Synthetic applications of the catalytic asymmetric 1,4-addition
Naasz, Robert

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Naasz, R. (2002). Synthetic applications of the catalytic asymmetric 1,4-addition. [Thesis fully internal (DIV), University of Groningen]. s.n.

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 10-12-2023
Chapter 6

Enantioselective synthesis of bicyclic compounds via catalytic 1,4-addition and ring closing metathesis

6.1 Introduction

The synthesis of enantiomerically pure bicyclic compounds constitutes an important synthetic challenge, as has already been indicated in the introduction to Chapter 4. As an extension of the aldol based annulations discussed in that chapter, we envisioned that a variety of enantiomerically pure bicyclic products would become readily accessible by using a combination of ring closing metathesis (RCM) and the enantioselective 1,4-addition. In these bicyclic products the size of each ring can easily be varied, independent of one another (Scheme 6.1).

The following considerations were made: (i) Cyclic enones with different ring sizes and substituents can be employed in the catalytic 1,4-addition with enantioselectivities generally exceeding 96% in the products. These products can subsequently act as templates onto which a second ring can be annulated; (ii) The use of RCM for this annulation would make it possible to vary the size of the second ring.2

Scheme 6.1 Concept of the RCM based enantioselective synthesis of bicyclic systems.
Chapter 6

6.2 Ring closing metathesis (RCM)

Olefin metathesis can be defined as the metal catalyzed redistribution of carbon-carbon double bonds. After the first report of such double bond scrambling reactions in 1955, olefin metathesis initially found relatively few applications, but became one of the most important organic reaction of the 90’s with the introduction of well defined catalysts. Although the topic of olefin metathesis has been reviewed extensively, a short historic overview of the development of olefin metathesis and its major applications, focussing on ring closing metathesis, will be given below.

The olefin metathesis reaction has various applications and some examples are depicted in Scheme 6.2. The most important applications are ring closing metathesis (RCM) and ring opening metathesis polymerization (ROMP), but other reactions, such as acyclic diene metathesis polymerization (ADMET), ring opening metathesis (ROM), and cross metathesis (CM) are also possible.

The main reasons as to why olefin metathesis reactions initially found little application (vide supra) were the poorly defined, multicomponent catalyst systems that were used together with the harsh conditions and strong Lewis acids that were required to perform the reaction. Two important contributions allowed the development of olefin metathesis into a synthetically useful tool. The first one was the observation of Calderon et al, that the ring opening polymerization reaction of cyclic alkenes and the disproportionation of linear alkenes were actually examples of the same reaction, as was not recognized previously. Incidentally, Calderon was also the first to use the term “olefin metathesis” in the same
publication. The second major contribution was the mechanism proposed by Chauvin, which is still generally accepted today.\(^8\) Chauvin suggested that olefin metathesis involved the interconversion of an olefin and a metalalkylidene. This process is believed to occur via a metallacyclobutane intermediate, by alternating [2+2] cycloadditions and cycloreversions as exemplified for RCM in Scheme 6.3. Note that all the individual steps in the catalytic cycle are reversible, it therefore is necessary to shift the equilibrium in one direction to make this reaction useful in preparative terms. In the case of RCM, the forward process is entropically driven because RCM cuts one substrate molecule into two products. In most cases one of the products will be volatile (e.g. ethene or propene) and the desired cycloalkene product will accumulate in the reaction mixture.

![Scheme 6.3 General mechanism for RCM.](image)

This mechanistic proposal was the starting point for a more rational design of catalysts and understanding of catalyst activity. This eventually led to the development of the first single component catalysts such as (CO)\(_5\)W=CPh\(_2\),\(^9\) bis(cyclopentadienyl) titanocyclobutanes,\(^10\) tris(aryloxide) tantalacyclobutanes,\(^11\) and various tungsten dihaloalkoxide-alkylidene complexes\(^12\) in the late 1970s and early 1980s. The real breakthrough for RCM came in 1992, when Fu and Grubbs reported the successful application of the molybdenum complex \(6.1\), previously described by Schrock \textit{et al.},\(^13\) for the RCM of several substrates, resulting in the formation of 5-, 6-, and 7-membered rings.\(^14\) A year later, Grubbs reported the use of the ruthenium alkylidene complex \(6.2a\) which also gave excellent results in the RCM of various substrates.\(^15\) In 1995, the ruthenium complex now widely known as “Grubbs catalyst” \(6.2b\), was reported for the first time.\(^16\) Both \(6.1\) and \(6.2b\) are commercially available nowadays.
The catalysts 6.1 and 6.2b turned out to be complementary in their reactivity. Ruthenium complex 6.2b is very stable, easy to handle, and tolerates a wide variety of functional groups in the substrates. Complex 6.1, although being sensitive to moisture and air and consequently difficult to handle, is very efficient in catalyzing the RCM of sterically hindered alkenes that do not react in the presence of 6.2b. Furthermore, RCM proved to be a valuable tool for the construction of medium sized and macrocyclic ring systems that are not readily available by other methods. As a consequence, RCM started to be used increasingly in organic synthesis as is nicely illustrated by the numerous examples of total syntheses of natural compounds using RCM in at least one of the key steps. An illustrative example is found in the synthesis of epothilone A, as shown in Scheme 6.4.

**Scheme 6.4 Synthesis of epothilone A through RCM as reported by both Nicolaou and Schinzer.**

Apart from being a nice example of the power of RCM as a synthetic tool, the synthesis of epothilone A also illustrates a major challenge in the development of new catalysts for RCM.
The complete lack of $E/Z$ stereoselectivity in the closure of such large rings emphasizes the need for better catalysts. Fürstner et al. have partially solved this problem by using molybdenum catalyst 6.6 (Figure 6.2) for the RCM of alkynes instead of alkenes.\textsuperscript{20} The resulting cyclic alkynes are subsequently reduced selectively to give $Z$-alkenes with the use of Lindlar catalyst. This strategy has been successfully applied in the total syntheses of epothilone A and C,\textsuperscript{21} but the development of $E$ and $Z$ selective catalysts for RCM of macrocyclic structures remains one of the biggest challenges in this field. Other interesting recent developments in catalyst design have been the introduction of water soluble RCM catalysts\textsuperscript{22} and the development of cheap and more user friendly RCM catalysts.\textsuperscript{18a,23} Very important has been the development of ruthenium-based catalysts bearing $N$-heterocyclic carbene ligands, \textit{e.g.} 6.7, almost simultaneously reported by three groups.\textsuperscript{24} These catalysts have the advantage that they are (at least) as stable and tolerant towards functional groups as the Grubbs catalyst (6.2b), but are able to catalyze the RCM of sterically hindered olefins to form tetrasubstituted cycloalkenes which are beyond the reach of the “normal” Grubbs catalyst.\textsuperscript{25} Another interesting development is the successful application of chiral “Schrock-like” molybdenum complexes, \textit{e.g.} 6.8, in asymmetric catalysis and kinetic resolutions.\textsuperscript{26}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/figure6.2.png}
\caption{New generation of RCM catalysts.}
\end{figure}

### 6.3 Catalytic enantioselective tandem 1,4-addition-allylic substitution

As mentioned in Chapter 4, zinc enolates resulting from the catalytic 1,4-addition of dialkylzinc reagents to 2-cyclohexenone or 2-cycloheptenone can be trapped stereo- and regioselectively by a Pd-allyl complex, generated \textit{in situ} from allyl acetate and a catalytic amount of Pd($\text{PPh}_3)_4$ to give disubstituted cycloalkanones in good yields. To test the concept shown in Scheme 6.1, we extended the tandem 1,4-addition-allylic substitution reaction to different substrates and zinc reagents (Scheme 6.5, Table 6.1). Note that entries 1 and 2 of Table 6.1 have already been presented in Chapter 4; they have been included here for the purpose of comparison.
Scheme 6.5 Tandem 1,4-addition-allylic substitution (m, R and R'; see Table 6.1).

The results summarized in Table 6.1 demonstrate that the tandem 1,4-addition allylic substitution reaction proceeds readily also with other substrates and organozinc reagents. The tandem addition to 2-cyclooctenone (6.9c) proceeded in a reasonable yield with high ee and was virtually diastereoselective. Addition to 4,4-disubstituted cyclohexenone 6.9d was completely diastereoselective. The use of Me₂Zn resulted in a high ee of 96%, but the diastereoselectivity was slightly lower compared to the other entries (entry 5). This probably is due to the lower steric requirements of the methyl group. On the other hand the use of n-Bu₂Zn led to a good trans/cis selectivity of 9/1 but a slightly lower ee of 93% (entry 6).

### Table 6.1 Tandem 1,4-addition-allylic substitution to 2-cycloalkenones.

<table>
<thead>
<tr>
<th>entry</th>
<th>enone</th>
<th>m</th>
<th>R</th>
<th>R¹</th>
<th>product</th>
<th>c.y. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>trans/cis&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.9a</td>
<td>1</td>
<td>H</td>
<td>Et</td>
<td>6.10a</td>
<td>88</td>
<td>96</td>
<td>9/1</td>
</tr>
<tr>
<td>2</td>
<td>6.9b</td>
<td>2</td>
<td>H</td>
<td>Et</td>
<td>6.10b</td>
<td>86</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>trans&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>6.9c</td>
<td>3</td>
<td>H</td>
<td>Et</td>
<td>6.10c</td>
<td>79</td>
<td>97</td>
<td>196/1</td>
</tr>
<tr>
<td>4</td>
<td>6.9d</td>
<td>1</td>
<td>Me</td>
<td>Et</td>
<td>6.10d</td>
<td>82</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>trans&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>6.9a</td>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>6.10e</td>
<td>92</td>
<td>96</td>
<td>5.3/1</td>
</tr>
<tr>
<td>6</td>
<td>6.9a</td>
<td>1</td>
<td>H</td>
<td>n-Bu</td>
<td>6.10f</td>
<td>83</td>
<td>93</td>
<td>9/1</td>
</tr>
</tbody>
</table>

(a) Isolated yield after column chromatography. (b) Determined by chiral GC (see experimental section). (c) Determined by GC. (d) Not determined. (e) Only trans detected.

### 6.4 Annulation of a 6-membered ring through RCM

To form a 6-membered ring starting from disubstituted cycloalkenones 6.10a-f according to Scheme 6.1, an allyl group has to be introduced. One way to do so is by a simple 1,2-addition of an allylic Grignard reagent onto the carbonyl functionality, as shown in Scheme 6.6.
Scheme 6.6 1,2-Addition to 6.10a-f and subsequent formation of a 6-membered ring through RCM.

Table 6.2 summarizes the results obtained in the 1,2-addition. As expected, a reasonable selectivity was observed in all cases for the addition of allylmagnesium chloride to 6.10a-f and the major isomer most likely resulted from attack of the Grignard reagent trans to the allyl group, leading to the all-trans isomer as the major product (Scheme 6.6). Addition to a 90/10 trans/cis mixture of 6.10a (entry 1) yielded three out of four possible diastereomers of 1,2-diallyl-3-ethylcyclohexanol (6.11a) in a ratio of 74:16:10, as determined by GC. This result is explained as follows: addition of the Grignard reagent to the trans compound (2R,3S)-6.10a proceeds preferably trans to the allyl group (equatorial approach), but not with complete selectivity, accounting for 74% (1R,2R,3S)-1,2-diallyl-3-ethylcyclohexanol (6.11a) and 16% (1S,2R,3S)-6.11a. The relative configuration of the major isomer was determined by COSY, HSQC, and NOESY NMR experiments on the p-nitrobenzoate ester of 6.12a (Section 6.5). Addition to the minor cis compound (2S,3S)-6.10a accounts for the 10% of another isomer of 6.11a, most probably (1S,2S,3S)-6.11a. This is in accordance with results reported in the literature for the stereochemistry of the 1,2-addition of methyllithium to both trans- and cis-2-ethyl-3-methylcyclohexanone. The stereochemical outcome of the 1,2-addition can also be explained using the Felkin model for nucleophilic additions to cyclic enones (Scheme 6.7).
According to this model, formation of the axial alcohol (equatorial approach) requires a partially eclipsed transition state (E‡) involving torsional strain between the nucleophile and the axial hydrogen in the α-position. On the other hand, formation of the equatorial alcohol proceeds through a staggered transition state A‡, generating steric strain between the nucleophile and the β-axial substituents. From Scheme 6.7 it can be seen that sterically demanding nucleophiles (i.e. allylmagnesium chloride) and/or bulky substituents in the β-position, increase the energy of A‡, thus favoring the formation of the axial alcohol. 30

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>R</th>
<th>R'</th>
<th>m</th>
<th>product</th>
<th>c.y. a (%)</th>
<th>ee b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.10a</td>
<td>Et</td>
<td>H</td>
<td>1</td>
<td>6.11a</td>
<td>92</td>
<td>c</td>
</tr>
<tr>
<td>2</td>
<td>6.10b</td>
<td>Et</td>
<td>H</td>
<td>2</td>
<td>6.11b</td>
<td>68d</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>6.10c</td>
<td>Et</td>
<td>H</td>
<td>3</td>
<td>6.11c</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>6.10d</td>
<td>Et</td>
<td>Me</td>
<td>1</td>
<td>6.11d</td>
<td>70</td>
<td>c</td>
</tr>
<tr>
<td>5</td>
<td>6.10e</td>
<td>Me</td>
<td>H</td>
<td>1</td>
<td>6.11e</td>
<td>82</td>
<td>c</td>
</tr>
<tr>
<td>6</td>
<td>6.10f</td>
<td>Bu</td>
<td>H</td>
<td>1</td>
<td>6.11f</td>
<td>92</td>
<td>c</td>
</tr>
</tbody>
</table>

(a) Isolated yield as a mixture of diastereomers. (b) Determined by chiral GC (Chiraldex G-TA). (c) Not determined. (d) Isolated yield of the all-trans isomer after column chromatography.

In the case of trans-6.10b the ratio of addition trans and cis to the allyl group was 80:20 (GC). The major product was assumed to be the all-trans diastereomer as shown in Scheme 6.6, based on analogy with the results with 6.10a and results reported in literature, which demonstrate that the Felkin model also holds for 2-substituted cycloheptanones.31 Diastereomerically pure all trans-6.11b was isolated by column chromatography in a yield of 68% (entry 2). The 1,2-addition to trans-6.10c proceeded with a moderate selectivity giving a trans:cis ratio of 63:37 (entry 3).32 Addition to the cyclohexanones 6.10d-f also proceeded with good selectivity. In the case of 6.11d, GC analysis of the crude product on a DB-1 dimethylpolysiloxane column showed one peak only, indicating that the 1,2-addition was completely diastereoselective. Analysis of the crude addition products 6.11e and f by GC showed only two peaks in both cases, but analysis of the ring closed product 6.11e after RCM on 6.11e revealed the presence of a third isomer (vide infra). All dienes 6.11a-f readily underwent ring closure in benzene at room temperature in the presence of 7.5 mol% of Grubbs catalyst 6.2b (Scheme 6.6 and Table 6.3). As expected (see Section 6.2), the presence of an unprotected alcohol functionality presented no problems for the Grubbs catalysts. The RCM reaction of 6.11a was relatively fast, reaching approximately 90% conversion after 15 min, 95% conversion after 75 min and full conversion overnight (GC). Although the reaction slowed down considerably towards the end, the RCM reaction did not strongly favor one of the diastereomers over the others, since the product ratio did not change significantly during the reaction. As expected, reaction of the 74:16:10 mixture of isomers of 6.11a led to the formation of a mixture of isomers of 6.12a in the same ratio. All the diastereomers and
Enantioselective synthesis of bicyclic compounds via catalytic 1,4-addition-ring closing metathesis

Enantiomers could be separated by chiral GC on a Chiraldex G-TA column in one run which showed that no racemization had taken place and that all isomers were present with 96% ee (see Experimental Section). Separation by column chromatography allowed isolation of the major isomer, (1S,9R,9aR)-6.12a (vide infra), in 60% yield.

Table 6.3 RCM of dialkenes 6.11a-f.

<table>
<thead>
<tr>
<th>entry</th>
<th>dialkene</th>
<th>R</th>
<th>R¹</th>
<th>m</th>
<th>ring system</th>
<th>product</th>
<th>c.y.a (%)</th>
<th>eeª (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.11a</td>
<td>Et</td>
<td>H</td>
<td>1</td>
<td>[6,6]</td>
<td>6.12a</td>
<td>60</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>6.11c</td>
<td>Et</td>
<td>H</td>
<td>3</td>
<td>[8,6]</td>
<td>6.12c</td>
<td>43</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>6.11d</td>
<td>Et</td>
<td>Me</td>
<td>1</td>
<td>[6,6]</td>
<td>6.12d</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>6.11e</td>
<td>Me</td>
<td>H</td>
<td>1</td>
<td>[6,6]</td>
<td>6.12e</td>
<td>46</td>
<td>96c</td>
</tr>
<tr>
<td>6</td>
<td>6.11f</td>
<td>Bu</td>
<td>H</td>
<td>1</td>
<td>[6,6]</td>
<td>6.12f</td>
<td>68</td>
<td>93</td>
</tr>
</tbody>
</table>

(a) Isolated yield of major isomer after column chromatography.
(b) Determined by chiral GC (see experimental section). (c) Determined by chiral HPLC after conversion into the p-nitrobenzoate ester (vide infra).

Formation of the 6-membered ring also proceeded well in all other cases and full conversion was observed after reaction overnight (GC), showing that both cis- and trans-fused [5+m,6] bicyclic systems are formed readily. RCM on the isomerically pure trans-diene 6.11b provided the [7,6] bicyclic product 6.12b in >99% isolated yield (Table 6.3, entry 2). Quantitative isolation of the product was readily achieved because of the simple workup procedure; after reaching full conversion, the catalyst was oxidized by bubbling air through the reaction mixture and the oxidized catalyst was removed by filtration over silica followed by removal of the solvents.

In all other cases the major isomer of the resulting carbobicyclic products from this annulation protocol were isolated in moderate to good yield by simple chromatographic procedures with e.e.’s ranging from 93% to 97%. The somewhat low isolated yields of isomerically pure 6.12c and e are due to the low selectivity in the 1,2-addition of allylmagnesium chloride in the case of 6.12c and in the tandem 1,4-addition-allylic substitution step in the case of 6.12e, resulting in a diminished yield after separation of the isomers. GC analysis of the crude RCM product 6.12d again showed one peak only, confirming the diastereoselective formation of 6.11d (vide supra).

6.5 Determination of the relative stereochemistry of the 6.12a

To determine its relative configuration, 6.12a was converted into the corresponding p-nitrobenzoate ester in order to obtain crystals suitable for X-ray analysis. Esterification of the major isomer of the sterically hindered tertiary alcohol 6.12a was accomplished using n-BuLi
in refluxing hexane, followed by addition of the resulting lithium alkoxide to $p$-nitrobenzoyl chloride (Scheme 6.8).\(^{33}\)

\[
\begin{align*}
\text{6.12a} & \xrightarrow{1) \ n\text{-BuLi (1.1 equiv), hexane}} \ x \rightarrow \text{6.13} \\
0 \ ^\circ \text{C to reflux} & \rightarrow \\
\text{2) RT to reflux, 3 h} & \rightarrow \\
c.y. 37\% & \rightarrow \\
\end{align*}
\]

Scheme 6.8 Synthesis of ester 6.13.

Unfortunately, no crystals of 6.13 suitable for X-ray analysis were obtained using various solvents and methods of crystallization. A fortunate side effect of derivatizing 6.12a to 6.13 is that the resolution of the $^1$H-NMR spectrum of 6.13 was strongly enhanced (Figure 6.3) compared to the spectrum of 6.12a. Therefore, the configuration of the major isomer of 6.12a was deduced from the HSQC, COSY, and NOESY NMR spectral data of 6.13.\(^{34}\) All protons were assigned by COSY and HSQC experiments. The methyl protons ($\delta = 0.90$ ppm, $t$, $3H$) were unambiguously assigned by their characteristic chemical shift, integration, and splitting pattern. A COSY interaction identified the two diastereotopic $H_7$ neighbour protons at 1.21 and around 1.6 ppm (partial overlap with other proton). Both $H_7$ protons have a COSY interaction with one other proton: $H_6$ at 1.55 ppm. $H_5$ was identified by HSQC as the proton connected to the other non-vinylic doublet carbon which was confirmed by an interaction between this proton ($H_5$ at 1.46 ppm) and $H_6$. Starting from $H_6$ additional interactions with two other protons were observed. Both protons are attached to the same carbon (HSQC) and therefore were assigned as the two $H_5$’s at 1.10 and 1.81 ppm. Both these protons gave a COSY interaction with two protons at around 1.35 and 1.6 ppm (both overlap with other signals) which were thus identified as the $H_9$ protons. The signal at 1.6 ppm couples with a proton at 3.05 ppm ($H_{1\beta}$). HSQC identified the other $H_{1\alpha}$ at around 1.35 ppm. Starting from $H_5$ additional COSY interactions with two protons were observed (both $H_4$’s at 2.07 and 2.38 ppm). Both of these coupled with a proton at 5.72 ppm ($H_3$). This proton coupled with its neighbor $H_2$ at 5.50 ppm which in turn coupled with one of the $H_1$ protons (3.32 ppm). Through HSQC the other $H_1$ proton was found at 2.09 ppm.

If the two six membered rings are fused in a trans fashion as is expected from addition of the Grignard reagent trans to the allylic group, NOE interactions should be observed between $H_{1\beta}$ and $H_{10b}$, $H_{1\beta}$ and $H_3$, $H_5$ and $H_{10b}$, $H_3$ and $H_{10b}$, and $H_{10b}$ and $H_{1\beta}$. A NOE interaction was observed between $H_5$ and one of the $H_1$’s which is therefore $H_{1\beta}$ at 2.09 ppm (Figure 6.4). Additionally, NOE interactions between $H_5$ and $H_{10b}$ (1.10 ppm), $H_3$ and $H_{10b}$ (1.35 ppm) and $H_{1\beta}$ and $H_{10b}$ are observed. Especially the presence of both a $H_3$-$H_{1\beta}$ and a $H_{1\beta}$-$H_{10b}$ NOE interaction excluded a cis fused bicycle in a steroid or non-steroid conformation. Since the addition of the ethyl group to 2-cyclohexenone in the presence of (S,R,R)-L1 gives the $S$
configuration at C1, the major isomer of 6.12a was identified as (1S,4aR,8aR)-1-ethyl-1,3,4,5,8,8a-hexahydro-4a(2H)-naphthalenol, as depicted in Figure 6.3 for the PNB ester 6.13.

Figure 6.3 500 MHz 1H-NMR spectrum of p-nitrobenzoate ester 6.13.

Figure 6.4 NOESY spectrum of p-nitrobenzoate ester 6.13.
Chapter 6

6.6 Annulation of other rings using RCM

The results described in Section 6.4 demonstrate that variation in size and substitution pattern on the left ring (Scheme 6.1) is readily achieved. To investigate the possibilities for variation in size of the right ring, 6.10a was chosen as a test substrate and addition of three different Grignard reagents to this ketone were performed (Scheme 6.9, Table 6.4).

The Grignard reagents used were: vinylmagnesium bromide (n=0) eventually leading to the annihilation of a 5-membered ring, butenylmagnesium bromide (n=2) leading to a 7-membered ring, and octenylmagnesium bromide (n=6), eventually leading to the formation of an 11-membered ring. Addition of vinylmagnesium bromide to 6.10a led to a mixture of isomers of 6.14a in a 81:15:4 ratio, the major isomer resulting from attack of the nucleophile trans to the allyl group, as is depicted in Scheme 6.9. Attempts to perform a RCM on the mixture of isomers of 6.14a using 7.5 mol% of the Grubbs catalyst in benzene at RT were unsuccessful. Prolonged reaction times (3 d) and elevated temperature did not result in significant conversion to product 6.15a. Only the minor isomer of 6.14a (4%) was converted to a product as judged by GC, most likely the cis-fused isomer of 6.15a. Similar difficulties in the preparation of trans-fused [6,5]-bicyclic products have been reported by others. The reason for the difficult formation of such trans-fused bicyclic systems with a double bond in the 5-membered ring is the high strain in such a system.

![Scheme 6.9 1,2-Addition and RCM to annulate rings of different sizes.](image)

Table 6.4 1,2-Addition to 6.10a and subsequent RCM.

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>dialkene</th>
<th>c.y.</th>
<th>product</th>
<th>ring</th>
<th>c.y.</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>6.14a</td>
<td>64</td>
<td>6.15a</td>
<td>[6,5]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6.14b</td>
<td>52</td>
<td>6.15b</td>
<td>[6,7]</td>
<td>65</td>
<td>96</td>
</tr>
<tr>
<td>3d</td>
<td>2</td>
<td>6.14b</td>
<td>98</td>
<td>6.15b</td>
<td>[6,7]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>6.14c</td>
<td>50</td>
<td>6.15c</td>
<td>[6,11]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) Isolated yield as a mixture of diastereomers. (b) Isolated yield of the major diastereomer (c) Determined by chiral GC (Chiraldex G-TA). (d) Reaction performed with the corresponding organocerium reagent. (e) Small amount (<5%) of cis-fused 6.15a was detected by GC.
Addition of butenylmagnesium bromide \((n = 2)\) to a 9:1 \(trans/cis\) mixture of 6.10a in THF at 0°C did not give satisfactory results. GC analysis showed that complete conversion was not achieved and the reaction stopped at between 50 and 70% conversion in various attempts (GC). Addition of extra Grignard reagent at this point did not result in any conversion to the product. This led to the conclusion that 6.10a is partially deprotonated by the basic Grignard reagent, thus generating the magnesium enolate of 6.10a. Since in the absence of a proton donor this reaction is irreversible, the 1,2-addition cannot reach completion. This problem was overcome by a well known trick; transmetallation of the Grignard reagent to the organocerium reagent to prevent enolization. Use of the organocerium reagent gave complete conversion to 6.15b as a mixture of 3 isomers (87:12:1, GC) with \((1R,2R,3S)-6.14b\) as the major product.\(^{37}\) Annulation of the seven-membered ring through RCM using 7.5 mol% of 6.2b in benzene at RT was successful, allowing the isolation of isomerically pure \((1S,4aR,9aR)-6.15b\) in 65% yield with an ee of 96% after column chromatography. Addition of octenylmagnesium bromide did not give full conversion either, but 6.15c could be isolated in 50% as a mixture of isomers in a ratio of 85:13:2. However, attempts at RCM with 6.15c failed, no conversion was observed (GC), not even in refluxing benzene. Presumably, the target of an 11-membered ring was an unfortunate one, since to the best of our knowledge the formation of such a ring using RCM has not been reported previously.

### 6.7 Conclusions and discussion

New methodology for the synthesis of enantiomerically pure carbobicyclic compounds has been developed, based on an enantioselective tandem 1,4-addition-allylic substitution, Grignard addition, and RCM 3-step sequence. This method allows the construction of a variety of bicyclic structures with high ee’s. Products with [6,6], [7,6], [8,6] and [6,7] carbobicyclic skeletons and different alkyl substituents have been prepared with ee’s ranging from 93-97%.

An elegant feature of this methodology is that the synthesis is highly modular, \textit{i.e.} several structural features such as ring size and substituents can be easily varied without serious depletion of the enantioselectivity (Figure 6.5).

![Figure 6.5 General structure of the RCM products.](image)

For instance, the broad range of substrates tolerated by the copper-phosphoramidite catalyst, allows the use of different cyclic enones leading to different ring sizes and
substituents on the A-ring. Also very important, the use of different organozinc reagents leads to the introduction of various R substituents. Functionalized organozinc reagents have not been used in this methodology yet, but there is no basic reason why this should not be possible. Finally, variation in the organometallic reagent used for the 1,2-addition and subsequent RCM leads to different sizes for the B-ring. So far, only 6- and 7-membered rings have been prepared. Formation of a \textit{trans}-fused 5-membered ring through RCM is very difficult because of the high strain present in such a [5,6] bicyclic system. Attempts to form an 11-membered ring were unsuccessful, but systematic variation of n (Figure 6.5) is necessary to see whether the formation of 8-, 9-, or 10-membered or even larger rings is possible, with or without the protection of the hydroxy group, and possibly using a next generation RCM catalyst such as \textit{6.7}. The successful formation of the 7-membered B-ring also makes the synthesis of [7,7]- and [8,7]-bicyclic systems with high ee possible.

\section*{6.8 Experimental section}

For general information: see Chapter 3. All the 1,2-additions and RCM procedures were performed in flame dried Schlenk vessels under argon. Grubbs catalyst (\textit{6.2b}) was purchased from Strem Chemicals and used as received. Vinylmagnesium bromide and allylmagnesium chloride were purchased from Aldrich as 1.0 M and 2.0 M solutions in THF, respectively. Butenylmagnesium bromide and octenylmagnesium bromide were prepared using standard procedures for the formation of Grignard reagents. The syntheses of \textit{6.10a} and \textit{b} were already described in the Experimental Section of Chapter 4 and compounds \textit{6.10c-f} were prepared using analogous procedures.

\textit{(2R*,3S*)-2-Allyl-3-ethylcyclooctane (6.10c)}

\begin{itemize}
\item \textit{1H-NMR} (300 MHz, CDCl\textsubscript{3}): \( \delta \) 0.81 (t, \( J = 7.3 \) Hz, 3H), 1.2-1.8 (m, 10H), 1.9 (m, 1H), 2.1-2.4 (m, 4H), 2.57 (m, 1H), 4.89 (m, 2H), 5.58 (m, 1H). \textit{13C-NMR} (300MHz, CDCl\textsubscript{3}): \( \delta \) 10.28 (q), 23.23 (t), 24.04 (t), 25.10 (t), 28.18 (t), 29.62 (t), 35.27 (t), 42.78 (d), 44.85 (t), 53.51 (d), 126.43 (t), 125.93 (d), 219.26 (s). An ee of 97\% was determined by chiral GC on a Chiraldex G-TA column, 50 m x 0.25 mm, He-flow: 1.0 ml/min, 120 °C isothermic, \( t_{\text{ret}} \) 68.5 min (major enantiomer \textit{6.10c}), \( t_{\text{ret}} \) 70.0 min (minor enantiomer \textit{6.10c}).
\end{itemize}

\textit{(2R*,3R*)-2-Allyl-3-ethyl-4,4-dimethylcyclohexanone (6.10d)}

\begin{itemize}
\item \textit{1H-NMR} (300 MHz, CDCl\textsubscript{3}): \( \delta \) 0.90 (t, \( J = 7.3 \) Hz, 3H), 0.94 (s, 3H), 0.97 (s, 3H), 1.20 (m, 2H), 1.4-1.7 (m, 4H), 2.2-2.5 (m, 6H), 4.94 (m, 2H), 5.76 (m, 1H). \textit{13C-NMR} (300MHz, CDCl\textsubscript{3}): \( \delta \) 14.59 (q), 20.30 (q), 22.99 (t), 29.53 (q), 31.92 (t), 34.30 (s), 38.10 (t), 40.79 (t), 52.14 (d), 52.67 (d), 115.80 (t), 137.17 (d), 212.99 (s).
\end{itemize}

\textit{(2R*,3S*)-2-Allyl-3-methylcyclohexanone (6.10e)}

\begin{itemize}
\item \textit{1H-NMR} (300 MHz, CDCl\textsubscript{3}): \( \delta \) 0.98 (d, \( J = 6.2 \) Hz, 3H), 1.3-1.4 (m, 1H), 1.5-2.1 (m, 6H), 2.1-2.4 (m, 5H), 4.98 (m, 2H), 5.72 (m, 1H). \textit{13C-NMR} (300MHz, CDCl\textsubscript{3}): \( \delta \) 20.29 (q), 25.47 (t), 30.84 (t),
Enantioselective synthesis of bicyclic compounds via catalytic 1,4-addition-ring closing metathesis

33.41 (t), 37.81 (d), 41.49 (t), 56.72 (d), 115.77 (t), 136.53 (d), 212.10 (s). An ee of 96% was determined by chiral GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 120 °C isothermic, \( t_{ret} \) 21.2 min (minor enantiomer 6.10e), \( t_{ret} \) 22.0 min (major enantiomer 6.10f).

(2R*,3S*)-2-Allyl-3-butyrcyclohexanone (6.10f)

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta \) 0.83 (t, \( J = 7.3 \) Hz, 3H), 1.1-1.3 (m, 5H), 1.3-1.5 (m, 2H), 1.5-1.7 (m, 2H), 1.8-2.0 (m, 2H), 2.1-2.4 (m, 5H), 4.93 (m, 2H), 5.70 (m, 1H). \(^{13}\)C-NMR (300 MHz, CDCl\(_3\)): \( \delta \) 14.02 (q), 22.82 (t), 24.86 (t), 28.48 (t), 28.81 (t), 31.67 (t), 32.97 (t), 41.11 (t), 41.85 (d), 55.03 (d), 115.97 (d), 136.43 (d), 212.93 (s). An ee of 93% was determined by chiral GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 130 °C isothermic, \( t_{ret} \) 44.7 min (minor enantiomer 6.10f), \( t_{ret} \) 45.9 min (major enantiomer 6.10f).

General procedure for the 1,2-addition of Grignard reagents to cyclalkanones: (1R, 2R, 3S)-1,2-Diallyl-3-ethylcyclohexanol (6.11a)

Disubstituted cyclohexanone 6.10a (400 mg, 2.41 mmol) was dissolved in dry THF (10 ml). The solution was cooled to 0 °C after which allylmagnesium chloride (1.8 ml, 2.0 M solution in THF, 3.6 mmol) was added dropwise and the solution was stirred overnight. The reaction mixture was quenched with 1 M aqueous HCl (15 ml) and the aqueous layer was extracted with ether (3 × 20 ml). The combined organic layers were washed with brine (30 ml) and dried over Na\(_2\)SO\(_4\). Filtration and evaporation of the solvent was followed by filtration through a short column (SiO\(_2\), hexanes:ether 5:1) giving >95% pure 6.11a as a mixture of isomers as a slightly yellow oil (463 mg, 2.23 mmol, 92%). \(^1\)H-NMR (CDCl\(_3\)): \( \delta \) 0.80 (t, 3H), 1.0-1.4 (m, 11H), 2.1-2.4 (m, 4H), 4.8-5.1 (m, 4H), 5.7-6.0 (m, 2H). (1R, 2R, 3S)-6.11a: \(^{13}\)C-NMR (CDCl\(_3\), 300 MHz): \( \delta \) 10.53 (q), 20.94 (t), 25.73 (t), 30.92 (t), 31.43 (t), 37.42 (t), 37.38 (d), 46.44 (t), 46.78 (d), 74.75 (s), 115.64 (t), 118.06 (t), 134.11 (d), 139.13 (d).

Compounds 6.11b-f, 6.14a and c were prepared according to the general procedure described for 6.11a.

(1R*,2R*,3S*)-1,2-Diallyl-3-ethylcycloheptanol (6.11b)

Separation of the diastereomers of 6.11b was carried out using column chromatography (SiO\(_2\), hexanes:ether 12:1). \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \( \delta \) 0.80 (t, \( J = 7.3 \) Hz, 3H), 1.2-1.4 (m, 6H), 1.4-2.1 (m, 8H), 2.2 (m, 1H), 2.4-2.6 (m, 2H), 4.9-5.2 (m, 4H), 5.8 (m, 2H). (1R, 2R, 3S)-6.11b: \(^{13}\)C-NMR (CDCl\(_3\), 300 MHz): \( \delta \) 12.47 (q), 24.88 (t), 25.40 (t), 30.55 (t), 32.31 (t), 36.66 (t), 37.66 (t), 40.39 (d), 46.15 (t), 51.50 (d), 76.88 (s), 115.66 (t), 119.67 (t), 134.06 (d), 139.13 (d). An ee of 96% was determined by chiral GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 117 °C isothermic, \( t_{ret} \) 131.0 min (major enantiomer 6.11b), \( t_{ret} \) 133.5 min (minor enantiomer 6.11b).
(1R*,2R*,3S*)-1,2-Diallyl-3-ethylcyclooctanol (6.11c)
1H-NMR (CDCl₃, 300 MHz): δ 0.87 (t, J = 7.3 Hz, 3H), 1.0-1.9 (m, 13H), 2.0-2.5 (m, 6H), 4.9-5.1 (m, 4H), 5.7-5.9 (m, 2H). (1R, 2R, 3S)-6.11c: 13C-NMR (CDCl₃, 300 MHz): δ 13.41 (q), 26.91 (t), 27.07 (t), 28.30 (t), 30.13 (t), 33.00 (t), 36.70 (d), 39.05 (t), 41.41 (t), 43.18 (t), 43.27 (d), 78.21 (s), 114.71 (t), 118.09 (t), 134.73 (d), 140.70 (d). An ee of 97% was determined by chiral GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 125 °C isothermic, t<sub>ret</sub> 146.6 min (major enantiomer 6.11b), t<sub>ret</sub> 150.3 min (minor enantiomer 6.11b).

(1R*,2R*,3R*)-1,2-Diallyl-3-ethyl-4,4-dimethylcyclohexanol (6.12d)
1H-NMR (CDCl₃, 300 MHz): δ 0.72 (s, 3H), 0.88 (s, 3H), 0.93 (t, J = 7.3 Hz, 3H), 1.0-1.6 (m, 9H), 2.1-2.5 (m, 4H), 4.9-5.1 (m, 4H), 5.8 (m, 1H), 6.0 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 16.44 (q), 19.47 (q), 21.67 (t), 30.65 (q), 31.71 (t), 32.81 (t), 34.33 (s), 36.48 (t), 44.41 (d), 46.32 (t), 47.26 (d), 74.63 (s), 115.21 (t), 118.19 (t), 134.02 (d).

(1R*,2R*,3S*)-1,2-Diallyl-3-methylcyclohexanol (6.12e)
1H-NMR (CDCl₃, 300 MHz): δ 0.79 (t, J = 7.3 Hz, 3H), 1.0-1.8 (m, 9H), 2.1-2.4 (m, 4H), 4.9-5.1 (m, 4H), 5.8 (m, 1H), 6.0 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 35.69 (t), 37.24 (t), 46.32 (t), 49.46 (d), 74.58 (s), 115.71 (t), 118.04 (t), 134.11 (d), 138.97 (d).

(1R*,2R*,3S*)-1,2-Diallyl-3-butylcyclohexanol (6.12f)
1H-NMR (CDCl₃, 300 MHz): δ 0.87 (t, J = 7.3 Hz, 3H), 1.0-1.9 (m, 13H), 2.0-2.5 (m, 6H), 4.9-5.1 (m, 4H), 5.8 (m, 1H), 5.9 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 23.08 (t), 28.44 (t), 31.51 (t), 31.64 (t), 33.07 (t), 36.14 (d), 37.24 (t), 46.47 (t), 47.25 (d), 74.74 (s), 115.64 (t), 118.08 (t), 134.12 (d), 139.19 (d).

(1R, 2R, 3S)-2-Allyl-3-ethyl-1-vinylcyclohexanol (6.14a)
1H-NMR (CDCl₃, 300 MHz): δ 0.87 (t, J = 7.3 Hz, 3H), 1.0-1.9 (m, 11H), 2.0-2.4 (m, 2H), 4.9-5.1 (m, 2H), 5.08 (dd, J<sup>1</sup> = 17.6 Hz, J<sup>2</sup> = 1.5 Hz, 1H), 5.26 (dd, J<sup>1</sup> = 17.6 Hz, J<sup>2</sup> = 1.5 Hz, 1H), 5.86 (dd, J<sup>1</sup> = 17.6 Hz, J<sup>2</sup> = 10.6 Hz, 1H), 6.0 (m, 1H). Compound 6.14a was prepared in racemic form only, but ee determination and separation of all three diastereomers by chiral GC was possible: Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 105 °C isothermic, t<sub>ret</sub> 82.4 min (major diastereomer 6.11b), t<sub>ret</sub> 84.2 min (major diastereomer 6.11b).

(1S, 2R, 3S)-2-Allyl-3-ethyl-1-(7-octenyl)cyclohexanol (6.14d)
1H-NMR (CDCl₃, 300 MHz): δ 0.8-1.0 (m, 3H), 1.1-2.5 (m, 25 H), 4.9-5.2 (m, 4H), 5.7-6.2 (m, 2H).

(1R, 2R, 3S)-2-Allyl-1-(3-butenyl)-3-ethylcyclohexanol (6.14b)
Powdered CeCl₃·7H₂O (2.31 g, 6.2 mmol) was dried according to the procedure described by Imamoto et al. The anhydrous CeCl₃ thus obtained was suspended in THF (10 ml) and stirred overnight under argon at room temperature. The resulting milky suspension was cooled to 0 °C and butenylmagnesium bromide, freshly prepared from magnesium turnings
(181 mg, 7.4 mmol) and 4-bromo-1-butene (837 mg, 6.2 mmol) in THF (10 ml) was added dropwise with a syringe. The resulting yellow suspension was stirred for 30 min at 0 °C after which 6.10a (515 mg, 3.1 mmol) was added dropwise over a period of 2 min. After 2 h the reaction was complete according to GC, the reaction mixture was quenched with 1N aqueous HCl (20 ml) and treated according to the workup procedure described for 6.11a, yielding 6.14b (677 mg, 3.05 mmol, 98%) as a colorless oil. 1H-NMR (CDCl3) (t, J = 7.3 Hz, 3H), 1.0-1.3 (m, 4H), 1.4-1.8 (m, 9H), 2.0-2.4 (m, 4H), 4.9-5.1 (m, 4H), 5.8 (m, 1H), 6.0 (m, 1H). 13C-NMR (CDCl3) (t), 31.30 (t), 36.74 (t), 37.26 (d), 41.03 (t), 46.79 (d), 74.93 (s), 114.21 (t), 115.71 (t), 138.95 (d), 139.08 (d).

General procedure for RCM: (1S,4aR,8aR)-1-Ethyl-1,3,4,5,8,8a-hexahydro-4a(2H)-naphthalenol (6.12a)
Grubbs catalyst 6.2b (62 mg, 0.10 mmol) was dissolved in dry benzene (30 ml). Dialkene 6.11a (310 mg, 1.49 mmol) was added dropwise and the mixture was stirred overnight at RT. After oxidation of the catalyst by exposing the reaction mixture to air for 24 h and removal of the solvent, pure (1S, 4aR, 8aR)-6.12a (161 mg, 0.89 mmol, 60%) was obtained by column chromatography (SiO2, hexanes:ether 6:1). 1H-NMR (CDCl3, 300 MHz): δ 0.78 (t, 3H), 2.0-2.3 (m, 15H), 5.54 (m, 1H), 5.68 (m, 1H). 13C-NMR (CDCl3, 300 MHz): δ 10.23 (q), 21.23 (t), 24.97 (t), 26.54 (t), 30.78 (t), 38.86 (d), 38.97 (t), 40.86 (t), 42.79 (d), 73.77 (s), 124.07 (d), 127.04 (d). The ee of  (1S, 4aR, 8aR)-6.12a was determined by GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow 1.0 ml/min, isothermic 125 °C. tret 53.1 min: (1S, 4aR, 8aR)-6a, tret 54.4 min: (1R, 4aS, 8aS)-6a.

Compounds 6.12b-f and 6.15b were prepared according to the general procedure described for 6.12a. In all cases, the major isomer of the product was isolated by column chromatography (SiO2) with hexane-ether mixtures as the eluens. The diastereomeric purity of the fractions obtained after column chromatography was checked by GC on a DB-1 dimethylpolysiloxane column.

(4aR*,9S*,9aR*)-9-Ethyl-1,4,5,6,7,8,9a-octahydro-4aH-benzo[a]cyclohepten-4a(1H)-ol (6.12b)
1H-NMR (CDCl3, 300 MHz): 0.79 (t, 3H), 1.16 (m, 2H), 1.37 (m, 5H), 2.0-2.3 (m, 2H), 5.53 (m, 1H), 5.68 (m, 1H). 13C-NMR (CDCl3, 300 MHz): 10.56 (q), 20.71 (t), 25.92 (t), 27.15 (t), 27.91 (t), 32.12 (t), 38.24 (d), 39.87 (t), 42.69 (t), 46.47 (d), 72.38 (s), 124.41 (d), 127.68 (d). Determination of the ee of 6.12b was performed on a Chiraldex G-TA column, 50 m × 0.25 mm, He flow: 1.0 ml/min, isothermic 135 °C. tret 53.1 min: (4aR, 9S, 9aR)-6.12b, tret 54.3 min: (4aS, 9R, 9aR)-6.12b.

(4aR*,10S*,10aR*)-10-Ethyl-1,5,6,7,8,9,10a-octahydrobenzo[a]cycloocten-4a(2H)-ol (6.12c)
1H-NMR (CDCl3, 300 MHz): 0.85 (t, 3H), 1.0-1.4 (m, 4H), 1.4-1.8 (m, 11H), 1.9-1.2 (m, 3H), 2.4 (m, 1H), 5.54 (m, 1H), 5.70 (m, 1H). 13C-NMR (CDCl3, 300 MHz): 12.92 (q), 24.98 (t), 25.13 (t), 25.71 (t), 26.48 (t), 27.76 (t), 33.06 (t), 35.95 (d), 39.27 (d), 39.55 (t), 40.01 (t), 73.77 (s), 124.07
Chapter 6

(d), 127.39 (d). MS(EI) for C_{14}H_{24}O: m/z = 208 (M^+). Ee determination of 6.12c was performed on a Chiraldex G-TA column, 50 m × 0.25 mm, He flow: 1.0 ml/min, 140 °C isothermic: \( t_{\text{ret}} 77.8 \) min: (4aR, 10S, 10aR)-6.12c, \( t_{\text{ret}} 79.6 \) min: (4aS, 10R, 10aR)-6.12c.

\( (1R^*, 4aR^*, 8aR^*)\)-1-Ethyl-2,2-dimethyl-1,3,4,5,8,8a-hexahydro-4a(2H)-napthalenol (6.12d)

\(^1\)H-NMR (CDCl\(_3\), 300 MHz): 0.74 (s, 3H), 0.88 (s + t, 6H), 0.9-1.2 (m, 3H), 1.3-1.7 (m, 6H), 1.79 (m, 1H), 1.9-2.3 (m, 3H), 5.54 (m, 1H), 5.71 (m, 1H). \(^1^3\)C-NMR (CDCl\(_3\), 300 MHz): 16.12 (q), 19.45 (q), 21.59 (t), 30.39 (q), 34.34 (s), 34.60 (t), 36.64 (t), 41.06 (t), 41.11 (d), 48.32 (d), 69.14 (s), 123.72 (d), 127.35 (d). MS(CI) for C\(_{14}\)H\(_{24}\)O: m/z = 226 (M+NH\(_4^+\)). Ee determination of 6.12d was performed on a Chiraldex G-TA column, 50 m × 0.25 mm, He flow: 1.0 ml/min, 125 °C isothermic: \( t_{\text{ret}} 76.1 \) min: (1S, 4aR, 8aR)-6.12d, \( t_{\text{ret}} 78.4 \) min: (1R, 4aS, 8aS)-6.12d.

\( (1S^*, 4aR^*, 8aR^*)\)-1-Methyl-1,3,4,5,8,8a-hexahydro-4a(2H)-napthalenol (6.12e)

\(^1\)H-NMR (CDCl\(_3\), 300 MHz): 0.80 (d, 3H), 0.97 (m, 1H), 1.1-1.3 (m, 3H), 1.3-1.5 (m, 2H), 1.5-1.8 (m, 4H), 1.9-2.1 (m, 2H), 2.2 (m, 1H), 5.55 (m, 1H), 5.68 (m, 1H). \(^1^3\)C-NMR (CDCl\(_3\), 300 MHz): 19.56 (q), 21.31 (t), 26.75 (t), 33.14 (d), 35.42 (t), 38.92 (t), 40.75 (t), 45.51 (d), 68.81 (s), 123.84 (d), 127.04 (d). Ee determination was performed on the \( p \)-nitrobenzoate ester of 6.12e, prepared according to the procedure described for 6.13, by chiral HPLC: Chiralcel OD, heptane/2-propanol: 99/1, 1.0 ml/min, \( \lambda_{\text{det}} \): 254 nm. \( t_{\text{ret}} 6.7 \) min and \( t_{\text{ret}} 7.9 \) min.

\( (1S^*, 4aR^*, 8aR^*)\)-1-Butyl-1,3,4,5,8,8a-hexahydro-4a(2H)-napthalenol (6.12f)

\(^1\)H-NMR (CDCl\(_3\), 300 MHz): 0.83 (t, 3H), 0.9-1.8 (m, 14H), 1.9-2.1 (m, 2H), 2.21 (m, 1H), 5.54 (m, 1H), 5.68 (m, 1H). \(^1^3\)C-NMR (CDCl \(_3\), 300 MHz): 14.10 (q), 21.82 (t), 23.13 (t), 26.62 (t), 28.23 (t), 31.50 (t), 32.34 (t), 37.64 (d), 38.96 (t), 40.90 (t), 43.32 (d), 45.51 (d), 68.98 (s), 123.73 (d), 127.08 (d). MS(CI) for C\(_{14}\)H\(_{24}\)O: m/z = 226 (M+NH\(_4^+\)). Ee determination of 6.12f was performed on a Chiraldex G-TA column, 50 m × 0.25 mm, He flow: 1.0 ml/min, 135 °C isothermic: \( t_{\text{ret}} 67.0 \) min: (1S, 4aR, 8aR)-6.12f, \( t_{\text{ret}} 68.5 \) min: (1R, 4aS, 8aS)-6.12f.

\( (1S^*, 4aR^*, 8aR^*)\)-1-Ethyl-1,2,3,4,5,6,9,9a-octahydro-4aH-benzo[a]cyclohepten-4a-ol (6.15b)

\(^1\)H-NMR (CDCl\(_3\), 300 MHz): 0.77 (t, 3H), 0.95 (m, 2H), 1.1-1.7 (m, 5H), 1.8-2.4 (m, 5H), 5.7 (m, 2H). \(^1^3\)C-NMR (CDCl\(_3\), 300 MHz): 10.11 (q), 21.40 (t), 22.92 (t), 24.59 (t), 26.08 (t), 31.35 (t), 37.07 (d), 40.61 (t), 42.25 (t), 48.14 (d), 74.00 (s), 132.07 (d), 132.23 (d). Ee determination of 6.15b was performed on a Chiraldex G-TA column, 50 m × 0.25 mm, He flow: 1.0 ml/min, 135 °C isothermic: \( t_{\text{ret}} 51.9 \) min: (1S, 4aR, 9aR)-6.15b, \( t_{\text{ret}} 53.6 \) min: (1R, 4aS, 9aS)-6.15b.

Alcohol 6.12a (678 mg, 3.8 mmol) was dissolved in hexane (10 ml) and the solution was cooled to 0 °C. n-Butyllithium (2.5 ml, 1.6 M solution in hexanes, 4.0 mmol) was added dropwise to this solution and the reaction mixture was refluxed subsequently for 20 min. After cooling to RT the resulting lithiumalkoxide solution was added dropwise to a solution of \( p \)-nitrobenzoyl chloride (700 mg, 3.8 mmol) in hexane (10 ml) at RT via a syringe, and the reaction mixture was refluxed for 3 h. The resulting yellow suspension was filtered while
still hot and the filtrate was kept at RT to allow 6.13 to crystallize. The crystals were collected on a glass filter and recrystallized from hexane, yielding 6.13 as colorless crystals (457 mg, 1.4 mmol, 37%). For 1H-NMR (CDCl3, 500 MHz) see Figure 6.3. 13C-NMR (CDCl3): δ 10.04 (q), 21.06 (t), 25.09 (t), 27.21 (t), 30.44 (t), 34.02 (t), 34.17 (t), 39.10 (d), 44.46 (d), 83.79 (s), 118.48 (s), 122.63 (d), 123.50 (d), 126.50 (d), 130.33 (d), 150.67 (s), 160.14 (s). MS(CI) for C19H23NO4: m/z = 347 (M + NH4)+. Anal. Calcd. for C19H23NO4: C 69.28%; H 7.04%; N 4.25%, found: C 69.22%; H 7.05%; N 4.25%.

6.9 References and notes

1 Part of this chapter has been published: R. Naasz, L. A. Arnold, A. J. Minnaard, B. L. Feringa, Chem. Commun. 2001, 735.


4 C&EN, August 2001, 57-58.


8 a) J-L. Hérisson, Y. Chauvin, Makromol. Chem. 1970, 141, 161; b) For a description of the evidence for the metallacyclobutane mechanism and references on this topic see ref. 6, chapter 3.


28 Note that addition of MeMgBr trans to the methyl group of e.g. 2-methylcyclohexanone formally yields cis-1,2-dimethylcyclohexanol, due to the higher priority that is given to the hydroxy group over the methyl group in the Cahn-Ingold-Prelog system. Throughout this chapter however, the terms trans and cis are used to describe the stereochemical relations between the different alkyl and allyl groups.
30 Collected experimental data for the selectivities in the 1,2-addition of different nucleophiles to various substituted cycloalkenones can be found in: E. C. Ashby, J. T. Laemmle, Chem. Rev. 1975, 75, 521. All cases of 1,2-addition of allylmagnesium chloride to
cyclohexanones mentioned in this review show a strong preference for formation of the axial alcohol.


34 HSQC and COSY spectra of 6.13 can be found in the electronic supplementary information to ref. 1.


