Enantioselective Intramolecular Aldol Addition/Dehydration Reaction of a Macrocyclic Diketone: Synthesis of the Musk Odorants (*R*)-Muscone and (*R*,*Z*)-5-Muscenone**

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One hundred years after the isolation of natural (R)-muscone [(R)-1] by Walbaum,^[1] we describe a short and efficient synthesis of (R)-1 and (R,Z)-5-muscenone [(R)-2] (up to



76% *ee*) by using an unprecedented, enantioselective intramolecular aldol addition/dehydration reaction as the key step.

Compounds (*R*)-1 and (*R*)-2 are macrocyclic musks in which the configuration at C3 influences very strongly the odor character and the human olfactory threshold.^[2] Musk (*R*)-2 has an extremely low threshold (0.027 ng L^{-1}) and possesses a highly desired nitromusk character [(*S*)-2: 3 ng L⁻¹]. Compound (*R*)-1 is appreciated for its strong animal musk character [(*S*)-1: weakly musky].

To our knowledge, neither of the two musk odorants has ever been found in commercial fragrances, which indicates that the published syntheses do not completely fulfill the requirements for a large-scale preparation.^[3] In view of the growing interest from the fragrance industry^[4] and academia^[5] in (*R*)-1, and the exceptional olfactory characteristics of (*R*)-2, practical syntheses of both of these compounds are highly desirable.

Our synthetic strategy was to develop an enantioselective aldol condensation of the readily available macrocyclic diketone $3^{[6a]}$ for the formation of product (*S*)-4, which then could be easily transformed into both (*R*)-1 and (*R*)-2 following the previously published synthesis (Scheme 1).^[2,6b-e]

Over the last decade impressive achievements in direct asymmetric aldol methodology have been made for the reaction between ketones and aldehydes.^[7] However, our attempts with the use of alkoxides ([Zn]OR*,^[8a] [Ba]OR*,^[8b] [Ca]OR*,^[8c] [La]OR*,^[8d] [Ti]OR*,^[8c]) or L-proline^[8f] were

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Scheme 1. Synthetic strategy for the synthesis of (*R*)-1 and (*R*)-2 from **3**: a) EF = Eschenmoser fragmentation: H_2NNHTs , cat. AcOH, toluene, reflux; then AcOOH; b) H_2 , cat. Lindlar, EtOH; c) H_2 , cat. Pd/C, EtOH.^[2,6b-c]

unsuccessful (low conversion of **3**). In view of the low reactivity of diketones, it is not surprising that there are only two known direct asymmetric intramolecular aldol reactions, from Agami et al.,^[9] Hajos and Parrish,^[10a] and Wiechert and co-workers,^[10b]

As **3** was inert to the reported reaction conditions (Lproline, *N*,*N*-dimethylformamide), we decided to study systematically the reactivity of **3** towards metal isopropoxides, $MOiPr.^{[11]}$ Surprisingly, quantitative formation of **4** at room temperature was observed in the presence of two equivalents of NaO*i*Pr after one day.

After screening a selection of Na alkoxides 8–11 (Table 1) derived from chiral β -amino alcohols, we were delighted to

Table 1: The effect of alkoxides **8–11** on the yield and enantioselectivity of the formation of **4** from **3** in THF.^[12]

\bigcirc		Alkoxide THF, RT 4-Å M.S.			
Pł	ONa 3	Ph 9	N Ph 10		Ph 11 Ph
Entry	Alkoxide	t [days]	с [mol L ⁻¹] ^[а]	Conv. [%] ^[b]	ee [%] ^[e]
1	4 equiv 8	3	0.1	88	53 (S)
2	4 equiv 9	3	0.1	85	36 (S)
3	4 equiv 10	3	0.1	49	25 (S)
4	4 equiv 11	3	0.1	56	50 (S)
5	4 equiv 8	1	0.8	99 (95) ^[c]	64 (96) ^[d] (S)
6	2 equiv 8	1	0.8	91	56 (<i>S</i>)
7	8 equiv 8	2	1	90	76 (<i>S</i>)

[a] Concentration of **3** at the beginning of the reaction. [b] Conversion was determined by GC. [c] Yield of isolated products. [d] *ee* value after 2 recrystallizations. [e] Determined by chiral GC analysis (CHIRASIL DEX CB) after reduction to the alcohol.



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obtain (*S*)-**4** in an enantiomeric excess of 53 % in the presence of four equivalents of the Na alkoxide of (+)-*N*-methylephedrine (**8**) (Table 1, entry 1, 88 % yield, 3 days in THF).^[12] Notably, transient aldol **7** was not observed during the course of this reaction.

Interestingly, the enantiomeric excess was strongly dependent on the configuration at C2 of the β -amino alcohol (Table 1, entry 2, 9, 36% *ee*) and the relative size of the amino moiety (Table 1, entry 3, 10, 25% *ee*), whereas a more bulky phenyl group at C2 gave nearly the same enantiomeric excess (Table 1, entry 4, 11, 50% *ee*).

An even higher *ee* value and a higher reaction rate could be obtained with four equivalents of **8** by performing the reaction at a higher concentration (Table 1, entry 5, 0.8 mol L^{-1}). After allowing the reaction to run for one day at room temperature, we obtained (*S*)-**4** in quantitative yield and with an enantiomeric excess of 64%. Importantly, lower quantities of **8** (2 equiv) gave a lower *ee* value (Table 1, entry 6, 56% *ee*), and higher quantities of **8** (8 equiv) gave a higher *ee* value (Table 1, entry 7, 76% *ee*). (+)-*N*-Methylephedrine could be easily recycled (up to 98%) and reused for the formation of **8**.

Subsequently, (S)-4 was transformed into the musk odorants (R)-muscone (1) and (R,Z)-5-muscenone (2) in high yield (two steps, $70\%)^{[2]}$ without any loss of enantiomeric excess.

One way to answer the question of whether the aldol reaction or the dehydration step (or both) were responsible for the high enantioselectivity would be the determination of the enantiomeric excess of aldol intermediate 7. As the quantity of transient 7 was too low (<1%),^[13] racemic (\pm) -7^[14] was prepared from 3 and treated with two equivalents of Na alkoxide 8 to determine the enantioselectivity in the dehydration step (Scheme 2). In less than one minute, 3 was



Scheme 2. Preparation of (\pm) -7: a) 1.5 equiv ZrCl₃OPr, 1.7 equiv NBu₃, CH₂Cl₂, -10°C. Reactivity of aldol (\pm) -7 towards Na alkoxide 8.

formed quantitatively,^[15] which indicates that the retro-aldol reaction is much faster than the aldol dehydration reaction. Not surprisingly, relative energy calculations showed that retro-aldol product **3** ($-12.1 \text{ kcal mol}^{-1}$) is much lower in energy than aldol **7** (0 kcal mol⁻¹) and dehydration product (*S*)-**4** ($-2.7 \text{ kcal mol}^{-1}$).^[16,17]

On the basis of the experimental results, we suggest the following mechanism for the formation of (S)-4: In the presence of a large excess of 8, both enantiomers of transient 7 are formed from 3 in small amounts by reversible steps (Na enolate formation, aldol addition, and protonation; Scheme 3).^[18]



Scheme 3. Simplified illustration of the dynamic kinetic resolution of aldol intermediate (±)-7 mediated by Na alkoxide 8 [NaOR], :[THF],...^[18]

Owing to the fact that Na alkoxide **8** has already been used by Plaquevent and co-workers^[19] for enantioselective dehydrohalogenations, it is reasonable to assume that (*S*)-**4** is formed by the enantiomer-differentiating dehydration of **7** (pathway **A** is faster than pathway **B**).^[20,21] Interconversion between the enantiomers of **7** through a retro-aldol/aldol addition sequence enables the transformation of undesired aldol (*R*)-**7** to desired aldol (*S*)-**7** (dynamic kinetic resolution).

Conformational analysis of 7 (Figure 1)^[17] shows that its sterically very demanding 11-membered ring hinders attack of 8 on one side of the bridgehead proton. Chelation of the sodium cation of 8 to the oxygen and nitrogen atoms should give a rigid conformer with a sterically demanding face (methyl and phenyl groups).^[22] We speculate that in the faster deprotonation of 7 with 8, the methyl and phenyl groups of 8 point away from the bulky 11-membered ring (Figure 1 and Scheme 3, pathway A).^[19,23] This mechanism is consistent with the observation that the Na alkoxide of (+)-N-methylpseudoephedrine (9) gives a lower enantiomeric excess^[24] than 8 and that 11 (2 phenyl groups on the same side) affords high enantioselectivities. The observation that sterically demanding alkyl substituents on the nitrogen atom (10) lower the enantiomeric excess and slow down the reaction rate could be a result of a stronger steric interaction of the alkyl groups with the 11-membered ring during the deprotonation step.

We have thus developed a short and efficient synthesis of (R)-muscone (1) and (R,Z)-5-muscenone (2) (up to 76% *ee*) from a macrocyclic diketone by using an unprecedented, reversible intramolecular aldol addition/enantioselective dehydration reaction.^[25] This sodium ephedrate mediated



Figure 1. Preferred conformation of aldol (15,115,145)-7.^[17] Simplified illustration of the enantiomer-differentiating aldol dehydration of 7.^[18]

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reaction represents an efficient and hitherto unknown type of dynamic kinetic resolution, which involves a new class of aldol intermediates.^[26] Currently, we are expanding this novel reaction to other ring sizes and acyclic diketones.

Experimental Section

Sodium alkoxides **8–11** can be prepared from the corresponding β amino alcohols in several ways (for example by the addition of 1 equiv of NaH in THF, followed by heating at reflux and stirring for 30 min).^[19]

(*S*)-4 (64% ee): A mixture of (+)-*N*-methylephedrine (2.9 g, 16 mmol), NaH (60 wt% dispersion in mineral oil, 0.64 g, 16 mmol), and 4–Å molecular sieves (0.8 g) in dry THF (5 mL) was heated at reflux and stirred for 30 min. The mixture was cooled to room temperature, **3** (4 mmol, 1.0 g) was added, and the mixture was stirred. The reaction was followed by GC. To stop the reaction, the mixture was hydrolyzed with an aqueous HCl solution (2 N, 15 mL). After extraction of the aqueous layer with diethyl ether, the organic layer was washed with water, dried over MgSO₄, and filtered. The solvent was removed under vacuum, and the residue was purified by flash chromatography. The *ee* value was determined by reduction of (*S*)-**4** to the corresponding alcohol (LiAlH₄ in dry THF) and injection onto a chiral GC column (CHIRASIL DEX CB).^[2]

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- [13] Reaction intermediates (aldol 7, Na enolate of 3) were not detected during the slow formation of 4 from 3 with the use of four equivalents of 8 (13 C NMR in [D₈]THF). It should be noted that 8 acts in the presence of 4 like a chiral shift reagent [different shift of the 13 C NMR signals of the carbonyl functionality and the double bond of (*S*)-4 and (*R*)-4]. This suggests that there is coordination of 8 to 4. No shift in the 13 C NMR signal of the keto group of diketone 3 was observed.
- [14] Aldol product 7 with the indicated configuration (1*R*,11*R*,14*R*)/(1*S*,11*S*,14*S*) is the major product. Only small amounts (1%) of 7 with the (1*R*,11*S*,14*R*)/(1*S*,11*R*,14*S*) configuration were isolated. Calculation of the relative energy showed that aldol product (1*R*,11*S*,14*R*)/(1*S*,11*R*,14*S*)-7 is higher in energy (0.9 kcal mol⁻¹).^[17]
- [15] Upon continued stirring at room temperature, aldol condensation product (S)-4 was slowly formed from 3 in 53% ee (3 days, 88%).
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