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New *exo*/*endo* selectivity observed in monohydrolysis of dialkyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylates

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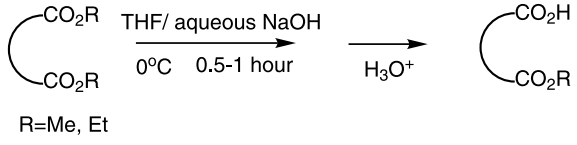
Abstract—New monohydrolysis reactions of several *exo* or *endo* dimethyl or diethyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylates showed higher selectivity toward monohydrolyses of *exo*-carboalkoxy groups, although the reaction centers are located away from the norbornene rings.

The *exo*/*endo* facial selectivities of electrophilic or nucleophilic additions as well as cyclic additions to norbornene or 2-norbornanone derivatives have been extensively studied for several decades both experimentally and theoretically.[1] The general *exo* selectivities observed during these reactions have been explained, for example, by torsional effects and/or stereoelectronic effects based on the distorted sp^2-trigonal centers of the olefin or the carbonyl group on the C_2 and/or C_3 positions within the uniquely strained bicyclic structure.

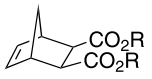
However, with respect to the reactions that occur on the sp^2 carbons attached to these C_2 or C_3 positions, examples for *exo*/*endo* facial selectivities are quite rare, since the characteristic trigonal distortions are no longer expected due to the distance from the strained norbornene ring. The stereochemical effects from methano and ethano bridges are also expected to be negligible. Only a few examples have been reported in enzymatic hydrolysis reactions, where the mechanisms are not understood.[2] The bottom-face preference in Diels–Alder cycloadditions toward isodicyclopentadiene may be an intriguing example where the new carbon–carbon bond formations occur at the olefinic carbons that are next to the norbornane ring,[3] although the other olefinic ends are still on the strained bicyclic ring.

Here we report unexpectedly high *exo*-facial selectivities observed during monohydrolysis reactions of several *exo* and/or *endo* dialkyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylates.

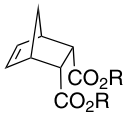
Earlier, Niwayama reported a highly efficient selective monohydrolysis of a series of symmetric diesters applying THF and aqueous NaOH solution at 0°C. In contrast to classical saponification, this reaction is quite clean and produces the corresponding half-esters in near-quantitative to modestly high yields for a series of symmetric diesters (Scheme 1).[4]



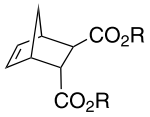
Scheme 1.



1a: R=CH_3
1b: R=CH_2CH_3



2a: R=CH_3
2b: R=CH_2CH_3



3a: R=CH_3
3b: R=CH_2CH_3

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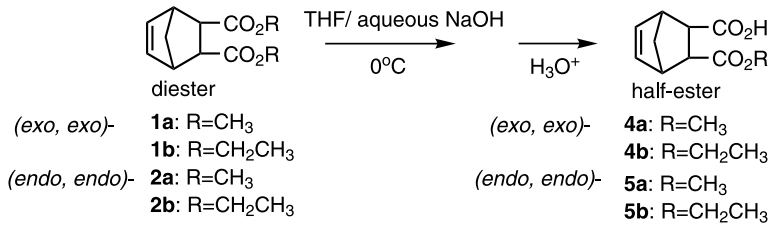
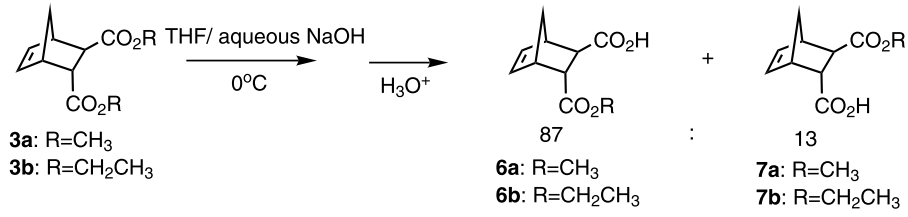
Table 1.



Starting diester	Reaction time (h)	Yield (%) of half-ester	Recovered diester (%)
1a	1	**4a** 31.7	**1a** 61.9
2a	1	**5a** 21.2	**2a** 76.9
1a	5	**4a** 88.4	**1a** 8.7
2a	24	**5a** 93.7	**2a** 4.7
1b	24	**4b** 51.7	**1b** 40.1
2b	24	**5b** 53.7	**2b** 45.5
1b	72	**4b** 83.8	**1b** 2.9
2b	72	**5b** 82.9	**2b** 8.3

Table 2.



Starting diester	Reaction time (h)	Yield (%) of half-ester	Ratio of **6**:**7**	Recovered diester (%)
3a	0.5	**6a**+**7a** 81.6	87:13	**3a** 9.5
3b	6	**6b**+**7b** 69.2	87:13	**3b** 9.8

We applied this reaction to monohydrolyses of a series of dimethyl and diethyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylates **1a**,**b**–**3a**,**b** which possess two carbomethoxy or carboethoxy groups in (*exo*, *exo*)-, (*endo*, *endo*)-, or (*exo*, *endo*)-positions. All of these diesters were readily obtained in high yields by following reported procedures.[5]

Table 1 summarizes the results of monohydrolyses of the *cis*-diesters, **1a**,**b** and **2a**,**b**, applying the same conditions Niwayama reported earlier.[4] All the reactions were repeated at least two times and therefore the results were reproducible.

As can be seen from Table 1, the monohydrolysis successfully desymmetrized all the symmetric dimethyl and diethyl esters for both (*exo*, *exo*)- and (*endo*, *endo*)-stereochemistries,[6] although reactivities of these diesters appeared to be lower and monohydrolyses of these diesters required a longer time than those reported earlier, probably due to the low solubility of these diesters in the reaction mixture.[7] Under the reaction conditions, no changes in the stereochemistry of the compounds were observed in any of the reactions. The somewhat lower reactivities observed for diethyl esters than for dimethyl esters are consistent with our earlier observation, due to the lower solubility of the diethyl esters in the reaction mixture caused by the higher hydrophobicity.[4,8]

Interestingly, when the reactivities between *endo* and *exo* ester groups are compared applying the same equivalent of aqueous NaOH solution, judging from the reaction times and conversions, the (*exo*, *exo*)-diesters showed higher reactivities than the corresponding (*endo*, *endo*)-diesters, despite the fact that the reaction center is located next to the norbornene ring rather than within the ring. This tendency appears to be especially prominent for dimethyl esters, **1a** and **2a**.[9] In order to confirm this stereoselectivity, we pitted an *exo* carboalkoxy group against an *endo* carboalkoxy group in the same molecule as in **3a** and **3b**, and these two diesters were monohydrolyzed under the same conditions (Table 2).

As expected from the above results, the *exo* ester groups in both **3a** and **3b** predominantly produced half-esters where the *exo* carboalkoxy group was monohydrolyzed (**6a** and **6b**). The product ratios of **6a** and **7a** as well as **6b** and **7b** were determined to be 87:13 in both cases from the relative intensities of the integral

curves of the methyl or ethyl signals in the ^{1}H NMR spectra. The structures of half-esters, **6a**, **6b**, **7a**, and **7b** were determined based on ^{1}H-^{1}H COSY and HMBC analyses as well as differential NOE experiments, after separation and purification of these half-esters.[10] In particular, the ^{1}H NMR and ^{13}C NMR data of half-esters, **6b** and **7b**, were found to be identical to those reported.[11] These diesters, **3a** and **3b** showed higher reactivity than *exo*-*cis* diesters, **1a** and **1b**, probably due to the less crowded *trans* stereochemistry.

From these data, we safely conclude that the characteristic *exo*-facial selectivity applies to the carbonyl carbons that are attached on the norbornene skeleton in our new monohydrolysis of a series of *exo*- and/or *endo* norbornene diesters, despite the fact that the reaction sites are one covalent bond from the norbornene ring. To our knowledge, among non-enzymatic reactions, these reactions are the first examples of such unique *exo* selectivities.

Acknowledgements

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3. For example, see: (a) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328–334; (b) Kobuke, Y.; Sugimoto, T.; Furukawa, J. *J. Org. Chem.* **1976**, *41*, 1457–1459; (c) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *107*, 1971–1978.
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6. The spectral data for these products are as follows:
Half-ester (**4a**); colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (2H, m), 3.62 (3H, s), 3.08 (2H, m), 2.61 (2H, m), 2.06 (1H, br.d, $J=9.2$), 1.47 (1H, br.d, $J=9.2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.8, 173.8, 138.0. 137.9, 51.8, 47.4, 47.3, 45.7, 45.4, 45.3; IR (neat, cm^{-1}): 1707, 1735, 2950–3000; HRMS(EI) calcd for $C_{10}H_{12}O_4$: 196.0736, found 196.0736.
Half-ester (**5a**); white solid (mp 71–72°C), ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (1H, dd, $J=3.0$. 5.5), 6.17 (1H, dd, $J=3.0$, 5.5), 3.55 (3H, s), 3.29 (1H, dd, $J=3.2$, 10.3), 3.25 (1H, dd, $J=3.2$, 10.3), 3.15 (1H, m), 3.12 (1H, m), 1.45 (1H, br.d, $J=8.7$), 1.30 (1H, br.d, $J=8.7$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 172.8, 135.5. 134.3, 51.4, 48.7, 48.2, 48.0, 46.5, 46.0; IR (neat, cm^{-1}): 1711, 1739, 2950–3000; HRMS(EI) calcd for $C_{10}H_{12}O_4$: 196.0736, found 196.0735.
Half-ester (**4b**); colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (2H, m), 4.09 (2H, q, $J=7.1$), 3.09 (2H, m), 2.61 (2H, m), 2.09 (1H, br.d, $J=9.2$), 1.47 (1H, br.d, $J=9.2$), 1.21 (3H, t, $J=7.1$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.1, 173.3, 138.1, 137.9, 60.8, 47.5, 47.2, 45.8, 45.5, 45.4, 14.0; IR (neat, cm^{-1}): 1708, 1735, 2950–3000; HRMS(EI) calcd for $C_{11}H_{14}O_4$: 210.0892, found 210.0891.
Half-ester (**5b**); colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (1H, dd, $J=3.0$, 5.5), 6.20 (1H, dd, $J=3.0$, 5.5), 4.03 (2H, m), 3.30 (1H, dd, $J=3.2$, 10.3), 3.25 (1H, dd, $J=3.2$, 10.3), 3.16 (1H, m), 3.14 (1H, m), 1.46 (1H, br.d, $J=8.7$), 1.31 (br. d, $J=8.7$), 1.19 (3H, t, $J=7.1$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 172.3, 135.4. 134.4, 60.4, 48.7, 48.5, 48.0, 46.6, 46.2, 14.0; IR (neat, cm^{-1}): 1711, 1737, 2950–3000; HRMS(EI) calcd for $C_{11}H_{14}O_4$: 210.0892, found 210.0892.
7. Formation of a small amount of dicarboxylic acids was occasionally observed due to this prolonged reaction time.
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9. The somewhat smaller difference in the yields for monohydrolyses of **1b** and **2b** than those of **1a** and **2a** may be attributed to the differences in their solubilities in this reaction mixture.
10. The spectral data for these products are as follows:
Half-ester (**6a**); white solid (mp 121–122°C), ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (1H, dd, $J=3.2$, 5.5), 6.07 (1H, dd, $J=2.8$, 5.5), 3.64 (3H, s), 3.36 (1H, dd, $J=3.7$, 4.6), 3.26 (1H, m), 3.19 (1H, m), 2.71 (1H, dd, $J=1.6$, 4.6), 1.60 (1H, br.d, $J=8.9$), 1.47 (1H, dq, $J=1.6$, 8.9); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.0, 173.6, 137.5. 135.3, 51.9, 47.8, 47.6, 47.4, 47.1, 45.6; IR (neat, cm^{-1}): 1696, 1724, 2950–3000; HRMS(EI) calcd for $C_{10}H_{12}O_4$: 196.0736, found 196.0735.
Half-ester (**7a**); colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (1H, dd, $J=3.2$, 5.5), 6.12 (1H, dd, $J=2.8$, 5.5), 3.71 (3H, s), 3.41 (1H, dd, $J=3.7$, 4.6), 3.28 (1H, m), 3.13 (1H, m), 2.64 (1H, dd, $J=1.6$, 4.6), 1.59 (1H, br.d, $J=8.7$), 1.47 (1H, dq, $J=1.6$, 8.7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 174.7, 137.8. 135.2, 52.2, 47.6, 47.6, 47.5, 47.1, 45.6; IR (neat, cm^{-1}): 1696, 1724, 2950–3000; HRMS(EI) calcd for $C_{10}H_{12}O_4$: 196.0736, found 196.0735.
Half-ester (**6b**); colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (1H, dd, $J=3.2$, 5.5), 6.06 (1H, dd, $J=2.6$, 5.5), 4.08 (2H, m), 3.34 (1H, dd, $J=3.7$, 4.6), 3.25 (1H, m), 3.18 (1H, m), 2.71 (1H, dd, $J=1.6$, 4.6), 1.60 (1H, br.d, $J=8.9$), 1.46 (1H, dd, $J=1.6$, 8.9), 1.22 (3H, t, $J=7.1$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.0, 173.1, 137.5. 135.2, 60.7, 47.9, 47.7, 47.3, 47.2, 45.7, 14.2; IR (neat, cm^{-1}): 1704, 1732, 2950–3000; HRMS(EI) calcd for $C_{11}H_{14}O_4$: 210.0892, found 210.0892.

Half-ester (**7b**); colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (1H, dd, $J=3.2$, 5.5), 6.11 (1H, dd, $J=2.8$, 5.5), 4.15 (2H, q, $J=7.1$), 3.42 (1H, dd, $J=3.7$, 4.6), 3.3 (1H, m), 3.1 (1H, m), 2.62 (1H, dd, $J=1.6$, 4.6), 1.59 (1H, br.d, $J=8.7$), 1.45 (1H, dq, $J=1.6$, 8.7), 1.25 (3H, t, $J=7.1$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 174.2, 137.8, 135.2, 61.0, 47.7, 47.6, 47.4, 47.3, 45.6, 14.2; IR (neat, cm^{-1}): 1704, 1732, 2950-3000; HRMS(EI) calcd for $C_{11}H_{14}O_4$: 210.0892, found 210.0892.

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