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Enantioselective reduction of 2-substituted tetrahydropyran-4-ones using *Daucus carota* plant cells

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Abstract

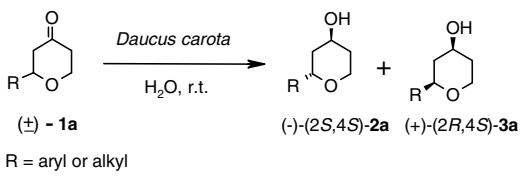
Enzymatic reduction of 2-substituted tetrahydropyran-4-ones with *Daucus carota*, plant cells as biocatalyst occurred in water under extremely mild and environmentally benign conditions giving a 1:1 mixture of diastereoselectively (2*R*,4*S*)- and (2*S*,4*S*)-2-aryl- or 2-alkyl-tetrahydropyranols in high yields.

Keywords: Biocatalytic transformation; Carrot root; Enantioselective reduction; Chiral tetrahydropyranols

Tetrahydropyranols are present as structural units in a number of natural products such as avermectins, aplysiatoxin, oscillatoxins, latrunculins, talaromycins and acutiphycins.[1] Optically pure tetrahydropyranols are potential chiral building blocks for the synthesis of *anti*-1,3-diols.[2] The Prins-cyclization is one of the most simple and straightforward approaches for the construction of a tetrahydropyran ring system.[3–6] However, there is no report on an asymmetric Prins-cyclization for the direct preparation of enantiomerically pure hydroxy tetrahydropyrans. Therefore, we have developed an enzymatic approach for the preparation of optically active tetrahydropyranols by means of kinetic resolution of racemic tetrahydropyranols via lipase mediated transesterification.[7] Recently, plants have been considered as suitable biochemical systems for the biotransformation of exogenous substrates.[8,9] Among plants, carrots (*Daucus carota*) are effective biocatalysts for the stereoselective reduction of ketones, both as immobilized plant cell cultures[10] and whole plant tissues.[11] *D. carota* root has been used previously for the enantioselective reduction of prochiral ketones to produce chiral secondary alcohols.[12]

In this Letter, we describe an enzymatic approach for the preparation of chiral tetrahydropyranols by means of enantioselective reduction of 2-substituted tetrahydropyran-4-ones using *D. carota* roots in water (Scheme 1).

The 2-susbtituted tetrahydropyran-4-ones were easily prepared by the oxidation of (±)-tetrahydropyranols obtained via the condensation of an aldehyde with 3-buten-1-ol via the Prins-cyclization.[13] Subsequently, these tetrahydropyran-4-ones were subjected to *D. carota* reduction. The bioreduction of the keto group was performed using fresh carrot roots obtained from a local market. Initially, the reduction was carried out using a solution



Scheme 1. Reduction of tetrahydropyran-4-ones with *Daucus carota* roots.

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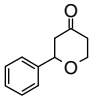
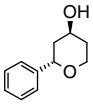
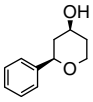
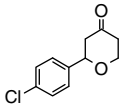
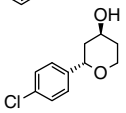
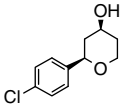
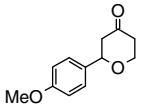
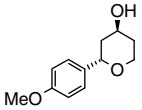
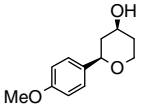
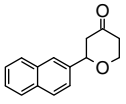
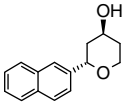
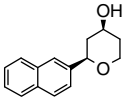
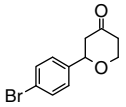
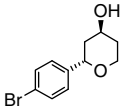
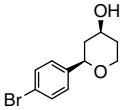
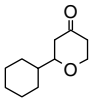
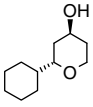
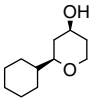
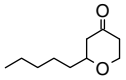
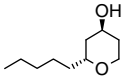
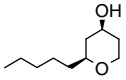
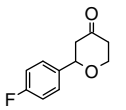
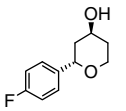
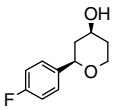
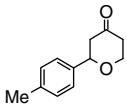
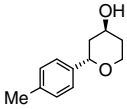
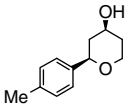
of the ketone (1 mmol) in ethanol (1 mL) with fresh carrot (10 g) in water (70 mL) followed by incubation in an orbital shaker at 30 °C. The progress of the reaction was monitored by TLC analysis. The results are summarized in Table 1.

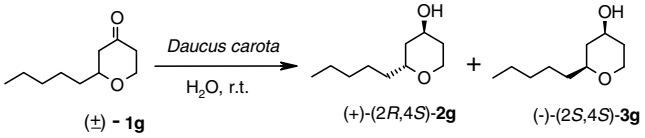
For example, reduction of (±)-2-phenyl-tetrahydro-2*H*-pyran-4-one with *D. carota* in water afforded (2*S*,4*S*)-2-phenyl-tetrahydropyranol and (2*R*,4*S*)-2-phenyl-tetrahydropyranol in a 1:1 ratio. These stereoisomers could be easily separated by column chromatography. The enantiomeric excesses of both the *cis*- and *trans*-tetrahydropyranols were determined by HPLC using chiral columns and were higher than 92%. The structures of the products were established by ^{1}H NMR, IR and mass spectrometry and also by comparison with authentic samples.[14] The absolute stereochemistry of (2*R*,4*S*)- and (2*S*,4*S*)-2-aryl- or 2-alkyl-tetrahydropyranols was established by comparison with authentic samples.[14] The reductions in water gave the best results. The effects of ring substituents on the reduction of aryl-substituted tetrahydropyran-4-ones by *D. carota* are quite general. First, the corresponding (*S*)-alcohols were obtained in all cases, with enantiomeric excesses ranging from 83% to 94%. With aryl-substituted tetrahydropyran-4-ones, it was observed that electron-donating substituents slowed the reaction, highlighting the sensitivity of bioreduction kinetics to electronic effects, which is in accordance with results reported in the literature.[12] As with aryl-substituted tetrahydropyran-4-ones, 2-hexyl-tetrahydropyran-4-one underwent smooth reduction with *D. carota* roots to give optically active 2-hexyl-4-hydroxy tetrahydropyrans in good yields and with high degrees of enantioselectivity (Scheme 2).

The use of cut carrot roots in water offers several advantages compared to Baker's yeast, such as low cost, ease of

Table 1
Enantioselective reduction of tetrahydropyranones using *Daucus Carota*

Entry	Substrate	Alcohol **2**[a]	$[\alpha]_D^{25}$[b]	ee (%)[c]	Alcohol **3**	$[\alpha]_D^{25}$[b]	ee (%)[c]	Time (h)	Yield (%)[d]
a			−18.8	94		+15.6	92	24	92
b			−14.7	90		+25.3	86	26	94
c			−16.0	87		+17.8	85	30	90
d			−27.9	94		+25.6	89	29	90
e			−18.6	90		+16.6	83	24	92
f			−9.9	88		+9.6	86	32	88
g			−8.6	92		+6.6	87	38	85
h			−11.2	90		+9.5	87	24	91
i			−28.2	92		+21.7	88	24	92

[a] All products were characterized by IR, NMR and mass spectroscopy.
[b] Optical rotations were recorded in $CHCl_3$ ($c = 1.0$).
[c] Enantiomeric excesses of alcohols were determined using chiral HPLC.
[d] Yield refers to pure products after chromatography.



Scheme 2. Reduction of 2-hexyl-tetrahydropyran-4-one with *Daucus carota* roots.

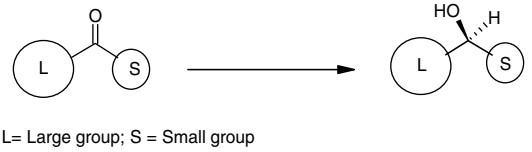


Fig. 1. Prelog's rule for the bioreduction of ketones.

availability of the biocatalyst, simple work-up and product recovery. No specific match/mismatch effect from the adjacent stereocentre was observed, as can be seen from the reduction of 2-phenyl-tetrahydropyran-4-one (±)-**1a** (Table 1).[15] At 100% conversion, an equal amount of enantiopure tetrahydropyranols **2a** and **3a** were isolated in 92% yield. Reduction occurs from the *re*-face only of the prochiral ketone, independently of the configuration of the 2-aryl- or alkyl-substituted stereocentre. The stereochemical course of many bioreductions of ketones may be predicted from a simple model which is generally referred to as Prelog's rule.[16] This empirical model, originally designed for the reduction of ketones by the fungus *Curvularia falcata* implies that the outcome is mainly dependent on the steric requirements of the substrate (Fig. 1).

The observed enantioselectivity is in accordance with Prelog's rule. The presence of several competing oxidoreductases with opposite stereoselectivities in the plant tissues may be the origin of the stereochemical outcome with these substrates. Hence, this biocatalytic approach is found to be suitable for the preparation of a wide range of tetrahydropyranols. Finally, the recovered carrot could be used for composting.

In conclusion, the enantioselective reduction of a series of 2-substituted tetrahydropyran-4-ones was achieved using *D. carota* roots in water, which afforded the corresponding (*S*)-alcohols with ee ranging from 83% to 94%. The low cost and the easy availability of the biocatalyst besides the experimental simplicity suggest the possible use of the present method for large scale preparations of important chiral tetrahydropyranols.

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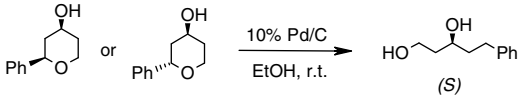

$[\alpha]_D^{25}$ -7.2 (*c* 1.5, EtOH)

15. *Reduction of ketones with D. carota roots*: Twelve carrots were obtained from a local market. The external layer was removed and the remainder was cut into small thin pieces (1 cm long slices). Ketone (100 mg) was added to a suspension of the freshly cut carrot root (10 g) in 70 mL of water and the reaction mixture was incubated in an orbital shaker at room temperature. The suspension was then filtered off and the carrot root was washed three times with water. The filtrates were extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude products were purified by flash chromatography to furnish the corresponding diastereomerically pure *cis*- and *trans*-tetrahydropyr-

anols in approximately 1:1 ratios. All the compounds were characterized by ^{1}H NMR, IR, and mass spectroscopy and HPLC. The enantiomeric excess of the product was determined using a Shimadzu high-performance liquid-chromatography (HPLC) system equipped with a chiral HPLC column (Chiralcel OD) and a UV detector at an absorbance of 225 nm. A solvent system of *n*-hexane and isopropanol (8:2) at a flow rate of 1.0 ml/min was used. Spectroscopic data for selected products: *Compound* **2b**: *(2S,4S)-2-(4-chlorophenyl)tetrahydro-2H-4-pyranol*: Solid, mp 92–94 °C, $[\alpha]_D^{25}$ −14.7 (*c* 1.0, $CHCl_3$, ee = 90%); IR (KBr): ν_{max} 3380, 2952, 2921, 2858, 1515, 1448, 1371, 1284, 1125, 1068, 1044, 985, 813 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.17 (d, 2H, J = 8.3 Hz), 7.08 (d, 2H, J = 8.3 Hz), 4.72 (m, 1H), 4.27 (m, 1H), 4.06 (dt, 1H, J = 2.2, 12.0 Hz), 3.90 (ddd, 1H, J = 1.5, 5.2, 12.0 Hz), 2.01 (br s, 1H), 1.90 (m, 1H), 1.81 (m, 1H), 1.63 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 128.3, 127.3, 125.8, 73.8, 64.2, 62.8, 40.6, 32.8; LCMS: (M+H$^+$): 213. HRMS calcd for $C_{11}H_{14}O_2Cl$: 213.0682. Found: 213.0686. *Compound* **3b**: *(2R,4S)-2-(4-chlorophenyl)tetrahydro-2H-4-pyranol*: Solid, mp 69–71 °C, $[\alpha]_D^{25}$ +25.3 (*c* 1.0, $CHCl_3$, ee = 86%); IR (KBr): ν_{max} 3382, 2940, 2842, 1489, 1448, 1409, 1364, 1301, 1249, 1163, 1142, 1085, 1015, 987, 691, 885, 823, 717, 689, 594 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.3 Hz), 4.24 (dd, 1H, J = 2.2, 11.3 Hz), 4.14 (ddd, 1H, J = 2.2, 4.5, 12.0 Hz), 3.87 (m, 1H), 3.52 (dt, 1H, J = 2.2, 12.0 Hz), 2.15 (m, 1H), 2.01 (br s, 1H), 1.93 (m, 1H), 1.68–1.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 128.3, 127.3, 125.8, 73.8, 64.2, 62.8,40.6, 32.8; LCMS: (M+H$^+$): 213. HRMS calcd for $C_{11}H_{14}O_2Cl$: 213.0682. Found: 213.0688. *Compound* **2f**: *(2S,4S)-2-cyclohexyl-tetrahydro-2H-4-pyranol*: Liquid, $[\alpha]_D^{25}$ −9.9 (*c* 1.0, $CHCl_3$, ee = 88%); IR (KBr): ν_{max} 3388, 2938, 2848, 1458, 1372, 1251, 1147, 1083, 1045, 980, 874 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.19 (m, 1H), 3.78 (m, 1H), 3.68 (m, 1H), 3.40 (m, 1H), 1.92–1.42 (m, 5H), 1.34–0.83 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.6, 64.4, 58.8, 44.7, 39.5, 35.7, 31.0, 29.8, 25.6; LCMS: (M+H$^+$): 185. HRMS calcd for $C_{11}H_{21}O_2$: 185.1541. Found: 185.1546. *Compound* **3f**: *(2R,4S)-2-cyclohexyl-tetrahydro-2H-4-pyranol*: Liquid, $[\alpha]_D^{25}$ +9.6 (*c* 1.0, $CHCl_3$, ee = 86%); IR (KBr): ν_{max} 3275, 2927, 2851, 1448, 1364, 1320, 1123, 1071, 1040, 996 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.90 (dd, 1H, J = 4.7, 11.5 Hz), 3.61 (m, 1H), 3.24 (m, 1H), 2.89 (dd, 1H, J = 6.0, 11.1 Hz), 1.89–1.51 (m, 5H), 1.44–0.77 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.6, 64.4, 58.8, 44.7, 39.5, 35.7, 31.0, 29.8, 25.6; LCMS: (M+H$^+$): 185. HRMS calcd for $C_{11}H_{21}O_2$: 185.1541. Found: 185.1549. *Compound* **2i**: *(2R,4S)-2-(4-methylphenyl)tetrahydro-2H-4-pyranol*: Liquid, $[\alpha]_D^{25}$ −28.2 (*c* 1.0, $CHCl_3$, ee = 92%); IR (KBr): ν_{max} 3386, 2932, 2856, 1447, 1366, 1256, 1175, 1073, 970, 807 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17 (d, 2H, J = 8.3 Hz), 7.08 (d, 2H, J = 8.3 Hz), 4.80–4.66 (m, 1H), 4.40–4.24 (m, 1H), 4.01 (dt, 1H, J = 2.2, 12.0 Hz), 3.88 (ddd, 1H, J = 1.5, 5.3, 12.0 Hz), 2.32 (s, 3H), 1.99–1.87 (m, 1H), 1.85–1.77 (m, 1H), 1.66–1.59 (m, 1H), 1.59–1.54 (m, 1H); 13C NMR (75 MHz, $CDCl_3$): δ 138.9, 137.4, 129.1, 125.9, 78.3, 68.4, 66.4, 43.2, 35.4, 21.2; LCMS: (M+H$^+$): 193. HRMS calcd for $C_{12}H_{17}O_2$: 193.1228. Found: 193.1236. *Compound* **3i**: *(2R,4S)-2-(4-methylphenyl)tetrahydro-2H-4-pyranol*: Liquid, $[\alpha]_D^{25}$ +21.7 (*c* 1.0, $CHCl_3$, ee = 88%); IR (KBr): ν_{max} 3387, 2923,2851, 1493, 1365, 1250, 1139, 1083, 1014, 987, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (d, 2H, J = 8.3 Hz), 7.08 (d, 2H, J = 8.3 Hz), 4.21 (dd, 1H, J = 1.5, 12.0 Hz), 4.11 (ddd, 1H, J = 1.5, 4.5, 12.0 Hz), 3.83 (m, 1H), 3.51 (dt, 1H, J = 1.5, 12.0 Hz), 2.32 (s, 3H), 2.09 (m, 1H), 1.89 (m, 1H), 1.66–1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 137.4, 129.1, 125.9, 78.3, 68.4, 66.4, 43.2, 35.4, 21.2; LCMS: (M+H$^+$): 193. HRMS calcd for $C_{12}H_{17}O_2$: 193.1228. Found: 193.1230.

16. Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119.