A Catalytic Route to Acyclic Chiral Building Blocks: Applications of the Catalytic Asymmetric Conjugate Addition of Organozinc Reagents to Cyclic Enones

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Abstract. Through the Cu-phosphoramidite-catalyzed asymmetric conjugate addition a number of chiral cyclic enones are available with high ee. Here 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 synthons containing multiple stereocenters. This procedure represents a short, catalytic, and highly enantioselective route to a variety of acyclic chiral building blocks.

INTRODUCTION

Acyclic chiral building blocks play a major role in organic synthesis, as is particularly evident in total synthesis of macrolide antibiotics[1] and pheromones.[2] Linear fragments containing methyl-substituted stereogenic centers are especially of interest. Two general routes to obtain these linear building blocks in enantiomerically pure form comprise a synthesis starting from a precursor from the chiral pool, and methodology based on a chiral auxiliary in the crucial steps where the asymmetry is introduced.[3]

Alternatively, catalytic methods might be employed to generate acyclic chiral building blocks. Recent approaches include, among other methods, catalytic enantioselective (Mukaiyama) aldol reaction,[4] isomerization,[5] hydrogenation,[6] and allylic substitution.[7]

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.[8] Catalytic 1,4-addition to 5-substituted-cyclohexenones, readily accessible through kinetic resolution or asymmetric conjugate addition, provides *trans*-3,5-disubstituted cyclohexenones. Subsequent ring-opening of the chiral cyclic products allows the formation of the desired acyclic building blocks, with multiple stereocenters (see Scheme 1).

Recently, we realized the first catalytic 1,4-addition of organometallic reagents to enones with complete stereocontrol.[9] The asymmetric conjugate addition of dialkylzinc reagents to various cyclic enones, using a Cu-phosphoramidite complex as catalyst, proceeds with high yields and excellent ee's of >96% (Scheme 2). Shortly after these findings, two routes to chiral cyclohexenones were developed in our laboratories. The $Cu(OTf)_2$-**L*-1** catalyst proved to be very efficient for kinetic resolutions of racemic 5-substituted cyclohexenones, providing the starting compounds **1a**,**1b**, and **1c** with ee's >99%, >99%, and 89%, respectively[10] (Scheme 3a). Furthermore, not only cyclic enones, but also cyclohexadienone monoketals are excellent substrates for the asymmetric conjugate addition,[11] yielding the corresponding chiral cyclohexenones with >99% ee (Scheme 3b).

Herein we report the use of these easily accessible chiral cyclohexenones **1a–c**, as well as the use of enantiomerically pure (ee > 99%) 6-methyl-cycloheptenone **8** (available through asymmetric conjugate addition to cycloheptadienone) in the synthesis of linear building blocks containing 2 stereocenters. The route involves an asymmetric $Cu(OTf)_2$-**L*-1**-catalyzed conjugate addi-

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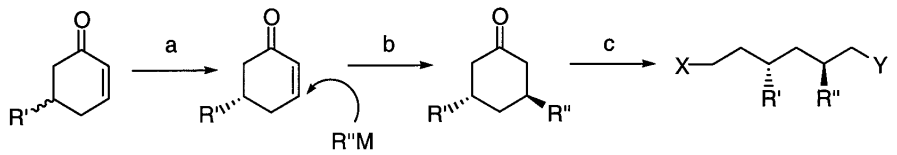
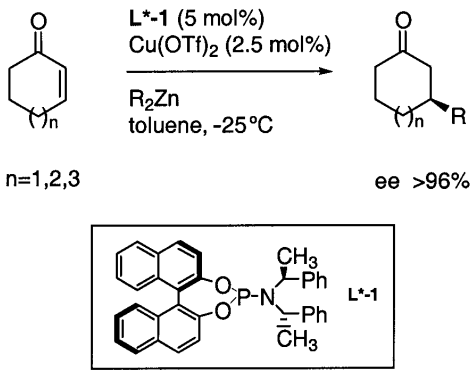
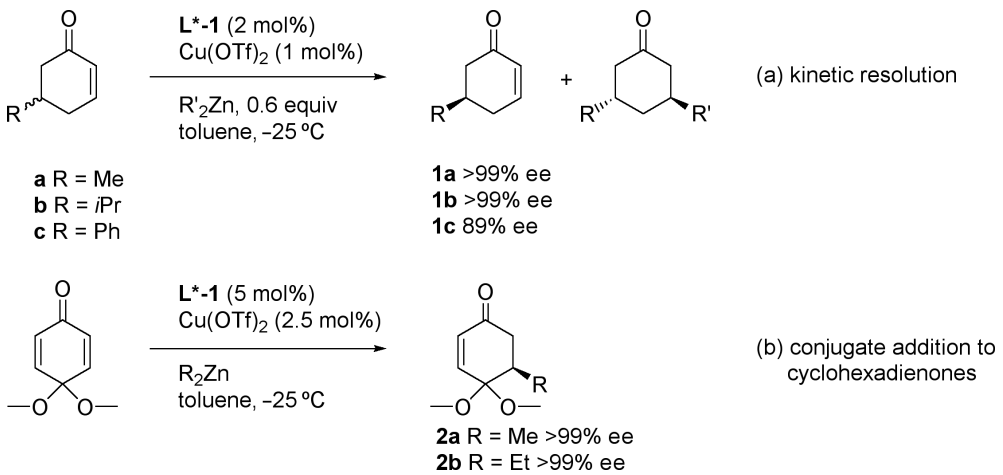


Scheme 1. (a) kinetic resolution, (b) conjugate addition, (c) ring opening.



Scheme 2. Asymmetric conjugate addition of dialkylzinc reagents to cycloalkenones catalyzed by a $Cu(OTf)_2$/ **L*-1** complex.



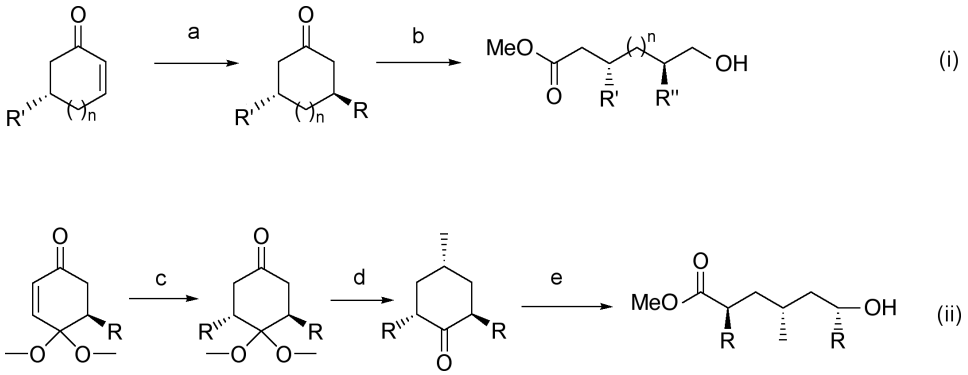
Scheme 3. Catalytic asymmetric route to chiral cyclohexenones using the Cu/**L*-1**-catalyzed conjugate addition of R_2Zn reagents.

tion of Me_2Zn to create the second stereocenter, followed by a Baeyer–Villiger oxidation and subsequent ring-opening by transesterification (See Scheme 4 (i)). Furthermore, the chiral cyclohexenone-monoketals **2a** and **2b** provide, through a similar sequence, a method to obtain linear building blocks with three stereocenters (see Scheme 4 (ii)).

EXPERIMENTAL

*General Procedure for the Conjugate Addition of Dialkylzinc to Cyclic Enones Employing a Chiral Catalyst Derived from Cu(OTf)$_2$ and **L*-1***

A solution of 2.5 mol% $Cu(OTf)_2$ and 5 mol% of **L*-1** in 5 mL of freshly distilled toluene was stirred under a nitrogen atmosphere at ambient temperature for 1 h, after



Scheme 4. General schemes for chiral linear building blocks, starting from (i) cycloalkenones leading to linear fragments containing 2 stereogenic centers, (ii) cyclohexenone monoacetals, yielding acyclic building block containing 3 stereogenic centers. 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.

which the enone was added. The mixture was cooled to –25 °C and 1.2 equiv of R_2Zn in toluene was added. Stirring was continued at –25 °C for 16 h. Conversion was determined by TLC. After complete conversion, the reaction mixture was poured into 50 mL of 2N NaOH and extracted three times with diethyl ether (100 mL). The combined organic layers were washed with brine (50 mL) and dried on Na_2SO_4, 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 **3a–3c** and **14a–b***

A suspension of 3.90 mmol *m*CPBA and $NaHCO_3$ (3.90 mmol) in 50 mL of freshly distilled dichloromethane was stirred under a nitrogen atmosphere at ambient temperature for 1 h, after which 1.3 mmol of di- or tri-substituted cyclohexanone was added. Stirring was continued for 16 h, during which a precipitate was formed. Conversion was shown to be complete by TLC. The reaction mixture was washed with 10% $NaHSO_3$, saturated $NaHCO_3$, and brine. The last three steps were repeated until the brine layer tested negative on peroxides. Subsequently, the organic layer was dried with Na_2SO_4, filtered, and the solvent evaporated. The resulting crude products were purified by column chromatography (SiO_2, hexane/Et_2O = 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 into 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 Na_2SO_4, filtered, and the solvent evaporated to yield the product.

*(3*R*,5*R*)-3,5-Dimethylcyclohexanone (**3a**)*

Isolated yield 68% after purification by column chromatography (SiO_2, pentane/Et_2O = 4/1). ^{1}H NMR shows >99% *trans* adduct. $[\alpha]_D$ = –8.2° (c = 1.0, $CHCl_3$). (Reported: $[\alpha]_D$ = –12.28° (c 1.18, $CHCl_3$)[12]) ^{1}H 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). ^{13}C 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 previously.[13] CIMS (M+1) 127, (M+18) 144. Ee determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 75 °C for 10 min, T_f = 150 °C, rate 10 °C/min, rt 14.4 (3*S*, 5*S*), 14.6 (3*R*, 5*R*) min.

*(–)-3-Isopropyl-5-methylcyclohexanone (**3b**)*

Isolated yield 75% after purification by column chromatography (SiO_2, hexane/Et_2O = 4/1). ^{1}H NMR shows no *cis* adduct. $[\alpha]_D$ = –49.6° (c = 1.0, $CHCl_3$). ^{1}H 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). ^{13}C 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. Ee determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 90 °C for 10 min, T_f = 150 °C, rate 10 °C/min, rt 19.0, 19.3 min.

*(–)-3-Methyl-5-phenylcyclohexanone (**3c**)*

Isolated yield 78% after purification by column chromatography (SiO_2, hexane/Et_2O = 4/1). ^{1}H NMR shows no *cis* adduct. $[\alpha]_D$ = –32.3° (c = 0.9, $CHCl_3$). ^{1}H 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). ^{13}C NMR: δ 20.20 (q), 29.16 (d), 39.21 (t), 39.44 (d), 47.06 (t), 48.34 (t), 126.40 (d), 126.85 (d), 128.48 (d), 144.23 (s), 211.48 (s). CIMS (M+1) 189, (M+18) 206.

*(4*R*,6*R*)-Dimethyl-2-oxepanone (**4a**)*

Isolated yield 70%. $[\alpha]_D$ = –31.9° (c = 1.1, $CHCl_3$). ^{1}H 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). ^{13}C 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. Ee determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 125 °C for 10 min, T_f = 180 °C, rate 10 °C/min, rt 14.9 (4*S*, 6*S*), 15.5 (4*R*, 6*R*) min.

*6-Isopropyl-4-methyl-2-oxepanone and 4-isopropyl-6-methyl-2-oxepanone (**4b/5b**)*

Isolated yield 81%. Ratio **4b/5b** = 56/44 ^{1}H 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). ^{13}C 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. Ee and de determinations: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 100 °C for 10 min, T_f = 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 (**4c/5c**)*

Isolated yield 68%. Ratio **4c**/**5c** = 70/30. mp 132–133 °C. ^{1}H 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). ^{13}C 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. De determination: GC CP 57 CB, 5 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 75 °C for 10 min, T_f = 250 °C, rate 10 °C/min, rt 19.6, 19.8 min.

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

Isolated yield 91% (colorless oil). $[\alpha]_D$ = +19.4° (c = 1.1, $CHCl_3$). ^{1}H 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). ^{13}C NMR: δ 16.13 (q), 19.37 (q), 27.56 (d), 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 (**6b'**) and Methyl 6-hydroxy-3-isopropyl-5-methylhexanoate (**6b**)*

Isolated yield 81% (colorless oil). ^{1}H NMR: δ 0.74 (d, *J* = 6.6 Hz), 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). ^{13}C 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 (**6c'**) and Methyl 6-hydroxy-5-methyl-3-phenylhexanoate (**6c**)*

Isolated yield 73% (oil). ^{1}H 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). ^{13}C 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. De determination: GC HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T_i = 75 °C for 1 min, T_f = 300 °C, rate 10 °C/min, rt 14.2, 14.5 min. Ee determination major diastereomer: HPLC OD, Heptane/IPA = 97.5/2.5, rt 15.6, 16.9 min.

*(*S*)-6-Methyl-2-cyclohepten-1-one (**8**)*

Isolated yield 76% (after column chromatography (SiO_2, pentane/Et_2O = 4/1). $[\alpha]_D$ = –46.3° (c = 1.1, $CHCl_3$) (literature: $[\alpha]_D$ = –59° (c = 1.0, $CHCl_3$), $[\alpha]_D$ = + 64.6° (c = 1.3, $CHCl_3$, *R* enantiomer). ^{1}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). ^{13}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. Ee determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 75 °C for 10 min, T_f = 150 °C, rate 10 °C/min, rt 17.1 (*S*), 17.2 (*R*) min.

*(–)*trans-*(3*S*,6*S*)-Dimethylcycloheptanone (**9**)*

Isolated yield 79% after purification by column chromatography (SiO_2, pentane/Et_2O = 4/1). ^{1}H NMR shows no *cis* adduct. $[\alpha]_D$ = –50.0° (c = 1.0, $CHCl_3$). ^{1}H NMR: δ 0.94 (d, *J* = 6.6 Hz, 6H), 1.20 (m, 2H), 1.66 (m, 4H), 2.32 (m, 4H). ^{13}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. Ee determination: GC Chiraldex B-TA, 30 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 75 °C for 10 min, T_f = 150 °C, rate 10 °C/min, rt 15.5, 15.6 min.

*(–)-4,7-Dimethyl-2-oxocanone (**10**)*

A mixture of 1.14 mL of acetic anhydride and 0.9 mL of 30% H_2O_2 (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 (**9**) was added. After 16 h, ^{1}H NMR showed 87% conversion. The reaction mixture was extracted with 10% $NaHSO_3$, 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_2SO_4, filtered, and the solvent evaporated. The resulting crude product was purified by column chromatography (SiO_2, hexane/Et_2O = 4/1). 65% isolated yield. $[\alpha]_D$ = –4.6° (c = 1.0, $CHCl_3$). ^{1}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). ^{13}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 (**11**)*

Isolated yield 70% (oil). $[\alpha]_D$ = –5.8° (c = 1.2, $CHCl_3$). ^{1}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). ^{13}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.

(+)-trans-*3,5-Dimethyl-4,4-dimethoxycyclohexanone* ***(12a)***

Colorless oil, 65% isolated yield after purification by column chromatography (SiO_2, hexane/EtOAc = 10/1). $[\alpha]_D$ = +15.4° (c = 1.3, $CHCl_3$). ^{1}H NMR shows >99% *trans* adduct. ^{1}H NMR: δ 0.98 (d, *J* = 7.0 Hz, 6H), 2.19 (m, 2H), 2.30 (m, 2H), 2.44 (td, *J* = 18.7, *J* = 4.8, *J* = 1.5 Hz, 2H), 3.30 (s, 6H). ^{13}C NMR: δ 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.

(+)-trans-*3,5-Diethyl-4,4-dimethoxycyclohexanone* ***(12b)***

Oil, 77% isolated yield after purification by column chromatography (SiO_2, hexane/EtOAc = 10/1). ^{1}H NMR shows >98% *trans* adduct. $[\alpha]_D$ = +20.3° (c = 1.2, $CHCl_3$). ^{1}H NMR: δ 0.84 (t, *J* = 7.3 Hz, 6H), 1.01 (m, 2H), 1.75 (m,4H), 1.95 (m, 2H), 2.10 (dd, *J* = 5.0, 1.0 Hz, 2H), 3.26 (s, 6H). ^{13}C NMR: δ 12.69 (q), 22.48 (t), 42.06 (d), 43.89 (t), 49.80 (q), 101.46 (s), 211.34 (s). CIMS (M+1) 215, (M+18) 232.

(–)-trans-*2,6-Dimethyl-4-methylenecyclohexanone* ***(13a)***

A suspension of triphenylmethylphosphonium iodide (3.8 mmol) in 20 mL of freshly distilled THF was stirred under a nitrogen atmosphere at 0 °C. *n*BuLi (3.8 mmol, 1.6 M in hexanes) was added dropwise, resulting in a yellow solution. The 3,5-dialkyl-4,4-dimethoxycyclohexanone **12a** (2.55 mmol) was added and the reaction mixture was stirred for 16 h at ambient temperature, during which a precipitate was formed. Conversion was shown to be complete by TLC. 50 mL of 10% citric acid (aq) was added. After 5 h, ^{1}H NMR showed that deprotection of the ketone was complete and no epimerization 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_2SO_4, filtered, and the solvent evaporated. The product was purified by column chromatography (SiO_2, hexane/Et_2O = 4/1). Oil, 87% isolated yield. $[\alpha]_D$ = -164.1° (c = 0.41, $CHCl_3$). ^{1}H NMR: δ 1.04 (d, *J* = 3.3 Hz, 6H), 2.15 (m, 2H), 2.56 (m, 4H), 4.84 (s, 2H). ^{13}C NMR: δ 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.

(–)-trans-*2,6-Diethyl-4-methylenecyclohexanone* ***(13b)***

A suspension of triphenylmethylphosphonium iodide (3.8 mmol) in 20 mL of freshly distilled THF was stirred under a nitrogen atmosphere at 0 °C. 3.8 mmol of *n*BuLi (1.6 M in hexanes) was added dropwise, upon which a yellow solution formed. The 3,5-dialkyl-4,4-dimethoxycyclohexanone **12b** (2.55 mmol) was added and the reaction mixture was stirred for 16 h at ambient temperature, during which a precipitate was formed. Complete conversion was determined by TLC. 50 mL of 10% citric acid (aq) was added and after 5 h, ^{1}H NMR showed that deprotection of the ketone was complete and no epimerization 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_2SO_4, filtered, and the solvent evaporated. The products were purified by column chromatography (SiO_2, hexane/Et_2O = 4/1). 88% isolated yield. $[\alpha]_D$ = –59.1° (c = 0.89, $CHCl_3$). ^{1}H NMR: δ 0.86 (t, *J* = 7.4 Hz, 6H), 1.33 (m, 2H), 1.60 (m, 2H), 2.26 (m, 4H), 2.57 (dd, *J* = 12.9, 5.4 Hz, 2H), 4.86 (s, 2H). ^{13}C NMR: δ 11.45 (q), 23.49 (t), 39.61 (t), 50.20 (d), 111.99 (t), 142.75 (s), 215.03 (s). CIMS (M+1) 167, (M+18) 184.

(–)-trans-*2,6-Dimethyl-4-methylcyclohexanone* ***(14a)***

A mixture of 2,6-dimethyl-4-methylenecyclohexanone **13a** (1.70 mmol), ethyl acetate (40 mL), PtO_2 (0.12 mmol), and activated carbon (13 mmol) was stirred under 1 atm of H_2 for 16 h. Conversion was shown 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_2, hexane/Et_2O = 4/1). 53% isolated yield. $[\alpha]_D$ = -88.3° (c = 1.2, $CHCl_3$). ^{1}H NMR: δ 0.90 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.04 (q, *J* = 12.7 Hz, 1H), 1.30 (d, *J* = 7.3 Hz, 3H), 1.47 (m, 1H), 1.70 (m,1H), 1.91 (m, 1H), 2.11 (m, 1H), 2.53 (m, 2H). ^{13}C NMR: δ 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.

(–)-trans-*2,6-Diethyl-4-methylcyclohexanone* ***(14b)***

A mixture of 2,6-diethyl-4-methylenecyclohexanone **13b** (1.70 mmol), ethyl acetate (40 mL), PtO_2 (0.12 mmol), and activated charcoal powder (13 mmol) was stirred under 1 atm of H_2 for 16 h.[16] Full conversion was determined by TLC. The reaction mixture was filtered over Celite, the filtrate was concentrated, and the resulting crude product was purified by column chromatography (SiO_2, hexane/Et_2O = 4/1). 82% isolated yield. $[\alpha]_D$ = –84.7° (c = 1.1, $CHCl_3$). ^{1}H NMR: δ 0.90 (m, 9H), 1.04 (q, *J* = 7.0 Hz, 1H), 1.13 (m, 1H), 1.42 (m, 2H), 1.66 (m, 3H), 1.99 (m, 2H), 2.24 (m, 2H). ^{13}C NMR: δ 11.60 (q), 11.88 (q), 21.49 (q), 22.04 (t), 25.10 (t), 26.85 (d), 40.00 (t), 41.77 (t), 47.19 (d), 52.16 (d), 216.61 (s). CIMS (M+1) 169, (M+18) 186.

3,5,7-Trimethyl-2-oxepanone ***(15a, 16a)***

Oil, 92% isolated yield. ^{1}H NMR major diastereomer: δ 1.91 (d, *J* = 15.6 Hz, 3H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.36 (d, *J* = 7.81 Hz, 3H), 1.20–1.70 (m, 3H), 1.85 (m, 1H), 2.03 (m, 1H), 3.08 (m, 1H), 4.65 (m, 1H). ^{13}C NMR major diastereomer: δ 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). de determination: GC HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T_i = 75 °C for 10 min, T_f = 200 °C, rate 10 °C/min, rt 18.5, 18.7 min.

3,7-Diethyl-5-methyl-2-oxepanone ***(15b, 16b)***

Oil, 72% isolated yield. ^{1}H NMR major diastereomer: δ 0.95 (m, 9H), 1.20–1.95 (m, 9H), 2.80 (m, 1H), 4.32 (m, 1H). ^{13}C NMR major diastereomer: δ 9.76 (q), 12.15 (q), 21.98 (q), 23.09 (t), 28.71 (t), 29.83 (d), 35.47 (t), 42.68 (t), 48.71 (d), 79.67 (d), 176.42 (s). CIMS (M+1) 185, (M+18) 202. De determination: GC HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T_i = 75 °C for 10 min, T_f = 200 °C, rate 10 °C/min, rt 18.5, 18.6 min. Ee determination major diasteroisomer: GC CP Cyclodex CB, 25 m × 0.25 mm, He-flow = 1.0 mL/min, T_i = 50 °C for 5 min, T_f = 160 °C, rate 5 °C/min, rt 26.5, 26.7 min.

Methyl 6-hydroxy-2,4-dimethylheptanoate ***(17a)***

Oil, 86% isolated yield. ^{1}H 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). ^{13}C 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. De determination: GC HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T_i = 50 °C for 10 min, T_f = 250 °C, rate 10 °C/min, rt 14.2, 14.5 min.

*Methyl 2-ethyl-6-hydroxy-4-methyloctanoate (**17b**)*

Oil, 72% isolated yield. ^{1}H NMR major diastereomer: δ 0.83 (t, J = 7.32 Hz, 3H), 0.88 (t, J = 7.32 Hz, 3H), 1.05–1.64 (m, 13H), 2.26 (m, 1H), 3.53 (m, 1H), 3.62 (s, 3H). ^{13}C NMR major diastereomer: δ 9.94 (q), 11.78 (q), 19.65 (q), 25.67 (t), 27.53 (d), 31.15 (t), 40.22 (t), 43.94 (t), 44.94 (d), 51.37 (q), 70.82 (d), 177.01 (s). CIMS (M+1) 217, (M+18) 234. De determination: GC HP-5, 30 m × 0.25 mm, He-flow = 1.3 mL/min, T_i = 50 °C for 10 min, T_f = 250 °C, rate 10 °C/min, rt 16.4, 16.6 min.

RESULTS AND DISCUSSION

Optically active cyclohexenones **1a–c** are easily accessible through the kinetic resolution procedure (see Scheme 3a)[10] employing chiral ligand **L*-1**.

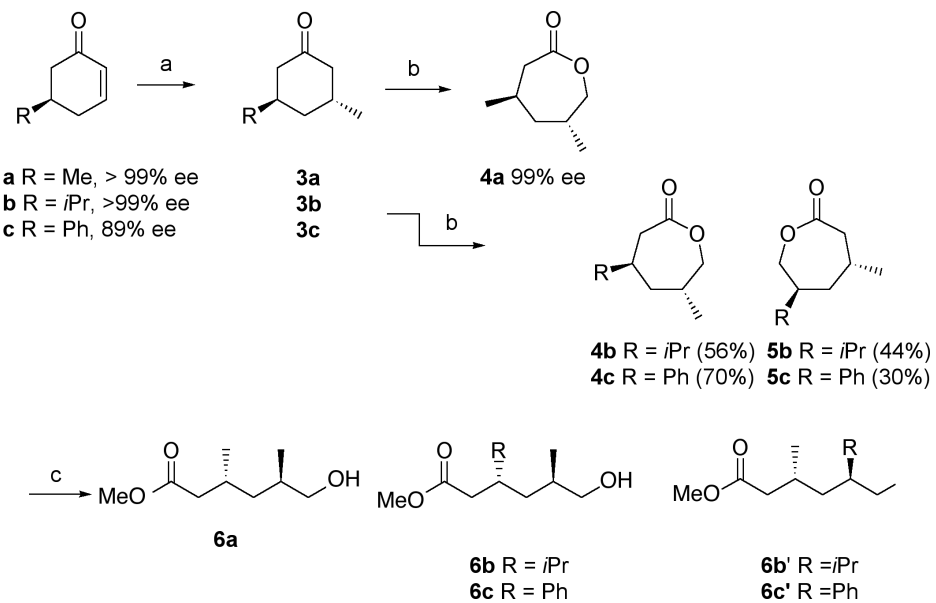
Cyclohexenones **1a–c** were subjected to a subsequent catalytic enantioselective conjugate addition. The enantiomer of the ligand (**L*-1**) was chosen in such a way that the chiral catalyst provided the *trans*-diadduct, i.e., the second stereogenic center would be of the same handedness as the first, leading to *R,R*-disubstituted cyclohexanones. Products **3a–c** were formed in good yields with >99% *trans* selectivity (^{1}H and ^{13}C NMR spectra showed no *cis*-product), with retention of ee (Scheme 5).

Treatment of the symmetrical cyclohexanone **3a** with *m*CPBA afforded, due to C_2 symmetry in **3**, the lactone **4a** as a single diastereomer with 99% ee. The Baeyer–Villiger reaction with nonsymmetrical cyclohexanones **3b** and **3c** would provide a mixture of two regioisomers if there was no *side*-selectivity. Indeed, for the *i*Pr-substituted cyclohexanone **3b** the regioselectivity was poor, giving products **4b** and **5b** as a mixture of two regioisomers in a ratio of 56:44. For the phenyl-substituted cyclohexanone **3c**, the regioselectivity improved to 70:30. Based on NMR analysis, structure **4c** was assigned to the major regioisomer.

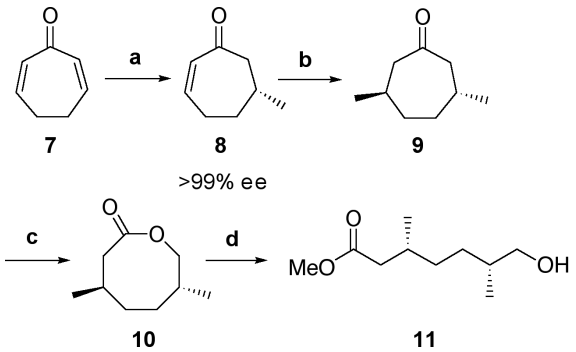
The ring-opening of the lactones using MeOH/NaOMe proceeded smoothly, and linear building block **6a**[17] (comprizing a 1,3-arrangement of stereocenters) was obtained in high yield (91%). The linear hydroxyesters **6b** and **6c** were formed as a mixture of the two isomers.

No separation of enantiomers could be found on any chiral GC or HPLC column for acyclic synthons **6a–6c**. However, the Baeyer–Villiger/saponification procedure is unlikely to give any epimerization for these compounds, so the ee's of the products **6a–6c** are likely to be equal to the ee's of starting compounds (i.e., >99%, >99%, and 89%, respectively).

The conjugate addition of Me_2Zn to cyclohepta-



Scheme 5. Reaction conditions: (a) Me_2Zn, 1.4 equiv, toluene, **L*-1** (5 mol%), $Cu(OTf)_2$ (2.5 mol%), (b) mCPBA, $NaHCO_3$, CH_2Cl_2, (c) NaOMe, MeOH.



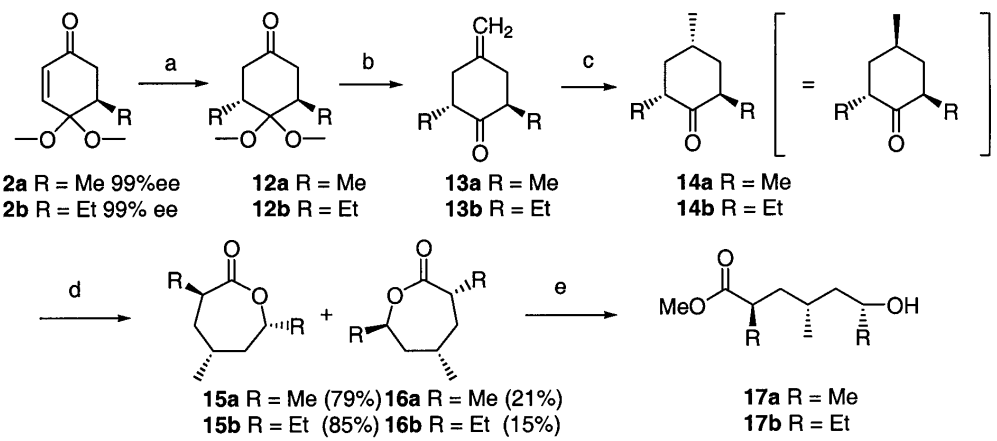
Scheme 6. Reaction conditions: (a) Me_2Zn, 1.4 equiv, toluene, **L*-1** (5 mol%), $Cu(OTf)_2$ (2.5 mol%), (b) Me_2Zn, 1.4 equiv, toluene, **L*-1** (5 mol%), $Cu(OTf)_2$ (2.5 mol%), (c) H_2O_2, maleic anhydride, acetic anhydride, CH_2Cl_2, (d) NaOMe, MeOH.

dienone **7**,[18] catalyzed by **L*-1**/$Cu(OTf)_2$, affords 3-methyl cycloheptenone **8** in good yield and with >99% ee. A conjugate addition of Me_2CuLi to racemic methyl cycloheptenone **8** has been reported to give the product as a 1:1 mixture of the *cis*:*trans* disubstituted product. However, a second conjugate addition of Me_2Zn to **8** using the same **L*-1**/$Cu(OTf)_2$ catalyst lead to the selective formation of the *trans*-disubstituted cyclo-heptanone **9**, with retention of ee (see Scheme 6, no *cis*-product was identified by ^1H and ^{13}C NMR spectroscopy).

Lactonization of cycloheptanone **9** with *m*CPBA proved to be difficult (<10% conversion after refluxing the mixture for 5 d), presumably due to unfavorable seven- to eight-membered ring enlargement.[20] Fortunately, by using the more powerful H_2O_2/maleic anhydride method reported by Bidd et al.[21] we were able to isolate product **10** in 65% yield. Ring-opening of **10** using MeOH/NaOMe proceeded smoothly, and linear building block **11** (comprising a 1,4-arrangement of stereocenters) was obtained in good yield (70%).

The chiral cyclohexenone monoacetals **2a** and **2b**, obtained through catalytic enantioselective conjugate addition of dialkylzinc reagents to cyclohexadienones (see Scheme 3b) provide a way of synthesizing linear building blocks with three stereocenters in a 2,4,6-array. The bisadduct **12b** of Et_2Zn to 4,4-dimethoxycyclohexadienone was previously reported[11] to be, selectively, the *trans* isomer when, in both conjugate addition-steps in the sequential conjugate addition, the (*S*, *R*, *R*)-enantiomer of ligand **L*-1** was used for the preparation of the catalyst. Since in natural products, linear fragments with methyl substituents occur more frequently than those with ethyl substituents, it would be interesting to know if Me_2Zn would behave in a similar way. Indeed, starting from the enantiomerically pure monoadduct **2a**, also *trans*-bisadduct **12a** was formed selectively (based on ^1H and ^{13}C NMR) through a Cu/**L*-1**-catalyzed conjugate addition of Me_2Zn (see Scheme 7).

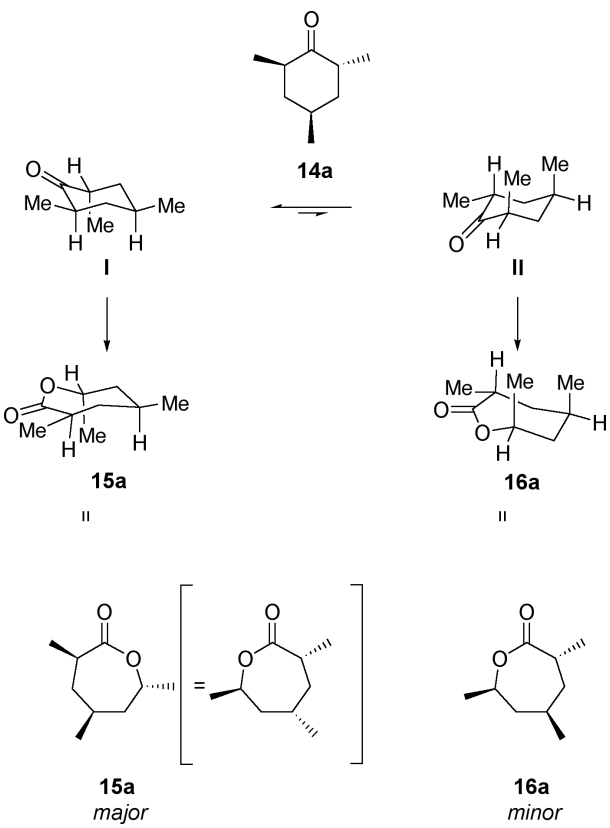
A Wittig reaction of **12a** and **12b** with CH_3PPh_3I followed by mild hydrolysis of the acetal in the presence of citric acid (10%) smoothly gave **13a** and **13b**. Based on ^1H and ^{13}C NMR, it was established that no epimerization occurs. However, reduction of the methylene groups in the presence of Pd/C and H_2 afforded, not the desired cyclohexanones **14a** and **14b**, but isomers of the starting compound (^1H NMR indicates that the exocyclic alkene isomerized to the endocyclic alkene). We were pleased to see that reduction of the methylene group in the presence of PtO_2/C[16] was successful, giving **14a** and **14b** in satisfactory yields. No epimerization of the C-2 and C-6 centers was observed (based on ^1H and ^{13}C NMR, as no *cis*-2,6-dialkyl signals were seen).



Scheme 7. Reaction conditions: (a) R_2Zn, 1.4 equiv, toluene, **L*-1** (5 mol%), $Cu(OTf)_2$ (2.5 mol%), (b) (1) CH_3PPh_3I, nBuLi, THF, (2) 10% citric acid, (c) PtO_2/C, H_2, EtOAc (d) mCPBA, $NaHCO_3$, CH_2Cl_2, (e) NaOMe, MeOH.

The C-4 methyl substituent in these 2,4,6-trisubstituted cyclohexanones is positioned on the C_2-axis, and therefore compounds **14a** and **14b** contain only 2 stereocenters (at C-2 and C-6), but after a Baeyer–Villiger reaction C-4 in lactones **15a,b** and **16a,b** is also a stereocenter. The Baeyer–Villiger is expected to proceed with some regioselectivity; the reaction has preference for oxygen insertion between the carbonyl and the adjacent carbon atom bearing an axial methyl group.[22,23]

In our case, tri-substituted cyclohexanone **14a** will be preferentially in chair-conformation **I** with two equatorial and one axial oriented methyl substituent (Scheme 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 **15a** or **16a**, respectively.[22] Assuming that there is not a large energy difference for these two oxygen insertion pathways, we expect **15a** to be the major regioisomer. For the tri-substituted cyclohexanone **14b**, similar reasoning might indicate that **15b** would be formed preferentially (see Scheme 8). Starting from **14a** and **14b**, the major regioisomer is formed in 79% (**15a**) and in 85% (**15b**), respectively. Unequivocal assignment of major isomers was not possible so far, despite the fact that extensive NMR experiments have been performed.



Scheme 8. Regioselectivity in the Baeyer–Villiger oxidation of **14a**.

Ring-opening proceeds smoothly, and the linear building blocks, **17a** and **17b**, with three stereocenters at positions 2, 4, and 6, are obtained, together with small amounts of the C4 epimers.

CONCLUSIONS

By using chiral cyclohexenones, which are easily accessible through the kinetic resolutions based on the asymmetric Cu/**L*-1**-catalyzed conjugate additions, it is possible to obtain, through a subsequent catalytic conjugate addition/ring-opening approach, linear building blocks **6a–c** with two stereocenters (at C3 and C5) in satisfactory yields and with ee's of >99%, >99%, and 89%, respectively. Linear building block **11** (with two stereocenters at C3 and C6) is easily formed in 4 steps (>99% ee) from 2,6-cycloheptadien-2-one through a sequential asymmetric Cu/**L*-1**-catalyzed conjugate addition of Me_2Zn (yielding the *trans* di-adduct **9** in 99% ee), followed by subsequent lactonization and ring-opening.

Trans-selective sequential Cu/**L*-1**-catalyzed asymmetric conjugate additions of dialkylzinc reagents to 4,4-dimethoxycyclohexadienone, followed by a Wittig reaction, reduction of the formed olefinic bond, lactonization, and ring-opening, results in linear building blocks **17a** and **17b**, which contain three stereocenters (at C2, C4, and C6) in good yield and excellent ee's (>99%).

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.

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