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

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 enyme metathesis,28 or one-pot consecutive Pd-catalyzed Overman rearrangement, Ru-catalyzed ring closing enyme metathesis, and hydrogen bond-directed Diels–Alder reaction.29 Particular valuable hydrindanes are hexa-
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hydroindenones whose enone moiety allows further functionalization. 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 hexahydroindene 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.32–38 On the other hand, simple 1,3-carbonyl compounds such as acetylacetone and ethyl acetooacetate 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.

Next, the robustness of the Michael addition with respect to catalyst loading and scale 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 deteri- orated 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)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>EtOH</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>13a (50)</td>
<td>EtOH</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>13b (30)</td>
<td>EtOH</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>13c (20)</td>
<td>EtOH</td>
<td>58b</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>13c (20)</td>
<td>MeOH</td>
<td>43</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>13c (20)</td>
<td>H2O</td>
<td>45</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>13c (20)</td>
<td>THF</td>
<td>55</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>13c (20)</td>
<td>MeCN</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>13c (20)</td>
<td>CHCl3</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>13c (20)</td>
<td>hexane</td>
<td>39</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>13c (20)</td>
<td>toluene</td>
<td>70</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>13c (20)</td>
<td>toluenec</td>
<td>52</td>
<td>92</td>
</tr>
</tbody>
</table>

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.
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 cyclopentanone enolate 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 cyclopentanone enolate 15 in 27% yield (E/Z >95:5, d.r. 55:45).

Taking the preferred formation of the trans-disubstituted cyclopentanonecarbaldehyde (1R,2R)-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 (1R,2R,1’S)-10b and (1R,2R,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 cyclopentanone enolates 15 (d.r. 47:40:8:5) under racemic conditions presumably coming from four diastereomeric cyclopentanone carbaldehydes 10b with a similar ratio suggested that besides the two trans-disubstituted diastereomers (1R,2R,1’S)-10b and (1R,2R,1’R)-10b also the corresponding cis-diastereomers (1R,2S,1’S)-10b and (1R,2S,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

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**Table 2** Optimization of Catalyst Loading and Scale

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

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*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.
With cyclopentanecarbaldehydes \(10a, b\) 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 \(\text{CH}_2\text{Cl}_2\). 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, acetacetate-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 addi-
tion of 1 equivalent of (−)-CSA to the reaction mixture and stir-
ring 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 CH2-
Cl2, the crude product was treated with mesyl chloride,
DMAP, and NEt3 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 triclinic space
group P2(1)2(1)2(1). The absolute configuration could be
determined from X-ray data by anomalous dispersion char-
acterized as a potential scaffold for convenient functionaliza-
tion 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).

As the determination of the enantioselectivity of the
Michael addition product 10b had not yet been solved, a se-
quencing of Michael addition/aldol condensation was studied
in 35% and enantioenriched
9b in 30%
product 10b in 35% and enantioenriched 9b in 35%
determination of the enantioselectivity of the
Michael addition product 10b had not yet been solved, a se-
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9b in 30%
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9b in 30%
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9b in 30%
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in 35% and enantioenriched
9b in 30%
product 10b in 35% and enantioenriched 9b in 35%
comparison with known 1,3-dicarbonyl derivatives\textsuperscript{50} 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 4R-configuration of the acetyl-carrying carbon atom, while the corresponding epimer with 4S-configuration was not detected. Presumably, the diastereofacial preference of the protonation step is governed by formation of the thermodynamically more stable (4R)-keto-18 with an equatorial acetyl moiety as compared to the (4S)-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.\textsuperscript{51} Furthermore, upon prolonged storage of tetracycle 18 in CDCl\textsubscript{3}, the equilibrium shifted from (4R)-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 (4R)-keto-18 and (4S)-keto-18 (Figure 3). Comparing the two configurations we found that (4R)-keto-18 to be 85 kJ/mol more stable than (4S)-keto-18. This result is consistent with the observed diastereofacial preference of (4R)-keto-18 due to a thermodynamically driven tautomerization.

In conclusion, we have demonstrated the first organocatalytic Michael addition of acetylacetone (12a) and ethyl acetooacetate (12b) with 1-cyclopentene-1-carboxaldehyde (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-5H-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 (4R)-keto-18/enol-18. Surprisingly, despite the keto/enol tautomeric equilibrium the 4R-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-cyclohexanedione]\textsuperscript{52}. 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.\textsuperscript{32}

\( ^{1} \text{H} \) and \( ^{13} \text{C} \) 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 CDCl\textsubscript{3}, 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 equipped 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 Chiralcel 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.

\( ^{1} \text{H} \) and \( ^{13} \text{C} \) NMR assignments are described in Table S1.
Method A: 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 to a solution of (1R,2R)-2-Formylcyclopentyl-3-oxobutanoate (10b) (237 mg, 1.82 mmol, 1 equiv) in toluene (4.5 mL) was cooled to 0 °C and 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 removed under reduced pressure. The residue was purified by chromatography on SiO2 with hexanes/EtOAc (10:1) to give 10c as a yellow oil; yield: 373 mg (968 μmol, 33%); d.r. 47:40:8:5 by GC achiral.

Method B: A solution of 11 (Et2O = 87:12, 500 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 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 30:1 → 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.

Ethyl (Z)-2-(15,2R)-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 (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 and 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 (Et2O = 87:12, 500 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 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 30:1 → 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.

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

under reduced pressure. Sat. aq NH4Cl was added to the residue (under ice cooling), and the mixture was extracted with CH2Cl2 (3 × 30 mL). The combined organic layers were dried (MgSO4) and the solvent was removed under reduced pressure. To the yellow residue in anhyd CH2Cl2 (13 mL) were added NEt3 (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 rt. After the addition of H2O (20 mL), the mixture was extracted with CH2Cl2 (3 × 25 mL). The combined organic extracts were dried (MgSO4) and the solvent was removed under reduced pressure. The residue was chromatographed on SiO2 with hexanes/EtOAc (20:1) to give 7 as a yellow oil; yield: 184 mg (1.35 mmol, 50%); Rf = 0.35 (hexanes/EtOAc 10:1).

**FT-IR:** 3025 (w), 2871 (w), 1736 (w), 1673 (s), 1604 (w), 1546 (w), 1415 (w), 1386 (w), 1356 (w), 1308 (w), 1244 (w), 1199 (w), 1152 (w), 1117 (w), 1083 (w), 1043 (w), 895 (w), 671 (w), 576 (w), 556 (w), 510 (w), 452 cm⁻¹ (w).

**1H NMR (500 MHz, CDCl3):** δ = 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, 9–H), 1.95 (dddd, J = 11.9, 7.1, 7.1, 4.4 Hz, 1 H, 1 × 3-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).

**13C NMR (126 MHz, CDCl3):** δ = 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).

**HRMS (EI):** m/z (3 × 30 mL). The combined organic layers were washed with sat. aq NaHCO3 (20 mL), dried (MgSO4), and the remaining solvent was removed under reduced pressure. The residue was purified by chromatography on SiO2 with hexanes/EtOAc (30:1) to give 9b as a yellow oil; yield: 660 mg (370 μmol, 73%); d.r. 4:6. Repeated recrystallization from hexane (0.5 mL) at –20 °C gave optically pure 9a; Rf = 0.39 (hexanes/EtOAc 5:1); [α]D20 +6.4 (c = 0.63, CHCl3).

**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, CDCl3):** δ = 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, 3–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).

**13C NMR (126 MHz, CDCl3):** δ = 22.0 (C-8), 28.2 (C-7), 28.7 (C-9), 30.9 (C-11), 44.2 (C-1), 462 (C-2), 67.5 (C-3), 129.8 (C-6), 152.9 (C-5), 196.7 (C-4), 205.7 (C-10).


**Ethyl (3aR,4S,7aS)-5-Oxo-2,3a,3,4,5,7a-hexahydro-1H-inden-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 NaHCO3 (20 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 9b as a yellow oil; yield: 237 mg (30%); d.r. 83:17.

**From enantioenriched 10b:** A solution of (3aR,4S,7aS)-10b (3.44 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 NaHCO3 (30 mL), dried (MgSO4), and the solvent removed under reduced pressure. The residue was purified by chromatography on SiO2 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,4R,5aR,6S,9R,9aS,9bR)-4-Acetyl-1,2,3,4,5a,6,9,9a,9b-decahydro-SH-6,9-methanocyclopenta[a]naphthalene-5-one keto-18 and 1-[(3aR,8S,5aR,6S,9aR,9bS)-5-Hydroxy-2,3,3a,5a,6,9,9a,9b-octahydro-1H-6,9-methanocyclopenta[a]naphthalene-4-yl]ethanone enol-18

Method B: To a solution of (3aR,4R,5aS)-9a (127 mg, 713 μmol, 1 equiv) in anhyd toluene (3.6 mL) under N₂ atmosphere at –100 °C (Method B): To a solution of (3aR,4R,5aS)-9a (127 mg, 713 μmol, 1 equiv) and 1-[(3aR,8S,5aR,6S,9aR,9bS)-5-Hydroxy-2,3,3a,5a,6,9,9a,9b-octahydro-1H-6,9-methanocyclopenta[a]naphthalene-4-yl]ethanone 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), 3.94 (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-16), 46.5 (C-15), 46.7 (C-7), 47.0 (C-12), 51.4 (C-16), 112.3 (C-3), 134.3 (C-13), 136.3 (C-14), 139.3, 196.0 (C-4, C-10).

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

**Keto-18**

FT-IR: 3057 (w), 2960 (w), 2869 (w), 1716 (s), 1687 (s), 1570 (w), 1453 (s), 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, 3 × 7-H, 1 × 9-H, 8-H), 1.86 (dd, J = 12.4, 12.4, 7.1 Hz, 1 H, 1-H), 1.98 (dd, J = 12.4, 12.4, 10.8, 6.2 Hz, 1 H, 1-H), 2.11 (s, 3 H, 11-H), 2.27 (dd, 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 (ddd, 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-15), 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.


**DFT Calculations**

The calculations were performed at the B3LYP level of theory using the AUG-cc-pVTZ basis set as implemented in the Gaussian 16 program package. The X-ray crystal structure of enone 9a (Figure 2) was used as a starting point to calculate optimized minimum energy structures of neutral (4R)-keto-18 and (4S)-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 (ΔGº) 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.

**References**

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