Novel asymmetric copper-catalysed transformations
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Chapter 4
Catalytic Asymmetric Conjugate Addition/Oxidative Dearomatization Towards Multifunctional Spiroyclic Compounds

In this chapter a sequential asymmetric conjugate addition/oxidative cyclization protocol is reported. This methodology allows for the synthesis of highly functionalized benzofused spirocyclic compounds and a high degree of molecular complexity is achieved in a one-pot transformation.*

* Parts of this chapter have been published: Rudolf, A.; Bos, P. H.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. Angew. Chem. Int. Ed. 2011, 50, 5834; Angew. Chem. 2011, 123, 5956.
4.1 Introduction

The development of highly efficient methods that provide access to chiral small molecules that display a high degree of skeletal complexity, diversity, and functionality is a substantial challenge in organic chemistry.\textsuperscript{1, 2} A powerful approach towards the introduction of multiple stereocenters in a one-pot procedure is the use of catalytic asymmetric tandem transformations. This strategy is particularly attractive as a high degree of structural and stereochemical complexity can be achieved in a sequential process using small amounts of chiral catalyst.\textsuperscript{3-14}

4.1.1 Asymmetric copper-catalyzed conjugate addition of Grignard reagents

The asymmetric copper-catalyzed conjugate addition of Grignard reagents to $\alpha,\beta$-unsaturated carbonyl compounds has established itself as a reliable and efficient method for the preparation of chiral building blocks that contain a new carbon-carbon bond and a single stereogenic center generally giving excellent enantiomeric excess and isolated yields (see Chapter 1 of this thesis).\textsuperscript{5, 15, 16}

4.1.2 Sequential transformations based on copper-catalyzed asymmetric conjugate addition of organometallic reagents

As already described, both in the introduction of this chapter as well as in Chapter 1, the use of asymmetric tandem transformations is a very powerful approach in organic synthesis.\textsuperscript{3} Tandem transformations based on the asymmetric conjugate addition of organometallic reagents generally take advantage of the high enantioselectivities obtained in the conjugate addition reaction. The enolate formed in the asymmetric conjugate addition lends itself towards the development of sequential processes, in which trapping of the enolate leads to the formation of two or more stereocenters in a one-pot procedure (see Scheme 1).

Scheme 1  Tandem transformation triggered by asymmetric conjugate addition. E = electrophile; R = alkyl/aryl group; M = metal; L = chiral ligand; * = stereogenic center.
One of the first examples of such an asymmetric tandem transformation was developed in 1997 by our group. After an asymmetric copper-catalyzed conjugate addition of organozinc reagents to cyclohexenone 4, the resulting zinc enolate was quenched with an aldehyde affording trans-2,3-disubstituted cyclohexanones with excellent enantiomeric excess (>90%) in all cases (Scheme 2).

Another impressive example demonstrating the versatility of the tandem conjugate addition/electrophilic trapping reaction was the total synthesis of prostaglandin E1 methyl ester (11) reported in 2001. Asymmetric copper-catalyzed conjugate addition of dialkyl zinc reagent 9 to α,β-unsaturated cyclopentenone 7, in the presence of aldehyde 8, led to the formation of aldol product 10 with high enantioselectivity and three contiguous stereocenters (Scheme 3). Using this tandem approach prostaglandin E1 methyl ester 11 could be synthesized in seven steps with an overall yield of 7% and 94% enantiomeric excess.

Scheme 2  Copper-catalyzed asymmetric conjugate addition/aldol reaction.

Scheme 3  Total synthesis of prostaglandin E1 methyl ester 11.
An efficient method for a tandem transformation based on the copper-catalyzed asymmetric conjugate addition of Grignard reagents to $\alpha,\beta$-unsaturated thioesters was reported in 2006. Efficient acyclic stereocontrol was achieved in a tandem 1,4-addition/aldol reaction. This tandem process afforded a range of products bearing three contiguous stereocenters with excellent control of relative and absolute stereochemistry. The utility of this protocol was demonstrated by the concise total synthesis of (-)-phaseolinic acid 14 (Scheme 4).

![Scheme 4](image)

4.1.3 Oxidative dearomatization

To develop new sequential transformations compatible with the copper-catalyzed conjugate addition of Grignard reagents, we explored the synthetic utility of oxidative dearomatization processes of phenol and naphthol compounds. Oxidative dearomatization is an important pathway in the biosynthesis of many natural products. As a consequence, oxidative dearomatization is a method regularly used for the total synthesis of these compounds. During the oxidative dearomatization event, the reactivity of the phenol moiety changes from nucleophilic to electrophilic. Subsequent nucleophilic addition can afford chiral products from substrates that once featured planar structures.

The utility of oxidative dearomatization in the synthesis of complex organic molecules was illustrated nicely by Sorensen et al. in the total synthesis of the potent immunosuppressant FR901483 (17) (Scheme 5).

![Scheme 5](image)
Recently, the research groups of Gaunt and Jørgensen employed an oxidative dearomatization strategy of phenols in conjunction with enamine catalysis for the synthesis of chiral cyclohexenone derivatives. The process of Gaunt et al. involves the oxidative dearomatization of substituted phenols by oxidation with the hypervalent iodine reagent phenyliodine(III) diacetate (PIDA) followed by a catalytic asymmetric intramolecular conjugate addition of an \textit{in situ} formed enamine. Employing bulky secondary amine \((R)-19\) as the chiral catalyst led to the formation of a range of highly functionalized molecules with excellent selectivity (up to >20:1 dr, up to 99% ee) (Scheme 6).\(^{31}\)

The strategy of Jørgensen et al. utilizes a combination of electrochemistry and asymmetric organocatalysis in order to synthesize optically active dihydrobenzofurans (Scheme 7).\(^{32}\) Anodic oxidation of the phenol moiety led to the formation of an electrophilic intermediate \((22)\) which, combined with the catalytic formation of an electron-rich enamine, generated \textit{in situ}, afforded \(\alpha\)-arylated aldehydes, \textit{i.e.} hemiacetal 24. This method represents a formal \textit{meta}-addition to anilines.

\begin{equation}
\text{Scheme 6} \quad \text{Oxidative dearomatization/intramolecular organocatalytic Michael addition}\,.\(^{31}\)
\end{equation}

\begin{equation}
\text{Scheme 7} \quad \text{Regio- and stereoselective anodic oxidation/organocatalytic } \alpha\text{-arylation of aldehydes}\,.\(^{32}\)
\end{equation}
4.1.4 Intra- and intermolecular oxidative enolate heterocoupling

Although oxidative dimerization of enolates has been known since 1935, the oxidative coupling of two different types of coupling partners remained largely unexplored. Recently, the group of Baran made enormous progress in this area of research by developing novel methods for the intra- as well as intermolecular heterocoupling of two different types of coupling partners (*vide infra*).

Initially, Baran *et al.* reported a method for the direct coupling of indole and pyrrole derived heterocycles to various carbonyl compounds through enolate heterocoupling. This methodology was applied successfully in the total synthesis of a number of natural products. One representative example is the protecting-group-free total synthesis of three different indole alkaloids (welwitindolinone A and fischerindoles I and G) in 7-9 steps starting from carvone oxide (Scheme 8). Compound 25 was synthesized in two steps from (R)-carvone oxide. Oxidative enolate coupling of the Li-enolate of 25 and indole using copper(II) 2-ethylhexanoate as the oxidant led to the formation of 26 in 55% yield which contains all the necessary carbon atoms (except the isocyanide) to complete the synthesis of the three natural products.

![Scheme 8](image)

Scheme 8  Total synthesis of (-)-fischerindole G.  

Shortly after the development of the heterocoupling of enolates with nitrogen containing heterocycles, Baran *et al.* reported methodology for the intra- and intermolecular coupling of two different types of carbonyl species. In the intermolecular oxidative enolate coupling protocol, oxazolidinones and oxindoles could be used in the cross-coupling with ketones, esters and lactones using either iron(III) acetylacetonate or copper(II) 2-ethylhexanoate in moderate to good yields (51-91%) (Scheme 9). A major disadvantage is that the diastereoselectivity is modest in all cases. This could partly be overcome in some cases by thermodynamic equilibration to one of the diastereomers. The utility of this method was demonstrated by the enantioselective total synthesis of (-)-bursehermin in three synthetic steps with only one purification step (Scheme 10).
4.2 Goal

The aim of this research project was to develop a sequential asymmetric conjugate addition/oxidative cyclization protocol. Despite existing strategies for the synthesis of chiral molecules through oxidative dearomatization/nucleophilic addition,\textsuperscript{28, 31, 32, 41-47} this would be the first method to use the enolate intermediate of the catalytic asymmetric conjugate addition of Grignard reagents. This methodology would allow for the synthesis of highly functionalized benzofused spirocyclic compounds bearing multiple stereogenic centers. Using this methodology a high degree of structural and stereochemical complexity would be achieved in a one-pot transformation using small amounts of chiral catalyst.
4.3 Results and Discussion

4.3.1 Strategy
To develop new sequential transformations compatible with the copper-catalyzed conjugate addition of Grignard reagents, we explored the synthetic utility of oxidative dearomatization processes of naphthol and phenol compounds. Our proposed reaction scheme comprises a substrate bearing a phenol or naphthol group (34) bearing an ortho-tethered α,β-unsaturated carbonyl group (Scheme 11).

Asymmetric copper-catalyzed conjugate addition to afford enolate intermediate 35 and subsequent intramolecular oxidative coupling, involving a naphtholate/phenolate and an enolate, would yield a chiral spirocyclic five- or six-membered ring compound. This one-pot transformation would provide, besides the spirocyclic framework, two new carbon-carbon bonds and three contiguous stereocenters— including one quaternary stereocenter— in a single transformation (Scheme 12). The products are architecturally complex, possessing optically active cyclohexenone and spirocyclic moieties, both of which have been used as intermediates in the synthesis of natural products and pharmaceuticals (see Scheme 11).48-52
Substituents R² and R³ are easily varied, depending on the substrate or the Grignard reagent employed in the reaction. Spirocyclic structure 36 also contains a number of functional groups, including an α,β-unsaturated ketone and one carbonyl unit, which are amenable to further transformations such as [4+2] cycloadditions as well as 1,4- and 1,2-additions.

4.3.2 Synthesis of naphthol-based substrates

4.3.2.1 Synthesis of 6-substituted 2-naphthol-based substrates 43a-c

The 2-naphthol-based substrates were synthesized in a three step procedure (Scheme 13). Friedel-Crafts alkylation of 6-substituted 2-naphthols 40a-c with acrylic acid using amberlyst-15 as a catalyst led to the formation of 41a-c in good to moderate yields (50-82%). The resulting lactones were reduced to the corresponding hemiacetals 42a-c in 41-94% yield using diisobutylaluminium hydride in dichloromethane at -78 °C. After a Wittig reaction the 2-naphthol-based α,β-unsaturated esters 43a-c were obtained in good to excellent yield (80-100%) with full selectivity for the E-isomer.
4.3.2.2 Synthesis of 2-naphthol-based substrate 51

In order to obtain a substrate that after the tandem conjugate addition/oxidative cyclization would afford a six-membered spirocyclic ring a slightly different synthetic route was necessary (Scheme 14). Allylation of 1-naphthol with allylbromide under basic conditions provided 44, which was converted into 45 via a Claisen rearrangement in good yield (85%).

![Scheme 14 Synthesis of 2-naphthol-based substrate 51.](image)

After protection of the resulting free alcohol using TBDMSCI followed by cross-metathesis with ethyl acrylate, catalyzed by Hoveyda-Grubbs 2nd generation catalyst (HG-2), compound 47 was isolated in 64% yield over two steps. The double bond of this α,β-unsaturated ester was reduced selectively using palladium on charcoal and the resulting ester 48 was reduced to aldehyde 49 with Dibal-H in 66% yield. A Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate provided 50, which was subsequently deprotected to provide 2-naphthol-based substrate 51.

4.3.2.3 Synthesis of 1-naphthol substrate 55

The substrate based upon 1-naphthol was synthesized in a similar fashion as substrate 43 described in paragraph 4.3.2.1 (vide supra). Friedel-Crafts alkylation of 1-naphthol with acrylic acid followed by Dibal-H reduction afforded hemiacetal 54. Subsequent Wittig reaction led to the formation of the desired substrate 55 in 80% yield (Scheme 15).
4.3.2.4 Synthesis of 1-naphthol-based substrate 62

In order to explore the synthesis of different spirocyclic architectures a 1-naphthol derivative, with the pendant arm in the para-position, was synthesized in six steps (Scheme 16). Protection of 4-hydroxy-1-naphthaldehyde 56 using TBDMSCI and imidazole gave 57 in 87% yield. Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate and n-BuLi in THF provided 58. Selective reduction of the double bond with palladium on charcoal followed by Dibal-H reduction of the ester afforded aldehyde 60. After another HWE reaction product 61 was isolated in 58% yield. Subsequent deprotection of the TBDMS-group (97% yield) completed the synthesis of substrate 62.

4.3.3 Optimization of the enantioselective Cu-catalyzed conjugate addition

Initial investigations focused on the optimization of the asymmetric copper-catalyzed conjugate addition of EtMgBr to 2-naphthol-based substrate 43a (Table 1). A catalytic system comprising CuBr·Me2S (5 mol%) and JosiPhos (6 mol%) in t-BuOMe at -78 °C did not afford the desired conjugate addition product (Table 1, entry 1). Changing the solvent to dichloromethane led to an increase in the conversion and good enantiomeric excess (Table 1, entry 2). Switching from a ferrocenyl-type ligand to a Binap-based system with Cul led to full conversion at -40 °C without influencing the enantiomeric excess dramatically. (Table 1, entry 3). Upon further screening of the Binap ligand family and
copper/ligand ratio (Table 1, entries 3-7), the optimized conditions were found and the desired product could be isolated in 84% yield with 88% ee using CuI (5 mol%), (R)-L4 (7.5 mol%) at -40 °C (Table 1, entry 7).

Table 1  Optimization of the copper-catalyzed asymmetric conjugate addition of EtMgBr to 43a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(I) 5 mol%</th>
<th>Ligand</th>
<th>Solvent</th>
<th>ee † (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr·Me₂S</td>
<td>(R,S,S)-L₂</td>
<td>t-BuOMe</td>
<td>nd*</td>
</tr>
<tr>
<td>2</td>
<td>CuBr·Me₂S</td>
<td>(R,S,S)-L₂</td>
<td>CH₂Cl₂</td>
<td>84 ‡</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>(R)-L₃</td>
<td>CH₂Cl₂</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>CuI</td>
<td>(R)-L₄</td>
<td>CH₂Cl₂</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>CuI</td>
<td>(R)-L₅</td>
<td>CH₂Cl₂</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>CuI</td>
<td>(R)-L₃</td>
<td>CH₂Cl₂</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>CuI</td>
<td>(R)-L₄</td>
<td>CH₂Cl₂</td>
<td>88 †</td>
</tr>
</tbody>
</table>

* Conditions: 43a (1.0 eq. 0.25 mmol in 0.8 mL of CH₂Cl₂) was added over 1 h to EtMgBr (2.5 eq.), Cu(I) (5 mol%) and L₂-5 (6-7.5 mol%) in t-BuOMe or CH₂Cl₂ and the reaction mixture was stirred for 4-16 h at the indicated temperature. ‡ Enantiomeric excess determined by chiral HPLC. * Incomplete conversion. † 84% isolated yield

4.3.4 One-pot conjugate addition/oxidative cyclization

After optimization of the copper-catalyzed asymmetric conjugate addition of Grignard reagents the one-pot conjugate addition/oxidative cyclization protocol was studied. Under racemic reaction conditions (using rac-Binap), the conjugate addition of EtMgBr to 43a was followed by the addition of copper(II) 2-ethylhexanoate as the oxidant, in the same pot (Scheme 17).
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Scheme 17 Initial result for the sequential conjugate addition/oxidative cyclization reaction.

The desired spirocyclic product 64 was obtained in 59% yield as a single diastereomer. Under the asymmetric reaction conditions employing (R)-Binap-L4 as the chiral ligand, the same transformation afforded product 64 with high yield (69%) and enantiomeric excess (88%). Further screening of oxidizing reagents (other sources of Cu(II), Fe(III), phenyliodine(III) diacetate, and phenyliodine(III) bis(trifluoroacetate)) did not improve on these results. The enantiomeric excess of 64 matches exactly that of 63 obtained under the same reaction conditions for the conjugate addition (see Table 1). The high diastereoselectivity (>20:1 dr) achieved in the cyclization to 64 suggests that once the first stereocenter is established during the conjugate addition, it controls the formation of the two subsequent stereocenters.

Next, we focused our efforts on the scope of the reaction (Table 2). Linear alkyl Grignard reagents provided the desired products in good to excellent yields (Table 2, entries 1-3) and good diastereoselectivities and enantioselectivities (Table 2, entries 1-3, 5, and 6). The addition of i-PrMgBr proceeded in good yield, but with lower enantioselectivity, which is common for this particular Grignard reagent in the copper-catalyzed asymmetric conjugate addition reaction (Table 2, entry 4).15 Electron-withdrawing (Table 2, entry 8) or electron-donating (Table 2, entry 9) groups in the 6-position of the naphthol core were both compatible under the reaction conditions and provided the cyclized products in good yields and enantioselectivities. The use of a Grignard reagent bearing a terminal olefin afforded the product in a lower yield as a result of the instability of the terminal olefin towards the oxidative conditions (Table 2, entry 5). Grignard reagents MeMgBr (Table 2, entry 6) and PhMgBr (Table 2, entry 7) gave low yields due to the reactivity of these particular Grignard reagents.

It should be noted that the conjugate addition of MeMgBr to α,β-unsaturated esters requires specific reaction conditions to proceed in high yield and ee.25 In the case of PhMgBr (Table 2, entry 7) a by-product, originating from 1,2-addition of PhMgBr to the ethyl ester moiety to afford the aryl ketone, accounts for an additional 16% of the reaction mixture. Furthermore, low or no enantioselectivity with PhMgBr in copper-catalyzed conjugate addition reactions is a common problem.15, 16 Substrate 51 gave an excellent
enantiomeric excess, but the resulting product 73 was isolated in only 13% yield (Table 2, entry 10). The high enantioselectivity can be rationalized by the position of the alcohol moiety with respect to the \( \alpha, \beta \)-unsaturated ester. The further the alcohol is positioned away from the \( \alpha, \beta \)-unsaturated ester, the higher the enantiomeric excess. The same behavior was also seen with phenol-based substrates (\textit{vide infra}).

### Table 2 Reaction scope of substituted 2-naphthols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>( R^2 )</th>
<th>Product (dr)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43a</td>
<td>ethyl</td>
<td>64 (&gt;20:1)</td>
<td>69</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>43a</td>
<td>hexyl</td>
<td>65 (&gt;20:1)</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>43a</td>
<td>( \text{CH}_2\text{CH}_2\text{Ph} )</td>
<td>66 (&gt;20:1)</td>
<td>51</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>43a</td>
<td>\textit{i}-propyl</td>
<td>67 (&gt;20:1)</td>
<td>70</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>43a</td>
<td>but-3-enyl</td>
<td>68 (&gt;20:1)</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>43a</td>
<td>methyl</td>
<td>69 (&gt;20:1)</td>
<td>32</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>43a</td>
<td>phenyl</td>
<td>70 (&gt;20:1)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>43b</td>
<td>ethyl</td>
<td>71 (&gt;20:1)</td>
<td>63</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>43c</td>
<td>ethyl</td>
<td>72 (&gt;20:1)</td>
<td>63</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>ethyl</td>
<td>73 (&gt;20:1)</td>
<td>13</td>
<td>94</td>
</tr>
</tbody>
</table>

\( a \) Reaction conditions: 43a-c or 51 (0.25 mmol) in CH\(_2\)Cl\(_2\) (0.8 mL) was added over 1 h to a solution of CuI (5 mol%), (\( R \))-L4 (7.5 mol%), and Grignard reagent (2.5 eq) in CH\(_2\)Cl\(_2\) (0.4 mL) at -40 °C. The reaction mixture was stirred at -40 °C for 4-12 h, and solid copper(II) 2-ethylhexanoate (2.5 eq) was added to the reaction mixture followed by warming to rt. \( b \) Determined by \(^1\)H-NMR analysis of the crude reaction mixture. \( c \) Isolated yield. \( d \) Determined by chiral HPLC analysis (see Experimental Section).

To explore the synthesis of different spirocyclic architectures using this method, 1-naphthol based substrate 55, with the pendant \( \alpha, \beta \)-unsaturated ester in the 2-position on the naphthol core, and 1-naphthol-based substrate 62, with the pendant \( \alpha, \beta \)-unsaturated ester in the 4-
position on the naphthol core were employed. In the case of substrate 55, the desired product 74 was obtained in 41% yield, with a diastereoselectivity of 8:1 and good enantiomeric excess of the major isomer (89% ee) (Scheme 18). Substrate 62 only afforded trace amounts of the desired product 75 despite numerous attempts at its isolation. However, conjugate addition of EtMgBr under the optimized conditions (vide supra) afforded product 76 with excellent enantiomeric excess (91% ee) (Scheme 19).

Scheme 18 Conjugate addition/oxidative cyclization of 1-naphthol-based substrate 55.

Scheme 19 Attempted conjugate addition/oxidative cyclization of substrate 62
4.3.5 **Determination of the absolute configuration of the spirocyclic product**

To determine the relative and absolute configuration of the spirocyclic products the bromo-substituted ethyl ester 71 was converted into the corresponding carboxylic acid 77 by treatment with sodium hydroxide in ethanol. Slow diffusion of hexanes into a solution of 77 in ethyl acetate afforded crystals that were suitable for X-ray diffraction, and using the Patterson method the absolute configuration of 77 could be established (Figure 1).

![Figure 1](image)

**Figure 1** PLUTO drawing of 77. The unit cell consists out of two molecules of 77 linked by intermolecular hydrogen bonds of the carboxyl groups. Only one half of the dimeric species is shown.

The X-ray crystal structure of 77 verifies the *trans* configuration between the ethyl and carboxylic acid substituents on the five-membered ring. The vicinal proton coupling constant measured for the *trans* substituents on the cyclopentane ring of 77 is $J = 9.4$ Hz. The analogous coupling constant for 71 (the ester precursor of 77) is $J = 9.8$ Hz. Similarly, the vicinal coupling constant of these two protons for all the spirocyclic products (64-73) have values between $J = 9.8$-10.8 Hz. Owing to the similarity of the $^1$H-NMR spectra, we assume the absolute configuration to be the same for all products 64-73.

The stereoselectivity in the formation of the quaternary center can be rationalized by comparison of three-dimensional models of the enolate-intermediate (Scheme 20). Bridging of both the oxygen atom of the enolate and the oxygen atom of the naphthol moiety by a magnesium ion would favor the cyclization (Scheme 20, TS-1) and would lead to formation of the product with the correct stereochemistry as displayed in Figure 1. In the transition state leading to the other diastereomer (Scheme 20, TS-2), bridging of the two oxygen anions cannot occur (Scheme 20).
Catalytic Asymmetric Conjugate Addition/Oxidative Dearomatization Towards Multifunctional Spirocyclic Compounds

Scheme 20   Rationalization of the absolute stereochemistry of 71.

The precise mechanism of the oxidative cyclization described in this paragraph is not yet known. The oxidative coupling of enolates with copper(II) 2-ethylhexanoate has been shown to operate via a single-electron transfer (SET) mechanism, where both enolates may be bound to a single copper(II) atom.57 Recent work by Roithová and Milko on the oxidative dimerization of naphthol, mediated by copper(II), indicates that it occurs via dinuclear clusters, where both naphthol units are activated towards dimerization by binding to their own copper(II) center through the phenoxy group.60 On the other hand, for the oxidation and dearomatization of phenols, an ionic mechanism was proposed by Quideau et al. in which an oxocyclohexadienylum cation is the intermediate at which nucleophilic addition occurs.20 So far, we are unable to distinguish between an ionic or radical mechanism for this reaction.

4.3.6 Synthesis of phenol-based substrates

In order to study if the conjugate addition/oxidative cyclization method of naphthol-based substrates described earlier in this chapter could be extended to phenol-based compounds, three substrates were synthesized.

4.3.6.1 Synthesis of ortho-substituted phenol-based substrate 80

Reduction of the commercially available lactone 78 with Dibal-H in dichloromethane at -78 °C afforded hemiacetal 79 in excellent yield (99%). Subsequent Wittig reaction in benzene led to the isolation of substrate 80 in 81% yield over a simple two step procedure (Scheme 21).
4.3.6.2 Synthesis of meta-substituted phenol-based substrate 87

For the synthesis of phenol-based substrate 87 a slightly more elaborate synthetic route was necessary. Esterification of the commercially available acid 81, followed by protection of the alcohol group with TBDMSCl catalyzed by imidazole gave 83 in 95% yield over two steps. Selective reduction of the double bond with palladium on charcoal provided 84. Dibal-H reduction of the ester moiety at low temperature (-78 °C) followed by a Wittig reaction afforded TBDMS-protected substrate 86. In the final step the TBDMS-group was removed in order to obtain substrate 87 in 88% isolated yield (Scheme 22).
4.3.6.3 Synthesis of para-substituted phenol-based substrate 93
A similar route compared to substrate 87 was chosen for the synthesis of substrate 93. Starting with the esterification of commercially available acid 88, ethyl ester 89 was obtained in quantitative yield. TBDMS-protection of the phenol afforded 90, which was subsequently reduced to aldehyde 91 with Dibal-H. The crude aldehyde was then converted into the \( \alpha,\beta \)-unsaturated ester in moderate yield (52% over 2 steps). Finally, after deprotection of the TBDMS-group, the desired substrate 93 was isolated in 98% yield. (Scheme 23).

![Scheme 23](image)

4.3.7 Conjugate addition of EtMgBr to phenol-based substrates
After successful synthesis of the phenol-based substrates, the optimized protocol for the conjugate addition reaction (see section 4.3.3) was applied (Table 3). A comparison between the structure and the observed enantiomeric excess revealed that for these substrates the proximity of the hydroxy moiety to the \( \alpha,\beta \)-unsaturated ester unit has a pronounced impact on the attainable level of enantioselectivity. A hydroxy moiety in the ortho-position to the \( \alpha,\beta \)-unsaturated ester unit led to a significantly lower enantiomeric excess (Table 3, entry 1). However, for substrates in which the hydroxy group was positioned at the meta- or para-position excellent enantioselectivities were obtained (Table 3, entries 2 and 3). This can be rationalized by a possible coordination of the ortho-phenol moiety to the copper atom which negatively influences the enantioselectivity of the catalytic system. A similar effect was also observed for the naphthol-based substrates (vide supra).
Table 3  Catalytic asymmetric conjugate addition of EtMgBr to phenol-based substrates.  

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>1</td>
<td>80</td>
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</tbody>
</table>

Reaction conditions: 80, 87 or 93 (0.25 mmol) in CH₂Cl₂ (0.8 mL) was added over 1 h to a solution of CuI (5 mol%), (R)-L₄ (7.5 mol%), and Grignard reagent (2.5 eq) in CH₂Cl₂ (0.4 mL) at -40 °C. The reaction mixture was stirred at -40 °C over night. Isolated yield. Determined by chiral HPLC analysis (see Experimental Section).

4.3.8 Attempted oxidative cyclization

Initially, the one-pot conjugate addition/oxidative cyclization was studied using the same conditions as for the naphthol-based system. Unfortunately, the main product that was isolated in this reaction was not the desired product 98 but dimer 99, originating from intermolecular enolate-enolate dimerization. In this reaction, phenol-oxidation apparently does not take place and therefore enolate-enolate dimerization occurs instead (Scheme 24). When the same conditions were applied to the other phenol-based substrates 87 and 93 the major products isolated were the conjugate addition products 95 and 96, so in these examples no oxidative cyclization takes place. The use of phenyliodine(III) diacetate as the oxidant gave a complex reaction mixture due to the formation of a lot of different side-products.
In order to gain a better understanding of the oxidation step, we decided to switch to a two-step procedure. After isolation of the product from the asymmetric conjugate addition reaction, the oxidative cyclization step was performed in a separate flask (Table 4). A range of different bases was used to form the enolate of 95 in situ, which upon addition of the oxidant should provide the desired product 100. Different oxidants were used and in some cases a mixture of product and starting material, inseparable by column chromatography, was isolated (Table 4, entries 1-3). In most cases substrate 95 was isolated or complex mixtures of side-products were obtained (Table 4, entries 4-11).

Table 4  Attempted oxidative cyclization of 95.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base eq</th>
<th>Oxidant eq</th>
<th>Time, temperature</th>
<th>100:95</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA 2.1</td>
<td>Fe(III)acac$^e$</td>
<td>2.0, 30 min, rt</td>
<td>1:1.5 (87)</td>
</tr>
<tr>
<td>2</td>
<td>LDA 2.1</td>
<td>Cu(II) 2-ethylhexanoate$^f$</td>
<td>2.0, 30 min, 0 °C - rt</td>
<td>1:6.1 (95)</td>
</tr>
<tr>
<td>3</td>
<td>LDA 2.1</td>
<td>Cu(II) 2-ethylhexanoate$^f$</td>
<td>2.0, 30 min, 0 °C - rt</td>
<td>1:1.3 (81)</td>
</tr>
<tr>
<td>4$^f$</td>
<td>LDA 2.1</td>
<td>Ferrocenium PF$_6$</td>
<td>2.0, 30 min, 0 °C - rt</td>
<td>0:100 (41)</td>
</tr>
<tr>
<td>5$^f$</td>
<td>LDA 2.1</td>
<td>Cu(II) 2-ethylhexanoate$^f$</td>
<td>5.0, overnight, rt</td>
<td>0:100 (42)</td>
</tr>
<tr>
<td>6$^f$</td>
<td>LDA 2.1</td>
<td>Mn(III)acac$_3$</td>
<td>2.5, overnight, rt</td>
<td>-- (0)</td>
</tr>
<tr>
<td>7$^f$</td>
<td>LDA 3.1</td>
<td>Mn(III)acac$_3$</td>
<td>2.0, 30 min, 0 °C - rt</td>
<td>1:99 (nd)</td>
</tr>
<tr>
<td>8$^f$</td>
<td>EtMgBr 2.05</td>
<td>Mn(III)acac$_3$</td>
<td>2.0, 120 min, 0 °C</td>
<td>0:100 (nd)</td>
</tr>
<tr>
<td>9$^f$</td>
<td>LDA 4.1$^f$</td>
<td>Mn(III)acac$_3$</td>
<td>4.0, 60 min, rt</td>
<td>-- (nd)</td>
</tr>
<tr>
<td>10$^f$</td>
<td>BMDA$^h$</td>
<td>Mn(III)acac$_3$</td>
<td>2.0, 30 min, rt</td>
<td>0:100 (nd)</td>
</tr>
<tr>
<td>11$^f$</td>
<td>LDA 2.05</td>
<td>Cu(II) pivalate</td>
<td>2.2, 30 min, rt</td>
<td>0:100 (nd)</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 95 (0.06 mmol) was dissolved in THF (0.2 mL), cooled to -78 °C, the base was added slowly and the mixture was stirred for 30 min and warmed to 0 °C or rt and the oxidant was added and the reaction mixture was stirred for the indicated time. $^b$ Temperature at which the oxidant was added. $^c$ Determined by GC-MS. $^d$ Isolated yield in parentheses. $^e$ A solution of the oxidant in THF was used (0.5 M). $^f$ Next to 95, the formation of undesired side products was observed. $^g$ The reagents were added in two batches at 30 min intervals. $^h$ BMDA = Bromomagnesium diisopropylamide.
4.3.9 Synthesis of pyrrole-based substrate

Next to naphthol- and phenol-based substrates, we also looked at the use of pyrrole-based substrates for the development of an asymmetric conjugate addition/oxidative cyclization protocol. For this purpose the synthesis of substrates 106 and 109 was attempted. 1-(2-Hydroxyethyl)pyrrole 102 was synthesized in one step from 2,5-dimethoxytetrahydrofuran (101) and ethanolamine in glacial acetic acid in 65% yield (Scheme 25, route 1). Several attempts were made to oxidize the alcohol to aldehyde (103) in order to perform a Wittig-reaction to obtain the desired substrate. In the case of the IBX oxidation of 102 (Scheme 24, route 1) no product could be isolated and upon Swern oxidation unreacted starting material was isolated. A base-catalyzed substitution reaction of pyrrole and 105 afforded a complex mixture of products and the desired product could not be isolated (Scheme 25, route 2).

\[
\text{Scheme 25}\quad \text{Attempted synthesis of 106.}
\]

Reduction of nitrile 107 with Dibal-H in CH₂Cl₂ at low temperature (-78 to 0 °C) afforded 108. Although ¹H-NMR indicated that the conversion to aldehyde 108 was not very high, the crude product was used without further purification in the next step. After a Wittig reaction the desired pyrrole substituted α,β-unsaturated ester 109 was isolated in 25% yield over two steps (Scheme 26).

\[
\text{Scheme 26}\quad \text{Synthesis of pyrrole-based substrate 109.}
\]
### 4.3.10 Asymmetric conjugate addition of EtMgBr to pyrrole-based substrate

Before studying the one-pot conjugate addition/oxidative cyclization, the conjugate addition of EtMgBr to pyrrole substituted $\alpha,\beta$-unsaturated ester 109 was examined (Scheme 27). Using 1 mol% of copper(I) iodide together with 1.5 mol% of (S)-Tol-Binap as the catalytic system and EtMgBr (5.0 eq) at -40 °C in $\tau$-BuOMe afforded the conjugate addition product with excellent yield (91%) and enantiomeric excess (92%).

![Scheme 27](image)

Scheme 27 Asymmetric conjugate addition of EtMgBr to substrate 109.

### 4.3.11 Oxidative cyclization of pyrrole-based substrate 109

Based on the fact that the asymmetric conjugate addition of EtMgBr works very well with the pyrrole substituted $\alpha,\beta$-unsaturated ester 109, the resulting product 110 was submitted to the oxidative conditions (Scheme 28). Based on literature precedents on intramolecular enolate-pyrrole coupling developed by Baran et al., we decided to use ferrocenium hexafluorophosphate 111 as the oxidant. The preliminary results of this reaction are shown in Scheme 28. In both cases an inseparable mixture of starting material and desired product was isolated in good yield. The $^1$H-NMR spectrum of the crude mixture of product and starting material shows only one set of signals, besides the signals belonging to the starting material, indicating the formation of only one diastereomer of product 112 in the oxidative cyclization reaction. Also, GC-MS analysis shows only two peaks: one of the starting material and one for the product. Furthermore, the $^1$H-NMR spectrum of the product shows only one doublet at 5.5 ppm with a $J$-coupling of 9.2 Hz suggesting a trans-configured system. Increasing the amount of base and oxidant, the product to starting material ratio increased to 1.3:1. Further screening of oxidants and optimization of reaction conditions could lead to the development of general method for the enantioselective synthesis of these valuable pyrrole-containing bicyclic systems. If, after careful screening, full conversion cannot be obtained for this reaction, separation of the products by derivatization (i.e. reduction to the alcohol) could be a viable alternative.
4.4 Conclusion and future prospects

In summary, we have developed a sequential asymmetric copper-catalyzed conjugate addition/oxidative cyclization of naphthol-based substrates for the synthesis of highly functionalized benzofused spirocyclic cyclohexenones. A high degree of molecular complexity was achieved in this one-pot transformation, along with the formation of three contiguous stereocenters. The chiral catalyst controls the configuration of the first stereocenter, achieving excellent enantiomeric excess up to 94% and the subsequent two stereocenters are formed with high diastereoselectivity (up to >20:1), governed by the first stereocenter. So far, the oxidative cyclization of phenol-based substrates has proven to be more challenging as no effective methods were discovered for this transformation. Preliminary results of the oxidative cyclization of pyrrole-based substrates were promising and further optimization of the reaction conditions could lead to the development of novel methodology for the synthesis of enantiopure pyrrole-based bicyclic systems.
4.5 Experimental Section

General Experimental
Starting materials were purchased from Acros, Sigma-Aldrich, Strem, or Alfa Aesar and were used as received unless stated otherwise. All solvents were reagent grade and were dried and distilled prior to use, if necessary. Tetrahydrofuran and diethyl ether were distilled over sodium. Toluene, dichloromethane and tert-butyl methyl ether were distilled over calcium hydride. Column chromatography was performed on silica gel (Silica-P flash silica gel from Silicycle, size 40-63 μm). TLC was performed on silica gel 60/Kieselguhr F254. 1H and 13C NMR spectra were recorded in CDCl3 on a Varian VXR300 (300 MHz for 1H, 75 MHz for 13C) or a Varian AMX400 (400 MHz for 1H, 100.59 MHz for 13C) spectrometer. Chemical shifts are reported in values (ppm) relative to the solvent peak (CHCl3 =7.26 (1H), 77.0 ppm (13C)), or TMS (0 ppm). The following abbreviations are used to indicate multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Mass spectra (HRMS) were performed on a LTQ Orbitrap XL. HPLC analysis was performed on a Shimadzu HPLC system equipped with two LC-10AD vp solvent delivery systems, a DGU-14 A degasser, a SIL-10AD vp auto injector, a SPD-M10 A vp diode array detector, a CTO-10 A vp column oven and a SCL-10A vp system controller by using the columns indicated for each compound separately. Optical rotations were measured in CH2Cl2 or CHCl3 on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL).
Chapter 4

1H-Benzof[\textit{f}]chromen-3(2\textit{H})-one (41a)

This compound was synthesized according to the literature procedure.\textsuperscript{63} Amberlyst 15 (1 g) was added to a solution of 2-naphthol (10 g, 69 mmol) and acrylic acid (9.5 mL, 139 mmol) in toluene (140 mL). The reaction mixture was heated to reflux for 12 h. The reaction mixture was filtered and concentrated. The crude product was purified by column chromatography using n-pentane/diethyl ether (4:1) to yield 41a as a colorless oil (1:1 mixture of regioisomers, 82% yield). The spectroscopic data matched those reported in the literature\textsuperscript{63} and the mixture was carried on to the next step without further purification.

2,3-Dihydro-1H-benzof[\textit{f}]chromen-3-ol (42a)

To a solution of 41a (1:1 mixture of regioisomers, 5.7 g, 28.6 mmol), in dichloromethane (65 mL) at -78 °C was added diisobutylaluminium hydride (1 M in toluene, 32 mL, 32 mmol) by syringe pump over 30 min. The reaction mixture was left stirring at -78 °C for 2 h and then poured into an aqueous solution of Rochelle’s salt (150 mL). After stirring at room temperature for 2 h, the organic layer was separated and the aqueous later was extracted twice with dichloromethane (2×30 mL). The combined organic layers were dried over MgSO\textsubscript{4} and concentrated. The crude product was purified by column chromatography using n-pentane/diethyl ether (9:1 – 4:1) to afford 42a as a colorless oil and a single regioisomer (2.36 g, 41% yield). The spectroscopic data matched those reported in the literature.\textsuperscript{64}

(E)-Ethyl 5-(2-hydroxynaphthalen-1-yl)pent-2-enoate (43a)

To a solution of (carbethoxymethylene)triphenylphosphorane (4.0 g, 11.4 mmol) in benzene (100 mL) was added a solution of 42a (2.1 g, 10.4 mmol) in benzene (100 mL). The reaction mixture was left stirring at room temperature for 12 h. The reaction was then quenched with water and the solution was diluted with diethyl ether (100 mL). The organic layer was separated and the aqueous layer was extracted twice with diethyl ether (2×50 mL). The combined organic layers were dried over MgSO\textsubscript{4} and concentrated. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (4:1 – 5:2) to afford 43a as an off-white solid (2.25 g, 80%), mp: 82-85 °C. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.86 (d, \(J = 8.5\) Hz, 1H), 7.76 (d, \(J = 8.1\) Hz, 1H), 7.60 (d, \(J = 8.8\) Hz, 1H), 7.47 (dd, \(J = 7.4, 7.9\) Hz, 1H), 7.31 (t, \(J = 7.4\) Hz, 1H), 7.21-7.13 (m, 1H), 7.05 (d, \(J = 8.8\) Hz, 1H), 6.16 (s, 1H), 5.92 (d, \(J = 15.6\) Hz, 1H), 4.20 (q, \(J = 7.1\) Hz, 2H), 3.24-3.20 (m, 2H), 2.56 (dd, \(J = 7.5, 15.0\) Hz, 2H), 1.28 (t, \(J = 7.1\) Hz, 3H). \textsuperscript{13}C-
NMR (100 MHz, CDCl₃): δ 167.6, 151.1, 149.7, 133.2, 129.5, 128.9, 128.1, 126.7, 123.2, 122.7, 121.5, 119.1, 118.0, 60.7, 32.5, 23.8, 14.4. HRMS (ESI+, m/z): calcd. for C₁₇H₁₉O₃ [M+H]⁺: 271.1329; found: 271.1329.

8-Bromo-1H-benzo[f]chromen-3(2H)-one (41b)

Compound 41b was prepared as compound 41a above, from 6-bromo-2-naphthol (5.0 g, 22.0 mmol). The crude product was purified by a single recrystallization from hot toluene to afford 41b as pink crystals and as a single regioisomer (3.2 g, 52% yield). The spectroscopic data matched those reported in the literature.⁶⁵

8-Bromo-2,3-dihydro-1H-benzo[f]chromen-3-ol (42b)

Compound 42b was prepared according to the procedure for compound 42a above, using 41b (700 mg, 2.5 mmol). The crude product was purified by column chromatography using n-pentane/diethyl ether (9:1) to afford 42b as a white solid (607 mg, 87% yield), mp: 116-119 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.90 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.05 (d, J = 8.9 Hz, 1H), 5.67 (dd, J = 4.1, 6.5 Hz, 1H), 3.18 – 2.99 (m, 3H), 2.25 – 2.05 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃): δ 149.5, 131.2, 130.4, 130.3, 129.5, 127.0, 123.8, 120.1, 117.2, 114.1, 91.9, 26.7, 17.0. HRMS (ESI−, m/z): calcd. for C₁₃H₁₀BrO₂ [M−H]⁻: 276.9859; found: 276.9862.

(E)-Ethyl 5-(6-bromo-2-hydroxynaphthalen-1-yl)pent-2-enoate (43b)

Compound 43b was prepared according to the procedure for compound 43a above, using 42b (607 mg, 2.17 mmol). The crude product was purified by column chromatography using n-pentane/diethyl ether (4:1) to afford 43b as a white solid (619 mg, 82% yield), mp: 95-96 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.90 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.13 (dt, J = 6.9, 15.6 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 5.90 (dt, J = 1.4, 15.6 Hz, 1H), 5.86 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.25 – 3.11 (m, 2H), 2.59 – 2.47 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 167.2, 151.1, 148.8, 131.6, 130.6, 130.5, 129.7, 127.1, 124.4, 121.6, 119.2, 118.7, 116.7, 60.5, 32.2, 23.6, 14.2. HRMS (ESI+, m/z): calcd. for C₁₇H₁₈BrO₃ [M+H]⁺: 349.0434; found: 349.0434.

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8-Methoxy-1H-benzo[f]chromen-3(2H)-one (41c)

Compound 41c was prepared as compound 41a above, from 6-methoxy-2-naphthol (1.9 g, 10.91 mmol). The crude product was purified by column chromatography using dichloromethane/acetone (150:1) to afford 41c as a white solid (1.24 g, 50% yield). The spectroscopic data matched those reported in the literature.\(^6^3\)

8-Methoxy-2,3-dihydro-1H-benzo[f]chromen-3-ol (42c)

Compound 42c was prepared according to the procedure for compound 42a above, using 41c (1.15 g, 5.04 mmol). The crude product was purified by column chromatography using dichloromethane/acetone (25:1) to afford 42c as a colorless oil (1.1 g, 94% yield). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.76 (d, \(J = 9.2\) Hz, 1H), 7.55 (d, \(J = 8.9\) Hz, 1H), 7.18 – 7.08 (m, 3H), 7.02 (d, \(J = 8.8\) Hz, 1H), 5.68 – 5.64 (m, 1H), 3.90 (s, 3H), 3.20 – 3.05 (m, 2H), 3.05 – 3.00 (m, 1H), 2.23 – 2.11 (m, 2H). \(^1\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 156.0, 147.7, 130.1, 127.9, 126.7, 123.5, 119.3, 118.6, 114.0, 106.9, 91.9, 55.3, 27.0, 17.3.

(E)-Ethyl 5-(2-hydroxy-6-methoxynaphthalen-1-yl)pent-2-enoate (43c)

Compound 43c was prepared according to the procedure for compound 43a above, using 42c (1 g, 4.34 mmol). The crude product was purified by column chromatography using n-pentane/diethyl ether (4:1 – 7:3) to afford 43c as a white solid (1.3 g, 100% yield), mp: 90.5 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.78 (d, \(J = 9.3\) Hz, 1H), 7.51 (d, \(J = 8.8\) Hz, 1H), 7.22 – 7.08 (m, 3H), 7.02 (d, \(J = 8.8\) Hz, 1H), 5.97 - 5.88 (m, 1H), 5.66 (s, 1H), 4.21 (q, \(J = 7.1\) Hz, 2H), 3.90 (s, 3H), 3.25 - 3.15 (m, 2H), 2.60 - 2.50 (m, 2H), 1.29 (t, \(J = 7.1\) Hz, 3H). \(^1\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.2, 155.6, 149.2, 149.1, 130.2, 128.3, 126.5, 124.1, 121.4, 119.4, 119.0, 118.2, 107.0, 60.4, 55.3, 32.4, 23.7, 14.3. HRMS (ESI+, \(m/z\)): calcd. for C\(_{18}\)H\(_{21}\)O\(_4\) [M + H]\(^+\): 301.14344; found: 301.14456.
2-(Allyloxy)naphthalene (44)

Allyl bromide (9 mL, 104 mmol) was added to a suspension of 2-naphthol (5 g, 35 mmol) and potassium carbonate (14 g, 104 mmol) in acetone (100 mL). The reaction mixture was heated to 60 °C for 12 h, cooled to room temperature, diluted with diethyl ether (100 mL) and quenched with water (100 mL). The organic layer was separated and the aqueous layer was extracted twice with diethyl ether (2×50 mL). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The crude product was purified by column chromatography using n-pentane/diethyl ether (100:0 – 98:2) to obtain 44 as a colorless oil (5.9 g, 91% yield). The spectroscopic data matched those reported in the literature.\(^{66}\)

1-Allylnaphthalen-2-ol (45)

Compound 44 (737 mg, 4 mmol) was dissolved in xylenes (10 mL) and heated to 210 °C for 12 h in a sealed tube. The reaction mixture was cooled and the solvent removed in vacuo. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (95:5) to obtain 45 as a colorless oil (635 mg, 85% yield). The spectroscopic data matched those reported in the literature.\(^{66}\)

(1-Allylnaphthalen-2-yloxy)(tert-butyldimethyl)silane (46)

A solution of compound 45 (1.3 g, 6.8 mmol) and imidazole (694 mg, 10.19 mmol) in dichloromethane (25 mL) was cooled to 0 °C. tert-Butyldimethylsilylchloride (1.1 g, 7.5 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched with water (50 mL) and the organic layer was separated. The aqueous layer was extracted twice with dichloromethane (2×20 mL) and the combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (100:0 – 98:2) to obtain 46 as a colorless oil (1.73 g, 85% yield). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.90 (d, \(J = 8.6\) Hz, 1H), 7.76 (d, \(J = 8.1\) Hz, 1H), 7.63 (d, \(J = 8.8\) Hz, 1H), 7.45 (ddd, \(J = 1.3, 6.8, 8.4\) Hz, 1H), 7.32 (ddd, \(J = 1.1, 6.8, 8.0\) Hz, 1H), 7.10 (d, \(J = 8.8\) Hz, 1H), 6.01 (tdd, \(J = 5.8, 10.2, 17.0\) Hz, 1H), 4.98 (qdd, \(J = 1.8, 17.0, 22.7\) Hz, 2H), 3.83 (td, \(J = 1.7, 5.7\) Hz, 2H), 1.05 (s, 9H), 0.26 (s, 6H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 150.7, 136.6, 133.6, 129.5, 128.3, 127.6, 126.0, 123.8, 123.2, 122.6, 120.4, 115.1, 29.7, 25.9, 18.3, -3.9. HRMS (ESI+, \(m/z\)): calcd. for C\(_{16}\)H\(_{27}\)OSi [M+H]\(^+\): 299.1826; found: 299.1818.
(E)-Ethyl 4-(2-(tert-butyldimethylsilyloxy)naphthalen-1-yl)but-2-enoate (47)

To a solution of compound 46 (1.6 g, 5.4 mmol) and ethyl acrylate (1.2 mL, 10.7 mmol) in toluene (125 mL) was added Hoveyda-Grubbs second generation catalyst (101 mg, 0.16 mmol, 3 mol%). The reaction mixture was heated to 70 °C for 16 h. The solvent was removed in vacuo and the crude mixture was purified by column chromatography using n-pentane/diethyl ether (95:5) to obtain 47 as a colorless oil (1.49 g, 75% yield). 1H-NMR (400 MHz, CDCl3): δ 7.77 (d, J = 9.4 Hz, 2H), 7.67 (d, J = 8.9 Hz, 1H), 7.47-7.43 (m, 1H), 7.35-7.31 (m, 1H), 7.18 (td, J = 5.8, 15.7 Hz, 1H), 7.10 (d, J = 8.9 Hz, 1H), 5.64 (td, J = 1.8, 15.6 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.96 (dd, J = 1.8, 5.8 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.03 (s, 9H), 0.27 (s, 3H). 13C-NMR (100 MHz, CDCl3): δ 173.5, 166.6, 151.0, 147.1, 133.3, 129.4, 128.5, 128.3, 126.5, 123.4, 123.3, 121.8, 120.4, 120.2, 60.1, 28.3, 25.8, 18.3, 14.2, -3.9. HRMS (ESI+, m/z): calcd. for C22H30O3SiNa [M+Na]+: 393.1875; found: 393.1841.

Ethyl 4-(2-(tert-butyldimethylsilyloxy)naphthalen-1-yl)butanoate (48)

To a solution of 47 (1.5 g, 4.0 mmol) in methanol (45 mL) was added palladium on activated carbon (5 wt% Pd, 300 mg). The reaction mixture was placed under an atmosphere of hydrogen at atmospheric pressure and left stirring for 5 d. The mixture was filtered over celite and the solvent removed in vacuo. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (98:2 – 95:5) to obtain 48 as a colorless oil (1.47 g, 98% yield). 1H-NMR (400 MHz, CDCl3): δ 7.98 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.47 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 7.33 (ddd, J = 1.1, 6.8, 8.0 Hz, 1H), 7.07 (d, J = 8.9 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.11-3.07 (m, 2H), 2.42 (t, J = 7.5 Hz, 2H), 2.00-1.92 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H), 0.27 (s, 3H). 13C-NMR (100 MHz, CDCl3): δ 173.6, 150.5, 133.4, 129.5, 128.4, 127.3, 126.1, 124.7, 123.3, 123.2, 120.2, 60.2, 34.3, 25.8, 25.0, 24.9, 18.3, 14.2, -3.9. HRMS (ESI+, m/z): calcd. for C22H32O3SiNa [M+Na]+: 395.2031; found: 393.1841.

4-(2-(tert-Butyldimethylsilyloxy)naphthalen-1-yl)butanal (49)

To a solution of 48 (1.4 g, 3.7 mmol) in dichloromethane (15 mL) was slowly added diisobutylaluminum hydride (1.0 M in toluene, 4.5 mL, 4.5 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h and poured into a saturated aqueous solution of Rochelle’s salt (50 mL). The biphasic mixture was stirred at room temperature for 5 h, at which time the organic phase was separated. The aqueous phase was
extracted with dichloromethane (2×25 mL) and the combined organic phases were dried over MgSO₄, filtered and concentrated. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (98:2 – 95:5) to obtain 49 as a colorless oil (0.80 g, 66% yield). ¹H-NMR (400 MHz, CDCl₃): δ 9.76 (t, J = 1.6 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.9 Hz, 1H), 7.48 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 7.33 (ddd, J = 1.0, 6.9, 7.9 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 3.12-3.09 (m, 2H), 2.52 (dt, J = 1.6, 7.3 Hz, 2H), 2.01-1.94 (m, 2H), 1.05 (s, 9H), 0.27 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 202.5, 150.6, 133.3, 129.5, 128.5, 127.5, 126.2, 124.4, 123.3, 123.2, 120.3, 43.6, 25.9, 24.7, 22.2, 18.3, -3.9. HRMS (ESI+, m/z): calcd. for C₂₀H₂₈O₂SiNa [M+Na]^+: 351.1767; found: 351.1740.

(E)-Ethyl 6-(2-(tert-butyldimethylsilyloxy)naphthalen-1-yl)hex-2-enoate (50)

n-Butyllithium (1.6 M in hexanes, 1.9 mL, 3.0 mmol) was added to a solution of triethyl phosphonoacetate (0.6 mL, 3.5 mmol) in THF (15 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min and warmed to room temperature and stirred for an additional 30 min at rt. The reaction mixture was then cooled back to 0 °C and a solution of 49 (760 mg, 2.31 mmol) in THF (5 mL) was added via a cannula. The reaction mixture was allowed to warm slowly to room temperature and stirred for an additional 12 h. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate (40 mL) and the resulting mixture was diluted with diethyl ether (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×20 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (98:2 – 95:5) to obtain 50 as a colorless oil (0.69 g, 75% yield). ¹H-NMR (400 MHz, CDCl₃): δ 7.89 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 8.9 Hz, 1H), 7.01 (dd, J = 7.2, 15.4 Hz, 1H), 5.84 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.10-3.06 (m, 2H), 2.34 (dd, J = 7.3, 14.6 Hz, 2H), 1.79 (td, J = 7.8, 15.4 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H), 0.26 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 166.6, 150.5, 148.9, 133.2, 129.5, 128.5, 127.2, 126.1, 124.8, 123.2, 123.1, 121.5, 120.2, 60.1, 32.5, 28.2, 25.8, 25.1, 18.3, 14.2, -3.9. HRMS (ESI+, m/z): calcd. for C₂₄H₃₄O₃SiNa [M+Na]^+: 421.2175; found: 421.2168.
(E)-Ethyl 6-(2-hydroxynaphthalen-1-yl)hex-2-enoate (51)

To a solution of 50 (135 mg, 0.34 mmol) in THF (3 mL) at -40 °C was added tetrabutylammonium fluoride (1.0 M in THF, 0.4 mL, 0.4 mmol) dropwise. The reaction mixture was stirred at -40 °C for 10 min, quenched with a saturated aqueous ammonium chloride solution (5 mL) and diluted with diethyl ether (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (90:10 – 80:20) to obtain 51 as a colorless oil (94 mg, 97% yield). 1H-NMR (400 MHz, CDCl₃): δ 7.86 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.08-7.01 (m, 2H), 6.07 (s, 1H), 5.86 (d, J = 15.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.09-3.06 (m, 2H), 2.31 (q, J = 7.2 Hz, 2H), 1.88-1.78 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H). 13C-NMR (100 MHz, CDCl₃): δ 167.4, 150.8, 149.7, 133.2, 129.2, 128.6, 127.6, 126.3, 122.8, 128.7, 121.2, 119.7, 117.7, 60.4, 32.1, 27.9, 24.3, 14.2. HRMS (ESI+, m/z): calcd. for C₁₈H₂₀O₃Na [M+Na]+: 307.1313; found: 307.1299.

3,4-Dihydro-2H-benzo[h]chromen-2-one (53)

Compound 53 was prepared as compound 41a above, from 1-naphthol (1.0 g, 6.9 mmol). The crude product was purified by column chromatography using n-pentane/diethyl ether (9:1 – 4:1) to afford 53 as a white crystalline solid and as a single regioisomer (341 mg, 25% yield). The spectroscopic data matched those reported in the literature.⁶³

3,4-Dihydro-2H-benzo[h]chromen-2-ol (54)

Compound 54 was prepared according to the procedure for compound 42a above, using 53 (298 mg, 1.50 mmol). The crude product was purified by column chromatography using n-pentane/diethyl ether (9:1 – 4:1) to afford 54 as a colorless oil (265 mg, 88% yield). 1H-NMR (300 MHz, CDCl₃): δ 8.15-8.12 (m, 1H), 7.75-7.72 (m, 1H), 7.45-7.38 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 5.75-5.72 (m, 1H), 3.34 (d, J = 3.2 Hz, 1H), 3.04 (ddd, J = 6.8, 9.6, 16.5 Hz, 1H), 2.77 (td, J = 5.4, 16.6 Hz, 1H) 2.14-1.98 (m, 2H). 13C-NMR (100 MHz, CDCl₃): δ 146.6, 133.3, 127.4, 127.3, 125.6, 125.3, 125.1, 121.2, 120.1, 115.6, 92.4, 27.0 20.6. HRMS (ESI+, m/z): calcd. for C₁₃H₁₃O₂ [M+H]+: 201.0910; found: 201.0910.
(E)-Ethyl 5-(1-hydroxynaphthalen-2-yl)pent-2-enoate (55)

Compound 55 was prepared according to the procedure for compound 43a above, using 54 (265 mg, 1.32 mmol). The crude product was purified by column chromatography using n-pentane/diethyl ether (9:1 – 4:1) to afford 55 as a white crystalline solid (268 mg, 80% yield), mp: 65-67 °C.  

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.06-8.04 (m, 1H), 7.78 (dd, $J = 2.1$, 7.2 Hz, 1H), 7.48-7.43 (m, 2H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.06 (td, $J = 6.9$, 15.6 Hz, 1H), 5.88 (td, $J = 1.5$, 15.6 Hz, 1H), 5.68 (s, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 2.94-2.90 (m, 2H), 2.60-2.54 (m, 2H), 1.27 (t, $J = 7.1$ Hz, 3H).  

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 166.9, 148.3, 133.4, 127.9, 127.8, 125.5, 125.4, 124.6, 121.9, 120.62, 120.60, 120.5, 60.4, 32.6, 28.7, 14.2. HRMS (ESI+, m/z): calcd. for C$_{17}$H$_{19}$O$_3$ [M+H]$^+$: 271.1329; found: 271.1335.

4-(tert-Butyldimethylsilyloxy)-1-naphthaldehyde (57)

To a solution of 4-hydroxy-1-naphthaldehyde (5 g, 29 mmol) and imidazole (3 g, 44 mmol) in dichloromethane (60 mL) at 0 °C was added tert-butyldimethylsilyl chloride (5 g, 32 mmol). The reaction mixture was allowed to warm slowly to room temperature and stirring was continued over 12 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (50 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2×30 mL) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated. The crude product was purified by column chromatography using n-pentane/diethyl ether (100:0 – 95:5) to afford 57 as an off-white solid (7.2 g, 87% yield), mp: 87-88 °C.  

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 10.21 (s, 1H), 9.31 (d, $J = 8.5$ Hz, 1H), 8.28 (d, $J = 8.3$ Hz, 1H), 7.86 (d, $J = 7.9$ Hz, 1H), 7.68 (ddd, $J = 1.4$, 6.9, 8.4 Hz, 1H), 7.57 (ddd, $J = 1.1$, 6.9, 8.2 Hz, 1H), 6.94 (d, $J = 7.9$ Hz, 1H), 1.10 (s, 9H), 0.36 (s, 6H).  

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 192.2, 158.0, 139.1, 132.5, 129.4, 127.8, 126.3, 125.3, 124.9, 122.9, 111.3, 25.7, 18.5, -4.2. HRMS (ESI+, m/z): calcd. for C$_{17}$H$_{23}$O$_3$Si [M+H]$^+$: 287.1462; found: 287.1459.
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Ethyl 3-(4-(tert-butyldimethylsilyloxy)naphthalen-1-yl)acrylate (58)

To a solution of (carbethoxymethylene)triphenylphosphorane (9.0 g, 25.7 mmol) in benzene (200 mL) was added a solution of 57 (6.7 g, 23.4 mmol) in benzene (50 mL). The reaction mixture was left stirring at room temperature for 12 h. The reaction mixture was then quenched with water (100 mL) and the mixture was diluted with diethyl ether (100 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×100 ml). The combined organic layers were dried over MgSO₄ and concentrated. The crude mixture was filtered over silica and the product was carried on to the next step without further purification.

Ethyl 3-(4-(tert-butyldimethylsilyloxy)naphthalen-1-yl)propanoate (59)

To a solution of 58 (4.3 g, 12.0 mmol) in methanol (100 mL) was added palladium on activated carbon (5 wt% Pd, 250 mg). The reaction mixture was placed under an atmosphere of hydrogen at atmospheric pressure and left stirring for 5 d. The mixture was filtered over celite and the solvent removed in vacuo. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (98:2 – 95:5) to obtain 59 as a colorless oil (3.5 g, 42% yield over two steps). ¹H-NMR (400 MHz, CDCl₃): δ 8.24 (d,  𝐽 = 8.1 Hz, 1H), 7.96 (d,  𝐽 = 7.9 Hz, 1H), 7.52 (ddd,  𝐽 = 1.5, 6.8, 8.4 Hz, 1H), 7.47 (ddd,  𝐽 = 1.3, 6.8, 8.0 Hz, 1H), 7.18 (d,  𝐽 = 7.7 Hz, 1H), 6.77 (d,  𝐽 = 7.7 Hz, 1H), 4.14 (q,  𝐽 = 7.1 Hz, 2H), 3.35-3.31 (m, 2H), 2.71 (dd,  𝐽 = 7.2, 8.7 Hz, 2H), 1.24 (t,  𝐽 = 7.1 Hz, 3H), 1.09 (s, 9H), 0.27 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 173.2, 150.6, 132.8, 129.1, 128.2, 126.2, 125.9, 124.8, 123.4, 112.0, 60.4, 35.4, 27.8, 25.9, 18.4, 14.2, -4.3. HRMS (ESI⁺, m/z): calcd. for C₂₁H₃₁O₃Si [M+H]⁺: 359.2037; found: 359.2010.

3-(4-(tert-Butyldimethylsilyloxy)naphthalen-1-yl)propanal (60)

To a solution of 59 (0.75 g, 2.1 mmol) in dichloromethane (4 mL) was slowly added disobutylaluminum hydride (1.0 M in toluene, 2.3 mL, 2.3 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h and poured into an aqueous solution of Rochelle’s salt (10 mL). The biphasic mixture was stirred at room temperature for 5 h, at which time the organic phase was separated. The aqueous phase was extracted with dichloromethane (2×5 mL) and the combined organic phases were dried over MgSO₄, filtered and concentrated. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (95:5 – 90:10) to obtain 60.
60 as a colorless oil (0.50 g, 75% yield). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 9.88 (t, $J = 1.4$ Hz, 1H), 8.24 (dd, $J = 1.1$, 8.2 Hz, 1H), 7.91 (dd, $J = 1.0$, 7.7 Hz, 1H), 7.53 (dd, $J = 1.6$, 6.8, 8.4 Hz, 1H), 7.48 (dd, $J = 1.4$, 6.8, 8.0 Hz, 1H), 7.17 (d, $J = 7.7$ Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 1H), 3.34 (t, $J = 7.6$ Hz, 2H), 2.88 (dt, $J = 1.4$, 7.7 Hz, 2H), 1.09 (s, 9H), 0.28 (s, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 201.7, 150.6, 132.7, 128.7, 128.2, 126.3, 125.9, 124.9, 123.4, 123.2, 111.9, 44.6, 25.9, 24.8, 18.4, -4.3. HRMS (ESI+, $m/z$): calcd. for C$_{10}$H$_{25}$O$_3$Si $[M+H]^+$: 297.1669; found 297.1671.

$^{(E)}$-Ethyl 5-(4-(tert-butyldimethylsilyloxy)naphthalen-1-yl)pent-2-enoate (61) 

$\textit{n}$-Butyllithium (1.6 M in hexanes, 2.6 mL, 4.2 mmol) was added to a solution of triethyl phosphonoacetate (0.8 mL, 5.0 mmol) in THF (10 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min and warmed to room temperature and stirred for an additional 30 min at rt. The reaction mixture was then cooled back to 0 °C and a solution of 60 (1.20 g, 3.82 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm slowly to room temperature and stirred for an additional 12 h. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate (40 mL) and the mixture was diluted with diethyl ether (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×20 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated. The crude mixture was purified by column chromatography using $\textit{n}$-pentane/diethyl ether (98:2 – 95:5) to afford 61 as a colorless oil (0.85 g, 58% yield). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.24 (dd, $J = 1.3$, 8.2 Hz, 1H), 7.91 (dd, $J = 1.1$, 7.5 Hz, 1H), 7.52-7.47 (m, 2H), 7.14 (d, $J = 7.7$ Hz, 1H), 7.08 (td, $J = 6.9$, 15.6 Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 1H), 5.88 (td, $J = 1.5$, 15.6 Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.15-3.11 (m, 2H), 2.64-2.58 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.09 (s, 9H), 0.28 (s, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 166.5, 150.5, 148.3, 132.8, 129.4, 128.2, 126.1, 125.8, 124.7, 123.4, 123.3, 121.7, 112.0, 60.1, 33.2, 31.1, 25.9, 18.4, 14.2, -4.3. HRMS (ESI+, $m/z$): calcd. for C$_{23}$H$_{32}$O$_3$SiNa $[M+Na]^+$: 407.2013; found: 407.2003.

$^{(E)}$-Ethyl 5-(4-hydroxynaphthalen-1-yl)pent-2-enoate (62)

To a solution of 61 (0.85 g, 2.2 mmol) in THF (25 mL) at - 40 °C was added tetrabutylammonium fluoride (1.0 M in THF, 2.4 mL, 2.4 mmol) dropwise. The reaction mixture was stirred at -40 °C for 10 min, quenched with saturated aqueous ammonium chloride solution (15 mL) and diluted with diethyl ether (10 mL). The organic layer was
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separated and the aqueous layer was extracted with diethyl ether (2×10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude mixture was purified by column chromatography using n-pentane/diethyl ether (90:10 – 70:30) to obtain 62 as a colorless oil (0.58 g, 97% yield). ¹H-NMR (300 MHz, CDCl₃) δ 8.24 (dd, J = 1.3, 8.1 Hz, 1H), 7.93 (dd, J = 1.5, 7.5 Hz, 1H), 7.57-7.47 (m, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.09 (td, J = 6.8, 15.6 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 5.89 (td, J = 1.4, 15.6 Hz, 1H), 5.37 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.17-3.12 (m, 2H), 2.62 (dt, J = 1.3, 8.0 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 167.0, 150.6, 148.7, 132.6, 128.9, 126.4, 125.8, 124.9, 124.8, 123.4, 122.6, 121.6, 108.0, 60.4, 33.3, 31.0, 14.2. HRMS (ESI+, m/z): calcd for C₁₇H₁₈O₃Na [M+Na]⁺: 293.1148; found: 293.1149.

General Procedure for the Asymmetric Conjugate Addition/Oxidative Dearomatization

In an oven-dried Schlenk tube, under an atmosphere of nitrogen, CuI (2.38 mg, 13 µmol, 5 mol%) and (R)-BINAP (6.38 mg, 19 µmol, 7.5 mol%) in dichloromethane (0.4 mL) were allowed to stir at room temperature for 15 min until a clear yellow solution resulted. The catalyst solution was cooled to -40 °C and to this, ethylmagnesium bromide (2.5 eq, 3.0 M solution in Et₂O, 0.21 mL, 0.63 mmol) was added. The reaction mixture was stirred at -40 °C for 10 additional min before a solution of the naphthol substrate (0.25 mmol) in dichloromethane (0.8 mL) was added slowly to the reaction mixture over 1 h via syringe pump. The resulting reaction mixture was stirred at -40 °C for 4-16 h until analysis by TLC showed the reaction to be complete. Copper (II) 2-ethylhexanoate (2.5 eq, 220 mg, 0.63 mmol) was added to the reaction mixture in one portion at -40 °C. The mixture was further diluted with dichloromethane (0.5-2.0 mL) if necessary. The mixture was allowed to warm to room temperature and stirred at rt for an additional 5-16 h, during which time the reaction mixture turned from a turquoise color to pale yellow. The reaction was quenched with saturated aqueous NH₄Cl (5 mL) and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2×5 mL). The combined organic layers were washed with a 10% aqueous ammonia solution and brine, separated, dried over MgSO₄, filtered and the solvent removed in vacuo. The crude product was purified by column chromatography using n-pentane/diethyl ether. Enantiomeric excess was determined by chiral HPLC analysis. The absolute configuration depicted for all compounds is assumed to be the same to that of 77, as determined by X-ray crystallography (see section 4.3.5).
(1R,2S,3R)-Ethyl 3-ethyl-2'-oxo-2'H-spiro[cyclopentane-1,1'-naphthalene]-2-carboxylate (64)

Substrate 43a was reacted with ethylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 64 as a colorless oil (51 mg, 68% yield). Enantiomeric excess: 88% determined by chiral HPLC analysis, Chiralpak AD 1.0 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 230 nm, retention times (min): 13.7 (minor) and 14.7 (major). [α]D20 = +49.5 (c 2.8, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.46-7.28 (m, 4H), 7.39 (d, J = 9.8 Hz, 1H), 6.12 (d, J = 9.8 Hz, 1H), 3.97 (qd, J = 7.1, 10.8 Hz, 1H), 3.85 (qd, J = 7.1, 10.7 Hz, 1H), 3.00 (d, J = 9.8 Hz, 1H), 2.85-2.75 (m, 1H), 2.33-2.22 (m, 2H), 1.99-1.91 (m, 1H), 1.89-1.79 (m, 1H), 1.66-1.56 (m, 1H), 1.43-1.26 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H), 1.01 (t, J = 7.1 Hz, 1H). 13C-NMR (100 MHz, CDCl3): δ 203.1, 172.3, 146.9, 144.5, 130.2, 129.5, 129.3, 126.7, 125.8, 125.2, 63.9, 61.5, 60.3, 43.7, 41.0, 30.6, 28.3, 13.8, 12.5. HRMS (ESI+, m/z): calcd. for C19H23O3 [M+H]+: 299.1642; found: 299.1642.

(1R,2S,3R)-Ethyl 3-hexyl-2'-oxo-2'H-spiro[cyclopentane-1,1'-naphthalene]-2-carboxylate (65)

Substrate 43a was reacted with hexylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 65 as a colorless oil (74 mg, 84% yield). Enantiomeric excess: 83% determined by chiral HPLC analysis, Chiralpak AD 1.0 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 230 nm, retention times (min): 14.0 (minor) and 16.6 (major). [α]D20 = +24.7 (c 3.0, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.46-7.26 (m, 4H), 7.38 (d, J = 9.9 Hz, 1H), 6.12 (d, J = 9.8 Hz, 1H), 3.97 (qd, J = 7.2, 10.7 Hz, 1H), 3.86 (qd, J = 6.9, 10.6 Hz, 1H), 2.98 (d, J = 9.9 Hz, 1H), 2.89-2.81 (m, 1H), 2.27 (tt, J = 8.0, 13.4, 2H), 1.96 (td, J = 7.3, 13.0 Hz, 1H), 1.81-1.74 (m, 1H), 1.65-1.55 (m, 1H), 1.44-1.18 (m, 9H), 1.01 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 6.2 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 203.0, 172.3, 147.0, 144.5, 130.2, 129.5, 129.2, 126.7, 125.8, 125.2, 64.4, 61.4, 60.2, 42.3, 41.1, 35.7, 31.8, 31.1, 29.5, 28.2, 22.7, 14.1, 13.8. HRMS (ESI+, m/z): calcd. for C23H31O3 [M+H]+: 355.2268; found: 355.2244.
(1R,2S,3R)-Ethyl 2’-oxo-3-phenethyl-2’H-spiro[cyclopentane-1,1’-naphthalene]-2-carboxylate (66)

Substrate 43a was reacted with phenethylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-80:20) afforded 66 as an opaque oil (48 mg, 51% yield). Enantiomeric excess: 80% determined by chiral HPLC analysis, Chiralpak AD 1.0 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 240 nm, retention times (min): 29.2 (minor) and 31.3 (major). \([\alpha]_D^{20} = +19.6 (c 3.1, \text{CHCl}_3)\). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.45 – 7.42 (m, 3H), 7.39 (d, \(J = 9.8\) Hz, 1H), 7.33 – 7.21 (m, 5H), 7.18 (t, \(J = 7.1\) Hz, 1H), 6.12 (d, \(J = 9.8\) Hz, 1H), 3.97 (dq, \(J = 7.1, 10.8\) Hz, 1H), 3.85 (dq, \(J = 7.1, 10.8\) Hz, 1H), 3.04 (d, \(J = 9.8\) Hz, 1H), 3.01 – 2.88 (m, 1H), 2.84 – 2.65 (m, 2H), 2.40 – 2.25 (m, 2H), 2.24 – 2.09 (m, 1H), 2.05 – 1.90 (m, 1H), 1.76 – 1.53 (m, 2H), 1.00 (t, \(J = 7.1\) Hz, 3H). \(^1\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 203.0, 172.1, 146.8, 144.6, 142.5, 130.2, 129.5, 129.3, 128.3, 128.3, 126.8, 125.7, 125.7, 125.2, 64.2, 61.3, 60.3, 42.2, 41.1, 37.8, 34.8, 31.1, 13.8. HRMS (ESI+, \(m/z\)): calcd. for C\(_{25}\)H\(_{27}\)O\(_3\) [M+H]\(^+\): 375.1955; found: 375.1960.

(1R,2S,3S)-Ethyl 3-isopropyl-2’-oxo-2’H-spiro[cyclopentane-1,1’-naphthalene]-2-carboxylate (67)

Substrate 43a was reacted with isopropylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 67 as a yellow oil (55 mg, 70% yield). Enantiomeric excess: 54% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 240 nm, retention times (min): 17.6 (major) and 20.1 (minor). \([\alpha]_D^{20} = +34.4 (c 4.6, \text{CHCl}_3)\). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.48-7.26 (m, 4H), 7.37 (d, \(J = 9.8\) Hz, 1H), 6.11 (d, \(J = 9.8\) Hz, 1H), 3.96 (qd, \(J = 7.1, 10.7\) Hz, 1H), 3.84 (qd, \(J = 7.1, 10.8\) Hz, 1H), 3.16 (d, \(J = 9.6\) Hz, 1H), 2.88-2.81 (m, 1H), 2.26 (ddd, \(J = 5.1, 7.8, 12.9\) Hz, 1H), 2.12 (ddd, \(J = 8.1, 12.9, 16.7\) Hz, 1H), 1.93 (dq, \(J = 7.4, 13.3\) Hz, 2H), 1.75-1.66 (m, 1H), 0.99 (m, 9H, 3×CH\(_3\)). \(^1\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 202.7, 172.6, 146.5, 144.3, 130.2, 129.6, 129.3, 126.7, 125.6, 125.2, 61.9, 50.9, 60.2, 47.4, 40.9, 30.9, 26.2, 21.8, 18.1, 13.7. HRMS (ESI+, \(m/z\)): calcd. for C\(_{29}\)H\(_{55}\)O\(_3\) [M+H]\(^+\): 375.1798; found: 373.1776.
(1R,2S,3R)-Ethyl 3-(but-3-enyl)-2'-oxo-2'H-spirocyclopentane-1,1'-naphthalene)-2-carboxylate (68)

Substrate 43a was reacted with but-3-enylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 68 as a colorless oil (20 mg, 24% yield). Enantiomeric excess: 87% determined by chiral HPLC analysis, Chiralpak AD 1.0 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 240 nm, retention times (min): 16.0 (minor) and 18.8 (major). $\lbrack \alpha \rbrack_\text{D}^{20} = +31.9$ ($c$ 1.8, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.45-7.28 (m, 4H), 7.39 (d, $J$ = 10.3 Hz, 1H), 6.12 (d, $J$ = 9.7 Hz, 1H), 5.94-5.84 (m, 1H), 5.06 (d, $J$ = 16.9 Hz, 1H), 4.98 (d, $J$ = 10.2 Hz, 1H), 3.97 (qd, $J$ = 7.3, 10.5 Hz, 1H), 3.86 (qd, $J$ = 7.4, 11.0 Hz, 1H), 3.01 (d, $J$ = 9.9 Hz, 1H), 2.93-2.83 (m, 1H), 2.33-2.10 (m, 4H), 2.00-1.88 (m, 2H), 1.67-1.57 (m, 1H), 1.47-1.38 (m, 1H), 1.01 (t, $J$ = 7.1 Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 203.0, 172.2, 146.9, 144.5, 138.8, 130.2, 129.5, 129.3, 126.7, 125.8, 125.2, 114.4, 64.3, 61.3, 60.3, 41.9, 41.1, 35.0, 32.5, 31.0, 13.8. HRMS (ESI+, $m/z$): calcd. for C$_{21}$H$_{25}$O$_3$ [M+H]$^+$: 325.1798; found: 325.1776.

(1R,2S,3R)-Ethyl 3-methyl-2'-oxo-2'H-spirocyclopentane-1,1'-naphthalene)-2-carboxylate (69)

Substrate 43a was reacted with methyl magnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 69 as a colorless oil (23 mg, 32% yield). Enantiomeric excess: 82% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 230 nm, retention times (min): 21.9 (major) and 24.9 (minor). $\lbrack \alpha \rbrack_\text{D}^{20} = +43.8$ ($c$ 0.8, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.47 – 7.41 (m, 2H), 7.39 (d, $J$ = 9.8 Hz, 1H), 7.32 – 7.27 (m, 2H), 6.12 (d, $J$ = 9.8 Hz, 1H), 3.98 (dq, $J$ = 7.1, 10.8 Hz, 1H), 3.87 (dq, $J$ = 7.1, 10.8 Hz, 1H), 2.98 – 2.85 (m, 2H), 2.38 – 2.17 (m, 2H), 2.02 – 1.88 (m, 1H), 1.68 – 1.54 (m, 1H), 1.24 (d, $J$ = 8.0 Hz, 3H), 1.02 (t, $J$ = 4.0 Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 203.2, 172.1, 147.3, 144.5, 138.8, 130.2, 129.5, 129.2, 126.7, 125.9, 125.3, 66.2, 61.3, 60.3, 41.3, 37.4, 34.1, 20.1, 13.8. HRMS (ESI+, $m/z$): calcd. for C$_{18}$H$_{21}$O$_3$ [M+H]$^+$: 285.1485; found: 285.1481.
(1R*,2S*,3R*)-Ethyl 2’-oxo-3-phenyl-2'H-spiro[cyclopentane-1,1'-naphthalene]-2-carboxylate (70)

Substrate 43a was reacted with phenylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 70 as a colorless oil (7 mg, 8% yield). Enantiomeric excess: 0% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 230 nm, retention times (min): 29.3 and 74.5. 1H-NMR (400 MHz, CDCl3): δ 7.58 (d, J = 7.9 Hz, 1H), 7.50-7.46 (m, 1H), 7.44-7.40 (m, 2H), 7.36-7.31 (m, 2H), 7.24-7.20 (m, 1H), 6.17 (d, J = 9.8 Hz, 1H), 4.09 (td, J = 8.4, 10.0 Hz, 1H), 3.88 (qd, J = 7.1, 10.8 Hz, 1H). 13C-NMR (100 MHz, CDCl3): δ 202.9, 171.4, 146.7, 144.8, 144.3, 130.4, 129.6, 129.4, 128.5, 127.5, 126.9, 126.4, 125.8, 125.2, 66.1, 61.3, 60.4, 47.7, 41.5, 34.2, 13.7. HRMS (ESI+, m/z): calcd. for C23H22O3Na [M+Na]+: 369.1461; found: 369.1463.

(1R,2S,3R)-Ethyl 6’-bromo-3-ethyl-2’-oxo-2'H-spiro[cyclopentane-1,1'-naphthalene]-2-carboxylate (71)

Substrate 43b was reacted with ethylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 71 as a colorless oil (59 mg, 63% yield). Enantiomeric excess: 83% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 240 nm, retention times (min): 19.2 (major) and 23.4 (minor). [α]D²⁰ = +45.0 (c 3.7, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.53 (dd, J = 2.1, 8.4 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.32 (d, J = 3.4 Hz, 1H), 7.29 (d, J = 4.8 Hz, 1H), 6.15 (d, J = 9.9 Hz, 1H), 3.97 (qd, J = 7.1, 10.8 Hz, 1H), 3.87 (qd, J = 7.1, 10.8 Hz, 1H), 2.94 (d, J = 9.8 Hz, 1H), 2.84-2.74 (m, 1H), 2.31-2.21 (m, 2H), 1.96-1.88 (m, 1H), 1.88-1.79 (m, 1H), 1.64-1.55 (m, 1H), 1.41-1.29 (m, 1H), 1.03 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 202.2, 172.0, 145.6, 142.8, 132.8, 131.6, 131.5, 127.5, 126.4, 120.3, 63.9, 61.2, 60.4, 43.6, 40.9, 30.5, 28.4, 13.8, 12.4. HRMS (ESI+, m/z): calcd. for C19H22BrO3 [M+H]+: 377.0747; found: 377.0747.
(1R,2S,3R)-Ethyl 3-ethyl-6’-methoxy-2’-oxo-2’H-spiro[cyclopentane-1,1’-naphthalene]-2-carboxylate (72)

Substrate 43c was reacted with ethylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 72 as a colorless oil (52 mg, 63% yield). Enantiomeric excess: 86% determined by chiral HPLC analysis, Chiralpak AD 1.0 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 250 nm, retention times (min): 17.6 (minor) and 23.9 (major). \([\alpha]_D^{20} = +45.4\) (c 4.1, CHCl₃). \(^1\)H-NMR (400 MHz, CDCl₃): \(\delta \)

\[
\begin{align*}
7.35 & (d, J = 8.6 Hz, 1H), \\
7.32 & (d, J = 9.8 Hz, 1H), \\
6.98 & (dd, J = 2.8, 8.6 Hz, 1H), \\
6.81 & (d, J = 2.7 Hz, 1H), \\
6.12 & (d, J = 9.8 Hz, 1H), \\
3.97 & (qd, J = 7.1, 10.8 Hz, 1H), \\
3.86 & (qd, J = 7.1, 10.7 Hz, 1H), \\
3.84 & (s, 3H), \\
2.94 & (d, J = 9.9 Hz, 1H), \\
2.77 & (ddt, J = 4.4, 9.4, 12.5 Hz, 1H), \\
2.30-2.21 & (m, 2H), \\
1.97 & (m, 1H), \\
1.87 & (m, 1H), \\
1.64-1.54 & (m, 1H), \\
1.40-1.29 & (m, 1H), \\
1.02 & (t, J = 7.0 Hz, 3H), \\
1.01 & (t, J = 7.2 Hz, 3H).
\end{align*}
\]

\(^{13}\)C-NMR (100 MHz, CDCl₃): \(\delta \) 203.3, 172.4, 158.0, 144.3, 138.8, 130.5, 126.9, 125.7, 116.1, 113.7, 64.1, 60.9, 60.2, 55.4, 43.6, 40.9, 30.5, 28.3, 13.8, 12.4. HRMS (ESI+, m/z): calcd. for C₂₀H₂₄O₄Na [M+Na]⁺: 351.1567; found: 351.1561.

(1R,2S,3R)-Ethyl 3-ethyl-2’-oxo-2’H-spiro[cyclohexane-1,1’-naphthalene]-2-carboxylate (73)

Substrate 51 was reacted with ethylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 73 as a colorless oil (10 mg, 13% yield). Enantiomeric excess: 94% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 230 nm, retention times (min): 15.9 (minor) and 17.7 (major). \([\alpha]_D^{20} = +38.9\) (c 0.75, CHCl₃). \(^1\)H-NMR (400 MHz, CDCl₃): \(\delta \)

\[
\begin{align*}
7.55 & (d, J = 8.1 Hz, 1H), \\
7.43-7.39 & (m, 1H), \\
7.29-7.23 & (m, 3H), \\
6.11 & (d, J = 9.8 Hz, 1H), \\
3.81 & (qd, J = 6.6, 10.3 Hz, 1H), \\
3.75 & (qd, J = 6.6, 10.3 Hz, 1H), \\
2.79 & (d, J = 11.4 Hz, 1H), \\
2.75-2.66 & (m, 1H), \\
2.22-2.08 & (m, 2H), \\
1.86-1.81 & (m, 1H), \\
1.75-1.67 & (m, 1H), \\
1.59-1.52 & (m, 1H), \\
1.45 & (dddd, J = 4.5, 7.9, 12.1, 15.3 Hz, 1H), \\
1.15-0.97 & (m, 2H), \\
0.93 & (t, J = 7.4 Hz, 3H), \\
0.85 & (t, J = 7.1 Hz, 1H).
\end{align*}
\]

\(^{13}\)C-NMR (100 MHz, CDCl₃): \(\delta \) 201.3, 172.9, 145.2, 142.8, 129.84, 129.77, 129.2, 127.0, 126.9, 126.8, 59.9, 59.3, 51.3, 37.6, 34.7, 30.2, 27.6, 19.7, 13.8, 10.7. HRMS (ESI+, m/z): calcd. for C₂₀H₂₂O₃Na [M+Na]⁺: 335.1618; found: 335.1617.
Ethyl 3-ethyl-1’-oxo-1’H-spiro[cyclopentane-1,2’-naphthalene]-2-carboxylate (74)

Substrate 55 was reacted with ethylmagnesium bromide under the general reaction conditions. Column chromatography using n-pentane/diethyl ether (90:10-85:15-80:20) afforded 74 as a colorless oil as a mixture of diastereomers (8:1 dr, 31 mg, 41% yield). Enantiomeric excess: 89% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane: i-PrOH 98:2, 40 °C, 230 nm, retention times (min): 12.3 (major) and 14.1 (minor). [α]D20 = -66.4 (c 1.4, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.99 (d, J = 7.7 Hz, 1H), 7.53 (dt, J = 1.3, 7.5 Hz, 1H), 7.32 (dt, J = 1.1, 7.6 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.55 (d, J = 9.6 Hz, 1H), 6.13 (d, J = 9.7 Hz, 1H), 3.87-3.75 (m, 2H), 2.81-2.71 (m, 1H), 2.54 (d, J = 9.9Hz, 1H), 2.30-2.21 (m, 1H), 2.07 (ddd, J = 6.2, 7.8, 13.8 Hz, 1H), 1.84-1.71 (m, 2H), 1.51-1.40 (m, 1H), 1.33-1.22 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.1 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 201.8, 172.2, 139.7, 137.9, 134.0, 129.6, 127.7, 126.9, 126.8, 123.3, 61.6, 60.3, 59.0, 43.7, 37.1, 29.7, 28.5, 13.5, 12.5. HRMS (ESI+, m/z): calcd for C19H23O3 [M+H]+: 299.1642; found: 299.1632.

(1R,2S,3R)-6'-Bromo-3-ethyl-2’-oxo-2’H-spiro[cyclopentane-1,1’-naphthalene]-2-carboxylic acid (77)

In a solution of ethanol (2 mL) and 2N NaOH (2 mL) in a Schlenk tube, 71 was heated to 100 °C for 4 h. The reaction mixture was cooled to room temperature and acidified to pH 1. The aqueous layer was then extracted with dichloromethane (3×3 mL) and the combined organic layers were dried over MgSO4, filtered and concentrated to afford 77 as an off-white solid. Crystals suitable for X-ray analysis were obtained by slow diffusion of hexanes into a solution of 77 in ethyl acetate. Mp: 195-197 °C. 1H-NMR (400 MHz, CDCl3): δ 7.51 (dd, J = 2.1, 8.4 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 5.1, 9.7 Hz, 2H), 6.12 (d, J = 9.9 Hz, 1H), 2.99 (d, J = 9.3 Hz, 1H), 2.85 – 2.67 (m, 1H), 2.30 – 2.10 (m, 2H), 1.92 – 1.74 (m, 2H), 1.62 – 1.47 (m, 1H), 1.42 – 1.23 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 202.0, 178.1, 144.9, 143.2, 132.8, 131.9, 131.5, 127.1, 126.1, 120.5, 62.1, 61.6, 43.5, 41.2, 29.9, 28.6, 12.4. HRMS (ESI+, m/z): calcd for C19H16BrO3Na [M+Na]+: 371.0253; found: 371.0242. The supplementary crystallographic data can be obtained from The Cambridge Crystallographic Data Centre CCDC 816689 via www.ccdc.cam.ac.uk/data_request/cif.
Catalytic Asymmetric Conjugate Addition/Oxidative Dearomatization Towards Multifunctional Spirocyclic Compounds

Chroman-2-ol (79)

To a solution of chroman-2-one (7.4 g, 50 mmol) in dry dichloromethane (100 mL) at -78 °C was added diisobutylaluminum hydride (1.1 eq, 1 M in toluene, 55 mL, 55 mmol) by syringe pump over 2 h. The reaction mixture was left stirring at -78 °C for 2 h and 50 mL of water was added dropwise while the reaction mixture was allowed to warm to room temperature. Celite was added and the reaction mixture was filtered. The celite was washed with diethyl ether. The remaining salts and the celite were stirred with diethyl ether and filtered again. The combined organic layers were washed with brine (2x) and dried with Na2SO4, filtered and the solvent evaporated to yield chroman-2-ol 79 (7.42 g, 49.4 mmol, 99% yield) The crude product was used without further purification in the next step. The spectroscopic data matched those reported in the literature.67

(E)-Ethyl 5-(2-hydroxyphenyl)pent-2-enoate (80)

Chroman-2-ol 79 (7.33 g, 48.8 mmol) was dissolved in benzene (100 mL) and (carbethoxymethylene)triphenyl phosphorane (17.90 g, 48.8 mmol, 1 eq) dissolved in benzene (100 mL) was added and the mixture was stirred for 2 d at room temperature. The solvent was evaporated and the crude mixture was purified by column chromatography on silica (n-pentane/diethyl ether, 25:1 to 5:1) to give 80 (8.83 g, 40.1 mmol, 82% yield). The data spectroscopic matched those reported in the literature.67

(E)-Ethyl 3-(3-hydroxyphenyl)acrylate (82)

(E)-3-(3-Hydroxyphenyl)acrylic acid (8.2 g, 50 mmol) was dissolved in ethanol (50 mL) and sulfuric acid (2.67 mL, 50 mmol, 1 eq) was added dropwise. The reaction mixture was heated at reflux overnight. Most of the solvent was evaporated by rotatory evaporation and saturated aqueous Na2CO3 was added carefully. The aqueous layer was extracted with diethyl ether (3x) and the organic layers were washed with aqueous saturated aqueous Na2CO3 and brine, dried with MgSO4, filtered. The solvent was evaporated to give 82 (9.7 g, 49.9 mmol, 100 % yield) as a colorless oil. The spectroscopic data matched those reported in the literature.68
(E)-Ethyl 3-((tert-butyldimethylsilyl)oxy)phenyl)acrylate (83)

(E)-Ethyl 3-(3-hydroxyphenyl)acrylate 82 (5.0 g, 26.0 mmol) was dissolved in dry dichloromethane under a nitrogen atmosphere in a dry flask, imidazole (4.0 g, 59 mmol, 2.6 eq) and TBDMSCl (4.72 mL, 27.2 mmol, 1.2 eq) were added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was washed with an aqueous HCl solution (1M, 15 mL), aqueous sat. NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated. The crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 100:1 to 50:1) to give 83 as a colorless oil (7.54 g, 24.6 mmol, 95% yield). ¹H-NMR (400 MHz, CDCl₃): δ 7.62 (d, J = 16.0 Hz, 1H), 7.29 – 7.18 (m, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.00 – 6.98 (m, 1H), 6.86 (ddd, J = 8.1, 2.4, 0.9 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.01 – 0.98 (m, 9H), 0.22 – 0.19 (m, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 167.0, 156.0, 144.5, 135.8, 129.8, 122.1, 121.4, 119.3, 118.3, 61.5, 25.6, 18.2, 14.3, -4.4. HRMS (ESI+, m/z): calcd. for C₁₇H₂₅O₃SiNaNa [M+Na]+: 331.16999; found: 331.16937.

Ethyl 3-((tert-butyldimethylsilyl)oxy)phenyl)propanoate (84)

(E)-Ethyl 3-((3-((tert-butyldimethylsilyl)oxy)phenyl)acrylate 83 (7.0 g, 22.85 mmol) was dissolved in a mixture of EtOAc (20 mL) and EtOH (20 mL) under a nitrogen atmosphere and palladium on activated carbon (10 wt% Pd, 1.72 g, 1.61 mmol) was added to the reaction mixture. The reaction mixture was brought under a hydrogen atmosphere with a balloon (1 atm) and stirred for two nights. The reaction mixture was filtered over celite and the celite was subsequently washed with EtOAc. The solvent was evaporated and the crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 50:1) to give 84 (5.18 g, 16.8 mmol, 74% yield). ¹H-NMR (400 MHz, CDCl₃): δ 7.16 – 7.10 (m, 1H), 6.82 – 6.76 (m, 1H), 6.70 – 6.65 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.89 (t, J = 8.0 Hz, 2H), 2.59 (t, J = 8.0 Hz, 2H), 1.24 (td, J = 7.1, 0.8 Hz, 4H), 0.99 – 0.97 (m, 9H), 0.19 – 0.18 (m, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 172.9, 155.7, 142.1, 129.3, 121.3, 120.0, 117.9, 60.4, 35.9, 30.8, 25.7, 18.2, 14.2, -4.4. HRMS (ESI+, m/z): calcd. for C₁₇H₂₅O₃SiNa [M+Na]+: 331.16999; found: 331.16937.
3-(3-((tert-Butyldimethylsilyl)oxy)phenyl)propanal (85)

Ethyl 3-(3-((tert-butylidemethylsilyl)oxy)phenyl)propanoate 84 (3.0 g, 9.72 mmol) was dissolved in dry dichloromethane (20 mL) under a nitrogen atmosphere and cooled to -78 °C. Diisobutylaluminium hydride (1.0 M in toluene, 14.6 mL, 14.6 mmol, 1.5 eq) was added slowly in order to maintain the temperature. The reaction was followed by TLC (n-pentane/diethyl ether, 25:1). After 30 min full conversion of the starting material was reached. The reaction was quenched with a saturated aqueous NH₄Cl solution and after warming to room temperature, the organic layer was washed with a saturated aqueous Rochelle’s salt solution (potassium sodium tartrate tetrahydrate) and the aqueous layer was extracted with dichloromethane and the solvent evaporated. Although ¹H-NMR analysis showed quite some overreduction to the alcohol, the crude product was used without any further purification in the next step.

(E)-Ethyl 5-(3-((tert-Butyldimethylsilyl)oxy)phenyl)pent-2-enoate (86)

3-(3-((tert-Butyldimethylsilyl)oxy)phenyl)propanal 85 (2.57 g, 9.72 mmol) was dissolved in benzene (20 mL) and (carbethoxymethylene)triphenylphosphorane (3.56 g, 9.72 mmol, 1 eq) dissolved in benzene (20 mL) was added and the mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (n-pentane/diethyl ether, 25:1) to give 86 (2.17 g, 6.49 mmol, 67% yield) over two steps. ¹H-NMR (400 MHz, CDCl₃): δ 7.14 (t, J = 7.7 Hz, 1H), 6.99 (ddt, J = 15.5, 6.8, 0.6 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.71 – 6.64 (m, 2H), 5.83 (ddd, J = 15.6, 2.5, 1.4 Hz, 1H), 4.18 (qd, J = 7.1, 0.9 Hz, 2H), 2.72 (t, J = 7.7 Hz, 2H), 2.50 (dd, J = 14.6, 7.7 Hz, 2H), 1.28 (td, J = 14.6, 7.7 Hz, 2H), 0.98 (d, J = 1.0 Hz, 9H), 0.19 (d, J = 1.0 Hz, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 166.5, 155.7, 148.0, 142.3, 129.3, 121.8, 121.3, 120.1, 117.8, 60.2, 34.2, 33.8, 25.7, 18.2, 14.3, -4.4. HRMS (ESI+, m/z): calcd. for C₁₉H₂₇O₃Si [M+H]+: 335.20370; found: 335.20358.

(E)-ethyl 5-(3-hydroxyphenyl)pent-2-enoate (87)

(E)-ethyl 5-(3-((tert-Butyldimethylsilyl)oxy)phenyl)pent-2-enoate 86 (2.11 g, 6.31 mmol) was dissolved in THF (30 mL) and cooled down to 0 °C and TBAF (1.0 M in THF, 12.6 mL, 12.6 mmol, 2 eq) was added. The reaction mixture was stirred overnight while slowly warming to room temperature. Full conversion was reached (TLC, n-pentane/diethyl ether, 9:1) and the reaction mixture was diluted with diethyl ether and washed with brine (3x). The organic layer was dried with Na₂SO₄, filtered and the solvent
evaporated. The crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 9:1 - 3:1) to give 87 (1.23 g, 5.58 mmol, 88 % yield) as a slightly yellow oil. ¹H-NMR (400 MHz, CDCl₃): δ 7.14 (t, J = 7.8 Hz, 1H), 7.02 (dt, J = 15.7, 6.8 Hz, 1H), 6.78 – 6.66 (m, 3H), 6.13 (s, 1H), 5.86 (dt, J = 15.6, 1.6 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.73 – 2.68 (m, 2H), 2.53 – 2.46 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 167.2, 155.9, 148.6, 142.5, 129.6, 121.6, 120.4, 115.3, 113.2, 60.5, 34.1, 33.7, 14.2.

**Ethyl 3-(4-hydroxyphenyl)propanoate (89)**

Compound 89 was prepared according to the procedure for compound 82 above, using 88 (8.31 g, 50.0 mmol). The crude product was purified by column chromatography on silica to give 89 (9.7 g, 49.9 mmol, 100% yield). ¹H-NMR (400 MHz, CDCl₃): δ 7.06 – 7.01 (m, 2H), 6.77 – 6.72 (m, 2H), 6.19 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 173.6, 154.3, 132.2, 129.3, 115.3, 60.6, 36.3, 30.1, 14.1. HRMS (ESI+, m/z): calcd. for C₁₁H₁₄O₃Na [M+Na]+: 217.08352; found: 217.08296.

**Ethyl 3-((tert-butyldimethylsilyl)oxy)phenyl)propanoate (90)**

Compound 90 was prepared according to the procedure for compound 83 above, using 89 (4.6 g, 23.7 mmol). The crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 50:1) to give 90 (6.24 g, 20.2 mmol, 85% yield). ¹H-NMR (400 MHz, CDCl₃): δ 7.05 (d, J = 8.3 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.88 (t, J = 7.8 Hz, 2H), 2.58 (t, J = 7.8 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.00 – 0.96 (m, 9H), 0.19 – 0.16 (m, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 173.0, 153.9, 133.2, 129.1, 119.9, 60.3, 36.2, 30.2, 25.7, 18.2, 14.2, -4.5. HRMS (ESI+, m/z): calcd. for C₁₇H₂₉O₃Si [M+H]+: 309.18805; found: 309.18787.

**3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanal (91)**

Ester 90 (6.2 g, 20.1 mmol) was dissolved in dry dichloromethane (40 mL) in a dry flask under nitrogen. The mixture was cooled down to -78 °C and disobutylaluminium hydride (1.0 M in toluene, 21.1 mL, 21.1 mmol, 1.05 eq) was added slowly and the mixture was stirred at -78 °C and the conversion was followed by TLC (n-pentane/diethyl ether, 20:1). The reaction was quenched after 1 h with a saturated aqueous NH₄Cl solution.
The layers were separated and the organic layer was washed with a saturated aqueous Rochelle's salt solution and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried with Na$_2$SO$_4$. The solvent was evaporated and the crude product was used without further purification in the next step.

**(E)-Ethyl 5-((tert-butyldimethylsilyl)oxy)phenyl)pent-2-enoate (92)**

Compound 92 was prepared according to the procedure for compound 80 above, using 91 (5.05 g, 19.1 mmol). The crude product was purified by column chromatography on silica (n-pentane/diethyl ether 100:1 – 75:1) to give 92 (3.29 g, 9.83 mmol, 52% yield over two steps). $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.06 – 6.94 (m, 3H), 6.79 – 6.74 (m, 2H), 5.83 (dt, $J$ = 15.6, 1.5 Hz, 1H), 4.18 (qd, $J$ = 7.1, 2.3 Hz, 2H), 2.77 – 2.64 (m, 2H), 2.54 – 2.42 (m, 2H), 1.28 (td, $J$ = 7.1, 2.3 Hz, 3H), 1.00 – 0.97 (m, 9H), 0.20 – 0.18 (m, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 166.6, 153.9, 148.2, 133.5, 129.1, 121.7, 119.9, 60.1, 34.1, 33.5, 25.7, 18.2, 14.2, -4.5. HRMS (ESI+, m/z): calcd. for C$_{19}$H$_{31}$O$_3$Si [M+H]$^+$: 335.20370; found: 335.20386.

**(E)-Ethyl 5-(4-hydroxyphenyl)pent-2-enoate (93)**

Compound 93 was prepared according to the procedure for compound 87 above, using 92 (1.5 g, 4.48 mmol). The crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 10:1 – 3:1) to give 93 (966 mg, 4.39 mmol, 98% yield). $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.06 – 6.96 (m, 3H), 6.77 (d, $J$ = 8.6 Hz, 2H), 5.84 (dt, $J$ = 15.7, 1.6 Hz, 1H), 5.76 (s, $J$ = 9.7 Hz, 1H), 4.19 (q, $J$ = 7.1 Hz, 2H), 2.69 (t, $J$ = 7.7 Hz, 2H), 2.52 – 2.44 (m, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 167.1, 154.2, 148.7, 132.6, 129.6, 129.3, 121.6, 115.3, 115.2, 60.4, 34.2, 33.4, 14.2. HRMS (ESI+, m/z): calcd. for C$_{13}$H$_{17}$O$_3$ [M+H]$^+$: 221.11722; found: 221.11700.

**(+-)Ethyl 3-ethyl-5-(2-hydroxyphenyl)pentanoate (94)**

Copper(I) iodide (2.4 mg, 12 μmol, 5 mol%) and (R)(+)-BINAP (11.7 mg, 19 μmol, 7.5 mol%) were dissolved in dry dichloromethane (0.4 mL) in a flame dried Schlenk vessel and stirred for 15 min after which the reaction mixture was cooled to -40 °C. Ethylmagnesium bromide (1.0 M in t-BuOMe, 624 μL, 0.624 mmol, 2.5 eq) was added and the mixture was stirred for another 10 min. (E)-ethyl 5-(2-hydroxyphenyl)pent-2-enoate (55.0 mg, 0.25 mmol) 80 dissolved in dichloromethane (0.8 mL) was added over one hour by a
syringe pump and the mixture was stirred overnight. Upon full conversion (TLC, n-pentane/diethyl ether, 10:1) the reaction mixture was quenched with a saturated aqueous NH₄Cl solution and extracted with dichloromethane. The combined organic layers were dried with Na₂SO₄, filtered and the solvent evaporated. The crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 9:1 - 6:1) to yield 94 (49 mg, 0.196 mmol, 78% yield). Enantiomeric excess: 83% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane: i-PrOH 99:1, 40 °C, 275 nm, retention times (min): 58.9 (minor) and 61.0 (major). [α]₂₀° = +2.79 (c 1.0, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 7.12 – 7.06 (m, 2H), 6.87 – 6.80 (m, 2H), 5.82 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.71 – 2.55 (m, 2H), 2.40 (qd, J = 14.3, 6.7 Hz, 2H), 1.87 (dp, J = 13.1, 6.6 Hz, 1H), 1.70 – 1.53 (m, 2H), 1.50 – 1.33 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 174.1, 153.9, 130.0, 128.1, 127.2, 120.5, 115.7, 60.6, 38.1, 36.6, 33.5, 27.1, 26.8, 14.2, 11.1. HRMS (ESI+, m/z): calcd. for C₁₅H₂₃O₃ [M+H]+: 251.16417; found: 251.16429.

(+)‐Ethyl 3‐ethyl‐5‐(3‐hydroxyphenyl)pentanoate (95)

Compound 95 was prepared according to the procedure for compound 94 above, using 87 (55 mg, 0.25 mmol). The crude product was purified by column chromatography on silica (n-pentane/diethyl ether 9:1 – 3:1) to give 95 (50 mg, 0.2 mmol, 80% yield). Enantiomeric excess: 97% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane/i-PrOH 97:3, 40 °C, 275 nm, retention times (min): 35.4 (minor) and 37.5 (major). [α]₂₀° = +8.16 (c 1.0, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 7.16 – 7.09 (m, 1H), 6.77 – 6.62 (m, 3H), 5.99 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 2.55 (dd, J = 9.0, 7.4 Hz, 2H), 2.31 (dd, J = 6.9, 1.9 Hz, 2H), 1.89 (dp, J = 13.2, 6.6 Hz, 1H), 1.68 – 1.53 (m, 2H), 1.49 – 1.32 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 174.1, 155.8, 144.3, 129.4, 120.5, 115.3, 112.7, 60.5, 38.7, 36.1, 35.0, 32.8, 26.1, 14.2, 10.6. HRMS (ESI+, m/z): calcd. for C₁₅H₂₃O₃ [M+H]+: 251.16417; found: 251.16429.

(+)‐Ethyl 3‐ethyl‐5‐(4‐hydroxyphenyl)pentanoate (96)

Compound 96 was prepared according to the procedure for compound 94 above, using 93 (55 mg, 0.25 mmol). The crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 9:1 – 5:1) to give 96 (58.6 mg, 0.234 mmol, 94% yield). Enantiomeric excess: 96% determined by chiral HPLC analysis, Chiralpak AD 1.0 mL/min, n-heptane/i-PrOH 97:3, 40 °C, 275 nm, retention times (min): 23.9 (minor) and 29.2 (major). [α]₂₀° = +9.17 (c 1.0, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 7.05 – 6.98
(m, 2H), 6.79 – 6.73 (m, 2H), 5.75 (br s, 1H), 4.14 (q, \( J = 7.1 \text{ Hz}, 2\text{H} \)), 2.53 (t, \( J = 7.1 \text{ Hz}, 2\text{H} \)), 2.31 (dd, \( J = 6.9, 2.1 \text{ Hz}, 2\text{H} \)), 1.87 (dp, \( J = 13.1, 6.6 \text{ Hz}, 1\text{H} \)), 1.65 – 1.50 (m, 2H), 1.50 – 1.33 (m, 2H), 1.26 (t, \( J = 7.1 \text{ Hz}, 3\text{H} \)), 0.89 (t, \( J = 7.4 \text{ Hz}, 3\text{H} \)). \(^{13}\text{C}-\text{NMR} (100 \text{ MHz, CDCl}_3): \delta 174.0, 153.8, 134.3, 129.3, 115.2, 60.4, 38.7, 36.2, 35.5, 32.0, 26.2, 14.2, 10.7. \text{HRMS (ESI+}, m/z): \text{calcd. for C}_{15}\text{H}_{23}\text{O}_3 [\text{M+H}]^+: 251.16417; \text{found: 251.16435.}

2-(1\text{H}-\text{Pyrrol-1-yl})ethanol (102)

[Chemical structure]

Ethanolamine (50 g, 0.82 mol) was added to glacial acetic acid (100 mL) while cooling with an ice-salt bath to keep the temperature between 15-25 °C. After the addition was completed, 2,5-dimethoxytetrahydrofuran (25 g, 0.189 mol) was added in one portion and the ice bath was removed and the reaction was set up for distillation. At 125 °C distillation of a liquid commenced. After 1.5 h the reaction mixture was cooled down to rt, diluted with water (200 mL) and extracted with dichloromethane (3x). The organic layer was washed with brine and a saturated aqueous Na\(_2\)CO\(_3\) solution, dried with Na\(_2\)SO\(_4\), filtered and the solvent evaporated. The residue, containing the product and the corresponding acetate, was dissolved in methanol (65 mL) and an aqueous solution of NaOH (50 mL, 20 wt%) and the solution was left at rt for 1 h. The solution was poured into brine, extracted with dichloromethane, dried with Na\(_2\)SO\(_4\), filtered and the solvent evaporated. The crude product was purified by flash chromatography on silica (n-pentane/diethyl ether, 2:1) to give 102 (13.6 g, 0.122 mol, 65% yield) as a slightly yellow oil. \(^1\text{H}-\text{NMR} (400 \text{ MHz, CDCl}_3): \delta 6.71 (t, \( J = 2.1 \text{ Hz}, 2\text{H} \)), 6.18 (t, \( J = 2.1 \text{ Hz}, 2\text{H} \)), 4.02 (t, \( J = 4.0 \text{ Hz}, 2\text{H} \)), 3.84 (br s, 2H), 1.84 (br s, 1H). \(^{13}\text{C}-\text{NMR} (100 \text{ MHz, CDCl}_3): \delta 120.8, 108.5, 62.9, 51.9.

3-(1\text{H}-\text{Pyrrol-1-yl})propanal (108)

[Chemical structure]

3-(1\text{H}-pyrrol-1-yl)propanenitrile 107 (5.0 g, 41.6 mmol) was dissolved in dry dichloromethane (83 mL) under a nitrogen atmosphere and cooled down to -78 °C. Diisobutylaluminium hydride (1.0 M in dichloromethane, 43.7 mL, 43.7 mmol, 1.05 eq) was added dropwise and the reaction mixture was stirred at this temperature for 2 h and then for 2 h at 0 °C. The reaction mixture was quenched by adding a saturated aqueous NH\(_4\)Cl solution (12 mL) and diluted with diethyl ether. The reaction mixture was washed with a saturated aqueous Rochelle’s salt solution and the layers were separated. The aqueous layer was extracted with dichloromethane (3x) and the combined organic layers were washed with brine, dried with Na\(_2\)SO\(_4\), filtered and the solvent evaporated. Although \(^1\text{H}-\text{NMR} analysis showed that the conversion to the aldehyde was not very high, the crude product was used without further purification in the next step.
(E)-Ethyl 5-(1H-pyrrol-1-yl)pent-2-enoate (109)

3-(1H-pyrrol-1-yl)propanal 108 (5.12 g, 41.6 mmol) was dissolved in benzene (80 mL) and (carbethoxymethylene)triphenylphosphorane (14.5 g, 41.6 mmol, 1.0 eq) dissolved in benzene (80 mL) was added and the reaction mixture was stirred for two days at room temperature. The solvent was evaporated and the crude mixture was purified by column chromatography on silica (n-pentane/diethyl ether, 9:1) to give 109 (1.89 g, 9.78 mmol, 24% yield over 2 steps) as a light yellow oil. 1H-NMR (400 MHz, CDCl 3): δ 6.90 (dt, J = 15.7, 7.1 Hz, 1H), 6.65 (t, J = 2.1 Hz, 2H), 6.15 (t, J = 2.0 Hz, 2H), 5.85 (dt, J = 15.6, 1.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.02 (t, J = 7.2 Hz, 2H), 2.67 (qd, J = 7.2, 1.5 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). 13C-NMR (100 MHz, CDCl 3): δ 166.0, 144.1, 123.6, 120.3, 108.4, 60.3, 48.0, 34.3, 14.2. HRMS (ESI+, m/z): calcd. for C 11H 16NO 2 [M+H] +: 194.11756; found: 194.11719.

(-)-Ethyl 3-ethyl-5-(1H-pyrrol-1-yl)pentanoate (110)

In a flame-dried Schlenk tube equipped with a septum and a stirring bar, (S)-Tol-BINAP (5.1 mg, 7.5 μmol, 1.5 mol%) and copper(I) iodide (0.96 mg, 5.0 μmol, 1.0 mol%) were dissolved in dry t-BuOMe (1.0 mL). The mixture was stirred for 15 min, cooled to -40 °C followed by addition of ethylmagnesium bromide (1.0 M in t-BuOME, 2.5 mL, 2.5 mmol, 5 eq). After stirring for 5 min, a solution of (E)-ethyl 5-(1H-pyrrol-1-yl)pent-2-enoate 109 (97 mg, 0.50 mmol) in t-BuOMe (250 μL) was added dropwise over 1 h using a syringe pump and the reaction mixture was stirred overnight. The reaction mixture was quenched by subsequent addition of methanol (0.5 mL) and aqueous NH 4Cl solution (1N, 2.0 mL) followed by warming to room temperature. The reaction mixture was extracted with diethyl ether (3×5 mL) and the combined organic layers were dried with Na 2SO 4, filtered and the solvent evaporated. The crude product was purified by column chromatography on silica (n-pentane/diethyl ether, 20:1) to give 110 (102 mg, 0.46 mmol, 92% yield) as a colorless oil. Enantiomeric excess: 92% determined by chiral HPLC analysis, Chiralcel OD-H 0.5 mL/min, n-heptane/i-PrOH 99.5:0.5, 40 °C, 215 nm, retention times (min): 24.2 (major) and 26.0 (minor). [α] D 20 = - 5.80 (c 1.0, CHCl 3). 1H-NMR (400 MHz, CDCl 3): δ 6.66 (t, J = 1.9 Hz, 2H), 6.14 (t, J = 1.9 Hz, 2H), 4.14 (qd, J = 7.1, 0.8 Hz, 2H), 3.91 (dd, J = 8.0, 6.9 Hz, 2H), 2.27 (ddd, J = 39.1, 15.1, 6.3 Hz, 2H), 1.90 – 1.75 (m, 3H), 1.48 – 1.32 (m, 2H), 1.26 (t, J = 7.1, 0.9 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). 13C-NMR (100 MHz, CDCl 3): δ 172.9, 120.3, 107.9, 60.3, 47.3, 38.3, 35.2, 34.1, 26.2, 14.2, 10.7. HRMS (ESI+, m/z): calcd. for C 13H 22NO 2 [M+H] +: 224.16451; found: 224.16411.
(7R*,8S*)-Ethyl 7-ethyl-5,6,7,8-tetrahydroindolizine-8-carboxylate

(–)-Ethyl 3-ethyl-5-(1H-pyrrol-1-yl)pentanoate 110 (56.0 mg, 0.251 mmol, 92% ee) was dissolved in dry THF (25 mL) under a nitrogen atmosphere in a dried Schlenk flask. The solution was cooled to -78 °C and LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol, 2.2 eq) was added. After stirring for 1 h the reaction mixture was allowed to warm to 10 °C and ferrocenium hexafluorophosphate (91 mg, 0.276 mmol, 1.1 eq) was added. The reaction mixture was stirred for an additional 10 min followed by filtration over a plug of silica gel (n-pentane:ethyl acetate, 3:1) The solvent was evaporated and the crude product was purified by column chromatography using n-pentane as the eluent to wash away the ferrocenium hexafluorophosphate followed by a mixture of n-pentane/diethyl ether (30:1) to give an inseparable mixture of product (112) and starting material (110) (43 mg, 77% combined yield).

4.6 References

Chapter 4
