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Intramolecular Michael Reactions by Iron(III) Catalysis

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Abstract—Seven-membered ring annulation is achieved by an intramolecular Michael reaction catalyzed by iron(III) chloride hexahydrate. Reaction conditions are mild and non-basic, and chemo- and stereoselectivity is excellent. Contrastingly, this method fails for a 17-membered ring annulation.

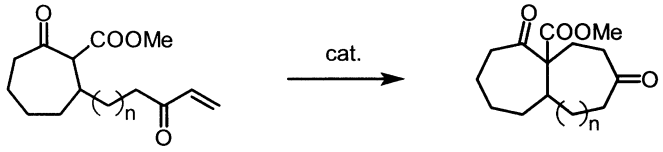
Introduction

Iron(III) chloride hexahydrate is to date the most efficient catalyst for the Michael reaction of β-keto esters with vinyl ketones.[1–3] Owing to the mild and non-basic reaction conditions, the chemoselectivity of this process is superior to that offered by base catalysis,[4–8] since the latter suffers from various unwanted side- and subsequent reactions, such as aldol cyclizations, ester solvolysis or retro-Claisen type decompositions. Moreover, since conversions are quantitative within hours at room temperature, the isolated yields are generally very good.[9] Inspired by these results on intermolecular Michael reactions we considered $FeCl_3 \cdot 6H_2O$ to be also an efficient catalyst for intramolecular conversions,[10–15] with special respect to macrocyclizations still being a challenging goal in synthetic organic chemistry. In the past some reports on macrocyclizations by intramolecular Michael reactions have been reported by others.[16–19] Herein we wish to report on our results on seven-[20] and seventeen-membered carboannulations by intramolecular Michael reactions catalyzed by $FeCl_3 \cdot 6H_2O$.

Results and Discussion

Seven-membered ring annulation

Donor–acceptor functionalized precursor **1a** was cleanly converted with a catalytic amount of $FeCl_3 \cdot 6H_2O$ to the bicyclo[5.5.0]-dodecane derivative **2a** (Scheme 1). The reaction proceeded at ambient temperature in CH_2Cl_2 as solvent within a few hours, and the isolated yield was good (80%). Separation of the product from all iron-containing materials was simply accomplished by filtration through SiO_2. Basic reaction conditions were avoided, thus, no side- or subsequent products were observed. Moreover, no dimeric or oligomeric species resulting from an intermolecular process were detectable by GC-MS. Besides a very high chemoselectivity, quantitative stereoselectivity was observed: only one diastereoisomer of the racemic material **2a** was isolated. After assignment of all proton and carbon NMR resonances by H,H-COSY, DEPT, HMBC and HMQC experiments the relative configuration was established to be *trans*: A *J*-resolved 500 MHz ^{1}H NMR



1a, n = 1
1b, n = 11

2a, n = 1, 80%
2b, n = 11, 8%

Scheme 1. Iron(III) chloride catalyzed intramolecular Michael reactions; reagents and conditions: **1a**, 5 mol% $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, 23°C, 12 h, 80% yield of **2a**, 11% of **1a** was recovered; **1b**, 10 mol% $FeCl_3$, CH_2Cl_2, 2 h ultrasonication at 23°C, then 6 h stirring at 23°C.

Keywords: annulation; catalysis; iron compounds; Michael reactions.
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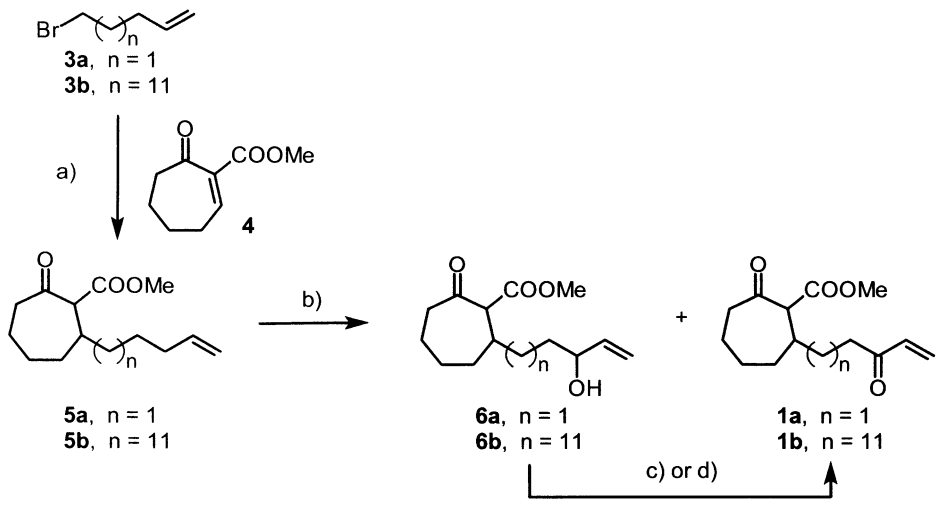


Scheme 2. Reagents, conditions, and yields: (a) 1. Mg, THF (ultrasound for **3b**), 2. CuI, −20°C, 1 h, 3. **4** (0.7 equiv.), −78°C to 23°C, **5a**: 85%, **5b**: 36%; (b) SeO_2 (2 equiv.), $tBuO_2H$ (5 equiv.), CH_2Cl_2, 23°C, 15 h, **6a**: 38% (**1a**: 30%, **5a**: 27% recovered), **6b**: 60%; (c) for **6a**: 1. PCC (1.5 equiv.), CH_2Cl_2, 23°C, 4 h, 2. HCl–H_2O, **1a**: 80%; (d) for **6b**: NMO (6 equiv.), TPAP (0.07 equiv.), mol. sieves (4 Å), CH_2Cl_2, 0°C, 1 h, **1b**: 86%.

spectrum gave a triplet–triplet coupling pattern of the 7-H (methine) signal at 1.71 ppm, representing a strictly symmetrical environment of this proton with two equatorial (J=3 Hz) and two axial (J=11 Hz) vicinal protons. Such a high symmetry can only be achieved with *trans*-connection of the two seven-membered rings.

Seventeen-membered ring annulation

Encouraged by the latter result we converted the starting material **1b** bearing a C_{15}-side chain with a catalytic amount of $FeCl_3 \cdot 6H_2O$ under both high-dilution and pseudo-high-dilution conditions.[21] To our surprise we found conversion of **1b** to products with either water or MeOH (from the CH_2Cl_2 solvent applied) being added to the vinyl ketone moiety. Consequently, in further experiments we excluded moisture, applied anhydrous $FeCl_3$ and used MeOH-free CH_2Cl_2 as solvent.

However, at ambient temperature under pseudo-high-dilution conditions (addition of a solution of substrate **1b** to up to 10 equiv. of a 10 g/l solution of $FeCl_3$ in CH_2Cl_2 over a period up to 5 days) only starting material was recovered almost quantitatively. Thus, we decided to run the reaction at elevated temperature (up to 70°C in a sealed flask) under diluted conditions (1.5–25 mmol/l in THF or CH_2Cl_2 with 0.1–1 equiv. $FeCl_3$), but again only starting material was recoverable after workup in 14–40% yield, and no other unique material was identified after chromatography. It is important to note, that we were neither able to accomplish the conversion of **1b** to **2b** with a basic catalyst (Cs_2CO_3 in THF).

Finally, compound **1b** was converted with 0.1 equiv. $FeCl_3$ in 100 mmol/l CH_2Cl_2. Immediate precipitation of a iron-dionato complex occurred, but after 2 h of ultrasonication at ambient temperature a homogeneous mixture was obtained, which was further stirred for 6 h. After workup and twice chromatography about 8% of product **2b** was isolated besides various presumably dimeric or oligomeric species (Scheme 1). Characterization of **2b** is based on HRMS and ^{1}H NMR spectroscopy. The latter shows no more olefinic signals, but four distinguished MeO resonances in equal ratio at 3.70 to 3.75 ppm being due to the existence of two relatively stable conformers each of two diastereoisomers.

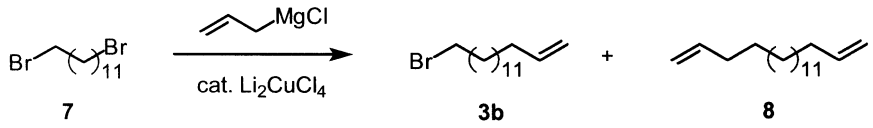
Syntheses of precursors

Syntheses of donor–acceptor functionalized substrates **1a**,**b** started with ω-bromo-α-olefins **3a,b** being converted after Grignard formation (ultrasonication was required in case of **3b**) and transmetallation with CuI[22] with the 2-acceptor substituted cycloalkenone **4** to yield cyclic oxoesters **5a**,**b** with an ω-alkenyl side chain. In case of **5b** the low yield (36%) might be due to the tautomerization of **4** to the corresponding dienol,[23] which was isolated in 34% yield as a byproduct and could protonate the cuprate derived from **3b** under reaction conditions.

Subsequently, compounds **5a**,**b** were submitted to allylic oxidation with freshly sublimated SeO_2 and $tBuO_2H$.[24–26] In case of **5a** besides the product **6a** (38%), enone **1a** (30%) was formed and starting material **5a** was recovered (27%). All three compounds were separable by column chromatography. In case of **5b** allylic alcohol **6b** was obtained in 60% yield. In both cases increase of reaction times or temperatures did not raise yields, but lead to unspecified decomposition making the purification of products more difficult.

Allylic alcohol **6a** was oxidized to the enone **1a** by PCC[27] in 80% yield, compound **6b** was oxidized by the system TPAP-NMO[28] to give **1b** in 86% yield (Scheme 2).

Whereas ω-bromo-α-olefin **3a** was commercially available, compound **3b** was not and had to be prepared by copper cross-coupling reaction[29] of a α,ω-dibromo alkane **7** with an allyl Grignard reagent (Scheme 3). An optimal yield of 47% of **3b** was obtained and α,ω-diolefin **8** was isolated as the byproduct in 12% yield. The separation of **7**, **3b** and **8** was accomplished by column chromatography.



Scheme 3. Cu-catalyzed cross-coupling reaction to yield a ω-bromo-α-olefin, reagents, conditions, and yields: LiCl (0.4 equiv.), $CuCl_2$ (0.2 equiv.), allyl-MgCl (1.5 equiv.), THF, 0°C, 1 h, **3b**: 47%, **7**: 24% recovered, **8**: 12%.

Conclusion

Iron(III) chloride hexahydrate is an efficient catalytic system for seven-membered carboannulation by intramolecular Michael reaction of a cyclic oxoester with a vinyl ketone moiety. The reaction conditions are mild and not basic, the separation of the product from the catalyst is simply accomplished by filtration through SiO_2, the yield is high and the diastereoselectivity quantitatively *trans*. In contrast to this, the above mentioned method is not suitable for a macrocarboannulation reaction. The synthesis of substrates for an intramolecular Michael reaction was achieved in a straightforward manner by introduction of an ω-alkenyl side chain by cuprate addition to an α,β-unsaturated oxoester followed by stepwise allylic oxidation to the enone moiety.

Experimental

General

^1H NMR spectra were recorded with Bruker DRX 500 (500 MHz), AM 400 (400 MHz) and AC 200 (200 MHz). ^{13}C NMR spectra were recorded with Bruker DRX 500 (125 MHz) and AC 200 (50 MHz). ^1H and ^{13}C resonances were assigned by DEPT, HMBC, HMQC and H,H-COSY experiments. MS spectra were obtained with a Varian MAT 711 and MAT 955Q (high resolution). IR spectra were recorded with a Nicolet Magna IR 750. Elemental analyses were obtained with an Analytik Jena Vario EL.

Column chromatography was accomplished with Merck silica gel (Type 60, 0.063–0.200 mm). All manipulations involving Grignard or cuprate reagents were carried out in flame dried glassware under an atmosphere of N_2 and with absolute THF, which was freshly distilled from potassium. $CuCl_2$, CuI, and LiCl were dried in high vacuum, Mg was activated with I_2, and SeO_2 freshly sublimated prior to use. All other reagents were used as purchased. All starting materials were commercially available, except methyl 7-oxo-1-cycloheptene-1-carboxylate (**4**), which was obtained according to a literature protocol.[30] Solutions of allyl magnesium chloride and *tert*-butyl hydroperoxide were purchased from the Aldrich Chemical Co.

15-Bromo-1-pentadecene (3b). Solutions of LiCl (672 mg, 15.8 mmol) and $CuCl_2$ (1.07 g, 7.92 mmol) in abs. THF (each 30 ml) were combined and stirred over night at room temperature. 1,12-Dibromododecane (**7**) (13.0 g, 39.6 mmol) was added in one portion, and allyl magnesium chloride (60.0 mmol, 30.0 ml of a 2 mol/l solution in THF) was added within 30 min at 0°C, and the resulting mixture was stirred for 60 min at this temperature. Hydrochloric acid (100 ml, 1 mol/l) was added, and the mixture was stirred for 30 min at room temperature. Then the layers were separated, and the aqueous layer extracted with MTB (three times 50 ml). The combined organic layers were washed with brine (20 ml) and dried over $MgSO_4$. After filtration and evaporation of the solvent the crude product mixture was separated by chromatography (SiO_2, PE) to give three fractions: First, byproduct **8** (colorless wax, R_f=0.56, 1.19 g, 4.75 mmol, 12%) was obtained. Secondly, title compound **3b** was eluted (colorless oil, R_f=0.41, 5.37 g, 18.6 mmol, 47%). As the third fraction, starting material **7** was recovered (R_f=0.35, 3.15 g, 9.60 mmol, 24%). ^1H NMR ($CDCl_3$, 400 MHz): δ=1.26–1.54 (m, 20H), 1.85 (pentet, J=7.1 Hz, 2H, 14-CH_2), 2.04 (q, J=7.1 Hz, 2H; 3-CH_2), 3.40 (t, J=6.9 Hz, 2H; 15-CH_2), 4.93 (d, J=10.2 Hz, 1H; *E*-1-CH), 5.01 (dq, J=17.1 Hz, J=1.7 Hz, 1H; *Z*-1-CH), 5.82 (ddt, J=17.0 Hz, J=10.2 Hz, J=6.6 Hz, 1H; 2-CH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz): δ=28.18 (CH_2), 28.77 (CH_2), 28.94 (CH_2), 29.14 (CH_2), 29.44 (CH_2), 29.50 (CH_2), 29.53 (CH_2), 29.59 (CH_2), 29.62 (CH_2), 29.69 (CH_2), 32.85 (CH_2), 33.81 (CH_2), 33.87 (CH_2), 114.05 (CH_2), 139.16 (CH) ppm. IR (ATR): 1/λ=2917 (vs), 2851 (vs), 1641 (m), 1472 (m), 1463 (m), 1438 (m), 992 (m), 909 (s), 717 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 288 (2) [M^+], 97 (66), 83 (80), 69 (83), 55 (100) [CH_2=CH–$(CH_2)_2^+$]. $C_{15}H_{29}Br$ (289.30): Anal. calcd C 62.28, H 10.10; found C 62.30, H 10.46. Mol. mass calcd 288.1453, found 288.1457 (M^+, HRMS).

1,17-Octadecadiene (8). R_f (SiO_2, PE)=0.56. ^1H NMR ($CDCl_3$, 400 MHz): δ=1.17–1.38 (m, 24H), 2.04 (q, J=7.1 Hz, 4H; 3-CH_2, 16-CH_2), 4.92 (dq, J=10.2 Hz, J=1.7 Hz, 2H; *E*-1-CH, *E*-18-CH), 4.99 (dq, J=17.1 Hz, J=1.6 Hz, 2H; *Z*-1-CH, *Z*-18-CH), 5.81 (ddt, J=17.0 Hz, J=10.3 Hz, J=6.8 Hz, 2H; 2-CH, 17-CH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz): δ=26.93 (CH_2), 28.97 (CH_2), 29.18 (CH_2), 29.53 (CH_2), 29.64 (CH_2), 29.72 (CH_2), 33.84 (CH_2), 114.06 (CH_2), 139.27 (CH) ppm. IR (ATR): 1/λ=3077 (m), 2977 (m), 2923 (vs), 2853 (s), 1641 (m), 1466 (m), 1440 (m), 992 (m), 909 (s), 721 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 250 (1) [M^+], 97 (42), 83 (49), 69 (62), 55 (100) [CH_2=CH–$(CH_2)_2^+$]. $C_{18}H_{34}$ (250.46): Mol. mass calcd 250.2661, found 250.2663 (M^+, HRMS).

Methyl 3-(4-penten-1-yl)cycloheptanone-2-carboxylate (5a). A Grignard solution prepared from 5-bromo-1-pentene (**3a**) (1.77 g, 11.9 mmol) and Mg turnings (442 mg, 18.2 mmol) in THF (10 ml) was added at −20°C to a suspension of CuI (1.82 g, 9.55 mmol) in THF (20 ml). After stirring for 1 h at −20°C the mixture was cooled to −78°C, and a solution of acceptor **4** (1.42 g, 8.42 mmol) in THF (2 ml) was added. The mixture was stirred for 15 min at −78°C, then warmed up to room temperature within 1 h. NH_4Cl (50 ml of a saturated solution in H_2O) and conc. hydrochloric acid (2 ml) were added, and the resulting

suspension was extracted with MTB (three times 50 ml). After drying (Na_2SO_4) and filtration the combined organic layers were evaporated and the residue chromatographed on SiO_2 (PE/MTB 1:1, R_f=0.50) to yield the compound **5a** as a colorless oil (1.70 g, 7.13 mmol, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz), a mixture of two diastereoisomers, *trans*/*cis*=2:1, *trans*: δ=1.73–2.08 (m, 12H), 2.18–2.24 (m, 1H), 2.36–2.43 (m, 1H), 2.63–2.82 (m, 1H), 3.27 (d, J=9.6 Hz, 1H; 2-CH), 3.71 (s, 3H; OMe), 4.92–5.01 (m, 2H; 5′-CH_2), 5.71–5.83 (m, 1H; 4′-CH) ppm; *cis*: δ=1.73–2.08 (m, 13 H), 2.44–2.50 (m, 1H), 2.55–2.61 (m, 1H), 3.71 (s, 3H; OMe), 3.73 (d, J=6.3 Hz, 1H; 2-CH), 4.92–5.01 (m, 2H; 5′-CH_2), 5.71–5.83 (m, 1H; 4′-CH) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz), a mixture of two diastereoisomers, *trans* (major): δ=25.74 (CH_2), 25.89 (CH_2), 27.79 (CH_2), 31.71 (CH_2), 33.63 (CH_2), 34.26 (CH_2), 37.81 (CH), 41.88 (CH_2), 52.32 (CH_2), 65.89 (CH_3), 114.68 (CH_2), 138.40 (CH), 170.21 (C=O), 208.05 (C=O) ppm; *cis* (minor): δ=24.03 (CH_2), 26.65 (CH_2), 26.88 (CH_2), 27.03 (CH_2), 31.24 (CH_2), 32.00 (CH_2), 37.33 (CH), 43.30 (CH_2), 51.77 (CH), 62.34 (CH_3), 114.55 (CH_2), 138.56 (CH), 170.54 (C=O), 208.63 (C=O) ppm. IR (ATR): 1/λ=2930 (s), 2859 (m), 1744 (vs), 1707 (vs), 1640 (m), 1435 (s), 1303 (m), 1232 (s), 1200 (s), 1157 (s), 995 (m), 911 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 238 (2) [M^+], 206 (17), 169 (100) [$M^+-(CH_2)_3CH{=}CH_2$], 137 (44). $C_{14}H_{22}O_3$ (238.33): Mol. mass calcd 238.1569, found 238.1567 (HRMS).

Methyl 3-(14-pentadecen-1-yl)cycloheptanone-2-carboxylate (5b). A Grignard solution prepared from **3b** (2.54 g, 8.77 mmol) and activated Mg turnings (320 mg, 13.2 mmol) in THF (20 ml, ultrasonication was required to start the reaction) was added at −30°C to a suspension of CuI (1.31 g, 6.89 mmol) in THF (20 ml). After stirring for 2 h at −15°C the mixture was cooled to −78°C, and a solution of acceptor **4** (1.05 g, 6.27 mmol) in THF (10 ml) was added. The mixture was stirred for 15 min at −78°C, then warmed up to room temperature within 1 h. NH_4Cl (300 ml of a saturated solution in H_2O) was added, and the resulting suspension was filtered through a glass frit. The aqueous layer was extracted with MTB (three times 100 ml). After drying (Na_2SO_4) and filtration the combined organic layers were evaporated and the residue chromatographed twice on SiO_2 (1. PE/MTB 2: 1, R_f=0.50; 2. PE/MTB 10:1, R_f=0.16) to yield the compound **5b** as a colorless oil (845 mg, 2.23 mmol, 36%). ^{1}H NMR ($CDCl_3$, 400 MHz), *trans*-isomer (the *cis*-isomer is less than 5%): δ=1.09–1.89 (m, 30H; 15 CH_2), 2.01 (q, J=7.0 Hz, 2H; 13′-CH_2), 2.18–2.47 (m, 3H; 7-CH_2, 3-CH), 3.26 (d, J=9.5 Hz, 1H; 2-CH), 3.70 (s, 3H; OMe), 4.90 (d, J=10.1 Hz, 1H; 15′-*E*-C*H*H), 4.97 (dd, J=17.0 Hz, J=1.8 Hz, 1H; 15′-*Z*-CH*H*), 5.79 (ddt, J=17.0 Hz, J=10.2 Hz, J=6.7 Hz, 1H; 14′-CH) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz), a mixture of two diastereoisomers, *trans* (major): δ=23.97 (CH_2), 25.76 (CH_2), 26.33 (CH_2), 27.54 (CH_2), 27.68 (CH_2), 28.80 (CH_2), 29.00 (CH_2), 29.37 (CH_2), 29.50 (br., 5 CH_2), 31.61 (CH_2), 33.66 (CH_2), 34.70 (CH_2), 37.77 (3-CH), 41.70 (CH_2), 52.01 (OMe), 65.75 (2-CH), 113.91 (15′-CH_2), 138.90 (14′-CH), 170.03 (C=O), 207.63 (C=O) ppm; *cis*-isomer (missing signals are hidden by the major isomer): δ=22.53 (CH_2), 24.51 (CH_2), 24.78 (CH_2), 26.67 (CH_2), 26.75 (CH_2), 29.71 (CH_2), 31.72 (CH_2), 31.76 (CH_2), 31.87 (CH_2), 34.99 (CH_2), 43.10 (CH_2), 37.33 (3-CH), 51.47 (OMe), 62.22 (2-CH), 113.91 (15′-CH_2), 138.90 (14′-CH), 170.32 (C=O), 208.23 (C=O) ppm. IR (ATR): 1/λ=2923 (vs), 2852 (vs), 1746 (s), 1708 (vs), 1640 (m), 1462 (m), 1435 (m), 1230 (m), 1198 (m), 1158 (m), 994 (m), 908 (m), 720 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 378 (1) [M^+], 169 (92), 137 (46), 111, 97 (50), 83 (85), 69 (63), 55 (100) [$CH_2{=}CH(CH_2)_2^+$]. $C_{24}H_{42}O_3$ (378.59): Anal. calcd C 76.14, H 11.18; found C 76.04, H 11.33. Mol. mass calcd 378.3134, found 378.3134 (M^+, HRMS).

Methyl 3-(3-hydroxy-4-penten-1-yl)cycloheptanone-2-carboxylate (6a). Oxoester **5a** (1.50 g, 6.30 mmol), SeO_2 (1.36 g, 12.6 mmol), *t*BuO_2H (33 mmol, 5.5 ml of a 6.0 mol/l solution in decane) and CH_2Cl_2 (10 ml) were mixed and stirred for 15 h at room temperature. The supernatant was decanted, the residue washed twice with CH_2Cl_2 (after drying, this material could be resubmitted to SeO_2 sublimation), and from the combined CH_2Cl_2 solutions all volatile materials were removed in vacuo. The resulting crude oil was chromatographed on SiO_2 (PE/MTB 1:1) to yield three fractions: First, starting material **5a** was recovered (colorless oil, R_f=0.50, 789 mg of a mixture with *t*BuO_2H, molar ratio 1:2.5 by ^{1}H NMR, 1.70 mmol, 27%; this mixture was directly resubmitted to another SeO_2 oxidation). Secondly, enone **1a** was yielded (colorless oil, R_f=0.17, 476 mg, 1.89 mmol, 30%). And finally, allylic alcohol **6a** was obtained as a colorless oil (R_f=0.12, 608 mg, 2.39 mmol, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz), a mixture of four diastereoisomers: δ=1.24–2.77 (m, 13 H), 3.13–3.32 (m, 1H; 3-CH), 3.71 (s, 3 H; OMe), 3.66–3.82 (m, 1H; 2-CH), 4.04–4.11 (m, 1H; 3′-CH), 5.07–5.11 (m, 1H; 5′-C*H*H), 5.18–5.24 (m, 1H; 5′-CH*H*), 5.77–5.88 (m, 1H; 4′-CH) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz), a mixture of four diastereoisomers, two major and two minor isomers, major isomers: δ=25.62 (2 CH_2), 27.45 (2 CH_2), 30.17 (CH_2), 30.28 (CH_2), 31.44 (CH_2), 31.57 (CH_2), 33.54 (CH_2), 33.59 (CH_2), 37.38 (CH), 37.49 (CH), 41.72 (2 CH_2), 52.21 (CH), 52.24 (CH), 65.45 (CH_3), 65.48 (CH_3), 72.36 (CH), 72.76 (CH), 114.43 (CH_2), 114.68 (CH_2), 140.75 (CH), 140.84 (CH), 170.04 (C=O), 170.12 (C=O), 207.79 (C=O), 207.86 (C=O) ppm; minor isomers: δ=23.72 (CH_2), 23.79 (CH_2), 24.62 (CH_2), 25.98 (CH_2), 26.31 (CH_2), 26.61 (CH_2), 31.84 (CH_2), 34.70 (CH_2), 34.84 (CH_2), 34.97 (CH_2), 36.49 (CH), 37.11 (CH), 43.13 (CH_2), 43.18 (CH_2), 51.69 (CH), 51.73 (CH), 61.87 (CH_3), 62.05 (CH_3), 72.04 (2 CH), 114.29 (CH_2), 114.54 (CH_2), 141.10 (2 CH), 170.69 (C=O), 174.09 (C=O), 208.41 (C=O), 208.46 (C=O) ppm. IR (ATR): 1/λ=3460 (s), 2934 (s), 2861 (m), 1738 (vs), 1703 (vs), 1435 (m), 1349 (m), 1318 (m), 1265 (m), 1227 (m), 1199 (s), 1158 (s), 1057 (m), 993 (m), 923 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 253 (1) [M^+-H], 237 (10), 219 (17), 205 (100) [$M^+-OH-MeOH$], 137 (80). $C_{14}H_{22}O_4$ (254.33): Mol. mass calcd 253.1439 (for $C_{14}H_{21}O_4$), found 253.1436 (M^+-H, HRMS).

Methyl 3-(13-hydroxy-14-pentadecen-1-yl)cycloheptanone-2-carboxylate (6b). A mixture of oxoester **5b** (766 mg, 2.02 mmol), SeO_2 (460 mg, 4.14 mmol) and *t*BuO_2H (12 mmol, 2.0 ml of a 6.0 mol/l solution in decane) was stirred for 16 h at ambient temperature. After filtration and evaporation of volatile materials the filtrate was

chromatographed on SiO_2 (PE/MTB 1:1, R_f=0.38) to yield the title compound **6b** (481 mg, 1.21 mmol, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz), only one signal set, minor diastereoisomer not detectable: δ=1.15–1.30 (m, 21H), 1.45–1.65 (m, 7H), 1.72–1.90 (m, 3H), 2.15–2.25 (m, 1H), 2.35–2.45 (m, 1H), 2.70–2.83 (m, 1H), 3.27 (d, J=9.5 Hz, 1H; 2-CH), 3.71 (s, 3H; OMe), 4.08 (q, J=6.3 Hz, 1H; 13′-CH), 5.08 (dt, J=10.4 Hz, J=1.1 Hz, 1H; *E*-15′-CH), 5.20 (dt, J=17.3 Hz, J=1.1 Hz, 1H; *Z*-15′-CH), 5.85 (ddd, J=16.8 Hz, J=10.4 Hz, J=6.2 Hz, 1H; 14′-CH) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz), a mixture of two diastereoisomers, major: δ=25.30 (CH_2), 25.92 (CH_2), 26.47 (CH_2), 27.81 (CH_2), 29.43 (CH_2), 29.49 (CH_2), 29.57 (CH_2), 29.62 (CH_2), 31.71 (CH_2), 34.82 (CH_2), 37.04 (CH_2), 37.93 (CH), 41.89 (CH_2), 52.29 (CH), 65.97 (CH_3), 73.24 (CH), 114.45 (CH_2), 141.34 (CH), 170.31 (C=O), 208.22 (C=O) ppm; minor isomer (missing signals are hidden by the major isomer): δ=26.76 (CH_2), 27.68 (CH_2), 31.82 (CH_2), 31.99 (CH_2), 37.45 (CH), 43.30 (CH_2), 51.76 (CH), 62.44 (CH_3), 170.60 (C=O), 208.42 (C=O) ppm. IR (ATR): 1/λ=3446 (br, m), 2925 (vs), 2853 (vs), 1743 (s), 1706 (s), 1457 (m), 1435 (m), 1318 (m), 1262 (m), 1231 (m), 1198 (m), 1158 (m), 991 (m), 919 (m), cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 376 (2) [M^+-H_2O], 323 (5), 291 (10), 169 (100) [$M^+-(CH_2)_{12}CH(OH)CH{=}CH_2$], 137 (40), 111 (30). $C_{24}H_{42}O_4$ (394.59 g/mol): Mol. mass calcd 376.2977 (for $C_{24}H_{40}O_3$), found 376.2973 (M^+-H_2O, HRMS).

Methyl 3-(3-oxo-4-penten-1-yl)cycloheptanone-2-carboxylate (1a). A mixture of the allylic alcohol **6a** (500 mg, 1.98 mmol), PCC (641 mg, 2.97 mmol) and CH_2Cl_2 (10 ml) was stirred for 4 h at room temperature, then hydrochloric acid was added (20 ml, 1 mol/l). The liquid layers were decanted, and the residue dissolved in hydrochloric acid (2 ml, 6 mol/l). The combined aqueous layers were extracted with CH_2Cl_2 (2×10 ml), and finally, the combined organic layers were filtered through a SiO_2 column (10 cm, elution with MTB), which yielded compound **1a** (400 mg, 1.58 mmol, 80%) as a colorless oil pure by TLC (PE/MTB 1:5, R_f=0.43) and ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz), a mixture of two diastereoisomers, *trans*/*cis*=2:1, *trans*: δ=1.51–1.94 (m, 8H; 4 CH_2), 2.22–2.78 (m, 5H; 3-CH, 2 CH_2), 3.31 (d, J=9.5 Hz, 1H; 2-CH), 3.71 (s, 3H; OMe), 5.83 (d, J=10.4 Hz, 1H; *E*-5′-CH*H*), 6.21 (dd, J=17.6 Hz, J=0.9 Hz, 1H; *Z*-5′-C*H*H), 6.34 (dd, J=17.7 Hz, J=10.4 Hz, 1H; 4′-CH) ppm; *cis*: δ=1.51–1.94 (m, 8H; 4 CH_2), 2.22–2.78 (m, 5H; 3-CH, 2 CH_2), 3.71 (s, 3H; OMe), 3.72 (d, J=4.1 Hz, 1H; 2-CH), 5.83 (d, J=10.4 Hz, 1H; *E*-5′-CH*H*), 6.22 (dd, J=17.7 Hz, J=1.0 Hz, 1H; *Z*-5′-C*H*H), 6.35 (dd, J=17.7 Hz, J=10.5 Hz, 1H; 4′-CH) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz), a mixture of two diastereoisomers, *trans* (major): δ=25.70 (CH_2), 27.52 (CH_2), 28.61 (CH_2), 31.69 (CH_2), 36.63 (CH_2), 37.35 (CH), 41.87 (CH_2), 52.45 (CH_3), 65.38 (CH), 128.23 (5′-CH_2), 136.32 (4′-CH), 169.98 (C=O), 199.81 (C=O), 207.60 (C=O) ppm; *cis* (minor): δ=23.93 (CH_2), 26.36 (CH_2), 26.69 (CH_2), 32.29 (CH_2), 36.93 (CH), 37.76 (CH_2), 43.25 (CH_2), 51.91 (CH_3), 62.04 (CH), 127.69 (5′-CH_2), 136.50 (4′-CH), 170 (C=O), 200.12 (C=O), 208.19 (C=O) ppm. IR (ATR): 1/λ=2932 (s), 2862 (m), 1739 (s), 1704 (vs), 1616 (m), 1447 (m), 1436 (m), 1405 (m), 1352 (m), 1317 (m), 1264 (m), 1199 (s), 1156 (s), 1092 (m), 1017 (m), 993 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 252 (1) [M^+], 193 (4), 182 (38), 169 (14), 150 (34), 137 (36), 55 (100) [CH_2CHCO^+]. $C_{14}H_{20}O_4$ (252.31): Mol. mass calcd 252.1362, found 252.1367 (M^+, HRMS).

Methyl 3-(13-oxo-14-pentadecen-1-yl)cycloheptanone-2-carboxylate (1b). NMO (874 mg, 6.47 mmol) and ground molecular sieves (4 Å, 828 mg) were added at ambient temperature to a solution of alcohol **6b** (426 mg, 1.08 mmol) in abs. CH_2Cl_2 (10 ml). TPAP (60 mg, 0.16 mmol) was added and the mixture stirred for 1 h at 0°C. After filtration through SiO_2 (MTB) and evaporation, chromatography on SiO_2 (PE/MTB 2:1, R_f=0.30) yielded the compound **1b** (366 mg, 0.932 mmol, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz), only one signal set, minor diastereoisomer not detectable: δ=1.19–1.33 (m, 13H), 1.51–1.62 (m, 8H), 1.74–2.04 (m, 5H), 2.30–2.43 (m, 3H), 2.57 (t, J=7.4 Hz, 2H; 12′-CH_2), 2.74–2.80 (m, 2H; 7-CH_2), 3.27 (d, J=9.5 Hz, 1H; 2-CH), 3.72 (s, 3H; OMe), 5.81 (dd, J=10.4 Hz, J=0.9 Hz, 1H; *E*-15′-CH), 6.21 (dd, J=17.5 Hz, J=0.8 Hz, 1H; *Z*-15′-CH), 6.35 (dd, J=17.7 Hz, J=10.4 Hz, 1H; 14′-CH) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz), a mixture of two diastereoisomers, major: δ=24.03 (CH_2), 25.34 (CH_2), 26.49 (CH_2), 27.83 (CH_2), 29.26 (CH_2), 29.41 (CH_2), 29.45 (CH_2), 29.57 (CH_2), 29.64 (CH_2), 31.73 (CH_2), 34.85 (CH_2), 39.67 (CH_2), 41.92 (CH_2), 52.30 (CH), 65.99 (CH_3), 127.80 (CH_2), 136.61 (CH), 170.30 (C=O), 201.12 (C=O), 208.21 (C=O) ppm; minor isomer (missing signals are hidden by the major isomer): δ=24.11 (CH_2), 26.79 (CH_2), 26.91 (CH_2), 27.70 (CH_2), 32.01 (CH_2), 43.32 (CH_2), 51.76 (CH), 170.60 (C=O), 208.78 (C=O) ppm. IR (ATR): 1/λ=2925 (vs), 2853 (s), 1743 (s), 1706 (s), 1457 (m), 1435 (m), 1262 (m), 1231 (m), 1198 (m), 1158 (m), 991 (m), 919 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 392 (4) [M^+], 361 (18), 333 (12), 323 (22), 291 (38), 169 (100) [$M^+-(CH_2)_{12}COCH{=}CH_2$]. $C_{24}H_{40}O_4$ (392.58): Mol. mass calcd. 392.2927, found 392.2929 (M^+, HRMS).

***trans*-Methyl bicyclo[5.5.0]dodecan-2,11-dione-1-carboxylate (2a).** Compound **1a** (89 mg, 0.35 mmol) and $FeCl_3{\cdot}6H_2O$ (4.7 mg, 0.017 mmol) were stirred in CH_2Cl_2 (1 ml) for 12 h at ambient temperature. Subsequently, the reaction mixture was transferred onto the top of a silica gel column, and the product **2a** was eluted with PE/MTB (1:2, R_f=0.33) to yield 71 mg (80%) of **2a** as a colorless oil. Also, an amount of about 10 mg (11%) of the starting material **1a** was recovered (R_f=0.38). ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.36 (m, 1H; 5-H), 1.56 (m, 1 H; 4-H), 1.71 (tt, J=11 Hz, J=3 Hz, 1H; 7-H), 1.71–1.81 (m, 2H; 6-H, 8-H), 1.89–1.95 (m, 2H; 4-H, 5-H), 2.08–2.22 (m, 3H; 6-H, 8-H, 12-H), 2.27 (ddd, J=15 Hz, J=6 Hz, J=3 Hz, 1H; 12-H), 2.51 (ddd, J=16 Hz, J=6 Hz, J=3 Hz, 1H; 11-H), 2.54 (ddd, J=15 Hz, J=6 Hz, J=4 Hz, 1H; 9-H), 2.57 (m, 1H; 3-H), 2.61 (m, 1H; 9-H), 2.65 (ddd, J=16 Hz, J=12 Hz, J=3 Hz, 1H; 11-H), 2.70 (ddd, J=13 Hz, J=6 Hz, J=5 Hz, 1H; 3-H), 3.83 (s, 3H; CH_3) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz): δ=24.36 (4-C), 28.44 (5-C), 29.51 (8-C), 31.20 (12-C), 36.17 (6-C), 39.47 (11-C), 41.49 (3-C), 42.57 (9-C), 46.11 (7-C), 52.02 (OMe), 66.14 (1-C), 171.84 (*C*O_2Me), 209.68 (2-C), 212.71 (10-C) ppm. IR (ATR): 1/λ=2935 (s), 2862 (m), 1735 (vs), 1703 (vs), 1447 (s), 1449 (m), 1225 (s), 1158 (s), 1106 (m), 1019

(m), 936 (m), 799 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 252 (27) [M^+], 234 (10), 220 (16), 192 (26), 182 (52), 169 (46), 137 (100) [*cyclo*–$(CH_2)_4CHC(CO)CO^+$]. $C_{14}H_{20}O_4$ (252.31): Mol. mass calcd 252.1362, found 252.1366 (HRMS).

Methyl bicyclo[15.5.0]docosan-4,22-dione-1-carboxylate (2b). Anhydrous $FeCl_3$ (97.5 mg, 0.0601 mmol) was added to a solution of oxoester **1b** (236 mg, 0.601 mmol) in abs. CH_2Cl_2 (6 ml). After stirring for 15 min a brown material precipitated. The mixture was kept for 2 h in an ultrasound bath resulting in a homogeneous dark brown solution, which was further stirred for 16 h at room temperature. Half conc. HCl (5 ml) was added, and the mixture extracted three times with CH_2Cl_2. The combined extracts were filtered through SiO_2 (CH_2Cl_2) and evaporated. Twice chromatography on SiO_2 (PE/MTB 2:1, R_f=0.24) yielded the macrocyclic product **2b** (20 mg, 0.051 mmol, 8%) as a colorless material. IR (ATR): $1/\lambda$=2925 (vs), 2853 (s), 1736 (s), 1707 (vs), 1447 (m), 1435 (m), 1365 (m), 1350 (m), 1319 (m), 1223 (m), 1197 (m), 1158 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 392 (8) [M^+], 364 (17), 360 (24), 332 (38), 304 (26), 277 (16), 169 (93), 137 (46), 109 (40), 95 (48), 81 (67), 69 (51), 67 (49), 57 (43), 55 (100). $C_{24}H_{40}O_4$ (392.58): Mol. mass calcd 392.2927 (for $C_{24}H_{40}O_4$), found 392.2928 (M^+, HRMS). ^1H NMR ($CDCl_3$, 500 MHz): very broad multiplets between 1.00 and 2.80 ppm, four signals to be assigned to CO_2Me groups of four isomers: two diastereoisomers each having two conformers, δ=3.70, 3.71, 3.73, 3.74 ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): very broad signals, due to bad signal to noise ratio no assignments possible.

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