A Versatile Access to Enantiomerically Pure 5-Substituted 4-Hydroxycyclohex-2-enones: An Advanced Hemisecalonic Acid A Model

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Abstract: A convenient route for the versatile preparation of 5-substituted 4-hydroxycyclohex-2-enones via the addition of an organocuprate to a cyclohex-2-enone is reported. These compounds are important intermediates in our synthetic studies towards the mycotoxin secalonic acid A.

Keywords: stereoselective synthesis, cyclohexenone, Michael addition, domino reaction, natural products

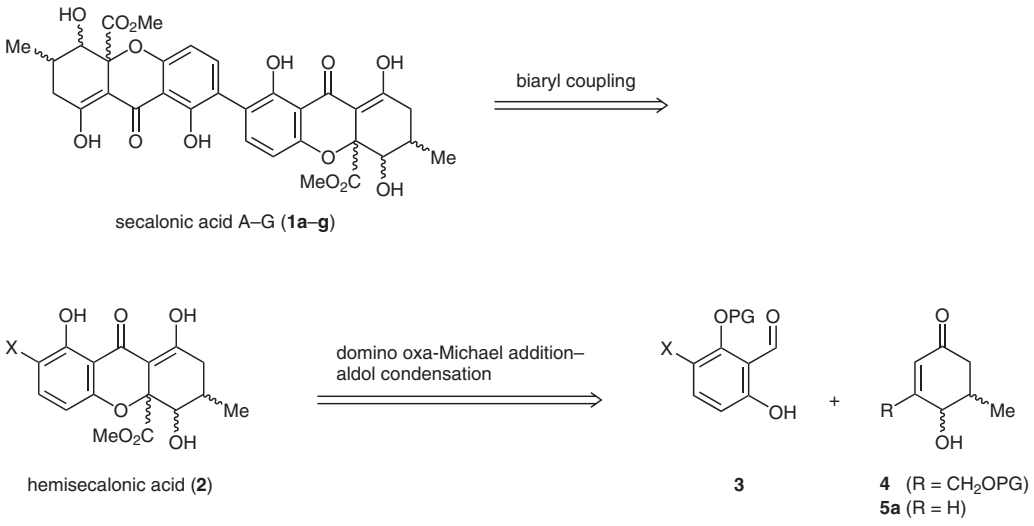
Mycotoxins are both an increasing threat for humankind and a challenge for synthetic chemists due to their biological activity and demanding molecular architecture. Aiming at the total synthesis of the challenging secalonic acids **1**[1] by use of the domino oxa-Michael addition–aldol condensation as the key step of our synthetic strategy,[2] we found that this reaction could not be realized using a cyclohexenone building block carrying a substituent at C3 **4** (Scheme 1).[3] Therefore, the complexity of the building block had to be reduced from the 3,4,5-trisubstituted cyclohex-2-enones **4** to the simpler, but sterically less hindered, 4,5-substituted cyclohex-2-enones, such as 4-hydroxy-4-methylcyclohex-2-enone (**5a**).

A flexible and reliable pathway for the stereoselective preparation of this compound was required.

Two articles reporting the synthesis of fairly similar compounds have been published by the groups of Maycock[4] and Matsuo.[5] Both made use of the same strategy, the conjugate addition of an organocuprate to the building block **6** accessible via a procedure developed by both Trost and Danishefsky.[6,7] Independently, both groups reported that they isolated the product of the addition together with significant, but strongly varying, amounts of the cyclohexenone formed by elimination of acetone from the product of conjugate addition.

When attempting to utilize this reaction for the addition of a methylcuprate using the conditions described in the literature,[5] we also found that the product was contaminated with the corresponding elimination product (Table 1). As the elimination product is identical with the target molecule, 4-hydroxy-5-methylcyclohex-2-enone (**5a**), a more thorough investigation of its mode of formation was conducted.

A change of the temperature profile of the conjugate addition reaction shows that the elimination takes place if the reaction is conducted above –40 °C (Table 1, entries 1, 2); for any temperature below, no cyclohexenone **5a** was formed (Table 1, entries 3, 4). However, lower tempera-



Scheme 1 Retrosynthesis of the secalonic acids **1**

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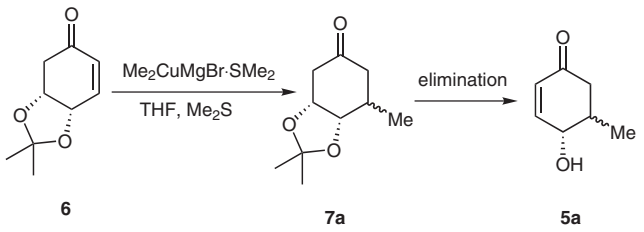
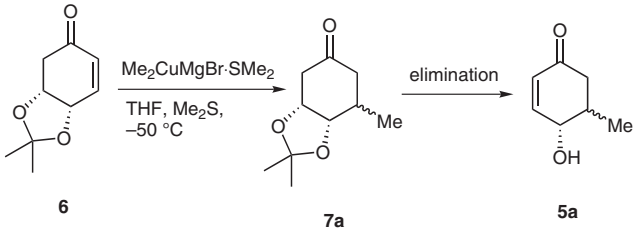
Table 1 Effect of Temperature Variation on the Conjugate Addition of $Me_2CuMgBr{\cdot}SMe_2$



Entry	Temp (°C)	Time (h)	Yield (%)	
			7a	**5a**
1	–20	1	57	6
2	–40	1	59	6
3	–60	1	56	0
4	–50	14	73	0

Table 2 Ratio of Addition Product **7a** to Addition/Elimination Product **5a** Depending on the Workup Conditions



Entry	Workup conditions[a]	Yield (%)		Overall yield (%)
		7a	**5a**	
1	r.t., 10 min	44	traces	44
2	r.t., 2 h	31	10	41
3	r.t., 15 h	15	23	38
4	40 °C, 2 d	0	10	10

[a] Temperature and time of stirring after addition of sat. NH_4Cl soln.

tures need to be compensated for by a prolonged reaction time; the conditions described in Table 1, entry 4 resulted in the highest yield (73%) of the 1,4-addition product without any detectable amount of **5a**. Furthermore, the removal of copper salts after quenching, which could not be fully realized following the procedure published by Matsuo,[5] could be accomplished by addition of saturated ammonium chloride solution followed by bubbling air through the reaction mixture; this accelerated the oxidation to copper(II) significantly.

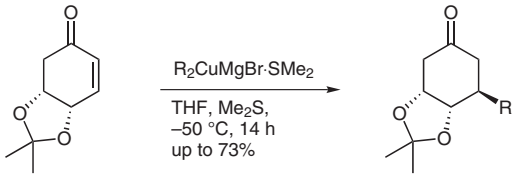
A 6:1 ratio of the initially formed **7a** and the cyclohexenone **5a** was found for both reactions conducted at higher temperatures. Attempts to alter this ratio by modification of the workup conditions were not successful: prolonged stirring after the addition of saturated ammonium chloride solution resulted in an alteration of the ratio to up to 1:1.5 (Table 2, entry 3), but gave only a moderate overall yield.

The scope and limitations of the addition reaction were investigated by reacting **6** with cuprates of variable size and stability (Table 3).

For any of the addition reactions performed, the diastereoselectivity was >99:1 in favor of *anti* addition. In all cases, the nucleophile had attacked from the side of **6** that does not contain the oxygen substituent on C4. This observation is consistent with the result found by Maycock and with the conjugate addition of cuprates to a very similar system reported in the literature that also showed *anti* diastereoselectivity.[8] By using functionalized Knochel-type cuprates, this procedure should also allow the synthesis of higher functionalized cyclohexenones.[9] This issue is currently under investigation in our group.

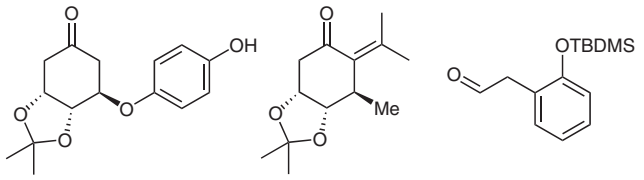
Interestingly, the unusual side product **8** (Figure 1) was isolated from the addition of allylcuprate to **6** (Table 3, entry 7). Instead of reacting with the allylcuprate, which seems to decompose rapidly, the cyclohexenone **6** slowly transforms into hydroquinone, due to the basic conditions, and **8** is formed by conjugate addition of hydroquinone to the substrate. This unexpected reaction outcome depicts a remarkable example for a nonreversible oxa-Michael addition.

Table 3 Conjugate Addition of Various Nucleophiles to **6**



Entry	R	Product	Yield (%)	Side product (%)
1	Me	**7a**	73	–
2	Et	**7b**	66	–
3	Pr	**7c**	40[a]	24 (**5c**)
4	*i*-Pr	**7d**	0	–
5	CH_2-*t*-Bu	**7e**	28	–
6	$CH{=}CH_2$	**7f**	n.d.[b]	–
7	$CH_2CH{=}CH_2$	**7g**	4	4 (**8**)[c]
8	Ph	**7h**	27	–

[a] Overall yield of the addition reaction was 64%; reaction was conducted at –20 °C.
[b] The yield was not determined because **7f** is unstable towards column chromatography.
[c] Compound **8** was formed by conjugate addition of hydroquinone, a degradation product of **6** under basic conditions.



8 9 10

Figure 1 Unexpected side products of the conjugate addition and the elimination step

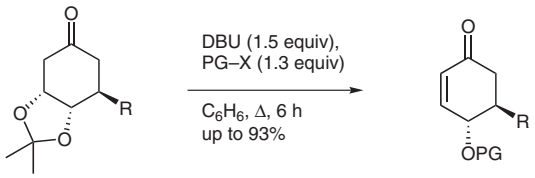
As the direct transformation of the addition products **7** to the building block **5** resulted in only very low yields due to the high solubility of the unprotected 5-substituted 4-hydroxycyclohex-2-enones **5** in water, the introduction of an additional step was required to render this reaction more efficient.[7] When the elimination step was performed in the presence of *tert*-butylchlorodimethylsilane, the silyl-protected derivatives of **7** could be isolated in satisfying yields (Table 4, entry 1).

Table 4, entries 1–6 summarize the outcome of the elimination/protection reaction resulting when the conditions reported by Danishefsky [DBU (1.12 equiv), TBDMSCl (1.07 equiv), benzene, heat, 3 h; DBU (0.28 equiv), heat, 2.5 h] were applied.[7] Even the results obtained using the standard protecting reagents *tert*-butylchlorodimethylsilane and chlorotriisopropylsilane for the transformation of **7a** (49% and 47%; entries 1, 2), are not comparable to the yield reported for the unsubstituted system (87%, R = H).[7] The installation of less bulky protecting groups was impossible if the protection reaction proceeded by an S_N2 mechanism, as it is necessary for an allylation or benzylation reaction (Table 4, entries 3, 4). Yet, the esterification to the 4-bromobenzoic acid ester **15** could be realized in 23% yield (Table 4, entry 5), whereas only traces of the corresponding acetate **16** were isolated from the reaction with acetic acid anhydride (Table 4, entry 6).

After altering the reaction conditions to 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 equiv) and *tert*-butylchlorodimethylsilane (1.3 equiv), the *tert*-butyldimethylsilyl-protected cyclohex-2-enone **11a** could be isolated in a very satisfying 93% yield (Table 4, entry 7). The optimized elimination/protection procedure was applied to the transformation of the cyclohexanones **7a–c**,**f–h** to the corresponding unsaturated compounds (Table 4, entries 8–12). A significant decrease in yield with increasing size of the substituent at C5 was observed, showing that the protection reaction is also sensitive to sterical hindrance near the reaction site on the cyclic system.

The vinylated derivative **7f** could only be isolated in 9% yield (Table 4, entry 10) as it tends to undergo a Claisen

Table 4 Elimination and Simultaneous Protection



7 11

Entry	Substrate	R	PG-X	Product	Yield (%)
1	**7a**	Me	TBDMSCl	**11a**	49[a]
2	**7a**	Me	TIPSCl	**12**	47[a]
3	**7a**	Me	$H_2C{=}CHCH_2Br$	**13**	0[a]
4	**7a**	Me	BnBr	**14**	0[a]
5	**7a**	Me	$4\text{-}BrC_6H_4COCl$	**15**	23[a]
6	**7a**	Me	Ac_2O	**16**	trace[a]
7	**7a**	Me	TBDMSCl	**11a**	93
8	**7b**	Et	TBDMSCl	**11b**	74
9	**7c**	Pr	TBDMSCl	**11c**	67
10	**7f**	$CH{=}CH_2$	TBDMSCl	**11f**	9[b]
11	**7g**	$CH_2CH{=}CH_2$	TBDMSCl	**11g**	55
12	**7h**	Ph	TBDMSCl	**11h**	11

[a] These experiments were performed under the conditions reported by Danishefsky.
[b] Yield after two steps (see also Table 3, entry 6).

rearrangement to the phenylacetaldehyde **10** (Figure 1). However, due to the instability of this compound, neither its yield nor its complete characterization could be assigned.

Most interestingly, a very small amount of a side product was isolated and identified as the cyclohexanone **9** with a conjugated, but exocyclic, double bond (Figure 1). This compound is formed when the deprotonation does not abstract a proton from C2 but C6 of the saturated cyclohexanone **7a**. The enolate thus formed cannot eliminate acetone, but instead it is consumed by an aldol condensation reaction with acetone liberated by molecules that are pursuing the intended reaction course. As the formation of the condensation product **9** was only observed for the methyl-substituted compound **7a**, the conclusion can be derived that the presence of any larger substituent at C5 most probably prevents the deprotonation at C6 of **7**, and certainly averts the subsequent aldol condensation.

As we have already reported, cyclohexenones with a large substituent at C4 are not suitable for the key domino oxa-Michael–addition aldol reaction planned for the total synthesis of the secalonic acids **1**.[3] Therefore, the preliminary deprotection of the cyclohexenone building block **11** is essential. Initially experiments with **11a** using standard conditions (TBAF, THF, r.t.), resulted in the formation of the dimers **17** and **18** instead of the target molecule **5a** (Table 5).

The formation of dimer **17** (Table 5, entry 1) is accomplished by the dimerization of the primarily formed alcoholate of **5a**, which cannot be protonated immediately under the aprotic deprotection conditions. The alcoholate is presumed to form an epoxy enolate and to undergo standard Michael addition to another cyclohexenone moiety. Regeneration of the cyclohexenone by a proton shift with subsequent protonation upon workup results in **17**. Epoxide opening by addition of water instead led to **18**.

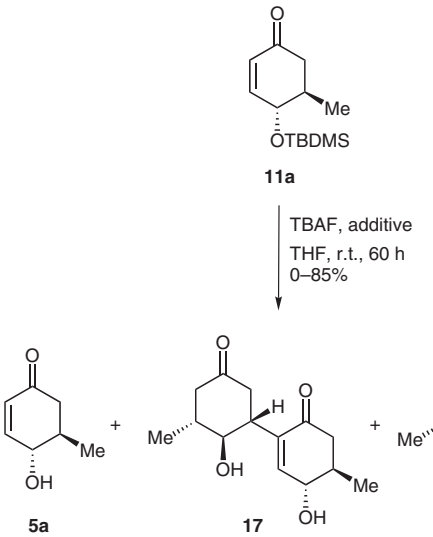
The addition of a proton source seemed the easiest way to shorten the lifespan of the alcoholate of **5a**. The application of methanol in varying amounts led to the formation of byproduct **18**, a hydrate of **17** whose stereochemistry could not be elucidated completely. The best result for methanol as additive was 36% of the desired product **5a** contaminated with **18** (Table 5, entries 2, 3). Adding the more acidic phenol as proton source merely resulted in the isolation of traces of **5a**, showing that the alcoholate could still dimerize before being protonated (Table 5, entry 4). Only the presence of acetic acid allowed the isolation of **5a** in a satisfying 75% yield (Table 5, entry 5). The need for nonaqueous workup conditions was recently also addressed by Kishi et al.[10]

The general applicability of this procedure was investigated by using these conditions for the deprotection of variably substituted cyclohexenones of type **11** (Table 6). All substrates could be transformed in good to excellent yields.

The method described above is generally applicable to the stereoselective synthesis of a large variety of silyl-protected or unprotected 5-substituted 4-hydroxycyclohex-2-enones.

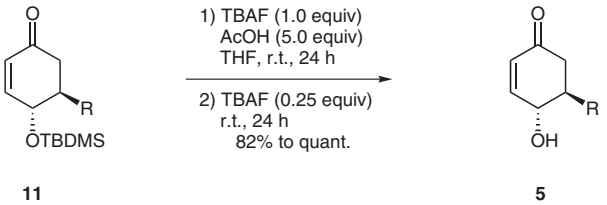
Finally, these unprotected 5-substituted 4-hydroxycyclohex-2-enones **5** were employed as building blocks for the domino oxa-Michael addition–aldol[2,3] condensation together with 5-methoxysalicylaldehyde (**19**) to give access

Table 5 Effect of Variation of the Proton Source on the Deprotection Step



Entry	Additive	Equiv of additive	Product	Yield (%)
1	–	–	**17**	37
2	MeOH	25	**18**	traces
3	MeOH	5	**5a** **18**	36 traces
4	PhOH	5	**5a**	traces
5	AcOH	5	**5a**	75

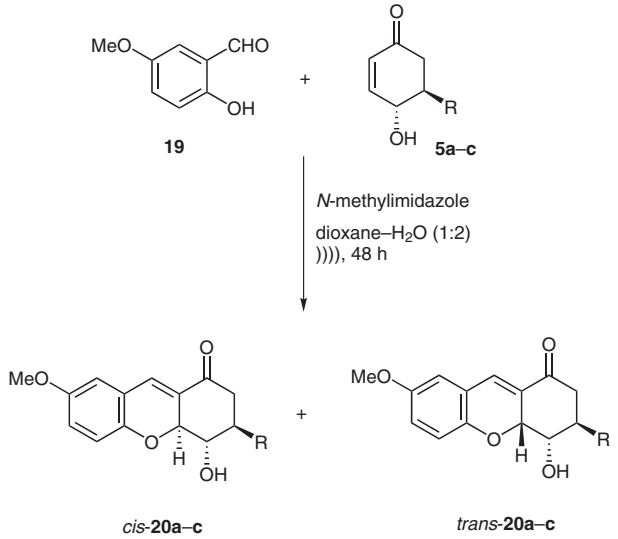
Table 6 Deprotection of Variably Substituted 4-Hydroxycyclohex-2-enones **11**



Entry	Substrate	R	Product	Yield (%)
1	**11a**	Me	**5a**	75
2	**11b**	Et	**5b**	99.5
3	**11c**	Pr	**5c**	70
4	**11h**	Ph	**5h**	93

to tetrahydroxanthenones cores **20** with excellent yields (Table 7). All compounds were obtained as mixture of diastereomers at the 4a-position, in some cases as separable mixture. However, we developed a route to 4a-substituted tetrahydroxanthenones by addition of cuprates generating a new stereogenic center at the 4a-position, thus this obstacle is not a drawback. Finally, the xanthone **20a** can be considered as an advanced enantiomerically pure hemisecalonic acid A model.[1] To our knowledge, this is the first synthesis of such an advanced model compound.

Table 7 Application of the Substituted 4-Hydroxycyclohex-2-enones **5** to the Domino Oxa-Michael–Aldol Condensation



Entry	Substrate	R	Product	Ratio *cis*/*trans*	Yield (%)
1	**5a**	Me	**20a**	1.5:1	62
2	**5b**	Et	**20b**	1:1.2	82
3	**5c**	Pr	**20c**	1.3:1	82

In summary, we developed a robust route to enantiomerically pure 4,5-disubstituted cyclohex-2-enones suitable as building blocks in the total synthesis of mycotoxins with the xanthone skeleton. As a first attempt, we have synthesized tetrahydroxanthenone derivatives employing the domino oxa-Michael addition–aldol condensation with excellent yields.

Substrates were purchased from commercial sources and used without further purification. Column chromatography was performed using Macherey-Nagel silica gel 60 (230–400 mesh) under flash conditions. For TLC, aluminum foil layered with silica gel with fluorescence indicator (silica gel 60 F_{254}) produced by Merck were employed. Melting points were determined using a Laboratory Devices Inc. MelTemp II device. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM400 (400 MHz/100 MHz) or Bruker DRX500 (500 MHz/125 MHz) instrument using $CDCl_3$ as the solvent and residual $CHCl_3$/$CDCl_3$ as shift reference [δ ($CHCl_3$) = 7.28 /δ ($CDCl_3$) = 77.00]. NMR signals that are labeled with an asterix (*) are interchangeable within their corresponding numbers. ^{13}C signals are labeled with '+' for positive signals in the DEPT 135 spectrum and with '–' for negative signals, respectively. IR spectra were recorded using the Bruker FTIR device IFS 88. EI-MS and EI-HRMS spectra were recorded on a Finnigan MAT 90 instrument; elemental analyses were performed using a Heraeus CHN-O-Rapid device. Specific rotations $[\alpha]_D^{20}$ were determined using the Perkin-Elmer device Polarimeter 241.

1,4-Addition of Copper Nucleophiles to 6; General Procedure A

$CuBr{\cdot}SMe_2$ (1.30 equiv) was completely dissolved in Me_2S (2.00 mL/mmol $CuBr{\cdot}SMe_2$) and then diluted with THF (4.00 mL/mmol $CuBr{\cdot}SMe_2$. At –30 to –20 °C, this soln was then slowly added to a 1 M soln of the corresponding alkyl or aryl Grignard reagent in THF (2.60 equiv). The mixture was stirred at –20 °C for 1 h and then it was cooled to –50 °C and treated with a soln of **6** (1.00 equiv) in THF (2.00 mL/mmol **6**) by dropwise addition and then stirred at –50 °C for 14 h. Sat. aq NH_4Cl soln was added and the mixture was brought up to r.t. Oxidation of residual copper(I) species was accomplished by conducting a stream of air through the reaction slurry for 30 min. The aqueous phase was then separated and extracted several times with EtOAc. The combined organic phases were freed from copper by washing with 10% aq NH_4Cl, dried (Na_2SO_4), and filtered. After removal of the solvent, the crude product was purified by flash column chromatography (silica gel, cyclohexane–EtOAc).

5-Alkyl/aryl-4-(trialkylsiloxy)cyclohex-2-enones 11; General Procedure B

Compound **7** (1.00 equiv) was dissolved in benzene (4.00 mL/mmol **7**) and treated with a trialkylsilyl chloride (1.30 equiv). DBU (1.50 equiv) was added and the mixture was heated to 100 °C for 5–7 h. The mixture was cooled to r.t., diluted with Et_2O, and washed with H_2O (2 ×), 1 M HCl (2 ×), and sat. aq $NaHCO_3$ soln (2 ×). The soln was dried (Na_2SO_4) and filtered, the solvent was removed, and the crude product was purified by flash column chromatography (silica gel, cyclohexane–EtOAc).

Deprotection of 5-Alkyl/aryl-4-(trialkylsiloxy)cyclohex-2-enones 11; General Procedure C

The 5-alkyl- or 5-aryl-4-(trialkylsiloxy)cyclohex-2-enone (1.00 equiv) was dissolved in THF (4.00 mL/mmol cyclohexenone derivative) and treated with AcOH (5.00 equiv) followed by the addition of 1 M TBAF in THF (1.00 equiv). The mixture was stirred at r.t. for 24 h and then another portion of TBAF soln (0.25 equiv) was added and stirring was continued at r.t. for an additional 24 h. The solvent was removed in vacuo with a minimum pressure of 100 mbar at 40 °C. The residue was purified by flash column chromatography (silica gel, cyclohexane–EtOAc).

Tetrahydroxanthones 20; General Procedure D

Argon was passed through H_2O (1.2 mL/mmol) for 15 min with simultaneous sonication. *N*-Methylimidazole (0.50 equiv), 5-methoxysalicylaldehyde (**19**, 1.00 equiv) and the corresponding 5-substituted 4-hydroxycyclohex-2-enone **5** (2.00 equiv) were then suspended in the degassed solvent and treated with ultrasound for 48 h. After this time, H_2O was added and the mixture was extracted several times with EtOAc. The resulting combined organic phases were dried (Na_2SO_4), and filtered. After removal of the solvent, the crude product was purified by flash column chromatography (silica gel, cyclohexane–EtOAc).

(3*R*,4*S*,5*R*)-3,4-(Isopropylidenedioxy)-5-methylcyclohexanone (7a)

Following general procedure A. Scale: **6** (500 mg, 2.97 mmol). Chromatography (cyclohexane–EtOAc, 5:1) gave a colorless oil; yield: 402 mg (73%); R_f = 0.47 (cyclohexane–EtOAc, 2:1).

$[\alpha]_D^{20}$ –36.93 (*c* 1.61, $CHCl_3$).

IR (KBr): 2985 (m, ν C–H), 2935 (m, ν C–H), 2908 (m, ν C–H), 1719 (s, ν C=O), 1381 (m, δ C–H), 1211 (m), 1049 cm^{-1} (s, ν C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.10 (d, ^3J = 7.2 Hz, 3 H, 5-CH_3), 1.35 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 2.04 (dd, ^2J = 17.0 Hz, ^3J = 8.8 Hz, 1 H, H6$_a$), 2.17–2.26 (m, 1 H, H5), 2.41 (dd, ^2J = 17.0 Hz, ^3J = 4.4 Hz, 1 H, H6$_b$), 2.57 (dd, ^2J = 16.9 Hz, ^3J = 5.0 Hz, 1 H, H2$_a$), 2.69 (dd, ^2J = 16.8 Hz, ^3J = 5.5 Hz, 1 H, H2$_b$), 4.13 (dd, ^3J = 6.6 Hz, ^3J = 6.6 Hz, 1 H, H4), 4.61 (ddd, ^3J = 6.9 Hz, ^3J = 5.3 Hz, ^3J = 5.3 Hz, 1 H, H3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.1 (+, 5-CH_3), 23.8 (+, CH_3), 26.6 (+, CH_3), 32.4 (+, C5), 41.8 (–, C2), 42.0 (–, C6), 72.5 (+, C3), 78.2 (+, C4), 107.7 (C_q, C8), 207.3 (C_q, C1).

MS (ESI): *m*/*z* (%) = 185 (37) [(M + H)$^+$], 169 (100) [(M – CH_3)$^+$], 127 (99) [($C_7H_{11}O_2$)$^+$], 109 (49) [(C_6H_9O)$^+$], 97 (35), 85 (78), 81 (39), 59 (49), 43 (69) [(C_2H_3O)$^+$].

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{17}O_3$: 185.1178; found: 185.1176.

(3*R*,4*S*,5*R*)-5-Ethyl-3,4-(isopropylidenedioxy)cyclohexanone (7b)

Following general procedure A. Scale: **6** (1.00 g, 5.95 mmol). Chromatography (cyclohexane–EtOAc, 5:1) gave a colorless oil; yield: 775 mg (66%); R_f = 0.29 (cyclohexane–EtOAc, 5:1).

$[\alpha]_D^{20}$ –24.25 (*c* 1.04, $CHCl_3$).

IR (KBr): 2965 (m, ν C–H), 2936 (m, ν C–H), 1719 (s, ν C=O), 1382 (m, δ C–H), 1055 cm^{-1} (m, ν C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 7.4 Hz, 3 H, 2′-CH_3), 1.23–1.33 (m, 1 H, H1′$_a$), 1.37 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.57–1.68 (m, 1 H, H1′$_b$), 1.99–2.10 (m, 2 H, H5, H6$_a$), 2.54–2.60 (m, 1 H, H6$_b$), 2.61–2.68 (m, 2 H, 2 H2), 4.16 (dd, ^3J = 6.0 Hz, ^3J = 6.0 Hz, 1 H, H4), 4.51–4.57 (m, 1 H, H3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5 (+, C2′), 24.4 [+, C(CH_3)$_2$], 24.9 (–, C1′), 27.0 [+, C(CH_3)$_2$], 39.1 (+, C5), 39.7 (–, C6), 42.0 (–, C2), 72.3 (+, C3), 76.7 (+, C4), 108.3 [C_q, *C*(CH_3)$_2$], 209.1 (C_q, C1).

MS (EI): *m*/*z* (%) = 198 (1) [M$^+$], 183 (77) [(M – CH_3)$^+$], 141 (100) [($C_8H_{13}O_2$)$^+$], 123 (51) [($C_8H_{11}O$)$^+$], 95 (71) [(C_6H_7O)$^+$], 81 (35), 43 (63) [(C_2H_3O)$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for ($C_{11}H_{18}O_3$): 198.1256; found: 198.1254.

(3*R*,4*S*,5*R*)-3,4-(Isopropylidenedioxy)-5-propylcyclohexanone (7c)

Following general procedure A. Scale: **6** (1.07 g, 6.37 mmol). Chromatography (cyclohexane–EtOAc, 5:1) gave a light-brown oil; yield: 535 mg (40%); R_f = 0.34 (cyclohexane–EtOAc, 5:1). Additionally, 236 mg (24%) of **5c** were isolated.

$[\alpha]_D^{20}$ –22.30 (*c* 4.73, $CHCl_3$).

IR (KBr): 2959 (m, ν C–H), 2933 (m, ν C–H), 2874 (w, ν C–H), 1719 (s, ν C=O), 1381 (m, δ C–H), 1056 cm^{-1} (m, ν C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.2 Hz, 3 H, 3′-CH_3), 1.17–1.27 (m, 1 H, H1′$_a$), 1.29–1.56 (m, 3 H, H1′$_b$, 2 H2′), 1.37 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 2.05 (dd, ^2J = 16.9 Hz, ^3J = 7.6 Hz, 1 H, H6$_a$), 2.08–2.16 (m, 1 H, H5), 2.57 (dd, ^2J = 16.9 Hz, ^3J = 4.1 Hz, 1 H, H6$_b$), 2.58–2.68 (m, 2 H, 2 H2), 4.15 (dd, ^3J = 6.0 Hz, ^3J = 6.0 Hz, 1 H, H4), 4.51–4.56 (m, 1 H, H3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (+, C3′), 20.2 (–, C2′), 24.3 (+, CH_3), 27.0 (+, CH_3), 34.3 (–, C1′), 37.2 (+, C5), 40.1 (–, C6), 41.9 (–, C2), 72.3 (+, C3), 76.9 (+, C4), 108.3 [C_q, *C*(CH_3)$_2$], 209.1 (C_q, C1).

MS (EI): *m*/*z* (%) = 212 (1) [M$^+$], 197 (59) [(M – CH_3)$^+$], 155 (100) [(M – C_3H_5O)$^+$], 137 (32), 109 (20), 95 (29), 67 (18), 43 (21) [(C_2H_3O)$^+$].

HRMS (EI): *m*/*z* [M – CH_3]$^+$ calcd for ($C_{11}H_{17}O_3$): 197.1178; found: 197.1172.

(3*R*,4*S*,5*R*)-3,4-(Isopropylidenedioxy)-5-neopentylcyclohexanone (7e)

Neopentylmagnesium bromide was prepared by the dropwise addition of a soln of neopentyl bromide (0.876 g, 5.80 mmol, 2.60 equiv) in THF (800 μL) to thermally and mechanically activated Mg shavings (141 mg, 5.80 mmol, 2.60 equiv) suspended in THF (5.80 mL). To ensure complete consumption of the magnesium shavings, 1,2-dibromoethane (0.129 mL, 0.691 mmol, 0.31 equiv) was added and the mixture was heated to 65 °C for 14 h. The greyish green soln was diluted with THF (5.00 mL) and was added dropwise to a soln of CuBr·SMe_2 (596 mg, 2.90 mmol, 1.30 equiv) in Me_2S (4.50 mL) and THF (9.00 mL) according to general procedure A. After 2 h stirring at –20 °C, a greyish brown suspension had formed, which was cooled down to –50 °C. A soln of the unsaturated acetonide **6** (375 mg, 2.23 mmol, 1.00 equiv) in THF (4.50 mL) was slowly added. The mixture was stirred at –50 °C for 14 h followed by the workup procedure described in general procedure A. Chromatography (cyclohexane–EtOAc, 9:1) gave a colorless oil; yield: 151 mg (28%); colorless oil; R_f = 0.34 (cyclohexane–EtOAc, 9:1).

$[\alpha]_D^{20}$ +54.54 (*c* 5.58, $CHCl_3$).

IR (KBr): 2958 (m, ν C–H), 2910 (m, ν C–H), 2868 (m, ν C–H), 1704 (s, ν C=O), 1062 cm^{-1} (m, ν C–O).

^1H NMR [400 MHz, $CDCl_3$ (spectrum shows contamination by hydroquinone, δ = 6.80)]: δ = 0.93 [s, 9 H, C(CH_3)$_3$], 1.09 (dd, ^2J = 13.9 Hz, ^3J = 5.5 Hz, 1 H, H1′$_a$), 1.34 (dd, ^2J = 13.9 Hz, ^3J = 4.1 Hz, 1 H, H1′$_b$), 1.37 [s, 3 H, C(CH_3)$_2$], 1.48 [s, 3 H, C(CH_3)$_2$], 2.14 (ddd, ^2J = 17.3 Hz, ^3J = 5.0 Hz, ^4J = 1.1 Hz, 1 H, H6$_a$), 2.16–2.23 (m, 1 H, H5), 2.50 (dd, ^2J = 17.6 Hz, ^3J = 4.7 Hz, 1 H, H2$_a$), 2.63–2.71 (m, 2 H, H2$_b$, H6$_b$), 4.19 (ddd, ^3J = 7.2 Hz, ^3J = 3.6 Hz, ^4J = 1.1 Hz, 1 H, H4), 4.62 (ddd, ^3J = 7.2 Hz, ^3J = 4.7 Hz, ^3J = 3.4 Hz, 1 H, H3).

^{13}C NMR [100 MHz, $CDCl_3$ (spectrum shows contamination by hydroquinone, δ = 136.5)]: δ = 24.0 (+, CH_3), 26.5 (+, CH_3), 29.2 [+, C(*C*H_3)$_3$], 31.5 [C_q, *C*(CH_3)$_3$], 33.4 (+, C5), 41.8 (–, C2)*, 41.9 (–, C6)*, 45.5 (–, C1′), 72.1 (+, C3), 77.6 (+, C4), 108.1 [C_q, *C*(CH_3)$_2$], 209.5 (C_q, C1).

MS (EI): *m*/*z* (%) = 240 (34) [M$^+$], 225 (83) [(M – CH_3)$^+$], 183 (41) [(M – C_4H_9)$^+$], 165 (26), 125 (55), 109 (28), 100 (32), 85 (33), 71 (45), 57 (100) [(C_4H_9)$^+$], 43 (37) [(C_2H_3O)$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for ($C_{14}H_{24}O_3$): 240.1725; found: 240.1728.

(3*R*,4*S*,5*R*)-5-Allyl-3,4-(isopropylidenedioxy)cyclohexanone (7g)

Following general procedure A. Scale: **6** (1.50 g, 8.92 mmol). Chromatography (cyclohexane–EtOAc, 5:1) gave a brown oil; yield: 80 mg (4%); R_f = 0.49 (cyclohexane–EtOAc, 2:1). The analytical data are in accordance with those reported in the literature.[8] Additionally, starting material **6** (228 mg, 15%) and **8**[11] (87 mg, 4%) were isolated.

$[\alpha]_D^{20}$ +19.45 (*c* 1.83, $CHCl_3$)

IR (KBr): 3077 (vw, ν C=C–H), 2987 (w, ν C–H), 2916 (w, ν C–H), 1719 (s, ν C=O), 1382 (m, δ C–H), 1045 cm^{-1} (m, ν C–O).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.98–2.05 (m, 1 H, H1′$_a$), 2.05 (dd, ^2J = 17.3 Hz, ^3J = 8.4 Hz, 1 H, H6$_a$), 2.16–2.25 (m, 1 H, H5), 2.31–2.40 (m, 1 H, H1′$_b$), 2.56 (dd, ^2J = 17.3 Hz, ^3J = 4.5 Hz, 1 H, H6$_b$), 2.64 (dd, ^2J = 17.1 Hz,

^3J = 5.4 Hz, 1 H, H2$_a$), 2.69 (dd, ^2J = 17.1 Hz, ^3J = 5.2 Hz, 1 H, H2$_b$), 4.16 (dd, ^3J = 6.6 Hz, ^3J = 6.3 Hz, 1 H, H4), 4.54 (ddd, ^3J = 6.6 Hz, ^3J = 5.4 Hz, ^3J = 5.2 Hz, 1 H, H3), 5.05–5.13 (m, 2 H, 2 H3′), 5.76 (dddd, ^3J = 16.9 Hz, ^3J = 10.3 Hz, ^3J = 7.5 Hz, ^3J = 6.6 Hz, 1 H, H2′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (+, *C*H$_3$), 27.1 (+, *C*H$_3$), 36.3 (–, C1′), 37.2 (+, C5), 39.9 (–, C6), 42.2 (–, C2), 72.2 (+, C3), 76.3 (+, C4), 108.5 [C$_q$, *C*(CH$_3$)$_2$], 117.6 (–, C3′), 134.9 (+, C2′), 208.7 (C$_q$, C1).

MS (EI): *m*/*z* (%) = 210 (10) [M$^+$], 195 (100) [(M – CH$_3$)$^+$], 153 (80) [(M – C$_3$H$_5$O)$^+$], 135 (30), 107 (52), 93 (82), 79 (27), 43 (56) [(C$_2$H$_3$O)$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for (C$_{12}$H$_{18}$O$_3$): 210.1256; found: 210.1251.

(3*R*,4*S*,5*S*)-3,4-(Isopropylidenedioxy)-5-phenylcyclohexanone (7h)

Following general procedure A. Scale: **6** (850 mg, 5.05 mmol). Chromatography (cyclohexane–EtOAc, 5:1) gave a light-yellow oil; yield: 334 mg (27%); R_f = 0.24 (cyclohexane–EtOAc, 5:1).

$[\alpha]_D^{20}$ –56.96 (*c* 10.7, $CHCl_3$).

IR (KBr): 3062 (vw, ν C=C–H), 3030 (w, ν C$_{ar}$–H), 2987 (m, ν C–H), 2935 (w, ν C–H), 1719 (s, ν C=O), 1381 (s, δ C–H), 1047 cm^{-1} (s, ν C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, C*H*$_3$), 1.55 (s, 3 H, C*H*$_3$), 2.63 (dd, ^2J = 17.8 Hz, ^3J = 8.9 Hz, 1 H, H6$_a$), 2.67 (dd, ^2J = 17.0 Hz, ^3J = 4.9 Hz, 1 H, H2$_a$), 2.74 (dd, ^2J = 17.0 Hz, ^3J = 4.4 Hz, 1 H, H2$_b$), 2.76 (dd, ^2J = 17.8 Hz, ^3J = 4.7 Hz, 1 H, H6$_b$), 3.43 (ddd, ^3J = 8.9 Hz, ^3J = 4.7 Hz, ^3J = 4.7 Hz, 1 H, H5), 4.60–4.66 (m, 2 H, H3, H4), 7.24–7.30 (m, 3 H, H2′, H4′, H6′), 7.37 (dd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, 2 H, H3′, H5′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3 (+, *C*H$_3$), 27.0 (+, *C*H$_3$), 40.9 (–, C6), 42.3 (–, C2), 42.6 (+, C5), 72.4 (+, C3)*, 77.7 (+, C4)*, 108.6 [C$_q$, *C*(CH$_3$)$_2$], 127.1 (+, C4′), 127.4 (+, C2′, C6′), 128.8 (+, C3′, C5′), 140.0 (C$_q$, C1′), 208.5 (C$_q$, C1).

MS (EI): *m*/*z* (%) = 246 (81) [M$^+$], 231 (62) [(M – CH$_3$)$^+$], 189 (21) [(M – C$_3$H$_6$O)$^+$], 171 (26), 143 (35), 131 (72), 129 (67), 104 (100), [(C$_8$H$_8$)$^+$], 43 (54) [(C$_2$H$_3$O)$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for (C$_{15}$H$_{18}$O$_3$): 246.1256; found: 246.1259.

(4*S*,5*R*)-4-(*tert*-Butyldimethylsiloxy)-5-methylcyclohex-2-enone (11a)

Following general procedure B. Scale: **7a** (1.38 g, 7.50 mmol). Chromatography (cyclohexane–EtOAc, 9:1) gave a light-yellow oil; yield: 1.67 g (93%); R_f = 0.46 (cyclohexane–EtOAc, 9:1).

$[\alpha]_D^{20}$ –157.44 (*c* 0.80, $CHCl_3$).

IR (KBr): 3041 (m, ν C=C–H), 2956 (m, ν C–H), 2930 (w, ν C–H), 2894 (w, ν C–H), 2858 (m, ν C–H), 1687 cm^{-1} (s, ν C=O).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.12 (s, 3 H, SiC*H*$_3$), 0.13 (s, 3 H, SiC*H*$_3$), 0.93 [s, 9 H, Si-C(C*H*$_3$)$_3$], 1.08 (d, ^3J = 6.1 Hz, 3 H, 5-C*H*$_3$), 2.08–2.19 (m, 2 H, H5, H6$_a$), 2.50 (d, ^3J = 13.0 Hz, 1 H, H6$_b$), 4.10 (d, ^3J = 8.7 Hz, 1 H, H4), 5.91 (d, ^3J = 10.2 Hz, 1 H, H2), 6.78 (dd, ^3J = 10.2 Hz, ^3J = 1.7 Hz, 1 H, H3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.8 (+, Si*C*H$_3$), –4.4 (+, Si*C*H$_3$), 18.0 [C$_q$, Si-*C*(CH$_3$)$_3$], 18.5 (+,5-*C*H$_3$), 25.8 [+, Si-C(*C*H$_3$)$_3$], 39.4 (+, C5), 44.1 (–, C6), 73.5 (+, C4), 128.6 (+, C2), 154.2 (+, C3), 199.1 (C$_q$, C1).

MS (EI): *m*/*z* (%) = 240 (11) [M$^+$], 225 (87) [(M – CH$_3$)$^+$], 183 (100) [(M – C$_4$H$_9$)$^+$], 165 (17) [(M – C$_2$H$_7$OSi)$^+$], 75 (74) [(C$_2$H$_7$OSi)$^+$].

HRMS (EI): *m*/*z* [M – C$_4$H$_9$]$^+$ calcd for (C$_9$H$_{15}$O$_2$Si): 183.0841; found: 183.0844.

Anal. Calcd for C$_{13}$H$_{24}$O$_2$Si: C, 64.95; H, 10.06. Found: C, 65.12; H, 10.14.

(4*S*,5*R*)-4-(*tert*-Butyldimethylsiloxy)-5-ethylcyclohex-2-enone (11b)

Following general procedure B. Scale: **7b** (700 mg, 3.53 mmol). Chromatography (cyclohexane–EtOAc, 9:1) gave a light yellow oil; yield: 662 mg (74%); R_f = 0.35 (cyclohexane–EtOAc, 9:1).

IR (KBr): 3041 (m, ν C=C–H), 2959 (m, ν C–H), 2931 (m, ν C–H), 2885 (w, ν C–H), 2858 (m, ν C–H), 1689 (s, ν C=O), 1092 cm^{-1} (m, ν C–O).

$[\alpha]_D^{20}$ –198.00 (*c* 0.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.14 (s, 3 H, SiC*H*$_3$), 0.15 (s, 3 H, SiC*H*$_3$), 0.92 (t, ^3J = 7.5 Hz, 3 H, 2′-C*H*$_3$), 0.94 [s, 9 H, SiC(C*H*$_3$)$_3$], 1.19–1.31 (m, 1 H, H1′$_a$), 1.82 (dqd, ^2J = 13.4 Hz, ^3J = 7.6 Hz, ^3J = 3.4 Hz, 1 H, H1′$_b$), 1.95–2.04 (m, 1 H, H5), 2.07 (dd, ^2J = 15.5 Hz, ^3J = 12.7 Hz, 1 H, H6$_a$), 2.64 (ddd, ^2J = 15.5 Hz, ^3J = 2.6 Hz, ^4J = 1.5 Hz, 1 H, H6$_b$), 4.21 (ddd, ^3J = 8.4 Hz, ^3J = 2.0 Hz, ^4J = 1.5 Hz, 1 H, H4), 5.93 (ddd, ^3J = 10.2 Hz, ^3J = 2.0 Hz, ^4J = 1.2 Hz, 1 H, H2), 6.81 (dd, ^3J = 10.2 Hz, ^4J = 2.1 Hz, 1 H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 (+, Si*C*H$_3$), –4.3 (+, Si*C*H$_3$), 10.5 (+, C2′), 13.0 [C$_q$, Si*C*(CH$_3$)$_3$], 24.4 (–, C1′), 25.8 [+, SiC(*C*H$_3$)$_3$], 40.6 (–, C6), 45.6 (+, C5), 71.6 (+, C4), 128.4 (+, C2), 154.1 (+, C3), 199.4 (C$_q$, C1).

MS (EI): *m*/*z* (%) = 254 (1) [M$^+$], 239 (3) [(M – CH$_3$)$^+$], 197 (79) [(M – C$_4$H$_9$)$^+$], 179 (13) [(M – C$_2$H$_7$OSi)$^+$], 155 (16), 105 (17), 75 (100) [(C$_2$H$_7$OSi)$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for (C$_{14}$H$_{26}$O$_2$Si): 254.1702; found: 254.1700.

(4*S*,5*R*)-4-(*tert*-Butyldimethylsiloxy)-5-propylcyclohex-2-enone (11c)

Following general procedure B. Scale: **7c** (332 mg, 1.56 mmol). Chromatography (cyclohexane–EtOAc, 9:1) gave a colorless oil; yield: 281 mg (67%); R_f = 0.39 (cyclohexane–EtOAc, 9:1).

$[\alpha]_D^{20}$ –409.23 (*c* 0.79, $CHCl_3$).

FT-IR (film on KBr): 3041 (vw, ν C=C–H), 2957 (m, ν C–H), 2932 (m, ν C–H), 2897 (w, ν C–H), 2858 (m, ν C–H), 1688 (s, ν C=O), 1094 cm^{-1} (w, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.14 (s, 3 H, SiC*H*$_3$), 0.15 (s, 3 H, SiC*H*$_3$), 0.90–0.95 [m, 12 H, 3′-CH$_3$, SiC(C*H*$_3$)$_3$], 1.15–1.32 (m, 2 H, H1′$_a$, H2′$_a$), 1.36–1.49 (m, 1 H, H2′$_b$), 1.66–1.77 (m, 1 H, H1′$_b$), 2.02–2.13 (m, 2 H, H5, H6$_a$), 2.58–2.68 (m, 1 H, H6$_b$), 4.16–4.21 (m, 1 H, H4), 5.87 (ddd, ^3J = 10.2 Hz, ^4J = 1.3 Hz, ^4J = 1.3 Hz, 1 H, H2), 6.80 (dd, ^3J = 10.2 Hz, ^3J = 2.1 Hz, 1 H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (+, Si*C*H$_3$), –4.3 (+, Si*C*H$_3$), 14.1 (+, C3′), 18.0 [C$_q$, Si*C*(CH$_3$)$_3$], 19.2 (–, C2′), 25.7 [+, SiC(*C*H$_3$)$_3$], 4.0 (–, C1′), 41.1 (–, C6), 43.8 (–, C5), 71.7 (–, C4), 128.4 (–, C2), 153.9 (–, C3), 199.3 (C$_q$, C1).

MS (EI): *m*/*z* (%) = 268 (1) [M$^+$], 253 (3) [(M – CH$_3$)$^+$], 211 (100) [(M – C$_4$H$_9$)$^+$], 155 (9), 75 (39) [(C$_2$H$_7$OSi)$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for (C$_{15}$H$_{28}$O$_2$Si): 268.1859; found: 268.1856.

(4*S*,5*S*)-4-(*tert*-Butyldimethylsiloxy)-5-vinylcyclohex-2-enone (11f)

Divinylcuprate was prepared according to general procedure A and added to the unsaturated acetonide **6** (100 mg, 595 μmol). The workup was conducted by addition of sat. aq NH_4Cl soln (5 mL), filtration and washing of the filter cake with EtOAc (20 mL). The organic phase was separated and the solvents removed. The residue was dissolved in H_2O and extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with 10% aq NH_4Cl (2 × 10

mL), H_2O (10 mL), and brine (10 mL), dried (Na_2SO_4), and filtered. After removal of the solvent, the crude product (40 mg, ca. 200 μmol) was directly used in the next transformation step corresponding to general procedure B. The crude product, DBU (33.0 mg, 218 μmol, 1.07 equiv) and TBDMSCl (75.0 mg, 500 μmol, 2.45 equiv) were dissolved in benzene (2 mL) and heated to 100 °C for 5.5 h. The workup also followed general procedure C. Chromatography (cyclohexane–EtOAc, 20:1, 1% Et_3N) gave a colorless oil; yield: 13 mg (9%); R_f = 0.17 (cyclohexane–EtOAc, 20:1, 1% Et_3N). The analytical data are in accordance with those reported in the literature as far as they have been reported before.[4]

IR (KBr): 3081 (vw, ν C=C–H), 3040 (vw, ν C=C–H), 2955 (m, ν C–H), 2928 (s, ν C–H), 2856 (m, ν C–H), 1694 (m, ν C=O), 1463 (w, ν C=C), 1380 (w), 1252 (m), 1100 cm^{-1} (m ν C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, SiCH_3), 0.11 (s, 3 H, SiCH_3), 0.90 [s, 9 H, SiC(CH_3)$_3$], 2.32 (dd, ^2J = 16.6 Hz, ^3J = 12.6 Hz, 1 H, H6$_a$), 2.57 (ddd, ^2J = 16.6 Hz, ^3J = 4.1 Hz, ^4J = 0.9 Hz, 1 H, H6$_b$), 2.70–2.79 (m, 1 H, H5), 4.26 (ddd, ^3J = 8.8 Hz, ^3J = 2.0 Hz, ^4J = 2.0 Hz, 1 H, H4), 5.10 (br d, ^3J = 17.0 Hz, 1 H, H2′$_a$), 5.13 (br d, ^3J = 10.6 Hz, 1 H, H2′$_b$), 5.81 (ddd, ^3J = 17.0 Hz, ^3J = 10.6 Hz, ^3J = 7.5 Hz, 1 H, H1′), 5.92 (br d, ^3J = 10.2 Hz, 1 H, H2), 6.78 (dd, ^3J = 10.1 Hz, ^3J = 2.1 Hz, 1 H, H3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6 (+, Si*C*H$_3$), –4.5 (+, Si*C*H$_3$), 18.1 [C_q, Si*C*(CH$_3$)$_3$], 25.7 [+, Si*C*(CH$_3$)$_3$], 40.9 (–, C6), 48.2 (+, C5), 71.4 (+, C4), 116.7 (–, C2′), 128.5 (+, C2), 138.0 (+, C1′), 153.4 (+, C3), 198.3 (C_q, C1).

MS (EI): *m*/*z* (%) = 252 (1) [M^+], 237 (2) [$(M - CH_3)^+$], 223 (4) [$(C_{13}H_{23}OSi)^+$], 209 (4) [$(M - C_2H_3O)^+$], 195 (100) [$(M - C_4H_9)^+$], 167 (20), 113 (30), 75 (87) [$(C_2H_7OSi)^+$].

HRMS (EI): *m*/*z* [$M]^+$ calcd for ($C_{14}H_{24}O_2Si$): 252.1546; found: 252.1541.

(4*S*,5*R*)-5-Allyl-4-(*tert*-butyldimethylsiloxy)cyclohex-2-enone (11g)

Following general procedure B. Scale: **7g** (50.0 mg, 238 μmol). Chromatography (cyclohexane–EtOAc, 9:1) gave a light yellow oil; yield: 35 mg (55%); R_f = 0.39 (cyclohexane–EtOAc, 9:1). The analytical data are in accordance with those reported in the literature.[4]

$[\alpha]_D^{20}$ –109.47 (*c* 1.13, $CHCl_3$).

IR (KBr): 3078 (w, ν C=C–H), 3041 (w, ν C=C–H), 2957 (m, ν C–H), 2931 (w, ν C–H), 2859 (m, ν C–H), 1689 (s, ν C=O), 1100 cm^{-1} (s, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 3 H, SiCH_3), 0.16 (s, 3 H, SiCH_3), 0.95 [s, 9 H, SiC(CH_3)$_3$], 1.98 (ddd, ^2J = 13.7 Hz, ^3J = 8.5 Hz, ^3J = 8.1 Hz, 1 H, H1′$_a$), 2.07 (dd, ^2J = 15.8 Hz, ^3J = 12.7 Hz, 1 H, H6′$_a$), 2.10–2.22 (m, 1 H, H5), 2.51–2.58 (m, 1 H, H1′$_b$), 2.62 (ddd, ^2J = 15.8 Hz, ^3J = 2.9 Hz, ^4J = 1.3 Hz, 1 H, H6′$_b$), 4.23 (ddd, ^3J = 8.5 Hz, ^3J = 2.4 Hz, ^3J = 2.0 Hz, 1 H, H4), 5.05–5.13 (m, 2 H, 2 H3′), 5.73 (dddd, ^3J = 16.7 Hz, ^3J = 10.3 Hz, ^3J = 8.1 Hz, ^3J = 6.2 Hz, 1 H, H2′), 5.94 (ddd, ^3J = 10.2 Hz, ^3J = 2.0 Hz, ^4J = 1.3 Hz, 1 H, H2), 6.81 (dd, ^3J = 10.2 Hz, ^3J = 2.4 Hz, 1 H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 (+, Si*C*H$_3$), –4.2 (+, Si*C*H$_3$), 18.0 [C_q, Si*C*(CH$_3$)$_3$], 25.7 [+, SiC(*C*H$_3$)$_3$], 36.2 (–, C1′), 40.9 (–, C6), 43.7 (+, C5), 71.3 (+, C4), 117.6 (–, C3′), 128.6 (+, C2), 134.9 (+, C2′), 153.6 (+, C3), 199.0 (C_q, C1).

MS (EI): *m*/*z* (%) = 257 (15) [$(M - CH_3)^+$], 209 (81) [$(M - C_4H_9)^+$], 191 (63) [$(M - C_2H_7OSi)^+$], 167 (61), 151 (21) [$(M - C_6H_{15}Si)^+$], 75 (100) [$(C_2H_7OSi)^+$].

HRMS (EI): *m*/*z* [$M - C_4H_9]^+$ calcd for ($C_{11}H_{17}O_2Si$): 209.0998; found: 209.1000.

(4*R*,5*S*)-4-(*tert*-Butyldimethylsiloxy)-5-phenylcyclohex-2-enone (11h)

Following general procedure B. Scale: **7h** (250 mg, 1.02 mmol). Chromatography (cyclohexane–EtOAc, 9:1) gave a colorless solid; yield: 35 mg (11%); mp 74–75 °C; R_f = 0.26 (cyclohexane–EtOAc, 5:1).

$[\alpha]_D^{20}$ –158.40 (*c* 0.50, $CHCl_3$).

IR (KBr): 3032 (w, ν C=C–H), 2951 (m, ν C–H), 2929 (m, ν C–H), 2896 (w, ν C–H), 2855 (m, ν C–H), 2817 (w, ν C–H), 1682 (s, ν C=O), 1093 cm^{-1} (m, ν C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.48 (s, 3 H, SiCH_3), –0.12 (s, 3 H, SiCH_3), 0.77 [s, 9 H, SiC(CH_3)$_3$], 2.68 (dd, ^2J = 16.5 Hz, ^3J = 4.0 Hz, 1 H, H6$_a$), 2.79 (dd, ^3J = 16.5 Hz, ^3J = 13.7 Hz, 1 H, H6$_b$), 3.27 (ddd, ^3J = 13.7 Hz, ^3J = 9.4 Hz, ^3J = 4.0 Hz, 1 H, H5), 4.54 (ddd, ^3J = 9.4 Hz, ^3J = 1.8 Hz, ^4J = 1.8 Hz, 1 H, H4), 6.04 (br d, ^3J = 10.2 Hz, 1 H, H2), 6.86 (dd, ^3J = 10.2 Hz, ^3J = 1.8 Hz, 1 H, H3), 7.24–7.30 (m, 3 H, H2′, H4′, H6′), 7.35 (dd, ^3J = 7.35 Hz, ^3J = 7.3 Hz, 2 H, H3′, H5′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.8 (+, Si*C*H$_3$), –5.2 (+, Si*C*H$_3$), 17.9 [C_q, Si*C*(CH$_3$)$_3$], 25.6 [+, SiC(*C*H$_3$)$_3$], 42.6 (–, C6), 50.7 (+, C5), 73.0 (+, C4), 127.3 (+, C4′), 128.2 (+, C2′, C6′), 128.4 (+, C2), 128.5 (+, C3′, C5′), 140.7 (C_q, C1′), 153.9 (+, C3), 198.5 (C_q, C1).

MS (EI): *m*/*z* (%) = 302 (1) [M^+], 287 (3) [$(M - CH_3)^+$], 245 (100) [$(M - C_4H_9)^+$], 198 (10), 75 (16) [$(C_2H_7OSi)^+$].

HRMS (EI): *m*/*z* [$M]^+$ calcd for ($C_{18}H_{26}O_2Si$): 302.1702; found: 302.1701.

(4*S*,5*R*)-4-Hydroxy-5-methylcyclohex-2-enone (5a)

Following general procedure C. Scale: **11a** (1.47 g, 6.11 mmol). Chromatography (cyclohexane–EtOAc, 1:1) gave a colorless oil; yield: 578 mg (75%); R_f = 0.21 (cyclohexane–EtOAc, 1:1).

$[\alpha]_D^{20}$ –135.71 (*c* 1.06, $CHCl_3$).

IR (KBr): 3415 (m, ν O–H), 2959 (w, ν C–H), 2878 (w, ν C–H), 1665 (m, ν C=O), 1053 cm^{-1} (m, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, ^3J = 6.1 Hz, 3 H, 5-CH_3), 2.12–2.22 (m, 2 H, H5, H6$_a$), 2.47 (br s, 1 H, OH), 2.53 (dd, ^2J = 12.7 Hz, ^3J = 1.2 Hz, 1 H, H6$_b$), 4.14–4.19 (m, 1 H, H4), 5.97 (ddd, ^3J = 10.2 Hz, ^4J = 2.3 Hz, ^4J = 1.3 Hz, 1 H, H2), 6.92 (dd, ^3J = 10.2 Hz, ^3J = 2.0 Hz, 1 H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (+, 5-*C*H$_3$), 39.2 (+, C5), 44.0 (–, C6), 72.9 (+, C4), 129.0 (+, C2), 153.3 (+, C3), 199.2 (C_q, C1).

MS (EI): *m*/*z* (%) = 126 (24) [M^+], 109 (2) [$(M - OH)^+$], 84 (100) [$(C_4H_4O_2)^+$], 68 (28), 55 (52).

HRMS (EI): *m*/*z* [$M]^+$ calcd for ($C_7H_{10}O_2$): 126.0681; found: 126.0684.

(4*S*,5*R*)-5-Ethyl-4-hydroxycyclohex-2-enone (5b)

Following general procedure C. Scale: **11b** (640 mg, 2.52 mmol). Chromatography (cyclohexane–EtOAc, 1:1) gave a light yellow oil; yield: 352 mg (99.5%); R_f = 0.25 (cyclohexane–EtOAc, 1:1).

$[\alpha]_D^{20}$ –170.14 (*c* 0.71, $CHCl_3$).

IR (KBr): 3413 (s, ν O–H), 2965 (m, ν C–H), 2936 (m, ν C–H), 2879 (m, ν C–H), 1680 (s, ν C=O), 1058 cm^{-1} (m, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, ^3J = 7.5 Hz, 3 H, 2′-CH_3), 1.32–1.44 (m, 1 H, H1′$_a$), 1.82–2.04 (m, 2 H, H1′$_b$, H5), 2.11 (dd, ^2J = 16.2 Hz, ^3J = 13.1 Hz, 1 H, H6$_a$), 2.43 (br s, 1 H, OH), 2.62 (ddd, ^2J = 16.2 Hz, ^3J = 3.6 Hz, ^4J = 1.0 Hz, 1 H, H6$_b$), 5.24 (ddd, ^3J = 9.2 Hz, ^3J = 2.1 Hz, ^4J = 2.1 Hz, 1 H, H4), 5.97 (ddd, ^3J = 10.2 Hz, ^3J = 2.2 Hz, ^4J = 1.3 Hz, 1 H, H2), 6.92 (dd, ^3J = 10.2 Hz, ^3J = 2.1 Hz, 1 H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.4 (+, C2′), 24.5 (–, C1′), 40.7 (–, C6), 45.4 (+, C5), 70.9 (+, C4), 128.8 (+, C2), 153.5 (+, C3), 199.4 (C_q, C1).

MS (EI): *m*/*z* (%) = 140 (71) [M^+], 98 (75) [$(M - C_2H_2O)^+$], 84 (100) [$(C_4H_4O_2)^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for ($C_8H_{12}O_2$): 140.0837; found: 140.0839.

(4*S*,5*R*)-4-Hydroxy-5-propylcyclohex-2-enone (5c)

Following general procedure C. Scale: **11c** (281 mg, 1.05 mmol). Chromatography (cyclohexane–EtOAc, 1:1) gave a colorless oil; yield: 113 mg (70%); R_f = 0.37 (cyclohexane–EtOAc, 1:1).

$[\alpha]_D^{20}$ –157.11 (*c* 0.45, $CHCl_3$).

IR (KBr): 3420 (m, ν O–H), 3037 (vw, ν C=C–H), 2959 (m, ν C–H), 2933 (m, ν C–H), 2873 (m, ν C–H), 1677 (s, ν C=O), 1053 cm^{-1} (m, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.1 Hz, 3 H, 3′-CH_3), 1.21–1.38 (m, 2 H, H1′$_a$, H2′$_a$), 1.41–1.54 (m, 1 H, H2′$_b$), 1.73–1.84 (m, 1 H, H1′$_b$), 1.98–2.15 (m, 3 H, H5, H6$_a$, OH), 2.60–2.66 (m, 1 H, H6$_b$), 4.24 (ddd, ^3J = 8.9 Hz, ^3J = 1.9 Hz, ^3J = 1.9 Hz, 1 H, H4), 5.97 (br d, ^3J = 10.2 Hz, 1 H, H2), 6.92 (dd, ^3J = 10.2 Hz, ^3J = 6.1 Hz, 1 H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (+, C3′), 19.2 (–, C2′), 34.1 (–, C1′), 41.2 (–, C6), 43.8 (+, C5), 71.4 (+, C4), 128.9 (+, C2), 153.2 (+, C3), 199.2 (C_q, C1).

MS (EI): *m*/*z* (%) = 154 (50) [M^+], 112 (66) [$(M - C_2H_2O)^+$], 84 (100) [$(C_4H_4O_2)^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for ($C_9H_{14}O_2$): 154.0994; found: 154.0992.

(4*R*,5*S*)-4-Hydroxy-5-phenylcyclohex-2-enone (5h)

Following general procedure C. Scale: **11h** (143 mg, 473 μmol). Chromatography (cyclohexane–EtOAc, 1:1) gave a colorless oil; yield: 83 mg (93%); R_f = 0.27 (cyclohexane–EtOAc, 1:1).

$[\alpha]_D^{20}$ –175.42 (*c* 0.12, $CHCl_3$).

IR (KBr): 3407 (m, ν O–H), 3062 (w, ν C_{ar}–H), 3031 (w, ν C_{ar}–H), 2957 (w, ν C–H), 2896 (w, ν C–H), 1676 (s, ν C=O), 1074 cm^{-1} (m, ν C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.05 (br d, ^3J = 3.8 Hz, 1 H, OH), 2.66–2.76 (m, 2 H, 2 H6), 3.26 (ddd, ^3J = 11.6 Hz, ^3J = 10.0 Hz, ^3J = 6.3 Hz, 1 H, H5), 4.66–4.72 (m, 1 H, H4), 6.08 (dd, ^3J = 10.2 Hz, ^3J = 2.0 Hz, 1 H, H2), 7.01 (dd, ^3J = 10.2 Hz, ^3J = 1.7 Hz, 1 H, H3), 7.30–7.36 (m, 3 H, H2′, H4′, H6′), 7.42 (dd, ^3J = 7.4 Hz, 2 H, H3′, H5′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.0 (–, C6), 50.7 (+, C5), 71.8 (+, C4), 127.7 (+, C2′, C6′), 127.9 (+, C4′), 129.0 (+, C2), 129.2 (+, C3′, C5′), 139.4 (C_q, C1′), 152.1 (+, C3), 198.0 (C_q, C1).

MS (EI): *m*/*z* (%) = 188 (42) [M^+], 146 (12) [$(M - C_2H_2O)^+$], 104 (15), 84 (100) [$(C_4H_4O_2)^+$], 77 (12) [$(C_6H_5)^+$], 55 (22), 43 (30) [$(C_2H_3O)^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for ($C_{12}H_{12}O_2$): 188.0837; found: 188.0839.

(4*S*,5*R*)-5-Methyl-4-(triisopropylsiloxy)cyclohex-2-enone (12)

Following general procedure B. Scale: **7a** (255 mg, 1.38 mmol) and TIPSCl (285 mg, 1.48 mmol, 1.07 equiv) instead of TBDMSCl. Chromatography (cyclohexane–EtOAc, 9:1) gave a colorless oil; yield: 177 mg (47%); R_f = 0.35 (cyclohexane–EtOAc, 9:1).

IR (KBr): 3041 (vw, ν C=C–H), 2945 (s, ν C–H), 2892 (m, ν C–H), 2867 (s, ν C–H), 1686 cm^{-1} (s, ν C=O).

$[\alpha]_D^{20}$ –128.61 (*c* 0.76, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08–1.20 [m, 24 H, 5-CH_3, Si(CH(CH_3)$_2$)$_3$], 2.16 (dd, ^2J = 16.0 Hz, ^3J = 11.3 Hz, 1 H, H6$_a$), 2.17–2.28 (m, 1 H, H5), 2.60 (dd, ^2J = 16.0 Hz, ^3J = 3.3 Hz, 1 H, H6$_b$), 4.28–4.32 (m, 1 H, H4), 5.94 (d, ^3J = 10.4 Hz, 1 H, H2), 6.88 (dd, ^3J = 10.4 Hz, ^3J = 2.5 Hz, 1 H, H3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7 [+, Si(CH(CH_3)$_2$)$_3$], 18.11 [+, Si(CH(CH_3)(CH_3))$_3$], 18.13 [+, SiCH(CH_3)(CH_3)], 18.5 (+, 5-CH_3), 39.4 (+, C5), 43.6 (–, C6), 73.1 (+, C4), 128.6 (+, C2), 152.7 (+, C3), 199.2 (C_q, C1).

MS (EI): *m*/*z* (%) = 282 (1) [M+], 239 (100) [$(M - C_3H_7)^+$], 165 (26), 103 (29), 75 (54).

HRMS (EI): *m*/*z* [M]$^+$ calcd for ($C_{16}H_{30}O_2Si$): 282.2015; found: 282.2012.

(4*S*,5*R*)-4-(4-Bromobenzoyloxy)-5-methylcyclohex-2-enone (15)

Following general procedure B. Scale: **7a** (82.0 mg, 445 μmol) and 4-bromobenzoyl chloride (294 mg, 1.34 mmol, 3.01 equiv) instead of TBDMSCl. Chromatography (cyclohexane–EtOAc, 9:1) gave an off-white solid; yield: 31 mg (23%); mp 108 °C; R_f = 0.48 (cyclohexane–EtOAc, 5:1).

$[\alpha]_D^{20}$ – 197.32 (*c* 1.10, $CHCl_3$).

IR (KBr): 3104 (w, ν C=C–H), 3089 (w, ν C=C–H), 3059 (w, ν C_{ar}–H), 3041 (w, ν C_{ar}–H), 2962 (m, ν C–H), 2929 (m, ν C–H), 2873 (m, ν C–H), 2373 (vw), 2295 (vw), 2214 (vw), 1708 [s, ν C=O (RCO_2R')], 1689 (s, ν C=O), 1587 cm^{-1} (m, ν C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (d, ^3J = 6.6 Hz, 3 H, 5-CH_3), 2.30 (dd, ^2J = 16.5 Hz, ^3J = 12.7 Hz, 1 H, H6$_a$), 2.54 (ddqd, ^3J = 12.7 Hz, ^3J = 9.4 Hz, ^3J = 6.6 Hz, ^3J = 4.1 Hz, 1 H, H5), 2.63 (dd, ^2J = 16.5 Hz, ^3J = 4.1 Hz, 1 H, H6$_b$), 5.57 (ddd, ^3J = 9.4 Hz, ^3J = 2.0 Hz, ^4J = 1.5 Hz, 1 H, H4), 6.06 (dm, ^3J = 10.1 Hz, 1 H, H2), 6.85 (dd, ^3J = 10.1 Hz, ^3J = 2.0 Hz, 1 H, H3), 7.58–7.61 (m, 2 H, H$_{ar}$), 7.90–7.94 (m, 2 H, H$_{ar}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (+, 5-CH_3), 36.2 (+, C5), 43.8 (–, C6), 74.6 (+, C4), 128.4 (C_q, C_{ar}), 128.7 (C_q, C_{ar}), 130.5 (+, C2), 131.3 (+, C2′, C6′)*, 131.9 (+, C3′, C5′)*, 148.1 (+, C3), 165.5 (C_q, RCO_2R′), 197.9 (C_q, C1).

MS (EI): *m*/*z* (%) = 310/308 (8/9) [M^+], 185/183 (100/87) [$(C_7H_4BrO)^+$], 157/155 (15/16) [$(C_6H_4Br)^+$], 124 (12), 108 (60) [$C_7H_8O)^+$], 80 (15).

HRMS (EI): *m*/*z* [M]$^+$ calcd for ($C_{14}H_{13}BrO_3$): 310.0028; found: 310.0031.

(4*S*,5*R*)-4-Hydroxy-2-[(1*R*,2*S*,3*R*)-2-hydroxy-3-methyl-5-oxocyclohexyl]-5-methylcyclohex-2-enone (17)

A soln of **11a** (84.0 mg, 351 μmol, 1.00 equiv) in THF (2.00 mL) was treated with a soln of 1 M TBAF in THF (351 μL, 351 μmol, 1.00 equiv) and stirred at r.t. for 1 h. The solvent was removed in vacuo. Chromatography (cyclohexane–EtOAc, 1:1) gave a colorless solid; yield: 16 mg (37%); R_f = 0.12 (cyclohexane–EtOAc, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (d, ^3J = 7.2 Hz, 3 H, 3′-CH_3), 1.18 (d, ^3J = 6.2 Hz, 3 H, 5-CH_3), 2.00 (br s, 1 H, OH), 2.07–2.22 (m, 4 H, H5, H6$_a$, H6′$_a$, H4′$_a$), 2.35–2.42 (m, 1 H, H3′), 2.60 (dd, ^2J = 15.7 Hz, ^3J = 3.1 Hz, 1 H, H6$_b$), 2.73 (dd, ^2J = 13.4 Hz, ^3J = 12.5 Hz, 1 H, H6′$_b$), 2.81 (dd, ^2J = 14.4 Hz, ^3J = 6.1 Hz, 1 H, H4′$_b$), 3.16 (br s, 1 H, OH), 3.39 (br d, ^3J = 12.5 Hz, 1 H, H1′), 3.76–3.79 (m, 1 H, H2′), 4.16 (br d, ^3J = 7.3 Hz, 1 H, H4), 6.67 (s, 1 H, H3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8 (+, CH_3), 17.9 (+, CH_3), 36.2 (+, C1′), 36.7 (+, C3′), 38.7 (+, C5), 40.0 (–, C6′), 43.0 (–, C4′), 43.9 (–, C6), 71.5 (+, C2′), 72.7 (+, C4), 137.8 (C_q, C2), 149.5 (+, C3), 198.6 (C_q, C1), 211.5 (C_q, C5′).

MS (EI): *m/z* (%) = 252 (1) [M$^+$], 234 (2) [(M – H_2O)$^+$], 169 (72) [($C_9H_{13}O_3$)$^+$], 153 (45), 127 (83) [($C_7H_{11}O_2$)$^+$], 110 (100) [($C_7H_{10}O$)$^+$], 81 (40), 55 (34), 43 (66) [(C_2H_3O)$^+$].

HRMS (EI): *m/z* [M]$^+$ calcd for ($C_{14}H_{20}O_4$): 252.1362; found: 252.1360.

(1*R*,1′*R*,4*R*,5*S*,5′*R*,6*R*,6′*S*)-5,6,6′-Trihydroxy-4,5′-dimethylbicyclohexyl-2,3′-dione (18)

A soln of **11a** (200 mg, 832 μmol, 1.00 equiv) in THF (4.00 mL) was treated with MeOH (170 μL, 4.16 mmol, 5.00 equiv) and, subsequently, with 1 M TBAF in THF (832 μL, 832 μmol, 1.00 equiv). The mixture was stirred at r.t. for 48 h and then the solvent was removed and the residue was purified by flash column chromatography. Chromatography (cyclohexane–EtOAc, 1:1) gave a colorless solid; yield: 31 mg (32%); R_f = 0.10 (cyclohexane–EtOAc, 1:1).

[α]$_D^{20}$ –140.33 (*c* 1.20, $CHCl_3$).

IR (KBr): 3483 (s, ν O–H), 2957 (m, ν C–H), 2875 (w, ν C–H), 1712 (vs, ν C=O), 1067 cm^{-1} (s, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (d, ^3J = 6.6 Hz, 3 H, 5′-CH_3), 1.17 (d, ^3J = 6.4 Hz, 3 H, 4-CH_3), 1.98 (dd, ^2J = 17.0 Hz, ^3J = 11.8 Hz, 1 H, H4′$_a$), 2.06–2.18 (m, 1 H, H5′), 2.13 (dd, ^2J = 13.8 Hz, ^3J = 11.7 Hz, 1 H, H3$_a$), 2.15–2.28 (m, 1 H, H4), 2.38 (dd, ^2J = 15.9 Hz, ^3J = 11.6 Hz, 1 H, H2′$_a$), 2.42 (dd ^2J = 17.0 Hz, ^3J = 3.6 Hz, 1 H, H4′$_b$), 2.45 (dd, ^2J = 15.9 Hz, ^3J = 6.8 Hz, 1 H, H2′$_b$), 2.52 (dd, ^2J = 13.8 Hz, ^3J = 3.4 Hz, 1 H, H3$_b$), 2.60 (dd, ^3J = 5.4 Hz, ^3J = 2.2 Hz, 1 H, H1), 3.35 (dddd, ^3J = 11.6 Hz, ^3J = 7.4 Hz, ^3J = 6.8 Hz, ^3J = 2.2 Hz, 1 H, H1′), 3.75 (dd, ^3J = 9.2 Hz, ^3J = 3.4 Hz, 1 H, H5), 3.87 (dd, ^3J = 7.7 Hz, ^3J = 7.4 Hz, 1 H, H6′), 4.57 (dd, ^3J = 5.4 Hz, ^3J = 3.4 Hz, 1 H, H6); the protons of the OH moieties could not be detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (+, 4-*C*H_3), 18.9 (+, 5′-*C*H_3), 32.4 (+, C5′), 33.7 (+, C4), 37.2 (+, C1′), 40.7 (–, C2′), 43.4 (–, C4′), 45.8 (–, C3), 56.8 (+, C1), 74.1 (+, C5), 78.7 (+, C6), 82.2 (+, C6′), 207.1 (C$_q$, C2)*, 210.2 (C$_q$, C3′)*.

MS (EI): *m/z* (%) = 253 (10) [(M – OH)$^+$], 234 (94) [(M – 2 H_2O)$^+$], 219 (21) [($C_{13}H_{15}O_3$)$^+$], 143 (100) [($C_7H_{11}O_3$)$^+$], 126 (53) [($C_7H_{10}O_2$)$^+$], 109 (73) [(C_7H_9O)$^+$], 95 (63), 71 (47), 43 (78) [(C_2H_3O)$^+$].

HRMS (EI): *m/z* [M – 2 H_2O]$^+$ calcd for ($C_{14}H_{18}O_3$): 234.1256; found: 234.1259.

(3*R*,4*S*,4a*S*)-4-Hydroxy-7-methoxy-3-methyl-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (*cis*-20a)

Following general procedure D. Scale: **19** (463 mg, 3.05 mmol, 1.00 equiv), **5a** (770 mg, 6.09 mmol, 2.00 equiv), *N*-methylimidazole (125 mg, 1.52 mmol, 0.50 equiv). Chromatography (cyclohexane–EtOAc, 2:1) resulted in *trans*-**20a** (184 mg, 23%), a diastereomeric mixture of *cis*/*trans*-**20a** (8.5:1, 226 mg, 28%), and *cis*-**20a** as a yellow solid (87 mg, 11%). The overall yield of diastereomers was 62%. R_f = 0.29 (cyclohexane–EtOAc 2:1).

[α]$_D^{20}$ –135.33 (*c* 2.03, $CHCl_3$).

IR (KBr): 3398 (s, ν O–H), 3023 (w, ν C_{ar}–H), 2994 (m, ν C=C–H), 2965 (m, ν C–H), 2890 (m, ν C–H), 2878 (m, ν C–H), 2837 (m, ν OCH_3), 2056 (vw), 1905 (vw), 1658 (s, ν C=O), 1598 (s, ν C=C), 1558 (s, ν C_{ar}=C_{ar}), 1244 (s, ν C_{ar}–O–C), 1032 cm^{-1} (m, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, ^3J = 6.4 Hz, 3 H, 3-C*H*$_3$), 1.96–2.09 (m, 1 H, H3), 2.24 (dd, ^2J = 18.0 Hz, ^3J = 13.2 Hz, 1 H, H2$_a$), 2.70 (br s, 1 H, OH), 2.67 (dd, ^2J = 18.0 Hz, ^3J = 4.5 Hz, 1 H, H2$_b$), 3.80 (s, 3 H, OC*H*$_3$), 3.93 (dd, ^3J = 10.8 Hz, ^3J = 8.7 Hz, 1 H, H4), 4.79 (dd, ^3J = 8.7 Hz, ^4J = 2.5 Hz, 1 H, H4a), 6.77 (d, ^4J = 2.7 Hz, 1 H, H8), 6.875 (dd, ^3J = 8.9 Hz, ^4J = 2.76 Hz, 1 H, H6), 6.90 (d, ^3J = 8.9 Hz, 1 H, H5), 7.45 (d, ^4J = 2.62 Hz, 1 H, H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3 (+, 3-*C*H_3), 30.9 (+, C3), 45.7 (–, C2), 55.8 (+, O*C*H_3), 76.1 (+, C4), 79.9 (+, C4a), 113.7 (+, C8), 116.8 (+, C5), 118.5 (+, C6), 122.0 (C$_q$, C$_{ar}$), 128.5 (C$_q$, C$_{ar}$), 132.6 (+, C9), 149.1 (C$_q$, C9a), 154.7 (C$_q$, C$_{ar}$), 195.4 (C$_q$, C1).

MS (EI): *m/z* (%) = 260 (28) [M$^+$], 203 (100) [($C_{13}H_{15}O_2$)$^+$], 174 (29), 160 (22).

HRMS (EI): *m/z* [M]$^+$ calcd for ($C_{15}H_{16}O_4$): 260.1049; found: 260.1042.

(3*R*,4*S*,4a*R*)-4-Hydroxy-7-methoxy-3-methyl-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (*trans*-20a)

The synthesis of *trans*-**20a** was realized in accordance to the procedure described for *cis*-**20a**, yielding clean *trans*-**20a** as yellow-brown oil (184 mg, 23%) and a *cis*/*trans* diastereomeric mixture (8.5:1). R_f = 0.35 (cyclohexane–EtOAc, 2:1).

[α]$_D^{20}$ +105.02 (*c* 1.45, $CHCl_3$).

IR (KBr): 3467 (w, ν O–H), 3039 (vw, ν C_{ar}–H), 2958 (w, ν C–H), 2909 (w, ν C–H), 2839 (w, ν OCH_3), 1681 (m, ν C=O), 1614 (m, ν C=C), 1570 (m, ν C_{ar}=C_{ar}), 1233 (s, ν C_{ar}–O–C), 1036 cm^{-1} (m, ν C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, ^3J = 7.6 Hz, 3 H, 3-C*H*$_3$), 2.28 (dd, ^2J = 17.7 Hz, ^3J = 1.6 Hz, 1 H, H2$_a$), 2.55-2.63 (m, 1 H, H3), 2.75 (br s, 1 H, OH), 3.04 (dd, ^2J = 17.7 Hz, ^3J = 6.2 Hz, 1 H, H2$_b$), 3.80 (s, 3 H, OC*H*$_3$), 4.30 (dd, ^3J = 3.7 Hz, ^3J = 3.3 Hz, 1 H, H4), 5.09 (dd, ^3J = 3.3 Hz, ^4J = 2.6 Hz, 1 H, H4a), 6.78 (d, ^4J = 2.6 Hz, 1 H, H8), 6.85 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1 H, H6), 6.88 (d, ^3J = 8.9 Hz, 1 H, H5), 7.45 (d, ^4J = 2.62 Hz, 1 H, H9).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.0 (+, 3-*C*H_3), 30.6 (+, C3), 39.8 (–, C2), 55.8 (+, O*C*H_3), 69.6 (+, C4), 74.8 (+, C4a), 113.7 (+, C8), 117.0 (+, C5), 118.1 (+, C6), 122.2 (C$_q$, C$_{ar}$), 128.4 (C$_q$, C$_{ar}$), 132.3 (+, C9), 149.0 (C$_q$, C9a), 154.8 (C$_q$, C$_{ar}$), 197.4 (C$_q$, C1).

MS (EI): *m/z* (%) = 260 (14) [M$^+$], 243 (1) [(M – OH)$^+$], 232 (1), 203 (16) [($C_{13}H_{15}O_2$)$^+$], 174 (5), 160 (4), 84 (38) [($C_4H_4O_2$)$^+$], 69 (16), 56 (100) [(C_3H_4O)$^+$], 43 (14) [(C_2H_3O)$^+$].

HRMS (EI): *m/z* [M]$^+$ calcd for ($C_{15}H_{16}O_4$): 260.1049; found: 260.1052.

(3*R*,4*S*,4a*R*/*S*)-3-Ethyl-4-hydroxy-7-methoxy-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (*cis*/*trans*-20b)

Following general procedure D. Scale: **19** (163 mg, 1.07 mmol, 1.00 equiv), **5b** (330 mg, 2.14 mmol, 2.00 equiv), *N*-methylimidazole (43 mg, 535 μmol, 0.50 equiv). Chromatography (cyclohexane–EtOAc, 5:1) gave a diastereomeric mixture *cis*/*trans*-**20b** (1:1.2); yield: 242 mg (82%); R_f = 0.41 (cyclohexane–EtOAc, 2:1).

IR (KBr): 3432 (s, ν O–H), 3063 (vw, ν C_{ar}–H), 2968 (m, ν C–H), 2913 (m, ν C–H), 2839 (m, ν OCH_3), 1682 (s, ν C=O), 1615 (s, ν C=C), 1570 (s, ν C_{ar}=C_{ar}), 1237 (s, ν C_{ar}–O–C), 1034 cm^{-1} (m, ν C–O).

^{1}H NMR (500 MHz, $CDCl_3$, *trans*/*cis* 1.2:1): δ = 0.98 (t, ^3J = 7.5 Hz, 3 H$_{cis}$, *cis*-2′-CH_3), 1.02 (t, ^3J = 7.3 Hz, 3 H$_{trans}$, *trans*-2′-CH_3), 1.18–1.29 (m, 1 H$_{trans}$, *trans*-H1′$_a$), 1.36–1.49 (m, 1 H$_{cis}$, 1 H$_{trans}$, *cis*-H1′$_a$, *trans*-H1′$_b$), 1.83–1.92 (m, 1 H$_{cis}$, *cis*-H3), 1.93–2.02 (m, 1 H, *cis*-H1′$_b$), 2.21 (dd, ^2J = 18.0 Hz, ^3J = 13.2 Hz, 1 H$_{cis}$, *cis*-H2$_a$), 2.28–2.35 (m, 1 H$_{trans}$, *trans*-H3), 2.39 (dd, ^2J = 17.8 Hz, ^3J = 1.2 Hz, 1 H$_{trans}$, *trans*-H2$_a$), 2.72 (dd, ^2J = 18.0 Hz, ^3J = 4.5 Hz, 1 H$_{cis}$, *cis*-H2$_b$), 2.79 (br s, 1 H$_{cis}$, 1 H$_{trans}$, *cis*-OH, *trans*-H), 2.99 (dd, ^2J = 17.8 Hz, ^3J = 6.2 Hz, 1 H$_{trans}$, *trans*-H2$_b$), 3.79 (s, 3 H$_{cis}$, 3 H$_{trans}$, *cis*-OCH_3, *trans*-OCH_3), 4.00 (dd, ^3J = 10.7 Hz, ^3J = 8.8 Hz, 1 H$_{cis}$, *cis*-H4), 4.38 (dd, ^3J = 3.6 Hz, ^3J = 3.6 Hz, 1 H$_{trans}$, *trans*-H4), 4.79 (dd, ^3J = 8.8 Hz, ^3J = 2.3 Hz, 1 H$_{cis}$, *cis*-H4a), 5.04 (dd, ^3J = 2.8 Hz, ^4J = 2.0 Hz, 1 H$_{trans}$, *trans*-H4a), 6.75–6.77 (m, 1 H$_{cis}$, 1 H$_{trans}$, *cis*-H$_{ar}$, *trans*-H$_{ar}$), 6.80–6.90 (m, 2 H$_{cis}$, 2 H$_{trans}$, *cis*-H$_{ar}$, *trans*-H$_{ar}$), 7.39

(d, ^3J = 2.3 Hz, 1 H_{cis}, *cis*-H9), 7.43 (d, ^4J = 2.0 Hz, 1 H_{trans}, *trans*-H9).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.8 (+, *cis*-C2′), 12.0 (+, *trans*-C2′), 23.4 (–, *cis*-C1′), 24.5 (–, *trans*-C1′), 36.4 (+, *cis*-C3), 37.8 (–, *trans*-C2), 37.8 (+, *trans*-C3), 42.2 (–, *cis*-C2), 55.7 (+, *cis*-O*C*H_3, *trans*-O*C*H_3), 68.5 (+, *trans*-C4), 74.3 (+, *cis*-C4), 74.8 (+, *trans*-C4a), 80.1 (+, *cis*-C4a), 113.6 (+, C_{ar}), 113.7 (+, C_{ar}), 116.8 (+, C_{ar}), 116.9 (+, C_{ar}), 118.0 (+, C_{ar}), 118.4 (+, C_{ar}), 122.0 (C_q, C_{ar})*, 122.2 (C_q, C_{ar})*, 128.4 (C_q, *cis*-C9a)*, 128.4 (C_q, *trans*-C9a)*, 132.2 (+, *trans*-C9), 132.5 (+, *cis*-C9), 148.9 (C_q, C_{ar}), 149.1 (C_q, C_{ar}), 154.67 (C_q, C_{ar}), 154.73 (C_q, C_{ar}), 195.8 (C_q, *trans*-C1)**, 197.4 (C_q, *cis*-C1)**.

MS (EI): *m*/*z* (%) = 274 (11) [M^+], 203 (17) [$(C_{12}H_{11}O_3)^+$], 153 (11), 105 (13), 77 (20) [$(C_6H_5O)^+$], 57 (12), 43 (100) [$(C_2H_3O)^+$].

HRMS (EI): *m*/*z* [$M]^+$ calcd for ($C_{16}H_{18}O_4$): 274.1205; found: 274.1203.

(3*R*,4*S*,4a*R*/*S*)-4-Hydroxy-7-methoxy-3-propyl-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (*cis*/*trans*-20c)

Following general procedure D. Scale: **19** (159 mg, 1.05 mmol, 1.00 equiv), **5c** (324 mg, 2.10 mmol, 2.00 equiv), *N*-methylimidazole (43.5 mg, 539 μmol, 0.50 equiv). Chromatography (cyclohexane–EtOAc, 5:1) gave a diastereomeric mixture *trans*/*cis* (1.3:1) as a yellow solid; yield: 246 mg (82%); R_f = 0.54 (cyclohexane–EtOAc, 2:1).

IR (KBr): 3451 (m, ν O–H), 2959 (m, ν C–H), 2930 (m, ν C–H), 2872 (m, ν OCH_3), 1682 (m, ν C=O), 1613 (m, ν C=C), 1570 (s, ν C_{ar}=C_{ar}), 1236 (s, ν C_{ar}–O–C), 1034 cm^{-1} (m, ν C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.2 Hz, 3 H_{trans}, *trans*-3′-CH_3), 0.97 (t, ^3J = 7.0 Hz, 3 H_{cis}, *cis*-3′-CH_3), 1.12–1.24 (m, 1 H_{trans}, *trans*-H1′$_a$), 1.25–1.41 (m, 3 H_{cis}, 2 H_{trans}, 2 *cis*-H1′, *cis*-H2′$_a$, *trans*-H1′$_b$, *trans*-H2′$_a$), 1.43–1.55 (m, 1 H_{cis}, 1 H_{trans}, *cis*-H2′$_b$, *trans*-H2′$_b$), 1.85–1.98 (m, 1 H_{cis}, *cis*-H3), 2.18 (dd, ^2J = 18.0 Hz, ^3J = 13.1 Hz, 1 H_{cis}, *cis*-H2$_a$), 2.36 (br d, ^2J = 17.8 Hz, 1 H_{trans}, *trans*-H2$_a$), 2.38–2.45 (m, 1 H_{trans}, *trans*-H3), 2.73 (dd, ^2J = 18.0 Hz, ^3J = 4.3 Hz, 1 H_{cis}, *cis*-H2$_b$), 2.83–2.87 (m, 1 H_{cis}, 1 H_{trans}, *cis*-OH, *trans*-OH), 2.99 (dd, ^2J = 17.6 Hz, ^3J = 6.0 Hz, 1 H_{trans}, *trans*-H2$_b$), 3.78 (s, 3 H_{cis}, 3 H_{trans}, *cis*-OCH_3, *trans*-OCH_3), 3.98 (dd, ^3J = 9.3 Hz, ^3J = 9.3 Hz, 1 H_{cis}, *cis*-H4), 4.35 (dd, ^3J = 3.5 Hz, ^3J = 3.5 Hz, 1 H_{trans}, *trans*-H4), 4.78 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1 H_{cis}, *cis*-H4a), 5.04 (dd, ^3J = 2.7 Hz, ^4J = 2.7 Hz, 1 H_{trans}, *trans*-H4a), 6.74–6.76 (m, 1 H_{cis}, 1 H_{trans}, *cis*-H8, *trans*-H8), 6.81–6.90 (m, 2 H_{cis}, 2 H_{trans}, *cis*-H5, *cis*-H6, *trans*-H5, *trans*-H6), 7.38 (d, ^4J = 2.3 Hz, 1 H_{cis}, *cis*-H9), 7.42 (d, ^4J = 1.6 Hz, 1 H_{trans}, *trans*-H9).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (+, *trans*-C3′), 14.2 (+, *cis*-C3′), 18.9 (–, *cis*-C2′), 20.4 (–, *trans*-C2′), 33.0 (–, *cis*-C1′), 33.6 (–, *trans*-C1′), 35.2 (+, *cis*-C3), 35.6 (+, *trans*-C3), 38.1 (–, *trans*-C2), 42.7 (–, *cis*-C2), 55.7 (+, *cis*-O*C*H_3, *trans*-O*C*H_3), 68.6 (+, *trans*-C4), 74.7 (+, *cis*-C4), 74.9 (+, *trans*-C4a), 80.0 (+, *cis*-C4a), 113.59 (+, *trans*-C8), 113.64 (+, *cis*-C8), 116.8 (+, C_{ar}), 116.9 (+, C_{ar}), 118.0 (+, C_{ar}), 118.4 (+, C_{ar}), 122.0 (C_q, C_{ar}), 122.2 (C_q, C_{ar}), 128.3 (C_q, C_{ar}), 128.4 (C_q, C_{ar}), 132.1 (+, *trans*-C9), 132.4 (+, *cis*-C9), 148.9 (C_q, *trans*-C9a), 149.1 (C_q, *cis*-C9a), 154.66 (C_q, C_{ar}), 154.70 (C_q, C_{ar}), 195.7 (C_q, *cis*-C1), 197.5 (C_q, *trans*-C1).

MS (EI): *m*/*z* (%) = 288 (25) [M^+], 203 (38) [$(C_{12}H_{11}O_3)^+$], 84 (64) [$(C_4H_4O_2)^+$], 56 (100) [$(C_3H_4O)^+$], 43 (21) [$(C_2H_3O)^+$].

HRMS (EI): *m*/*z* [$M]^+$ calcd for ($C_{17}H_{20}O_4$): 288.1362; found: 288.1360.

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