Regio- and Stereoselectivity of Water Elimination as a Function of Ring Size

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The elimination of water from tertiary alcohols was studied for carbocycles of ring size 5−16. The resulting olefins **3**−**5** were discriminated by NMR spectroscopy. The relative amount of their formation reflects the steric idiosyncrasies of the respective ring systems. The behavior of the medium-sized rings yielded experimental proof to the I-strain concept.

Introduction

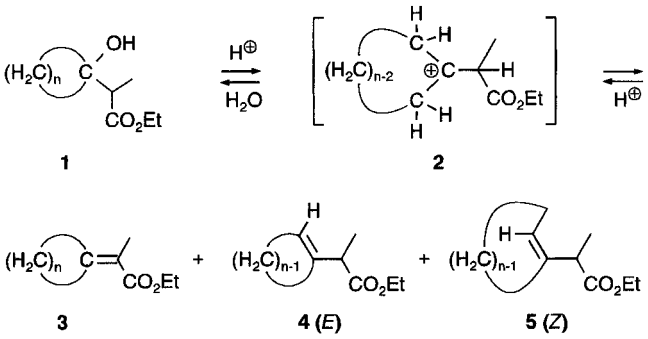
We recently developed a new class of potent cyclooxygenase and lipoxygenase inhibitors[1] as potential dual-action antirheumatics.[2] Their preparation involved the synthesis of a homologous series of monosubstituted cycloalkenes **3**−**5** from the tertiary alcohols **1** (Scheme 1). We herein report the influence of ring size on the position and stereochemistry of the double bond in **3**−**5**. This is the first study on elimination regioselectivity covering normal, medium, and large rings.

Results and Discussion

Mechanism of the Reaction and Product Stabilities. The elimination of water from the cycloalkanols **1** was performed in refluxing toluene in a Dean−Stark apparatus, adding a catalytic amount of 4-toluenesulfonic acid. The reaction was run under identical conditions for all ring systems investigated (amount of substrate, time, etc.). After a short workup (see Experimental Section), the raw product was isolated in a yield of approximately 90% and examined by ^{1}H and ^{13}C NMR spectroscopy.

Following the literature,[3] we assume that the reaction proceeds by an E1 mechanism. Consequently, the abstraction of a proton from the intermediate carbenium ion **2** will determine which of the regioisomers **3**−**5** will be formed. Statistics would predict a 4:1 ratio in favor of the endocyclic isomers, but in such cases the direction the new double bond takes is determined almost entirely by the relative stabilities of the possible olefins.[4] The following factors influence the relative stabilities of the cycloalkenes **3**−**5**. In the semicyclic[5] isomers **3**, the double bond has gone to the most highly substituted carbon according to Zaitsev's rule, and it is also in conjugation with the ester carbonyl group. These advantages are counterbalanced, for some ring sizes, by steric interactions of the methyl and ester groups with the ring methylene groups attached to the ring sp^2 carbon, as can be visualized by models. The endocyclic olefins **4** and **5** lack the advantages **3** has, but with some ring systems (vide infra), the positioning of *two* sp^2 centers *within* the ring reduces steric interactions. As expected, the formation of the *trans*[6] olefins **5** was not observed up to a ring size of eight.

Scheme 1. Preparation of the Homologous Monosubstituted Cycloalkenes 3−5 from the Tertiary Alcohols 1 (*n* = 4−15)



Assignment of NMR signals. The discrimination of the isomeric olefins **3**−**5** rests on the following data. Only the endocyclic alkenes **4** and **5** have a proton attached to an sp^2 center, giving rise to a triplet at approximately 5.1 ppm. The assignment of these signals to **4** or **5** by the increment method[7] was not possible since the chemical shift difference was small, preventing a decision. However, the presence or absence of one or two olefinic proton resonances showed the formation of **4** and **5**.

The identification of **3** was straightforwardly possible by ^{13}C NMR. Due to the conjugation of double bond and ester group, the carbonyl and α-carbon atoms were shifted to high field (to approximately 170 and 120 ppm) and the *β*-carbon to low field (to approximately 150 ppm) as compared to **4** and **5** with isolated double bonds.

According to the literature on ^{13}C NMR spectroscopy,[8] sp^2 centers of cis-configured alkenes usually show a small high field shift as compared to their trans isomers. In the cycloalkenes studied by us, we did not find this trend, but one of the sp^2 signals of one of the isomers was at higher and the other signal at lower field than the signals

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(1) Greve, B.; Imming, P.; Laufer, S. *Angew. Chem.* **1996**, *108*, 1312−1314 (*Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1221−1223).

(2) Laufer, S. A.; Augustin, J.; Dannhardt, G.; Kiefer, W. *J. Med. Chem.* **1994**, *37*, 1894−1897.

(3) Knözinger, H. In *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; Interscience Publishers: New York, 1971; pp 641−718.

(4) (a) Hückel, W.; Hanack, M. *Angew. Chem.* **1967**, *79*, 555−565 (*Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 534−544). (b) March, J. *Advanced Organic Chemistry*; Wiley: New York, 1992; p 998.

(5) We use the term "semicyclic" to denote a double bond shared by a ring and an exocyclic atom, as distinguished from a fully "exocyclic" double bond.

(6) We use the more familiar cis/trans nomenclature to designate the stereochemistry of the (unsubstituted) rings themselves. Trans corresponds to *Z* with our 1-substituted cycloalkenes.

(7) Friedrich, E. C.; Runkle, K. G. *J. Chem. Educ.* **1984**, *61*, 830−831.

(8) Kalinowsky, H.-O.; Berger, S.; Braun, S. *^{13}C NMR-Spektroskopie*, Thieme: Stuttgart, 1984; pp 118−119.

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Table 1. Amount of Isomers as a Function of Ring size

ring size	semi (**3**)	endo *E* (**4**)	endo *Z* (**5**)
5	34	66	0
6	0	100	0
7	20	80	0
8	8	92	0
9	2	96	2
10	0	100	0
11	1	89	10
12	1	86	13
13	4	68	28
14*	15	60	25
15	28	54	18
16	7	73	20

* Data for cyclotetradecenyl system not determined experimentally, but calculated by extrapolation.

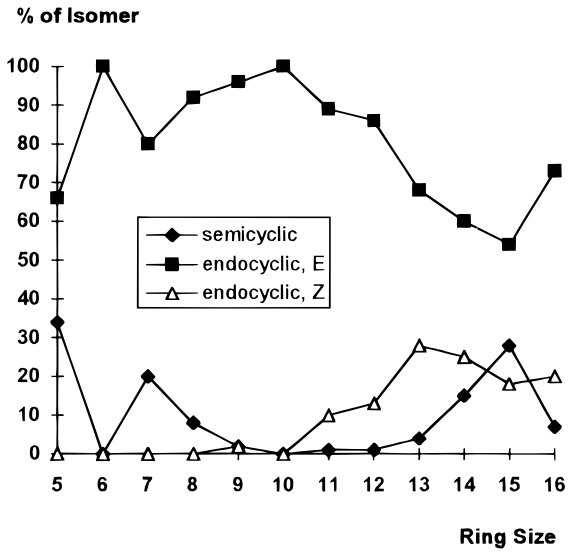
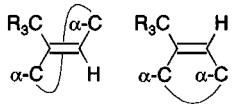


Figure 1. Ratio of isomeric cycloalkenes **3** (semicyclic), **4** (endocyclic, *E*), and **5** (endocyclic, *Z*) formed during the elimination reaction.

of the isomer. The cycloalkenes studied also did not show the larger shift difference of the sp^2 signals reported[9] for cyclic trans in comparison to cis olefins.

We found the methine carbon signals to be an unambiguous probe of stereochemistry. In trans alkenes, the signals of the α-carbon atoms are shifted to lower field relative to their cis isomers[10] (α-C in **6-Z** and **6-E**). Due



to the large number of signals, we could not identify the relative positions of the α-*ring* carbon signals. But the α-carbon of the propionate side chain resonated well off the ring atoms, allowing assignments and quantitative comparison of the **6-Z** (R_3C, approximately 40 ppm) and **6-E** (R_3C, approximately 45 ppm) isomers. Further corroboration stems from comparison with the NMR data of the 5−7-membered cycloalkene products that cannot form **5** with a trans double bond.

Ratio of isomers. The Table 1 and Figure 1 summarize the relative ratio of the isomers **3**−**5** for the ring systems studied. The ratios were determined on the basis of the integrals of the olefinic, methine, and ester methylene proton signals and the relative height of the olefinic carbon signals. With the exception of the cyclohexenyl derivative that gave rise to 100% endocyclic isomer **4**, we observed a steady decline of the proportion of the semicyclic isomers **3** on going from the 5- to the 10-membered system. The latter formed the endocyclic *E*-isomer **4** exclusively. The proportion of **3** then rises steadily, at the 15-membered system reaching the value of approximately 30% it had with the 5-membered ring.

As expected, for the 5−7-membered systems we did not detect any trans isomers **5** (*Z* for our system). This was first observed in 2% amount for the cyclononenyl derivative, but was not detectable in the next higher homolog, then steadily rising to a proportion of 20−25% for the large ring systems. The endocyclic *E* isomer **4** always was the main product, in some cases being formed with high regio- and stereoselectivity. Data for the cyclotetradecenyl system were not determined experimentally, but calculated by extrapolation. The calculated numbers of course have to be considered with care since the relation of the isomers may not change linearly, but follow an oscillating behavior (cf. the deviation from the trend we found for the 16-membered ring, Figure 1). Such a behavior has long been known e.g. for the melting points of homologous fatty acids and the yield of ketones from the cyclization of dinitriles.[11]

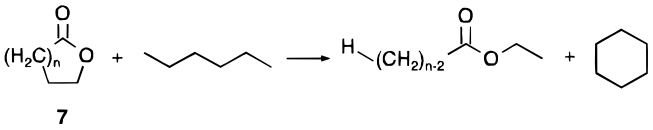
Discussion of the Data and Relation to the Literature. The reluctance of six-membered rings to accommodate semicyclic double bonds can be demonstrated by several literature examples, e.g.: elimination reactions;[12] the fact that the enol content of cyclohexanone is about 25 times that of cyclopentanone and cycloheptanone;[13] and the finding that in the cycloalkanone series, the reactivity of cyclohexanone is surpassed by cyclopropanone and cyclobutanone only.[14] This tendency has been attributed to unfavorable interactions of especially ring hydrogen atoms with the carbonyl oxygen and also to the ecliptic positioning of protons in the ring.[15]

We explain as follows the low or vanishing proportion of semicyclic olefins **3** in the medium-ring derivatives. Medium rings are strained because of transannular interactions (Prelog strain) and too large bond angles (Baeyer strain).[16] Thus it is advantageous for medium-sized rings to have sp^2 centers *in* the ring, relieving the strain because they have one substituent less and can accommodate larger bond angles. Since the 8−12-membered rings predominantly formed the endocyclic olefins **4** and **5**, the introduction of two sp^2 centers in the ring was more favorable than the conjugation with an ester group. (The latter would have been regarded more favorable at first glance, assuming Zaitsev's rule and normal double-bond preferences[17] to direct product formation.) Typical medium-ring strain effects vanishing

(9) *Ibid.* pp 267−269.
(10) *Ibid.* p 119.

(11) Ziegler, K.; Hechelhammer, W. *Liebigs Ann. Chem.* **1937**, *528*, 114−142.
(12) Askani, R. *Methods in Organic Chemistry (Houben/Weyl)*; Thieme: Stuttgart, 1972; Vol. 5/1b, pp 63−70.
(13) (a) Toullec, J. *Tetrahedron Lett.* **1984**, *25*, 4401−4402. (b) Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1990**, *112*, 4862−4868.
(14) Prelog, V.; Kobelt, M. *Helv. Chim. Acta* **1949**, *32*, 1187−1192.
(15) For a discussion, see Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1972**, *28*, 1173−1190.
(16) Eliel, E. H.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 762−771.
(17) Hine, J.; Skoglund, M. J. *J. Org. Chem.* **1982**, *47*, 4766−4770.

Scheme 2. The Strain Energies of the Lactones 7 Were Calculated on the Basis of This Isodesmic Reaction[21]



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with increasing ring size, the proportion of the semicyclic conjugated Zaitsev product **3** again rose for the large rings.

This was not taken into account in a paper[18] that dealt with the elimination of water from ethyl 1-hydroxy-1-cycloalkyl acetates (ring size 5−10) under acid catalysis. The authors, without commenting on the possibility of *E*/*Z*-isomers, noted an increase of the amount of the endo-(cyclic) olefin, corresponding to **3**. They did not offer an explanation for this, but predicted that "in the case of a C_{12} or larger ring, dehydration will afford just one product, the endo one". Our study proves this prediction not to be true since one has to take into account the different factors operating with normal, medium, and large rings.

Our data can also be interpreted in terms of Brown's internal (I-)strain concept, furnishing experimental proof for a concept that was supported theoretically by force field analyses some years ago.[19] In the original rendering, "I-strain is that change in internal strain of a ring compound which results from a change in the coordination number (and the preferred bond angle) of a ring atom involved in the reaction".[20] Two ring atoms were involved in the reaction leading to the endocyclic olefins **4** and **5**. Both changed from coordination number 4 to 3, and from a preferred bond angle of approximately 109° to 120°. The outcome of the elimination verified a reduction in I-strain by this change for the medium-sized rings.

The product ratios highlight the sensitivity of the quantitative outcome of a reaction to the stereochemical demands of the ring involved. These data complement well the findings of a recent thermodynamic study on the strain energies of lactones **7** as a function of ring size.[21] The strain energies were calculated from the isodesmic reaction shown in Scheme 2, the enthalpies of formation being derived from the enthalpies of reduction of **7**. The shape of the curve (Figure 2, based on the authors' data) reflects the same trend we extracted from the product pattern changes in the elimination reactions. They noted a relatively high strain energy of the six-membered lactone, accompanied by a second strain maximum in the region of the medium rings with the eight-membered ring as the extreme. This also exemplifies that in the case of carbocycles with a semicyclic double bond, the six-membered ring is more akin to its medium-sized congeners.[22] In contrast, the well-known relative stabilities of saturated cycloalkanes, based on combustion enthalpies and comparison with open-chain alkanes,[23] show strain maxima for the small and medium rings, and minimal strain for cyclohexane.

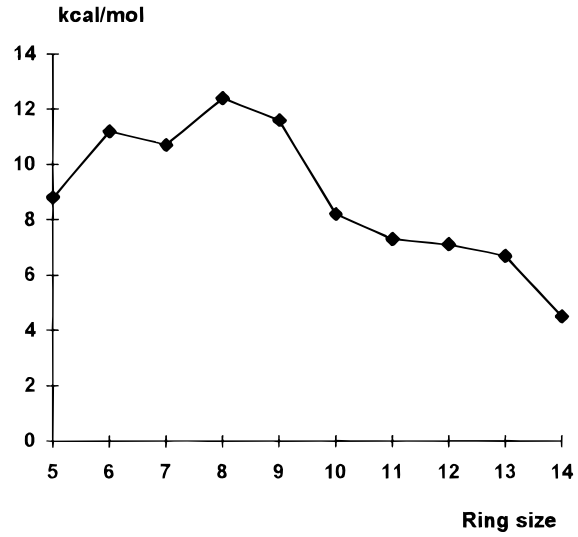

Figure 2. Strain energies of lactones **7** as a function of ring size (from data in lit.,[21] Table 5).

Numerically, the differences in our study were more pronounced than in the lactone series and provided more insight into the reactivity changes with increasing ring size.

Conclusion

The elimination study presented furnishes an instance of a reaction that reflects and illustrates the characteristics of normal (5−7), medium (8−11), and large rings (12−16) on both regio- and stereoselectivity. The trends observed should be of use in the design of preparations involving transformations at carbocycles of various size.

Experimental Section

High-resolution masses were determined by peak matching with tris(nonafluorobutyl)amine at a resolution of 0.2 mmu or better. The tertiary alcohols **1** were prepared from the respective cycloalkanones as described previously.[1]

General Procedure for the Elimination of Water from the Tertiary Alkanols 1. Alkanol **1** (7 mmol) was dissolved in 70 mL of toluene. After the addition of 4-toluenesulfonic acid monohydrate (25 wt % of **1**), the mixture was refluxed in a Dean−Stark apparatus for 24 h. The solvent was partially distilled off (40 mL), and the cooled solution was poured into 100 mL of 10% sodium hydrogen carbonate and 50 mL of diethyl ether. The aqueous phase was extracted twice with diethyl ether (60 mL each). The ether extracts were dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure, and the residue was taken to NMR analysis for the determination of the isomer ratio, followed by flash chromatography or vacuum distillation to isolate the main product.

***(E)*-Ethyl 2-(Cyclohexadec-1-enyl)propionate (4a).** Ethyl 2-(1-hydroxycyclohexadecyl)propionate (**1a**) (1.5 g, 4.4 mmol), after flash chromatography (hexane/diethyl ether 4:1, R_f = 0.52), furnished 1.0 g (73%) of **4a** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.31 (t, J = 8 Hz, 1H), [5.21 (t, J = 8 Hz, 1H)], 4.17−4.02 (m, 2H), [3.44 (q, J = 7 Hz, 1H)], 3.02 (q, J = 7 Hz, 1H,), 2.09−1.95 (m, 4H), 1.46−1.15 (m, 30H), (recognizable signals

(18) Screttas, S. G.; Smonou, I. C. *J. Org. Chem.* **1988**, *53*, 893−894. See also Screttas, S. G.; Smonou, I. C. *J. Organomet. Chem.* **1988**, *342*, 143−152.

(19) (a) Schneider, H.-J.; Thomas, F. *J. Am. Chem. Soc.* **1980**, *102*, 1424−1425. (b) Schneider, H.-J.; Schmidt, G.; Thomas, F. *J. Am. Chem. Soc.* **1983**, *105*, 3556−3563.

(20) Brown, H. C.; Gerstein, M. *J. Am. Chem. Soc.* **1950**, *72*, 2926−2933. See also Eliel, E. H.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 769−771.

(21) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7697−7705 and work cited therein.

(22) Cf. also Thalhammer, F.; Wallfahrer, U.; Sauer, F. *Tetrahedron Lett.* **1990**, *47*, 6851−6854.

(23) (a) Kaarsemaker, S.; Coops, J. *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 261−276. (b) Dunitz, J. D.; Prelog, V. *Angew. Chem.* **1960**, *23*, 896−902. See also Eliel, E. H.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 675−678.

of the *Z*-isomer **5a** in square brackets); ^{13}C NMR ($CDCl_3$): δ 175.3, [174.9], [150.4], 138.4, [136.7], [128.4], 127.2, [122.9], [60.3], 60.2, [60.0], 45.5, [40.8], [34.2], [33.4], [33.3], 30.0, [29.8], [29.1], 28.6, [28.2], 28.11, 28.08, 27.94, 27.87, 27.7, [27.6], 27.39, [27.36], [27.33], [27.28], [27.2], [27.14], 27.07, 27.04, [26.97], 26.9, [26.75], [26.69], [26.65], 26.4, 26.3, [26.04], [25.98], [25.6], 25.4, 16.9, [15.5], 14.2, (recognizable signals of the semicyclic and *Z*-isomers **3a** and **5a** in square brackets); IR (neat) 2928 (vs), 2857 (s), 1735 (s), 1461 (m), 1180 (m); MS (EI) *m*/*z* (rel int) 323 (M + 1, 6), 322 (M^+, 26), 102 (100), 97 (35), 95 (31), 83 (43), 81 (35), 69 (35), 67 (39), 55 (47), 41 (38); HRMS (EI) calcd for $C_{21}H_{38}O_2$ 322.2872, found 322.2866.

(*E*)-Ethyl 2-(Cyclopentadec-1-enyl)propionate (4b). Ethyl 2-(1-hydroxycyclopentadecyl)propionate (**1b**) (3.8 g, 12 mmol), after distillation at 1.8×10^{-2} mmHg, furnished 2.5 g (67%) of **4b** as a colorless oil; bp 138−142 °C (1.8×10^{-2} mmHg); ^{1}H NMR ($CDCl_3$) δ 5.31 (t, J = 7 Hz, 1H), [5.22 (t, J = 7 Hz, 1H)], 4.20−4.06 (m, 2H), 3.05 (q, J = 7 Hz, 1H), 2.17−2.00 (m, 8H), 1.37−1.20 (m, 24H), (recognizable signals of the *Z*-isomer **5b** in square brackets); ^{13}C NMR ($CDCl_3$) δ 175.1, [174.7], [169.8], [150.9], 138.3, [136.5], [127.7], 127.3, [122.7], 60.1, [59.8], 45.8, [40.7], [34.3], [33.5], 29.5, [28.9], 28.0, [27.8], [27.6], 27.4, 27.3, [27.24], 27.17, [27.00], 26.96, [26.93], [26.87], [26.81], 26.76, [26.7], 26.59, 26.56, [26.5], [26.4], 26.22, 26.17, 26.1, [26.0], 25.8, [25.7], [25.6], 16.6, [14.14], [14.08], 14.0 (recognizable signals of the semicyclic and *Z*-isomer **3b** and **5b** in square brackets); IR (neat) 2931 (vs), 2858 (vs), 1779 (m), 1735 (vs), 1459 (s), 1181 (s). MS (EI) *m*/*z* (rel int) 309 (M + 1, 6), 308 (M^+, 28), 293 (9), 102 (100), 97 (35), 83 (43), 69 (38), 55 (42), 41 (48). $C_{20}H_{36}O_2$ (308.50) calcd C 77.87, H 11.76, found C 78.00, H 11.51.

(*E*)-Ethyl 2-(Cyclotridec-1-enyl)propionate (4d). Ethyl 2-(1-hydroxycyclotridecyl)propionate (**1d**) (1.7 g, 5.7 mmol) yielded **4d** (1.2 g, 75%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.22−5.13 (m, 1H), 4.12−3.97 (m, 2H), [3.43 (q, J = 7 Hz, 1H)], 2.98 (q, J = 7 Hz, 1H), 2.04−1.93 (m, 4H), 1.44−1.12 (m, 24H) (recognizable signals of the *Z*-isomer **5a** in square brackets); ^{13}C NMR ($CDCl_3$) δ 175.1, [174.6], [169.8], [150.2], 138.7, [136.2], [128.9], 127.7, [123.0], [60.2], 60.1, 45.5, [41.9], [31.2], 28.2, [28.0], 27.6, [27.1], [26.9], 26.7, 26.6, [26.4], 26.2 (double intensity), 26.1, [25.9], [25.84], 25.78, 25.72, [25.68], [25.6], 25.4, 24.81, [24.77], [24.7], [24.6], [24.4], [24.3], [23.2], 16.6, [15.1], 14.0 (recognizable signals of the semicyclic and *Z*-isomers **3** and **5a** in square brackets); IR (neat) 2927 (vs), 2855 (vs), 1734 (vs), 1461 (s), 1179 (vs), 1097 (s).

(*E*)-Ethyl 2-(Cyclododec-1-enyl)propionate (4e). Ethyl 2-(1-hydroxycyclododecyl)propionate (**1e**) (2.0 g, 7.0 mmol), after flash chromatography (hexane/diethyl ether 4:1, R_f = 0.52), furnished 1.2 g (64%) of **4e** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ [5.45 (t, J = 8 Hz, 1H], 5.21 (t, J = 8 Hz, 1H), 4.08−3.96 (m, 2H), [3.47 (q, J = 7 Hz, 1H)], 2.98 (q, J = 7 Hz, 1H,), 2.13−1.91 (m, 4H), 1.48−1.10 (m, 22H) (recognizable signals of the *Z*-isomer **5a** in square brackets); ^{13}C NMR ($CDCl_3$) δ 175.1, [174.5], 138.0, [135.2], [129.2], 127.3, [60.1], 59.9, 43.8, [40.2], [31.4], [27.3], 26.8, 26.3, [26.2], [26.1], 25.1, 24.7, 24.6, 24.5, 24.2, 23.8, [23.6], [23.1], 22.5, 22.1, 16.6, [15.3], 13.9, [13.8] (recognizable signals of the *Z*-isomer **5a** in square brackets); IR (neat) 2928 (vs), 2863 (vs), 1735 (vs), 1712 (s), 1600 (w), 1469 (s), 1446 (s), 1180 (vs), 1097 (s), 805 (m), 726 (m); MS (EI) *m*/*z* (rel int) 267 (M + 1, 3), 266 (M^+, 16), 251 (7), 200 (18), 155 (26), 109 (32), 102 (100), 95 (56), 92 (27), 91 (79), 83 (47), 81 (49), 79 (33), 69 (38), 67 (54), 65 (31), 55 (72), 41 (50); HRMS (EI) calcd for $C_{17}H_{30}O_2$ 266.2246, found 266.2231.

(*E*)-Ethyl 2-(Cycloundec-1-enyl)propionate (4f). Ethyl 2-(1-hydroxycycloundecyl)propionate (**1f**) (2.0 g, 7.0 mmol), after distillation at 2.5×10^{-2} mmHg, furnished 1.2 g (64%) of **4f** as a colorless oil; bp, 100 °C (2.5×10^{-2} mmHg); ^{1}H NMR ($CDCl_3$) δ [5.49 (t, J = 4 Hz, 1H], 5.24 (t, J = 7 Hz, 1H), 4.17−4.07 (m, 2H), [3.67 (q, J = 7 Hz, 1H], 3.10 (q, J = 7 Hz, 1H), 2.27−218 (m, 4H), 1.53−1.17 (m, 20H) (recognizable signals of the *Z*-isomer **5a** in square brackets); ^{13}C NMR ($CDCl_3$) δ 175.4, [174.7], 138.4, [135.7], [127.9], 128.3, [60.4], 60.3, 43.6, [41.1], [31.1], 29.8, [28.1], 27.9, 27.3, [26.93], 26.88, [26.8], [26.7], [26.0], 25.8, [25.4], 25.2, [24.9], 24.7, 24.6, [23.66], [23.51], 22.9, [22.6], 17.0, [15.4], [14.7], 14.2, [14.1] (recognizable signals of the semicyclic and *Z*-isomers **3** and **5a** in square brackets); IR (neat) 2931 (vs), 2860 (s), 1735 (vs), 1468 (m), 1446 (m), 1373 (m), 1180 (s), 1096 (m), 916 (w); MS (EI) *m*/*z* (rel int) 252 (M + 1, 3), 237 (3), 168 (19), 125 (26), 111 (32), 102 (92), 98 (28), 97 (26), 95 (35), 92 (65), 91 (100), 69 (40), 67 (39), 58 (46), 55 (86), 43 (72), 41 (61), 39 (37); HRMS (EI) calcd for $C_{16}H_{28}O_2$ 252.2089, found 252.2087.

(*E*)-Ethyl 2-(Cyclodec-1-enyl)propionate (4g). Ethyl 2-(1-hydroxycyclodecyl)propionate (**1g**) (1.8 g, 7.0 mmol), after distillation at 1.9×10^{-2} mmHg, furnished 1.3 g (79%) of **4g** as a colorless oil; bp, 84 °C (1.9×10^{-2} mmHg); ^{1}H NMR ($CDCl_3$) δ 5.34 (t, J = 7 Hz, 1H), 4.17−4.08 (m, 2H), 3.06 (q, J = 7 Hz, 1H), 2.29−2.26 (m, 4H), 1.57−1.51 (m, 4H), 1.40−1.21 (m, 14H).; ^{13}C NMR ($CDCl_3$) δ 175.4, 137.7, 127.4, 60.3, 43.9, 27.9, 27.4, 26.8, 26.7, 25.2, 24.6, 20.9, 20.7, 16.8, 14.2; IR (neat) 3510 (vs), 2920 (vs), 1705 (vs), 1470 (vs), 770 (vs); MS (EI) *m*/*z* (rel int) 238 (M^+, 0.4), 223 (2), 102 (100), 95 (25), 81 (30), 67 (25), 55 (31), 41 (36); HRMS (EI) calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1935.

(*E*)-Ethyl 2-(Cyclonon-1-enyl)-propionate (4h). According to the general procedure, ethyl 2-(1-hydroxycyclononyl)-propionate (**1h**) (4.5 g, 19 mmol), after distillation at 2×10^{-2} mmHg, yielded **4h** (3.1 g, 14 mmol, 74%) as a colorless oil; bp, 74−76 °C (2×10^{-2} mmHg); ^{1}H NMR ($CDCl_3$) δ 5.43 (t, J = 8 Hz), 4.16−4.08 (m, 2H), 3.07 (q, J = 7 Hz, 1H), 2.21−2.12 (m, 4H), 1.51−1.45 (m, 10H), 1.62−1.22 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 175.2, [170.4], [152.2], 139.2, 127.2, [123.7], 60.3, [60.0], 46.9, [35.5], [35.1], 29.1, [28.6], [28.3], [27.1], 26.8, 26.7, 26.6, [26.4], 26.2, [25.8], 25.5, 24.0, 16.6, [14.3], 14.2 (recognizable signals of the semicyclic isomer **3** in square brackets); IR (neat) 2977 (s), 2929 (vs), 2862 (s), 1734 (vs), 1451 (m), 1180 (s); MS (EI) *m*/*z* (rel int) 224 (M^+, 1), 209 (3), 102 (100), 95 (33), 81 (40), 67 (32), 55 (27), 41 (32); HRMS (EI) calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1765.

(*E*)-Ethyl 2-(Cyclooct-1-enyl)propionate (4i). According to the general procedure, ethyl 2-(1-hydroxycyclooctyl)propionate (**1i**) (22.8 g, 99 mmol), after distillation at 1.8×10^{-2} mmHg, yielded **4i** (15.1 g, 72 mmol, 73%) as a colorless oil; bp, 70 °C (1.8×10^{-2} mmHg); ^{1}H NMR ($CDCl_3$) δ 5.52 (t, J = 8 Hz, 1H), 4.11 (q, J = 7 Hz, 2H), 3.09 (q, J = 7 Hz, 1H), 2.23−2.09 (m, 4H), 1.56−1.42 (m, 6H), 1.26−1.22 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 175.1, [151.5], 139.3, 126.6, [123.9], 60.3, 47.1, 29.6, 29.2, 27.8, 26.4, 26.3, 26.2, 16.4, 14.2 (recognizable signals of the semicyclic isomer **3** in square brackets); IR (neat) 2980 (s), 2927 (vs), 2854 (s), 1733 (vs), 1650 (w), 1469 (m), 1183 (s); HRMS (EI) calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1614.

(*E*)-Ethyl 2-(Cyclohept-1-enyl)propionate (4j). Ethyl 2-(1-hydroxycycloheptyl)propionate (**1j**) (21.2 g, 99 mmol), after flash chromatography (pentane/diethyl ether 4:1, R_f = 0.52), furnished 13.9 g (72%) of **4j** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.71 (t, J = 7 Hz, 1H), 4.19−4.08 (m, 2H), 3.07 (q, J = 7 Hz, 1H), 2.14−2.09 (m, 3H), 1.49−1.43 (m, 3H), 1.31−1.21 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 174.7, [170.1], [150.5], 143.1, 128.6, [122.6], 60.2, [60.1], 48.7, [33.3], [33.2], 32.6, 30.3, [29.0], [28.6], 28.3, [27.7], 26.9, 26.8, [26.1], 15.8, [15.7], 14.2, [14.1]; (signals of the semicyclic isomer **3** in square brackets); IR (neat) 2923 (vs), 2855 (vs), 1712 (vs), 1623 (s), 1433 (vs), 1276 (vs), 1226 (vs), 1190 (vs), 1113 (vs), 1044 (s), 773 (s); MS (EI) *m*/*z* (rel int) 196 (M^+, 3), 182 (97), 151 (100), 150 (52), 125 (48), 123 (24), 122 (38), 101 (27), 96 (28), 95 (36), 93 (33), 88 (25), 83 (50), 82 (30), 81 (90), 79 (40), 77 (24), 67 (82), 55 (78), 54 (20), 53 (22), 43 (28), 41 (43), 39 (34); HRMS (EI) calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1484.

(*E*)-Ethyl 2-(Cyclohex-1-enyl)propionate (4k). Ethyl 2-(1-hydroxycyclohexyl)propionate (**1k**) (3.4 g, 17 mmol), after flash chromatography (pentane/diethyl ether 4:1, R_f = 0.52), furnished 2.4 g (76%) of **4k** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.59−5.55 (m, 1H), 4.21−4.10 (m, 2H), 3.02 (q, J = 7 Hz, 1H), 2.04−1.86 (m, 4H), 1.65−1.52 (m, 4H), 1.33−1.21 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.9, 136.6, 123.4, 60.3, 47.1, 26.3, 25.3, 22.9, 22.3, 15.7, 14.3. The compound was mentioned in the literature[24] with no characterization and analytical data.

(24) Patel, Sh. K.; Paterson, I. *Tetrahedron Lett.* **1983**, *24*, 1315.

(*E*)-Ethyl 2-(Cyclopent-1-enyl)propionate (4l). Ethyl 2-(1-hydroxycyclopentyl)propionate (**1l**) (3.3 g, 18 mmol) furnished 2.6 g (88%) of **4l** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.52−5.51 (m, 1H), 4.19−4.10 (m, 2H), 3.23 (q, J = 7 Hz, 1H), 2.36−2.26 (m, 2H), 1.90−1.82 (m, 2H), 1.30−1.23 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 174.5, [168.4], [160.2], 142.7, 125.3, [118.6], 60.4, [59.8], 41.7, [34.2], [34.1], 33.3, 32.3, [27.2], [25.6], 23.3, [21.5], 15.9, [14.5], 14.2 (signals of the semicyclic isomer **3l** in square brackets).

Supporting Information Available: ^{13}C NMR spectra of compounds **4a**,**d**−**j**,**l** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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