

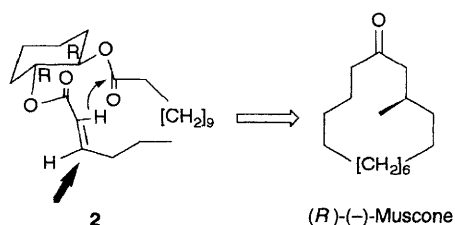
## Asymmetric Syntheses of (*R*)-(-)-Muscone based on Diastereoselective Conjugate Addition

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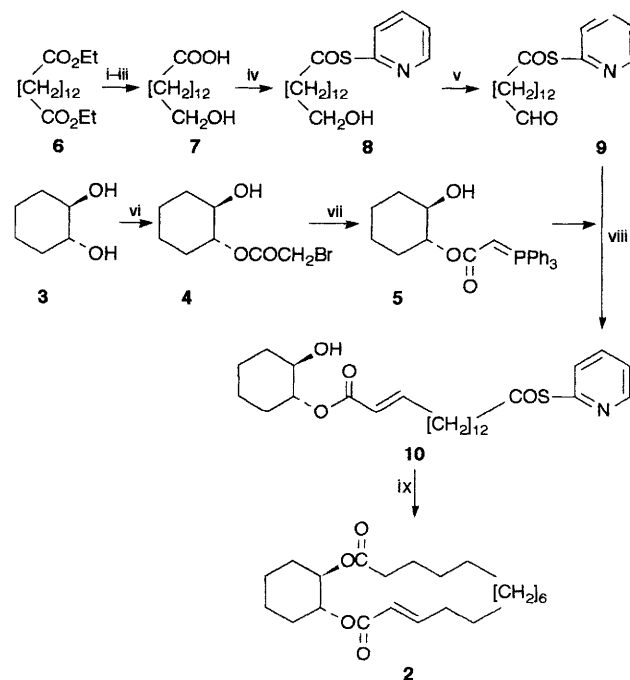
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(*R*)-(-)-Muscone was synthesized in a stereocontrolled manner via the diastereoselective conjugate addition to a cyclic  $\alpha,\beta$ -unsaturated ester of (*R,R*)-cyclohexane-1,2-diol accompanied by spontaneous Dieckmann condensation.

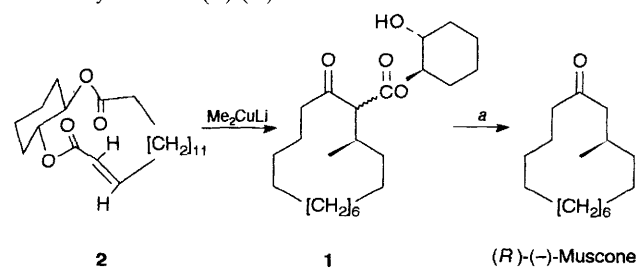
(*R*)-(-)-Muscone is a principal odoriferous constituent isolated from the male musk deer, *Moschus moschiferus*.<sup>1</sup> The limited supply of this compound from nature requires new synthetic methods,<sup>2,3</sup> and we now describe a new approach. We have already reported that the conjugate addition of organocuprate reagents to  $\alpha,\beta$ -unsaturated esters of chiral *trans*-cyclohexanediols proceeds in a highly diastereoselective manner, and, in addition, the intramolecular trapping of this reaction affords *trans*-cyclized products diastereoselectively.<sup>4</sup> The 20-membered ring diesters **2** contain an (*R,R*)-cyclohexane-1,2-diol unit readily prepared by enzymatic procedures, and should have several synthetic advantages: (i) the  $\alpha,\beta$ -unsaturated ester in the 20-membered ring conformationally favours the *s-trans* form; (ii) reagents attack, in a diastereoselective manner, the  $\alpha,\beta$ -unsaturated ester from outside the 20-membered ring and the two closely located esters subsequently undergo Dieckmann cyclization; (iii) the 3-methylated 15-membered cyclic  $\beta$ -ketoester is converted to (*R*)-(-)-muscone (Scheme 1) under decarboxylation conditions, with recovery of the chiral (*R,R*)-cyclohexane-1,2-diol.



Scheme 1



**Scheme 2** Reagents and conditions: i, KOH (1 equiv.), MeOH-H<sub>2</sub>O, 30%; ii, BH<sub>3</sub>-Me<sub>2</sub>S, tetrahydrofuran (THF), 89%; iii, KOH, MeOH-H<sub>2</sub>O, 88%; iv, di-2-pyridyl disulphide, PPh<sub>3</sub>, THF, 79%; v, Swern oxidation, 70%; vi, BrCH<sub>2</sub>COCl, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 4 h, 64%; vii, PPh<sub>3</sub>, C<sub>6</sub>H<sub>6</sub>, reflux, 66%, then KHCO<sub>3</sub>, 92%; viii, toluene, 71%; ix, xylene, reflux, 24 h, 57%

**Table 1** Synthesis of (*R*)-(-)-muscone from **2**

Entry	Solvent	<i>T</i> /°C	Yield (%) (1 from 2)	Muscone		Yield (%) (from 1)
				[α] <sub>D</sub> <sup>23</sup> (MeOH)	E.e. (%) <sup>b</sup>	
1	Et <sub>2</sub> O	-10	71	-9.9° (c 1.02)	71	49
2	Toluene	-10	73	-11.4° (c 1.33)	85	52
3	Toluene	-45	69	-11.1° (c 1.42)	78	55
4	Hexane	-10	Complex			
5	THF	-10	Recovery of 2			
6	DME	-10	Recovery of 2			

<sup>a</sup> LiAlH<sub>4</sub>; Jones oxidation; then 50 °C. <sup>b</sup> E.e. = enantiomeric excess.

Compound **2** was prepared by the reactions in Scheme 2. (*R,R*)-Cyclohexane-1,2-diol<sup>5</sup> was converted to its monobromoacetate **4**, and treatment with PPh<sub>3</sub> afforded the phosphonium salt which was converted to the ylide **5** with 5% aqueous KHCO<sub>3</sub>. Selective hydrolysis of diethyl tetradecanedioate **6** to the monocarboxylic acid, and subsequent reduction to the primary alcohol followed by hydrolysis of the remaining ester unit gave the hydroxy acid **7**. Conversion of **7** to the thioester **8**, and subsequent Swern oxidation afforded the aldehyde **9**. Wittig reaction of **9** with **5** (toluene, room temperature, overnight) afforded the α,β-unsaturated monoester **10** (mixture of *trans*- and *cis*-isomers in 1:1 ratio) of (*R,R*)-cyclohexane-1,2-diol, which was subjected to the intramolecular transesterification<sup>6</sup> under high dilution conditions to give **2** in 57% yield. In this process, isomerization to the desired *trans*-isomer was observed, and **2** was obtained in a 94:6 (*trans*:*cis*) ratio.

Conjugate addition of dimethylcuprate to **2** and spontaneous cyclization were examined under various conditions. In accord with our assumption, conjugate addition accompanied by spontaneous Dieckmann condensation was observed in all cases. Reduction of the 15-membered cyclic β-ketoester **1** with LiAlH<sub>4</sub>, and subsequent Jones oxidation followed by

decarboxylation (50 °C) afforded (*R*)-(-)-muscone (49–55% yield from **1**),<sup>†</sup> whose spectroscopic data were identical with the reported values.<sup>3d</sup> In this reaction, (*R,R*)-cyclohexane-1,2-diol was also recovered without any loss of optical purity. As shown in Table 1, this reaction is markedly influenced by the solvent. The conditions of entry 2 showed the best optical purity (85% e.e.). (*S*)-(+)-Muscone (unnatural form) was also prepared in 40% yield (87% e.e.) from the corresponding **2** by using (*S,S*)-cyclohexane-1,2-diol.

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<sup>†</sup> The optical yield of (*R*)-(-)-muscone was determined from its 270 MHz <sup>13</sup>C NMR spectra, after conversion to the acetal with chiral (*R,R*)-butanediol. Although muscone ([α]<sub>D</sub> -11.4°) in entry 2 shows high optical purity corresponding to that of the natural compound ([α]<sub>D</sub> -11.7°), the <sup>13</sup>C NMR spectrum of the chiral acetal showed 85% e.e.

Selected spectral data of main products. **10**: IR (neat) ν/cm<sup>-1</sup> 3400, 1710, 1650, 1570, 850 and 720; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.61 (4H, m), 3.60 (1H, m), 4.61 (1H, m), 5.77 (0.5H, dt, *J* 11.5 and 1.7 Hz), 5.83 (0.5H, dt, *J* 15.6 and 1.6 Hz), 6.26 (0.5H, dt, *J* 11.5 and 7.3 Hz), 7.00 (0.5H, dt, *J* 15.6 and 6.8 Hz) and 7.21–8.66 (4H, m); *m/z* 475 (M<sup>+</sup>), 364, 345, 267, 111 and 98. **2**: [α]<sub>D</sub><sup>22</sup> -10.4° (CHCl<sub>3</sub>, c 1.55); IR (neat) ν/cm<sup>-1</sup> 2830, 1720, 1650 and 1210; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.23 (4H, m), 4.83 (2H, m), 5.78 (1H, dt, *J* 15.5 and 1.7 Hz) and 6.97 (1H, ddd, *J* 15.5, 8.3 and 5.7 Hz); *m/z* 364 (M<sup>+</sup>), 267, 250 and 98. **1**: IR (neat) ν/cm<sup>-1</sup> 3450, 2930, 1730 and 1190; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.91–0.97 (3H, m), 2.30–2.60 (3H, m), 3.60 (1H, m), 3.40, 4.62 (1H, m) and 4.83 (1H, m); *m/z* 380 (M<sup>+</sup>), 362, 282 and 265.