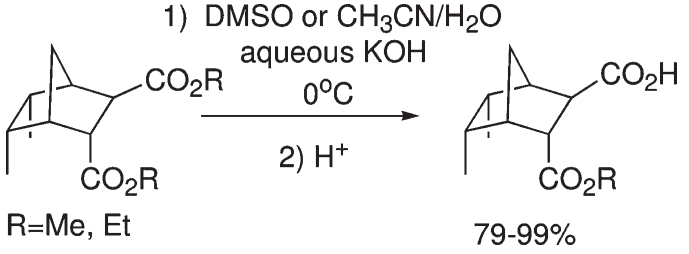

High exo-facial selectivity was observed in the selective monohydrolysis of a series of near-symmetric diesters that possess an exo-ester group and an endo-ester group attached on a norbornane or norbornene skeleton. The selectivities were found to be clear-cut, although the reaction center in these reactions is one covalent bond distant from the norbornane or norbornene ring, where the difference of the environment between the exo face and endo face is therefore expected to be negligible. The effect of the co-solvent we studied earlier for the selective monohydrolysis reaction was also confirmed and contributed to improvement of the yields of the half-esters.

Introduction

It has been well documented that norbornene, norbornadiene, or norbornanone systems in general show high exo-facial selectivity in the electrophilic, nucleophilic, or cyclic additions. Many research groups have reported extensive studies to explain the exo-facial selectivity from theoretical and experimental points of view. These explanations include steric effects due to the fact that the ethano bridge is larger than the methano bridge,[1] a torsional effect that is relieved by exo attack but increased by endo attack in the transition state,[2] pyramidalization of the sp^2 carbons toward the endo directions leading to the favored attack on the convex face of the pyramidalized sp^2 carbons,[3] and nonequivalent orbital extension caused by the mixing of σ orbitals and π orbitals, inducing higher exo reactivity.[4] Since norbornene, norbornadiene, or norbornanone and their derivatives are versatile synthetic building blocks for further skeletal conversions, the high exo selectivity has been applied to development of a variety of useful stereospecific or stereoselective reactions in organic synthesis such as epoxidation and hydroboration.

However, for the sp^2 carbons that are one covalent bond away from the norbornane skeleton, such exo/endo-facial selectivities are not systematically studied, because the differences of the reported steric effects are anticipated to be too small, and the torsional effects considered within the norbornane ring are not expected. Electrophilic additions to 2-methylenenornornene are still known to show the predominant exo selectivity due to the fact that C2 carbon is part of the norbornane ring. The Diels−Alder reactions toward isodicyclopentadiene, showing the bottom-face selectivity with a variety of dienophiles, are interesting exceptions in which the new bond forms on the sp^2 carbons next to

[§] The author to whom correspondence regarding X-ray crystallographic analysis should be directed.

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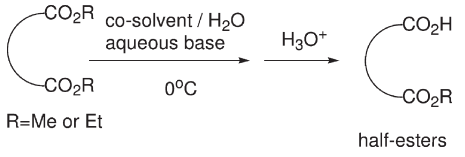
the C2 and C3 sp^2 carbons of the norbornane ring.[5] For these reactions, as the olefinic ends are still within the strained norbornane ring, the selectivity is explained by the out-of-plane bending of groups at C2 and C3 on the ring, although it appears that the steric bulkiness of the dienophile also affects the selectivity.[6] Therefore, the only studies reported as remote exo/endo-facial selectivity away from the norbornane or norbornene ring were enzyme reactions, for which the mechanisms of selectivity are not understood.[7]

To this end, we previously observed unusually prominent exo-facial selectivity on the sp^2 carbons that are one covalent bond distant from the norbornene ring in the selective monohydrolysis reactions we reported earlier.[8] We attempted selective monohydrolysis of (exo, exo), (endo, endo), and (exo, endo)-dimethyl and diethyl esters attached to the norbornene skeleton and observed enhanced reactivity on hydrolysis of the exo esters in all cases, perhaps due to the mild reaction conditions. Here we report the fuller details of this unusually prominent exo-facial selectivity observed during the selective monohydrolysis.

Earlier, we reported the highly selective monohydrolysis of symmetric diesters that monohydrolyzes a series of symmetric diesters with high selectivity and reactivity, yielding half-esters in a racemic form (Scheme 1).[9] This reaction is particularly powerful when it is necessary to hydrolyze only one of the two identical ester groups. However, we find that this reaction can recognize subtle steric differences and can also selectively hydrolyze one of the two ester groups in near-symmetrical diesters, and therefore, this reaction can selectively monohydrolyze the ester group of the exo position in *exo*,*endo*-dimethyl- and -diethylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxylates, **1a** and **1b** (Scheme 1).[8]

SCHEME 1. Selective Monohydrolysis of Symmetric Diesters



Initially, we applied THF as a co-solvent, 10 times the volume of water, and aqueous NaOH solution for the selective monohydrolysis reaction. This practical reaction was found to monohydrolyze all the diesters thus far tried, forming a clean reaction mixture leading to straightforward purification unlike the classical saponification. Later, we reported additional studies on solvent effects, types of base, and steric effects and found conditions that improve the selectivity and reactivity. For example, polar aprotic solvents are in general appropriate for an accelerated reaction rate and higher selectivity, while protic solvents are not as effective.[10] KOH is often more effective than NaOH as a base, perhaps due to the enhanced electropositive character of the countercation, while LiOH tends to be inferior to NaOH.[11]

Our current hypothesis for the high selectivity for monohydrolysis of only one of the two ester groups is that once one of the ester groups is monohydrolyzed, in water the intermediary monocarboxylate will form aggregates in which the remaining hydrophobic portions point inside and the hydrophilic CO_2^- groups point outside, thus prohibiting further hydrolysis. The solvent effects we have observed thus far are consistent with this hypothesis.

The selectivity was initially observed to be especially high when the two ester groups possess the stereochemistry of "*cis*". We explained the potential reasons based on the electrostatic attractive interaction due to the two closely located carbonyl groups before formation of the potential aggregate above.[9,12] However, applying the conditions we found later based on the information obtained from these basic studies, we have also been successful in selectively monohydrolyzing linear diesters[13] or those with "*trans*" stereochemistry as in this study.

Results and Discussion

We first tried selective monohydrolysis of *exo*,*endo*-dimethyl- and -diethylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxylates, **1a** and **1b**, both of which we reported earlier, in order to improve the reaction conditions. We first changed the type of base (Table 1) for dimethyl ester **1a** and found that all bases predominantly produced half-ester **2a** in which the *exo*-carbomethoxy group was monohydrolyzed. The product ratios of **2a** and **3a** and **2b** and **3b** were determined from the relative intensities of the integral curves of the methyl or ethyl signal in the reaction mixture of the ^{1}H NMR spectra. The structures of half-esters were determined from the ^{1}H NMR and ^{13}C NMR data we reported. Among these bases, KOH produced the highest yields (97%). This enhanced reactivity by KOH is also consistent with the results we reported earlier.[11,13] The amount of the base was also slightly reduced because of the stereochemistry of the starting diester, which appears to have helped improve the yield for this particular diester. Therefore, for selective monohydrolysis of the corresponding diethyl ester, **1b**, only this KOH was applied. Since it was anticipated that the hydrolysis of diethyl ester would require more time than the corresponding dimethyl ester due to the increased hydrophobicity, the co-solvent was changed to acetonitrile from THF according to our previous study about solvent effects.[10] As a result, the yield of the half-ester also significantly improved to 96% in 7.5 h, while we found that the use of 1.7 equiv of base is preferable to 1.2 equiv. These ratios for exo-carboxylic acid and endo-carboxylic acid are comparable to those we reported earlier,[8] while the yields improved significantly, without production of the corresponding diacid despite the fact that the stereochemistry of these diesters is "*trans*".

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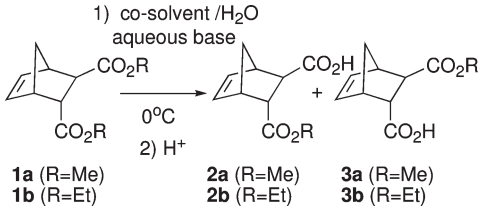
TABLE 1. Selective Monohydrolysis of 1a and 1b



run	diester	cosolvent	base	base (equiv)	time (h)	yield[a] (%)	ratio (**2**:**3**)
1	**1a**	THF	LiOH	1.2	1	77 (22)	82:18
2	**1a**	THF	NaOH	1.2	1	93 (4)	80:20
3	**1a**	THF	KOH	1.2	1	97 (2)	82:18
4	**1a**	THF	CsOH	1.2	1	87 (11)	80:20
5	**1b**	THF	KOH	1.7	7	91 (2)	87:13
6	**1b**	CH_3CN	KOH	1.7	7.5	96 (0)	87:13
7	**1b**	CH_3CN	KOH	1.2	6	65 (34)	86:14

[a]Isolated yield of the half-ester. The recovered diester is shown in parentheses (%).

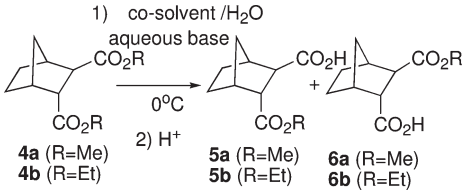
Since the reaction center is not on the norbornene ring, we hypothesize that this remote exo-facial selectivity was induced by the difference of the steric bulkiness of the methano bridge and the etheno bridge on the C5−C6 carbons. Therefore, for close assessment of the exo/endo-facial selectivity on this carbon, selective monohydrolysis reactions were applied to structural variants of the C5−C6 positions.

Diesters **4a** and **4b** were synthesized by hydrogenation of diesters **1a** and **1b**, respectively. The selective monohydrolyses of these diesters were conducted, and the results are summarized in Table 2.

From these results, this exo-selectivity was found to be more prominent when selective monohydrolysis was conducted with diesters **4a** and **4b**, in which the double bond in **1a** and **1b** is hydrogenated to introduce two additional hydrogens on the C5−C6 positions. The exo selectivities are increased by more than 10% for both diesters **4a** and **4b**. Interestingly, the extent of the enhancement is comparable to that observed in the addition of ethyl bromoacetate to 2-norbornenone (90% exo) versus 2-norbornanone (100% exo) in the Reformatsky reaction,[14] even though in our selective monohydrolysis, the nucleophile, OH^-, is far smaller than ethyl bromoacetate and thus may appear less influenced by the steric environment, especially in this remote position. It is also noteworthy that sodium borohydride reduction of the carbonyl of 2-norbornenone and 2-norbornanone showed slightly enhanced exo-selectivity in the reduction of 2-norbornenone (95% exo) than of 2-norbornanone (86% exo). The reasons are perhaps due to the enhanced ring strain by introduction of the olefinic bond within the ring and the small size of the nucleophile, H^- in this case,[15] although the extent of the enhancement of the selectivity is again comparable to our results in **4a** and **4b**.

The structures of these half-esters, **5a**, **6a**, **5b**, and **6b**, were determined by the matching of ^1H and ^{13}C NMR data of the authentic **5a**, **6a**, **5b**, and **6b**, synthesized by hydrogenation of the purified major and minor half-esters **2a**, **3a**, **2b**, and **3b** above. For monohydrolysis of diethyl ester **4b**, the solvent

TABLE 2. Selective Monohydrolysis of 4a and 4b



run	diester	cosolvent	base	base (equiv)	time	yield[a] (%)	ratio (**5**:**6**)
1	**4a**	THF	LiOH	1.7	2.5 h	96 (4)	97:3
2	**4a**	THF	NaOH	1.7	2 h	>99	91:9
3	**4a**	THF	KOH	1.7	2 h	>99	95:5
4	**4a**	THF	CsOH	1.7	2 h	>99	92:8
5	**4b**	CH_3CN	KOH	2.0	12 h	73 (17)	96:4
6	**4b**	DMSO	KOH	1.7	11 h	91 (0)	97:3

[a]Isolated yield of the half-ester. The recovered diesteris shown in parentheses (%).

effect we studied earlier again contributed to the increase in reactivity, as DMSO is a polar aprotic solvent, and improved the yield of this selective monohydrolysis of **4b** (run 6).[9b,10]

From these results, it was obvious that the most responsible factor that governs these remote exo-facial selectivities is the enhanced steric hindrance by the C5−C6 bridges compared to the C7 bridge. Therefore, it was assumed that further modification of the C5−C6 bridge would lead to more exclusive selectivity. We next examined diesters **7a** and **7b**, in which the exo positions of the C5−C6 positions are blocked by bulkier 1,2-*O*-isopropylidene. These diesters were synthesized by osmium-catalyzed dihydroxylation of **1a** and **1b** and subsequent protection of the formed diols as acetonides.[16] The selective monohydrolysis was conducted on these diesters with the use of aqueous KOH. The results are summarized in Table 3.

The ratios for half-esters **8**/**9** are 98:2 for both methyl and ethyl esters, due to the enhanced steric hindrance on the exo direction of the C5−C6 bond, showing higher exo-facial selectivity than monohydrolysis of **4a** or **4b**. We also examined the effects of the co-solvent and again found that the polar aprotic solvents, CH_3CN and DMSO, in particular DMSO, improved the yield (run 3). Therefore, only DMSO was applied for selective monohydrolysis of diethyl ester **7b**, which led to high yields of the half-esters (run 4).

Next, we examined the steric effect of the endo positions of the C5−C6 bond, as we expected that blocking the endo position would most effectively lead to the high exo selectivity. We synthesized *endo*,*endo*-dimethyl-substituted diesters **10a** and **10b** by the Diels−Alder reaction of 2,3-dimethylcyclopentadiene prepared *in situ*[17] with dimethyl fumarate and subsequent hydrogenation. The selective monohydrolyses of both of these dimethyl and diethyl esters were conducted with the use of aqueous KOH, and the results are shown in Table 4.

As can shown in Table 4, even though the methyl groups are far smaller than the *O*-isopropylidene, only the ester groups on the exo position were hydrolyzed exclusively for both dimethyl and diethyl esters, demonstrating the importance of the steric effects toward the endo directions.

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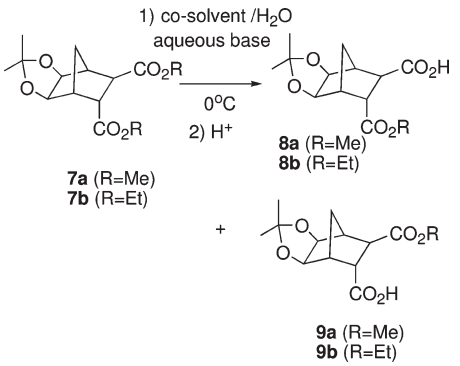
TABLE 3. Selective Monohydrolysis of 7a and 7b



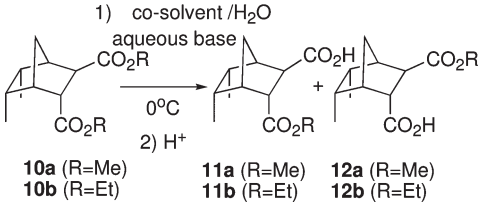
run	diester	cosolvent	base	equivalent of base	time (h)	yield[a] (%)	ratio (**8**:**9**)
1	**7a**	THF	KOH	1.7	3	83 (5)	98:2
2	**7a**	CH_3CN	KOH	1.7	3	87 (4)	98:2
3	**7a**	DMSO	KOH	1.7	3	89 (3)	98:2
4	**7b**	DMSO	KOH	1.7	6	92 (3)	98:2

[a]Isolated yield of the half-ester. The recovered diester is shown in parentheses (%).

The structure was confirmed by X-ray crystal analysis of the half-ester **11a**. Therefore, we conclude that the most critical factor appears to be the steric effect that blocked approach of the nucleophile OH^- from the endo direction on the C5−C6 bridge.

The results in Table 4 also demonstrate effects of the cosolvents, indicating that polar aprotic solvents improve the reactivity. DMSO was the most efficient solvent in these reactions as well. In particular, the yield of the half-ester for the methyl ester, **11a**, was near-quantitative (runs 2 and 3).

TABLE 4. Selective Monohydrolysis of 10a and 10b



run	diester	cosolvent	base	equivalent of base	time	yield[a] (%)	ratio (**11**:**12**)
1	**10a**	THF	KOH	1.7	9 h	63 (26)	100:0
2	**10a**	CH_3CN	KOH	1.7	9 h	99	100:0
3	**10a**	DMSO	KOH	1.7	8 h	49	100:0
4	**10b**	DMSO	KOH	1.7	1 d	79 (18)	100:0
5	**10b**	DMSO	KOH	2.5	2 d	79 (16)	100:0

[a]Isolated yield of the half-ester. The recovered diester is shown in parentheses (%).

There have been very few systematic studies reported about the effects of substituents on C5 and/or C6 positions of norbornene or norbornanone on the exo/endo-facial selectivities, perhaps because the effects of substituents on such positions have been perceived as too remote even for the reactions that occur on the norbornene or norbornanone ring, and the reported selectivities are rather complicated. Studies about addition of Br_2 to several 5,6-disubstituted norbornenes are among those examples.[18] The initial bromonium cation is expected to form on the exo position, but the second bromide ion may attack either from the endo or exo face, forming *trans*- or *cis*-dibromide, respectively. Interestingly, it appears that the selectivity toward formation of the *cis*-dibromide/*trans*-dibromide from *cis*-*exo*,*exo*-5,6-dicyanonorbornene in acetic acid is not necessarily high (11% *cis*, 89% *trans*). Bromination of *trans*-5,6-dichloro- or -dicyanonorbornene is reported to form a considerable extent of the *trans* dibromide depending on the reaction conditions (33−100%), even though these functional groups are not as bulky as *O*-isopropylidene. Although the *cis*-*endo*,*endo*-5,6-dichloro- or -dicyanonorbornenes appear to retard the reaction rate of bromination more than the corresponding *trans*- or *cis*-*exo*,*exo*-5,6-dichloro- or -dicyanonorbornene, the order of reaction rate for epoxidation on the same norbornene derivatives appears to be the opposite, while that for addition of diazomethane was the same.[19] Therefore, our reaction demonstrates unique examples for distinguishing the exo and endo selectivity by the C5 and C6 functional groups in a clear-cut manner.

Conclusions

In summary, while the exo-/endo-facial selectivities are perceived as negligible for the carbons that are one covalent bond distant from the norbornane ring, we have demonstrated that such carbons can be successfully distinguished by our selective monohydrolysis reaction with high exo-facial selectivity. We have shown that the selectivity is controllable in a predictable manner based on the steric effect on the C5−C6 ethano bridge. In particular, introduction of the smallest alkyl groups, methyl groups, on the endo positions of the C5−C6 bonds leads to the exclusive exo selectivity.

To our knowledge, these results are the first examples of systematic studies for remote exo-facial selectivities that occur one covalent bond away from the norbornyl system. Since norbornyl systems with various endo and exo functional groups are often applied to synthesis of polymers with different physical properties,[20] our new finding is expected to expand the scope of exo/endo-facial selectivity observed in the norbornyl systems with the use of this selective monohydrolysis reaction, in particular on dimethyl and diethyl esters.

In addition, it has become more apparent that a polar aprotic cosolvent significantly improves the reactivity and selectivity of the selective monohydrolysis of diesters, confirming results of our previous studies about the influence of cosolvents in the monohydrolyses of other diesters. This solvent effect is expected to improve yields of half-esters by selective monohydrolysis of other diesters.

Experimental Section

General Methods. The melting points are uncorrected. ^1H NMR at 300 MHz and ^{13}C NMR at 75 MHz spectra were

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measured as solutions in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. The IR spectra were recorded on an FTIR instrument.

General Procedures for Selective Monohydrolysis. A diester (1.2 mmol) was dissolved in 2 mL of a co-solvent, and 20 mL of water was added. The reaction mixture was cooled to 0 °C in an ice−water bath. To this mixture was added dropwise with stirring 0.25 M KOH aqueous solution in the amount indicated in Tables 1−4 (1.2, 1.7, 2.0, or 2.5 equiv). The reaction mixture was stirred until the consumption of the starting diester was observed by TLC, acidified with 1 M HCl at 0 °C, saturated with NaCl, extracted with ethyl acetate (×4), and dried over sodium sulfate. This extract was concentrated in vacuo and purified by silica gel column chromatography. The product ratios of the two diastereomeric half-esters were determined from the relative intensities of the integral curves of the methyl or ethyl protons or protons attached on C2 in the reaction mixture of ^{1}H NMR spectra.

The separation of the two half-esters was performed by a combination of HPLC and preparative TLC for **2a** and **3a**, **2b** and **3b**, **8a** and **9a**, and **8b** and **9b**. The authentic samples for **5a**, **6a**, **5b**, and **6b** were prepared by hydrogenation of **2a**, **3a**, **2b**, and **3b**, respectively.

***endo*-3-Methoxycarbonylbicyclo[2.2.1]hept-2-ene-2-*exo*-carboxylic acid (2a):** white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (1H, dq, J = 1.6, 8.9 Hz), 1.60 (1H, br. d, J = 8.9 Hz), 2.71 (1H, dd, J = 1.5, 4.7 Hz), 3.19 (1H, m), 3.26 (1H, m), 3.36 (1H, t, J = 4.0 Hz), 3.64 (3H, s), 6.07 (1H, dd, J = 2.8, 5.7 Hz), 6.28 (1H, dd, J = 3.2, 5.6 Hz), 11.41 (1H, br); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 45.6, 47.1, 47.4, 47.6, 47.8, 51.9, 135.3, 137.5, 173.6, 178.8; IR (neat, cm^{-1}) 1696, 1724, 2950−3000; mp 121−122 °C (lit.[8] mp 121−122 °C); HRMS calcd for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0813, found 197.0817.

***exo*-3-Methoxycarbonylbicyclo[2.2.1]hept-2-ene-*endo*-2-carboxylic acid (3a):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.45 (1H, dq, J = 1.6, 8.9 Hz), 1.60 (1H, br. d, J = 8.9 Hz), 2.64 (1H, dd, J = 1.6, 4.4 Hz), 3.12 (1H, m), 3.28 (1H, m), 3.41 (1H, t, J = 4.0 Hz), 3.71 (3H, s), 6.12 (1H, dd, J = 2.9, 5.6 Hz), 6.28 (1H, dd, J = 3.2, 5.6 Hz), 10.44 (1H, br); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 45.6, 47.0, 47.4, 47.6, 47.7, 52.2, 135.1, 137.8, 174.7, 177.9; IR (neat, cm^{-1}) 1696, 1724, 2950−3000; HRMS calcd for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0813, found 197.0820.

***endo*-3-Methoxycarbonylbicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (5a):** white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.60−1.22 (6H, m), 2.62 (2H, t, J = 1.5 Hz), 2.85 (1H, d, J = 5.4 Hz), 3.17 (1H, t, J = 4.5 Hz), 3.69 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 24.2, 28.8, 38.2, 40.2, 41.7, 48.4, 49.4, 51.9, 173.8, 178.8; IR (neat, cm^{-1}) 1693, 1704, 2880−3550; mp 81−82 °C; HRMS calcd for $C_{10}H_{14}O_4Na$ $[M + Na]^+$ 221.0790, found 221.0801.

***exo*-3-Methoxycarbonylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (6a):** white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.61−1.23 (6H, m), 2.57 (1H, t, J = 3.6 Hz), 2.67 (1H, s), 2.76 (1H, d, J = 5.1 Hz), 3.25 (1H, t, J = 4.5 Hz), 3.67 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 24.2, 28.8, 38.2, 40.1, 41.6, 48.4, 49.1, 52.1, 175.0, 177.4; IR (neat, cm^{-1}) 1698, 1720, 2880−3500; mp 79 °C; HRMS calcd for $C_{10}H_{14}O_4Na$ $[M + Na]^+$ 221.0790, found 221.0780.

***endo*-3-Methoxycarbonyl-*exo*,*exo*-5,6-isopropylidenedioxybicyclo[2.2.1]heptane-*exo*-2-carboxylic acid (8a):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.26 (3H, s), 1.36 (1H, d, J = 11.1 Hz), 1.42 (3H, s), 1.80 (1H, d, J = 11.1 Hz), 2.65 (2H, s), 2.70 (1H, d, J = 4.5 Hz), 3.19 (1H, t, J = 5.1 Hz), 3.71 (3H, s), 4.01 (1H, d, J = 5.1 Hz), 4.15 (1H, d, J = 5.1 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 24.1, 25.3, 31.5, 43.4, 43.4, 45.0, 45.1, 52.3, 78.2, 80.9, 109.6, 172.7, 177.2; IR (neat, cm^{-1}) 1700, 1733, 2937−3389; HRMS calcd for $C_{13}H_{18}O_6Na$ $[M + Na]^+$ 293.1001, found 293.1003.

***exo*-3-Methoxycarbonyl-*exo*,*exo*-5,6-isopropylidenedioxybicyclo[2.2.1]heptane-*endo*-2-carboxylic acid (9a):** colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26 (3H, s), 1.36 (1H, d, J = 11.1 Hz), 1.42 (3H, s), 1.80 (1H, d, J = 11.1 Hz), 2.59 (2H, s), 2.70 (1H, d, J = 4.5 Hz), 3.26 (1H, t, J = 5.1 Hz), 3.70 (3H, s), 4.01 (1H, d, J = 5.1 Hz), 4.13 (1H, d J = 5.1 Hz), 7.82 (1H, br); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 24.1, 25.3, 29.7, 43.4, 43.4, 44.9, 45.2, 52.4, 78.3, 80.9, 109.8, 173.9, 177.7.

***endo*-3-Methoxycarbonyl-*endo*,*endo*-5,6-dimethylbicyclo[2.2.1]heptane-*exo*-2-carboxylic acid (11a):** white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.73 (3H, d, J = 7.5 Hz), 0.93 (3H, d, J = 6.9 Hz), 1.42 (1H, dd, J = 9.9 Hz, 1.5 Hz), 1.53 (1H, dt, J = 9.9 Hz, 1.8 Hz), 2.13 (2H, m), 2.46 (1H, d, J = 2.4 Hz), 2.62 (1H, m), 3.11 (1H, m), 3.22 (1H, dd, J = 6.6 Hz, 1.5 Hz), 3.65 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 11.2, 11.8, 34.8, 35.0, 39.7, 40.6, 46.5, 47.0, 48.6, 51.6, 174.5, 181.3; IR (neat, cm^{-1}) 1704, 1714, 2850−3400; mp 75−76 °C. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.74; H, 7.58.

Crystal data for **11a**: space group $P\bar{1}$, No. 2; a = 6.9411(8) Å, b = 9.2660(11) Å, c = 10.4142(12) Å, α = 98.810(1)°, β = 101.150(1)°, γ = 109.229(1)°, V = 603.26(12) Å^3, Z = 2, M = 226.26 for $C_{12}H_{18}O_4$, density (calcd) = 1.246 g cm^{-3}, T = 293(2) K, μ = 0.093 mm^{-1} for Mo Kα radiation (λ = 0.71073 Å, fine-focus sealed tube). Measured reflections = 6879, unique reflections = 2643 (merging R for equivalents = 0.0161), unique reflections with $I > 2\sigma(I)$ = 2058. Final R factors (all data, 150 parameters refined): R = 0.0636, R_w = 0.1544. For $I > 2\sigma(I)$: R = 0.0504, R_w = 0.1428, Gof = 1.056.

***endo*-3-Ethoxycarbonylbicyclo[2.2.1]hept-2-ene-2-*exo*-carboxylic acid (2b):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.21 (3H, t, J = 7.0 Hz), 1.46 (1H, dd, J = 1.6, 8.9 Hz), 1.60 (1H, br d, J = 8.9 Hz), 2.71 (1H, dd, J = 1.5, 4.5 Hz), 3.18 (1H, m), 3.26 (1H, m), 3.40 (1H, t, J = 4.0 Hz), 4.08 (2H, m), 6.06 (1H, dd, J = 2.8, 5.7 Hz), 6.28 (1H, dd, J = 3.2, 5.6 Hz), 11.0 (1H, br); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 14.2, 45.6, 47.1, 47.4, 47.7, 47.9, 60.7, 135.2, 137.5, 173.1, 180.0; IR (neat, cm^{-1}) 1704, 1732, 2950−3000; HRMS calcd for $C_{11}H_{15}O_4$ $[M + H]^+$ 211.0970, found 211.0961.

***exo*-3-Ethoxycarbonylbicyclo[2.2.1]hept-2-ene-*endo*-2-carboxylic acid (3b):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.26 (3H, t, J = 7.0 Hz), 1.47 (1H, dd, J = 1.6, 8.7 Hz), 1.61 (1H, br d, J = 8.7 Hz), 2.63 (1H, dd, J = 1.6, 4.4 Hz), 3.12 (1H, m), 3.28 (1H, m), 3.43 (1H, t, J = 4.0 Hz), 4.16 (2H, q, J = 7.1 Hz), 6.12 (1H, dd, J = 2.9, 5.6 Hz), 6.28 (1H, dd, J = 3.2, 5.6 Hz), 11.0 (1H, br); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 14.2, 45.6, 47.2, 47.4, 47.6, 47.7, 61.0, 135.1, 137.8, 174.2, 177.5; IR (neat, cm^{-1}) 1704, 1732, 2950−3000; HRMS calcd for $C_{11}H_{15}O_4$ $[M + H]^+$ 211.0970, found 211.0960.

***endo*-3-Ethoxycarbonylbicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (5b):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.60−1.23 (9H, m), 2.62 (2H, t, J = 1.5 Hz), 2.86 (1H, d, J = 5.1 Hz), 3.15 (1H, t, J = 0.9 Hz), 4.15 (2H, q, J = 7.2 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 14.3, 24.1, 28.8, 38.2, 40.2, 41.6, 48.3, 49.4, 60.7, 173.4, 178.7; IR (neat, cm^{-1}) 1695, 1730, 2880−3400; HRMS calcd for $C_{11}H_{16}O_4Na$ $[M + Na]^+$ 235.0946, found 235.0935.

***exo*-3-Ethoxycarbonylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (6b):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.60−1.23 (9H, m), 2.56 (1H, d, J = 4.8 Hz), 2.67(1H, m), 2.74 (1H, d, J = 5.1 Hz), 3.26 (1H, t, J = 0.9 Hz), 4.12 (2H, q, J = 7.2 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 14.2, 24.2, 28.9, 38.1, 40.2, 41.8, 48.7, 48.9, 60.8, 174.5, 177.3; IR (neat, cm^{-1}): 1695, 1730, 2880−3400; HRMS calcd for $C_{11}H_{17}O_4$ $[M + H]^+$ 213.1126, found 213.1130.

***endo*-3-Ethoxycarbonyl-*exo*,*exo*-5,6-isopropylidenedioxybicyclo[2.2.1]heptane-*exo*-2-carboxylic acid (8b):** white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.29−1.24 (6H, m), 1.35 (1H, d, J = 11.1 Hz), 1.42 (3H, s), 1.81 (1H, d, J = 11.1 Hz), 2.65 (2H, s), 2.71 (1H, d, J = 0.9 Hz), 3.17 (1H, t, J = 5.1 Hz), 4.02 (1H, d, J = 5.4 Hz), 4.19−4.12 (3H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 14.2, 24.1, 25.3, 31.5, 43.4, 43.4, 45.1, 45.3, 61.2, 78.2, 80.9, 109.5, 172.2, 178.5; IR (neat, cm^{-1}) 1720, 1730, 2935−3473; mp 64−66 °C; HRMS calcd for $C_{14}H_{20}O_6Na$ $[M + Na]^+$ 307.1158, found 307.1143.

***exo*-3-Ethoxycarbonyl-*exo*,*exo*-5,6-isopropylidenedioxybicyclo-[2.2.1]heptane-*endo*-2-carboxylic acid (9b):** white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.29−1.24 (6H, m), 1.35 (1H, m, J = 11.1 Hz), 1.42 (3H, s), 1.81 (1H, d, J = 11.1 Hz), 2.65 (2H, s), 2.71 (1H, d, J = 0.9 Hz), 3.26 (1H, t, J = 5.1 Hz), 4.02 (1H, d, J = 5.4 Hz), 4.19−4.12 (3H, m).

***endo*-3-Ethoxycarbonyl-*endo*,*endo*-5,6-dimethylbicyclo[2.2.1]-heptane-*exo*-2-carboxylic acid (11b):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.75 (3H, d, J = 7.5 Hz), 0.93 (3H, d, J = 6.9 Hz), 1.27 (3H, m), 1.42 (1H, dd, J = 9.9, 1.5 Hz), 1.53 (1H, dt, J = 9.9, 1.8 Hz), 2.13 (2H, m), 2.45 (1H, d, J = 2.4 Hz), 2.63 (1H, s), 3.11 (1H, m), 3.12 (1H, dd, J = 6.6, 1.5 Hz), 4.12 (2H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 11.2, 12.0, 14.0, 35.0, 35.1, 39.7, 40.5, 46.5, 47.4, 48.6, 60.6, 174.1, 180.9; IR (neat, cm^{-1}) 1705, 1715, 2932−3400; mp 75−76 °C. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.24; H, 8.49.

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Supporting Information Available: Crystal structure of compound **11a** (CIF). The synthetic procedure for diesters **1a**, **1b**, **4a**, **4b**, **7a**, **7b**, **10a**, and **10b**, and the NMR spectra for the new compounds. They are available free of charge via the Internet at http://pubs.acs.org.