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Daucus carota and baker's yeast mediated bio-reduction of prochiral ketones☆

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Abstract—Stereoselective reduction of prochiral ketones to the corresponding alcohols using biocatalysts has attracted much attention, from the viewpoint of green chemistry. Asymmetric reduction of indanone, tetralone and hydroxyl trimonoterpene ketones to the corresponding enantiomerically pure (*S*)-alcohols, using *Daucus carota* plant homogenate and fermented baker's yeast cells, is described. The present study illustrates the broad substrate selectivity of the dehydrogenase enzymes present in the *D. carota* in the synthesis of a wide range of chiral secondary alcohols of biological importance.

1. Introduction

Asymmetric reduction of prochiral ketones into chiral non-racemic secondary alcohols is a fundamental process in the synthesis of organic molecules of biological interest.[1] Chiral alcohols are versatile building blocks for a number of natural and unnatural compounds used in the synthesis of pharmaceuticals, agrochemicals, pheromones, flavors, fragrances and can also act as chiral auxiliaries in asymmetric synthesis of chiral molecules.[2] Though numerous chemical and biological methodologies are known in the synthesis of these secondary chiral alcohols, difficulties still remain in attaining high yields and enantiomeric excess due to the use of expensive chiral reagents (chemical /metal catalysts) and in isolation of pure product from reaction/fermentation medium.[3] Biocatalysts catalyze the reactions, in aqueous medium under mild and economically viable conditions, in a eco-friendly environment when compared to chemical (homogeneous and heterogeneous) or organo metallic catalysts used in chemical reactions.[4] Recently, plant cell cultures/cut carrot root homogenates have been used in transformation of the exogenous substrates.[5] In our earlier articles, we reported the reduction of prochiral ketones using *Daucus carota* homogenate as a further tool for the organic chemists in addition to baker's yeast cells in the synthesis of homochiral secondary alcohols.[6] Herein we report a non-conventional simple asymmetric bio-reduction of prochiral ketones to corresponding alcohols of biological importance.

2. Results and discussion

D. carota and baker's yeast cells show promising redox potential in catalyzing prochiral ketones, indanones, tetralone and terpenoids. Herein we explore the potential usefulness of the enzymes dehydrogenases in the reduction of carbonyl groups with broad substrate specificity and high yields to corresponding alcohols of biological significance.

2.1. Reduction of substituted 1-oximino indanones to substituted 1-amino-2-indanol

The asymmetric reductions of the substituted 1-oximino indanones **4a–d** and **10a–b** were carried out using *D. carota* or baker's yeast cells (Schemes 1 and 2) to obtain pure substituted *cis*-2-hydroxy-1-indanone-oximes **5a–d** and **11a–b**, with high stereoselectivities and yields. Thus the obtained oximes are subjected to hydrogenation to give the corresponding target molecule of substituted *cis*-(1*R*,2*S*)-1-amino-2-indanols **6a–d** and **12a–b** with excellent isolated yield, diastereoselectivity and enantiomeric excess (Table

☆ Part of the work granted US Patent.[6c]

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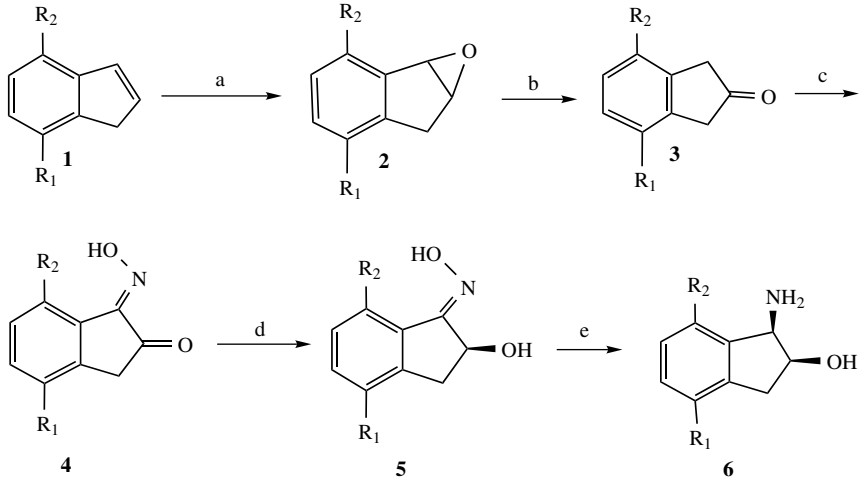
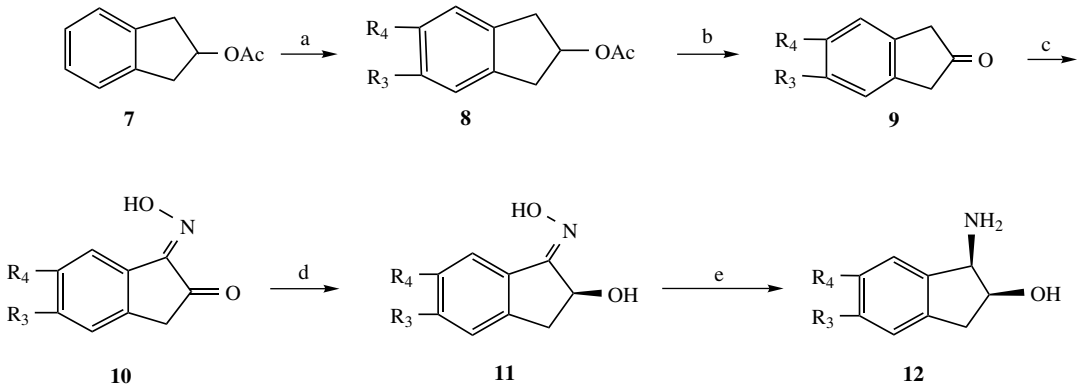


Scheme 1. Synthesis of substituted *cis*-1-amino-2-indanols: Reagents and conditions: (a) MCPBA, DCM, rt; (b) HNO_3, IBX; (c) isoamyl nitrite, TMSCl, −20 °C; (d) biocatalyst (*D carota* or Baker's yeast), 0.1 mM phosphate buffer, pH 6.5; (e) 10% Pd/C, H_2/MeOH. Compounds (**6a**) $R_1 = R_2 = H$; (**6b**) $R_2 = Me$; (**6c**) $R_1 = Me$; (**6d**), $R_2 = (CH_3)_2CH$.



Scheme 2. Synthesis of substituted *cis*-1-amino-2-indanols: Reagents and conditions: (a) NBS, (1 equiv) CH_3CN, 25 °C for mono bromo and NBS (2 equiv), Br_2 (1.1 equiv), CH_3CN 0–25 °C; (b) 10% aq NaOH, MeOH, 0–25°C; (2) IBX, CH_3CN, rt; (c) isoamyl nitrite, TMSCl, −20 °C; (d) biocatalyst (*D. carota* or Baker's yeast), 0.1 mM phosphate buffer, pH 6.5; (e) 10% Pd/C, H_2/MeOH. Compounds (**12a**) $R_3 = Br$; (**12b**) R_3, $R_4 = Br$.

Table 1. Reduction of substituted 2-indanones

Entry	Product	*Daucus carota*				Baker's yeast			
		Time (h)	Conversion (%)	ee%	Configuration	Time (h)	Conversion (%)	ee%	Configuration
1	**6a**	6	95	99	*S*	8	85	88	*S*
2	**6b**	18	75	98	*S*	20	72	90	*S*
3	**6c**	20	70	95	*S*	24	75	92	*S*
4	**6d**	28	45	90	*S*	72	60	77	*S*
5	**12a**	24	80	95	*S*	48	65	89	*S*
6	**12b**	24	75	96	*S*	48	65	91	*S*

(a) Absolute configuration was determined by optical rotation or by ^1H NMR by preparing Mosher esters of the products.

(b) The specific activity of the enzyme carbonyl reductase present in (i) *D. carota* 245 mmol min^{-1}, mg^{-1} protein (protein 15 μg/ml); (ii) yeast 465 mmol min^{-1}, mg^{-1} protein (protein 25 μg/ml).

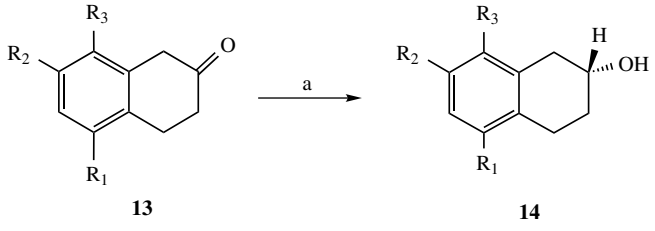
1). The stereochemistry of *cis*-(*S*)-2-hydroxy-1-indanone-oxime **5a** is confirmed by derivatising the compound to acetate to give (*E*)-(*S*)-2-acetoxy-1-acetoxyiminoindanol and the spectrum was compared with reported values,[7b] thus the obtained (*E*)-(*S*)-2-acetoxy-1-acetoxyiminoindanol recrystallized from ethyl acetate/hexane (5:95) gave white crystals. Mp 117–119 °C IR (neat): *v* 1778, 1765, 1633, 1603 1461, 1338, 1365, 1254, 1233, 1032, 924, 829. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.10 (s, 3H), 2.35 (s, 3H), 3.0 (d, 1H, $J = 17.5$ Hz), 3.60 (dd, 1H, $J = 7.5$, 17.5 Hz), 5.90 (m, 1H) multiplet for EH proton, 7.35 (t, 2H, $J = 7.8$ Hz), 7.48 (t, 1H, $J = 7.8$ Hz), 8.21 (d, 1H,

$J = 8.0$ Hz) EIMS: m/z: 206 M^+. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 63.04; H 5.32; N, 6.80. Specific rotation $[\alpha]_D^{25} = +65.5$ (c 0.8, MeOH), optical purity 96% ee.

From the results obtained (Table 1), it was observed that the *D. carota* plant homogenate shows good enantioselectivity in the chiral reduction of the indanones in comparison with yeast cells. This method provides an efficient route in the synthesis of enantiomerically pure 1-amino-2-indanol, which is somewhat difficult to obtain by chemical methods.[8] From the optical studies, it was concluded that the bio-reduction of *cis*-(*S*)-2-hydroxy-1-indanone-oxime to the corresponding secondary amino alcohols exclusively gave an (*S*)-configuration with yields ranging from 80% to 90%, diastereomeric purity of >95–98%. In comparison with the chemical synthesis of enantiomerically pure *cis*-1-amino-2-indanol, the use of *D. carota* root homogenate as a source of the biocatalyst for the bio-reduction processes is simple and economical, and showed high enantioselectivity.[9] The present methodology describes the synthesis/design of a number of natural/synthetic conventional chiral indole libraries and chiral ligands for advanced asymmetric reactions.[10]

2.2. Reduction of cyclic ketones (tetralones)

The enantioselective reductions of substituted 2-tetralone were studied using *D. carota* and yeast cells (Scheme 3). From the results obtained (Table 2), it was observed that the *D. carota* homogenate reduced compounds **13a–c** in modest yields (50–60%) and enantioselectivity (70–80%) with long incubation periods. In comparison with earlier studies on the bio-reduction of tetralones, the present study using *D. carota* homogenate and fermented yeast cells produced good yields and enantioselectivity.[11] The methodology developed is simple and easy in the synthesis of important chiral tetralols and is of great significance since some of these are key intermediates in the synthesis of biologically active molecules.[12]



13 **14**

Scheme 3. Synthesis of substituted tetralols. Reagents and conditions: (a) biocatalyst (*D. carota* or Baker's yeast), 0.1 mM phosphate buffer pH 6.5. Compounds (**14a**) R_1, R_2, $R_3 = H$; (**14b**) $R_2 = OCH_3$; (**14c**) $R_2 = R_3 = OCH_3$.

2.3. Reduction of monoterpene ketones

The monoterpenes of the *p*-menthane family are widely spread in Nature and exhibit significant biological activities such as perfumery, flavor and herbicide and in the pharmaceutical industry.[13] Biotransformation of monoterpene ketones **15**, **17** and **20** to the corresponding alcohols is studied (Scheme 4). It was observed from the results in Table 3 that the *D. carota* plant enzymes and yeast cells reduced both C–C double bonds and the carbonyl group present in the terpenoids pharmacophores **17** and **20**. Thus the enzyme present in *D. carota* and yeast cells showed broad substrate specificity, good yields (80–90%) and enantioselectivities (88–99%).

The bio reduction of the carbonyl groups studied by the carrot and baker's yeast cell systems proceeded stereoselectively, following Prelog's rule, which resulted in the predominant formation of (*S*)-alcohols.[14] The repetitive use of the carrot root homogenate was attempted on the biotransformation of the prochiral ketones, where it was observed that the bio-catalytic activity of the carrot root homogenate maintained after 3–4 consecutive reuses high chemical yields and enantiomeric excesses.[15] The use of *D. carota* in asymmetric bio-reduction was accompanied by several limitations such as the large biocatalyst to substrate (*B*/*S*) ratios, thus effecting conversion and commercial application. Work is currently in progress to overcome these difficulties by natural genetic transformation.[16]

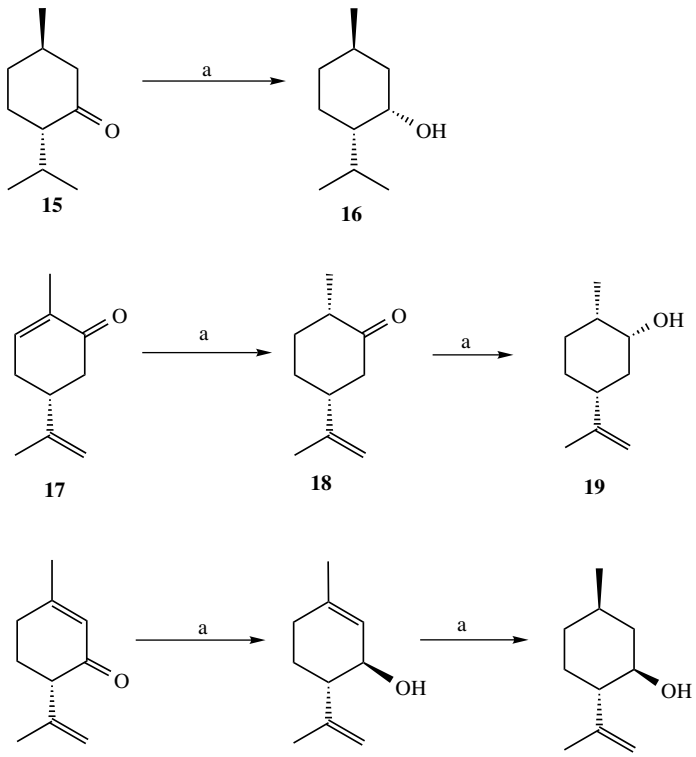
3. Conclusions

Bio-reduction catalyzed by dehydrogenases enzymes present in *D. carota* and yeast cells provides an attractive approach in selectively reducing a broad range of ketone substrates with excellent yields and selectivity. Intact cells from cut portion plants can mediate useful asymmetric transformations, thus offering new possibilities to synthetic chemists in terms of simplicity, efficiency and cost (in the absence of an external addition of coenzyme NAD (P) H to the medium). This methodology could also provide as a new tool for bio-reduction and exploitation of the biomass mainly towards production of functional molecules of biological importance.

Table 2. Reduction of cyclic ketones

Entry	Product	*Daucus carota*				Baker's yeast			
		Time (h)	Conversion (%)	ee%	Configuration	Time (h)	Conversion (%)	ee%	Configuration
1	**14a**	36	45	85	*S*	96	35	70	*S*
2	**14b**	40	40	70	*S*	72	30	70	*S*
3	**14c**	62	40	80	*S*	72	40	75	*S*

(a) Absolute configuration was determined by specific rotation or by ^{1}H NMR by preparing Mosher Esters of the products.
(b) The specific activity of the enzyme carbonyl reductase present in (i) *D. carota* 245 mmol min^{-1}, mg^{-1} protein (protein 15 μg/ml); (ii) yeast 465 mmol min^{-1}, mg^{-1} protein (protein 25 μg/ml).



Scheme 4. Synthesis of mono terpenols. Reagents and conditions: (a) biocatalyst (*D. carota* or Baker's yeast), 0.1 mM phosphate buffer pH 6.5.

Table 3. Reduction of terpenoid ketones

Entry	Product	*Daucus carota*				Baker's yeast			
		Time (h)	Conversion (%)	ee%	Configuration	Time (h)	Conversion (%)	ee%	Configuration
1	**16**	8	70	99	*S*	16	40	89	*S*
2	**19**	10	60	95	*S*	16	45	91	*S*
3	**22**	14	50	90	*S*	24	25	85	*S*

(a) Absolute configuration was determined by specific rotation or by ^{1}H NMR by preparing Mosher esters of the products.
(b) The specific activity of the enzyme carbonyl reductase present in (i) *D. carota* 245 mmol min^{-1}, mg^{-1} protein (protein 15 μg/ml); (ii) yeast 465 mmol min^{-1}, mg^{-1} protein (protein 25 μg/ml).
(c) Diastereoselectivity (*trans*/*cis*) ratio determined by GC/mass.

In summary, we have established an attractive, alternative, simple and convenient procedure for the preparation of both natural and unnatural secondary chiral alcohols under mild and eco-friendly conditions.

4. Experimental

All the chemicals and solvents used are of analytical/spectral grade obtained from commercial suppliers. Compound **4a** was prepared as shown in Scheme 1. The treatment of 1-oximination of 2-indanone **3** with TMSCl and isoamyl nitrite taken either neatly or in dichloromethane at −20 °C afforded 1-oximino-2-indanone **4a** in 80% yield. Compounds **4b–d** and **7a** were made according to the published procedures.[7,17] 5-Bromo 2-indanone **9a** was synthesized from indane-2-ol acetate **8a** with 1 equiv of NBS at −25 °C. Similarly, 5,6-dibromo 2-indanone **9b** was prepared from indane-2-ol acetate **8a** with 2 equiv of NBS in acetonitrile at 25 °C and subsequent hydrolysis with NaOH/oxidation (IBX) gave the bromo substituted 2-indanones. 7,8-Dimethoxy–2-tetralone **13c**, was synthesized according to the published procedure.[18] Isopiperitenone **20** was obtained by allylic oxidation of limonene with CrO_3–pyridine complex. Compounds **13a**, **13b**, **15** and **17** and limonene were obtained from Aldrich Chemicals, USA. *Saccharomyces cerevisiae* (baker's yeast) Type II was procured from Sigma Chemical Co., USA. *D. carota* (carrot) was purchased from local super market, and the carrot root cut into small graded pieces (approximately 4 mm long slices) for the study. Progress of the reduction reactions was followed by TLC and HPLC using normal phase column in a hexane/ethyl acetate (70:30) as a mobile phase at 254 nm wavelength. The products obtained were purified by silica gel (60–120 mesh) column chromatography using hexane: ethyl acetate (analytical grade) solvent system and the yields refer to purified homogeneous compounds unless otherwise stated. The products were fully characterized with specific rotation, mass, infrared spectra, ^{1}H and ^{13}C NMR spectra and the data obtained were used

to compare to those reported in the literature. The diastereomeric purity and enantiomeric excess of the chiral products obtained were determined either by GC/MS, 5% phenyl methyl silicone 30 m × 0.25 mm × 0.25 m thickness, carrier gas helium, or by HPLC using chiral column OD-H Daicel column (0.46 × 25 cm OD) with a mobile phase, hexane/isopropanol (85:15) at a wavelength of 254 nm. The absolute configurations of the chiral molecules were determined either by specific rotations or by the preparation of Mosher esters (MTPH) of the products. ^{1}H and ^{13}C NMR spectra are recorded in $CDCl_3$/DMSO solution using Varian Gemini-200/400/75 MHz NMR spectroscopy. Mass and IR spectra were recorded using VG, Micro mass 7070H and Nicolet-740, respectively. Optical rotations were taken on Jasco Dip-360 digital polarimeter.

4.1. *Daucus carota*

Freshly cut *D. carota* root pieces (10 g) were suspended in 100 mL of 0.1 mM sodium phosphate buffer pH 6.5. To this were added (200 mg) the ketones (indanones, tetralones and monoterpenoids) in 500 mL conical flask. The reaction was incubated in an orbital shaker (150 rpm) at room temperature for different time intervals. The progress of the reaction was monitored by TLC or by HPLC. On obtaining the optimal product formation, the reaction was terminated by filtering the carrot suspension and the filtrate was extracted with organic solvent (ethyl acetate, 3 × 100 mL), the organic phase separated, dried and concentrated in vacuum at low temperature. The product in the medium was extracted, purified and the chemical structure characterized. The specific activity of the dehydrogenase enzyme (enzyme known for reduction of ketones) present in the homogenate was determined by spectrophotometrically measuring the oxidation of NAD (P) H at 340 nm at room temperature. The protein concentration in the *D. carota* homogenate was measured by the Lowry method.[19]

4.2. Fermented yeast cells (*Saccharomyces cerevisiae*)

Lyophilized baker's yeast (2 g) was incubated in a nutrient medium containing sucrose (2 g), peptone (0.5 g), yeast extract (0.2 g) and $MgCl_2$/$ZnCl_2$ (0.1 g) dissolved in 0.1 mM sodium phosphate buffer, pH 6.5 (200 mL), and incubated at 28–37 °C for 24 h. The fermented cells were treated with allyl alcohol (20 mL), stirred for 3 h and later the solvent was decanted. To the treated fermented yeast cells, the aromatic ketones (500 mg) were added and incubated in an orbital shaker for their optimal product transformation. The final products were purified by flash chromatography and the structures confirmed by spectral data.

4.3. (*R*)-2-Hydroxy-1-indanone-oxime 5a

$[\alpha]_D^{25} = +48.2$ (*c* 0.8, MeOH); compared with opposite isomer values. lit.[7b] $[\alpha]_D^{25} = -55.0$ (*c* 1.0, MeOH). Solid mp 148–149 °C. IR (KBR): *v* 3220, 2900, 1604, 1461, 1428, 1306, 1042, 976, 734 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.80 (dd, 1H, $J = 2.6$, 17.5 Hz), 3.22 (dd, 1H, $J = 8.0$, 17.5 Hz), 4.60 (br s, 1H, OH), 4.78 (m, 1H), 7.10–7.30 (m, 3H), 8.25 (d, 1H, $J = 8.0$ Hz), 10.80 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 40.12, 76.47, 125.05, 127.98, 128.41, 128.82, 129.42, 138.02, 152.64 (EI) *m*/*z* 163 (M^+).

4.4. 7-Methyl (*R*)-2-hydroxy-1-indanone-oxime 5b

$[\alpha]_D^{25} = +58.5$ (*c* 0.7, MeOH). Solid mp 159–162 °C. IR (KBR): *v* 3231, 2882, 1621, 1469, 1452, 1329 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.4 (s, 3H), 2.71 (dd, 1H, $J = 2.5$, 17.2 Hz), 3.34 (dd, 1H, $J = 7.3$, 17.4 Hz), 4.35 (br s, 1H, OH), 4.50 (m, 1 H), 7.02–7.04 (m, 2H), 7.13 (dd, 1H, $J = 7.5$, 7.2 Hz) 11.1 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.4, 39.4, 79.0, 117.8, 124.7, 125.3, 126.9, 132.1, 138.56, 153.13; HRMS *m*/*z* calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0790; found, 177.0793.

4.5. 4-Methyl (*R*)-2-hydroxy-1-indanone-oxime 5c

$[\alpha]_D^{25} = +78.5$ (*c* 0.9, MeOH). Solid mp 165–167 °C. IR (KBR): *v* 3321, 2961, 1629, 1465, 1424, 1001, 651 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.63 (s, 3H), 2.83 (dd, 1H, $J = 2.4$, 17.3 Hz), 3.56 (dd, 1H, $J = 7.5$, 17.3 Hz), 4.42 (br s, 1H, OH), 4.62 (m, 1H), 7.05 (d, 1H, $J = 7.2$ Hz), 7.21–7.29 (m, 2H), 10.61 (s, 1H); ^{13} C NMR (75 MHz, DMSO-d_6): δ 21.4, 38.4, 78.0, 119.8, 123.7, 127.1, 129.1, 133.9, 139.3, 152.7; HRMS *m*/*z* calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0791; found, 177.0796.

4.6. 7-Isopropyl (*R*)-2-hydroxy-1-indanone-oxime 5d

$[\alpha]_D^{25} = +23.5$ (*c* 1, MeOH). Solid mp 204–206 °C. IR (KBR): *v* 3301, 2981, 1680, 1445, 1421, 1023, 750, 621 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.27 (d, 3H, $J = 6.6$ Hz), 1.32 (d, 3H, $J = 6.7$ Hz), 2.71 (dd, 1H, $J = 15.6$, 8.2 Hz), 3.17 (dd, 1H, $J = 15.5$, 7.7 Hz), 3.19–3.27 (m, 1H), 4.28 (br s, 1 H, OH), 4.37–4.41 (m, 1H), 7.15 (d, 1H, $J = 7.2$ Hz), 7.29 (d, 1H, $J = 7.8$ Hz), 7.4 (dd, 1H, $J = 7.5$, 7.5 Hz), 10.92 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.21, 31.9, 40.5, 79.8, 115.4, 119.1, 127.4, 129.2, 138.4, 139.9, 152.8; HRMS *m*/*z* calcd for $C_{12}H_{15}NO_2$ (M^+) 205.1103; found, 205.1107.

4.7. 5-Bromo (*R*)-2-hydroxy-1-indanone-oxime 11a

$[\alpha]_D^{25} = +39.5$ (*c* 0.6, MeOH). Solid mp 281–283 °C. IR (KBR): *v* 3300, 2989, 1645, 1445, 1433, 1049, 722 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.82 (dd, 1H, $J = 16.3$, 7.2 Hz), 3.23 (dd, 1H, $J = 16.3$, 6.1 Hz), 4.31 (br s, 1H, OH), 4.43–4.49 (m, 1H), 7.33 (s, 1H), 7.42 (d, 1H, $J = 7.6$ Hz), 7.57 (d, 1H, $J = 7.6$ Hz), 10.78 (s, 1H); ^{13} C NMR (75 MHz, DMSO-d_6): δ 38.5, 77.4, 119.9, 123.4, 128.7, 129.9, 130.2, 139.1, 151.6; HRMS *m*/*z* calcd for $C_9H_8BrNO_2$ (M^+) 240.9738; found, 240.9735.

4.8. 5,6-Di-bromo (*R*)-2-hydroxy-1-indanone-oxime 11b

$[\alpha]_D^{25} = +52.5$ (*c* 0.9 MeOH). Solid mp 261–263 °C. IR (KBR): *v* 3400, 2961, 2881, 1681, 1465, 1423, 1028, 633 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.63 (dd, 1H, $J = 16.4$, 5.6 Hz), 3.25 (dd, 1H, $J = 16.4$, 5.9 Hz), 4.39 (br s, 1H, OH), 4.47–4.49 (m, 1H), 7.61 (s, 1H), 8.42 (s, 1H), 11.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ

37.2, 76.4, 118.9, 122.4, 129.7, 132.5, 134.2, 140.1, 158.6; HRMS m/z calcd for $C_9H_7Br_2NO_2$ (M^+) 318.8844; found, 318.8850.

4.9. *cis*-1-Amino-2-indanol 6a

Liquid. IR (KBr): ν 3363, 2963, 1494, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.95 (dd, $J = 3.0$, 16.5 Hz for H^1), 3.10 ($J = 5.5$, 16.5 Hz)′ 4.30 (d, 1H, $J = 5.5$ Hz), 4.40 (m, 1H), 7.20–7.35 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.45, 64.39, 75.76, 124.39, 126.65, 127.48, 127.92, 138.39, 140.33. (EI) $m/z = 149$ M^+. Optical rotation $[\alpha]_D^{25} = +56.6$ (c 0.8, MeOH).

4.10. 7-Methyl-*cis*-1-amino-2-indanol 6b

Liquid: IR (KBr): ν 3313–2561, 1592, 1470, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.21 (br s, 3H), 2.42 (s, 3H), 2.91 (dd, 1H, $J = 15.7$, 7.7 Hz), 3.17 (dd, 1H, $J = 15.9$, 7.3 Hz), 4.31 (d, 1H, $J = 6.7$ Hz), 4.41 (ddd, $J = 7.2$, 7.2, 7.2 Hz) 7.01–7.03 (m, 2H), 7.13 (dd, 1H, $J = 7.7$, 7. 4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 39.2, 55.5, 71.1, 123.7, 128.57, 128.48, 134.4, 141.7, 143.5 EIMS: m/z; 163 M^+ $[\alpha]_D^{25} = -112.2$ (c 0.6, $CHCl_3$). lit.[18] $[\alpha]_D^{25} = -110.8$ ($c = 0.6$, $CHCl_3$).

4.11. 4-Methyl-*cis*-1-amino-2-indanol 6c

Liquid: IR (KBr): ν 3342, 1602, 1480, 1325, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.71 (dd, 1H, $J = 16.5$, 2.5 Hz), 3.0 (dd, 1H, $J = 16.2$, 5.5 Hz), 4.21 (d, 1H, $J = 5.2$ Hz), 4.31 (ddd, 1H, $J = 5.5$, 5.3, 2.5 Hz), 7.02 (d, 1H, $J = 7.2$ Hz), 7.23–7.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 37.9, 59.1, 71.9, 122, 128, 128.6, 133.9, 140.1, 144.4. EIMS m/z: 163 M^+ $[\alpha]_D^{25} = -29.6$ (c 0.7, $CHCl_3$). lit.[18] $[\alpha]_D^{25} = -30.7$ (c 0.9, $CHCl_3$).

4.12. 7-Isopropyl-*cis*-1-amino-2-indanol 6d

Liquid: IR (KBr): ν 3294, 1489, 1455, 1381, 1343, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, 3H, $J = 6.7$ Hz), 1.32 (d, 3H, $J = 6.7$ Hz), 2.32 (br s, 3H), 2.90 (dd, 1H, $J = 15.7$, 8.4 Hz), 3.12 (dd, 1H, $J = 15.7$, 7.6 Hz), 3.15–3.24 (m, 1H), 4.20 (br, d, 1H, $J = 6.6$ Hz), 4.36–4.38 (m, 1H), 7.05 (d, 1H, $J = 7.5$ Hz), 7.13 (d, 1H, $J = 7.6$ Hz), 7.24 (dd, 1H, $J = 7.6$, 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 24.1, 31.1, 39.2, 54.8, 70.0, 122.5, 123.8, 128.5, 139.5, 140.9, 145.6. EIMS m/z: 192 (M+1). $[\alpha]_D^{25} = -113.1$ (c 0.5, $CHCl_3$). lit.[18] $[\alpha]_D^{25} = -114.2$ (c 0.5, $CHCl_3$).

4.13. 5-Bromo-*cis*-1-amino-2-indanol 12a

Liquid: IR (KBr): ν 3293, 1592, 1450, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.82 (dd, 1H, $J = 16.1$, 2.5 Hz), 3.11 (dd, 1H, $J = 16.2$, 5.5 Hz), 4.23 (d, 1H, $J = 5.6$ Hz), 4.45 (ddd, 1H, $J = 5.7$, 5.4, 2.7 Hz), 6.91 (d, 1H, $J = 8.13$), 7.65 (s, 1H), 7.72 (d, 1H, $J = 8.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.63, 62.38, 76.74, 118.73, 122.88, 125.12, 129.38, 137.30, 139.57. EIMS: m/z: 230 (M^++2). $[\alpha]_D^{25} = -32.1$ (c 0.8, MeOH).

4.14. 5,6-Dibromo-*cis*-1-amino-2-indanol 12f

Liquid: IR (KBr): ν 3380, 1581, 1478, 1208, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.78 (dd, 1H, $J = 16.0$, 2.6 Hz), 3.8 (dd, 1H, $J = 16.1$, 5.6 Hz), 4.35 (d, 1H, $J = 5.7$ Hz), 4.42 (ddd, 1H, $J = 5.6$, 5.4, 2.6 Hz), 7.32 (s, 1H), 7.45 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.63, 64.19, 77.17, 120.42, 122.38, 127.57, 130.29, 139.19, 140.15. EIMS: m/z: 308 (M^++2), $[\alpha]_D^{25} = -33.5$ (c 1.5, $CHCl_3$).

4.15. 2-Tetralol 14a

Liquid: IR (KBr): ν 3450, 2922, 1609, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.74–1.88 (m, 1H), 2.01–2.12 (m, 2H), 2.79 (dd, 1H, $J = 16.4$, 7.9 Hz), 2.82–3.05 (m, 2H), 3.12 (dd, 1H, $J = 16.4$, 5.2 Hz), 4.15–4.21 (m, 1H), 7.08–7.18 (m, 4H). EIMS m/z: 148 M^+, $[\alpha]_D^{25} = -19.2$ (c 0.9, $CHCl_3$) lit.[11c] $[\alpha]_D^{25} = -20.8$ (c 0.25, $CHCl_3$).

4.16. 7-Methoxy-2-tetralol 14b

Liquid: IR (KBr): ν 3422, 2928, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.64 (s, OH), 1.70–1.88 (m, 1H), 1.99–2.07 (m, 1H), 2.72–2.83 (m, 2H), 2.88 (dt, 1H, $J = 16.6$, 5.8 Hz), 3.03 (dd, 1H, $J = 16.3$, 4.7 Hz), 3.77 (s, 3H), 4.08–4.19 (m, 1H) 6.62 (d, 1H, $J = 2.7$ Hz), 6.71 (dd, 1H, $J = 8.5$, 2.7 Hz), 7.05 (d, 1H, $J = 8.5$ Hz). EIMS: m/z: 178 M^+, $[\alpha]_D^{25} = +16.1$ (c 1.0, $CHCl_3$). lit.[11c] $[\alpha]_D^{25} = +16.3$ (c 0.23, $CHCl_3$).

4.17. 7,8-Dimethoxy-2-tetralol 14c

Liquid IR (KBr): ν 3388, 2938, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.71–1.84 (m, 2H), 1.98–2.05 (m, 1H), 2.68 (dd, H, $J = 18.0$, 7.6 Hz), 2.77 (ddd, 1H, $J = 16.6$, 8.9 and 5.8 Hz), 2.89 (dt, 1H, $J = 16.5$ and 5.7 Hz), 3.18 (dd, 1H, $J = 17.1$ and 5.7 Hz), 3.72 (s, 3H), 3.88 (s, 3H), 4.05–4.18 (m, 1H), 6.75 (d, 1H), 6.84 (d, 1H, $J = 8.6$ Hz). EIMS: m/z: 208 M^+ $[\alpha]_D^{25} = +19.1$ (c 0.43, $CHCl_3$). lit.[11c] $[\alpha]_D^{25} = +18.1$ ($c = 0.41$, $CHCl_3$).

4.18. Neomenthol 16

Liquid IR (KBr): ν 3381, 2952, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ, 0.81 (s, 3H), 1.21 (s, 3H), 1.34 (s, 3H), 2.49 (m, 1H), 2.52 (m, 1H), 2.70 (m, 1H), 3.12 (s, OH). EI: m/z: 156 (M^+). $[\alpha]_D^{25} = -21.2$ (c 0.2 $CHCl_3$).[13]

4.19. Sodihydrocarvone 18

Liquid IR (KBr): ν 1681, 1708, 2980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (s, 3H), 1.69 (s, 3H), 2.00 (m, 1H), 2.25 (m, 1H), 4.79 (m, 1H), 4.81 (m, 1H); EIMS: m/z: 152 M^+. $[\alpha]_D^{25} = -34$ (c 0.5, $CHCl_3$).[13]

4.20. Neoisodihydrocarveol 19

Liquid; IR (KBr): ν 3388, 1680, 2948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (s, 3H), 1.70 (s, 3H), 1.81 (m, 1H), 2.60 (m, 1H), 2.72 (m, 1H), 3.11 (s, OH), 4.75 (m,

1H), 4.78 (m, 1H). EIMS: m/z: 154 M^+ $[\alpha]_D^{25} = -18.1$ (c 0.7, $CHCl_3$). lit.[13] $[\alpha]_D^{25} = -20.0$ (c 0.2 EtOH).

4.21. Isopiperitenol 21

Liquid. IR (KBr): ν 3341, 2981, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 156 (s, 3H), 1.78 (s, 3H), 2.60 (s, OH), 2.34 (m, 1H), 4.83 (m, 1H), 5.17 (m, 1H), 5.73 (m, 1H). EIMS: m/z: 152 M^+. $[\alpha]_D^{25} = -41.1$ (c 0.5, $CHCl_3$).[13]

4.22. Isopulegol: liquid 22

IR (KBr): ν 3341, 2981, 1650 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (s, 3H), 1.52 (s, 3H), 1.62 (m, 1H), 1.82 (m, 1H), 2.40 (s, OH), 3.72 (s, 3H), 4.93 (m, 1H), 4.98 (m, 1H). EIMS m/z: 154 M^+. $[\alpha]_D^{25} = -22.1$ (c 0.9, $CHCl_3$) lit.[14] $[\alpha]_D^{25} = -13.4$ (c 1.0, $CHCl_3$).

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