Stereoselective Synthesis of *cis-p*-Menth-8-ene-1,7-diol, *cis-p*-Menthane-1,7-diol, and *cis-p*-Menthane-1,7,8-triol**

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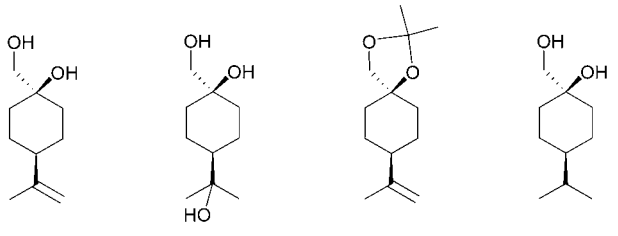
Abstract: The natural products *cis-p*-menthane-1,7-diol (*cis*-**IV**), *cis-p*-menth-8-ene-1,7-diol (*cis*-**I**) and *cis-p*-menthane-1,7,8-triol (*cis*-**II**) are obtained starting from the corresponding *cis*-cyanohydrins, *cis*-**2** and *cis*-**7**, respectively, by chemical transformation of the cyano into the hydroxymethyl group. The key step of the synthesis is the very high *cis*-selectivity ($\geq$ 96%) of the MeHNL-catalyzed HCN addition to 4-alkylcyclohexanones. From 4-isopropylcyclohexanone (**1**) the cyanohydrin *cis*-**2** and from 4-(1-methylvinyl)cyclohexanone (**6**) the cyanohydrin *cis*-**7** result almost quantitatively. Regioselective hydroxylation of *cis*-**I** affords the triol *cis*-**II**. X-ray crystal structure determinations of the final products confirm their *cis*-configuration.

Keywords: cyanohydrins · hydroxynitrile lyase · natural products · total synthesis

Introduction

The monoterpene *cis-p*-menthane-1,7,8-triol (*cis*-**II**) was first isolated, but not completely characterized, in 1992 by Konda et al., from the roots of *Cynanchum hancockianum* in addition to the antitumor active Antofin.[1] In 1998 the isolation and characterization of both the *cis*- and the *trans*-isomer of *p*-menthane-1,7,8-triol (**II**) from the methanolic extract of *Foeniculum vulgare* was achieved by Ishikawa et al.[2] The dehydration product of *cis*-**II**, *cis-p*-menth-8-ene-1,7-diol (*cis*-**I**) was isolated from urine of rats after treatment with β-Myrcen.[3]



cis-**I** *cis*-**II** *cis*-**III** *cis*-**IV**

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[**] Enzyme-catalyzed Reactions, Part 51. For Part 50 see: C. Kobler, F. Effenberger, *Tetrahedron: Asymmetry* **2004**, *15*, 3731–3742.

The acetonide of *cis*-**I**, the farnesyl protein transferase inhibitor XR3054 (*cis*-**III**), is a promising antitumor candidate and, therefore, stereoselective chemical syntheses have been developed.[4] Carman and Garner[4a] obtained **II** as a side product in 10–20% yield after oxymercuration and reduction of (*S*)-(−)-perillylalcohol. A straightforward synthesis of both **I** and **III** was achieved by Donaldson et al.[4b] starting from (*S*)-(−)-perillylalcohol; Sharpless epoxidation and subsequent hydrogenation with $LiAlH_4$ gave **I**, which easily can be treated with acetone to give **III**. The only known synthesis of a *cis*/*trans*-mixture of triol **II** was published in 1993, starting from δ-terpineol.[5] The direct oxidation of δ-terpineol with alkaline $KMnO_4$ gives only *trans-p*-menthane-1,8-diol.

A structural analogue of the monoterpenes **I**–**III** is the monoterpenediol **IV**, which was obtained as a byproduct in the stereoselective hydroxylation of *cis*/*trans-p*-menthane by *Pseudomonas mandocina-SF*.[6]

The natural products discussed so far (**I**, **II**, and **IV**) are 4-alkyl-1-hydroxymethyl cyclohexanols, all of which can be retro-synthetically derived from cyanohydrins of the corresponding 4-alkylcyclohexanones. Recently, we have published hydroxynitrile lyase (HNL)-catalyzed additions of HCN to 4-substituated cyclohexanones.[7] In nonenzymatic-catalyzed chemical additions the *cis/trans*-ratio of the HCN addition to 4-alkylcyclohexanones is roughly 13:87.[7b] Therefore, chemical syntheses of compounds **I**–**IV** via the corresponding cyanohydrins, all with *cis*-configuration, would be very unfavourable, because of the very high *trans*-ratio. In our methodically oriented investigations of applications of hy-

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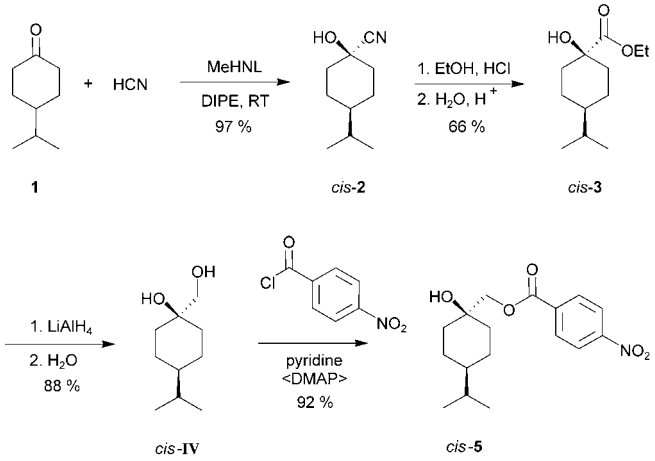
droxynitrile lyases (HNL) we observed very high *cis*/*trans*-selectivity in the HNL-catalyzed cyanohydrin formations of 4-alkylcyclohexanones.[7] We obtained *trans*-selectivity with (*R*)-PaHNL from almonds and *cis*-selectivity with (*S*)-MeHNL from cassava as catalysts.[7]

Since the transformation of a cyano function into a hydroxymethyl group is well known, the stereoselective synthesis of the natural products **I**, **II**, and **IV** starting from *cis*-4-alkylcyclohexanone cyanohydrins should be possible.

Results and Discussion

Synthesis of *cis-p*-methane-1,7-diol (*cis*-IV): In Scheme 1 the synthesis of *cis*-**IV**, starting from 4-isopropylcyclohexanone (**1**) is illustrated.



Scheme 1. Synthesis of *cis-p*-menthane-1,7-diol (*cis*-**IV**) from 4-isopropylcyclohexanone (**1**).

The MeHNL-catalyzed addition of HCN to **1** was performed under the optimized conditions described earlier.[7b] The cyanohydrin **2** was obtained almost quantitatively in a *cis*/*trans*-ratio of 96:4. After recrystallization from diisopropyl ether (iPr$_2$O) pure *cis*-**2** results as colorless needles. By dissolving *cis*-**2** in a saturated solution of HCl in absolute ethanol and heating for 16 h in a glass autoclave at 95 °C, the corresponding imidate hydrochloride separates as amorphous solid, which was not isolated. Workup in ice water resulted in the ester *cis*-**3**, which was isolated and purified by extraction with diethyl ether and vacuum distillation. The hydrogenation of *cis*-**3** with $LiAlH_4$ was performed in THF at room temperature. The final product, *cis*-**IV**, was obtained as a colorless powder and after recrystallization from iPr$_2$O gave colorless, rhombic crystals with a melting point of 89 °C.

Since the crystals of *cis*-**IV** were not suitable for an X-ray structure determination, it was transformed to the *p*-nitrobenzoyl derivative *cis*-**5** by reaction with *p*-nitrobenzoyl chloride in pyridine (Scheme 1). The X-ray structure of *cis*-**5** in Figure 1 demonstrates unambiguously the *cis*-configuration not only for *cis*-**5**, but also for *cis*-**IV**, *cis*-**3**, and *cis*-**2** (Scheme 1).[9]

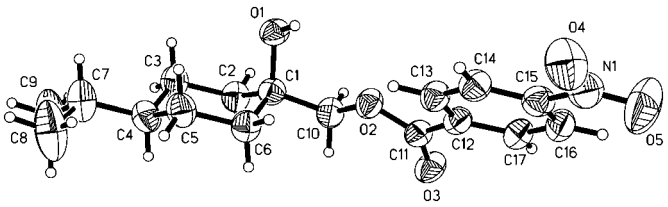
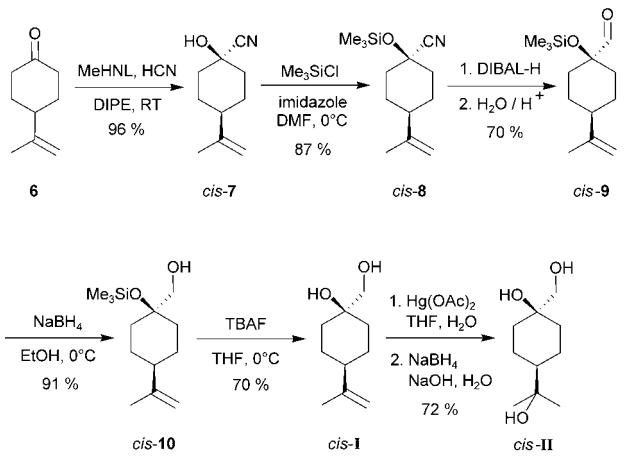


Figure 1. ORTEP view of *cis*-(1-hydroxy-4-isopropylcyclohexyl)-methyl-4-nitrobenzoate (*cis*-**5**).

Syntheses of *cis-p*-menth-8-ene-1,7-diol (*cis*-I) and *cis-p*-menthane-1,7,8-triol (*cis*-II): In Scheme 2 the synthesis of *cis*-**I** and *cis*-**II** is summarized.



Scheme 2. Synthesis of *cis-p*-menth-8-ene-1,7-diol (*cis*-**I**) and *cis-p*-menthane-1,7,8-triol (*cis*-**II**) from 4-isopropenylcyclohexanone (**6**).

4-(1-Methylvinyl)cyclohexanone (4-isopropenylcyclohexanone) (**6**) was prepared as described in the literature.[8] The MeHNL-catalyzed addition of HCN to **6** was carried out as described earlier.[7b] The cyanohydrin **7** was obtained in 99 % yield with a *cis*/*trans*-ratio of 96:4. After recrystallization from *n*-hexane/methylenechloride pure *cis*-**7** was obtained as colorless, cuboid crystals.[7a,9] Before the reduction of the nitrile function with DIBAL-H, the hydroxyl group of *cis*-**7** was protected with a trimethylsilyl group to give *cis*-**8**.[10] The reduction of *cis*-**8** with DIBAL-H was performed in *n*-hexane at −45 °C. The resulting "aminoalane" as an intermediate was transformed to the aldehyde *cis*-**9** in a two-phase system (CH_2Cl_2/H_2O) by careful treatment with diluted sulfuric acid. The hydrogenation of the *O*-protected aldehyde *cis*-**9** to the corresponding hydroxymethyl derivative *cis*-**10** was performed in absolute ethanol at 0 °C.[11] Deprotection of *cis*-**10** with TBAF in THF yielded *cis*-**I**, the precursor of the farnesylprotein transferase inhibitor XR3054.[4] Compound *cis*-**I** was recrystallized from iPr$_2$O to give colorless crystals suitable for X-ray structure analysis.[9]

The X-ray structure of the synthesized compound **I** in Figure 2 clearly demonstrates the *cis*-configuration of the diol **I**, which is also evidence for the *cis*-configurations of compounds **7**, **8**, **9**, and **10**.

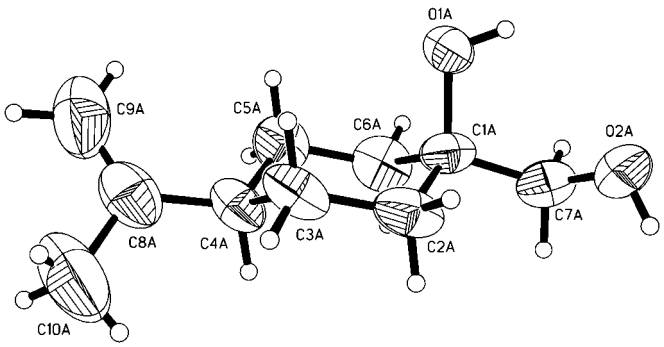


Figure 2. ORTEP view of *cis-p*-menth-8-ene-1,7-diol (*cis*-**I**).

The regioselective hydroxylation of the olefinic double bond of *cis*-**I** was performed with mercury(II) acetate and subsequent demercuration with an alkaline sodium borohydride solution.[12] The natural product *cis*-**II** was recrystallized from a mixture of $CHCl_3$/iPr_2O/EtOH as colorless, crystalline needles. The X-ray structure analysis of these crystals proves the *cis*-configuration of **II** unambiguously, as shown in Figure 3.

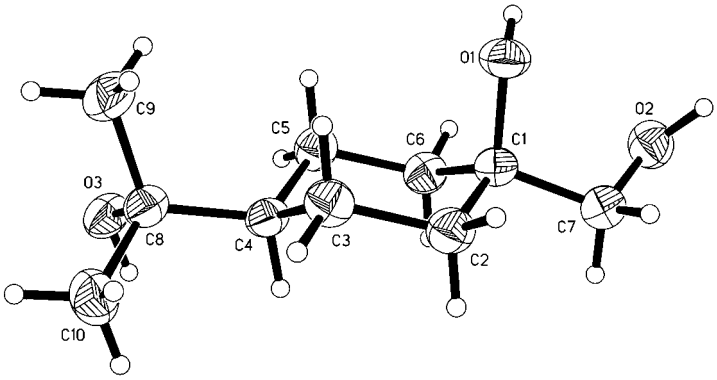


Figure 3. ORTEP view of *cis-p*-menthane-1,7,8-triol (*cis*-**II**).

Conclusion

The very high *cis*-selectivity ($\geq 96\,\%$) of MeHNL-catalyzed HCN additions to 4-alkylcyclohexanones, resulting in the corresponding *cis*-cyanohydrins, is an excellent starting basis for the stereoselective synthesis of *cis*-4-alkly-hydroxymethylcyclohexanols, which are interesting monoterpenes in natural products. Starting from 4-isopropylcyclohexanone (**1**) the corresponding *cis*-cyanohydrin (*cis*-**2**) is obtained almost quantitatively. The chemical transformations of *cis*-**2** to the final product, *cis-p*-methane-1,7-diol (*cis*-**IV**) is straightforward and can be performed without problems in only two steps. Starting from 4-(1-methylvinyl)cyclohexanone (**6**) the MeHNL-catalyzed HCN addition results in the almost quantitative formation of the *cis*-cyanohydrin, *cis*-**7**. The stereoselective transformation of the cyano group of *cis*-**7** to the hydroxymethyl group in the final product *cis-p*-menth-8-ene-1,7-diol (*cis*-**I**) can be performed easily by known chemical procedures. *Cis-p*-menthane-1,7,8-triol (*cis*-**II**) is obtained by regioselective hydroxylation of *cis*-**I**. The *cis*-configuration of all synthesized natural products, that is *cis*-**I**, *cis*-**II**, and *cis*-**IV**, was assured by X-ray crystal structure analysis. The farnesyl transferase inhibitor XR3054 (*cis*-**III**) is now conveniently available through the novel synthesis of *cis*-**I**.

Experimental Section

General: Melting points were determined on a Büchi SMP-20 and are uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 F (250 MHz) and ARX 500 (500 MHz) in $CDCl_3$ with TMS as internal standard. ^{13}C NMR multiplicities were determined with DEPT experiments. Chromatography was performed using silica gel, grain size 0.040–0.063 mm (Fluka). *Cis*/*trans*-ratios: GC separations were conducted by using: 1) capillary glass columns (20 m) with OV 1701, carrier gas 0.4–0.6 bar hydrogen; 2) a Chiraldex B-TA and G-TA column (30 m × 0.32 mm), carrier gas hydrogen. Details of the X-ray crystallographic measurements are given in Table 1. 4-Isopropylcyclohexanone (**1**) is commercially available. 4-(1-Methylvinyl)cyclohexanone (4-isopropenylcyclohexanone; **6**) was prepared according to known literature procedures.[8] All solvents were dried and distilled. All yields are not optimized.

***cis*-1-Hydroxy-4-isopropylcyclohexanecarbonitrile (*cis*-2)**:[7b] A solution of (*S*)-MeHNL (7990 U, 2.88 mL, $P_w = 40.8$ mg mL^{-1}) was added to nitrocellulose (2.20 g) [Pro-Celloidin (Fluka): 1 g (dry), soaked in a 0.02 M sodium citrate buffer (50 mL), pH 3.3, for 0.5 h; the buffer was decanted and nitrocellulose centrifuged (5700 × *g* for 30 min) and dried under high vacuum for 5 h], followed after 15 min by addition of diisopropyl ether (75 mL), compound **1** (2.31 g, 16.47 mmol) and anhydrous HCN[13] (2.5 mL, 63.6 mmol). After stirring at room temperature for 5 h, the support was removed by filtration and was washed twice with diethyl ether; the combined filtrates were concentrated under vacuum. The white residue (2.68 g, 97 %, *cis/trans*-ratio = 96:4) was recrystallized from *i*Pr_2O to give colorless crystals of pure *cis*-**2**. M.p. 52 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.87$ (d, $^3J = 6.8$ Hz, 6H; $CH(CH_3)_2$), 1.04–1.18 (m, 1H; C^4H), 1.33–1.51 (m, 3H; C^3H_{ax}, C^5H_{ax}, $CH(CH_3)_2$), 1.56–1.64 (m, 2H; C^3H_{eq}, C^5H_{eq}), 1.81 (ddd, $^3J(C^2H_{ax},C^3H_{eq}) = 4.2$ Hz, $^2J(C^2H_{ax},C^2H_{eq}) \approx {}^3J(C^2H_{ax},C^3H_{ax}) = 13.2$ Hz, 2H; C^2H_{ax}, C^6H_{ax}), 2.07–2.14 (m, 2H; C^2H_{eq}, C^6H_{eq}), 3.57 ppm (br s, 1H; OH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 19.73$ ($CH(CH_3)_2$), 23.24 (C^3H_2, C^5H_2), 32.03 ($CH(CH_3)_2$), 36.50 (C^2H_2, C^6H_2), 42.27 (C^4H), 66.87 (C^1), 123.04 ppm (CN).

***cis*-Ethyl-1-hydroxy-4-isopropylcyclohexanecarboxylate (*cis*-3)**:[7b] A solution of *cis*-**2** (2.47 g, 14.77 mmol) in ethanolic HCl (30 mL) was stirred at 95 °C for 18 h in a pressure vessel. To open the vessel, it was cooled with ice water. The reaction mixture was diluted with diethyl ether (50 mL), and ice water was added until the white precipitate dissolved. The layers were separated, and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The residue was distilled under vacuum to give *cis*-**3** (2.09 g, 66 %) as a colorless oil. B.p. 71 °C, 0.01 Torr; IR (neat): $\tilde{\nu}_{max} = 2954$, 2937, 1724, 1367, 1255, 1223, 1152, 1094, 1052, 1022, 987 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 0.89 (d, $^3J = 6.9$ Hz, 6H; $CH(CH_3)_2$), 1.07–1.17 (m, 1H; C^4H), 1.29 (t, $^3J =$ 7.1 Hz, 3H; CH_2CH_3), 1.38–1.49 (m, 3H; C^3H_{ax}, C^5H_{ax}, $CH(CH_3)_2$), 1.58–1.61 (m, 2H; C^3H_{eq}, C^5H_{eq}), 1.69–1.81 (m, 4H; C^2H_{ax}, C^6H_{ax}, C^2H_{eq}, C^6H_{eq}), 2.89 (br s, 1H; OH), 4.22 ppm (q, $^3J = 7.1$ Hz, 2H; CH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.24$ (CH_2CH_3), 19.84 ($CH(CH_3)_2$),

Table 1. X-ray crystal data collection and refinement for *cis*-**5**, *cis*-**I**, and *cis*-**II**.

	cis-**5**	*cis*-**I**	*cis*-**II**
formula	$C_{17}H_{23}NO_5$	$C_{10}H_{18}O_2$	$C_{10}H_{20}O_3$
M_r	321.37	170.25	188.27
crystal system	monoclinic	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/c$	$P2_1/n$
a [Å]	14.9154(8)	16.201(4)	6.3415(3)
b [Å]	5.6903(4)	17.239(5)	13.8270(7)
c [Å]	20.9257(17)	11.766(5)	12.1563(4)
α [°]	90	90	90
β [°]	107.691(5)	107.67(2)	99.665(4)
γ [°]	90	90	90
V [Å^3]	1692.0(2)	3132.8(18)	1050.78(8)
Z	4	12	4
ρ_{calcd} [mg m^{-3}]	1.262	1.083	1.190
$F(000)$	688	1128	416
μ [mm^{-1}]	0.765	0.073	0.694
θ range [°]	3.22–64.99	1.77–22.49	4.88–67.95
data collection[a]			
reflections collected/unique	3818/2788	4263/4096	2607/1857
data/restraints/parameters	2788/0/213	4096/0/332	1857/0/131
goodness-of-fit on F^2	1.068	1.047	1.070
final R indices [$I>2\sigma(I)$]			
$R1$	0.0801	0.1225	0.0539
w$R2$	0.2089	0.2157	0.1501
R indices (all data)			
$R1$	0.1027	0.2379	0.0639
w$R2$	0.2630	0.2545	0.1642
largest diff. peak/hole [e Å^{-3}]	0.416/−0.357	0.220/−0.172	0.192/−0.217

[a] $T=293$ K, Nicolet P3 diffractometer, $Mo_{K\alpha}$ ($\lambda=0.71073$ Å) or Siemens P4 diffractometer, $Cu_{K\alpha}$ ($\lambda=1.54178$ Å) radiation.

24.31 (C^3H_2, C^5H_2), 32.82 ($CH(CH_3)_2$), 34.90 (C^2H_2, C^6H_2), 43.17 (C^4H), 61.71 (CH_2CH_3), 73.36 (C^1), 177.84 ppm (COO); elemental analysis calcd (%) for $C_{12}H_{22}O_3$ (214.30): C 67.26, H 10.35; found: C 67.18, H 10.13.

***cis*-1-(Hydroxymethyl)-4-isopropylcyclohexane-1-ol (*cis*-IV)**: A solution of *cis*-**3** (1.0 g, 4.67 mmol) in THF (10 mL) at 0 °C was added dropwise to a stirred suspension of $LiAlH_4$ (231.0 mg, 6.07 mmol) in THF (5 mL). After stirring for 15 min, the reaction mixture was allowed to warm slowly to room temperature and stirred for a further 1 h. After cooling down to 0 °C, the mixture was hydrolyzed with brine (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The pure white residue recrystallized from iPr_2O to afford *cis*-**IV** (0.71 g, 88 %) as colorless, rhombic crystals. M.p. 89 °C; IR (neat): $\tilde{\nu}_{max}=3276$, 2936, 2865, 1228, 1175, 1074, 1050, 1025, 992, 976, 900, 739, 671, 643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.88$ (d, $^3J=6.8$ Hz, 6H; $CH(CH_3)_2$), 0.99–1.06 (m, 1H; C^4H), 1.21–1.37 (m, 4H; C^2H_{ax}, C^6H_{ax}, C^3H_{ax}, C^5H_{ax}), 1.43–1.50 (m, 1H; $CH(CH_3)_2$), 1.56–1.59 (m, 2H; C^3H_{eq}, C^5H_{eq}), 1.72–1.75 (m, 2H; C^2H_{eq}, C^6H_{eq}), 2.28 (br s, 1H; OH), 2.75 (t, $^3J=5.9$ Hz, 1H; CH_2OH), 3.39 ppm (d, $^3J=5.6$ Hz, 2H; CH_2OH); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=20.01$ ($CH(CH_3)_2$), 24.47 (C^3H_2, C^5H_2), 32.03 ($CH(CH_3)_2$), 33.84 (C^2H_2, C^6H_2), 44.09 (C^4H), 71.57 (C^1), 71.86 ppm (CH_2OH); elemental analysis calcd (%) for $C_{10}H_{20}O_2$ (172.27): C 69.72, H 11.70; found: C 69.87, H 11.71.

***cis*-(1-Hydroxy-4-isopropylcyclohexyl)methyl-4-nitrobenzoate (*cis*-5)**:[7b] DMAP (15 mg) and *p*-nitrobenzoyl chloride (0.23 g, 1.24 mmol) were added to a vigorously stirred solution of *cis*-**IV** (0.18 g, 1.04 mmol) in pyridine (4 mL), and the reaction mixture was stirred for 14 d at room temperature. Then water (5 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined extracts were washed with diluted HCl until neutral, dried (Na_2SO_4), and concentrated. The residue was subjected to chromatography on SiO_2 with petroleum ether/EtOAc (7:1) and recrystallized from iPr_2O to afford pure *cis*-**5** (0.31 g, 92 %) as colorless crystals.[9] M.p. 103 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=0.90$ (d, $^3J=6.8$ Hz, 6H; $CH(CH_3)_2$), 0.99–1.16 (m, 1H; C^4H), 1.31–1.55 (m, 5H; C^2H_{ax}, C^6H_{ax}, C^3H_{ax}, C^5H_{ax}, $CH(CH_3)_2$), 1.60–1.64 (m, 2H; C^3H_{eq}, C^5H_{eq}), 1.72 (br s, 1H; OH), 1.80–1.84 (m, 2H; C^2H_{eq}, C^6H_{eq}), 4.42 (s, 2H; CH_2O), 8.21–8.32 ppm (m, 4H; H_{Ph}); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=19.84$ ($CH(CH_3)_2$), 24.08 (C^3H_2, C^5H_2), 32.64 ($CH(CH_3)_2$), 34.13 (C^2H_2, C^6H_2), 43.67 (C^4H), 70.44 (C^1), 73.88 (CH_2O), 123.61, 130.78, 135.46, 150.62 (C_{Ph}), 164.72 ppm (OCO); elemental analysis calcd (%) for $C_{17}H_{23}NO_5$ (321.37): C 63.54, H 7.21, N 4.36; found: C 63.46, H 7.06, N 4.37.

***cis*-1-Hydroxy-4-isopropenylcyclohexanecarbonitrile (*cis*-7)**:[7b] Reaction conditions and workup as for *cis*-**2**. (*S*)-MeHNL (10000 U, 3.61 mL, $P_w=40.8$ mg mL^{-1}), nitrocellulose (2.70 g), diisopropyl ether (125 mL), compound **6** (4.11 g, 29.73 mmol), and anhydrous HCN[13] (4.5 mL, 114.4 mmol), reaction time 5 h. The white residue (4.71 g, 96 %, *cis/trans*-ratio = 96:4) was recrystallized from *n*-hexane/CH_2Cl_2 to afford *cis*-**7** as colorless crystals.[9] M.p. 65 °C; IR (neat): $\tilde{\nu}_{max}=3420$, 2939, 1645, 1434, 1399, 1373, 1230, 1140, 1060, 972, 932, 893 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.60–1.68$ (m, 4H; C^3H_{ax}, C^5H_{ax}, C^3H_{eq}, C^5H_{eq}), 1.72 (s, 3H; CH_3), 1.85–1.99 (m, 3H; C^2H_{ax}, C^6H_{ax}, C^4H), 2.15–2.18 (m, 2H; C^2H_{eq}, C^6H_{eq}), 2.86 (br s, 1H; OH), 4.71–4.74 ppm (m, 2H; =CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=20.89$ (CH_3), 25.00 (C^3H_2, C^5H_2), 36.49 (C^2H_2, C^6H_2), 43.26 (C^4H), 66.59 (C^1), 109.44 (=CH_2), 122.89 (CN), 148.76 ppm (C=); elemental analysis calcd (%) for $C_{10}H_{15}NO$ (165.24): C 72.69, H 9.15, N 8.48; found: C 72.65, H 9.05, N 8.55.

***cis*-4-Isopropenyl-1-trimethylsilyloxycyclohexanecarbonitrile (*cis*-8)**:[10] Chlorotrimethylsilane was added (3.11 g, 28.63 mmol) to a stirred solution of imidazole (3.43 g, 49.62 mmol) in DMF (65 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 15 min, a solution of *cis*-**7** (4.10 g, 24.81 mmol) in DMF (15 mL) was added dropwise and allowed to warm slowly to room temperature and stirred for a further 1 h. Then water (125 mL) was added, and the resulting mixture was extracted with diethyl ether (3×25 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 using a short column eluting with petroleum ether/EtOAc (7:1) ($R_f=0.60$) to afford *cis*-**8** (5.14 g, 87 %) as colorless oil. IR (neat): $\tilde{\nu}_{max}=1645$ (w), 1252, 1079, 1054, 1030, 889, 840, 754 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=0.26$ ($Si(CH_3)_3$), 1.56–1.64 (m, 4H; C^3H_{ax}, C^5H_{ax}, C^3H_{eq}, C^5H_{eq}), 1.71 (s, 3H; CH_3), 1.72–1.99 (m, 3H; C^2H_{ax}, C^6H_{ax}, C^4H), 2.06–2.15 (m, 2H; C^2H_{eq}, C^6H_{eq}), 4.70–4.73 ppm (m, 2H; =CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=1.18$ ($Si(CH_3)_3$), 20.80 (CH_3), 25.16 (C^3H_2, C^5H_2), 37.96 (C^2H_2, C^6H_2), 43.19 (C^4H), 67.39 (C^1), 109.17 (=CH_2), 122.86 (CN), 149.00 ppm (C=); elemental analysis calcd (%) for $C_{13}H_{23}NOSi$ (237.42): C 65.77, H 9.76, N 5.90; found: C 65.76, H 9.74, N 5.70.

***cis*-4-Isopropenyl-1-trimethylsilyloxycyclohexanecarbaldehyde (*cis*-9)**: A DIBAL-H solution (1 M in *n*-hexane, 25 mL) at −45 °C was added dropwise to a vigorously stirred solution of *cis*-**8** (3.57 g, 15.0 mmol) in *n*-hexane (25 mL) under an inert atmosphere. The reaction mixture then was allowed to warm up slowly to 15 °C and stirred at this temperature for 15 h. The mixture was diluted with CH_2Cl_2 (50 mL) and quenched with 0.5 M aqueous H_2SO_4 (75 mL). After vigorous stirring for 0.5 h at room temperature, the organic layer was separated and the aqueous

layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 using a short column eluting with petroleum ether/EtOAc (10:1) (R_f=0.54) to afford *cis*-**9** (2.53 g, 70%) as a colorless oil. IR (neat): $\tilde{\nu}_{max}$=1713, 1645 (w), 1164, 888, 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.16 ($Si(CH_3)_3$), 1.51–1.77 (m, 8H; 8 CH), 1.73 (s, 3H; CH_3), 1.86–1.93 (m, 1H; C^4H), 4.72 (s, 2H; $=CH_2$), 9.56 ppm (s, 1H; CHO); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=2.26 ($Si(CH_3)_3$), 20.70 (CH_3), 25.50 (C^3H_2, C^5H_2), 32.13 (C^2H_2, C^6H_2), 44.24 (C^4H), 80.10 (C^1), 108.73 ($=CH_2$), 149.96 (C=), 204.25 ppm (CHO); elemental analysis calcd (%) for $C_{17}H_{24}O_2Si$ (240.42): C 64.95, H 10.06; found: C 64.86, H 10.05.

***cis*-(4-Isopropenyl-1-trimethylsilyloxycyclohexyl)methanol (*cis*-10)**:[11] $NaBH_4$ (60.0 mg, 1.58 mmol) was added slowly to a stirred solution of *cis*-**9** (250.0 mg, 1.04 mmol) in absolute EtOH (2.5 mL) at 0°C under an atmosphere of nitrogen. After stirring for 30 min, concentrated CH_3COOH (35 μL) was added. The mixture was concentrated under reduced pressure, and the residue was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 with a short column eluting with petroleum ether/EtOAc (7:1) (R_f=0.47) to afford *cis*-**10** (229.5 mg, 91%) as a colorless oil, which after some time began to crystallize. M.p. 81°C; IR (neat): $\tilde{\nu}_{max}$=1643 (w), 1250, 1067, 869, 837, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.12 (s, 9H; $Si(CH_3)_3$), 1.25 (ddd, $^3J(C^2H_{ax},C^3H_{eq})$=4.7 Hz, $^2J(C^2H_{ax},C^2H_{eq}) \approx {}^3J(C^2H_{ax},C^3H_{ax})$=13.1 Hz, 2H; C^2H_{ax}, C^6H_{ax}), 1.58–1.74 (m, 6H; C^3H_{ax}, C^5H_{ax}, C^2H_{eq}, C^6H_{eq}, C^3H_{eq}, C^5H_{eq}), 1.74 (s, 3H; CH_3), 1.85 (tt, $^3J(C^4H_{ax},C^3H_{eq})$=4.0 Hz, $^3J(C^4H_{ax},C^3H_{ax})$=11.3 Hz, 1H; C^4H), 2.12 (s, 1H; OH), 3.34 (s, 2H; CH_2OH), 4.69–4.72 ppm (m, 2H; $=CH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=−0.56 ($Si(CH_3)_3$), 20.88 (CH_3), 26.47 (C^3H_2, C^5H_2), 33.94 (C^2H_2, C^6H_2), 45.47 (C^4H), 70.26 (C^1), 71.37 (CH_2OH), 108.35 ($=CH_2$), 150.58 ppm (C=); HRMS (70 eV, EI) calcd for $C_{13}H_{26}O_2Si^+$: 242.1702; found 242.1702.

***cis*-1-(Hydroxymethyl)-4-isopropenylcyclohexane-1-ol (*cis*-I)**: A solution of nBu_4NF (359.7 mg, 1.14 mmol) in THF (1.2 mL) was added slowly to a stirred solution of *cis*-**10** (229.5 mg, 0.95 mmol) in THF (5 mL) at 0°C. The reaction was stirred for 0.5 h. Then H_2O (6.0 mL) and CH_2Cl_2 (8.0 mL) were added, and the organic layer was separated, reextracting with CH_2Cl_2 (3×8 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 with petroleum ether/EtOAc (1:1) (R_f=0.21) to give *cis*-**I** (120.0 mg, 74%) as a white solid. Recrystallization from iPr_2O afforded colorless crystals.[9] M.p. 76°C; IR (neat): $\tilde{\nu}_{max}$= 3290, 2926, 2856, 1644 (w), 1434, 1222, 1158, 1051, 992, 959, 883, 736, 642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.25–1.34 (m, 2H; C^2H_{ax}, C^6H_{ax}), 1.53–1.65 (m, 4H; C^3H_{ax}, C^5H_{ax}, C^3H_{eq}, C^5H_{eq}), 1.71–1.79 (m, 2H; C^2H_{eq}, C^6H_{eq}), 1.74 (s, 3H; CH_3), 1.87 (tt, $^3J(C^4H_{ax},C^3H_{eq})$=3.4 Hz, $^3J(C^4H_{ax}, C^3H_{ax})$=11.7 Hz, 1H; C^4H_{ax}), 2.45 (br s, 1H; OH), 2.72 (br s, 1H; OH), 3.42 (s, CH_2OH), 4.70–4.71 ppm (m, 2H; $=CH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=20.93 (CH_3), 26.29 (C^3H_2, C^5H_2), 33.66 (C^2H_2, C^6H_2), 45.18 (C^4H), 71.12 (C^1), 71.70 (CH_2OH), 108.50 ($=CH_2$), 150.22 ppm (C=); elemental analysis calcd (%) for $C_{10}H_{18}O_2$ (170.25): C 70.55, H 10.66; found: C 70.38, H 10.71.

***cis*-1-Hydroxymethyl-4-(1-hydroxy-1-methylethyl)cyclohexane-1-ol) (*cis*-II)**:[12] A solution of *cis*-**I** (364.6 mg, 2.14 mmol) in THF (0.8 mL) was added to a stirred suspension of mercuric acetate (732.0 mg, 2.27 mmol) in a 1:1 mixture of THF/H_2O (4.6 mL). The yellow color disappeared after 2 min. The reaction mixture was stirred for 40 min at room temperature and then an aqueous solution of NaOH (3.0 M, 2.3 mL) and a solution of $NaBH_4$ (0.5 M) in NaOH (3 M, 2.3 mL) were added. The gray mixture was stirred until it clarified and mercury settled out. The reaction mixture was neutralized with citrus acid monohydrate and extracted with Et_2O in a perforator. After the extraction the organic solution was concentrated under reduced pressure. Traces of AcOH were removed under high vacuum. The white residue (mp 131–133°C) was recrystallized from a mixture of $CHCl_3$/iPr_2O/EtOH to yield *cis*-**II** (290.6 mg, 72%) as colorless, crystalline needles.[9] M.p. 133–135°C; IR (neat): $\tilde{\nu}_{max}$=3269, 2934, 1367, 1173, 1130, 1043, 1026, 1006, 952, 927, 913, 900, 736, 641 cm^{-1}; ^1H NMR (500 MHz, [D$_4$]methanol):[2] δ=1.15 (s, 6H; CH_3), 1.22–1.27 (m, 1H; C^4H), 1.34–1.49 (m, 4H; C^3H_{ax}, C^5H_{ax}, C^2H_{ax}, C^6H_{ax},), 1.64–1.66 (m, 4H; C^3H_{eq}, C^5H_{eq}, C^2H_{eq}, C^6H_{eq}), 3.30 ppm (br s, 2H; CH_2OH); ^{13}C NMR (125.8 MHz, [D$_4$]methanol): δ=23.21 (C^3H_2, C^5H_2), 26.88 (CH_3), 34.44 (C^2H_2, C^6H_2), 50.24 (C^4H), 72.05 (C), 72.23 (CH_2OH), 73.42 ppm (C); ^1H NMR (500 MHz, [D$_5$]pyridine): δ=1.40 (s, 6H; CH_3), 1.58–1.76 (m, 3H; 2 CH_{ax}, C^4H), 2.00–2.16 (m, 6H; 2 CH_{ax}, C^3H_{eq}, C^5H_{eq}, C^2H_{eq}, C^6H_{eq}), 3.84 ppm (br s, 2H; CH_2OH); ^{13}C NMR (125.8 MHz, [D$_5$]pyridine): δ=23.08 (C^3H_2, C^5H_2), 27.77 (CH_3), 34.92 (C^2H_2, C^6H_2), 50.17 (C^4H), 71.08 (C), 71.61 (C), 72.39 ppm (CH_2OH); elemental analysis calcd (%) for $C_{10}H_{20}O_3$ (188.27): C 63.80, H 10.71; found: C 63.79, H 10.69.

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