Asymmetric Organocatalysis Revisited: Taming Hydrindanes with Jørgensen–Hayashi Catalyst

Yannick Stöckl
Wolfgang Frey
Johannes Lang
Birgit Claasen
Angelika Baro
Sabine Laschat*

Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
sabine.laschat@oc.uni-stuttgart.de

Published as part of the 50 Years SYNTHESIS – Golden Anniversary Issue

Received: 12.11.2018
Accepted: 15.11.2018
Published online: 14.12.2018

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 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 annihilations,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 characterization of liquid crystalline merocyanines (2016) and in his M.Sc. thesis, he worked on the formation of bi- and polycyclic natural product scaffolds (2018). In 2016, he joined the research group of Louis C. Morril, Cardiff University, for 3 months (DAAD-RISE fellowship). The aim of his Ph.D. project is the synthesis of polycyclic natural products.

**Wolfgang Frey** received his Ph.D. in 1991 in Organic Structure Chemistry at the University of Stuttgart, Germany. Since 1996 he is responsible for the structure determination of single crystal X-ray diffraction data at the Institute of Organic Chemistry.

**Johannes Lang** is an independent researcher within the Institute of Organic Chemistry at the University of Stuttgart, Germany. He obtained his Ph.D. at the University of Kaiserlautern elucidating geometrical and electronic structures of gaseous ions. His current research interests include spectroscopic and theoretical studies of organic molecules and coordination compounds.

**Birgit Claasen** studied chemistry in Hamburg and obtained her Ph.D. in the research group of Prof. Meyer, where she studied biomolecular interactions by NMR spectroscopy. In her post-doctoral fellowship in the group of Prof. Giralt at the Barcelona Science Park, Spain, she applied NMR spectroscopy to large proteins to study protein dynamics. In 2009, she joined the analytical department of organic chemistry in Stuttgart, where she is focused on structure elucidation by spectroscopic techniques.

**Angelika Baro** studied chemistry at the Georg-August-Universität Göttingen (Germany), where she received her Ph.D. in Clinical Biochemistry (1987). Since 1991 at the Institute of Organic Chemistry, University of Stuttgart, she is responsible for scientific documentation and publication.

**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 at the University of Münster, she was appointed as Associate Professor at the TU Braunschweig (1997–2002). Since 2002 she is Full Professor of Organic Chemistry at the University of Stuttgart. She was speaker of the Cooperative Research Centre SFB 706 ‘Selective catalytic oxidations with C–H bonds with molecular 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. Their archetypal organocatalytic synthesis relies on the proline-catalyzed aldol condensation towards Hajos–Parrish diketone (Scheme 1), which was further functionalized in multiple ways to the desired hyridnane target compounds. The unsubstituted member of the hexahydroindenones family was obtained via sequential intramolecular Michael addition/aldol condensation of enone (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. On the other hand, simple 1,3-carbonyl compounds such as acetylacetone and ethyl acetoacetate were only rarely employed in organocatalytic Michael additions. Thus, we aimed at a robust and reliable route towards hyridnanes 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 Michael addition of acetylacetone (12a) to 1-cyclopentene-1-carbaldehyde (11) 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).

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 conditions 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)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</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>58&lt;sup&gt;b&lt;/sup&gt;</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>toluene&lt;sup&gt;c&lt;/sup&gt;</td>
<td>52</td>
<td>92</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC on a chiral stationary phase.
<sup>b</sup> Determined by 1H NMR spectroscopy with 1,3,5-trimethylbenzene (0.53 equiv) as an internal standard.
<sup>c</sup> 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, cyclopentane-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 enolate 15 in 27% yield (E/Z >95:5, d.r. 55:45).

Taking the preferred formation of the trans-disubstituted cyclopentanecarbaldehyde (1R,2R)-10a with excellent enantioselectivity (e.e. 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-dicarboxyl 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 (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

### 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>1a</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>6e</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>7f</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>8g</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>

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.

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**Scheme 2** Sequential Michael addition/Wittig olefination

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**Figure 1** Molecular structures of the key compounds.

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**Figure 2** Spectroscopic data for the key compounds.

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**Figure 3** Synthetic pathway for the key compounds.

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**Figure 4** Optical rotation data for the key compounds.
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-5H-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 acetoacetone 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-

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH b</td>
<td>MeOH</td>
<td>0 → r.t.</td>
<td>2</td>
<td>9a</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1) KOH</td>
<td>MeOH</td>
<td>0 → r.t.</td>
<td>2</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>2) MeCl2</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>17</td>
<td>9b</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>TsOH (0.1)</td>
<td>toluene</td>
<td>reflux</td>
<td>3</td>
<td>9a</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>TsOH (0.05)</td>
<td>toluene</td>
<td>r.t.</td>
<td>24</td>
<td>9a</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>TsOH (0.05)</td>
<td>toluene</td>
<td>50</td>
<td>36</td>
<td>9a</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>TsOH (0.05)</td>
<td>THF</td>
<td>50</td>
<td>24</td>
<td>9a</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>TsOH (0.05)</td>
<td>MeOH</td>
<td>50</td>
<td>16</td>
<td>9a</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>PPTS (0.05)</td>
<td>toluene</td>
<td>refluxb</td>
<td>7</td>
<td>9a</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>PPTS (1.0)</td>
<td>toluene</td>
<td>refluxb</td>
<td>3</td>
<td>9a</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>(–)-CSA (1.0)</td>
<td>toluene</td>
<td>refluxb</td>
<td>1</td>
<td>9a</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td>(–)-CSA (1.0)</td>
<td>toluene</td>
<td>50</td>
<td>72</td>
<td>9a</td>
<td>73, d.r. 94:6</td>
</tr>
<tr>
<td>12</td>
<td>(+)-CSA (1.0)</td>
<td>toluene</td>
<td>50</td>
<td>65</td>
<td>9a</td>
<td>71, d.r. 93:7</td>
</tr>
<tr>
<td>13</td>
<td>(–)-CSA (1.0)</td>
<td>toluene</td>
<td>50</td>
<td>96</td>
<td>9b</td>
<td>19</td>
</tr>
<tr>
<td>14</td>
<td>piperidine/CSA</td>
<td>toluene</td>
<td>50/reflux</td>
<td>24</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td>9b</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1) DBU</td>
<td>MeOH</td>
<td>0 → r.t.</td>
<td>2</td>
<td>9b</td>
<td>44, d.r. 91:9</td>
</tr>
</tbody>
</table>

* In the presence of NEt3, DMAP.
* Dean–Stark conditions.
* c = 0.03 M.
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 CH2Cl2, 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 acentric space group P2(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 (3aR,4R,7aS)-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

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 acetylacetone-derived enones 9a combined with the crystal structure of (3aR,4R,7aS)-9a, we assigned the major and the minor diastereomer of the non-racemic acetoacetate-derived enone as (3aR,4R,7aS)-9b and (3aR,4S,7aS)-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 Et3AlCl in CH2Cl2 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 NEt3 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 derivatives 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. Furthermore, upon prolonged storage of tetracycle 18 in CDCl3 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 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-5H-inden-5-ones 9 in moderate to good yields with high diastereoselectivities (up to 94:6). Hexahydropyridonene 9a was submitted to a [4 + 2] cycloaddition with cyclopentadiene (17) yielding the tetracyclic tautomers (4R)-keto-18/enol-18. Surpris-ingly, 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-cyclohexanediol]. 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 hexahydroindenediones without the use of protecting groups, which paves the way for their application in syntheses of complex target molecules.

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 Diamond. 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, μ-PChirasil 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.

Figure 3 Optimized minimum structures of (4R)-keto-18 and (4S)-keto-18 and their associated relative stabilities. ΔG° is the electronic energy corrected for the free energy at 300 K in the ground state. The DFT calculations were performed at the B3LYP/AUG-cc-pVTZ level of theory. Light gray: H; dark gray: C; red: O.

Figure 4 Numbering system for NMR assignment

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

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% mol, 3%); dr. = 50:50 (H 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. 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$_{\text{shat}}$ or by flash chromatography on SiO$_2$ with hexanes/EtOAc [gradient 5:1 → 2:1; R$_f$ = 0.16 (hexanes/EtOAc 5:1)] to give 10a (40%); >99% purity by GC$_{\text{shat}}$; [a]$_{D}^{20}$ = -129.1 (c = 0.77, CHCl$_3$, ee = 98%).

**FT-IR:** 2956 (w), 2871 (w), 1710 (s), 1651 (w), 1448 (w), 1368 (w), 914 (w), 904 (w), 862 (w), 730 (s), 647 (w), 540 cm$^{-1}$ (w).

**MS (ESI):** $m/z$ = 235 [M + K$^+$/2], 219 [M + Na$^+$].

**HRMS (ESI):** m/z [M + Na$^+$] calcd for C$_{13}$H$_{20}O$_{4}Na$: 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 (207.4 mg, 15.9 mmol, 1.02 equiv) in toluene (40 mL) was added 11 (23.7 mg, 7.21 mmol, 0.5 equiv) and the mixture was stirred for 22 h at r.t. Then it was washed with H$_2$O (10 mL), dried (MgSO$_4$), and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO$_2$ with hexanes/EtOAc (gradient 15:1 → 10:1) to give 12b as a colorless oil; yield: 287 mg (968 mg, 33%); d.r. 47:40:8:5 by GC$_{\text{shat}}$.

**FT-IR:** 237 (mg, 29.1 mmol, 1 equiv), 11a (104.4 mg, 1.48 mmol, 0.5 equiv), and 11 (111.6 mg, 0.87:13, 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 NEt$_3$ (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 H$_2$O (10 mL), dried (MgSO$_4$), and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO$_2$ with hexanes/EtOAc (gradient 15:1 → 10:1) to give rac-15 as a yellow oil; yield: 287 mg (968 mg, 33%); d.r. 47:40:8:5 by GC$_{\text{shat}}$.

**Method B:** A solution of 11 (111.6 mg, 0.87:12, 500 mg, 4.42 mmol, 1 equiv), 12b (757 mg, 4.42 mmol, 1 equiv), and 13c (28.8 mg, 88.4 mmol, 0.20 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 NEt$_3$ (0.7 mL, 671 mg, 6.63 mmol, 1.5 equiv), the reaction mixture was stirred for 8 h at r.t. Then H$_2$O (20 mL) was added and the mixture extracted with CHCl$_3$ (3 × 20 mL). The combined organic layers were dried (MgSO$_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO$_2$ 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 (118 mg, 27%); D$_{12}$D$_2$ = 55:40 by GC$_{\text{shat}}$; d.r. 55:45.

**FT-IR:** 2956 (w), 2871 (w), 1710 (s), 1448 (w), 1368 (w), 914 (w), 904 (w), 862 (w), 730 (s), 647 (w), 540 cm$^{-1}$ (w).

**HRMS (ESI):** m/z [M + Na$^+$] calcd for C$_{13}$H$_{20}O$_{4}Na$: 219.0992; found: 219.0973.

**Ethyl (2E)-2-[(15,2R)-2-[1-(Ethyloxycarbonyl)-2-oxopropyl]cyclopentyl]acetate (11a)**

**Method A:** A solution of 12b (379 mg, 2.91 mmol, 1 equiv), 13a (104 mg, 1.48 mmol, 0.5 equiv), and 11 (111.6 mg, 0.87:13, 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 NEt$_3$ (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 H$_2$O (10 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 → 10:1) to give rac-15 as a yellow oil; yield: 287 mg (968 mg, 33%); d.r. 47:40:8:5 by GC$_{\text{shat}}$.

**Method B:** A solution of 11 (111.6 mg, 0.87:12, 500 mg, 4.42 mmol, 1 equiv), 12b (757 mg, 4.42 mmol, 1 equiv), and 13c (28.8 mg, 88.4 mmol, 0.20 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 NEt$_3$ (0.7 mL, 671 mg, 6.63 mmol, 1.5 equiv), the reaction mixture was stirred for 8 h at r.t. Then H$_2$O (20 mL) was added and the mixture extracted with CHCl$_3$ (3 × 20 mL). The combined organic layers were dried (MgSO$_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO$_2$ 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 (118 mg, 27%); D$_{12}$D$_2$ = 55:40 by GC$_{\text{shat}}$; d.r. 55:45.

**FT-IR:** 2956 (w), 2871 (w), 1710 (s), 1448 (w), 1368 (w), 1206 (w), 1227 (w), 1194 (w), 1146 (s), 1096 (s), 1033 (s), 984 (w), 914 (w), 862 (w), 810 (w), 730 (s), 647 (w), 540 cm$^{-1}$ (w).

**HRMS (ESI):** m/z [M + Na$^+$] calcd for C$_{13}$H$_{20}O$_{4}Na$: 219.0992; found: 219.0973.
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 r.t. After the addition of H₂O (20 mL), the mixture was washed with sat. aq NaHCO₃ (20 mL), dried (MgSO₄), and the solvent removed under reduced pressure. Sat. aq NH₄Cl was added to the residue (un-dilution of H₂O (20 mL), the mixture was extracted with CH₂Cl₂ (13 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), 2958 (w), 2872 (w), 1736 (s), 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, 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, 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, 13.5 Hz, 1 H, 1 × 3-H), 2.68 (dd, J = 16.7, 3.0 Hz, 1 H, 1 × 3-H), 5.91 (dd, 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). MS (EI): m/z (%) = 136 (100) [M⁺], 81 (75), 68 (80), 55 (45).


**Synthesis**

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 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 (3αR,4S,7aS)-10b (3αR,4S,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 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.

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

**FT-IR:** 3025 (w), 2958 (w), 2872 (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, CDCl₃):** δ = 1.29 (t, J = 7.1 Hz, 3 H, OCH₂CH₃), 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, 4.4 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 Hz, 1.8 Hz, 1 H, 1-H), 3.18 (d, J = 13.1 Hz, 1 H, 3-H), 4.24 (m, 2 H, OCH₂CH₃), 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).

**13C NMR (176 MHz, CDCl₃):** δ = 33.2 (C-12), 20.8 (C-8), 27.3 (C-7), 27.6 (C-9), 43.0 (C-11), 45.8 (C-2), 60.0 (C-11), 60.2 (C-2), 128.5 (C-6), 151.5 (C-5), 168.7 (C-10), 194.1 (C-4).

**MS (ESI):** m/z = 231 [M + Na⁺], 209 [M + H⁺], 181, 163, 135.

**HRMS (ESI):** m/z [M⁺ + H⁺] calcd for C₁₄H₁₇O₃: 209.1172; found: 209.1170.

**Ethyl (3aR,4S,7aS)-5-Oxo-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylate (9b)**
HRMS (ESI): m/z [M + H+] calcd for C$_{11}$H$_{17}$O$_2$: 209.1172; found: 209.1192.

(3aR,4R,5aR,6S,9aS,9bR)-4-Acetyl-1,2,3a,4,5a,6,9,9a,9b-decahydro-SH-6,9-methanocyclopenta[a]naphthalen-5-one (keto-18) and 1-[3aR,4R,8aR,9aS,9bR]-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)D-4-acetyl-1,2,3a,4,5a,6,9,9a,9b-decahydro-SH-6,9-methanocyclopenta[a]naphthalen-5-one (keto-18) and 1-[3aR,4R,8aR,9aS,9bR]-5-Hydroxy-2,3,3a,5a,6,9,9a,9b-octahydro-1H-6,9-methanocyclopenta[a]naphthalen-4-yl]ethanone (enol-18)

1H NMR (700 MHz, CDCl$_3$): 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 × 9-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 (ddd, 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, CDCl$_3$): 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), 45.6 (C-15), 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).

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) served 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 (ΔG$_{0}$) were extracted at 300 K.

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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(47) (a) CDCD 1878438 contains supplementary crystallographic data for the structure (3aR,4R,7aS)-Sa. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures. (b) Formula C31H28O5; size 0.570 × 0.104 × 0.096 mm; crystal system: orthorhombic; space group: P2(1)2(1)2(1); unit cell dimensions: a = 5.3640(4) Å, b = 8.0159(6) Å, c = 22.3538(14) Å; α = β = γ = 90°.


