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Cyclobutanones through S_Ni' Ring Closure, a Mechanistic Study

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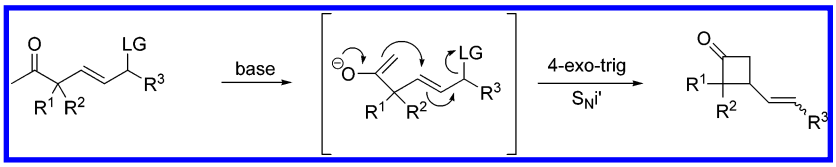

Mechanistic studies on the intramolecular nucleophilic substitution with allylic rearrangement (S_Ni' reaction) and a new stereoselective access to substituted cyclobutanones are reported. 4,4-Dialkyl-5-oxohex-2*E*-en-1-yl methanesulfonates **4** were converted to 2,2-dialkyl-3-vinylcyclobutanones **6** by S_Ni' ring closure. The stereochemical analysis of the reaction was achieved through ring closure of (6*S*)-6-chloro-3,3-diethylhept-4*E*-en-2-one (*S*)-**17**, defined by the absolute configuration of C(6), leading to (3*S*)-2,2-diethyl-3-(prop-1*E*-en-1-yl)cyclobutanone (*S*)-(*E*)-**18** and (3*R*)-2,2-diethyl-3-(prop-1*Z*-en-1-yl)cyclobutanone (*R*)-(*Z*)-**18**, in a ratio of 85:15, with almost complete transfer of chirality (>97%). The absolute configuration of (*S*)-**17** was determined by X-ray diffraction analysis of the camphanoate derivative **16**. The absolute configuration of the cyclobutanone products (*S*)-(*E*)-**18** and (*R*)-(*Z*)-**18** was determined by Raman optical activity spectroscopy. Comparison of the absolute configuration of (*S*)-**17** and the resulting (*E*)- and (*Z*)-cyclobutanones **18** allowed the conclusion that the S_Ni' reaction proceeds with *syn* geometry relative to the leaving group.

Introduction

The S_N2' reaction (bimolecular nucleophilic substitution with allylic rearrangement) was first postulated independently by Hughes and Winstein.[1] The regio- and stereoselectivity of the displacement was found to depend on both the nature of the nucleophiles and that of the leaving groups.[2] The intramolecular variant, the S_Ni' reaction, is strongly related to the S_N2' reaction, and the results from the stereochemical analysis of the S_N2' reaction apply to the intramolecular version as well.[3] Herein we discuss the results of our own mechanistic studies on the S_Ni' reaction and report a new enantioselective access to substituted cyclobutanones.[4]

The construction of four membered carbocycles is commonly achieved by the inter- or intramolecular photochemical [2+2] addition of olefins.[5] Cyclobutanones are frequently prepared by the thermal [2+2] addition of olefins with ketenes.[6] A diastereoselective variant was developed by Ghosez et al. involving chiral keteniminium salts.[7] Another asymmetric route to cyclobutanones was reported by Fráter et al. who employed a chiral ketene in the synthesis of (−)-blastmycinone.[8] Only few other methods for the enantioselective preparation of cyclobutanones can be found in the literature.[9]

During research on the stereoselective α-alkylation of chiral β-hydroxy esters, Fráter et al. reported the preparation of a 4:3 mixture of (*R*)-**2** and (*S*)-**3** via a base induced S_Ni reaction (intramolecular, nucleophilic substitution) of (*R*)-**1′** (′ indicates

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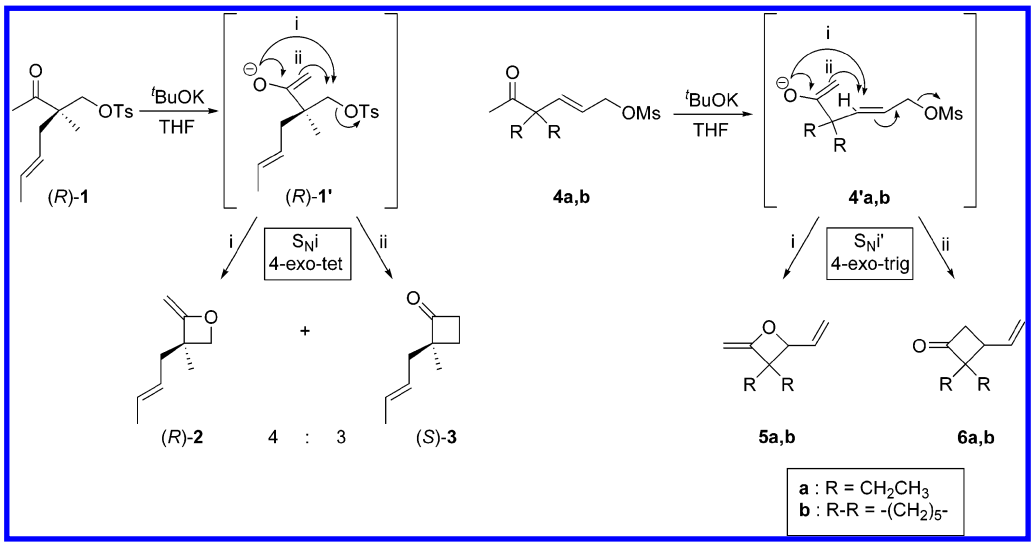
SCHEME 1



the enolate of the corresponding compound) (Scheme 1).[10] The efficient approach to chiral cyclobutanones prompted us to apply these findings in the synthesis of cyclobutanones by the S_Ni' reaction of an allylic analogue (Scheme 1). Several requirements must be met for this reaction to proceed: according to Baldwin's rules of ring closure, the 4-exo-trig mechanism is a favored process.[11] The double bond in **4** must have an *E* configuration, to prevent the reaction from following the allowed 6-exo-tet mechanism, leading to six-membered rings. In addition, disubstitution at C(3) prevents the formation of the alternative 2,3-enolate, which will provoke simple E2 elimination leading to hexa-3,5-dien-2-one. The allylic nucleophilic displacement of the leaving group may proceed either by attack of the oxygen anion (**i**) leading to oxetane **5** or by attack of the carbanion (**ii**) leading to cyclobutanone **6**.

Apart from the chemoselectivity of the reaction, it was of particular interest to determine whether the allylic nucleophilic displacement by the enolate takes place *syn* or *anti* with respect to the leaving group. Since its discovery, the mechanism of the S_N2' reaction has led to many disputes concerning its mechanism and the preferred trajectory of the incoming nucleophile. Today, the S_N2' reaction is commonly believed to involve a concerted allylic *syn* displacement of the nucleofuge by the incoming nucleophile. However, several examples exist in the literature that report selective *anti* displacements, especially when applying organometallic nucleophiles.[12] Stork and Kreft reported that S_N2' and S_Ni' reactions with thiolate nucleophiles led to predominant or even exclusive *anti* displacement of the nucleofuge in allylic systems.[13a] The authors reported a similar example to our S_Ni' ring closure where nucleophilic attack of a thiolate anion led to the formation of a tetrahydrothiophen ring by selective *anti* displacement of the leaving group.[13b] It was the objective of the current research to investigate the scope and limitations of the S_Ni' reaction for the synthesis of cyclobutanones and to determine the exact mechanistic course of the reaction.

Results and Discussion

The general feasibility and chemoselectivity of the S_Ni' reaction leading to cyclobutanones was explored by performing the reaction with **4a,b**, leading to cyclobutanones **6a,b** and/or oxetanes **5a,b** upon S_Ni' ring closure (Scheme 1). Stork enamine synthesis of 2-ethylbutanal **7a** and cyclohexanecarbaldehyde **7b** with morpholine,[14] followed by acetylation of the resulting enamines **8a,b** with acetyl chloride and hydrolysis of the resulting quaternary ammonium salt, led to the key intermediates **9a,b** (Scheme 2).[15] Subsequent reaction with triethyl phosphonoacetate at 0 °C selectively afforded (*E*)-**10a,b**.

Conversion of **10a,b** to the silyl-enol ether **11a,b**, followed by reduction of the ester group with $LiAlH_4$, led to the allylic alcohol **12a,b**, which was then converted to the corresponding methanesulfonate **4a,b**. Treatment of **4a** with 5% excess ^{t}BuOK 1 M in THF led to cyclobutanone **6a** in 45% yield. Formation of compound **13a**, the product of a formal ketene elimination, was indicated by the presence of ^{t}BuOAc, identified by gas chromatography mass spectroscopy (GC/MS). Accordingly, S_Ni' cyclization of **4b** under the same conditions led to a mixture of cyclobutanone **6b** in 56% yield and the ketene elimination product **13b** was isolated in 11% yield. In contrast to the S_Ni reaction reported by Fráter et al., the S_Ni' reactions did not lead to any detectable amount of oxetane **5a,b**, which would result from nucleophilic attack of the oxygen anion.[10] The observed trend can be rationalized by the HSAB rule: the allylic system in **4a,b** exhibits softer acid properties and is therefore prone to be attacked by the soft nucleophilic enolate-carbon rather than the hard oxygen anion.[16] The formal ketene-elimination reaction leading to **13**, found to be the major side reaction in the 4-exo-trig S_Ni' reaction, was not reported by Fráter et al. in the S_Ni reaction.

However, the analysis of the reaction mechanism and geometry of the transition state of the S_Ni' reaction leading to cyclobutanones requires more information than that which can

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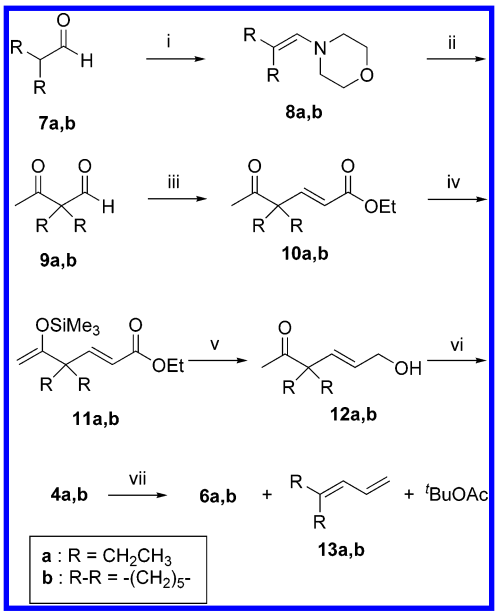
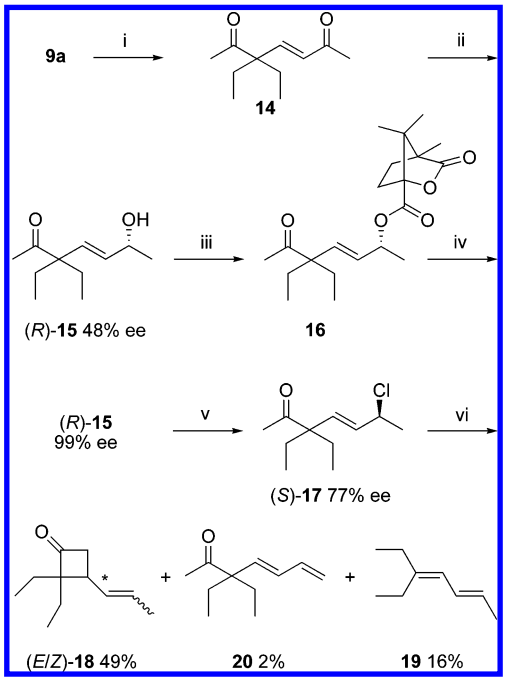
SCHEME 2[a]



[a] Reagents and conditions: (i) morpholine (1 mol. equiv), TsOH, $-H_2O$, **8a** 86% **8b** 89%. (ii) AcCl, CH_2Cl_2, **9a** 39%, **9b** 32%. (iii) $(Et_2O)_2P(O)$-CH_2CO_2Et, NaH, **10a** 84%, **10b** 62%. (iv) TMSCl, Et_3N, **11a** 82%, **11b** 66%. (v) $LiAlH_4$, THF, **12a** 80%, **12b** 45%. (vi) MsCl, pyridine, **4a** 47%, **4b** 40%. (vii) ^{t}BuOK, THF, **6a** 45%, **6b** 56%, **13a,b** 11%.

SCHEME 3[a]



[a] Reagents and conditions: (i) $Ph_3PCH_2COCH_3$, NaH, 72%. (ii) (+)-Ipc_2BCl, 77%. (iii) (−)-Camphanic acid chloride, crystallization. (iv) NaOH, H_2O, EtOH. (v) $(CCl_3)_2CO$, Ph_3P, 85%. (vi) ^{t}BuOK, THF.

be deduced from the cyclization of **4a,b**. Application of (*S*)-**17**, defined by the absolute configuration at the carbon bearing the leaving group, allows the analysis of the exact stereochemical route of the reaction.

Diketone (*E*)-**14** was prepared by Wittig reaction of 1-triphenyl-propan-2-one on **9a** (Scheme 3). The ketone function was reduced chemo- and enantioselectively by a modified Midland procedure[17a] using (+)-diisopinocampheylchloroborane ((+)-Ipc_2BCl), derived from (−)-α-pinene and $BH_3{\cdot}SMe_2$.[17b,c] (*R*)-**15** was obtained in 77% yield with 48% ee (for the determination of the enantiomeric excess, see Supporting Information). The enantiomerically pure product was obtained by reacting the enriched product with (*S*)-(−)-camphanic acid chloride, to give a solid camphanoate derivative **16**. Fractional crystallization of **16** from hexane/ether led to the pure diastereomer. X-ray crystallography of **16** allowed us to deduce the absolute configuration of (*R*)-**15**.

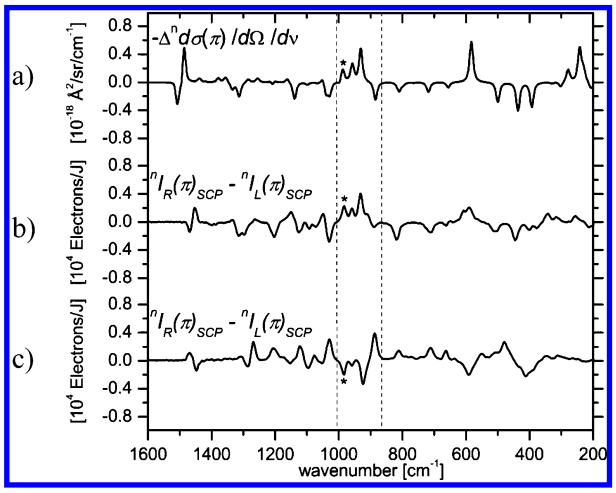


FIGURE 1. (a) Calculated ROA spectrum of (*S*)-(*E*)-**18**. (b) Measured spectrum of (*S*)-(*E*)-**18**. (c) Measured spectrum of (*R*)-(*Z*)-**18**.

The chloride ion was found to be a suitable leaving group for the S_Ni' reaction, and (*R*)-**15** was converted to (*S*)-**17** with hexachloroacetone in the presence of triphenylphosphine.[18] Although the reaction was reported to proceed with complete inversion of configuration, some loss of enantiomeric purity (77% ee) was observed in chloride (*S*)-**17**, possibly caused by partial formation of an allyl cation intermediate (S_N1).

Chloro-ketone (*S*)-**17** was cyclized using 1 M ^{t}BuOK in THF at 0 °C following the procedure by Fráter et al.[10] The reaction afforded a mixture of 85% (*E*)-**18** and 15% (*Z*)-**18** in 49% isolated yield together with 16% (GC) of the formal ketene elimination product **19**, as well as the dehydrochlorination product **20**. Analysis by chiral GC showed that the enantiomeric excesses of (*E*)- and (*Z*)-**18** was 75% for both isomers, indicating that the S_Ni' reaction proceeded with almost complete stereoselectivity.

To precisely analyze the mechanism of the S_Ni' reaction, it was necessary to separate (*E*)- and (*Z*)-**18** and to determine the absolute configuration of both products. The separation was accomplished by chromatography over silica gel impregnated with $AgNO_3$ (pentane/Et_2O 97.5:2.5).[19] The separated products were submitted for Raman optical activity (ROA) spectroscopy (Figure 1, spectrum b and c).[20] The absolute configuration of both isomers was determined by comparing the vibration at 988

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(20) Extensive analysis of all the conformers contributing to the ROA spectrum of (*E*)- and (*Z*)-**18** will be published shortly by W. Hug and D. Dudenko from the University of Fribourg, Switzerland.

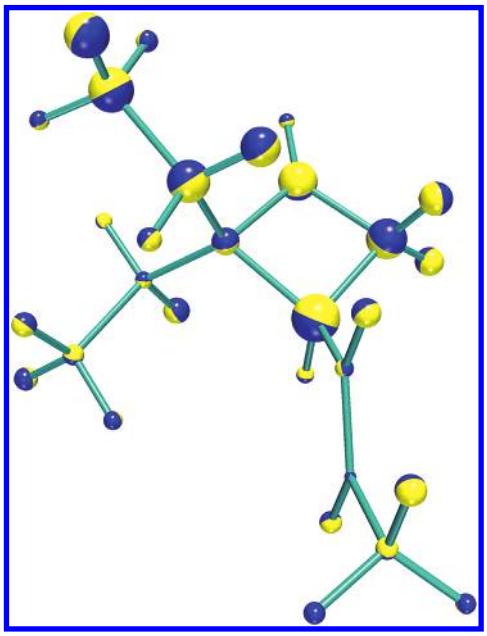


FIGURE 2. Vibration at 988 cm^{-1} in the ROA spectrum of (*S*)-(*E*)-**18**.

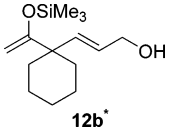


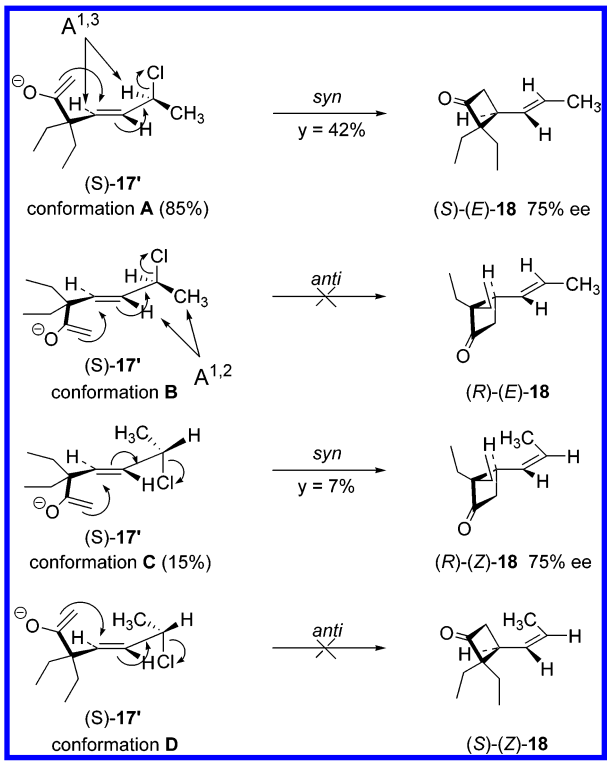
FIGURE 3.

cm^{-1}, marked with an asterisk, with that of the theoretical spectrum of (*S*)-(*E*)-**18** calculated at the B3LYP/6-311++G** level with the Gaussian program (Figure 1, spectrum a.). ROA calculation at the TDHF/rDP level was carried out with the Dalton program.[21]

The relevant vibration at 988 cm^{-1} was visualized as a 3-dimensional image (Figure 2). The image must be interpreted as follows: The size (volume) of the spheres represents the total vibration energy (kinetic and potential) of the corresponding atom. The direction of the movement of the atoms in the molecule is indicated by the two colored surfaces of the spheres. The atoms vibrate on an axis perpendicular to the colored surfaces, e.g., from blue to yellow or vice versa. The actual excursion of the motion of the nuclei is not represented by this delineation, which favors visibility of the motion of the heavier nuclei in comparison to that of the lighter ones. The ROA is proportional to the effective motion of the nuclei and to the gradients of the relevant optical tensors at their site, and not to vibrational energy. Despite the larger gradients at the site of the heavier nuclei, the hydrogen atoms therefore tend to contribute more to the computed ROA than implied by this delineation (Figure 2).[22] On the basis of the ROA analysis and the fact that (*E*)-**18** and (*Z*)-**18** show the opposite sign of optical rotation, the absolute configuration was assigned (*S*) for (*E*)-**18** and (*R*) for (*Z*)-**18**.

Now that the absolute configurations of the chloro-ketone (*S*)-**17** and the resulting cyclobutanones (*S*)-(*E*)-**18** and (*R*)-(*Z*)-**18** had been determined, it was possible to establish the

SCHEME 4



mechanistic course of the reaction, based on the conformational analysis of the possible reaction pathways. The reactive enolate (*S*)-**17′** can adopt 4 different conformations **A**−**D** (Scheme 4). Intramolecular displacement of the chloride ion in conformers **A** and **C** would proceed in a *syn* fashion, but conformer **A** is assumed to be lower in energy, because of a minor $A^{1,3}$ strain. However, both conformers interchange by a rapid equilibrium, as the energy difference between them is small (∼12 kJ/mol) at reaction temperature. Therefore, (*S*)-(*E*)-**18** derives from conformation **A**, where enolate attack at the *re* face of the molecule leads to the (*E*)-configured product upon *syn* displacement of the nucleofuge. The minor product is not only (*Z*)-configured but also displays the opposite absolute configuration: it results from conformation **C** in which the enolate attacks the allylchloride unit from the *si* face. The *E*/*Z* ratio of 85:15 represents the selectivity by which (*S*)-**17′** reacts through conformation **A** or **C**. As the enantiomeric purity of **18** was preserved to at least 97%, the *anti* displacements via conformations **B** and **D** are negligible, for they would lead to the formation of (*R*)-(*E*)-**18** and (*S*)-(*Z*)-**18**, respectively.

Conclusions

The current research has shown that substituted cyclobutanones **6a**,**b** can be prepared by a S_Ni' reaction of β,γ-unsaturated ketones of type **4a**,**b** (Scheme 1). Mechanistic studies with chloro-ketone (*S*)-**17** led to the conclusion that the nucleophilic displacement of the chloride ion by the ketone enolate proceeds exclusively with *syn* stereochemistry leading to (*E*)- and (*Z*)-**18** of opposite absolute configurations at C(3) of the cyclobutanone ring (Scheme 4). These findings were in accord with the results from Stork and White, who found that nucleophilic S_N2' displacement with enolates in sterically unbiased systems will take place *syn* to the leaving group.[23]

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Experimental Section

The ^1H and ^{13}C NMR spectra were recorded at 500 and 300 MHz and 100 and 75 MHz, respectively. Chemical shifts are expressed in parts per million (ppm). FTIR spectra were recorded in solution ($CDCl_3$) on Spectrum One FTIR and Bruker Vector 22 FTIR spectrometers. High-resolution mass spectra were recorded on a Finnigan MAT 95 double-focusing magnetic sector mass spectrometer. Thin layer chromatography was performed on commercial 60 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm) and $KMnO_4$ staining reagent. Chromatography was carried out with hexane (hex) and tert.-butyl methyl ether (MtBE) unless stated otherwise.

Ethyl 4,4-Diethyl-5-oxohex-2*E*-enoate (10a). Sodium hydride in paraffin oil (60%, 1.70 g, 42.30 mmol) was suspended in THF (40.0 mL). Triethyl phosphonoacetate (7.57 g, 33.80 mmol) was added dropwise. The mixture slowly became homogeneous, and the temperature rose to 35 °C. After stirring for 20 min, the mixture was cooled to 0−5 °C using an ice/NaCl bath. Keto-aldehyde **9a** (4.00 g, 28.20 mmol) was added slowly while maintaining the temperature at 0 °C. After the addition the cooling bath was removed and the reaction mixture stirred for an additional 30 min. The reaction mixture was poured onto ice/water and extracted with hexane. The hexane layers were combined and washed with aq. $NaHCO_3$, dried, and concentrated. Short-path distillation (90 °C, 0.05 mbar) afforded **10a** as a colorless oil (5.04 g, 84%). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.02 (d, J = 16.3 Hz, 1 H), 5.87 (d, J = 16.3 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 2.11 (s, 3 H), 1.82−1.78 (m, 4 H), 1.30 (t, J = 7,1 Hz, 3 H), 0.77 (t, J = 7.5 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.6, 166.1 (2 s), 149.5, 122.0 (2 d), 60.3 (t), 58.3 (s), 26.4 (2 t), 26.1, 14.1 (2 q), 8.2 (2 q). IR (CCl_4, cm^{-1}): ν 2971w, 1708s, 1646w. MS (EI): *m*/*z* 197 (1, $[M-CH_3]^+$), 170 (100, $[M-C_2H_4]^+$), 167 (7, $[M-C_2H_5O]^+$), 113 (12, $[M-C_5H_7O_2]^+$), 99 (13, $[M-C_7H_{13}O]^+$), 43 (80, $[C_2H_3O]^+$). Anal. Calcd. for $C_{12}H_{20}O_3$ (212): C 67.89, H 9.50. Found: C 67.64, H 9.31.

Ethyl (2*E*)-3-(1-Acetylcyclohexyl)acrylate (10b). Prepared from **9b** (11.50 g, 74.70 mmol) following the same procedure reported for the synthesis of **10a**. The crude product was purified by distillation over a 15-cm Vigreux column (0.05 mbar, 112 °C) to give **10b** as a colorless oil (10.45 g, 62%). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.85 (d, J = 16.1 Hz, 1 H), 5.87 (d, J = 16.1 Hz, 1 H), 4.2 (q, J = ?? 2 H), 2.11 (s, 3 H), 2.04−1.94 (m, 2 H), 1.72−1.61 (m, 2 H), 1.60−1.36 (m, 6 H), 1.30 (t, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.0, 166.0 (2 s), 150.2, 122.3 (2 d), 60.4 (t), 55.1 (s), 32.5 (2 t), 25.8 (1 q), 25.4, 22.4 (2 t), 14.1 (q). IR (CCl_4, cm^{-1}): ν 2935m, 2857w, 1707vs, 1643m. MS (EI): *m*/*z* 206 (1, $[M-H_2O]^+$), 182 (100, $[M-CH_2CO]^+$), 179 (6, $[M-C_2H_5O]^+$), 154 (10), 136 (15), 107 (44), 94 (16), 79 (31), 43 (65, $[C_2H_3O]^+$). HRMS (EI): calcd. for $C_{13}H_{21}O_3$ ($[M+H]^+$), 225.1491; found, 225.1496.

Ethyl 4,4-Diethyl-5-(trimethylsilanyloxy)hexa-2*E*,5-dienoate (11a). A solution of **10a** (26.46 g, 125.00 mmol) in of CH_3CN (50.0 mL) was prepared, and triethylamine (17.67 g, 175.00 mmol) was added. Trichloromethylsilane (18.90 g, 175.00 mmol) was added in portions to the stirred solution. A solution of NaI (26.26 g, 175.00 mmol) in CH_3CN (140.0 mL) was prepared and added dropwise at room temperature. After the addition was complete the mixture was heated to 50−60 °C and stirred for 3 h. The reaction mixture was poured onto a mixture of dilute $NaHCO_3$, and ice and was extracted with MtBE. The organic layers were washed with water and brine. After concentration of the combined ether layers the product was distilled over a 15-cm Vigreux column (97 °C, 0.05 mbar). **11a** was obtained as a colorless oil (29.00 g, 82%). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.73 (d, J = 16.2 Hz, 1 H), 5.59 (d, J = 16.2 Hz, 1 H), 4.01 (dd, J = 7.1, 14.1 Hz, 2 H), 3.93 (dd, J = 2.0, 29.6 Hz, 2 H), 1.48−1.30 (m, 4 H), 1.11 (t, J = 7.1 Hz, 3 H), 0.64−0.54 (m, 6 H), 0.00 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 167.0, 160.1 (2 s), 153.5, 120.0 (2 d), 90.4, 60.1 (2 t), 50.0 (s), 26.7 (2 t), 14.2, 8.4, 0.0 (6 q). IR (CCl_4, cm^{-1}): ν 2968w, 1720m, 1650w, 1620w. MS (EI): *m*/*z* 284 (5, $M^{+\cdot}$), 269 (7, $[M-CH_3]^+$), 255 (19, $[M-C_2H_5]^+$), 239 (3, $[M-OC_2H_5]^+$), 227 (3), 75 (31, $[C_2H_7OSi]^+$), 73 (100, $[C_3H_9Si]^+$). HRMS (EI): calcd. for $C_{15}H_{28}O_3Si$ (M^+): 284.1808; found, 284.1798.

Ethyl 3-[1-(1-Trimethylsilanyloxyvinyl)cyclohexyl]acrylate (11b). Prepared from **10b** (2.00 g, 8.93 mmol) following the same procedure reported for the synthesis of **11a**. Chromatography over silica gel with (hex/MtBE 95:5) afforded **11b** as a colorless liquid (1.75 g, 66%). ^1H NMR (300 MHz, C_6D_6; δ, ppm): 6.64 (d, J = 16.0 Hz 1 H), 5.62 (d, J = 16.0 Hz, 1 H), 4.00 (q, J = 7.1 Hz, 2 H), 3.961 (dd, J = 1.8, 11.1 Hz, 2H), 1.61−1.17 (m, 10 H), 1.10 (t, J = 7.1 Hz, 3 H), 0.17 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 167.0, 161.3 (2 s), 154.6, 120.2 (2 d), 89.5, 60.0 (2 t), 46.3 (s), 33.3, 26.0, 22.3 (5 t), 14.2 (q), 0.0 (3 q). IR (CCl_4, cm^{-1}): ν 2935m, 2860w, 1719m, 1648w, 1620w. MS (EI): *m*/*z* 296 (6, $M^{+\cdot}$), 223 (17), 281 (2, $[M-CH_3]^+$), 267 (3, $[M-C_2H_5]^+$), 253 (3, $[M-C_3H_7]^+$), 208 (19), 196 (15), 75 (31, $[C_2H_7OSi]^+$), 73 (100, $[C_3H_9Si]^+$). HRMS (EI): calc. for $C_{16}H_{28}O_3Si$ (M^+): 296.1808; found, 296.1797.

3,3-Diethyl-6-hydroxyhex-4*E*-en-2-one (12a). A solution of **11a** (250 mg, 0.88 mmol) in THF (5.0 mL) was cooled to −10 °C by means of an ice/NaCl bath. $LiAlH_4$ (21 mg, 0.55 mmol) was added in portions keeping the temperature at −10 °C. Cooling was removed, and the mixture was stirred for 1 h. The reaction was quenched by carefully adding water. The mixture was extracted with MtBE, the organic layers were combined, washed with water and brine, and concentrated. Chromatography over silica gel (hex/MtBE 3:7) and short-path distillation (0.05 mbar, 130 °C) gave **12a** as a colorless viscous oil (120 mg, 80%). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 5.72−5.69 (m, 2 H), 4.19−4.16 (m, 2 H), 2.09 (s, 3 H), 1.88 (s, 1H), 1.85−1.61 (m, 4H), 0.76 (t, J = 7.6 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 211.0 (s), 133.5, 130.3 (2 d), 63.5 (t), 57.5 (s), 26.0 (2 t), 25.8 (q), 8.2 (2 q). IR (CCl_4, cm^{-1}): ν 3402br, 2967m, 2940m, 2880w, 1702s. MS (EI): *m*/*z* 170 (1, $M^{+\cdot}$), 152 (1 $[M-H_2O]^+$), 141 (4, $[M-C_2H_4]^+$), 110 (52), 95 (26), 81 (64), 67 (33), 43 (100, $[C_2H_3O]^+$). HRMS (EI): calcd. for $C_9H_{15}O_2$ ($[M-CH_3]^+$): 155.1072; found, 155.1080.

1-[1-(3-Hydroxyprop-1*E*-en-1-yl)cyclohexyl]ethanone (12b). Prepared from **11b** (1.00 g, 3.40 mmol) by the same procedure reported for the synthesis of **12a**. Because of higher steric hindrance, the hydrolysis of the silylenolether was incomplete and a mixture of **12b*** and **12b** was obtained (Figure 3). The crude product was stirred in a 1 M solution of tetra-*n*-butylammonium fluoride in THF (2 mL) to complete the hydrolysis. For details on the isolation and characterization of **12b***, see Supporting Information. After purification by chromatography over silica gel (hex/MtBE 1:1) and drying in vacuo **12b** was obtained as a colorless oil (279 mg, 45%). ^1H NMR (300 MHz, C_6D_6; δ, ppm): 5.75−5.54 (m, 2 H), 4.15 (dd, J = 1.3, 5.3 Hz, 2 H), 2.53 (s 1 H), 2.10 (s, 3 H), 1.98−1.92 (m, 2 H), 1.57−1.53 (m, 4 H), 1.36−1.39 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 210.9 (s), 134.4, 130.7 (2 d), 63.2 (t), 54.2 (s), 32.9, 25.7 (3t), 25.5 (q), 22.6 (2t). IR (CCl_4, cm^{-1}): ν 3420br, 2932s, 2856m, 1702vs. MS (EI): *m*/*z* 182 (1, $M^{+\cdot}$), 164 (3, $[M-H_2O]^+$), 151 (5, $[M-CH_2OH]^+$), 122 (100), 107 (41), 93 (73), 79 (85).

2,2-Diethyl-3-vinylcyclobutanone (6a).[24] A solution of **12a** (1.00 g, 6.50 mmol) in pyridine (12.0 mL) was cooled to −10 °C by means of an ice/NaCl bath. Methanesulfonic acid chloride (0.55 mL, 7.15 mmol) was added dropwise, and the mixture was stirred at −10 °C for a total of 1.5 h. The mixture was poured onto water (50 mL) and extracted with MtBE. The combined organic layers were washed with aq. $CuSO_4$ solution until no more darkening of the solution occurred, indicating that all of the residual pyridine had been removed. The organic solutions were washed with water

(23) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956**, *78*, 4609−4619.
(24) Martin, J. C.; Gott, P. G. French Patent 1414457, priority, 15.10.1965, (to Eastman Kodak Co.).

and brine and concentrated. Chromatography over silica gel with (hex/MtBE 95:5) gave **4a** as a colorless oil (750 mg, 47%). The product is irritant and sensitive to air and humidity. A solution of **4a** (180 mg, 0.73 mmol) in THF (1.5 mL) was cooled to 0−5 °C by means of an ice/H_2O bath and 1 M ^{t}BuOK in ^{t}BuOH (0.75 mL, 0.75 mmol) was added dropwise. The yellow solution was stirred at 0 °C for 30 min. The mixture was poured onto water and extracted with MtBE. The ether layers were washed with water and brine, dried, and concentrated. The crude product was purified by column chromatography over silica gel (pentane/ Et_2O 9:1) and short path distillation (100 mbar, 80 °C). Cyclobutanone **6a** was obtained as a colorless, volatile liquid (50 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.04−5.89 (m, 1 H), 5.20−5.09 (m, 2 H), 3.11−2.92 (m, 2 H), 2.87−2.76 (m, 1 H), 1.75−1.46 (m, 4 H), 0.93−0.85 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 210.2 (s), 136.9 (d), 127.1 (t), 57.7 (s), 45.1 (t), 26.2 (2 t), 25.8 (d), 8.2 (2 q). IR (CCl_4, cm^{-1}): ν 2972m, 2941m, 1769s. MS (EI): *m*/*z* 110 (21, $[M-CH_2CO]^+$), 108 (21), 79 (67), 78 (49), 72 (60), 56 (47), 55 (100).

3-Vinylspiro[3.5]nonan-1-one (6b). Methanesulfonate **4b** was prepared from **12b** (1.50 g, 8.24 mmol) by the same procedure as **4a**. Purification of the crude product by chromatography over silica gel (hex/MtBE 95:5) and drying in vacuo afforded **4b** as a colorless liquid (850 mg, 40%). The product is irritant and sensitive to air and humidity. **4b** (800 mg, 3.07 mmol) was converted to **6b** by the same procedure reported for **6a**. After chromatography over silica gel (hex/Et_2O 8:2), cyclobutanone **6b** (280 mg, 56%) and the fragmentation product **13b** (60 mg, 11%) were obtained as colorless oils. Spectroscopic data for **6b**: ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.02−5.86 (m, 1 H), 5.17 (d, J = 1.1 Hz, 1 H), 5.15−5.09 (m, 1 H), 3.14 (dd, J = 17.5, 9.1 Hz, 1 H), 2.89 (dd, J = 7.0, 17.6 Hz, 1 H), 2.69 (q, J = 8.1 Hz, 1 H), 1.83−1.23 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 214.0 (s), 137.2 (d), 116.2 (t), 67.6 (s), 46.5 (t), 39.8 (d), 33.7, 28.0, 25.5, 22.7, 22.4 (5 t). IR (CCl_4, cm^{-1}): ν 2928m, 2853w, 1769vs. MS (EI): *m*/*z* 164 (1, $M^{+\cdot}$), 136 (1, $[M-CO]^+$), 122 (71), 110 (39), 107 (38), 93 (27), 79 (58), 67 (100), 54 (46, $[C_4H_6]^+$). HRMS (EI): calc. for $C_{11}H_{16}O$ (M^+): 164.1201; found, 164.1192. Spectroscopic data for **13b**: ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.62 (td, J = 17.1 Hz, 1 H), 5.79 (d, J = 11.0 Hz, 1 H), 5.09 (dd, J = 16.8, 2.0 1 H), 4.95 (dd, J = 10.1, 2.0 Hz, 1 H), 2.28 (s, 2 H), 2.14 (s, 2 H), 1.57−1.55 (m, 6 H). IR (CCl_4, cm^{-1}): ν 2977vs, 2935vs, 2858m, 1767vs. MS (EI): *m*/*z* 122 (40, $M^{+\cdot}$), 107 (45, $[M-CH_3]^+$), 93 (36, $[M-C_2H_5]^+$), 79 (100, $[M-C_3H_7]^+$). HRMS (EI): calcd. for $C_{11}H_{16}O$ (M^+), 164.1201; found, 164.1192.

5,5-Diethylhept-3*E*-ene-2,6-dione (14). To a solution of **9a** (24.43 g, 0.17 mol) in xylene (250.0 mL) 1-(triphenyl-λ^5-phosphanylidene)propan-2-one (60.42 g, 0.19 mol) was added, and the suspension was heated to reflux. After 24 h the mixture was cooled to room temperature, diluted with MtBE and washed with water and brine. The organic solution was concentrated and the residue distilled over a 20-cm Vigreux column (68 °C, 0.05 mbar). The diketone **14** was obtained as a colorless oil (23.00 g, 74%). The typical (*E*)-alkene absorption peaks at 1674 and 988 cm^{-1} in the IR spectrum as well as the vinylic proton spin-coupling constant of J = 16.8 Hz in the ^{1}H NMR (300 MHz, $CDCl_3$, δ 6.94 and 6.12) spectrum are good indicators that the product possesses *E* configuration. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.94 (d, J = 16.8 Hz, 1 H), 6.12 (d, J = 16.8 Hz, 1 H), 2.31 (s, 3 H), 2.13 (s, 3 H), 1.85−1.76 (m, 4 H), 0.78 (t, J = 7.6 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.7, 198.0 (2 s), 148.4, 131.0 (2 d), 58.5 (1 s), 27.1 (2 t), 27.0, 25.9 (2 q), 8.4 (2 q). IR (CCl_4, cm^{-1}): ν 2969w, 2881w, 1703s, 1674s, 1619m, 988m. MS (EI): *m*/*z* 153 (1, $[M-C_2H_5]^+$), 140 (37), 125 (15), 111 (46), 97 (13), 43 (100, $[C_2H_3O]^+$). Anal. calcd. for $C_{11}H_{18}O_2$ (182): C 72.49, H 9.95. Found: C 72.36, H 9.72.

(6*R*)-3,3-Diethyl-6-hydroxyhept-4*E*-en-2-one ((*R*)-15). A solution of (+)-Ipc_2BH (5.00 g, 27.50 mmol) in Et_2O (25.0 mL) was cooled to −60 °C and HCl in Et_2O (7.40 mL, 30.00 mmol) was added dropwise over 30 min. After stirring at 0 °C for 1 h the solution was concentrated and dried in vacuo. The active reagent (+)-Ipc_2BCl was obtained as a colorless, viscous liquid and was used without further purification. THF (25.0 mL) was added, and the solution was cooled to −60 °C by means of a CO_2/acetone bath. A solution of **14** (8.58 g, 30.00 mmol) in 10.0 mL of THF was added dropwise and stirring was continued at −60 °C for 1 h. The mixture was allowed to reach room temperature and stirring was continued for 16 h. The resulting dark-purple mixture was treated with diethanol amine (7.00 g, 66.60 mmol). The solids were removed by filtration and the orange liquid was diluted with MtBE, washed with water and brine, and concentrated. After chromatography over silica gel (hex/MtBE 1:1) and drying in vacuo, (*R*)-**15** was obtained as colorless oil (3.87 g, 77%, 48% ee). The product is sensitive to heat and cannot be distilled without decomposition. $[\alpha]^{25}_D$ = −6.45 (*c* 0.945, MeOH). The product was treated with (−)-camphanic acid chloride (6.84 g, 31.6 mmol) in pyridine (35 mL) at 0 °C and then stirred at room temperature for 3 h. The reaction mixture was diluted with MtBE and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. The solid residue was recrystallized (hex/MtBE 9:1) until the value of the optical rotation remained constant. $[\alpha]^{25}_D$ = +9.75 (*c* 1.005, MeOH). **16** was obtained as fine colorless crystals (1.64 g, 21.4%, 99% de). Mp 67−69 °C. The camphanoate **16** was dissolved in EtOH (20 mL) and hydrolyzed with 3 M NaOH (5 mL). The mixture was stirred for 1 h and then diluted with water (100 mL) and extracted with MtBE. The ether layers were combined, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was dried in vacuo to afford enantiomerically pure (*R*)-**15** (824 mg, 99%, 99% ee). $[\alpha]^{25}_D$ = −12.48 (*c* 1.307, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 5.56−5.34 (m, 2 H), 4.08−3.97 (m 1 H), 1.80 (s, 3 H), 1.69−1.44 (m, 4 H), 1.26 (d, J = 3.4 Hz, 1 H), 1.09 (d, J = 6.5 Hz, 3 H), 0.66 (dt, J = 11.2, 3.6 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 211.1 (s), 135.4, 131.5, 68.7 (3 d), 57.3 (s), 26.0, 25.9 (2 t), 25.7, 23.4 (2 q), 8.1 (2 q). IR (CCl_4, cm^{-1}): ν 3430br, 2968m, 2940w, 2880w, 1703vs. MS (EI): *m*/*z* 169 (1, $[M-CH_3]^+$), 155 (1, $[M-C_2H_5]^+$), 124 (40), 109 (12), 95 (59), 43 (100, $[C_2H_3O]^+$). Anal. calcd. for camphanoate **16** $C_{21}H_{32}O_5$ (364): C 69.20, H 8.85. Found: C 69.29, H 8.88.

(6*S*)-6-Chloro-3,3-diethylhept-4*E*-en-2-one ((*S*)-17). A mixture of (*R*)-**15** (280 mg, 1.52 mmol, 98% ee) and hexachloroacetone (0.51 mL, 3.34 mmol) was cooled to 0 °C and triphenylphosphine (420 mg, 1.60 mmol) was added at once. The mixture was stirred at 0 °C for 1 h and then at room temperature for 15 h. The mixture was diluted with MtBE and washed with water, sat. $NaHCO_3$ solution, and brine. After drying and concentration of the combined ether extracts the crude product was purified by chromatography over silica gel (hex/MtBE 95:5) and short-path distillation (80 °C, 0.05 mbar). (*S*)-**17** was obtained as a colorless liquid (260 mg, 85%, 77% ee). $[\alpha]^{25}_D$ = +20.70 (*c* 1.145, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 5.49−5.40 (m, 2 H), 4.16−4.20 (m, 1 H), 1.75 (s, 3 H), 1.59−1. 36 (m, 4 H), 1.28 (d, J = 6.6 Hz, 3 H), 0.60 (dd, J = 7.5, 7.9 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 210.2 (s), 133.5, 133.3, 57.9 (3 d), 57.3 (1 s), 26.2, 26.0 (2 t), 25.7, 25.2 (2 q), 8.1 (2 q). IR (CCl_4, cm^{-1}): ν 2969m, 2881w, 1706vs. MS (EI): *m*/*z* 173 (3, $[M-C_2H_5]^+$), 167 (2, $[M-Cl]^+$), 159 (2, $[M-CH_3CO]^+$), 124 (75), 109 (17), 95 (100), 81 (47), 67 (48). HRMS (EI): calcd. for $C_{10}H_{16}OCl$ ($[M-CH_3]^+$): 187.0890; found, 187.0881.

2,2-Diethyl-3-(prop-1*E*/*Z*-en-1-yl)cyclobutanone ((*E*/*Z*)-18). A solution of (*S*)-**17** (1.00 g, 4.95 mmol, 77% ee) in THF (22.0 mL) was cooled to 0 °C. ^{t}BuOK 1 M in ^{t}BuOH (5.00 mL, 5.00 mmol) was added dropwise to the stirred solution over the period of 1 h. The mixture was allowed to reach room temperature and stirring was continued for 4 h. The reaction was quenched with water and extracted with MtBE. The organic layers were combined, washed with water and brine, dried, and concentrated. The crude product mixture was purified by chromatography over silica gel (hex/MtBE

9:1) and short-path distillation (10 mbar, 80 °C). (*E*/*Z*)-**18** (ratio 85:15, GC) was obtained as a colorless oil (402 mg, 49%). $[\alpha]^{25}_D = -5.42$ (*c* 0.720, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 5.36−5.18 (m, 2 H), 2.78−2.56 (m, 2 H), 2.49−2.36 (m, 1 H), 1.54 (d, $J = 4.9$ Hz, 1 H), 1.52−1.25 (m, 4 H), 0.84 (t, $J = 7.4$ Hz, 3 H), 0.73 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 214.1 (s), 130.0, 127.1 (2 d), 70.6 (s), 47.5 (t), 36.9 (d), 25.0, 21.7 (2 t), 17.8, 13.2, 8.4, 7.7 (3 q). IR (CCl_4, cm^{-1}): ν 2967m, 2921w, 1771vs. MS (EI): *m*/*z* 166 (2, M^+), 151 (1, $[M-CH_3]^+$]), 138 (5, $[M-C_2H_4]^+$), 124 (40), 109 (18), 98 (57), 95 (68), 83 (100), 67 (46). Anal. calcd. for $C_{11}H_{18}O$ (166): C 79.46, H 10.91. Found: C 79.44, H 10.72. HRMS (EI): calc. for $C_{11}H_{18}O$ (M^+): 166.1358. Found: 166.1356.

Separation of (*E*)-18 and (*Z*)-18. $AgNO_3$ (6.00 g, 35.00 mmol) was dissolved in acetonitrile (100.0 mL) and silica gel (50.00 g) was added. The acetonitrile was removed by rotary evaporator (200 mbar) and the $AgNO_3$ impregnated silica gel was dried in vacuo (0.05 mbar) for 24 h. A chromatography column (12 × 1 cm) was filled with the treated silica gel, and a mixture of (*E*)-**18** and (*Z*)-**18** (*E*/*Z* = 85:15, 45 mg, 0.27 mmol) was separated over 48 fractions (hex/MtBE 97.5 : 2.5). The R_f values for (*E*)-**18** and (*Z*)-**18** on $AgNO_3$-impregnated silica gel thin-layer chromatography plates (hex/MtBE 95:5) were 0.3 and 0.2, respectively. The isolated *E* and *Z* isomers were purified by microscale distillation (0.05 mbar, 40 °C) under dust-free conditions. Analysis by ROA spectroscopy indicated (*S*)-configuration for (*E*)-**18** (32 mg, 71%, 75% ee) and (*R*)-configuration for (Z)-**18** (3 mg, 7%, 75% ee). $[\alpha]^{25}_D$ (*S*)-(*E*)-**18** = +0.96 (*c* 1.040, CH_2Cl_2). ^{1}H NMR for (*E*)-**18** (500 MHz, C_6D_6; δ, ppm): 5.31−5.19 (m, 2 H), 2.71 (dd, $J = 17.3$, 9.1 Hz, 1 H), 2.60 (dd, $J = 17.3$, 7.9 Hz, 1 H), 2.39−2.37 (m, 1 H), 1.53 (d, $J = 5.7$ Hz, 3 H), 1.52 (dq, $J = 14.3$, 7.5 Hz, 1 H), 1.42 (dq, $J = 14.4$, 7.5 Hz, 1 H), 1.39 (dq, $J = 14.3$, 7.5 Hz, 1 H), 1.31 (dq, $J = 14.4$, 7.5 Hz, 1 H), 0.83 (t, $J = 7.5$ Hz, 3 H), 0.71 (t, $J = 7.5$ Hz, 3 H). $[\alpha]^{25}_D$ (*R*)-(*Z*)-**18** = −5.94 (*c* 0.690, CH_2Cl_2). NMR analysis showed that (*Z*)-**18** contained 25% of the dehydrochlorination product **20**. The following NMR data was elaborated from the mixture and does therefore not necessarily correspond precisely to that of the corresponding pure compounds. ^{1}H NMR for (*Z*)-**18** (500 MHz, C_6D_6; δ, ppm): 5.39 (dqd, $J = 10.7$, 6.9, 1.0 Hz, 1 H), 5.24 (ddq, $J = 10.7$, 9.6, 1.8 Hz, 1 H), 280.−2.69 (m, 2 H), 2.49−2.47 (m, 1 H), 1.51−1.38 (m, 3 H), 1.42 (dd, $J = 6.9$, 1.8 Hz, 3 H), 1.33 (dq, $J = 14.5$, 7.5 Hz, 1 H), 0.82 (t, $J = 7.5$ Hz, 3 H), 0.73 (t, $J = 7.5$ Hz, 3 H). ^{1}H NMR for **20** (500 MHz, C_6D_6; δ, ppm): 6.22 (dtd, $J = 17.0$, 10.1, 0.6 Hz, 1 H), 6.00 (dd, $J = 15.8$, 10.3 Hz, 1 H), 5.51 (dd, $J = 15.8$, 0.6 Hz, 1 H), 5.05 (d, $J = 17.0$ Hz, 1 H), 4.95 (d, $J = 10.1$ Hz, 1 H), 1.75 (s, 3 H), 1.60 (dq, $J = 14.5$, 7.5 Hz, 2 H), 1.51 (dq, $J = 14.8$, 7.5 Hz, 2 H), 0.63 (t, $J = 7.5$ Hz, 6 H).

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Supporting Information Available: Experimental procedures for the synthesis of **8a,b**; **9a,b**; **12b***, X-ray crystallographic data for **16**, the determination of the ee for (*S*)-**15** by ^{1}H NMR, chiral GC analysis of (*S*)-**17** and (*E*/*Z*)-**18**, as well as ^{1}H and ^{13}C NMR data for **9a,b**, **10a,b**, **12a**, **12b***, **6a,b**, **14**, (*R*)-**15**, (*S*)-**17**, and (*E*/*Z*)-**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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