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Synthesis and odor of optically active rose oxide

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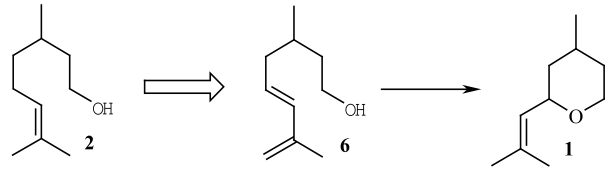
Abstract—Stereoselective synthesis of optically active rose oxide (**1**) by $KHSO_4$ and Pd–BINAP-catalyzed cyclization of (3*R*)- and (3*S*)-3,7-dimethyl-6,7-octadien-1-ol (**5**) is described. One-pot synthesis of the (3*R*)- and (3*S*)-allenyl alcohol **5** from (3*R*)- and (3*S*)-citronellol (**2**) (98% ee) is also described. Furthermore, the odor properties of the four diastereomers of **1** are reported. © 2002 Published by Elsevier Science Ltd.

Since rose oxide **1** was isolated from Bulgarian rose oil in 1959[1] for the first time, the four diastereomers have been identified in many plants, flowers and fruits such as Eucalyptus citriodora, geranium and tropical fruit, etc.,[2] and assumed to be responsible for the floral green top notes. Among the four diastereomers, the *l*-isomers {*l*-*cis*-**1**: (2*S*,4*R*)-**1** and *l*-*trans*-**1**: (2*R*,4*R*)-**1**} occur more profusely in nature, and the *l*-*cis*-**1** is found as the main component.[3] Ohloff et al.[4] already studied the odor properties of this important fragrance raw material; however, this seems to be inconclusive, because of the insufficient chemical and enantiomeric purities for a detailed evaluation.

The major synthetic strategy for **1** in many literature sources[5] has been focused on a pathway involving synthesizing 3,7-dimethyl-5,7-octadien-1-ol (**6**) from citronellol (**2**), followed by cyclization as shown in Scheme 1.



Scheme 1.

As one of the elegant similar selective cyclizations of an allenyl intermediate for **1**, only one study[6] of $HgCl_2$-catalyzed cyclization of 3,7-dimethylocta-5,6-dien-1-ol (**5**) has been reported. However, the synthesis of the allenyl alcohol **5** needed multi-step reactions and seems to be troublesome from a practical point of view as shown in Scheme 2.

We wish to report here a practical one-pot synthesis of the (3*S*)- and (3*R*)-allenyl alcohol **5** and stereoselective cyclization of the allenyl alcohol **5** to the diastereomers of **1** by $KHSO_4$ and Pd–BINAP catalysts and also the odor properties of the four diastereomers of **1**.[7]

As one approach to a practical synthesis, we successfully tried a simple one-pot synthesis of the (3*S*)-allenyl alcohol **5** starting from the (3*S*)-citronellol {(3*S*)-**2**}[8,9] as shown in Scheme 3. The reaction mixture of the (3*S*)-6,7-dibromo-3,7-dimethyloctan-1-ol {(3*S*)-**3**} produced by bromination of the (3*S*)-**2** was directly treated with KOH to yield the (3*S*)-**5**[10] via the (3*S*)-6-bromo-3,7-dimethyl-6-octen-1-ol {(3*S*)-**4**},[10] which can be selectively yielded by controlling reaction conditions such as the amounts of KOH relative to (3*S*)-**3** and the reaction temperature, etc.

Regarding the cyclization of (3*S*)-**5**, the result obtained by the cyclization using $KHSO_4$ catalyst was almost the same as the result[6] obtained with the $HgCl_2$ catalyst giving *l*-*cis*-**1** as the main product.

A typical procedure is as follows; bromine (159.8 g, 1.0 mol) was added dropwise to a suspension of Na_2CO_3 (1.56 g) and (3*S*)-**2**[11] (98% ee, 156 g, 1.0 mol) with stirring at 5–10°C for **3** h, followed by stirring for 1 h

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Keywords: diastereomer; rose oxide; odor; cyclization; (3*R*)- and (3*S*)-citronellol; (3*R*)- and (3*S*)-3,7-dimethyl-5,6-octadien-1-ol; Pd–(*R*)- and (*S*)-BINAP complexes.

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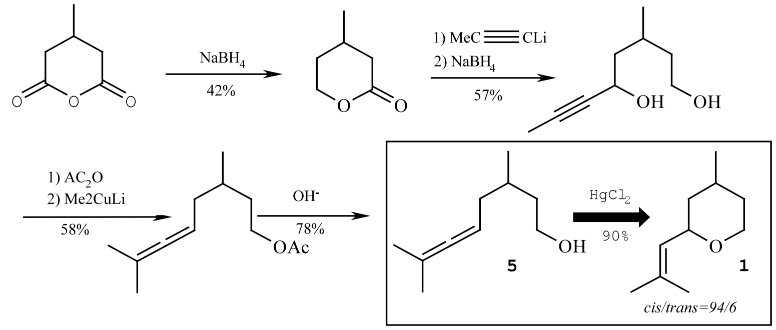


Scheme 2.

to complete the reaction. After acetonitrile (1.6 L) and Aliquat™ (3.12 g) were added to the reaction mixture at room temperature, KOH powder (224 g) was added over 30 minutes under a nitrogen atmosphere. The mixture was then heated at reflux for 16 h. After removal of acetonitrile in vacuo, the residue was combined with hexane (600 mL), and the solution was neutralized with 5% hydrochloric acid. The hexane layer was separated out, washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo to give the crude (3*S*)-**5** (158 g, GC; 80%) which was subjected to cyclization without any purification. That is, toluene (223 g) and $KHSO_4$ (3 g) was added to the crude (3*S*)-**5** (158 g), and the mixture was heated at refluxed for 8 h. The reaction mixture was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo followed by distillation to yield the *l*-oxide **1** (74 g, bp 75–77°C/ 80–85 mmHg, GC; 99.8%, *l*-*cis*-**1**/*l*-*trans*-**1** = 90/10) in 44% from the (*S*)-**2**. The optical purity of the *l*-oxide **1** was confirmed to be same as that of the starting material (3*S*)-**2** by gas chromatographic analysis with a chiral stationary phase [Chiraldex G-TA: 0.25 mm I.D.×30 m; conditions: 30°C (20 min) to 70°C (40 min) at 2°C/min]. In the same manner, *d*-oxide **1** can be synthesized starting from the (3*R*)-**2** (98% ee) as a raw material.

The synthesis of **1** from conjugated diene alcohol **6** by acid-catalyzed cyclization has been well studied, but the products always consist of a mixture of *cis*-**1** as a major product and *trans*-**1** as a minor product in different ratios depending on the reaction conditions.[12] Because the thermodynamically unstable *trans*-isomer was produced in less than 40% under ordinary conditions, it was troublesome to obtain pure *trans*-**1** for odor evaluation.

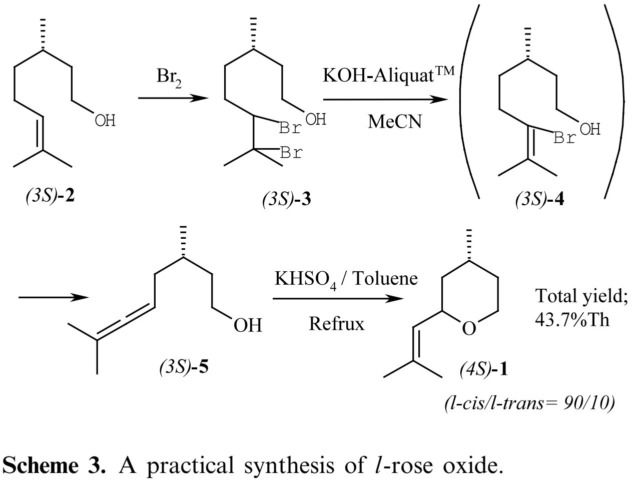
Thus we tried to produce optically active *trans*-rich **1** by diastereoselective Pd–BINAP-catalyzed cyclization of the (*R*)- and (*S*)-**5**. As a result, the *l*-*cis*-rich oxide **1** was obtained from the (3*S*)-allenyl alcohol **5** using the (3*R*)-BINAP–Pd complex. On the other hand, the *l*-*trans*-rich mixture was produced from the (3*S*)-allenyl alcohol **5** using the (*S*)-BINAP–Pd complex (Table 1).

It is interesting to note that diastereomeric combinations between the substrates and the ligands are very important to produce the *cis*- and *trans*-configurations selectively as shown in Scheme 4.

The typical procedure is as follows; the (3*S*)-allenyl alcohol **5** (5.0 g, 32.5 mmol) was stirred with catalytic amounts of palladium(II) acetate (73.0 mg, 0.33 mmol) and (*S*)-BINAP{2,2′-bis(diphenylphosphino)-1,1′-binaphthyl} (0.51 mg, 0.66 mmol) at room temperature for 16 h, and the reaction mixture was distilled (63–65°C/6 mmHg) to give 2.1 g of the *l*-oxide **1** (*cis*/*trans* = 37/63).

Recent remarkable progress in the methods and technologies for both synthesis and analysis has accelerated olfactory studies of optically active compounds.[13] Regarding the odor of optically active citronellyl derivatives, we had reported that the cyclic compounds show fairly large differences in odor properties between the diastereomeric pairs compared with the linear compounds.[14] In the case of rose oxide, Ohloff[4] had reported that the *d*-*cis*-oxide **1** has a sweet scent, whereas the *l*-*cis*-oxide **1** has a powerful fruity odor. Further detailed odor evaluation[15] of the four diastereomers synthesized in the present work has been conducted. (Table 2)

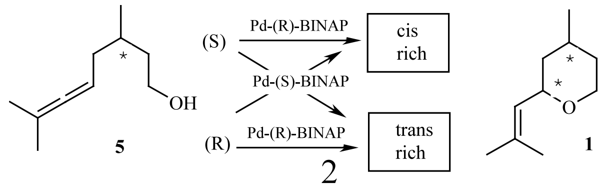
As suggested in previous reports,[4] there have been great differences in both odor quality and thresholds among the diastereomers. Namely, the *l*-*cis*-oxide **1**, a major diastereomer in Bulgarian rose, has shown the lowest odor threshold value of which the ratios relative to the other three diastereomers were 1/100 to 1/320 and has been evaluated to be superior in olfactory qualities to



Scheme 3. A practical synthesis of *l*-rose oxide.

Table 1. Cyclization of the allenyl alcohol **5** by Pd–BINAP complexes

Entry	Subst.	BINAP	Temp. (°C)	Time (h)	*cis*/*trans*
1	(*S*)-**5**	*R*	75	14	80/20
2	(*S*)-**5**	*S*	75	14	48/52
3	(*S*)-**5**	*S*	rt	16	37/63
4	(*R*)-**5**	*S*	75	14	83/17
5	(*R*)-**5**	*R*	75	14	47/53



Scheme 4. Stereochemical dependency of **1** upon the configuration of the substrate **5** and the catalyst.

the other diastereomers, all of which have herbal nuances in common.

Acknowledgements

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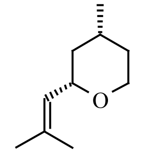
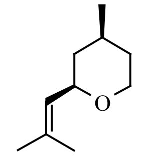
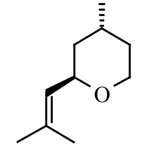
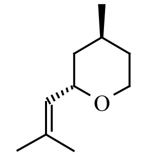
10. The purified compounds (3*S*)-**4** and (3*S*)-**5** were characterized. (3*S*)-**4**: IR (NaCl): 3342, 2945, 292, 2838, 1672, 1462, 1386, 1223, 1054 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.9 (d, 3H, J=6.5 Hz), 1.29–1.49 (m, 1H), 1.49–1.67 (m, 1H), 1.77 (s, 3H), 1.85 (s, 3H), 2.50 (brt, 2H, J=7.6 Hz), 3.61–3.75 (m, 2H). (3*S*)-**5**: d_{20}^{20}=0.8698,

Table 2. Odor properties[a)] of the diastereomeric rose oxide[b)] (98% ee)

l-Form	Odor	Threshold (ppb)	*d-Form*	Odor	Threshold (ppb)
 *l-cis-* **1**, *(2S,4R)*	**Floral-Green** clean, sharp, metallic light, rose, green	**0.5**	 *d-cis-* **1**, *(2R,4S)*	**Herbal-Green-Floral** hay, green, earthy heavy	**50**
 *l-trans-* **1**, *(2R,4R)*	**Floral-Green** green, herbal (minty), fruity	**160**	 *d-trans-* **1**, *(2S,4S)*	**Herbal-Green-Floral** fruity, herbal, rose citrus, (bitter peel)	**80**

a) All samples were purified by means of column chromatography on silica gel to obtain the pure *cis*- and the pure *trans*-isomers. The chemical purities of these samples were determined to be higher than 99% by capillary gas chromatography.

b) The specific rotations of the four diastereomers are as follows;

l-cis-**1**: $[\alpha]_D^{24}$=-78.4° (*c* 1.2, CHCl$_3$), *l-trans* -**1**: $[\alpha]_D^{24}$=-2.9° (*c* 1.4, CHCl$_3$),

d-cis-**1**: $[\alpha]_D^{25}$=+78.7° (*c* 1.0, CHCl$_3$), *d-trans* -**1**: $[\alpha]_D^{25}$=+3.2° (*c* 1.1, CHCl$_3$).

$n_D^{20}=1.4776$, $[\alpha]_D^{25}=-4.50°$ (*c* 1.036, $CHCl_3$); IR (NaCl): 3320, 2952, 2920, 2870, 1965, 1463, 1386, 1223, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.9 (d, 3H, $J=6.6$ Hz), 0.96–1.61 (m, 2H), 1.61–1.72 (m, 1H), 1.69 (s, 6H), 1.96 (m, 1H), 3.64–3.74 (m, 1H), 4.88 (m, 1H).

11. Commercial product (Takasago International Corporation) manufactured by the process described in the literature.[8,9]
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15. *Sensory evaluation*: The odor threshold concentrations were determined in an aqueous–ethanol solution by a triangular method similar to that reported by Acree et al.[16] Samples to be tested were dissolved in 95% ethanol to make specified concentrations, and 10 μL of the solution was added to 20 mL of distilled water in 50 mL glass bottles. The blank sample contained 10 μL of ethanol and 20 mL water. The evaluation panel was formed by male and female members of this laboratory and consisted of 11–13 panelists. The compounds were tested in 0.1 ppb–1.0 ppm concentrations. Each concentration was presented together with two blank samples in increasing concentrations and randomized order. Tests were repeated three times at each concentration. The judges chose the odd sample in each set and for each concentration. The mean score of a correct response was determined. The linear regression of the correct response ratio on a log concentration was calculated by iterative weighted least squares. We defined the threshold concentration as that concentration yielding fitted values equal to the level of correct responses which is 71.7% (5/7). The odor profiles of the four diastereomers were determined by five experienced perfumers.
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