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Practical optical resolution of *dl*-muscone using tartaric acid derivatives as a chiral auxiliary

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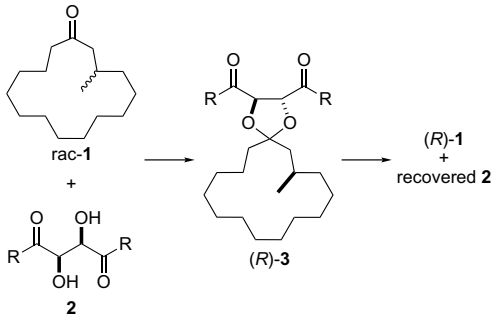
Abstract—A simple and practical synthesis of (*R*)-(−)-muscone was achieved by optical resolution of *dl*-muscone using tartaric acid derivatives. The acetalization of *dl*-muscone with *N*,*N*′-dibenzyl-L-tartaramide in the presence of $Sc(OTf)_3$ and methyl orthoformate furnished a diastereomeric mixture of acetals, which were readily separated by simple recrystallization. Diastereomerically pure acetal was hydrolyzed to give optically pure muscone and recovered *N*,*N*′-dibenzyl-L-tartaramide.

(*R*)-(−)-Muscone ((*R*)-**1**) is the most important classical source of musk odors for perfumes. Muscone is extracted from musk pods, which are the secretion from a gland of the endangered musk deer. Following Ruzicka's structural elucidation of natural muscone as (*R*)-3-methylcyclopentadecanone in 1926,[1] muscone has been synthesized by various synthetic approaches in racemic form[2] as well as enantiomerically pure form.[3] Although synthetic muscone **1** is commercially available in its racemic form, the enantiomerically pure synthesis of muscone is not practical. Therefore, a practical and simple process for the isolation of optically pure (*R*)-muscone is needed. This study focuses on the optical resolution of racemic muscone (*rac*-**1**), as the enantiomers are extremely difficult to separate by chiral chromatography due to the lack of steric and electrical difference between *S* and *R* isomers.[4] To the best of our knowledge, the optical resolution of racemic muscone **1** using chiral auxiliaries has not been reported.[5] As detailed in this letter, we investigated the optical resolution of racemic muscone **1** using tartaric acid derivatives **2** as a chiral auxiliaries to afford optically pure muscone (*R*)-**1** (Scheme 1).



Scheme 1. Optical resolution of *dl*-muscone (**1**).

One of the most useful chiral auxiliaries used to functionalize a carbonyl group is the cyclic acetal. The cyclic acetal is easily introduced by treating the carbonyl compound with 1,2-diol in the presence of a catalytic amount of acid. Conversely, acetals are easily removed by hydrolysis. We chose tartaric acid derivatives **2** as a chiral auxiliaries because both enantiomers are commercially available, and they are inexpensive, safe, and stable compounds. First we examined acetalization of racemic muscone **1** with dialkyl L-tartrate **4** in the presence of scandium trifluoromethanesulfonate ($Sc(OTf)_3$).[6] The results are shown in Table 1. Dimethyl L-tartrate (**4a**) and diethyl L-tartrate (**4b**) afforded the corresponding cyclic acetals **5a**, **5b** in good yield, but these acetals did not crystallize (entries 1 and 2). Crystallinity was remarkably changed by using dibenzyl L-tartrate (**4c**) (entry 3). Acetal **5c** was obtained in 47% yield with 23% de, which formed a colorless solid after

Keywords: (*R*)-(−)-Muscone; Optical resolution; Chiral auxiliary.
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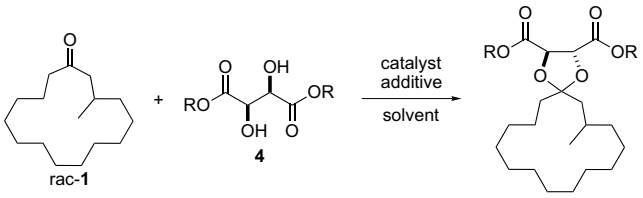
Table 1. Acetalization of racemic muscone (*rac*-**1**) with chiral dialkyl L-tartrate **4**[a]

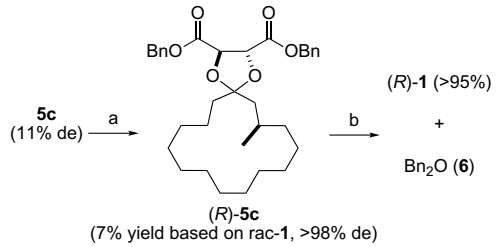


Entry	Diol	R	Catalyst	Additive	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	de[c] (%)	Product	Crystallinity
1	**4a**	Me	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	rt	7	75	7	**5a**	X
2	**4b**	Et	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	rt	21	82	8	**5b**	X
3	**4c**	$PhCH_2$–	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	0	26	47	23	**5c**	O
4	**4c**	$PhCH_2$–	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	0	48	64	11	**5c**	O
5	**4c**	$PhCH_2$–	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	rt	26	92	2	**5c**	Δ
6	**4c**	$PhCH_2$–	$McSc(OTf)_3$[d]	$HC(OMe)_3$	MeCN	rt	26	64	32	**5c**	O
7	**4c**	$PhCH_2$–	$Yb(OTf)_3$	$HC(OMe)_3$	MeCN	0	26	30	26	**5c**	O
8	**4c**	$PhCH_2$–	*p*-TsOH	—	Benzene	Reflux	37	24	39	**5c**	O
9	**4c**	$PhCH_2$–	CSA[e]	—	Benzene	Reflux	61	23	32	**5c**	O
10	**4d**	4-$Pr^iC_6H_4CH_2$–	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	0	26	57	14	**5d**	X
11	**4e**	4-$Bu^tC_6H_4CH_2$–	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	0	26	34	21	**5e**	X
12	**4f**	2-$MeOC_6H_4CH_2$–	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	rt	2	29	—	**5f**	X
13	**4g**	4-$NO_2C_6H_4CH_2$–	$Sc(OTf)_3$	$HC(OMe)_3$	MeCN	rt	4	16	—	**5g**	X

[a] Reactions were carried out using dialkyl L-tartrate (2 equiv), acid catalyst (5 mol %) and additive (2 equiv).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using CHIRALCEL OD.
[d] $mcSc(OTf)_3$ = microencapsulated scandium trifluoromethanesulfonate.
[e] CSA = (1*S*)-(+)-10-camphorsulfonic acid.

usual workup. We found that acetal **5c** with over 10% de was readily recrystallized to separate the diastereomers (entries 3–5, vide infra). Microencapsulated $Sc(OTf)_3$ and ytterbium trifluoromethanesulfonate ($Yb(OTf)_3$) also catalyzed the acetalization (entries 6 and 7). On the other hand, a Brønsted acid catalyst such as *p*-toluenesulfonic acid (*p*-TsOH) and (1*S*)-(+)-10-camphorsulfonic acid (CSA) gave the acetal **5c** in low yield along with dibenzyl ether (**6**), because hydrolysis of dibenzyl L-tartrate (**4c**) occurred during the actalyzation (entries 8 and 9). Substituents on the benzene ring, such as 4-isopropyl, 4-*tert*-butyl, 2-methoxy, and 4-nitro groups, did not show good results; oily products **5d**–**g** were obtained (entries 10–13).

Several recrystallizations of the acetal **5c** (11% de) from hexane afforded diastereomerically pure acetal (*R*)-**5c** in 7% yield based on the racemic muscone *rac*-**1** (Scheme 2). Deacetalization of (*R*)-**5c** was performed under standard conditions to give the enantiomerically pure natural muscone (*R*)-**1** in quantitative yield. Unfortunately, hydrolysis of dibenzyl L-tartrate (**4c**) also occurred, resulting in contamination with a small amount of inseparable dibenzyl ether (**6**).

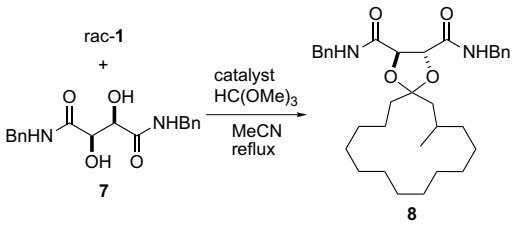


Scheme 2. Reagents and conditions: (a) 3 times recrystallization from hexane; (b) *p*-TsOH, 1,4-dioxane/H_2O = 4/1, 80 °C, 4 h.

A stable chiral auxiliary was needed that could be recovered intact and afford muscone in high optical purity. Therefore, we examined acetalization of *rac*-**1** using *N*,*N*′-dibenzyl-L-tartaramide **7** (Table 2).[7] Acetalization in the presence of $Sc(OTf)_3$ proceeded smoothly to give the acetal **8** in excellent yield after 2 h stirring under reflux (entry 1).[8,9] The acetal **8** with even 3% de was easily recrystallized. Microencapsulated $Sc(OTf)_3$ and $Yb(OTf)_3$ catalyzed the reaction in good yield (entries 2 and 3). *p*-TsOH acid and CSA also gave the acetal **8** in good yield without hydrolysis of *N*,*N*′-dibenzyl-L-tartaramide **7** (entries 4 and 5).

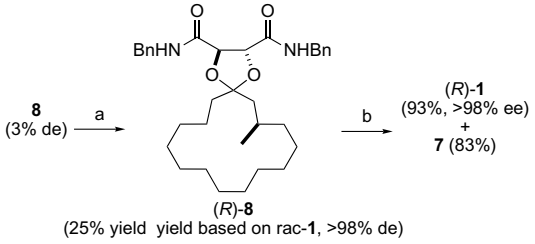
The first recrystallization of the acetal **8** (3% de) from methanol furnished diastereomerically pure acetal (*R*)-**8** in 15% yield, and the second recrystallization also gave (*R*)-**8** in 10% yield. The total yield of product based on the racemic muscone (*rac*-**1**) was 25% (Scheme 3). Purity of (*R*)-**1** as well as recovery of the chiral auxiliary was dramatically changed in the case of *N*,*N*′-dibenzyl-L-tartaramide (**7**) compared to that of dibenzyl L-tartrate (**4c**) (Scheme 2 vs 3). Deacetalization of (*R*)-**8** gave the enantiomerically pure natural muscone (*R*)-**1** in 93% yield without loss of optical purity.[10] No formation of dibenzyl ether (**6**) was observed with *N*,*N*′-dibenzyl-L-tartaramide (**7**) being recovered in 83% yield. The isolation

Table 2. Acetalization of racemic muscone (*rac*-**1**) with chiral *N*,*N*′-dibenzyl-L-tartaramide **7**[a]



Entry	Catalyst	Time (h)	Yield[b] (%)	De[c] (%)	Crystallinity
1	$Sc(OTf)_3$	2	94	3	O
2	$mcSc(OTf)_3$[d]	24	71	4	O
3	$Yb(OTf)_3$	17	50	0.4	O
4	*p*-TsOH	5	49	3	O
5	CSA[e]	8	70	13	O

[a] Reactions were carried out using *N*,*N*′-dibenzyl-L-tartaramide (0.9 equiv), acid catalyst (5 mol %) and $HC(OMe)_3$ (1 equiv).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using CHIRALPAK AD.
[d] $mcSc(OTf)_3$ = microencapsulated scandium trifluoromethanesulfonate.
[e] CSA = (1*S*)-(+)-10-camphorsulfonic acid.



Scheme 3. Reagents and conditions: (a) recrystallized twice from MeOH; (b) *p*-TsOH, 1,4-dioxane/H_2O = 8/1, 80 °C, 3 h.

of (*S*)-(+)-muscone was achieved in 19% yield based on racemic muscone by the same procedure as above using *N*,*N*′-dibenzyl-D-tartaramide.

In summary, tartaric acid derivatives, especially the *N*,*N*′-dibenzyl-L-tartaramide derivative, have proven to be good chiral auxiliaries for optical resolution of a racemic muscone. This method provides a practical access to optically pure (*R*)-muscone, which is one of the most important fragrance compounds.

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5. Previously, we reported that enzymatic resolution of racemic muscone derivatives such as alcohol and oxime was investigated. Chiral (*R*)-muscone with 99% ee was obtained via lipase AK-catalyzed acetylation of the corresponding hydroxy derivative. Takabe, K.; Aoyama, T.; Kawanishi, Y.; Yamada, T.; Yoda, H. In *39th TEAC*; Chemical Society of Japan: Utsunomiya, 1995; Vol. 1III-11, pp 177–178; Lately, Matsumura et al. reported enzymatic resolution of racemic muscone derivatives in a similar way to ours. See, Matsumura, Y.; Fukawa, H.; Terao, Y. *Chem. Pharm. Bull.* **1998**, *46*(9), 1484–1485.
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7. *N*,*N*′-Dibenzyl-L-tartaramide **7** was the most effective chiral auxiliary, while other substituted tartaramide derivatives, such as *N*,*N*′-dipyrrolidinyl- and *N*,*N*′-di-(4-methoxyphenyl)methyl-L-tartaramide, gave an inseparable diastereomeric mixture.
8. Typical procedure: To a solution of racemic muscone *rac*-**1** (1.0 mmol) and *N*,*N*′-dialkyl-L-tartaramide **7** (0.9 mmol) in MeCN (2.0 mL) were added trimethyl orthoformate (1.0 mmol) and $Sc(OTf)_3$ (0.05 mmol) at indicated temperature. The reaction mixture was stirred for the indicated time, then cooled to room temperature. After evaporation of MeCN, the solid was filtered and washed with ether

(10 mL). The filtrate was concentrated to give a crude oil, which was purified by column chromatography (silica gel, hexane/ethyl acetate as an eluent) to give a mixture of diastereomers **8** in excellent yield. These diastereomers were separated by recrystallization from MeOH to give (*R*)-**8** as a colorless solid with >99% de determined by chiral HPLC using CHIRALPAK AD. The acetal **8** would be used for the enantiopurity determination of muscone **1**, as the acetalization of **1** quantitatively proceeded.

9. Acetal (*R*)-**8**: $R_f = 0.37$ (hexane/AcOEt = 70/30); $[\alpha]_D^{18}$ −9.71 (*c* 0.780, $CHCl_3$); mp 136–137 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, $J = 6.5$ Hz, 3H, $-CH_3$), 0.97–1.47 (m, 23H), 1.47–1.90 (m, 4H), 4.37–4.59 (m, 4H, 2 × $-CH_2Ph$), 4.60 (d, $J = 6.9$ Hz, 1H, –CHOC–), 4.67 (d, $J = 6.9$ Hz, 1H, –CHOC–), 7.10–7.44 (m, 12H, 2 × –Ph, –NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.73, 169.67, 137.72, 137.66, 128.83, 127.81, 127.70, 116.87, 77.63, 77.14, 43.72, 43.31, 43.23, 35.85, 35.71, 27.59, 26.98, 26.87, 26.52, 26.45, 26.40, 26.17, 26.02, 25.89, 24.74, 22.23, 20.60; IR (KBr) 3363.6, 2927.7, 2856.4, 1685.7, 1672.2, 1649.0, 1525.6, 1456.2, 1109.0, 698.2; MS (EI) *m*/*z* 548 (M^+, 0.4), 379 (2), 310 (6), 176 (36), 106 (33), 91 (100); Anal. Calcd for $C_{34}H_{48}N_2O_4$: C, 74.42; H, 8.82; N, 5.10. Found: C, 74.36; H, 9.13; N, 4.91.
10. (*R*)-**1**: $[\alpha]_D^{25}$ −12.3 (*c* 1.0, MeOH), lit. $[\alpha]_D^{25}$ −12.3 (*c* 1.2, MeOH). See Ref. 3c.