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Cerium(III) chloride promoted addition of organometallic reagents to (–)-menthone—preparation of chiral neomenthyl derivatives†

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Abstract

The activation of (–)-menthone with anhydrous $CeCl_3$ led to high yielding additions of different organometallic reagents. Products of exclusively equatorial-addition of the reagents were obtained; only PhMgBr yielded additionally ca. 5% of the axial-addition product.

1. Introduction

The addition of organometallic compounds to menthone has been an object of interest for a long time.[1] The efforts were directed partly in the investigation of the stereoselectivity;[2,3] however, there is an increasing interest to use the addition of organometallics to enantiomerically pure menthone [mainly the (–)-isomer] for synthetic purposes.[4] In all addition reactions published to date[1–4] the attack of the reagent has been described to proceed exclusively from the equatorial side of the carbonyl C-atom, resulting in formation of neomenthol derivatives. Equatorial addition has been described even in the case of electroreductive coupling of (–)-menthone with *O*-methyl-acetaldoxime.[5] However, we recently obtained remarkable results; for the first time exclusively axial addition to (–)-menthone has been observed using $LiCH_2CN$ as the reagent.[6]

We describe now the addition of several organometallic reagents to (–)-menthone in order to optimize the synthetic procedure for the preparation of neomenthol derivatives in high yields as well as studying the stereoselectivity. It is interesting to note that, depending on the reagent, the addition reactions of organometallics to menthone often proceed with relatively low yields.[1c,4b,e] We apply herein highly active anhydrous $CeCl_3$ as a promoter of the additions, prepared by our previously published improved drying procedure,[8] which was also recently used by Imamoto

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† Dedicated to Professor Dr. Karl-Heinz Thiele on the occasion of his 70th birthday.

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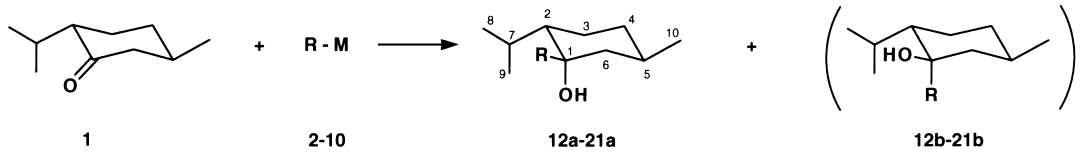
republishing the most significant details.[9] The use of in situ generated organocerium reagents for additions to carbonyl compounds, pioneered by Imamoto,[10] received in previous years considerable significance. Enantiomerically pure neomenthol derivatives are important auxiliaries[4d,e] or ligands[5,11] for the asymmetric synthesis.

2. Results and discussion

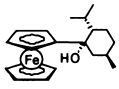
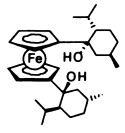
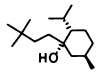
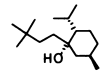
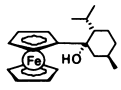
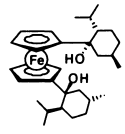
The addition of reagents **2**–**10** (Scheme 1 and Table 1) to (–)-menthone without the assistance of anhydrous $CeCl_3$ was carried out in THF or THF/Et_2O mixtures at –10°C with additional stirring for 2 h at room temperature. The yields realized for compounds **13a**, **15a** and **17a** were higher than described previously (no spectroscopic data were given)[1c] and for compound **12a** lower than recently published.[4e] In all cases, however, the conversion of (–)-menthone was not complete, resulting in some difficulties in the isolation of the products in pure form. The application of anhydrous $CeCl_3$ for activation of the carbonyl function, according to our previously published procedure,[8] brought in the case of reagents **2**, **3** and **7** small changes in the yields (entries 1, 3 and 11, Table 1). However, in all other cases a significant enhancement of the yields was observed. The addition of reagents **8** and **10** provided not only the products **18a** and **19a**, respectively, but also the disubstituted ferrocene derivative in the former case and the monosubstituted one in the latter case. The application of $CeCl_3$ improved the yields of the desired compounds (entries 14 and 17). The behavior of reagents **8** and **10** was in accordance with our previous observations on the additions to camphor and fenchone[7b] — **8** always contains dilithiated ferrocene and **10** can serve as precursor for monosubstituted ferrocene derivatives, despite the small quantity of monolithiated ferrocene, which is always present. In the case of reagent **8** we observed in addition a significant quantity of product **20a** (entries 13 and 14). This result is quite understandable, because during the monolithiation of ferrocene[12] with *t*-BuLi, an ether cleavage of the THF occurs and the ethene formed reacts further with the *t*-BuLi, present in excess, forming $LiCH_2CH_2C(CH_3)_3$ **9**. The formation of **9** from *t*-BuLi in THF has been reported previously.[13] This was proved preparing compound **9** separately and allowing it to react with **1** (entry 15 and Experimental).



Scheme 1.

The stereoselectivity of the addition reactions with reagents **2**–**10** was a result of equatorial attack. Only in the case of PhMgBr **7** could we obtain a small quantity of the axial addition product **17b** (entries 11 and 12). This may be explained by increased steric hindrance between the phenyl *ortho*-protons of the reagent and the axial protons of (–)-menthone. The anomalous behavior of phenyl reagents has been observed in additions to substituted cyclohexanones.[2,14] Further, it should be noted that menthone is prone to epimerization leading to isomenthone and we found evidence for this in recent investigations.[6] However, we could not find here any additional products indicating the presence of isomenthone.

Table 1
Addition of organometallic reagents **2**–**10** to (–)-menthone

Entry No.	R-M	$CeCl_3$ Equiv	Product (Yield %)[a]
1	MeMgJ **2**	-	**12a** (55)
2	MeMgJ **2**	1.0	**12a** (69)
3	EtMgBr **3**	-	**13a** (61)
4	EtMgBr **3**	1.0	**13a** (68)
5	i-PrMgCl **4**	-	**14a** (38)[b]
6	i-PrMgCl **4**	1.0	**14a** (81)
7	n-BuLi **5**	-	**15a** (50)[b]
8	n-BuLi **5**	1.0	**15a** (82)
9	t-BuLi **6**	-	**16a** (56)[b]
10	t-BuLi **6**	1.1	**16a** (80)
11	PhMgBr **7**	-	**17a** (71)/**17b** (2%)[b]
12	PhMgBr **7**	1.0	**17a** (76)/**17b** (5%)
13	 **8**	-	 **18a** (35)  **19a** (6)  **20a** (26)
14	 **8**	1.0	**18a** (40) **19a** (3) **20a** (8)
15	$(CH_3)_3CCH_2CH_2$-Li **9**	-	 **20a** (29)
16	 **10**	-	 **18a** (24)  **19a** (18)
17	 **10**	1.0	**18a** (22) **19a** (26)

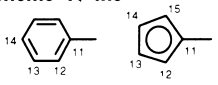
[a] Yields of isolated products. [b] Yields extrapolated by means of NMR spectra.

The unambiguous assignment of the proton and carbon-13 spectra (Table 2 and Experimental) was made on the basis of DEPT, HSQC[15] and NOESY experiments.

Table 2
^{13}C NMR chemical shifts of compounds **12–20** ($CDCl_3$, 300 K, δ in ppm from TMS)

Compound / No. C-atom	12a	13a	14a	15a	16a	17a	17b	18a	19a	20a
C1	72.93	75.31	77.00	75.07	78.67	78.26	79.40	73.79	74.21	75.36
C2	50.39	47.03	46.33	47.57	48.42	49.86	50.40	51.69	52.46	46.97
C3	20.76	20.43	20.52	20.45	20.79	21.23	16.50	20.97	21.14	20.42
C4	35.12	35.12	35.10	35.12	35.13	35.12	32.00	35.19	35.13	35.07
C5	28.04	27.93	27.77	27.97	28.71	28.39	27.90	27.88	27.87	28.01
C6	50.62	46.04	39.24	46.83	43.98	51.52	47.80	50.23	49.15	46.73
C7	25.98	25.33	24.57	25.40	27.26	26.60	26.80	26.21	26.18	25.34
C8	18.15	18.11	18.06	18.11	17.32	18.31	18.60	17.93	17.92	18.18
C9	23.73	23.54	23.41	23.55	23.07	23.66	23.90	23.44	23.52	23.52
C10	22.22	22.45	22.67	22.44	22.70	22.16	20.70	22.57	22.62	22.48
C11	28.77	33.53	34.36	41.09	38.40	148.56	149.30	99.49	98.65	35.77
C12	–	8.37	16.48	26.18	27.26	124.52	124.80	66.12	65.71	37.75
C13	–	–	17.57	23.39	–	127.98	128.00	66.64	66.63	30.08
C14	–	–	–	14.05	–	126.00	126.10	67.60	67.46	29.32
C15	–	–	–	–	–	–	–	66.26	68.82	–
unsubst. Cp	–	–	–	–	–	–	–	68.15	–	–

*For the numbering of the menthane moiety see Scheme 1; the alkyl substituents were numbered continuously; the Ph- and Cp-moieties were numbered as follows



In conclusion, we have shown that the use of anhydrous $CeCl_3$ as a promoter of the carbonyl reactivity enhanced the yields of the addition products of different organometallics to (–)-menthone, providing useful enantiomerically pure compounds on a preparative scale.

3. Experimental

3.1. General methods and starting materials

All reactions were carried out in flame-dried Schlenk flasks under argon atmosphere. The solvents were dried (sodium/benzophenone for Et_2O and THF, and $Na[Et_4Al]$ for hexane) and distilled. Thin layer chromatography (TLC): aluminum sheets precoated with silica gel 60 F_{254} (Merck). Column chromatography: at normal pressure, silica gel 60 (0.063–0.200 mm, Merck).

Melting point: Kofler block apparatus (uncorrected). $[\alpha]_D^{20}$: Perkin–Elmer 241 polarimeter. Mass spectra (MS): Finnigan MAT 90 or Finnigan SSQ 700; fragmentation in m/z with relative intensities (%) in parentheses. NMR spectra: Bruker Avance DRX-250 (^1H at 250.1 MHz; ^{13}C at 62.9 MHz; TMS as internal standard); samples for NOE difference experiments were prepared by

blowing argon through the $CDCl_3$ solution. Elemental analyses were performed by the Microanalytical Service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

The following starting materials (commercially available or prepared according to the literature) were used: (–)-menthone and ferrocene (Fluka AG); MeMgI, EtMgBr, *i*-PrMgCl, *n*-BuLi, *t*-BuLi and PhMgBr were prepared from the corresponding organic halides by known procedures;[16] LiCpFeCp,[12] $(LiCp)_2Fe$[7b] and anhydrous $CeCl_3$.[8]

3.2. General procedure for addition of organometallic reagents to (–)-menthone

3.2.1. Without the assistance of $CeCl_3$

To a THF solution of (–)-menthone **1** (1.94–3.57 mmol) was added the corresponding organometallic reagent at –10°C. After it was stirred for 2 h at room temperature the mixture was hydrolyzed (2N HCl) and extracted with Et_2O (3×20 ml). The organic layer was washed with 5% aq. $NaHCO_3$, H_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography or by distillation.

3.2.2. With the assistance of $CeCl_3$

(–)-Menthone **1** (0.91–4.47 mmol) and anhydrous $CeCl_3$ (0.93–4.50 mmol) in 7–11 ml THF were stirred at room temperature until a gel-like mixture (slightly yellow colored; activation time 40 min to 1 h) was formed. The mixture was cooled to –10°C and the corresponding organometallic reagent added. After it was stirred for 2 h at room temperature the mixture was hydrolyzed (2N HCl) and extracted with Et_2O (3×20 ml). The organic layer was washed with 5% aq. $NaHCO_3$, H_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography or by distillation.

3.3. (1S,2S,5R)-1,5-Dimethyl-2-isopropyl-cyclohexan-1-ol **12a**

Without $CeCl_3$. Following the general procedure, from 0.30 g (1.94 mmol) **1** in 4 ml THF and 1.8 ml of a 1.4 M MeMgI solution in Et_2O (2.52 mmol) were obtained after column chromatography (∅ 13 mm, h = 430 mm, 23 g silica gel, petroleum ether:Et_2O = 10:1) 0.05 g unconverted **1** and 0.18 g (55%) **12a** (colorless oil).

With $CeCl_3$. Following the general procedure, from 0.50 g (3.24 mmol) **1**, 0.81 g (3.29 mmol) $CeCl_3$ in 7 ml THF and 2.8 ml of a 1.4 M MeMgI solution in Et_2O (3.92 mmol) were obtained after column chromatography (∅ 13 mm, h = 500 mm, 40 g silica gel, petroleum ether:Et_2O = 15:1) 0.04 g unconverted **1** and 0.38 g (69%) **12a** (colorless oil). $[\alpha]_D^{20}$ 0 (c = 1.05, $CHCl_3$). Anal. calcd for $C_{11}H_{22}O$ (170.29): C, 77.58; H, 13.02. Found: C, 76.60; H, 12.81. ^{1}H NMR ($CDCl_3$, 300 K): δ = 0.86 (qd, 1H, 4-H_{ax}, J = 13.0, 4.0 Hz), 0.86 (d, 3H, 10-H, J = 6.4 Hz), 0.90 (d, 3H, 8-H, J = 7.1 Hz), 0.91 (d, 3H, 9-H, J = 7.1 Hz), 1.03 (ddd, 1H, 2-H, J = 12.5, 3.7, 2.2 Hz), 1.04 (t, 1H, 6-H_{ax}, J = 12.2 Hz), 1.16 (s, 1H, OH), 1.23 (s, 3H, 11-H), 1.36 (qd, 1H, 3-H_{ax}, J = 12.8, 3.3 Hz), 1.45–1.58 (m, 1H, 3-H_{eq}), 1.57 (dt, 1H, 6-H_{eq}, J = 12.0, 3.2 Hz), 1.60–1.74 (m, 1H, 5-H), 1.75 (dm, 1H, 4-H_{eq}, J = 12.2 Hz), 2.15 (quintd, 1H, 7-H, J = 7.0, 2.0 Hz).

3.4. (1S,2S,5R)-1-Ethyl-2-isopropyl-5-methyl-cyclohexan-1-ol **13a**

Without $CeCl_3$. Following the general procedure, from 0.30 g (1.94 mmol) **1** in 4 ml THF and 1.6 ml of a 1.59 M EtMgBr solution in Et_2O (2.54 mmol) were obtained after column

chromatography (∅ 13 mm, h = 430 mm, 23 g silica gel, petroleum ether:Et_2O = 10:1) 0.22 g (61%) **13a** (colorless oil).

With $CeCl_3$. Following the general procedure, from 0.52 g (3.37 mmol) **1**, 0.83 g (3.37 mmol) $CeCl_3$ in 7 ml THF and 3.2 ml of a 1.59 M EtMgBr solution in Et_2O (5.09 mmol) were obtained after column chromatography (∅ 17 mm, h = 490 mm, 40 g silica gel, petroleum ether:Et_2O = 10:1) 0.42 g (68%) **13a** (colorless oil). $[\alpha]_D^{20}$ +5.4 (c = 1.03, $CHCl_3$). Anal. calcd for $C_{12}H_{24}O$ (184.32): C, 78.20; H, 13.12. Found: C, 77.71; H, 12.98. MS (EI) m/z (rel. int.): 184 ($M^{+\cdot}$, 0.24), 166 ($[M–H_2O]^{+\cdot}$, 2), 155 (21), 137 (10), 99 (100), 95 (19), 81 (38), 69 (15), 57 (23), 43 (24). ^1H NMR ($CDCl_3$, 300 K): δ = 0.72–0.82 (m, 1H, H-4_{ax}), 0.80 (d, 3H, H-10, J = 6.4 Hz), 0.82 (d, 3H, H-8, J = 6.9 Hz), 0.83 (t, 3H, H-12, J = 7.6 Hz), 0.84 (d, 3H, H-9, J = 7.1 Hz), 1.04 (t, 1H, H-6_{ax}, J = 12.7 Hz), 1.09 (ddd, 1H, H-2, J = 13.7, 4.3, 1.8 Hz), 1.13 (s, 1H, OH), 1.39 (qd, 1H, H-3_{ax}, J = 13.2, 3.4 Hz), 1.43 (dt, 1H, H-6_{eq}, J = 12.5, 3.5 Hz), 1.38–1.68 (m, 2H, H-11), 1.43–1.54 (m, 1H, H-3_{eq}), 1.57–1.70 (m, 1H, H-5), 1.73 (dm, 1H, H-4_{eq}, J = 13.5 Hz), 2.05 (quintd, 1H, H-7, J = 6.9, 1.5 Hz).

3.5. (1R,2S,5R)-1,2-Diisopropyl-5-methyl-cyclohexan-1-ol **14a**

Without $CeCl_3$. Following the general procedure, from 0.30 g (1.94 mmol) **1** in 4 ml THF and 1.6 ml of a 1.64 M *i*-PrMgCl solution in Et_2O (2.62 mmol) were obtained after column chromatography (∅ 13 mm, h = 430 mm, 23 g silica gel, petroleum ether:Et_2O = 5:1) 0.20 g mixed fraction of **1** and **14a** (31:69 by NMR).

With $CeCl_3$. Following the general procedure, from 0.69 g (4.47 mmol) **1**, 1.11 g (4.50 mmol) $CeCl_3$ in 11 ml THF and 4 ml of a 1.64 M *i*-PrMgCl solution in Et_2O (6.56 mmol) were obtained after column chromatography (∅ 17 mm, h = 520 mm, 50 g silica gel, petroleum ether:Et_2O = 10:1) 0.72 g (81%) **14a** (colorless oil). $[\alpha]_D^{20}$ +8.9 (c = 1.00, $CHCl_3$). Anal. calcd for $C_{13}H_{26}O$ (198.35): C, 78.72; H, 13.21. Found: C, 77.31; H, 12.88. MS (EI) m/z (rel. int.): 198 ($M^{+\cdot}$, 11), 180 ($[M–H_2O]^{+\cdot}$, 1), 156 (11), 155 ($[M–C_2H_3O]^{+\cdot}$, 100), 137 (43), 113 (59), 99 (6), 95 (31), 81 (60), 69 (15), 55 (12), 43 (C_2H_3O, 38). ^1H NMR ($CDCl_3$, 300 K): δ = 0.81 (qd, 1H, H-4_{ax}, J = 11.6, 3.8 Hz), 0.82 (d, 3H, H-13, J = 7.1 Hz), 0.84 (t, 1H, H-6_{ax}, J = 13.0 Hz), 0.88 (d, 3H, H-10, J = 6.4 Hz), 0.88 (d, 3H, H-8, J = 6.8 Hz), 0.90 (d, 3H, H-9, J = 6.9 Hz), 0.94 (d, 3H, H-12, J = 6.9 Hz), 1.16 (s, 1H, OH), 1.24 (ddd, 1H, H-2, J = 11.9, 3.8, 1.7 Hz), 1.41 (qd, 1H, H-3_{ax}, J = 12.6, 3.2 Hz), 1.45–1.58 (m, 1H, H-3_{eq}), 1.50 (dm, 1H, H-6_{eq}), 1.58–1.72 (m, 1H, H-5), 1.75 (dm, 1H, H-4_{eq}, J = 12.2 Hz), 2.08 (quint, 1H, H-11), 2.10 (quint, 1H, H-7).

3.6. (1S,2S,5R)-1-Butyl-2-isopropyl-5-methyl-cyclohexan-1-ol **15a**

Without $CeCl_3$. Following the general procedure, from 0.55 g (3.57 mmol) **1** in 4 ml THF and 4 ml of a 1.78 M *n*-BuLi solution in hexane (7.12 mmol) were obtained after column chromatography (∅ 17 mm, h = 490 mm, 44 g silica gel, petroleum ether:Et_2O = 10:1) mixed fractions 0.18 g **1** and **15a** (43:57 by NMR), and 0.29 g **1** and **15a** (15:85 by NMR). Kugelrohr distillation of the latter fraction (70°C, 0.001 torr) gave 0.23 g (30%) **15a** (colorless oil). The conversion of **1** was 50% (extrapolated by means of the NMR spectra).

With $CeCl_3$. Following the general procedure, from 0.24 g (1.56 mmol) **1**, 0.38 g (1.54 mmol) $CeCl_3$ in 5 ml THF and 1.7 ml of a 1.78 M *n*-BuLi solution in hexane (3.03 mmol) were obtained after column chromatography (∅ 13 mm, h = 430 mm, 24 g silica gel, petroleum ether:Et_2O = 10:1) 0.27 g (82%) **15a** (colorless oil). $[\alpha]_D^{20}$ +3.2 (c = 1.08, $CHCl_3$). Anal. calcd for $C_{14}H_{28}O$ (212.38):

C, 79.18; H, 13.29. Found: C, 78.04; H, 12.79. MS (EI) m/z (rel. int.): 212 ($M^{+\cdot}$, 5), 155 (52), 137 (15), 127 (100), 95 (14), 81 (29), 69 (12), 57 (12), 55 (12), 43 (C_2H_3O, 16). ^{1}H NMR ($CDCl_3$, 300 K): $\delta = 0.82$ (qd, 1H, H-4_{ax}, J = 12.2, 4.4 Hz), 0.87 (d, 3H, H-10, J = 5.9 Hz), 0.89 (d, 3H, H-9, J = 6.6 Hz), 0.89 (d, 3H, H-8, J = 6.6 Hz), 0.91 (t, 3H, H-14), 1.07 (t, 1H, H-6_{ax}, J = 12.5 Hz), 1.10 (dm, 1H, H-2), 1.15–1.30 (m, 2H, H-12), 1.20–1.38 (m, 2H, H-13), 1.41 (qd, 1H, H-3_{ax}, J = 12.5, 3.4 Hz), 1.43–1.56 (m, 1H, H-3_{eq}), 1.47 (dm, 1H, H-6_{eq}), 1.38–1.50 (m, 1H, H-11), 1.57–1.70 (m, 1H, H-11), 1.59–1.75 (m, 1H, H-5), 1.75 (dm, 1H, H-4_{eq}), 2.08 (quintd, 1H, H-7, J = 6.9, 1.7 Hz).

3.7. (1S,2S,5R)-1-t-Butyl-2-isopropyl-5-methyl-cyclohexan-1-ol **16a**

Without $CeCl_3$. Following the general procedure, from 0.31 g (2.01 mmol) **1** in 4 ml THF and 3.4 ml of a 0.94 M *t*-BuLi solution in pentane (3.20 mmol) were obtained after column chromatography (∅ 13 mm, h = 430 mm, 26 g silica gel, petroleum ether:Et_2O = 10:1) 0.20 g (47%) **16a** and 0.06 g mixed fraction of **1** and **16a** (48:52 by NMR). The conversion of **1** was 56%.

With $CeCl_3$. Following the general procedure, from 0.30 g (1.94 mmol) **1**, 0.52 g (2.11 mmol) $CeCl_3$ in 7 ml THF and 3.3 ml of a 0.94 M *t*-BuLi solution in pentane (3.10 mmol) were obtained after column chromatography (∅ 17 mm, h = 490 mm, 41 g silica gel, petroleum ether:Et_2O = 5:1) 0.33 g (80%) **16a** (colorless oil). $[\alpha]_D^{20}$ –0.6 ($c = 1.13$, $CHCl_3$). Anal. calcd for $C_{14}H_{28}O$ (212.38): C, 79.18; H, 13.29. Found: C, 78.90; H, 12.83. MS (EI) m/z (rel. int.): 212 ($M^{+\cdot}$, 0.2), 155 (47), 137 (31), 127 (57), 109 (16), 95 (51), 85 (15), 81 (88), 69 (35), 57 (53), 55 (29), 43 (C_2H_3O, 100), 41 (46). ^{1}H NMR ($CDCl_3$, 300 K): $\delta = 0.79$ (qd, 1H, H-4_{ax}, J = 11.9, 4.3 Hz), 0.87 (d, 3H, H-10, J = 6.1 Hz), 0.88 (d, 3H, H-9, J = 6.9 Hz), 0.89 (d, 3H, H-8, J = 6.6 Hz), 0.94 (dd, 1H, H-6_{ax}, J = 14.4, 13.2 Hz), 1.02 (s, 9H, 3Me), 1.18 (s, 1H, OH), 1.28 (ddd, 1H, H-2, J = 11.3, 3.6, 2.0 Hz), 1.42 (qd, 1H, H-3_{ax}, J = 12.2, 3.2 Hz), 1.47–1.54 (m, 1H, H-3_{eq}), 1.58–1.70 (m, 1H, H-5), 1.62 (dm, 1H, H-6_{eq}, J = 12.2 Hz), 1.73 (dm, 1H, H-4_{eq}, J = 12.0 Hz), 2.41 (quintd, 1H, H-7, J = 6.9, 2.0 Hz).

3.8. (1S,2S,5R)-1-Phenyl-2-isopropyl-5-methyl-cyclohexan-1-ol **17a** and (1R,2S,5R)-1-phenyl-2-isopropyl-5-methyl-cyclohexan-1-ol **17b**

Without $CeCl_3$. Following the general procedure, from 0.30 g (1.94 mmol) **1** in 4 ml THF and 2.4 ml of a 1.06 M PhMgBr solution in Et_2O (2.54 mmol) were obtained after column chromatography (∅ 17 mm, h = 490 mm, 43 g silica gel, petroleum ether:Et_2O = 10:1) 0.34 g mixed fraction of **1** and **17a** (13:87 by NMR) and 0.01 g of **17b** (2%). The yield of **17** was 71% (extrapolated by means of NMR).

With $CeCl_3$. Following the general procedure, from 0.14 g (0.91 mmol) **1**, 0.23 g (0.93 mmol) $CeCl_3$ in 7 ml THF and 1.2 ml of a 1.06 M PhMgBr solution in Et_2O (1.27 mmol) were obtained after column chromatography (∅ 13 mm, h = 460 mm, 15 g silica gel, petroleum ether:Et_2O = 10:1) 0.16 g (76%) **17a** (colorless oil) and 0.01 g of **17b** (5%).

*Data of **17a**.* $[\alpha]_D^{20}$ –5.4 (c 1.05, $CHCl_3$). Anal. calcd for $C_{16}H_{24}O$ (232.37): C, 82.70; H, 10.41. Found: C, 82.35; H, 10.49. MS (EI) m/z (rel. int.): 232 ($M^{+\cdot}$, 19), 147 (100), 133 (4), 120 (12), 105 (21), 91 (6), 77 (14), 69 (12), 55 (11), 43 (C_2H_3O, 5), 41 (13). ^{1}H NMR ($CDCl_3$, 300 K): $\delta = 0.73$ (d, 3H, H-9, J = 7.1 Hz), 0.83 (d, 3H, H-8, J = 6.9 Hz), 0.90 (d, 3H, H-10, J = 6.4 Hz), 1.07 (dm, 1H, H-4_{ax}), 1.44 (dd, 1H, H-6_{ax}, J = 12.9, 12.0 Hz), 1.50 (quintd, 1H, H-7), 1.58–1.68 (m, 3H, H-2, H-3_{ax}, H-3_{eq}), 1.63 (dm, 1H, H-6_{eq}), 1.80–1.90 (m, 1H, H-5), 1.88 (dm, 1H, H-4_{eq}, J = 12.5 Hz), 7.22 (tt, 1H, H-14, J = 7.1, 1.6 Hz), 7.34 (td, 2H, H-13, J = 7.6, 0.8 Hz), 7.46 (d, 2H, H-12, J = 7.6 Hz).

3.9. 1-[(1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methyl-cyclohexyl]ferrocene **18a**, 1,1′-[(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-cyclohexyl]ferrocene **19a** and (1S,2S,5R)-1-(3,3-dimethylbutyl)-2-isopropyl-5-methyl-cyclohexan-1-ol **20a**

Without $CeCl_3$. Following a modified general procedure, to a THF/hexane/pentane solution of **8** (preparation: to a solution of ferrocene 0.93 g (5.00 mmol) in 2.5 ml THF and 2.5 ml hexane, cooled to 0°C, were added 12.5 ml 0.78 M *t*-BuLi in pentane (9.75 mmol), and the mixture stirred for 30 min at 0°C) were added 0.50 g (3.24 mmol) **1**. After work-up and column chromatography (∅ 23 mm, h = 580 mm, 100 g silica gel, petroleum ether:Et_2O = 20:1) were obtained 0.42 g mixed fraction of **1** and **18a**, 0.20 g (26%) of **20a** and 0.05 g (6%) of **19a**. The evaporation of **1** from the mixed fraction (70°C, 0.001 torr) gave 0.39 g (35%) **18a**.

With $CeCl_3$. Following a modified general procedure, to a stirred mixture of 0.38 g (2.46 mmol) **1** and 0.62 g (2.52 mmol) $CeCl_3$ in 12 ml THF was added a solution of **8** (preparation: to a solution of ferrocene 0.73 g (3.92 mmol) in 2.5 ml THF and 2.5 ml hexane, cooled to 0°C, were added 4 ml 0.94 M *t*-BuLi in pentane (3.76 mmol), and the mixture stirred for 30 min at 0°C). After work-up and column chromatography (∅ 24 mm, h = 520 mm, 85 g silica gel, petroleum ether:Et_2O = 20:1) were obtained 0.43 g mixed fraction of **1** and **18a**, 0.05 g (8%) of **20a** and 0.02 g (3%) of **19a**. The evaporation of **1** from the mixed fraction (70°C, 0.001 torr) gave 0.34 g (40%) **18a**.

*Data of **18a***. Mp 45–47°C. $[\alpha]_D^{20}$ –54.6 (c = 1.04, $CHCl_3$). Anal. calcd for $C_{20}H_{28}FeO$ (340.29): Fe, 16.45. Found: Fe, 14.32. MS (EI) m/z (rel. int.): 340 ($M^{+\cdot}$, 100), 322 ($[M–H_2O]^{+\cdot}$, 9), 256 (4), 255 (19), 186 (17), 138 (4), 121 (10), 69 (8), 55 (5), 43 (C_2H_3O, 4), 41 (5). ^1H NMR ($CDCl_3$, 300 K): δ = 0.68 (d, 3H, H-9, J = 7.1 Hz), 0.89 (d, 3H, H-8, J = 6.8 Hz), 0.85–0.95 (m, 1H, H-4_{ax}), 0.90–1.00 (m, 1H, H-2), 0.96 (d, 3H, H-10, J = 6.4 Hz), 1.33 (dd, 1H, H-6_{ax}, J = 13.2, 12.2 Hz), 1.45–1.64 (m, 2H, H-3_{ax}, H-3_{eq}), 1.82 (dm, 1H, H-4_{eq}, J = 12.2 Hz), 1.89 (quintd, 1H, H-7, J = 6.9, 2.1 Hz), 1.94–2.03 (m, 1H, H-5), 2.03 (dm, 1H, H-6_{eq}), 3.98 (dt, 1H, H-12, J = 2.5, 1.3 Hz), 4.12–4.21 (m, 2H, H-13, H-14), 4.20 (s, 5H, Cp), 4.30 (dt, 1H, H-15, J = 2.4, 1.3 Hz).

3.10. 1,1′-[(1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methyl-cyclohexyl]ferrocene **19a** and 1-[(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-cyclohexyl]ferrocene **18a**

Without $CeCl_3$. Following the general procedure, to a THF (8 ml) solution of 0.66 g (2.10 mmol) $(LiCp)_2Fe{\cdot}TMEDA$ were added 0.53 g (3.44 mmol) **1** in 2 ml THF and stirred for 2 h at rt. After work-up and column chromatography (∅ 24 mm, h = 520 mm, 78 g silica gel, petroleum ether:Et_2O = 20:1) were obtained 0.36 g mixed fraction of **1** and **18a**, and 0.15 g (18%) of **19a**. The evaporation of **1** from the mixed fraction (70°C, 0.001 torr) gave 0.28 g (24%) **18a**.

With $CeCl_3$. Following the general procedure, to a stirred mixture of 0.31 g (2.01 mmol) **1** and 0.50 g (2.03 mmol) $CeCl_3$ in 12 ml THF were added 0.36 g (1.15 mmol) solid $(LiCp)_2Fe{\bullet}TMEDA$ and the mixture stirred for 2 h at rt. After work-up and column chromatography (∅ 17 mm, h = 490 mm, 42 g silica gel, petroleum ether:Et_2O = 20:1) were obtained 0.15 g (22%) **18a** and 0.13 g (26%) of **19a**.

*Data of **19a***. Mp 147–150°C. $[\alpha]_D^{20}$ –127.8 (c = 1.04, $CHCl_3$). Anal. calcd for $C_{30}H_{46}FeO_2$ (494.54): Fe, 11.27. Found: Fe, 11.39. MS (EI) m/z (rel. int.): 494 ($M^{+\cdot}$, 100), 476 (8), 458 (3), 322 (4), 254 (5), 212 (4), 121 (3), 69 (5), 55 (4), 43 (C_2H_3O, 5), 41 (3). ^1H NMR ($CDCl_3$, 300 K): δ = 0.63 (d, 6H, H-9, J = 7.1 Hz), 0.86 (d, 6H, H-8, J = 6.9 Hz), 0.88 (qd, 2H, H-4_{ax}, J = 12.5, 4.2 Hz), 0.90 (dm, 2H, H-2), 0.98 (d, 6H, H-10, J = 6.4 Hz), 1.31 (dd, 2H, H-6_{ax}, J = 13.2, 12.5 Hz),

1.40 (qd, 2H, H-3_{ax}, J = 13.0, 3.4 Hz), 1.48–1.60 (m, 2H, H-3_{eq}), 1.80 (dm, 2H, H-4_{eq}), 1.80 (quintd, 2H, H-7, J = 6.9, 2.2 Hz), 2.18 (dm, 2H, H-6_{eq}, J = 12.7 Hz), 2.67 (s, 2H, OH), 3.93 (dt, 2H, H-12, J = 2.2, 1.4 Hz), 4.12–4.19 (m, 4H, H-13, H-14), 4.35 (dt, 2H, H-15, J = 2.2, 1.4 Hz).

3.11. (1S,2S,5R)-1-(3,3-Dimethylbutyl)-2-isopropyl-5-methyl-cyclohexan-1-ol **20a**

To 4 ml 0.78 M *t*-BuLi in pentane (3.12 mmol) were added 3 ml THF and the mixture stirred for several minutes. After cooling at 0°C 0.29 g (1.88 mmol) of **1** in 2 ml THF were added and then stirred for 4 h at rt. It was hydrolyzed (2N HCl), extracted with Et_2O (3×15 ml), washed with 5% aq. $NaHCO_3$, H_2O, dried ($NaSO_4$) and concentrated under reduced pressure. After column chromatography (∅ 11 mm, h = 350 mm, 13 g silica gel, petroleum ether:Et_2O = 4:1) were obtained 0.11 g (24%) of **20a** as colorless liquid. $[\alpha]_D^{20}$ +7.5 (c = 1.02, $CHCl_3$). Anal. calcd for $C_{16}H_{32}O$ (240.43): C, 79.93; H, 13.42. Found: C, 81.04; H, 13.03. MS (EI) m/z (rel. int.): 240 ($M^{+\cdot}$, 0.3), 222 ($[M–H_2O]^{+\cdot}$, 4), 183 (9), 155 (100), 137 (25), 123 (9), 109 (12), 95 (32), 81 (42), 69 (22), 57 (35), 43 (C_2H_3O, 27), 41 (24). ^{1}H NMR ($CDCl_3$, 300 K): δ = 0.82 (qd, 1H, H-4_{ax}, J = 12.2, 4.4 Hz), 0.88 (d, 3H, H-10, J = 6.4 Hz), 0.91 (d, 3H, H-8, J = 5.1 Hz), 0.89 (s, 9H, *t*-Bu), 0.91 (d, 3H, H-9, J = 5.9 Hz), 1.08–1.18 (m, 2H, H-12), 1.09 (t, 1H, H-6_{ax}, J = 12.2 Hz), 1.13 (dm, 1H, H-2), 1.20 (s, 1H, OH), 1.40 (qd, 1H, H-3_{ax}, J = 13.1, 3.5 Hz), 1.44 (dm, 1H, H-6_{eq}), 1.44–1.55 (m, 1H, H-3_{eq}), 1.34–1.48 (m, 1H, H-11), 1.58–1.72 (m, 1H, H-11′), 1.70 (dm, 1H, H-5), 1.76 (dm, 1H, H-4_{eq}, J = 12.7 Hz), 2.06 (quintd, 1H, H-7, J = 6.9, 1.6 Hz).

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