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A practical synthesis of (*E*)-2-cyclopentadecen-1-one: an important precursor of macrocyclic muscone

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Abstract—A practical synthesis of (*E*)-2-cyclopentadecen-1-one (*E*)-**2** which is an important precursor of macrocyclic muscone (**1**) was investigated. Olefination of 2-mesyloxycyclopentadecanone (**7c**) with strong acid such as sulfuric acid or trifluoromethanesulfonic acid afforded the desired (*E*)-**2** in high yield with extremely high stereoselectivity, which was treated with methylmagnesium cuprate to furnish the *dl*-muscone in good yield.
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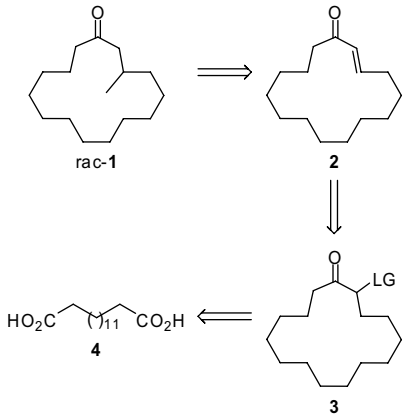
Muscone (**1**) is the primary contributor to the odor of natural musk. Natural muscone is obtained from musk pods, which are the secretion from a gland of the endangered musk deer. Naturally occurring muscone is composed of the (*R*)-(−)-enantiomer,[1,2] therefore, an efficient asymmetric synthesis of (*R*)-(−)-muscone is desirable.[2] Asymmetric conjugate addition of metal methyl reagents to (*E*)-2-cyclopentadecen-1-one (**2**) is a promising approach to enantiomerically pure muscone. In the early 1990s, Tanaka and co-workers developed the stoichiometric conjugate addition of chiral methylcuprate to **2** to give (*R*)-**1** with 100% optical purity.[3] Recently, several groups demonstrated catalytic asymmetric synthesis of (*R*)-**1** with moderate to high enantioselectivity.[4] To achieve the high enantioselectivity the configurationally fixed (*E*)-**2** is crucial, however, the preparation of (*E*)-**2** occasionally requires meticulous handling in commonly employed procedures such as halogen-, S-, Se, and Pd-based transformations.[5] On the other hand, Nicolaou and co-workers reported a direct one-step synthesis of (*E*)-**2** from cyclopentadecanone using *o*-iodoxybenzoic acid, however, a small amount of undesired dienone was also obtained.[6]

It is known that 2-hydroxycyclopentadecanone (**6**), which is readily prepared from diester **5** by acyloin condensation, is another important precursor for the synthesis of (*E*)-**2**. For example, thermal dehydration of **6** in the presence of silica–alumina catalyst afforded (*E*)-**2**.[7] Recently, Tanabe and co-workers reported that 2-mesyloxy- or 2-tosyloxycyclopentadecanone (**7b** or **7c**) with ammonium sulfonate in the presence of base was transformed to (*E*)-**2**.[8] Although these are simple manipulations, high temperature (140–220 °C) is essential to complete the reaction; in addition, the inseparable 3-cyclopentadecen-1-one (**8**) is also formed. Therefore, the preparation of (*E*)-**2** is still difficult to achieve in a truly efficient synthetic method. Herein, we report a straightforward and stereoselective synthesis of (*E*)-**2**



Scheme 1. Synthesis of muscone (**1**).

Keywords: Elimination; Muscone; Macrocycles.
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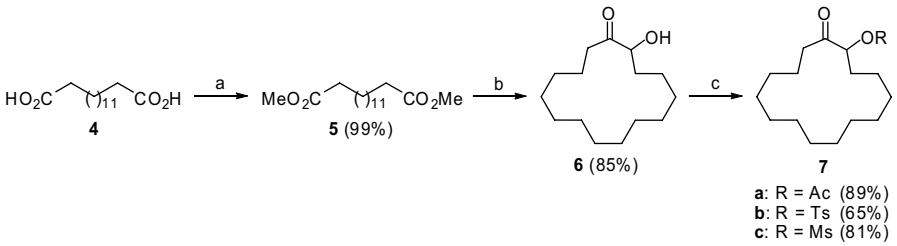
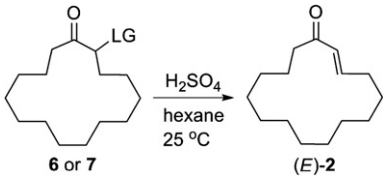


Scheme 2. Reagents and conditions: (a) *p*-TsOH, MeOH, reflux, 17 h; (b) Na, Me_3SiCl, toluene, 100 °C, 7 h, then *p*-TsOH·H_2O; (c) Ac_2O, pyridine, rt, 24 h for **7a**. TsCl, pyridine, rt, 24 h for **7b**. MsCl, pyridine, CH_2Cl_2, rt, 24 h for **7c**.

Table 1. Acid promoted elimination of acyloin derivatives[a]



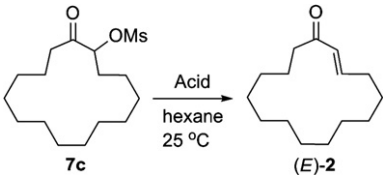
Entry	Substrate	LG	Time (h)	Conversion (%)	(*E*)-**2** yield[b] (%)
1	**6**	–OH	4	97	0
2	**7a**	–OAc	9	77	1
3	**7b**	–OTs	9	90	47
4	**7c**	–OMs	1	98	90

[a] Conditions: acyloin derivative (0.1 mmol) and sulfuric acid (0.4 mmol) in hexane (0.5 mL) at 25 °C with vigorous stirring.
[b] Isolated yield.

using acid promoted elimination of 2-mesyloxycyclopentadecanone (**7c**) (Scheme 1).

Acyloin derivatives **7** were prepared in 3 steps from readily available pentadecanedioic acid (**4**) as shown in Scheme 2. Fischer esterification of **4** with methanol gave diester **5** in quantitative yield. The acyloin condensation

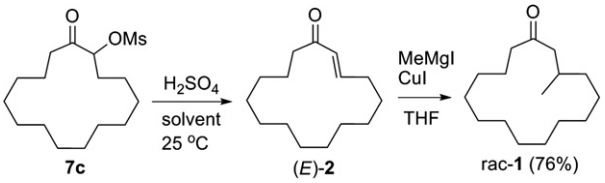
Table 2. Acid promoted elimination of 2-mesyloxycyclopentadecanone (**7c**)[a]



Entry	Acid	Time (h)	Conversion (%)	(*E*)-**2** yield[b] (%)
1	$AlCl_3$	9	85	5
2	$Sc(OTf)_3$	9	98	7
3	CH_3COOH	9	41	3
4	CF_3COOH	9	83	5
5	CH_3SO_3H	9	88	20
6	*p*-TsOH	9	83	63
7	H_2SO_4	1	98	90
8	CF_3SO_3H	0.3	99	94
9[c]	CF_3SO_3H	0.3	99	93

[a] Conditions: mesylate **7c** (0.1 mmol) and acid (0.4 mmol) in hexane (0.5 mL) at 25 °C with vigorous stirring.
[b] Isolated yield.
[c] CF_3SO_3H (0.1 mmol) was used.

Table 3. Solvent screening in acid promoted elimination of 2-mesyloxycyclopentadecanone (**7c**)[a]

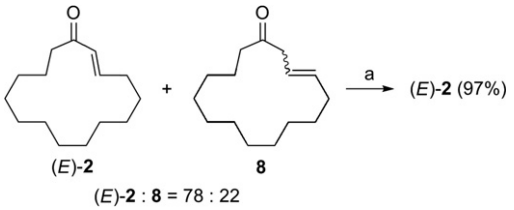


Entry	Solvent	Time (h)	Conversion (%)	(*E*)-**2** yield[b] (%)
1	Ether	9	23	9
2	DMSO	9	13	9
3	DMF	9	22	18
4	Hexane	1	98	90
5	CH_2Cl_2	3	97	93
6[c]	CH_2Cl_2	2	99	97

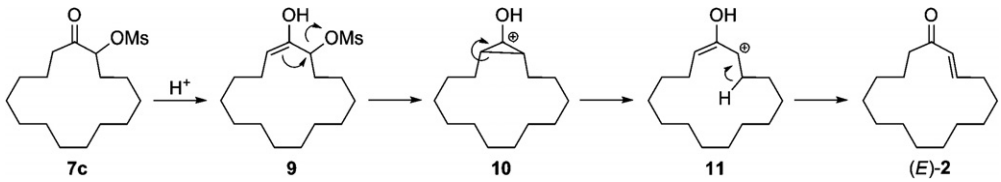
[a] Conditions: mesylate **7c** (0.1 mmol) and sulfuric acid (0.4 mmol) in hexane (0.5 mL) at 25 °C with vigorous stirring.
[b] Isolated yield.
[c] The reaction was carried out using mesylate **7c** (3.0 g, 9.4 mmol) and CF_3SO_3H (16 mmol) in CH_2Cl_2 (14 mL) at rt.

of **5** furnished acyloin **6** in high yield. Generally, to decrease the formation of intermolecular cyclized product, macrocyclization is performed in a highly diluted solution. In comparison, the acyloin condensation carried out in the presence of trimethylsilyl chloride gives acyloin **6** in 85% yield in toluene (0.53 M solution).[9] Acetylation, mesylation, and tosylation of acyloin **6** by standard reaction conditions furnished the acyloin derivatives **7** in good yields.

Sulfuric acid promoted elimination reactions of acyloin derivatives are compared in Table 1.[10] This elimination reaction depends on the leaving-group ability. Poor leaving-groups such as hydroxy and acetoxy groups did not give the desired enone **2** but an unidentified solid



Scheme 3. Reagents and conditions: (a) mixture of ketones (0.1 mmol) and sulfuric acid (0.4 mmol) in hexane (0.5 mL) at 25 °C for 1 h with vigorous stirring.



Scheme 4. Proposed reaction mechanism.

(entries 1 and 2). Sulfonate leaving groups in general were best for acid promoted elimination, but in particular, the mesylate was the best performing leaving group. The reaction of 2-mesyloxycyclopentadecanone (**7c**) took place in the presence of sulfuric acid at room temperature in a short reaction time and 90% yield (entry 4). Interestingly, the desired (*E*)-enone **2** was exclusively formed, confirmed by a single peak in capillary GC analysis. Neither (*Z*)-enone **2** nor 3-cyclopentadecen-1-one (**8**) was observed.

2-Mesyloxycyclopentadecanone (**7c**) was chosen for the further study of acid promoted elimination reactions with various acids (Table 2). Lewis acids and weak Brønsted acids were ineffective elimination reagents (entries 1–4), whereas sulfonic acids improved the reactivity as well as yield (entries 5–9). Trifluoromethanesulfonic acid was the best acid of those tested in the elimination reaction, giving (*E*)-enone **2** stereoselectively in a very short reaction time and 94% yield (entries 8 and 9).

Solvent screening studies were performed as shown in Table 3. Polar solvents such as DMF and DMSO resulted in low yields (entries 1–3). Whereas, dichloromethane and hexane gave high yields (entries 4 and 5).[11] These reaction conditions were readily scaled. To study a multi-gram-scale synthesis, trifluoromethanesulfonic acid (1.7 equiv) was added to a solution of mesylate **7c** (3.0 g, 9.4 mmol) in CH_2Cl_2 (14 mL) at room temperature. The reaction mixture was stirred for 2 h. Usual workup and purification to afford enone (*E*)-**2** (2.0 g, 97%, entry 6). Reacting (*E*)-**2** with a methyl Grignard reagent in the presence of cuprous iodide in THF produced a racemic mixture of muscone (*rac*-**1**) in 76% yield. Since optical resolution of *rac*-**1** using tartaric acid derivatives was recently achieved,[12] this simple and practical synthesis of *rac*-**1** from dicarboxylic acid **4** makes an immediate contribution to fragrance chemistry.

Thermal dehydration of **6** or ammonium sulfonates promoted elimination of **7c** results in the formation of enone (*E*)-**2** and ketone **8** as noted above. Although these compounds are inseparable by column chromatography, we found that sulfuric acid promoted isomerization of **8** into (*E*)-**2** proceeded with high stereoselectivity (Scheme 3). This result suggests that even if the undesired ketone **8** is formed during acid promoted elimination reaction, it must be converted to (*E*)-**2**. Therefore, no formation of **8** was observed.

The proposed mechanism for the elimination reaction is shown in Scheme 4.[13] Mesylate **7c** is protonated to form enol intermediate **9**, which undergoes intramolecular nucleophilic substitution. Cyclopropyl cationic intermediate **10** was transformed to the cation intermediate **11** with C–C bond fission. β-Elimination and tautomerization finally furnishes the desired enone (*E*)-**2**.

In summary, we have developed a practical synthesis of (*E*)-2-cyclopentadecen-1-one (**2**) from readily available pentadecanedioic acid (**4**). The strong acid promoted elimination reactions of acyloin derivatives demonstrate excellent stereoselectivity to give (*E*)-**2** which is an important precursor of macrocyclic muscone. No formation of undesired isomers was observed. Further studies focusing on the use of the acid promoted elimination reactions of acyloin derivatives are currently under investigation and will be reported in due course.

Acknowledgments

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10. *Typical procedure*: To a solution of 2-mesyloxycyclopentadecanone (**7c**) (0.1 mmol) in hexane (0.5 mL) were added sulfuric acid (0.4 mmol) and/or trifluoromethanesulfonic acid (0.1 mmol) at 25 °C. The reaction mixture was stirred for the indicated time, and quenched with saturated $NaHCO_3$ aq (1.0 mL). Aqueous layer was separated and extracted with ethyl acetate (3×1 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated to give the crude enone **2**, which was purified by column chromatography (silica gel) to give (*E*)-cyclopentadec-2-enone (*E*)-**2** as a colorless liquid: registry number (*E*)-56345-01-8, (*Z*)-56345-02-9, 32247-08-8; $R_f = 0.63$ (hexane–AcOEt = 80:20); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16–1.31 (m, 16H, $8 \times$ –CH_2–), 1.47–1.60 (m, 2H, –CH_2–CH$_2$–CH=CH–), 1.60–1.76 (m, 2H, –CH_2–CH$_2$–C=O), 2.20–2.33 (m, 2H, –CH_2–CH=CH–), 2.50 (t, $J = 6.4$ Hz, 2H, –CH$_2$–C=O), 6.19 (d,$J = 15.4$ Hz, 1H, –CH=CH–C=O), 6.82 (td, $J = 7.4$, 15.4 Hz, 1H, –CH=CH–C=O); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 25.07$ (CH_2), 25.16 (CH_2), 25.82 (CH_2), 26.01 (CH_2), 26.30 (CH_2), 26.47 (CH_2), 26.49 (CH_2), 26.69 (CH_2), 26.76 (CH_2), 31.45 (CH_2), 39.89 (CH_2), 115.90 (CH_2), 130.70 (CH), 148.07 (CH), 201.86 (O=C); GC $t_R = 23.24$ min (CBP1-M25-025, $N_2 = 0.6$ kg/cm^2, $H_2 = 0.5$ kg/cm^2, air = 0.5 kg/cm^2, INJ. 200 °C, DET.T. 250 °C, COL (initial temp; 170 °C, initial time; 10 min, PROG rate; 0.5 °C/min, final temp; 180 °C, final time; 10 min)).
11. We also prepared some other macrocyclic enones by the use of the same synthetic procedure (Table 3, entry 5); (*E*)-cycloicos-2-enone (y. 98%), (*E*)-cyclohexadec-2-enone (y. 98%), (*E*)-cyclotridec-2-enone (y. 66%), and (*E*)-cyclododec-2-enone (y. 38%). Elimination reactions of less than 10-membered ring mesylates did not proceed, probably due to a highly labile cyclopropyl cationic intermediate.
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13. Recently Tanabe and co-workers reported similar reaction mechanism of ammonium sulfonates promoted elimination of **7b** or **7c**. They have noted that the elimination reaction is considered to proceed through the cyclopropyl cationic intermediates, that is, via the 1,3-elimination pathway. Uchimura, D.; Funatomi, T.; Tanabe, Y. In the *48*th *Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics* (*TEAC*48); The Chemical Society of Japan: Yamaguchi, 2004, pp 120–122.