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Asymmetric Synthesis of the Epimeric (3*S*)-3-((*E*)-Hex-1-enyl)-2-methylcyclohexanones

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Abstract: The asymmetric rhodium-catalysed 1,4-addition of alkenylzirconium reagents to 2-cyclohexenone can be useful in the synthesis of 3-alkenyl-2-methylcyclohexanones, provided that formaldehyde is used in trapping the intermediate zirconium enolates. In this manner a four-step sequence leading to the two epimeric 3-hexenyl-2-methylcyclohexanones in enantiomeric form was developed.

Keywords: Enantioselective 1,4-addition, zirconium O-enolate trapping, 2-cyclohexenone.

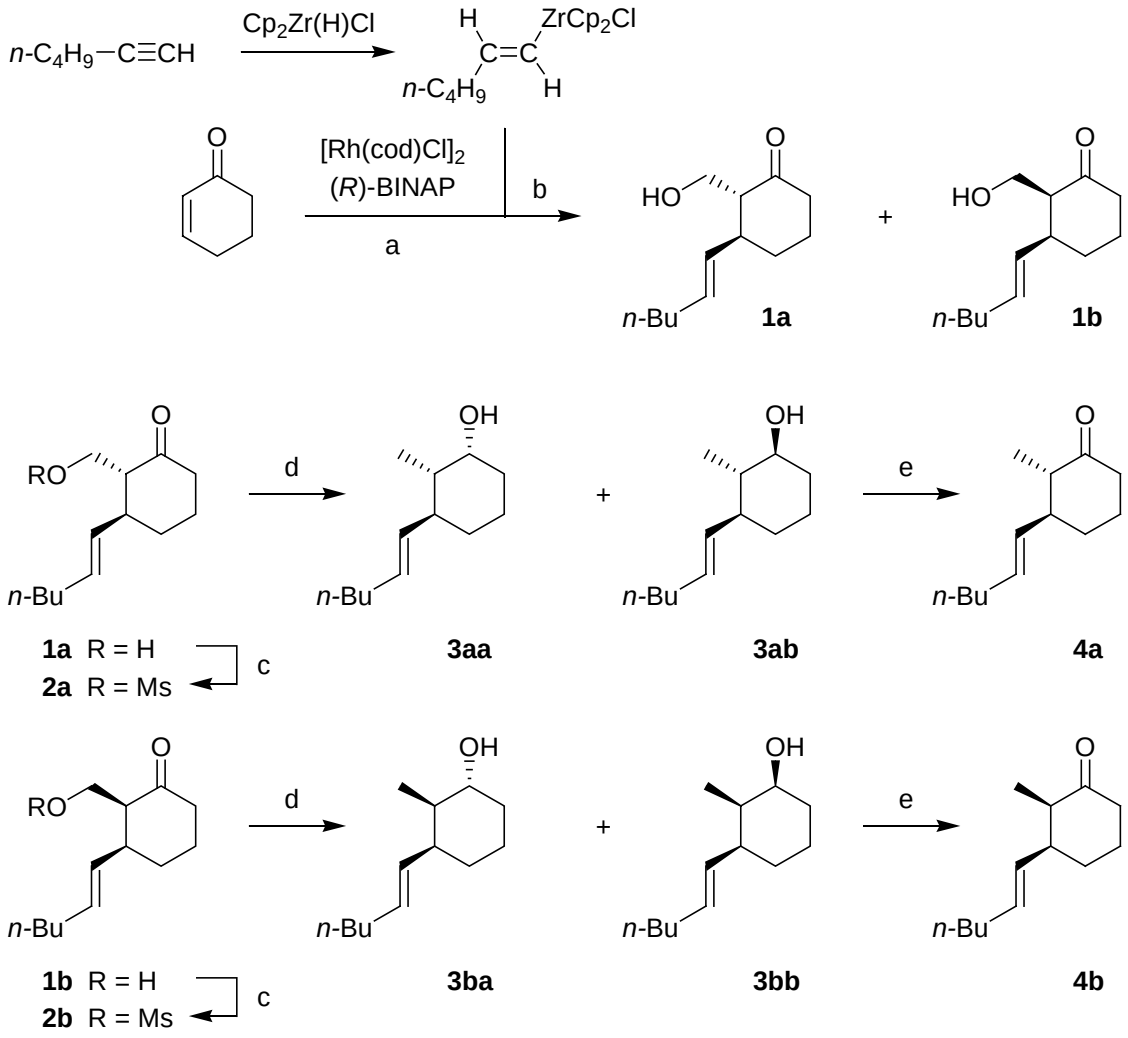
Introduction

In the context of the development of CD-ring modified structural analogs of calcitriol, the hormonally active metabolite of vitamin D_3 [1], we required the epimeric ketones **4a** and **4b** (Scheme 1) in enantiopure form. Both cyclohexanones are being converted to derivatives in which the bicyclic CD-entity is replaced by a single six-membered D-ring and in which the hexenyl substituent serves as a latent aldehyde for the introduction of the A-ring [2]. We describe herein in detail a synthesis of **4a** and **4b** featuring a highly enantioselective 1,4-addition of alkenylzirconocene to 2-cyclohexenone catalysed by the chiral rhodium complex generated from $[Rh(cod)Cl]_2$ and (*R*)-BINAP [3], followed by trapping of the O-enolate with formaldehyde.

Results and Discussion

The synthesis of the two epimeric cyclohexanones **4a** and **4b** rests on the asymmetric 1,4-introduction of the hexenyl side chain on 2-cyclohexenone followed by trapping of the resulting metal O-enolate with an electrophilic reagent.

Scheme 1. Synthetic pathway to epimeric (3*S*)-3-((*E*)-hex-1-enyl)-2-methylcyclohexanones **4a** and **4b**.

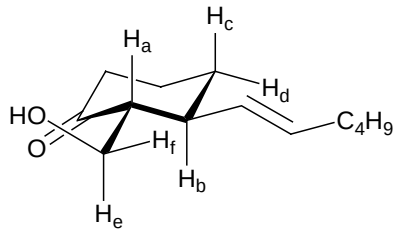


(a) $Cp_2Zr(H)Cl$, *n*-$C_4H_9C{\equiv}CH$, THF, rt, 45 min; $[Rh(cod)Cl]_2$, (*R*)-BINAP, THF, rt, 30 min; 2-cyclohexenone, rt, 3 h. (b) CH_2O (from paraformaldehyde), –78 °C (89%). (c) MsCl, Et_3N, CH_2Cl_2, 0 °C (**a**: 96%; **b**: 99%). (d) $LiAlH_4$, Et_2O, reflux, 2 h (**a**: 95%; **b**: 98%). (e) $(COCl)_2$, DMSO, Et_3N, –78 °C → rt (**a**: 89%; **b**: 96%).

Among several known enantioselective 1,4-additions of organometallic reagents to α,β-unsaturated ketones, we obtained the best results with the recently reported rhodium(I)-catalysed addition of alkenylzirconocene chlorides with BINAP as chiral ligand [3,4]. This result also follows Nicolaou's report of the tandem reaction of the rhodium-catalysed asymmetric additions of alkenylzirconium reagents followed by trapping of the zirconium enolate by aldehydes [5]. In our case, the 1,4-addition was performed on 2-cyclohexenone using (*E*)-1-hexenylzirconocene chloride [6], prepared from 1-

hexyne and bis(cyclopentadienyl)zirconium chloride hydride ($Cp_2Zr(H)Cl$ or Schwartz reagent) in the presence of a catalytic amount of the Rh(I)-complex $[Rh(cod)Cl]_2$ and (*R*)-BINAP as a chiral ligand. As previously observed by Schwartz, we were unable to directly alkylate the intermediate zirconium *O*-enolate [7]; however, reaction with gaseous formaldehyde at –78 °C led, after acid work-up, to a 2.7:1 mixture (89% yield) of **1a** and **1b**, respectively [8], with an excellent ee (better than 96%) [9]. The obtained mixture was readily separated by flash chromatography. The assignment of the *trans*- and *cis*-relationship to the alkyl substituents in the **a**- and **b**-series, respectively, rests on the analysis of NMR spectral data of **1a**. The diequatorial orientation in **1a** follows from the large vicinal *J*-value of 11.7 Hz for the coupling between H_a and H_b. The same coupling in epimer **1b** (5.3 Hz) is indicative of a *cis*-relationship (Figure 1). The absolute configuration was assigned on the basis of the results obtained by Oi and Inoue [3].

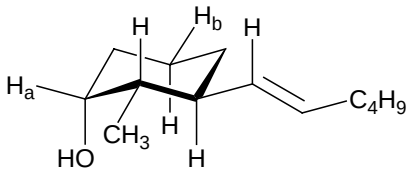
Figure 1. ^{1}H-NMR structural assignment of **1a**.



1a

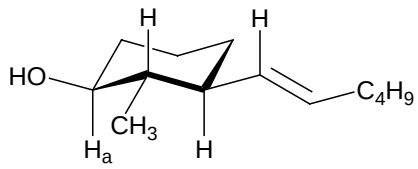
J_{ab} = 11.7 Hz, J_{bc} = 11.5 Hz
J_{bd} = 3.7 Hz, J_{ae} = 6.4 Hz
J_{af} = 3.2 Hz

Figure 2. ^{1}H-NMR structural assignments of the intermediate alcohols **3aa**, **3ab**, **3ba**, and **3bb**.



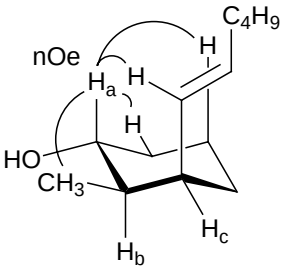
3aa

δH_a = 3.88 ppm
ΣJ = 25 Hz
W-coupling with H_b



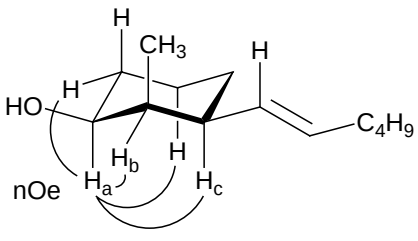
3ab

δH_a = 3.15 ppm
ΣJ = 39 Hz



3ba

δH_b = 1.59 ppm
δH_c = 2.41 ppm
H_a: dt, *J* = 3.8, 7.7 Hz



3bb

δH_b = 1.97 ppm
δH_c = 2.11 ppm
H_a: dt, *J* = 10.6, 4.1 Hz

The further conversion of **1a** and **1b** to **4a** and **4b**, respectively, first involves the reduction of the mesylates **2a** and **2b**, obtained by treatment with mesyl chloride and triethylamine in dichloromethane, to afford a mixture of the two epimeric alcohols. From **2a** there was obtained in 95% yield a 1:4

mixture of **3aa** and **3ab**; from **2b** there was obtained in 98% yield a 1:4 mixture of **3ba** and **3bb**, respectively. Again the structural assignment of the four isomeric alcohols rested on ^{1}H-NMR analysis (Figure 3). Within the *trans*-series distinction between **3aa** and **3ab** readily follows from the coupling constant pattern of the H_a proton, which indicates an axial hydroxyl group in **3aa** (cf. smaller sum of vicinal *J*-values for H_a) and an equatorial one in **3ab** (cf. larger sum of vicinal *J*-values for H_a). Furthermore a characteristic long range W coupling is observed between H_a and H_b in **3aa**. The structural assignment in the *cis*-series (**3ba** and **3bb**) on the other hand rests on the observed nOe's in both derivatives, in particular between H_a and the olefinic proton of the hexenyl side-chain in **3ba**. Finally, Swern oxidation of both mixtures led to the desired cyclohexanones **4a** and **4b** [10].

Conclusions

The two epimeric cyclohexanones **4a** and **4b** have been obtained in four steps starting from 2-cyclohexenone. The synthesis was based on the very efficient asymmetric 1,4-introduction of the 1-hexenyl chain using alkenylzirconocene and a chiral rhodium complex.

Experimental

General

Dichloromethane was distilled from CaH_2. Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl. TLC were run on glass plates precoated with silica gel (Merck, 60F-254). Column chromatography was performed on silica gel (Merck, 230-400 mesh). IR spectra (KBr films) were recorded on a Perkin–Elmer series 1600 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-500 spectrometer operating at 500 (^{1}H) and 125 MHz (^{13}C), respectively. Mass spectra (EI) were recorded on a Hewlett–Packard 5898A spectrometer at 70 eV.

(2R,3S)-3-((E)-Hex-1-enyl)-2-(hydroxymethyl)cyclohexanone (**1a**) *and (2S,3S)-3-((E)-hex-1-enyl)-2-(hydroxylmethyl)cyclohexanone* (**1b**).

Dry formaldehyde was prepared as follows: paraformaldehyde is predried overnight *in vacuo* at 60 °C in a three-necked 100-mL, round-bottom flask. The flask is equipped with an inlet for N_2 (dried over molecular sieves) and is connected via Teflon tubing to the reaction flask. The latter is then equipped with a $CaCl_2$ drying tube. The entire system is evacuated, filled with N_2 and the dried paraformaldehyde is depolymerised in a stream of N_2 by heating at 180 °C. To a suspension of Cp_2ZrHCl (6.20 g, 24 mmol) in dry THF (80 mL) under Ar was added 1-hexyne (2.76 mL, 24 mmol) and the mixture was stirred at rt for 45 minutes to give a solution of 1-hexenyl-zirconocene chloride. In a two-necked 250-mL flask under Ar, $[Rh(cod)Cl]_2$ (247 mg, 1 mmol) and (*R*)-BINAP (749 mg, 1.2 mmol) were dissolved in dry THF (40 mL) and the solution was stirred at rt for 0.5 h. To the solution of rhodium catalyst, cyclohexenone (1.94 mL, 20 mmol) and the solution of 1-hexenylzirconocene chloride were added and the mixture was stirred at rt for 3 h. The reaction mixture was cooled to –78 °C and quenched with gaseous dry formaldehyde (see above). After warming up the mixture to rt, an aqueous saturated NH_4Cl solution (3 mL) was added and the resulting mixture was stirred for 0.5 h. *t*-Butylmethyl ether (MTBE; 200 mL) was added and the precipitate formed was removed by filtration.

After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (*n*-pentane/EtOAc, 83:17 to 75:25) to give cyclohexanones **1a** (2.70 g) and **1b** (1.04 g) in 89% total yield.

1a: R_f (isooctane/EtOAc, 1:1) 0.38; $[\alpha]_D^{rt}$ –10.0 (*c* 1.0, $CHCl_3$); IR ν 3493 (br, m), 2929 (vs), 2871 (vs), 1701 (vs), 1459 (m), 1328 (m), 1222 (m), 1085 (m), 1052 (m), 969 (s) cm^{-1}; ^{1}H-NMR (C_6D_6) δ 5.29 (1 H, dt, *J* = 15.2, 6.7 Hz), 5.01 (1 H, ddt, *J* = 15.2, 8.8, 1.2 Hz), 3.85 (1 H, ddd, *J* = 11.6, 8.0, 3.2 Hz), 3.73 (1 H, dt, *J* = 11.6, 6.4 Hz), 2.85 (1 H, dd, *J* = 8.0, 6.4 Hz), 2.15 (1 H, app. d, *J* = 13.4 Hz), 2.04 (1 H, dddd, *J* = 11.7, 11.5, 8.8, 3.7 Hz), 1.86 (3 H, m), 1.75 (1 H, tdd, *J* = 13.4, 6.0, 1.0 Hz), 1.45 (2 H, m), 1.22 (4 H, m), 1.19 (1 H, tt, *J* = 13.5, 3.7 Hz), 1.11 (1 H, tdd, *J* = 13.4, 11.5, 3.7 Hz), 0.85 (3 H, t, *J* = 7.1 Hz) ppm; ^{13}C-NMR (C_6D_6) δ 212.7 (C=O), 132.4 (=CH), 131.8 (=CH), 60.6 (CH_2), 56.5 (CH), 45.0 (CH), 41.9 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 31.8 (CH_2), 25.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3) ppm; MS *m/z* (%) 210 (M^+, 3), 192 (8), 179 (100), 163 (6), 149 (13), 135 (26), 123 (54), 110 (33), 97 (21), 79 (81), 67 (97), 55 (87), 41 (99).

1b: R_f (isooctane/EtOAc, 1:1) 0.28; $[\alpha]_D^{rt}$ +7.0 (*c* 0.9, $CHCl_3$); IR ν 3408 (br, m), 2956 (vs), 2930 (vs), 2873 (vs), 1707 (vs), 1460 (m), 1379 (m), 1312 (m), 1238 (w), 1138 (m), 1025 (s), 969 (s) cm^{-1}; ^{1}H-NMR (C_6D_6) δ 5.26 (1 H, dt, *J* = 15.2, 6.4 Hz), 5.17 (1 H, dd, *J* = 15.2, 8.9 Hz), 4.00 (1 H, ddd, *J* = 11.5, 8.8, 2.1 Hz), 3.34 (1 H, ddd, *J* = 11.5, 8.5, 5.3 Hz), 2.42 (1 H, dq, *J* = 8.9, 3.6 Hz), 2.36 (1 H, dtd, *J* = 8.8, 5.3, 1.0 Hz), 2.17 (1 H, app. d, *J* = 13.8 Hz), 1.99 (1 H, app. d, *J* = 5.3 Hz), 1.82 (3 H, m), 1.58 (1 H, m), 1.30 (3 H, m), 1.19 (4 H, m), 0.83 (3 H, t, *J* = 7.0 Hz) ppm; ^{13}C-NMR (C_6D_6) δ 212.0 (C=O), 133.1 (=CH), 128.4 (=CH), 61.5 (CH_2), 55.8 (CH), 43.6 (CH), 41.7 (CH_2), 32.4 (CH_2), 31.8 (CH_2), 31.7 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 14.0 (CH_3) ppm; MS *m/z* (%) 210 (M^+, 2), 192 (10), 179 (14), 163 (6), 149 (9), 135 (32), 123 (50), 110 (98), 107 (29), 97 (47), 86 (48), 79 (83), 67 (100), 55 (82), 41 (98).

((1R,2S)-2-((E)-Hex-1-enyl)-6-oxocyclohexyl)methyl methanesulfonate (**2a**) *and ((1S,2S)-2-((E)-hex-1-enyl)-6-oxocyclohexyl)methyl methanesulfonate* (**2b**)

To an ice-cold solution of alcohol **1a** (458 mg, 2.18 mmol) and Et_3N (0.61 mL, 4.36 mmol) in CH_2Cl_2 (22 mL) was added MsCl (0.25 mL, 3.27 mmol). After stirring for 0.5 h, the reaction mixture was quenched with an aqueous saturated $NaHCO_3$ solution and the product was extracted with CH_2Cl_2. The combined organic extracts were consecutively washed with a HCl solution (0.5 M; 5 mL) and a saturated $NaHCO_3$ solution (8 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give mesylate **2a** (604 mg, 96%). The same procedure applied to alcohol **1b** afforded mesylate **2b** as a solid in 99% yield.

2a: R_f (isooctane/EtOAc, 6:4) 0.37; $[\alpha]_D^{rt}$ –17.0 (*c* 1.0, CH_3OH); IR ν 2956 (s), 2931 (s), 2860 (m), 1715 (vs), 1458 (m), 1356 (vs), 1251 (vw), 1174 (vs), 974 (s), 950 (s), 823 (w), 529 (s) cm^{-1}; ^{1}H-NMR (C_6D_6) δ 5.37 (1 H, dt, *J* = 15.3, 6.6 Hz), 4.95 (1 H, dd, *J* = 15.3, 9.0 Hz), 4.32 (1 H, dd, *J* = 9.5, 1.9 Hz), 4.21 (1 H, dd, *J* = 9.5, 5.7 Hz), 2.49 (3 H, s), 2.15 (1 H, app. d, *J* = 13.9 Hz), 2.02 (1 H, tdd, *J* = 11.8, 9.0, 3.7 Hz), 1.90 (2 H, m), 1.75 (1 H, ddd, J = 11.8, 5.7, 1.9), 1.69 (1 H, td, *J* = 13.9, 6.0 Hz), 1.42 (2 H, m), 1.27 (4 H, m), 1.15 (1 H, qt, *J* = 14.2, 3.5 Hz), 1.02 (1 H, qd, *J* = 12.9, 3.3 Hz), 0.91 (3

H, t, *J* = 7.3 Hz) ppm; ^{13}C-NMR (C_6D_6) δ 206.5 (C=O), 132.9 (=CH), 131.0 (=CH), 66.0 (OCH_2), 53.4 (CH), 44.4 (CH), 41.2 (CH_2), 36.3 (SCH_3), 32.4 (CH_2), 32.2 (CH_2), 31.6 (CH_2), 25.1 (CH_2), 22.4 (CH_2), 14.0 (CH_3) ppm; MS *m/z* (%) 289 (MH^+, 8), 205 (4), 192 (79), 179 (17), 163 (34), 149 (36), 135 (65), 122 (66), 107 (36), 93 (43), 79 (100), 67 (42), 55 (46), 41 (47).

2b: mp 39 °C; R_f (isooctane/EtOAc, 6:4) 0.37; $[\alpha]_D^{rt}$ –28.5 (*c* 1.0, CH_3OH); IR ν 2956 (s), 2932 (s), 2873 (m), 1711 (vs), 1459 (w), 1358 (vs), 1210 (vw), 1177 (vs), 1142 (vw), 959 (vs), 866 (w), 825 (w), 528 (m) cm^{-1}; ^{1}H-NMR (C_6D_6) δ 5.32 (1 H, dt, *J* = – 15.1, 6.8 Hz), 5.07 (1 H, dd, *J* = 15.1, 9.7 Hz), 4.51 (1 H, dd, *J* = 10.2, 6.5 Hz), 4.00 (1 H, dd, *J* = 10.2, 6.8 Hz), 2.61 (1 H, dq, *J* = 9.7, 3.4 Hz), 2.48 (1 H, app. q, *J* = 6.2 Hz), 2.26 (3 H, s), 2.11 (1 H, app. d, *J* = 13.2 Hz), 1.80 (2 H, m), 1.73 (1 H, td, *J* = 13.4, 6.0 Hz), 1.51 (1 H, m), 1.35 (3 H, m), 1.18 (4 H, m), 0.84 (3 H, t, *J* = 7.0 Hz) ppm; ^{13}C-NMR (C_6D_6) δ 208.0 (C=O), 134.9 (=CH), 126.3 (=CH), 68.0 (OCH_2), 52.4 (CH), 43.4 (CH), 41.5 (CH_2), 36.2 (SCH_3), 32.3 (CH_2), 31.5 (CH_2), 31.2 (CH_2), 22.9 (CH_2), 22.3 (CH_2), 13.9 (CH_3) ppm; MS *m/z* (%) 256 (5), 223 (4), 208 (14), 192 (24), 149 (24), 135 (16), 123 (14), 105 (16), 91 (35), 79 (56), 67 (51), 55 (76), 41 (100).

(2S,3S)-3-((E)-Hex-1-enyl)-2-methylcyclohexanol (**3aa**, **3ab**) *and (2R,3S)-3-((E)-hex-1-enyl)-2-methyl-cyclohexanol* (**3ba**, **3bb**)

$LiAlH_4$ (143 mg, 3.76 mmol) in dry Et_2O (7.5 mL) was refluxed for 30 min. Methanesulfonate **2a** (546 mg, 1.89 mmol) in dry Et_2O (7.5 mL) was dropwise added at reflux temperature over a period of 10 min. The reaction mixture was refluxed for 2 h, then cooled to 0 °C and quenched by the sequential addition of H_2O (145 μL), NaOH (15% solution; 145 μL) and H_2O (300 μL). After stirring at rt for 1h, the white precipitate was removed by filtration over Celite® and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (*n*-pentane/EtOAc, 9:1) to give alcohols **3aa** (70 mg) and **3ab** (285 mg) in 96% total yield. The same procedure applied to methanesulfonate **2b** (1.06 g) afforded alcohols **3ba** (141 mg) and **3bb** (563 mg) in 98% total yield.

3aa: R_f (isooctane/EtOAc, 6:4) 0.54; $[\alpha]_D^{rt}$ –45.7 (*c* 1.0, $CHCl_3$); IR ν 3392 (br, m), 2957 (s), 2928 (vs), 2872 (s), 1456 (m), 1376 (w), 1212 (w), 963 (w), 879 (w) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.37 (1 H, dt, *J* = 15.2, 6.2 Hz), 5.15 (1 H, ddt, *J* = 15.2, 8.6, 1.1), 3.88 (1 H, m, ΣJ = 25 Hz), 1.96 (3 H, m), 1.81 (1 H, app. d, *J* = 13.2 Hz), 1.64 (2 H, m), 1.46 (2 H, m), 1.35–1.24 (5 H, m), 1.11 (1 H, m), 0.92 (3 H, d, *J* = 7.0 Hz), 0.87 (3 H, t, *J* = 7.0 Hz) ppm; ^{13}C-NMR ($CDCl_3$) δ 134.7 (=CH), 130.1 (=CH), 71.1 (OCH), 41.7 (CH), 40.6 (CH), 33.3 (CH_2), 33.3 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 22.2 (CH_2), 19.6 (CH_2), 16.7 (CH_3), 14.0 (CH_3) ppm; MS *m/z* (%) 196 (M^+, <1), 178 (54), 163 (8), 149 (25), 135 (56), 121 (25), 111 (50), 93 (51), 79 (52), 67 (54), 55 (54), 41 (100).

3ab: R_f (isooctane/EtOAc, 6:4) 0.47; $[\alpha]_D^{rt}$ +12.3 (*c* 1.0, $CHCl_3$); IR ν 3350 (br, m), 2958 (s), 2926 (vs), 2857 (s), 1458 (m), 1376 (w), 1358 (w), 1294 (vw), 1117 (vw), 1032 (s), 966 (vs), 858 (vw) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.37 (1 H, dt, *J* = 15.2, 6.7 Hz), 5.17 (1 H, ddd, *J* = 15.2, 8.5, 1.2), 3.15 (1 H, m, ΣJ = 39 Hz), 1.96 (3 H, m), 1.72 (1 H, app. d, *J* = 13.0 Hz), 1.57 (2 H, m), 1.43 (1 H, s), 1.37–1.20 (6 H, m), 1.10 (1 H, m), 1.06 (1 H, m), 0.97 (3 H, d, *J* = 6.6 Hz), 0.87 (3 H, t, *J* = 6.9 Hz) ppm; ^{13}C-NMR

($CDCl_3$) δ 134.0 (=CH), 130.4 (=CH), 76.1 (OCH), 47.3 (CH), 44.6 (CH), 35.5 (CH_2), 33.4 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 23.9 (CH_2), 22.2 (CH_2), 16.0 (CH_3), 14.0 (CH_3) ppm; MS *m/z* (%) 196 (M^+, <1), 178 (22), 163 (5), 149 (22), 135 (29), 121 (42), 108 (21), 93 (40), 79 (47), 67 (52), 55 (59), 41 (100).

3ba: R_f (isooctane/EtOAc, 8:2) 0.47; $[\alpha]_D^{rt}$ –40.3 (*c* 1.0, $CHCl_3$); IR ν 3349 (br, m), 2956 (s), 2928 (vs), 2872 (s), 1460 (m), 1377 (w), 1142 (w), 1042 (m), 1017 (m), 967 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.40 (2 H, m), 3.56 (1 H, td, *J* = 7.7, 3.8 Hz), 2.41 (1 H, m), 2.20 (2 H, m), 1.85 (1 H, m), 1.59 (3 H, m), 1.50 (2 H, m), 1.41–1.28 (5 H, m), 0.90 (3 H, d, *J* = 6.9 Hz), 0.89 (3 H, t, *J* = 6.5 Hz) ppm; ^{13}C-NMR ($CDCl_3$) δ 131.2 (=CH), 130.9 (=CH), 72.4 (CH), 41.8 (CH), 41.6 (CH), 32.7 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 22.2 (CH_2), 20.4 (CH_2), 14.5 (CH_3), 14.0 (CH_3) ppm; MS *m/z* (%) 196 (M^+, 4), 178 (14), 163 (4), 149 (17), 135 (22), 121 (42), 111 (39), 93 (42), 79 (48), 67 (47), 55 (49), 41 (100).

3bb: R_f (isooctane/EtOAc, 8:2) 0.47; $[\alpha]_D^{rt}$ –10.3 (*c* 1.0, $CHCl_3$); IR ν 3350 (br, m), 2928 (vs), 2860 (s), 1466 (m), 1447 (m), 1378 (w), 1342 (w), 1301 (w), 1119 (w), 1053 (m), 1016 (m), 968 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.41 (1 H, dd, *J* = 15.5, 5.3 Hz), 5.38 (1 H, dt, *J* = 15.5, 5.8 Hz), 3.72 (1 H, dt, *J* = 10.6, 4.1 Hz), 2.11 (1 H, m), 1.97 (3 H, m), 1.72 (1 H, m), 1.59 (1 H, app. d, *J* = 12.3 Hz), 1.42 (1 H, m); 1.37–1.20 (7 H, m), 0.87 (3 H, t, *J* = 6.8 Hz), 0.80 (3 H, d, *J* = 7.0 Hz) ppm; ^{13}C-NMR ($CDCl_3$) δ 133.3 (=CH), 129.5 (=CH), 73.6 (CH), 42.8 (CH), 39.8 (CH), 32.4 (CH_2), 31.9 (CH_2), 29.0 (CH_2), 24.8 (CH_2), 23.2 (CH_2), 22.2 (CH_2), 14.0 (CH_3), 6.7 (CH_3) ppm; MS *m/z* (%) 196 (M^+,<1), 178 (40), 163 (6), 149 (22), 135 (32), 122 (28), 111 (36), 108 (25), 93 (36), 79 (50), 67 (34), 55 (51), 41 (100).

(2S,3S)-3-((E)-Hex-1-enyl)-2-methylcyclohexanone (**4a**) *and (2R,3S)-3-((E)-hex-1-enyl)-2-methyl-cyclohexanone* (**4b**)

To a solution of $(COCl)_2$ (113 μL, 1.33 mmol) in dry CH_2Cl_2 (4 mL) was dropwise added a solution of dimethyl sulfoxide (DMSO; 189 μL, 2.66 mmol) in dry CH_2Cl_2 (750 μL) at –78 °C. After 2 minutes of stirring, a mixture of alcohols **3aa** and **3ab** (238 mg, 1.21 mmol) in dry CH_2Cl_2 (3 mL) was dropwise added over a period of 5 min and the mixture was stirred for 15 min. Et_3N (845 μL, 6.66 mmol) was then added and the reaction mixture was stirred for an additional 5 min, followed by slow warming to rt. H_2O (10 mL) was added and the product was extracted with CH_2Cl_2. The combined organic layers were concentrated under reduced pressure and the residue was diluted with *t*-butyl methyl ether (MTBE). After washing with H_2O, the organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (*n*-pentane/EtOAc, 98:2) to give cyclohexanone **4a** (209 mg, 89%). The same procedure applied to the mixture of alcohols **3ba** and **3bb** afforded cyclohexanone **4b** in 96% yield.

4a: R_f (isooctane/EtOAc, 8:2) 0.44; $[\alpha]_D^{rt}$ –12.0 (*c* 1.0, CH_3OH); IR ν 2930 (vs), 2863 (vs), 1712 (vs), 1450 (m), 1376 (w), 1329 (w), 1307 (w), 1216 (w), 1181 (w), 1128 (bw), 1017 (w), 969 (s) cm^{-1}; ^{1}H-NMR (C_6D_6) δ 5.24 (1 H, dt, *J* = 15.2, 6.6 Hz), 5.05 (1 H, dd, *J* = 15.2, 8.4 Hz), 2.26 (1 H, app. d, *J* = 13.4 Hz), 1.92 (2 H, m), 1.86 (1 H, td, *J* = 13.6, 6.0 Hz), 1.77 (1 H, m), 1.73 (1 H, m), 1.56 (1 H, m), 1.48 (1 H, app. d, *J* = 13.0 Hz), 1.32 (1 H, m), 1.26 (4 H, m), 1.17 (1 H, m), 1.11 (3 H, d, *J* = 6.0 Hz),

0.86 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C-NMR (C_6D_6) δ 209.5 (C=O), 133.4 (=CH), 130.9 (=CH), 50.4 (CH), 49.4 (CH), 41.5 (CH_2), 32.9 (CH_2), 32.3 (CH_2), 31.1 (CH_2), 26.0 (CH_2), 21.6 (CH_2), 14.1 (CH_3), 13.0 (CH_3) ppm; MS *m/z* (%) 194 (M^+, 9), 137 (4), 123 (30), 110 (19), 96 (4), 81 (45), 79 (32), 67 (100), 47 (67).

4b: R_f (isooctane/EtOAc, 8:2) 0.44; $[\alpha]_D^{rt}$ –13.1 (*c* 1.0, $CHCl_3$); IR ν 2957 (s), 2930 (vs), 2872 (s), 1713 (vs), 1448 (m), 1377 (vw), 1312 (vw), 1222 (w), 1141 (w), 1078 (w), 995 (w), 968 (m) cm^{-1}; ^{1}H-NMR (C_6D_6) δ 5.32 (1 H, dtd, *J* = 15.3, 6.8, 1.1 Hz), 5.20 (1 H, ddd, *J* = 15.3, 8.8, 0.9 Hz), 2.36 (1 H, m), 2.20 (2 H, m), 1.87 (3 H, m), 1.65 (1 H, m), 1.44 (3 H, m), 1.22 (4 H, m), 0.97 (3 H, dd, *J* = 6.8, 1.3 Hz), 0.83 (3 H, t, *J* = 7.2 Hz) ppm; ^{13}C-NMR (C_6D_6) δ 210.6 (C=O), 133.1 (=CH), 129.0 (=CH), 48.5 (CH), 47.0 (CH), 41.0 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 31.1 (CH_2), 23.5 (CH_2), 22.5 (CH_2), 14.1 (CH_3), 12.9 (CH_3) ppm; MS *m/z* (%) 194 (M^+, 8), 179 (2), 149 (5), 138 (3), 123 (34), 110 (22), 95 (14), 81 (57), 67 (67), 55 (49), 49 (100), 41 (93).

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References and Notes

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6. Under the same conditions the introduction of the hexenyl side chain on 2-methyl-2-cyclohexenone was not successful.
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9. The ee was determined by HPLC based on the racemate using a chiral stationary phase column (Daicel CHIRALPAK® AD-H, eluent: *n*-hexane/EtOH, 95:5).
10. The ee of **4a** and **4b** was determined by HPLC based on the racemate using a chiral stationary phase column (Daicel CHIRALPAK® AD-H, eluent: *n*-hexane/EtOH, 99:1); for **4a**: 96.3% ee, for **4b**: better than 91% ee.

Sample Availability: No samples available.