Catalytic asymmetric conjugate additions and Heck reactions

Imbos, Rosalinde

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):

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).

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.
Chapter 4

A catalytic enantioselective route to acyclic chiral building blocks*

Applications of the catalytic asymmetric conjugate addition of organozinc reagents to cyclic enones

By means of the Cu-phosphoramidite catalysed asymmetric conjugate addition to cyclohexadienones and kinetic resolution of cycloalkenones a number of chiral cyclic enones are available with high e.e. In this chapter, we report the sequential conjugate addition to these enones as a route towards multisubstituted chiral cyclic ketones. A subsequent Baeyer-Villiger oxidation followed by ring-opening results in various linear chiral synthons containing multiple stereocenters. This procedure represents a short, catalytic and highly enantioselective route to a variety of acyclic chiral building blocks.

4.1 Introduction

Acyclic chiral building blocks play a major role in organic synthesis as is particularly evident in the total synthesis of macrolide antibiotics and pheromones. Especially linear fragments containing methyl-substituted stereogenic centres (either syndiotactic (stereochemistry at the stereogenic centers is alternating $R, S, R, S$ etc) or isotactic (all stereocenters have either $R$ or $S$ configuration)) are of interest. In Figure 4.1 a number of linear natural products containing methyl-substituted stereogenic centres are depicted, i.e. a pheromone of the cigarette beetle, a pheromone of the brownbanded cockroach, bourgeanic acid and lardolure.

There are two general routes to obtain these linear building blocks in enantiomerically pure form: the first route starts from a precursor from the chiral pool whereas the second route is based on the use of a chiral auxiliary in the steps where the asymmetry is introduced. Alternatively, catalytic methods might be employed to generate acyclic chiral building blocks. Recent approaches include catalytic enantioselective (Mukaiyama) aldol, isomerisation, hydrogenation and allylic substitution reactions. The use of cyclic substrates in catalytic asymmetric transformations has the distinct advantage of limited conformational flexibility and as a consequence usually strongly enhanced stereocontrol is observed. Recently, we have developed a highly stereoselective catalytic route to $\beta$-substituted cyclic enones, which offers attractive prospects in the synthesis of acyclic synthons.

Figure 4.1 A number of linear natural products containing methyl-substituted stereogenic centres.
A catalytic enantioselective route to acyclic chiral building blocks

**Scheme 4.1** Asymmetric conjugate addition of dialkylzinc reagents to cycloalkenones catalysed by a Cu(OTf)_{2}/ L1 complex.

The asymmetric conjugate addition of dialkylzinc reagents to various cyclic enones, using a Cu-phosphoramidite complex as catalyst, proceeds with high yields and excellent e.e.’s of >96%.\(^{15}\) (Scheme 4.1). Shortly after these findings, two other routes to chiral virtually enantiopure cyclohexenones were developed in our laboratories. The Cu(OTf)_{2} - L1 catalyst proved to be very efficient for kinetic resolutions of racemic 5-substituted cyclohexenones, providing the starting compounds 4.1a, 4.1b and 4.1c with e.e.’s of >99%, >99% and 89%, respectively.\(^{16}\) (Scheme 4.2, a) Furthermore, not only cyclic enones, but also cyclohexadienone monoketals are excellent substrates for the asymmetric conjugate addition,\(^{17}\) yielding the corresponding chiral cyclohexenones with >99% e.e. (Scheme 4.2b and Chapter 2)

**Scheme 4.2** Catalytic enantioselective routes to chiral cyclohexenones using the Cu/L1 catalysed conjugate addition of R_{2}Zn reagents
The catalytic 1,4-addition to 5-substituted-cyclohexenones provides trans-3,5-disubstituted cyclohexanones (see Chapter 3). Subsequent ring-opening of the chiral cyclic products allows the formation of the desired acyclic building blocks, with multiple stereocenters. (See Scheme 4.3)

Scheme 4.3 General route from cyclohexenones to linear chiral building blocks (a) conjugate addition, (b) ring-opening.

In this chapter the results are presented of the use of these easily accessible cyclohexenones in the synthesis of linear building blocks containing 2 or 3 stereocenters (starting from cyclohexenones or cyclohexadienones, respectively). The first route (i) involves an asymmetric Cu(OTf)$_2$-L$_1$ catalysed conjugate addition of Me$_2$Zn to create the second stereocenter, followed by a Baeyer-Villiger oxidation and subsequent ring-opening by transesterification (see Scheme 4.4). In the second method (ii), the chiral cyclohexenone-monoketal 4.3 provides, through a similar sequence, a method to obtain linear building blocks with three stereocenters. (see Scheme 4.4)

Scheme 4.4 General schemes for chiral linear building blocks, starting from (i) cycloalkenones leading to linear fragments containing 2 stereogenic centres, (ii) cyclohexenone monoacetals, yielding acyclic building blocks containing 3 stereogenic centres. Conditions: (a) trans-selective conjugate addition, (b) (1) Baeyer-Villiger oxidation (2) transesterification (c) trans-selective conjugate addition (d) (1) Wittig reaction, (2) reduction, (e) (1) Baeyer-Villiger oxidation (2) transesterification.
4.2 Results and Discussion

4.2.1 Linear building blocks starting from chiral cyclohexenones

Optically active cyclohexenones 4.1a-c are easily accessible through the kinetic resolution procedure (see Scheme 2a)\textsuperscript{16} employing chiral ligand (S, R, R) L1. These were subjected to a subsequent catalytic enantioselective conjugate addition. In this 1,4-addition the (R, S, S) enantiomer of the L1 was chosen to ensure that the chiral catalyst provided the trans-diadduct \emph{i.e.} the second stereogenic centre would be of the same handedness as the first, leading to (R,R)-disubstituted cyclohexanones. The products 4.4a-c were formed in good yields (68-78\%) and with >99\% trans selectivity (no cis-product could be observed in the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra) and 100\% d.e. (Scheme 5).

![Scheme 4.5](image)

\textbf{Scheme 4.5} Reaction conditions: (a) Me\textsubscript{2}Zn, 1.4 equiv., toluene, (R, S, S) L1 (5 mol\%), Cu(OTf)\textsubscript{2} (2.5 mol\%) (b) mCPBA, NaHCO\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2} (c) NaOMe, MeOH

Treatment of the C\textsubscript{2}-symmetrical cyclohexanone 4.4a with mCPBA afforded the lactone 4.5a as a single diastereomer with 99\% e.e. The Baeyer-Villiger reaction with non-symmetrical cyclohexanones 4.4b and 4.4c was expected to provide a mixture of two regioisomers. For the iPr substituted cyclohexanone 4.4b the regioselectivity was poor giving the products 4.5b and 4.6b in a ratio of 56:44. For the phenyl substituted cyclohexanone 4.4c the regioselectivity improved to 70:30. Based on NMR analysis structure 4.5c was assigned to the major regioisomer.

The ring opening of the lactones using MeOH/NaOMe proceeded smoothly and linear building block 4.7a\textsuperscript{18} (comprising a 1,3-arrangement of stereocenters) was obtained in high
yield (91%). The linear hydroxyesters 4.7b/4.8b and 4.7c/4.8c were formed as a mixture of the two isomers.

No separation of the enantiomers could be obtained on any chiral GC or HPLC column for acyclic synthons 4.7/4.8 so far. It is, however, unlikely that the Baeyer-Villiger oxidation/saponification procedure would cause any epimerisation for these compounds, so the e.e.’s of the products 4.7/4.8 are likely to be equal to the e.e.’s of the starting compounds (i.e. >99%, >99% and 89%, respectively).

4.2.2 Linear building blocks starting from cycloheptadienone

The conjugate addition of Me2Zn to cycloheptadienone 4.9,19 catalysed by (S,R,R) L1/Cu(OTf)2, afforded 3-methyl cycloheptenone 4.10 in 76% yield with >99% e.e. A conjugate addition of Me2CuLi to racemic methyl cycloheptenone 4.10 has been reported to give the product as a 1:1 mixture of the cis:trans disubstituted product.20 However, a second conjugate addition of Me2Zn to 4.10 using the same (S,R,R) L1/Cu(OTf)2 catalyst resulted in the exclusive formation of the trans-disubstituted cycloheptanone 4.11, with retention of e.e. (see Scheme 6, no cis-product was detected by 1H and 13C NMR spectroscopy).

Baeyer-Villiger oxidation of cycloheptanone 4.11 with mCPBA proved to be difficult (< 10% conversion after refluxing the mixture for 5 d), presumably due to the unfavourable seven to eight membered ring enlargement.21 Fortunately, by using the more powerful H2O2/maleic anhydride method reported by Bidd et al.22 we were able to isolate lactone 4.12 in 65 % yield. Ring opening of 4.12 using MeOH/NaOMe proceeded smoothly and linear building block 4.13 comprising a 1,4-arrangement of stereocenters was obtained in good yield (70%).
4.2.3 Linear building blocks containing three stereocenters starting from cyclohexadienones

The chiral cyclohexenone monocetal 4.3, obtained through catalytic enantioselective conjugate addition of dialkylzinc reagents to cyclohexadienones (see Scheme 4.2b), provides access to linear building blocks with three stereocenters in a 1,3,5-array. The bisaddition of Et₂Zn to 4,4-dimethoxy-cyclohexadienone was previously reported to provide selectively the trans isomer when in both addition steps in the sequential conjugate addition the (S, R, R)-enantiomer of ligand L1 was used for the preparation of the catalyst.

Scheme 4.7 Reaction conditions: (a) Me₂Zn, 1.4 equiv., toluene, (S, R, R) L1 (5 mol%), Cu(OTf)₂ (2.5 mol%), (b) (1) CH₃PPh₃I, nBuLi, THF (2) 10% citric acid, (c) PtO₂/C, H₂, EtOAc, (d) mCPBA, NaHCO₃, CH₂Cl₂ (e) NaOMe, MeOH

Since in natural products linear fragments with methyl substituents are more frequently occurring than those with ethyl substituents, it would be interesting to know if Me₂Zn would behave in a similar way. Indeed, starting from the enantiomerically pure monoadduct 4.3, trans- bisadduct 4.14 was also formed selectively (based on ¹H and ¹³C NMR) through a Cu/ (S, R, R) L1 catalysed conjugate addition of Me₂Zn. (see Scheme 4.7) A Wittig reaction of 4.14 with CH₃PPh₃I followed by mild hydrolysis of the acetal in the presence of aqueous citric acid (10%) smoothly gave 4.15. Based on ¹H and ¹³C NMR analysis it was established that no epimerisation had occurred. However, attempted hydrogenation of the methylene group in the presence of Pd/C did not afford the desired cyclohexanone 4.16, but isomers of the starting compound (¹H NMR indicated that the exocyclic alkene had isomerised to the endocyclic alkene). We were pleased to see that reduction of the methylene group in the presence of PtO₂/C was successful, providing 4.16 in satisfactory yields. No epimerisation...
at the C-2 and C-6 centres was observed (based on $^1$H and $^{13}$C NMR as no signals due to a cis 2,6-dialkyl moiety were seen).

The C-4 methyl substituent in these 1,3,5-trisubstituted cyclohexanones is positioned on the C$_2$-axis, and therefore compound 4.16 contains only two stereocenters (at C-2 and C-6). However, after a Baeyer-Villiger reaction C-4 in lactones 4.17 and 4.18 is also a stereocenter. The Baeyer-Villiger is expected to proceed with some regioselectivity. It has been reported that the reaction has preference for oxygen insertion between the carbonyl and the adjacent carbon atom bearing an axial methyl group.$^{23,24}$

Scheme 4.8  Regioselectivity in the Baeyer-Villiger oxidation of 4.16

In our case, tri-substituted cyclohexanone 4.16 will be preferentially in chair-conformation I with two equatorial and one axial methyl substituent (Scheme 4.8). This conformation will be lower in energy than the alternative chair conformation II, which contains two axial methyl groups. Oxygen insertion during the Baeyer-Villiger oxidation will be at the side that contains the axial methyl leading to 4.17 and 4.18, respectively.$^{23}$ Assuming that there is not
a large energy difference for these two oxygen insertion pathways, we expect 4.17 to be the major regioisomer. The major regioisomer 4.17 was formed in 79%. Unequivocal assignment of major isomer has not been possible so far, despite the fact that extensive NMR experiments have been performed on the pure major isomer. Ring opening proceeded smoothly, and the linear building block, 4.19, with three stereocenters at positions 2, 4 and 6, are obtained together with small amounts of the C4 epimer.

4.2.4 Routes to syndiotactic linear fragments

The previous paragraphs deal with the synthesis of isotactic (i.e. all stereocentres are either ‘R’ or ‘S’) methyl-substituted linear fragments. Synthesis of syndiotactic linear fragments would mean that the initial conjugate addition to cyclic enones has to be performed in a cis-fashion. Unfortunately, the cis-addition to Me- iPr- and Ph- substituted cyclohexenones 4.1a-e is extremely sluggish (this is inextricably linked to the fact that the kinetic resolution is successful) The cis-di-addition of Me₂Zn to cyclohexadienone 4.2 will be successful, but the product will be a meso isomer (i.e. not chiral). (see Scheme 4.9)

Scheme 4.9 Cis-diadducts leading to syndiotactic methyl substituted linear fragments.

Formation of syndiotactic methyl substituted linear fragments (that are still chiral) will be possible if the in situ formed zinc enolate of the diadduct can be trapped, e.g. as the silylenolether or as the aldol product. Subsequent ring opening will lead to the desired chiral linear fragments. Although the proposed rationale seems very promising, and is very
important for the synthesis of natural products, these routes to syndiotactic chiral building blocks have not been pursued.

4.3 Conclusions

By using chiral enantiopure cyclohexenones, which are easily accessible through the kinetic resolutions based on the asymmetric Cu/L1 catalysed conjugate additions or additions to cyclohexadienones, it is possible to obtain through a subsequent catalytic conjugate addition/ring-opening approach linear building blocks with two stereocenters in satisfactory yields and with excellent ee’s. Starting from cyclohexadienones, linear building blocks containing three stereocenters are easily obtained in good yield and with excellent ee. Although natural products have not been synthesised so far, we have shown that it is possible to use this method to obtain linear chiral fragments, which upon further reaction (e.g. chain elongation) might provide biologically active compounds. Furthermore, since in this chapter only the synthesis of linear compounds containing all R or all S stereocenters has been discussed, and most of the natural products have alternating absolute configuration at the stereocenters, the final section might provide a way to use the catalytic 1,4-addition to obtain these compounds.

In conclusion, we have demonstrated the versatility of sequential catalytic 1,4-addition, Baeyer Villiger oxidation/ring opening in new catalytic, diastereo- and enantioselective routes to acyclic chiral synthons.

4.4 Acknowledgement

We thank Mr. M. B. van Gelder for carrying out HPLC and GC measurements and Dr. R. Hulst for performing the NMR measurements. Dr. R. Naasz is gratefully acknowledged for generous gifts of 4.1a-c and 4.9.
4.5 Experimental

For general remarks, see chapter 2.

General procedure for the conjugate addition of dialkylzinc reagents to cyclic enones employing a chiral catalyst derived from Cu(OTf)₂ and L₁:
A solution of 2.5 mol% Cu(OTf)₂ and 5 mol% of L₁ in 5 mL of freshly distilled toluene was stirred under a nitrogen atmosphere at ambient temperature for 1 h, after which the enone was added. The mixture was cooled to -25°C and 1.2 equiv. of R₂Zn in toluene were added. Stirring was continued at -25°C for 16h. After complete conversion (as determined by TLC), the reaction mixture was poured in 50 mL of 2N NaOH and extracted three times with diethyl ether (100 mL). The combined organic layers were washed with brine (50 mL) dried on Na₂SO₄, filtered and the solvent evaporated to yield the crude 1,4-adduct.

General procedure for the Baeyer-Villiger oxidation of di- and tri-substituted cyclohexanones 4.4a-c and 4.17
A suspension of 3.90 mmol mCPBA and NaHCO₃ (3.90 mmol) in 50 ml of freshly distilled dichloromethane was stirred under a nitrogen atmosphere at ambient temperature for 1h, after which 1.3 mmol of di- or tri-substituted cyclohexanone was added. Stirring was continued for 16h, during which a precipitate was formed and TLC analysis showed the conversion to be complete. The reaction mixture was washed with 10% NaHSO₃, saturated NaHCO₃ and brine. The last three steps were repeated until the brine layer tested negative on peroxides. Subsequently, the organic layer was dried with Na₂SO₄, filtered and the solvent evaporated. The resulting crude products were purified by column chromatography (SiO₂, hexane/Et₂O = 4/1).

General procedure for the ring-opening of multi-substituted lactones
The lactones (0.25 mmol) were dissolved in 10 mL of methanol and treated with an excess of NaOMe for 16 h at ambient temperature. Conversion was shown to be complete by TLC. The reaction mixture was poured in 25 mL of water and extracted three times with diethyl ether (50 mL). The combined organic layers were washed with brine (25 mL) and dried on Na₂SO₄, filtered and the solvent evaporated to yield the product.

*(3R,5R)-3,5-Dimethylcyclohexanone (4.4a)*
Isolated yield 68% after purification by column chromatography (SiO₂, pentane/Et₂O = 4/1). ¹H NMR analysis: >99% trans adduct. [α]D = -8.2° (c 1.0, CHCl₃). (lit²⁶: [α]D = -12.28° (c 1.18, CHCl₃)) ¹H NMR δ 0.92 (d, J = 6.6 Hz, 6H), 1.54 (t, J = 5.7 Hz, 2H), 1.98 (m, 2H), 2.23 (m, 2H), 2.33 (d, J = 8.4 Hz, 1H), 2.36 (d, J = 3.7 Hz, 1H). ¹³C NMR: δ 20.79 (q), 29.54 (d), 39.45 (t), 48.70 (t), 212.11 (s). NMR data were in accordance with data published.²⁷ CIMS (M+1) 127, (M+18) 144. E.e. determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, Tᵢ = 75°C for 10 min, Tᵣ = 150°C, rate 10°C/min, rt 14.4 (3S, 5S), 14.6 (3R, 5R) min.
(-)-3-Isopropyl-5-methylcyclohexanone (4.4b)
Isolated yield 75% after purification by column chromatography (SiO₂, hexane/Et₂O = 4/1). No cis adduct could be detected by ¹H NMR. [α]₀ = -49.6° (c = 1.0, CHCl₃). ¹H NMR: δ 0.84 (d, J = 7.0 Hz, 6H), 0.91 (d, J = 7.0 Hz, 3H), 1.55 (m, 2H), 1.72 (m, 2H), 2.06 (m, 2H), 2.32 (m, 3H). ¹³C NMR: δ 19.76 (q), 19.91 (q), 20.18 (q), 29.60 (d), 31.40 (d), 34.79 (t), 40.40 (d), 44.88 (t), 48.34 (t), 212.65 (s). CIMS (M+1) 155, (M+18) 172. E.e. determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, Tᵢ = 90°C for 10 min, Tᵢ = 150°C, rate 10°C/min, rt 19.0, 19.3 min.

(-)-3-Methyl-5-phenylcyclohexanone (4.4c)
Isolated yield 78% after purification by column chromatography (SiO₂, hexane/Et₂O = 4/1). ¹H NMR shows no cis adduct. [α]₀ = -32.3° (c = 0.9, CHCl₃). ¹H NMR: δ 0.97 (d, J = 7.0 Hz, 3H), 1.81 (m, 1H), 1.99-2.27 (m, 3H), 2.54 (m, 3H), 3.33 (m, 1H), 7.18 (m, 3H), 7.27 (m, 2H). ¹³C NMR: δ 21.21 (s). CIMS (M+1) 189, (M+18) 206.

(4R,6R)-dimethyl-2-oxepanone (4.5a)
Isolated yield 70%. [α]₀ = -31.9° (c = 1.1, CHCl₃). ¹H NMR: δ 0.91 (d, J = 7.3 Hz, 3H), 0.98 (d, J = 7.0, 3H), 1.55 (m, 3H), 2.03 (m, 1H), 2.46 (dd, J = 13.7, 8.6 Hz, 1H), 2.61 (dd, J = 13.7, 2.0 Hz, 1H), 3.93 (dd, J = 12.8, 7.3 Hz, 1H), 4.09 (d, J = 12.8 Hz, 1H). ¹³C NMR: δ 16.75 (q), 20.46 (q), 25.72 (d), 30.25 (d), 41.04 (t), 43.84 (t), 73.46 (t), 174.72 (s). CIMS (M+1) 143, (M+18) 160. E.e. determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, Tᵢ = 125°C for 10 min, Tᵢ = 180°C, rate 10°C/min, rt 14.9 (4S, 6S), 15.5 (4R, 6R) min.

6-Isopropyl-4-methyl-2-oxepanone and 4-isopropyl-6-methyl-2-oxepanone (4.5b/4.6b)
Isolated yield 81%. Ratio 4.5b/4.6b = 56/44. ¹H NMR: δ 0.86 (m), 1.37 (m), 1.54 (m), 1.73 (m), 1.99 (m), 2.48 (m), 3.01 (dd, J = 12.6, 6.8 Hz), 4.08 (m). ¹³C NMR: δ 16.25 (q), 19.53 (q), 19.57 (q), 19.94 (q), 20.92 (q), 25.59 (d), 27.67 (d), 30.26 (d), 31.30 (d), 36.36 (d), 37.56 (t), 38.63 (t), 39.00 (t), 41.15 (t), 41.53 (d), 71.13 (t), 73.10 (t), 174.70 (s), 175.15 (s). CIMS (M+1) 171, (M+18) 188. E.e. and d.e. determinations: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, Tᵢ = 100°C for 10 min, Tᵢ = 170°C, rate 10°C/min, rt 28.7, 29.0, 30.1, 30.3 min.
4-Methyl-6-phenyl-2-oxepanone and 6-methyl-4-phenyl-2-oxepanone (4.5c/4.6c)

Isolated yield 68%. Ratio 4.5c/4.6c = 70/30. M.p. 132-133°C. 1H NMR: δ 1.09 (d, J = 7.0 Hz), 1.10 (d, J = 7.3 Hz), 1.61 (m), 4.46 (m), 2.58-3.13 (m), 4.10-4.41 (m), 7.02-7.30 (m). 13C NMR: δ 14.81 (q), 17.95 (q), 26.51 (d), 31.35 (d), 35.41 (d), 40.25 (t), 40.81 (d), 40.93 (t), 42.72 (t), 43.55 (t), 72.40 (t), 73.15 (t), 126.36 (d), 126.68 (d), 126.97 (d), 128.67 (d), 128.79 (d), 141.96 (s), 145.05 (s), 174.10 (s), 174.26 (s). CIMS (M+1) 205, (M+18) 222. D.e. determination: GC CP 57 CB, 5 m × 0.25 mm, He-flow = 1.0 mL/min, T1 = 250°C, rate 10°C/min, rt 19.6, 19.8 min.

(+)-Methyl-6-hydroxy-3,5-dimethylhexanoate (4.7a)

Isolated yield 91% (colorless oil). [α]D = +19.4° (c = 1.1, CHCl3). 1H NMR: δ 0.84 (d, J = 3.7 Hz, 3H), 0.87 (d, J = 3.7 Hz, 3H), 1.03 (m, 1H), 1.20 (m, 1H), 1.65 (m, 2H), 2.01 (m, 1H), 2.11 (dd, J = 14.6, 7.3 Hz, 1H), 2.37 (dd, J = 14.7, 6.6 Hz, 1H), 3.39 (m, 2H), 3.60 (s, 3H). 13C NMR: δ 33.13 (d), 40.17 (t), 42.38 (t), 51.40 (q), 68.68 (t), 173.61 (s). CIMS (M+1) 175, (M+18) 192.

Methyl-6-hydroxy-5-isopropyl-3-methylhexanoate (4.8b) and methyl 6-hydroxy-3-isopropyl-5-methylhexanoate (4.7b)

Isolated yield 81% (colorless oil). 1H NMR: δ 0.87 (m), 1.15 (m), 1.34 (m), 1.55-1.91 (m), 2.00 (m), 2.27 (m), 3.31-3.57 (m), 3.59 (s). 13C NMR: δ 16.91 (q), 17.38 (q), 19.06 (q), 19.21 (q), 19.71 (q), 20.46 (q), 27.69 (d), 28.39 (d), 29.18 (d), 33.24 (d), 35.02 (t), 35.25 (t), 35.73 (t), 37.77 (d), 41.53 (t), 43.73 (d), 51.38 (q), 51.46 (q), 63.88 (t), 68.21 (t), 173.78 (s), 174.54 (s). CIMS (M+1) 203, (M+18) 220.

Methyl-6-hydroxy-3-methyl-5-phenylhexanoate (4.8c) and methyl-6-hydroxy-5-methyl-3-phenylhexanoate (4.7c)

Isolated yield 73% (oil). 1H NMR: δ 0.85 (m), 1.03-1.51 (m), 1.81 (m), 2.15 (m), 2.54 (dd, J = 7.7, 4.0 Hz), 2.84 (m), 3.17 (m), 3.28 (d, J = 5.9 Hz), 3.52 (s), 3.56 (s), 3.62 (m), 3.67-4.96 (s), 7.02-7.37 (m). 13C NMR: δ 15.76 (q), 19.07 (q), 27.51 (d), 33.21 (d), 38.25 (t), 39.15 (t), 39.42 (d), 42.19 (t), 42.53 (t), 46.06 (d), 51.34 (q), 51.48 (q), 68.18 (t), 68.56 (t), 126.56 (d), 126.88 (d), 127.43 (d), 128.09 (d), 128.51 (d), 128.70 (d), 141.36 (s), 143.38 (s), 172.73 (s), 173.25 (s). CIMS (M+1) 237, (M+18) 254. D.e. determination: GC HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T1 = 75°C for 1 min, T2 = 300°C, rate 10°C/min, rt 14.2, 14.5 min. E.e. determination major diastereomer: HPLC OD, Heptane/IPA = 97.5/2.5, rt 15.6, 16.9 min.

(S)-6-Methyl-2-cyclohepten-1-one (4.10)

Isolated yield 76% (after column chromatography (SiO2, pentane/Et2O = 4/1). [α]D = -46.3° (c = 1.1, CHCl3) (literature: [α]D = -59° (c = 1.0, CHCl3)28, [α]D = +
64.6° (c = 1.3, CHCl3, R enantiomer).<sup>29</sup> <sup>1</sup>H NMR: δ 0.91 (d, J = 6.6 Hz, 3H), 1.42 (m, 1H), 1.81 (m, 1H), 1.99 (m, 1H), 2.41 (m, 3H), 2.57 (dd, J = 14.5, 4.6 Hz, 1H), 5.88 (d, J = 12.1 Hz, 1H), 6.53 (m, 1H). <sup>13</sup>C NMR: δ 21.87 (q), 28.20 (t), 28.36 (d), 34.72 (t), 51.24 (t), 132.56 (d), 147.29 (d), 202.91 (s). CIMS (M+1) 125, (M+18) 142. E.e. determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T<sub>i</sub> = 75°C for 10 min, T<sub>f</sub> = 150°C, rate 10°C/min, rt 17.1 (S), 17.2 (R) min.

**(-)-Trans- (3S,6S)-Dimethylcycloheptanone (4.11)**

Isolated yield 79% after purification by column chromatography (SiO<sub>2</sub>, pentane/Et<sub>2</sub>O = 4/1). <sup>1</sup>H NMR shows no cis adduct. [α]<sub>D</sub> = -50.0° (c = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR: δ 0.94 (d, J = 6.6 Hz, 6H), 1.20 (m, 2H), 1.66 (m, 4H), 2.32 (m, 4H). <sup>13</sup>C NMR: δ 24.15 (q), 31.58 (d), 38.28 (t), 52.23 (t), 213.56 (s). CIMS (M+1) 141, (M+18) 158. E.e. determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T<sub>i</sub> = 75°C for 10 min, T<sub>f</sub> = 150°C, rate 10°C/min, rt 15.5, 15.6 min.

**(-)-4,7-Dimethyl-2-oxocanone (4.12)**

A mixture of 1.14 mL of acetic anhydride and 0.9 mL of 30% H<sub>2</sub>O<sub>2</sub> (aq) in 10 mL of freshly distilled dichloromethane was stirred under a nitrogen atmosphere at 0°C for 1 h, after which 9.2 mmol of maleic anhydride was added. The mixture was heated to reflux, after which 0.64 mmol of 3,6-dimethylcycloheptanone (4.11) was added. After 16 h <sup>1</sup>H NMR showed 87% conversion. The reaction mixture was extracted with 10% NaHSO<sub>3</sub>, 2N NaOH and brine. The last three steps were repeated until the brine layer tested negative on peroxides. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated. The resulting crude product was purified by column chromatography (SiO<sub>2</sub>, hexane/Et<sub>2</sub>O = 4/1) to provide 4.12 in 65% isolated yield. [α]<sub>D</sub> = -4.6° (c = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR: δ 0.90 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 1.10 (m, 2H), 1.75 (m, 3H), 1.91 (m, 1H), 2.22 (dd, J = 12.1, 9.9 Hz, 1H), 2.48 (dd, J = 12.1, 4.0 Hz, 1H), 4.01 (dd, J = 12.3, 5.5 Hz, 1H), 4.27 (dd, J = 12.1, 3.7 Hz, 1H). <sup>13</sup>C NMR: δ 18.26 (q), 23.23 (q), 31.05 (t), 33.57 (t), 35.50 (d), 36.46 (d), 36.46 (t), 38.67 (t), 175.42 (s). CIMS (M+1) 157, (M+18) 174.

**(-)-Methyl-7-hydroxy-3,6-dimethylheptanoate (4.13)**

Isolated yield 70% (oil). [α]<sub>D</sub> = -5.8° (c = 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR: δ 8.54 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.09 (m, 1H), 1.22 (m, 3H), 1.34 (m, 1H), 1.52 (s, 1H), 1.89 (m, 1H), 2.09 (dd, J = 14.7, 7.7 Hz, 1H), 2.25 (dd, J = 11.8, 6.4 Hz, 1H), 3.41 (m, 2H), 3.61 (s, 3H). <sup>13</sup>C NMR: δ 16.43 (q), 19.64 (q), 30.19 (t), 30.51 (d), 33.76 (t), 35.79 (q), 41.62 (t), 51.39 (d), 68.26 (t), 216.07 (s). CIMS (M+1) 189, (M+18) 206.
A catalytic enantioselective route to acyclic chiral building blocks

(+)\textit{trans}-3,5-Dimethyl-4,4-dimethoxycyclohexanone (4.14)
Colourless oil, 65% isolated yield after purification by column chromatography (SiO\textsubscript{2}, hexane/Et\textsubscript{2}O = 10/1). [\alpha]_D = +15.4\textdegree (c = 1.3, CHCl\textsubscript{3}). \textsuperscript{1}H NMR shows >99% \textit{trans} adduct. \textsuperscript{1}H NMR: \(\delta 0.98 (d, J = 7.0 \text{ Hz}, 6H), 2.19 (m, 2H), 2.30 (m, 2H), 2.44 (td, J = 18.7, J = 4.8, J = 1.5 \text{ Hz}, 2H), 3.30 (s, 6H). \textsuperscript{13}C NMR: \(\delta 15.94 (q), 35.81 (d), 45.70 (t), 49.89 (q), 101.26 (s), 210.98 (s). CIMS (M+1) 187, (M+18) 204.

(-)\textit{trans}-2,6-Dimethyl-4-methylenecyclohexanone (4.15)
A suspension of triphenylmethylphosphonium iodide (3.8 mmol) in 20 mL of freshly distilled THF was stirred under a nitrogen atmosphere at 0\textdegree C. nBuLi (3.8 mmol, 1.6M in hexanes) was added dropwise, resulting in a yellow solution. The 3,5-dialkyl-4,4-dimethoxycyclohexanone 4.14 (2.55 mmol) was added and the reaction mixture was stirred for 16 h at ambient temperature, during which a precipitate was formed. Conversion showed to be complete by TLC. 50 mL of 10% citric acid (aq) was added. After 5h \textsuperscript{1}H NMR showed that deprotection of the ketone was complete and no epimerisation had occurred. The aqueous layer was extracted three times with diethyl ether (100 mL), the combined organic layers were washed with brine (50 mL) and dried on Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent evaporated. The product was purified by column chromatography (SiO\textsubscript{2}, hexane/Et\textsubscript{2}O = 4/1) to provide 4.15 (2.55 mmol) was added and the reaction mixture was stirred for 16 h at ambient temperature, during which a precipitate was formed. Conversion showed to be complete by TLC. 50 mL of 10% citric acid (aq) was added. After 5h \textsuperscript{1}H NMR showed that deprotection of the ketone was complete and no epimerisation had occurred. The aqueous layer was extracted three times with diethyl ether (100 mL), the combined organic layers were washed with brine (50 mL) and dried on Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent evaporated. The product was purified by column chromatography (SiO\textsubscript{2}, hexane/Et\textsubscript{2}O = 4/1) to provide 4.15 as an oil; 87% isolated yield. [\alpha]_D = -164.1\textdegree (c = 0.41, CHCl\textsubscript{3}). \textsuperscript{1}H NMR: \(\delta 1.04 (d, J = 3.3 \text{ Hz}, 6H), 2.15 (m, 2H), 2.56 (m, 4H), 4.84 (s, 2H). \textsuperscript{13}C NMR: \(\delta 15.97 (q), 41.43 (t), 42.71 (d), 111.97 (t), 142.38 (s, 215.85 (s). CIMS (M+1) 156, (M+18) 139.

(-)\textit{trans}-2,6-Dimethyl-4-methylcyclohexanone (4.16)
A mixture of 2,6-dimethyl-4-methylenecyclohexanone 4.15 (1.70 mmol), ethyl acetate (40 mL), PtO\textsubscript{2} (0.12 mmol), and activated carbon (13 mmol) was stirred under 1 atm of H\textsubscript{2} for 16 h.\textsuperscript{30} Conversion showed to be complete by TLC. The reaction mixture was filtered over Celite, the filtrate was concentrated and the resulting crude product was purified by column chromatography (SiO\textsubscript{2}, hexane/Et\textsubscript{2}O = 4/1) to provide 4.16 (1.70 mmol), ethyl acetate (40 mL), PtO\textsubscript{2} (0.12 mmol), and activated carbon (13 mmol) was stirred under 1 atm of H\textsubscript{2} for 16 h.\textsuperscript{30} Conversion showed to be complete by TLC. The reaction mixture was filtered over Celite, the filtrate was concentrated and the resulting crude product was purified by column chromatography (SiO\textsubscript{2}, hexane/Et\textsubscript{2}O = 4/1) to provide 4.15 as an oil; 87% isolated yield. [\alpha]_D = -88.3\textdegree (c = 1.2, CHCl\textsubscript{3}). \textsuperscript{1}H NMR: \(\delta 0.90 (d, J = 6.6 \text{ Hz}, 3H), 0.93 (d, J = 6.6 \text{ Hz}, 3H), 1.04 (q, J = 12.7 \text{ Hz}, 1H), 1.30 (d, J = 7.3 \text{ Hz}, 3H), 1.47 (m, 1H), 1.70 (m,1H), 1.91 (m, 1H), 2.11 (m, 1H), 2.53 (m, 2H). \textsuperscript{13}C NMR: \(\delta 14.56 (q), 17.83 (q), 21.39 (q), 26.23 (d), 39.81 (d), 41.64 (t), 43.97 (d), 44.08 (t), 217.26 (s). CIMS (M+1) 141, (M+18) 158.

3,5,7-Trimethyl-2-oxepanone (4.17, 4.18)
Oil, 92% isolated yield. \textsuperscript{1}H NMR major diastereomer: \(\delta 1.91 (d, J = 15.6 \text{ Hz}, 3H), 1.33 (d, J = 6.4 \text{ Hz}, 3H), 1.36 (d, J = 7.81 \text{ Hz}, 3H), 1.20-1.70 (m, 3H), 1.85 (m, 1H), 2.03 (m, 1H), 3.08 (m, 1H), 4.65 (m, 1H). \textsuperscript{13}C NMR major diastereomer: \(\delta 14.62 (q), 22.76 (q), 23.06 (q), 28.27 (d), 37.31 (t), 40.68 (d), 44.81 (t), 74.96 (d), 176.78 (s). CIMS (M+1), (M+18). D.e. determination: GC
HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T₁ = 75°C for 10 min, T₁ = 200°C, rate 10°C/min, rt 18.5, 18.7 min.

Methyl-6-hydroxy-2,4-dimethylheptanoate (4.19)

Oil, 86% isolated yield. ¹H NMR major diastereomer: δ 0.83 (d, J = 6.2 Hz, 3H), 0.87-1.34 (m, 2H), 1.06 (d, J =7.0 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H), 1.37-1.80 (m, 3H), 1.97 (s, 1H), 2.48 (m, 1H), 3.60 (s, 3H), 3.84 (m, 1H). ¹³C NMR major diastereomer: δ 17.00 (q), 19.14 (q), 24.37 (q), 27.26 (d), 37.07 (d), 41.52 (t), 46.63 (t), 51.54 (q), 65.59 (d), 177.56 (s). CIMS (M+1) 189, (M+18) 206. D.e. determination: GC HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T₁ = 50°C for 10 min, T₁ = 250°C, rate 10°C/min, rt 14.2, 14.5 min.

4.6 References

A catalytic enantioselective route to acyclic chiral building blocks


14 See chapters 2 and 3 and references therein.


25 The cis-diadduct of Et₂Zn was readily formed, Me₂Zn will behave in a similar way, see: Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2001**, *57*, 2485.


30 This was performed analogously to a method reported: Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909.