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A general approach to iridoids by applying a new Julia olefination and a tandem anion-radical-carbocation crossover reaction†

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A unified, asymmetric approach to the total synthesis of naturally occurring iridoids is presented. The synthesis features a recently discovered *ortho* → α transmetalation of alkyl aryl sulfone carbanions, thus enabling Julia reactions, by which so far hardly accessible disilylated olefins have been obtained. A subsequent tandem alkoxycarbonylation/oxidative radical cyclization afforded substituted cyclopentane building blocks with high diastereoselectivity. These compounds serve as unique central intermediates for short access to dihydronepetalactone, dolicholactone and potentially other iridoids.

Introduction

Cyclopentanoid monoterpenes (iridoids) have long been recognized as an important class of plant secondary metabolites displaying a wide range of biological activities.[1a–e] A number of iridoids including iridomyrmecin (**1**), isoiridomyrmecin (**2**) and dihydronepetalactone (**3**) were isolated from the volatile oils present in the cat-attracting plant *Actinidia polygama*.[2] These iridoids, accompanied by nepetalactone (**4**), were also isolated from *Nepeta cataria*, commonly known as catnip.[3] Catnip is famous for its irresistible action on cats and has been recently used in medical preparations as an antidiaphoretic, antispasmodic and mild sedative. Both, **3** and **4** have been identified as effective insect repellents.[4] Dolicholactone (**5**) was isolated from the wild plant *Teucrium marum* growing in the Mediterranean area.[5] The iridoid scaffold is biosynthesized by the enzyme iridoid synthase using 8-oxocitral as a substrate.[6] Recently, other iridoids have been found in nature. However, their isolation from plants with sufficient purity and amount is often complicated. Because of this their absolute or even their relative configuration as well as their biological activities could not be established.

Therefore, total synthesis serves best to gain access to the natural products and their analogs. A number of syntheses of iridoids have been published over the years.[7–12] Most of them target only individual members of the family, and are not suitable for the preparation of these compounds in larger amounts or provide the desired iridoid in racemic form.[8] More divergent approaches include Wolinski's synthesis of four of the eight possible stereoisomers of dihydronepetalactone (**3**),[9] Francke's synthesis of the eight *trans*-fused diastereomers,[10] Hofferberth's intramolecular Michael addition-based synthesis of iridoid lactols or lactones,[11] and the synthesis of iridolactones *via* a stereoselective Favorski rearrangement (Fig. 1).[12]

We developed previously a short approach to racemic (±)-dihydronepetalactone (**3**). Keysteps were a telescoped ozonolysis/Wittig reaction, which provided ω-silylated citronellate in only 30% yield as a 1 : 1 *E*/*Z* mixture, and an oxidative radical cyclization to obtain the cyclopentane unit of **3**, which was obtained as an inseparable 2 : 1 *trans*/*cis*-diastereomeric mixture.[13] Obviously, the strategy was far from ideal. We hypothesized that the Julia reaction[14] may serve as a better option and that a more symmetrical trisubstituted olefin unit would destabilize boat-type transition states in the crucial radical cyclization. However, recent attempts to promote Julia reactions with β,β′-branched alkyl phenyl sulfones have led to

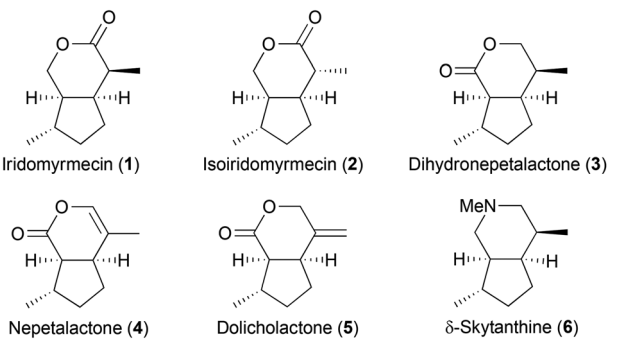

Fig. 1 Major naturally occurring iridoids.

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†Electronic supplementary information (ESI) available: Experimental procedures, analytical characterization and copies of ^{1}H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/c6ob01599a

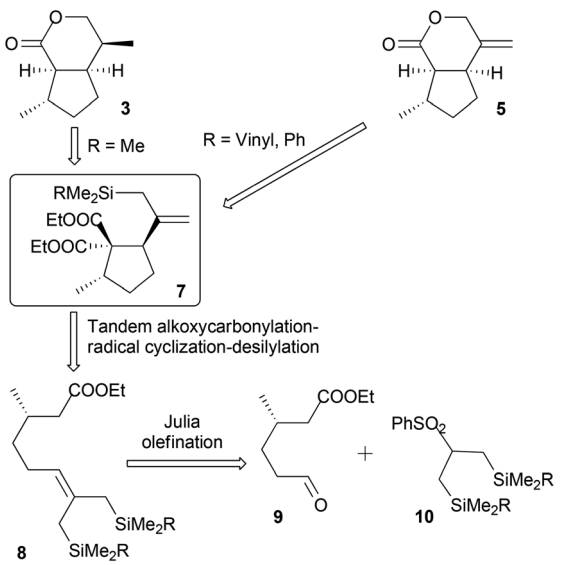
a surprising reversal in the metalation selectivity, in that such substrates are initially *ortho*-metalated despite having a significantly more acidic α-proton.[15] Further studies revealed that a rearrangement of the carbanion from the *ortho*- to the α-position is possible under thermodynamic conditions. Therefore, to successfully apply the Julia reaction in the total synthesis of iridoids, suitable silylated precursors and rearrangement conditions had to be found.

Here we describe an efficient integrated, asymmetric synthetic approach to iridoids, exemplified by dihydronepetalactone (**3**) and dolicholactone (**5**), by applying a carbanion rearrangement-driven Julia reaction and a highly diastereoselective tandem enolate alkoxycarbonylation-oxidative radical cyclization with cationic termination as the key steps.

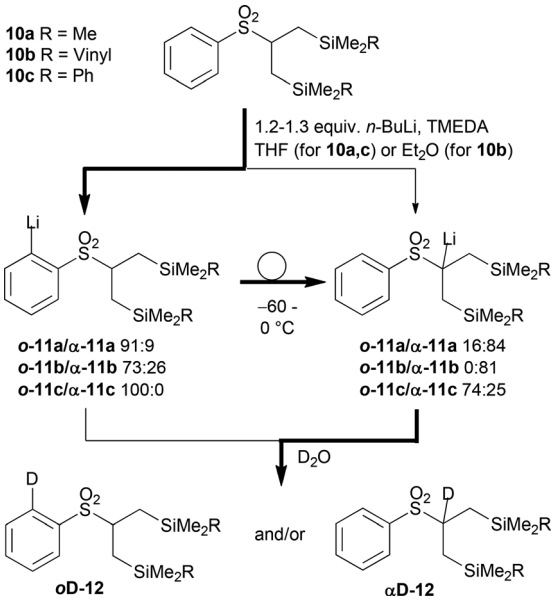
Results and discussion

The retrosynthesis of both, dihydronepetalactone (**3**) and dolicholactone (**5**), leads to the common cyclopentane building block **7** (Scheme 1). The effect of differently substituted silyl groups on this transformation must be investigated; since **3** will be accessed by protodesilylation, whereas **5** is envisaged to be formed by oxidative desilylation.[16] The cyclopentane building block **7** is envisaged to be obtained from bis(allylsilanes) **8**. Since the few known methods to access the so far synthetically rarely used allylic bis(silanes)[17] are not applicable for the synthesis of **8** because of functional group incompatibilities, the Julia reaction of sulfones **10** with aldehyde **9** seemed to be the most promising approach.

β,β′-Disilylated sulfones **10a–c** were prepared in good yields by a one-pot sequential alkylation of methyl phenyl sulfone with diverse (chloromethyl) silanes.[15] Their metalation selectivity was initially studied to enable the Julia olefination



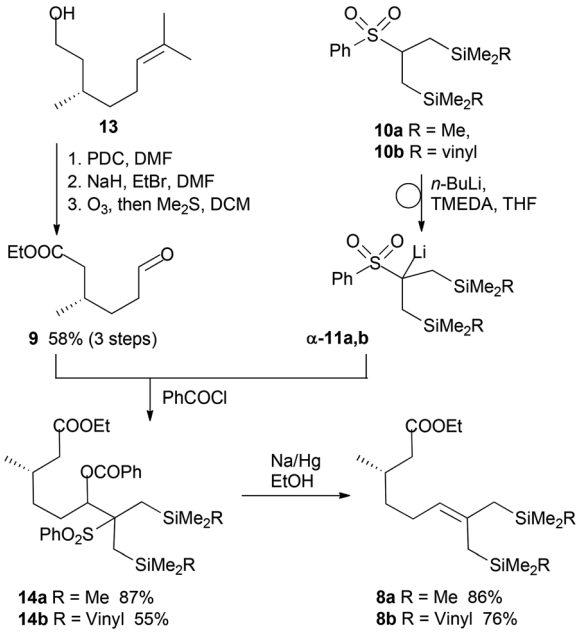
Scheme 1 Retrosynthetic analysis of dihydronepetalactone (**3**) and dolicholactone (**5**).



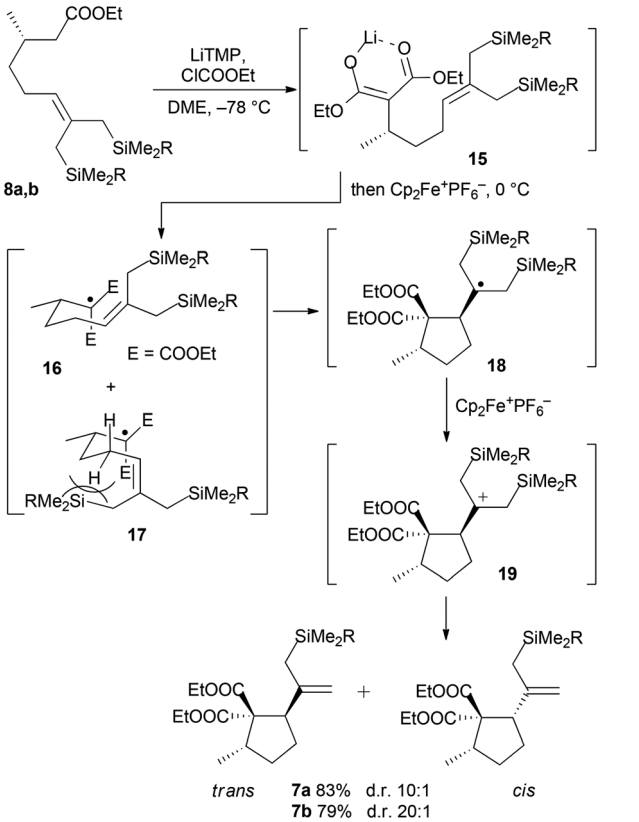
Scheme 2 Metalation selectivity of silylated sulfones **10a–c** and subsequent *ortho* → α transmetalation. The ratios were determined by taking aliquots and quenching by D_2O.

(Scheme 2, for full details, see the ESI†). Indeed, the initial deprotonation of all β,β-bis(silyl) sulfones **10a–c** by *n*-BuLi in the presence of TMEDA at −78 °C generated the undesired *ortho*-aryllithium ***o*-11a–c** with moderate to good selectivities. From ***o*-11a** the *ortho* → α transmetalation took place on warming from −60 to 0 °C as determined by quenching the reaction mixture with D_2O and isolation of deuterated sulfone **α-12a**.[15a] The deprotonation of silylated sulfone **10b** was slower and proceeded less selectively. Moreover, α-sulfonyllithium **α-11b** resulting after the rearrangement was not stable in THF and deteriorated to an appreciable extent. Therefore, the metalation/transmetalation was more conveniently performed in diethyl ether under otherwise similar conditions resulting in the clean formation of **α-12b**. In contrast *ortho*-sulfonylphenyllithium ***o*-11c** underwent the desired transmetalation to **α-11c** only very slowly, and did not proceed to completion. Thus, application of **10c** in the Julia olefination is not possible.

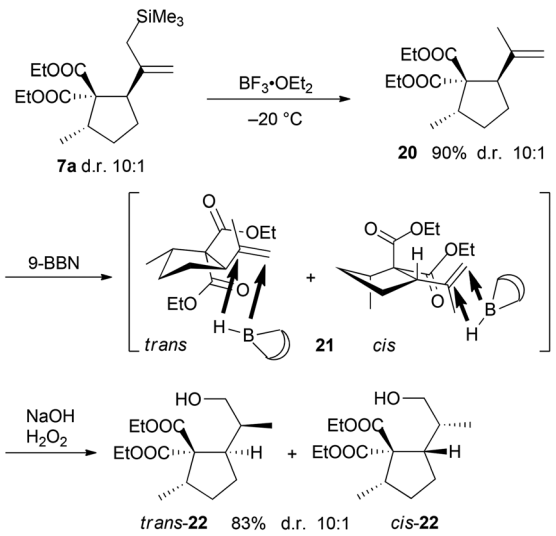
Aldehyde **9** was synthesized from (*S*)-citronellol (**13**) in three steps (Scheme 3). Initial oxidation by pyridinium dichromate (PDC) in dry DMF gave (*S*)-citronellic acid, which was esterified with sodium hydride and ethyl bromide. Subsequent ozonolysis provided aldehyde **9**, which was subsequently added to the reaction mixture of α-phenylsulfonyl lithium intermediates **α-11a,b**. The resulting alkoxide was acylated *in situ* with benzoyl chloride affording β-benzoyloxy sulfones **14**. In contrast to the reported Julia reactions with similar substrates,[15a] the olefination step of **14** using SmI_2 did not afford the desired olefins **8**. However, they were obtained by classical deoxygenation by using sodium amalgam in dry ethanol. It must be mentioned that compounds **14** and **8** are not stable to silica gel chromatography unless NEt_3 is added as a coeluent (see the ESI† for details).



Scheme 3 Preparations of olefins **8a,b** by Julia reactions.



Scheme 4 Tandem alkoxycarbonylation/oxidative radical cyclization of **8a,b**.

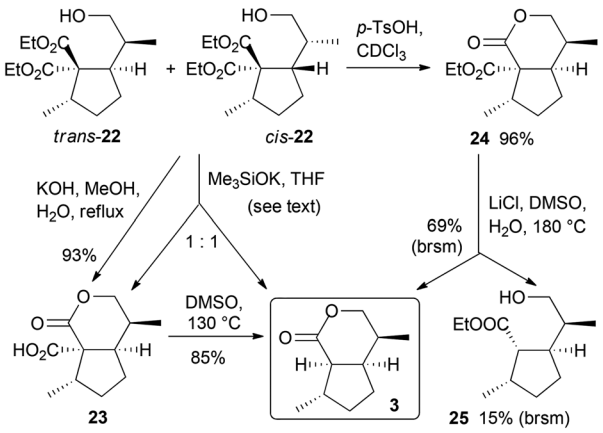


Scheme 5 Synthesis of hydroxy esters **22**.

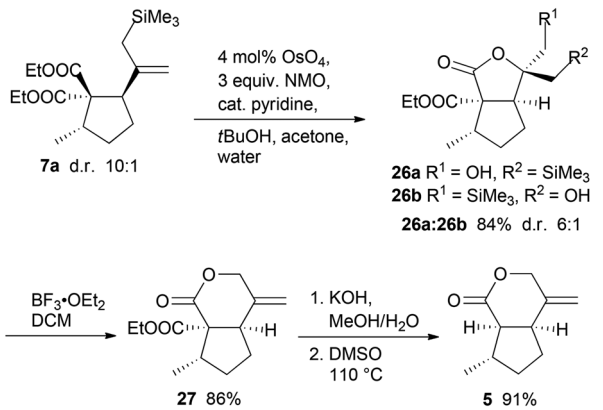
Disilylated esters **8a** and **8b** were subjected to tandem alkoxycarbonylation/oxidative radical cyclization by deprotonating with 2.6 equiv. of LiTMP and adding 1.2 equiv. of ethyl chloroformate followed by 2.3 equiv. of ferrocenium hexafluorophosphate (Scheme 4). In contrast to the previous synthesis,[13] the desired cyclopentanes **7a** and **7b** were obtained in good to excellent 10 : 1 and 20 : 1 *trans*/*cis* selectivities, respectively, as inseparable mixtures. The formation of cyclopentanes **7** is rationalized by deprotonation and alkoxycarbonylation giving malonate enolates **15**, which undergo selective oxidative single electron transfer mediated by ferrocenium hexafluorophosphate. Thus generated radicals cyclize efficiently to radicals **18**; the high *trans*-diastereoselectivity of the radical 5-*exo* cyclization is secured by favoring the chair-like transition state **16**. The (*Z*)-oriented allylic silyl group effectively increases the energy of the competing boat-like transition state **17** because of allylic strain.[18] Subsequently, carbocations **19** are generated by a second SET oxidation. Their desilylation affords predominately *trans*-cyclopentanes **7**.

For the synthesis of **3**, protodesilylation of the diastereomeric mixture **7a** by $BF_3{\cdot}OEt_2$ was carried out affording an inseparable 10 : 1 diastereomeric mixture of *trans*- and *cis*-cyclopentanedicarboxylates **20** in very good yield (Scheme 5). The remaining oxygen atom was introduced by a highly diastereoselective hydroboration/oxidation sequence providing alcohols **22**. The rationale for the diastereoselectivity of hydroboration is provided by a strongly preferred conformation of the isopropenyl group in **21** to minimize allylic strain.[18] In this conformation the two ester groups effectively shield the α-face, therefore the borane exclusively attacks the double bond from the opposite face.

The transformation of alcohols **22** into dihydronepetalactone (**3**) required some experimentation (Scheme 6). Saponification with an excess of potassium hydroxide selectively provided crude carboxylic acid **23** in high yield, but the transformation required seven days to go to completion. The



Scheme 6 Completion of the total synthesis of dihydronepetalactone (**3**).



Scheme 7 The successful approach to dolicholactone (**5**).

subsequent thermal decarboxylation furnished dihydronepetalactone (**3**) in 85% yield. The saponification can be performed with the mixture of *trans*- and *cis*-**22**, because the latter did not undergo lactonization and was therefore easily separable from **3** after decarboxylation (not shown). To reduce the rather long reaction time, lactonization and the hydrolysis of the ester function of **22** with 10 equiv. of potassium trimethylsilanolate[19] in THF under reflux for two days afforded an approximately 1 : 1 mixture of the corresponding carboxylic acid and dihydronepetalactone (**3**) in combined 96% yield, which converged to **3** by heating the crude mixture in DMSO at 130 °C for 5 h. Lactonization of *trans*-**22** was also promoted under acidic conditions using a catalytic amount of *p*-toluenesulfonic acid at room temperature in 96% yield, whereas unreacted *cis*-**22** was recovered and separated. However, the subsequent Krapcho dealkoxycarbonylation of lactone ester **24** did not proceed as expected, since conversion was slow and dihydronepetalactone formation was accompanied by the formation of the *cis*,*trans*-alcohol **25**.

Cyclopentane **7b** was envisaged to provide access to dolicholactone (**5**) *via* oxidative Tamao–Fleming desilylation[16] (*cf.* Scheme 2). However, the attempts to implement this strategy failed and resulted in protodesilylation instead. Therefore, allylsilane **7a** was alternatively subjected to dihydroxylation[20] to obtain a 6 : 1 diastereomeric mixture of *trans*-butyrolactones **26a** and **26b** (Scheme 7). The mixture converged to the optically pure compound **27** by a Peterson olefination using $BF_3{\cdot}OEt_2$.[21] Ethyl ester **27** was saponified by potassium hydroxide within 48 hours. The reaction with potassium trimethylsilanolate did in contrast not provide the desired carboxylic acid. The crude carboxylic acid was subjected to final thermal decarboxylation affording dolicholactone (**5**) in very good yield.

Conclusions

In conclusion, an efficient unified approach to iridoid type natural products was developed. The *ortho* → α-sulfonyl carbanion transmetalation-enabled Julia reaction is a well applicable reaction to provide bis(allylic silanes), whose potential is widely untapped. They undergo highly diastereoselective oxidative tandem polar-radical crossover processes. It was demonstrated that silylated *trans*-cyclopentanedicarboxylate **7** serves as a unique starting point for general syntheses of iridoids. Dihydronepetalactone and dolicholactone were synthesized in ten steps and 18% and 20% overall yields, respectively. Although not executed, the reported approach may serve as a basis for further diversification to other iridoid natural products, such as **1**, **2**, **4** or the related monoterpene alkaloid **6** by functional group interconversion as well as to those whose configuration and biological activities are not yet known.

Experimental

For general information see the ESI.† Compounds **9**[22] and **10a**[15a] are literature-known and their analytical data agree with those reported in the cited references.

Sequential dialkylation of methyl phenyl sulfone (General procedure)

n-BuLi (8.13 mL, 13 mmol, 1.6 M in hexane) was added dropwise to a stirred solution of methyl phenyl sulfone (10 mmol) and TMEDA (3 mL, 19.5 mmol) in dry THF (50 mL) at −78 °C under a nitrogen atmosphere. After stirring for 15 min, dimethylvinyl(chloromethyl)silane (13 mmol) for **10b** and dimethylphenyl(chloromethyl)silane (13 mmol) for **10c** were added dropwise at −78 °C. After stirring for 10 min, the reaction mixture was warmed to room temperature and stirred for 0.5 hour for **10b** and for two hours for **10c**. The reaction mixture was cooled to −78 °C, and TMEDA (3 mL, 19.5 mmol) and *n*-BuLi (8.13 mL, 13 mmol, 1.6 M in hexane) were added dropwise. After 10 min, the corresponding (chloromethyl) silane (13 mmol) was added, and the solution was stirred at −78 °C for 5 min, warmed to room temperature and stirred until completion as indicated by TLC. The reaction mixture was quenched with saturated NH_4Cl solution. The layers were

separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1 : 40, gradient to 1 : 10) gave sulfones **10b–c**.

1,3-Bis[dimethyl(vinyl)silyl]prop-2-yl phenyl sulfone (10b). 2.15 g (61%) as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.61; IR ν 3051, 3090, 2957, 2928, 2899, 2855, 2801, 1592, 1465, 1406, 1305, 1253, 1143, 1008, 958, 846, 830, 709; MS (ESI+), m/z (%) 727 (15) [2M + Na^+], 375 (100) [M + Na^+]; HRMS (ESI) m/z [M + Na^+] calcd for $C_{17}H_{28}O_2SSi_2Na^+$ 375.1241; found 375.1243; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 12H), 0.83 (dd, J = 7.3, 15.1 Hz, 2H), 1.10 (dd, J = 6.3, 15.1 Hz, 2H), 3.23 (tt, J = 6.3, 7.3 Hz, 1H), 5.66 (dd, J = 3.8, 20.1 Hz, 2H), 5.98 (dd, J = 3.8, 14.7 Hz, 2H), 6.14 (dd, J = 14.7, 20.1 Hz, 2H), 7.56 (m, 2H), 7.63 (m, 1H), 7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.8 (q), −2.4 (q), 18.1 (t), 59.4 (d), 128.9 (d), 129.4 (d), 132.4 (t), 133.3 (d), 136.9 (s), 138.5 (d).

1,3-Bis[dimethyl(phenyl)silyl]prop-2-yl phenyl sulfone (10c). Yield 2.63 g (58%) as colorless crystals, m.p. 67–68 °C. R_f (EtOAc/hexane 1 : 5) 0.52; IR ν 3069, 2954, 1427, 1304, 1251, 1143, 1113, 840, 732, 700, 647; MS (ESI+), m/z (%) 475 (100) [M + Na^+]; Anal. calcd for $C_{25}H_{32}O_2SSi_2$ (452.76) C 66.32, H 7.12, S 7.08; found C 66.12, H 7.15, S 7.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 12H), 0.92 (A part of the ABM system, J = 7.1, 15.3 Hz, 2H), 1.19 (B part of the ABM system, J = 6.3, 15.3 Hz, 2H), 3.10 (m, 1H), 7.31 (m, 10H), 7.45 (m, 2H), 7.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.4 (q), −1.8 (q), 18.7 (t), 59.3 (d), 128.0 (d), 129.0 (d), 129.28 (d), 129.30 (d), 133.4 (d), 133.9 (d), 137.1 (s), 138.1 (s).

Preparation of 2-benzoyloxy sulfones 14a,b (General procedure)

n-BuLi (1.4 mL, 2.23 mmol or 1.6 mL, 2.57 mmol, 1.6 M in hexane) was added dropwise to a stirred solution of sulfone **10a** or **10b** (1.88 mmol) and TMEDA (0.35 mL, 2.23 mmol or 0.4 mL, 2.57 mmol) in dry DME (12 mL) for **10a** or diethyl ether (12 mL) for **10b**, respectively, at −78 °C under a nitrogen atmosphere. The reaction mixture was warmed to room temperature over 2 h for **10a** or to 0 °C for 30 min for **10b** and aldehyde **9** (357 mg, 2.07 mmol) in DME (1.5 mL) or diethyl ether (1.5 mL), respectively, was added dropwise at −78 °C. The reaction mixture was stirred at this temperature for 15 min until completion as indicated by TLC. Benzoyl chloride (268 μL, 2.26 mmol) was added and the reaction mixture was warmed to room temperature after 20 min. 3-(Dimethylamino) propan-1-ol (292 μL, 2.5 mmol) was added and the reaction was quenched with water after 10 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane/Et_3N 1 : 20 : 0.05) gave benzoyloxy sulfones **14a,b**.

Ethyl (3*S*)-6-(benzoyloxy)-3-methyl-7-(phenylsulfonyl)-7-((trimethylsilyl)methyl)-8-(trimethylsilyl)octanoate (14a). Yield 989 mg (87%) as an inseparable 1 : 1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.31; IR ν 3091, 3072, 3065, 2957, 2932, 2907, 2875, 1719, 1602, 1585, 1452, 1447, 1393, 1373, 1315, 1296, 1271, 1265, 1251, 1177, 1162, 1134, 1106, 1095, 1080, 1070, 1026, 843, 711, 690; MS (ESI+), m/z (%) 627 (5) [M + Na^+], 485 (100) [M − $PhSO_2H$ + Na^+], 269 (20) [M^+ − $PhSO_2$ − $PhCO_2$ − TMS]; Anal. calcd for $C_{31}H_{48}O_6SSi$ (604.95) C 61.55, H 8.00, S 5.30; found C 61.82, H 8.14, S 5.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 36H), 0.82 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.19–1.37 (m, 10H), 1.45 (A part of the AB system, J = 14.6 Hz, 1H), 1.47 (A part of the AB system, J = 14.6 Hz, 1H), 1.63 (m, 3H), 1.86 (m, 3H), 1.98 (dd, J = 5.7, 14.7 Hz, 1H), 2.02 (dd, J = 8.2, 14.7 Hz, 1H), 2.15 (dd, J = 7.3, 14.7 Hz, 1H), 2.17 (dd, J = 6.0, 14.7 Hz, 1H), 3.98 (m, 2H), 4.05 (q, J = 7.2 Hz, 2H), 5.43 (dd, J = 2.9, 10.2 Hz, 2H), 7.23 (m, 4H), 7.32 (m, 10H), 7.44 (m, 2H), 7.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.6 (q), 1.7 (q), 14.3 (q), 14.4 (q), 19.7 (q), 19.8 (q), 20.56 (t), 20.60 (t), 21.57 (t), 21.61 (t), 29.6 (t), 29.7 (t), 30.6 (d), 30.7 (d), 33.7 (t), 33.8 (t), 41.78 (t), 41.81 (t), 60.30 (t), 60.34 (t), 76.78 (s), 76.81 (s), 77.1 (d, 2C), 128.19 (d), 128.20 (d), 128.95 (d), 128.96 (d), 129.4 (s), 129.5 (s), 129.52 (d), 129.54 (d), 130.3 (d, 2C), 132.9 (d), 133.1 (d), 139.3 (s), 139.4 (s), 165.8 (s), 165.9 (s), 172.89 (s), 172.92 (s).

Ethyl (3*S*)-6-benzoyloxy-3-methyl-7-(phenylsulfonyl)-7-((dimethyl(vinyl)silyl)methyl)-8-(dimethyl(vinyl)silyl)octanoate (14b). Yield 650 mg (55%) as an inseparable 1 : 1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.40; IR ν 3059, 2965, 2937, 2865, 1728, 1453, 1409, 1377, 1303, 1270, 1255, 1180, 1139, 1098, 1084, 1073, 1030, 1013, 957, 832, 760, 713, 693; MS (ESI+), m/z (%) 651 (30) [M + Na^+], 509 (100) [M − $PhSO_2H$ + Na^+]; HRMS (ESI) m/z [M + Na^+] calcd for $C_{33}H_{48}O_6SSi_2Na^+$ 651.2602; found 651.2604; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 6H), 0.29 (s, 6H), 0.30 (s, 6H), 0.31 (s, 6H), 0.85 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.19–1.34 (m, 8H), 1.45 (m, 2H), 1.57 (A part of the AB system, J = 14.6 Hz, 1H), 1.59 (A part of the AB system, J = 14.7 Hz, 1H), 1.72 (m, 3H), 1.87 (m, 3H), 2.00 (dd, J = 4.1, 8.2 Hz, 1H), 2.04 (dd, J = 4.2, 8.2 Hz, 1H), 2.17 (dd, J = 6.0, 8.8 Hz, 1H), 2.22 (m, 1H), 4.01 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 5.45 (m, 2H), 5.76 (dd, J = 3.7, 20.2 Hz, 2H), 5.78 (dd, J = 3.6, 20.5 Hz, 2H), 6.02 (m, 4H), 6.28 (dd, J = 14.4, 20.2 Hz, 1H), 6.30 (dd, J = 14.5, 20.3 Hz, 1H), 6.42 (dd, J = 14.3, 20.3 Hz, 1H), 6.44 (dd, J = 14.4, 20.2 Hz, 1H), 7.26 (m, 4H), 7.34 (m, 10H), 7.47 (m, 2H), 7.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.64 (q), −0.62 (q), −0.55 (q), −0.54 (q), −0.27 (q), −0.26 (q), −0.25 (q), −0.24 (q), 14.3 (q), 14.4 (q), 19.7 (q), 19.8 (q), 19.96 (t), 19.97 (t), 21.1 (t), 21.2 (t), 29.5 (t), 29.7 (t), 30.6 (d), 30.8 (d), 33.5 (t), 33.6 (t), 41.8 (t), 41.9 (t), 60.29 (t), 60.33 (t), 76.51 (s), 76.54 (s), 77.1 (d), 77.4 (d), 128.17 (d), 128.19 (d), 128.96 (d), 128.97 (d), 129.42 (s), 129.45 (s), 129.5 (d), 129.6 (d), 130.4 (d), 132.0 (t), 133.0 (d), 133.1 (d), 139.2 (s), 139.3 (s), 140.32 (d), 140.33 (d), 165.8 (s), 165.9 (s), 172.9 (s), 173.0 (s).

Julia olefination with sodium amalgam (General procedure)

Benzoyloxy sulfones **14a,b** (0.739 mmol) were dissolved in dry THF (5 mL) and dry ethanol (10 mL) under a nitrogen atmo-

sphere. Sodium amalgam (369 mg, 1.7 mmol) was added at −20 °C. After 3 h at this temperature, the reaction mixture was diluted with diethyl ether (15 mL) and decanted from mercury. The organic layer was washed with brine and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. Purification by column chromatography (EtOAc/hexane/NEt_3 1 : 50 : 1) afforded olefins **8a,b**. NEt_3 is mandatory as a coeluent, since partial decomposition occurs during chromatography in its absence.

Ethyl (*S*)-3-methyl-8-(trimethylsilyl)-7-((trimethylsilyl)methyl)oct-6-enoate (8a). Yield 218 mg (86%) as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.89; $[\alpha]_D^{20}$ −1.1 (*c* 1.116 in $CHCl_3$); IR ν 2986, 2957, 2927, 2876, 2854, 1726, 1645, 1478, 1462, 1447, 1415, 1394, 1382, 1371, 1352, 1259, 1248, 1115, 1095, 1032, 855, 840, 699; MS (ESI+), *m*/*z* (%) 365 (100) [M + Na^+]; HRMS (ESI) *m*/*z* [M + Na^+] calcd for $C_{18}H_{38}O_2Si_2Na^+$ 365.2303; found 365.2303; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.02 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.18–1.34 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.38 (s, 2H), 1.44 (AB system, *J* = 13.5 Hz, 2H), 1.81–2.02 (m, 3H), 2.09 (dd, *J* = 8.6, 14.4 Hz, 1H), 2.30 (dd, *J* = 5.8, 14.4 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.75 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.0 (q), −0.5 (q), 14.5 (q), 19.8 (q), 23.9 (t), 26.3 (t), 29.5 (t), 30.3 (d), 37.5 (t), 42.1 (t), 60.2 (t), 119.4 (d), 134.4 (s), 173.4 (s).

Ethyl (*S*)-8-(dimethyl(vinyl)silyl)-7-((dimethyl(vinyl)silyl)methyl)-3-methyloct-6-enoate (8b). Yield 201 mg (76%) as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.77; $[\alpha]_D^{20}$ −3.2 (*c* 0.437 in $CHCl_3$); IR ν 3058, 2967, 2936, 2864, 1743, 1467, 1409, 1375, 1291, 1252, 1194, 1159, 1100, 1071, 1038, 1012, 953, 835, 759, 619; MS (ESI+), *m*/*z* (%) 389 (100) [M + Na^+]; HRMS (ESI) *m*/*z* [M + Na^+] calcd for $C_{20}H_{38}O_2Si_2Na^+$ 389.2303; found 389.2303; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 6H), 0.93 (d, *J* = 6.5 Hz, 3H), 1.16–1.34 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 2H), 1.50 (AB system, *J* = 13.6 Hz, 2H), 1.81–2.02 (m, 3H), 2.10 (dd, *J* = 8.4, 14.5 Hz, 1H), 2.30 (dd, *J* = 5.7, 14.6 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.80 (t, *J* = 7.0 Hz, 1H), 5.65 (dd, *J* = 3.9, 20.3 Hz, 1H), 5.67 (dd, *J* = 3.9, 20.2 Hz, 1H), 5.92 (dd, *J* = 3.8, 14.6 Hz, 1H), 5.94 (dd, *J* = 3.8, 14.7 Hz, 1H), 6.13 (dd, *J* = 14.8, 20.4 Hz, 1H), 6.17 (dd, *J* = 14.7, 20.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.9 (q), −2.5 (q), 14.5 (q), 19.8 (q), 22.8 (t), 26.3 (t), 28.3 (t), 30.2 (d), 37.4 (t), 42.1 (t), 60.2 (t), 120.4 (d), 131.5 (t), 133.5 (s), 139.6 (d), 173.4 (s).

Alkoxycarbonylation/oxidative radical cyclization/carbocation desilylation (General procedure)

n-BuLi (1.14 mL, 1.82 mmol, 1.6 M in hexane) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.31 mL, 1.82 mmol) in dry DME (20 mL) at −78 °C under a nitrogen atmosphere. After stirring for 30 min, olefin **8a** or **8b** (0.70 mmol) in DME (0.5 mL) was added dropwise at −78 °C. After stirring for 30 min, ethyl chloroformate (0.08 mL, 0.84 mmol) was added. After completion of the carboxylation, ferrocenium hexafluorophosphate (534 mg, 1.61 mmol) was added in portions at 0 °C until a blue color of the mixture persisted. The reaction mixture was stirred for additional 30 min and quenched with a few drops of saturated NH_4Cl solution. The mixture was diluted with diethyl ether (25 mL) and filtered through a pad of silica gel. The solvent was evaporated and purification of the residue by column chromatography (EtOAc/hexane 1 : 200) afforded cyclopentanes **7a,b**.

Diethyl (2*S*,5*S*)-5-methyl-2-(3-(trimethylsilyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate and diethyl (2*R*,5*S*)-5-methyl-2-(3-(trimethylsilyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (7a). Yield 198 mg (83%) as an inseparable 10 : 1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.56; IR ν 3083, 2982, 2958, 2931, 2906, 2875, 2856, 1741, 1716, 1629, 1475, 1463, 1447, 1420, 1390, 1380, 1368, 1258, 1249, 1115, 1095, 1044, 1023, 880, 857, 841, 695; MS (CI+), *m*/*z* (%) 341 (95) [M + H^+], 325 (100) [M^+ − CH_3], 295 (30) [M^+ − OEt]; Anal. calcd for $C_{18}H_{32}O_4Si$ (340.54) C 63.49, H 9.47; found C 63.80, H 9.75; ^{1}H NMR (400 MHz, $CDCl_3$) major *trans*-diastereomer: δ 0.01 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.23 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.51 (dd, *J* = 13.3, 0.9 Hz, 1H), 1.61 (dd, *J* = 13.3, 1.0 Hz, 1H), 1.67 (m, 1H), 1.94 (m, 2H), 2.91 (m, 1H), 3.29 (dd, *J* = 7.5, 9.6 Hz, 1H), 3.93 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.13 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.57 (q, *J* = 1.1 Hz, 1H), 4.60 (t, *J* = 1.0 Hz, 1H); minor *cis*-diastereomer, detectable resonances: δ 2.29 (m, 1H), 3.20 (dd, *J* = 10.6, 8.8 Hz, 1H), 4.61 (s), 4.71 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major *trans*-diastereomer: δ −1.3 (q), 14.1 (q), 14.3 (q), 17.1 (q), 29.1 (t), 31.3 (t), 33.1 (t), 41.2 (d), 52.2 (d), 60.7 (t), 60.9 (t), 68.1 (s), 108.3 (t), 148.9 (s), 171.1 (s), 172.0 (s); minor *cis*-diastereomer: δ −2.3 (q), 14.20 (q), 14.25 (q), 15.6 (q), 27.6 (t), 29.8 (t), 31.5 (t), 45.1 (d), 53.0 (d), 60.3 (t), 61.1 (t), 67.8 (s), 108.7 (t), 146.6 (s), 169.3 (s), 172.6 (s).

Diethyl (2*S*,5*S*)-5-methyl-2-(3-(dimethyl(vinyl)silyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate, diethyl (2*R*,5*S*)-5-methyl-2-(3-(dimethyl(vinyl)silyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (7b). Yield 194 mg (79%) as a an inseparable 20 : 1 mixture of diastereomers as colorless oil. R_f (EtOAc/hexane 1 : 5) 0.63; IR ν 2967, 2939, 2883, 1728, 1636, 1467, 1409, 1299, 1252, 1212, 1184, 1118, 1099, 1075, 1048, 1013, 953, 879, 837, 760; MS (CI+), *m*/*z* (%) 353 (100) [M + H^+], 337 (50) [M^+ − CH_3], 325 (40) [M^+ − CH=CH_2], 307 (40) [M^+ − OEt], 279 (30) [M^+ − COOEt]; HRMS (CI) *m*/*z* [M + H^+] calcd for $C_{19}H_{33}O_4Si^+$ 353.2148; found 353.2136; ^{1}H NMR (400 MHz, $CDCl_3$) major *trans*-diastereomer: δ 0.09 (s, 3H), 0.10 (s, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.22 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.61 (d, *J* = 13.3 Hz, 1H), 1.64 (m, 1H), 1.68 (d, *J* = 13.3 Hz, 1H), 1.92 (m, 2H), 2.91 (dquint, *J* = 10.8, 6.9 Hz, 1H), 3.29 (dd, *J* = 7.4, 9.7 Hz, 1H), 3.94 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.13 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.60 (d, *J* = 1.1 Hz, 1H), 4.62 (d, *J* = 0.9 Hz, 1H), 5.67 (dd, *J* = 3.9, 20.3 Hz, 1H), 5.95 (dd, *J* = 3.9, 14.6 Hz, 1H), 6.17 (dd, *J* = 14.6, 20.3 Hz, 1H); minor *cis*-diastereomer, detectable resonances: δ 1.05 (d, *J* = 6.9 Hz, 3H), 2.28 (m, 1H), 3.29 (dd, *J* = 10.6, 8.8 Hz, 1H), 4.64 (s, 1H), 4.74 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major *trans*-diastereomer: δ −3.4 (q), −3.2 (q), 14.0 (q), 14.2 (q), 17.0 (q), 27.8 (t), 31.1 (t), 32.9 (t), 41.1 (d), 52.0 (d), 60.6 (t), 60.8 (t), 67.9 (s),

108.8 (t), 131.7 (t), 138.8 (d), 148.4 (s), 171.0 (s), 171.8 (s); minor *cis*-diastereomer: δ −2.5 (q), −2.3 (q), 14.08 (q), 14.14 (q), 15.5 (q), 26.3 (t), 28.6 (t), 31.5 (t), 44.9 (d), 52.8 (d), 60.2 (t), 61.0 (t), 67.6 (s), 109.1 (t), 131.6 (t), 138.9 (d), 146.0 (s), 169.1 (s), 172.5 (s).

Diethyl (2*S*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate and diethyl (2*S*,5*S*)-2-methyl-5-(prop-1-en-2-yl) cyclopentane-1,1-dicarboxylate (20). $BF_3{\cdot}OEt_2$ (130 μL, 1.03 mmol) was added dropwise to silylated ester **7a** (320 mg, 0.94 mmol) in dry DCM (19 mL) at −20 °C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature overnight. The reaction was quenched by adding a few drops of saturated $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1 : 100) afforded 227 mg (90%) of **20** as an inseparable 10 : 1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.41; IR ν 2982, 2959, 2873, 2855, 1717, 1646, 1636, 1465, 1457, 1448, 1437, 1419, 1394, 1374, 1369, 1252, 1113, 1094, 1032, 894, 849, 840; MS (ESI+), *m*/*z* (%) 291 (100) [M + Na^+]; Anal. calcd for $C_{15}H_{24}O_4$ (268.35) C 67.14, H 9.01; found C 67.39, H 9.20; ^{1}H NMR (400 MHz, $CDCl_3$) major *trans*-diastereomer: δ 0.90 (d, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.22 (m, 1H), 1.62 (m, 1H), 1.65 (d, *J* = 0.7 Hz, 3H), 1.81–1.99 (m, 2H), 2.85 (dquint, *J* = 10.3, 7.0 Hz, 1H), 3.33 (dd, *J* = 8.7, 8.1 Hz, 1H), 3.93 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.07 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.18 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.67 (br s, 1H), 4.70 (br s, 1H); minor *cis*-diastereomer, detectable resonances: δ 1.09 (d, *J* = 6.9 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.67 (m, 1H), 1.69 (s, 3H), 1.80 (m, 1H), 1.87 (m, 1H), 1.95 (m, 1H), 2.30 (m, 1H), 3.17 (dd, *J* = 10.7, 8.7 Hz, 1H), 3.98–4.22 (m, 4H), 4.73 (br s, 1H), 4.74 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major *trans*-diastereomer: δ 14.0 (q), 14.24 (q), 17.3 (q), 23.1 (q), 29.9 (t), 32.9 (t), 40.9 (d), 52.2 (d), 60.8 (t), 60.9 (t), 67.6 (s), 112.5 (t), 146.2 (s), 171.1 (s), 171.5 (s); minor *cis*-diastereomer: δ 14.1 (q), 14.16 (q), 15.5 (q), 23.3 (q), 27.9 (t), 30.9 (t), 44.7 (d), 53.5 (d), 60.3 (t), 61.0 (t), 66.9 (s), 112.4 (t), 144.8 (s), 169.3 (s), 172.2 (s).

Diethyl (2*R*,5*S*)-2-((*S*)-1-hydroxyprop-2-yl)-5-methylcyclopentane-1,1-dicarboxylate and diethyl (2*S*,5*S*)-2-((*R*)-1-hydroxyprop-2-yl)-5-methylcyclopentane-1,1-dicarboxylate (22). 9-BBN (2.26 mL, 1.13 mmol, 0.5 M in THF) was added dropwise to a mixture of olefin **20** (127 mg, 0.47 mmol) in dry THF (0.25 mL) at 0 °C under a nitrogen atmosphere. After stirring the mixture at room temperature for 15 h, the starting material was consumed as indicated by TLC. 10% NaOH solution (1.5 mL) was added slowly at 0 °C. After stirring for 15 min, 30% H_2O_2 solution (1.5 mL) was added dropwise to the reaction mixture. The mixture was stirred for 50 min and saturated NH_4Cl (10 mL) was added, the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 10% $Na_2S_2O_3$ solution (3 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and purification by column chromatography (EtOAc/hexane 1 : 30, gradient to 1 : 10) gave 111 mg (83%) of alcohol **22** as an in principle separable 10 : 1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.39; IR ν 3440, 2972, 2944, 2885, 1723, 1467, 1372, 1302, 1254, 1188, 1117, 1099, 1071, 1037, 865, 763; MS (ESI+), *m*/*z* (%) 309 (100) [M + Na^+]; HRMS (ESI) *m*/*z* [M + Na^+] calcd for $C_{15}H_{26}O_5Na^+$ 309.1673; found 309.1673; ^{1}H NMR (400 MHz, $CDCl_3$) major *trans*-diastereomer: δ 0.85 (d, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.10–1.32 (m, 7H), 1.36 (m, 1H), 1.63 (m, 1H), 1.86 (m, 1H), 2.09 (m, 1H), 2.65 (dt, *J* = 7.3, 11.7 Hz, 1H), 2.77 (sext, *J* = 7.2 Hz, 1H), 3.36 (dd, *J* = 6.8, 10.8 Hz, 1H), 3.54 (dd, *J* = 4.4, 10.8 Hz, 1H), 4.08 (m, 2H), 4.20 (m, 2H); minor *cis*-diastereomer, detectable resonances: δ 0.97 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 2.27 (m, 1H), 2.57 (m, 1H), 3.37 (m, 1H), 3.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major *trans*-diastereomer: δ 14.1 (q), 14.23 (q), 16.8 (q), 18.8 (q), 27.5 (t), 32.5 (t), 37.6 (d), 41.1 (d), 47.7 (d), 61.07 (t), 61.09 (t), 66.5 (t), 66.7 (s), 171.7 (s), 172.0 (s); minor *cis*-diastereomer: δ 14.15 (q), 14.20 (q), 15.3 (q), 16.6 (q), 27.8 (t), 31.0 (t), 38.6 (d), 45.3 (d), 50.2 (d), 60.5 (t), 61.10 (t), 65.9 (t), 66.9 (s), 169.9 (s), 172.6 (s).

(4*S*,4a*R*,7*S*,7a*R*)-4,7-Dimethyl-1-oxohexahydrocyclopenta[*c*]pyran-7a(1*H*)-carboxylic acid (23). Method A: Potassium hydroxide (500 mg, 8.9 mmol) was dissolved in water (5 mL) and added to a mixture of alcohol **22** (40 mg, 0.14 mmol) and methanol (5 mL). The reaction mixture was heated to reflux for a week. After completion, it was acidified by HCl (1 M) to pH 1. Methanol was evaporated under reduced pressure and DCM was added. The layers were separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. Evaporation gave 28 mg (93%) of crude acid **23** as a colorless oil. **Method B:** Potassium trimethylsilanolate (200 mg, 1.5 mmol) was added to alcohol **22** (45 mg, 0.15 mmol) and dry THF (5 mL) under an argon atmosphere. The reaction mixture was refluxed for two days and a few drops of hydrochloric acid (1 M) were added after cooling. The mixture was diluted with water, the layers were separated and the aqueous layer was extracted with DCM (3 × 5 mL). The organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure affording 16 mg of a crude 1 : 1 mixture of acid **23** and 12 mg of dihydronepetalactone (**3**) (overall 96%). MS (ESI+), *m*/*z* (%) 235 (40) [M + Na^+]; HRMS (ESI) *m*/*z* [M + Na^+] calcd for $C_{11}H_{16}O_4Na^+$ 235.0941; found 235.0941; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.56 (m, 1H), 1.69 (m, 1H), 1.85 (m, 1H), 1.94 (m, 1H), 2.21 (m, 1H), 2.25 (m, 1H), 3.33 (m, 1H), 4.20 (ddd, *J* = 1.9, 4.2, 11.2 Hz, 1H), 4.27 (dd, *J* = 11.2, 11.3 Hz, 1H), 12.04 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0 (q), 15.2 (q), 25.4 (t), 31.2 (d), 32.8 (t), 44.6 (d), 48.7 (d), 60.9 (s), 71.4 (t), 170.8 (s), 177.5 (s).

Dihydronepetalactone, (4*S*,4a*R*,7*S*,7a*R*)-4,7-dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (3). A carefully nitrogen-flushed mixture of carboxylic acid **23** (15 mg, 0.07 mmol) and DMSO (0.2 mL) was heated to 130 °C for 5 hours. After cooling to room temperature, water (3 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 3 mL) and

the organic extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (diethyl ether/pentane 1 : 30, gradient to 1 : 1) affording 10 mg (85%) of dihydronepetalactone (**3**) as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.30; $[\alpha]_D^{20}$ +66.9 (*c* 0.121 in $CHCl_3$); IR ν 2966, 2935, 2864, 1742, 1467, 1383, 1251, 1209, 1175, 1122, 1085, 1062, 968, 851, 830, 807, 670; MS (ESI+), *m*/*z* (%) 191 (100) [M + Na^+]; HRMS (EI) *m*/*z* [M^+] calcd for $C_{10}H_{16}O_2^+$ 168.1150; found 168.1151; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.1 Hz, 3H), 1.14–1.25 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.43 (m, 1H), 1.75 (m, 1H), 1.93 (m, 1H), 2.00 (m, 1H), 2.23 (m, 1H), 2.43 (dd, *J* = 9.3, 10.8 Hz, 1H), 2.52 (m, 1H), 4.02 (ddd, *J* = 1.6, 3.9, 11.1 Hz, 1H), 4.08 (dd, *J* = 10.4, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (q), 19.5 (q), 26.5 (t), 31.2 (d), 35.2 (t), 40.6 (d), 41.7 (d), 50.7 (d), 70.1 (t), 174.5 (s).

Ethyl (4*S*,4a*R*,7*S*,7a*R*)-4,7-dimethyl-1-oxohexahydrocyclopenta[*c*]pyran-7a(1*H*)-carboxylate (24). *p*-TsOH (6 mg, 0.030 mmol) was added to a diastereomeric mixture of alcohol **22** (29 mg, 0.1 mmol) and $CDCl_3$ (0.5 mL). The reaction mixture was directly monitored in the NMR tube. The reaction was completed after 1 h and a few drops of saturated Na_2CO_3 solution were added. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (diethyl ether/pentane 1 : 30, gradient to 1 : 10) giving 23 mg (96%) of lactone **24** as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.31; $[\alpha]_D^{20}$ +23.3 (*c* 0.300 in $CHCl_3$); IR ν 2966, 2933, 2863, 1749, 1732, 1467, 1382, 1257, 1237, 1208, 1176, 1126, 1043, 1017; MS (ESI+), *m*/*z* (%) 263 (100) [M + Na^+]; HRMS (ESI) *m*/*z* [M + Na^+] calcd for $C_{13}H_{20}O_4Na^+$ 263.1254; found 263.1254; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.40 (m, 1H), 1.47 (m, 1H), 1.78 (m, 2H), 2.32 (m, 1H), 2.47 (m, 1H), 2.96 (dt, *J* = 7.2, 10.9 Hz, 1H), 4.08 (d, *J* = 5.1 Hz, 2H), 4.17 (dq, *J* = 7.1, 10.9 Hz, 1H), 4.19 (dq, *J* = 7.0, 10.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (q), 14.3 (q), 15.7 (q), 26.5 (t), 29.7 (d), 33.4 (t), 44.2 (d), 47.3 (d), 61.5 (s), 61.8 (t), 72.0 (t), 171.1 (s), 172.0 (s).

Ethyl (1*S*,3a*R*,4*S*,6a*S*)-1-(hydroxymethyl)-4-methyl-3-oxo-1-((trimethylsilyl)methyl)tetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate (26a) and ethyl (1*R*,3a*R*,4*S*,6a*S*)-1-(hydroxymethyl)-4-methyl-3-oxo-1-((trimethylsilyl)methyl)tetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate (26b). *N*-Methylmorpholine *N*-oxide (155 mg, 1.32 mmol), OsO_4 (225 mL, 0.018 mmol, 2.5 wt% in *t*BuOH) and pyridine (1 drop) were added subsequently to a solution of silylated olefin **7a** (150 mg, 0.44 mmol) in an acetone/water/*t*-butanol mixture 1 : 1 : 1 (3 mL) at room temperature. The reaction mixture was stirred for 16 h, concentrated and diluted with water. The mixture was extracted with DCM, and the combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane 1 : 30, gradient to 1 : 2.5) giving 121 mg (84%) of alcohol **26** as an in principle separable 6 : 1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.34 (major diastereomer), 0.30 (minor diastereomer); IR ν 3523, 3489, 2964, 2934, 2863, 1776, 1734, 1466, 1373, 1303, 1253, 1189, 1140, 1082, 1033, 996, 919, 846, 695; MS (ESI+), *m*/*z* (%) 679 (20) [2M + Na^+], 351 (100) [M + Na^+]; Anal. calcd for $C_{16}H_{28}O_5Si$ (328.48) C 58.50, H 8.59; found C 58.71, H 8.69; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer: δ 0.11 (s, 9H), 0.98 (d, *J* = 14.8 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 14.9 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.48 (m, 1H), 1.59 (broad s, 1H), 1.72 (m, 1H), 1.82 (m, 1H), 1.94 (m, 1H), 2.52 (m, 1H), 3.26 (t, *J* = 8.5 Hz, 1H), 3.53 (d, *J* = 11.9 Hz, 1H), 3.62 (d, *J* = 11.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H); minor diastereomer: δ 0.09 (s, 9H), 1.05 (d, *J* = 14.7 Hz, 1H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 14.7 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.48 (m, 1H), 1.59 (broad s, 1H), 1.72 (m, 1H), 1.82 (m, 1H), 1.94 (m, 1H), 2.65 (m, 1H), 3.23 (t, *J* = 7.9 Hz, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer: δ 0.4 (q), 14.36 (q), 16.1 (q), 21.7 (t), 29.0 (t), 35.0 (t), 45.6 (d), 51.9 (d), 61.8 (t), 66.8 (s), 70.1 (t), 88.73 (s), 170.0 (s), 175.6 (s); detectable resonances of minor diastereomer: δ 0.1 (q), 14.38 (q), 15.9 (q), 26.4 (t), 28.5 (t), 35.6 (t), 44.0 (d), 53.6 (d), 62.2 (t), 66.1 (t), 88.75 (s).

Ethyl (4a*R*,7*S*,7a*R*)-7-methyl-4-methylene-1-oxohexahydrocyclopenta[*c*]pyran-7a(1*H*)-carboxylate (27). $BF_3{\cdot}OEt_2$ (9.3 μL, 0.074 mmol) was added dropwise to **26** (20 mg, 0.062 mmol) in dry DCM (1 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by adding a few drops of saturated $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted three times with diethyl ether and the organic extract was dried over $MgSO_4$. Purification by column chromatography (diethyl ether/pentane 1 : 5, gradient to 1 : 1) gave 13 mg (86%) of lactone ester **27** as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.35; $[\alpha]_D^{20}$ −15.9 (*c* 0.270 in $CHCl_3$); IR ν 2967, 2933, 2863, 1734, 1467, 1456, 1383, 1250, 1166, 671; MS (ESI+), *m*/*z* (%) 261 (100) [M + Na^+]; Anal. calcd for $C_{13}H_{18}O_4$ (238.28) C 65.53, H 7.61; found C 65.69, H 7.69; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.38 (m, 2H), 1.85 (m, 1H), 2.14 (m, 1H), 2.84 (m, 1H), 3.62 (m, 1H), 4.18 (dq, *J* = 7.1, 10.7 Hz, 1H), 4.20 (dq, *J* = 7.2, 10.7 Hz, 1H), 4.45 (dt, *J* = 0.7, 12.2 Hz, 1H), 4.47 (dtd, *J* = 0.5, 1.3, 12.3 Hz, 1H), 4.98 (d, *J* = 2.6 Hz, 1H), 5.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (q), 16.5 (q), 31.2 (t), 33.5 (t), 42.6 (d), 47.4 (d), 62.3 (t), 63.2 (s), 71.8 (t), 113.7 (t), 141.6 (s), 170.5 (s), 171.5 (s).

Dolicholactone, (4a*S*,7*S*,7a*R*)-7-methyl-4-methylenehexahydrocyclopenta[*c*]pyran-1(3*H*)-one (5). Potassium hydroxide (1 g, 17.8 mmol) was dissolved in water (2 mL) and added to a mixture of lactone ester **27** (40 mg, 0.17 mmol) and methanol (2 mL). The reaction mixture was heated to reflux for 48 h. After completion, it was acidified by hydrochloric acid (1 M) to pH 1. Methanol was evaporated under reduced pressure and DCM was added. The layers were separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. Evaporation gave 34 mg (96%) of the crude corresponding acid as a colorless oil. A carefully nitrogen-flushed mixture of the carboxylic acid (11 mg, 0.02 mmol) and DMSO (0.2 mL) was heated to 110 °C for 4 h. After cooling to room

temperature, water (2 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 3 mL) and the organic extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane 1 : 30, gradient to 10 : 1) affording 7.9 mg (91%) of dolicholactone (**5**) as a colorless oil. R_f (EtOAc/hexane 1 : 5) 0.29; $[\alpha]_D^{20}$ +44.0 (*c* 0.270 in $CHCl_3$); IR ν 2969, 2934, 2862, 1738, 1466, 1382, 1297, 1268, 1188, 1024, 972, 801; MS (EI), *m*/*z* (%) 166 (10) [M^+], 138 (20) [M^+ − CO], 121 (20) [M^+ − COOH], 82 (70) [M^+ − $COOCH_2C{=}CH_2$], 67 (10) [M^+ − $COOCH_2C{=}CH_2$ − Me]; HRMS (EI) *m*/*z* [M^+] calcd for $C_{10}H_{14}O_2^+$ 166.0993; found 166.0994; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.6 Hz, 3H), 1.16 (m, 1H), 1.45 (m, 1H), 1.89 (m, 1H), 2.05 (m, 1H), 2.29 (m, 1H), 2.45 (dd, *J* = 8.5, 10.7 Hz, 1H), 3.05 (m, 1H), 4.53 (dd, *J* = 1.0, 12.0 Hz, 1H), 4.61 (dd, *J* = 0.6, 12.0 Hz, 1H), 4.97 (m, 1H), 5.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 (q), 32.5 (t), 34.7 (t), 39.4 (d), 42.1 (d), 51.2 (d), 71.0 (t), 113.5 (t), 142.3 (s), 174.0 (s).

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