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First asymmetric synthesis of both enantiomers of Tropional® and their olfactory evaluation

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Abstract—The first asymmetric synthesis of both enantiomers of Tropional® is accomplished by asymmetric alkylation by employing the SAMP/RAMP-hydrazone method, respectively. The alkylated hydrazones were oxidatively cleaved with magnesium-monoperoxyphthalate (MMPP). Subsequent reduction of the resulting nitriles with diisobutyl aluminium hydride (DIBAL-H) led to the desired aldehydes in good overall yields (52–53%) and enantiomeric excesses (ee = 90%). Furthermore, the olfactory evaluation of both enantiomers showed remarkable differences in odour quality and intensity.

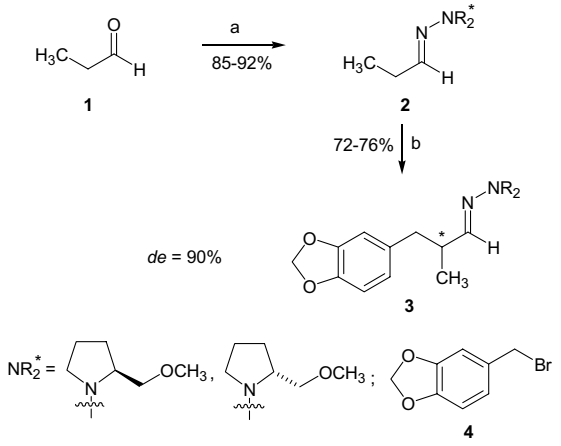
1. Introduction

Many well-known odourants are chiral compounds with their enantiomers sometimes exhibiting totally different scents [e.g., (+)-carvone: caraway; (−)-carvone: spearmint] and odour thresholds. Brenna et al. recently published a review about the enantioselective perception of chiral odourants.[1] Tropional® is an α-branched aldehyde, which is used in many perfumes that present a marine, fresh note.[2] In industry it is produced as a racemate via aldol condensation of piperonal and propanal and subsequent hydrogenation[3] with an annual production of about 300–350 tons.[4] To the best of our knowledge no asymmetric synthesis of Tropional® has been published. Furthermore nothing is known about the odour of the two enantiomers, although the human receptor for the recognition of Tropional® has been known for a few years.[5] Today this class of α-branched aldehydes is of considerable interest, as some promote the directed migration of sperm to the egg, and so may allow fertilization to be manipulated.[6]

2. Results and discussion

2.1. Asymmetric synthesis of Tropional®

Herein, we report the asymmetric synthesis of both enantiomers of Tropional® via an efficient four step synthesis employing our SAMP/RAMP-hydrazone methodology.[7] The synthesis of hydrazones **2** was achieved by reaction of freshly distilled propanal **1** with the corresponding hydrazines in good yields using standard conditions (Scheme 1).[8]



Scheme 1. Synthesis of the alkylated hydrazones **3**. Reagents and conditions: (a) $H_2NNR_2^*$, molecular sieves; (b) base, THF, **4** (Table 1).

In our first attempt, hydrazone **2** was deprotonated with lithium diisopropylamide (LDA) and reacted with 5-(bromomethyl)-1,3-benzodioxole **4** in THF at −78 °C. This reaction led only to a moderate diastereomeric excess of de = 74%. As it was not possible to determine the diastereomeric excesses of this reaction by NMR or

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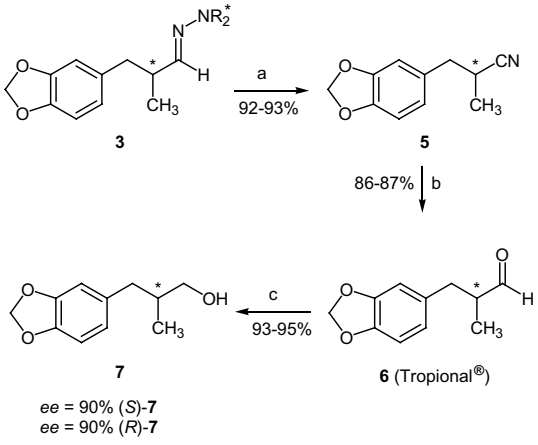
Table 1. Variation of the α-alkylation conditions

Entry	Hydrazone	Base	Temperature (°C)	Product	Yield	$[\alpha]_D^{24}$	De (%)[a]
1	(*S*)-**2**	LDA	−78	(*S*)-**3**	65	—	74
2	(*S*)-**2**	LDA	−100	(*S*)-**3**	76	+43.7	90
3	(*R*)-**2**	LDA	−100	(*R*)-**3**	71	−44.7	90
4	(*S*)-**2**	LTMP	−100	(*S*)-**6**	37[b]	—	89

[a] Determined by chiral stationary phase HPLC of the corresponding alcohols **7**.
[b] Direct conversion of the crude hydrazone (*S*)-**3** to aldehyde (*S*)-**6**.

HPLC, the selectivity was proven by HPLC on a chiral stationary phase of the corresponding alcohols **7**. In order to improve the diastereomeric excess, the temperature was lowered to −100 °C. This resulted in an increase of the observed diastereomeric excess to de = 90% (Table 1, entries 2 and 3). The change of the lithium base from LDA to lithium tetramethylpiperidide (LTMP) led to no significant change in the diastereomeric excess. A change of the solvent from THF to Et_2O also proved ineffective due to low solubility of bromide **4**.

For cleavage of the hydrazones, a great variety of methods are available.[9] As the cleavage with ozone was not successful, the 'salt method' was applied. Similar to the preparation of Lilial®, the desired aldehyde was obtained by refluxing hydrazones **3** in methyl iodide with subsequent hydrolysis in a two-phase system of 4 M aqueous HCl and pentane.[10] Unfortunately this procedure only gave moderate yields. The direct hydrolysis of the hydrazones in a two-phase system of 4 M aqueous HCl and pentane resulted in a significant drop in enantiomeric excess to ee = 79%. However, cleavage was successful by utilizing a two step procedure (Scheme 2).[11]



Scheme 2. Synthesis of Tropional® by cleavage of the hydrazones **3**. Reagents and conditions: (a) MMPP, MeOH, pH 7 buffer, 0 °C; (b) DIBAL-H, THF, 0 °C; (c) $BH_3 \cdot Et_2O$.

In the first step the N,N-bond was cleaved under oxidative conditions with MMPP to give nitriles **5** in very good yields. After reduction with DIBAL-H in THF at 0 °C, both enantiomers of Tropional® **6** could be obtained in 80% yield over two steps. To determine the enantiomeric excess, the aldehydes were reduced to the corresponding alcohols by employing $BH_3 \cdot DMS$ in Et_2O. At this stage the enantiomeric excess could be determined by HPLC on a chiral stationary phase to be ee = 90%. The absolute configuration of **6** was based on the general stereochemical outcome of the asymmetric-alkylation employing SAMP/RAMP hydrazones as chiral auxiliaries.[7]

2.2. Olfactory evaluation

The enantiomers of Tropional® **6** showed different odour characteristics (Table 2). Regarding the odour intensity the (*S*)-enantiomer (*S*)-**6** was about five times stronger than the (*R*)-enantiomer (*R*)-**6**. With respect to the odour quality some striking differences were also detected.

Table 2. Olfactory evaluation of both enantiomers of Tropional®

	(*S*)-Tropional®	(*R*)-Tropional®
Yield (%)[a]	53	90
Ee (%)[b]	90	90
$[\alpha]_D^{22}$	−2.8	+3.3
Odour description	• Green floral	• Floral (cyclamen/ lily of the valley)
	• Marine, ozone like	• Aldehydic
	• Cumin like	• Citrus like
Odour threshold value	0.64 ng/L	3.43 ng/L

[a] Overall yield.
[b] Determined by chiral stationary phase HPLC of the corresponding alcohols **6**.

The (*S*)-enantiomer exhibited a green-floral odour with a marine and ozone like note reminiscent of saltwater, as well as a sweet fruity cumin like scent. Thus, the (*S*)-enantiomer represented the typical odour of the industrially used racemate of Tropional®. In contrast, the (*R*)-enantiomer showed a floral scent reminding on cyclamen and lily of the valley. Furthermore this enantiomer smelled aldehydic with a sweet fruity citrus like note.[4]

It is worth mentioning, that the marine scent—typical for racemic Tropional®—was completely missing. Moreover, compared with the similar aldehyde Lilial®, also prepared in our group,[10] the odour intensity of the single enantiomers was different. Whereas in the case of Lilial® the (*R*)-enantiomer exhibited a slightly stronger scent, the (*S*)-enantiomer of Tropional® showed a remarkably stronger odour and the differences in odour quality were more considerable, too.

3. Conclusion

In summary, we have successfully applied our hydrazone-alkylation strategy in the first asymmetric synthesis of Tropional® **6**. Both enantiomers were obtained in good yields and high enantiomeric excesses. The olfactory evaluation showed remarkable differences in odour intensity as well as in odour quality between both enantiomers. Obviously, the scent of the industrially used racemic Tropional® is determined mainly by the (*S*)-enantiomer.

4. Experimental

4.1. General

n-Butyllithium (1.6 M in hexane) was purchased from Merck, Darmstadt. DIBAL-H (1.0 M in dichloromethane) and BH_3·DMS (2.0 M in THF) were purchased from Aldrich. SAMP/RAMP[8] and 5-(bromomethyl)-1,3-benzodioxole[12] **4** were prepared according to the literature. All reactions employing organometallic compounds were carried out under argon using standard *Schlenk* techniques. IR spectra were recorded on a Perkin–Elmer 1760 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 MHz and 75 or 100 MHz, respectively, on Varian Mercury 300 or Varian Inova 400 spectrometers.[3] $J_{H,H}$ coupling constants are expressed in Hz. All measurements were performed in $CDCl_3$ and chemical shifts expressed in ppm (δ) with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Finnigan SSQ 7000. Optical rotations were measured on a Perkin–Elmer P 241 polarimeter. Elemental analyses were carried out on Elementar Vario EL. Determination of the enantiomeric excesses was accomplished by analytical HPLC on a chiral stationary phase using a Hewlett Packard 1050 with UV-detector (DAD) utilizing a Chiracel OD (250 mm × 4.6 mm), as eluent a mixture of *n*-heptane/*i*-propanol 95/5 was employed.

4.2. Asymmetric synthesis of Tropional®

4.2.1. *N*-[(*R*)-2-methoxymethylpyrrolidin-1-yl]propan-1-imine (*R*)-2. To a mixture of 10.221 g (78.5 mmol) of RAMP and molecular sieves (4 Å) 7.5 mL (101.9 mmol) of freshly distilled propanal **1** were added slowly at 0 °C. The reaction was stirred overnight at room temperature and diluted with Et_2O. After filtration, the solvent was evaporated under reduced pressure and the hydrazone (*R*)-**2** (11.332 g, 66.6 mmol, 85%) obtained as a colourless oil by distillation in vacuo bp = 54–56 °C (1 mbar). $[\alpha]_D^{23} = +144.5$ (*c* 1.59, $CHCl_3$). {Lit.[8] $[\alpha]_D^{25} = +148.3$ (neat)}. ^{1}H NMR (300 MHz): δ 1.05 (t, 3H, $J = 7.6$), 1.75–1.97 (m, 4H), 2.23 (dq, 2H, $J = 5.4/7.6$), 2.71 (m, 1H), 3.39 (m, 3H), 3.38 (s, 3H), 3.57 (m, 1H), 6.65 (t, 1H, $J = 5.4$). ^{13}C NMR (75 MHz): δ 12.13, 22.17, 26.43, 26.62, 50.44, 59.19, 63.52, 74.89, 140.40. The spectroscopic data correspond with those of the literature.[8]

4.2.2. *N*-[(*S*)-2-methoxymethylpyrrolidin-1-yl]propan-1-imine (*S*)-2. The enantiomeric hydrazone was prepared in the same way as (*R*)-**2** by reaction of 20.277 g (155.7 mmol) of SAMP and 14.0 mL (190.2 mmol) of propanal **1** yielding 24.451 g (143.6 mmol, 92%) of hydrazone (*S*)-**2**. $[\alpha]_D^{23} = -143.3$ (*c* 1.11, $CHCl_3$). {Lit.[8] $[\alpha]_D^{25} = -145.2$ (neat)}. The spectroscopic data correspond with those of the literature.[8]

4.2.3. (2*R*)-3-(1,3-Benzodioxole-6-yl)-*N*-[(*R*)-2-methoxymethylpyrrolidin-1-yl]-2-methyl-propan-1-imine (*R*,*R*)-3. To a solution of 11.2 mmol of lithium diisopropylamide [LDA, prepared from 1.6 mL (11.3 mmol) diisopropyl-amine and 7.0 mL (11.2 mmol) *n*-butyllithium in 20 mL of anhydrous THF at 0 °C] 1.698 g (10.0 mmol) of the hydrazone (*R*)-**3** was slowly added and the reaction stirred for 3.5 h at 0 °C. After cooling to −100 °C, 2.276 g (10.6 mmol) of 5-(bromomethyl)-1,3-benzodioxole **4** dissolved in 5 mL anhydrous THF was added very slowly. The reaction was allowed to warm to room temperature overnight. After addition of satd aq NH_4Cl solution (10 mL) the two layers were separated and the aqueous layer extracted with Et_2O. The combined organic layers were washed with satd aq $NaHCO_3$ solution, brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (silica, pentane–Et_2O 4:1 + 5% NEt_3) and the hydrazone (*R*,*R*)-**3** (2.321 g, 7.6 mmol, 76%) obtained as a colourless oil. R_f (silica, pentane–Et_2O, 4:1): 0.38. De ⩾90% (HPLC of the corresponding alcohol (*R*)-**6**). $[\alpha]_D^{24} = +43.7$ (*c* 1.17, $CHCl_3$). ^{1}H NMR (400 MHz): δ 1.01 (d, 3H, $J = 6$), 1.78 (m, 1H), 1.89 (m, 3H), 2.47 (dd, 1H, $J = 8.1/13.4$), 2.55 (m, 1H), 2.66 (q, 1H, $J = 8.2$), 2.77 (dd, 1H, $J = 6.2/13.4$), 3.35 (m, 3H), 3.37 (s, 3H), 3.55 (dd, 1H, $J = 3.9/9.1$), 5.89 (s, 2H), 6.52–6.71 (m, 4H). ^{13}C NMR (100 MHz): δ 18.28, 22.06, 26.51, 38.76, 41.37, 50.21, 59.06, 63.31, 74.62, 100.51, 107.71, 109.44, 121.87, 133.99, 142.31, 145.37, 147.15. MS (EI): *m*/*z* (%) 304 (22, M^+), 260 (17), 259 (100), 170 (9), 169 (95), 160 (27), 135 (15), 70 (11). IR (film): $\nu = 2964$, 2881, 1490, 1443, 1341, 1247, 1194, 1120, 1040, 930, 809. Anal. Calcd for $C_{17}H_{24}O_3N_2$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.95; H, 7.68; N, 9.59.

4.2.4. (2*S*)-3-(1,3-Benzodioxole-6-yl)-*N*-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-2-methyl-propan-1-imine (*S*,*S*)-3. The enantiomeric hydrazone was prepared in the same way as (*R*,*R*)-**3** by reaction of 11.2 mmol of lithium diisopropylamide, 1.669 g (10.0 mmol) of hydrazone (*S*)-**3** and 2.195 g (10.2 mmol) of 5-(bromomethyl)-1,3-benzodioxole **4** to obtain hydrazone (*S*,*S*)-**3** (2.171 g, 7.1 mmol, 71%). De ⩾90% (HPLC of the corresponding alcohol (*S*)-**6**). $[\alpha]_D^{24} = -44.7$ (*c* 1.27, $CHCl_3$). The spectroscopic data correspond with those of the enantiomeric hydrazone (*R*,*R*)-**3**.

4.2.5. (2*R*)-2-Amino-3-(1,3-benzodioxole-5-yl)propannitrile (*R*)-5. A solution of 1.669 g (5.5 mmol) of hydrazone (*R*,*R*)-**3** in methanol (33 mL) was added dropwise to a suspension of pH 7 buffer (44 mL) and 6.826 g

(13.8 mmol) of MMPP at 0 °C. After the addition was complete, the reaction was stirred for 2 h at 0 °C and then finally diluted with 110 mL of Et_2O. The two layers were separated and the aqueous layer extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and after filtration and evaporation of the solvent, the residue was purified by column chromatography (silica, pentane–Et_2O 4:1). Nitrile (*R*)-**5** (0.971 g, 5.5 mmol, 93%) was obtained as a colourless liquid. R_f (silica, pentane–Et_2O, 4:1): 0.46. Ee $\geqslant$90% (HPLC of the corresponding alcohol (*R*)-**7**). $[\alpha]_D^{24} = -34.8$ (*c* 1.32, $CHCl_3$). ^{1}H NMR (300 MHz): δ 1.31 (d, 3H, $J = 6.9$), 2.79 (m, 3H), 5.95 (s, 2H), 6.23–6.78 (m, 3H). ^{13}C NMR (75 MHz): δ 17.52, 27.79, 39.74, 101.07, 108.42, 109.31, 122.24, 122.49, 130.55, 146.80, 147.86. MS (EI): *m*/*z* (%) 189 (22, M^+), 136 (10), 135 (100), 77 (12), 51 (7). IR (film): $\nu = 2934$, 2899, 1493, 1445, 1250, 1194, 1103, 1040, 931, 815. Anal. Calcd for $C_{11}H_{11}O_2N$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.86; N, 7.84.

4.2.6. (2*S*)-2-Amino-3-(1,3-benzodioxole-5-yl)propannitrile (*S*)-5. The enantiomeric nitrile was prepared in the same way as (*R*)-**5** by reaction of 8.063 g (16.3 mmol) of MMPP in pH 7 buffer (52 mL) and 1.979 g (6.5 mmol) of the hydrazone (*S*,*S*)-**3** in methanol (33 mL) to obtain nitrile (*S*)-**5** (1.139 g, 6.0 mmol, 92%). Ee $\geqslant$90% [HPLC of the corresponding alcohol (*S*)-**7**]. $[\alpha]_D^{24} = +35.2$ (*c* 0.88, $CHCl_3$). The spectroscopic data correspond with those of the enantiomeric nitrile (*R*)-**5**.

4.2.7. (2*R*)-3-(1,3-Benzodioxole-5-yl)-2-methylpropanal (*R*)-6 [(*R*)-Tropional®]. To a solution of 0.971 g (5.1 mmol) of nitrile (*R*)-**5** in anhydrous THF (10 mL), 7.7 mL (7.7 mmol) of DIBAL-H in dichloromethane were added via a syringe pump over 30 min at 0 °C. The cooling bath was removed and the reaction stirred for another 2 h at room temperature. It was then poured into a mixture of 25 mL of a solution of tartaric acid (25 mL, 1 M) and 10 mL Et_2O (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and after evaporation of the solvent the residue was purified by column chromatography (silica, pentane–Et_2O 4:1). Aldehyde (*R*)-**6** (0.857 g, 4.4 mmol, 86%) was obtained as a pale yellow liquid. R_f (silica, pentane–Et_2O, 4:1): 0.51. Ee $\geqslant$90% (HPLC of the corresponding alcohol (*R*)-**7**). $[\alpha]_D^{24} = +3.3$ (*c* 0.98, $CHCl_3$). ^{1}H NMR (300 MHz): δ 1.07 (d, 3H, $J = 6.9$), 2.59 (m, 2H), 2.99 (dd, 1H, $J = 5.6/13.3$), 5.91 (s, 2H), 6.59–6.74 (m, 3H), 9.69 (d, 1H, $J = 1.5$). ^{13}C NMR (75 MHz): δ 13.17, 36.39, 48.19, 100.91, 108.24, 109.30, 121.94, 132.52, 146.11, 147.75, 204.34. MS (EI): *m*/*z* (%) 192 (34, M^+), 136 (9), 135 (100), 122 (6), 105 (5), 77 (10), 51 (6). IR (film): $\nu = 2971$, 2895, 1725, 1492, 1444, 1364, 1248, 1193, 1124, 1101, 1039, 932, 813. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.58; H, 6.27.

4.2.8. (2*S*)-3-(1,3-Benzodioxole-5-yl)-2-methylpropanal (*S*)-6 [(*S*)-Tropional®]. The enantiomeric aldehyde was prepared in the same way as (*R*)-**6** by reaction of 1.139 g (6.0 mmol) of nitrile (*S*)-**5** and 9.0 mL (9.0 mmol) of DIBAL-H in dichloromethane to obtain aldehyde (*S*)-**6** (0.944 g, 5.2 mmol, 87%). Ee $\geqslant$90% [HPLC of the corresponding alcohol (*S*)-**7**]. $[\alpha]_D^{24} = -2.8$ (*c* 1.07, $CHCl_3$). The spectroscopic data correspond with those of the enantiomeric aldehyde (*R*)-**6**.

4.2.9. (2*R*)-3-(1,3-Benzodioxole-5-yl)-2-methylpropan-1-ol (*R*)-7. To a solution of 0.217 g (1.13 mmol) of aldehyde (*R*)-**6** in anhydrous THF (11 mL), 2.80 mL (5.60 mmol) of a solution of BH_3·DMS in THF were added slowly at 0 °C. After stirring for 45 min at 0 °C 4 M HCl (11 mL) was slowly added, the cooling bath removed and the reaction was stirred for another 2 h at room temperature. The organic layer was separated and the aqueous layer extracted with Et_2O. The combined organic layers were washed with satd aq sodium thiosulfate solution and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography (silica, pentane–Et_2O 1:1) and alcohol (*R*)-**7** (0.208 g, 1.07 mmol, 95%) obtained as a colourless liquid. R_f (silica, pentane–Et_2O, 1:1): 0.35. Ee $\geqslant$90% (HPLC, $t_R = 22.9$ min). $[\alpha]_D^{22} = +11.1$ (*c* 0.98, $CHCl_3$). ^{1}H NMR (400 MHz): δ 0.90 (d, 3H, $J = 6.6$), 1.51 (s, 1H), 1.88 (m, 1H), 2.34 (dd, 1H, $J = 8.0/13.7$), 2.67 (dd, 1H, $J = 6.3/13.5$), 3.48 (m, 2H), 5.91 (s, 2H), 6.60–6.73 (m, 3H). ^{13}C NMR (100 MHz): δ 16.38, 37.84, 39.33, 67.42, 100.59, 107.87, 109.29, 121.71, 134.21, 145.43, 147.28. MS (EI): *m*/*z* (%) 194 (28, M^+), 136 (29), 135 (100), 105 (5), 77 (9), 51 (5). IR (film): $\nu = 3367$, 2956, 2918, 1491, 1442, 1361, 1247, 1191, 1125, 1101, 1039, 935, 865, 808, 771. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.16; H, 7.55.

4.2.10. (2*S*)-3-(1,3-Benzodioxole-5-yl)-2-methylpropan-1-ol (*S*)-7. The enantiomeric alcohol was prepared in the same way as (*R*)-**7** by reaction of 0.213 g (1.11 mmol) of aldehyde (*S*)-**6** and 2.80 mL (5.60 mmol) of BH_3·DMS in THF to obtain alcohol (*S*)-**7** (0.201 g, 1.03 mmol, 93%). Ee $\geqslant$90% (HPLC, $t_R = 25.0$ min). $[\alpha]_D^{22} = -11.0$ (*c* 1.07, $CHCl_3$). The spectroscopic data correspond with those of the enantiomeric alcohol (*R*)-**7**.

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