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Chemo enzymatic synthesis of Rengyol and Isorengyol☆

Christoph Kobler† and Franz Effenberger*

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

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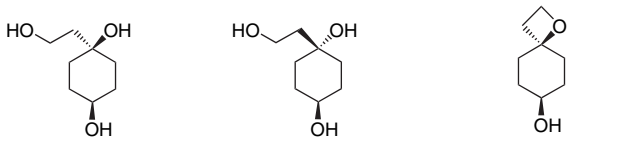
Abstract—Cyanohydrins **2** of *O*-protected 4-hydroxycyclohexanones **1** are excellent starting compounds for the synthesis of Isorengyol (**I**) and Rengyol (**II**). The cyano group of the *O*-benzyl derivative **2d** is first converted into the corresponding aldehyde **4**, which via Wittig olefination led to the vinyl compound **6**. Hydroboration of the trans-derivative (*trans*-**6**) leads, after debenzylation, to Isorengyol, whereas hydroboration and debenzylation of the cis-isomer (*cis*-**6**) gives Rengyol. With hydroxynitrile lyases (HNLs) as catalysts the stereoselective preparation of *cis*- as well as *trans*-cyanohydrin **2d** is possible, which enables the selective preparation of Isorengyol or Rengyol, respectively. The trans-configuration of Isorengyol and the cis-configuration of Rengyol were secured by X-ray crystal structure analysis.

1. Introduction

In 1984 Endo and Hikino have first isolated and characterized Rengyol (**I**) and Isorengyol (**II**) from the fruits of *Forsythia suspensa* Vahl (Scheme 1).[2] In traditional Chinese medicine these fruits, commonly called '*Rengyo*', are widely used because of their anti-inflammatory, antibactericidal, and antiemetic properties.[3] Isorengyol was not only found in *Forsythia* but also in the plants *Isoplexis chalcantha*,[4] *Millingtonia hortensis*,[5] and *Eurya tigang*.[6] Soon after its discovery chemical syntheses of Rengyol and Isorengyol have been developed.[7] The first stereoselective synthesis of Rengyol was performed by Hikino et al.[8] Starting from glucopyranosyl bromide, Rengyol was obtained in six steps and a total yield of 4%.[8] A completely different route was developed by the group of Ogasawara.[9] Starting from ethyl-2-(1-hydroxy-4-oxo-cyclohexa-2,5-dienyl)acetate Rengyol was obtained in 12 and Isorengyol in 16 steps.[9]



I: Rengyol **II**: Isorengyol **III**: Cleroindicin A

Scheme 1.

In 1996 Sun et al. isolated and characterized Cleroindicin A (**III**) from *Clerodendrum indicum*, which can be derived from Rengyol by intramolecular ether formation (Scheme 1).[10] Until today only one synthesis of Cleroindicin A is described in literature.[9]

The natural products **I**–**III**, contain a common 1,4-dihydroxy-cyclohexane substructure with an additional alkyl substituent in the 1-position (Scheme 1). In our methodically oriented investigations related to applications of hydroxynitrile lyases (HNL) in stereoselective organic syntheses, we have recently published the HNL-catalyzed addition of HCN to 4-substituted cyclohexanones.[11] Unexpectedly we observed trans-selectivity in the (*R*)-PaHNL-catalyzed additions and cis-selectivity with (*S*)-MeHNL as catalyst.[11] Since the transformation of a cyano group into a β-hydroxyethyl moeity can be achieved easily, cyanohydrins of 4-hydroxy-cyclohexanones should be ideal starting compounds for the syntheses of Rengyol, Isorengyol, and Cleroindicin A.

2. Results and discussion

In the publication mentioned above, the HNL-catalyzed reactions of *O*-protected 4-hydroxy-cyclohexanones **1** with hydrogen cyanide are described.[11b] With (*R*)-PaHNL from almonds (*Prunus amygdalus*) as catalyst the HCN addition preferentially gives the trans-products *trans*-**2**, with (*S*)-MeHNL from cassava (*Manihot esculenta*) as catalyst the cis-isomers *cis*-**2** are the major products (Scheme 2).[11b] In the nonenzymatic chemical addition of HCN to the cyclohexanones **1a–e** the isomeric cyanohydrins, *cis*-**2a–e** and *trans*-**2a–e** are obtained in almost equal amounts.[11b] Therefore, in the latter case a selective synthesis of either *cis*- or *trans*-1,4-substituted cyclohexanones is not possible.

☆ See Ref. 1.
Keywords: Rengyol; Isorengyol; Hydroxynitrile lyase; Cyanohydrins; cis/trans-Selectivity.
* Corresponding author. Tel.: +49 711 685 4265; fax: +49 711 685 4269; e-mail: franz.effenberger@oc.uni-stuttgart.de
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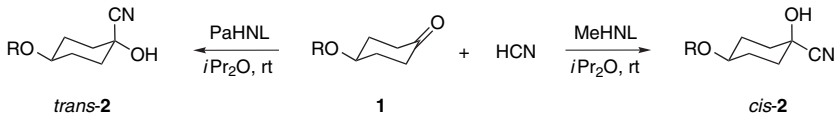


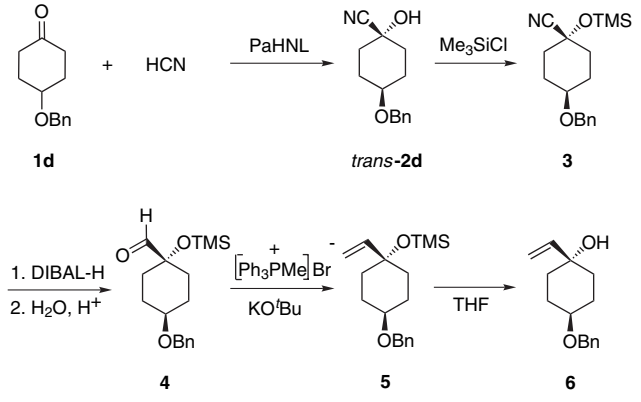
trans-**2** **1** *cis*-**2**

1, 2	a	b	c	d	e
R =	Me	*i*-Bu	allyl	benzyl	acetyl

Scheme 2.

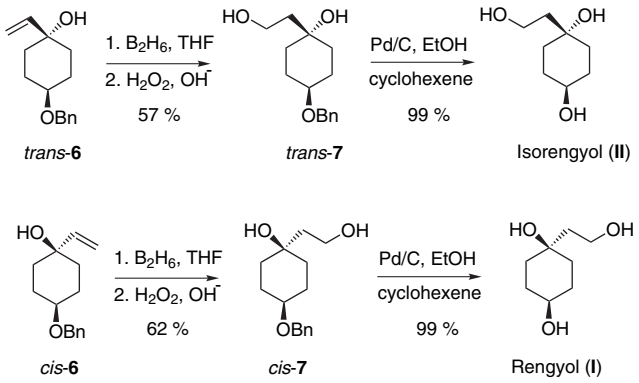
For the further transformations of the cyanohydrins **2** into Rengyol and Isorengyol, we have selected the benzyl protected cyanohydrin **2d** as educt for two reasons. The relatively high cis/trans-stereoselectivity of the HCN addition to **1d** with both the enzymes (cis/trans=2:98 with PaHNL and cis/trans=82:18 with MeHNL),[11b] and the mild reaction conditions for removal of the benzyl group by hydrogenolysis. For the synthesis of either Isorengyol or Rengyol the pure stereoisomers *trans*-**2d** and *cis*-**2d**, respectively, are required. However, since a separation of the cis/trans-isomers can be achieved without problems in a later stage in the synthesis, we first followed up reactions with the crude cyanohydrins obtained in the HNL-catalyzed reactions.

In Scheme 3 the synthesis of 4-benzyloxy-1-vinylcyclohexanol (**6**) starting from *trans*-**2d** is shown. Although the (*R*)-PaHNL-catalyzed HCN addition to **1d** using organic solvents and the enzyme supported on cellulose gives almost exclusively the *trans*-cyanohydrin, *trans*-**2d**,[11b] we have resorted to a two-phase reaction system,[12] which is easier to handle with defatted almond meal as enzyme source. This way **2d** was obtained as a cis/trans-mixture with a ratio of 25:75. Protection of the OH-function with a trimethylsilyl group[13] and hydrogenation with DIBAL-H[14] leads, after aqueous work up, to the corresponding (protected) aldehyde **4** (cis/trans=26:74). Wittig olefination of **4** results in the formation of the vinyl compound **5**.[15] The TMS-protecting group is removed by the treatment with *n*-Bu_4NF in THF leading to **6** (Scheme 3). At this stage the separation of the cis/trans-isomers was performed via chromatography on silica with PE/EE (7:1) to give pure *trans*-**6** and pure *cis*-**6**, respectively.



Scheme 3.

In Scheme 4 the straightforward transformations of *trans*-**6** to Isorengyol and *cis*-**6** to Rengyol are summarized. Hydroboration of the vinyl compounds *trans*-**6** and *cis*-**6**, with diborane in THF at 0 °C overnight and subsequent treatment of the reaction mixture with an alkaline solution of hydrogen peroxide (30%) at room temperature leads to the *O*-benzyl protected products *trans*-**6** and *cis*-**6**, respectively, which are isolated and purified.[16] The debenzylation to the natural products Isorengyol (**II**) and Rengyol (**I**) was performed via Pd/C catalyzed transfer hydrogenation using cyclohexene in abs EtOH (Scheme 4). Both Isorengyol and Rengyol are obtained quantitatively as colorless solids, which are recrystallized from acetone.



Scheme 4.

The cis/trans-isomer ratio of the starting cyanohydrin **2d** (Scheme 3) has been assigned by the chemical shift of the C-4 atom in ^{13}C NMR spectra. The absolute configuration of the 4-substituted cyclohexanone cyanohydrins has been determined earlier by X-ray crystallography of a corresponding 4-nitrobenzoyloxy derivative.[11b]

In none of the reactions performed (Schemes 3 and 4) isomerizations are to be expected. Thus structure assignments for the intermediates **3**–**6** are acceptable. The X-ray crystallographic structure of Isorengyol (**II**) (Fig. 1) confirms

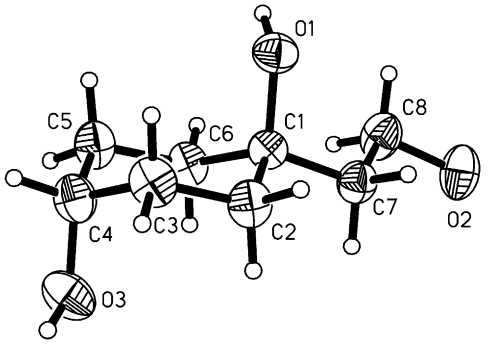


Figure 1. ORTEP plot of the trans-configurated Isorengyol (**II**).

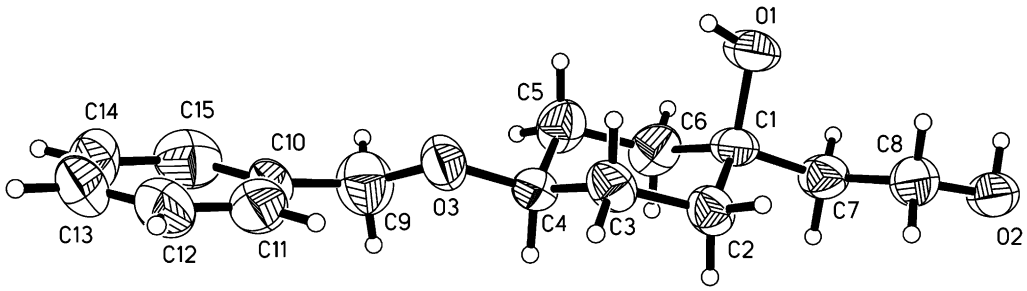


Figure 2. ORTEP plot of *cis*-4-benzyloxy-1-(2-hydroxyethyl)cyclohexane-1-ol (*cis*-**7**)—the *O*-benzyl derivative of Rengyol (**I**).

unambiguously the assigned trans-configuration.[17] The cis-configuration of Rengyol (**I**) is supported by the X-ray structure of the *O*-benzyl derivative *cis*-**7** (Fig. 2).[17]

3. Conclusions

Rengyol (**I**) and Isorengyol (**II**), isolated from *F. suspensa*, possess a variety of interesting biological activities, thus justifying that stereoselective chemical syntheses of these natural products are of great interest and importance. Cyanohydrins of 4-hydroxycyclohexanones are ideal starting materials for these naturally occurring 1,4-dihydroxycyclohexanones. *O*-Protected 4-hydroxycyclohexanones **1** are excellent substrates for hydroxynitrile lyase (HNL) catalyzed HCN additions leading to the corresponding cyanohydrins **2** for which an unexpected high cis- or trans-selectivity is observed.[11] With (*R*)-PaHNL from almonds the *trans*-1,4-dihydroxycyclohexanones are almost exclusively (≥98%) obtained, whereas with (*S*)-MeHNL from *cassava* high yields (≥82%) of the corresponding cis-compounds are obtained. The chemical transformations of the cyanohydrins **2** to the final products, i.e., Isorengyol (**II**) and Rengyol (**I**), are straightforward and can be performed without problems. By using almond meal as enzyme catalyst in a two-phase system, the cis/trans-ratio of the cyanohydrins **2d** is only 25:75. Nevertheless, the chemical transformations of this cis/trans-mixture of **2d** can be performed without difficulties. Separation of the cis/trans-isomers is best achieved via column chromatography of the vinyl compounds *trans*-**6** and *cis*-**6**, respectively. The last two steps to the final products Isorengyol (**II**) and Rengyol (**I**) are then performed separately with the pure isomers *trans*-**6** and *cis*-**6**, respectively.

A comparison of the syntheses of Rengyol and Isorengyol published already, with the procedures described in this paper, shows the following.

The synthesis of Rengyol by Hikino et al. was performed in six steps, starting from glucopyranosyl bromide, in 4% total yield. Ogasawara et al. synthesized Rengyol in 10 steps, starting from ethyl-2(1-hydroxy-4-oxo-cyclohexa-2.5-dienyl) acetate, in 14% total yield. Starting from 4-benzyloxy-cyclohexanone, we obtained Rengyol in seven steps and a total yield of 9.7%. The effort for the syntheses of the starting compounds in the three procedures cited is comparable.

For Isorengyol only one synthesis was published by Ogasawara et al. From the same starting compound as for Rengyol they obtained Isorengyol in 14 steps and a total yield of 3.64%. We obtained Isorengyol in seven steps and a total yield of 8.9%.

This comparison confirms the advantage of our approach if one combines the number of reaction steps and total yields, especially for the synthesis of Isorengyol.

4. Experimental

4.1. Materials and methods

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 using capillary glass columns (20 m) with OV 1701, carrier gas 0.4–0.6 bar hydrogen. 4-Benzyloxycyclohexanone (**1d**) was prepared according to literature procedures.[18] All solvents were dried and distilled. Yields are not optimized.

4.1.1. 4-Benzyloxy-1-hydroxycyclohexanecarbonitrile (2d).[11b] (a) HNL-catalyzed reactions in organic solvents: the *O*-protected 4-hydroxycyclohexanone cyanohydrins **2a**–**e** were prepared according to Effenberger et al.[12] (b) HNL-catalyzed reactions in the two-phase system: to a vigorously stirred two-phase system of 24.51 g (120 mmol) **1d**[18] in 120 mL diisopropylether and 200 mL of an aqueous solution of crude (*R*)-PaHNL[12] (42,200 U), 300 mL of a solution of 6.48 g (240 mmol) HCN, prepared in situ,[12] in 300 mL diisopropylether was added. To determine the conversion rate and the cis/trans-ratio, 2 mL of the reaction mixture was diluted with 2 mL of diisopropylether and dried (Na_2SO_4). The organic phase was decanted and concentrated under reduced pressure. The residue was dissolved in 1 mL anhydrous CH_2Cl_2 and 100 μL acetic anhydride and 20 mg DMAP were added. After 48 h of stirring at room temperature the reaction mixture was filtered through a Büchner funnel and washed several times with diisopropylether. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 26.21 g (94% yield) **2d** as a pale yellow oil, cis/trans-ratio=25:75. *cis*-**2d**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.71–2.07 (m, 8H, 8CH), 3.39 (br s, 1H, OH), 3.73–3.78 (m, 1H, C^4H), 4.51 (s, 2H, CH_2Ph), 7.26–7.38 (m, 5H, H_{Ph}). *cis*-**2d**: ^{13}C NMR (63 MHz,

$CDCl_3$) δ 26.74 (C^3H_2, C^5H_2), 33.30 (C^2H_2, C^6H_2), 68.85 (C^1), 69.96 (CH_2Ph), 71.63 (C^4H), 121.76 (CN), 127.44, 127.56, 128.40, 138.47 (C_{Ph}). *trans*-**2d**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.67–1.81 (m, 4H, 4CH), 1.95–2.03 (m, 2H, C^3H_{eq}, C^5H_{eq}), 2.19–2.29 (m, 2H, C^2H_{eq}, C^6H_{eq}), 2.93 (br s, 1H, OH), 3.45–3.54 (m, 1H, C^4H), 4.53 (s, 2H, CH_2Ph), 7.28–7.39 (m, 5H, H_{Ph}). *trans*-**2d**: ^{13}C NMR (63 MHz, $CDCl_3$) δ 26.54 (C^3H_2, C^5H_2), 33.99 (C^2H_2, C^6H_2), 68.34 (C^1), 70.17 (CH_2Ph), 73.27 (C^4H), 121.87 (CN), 127.46, 127.63, 128.45, 138.48 (C_{Ph}).

4.1.2. 4-Benzyloxy-trimethylsilyloxycyclohexanecarbonitrile (3).[13,14b] To a stirred solution of 15.74 g (224.82 mmol) imidazole in 280 mL dry DMF 14.25 g (131.15 mmol) chloro-trimethylsilane was added at 0 °C under an atmosphere of nitrogen. After stirring for 15 min, a solution of 26.00 g (112.41 mmol) **2d** in 50 mL dry DMF was added dropwise and the mixture was allowed to warm up slowly to room temperature with continued stirring for a further 1 h. Then 560 mL of water was added and the resulting mixture was extracted with diethyl ether (3×100 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude cis/trans-mixture was purified by chromatography on SiO_2 using petroleum ether–EtOAc (7:1) as eluant (R_f=0.56) to afford 28.51 g (84% yield) **3** as a colorless oil, cis/trans-ratio=25:75. *cis*-**3**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.25 (s, 9H, $Si(CH_3)_3$), 1.71–2.01 (m, 6H, 4CH, C^3H_{eq}, C^5H_{eq}), 2.02–2.16 (m, 2H, C^2H_{eq}, C^6H_{eq}), 3.53–3.55 (m, 1H, C^4H), 4.50 (s, 2H, CH_2Ph), 7.29–7.34 (m, 5H, H_{Ph}). *cis*-**3**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 1.40 ($Si(CH_3)_3$), 26.90 (C^3H_2, C^5H_2), 34.82 (C^2H_2, C^6H_2), 69.87 (C^1), 69.98 (CH_2Ph), 71.90 (C^4H), 121.82 (CN), 127.43, 127.54, 128.39, 138.62 (C_{Ph}). *trans*-**3**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.24 (s, 9H, $Si(CH_3)_3$), 1.64–2.11 (m, 6H, 4CH, C^3H_{eq}, C^5H_{eq}), 2.15–2.25 (m, 2H, C^2H_{eq}, C^6H_{eq}), 3.41–3.47 (m, 1H, C^4H), 4.52 (s, 2H, CH_2Ph), 7.29–7.34 (m, 5H, H_{Ph}). *trans*-**3**: ^{13}C NMR (126 MHz, $CDCl_3$) δ 1.30 ($Si(CH_3)_3$), 26.91 (C^3H_2, C^5H_2), 35.60 (C^2H_2, C^6H_2), 69.43 (C^1), 70.10 (CH_2Ph), 73.54 (C^4H), 121.80 (CN), 127.41, 127.54, 128.40, 138.64 (C_{Ph}). Anal. Calcd for $C_{17}H_{25}NO_2Si$ (303.48): C, 67.28; H, 8.30; N, 4.62. Found: C, 67.40; H, 8.30; N, 4.45.

4.1.3. 4-Benzyloxy-1-trimethylsilyloxycyclohexanecarbaldehyde (4).[14] To a vigorously stirred solution of 15.50 g (51.07 mmol) **3** in 125 mL dry *n*-hexane 86.8 mL of a DIBAL-H solution (1 M in *n*-hexane) was added dropwise at −45 °C under an inert gas atmosphere. Then the reaction mixture was allowed to warm up slowly to 15 °C and stirring at this temperature was continued for 5 h. The mixture was diluted with CH_2Cl_2 (100 mL) and quenched with a saturated aqueous solution of NH_4Cl (100 mL) and 0.5 M aqueous H_2SO_4 (250 mL). After vigorous stirring for 12 h at 15 °C, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude cis/trans-mixture was purified by chromatography on SiO_2 using petroleum ether–EtOAc (10:1) as eluant (R_f (*cis*-**4**)=0.54, R_f (*trans*-**4**)=0.57) to afford 7.54 g (48% yield) of **4** as a colorless oil, cis/trans-ratio=26:74. ^1H NMR (500 MHz, $CDCl_3$)[14b] δ 0.14 (s, 6.9H, *trans*-$Si(CH_3)_3$), 0.15 (s, 2.1H, *cis*-$Si(CH_3)_3$), 1.41–2.04 (m, 8H, 8CH), 3.37–3.40 (m, 0.25H, *cis*-C^4H), 3.60–3.63 (m, 0.75H, *trans*-C^4H), 4.51 (s, 1.45H, *trans*-CH_2Ph), 4.56 (s, 0.55H, *cis*-CH_2Ph), 7.25–7.36 (m, 5H, H_{Ph}), 9.49 (s, 0.75H, *trans*-CHO), 9.54 (s, 0.25H, *cis*-CHO).^{13}C NMR (126 MHz, $CDCl_3$) δ 2.25 ($Si(CH_3)_3$), 25.13 (*trans*-C^3H_2, *trans*-C^5H_2), 26.53 (*cis*-C^3H_2, *cis*-C^5H_2), 27.77 (*trans*-C^2H_2, *trans*-C^6H_2), 30.41 (*cis*-C^2H_2, *cis*-C^6H_2), 69.87 (*trans*-CH_2Ph), 69.96 (*cis*-CH_2Ph), 72.67 (*trans*-C^4H), 75.38 (*cis*-C^4H), 79.31 (*cis*-C^1), 79.69 (*trans*-C^1), 127.36, 127.40, 127.49, 127.53, 128.34, 128.38, 138.82, 138.96 (C_{Ph}), 202.89 (*trans*-CHO), 203.73 (*cis*-CHO). Anal. Calcd for $C_{17}H_{26}O_3Si$ (306.48): C, 66.62; H, 8.55. Found: C, 66.34; H, 8.63.

4.1.4. (4-Benzyloxy-1-vinyl-cyclohexyloxy)trimethylsilane (5).[15] To a stirred solution of 4.79 g (42.68 mmol) potassium *tert*-butoxide in 100 mL dry THF 16.06 g (44.81 mmol) methyl-triphenylphosphonium bromide was added under nitrogen atmosphere at room temperature. The bright yellow reaction mixture was stirred for 0.5 h, and then a solution of 7.40 g (24.14 mmol) **4** in 100 mL dry THF was added dropwise. After stirring for 2 h, the precipitate was filtered off and washed with Et_2O. The combined filtrates were quenched with water and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude cis/trans-mixture was purified by chromatography on SiO_2 using a short column with petroleum ether–EtOAc (3:1) as eluant to give 2.25 g (31% yield) **5** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6.4H, *trans*-$Si(CH_3)_3$), 0.10 (s, 2.6H, *cis*-$Si(CH_3)_3$), 1.26–1.49 (m, 8H, 8CH), 3.27–3.38 (m, 0.3H, *cis*-C^4H), 3.54–3.62 (m, 0.7H, *trans*-C^4H), 4.50 (s, 2H, *trans*-CH_2Ph), 4.56 (s, 0.6H, *cis*-CH_2Ph), 4.99–5.21 (m, 1.4H, CH=CH_2), 5.75–5.98 (m, 1H, CH=CH_2), 7.22–7.38 (5H, m, H_{Ph}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 2.53 (*cis*-$Si(CH_3)_3$), 2.56 (*trans*-$Si(CH_3)_3$), 26.62 (*trans*-C^3H_2, *trans*-C^5H_2), 27.48 (*cis*-C^3H_2, *cis*-C^5H_2)^{cis}, 33.47 (*trans*-C^2H_2, *trans*-C^6H_2), 35.39 (*cis*-C^2H_2, *cis*-C^6H_2), 69.79 (*trans*-CH_2Ph), 69.83 (*cis*-CH_2Ph), 73.34 (*cis*-C^1), 73.96 (*trans*-C^4H), 74.24 (*trans*-C^1), 76.64 (*cis*-C^4H), 112.27 (*cis*-CH=CH_2), 113.00 (*trans*-CH=CH_2), 127.29, 127.38, 127.54, 128.30, 128.33, 139.15, 139.24 (C_{Ph}), 145.10 (*trans*-CH=CH_2), 145.56 (*cis*-CH=CH_2). HRMS (EI, 70 eV) calcd for $C_{18}H_{28}O_2Si^+$: 304.1859. Found: 304.1850.

4.1.5. 4-Benzyloxy-1-vinylcyclohexan-1-ol (6). To a solution of 2.19 g (7.19 mmol) **5** in 36 mL dry THF a solution of 2.50 g (7.92 mmol) *n*-Bu_4NF in 8 mL dry THF was added slowly at 0 °C. The mixture was stirred for 0.5 h. Then 42 mL H_2O and 56 mL CH_2Cl_2 were added, the organic layer separated, and the aqueous layer was extracted twice with CH_2Cl_2 (2×25 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude cis/trans-mixture was purified and separated by chromatography on SiO_2 with petroleum ether–EtOAc (7:1) as eluant to give two main fractions as colorless oils: 0.55 g (33% yield) *cis*-**6** and 0.76 g (45% yield) *trans*-**6**. *cis*-**6**: IR (neat) 2928, 2855, 1453, 1363, 1252, 1229, 1068, 1028, 993, 959, 920, 841, 734, 695. ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (br s, 1H, OH), 1.48–1.54 (m, 2H, 2CH), 1.69–1.81 (m, 4H, 4CH), 1.86–1.91 (m, 2H, C^2H_{eq}, C^6H_{eq}), 3.34–3.40 (m, 1H, C^4H), 4.57 (s, 2H, CH_2Ph), 5.04 (dd, $^2J(H_C, H_B)$=1.3 Hz, *cis*-$^3J(H_C, H_A)$=10.8 Hz,

1H, $CH_A{=}CH_CH_B$), 5.26 (dd, 1H, $^2J(H_B, H_C)$=1.3 Hz, *trans*-$^3J(H_B, H_A)$=17.5 Hz, 1H, $CH_A{=}CH_CH_B$), 5.93 (dd, *cis*-$^3J(H_A, H_C)$=10.8 Hz, *trans*-$^3J(H_B, H_A)$=17.5 Hz, 1H, $CH_A{=}CH_CH_B$), 7.25–7.42 (m, 5H, H_{Ph}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.40 (C^3H_2, C^5H_2), 35.24 (C^2H_2, C^6H_2), 69.77 (CH_2Ph), 70.93 (C^1), 76.14 (C^4H), 111.85 ($CH{=}CH_2$), 127.39, 127.49, 128.34, 139.05 (C_{Ph}), 145.46 ($CH{=}CH_2$). HRMS (MH^+) calcd for $C_{15}H_{21}O_2$: 233.1542. Found: 233.1538.

trans-**6**: IR (neat) 2931, 2860, 1453, 1360, 1089, 1063, 1027, 968, 920, 907, 847, 732, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (br s, 1H, OH), 1.41–1.49 (m, 2H, 2CH), 1.72–1.78 (m, 2H, 2CH), 1.85–1.92 (m, 4H, C^3H_{eq}, C^5H_{eq}, C^2H_{eq}, C^6H_{eq}), 3.61–3.63 (m, 1H, C^4H), 4.52 (s, 2H, CH_2Ph), 5.07 (dd, $^2J(H_C, H_B)$=1.3 Hz, *cis*-$^3J(H_C, H_A)$=10.8 Hz, 1H, $CH_A{=}CH_CH_B$), 5.27 (dd, 1H, $^2J(H_B, H_C)$=1.3 Hz, *trans*-$^3J(H_B, H_A)$=17.3 Hz, 1H, $CH_A{=}CH_CH_B$), 6.01 (dd, *cis*-$^3J(H_A, H_C)$=10.8 Hz, *trans*-$^3J(H_B, H_A)$=17.3 Hz, 1H, $CH_A{=}CH_CH_B$), 7.25–7.36 (m, 5H, H_{Ph}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.14 (C^3H_2, C^5H_2), 32.84 (C^2H_2, C^6H_2), 69.85 (CH_2Ph), 71.64 (C^1), 73.35 (C^4H), 111.91 ($CH{=}CH_2$), 127.38, 128.33, 139.14 (C_{Ph}), 145.58 ($CH{=}CH_2$). HRMS (MH^+) calcd for $C_{15}H_{21}O_2$: 233.1542. Found: 233.1535. Anal. Calcd for $C_{15}H_{20}O_2$ (232.32): C, 77.55; H, 8.68. Found: C, 77.40; H, 8.83.

4.1.6. *cis*-4-Benzyloxy-1-(2-hydroxyethyl)cyclohexan-1-ol (*cis*-7).[16] To 480.9 mg (2.07 mmol) *cis*-**6** in 6 mL dry THF 4.5 mL of a 1 M solution of B_2H_6 in THF was added dropwise at 0 °C under nitrogen atmosphere and the mixture stirred overnight at 0 °C. The reaction mixture was oxidized by careful addition of 3.5 mL NaOH (3 M) and 0.78 mL 30% H_2O_2 and allowed to warm up slowly to room temperature. Stirring was continued for 30 min and then the mixture was extracted with CH_2Cl_2 (3×8 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 with petroleum ether–EtOAc (1:3) as eluant to afford 320.0 mg (62% yield) *cis*-**7** as a white amorphous solid, recrystallized from iPr_2O (colorless prismatic crystals): mp 102 °C. IR (neat) 3331, 2929, 2973, 1453, 1362, 1165, 1102, 1070, 1050, 1019, 962, 937, 741, 697. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33–1.38 (m, 2H, 2CH), 1.68–1.75 (m, 2H, 2CH), 1.69 (t, ^3J=5.7 Hz, CH_2CH_2OH), 1.83–1.85 (m, 4H, 4CH), 2.74 (br s, 1H, C^1OH), 2.96 (t, ^3J=4.6 Hz, 1H, CH_2CH_2OH), 3.33–3.39 (m, 1H, C^4H), 3.86 (dt, ^3J_d=4.6 Hz, ^3J_t=5.6 Hz, 2H, CH_2CH_2OH), 4.56 (s, 2H, CH_2Ph), 7.25–7.36 (m, 5H, H_{Ph}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.28 (C^3H_2, C^5H_2), 35.09 (C^2H_2, C^6H_2), 42.21 (CH_2CH_2OH), 59.51 (CH_2CH_2OH), 69.79 (CH_2Ph), 71.55 (C^1), 76.20 (C^4H), 127.42, 127.51, 128.35, 138.98 (C_{Ph}). Anal. Calcd for $C_{15}H_{22}O_3$ (250.34): C, 71.97; H, 8.86. Found: C, 71.93; H, 8.86.

4.1.7. *trans*-4-Benzyloxy-1-(2-hydroxyethyl)cyclohexan-1-ol) (*trans*-7).[16] For reaction conditions and workup see above for *cis*-**7**. 598.0 mg (2.57 mmol) of *trans*-**6**, 7.4 mL dry THF, and 5.6 mL B_2H_6 (1 M in THF). Purification by column chromatography (SiO_2) with petroleum ether–EtOAc (1:3) as eluant affording 365.0 mg (57% yield) *trans*-**7** as a white amorphous solid: mp 38 °C. IR (neat) 3324, 3271, 2939, 2922, 1440, 1250, 1087, 1066, 1029, 1004, 973, 940, 731, 695, 648. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49–1.54 (m, 2H, 2CH), 1.61–1.80 (m, 2H, 2CH), 1.74–1.80 (m, 2H, 2CH), 1.76 (t, ^3J=5.8 Hz, CH_2CH_2OH), 1.84–1.90 (m, 2H, 2CH), 3.14 (br s, 2H, C^1OH, CH_2CH_2OH), 3.56–3.60 (m, 1H, C^4H), 3.87 (t, ^3J=5.7 Hz, 2H, CH_2CH_2OH), 4.51 (s, 2H, CH_2Ph), 7.24–7.35 (m, 5H, H_{Ph}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.47 (C^3H_2, C^5H_2), 33.19 (C^2H_2, C^6H_2), 41.18 (CH_2CH_2OH), 59.30 (CH_2CH_2OH), 69.91 (CH_2Ph), 72.35 (C^1), 74.08 (C^4H), 127.41, 127.52, 128.34, 139.03 (C_{Ph}). Anal. Calcd for $C_{15}H_{22}O_3$ (250.34): C, 71.97; H, 8.86. Found: C, 71.80; H, 8.93.

4.1.8. Rengyol (*cis*-1-(2-hydroxyethyl)cyclohexane-1,4-diol) (I).[8,9] To a solution of 86.8 mg (0.35 mmol) *cis*-**7** in 7 mL abs EtOH and 0.75 mL freshly distilled cyclohexene, 20 mg 10% Pd/C (Degussa Type E) was added. The suspension was stirred under reflux for 1 h. The mixture was allowed to cool down and was then filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was recrystallized from acetone to afford 55.3 mg (99% yield) Rengyol (**I**) as a white amorphous solid: mp 120 °C. IR (neat) 2931, 2439, 2405, 1125, 1090, 1063, 1019, 959, 930, 907, 735, 666. ^{1}H NMR (500 MHz, methanol-d_4) δ 1.37–1.43 (m, 2H, C^2H_{ax}, C^6H_{ax}), 1.60–1.73 (m, 6H, C^3H_{ax}, C^5H_{ax}, C^3H_{eq}, C^5H_{eq}, C^2H_{eq}, C^6H_{eq}), 1.68 (t, ^3J=7.2 Hz, 2H, CH_2CH_2OH), 3.52 (tt, ^3J (C^4H_{ax}, C^3H_{ax})=^3J (C^4H_{ax}, C^5H_{ax})=9.9 Hz, ^3J (C^4H_{ax}, C^3H_{eq})=^3J (C^4H_{ax}, C^5H_{eq})=4.4 Hz, 1H, C^4H), 3.73 (t, ^3J=7.2 Hz, 2H, CH_2CH_2OH). ^{1}H NMR (300 MHz, pyridine-d_5)[5b,19] δ 1.51–1.61 (m, 2H, C^2H_{ax}, C^2H_{ax}), 2.01–2.12 (m, 4H, C^2H_{eq}, C^6H_{eq}, C^3H_{eq}, C^5H_{eq}), 2.04 (t, ^3J=6.6 Hz, 2H, CH_2CH_2OH), 2.24–2.38 (m, 2H, C^3H_{ax}, C^5H_{ax}), 3,94 (tt, ^3J (C^4H_{ax}, C^3H_{ax})=^3J (C^4H_{ax}, C^5H_{ax})=10.1 Hz, ^3J (C^4H_{ax}, C^3H_{eq})=^3J (C^4H_{ax}, C^5H_{eq})=4.0 Hz, 1H, C^4H), 4.22 (t, ^3J=6.6 Hz, 2H, CH_2CH_2OH). ^{13}C NMR (126 MHz, methanol-d_4) δ 31.28 (C^3H_2, C^5H_2), 36.04 (C^2H_2, C^6H_2), 45.57 (CH_2CH_2OH), 59.15 (CH_2CH_2OH), 70.76 (C^4H, C^1). ^{13}C NMR (126 MHz, pyridine-d_5)[5b,19] 31.86 (C^3H_2, C^5H_2), 36.26 (C^2H_2, C^6H_2), 45.21 (CH_2CH_2OH), 58.86 (CH_2CH_2OH), 69.80 (C^1), 70.03 (C^4H). Anal. Calcd for $C_8H_{16}O_3$ (160.21): C, 59.98; H, 10.07. Found: C, 59.92; H, 9.96.

4.1.9. Isorengyol (*trans*-1-(2-hydroxyethyl)cyclohexane-1,4-diol) (II).[9] To a solution of 242.2 mg (0.97 mmol) *trans*-**7** in 20 mL abs EtOH and 2.1 mL freshly distilled cyclohexene, 50 mg 10% Pd/C (Degussa Type E) was added. The suspension was stirred under reflux for 1 h. The mixture was allowed to cool down and was then filtered through Celite. The filtrate was concentrated under reduced pressure. Recrystallization from acetone afforded 153.8 mg (99% yield) Isorengyol (**II**) as colorless crystals: mp 109 °C. IR (neat) 3272, 2945, 2925, 2434, 1021, 979, 839, 730, 699, 672. ^{1}H NMR (500 MHz, methanol-d_4) δ 1.42–1.51 (m, 4H, 4CH), 1.74–1.87 (m, 4H, 4CH), 1.78 (t, ^3J=7.1 Hz, 2H, CH_2CH_2OH), 3.74–3.79 (m, 1H, C^4H), 3.75 (t, ^3J=7.1 Hz, 2H, CH_2CH_2OH). ^{1}H NMR (500 MHz, pyridine-d_5)[5b,19] δ 1.83–1.89 (m, 4H, 4CH), 2.15 (t, ^3J=6.5 Hz, 2H, CH_2CH_2OH), 2.18–2.29 (m, 4H, 4CH), 4.20–4.26 (m, 1H, C^4H), 4.25 (t, ^3J=6.5 Hz, 2H, CH_2CH_2OH). ^{13}C NMR (126 MHz, methanol-d_4) δ 30.69 (C^3H_2, C^5H_2), 34.22 (C^2H_2, C^6H_2), 43.03 (CH_2CH_2OH),

58.98 (CH_2CH_2OH), 68.52 (C^4H), 72.00 (C^1). ^{13}C NMR (126 MHz, pyridine-d_5)[5b,19] δ 31.24 (C^3H_2, C^5H_2), 34.59 (C^2H_2, C^6H_2), 43.26 (CH_2CH_2OH), 58.81 (CH_2CH_2OH), 67.41 (C^1), 71.29 (C^4H). Anal. Calcd for $C_8H_{16}O_3$ (160.21): C, 59.98; H, 10.07. Found: C, 60.11; H, 9.98.

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