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# New Practical Synthesis of the Exceptional Musk Odorants (*R*)-Muscone and (*R*,*Z*)-5-Muscenone

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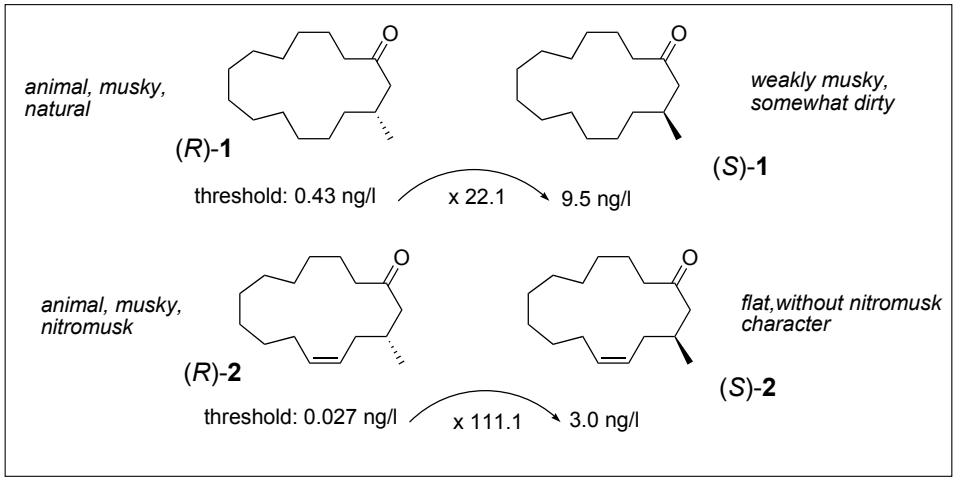
*Abstract:* Herein we describe a short and practical synthesis of the exceptional musk odorants (*R*)-muscone and (*R*,*Z*)-5-muscenone from a readily available achiral macrocyclic diketone. The key step of the synthesis is the first sodium *N*-methylephedrate mediated enantioselective aldol condensation reaction (up to 76% *ee*). This new type of reaction proceeds *via* a dynamic kinetic resolution of an aldol intermediate.

**Keywords:** Aldol reaction · Amino alcohol · Asymmetric synthesis · Dynamic kinetic resolution · Elimination

## 1. Introduction

Due to their unique olfactive characteristics the macrocyclic ketones (*R*)-muscone **1** ('*laevo* muscone') and (*R,Z*)-5-muscenone **2** ('*dextro* muscenone') are highly prestigious musk odorants (Scheme 1). In both molecules the configuration at C(3) influences very strongly the human olfactory threshold and olfactive characteristics.[1] Only the (*R*)-enantiomer of **2** posses an extremely low threshold (0.027 ng/l) and the highly desired nitromusk character. The (*R*)-enantiomer of muscone **1** is described by its warm, animalic musk character, whereas the (*S*)-enantiomer smells only weakly musky.

A recent literature search revealed 44 publications and 19 patent applications for the synthesis of (*R*)-**1**, none of them completely fulfilling the requirements for a large scale preparation.[2] Even more than 100 years after the first isolation in 1906 by Walbaum[3a] and 80 years after its characterization (Nobel price of Ružička),[3b] synthetic (*R*)-**1** is until now far too expensive to be used in a commercial fragrance. In view of the growing interest[4] and research activities[5] devoted to (*R*)-**1**, and the exceptional olfactive characteristics of (*R,Z*)-5-muscenone **2**, practical syntheses of both of these molecules are highly desired.




Scheme 1.

## 2. Results and Discussion

Recently Fehr *et al.* published a synthesis of (*R*)-muscone **1** and (*R,Z*)-5-muscenone **2** using an efficient kinetic resolution of a bicyclic enone **3** by CBS reduction[1a] and an Eschenmoser fragmentation[6] as the key steps (Scheme 2). The racemic enone **3** had to be prepared from the readily available macrocyclic diketone **4**[6a] by an aldol condensation reaction. For full conversion to the cyclohexenone **3**, the highly unreactive diketone **3** had to be refluxed 16 h in ethanol in the presence of 1 equiv. of KOH.

To shorten the synthesis and to increase the overall yield (23% over four steps) we were interested in investigating an enantioselective aldol condensation reaction of **4**, to directly obtain the desired product (*S*)-**3** in a one-step transformation. Herein we would like to discuss our recently published results[1b] more extensively.

Since direct asymmetric aldol chemistry was unsuccessful ([Zn]OR*,[7a] [Ba]OR*,[7b] [Ca]OR*,[7c] [La]OR*,[7d] [Ti]OR*,[7e] or L-proline;[7f–i] low conversion

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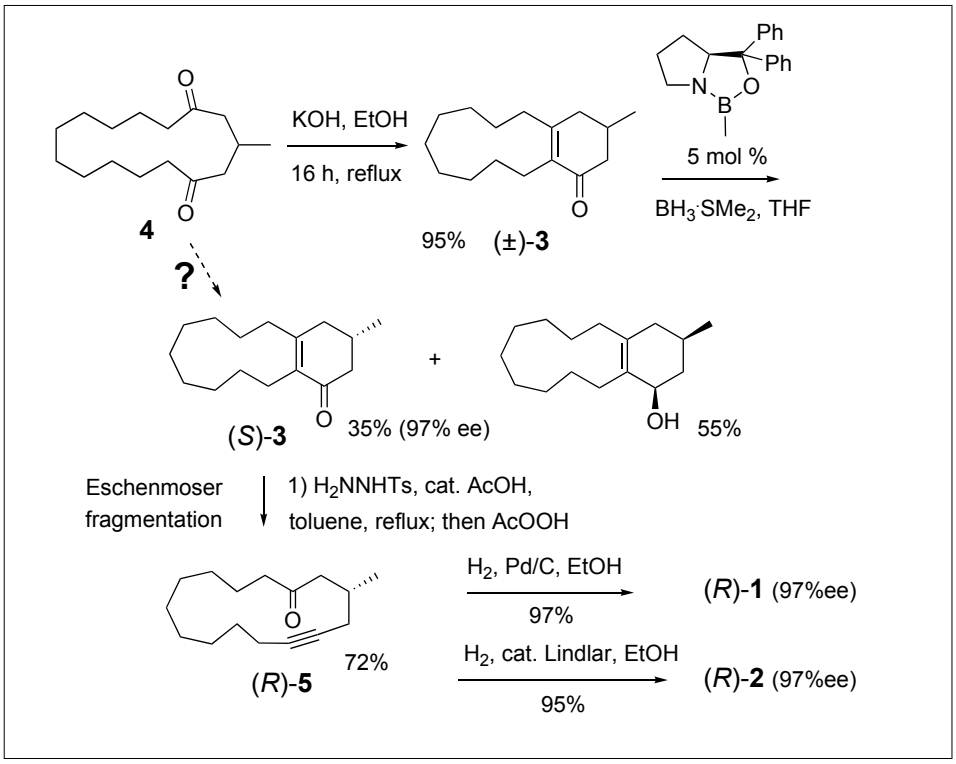
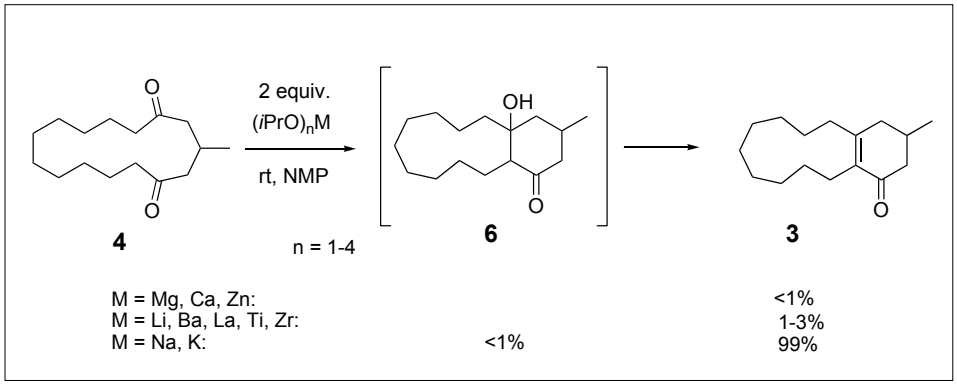



Scheme 2. Synthesis of (*R*)-**1** and (*R*)-**2**: kinetic resolution of (±)-**3** (CBS reduction) by Fehr *et al.*[1a] followed by Eschenmoser fragmentation[6] and hydrogenation




Scheme 3. Reactivity of **4** towards metal isopropoxides in NMP (1 d, RT)

of **4**) we therefore decided to study more systematically the reactivity of diketone **4** towards metal alkoxides (Scheme 3). When Mg-, Ca- and Zn-isopropoxides were employed, none of the product **3** was formed, and with Li-, Ba-, La-, Ti- and Zr-isopropoxides only 1–3% of **3** were obtained. To our delight the quantitative formation of **3** at room temperature was observed in the presence of 2 equiv. of NaO*i*Pr or KO*i*Pr after one day.

Having solved the problem of the low reactivity of **4**, we were now curious to test chiral Na-alkoxides for this transformation. To our surprise, the simple Na-alkoxide of L-menthol (2 equiv.) gave **3** in quantitative yield and 4% enantiomeric excess (at room temperature in THF). It should be noted that during the formation of **3** no trace of aldol **6** was observed.

Encouraged by our first enantiomeric excess, we screened a selection of Na-alkoxides which were all derived from optical pure secondary or tertiary alcohols. The common structural feature of the most promising alkoxides was the presence of a complexing amino group in the β-position of a secondary alcohol (Na-alkoxides of β-amino alcohols). As several β-amino alcohols are commercially available in optically pure form, we investigated the effect of the nitrogen substituents (NRR') and $R^1$ of **7** (Table) on the enantioselectivity.

The Table illustrates that using 4 equiv. of the Na-alkoxide of (+)-ephedrine **7a** a lower enantiomeric excess (30% *ee* (*S*)-**3**) was obtained than with (+)-*N*-methylephedrine **7b** (53% *ee* (*S*)-**3**). Sterically more demanding alkyl groups than methyl at the nitrogen (NRR') led to lower enantioselectivities (**7c**) and reaction rates. When $R^1$ = Me was changed to phenyl (**7d**) nearly the same enantiomeric excess (50% *ee* (*S*)-**3**) was obtained as with **7b**. The Na-alkoxide of (+)-N-methylpseudoephedrine (1*S*,2*S*)-**7e** gave a lower enantiomeric excess than (1*S*,2*R*)-**7b**.

An even higher enantiomeric excess and a higher reaction rate could be obtained with **7b** by increasing the concentration of the reaction (0.8 mol/l, THF, 64% *ee*, 95% isolated yield). Lower quantities of Na-alkoxide **7b** (2 equiv.) gave a lower *ee* (56% *ee*) and higher quantities of **7b** (8 equiv.) a higher *ee* (76% *ee*). (+)-*N*-methylephedrine could be easily recycled (up to 98%) and reused for the formation of **7b**.

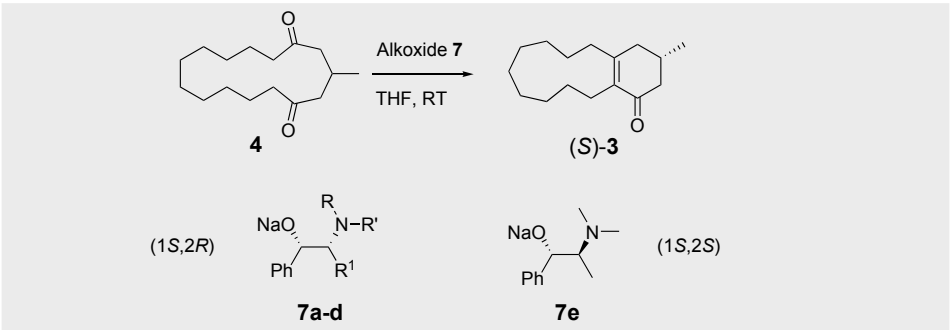
The obtained product (*S*)-**3** was transformed into the musk odorants (*R*)-muscone **1** and (*R*,*Z*)-5-muscenone **2** in high yield (2 steps, 70%) using the aforementioned literature procedure,[1a] without any loss of enantiomeric excess.

To shed some light onto the mechanism of this novel transformation we wanted to find out whether the aldol reaction or the dehydration step (or both) was responsible for the high enantioselectivity. The enantiomeric excess of the aldol intermediate **6** could not be measured, because it was never observed during the reaction ($^{13}$C-NMR experiments in THF-*d8*). For this reason (±)-**6** was prepared from **4** and treated with 2 equiv. of Na-alkoxide **7b** to determine the enantioselectivity in the dehydration step (Scheme 4). In less than 1 min the diketone **4** was formed, indicating that the retro aldol reaction is much faster than the aldol dehydration reaction. Calculation of the relative energy confirmed that the aldol product (±)-**6** (12.1 kcal/mol) and (*S*)-**3** (9.4 kcal/mol) are very high in energy compared to the diketone **4** (0 kcal/mol).[8]

On the basis of these experimental results we suggest that (*S*)-**3** is formed by a dynamic kinetic resolution of aldol **6** (Scheme 5).

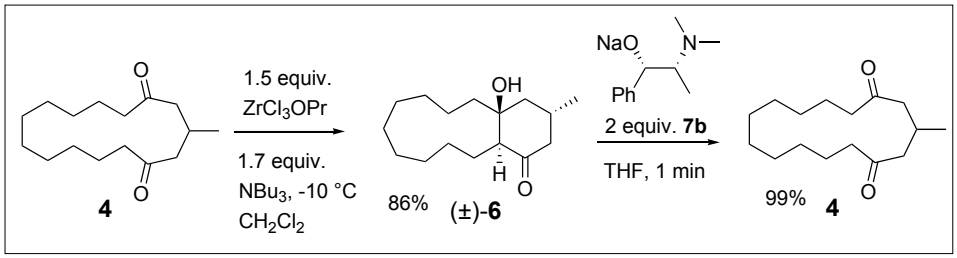
Conformational analysis of **6** (Fig.)[8] showed that the sterically very demanding 11-membered ring of the bicyclic aldol **6** is blocking an attack of **7b** on one side of the bridgehead proton. Chelation of the sodium cation of **7b** to oxygen and nitrogen should give a rigid conformer with a sterically demanding face (methyl and phenyl group).[10] We propose that in the faster deprotonation (pathway **A**) of **6** the methyl and the phenyl group of **7b** are pointing away from the 11-membered ring.[11] The retro-aldol reaction is faster than pathway **B** and converts the undesired enantiomer (*R*)-**6** to the starting diketone **4**. This mechanism is consistent with the observation that the Na-alkoxide of (+)-(1*S*,2*S*)-*N*-methylpseudoephedrine **7e** gives a lower enantiomeric excess[12] than (1*S*,2*R*)-**7b**, and that **7d** (two phenyl groups on the same side) gives high

Table. The effect of the NRR' and $R^1$ group of the alkoxides **7a**–**e** on the yield and enantioselectivity of the formation of **3** from **4** in THF.

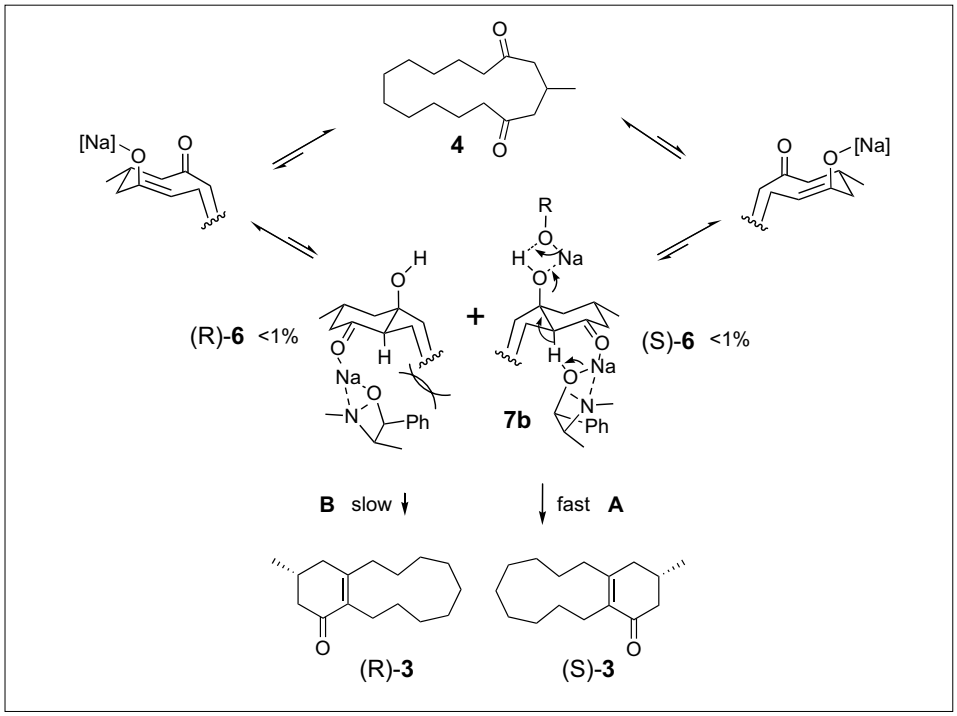



| Alkoxide | $NRR'_2$ | $R^1$ | t | Conv. [%][a] | ee [%] of 3[b] |
|---|---|---|---|---|---|
| 4 equiv. **7a**[c] | NHMe | Me | 4d | 99 | 30 (*S*) |
| 4 equiv. **7b**[cd] | $N(Me)_2$ | Me | 3d | 88 | 53 (*S*) |
| 4 equiv. **7c**[cd] | $N(Bu)_2$ | Me | 4d | 49 | 25 (*S*) |
| 4 equiv. **7d**[cd] | $N(Me)_2$ | Ph | 3d | 56 | 50 (*S*) |
| 4 equiv. **7e**[cd] | $N(Me)_2$ | Me | 4d | 85 | 36 (*S*) |
| 4 equiv. **7b**[de] | $N(Me)_2$ | Me | 1d | 95[f] | 64 (96)[g] (*S*) |
| 2 equiv. **7b**[de] | $N(Me)_2$ | Me | 1d | 91 | 56 (*S*) |
| 8 equiv. **7b**[h] | $N(Me)_2$ | Me | 2d | 90 | 76 (*S*) |

[a]Conversion was determined by GC; [b]determined by chiral GC analysis (CHIRASIL DEX CB) after reduction to the alcohol; [c]reactions were performed at a concentration of 0.1 mol/l **4**; [d]reactions were performed in the presence of 4 Å molecular sieves; [e]the concentration of **4** was 0.8 mol/l; [f]isolated yield; [g]*ee* after recrystallization; [h]the concentration of **3** was 1 mol/l.




Scheme 4. Preparation of the racemic aldol intermediate (±)-**6** and its reactivity towards **7b**




Scheme 5. Simplified illustration of the dynamic kinetic resolution of aldol intermediate (±)-**6** mediated by Na-alkoxide **7b**[9]

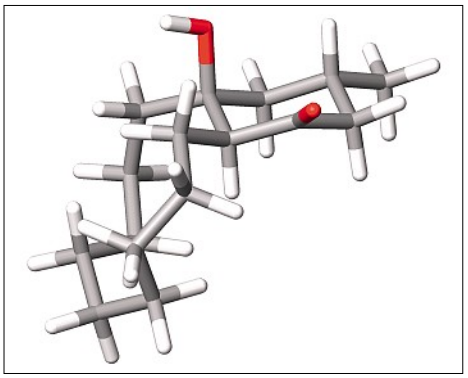


Fig. Preferred conformation of aldol (*S*)-**6**[8]

enantioselectivities. The observation that sterically demanding alkyl substituents on the nitrogen (NRR') lower the enantiomeric excess and slow down the reaction rate could be a result of a stronger interaction of the alkyl groups with the 11-membered ring during the deprotonation step.

## 3. Conclusion

100 years after the isolation of natural (*R*)-muscone **1** (Walbaum 1906) we have developed a short (three steps) and industrially feasible synthesis of (*R*)-**1** and (*R*,*Z*)-5-muscenone **2** (up to 76% *ee*) from a readily available achiral starting material using an unprecedented sodium N-methylephedrate mediated dynamic kinetic resolution of an aldol intermediate.[13]

## 4. Experimental Section

### 4.1. *Synthesis of Optically Active (S)-14-Methyl-bicyclo[9.4.0]pentadec-1(11)-en-12-one 3 (64% ee)*

The Na-alkoxides **7a**–**e** can be prepared from the corresponding β-amino alcohols in several ways (for example by addition of 1 equiv. NaH in THF, followed by stirring at reflux for 30 min).[11]

Procedure for the preparation of (*S*)-**3** (64% *ee*): a mixture of (+)-*N*-methylephedrine (2.9 g, 16 mmol), NaH (0.64 g, 16 mmol, 60 wt% dispersion in mineral oil) and 4 Å molecular sieves (0.8 g) in 5 ml of dry THF was stirred at reflux for 30 min. After cooling down to room temperature and the addition of **4** (4 mmol, 1.0 g) the mixture was stirred and followed by GC. To stop the reaction, the mixture was hydrolyzed with an aqueous 2N HCl solution (15 ml). After extraction of the aqueous layer with diethyl ether the organic layer was washed with water, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash chromatography. The *ee* was determined by reduction of (*S*)-**4** to the corresponding

alcohol ($LiAlH_4$ in dry THF) and injection onto a chiral stationary phase GC column (CHIRASIL DEX CB).[1a] (*S*)-**4** (64% *ee*): $^1$H-NMR ($CDCl_3$): δ = 1.04 (d, *J* = 6.1 Hz, 3H), 1.18–1.46 (m, 10H), 1.50–1.75 (m, 4H), 1.97–2.15 (m, 3H), 2.30–2.40 (m, 3H), 2.41–2.56 ppm (m, 3H). $^{13}$C-NMR ($CDCl_3$): δ = 21.3, 23.5, 24.6, 25.1, 25.3, 25.5, 26.0, 26.2, 26.6, 29.7, 32.3, 38.3, 46.7, 136.3, 158.2, 199.7 ppm. $[a]^{20}_D$ = +58.5 (c = 2.8, MeOH).

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