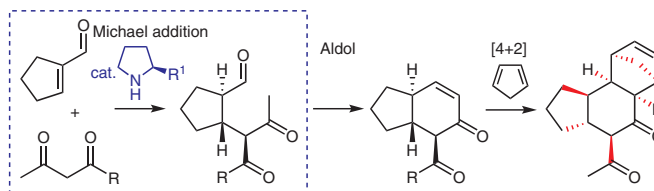


Asymmetric Organocatalysis Revisited: Taming Hydrindanes with Jørgensen–Hayashi Catalyst

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Abstract The organocatalytic Michael reaction of easily available 1-cyclopentene-1-carbaldehyde and 1,3-dicarbonyl compounds led to cyclopentanecarbaldehydes on a gram scale with low catalyst loading (2 mol%) and high enantioselectivity. The synthetic potential of 4-acylhexahydroindenones from intramolecular aldol condensation was demonstrated by Diels–Alder reaction to a tetracyclic derivative with seven stereogenic centers. The diastereofacial preference of the tetracyclic product was confirmed by DFT calculations. The described reaction sequence is characterized by few redox-economic steps and high degree of molecular complexity.

Key words organocatalysis, hydrindane, Jørgensen–Hayashi catalyst, Michael addition, aldol condensation, Diels–Alder reaction

Since the pioneering work by Wiechert¹ and Parrish² in the early seventies on proline-catalyzed aldol reactions,³ the field of asymmetric organocatalysis has made tremendous progress.⁴ Among the numerous organocatalysts developed so far, the Jørgensen–Hayashi catalyst and structurally related diarylprolinol silyl ethers have turned out very successful and reliable in a huge variety of different reactions.⁵ Depending on the substrates, Jørgensen–Hayashi catalyst operates either through HOMO activation of aldehydes via enamine intermediates or LUMO activation of enals via iminium ion intermediates. Detailed mechanistic insight was gained by NMR spectroscopy, kinetic experiments, reaction calorimetry, and computational studies.^{6,7} In addition, several strategies for immobilization have been successfully developed.⁸ Interesting targets for organocatalysis are substituted hydrindanes **1**, that is, bicyclo[4.3.0]nonanes, which are important scaffolds of natural products and synthetic bioactive compounds. Selected ex-

amples are amaminol A (**2**),⁹ the tricyclic unit of ikarugamycin (**3**),¹⁰ or the CD ring unit of deoxycholic acid (**4**)¹¹ (Figure 1).

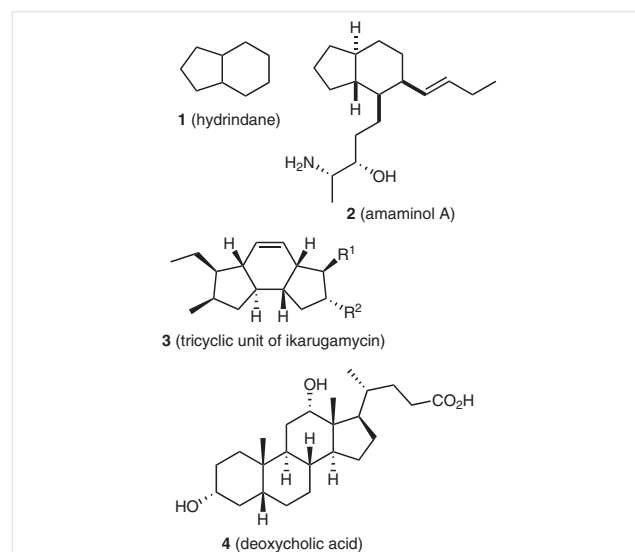


Figure 1 Bicyclo[4.3.0]nonane (hydrindane, **1**) and some selected examples of compounds **2–4** containing this structural motif

Various synthetic methods have been developed to access the bicyclo[4.3.0]nonane core,¹² most notably Diels–Alder reactions,^{13–17} Pauson–Khand reactions of alkenes and alkynes or enynes with carbon monoxide,¹⁸ radical cyclizations,¹⁹ titanacycle-mediated annulations,²⁰ intramolecular aldol and Michael reactions,²¹ Morita–Baylis–Hillman reactions,^{22–24} sequential ring-opening/ring-closing metathesis,^{25–27} and enyne metathesis,²⁸ or one-pot consecutive Pd-catalyzed Overman rearrangement, Ru-catalyzed ring closing enyne metathesis, and hydrogen bond-directed Diels–Alder reaction.²⁹ Particular valuable hydrindanes are hexa-

Biographical Sketches



Yannick Stöckl studied chemistry at the University of Stuttgart (2013–2016). In his B.Sc. thesis in the Laschat research group, he focused on the synthesis and characteriza-

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Wolfgang Frey received his Ph.D. in 1991 in Organic Structure Chemistry at the University of Stuttgart,

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Angelika Baro studied chemistry at the Georg-August-Universität Göttingen (Germany), where she re-

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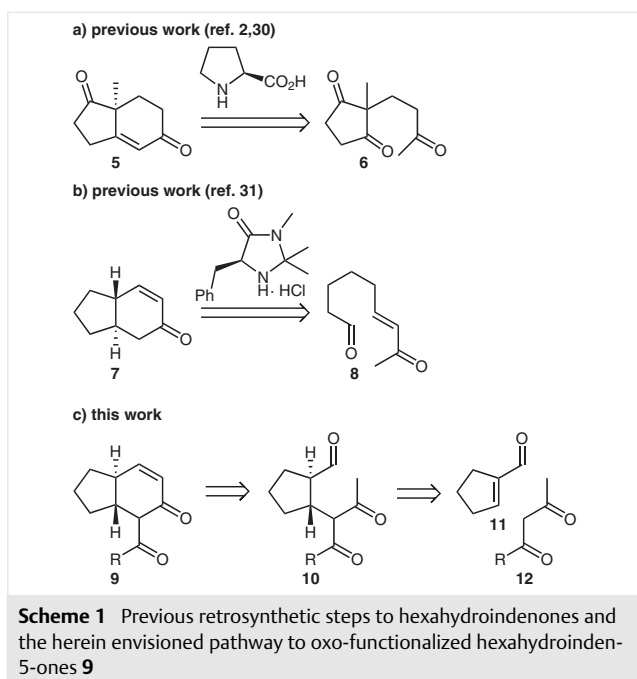


Sabine Laschat studied chemistry at the University of Würzburg (1982–1987) and did her Ph.D. at the University of Mainz under the supervision of Horst Kunz (1988–1990). After postdoctoral studies with Larry E. Overman at the University of California, Irvine (1990–1991), followed by her habilitation

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lar oxygen' (2005–2010), served as Vice Rector for Research and Technology of the University of Stuttgart (2010–2012), and is currently speaker of the project house 'NanoBioMater'. Her research interests include liquid crystals, natural product synthesis, and chemoenzymatic syntheses.

hydroindenones whose enone moiety allows further functionalization.¹² Their archetypal organocatalytic synthesis relies on the proline-catalyzed aldol condensation towards Hajos–Parrish diketone **5** (Scheme 1),^{2,30} which was further functionalized in multiple ways to the desired hydrindane target compounds. The unsubstituted member **7** of the hexahydroindenone family was obtained via sequential intramolecular Michael addition/aldol condensation of enone **8** in the presence of MacMillan imidazolidine catalyst (Scheme 1).³¹

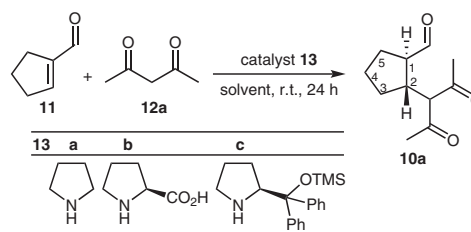


When considering potential organocatalytic routes to hexahydroindenones we identified the 4-substituted derivative **9** as a promising target for further manipulation. To access compound **9** from easily available starting materials, we envisaged an intermolecular Michael addition of 1,3-dicarbonyl compounds **12** to 1-cyclopentene-1-carbaldehyde (**11**) followed by aldol condensation of the resulting intermediate **10** (Scheme 1). Surprisingly, little is known about the use of 1-cyclopentene-1-carbaldehyde (**11**) in organocatalytic Michael additions.^{32–36} On the other hand, simple 1,3-carbonyl compounds such as acetylacetone and ethyl acetoacetate were only rarely employed in organocatalytic Michael additions.^{37,38} Thus, we aimed at a robust and reliable route towards hydrindanes **9**, which should be amenable to preparative scale while requiring a minimum catalyst loading. Furthermore, we wanted to probe functionalizations of compound **9** towards tri- or polycyclic scaffolds.

In preliminary experiments, the influence of different catalysts on the Michael addition of acetylacetone (**12a**) to 1-cyclopentene-1-carbaldehyde (**11**)³⁹ was studied

(Table 1). When **11** and **12a** were reacted in EtOH for 24 hours without catalyst, no conversion of the starting material **11** was observed by ¹H NMR analysis (Table 1, entry 1). In the presence of catalysts pyrrolidine (**13a**; 50 mol%) and L-proline (**13b**; 30 mol%), respectively, addition product **10a** was isolated in only 3% and 4% yield due to decomposition of **10a** upon chromatographic purification (entries 2 and 3). The use of Jørgensen–Hayashi catalyst **13c** (20 mol%), however, provided **10a** in 58% NMR yield with 94% *ee* (entry 4). A solvent screening for the Michael reaction (Table 1) resulted in toluene as optimal solvent giving **10a** in 70% yield and 97% *ee* (entry 11), while additives such as AcOH deteriorated yield and selectivity (entry 12).

Table 1 Optimization of Conditions for the Organocatalytic 1,4-Addition of Acetylacetone (**12a**) to 1-Cyclopentene-1-carbaldehyde (**11**)



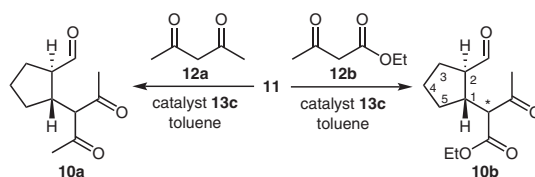
Entry	Catalyst (mol%)	Solvent	Yield (%)	<i>ee</i> (%) ^a
1	–	EtOH	–	–
2	13a (50)	EtOH	3	–
3	13b (30)	EtOH	4	5
4	13c (20)	EtOH	58 ^b	94
5	13c (20)	MeOH	43	89
6	13c (20)	H ₂ O	45	89
7	13c (20)	THF	55	89
8	13c (20)	MeCN	60	90
9	13c (20)	CHCl ₃	60	90
10	13c (20)	hexane	39	94
11	13c (20)	toluene	70	97
12	13c (20)	toluene ^c	52	92

^a Determined by GC on a chiral stationary phase.

^b Determined by ¹H NMR spectroscopy with 1,3,5-trimethylbenzene (0.53 equiv) as an internal standard.

^c AcOH as additive.

Next, the robustness of the Michael addition with respect to catalyst loading and scale was studied (Table 2). Reducing the amount of organocatalyst **13c** from 5 mol% to 2.5 mol% required longer reaction times but both yield and *ee* values remained constant (Table 2, entries 1 and 2). The best result was realized with 2 mol% of **13c** and convenient purification by simple filtration over a silica pad yielding **10a** in 72% with 98% *ee* even on a 10 mmol scale (entry 4). It should be emphasized that the catalyst loading under these

Table 2 Optimization of Catalyst Loading and Scale

Entry	11 (mmol)	13c (mol%)	12 (equiv)	Temp	Time (h)	10	Yield (%) ^a	ee (%) ^b	d.r.
1 ^c	10	5	1.0	r.t.	26	a	52	97	–
2 ^c	3	2.5	1.0	r.t.	38	a	52	97	–
3 ^c	3	0.5	1.0	r.t.	48	a	40	n.d.	–
4 ^d	10	2	1.0	0 °C → r.t.	60	a	72	98	–
5 ^d	1	2	1.5	0 °C → r.t.	18	a	61	n.d.	–
6 ^c	2	2	1.0	r.t.	24	b	91	–	50:50
7 ^d	4	2	1.0	r.t.	60	b	82	–	50:50
8 ^c	1	2	neat	0 °C → r.t.	24	b	30	–	50:50

^a Isolated yields.^b Determined by GC on a chiral stationary phase. n.d.: Not determined.^c Flash chromatography.^d Filtration over a silica pad.

optimized conditions is ten times lower than that of the initial experiments in Table 1. Further decrease of the catalyst loading was accompanied by reduced yield (entry 3).

When ethyl acetoacetate (**12b**) was employed as nucleophile under the optimized conditions, addition product **10b** was isolated in 91% as a (50:50) diastereomeric mixture after flash chromatography (Table 2, entry 6). Unfortunately, the enantioselectivity could not be determined by GC or HPLC on chiral stationary phases. Longer reaction time or the use of neat **12b** without any solvent reduced the yield (entries 7 and 8).

In order to determine the enantioselectivity of the Michael addition with acetoacetate **12b** by an indirect method, a sequential Michael addition/Wittig olefination was performed (Scheme 2). Following Method A, cyclopentene-

carbaldehyde **11** and acetoacetate **12b** were reacted in the presence of catalyst **13a** (50 mol%) in toluene for 24 hours at room temperature and subsequently treated with phosphonium salt **14** in toluene in the presence of NEt₃. After workup, racemic cyclopentane enoate *rac*-**15** was isolated with an *E/Z* ratio of >95:5 and a diastereomeric ratio of 47:40:8:5. In a parallel experiment Jørgensen–Hayashi catalyst **13c** (2 mol%) was used (Method B) resulting in the *trans*-disubstituted cyclopentane enoate **15** in 27% yield (*E/Z* >95:5, d.r. 55:45).

Taking the preferred formation of the *trans*-disubstituted cyclopentane carbaldehyde (1*R*,2*R*)-**10a** with excellent enantioselectivity (e.r. 99:1) into account, we surmised that a similar enantiofacial discrimination was obtained in the Michael addition of acetoacetate **12b**, resulting in the two diastereomeric products (1*R*,2*R*,1'*S*)-**10b** and (1*R*,2*R*,1'*R*)-**10b** in a diastereomeric ratio of (55:45) due to the lack of stereochemical control at the α-carbon of the 1,3-dicarbonyl unit. Moreover, the formation of four diastereomeric cyclopentane enoates **15** (d.r. 47:40:8:5) under racemic conditions presumably coming from four diastereomeric cyclopentane carbaldehydes **10b** with a similar ratio suggested that besides the two *trans*-disubstituted diastereomers (1*R*,2*R*,1'*S*)-**10b** and (1*R*,2*R*,1'*R*)-**10b** also the corresponding *cis*-diastereomers (1*R*,2*S*,1'*S*)-**10b** and (1*R*,2*S*,1'*R*)-**10b** were formed. Hence the Jørgensen–Hayashi catalyst **13c** not only exerts a stereochemical control on the enantiofacial differentiation but also on the diastereofacial differentiation of the C=C double bond of the Michael acceptor in agreement with previous work by Bernardi.³⁴

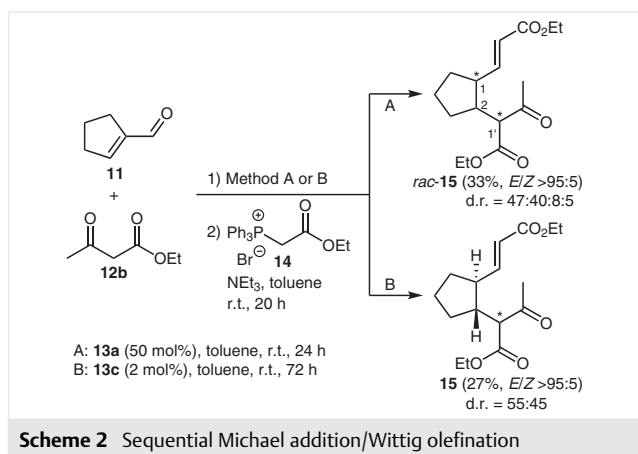
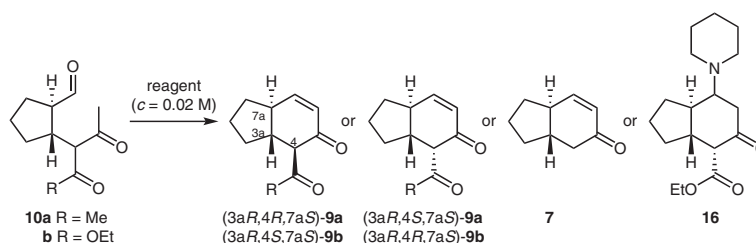


Table 3 Optimization of Intramolecular Aldol Condensation of **10**

Entry	Reagent (equiv)	Solvent	Temp (°C)	Time (h)	Product	Yield (%)
1	KOH	MeOH	0 → r.t.	2	9a	–
2	1) KOH 2) MsCl ^a	MeOH CH ₂ Cl ₂	0 → r.t. r.t.	2 17	7	50
3	TsOH (0.1)	toluene	reflux	3	9a	5
4	TsOH (0.05)	toluene	r.t.	24	9a	–
5	TsOH (0.05)	toluene	50	36	9a	23
6	TsOH (0.05)	THF	50	24	9a	–
7	TsOH (0.05)	MeOH	50	16	9a	–
8	PPTS (0.05)	toluene	reflux ^b	7	9a	50
9	PPTS (1.0)	toluene	reflux ^b	3	9a	55
10	(–)-CSA (1.0)	toluene	reflux ^b	1	9a	55
11	(–)-CSA (1.0)	toluene	50	72	9a	73, d.r. 94:6
12	(+)-CSA (1.0)	toluene	50	65	9a	71, d.r. 93:7
13	(–)-CSA (1.0)	toluene ^c	50	96	9b	19
14	piperidine/CSA	toluene ^c	50/reflux	24 1.5	16 9b	12
15	1) DBU 2) MsCl ^a	MeOH CH ₂ Cl ₂	0 0 → r.t.	2 4	9b	44, d.r. 91:9

^a In the presence of NEt₃, DMAP.

^b Dean-Stark conditions.

^c c = 0.03 M.

With cyclopentancarbaldehydes **10a,b** in hand, we examined the intramolecular aldol condensation to the hexahydroindenones **9** under various conditions (Table 3).

First we used bases as mediator. Treatment of **10a** with stoichiometric amounts of KOH in MeOH at 0 °C and warming to room temperature for 2 hours resulted in a complex mixture without any trace of the desired 4-acetylhexahydro-5*H*-inden-5-one (**9a**) (Table 3, entry 1). As other bases also failed [for details, see Table S1 in Supporting Information (SI)], we followed the method of List,³¹ in which **10a** was first deprotonated with KOH in MeOH at 0 °C and subsequently reacted with mesyl chloride in the presence of NEt₃ and DMAP in CH₂Cl₂. After workup, a single product was isolated in 50%, that, however, was identified as the deacetylated enone **7** (entry 2). Such deacetylation under basic conditions has been reported for several acetylacetone derivatives.^{40–43}

Due to the failure of the base-mediated cyclizations, we focused on the corresponding acid-catalyzed aldol condensation. Indeed, treatment of aldehyde **10a** with

0.1 equivalent of TsOH in toluene under reflux for 3 hours gave **9a** in 5% yield (Table 3, entry 3). Decrease of TsOH to 0.05 equivalent and the temperature to 50 °C with extended reaction time (36 h) improved the yield to 23% (entry 5). In contrast, neither further temperature decrease nor changing the solvent (THF or MeOH) gave any of the product **9a** (entries 4, 6, and 7). However, PPTS as acid catalyst (0.05 equiv) in toluene under Dean–Stark conditions provided **9a** in 50% yield (entry 8). Similar yields were obtained with 1 equivalent of PPTS or (–)-CSA (entries 9 and 10). With 1 equivalent of (–)-CSA in toluene at 50 °C the yield increased to 73% (d.r. 94:6), (entry 11). The sense of chirality of the Brønsted acid had no impact on yield and diastereoselectivity, that is, (+)-CSA gave **9a** in 71% yield (d.r. 93:7) (entry 12). Under these optimized conditions, however, acetoacetate-derived aldehyde **10b** cyclized to **9b** in a disappointingly low yield of 19% (entry 13). Other Brønsted acids failed completely (Table S2, SI). As piperidine has been reported to promote aldol condensations,^{44–46} aldehyde **10b** was submitted to condensation in the presence of piperi-

dine (1 equiv) in toluene at 50 °C for 24 hours. Monitoring the reaction by ^1H NMR spectroscopy and ESI-MS revealed formation of the aldol adduct **16**. Upon subsequent addition of 1 equivalent of (–)-CSA to the reaction mixture and stirring for 1.5 hours, only 12% of **9b** could be isolated (entry 14). Finally, a base-induced aldol addition was tested in which **10b** was reacted with 1 equivalent of DBU in MeOH at 0 °C for 2 hours. After acidic workup and addition of $\text{CH}_2\text{-Cl}_2$, the crude product was treated with mesyl chloride, DMAP, and NEt_3 for 4 hours to afford indenone **9b** in 44% yield with a high diastereoselectivity (d.r. 91:9) (entry 15).

A single crystal of **9a** was obtained by crystallization from a diluted solution, which was suitable for X-ray crystal structure analysis (Figure 2). Derivative **9a** crystallized with one molecule in the asymmetric unit of the acentric space group $\text{P}2(1)2(1)2(1)$. The absolute configuration could be determined from X-ray data by anomalous dispersion characterized by the Flack parameter of $x = 0.08(17)$ revealing the (3*aR*,4*R*,7*aS*)-configuration for the major product of **9a**. The five-membered ring system shows an envelope conformation, where C4 is 0.65 Å out of plane. The six-membered ring is characterized by a half-chair conformation with C3 out of plane (0.67 Å).⁴⁷

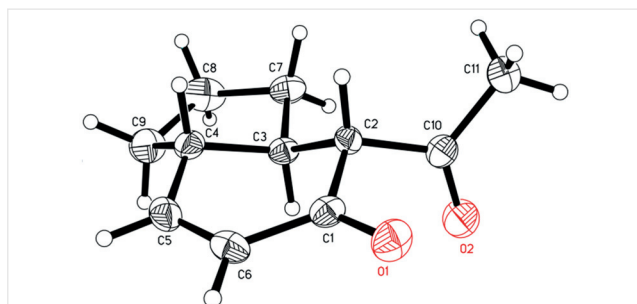
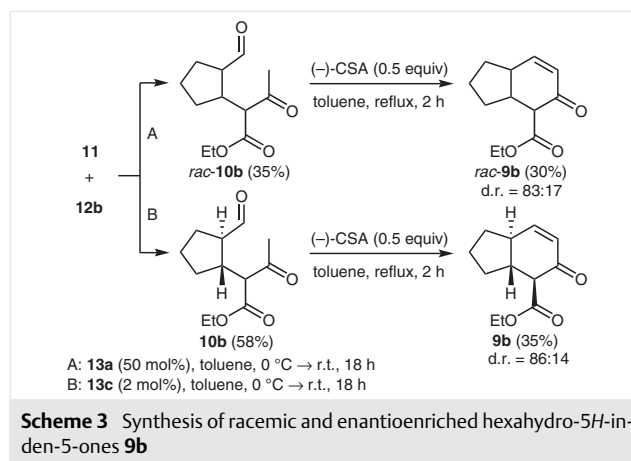


Figure 2 X-ray crystal structure of enone **9a**. The configuration is C2(*R*), C3(*R*), and C4(*S*) (X-ray label notation)

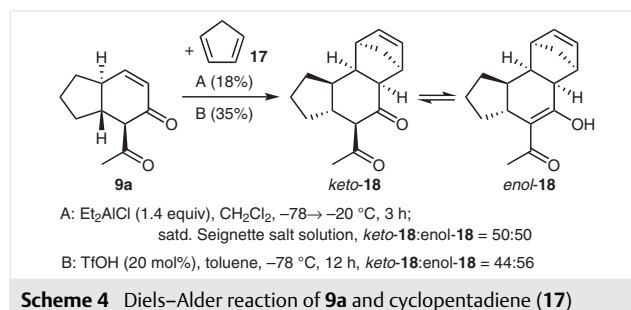
As the determination of the enantioselectivity of the Michael addition product **10b** had not yet been solved, a sequence of Michael addition/aldol condensation was studied (Scheme 3). For this purpose, **11** and acetoacetate **12b** were treated either with pyrrolidine **13a** (50 mol%, Method A) or Jørgensen–Hayashi catalyst **13c** (2 mol%, Method B) under the usual conditions to yield racemic addition product *rac*-**10b** in 35% and enantioenriched **10b** in 58%, respectively. Subsequent (–)-CSA-mediated aldol condensation gave 30% of *rac*-**9b** (d.r. 83:17) and 35% of enantioenriched **9b** (d.r. 86:14). Unfortunately, separation of enantiomers was neither possible via GC nor HPLC on chiral stationary phases.

The relative configuration of racemic enones *rac*-**9b** was assigned by 1D and 2D NMR experiments (Figures S1 and S2 in SI) as *trans,trans* for the major and *trans,cis* for the minor diastereomer, respectively. Due to the similarities of the



NMR spectra of acetylacetonone-derived enones **9a** combined with the crystal structure of (3*aR*,4*R*,7*aS*)-**9a**, we assigned the major and the minor diastereomer of the non-racemic acetoacetate-derived enone as (3*aR*,4*R*,7*aS*)-**9b** and (3*aR*,4*S*,7*aS*)-**9b**.

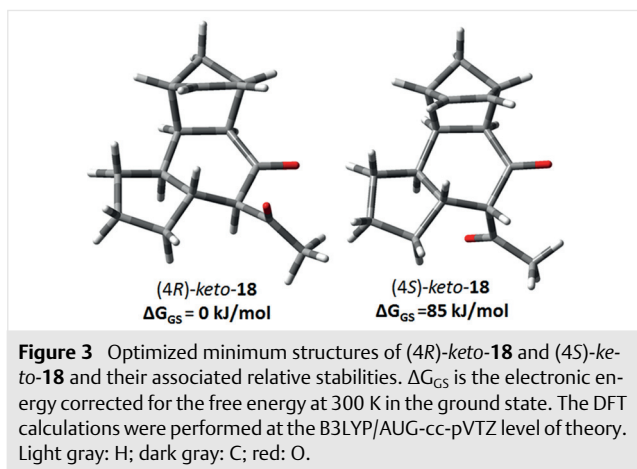
As mentioned above, hexahydroindenone **9a** was assumed as a potential scaffold for convenient functionalization to polycyclic compounds without the necessity to use protecting groups. To realize this goal, we studied the Diels–Alder reaction between **9a** and cyclopentadiene (**17**) (Scheme 4).



First, different Lewis or Brønsted acids and solvents were screened, but either decomposition or no conversion at all was observed (for details, see Schemes S2 and S3 in SI). However, the desired tetracycle **18** (50:50) could be isolated in 18% when employing 1.4 equivalents of Et_2AlCl in CH_2Cl_2 at -78 °C and warming the mixture to -20 °C over 3 hours followed by hydrolysis with aqueous Seignette salt solution (Method A). Both ^1H NMR spectra and GC-MS chromatograms indicated that the crude product contained cyclopentadiene-derived oligomer.^{48,49} Following Method B, that is, use of trifluoromethanesulfonic acid (20 mol%) in toluene at -78 °C and quenching after 12 hours with NEt_3 and aqueous workup, provided the tetracycle **18** in 35% (ratio 44:56). Initially, we surmised that the two sets of signals visible in the ^1H NMR spectrum of **18** might be caused by the two diastereomers. But HMBC measurements and

comparison with known 1,3-dicarbonyl derivatives⁵⁰ revealed the presence of keto- and enol-tautomer *keto-18*, *enol-18*, whose stereochemical structure was deduced from 2D NOESY experiments (Figures S3 and S4 in SI). It should be emphasized that *enol-18* stereoselectively equilibrates to *keto-18* with the 4*R*-configuration of the acetyl-carrying carbon atom, while the corresponding epimer with 4*S*-configuration was not detected. Presumably, the diastereofacial preference of the protonation step is governed by formation of the thermodynamically more stable (4*R*)-*keto-18* with an equatorial acetyl moiety as compared to the (4*S*)-*keto-18* with axial acetyl group. A thermodynamically driven tautomerization as the final step was also proposed by Carrillo and Vicario in the synthesis of *trans*-decalines.⁵¹ Furthermore, upon prolonged storage of tetracycle **18** in CDCl₃ the equilibrium shifted from (4*R*)-*keto-18*/*enol-18* = 44:56 to 57:43.

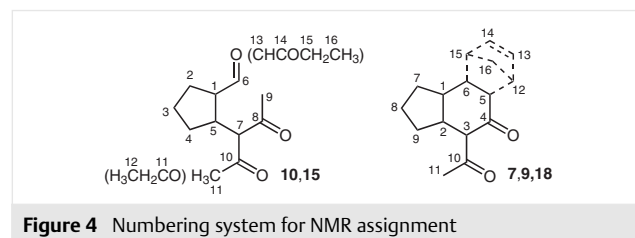
We performed first density functional theory (DFT)-based calculations to elucidate the relative thermodynamic stabilities of (4*R*)-*keto-18* and (4*S*)-*keto-18* (Figure 3). Comparing the two configurations we found that (4*R*)-*keto-18* to be 85 kJ/mol more stable than (4*S*)-*keto-18*. This result is consistent with the observed diastereofacial preference of (4*R*)-*keto-18* due to a thermodynamically driven tautomerization.



In conclusion, we have demonstrated the first organo-catalytic Michael addition of acetylacetone (**12a**) and ethyl acetoacetate (**12b**) with 1-cyclopentene-1-carbaldehyde (**11**) in the presence of Jørgensen–Hayashi catalyst **13c** providing highly oxo-functionalized cyclopentane derivatives **10** in good yields with high enantioselectivity up to 99:1 on gram scale with a catalyst loading of only 2 mol%. Acid-mediated intramolecular aldol condensation converted **10** into the corresponding *trans*-4-acylhexahydro-5*H*-inden-5-ones **9** in moderate to good yields with high diastereoselectivities (up to 94:6). Hexahydroindenone **9a** was submitted to a [4 + 2] cycloaddition with cyclopentadiene (**17**) yielding the tetracyclic tautomers (4*R*)-*keto-18*/*enol-18*. Surpris-

ingly, despite the keto/enol tautomeric equilibrium the 4*R*-configuration of the *exocyclic* acetyl moiety was maintained due to thermodynamic control of the scaffold supported by DFT calculations. Thus, a high degree of molecular complexity (4 rings, 7 stereogenic centers) was obtained in only four steps [including the synthesis of 1-cyclopentene-1-carbaldehyde (**11**) from commercially available 1,2-cyclohexanediol³⁹]. These results not only expand the scope of the Jørgensen–Hayashi catalyst, but also demonstrate the access to polycyclic derivatives in a few redox-economic steps via synthetically valuable, enantioenriched hexahydroindenones without the use of protecting groups, which paves the way for their application in syntheses of complex target molecules.⁵²

¹H and ¹³C NMR were recorded on a Bruker Avance 300, an Ascend 400, an Avance 500, and a Bruker Avance 700 spectrometer. Chemical shifts are reported in ppm relative to CDCl₃ as internal standard. Assignment of NMR spectra was based on correlation spectroscopy (COSY, HSQC, HMBC, and NOESY spectra). Mass spectra and GC-MS were recorded on a Bruker Daltonics micro-TOF-Q instrument, a Varian MAT 711 spectrometer, and an Agilent 6890N Network GC system gas-phase chromatograph equipped with a 5973 Network Mass Selective detector, respectively. FTIR spectra were recorded on a Bruker Vektor 22 spectrometer equipped with a MKII Golden Gate Single Reflection Diamand. GC was performed on a Thermo Scientific Trace 1300 gas-phase chromatograph with fused silica column (30 m × 0.32 mm, 0.25 μm thickness, TG-35 MS phase) (achiral) and on a Fisons Instrument HRGC Mega 2 series 8565 with a fused silica column (25 m × 0.25 mm, thickness 0.25 μm, CP Chirasil DEX CB phase) (chiral). HPLC was performed on a Shimadzu HPLC system on a MZ-Analytical Kromasil 100 Silica 5 μm column (250 × 4.6 mm), on a Chiracel OD-H or on a Chiracel OJ-H column. Optical rotation was performed on a PerkinElmer 241 polarimeter (cuvette l = 0.1 m). The numbering system shown in Figure 4 was used only for NMR assignment.



(1*R*,2*R*)-2-(1-Acetyl-2-oxopropyl)cyclopentanecarbaldehyde (**10a**)³⁴

Method A: A solution of **13a** (111 mg, 1.56 mmol, 0.5 equiv), **12a** (312 mg, 3.12 mmol, 1 equiv) and **11** (**11**/Et₂O = 80:20, 400 mg, 3.12 mmol, 1 equiv) in EtOH (8.0 mL) was stirred for 15 h at r.t. The solvent was removed under reduced pressure and the residue purified by chromatography on SiO₂ to give **10a** as a yellow oil; yield: 9.0 mg (96.8 μmol, 3%); d.r. = 50:50 (¹H NMR, 6-H).

Method B: To a solution of **12a** (2.12 g, 21.2 mmol, 2 equiv) and **13c** (69.1 mg, 212 μmol, 0.02 equiv) in cold toluene (26 mL) at 0 °C was added **11** (**11**/Et₂O = 80:20, 1.36 g, 10.6 mmol, 1 equiv), and the reaction mixture was warmed to r.t. After stirring for 48 h, the solvent was removed under reduced pressure.³⁴ The residue was purified ei-

ther by filtration over a silica pad with hexanes/EtOAc (2:1) to give **10a** as an orange oil; yield: 1.66 g (7.59 mmol, 72%); 88% purity by GC_{achiral} or by flash chromatography on SiO₂ with hexanes/EtOAc [gradient 5:1 → 2:1; R_f = 0.16 (hexanes/EtOAc 5:1)] to give **10a** (40%); >99% purity by GC_{achiral}; [α]_D²⁰ -129.1 (c = 0.77, CHCl₃, ee = 98%).

FT-IR: 2956 (w), 2871 (w), 1716 (s), 1694 (s), 1420 (w), 1357 (w), 1239 (s), 1185 (w), 1143 (w), 955 (w), 619 (w), 582 (w), 531 cm⁻¹ (w).

¹H NMR (500 MHz, CDCl₃): δ = 1.24 (dddd, J = 12.8, 8.3, 8.3, 8.2 Hz, 1 H, 1 × 4-H), 1.48–1.59 (m, 1 H, 1 × 3-H), 1.68 (dddd, J = 12.8, 11.0, 7.1, 5.3 Hz, 1 H, 1 × 3-H), 1.80–1.87 (m, 3 H, 1 × 4-H, 2-H), 2.13 (s, 3 H, 11-H), 2.16 (s, 3 H, 9-H), 2.33 (dddd, J = 9.7, 8.3, 6.9 Hz, 3.0 Hz, 1 H, 1-H), 2.95 (dddd, J = 10.3, 9.7, 9.7, 8.2 Hz, 1 H, 5-H), 3.62 (d, J = 10.3 Hz, 1 H, 7-H), 9.53 (d, J = 3.0 Hz, 1 H, 6-H).

¹³C NMR (126 MHz, CDCl₃): δ = 24.7 (C-3), 27.1 (C-2), 29.2 (C-9), 30.0 (C-11), 30.9 (C-4), 39.1 (C-5), 55.9 (C-1), 74.1 (C-7), 202.4 (C-6), 203.3 (C-10), 203.6 (C-8).

MS (ESI): m/z = 235 [M + K⁺], 219 [M + Na⁺].

HRMS (ESI): m/z [M + Na⁺] calcd for C₁₁H₁₆O₃Na⁺: 219.0992; found: 219.0973.

Ethyl 2-[(1R,2R)-2-Formylcyclopentyl]-3-oxobutanoate (**10b**)

Method A: To a solution of **13a** (555 mg, 7.80 mmol, 0.5 equiv) and **12b** (2.07 mg, 15.9 mmol, 1.02 equiv) in toluene (40 mL) was added **11** (**11**/Et₂O = 80:20, 2.00 g, 15.6 mmol, 1 equiv) and the reaction mixture was stirred for 60 h at r.t. The solvent was removed under reduced pressure and the residue purified by flash chromatography on SiO₂ with hexanes/EtOAc (5:1) to give **10b** as a yellow oil; yield: 1.24 g (3.84 mmol, 25%); 70% purity by ¹H NMR analysis.

Method B: A solution of **13c** (23.7 mg, 72.8 μmol, 0.02 equiv) and **12b** (237 mg, 1.82 mmol, 1 equiv) in toluene (4.5 mL) was cooled to 0 °C and **11** (**11**/Et₂O = 75:25, 250 mg, 1.82 mmol, 1 equiv) was added. The reaction mixture was stirred for 24 h at r.t. The solvent was removed under reduced pressure and the residue was filtered over a silica pad with hexanes/EtOAc (2:1) to give **10b** as a colorless oil; yield: 373 mg (1.65 mmol, 91%); D1:D2 = 50:50 by GC_{achiral}; [α]_D²⁰ -51.3 (c = 0.64, CHCl₃); d.r. = 50:50.

FT-IR: 3437 (w), 2958 (w), 2873 (w), 2725 (w), 1716 (s), 1449 (w), 1360 (w), 1246 (w), 1186 (w), 1148 (w), 1095 (w), 1023 (w), 857 (w), 540 cm⁻¹ (w).

¹H NMR (500 MHz, CDCl₃): δ (signals of both diastereomers, arbitrarily denoted) = 1.25 (t, J = 7.1 Hz, 3 H, OCH₂CH_{3,D2}), 1.28 (t, J = 7.1 Hz, 3 H, OCH₂CH_{3,D1}), 1.24–1.34 (m, 1 H, 1 × 4-H_{D2}), 1.40 (dddd, J = 12.6, 8.6, 8.6, 7.8 Hz, 1 H, 1 × 4-H_{D1}), 1.52–1.62 (m, 2 H, 1 × 3-H_{D1}, 1 × 3-H_{D2}), 1.66–1.75 (m, 2 H, 1 × 3-H_{D1}, 1 × 3-H_{D2}), 1.83–1.89 (m, 4 H, 2-H_{D1}, 2-H_{D2}), 1.93 (dddd, J = 12.6, 7.8, 7.8, 4.7 Hz, 1 H, 1 × 4-H_{D1}), 1.93 (dddd, J = 12.6, 7.8, 7.8, 4.7 Hz, 1 H, 1 × 4-H_{D2}), 2.21 (s, 3 H, 9-H_{D2}), 2.25 (s, 3 H, 9-H_{D1}), 2.45 (dddd, J = 7.6, 7.6, 7.6, 2.8 Hz, 1 H, 1-H_{D1}), 2.57 (dddd, J = 8.8, 7.0, 7.0, 3.0 Hz, 1 H, 1-H_{D2}), 2.92 (dddd, J = 9.5, 8.8, 7.8, 7.8 Hz, 1 H, 5-H_{D2}), 2.92 (dddd, J = 9.7, 8.3, 7.8, 7.8 Hz, 1 H, 5-H_{D1}), 3.43 (d, J = 9.5 Hz, 1 H, 7-H_{D2}), 3.44 (d, J = 9.7 Hz, 1 H, 7-H_{D1}), 4.15 (qd, J = 7.1, 1.2 Hz, 2 H, OCH₂CH_{3,D2}), 4.21 (qd, J = 7.2, 1.0 Hz, 2 H, OCH₂CH_{3,D1}), 9.58 (d, J = 3.0 Hz, 1 H, 6-H_{D2}), 9.60 (d, J = 2.8 Hz, 1 H, 6-H_{D1}).

¹³C NMR (126 MHz, CDCl₃): δ = 14.0 (OCH₂CH_{3,D2}), 14.1 (OCH₂CH_{3,D1}), 24.8 (C-3_{D1}), 25.0 (C-3_{D2}), 27.3 (C-2_{D1}), 27.4 (C-2_{D2}), 29.3 (C-9_{D2}), 29.3 (C-9_{D1}), 30.9 (C-4_{D1}), 31.4 (C-4_{D2}), 38.8 (C-5_{D2}), 39.1 (C-5_{D1}), 55.4 (C-1_{D2}), 55.7 (C-1_{D1}), 61.6 (OCH₂CH_{3,D1}), 61.7 (OCH₂CH_{3,D2}), 64.3 (C-7_{D1}), 64.4 (C-7_{D2}), 168.8 (C-10_{D1}), 168.8 (C-10_{D2}), 202.2 (C-8_{D1}), 202.5 (C-8_{D2}), 202.5 (C-6_{D2}), 202.6 (C-6_{D1}).

MS (ESI): m/z = 249 [M + Na⁺], 209, 184, 149, 131.

HRMS (ESI): m/z [M + Na⁺] calcd for C₁₂H₁₈O₄Na⁺: 249.1097; found: 249.1071.

Ethyl (2E)-3-[(1S,2R)-2-[1-(Ethoxycarbonyl)-2-oxopropyl]cyclopentyl]acrylate (**15**)

Method A: A solution of **12b** (379 mg, 2.91 mmol, 1 equiv), **13a** (104 mg, 1.48 mmol, 0.5 equiv), and **11** (**11**/Et₂O = 87:13, 400 mg, 2.91 mmol, 1 equiv) in toluene (8.0 mL) was stirred for 24 h at r.t. After filtration over a silica pad with hexanes/EtOAc (2:1), the filtrate was concentrated, and the residue dissolved in toluene (15 mL). Phosphonium bromide **14** (1.25 g, 2.91 mmol, 1 equiv) and NEt₃ (442 mg, 4.37 mmol, 1.5 equiv) were added, and the reaction mixture was stirred for 22 h at r.t. Then it was washed with H₂O (10 mL), dried (MgSO₄), and the solvent removed under reduced pressure. The residue was purified by chromatography on SiO₂ with hexanes/EtOAc (gradient 15:1 → 10:1) to give *rac*-**15** as a yellow oil; yield: 287 mg (968 μmol, 33%); d.r. 47:40:8:5 by GC_{achiral}.

Method B: A solution of **11** (**11**/Et₂O = 87:12, 500 mg, 4.42 mmol, 1 equiv), **12b** (575 mg, 4.42 mmol, 1 equiv), and **13c** (28.8 mg, 88.4 μmol, 0.02 equiv) in toluene (10 mL) was stirred for 72 h at r.t. After the addition of phosphonium bromide **14** (1.99 g, 4.64 mmol, 1.05 equiv) and NEt₃ (0.7 ml, 671 mg, 6.63 mmol, 1.5 equiv), the reaction mixture was stirred for 8 h at r.t. Then H₂O (20 mL) was added and the mixture extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (MgSO₄) and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO₂ with hexanes/EtOAc [gradient 30:1 → 10:1, R_f = 0.28, hexanes/EtOAc (10:1)] to give **15** as a colorless oil; yield: 351 mg (1.18 mmol, 27%); D1:D2 = 55:45 by GC_{achiral}; [α]_D²⁰ -52.6 (c = 0.54, CHCl₃); d.r. = 55:45.

FT-IR: 2956 (w), 2871 (w), 1710 (s), 1651 (w), 1448 (w), 1368 (w), 1306 (w), 1264 (w), 1227 (w), 1194 (w), 1146 (s), 1096 (w), 1033 (w), 984 (w), 914 (w), 862 (w), 810 (w), 730 (s), 647 (w), 540 cm⁻¹ (w).

¹H NMR (500 MHz, CDCl₃): δ (signals of both diastereomers, arbitrarily denoted) = 1.16 (t, J = 7.2 Hz, 3 H, 12-H_{D1}), 1.18–1.23 (m, 11 H, 1 × 4-H_{D1}, 1 × 4-H_{D2}, 12-H_{D2}, 16-H_{D1}, 16-H_{D2}), 1.39–1.50 (m, 2 H, 1 × 2-H_{D1}, 1 × 2-H_{D2}), 1.54–1.66 (m, 4 H, 3-H_{D1}, 3-H_{D2}), 1.76–1.84 (m, 2 H, 1 × 2-H_{D1}, 1 × 2-H_{D2}), 1.84–1.93 (m, 2 H, 1 × 4-H_{D1}, 1 × 4-H_{D2}), 2.09 (s, 3 H, 9-H_{D2}), 2.13 (s, 3 H, 9-H_{D1}), 2.27–2.34 (m, 3 H, 1-H_{D1}, 1-H_{D2}, 5-H_{D2}), 2.34–2.44 (m, 1 H, 5-H_{D1}), 3.26 (d, J = 9.5 Hz, 1 H, 7-H_{D1}), 3.34 (d, J = 6.9 Hz, 1 H, 7-H_{D2}), 3.93–4.05 (m, 2 H, 11-H_{D1}), 4.05–4.15 (m, 6 H, 11-H_{D2}, 15-H_{D1}, 15-H_{D2}), 5.66 (d, J = 15.5 Hz, 1 H, 13-H_{D1}), 5.69 (d, J = 15.2 Hz, 1 H, 13-H_{D2}), 6.69 (dd, J = 15.5, 3.1 Hz, 1 H, 6-H_{D1}), 6.71 (dd, J = 15.2, 3.3 Hz, 1 H, 6-H_{D2}).

¹³C NMR (126 MHz, CDCl₃): δ = 13.8 (C-12_{D1}), 14.1 (C-12_{D2}), 14.2 (C-16_{D2}), 14.2 (C-16_{D1}), 23.7 (C-3_{D1}), 23.8 (C-3_{D2}), 29.0 (C-9_{D1}), 29.1 (C-9_{D2}), 29.4 (C-4_{D2}), 30.7 (C-4_{D1}), 32.6 (C-2_{D2}), 32.8 (C-2_{D1}), 44.2 (C-5_{D2}), 44.4 (C-5_{D1}), 46.7 (C-1_{D2}), 47.4 (C-1_{D1}), 60.1 (C-15_{D1}), 60.2 (C-15_{D2}), 61.2 (C-11_{D2}), 61.2 (C-11_{D1}), 62.6 (C-7_{D2}), 64.7 (C-7_{D1}), 120.7 (C-13_{D1}), 121.3 (C-13_{D2}), 151.2 (C-6_{D1}), 151.4 (C-6_{D2}), 166.3 (C-14_{D1}), 166.3 (C-14_{D2}), 168.5 (C-10_{D1}), 168.9 (C-10_{D2}), 202.1 (C-8_{D1}), 202.3 (C-8_{D2}).

MS (ESI): m/z = 319 [M + Na⁺], 297, 251, 233, 205, 177, 121.

HRMS (ESI): m/z [M + Na⁺] calcd for C₁₆H₂₄O₅Na⁺: 319.1516; found: 319.1516.

(3aS,7aR)-1,2,3,3a,4,7a-Hexahydro-5H-inden-5-one (**7**)

To a solution of (1R,2R)-**10a** (530 mg, 2.70 mmol, 1 equiv) in MeOH (130 mL) at 0 °C was added KOH (607 mg, 10.8 mmol, 4 equiv), and the reaction mixture was stirred for 2.5 h at r.t. and then concentrated

under reduced pressure. Sat. aq. NH_4Cl was added to the residue (under ice cooling), and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried (MgSO_4) and the solvent was removed under reduced pressure. To the yellow residue in anhyd. CH_2Cl_2 (13 mL) were added NEt_3 (1.2 mL, 956 mg, 9.45 mmol, 3.5 equiv) and DMAP (32.9 mg, 270 μmol , 0.1 equiv) and the mixture was cooled to 0°C . Then MsCl (464 mg, 4.05 mmol, 1.5 equiv) was added dropwise and the mixture stirred for 17 h at r.t. After the addition of H_2O (20 mL), the mixture was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried (MgSO_4) and the solvent was removed under reduced pressure. The residue was chromatographed on SiO_2 with hexanes/ EtOAc (20:1) to give **7** as a yellow oil; yield: 184 mg (1.35 mmol, 50%); $R_f = 0.35$ (hexanes/ EtOAc 10:1).

FT-IR: 3025 (w), 2951 (w), 2871 (w), 1736 (w), 1673 (s), 1604 (w), 1456 (w), 1415 (w), 1386 (w), 1356 (w), 1308 (w), 1244 (w), 1199 (w), 1152 (w), 1117 (w), 1083 (w), 1043 (w), 895 (w), 817 (w), 756 (w), 556 (w), 510 (w), 452 cm^{-1} (w).

^1H NMR (500 MHz, CDCl_3): $\delta = 1.26$ – 1.36 (m, 2 H, 1×7 -H, 1×9 -H), 1.68 – 1.76 (m, 2 H, 8-H), 1.74 – 1.85 (m, 2 H, 2-H, 1×9 -H), 1.95 (dddd, $J = 11.9, 7.1, 7.1, 4.4$ Hz, 1 H, 1×7 -H), 2.05–2.15 (m, 1 H, 1-H), 2.09 (dd, $J = 16.7, 13.6$ Hz, 1 H, 1×3 -H), 2.68 (dd, $J = 16.7, 3.0$ Hz, 1 H, 1×3 -H), 5.91 (ddd, $J = 9.9, 2.9, 1.0$ Hz, 1 H, 6-H), 7.04 (dd, $J = 9.9, 1.9$ Hz, 1 H, 5-H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 22.2$ (C-8), 28.4 (C-7), 30.2 (C-9), 44.7 (C-3), 44.8 (C-2), 45.0 (C-1), 130.3 (C-6), 152.6 (C-5), 201.0 (C-4).

MS (EI): m/z (%) = 136 (100) [M^+], 81 (75), 68 (80), 55 (45).

HRMS (EI): m/z [M^+] calcd for $\text{C}_9\text{H}_{12}\text{O}^+$: 136.0888; found: 136.0887.

(3aR,4R,7aS)-4-Acetyl-1,2,3,3a,4,7a-hexahydro-5H-indene-5-one (9a)

A solution of (1R,2R)-**10a** (100 mg, 509 μmol , 1 equiv) and CSA (118 mg, 509 μmol , 1 equiv) in toluene (17 mL) was heated for 65 h under reflux. After cooling to r.t., the solution was washed with sat. aq. NaHCO_3 and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO_2 with hexanes/ EtOAc (30:1) to give **9a** as a yellow oil; yield: 66.0 mg (370 μmol , 73%); d.r. 94:6. Repeated crystallization from hexane (0.5 mL) at -20°C gave optically pure **9a**; $R_f = 0.39$ (hexanes/ EtOAc 5:1); $[\alpha]_D^{20} -6.4$ ($c = 0.63$, CHCl_3).

FT-IR: 3025 (w), 2958 (w), 2872 (w), 1713 (s), 1660 (s), 1603 (w), 1454 (w), 1421 (w), 1385 (w), 1353 (w), 1306 (w), 1285 (w), 1259 (w), 1224 (w), 1175 (w), 1140 (w), 1079 (w), 1048 (w), 1021 (w), 970 (w), 936 (w), 895 (w), 846 (w), 775 (w), 657 (w), 585 (w), 534 (w), 508 (w), 460 cm^{-1} (w).

^1H NMR (500 MHz, CDCl_3): $\delta = 1.28$ (dddd, $J = 11.4, 9.7, 9.7, 8.3$ Hz, 1 H, 1×9 -H), 1.41 (dddd, $J = 12.2, 10.1, 10.1, 8.6$ Hz, 1 H, 1×7 -H), 1.76–1.83 (m, 2 H, 8-H), 1.84–1.91 (m, 1 H, 1×9 -H), 2.04 (dddd, $J = 11.4, 7.2, 7.2, 3.9$ Hz, 1 H, 1×7 -H), 2.15 (dddd, $J = 12.9, 11.4, 6.2, 6.2$ Hz, 1 H, 2-H), 2.27 (s, 3 H, 11-H), 2.23–2.32 (m, 1 H, 1-H), 3.27 (d, $J = 12.9$ Hz, 1 H, 3-H), 5.98 (dd, $J = 9.8, 2.9$ Hz, 1 H, 6-H), 7.13 (dd, $J = 9.8, 1.7$ Hz, 1 H, 5-H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 22.0$ (C-8), 28.2 (C-7), 28.7 (C-9), 30.9 (C-11), 44.2 (C-1), 46.2 (C-2), 67.5 (C-3), 129.8 (C-6), 152.9 (C-5), 196.7 (C-4), 205.7 (C-10).

MS (ESI): $m/z = 201$ [$\text{M} + \text{Na}^+$], 179 [$\text{M} + \text{H}^+$], 161, 149, 137, 119.

HRMS (ESI): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_{11}\text{H}_{15}\text{O}_2^+$: 179.1081; found: 179.1067.

Ethyl (3aR,4S,7aS)-5-Oxo-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylate (9b)

From *rac*-**10b**: A solution of *rac*-**10b** (1.24 g, 70% purity, 3.84 mmol, 1 equiv) and CSA (445 mg, 1.92 mmol, 0.5 equiv) in toluene (40 mL) was heated under reflux (Dean–Stark conditions). After cooling to r.t., the solution was washed with sat. aq. NaHCO_3 (20 mL), dried (MgSO_4), and the solvent removed under reduced pressure. The residue was purified by chromatography on SiO_2 with hexanes/ EtOAc (gradient 15:1 \rightarrow 10:1) to give **9b** as a yellow oil; yield: 237 mg (30%); d.r. 83:17.

From *enantioenriched* **10b**: A solution of (3aR,4S,7aS)-**10b**:(3aR,4R,7aS)-**10b** (86:14) (282 mg, 1.25 mmol, 1 equiv) and CSA (144 mg, 623 μmol , 0.5 equiv) in toluene (40 mL) was heated for 2 h under reflux. After cooling to r.t., the solution was washed with sat. aq. NaHCO_3 (30 mL), dried (MgSO_4), and the solvent removed under reduced pressure. The residue was purified by chromatography on SiO_2 with hexanes/ EtOAc (30:1) to give **9b** as a yellow oil; yield: 55.0 mg (264 μmol , 35%). The product was further purified by crystallization from pentane (1.0 mL) at -20°C .

(3aR,4S,7aS)-9b

$R_f = 0.43$ (hexanes/ EtOAc 5:1); $[\alpha]_D^{20} -29.2$ ($c = 0.62$, CHCl_3).

FT-IR: 3025 (w), 2961 (w), 2873 (w), 1736 (s), 1673 (s), 1603 (w), 1455 (w), 1385 (w), 1321 (w), 1257 (w), 1178 (w), 1136 (s), 1079 (w), 1051 (w), 1024 (w), 929 (w), 909 (w), 792 (w), 710 (w), 533 (w), 487 cm^{-1} (w).

^1H NMR (700 MHz, CDCl_3): $\delta = 1.29$ (t, $J = 7.1$ Hz, 3 H, OCH_2CH_3), 1.39 (dddd, $J = 11.8, 11.8, 9.1, 9.1$ Hz, 1 H, 1×9 -H), 1.41 (dddd, $J = 12.3, 12.3, 8.9, 8.9$ Hz, 1 H, 1×7 -H), 1.77–1.84 (m, 2 H, 8-H), 1.89 (dddd, $J = 11.6, 6.0, 6.0, 5.4$ Hz, 1 H, 1×9 -H), 2.05 (dddd, $J = 11.7, 7.0, 7.0, 4.7$ Hz, 1 H, 1×7 -H), 2.20 (dddd, $J = 13.1, 11.7, 6.4, 6.4$ Hz, 1 H, 2-H), 2.29 (dddd, $J = 11.7, 7.0, 7.0, 2.8, 1.8$ Hz, 1 H, 1-H), 3.18 (d, $J = 13.1$ Hz, 1 H, 3-H), 4.24 (m, 2 H, OCH_2CH_3), 6.02 (dd, $J = 9.9, 2.8$ Hz, 1 H, 6-H), 7.13 (dd, $J = 9.9, 1.8$ Hz, 1 H, 5-H).

^{13}C NMR (176 MHz, CDCl_3): $\delta = 13.2$ (C-12), 20.8 (C-8), 27.3 (C-7), 27.6 (C-9), 43.0 (C-1), 45.8 (C-2), 60.0 (C-11), 60.2 (C-3), 128.5 (C-6), 151.5 (C-5), 168.7 (C-10), 194.1 (C-4).

MS (ESI): $m/z = 231$ [$\text{M} + \text{Na}^+$], 209 [$\text{M} + \text{H}^+$], 181, 163, 135.

HRMS (ESI): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_{12}\text{H}_{17}\text{O}_3^+$: 209.1172; found: 209.1170.

(3aR,4R,7aS)-9b

$R_f = 0.44$ (hexanes/ EtOAc 5:1).

FT-IR: 2958 (w), 2873 (w), 1727 (s), 1672 (s), 1605 (w), 1454 (w), 1378 (w), 1317 (w), 1263 (w), 1220 (w), 1177 (s), 1153 (s), 1082 (w), 1050 (w), 1020 (w), 954 (w), 902 (w), 803 (w), 716 (w), 609 (w), 567 (w), 527 (w), 489 (w), 442 cm^{-1} (w).

^1H NMR (700 MHz, CDCl_3): $\delta = 1.25$ (t, $J = 7.2$ Hz, 2 H, OCH_2CH_3), 1.35 (dddd, $J = 21.8, 12.3, 9.5, 9.5$ Hz, 1 H, 1×7 -H), 1.50–1.59 (m, 1 H, 1×9 -H), 1.75–1.83 (m, 2 H, 8-H), 1.85 (ddd, $J = 11.9, 6.1, 6.1$ Hz, 1 H, 1×9 -H), 2.00–2.10 (m, 2 H, 2-H, 1×7 -H), 2.61–2.68 (m, 1 H, 1-H), 3.59 (d, $J = 5.2$ Hz, 1 H, 3-H), 4.16 (m, 2 H, OCH_2CH_3), 6.04 (dd, $J = 9.9, 2.8$ Hz, 1 H, 6-H), 7.14 (dd, $J = 9.9, 1.8$ Hz, 1 H, 5-H).

^{13}C NMR (176 MHz, CDCl_3): $\delta = 14.3$ (OCH_2CH_3), 21.6 (C-8), 26.9 (C-9), 28.1 (C-7), 40.1 (C-1), 46.1 (C-2), 56.2 (C-3), 61.1 (OCH_2CH_3), 129.1 (C-6), 153.3 (C-5), 168.4 (C-10), 195.2 (C-4).

MS (ESI): $m/z = 231$ [$\text{M} + \text{Na}^+$], 209 [$\text{M} + \text{H}^+$], 163, 135.

HRMS (ESI): m/z [M + H⁺] calcd for C₁₂H₁₇O₃⁺: 209.1172; found: 209.1192.

(3aR,4R,5aR,6S,9R,9aS,9bR)-4-Acetyl-1,2,3,3a,4,5a,6,9,9a,9b-decahydro-5H-6,9-methanocyclopenta[*a*]naphthalen-5-one (keto-18) and 1-[(3aR,5aR,6S,9R,9aR,9bS)-5-Hydroxy-2,3,3a,5a,6,9,9a,9b-octahydro-1H-6,9-methanocyclopenta[*a*]naphthalen-4-yl]ethanone (enol-18)

Method B: To a solution of (3aR,4R,7aS)-**9a** (127 mg, 713 μmol, 1 equiv) in anhyd toluene (3.6 mL) under N₂ atmosphere at -100 °C was added dropwise TfOH (21.4 mg, 143 μmol, 0.2 equiv) and the mixture stirred for 10 min prior to the addition of freshly distilled **17** (120 μL, 94.2 mg, 1.43 mmol, 2 equiv). The reaction mixture was warmed to -75 °C and stirred for 12 h. After the addition of NEt₃ (0.3 mL), the mixture was warmed to r.t. and the solvent removed under reduced pressure. Then H₂O (5 mL) was added and the solution extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (20 mL) and filtered over a silica pad. The filtrate was concentrated under reduced pressure and the residue purified by chromatography on SiO₂ with hexanes/EtOAc (gradient 30:1 → 10:1) to give a mixture of *keto-18*/*enol-18* = 43:57 as a yellow oil; yield: 61.0 mg [250 μmol, 35%; 40% referred to reisolated **9a** (16.0 mg, 89.7 μmol)];⁵³ R_f = 0.47 (hexanes/EtOAc 10:1); [α]_D²⁰ -231.3 (*c* = 0.48, CHCl₃, *keto-18* : *enol-18* = 44:56).

Both derivatives were characterized as mixture. For clarity the signals are listed separately.

Enol-18

¹H NMR (700 MHz, CDCl₃): δ = 1.13–1.20 (m, 1 H, 1 × 9-H), 1.40 (ddd, *J* = 8.2, 1.6, 1.6 Hz, 1 H, 1 × 16-H), 1.43 (m, 1 H, 1 × 7-H), 1.50 (ddd, *J* = 8.2, 1.9, 1.9 Hz, 1 H, 1 × 16-H), 1.63–1.72 (m, 1 H, 1-H), 1.72–1.76 (m, 2 H, 8-H), 1.89–1.94 (m, 1 H, 1 × 7-H), 2.04–2.10 (m, 2 H, 2-H, 1 × 9-H), 2.12 (s, 3 H, 11-H), 2.64 (ddd, *J* = 9.2, 5.9, 3.2 Hz, 1 H, 6-H), 3.00 (dd, *J* = 9.2, 4.4 Hz, 1 H, 5-H), 3.01 (m, 1 H, 15-H), 3.17 (m, 1 H, 12-H), 5.94 (dd, *J* = 5.7, 3.0 Hz, 1 H, 13-H), 6.05 (dd, *J* = 5.7, 3.0 Hz, 1 H, 14-H), 16.67 (s, 1 H, OH).

¹³C NMR (176 MHz, CDCl₃): δ = 22.5 (C-8), 27.2 (C-7), 27.9 (C-11), 32.0 (C-9), 38.7 (C-2), 40.3 (C-6), 45.4 (C-15), 46.5 (C-1), 46.7 (C-5), 47.0 (C-12), 51.4 (C-16), 112.3 (C-3), 134.3 (C-13), 136.3 (C-14), 189.9, 196.0 (C-4, C-10).

Keto-18

FT-IR: 3057 (w), 2960 (w), 2869 (w), 1716 (s), 1687 (s), 1570 (w), 1453 (w), 1418 (w), 1358 (w), 1309 (w), 1252 (w), 1211 (w), 1146 (w), 1050 (w), 978 (w), 933 (w), 912 (w), 865 (w), 834 (w), 753 (w), 741 (w), 695 (w), 674 (w), 602 (w), 563 (w), 529 (w), 462 cm⁻¹ (w).

¹H NMR (700 MHz, CDCl₃): δ = 0.92–0.99 (m, 1 H, 1 × 9-H), 1.33 (ddd, *J* = 8.4, 1.6, 1.6 Hz, 1 H, 1 × 16-H), 1.43 (m, 2 H, 1 × 7-H, 1 × 16-H), 1.65–1.71 (m, 1 H, 1 × 9-H), 1.72–1.77 (m, 3 H, 1 × 7-H, 8-H), 1.86 (dddd, *J* = 12.4, 12.4, 7.1, 7.1 Hz, 1 H, 1-H), 1.98 (dddd, *J* = 12.4, 12.4, 10.8, 6.2 Hz, 1 H, 2-H), 2.11 (s, 3 H, 11-H), 2.77 (ddd, *J* = 9.2, 7.1, 3.2 Hz, 1 H, 6-H), 2.86 (d, *J* = 12.4 Hz, 1 H, 3-H), 2.91 (dd, *J* = 9.2, 4.4 Hz, 1 H, 5-H), 3.03–3.05 (m, 1 H, 15-H), 3.39 (dddd, *J* = 4.4, 2.9, 1.6, 1.6 Hz, 1 H, 12-H), 6.08 (dd, *J* = 5.7, 2.9 Hz, 1 H, 13-H), 6.18 (dd, *J* = 5.7, 2.9 Hz, 1 H, 14-H).

¹³C NMR (176 MHz, CDCl₃): δ = 22.2 (C-8), 27.3 (C-7), 29.2 (C-9), 29.8 (C-11), 39.4 (C-2), 40.0 (C-6), 44.6 (C-1), 45.6 (C-15), 47.9 (C-12), 50.3 (C-16), 51.8 (C-5), 70.3 (C-3), 135.9 (C-13), 137.3 (C-14), 206.3 (C-10), 210.4 (C-4).

MS (ESI): m/z = 267 [M + Na⁺], 245 [M + H⁺], 179, 137.

HRMS (ESI): m/z [M + H⁺] calcd for C₁₆H₂₀O₂⁺: 245.1536; found: 245.1538.

DFT Calculations

The calculations were performed at the B3LYP⁵⁴ level of theory using the AUG-cc-pVTZ⁵⁵ basis set as implemented in the Gaussian 16 program package.⁵⁶ The X-ray crystal structure of enone **9a** (Figure 2) served as a starting point to calculate optimized minimum energy structures of neutral (4*R*)-*keto-18* and (4*S*)-*keto-18* in their singlet ground states. Structures were optimized in the gas phase and confirmed to be true minima by frequency calculations (no imaginary frequencies). The relative free Gibbs energies (Δ*G*_{GS}) were extracted at 300 K.

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Supporting Information

Michael reaction, aldol condensation, and Diels–Alder reaction as well as characterization of the synthesized compounds (¹H, ¹³C and NOESY spectra). Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610409>.

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