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

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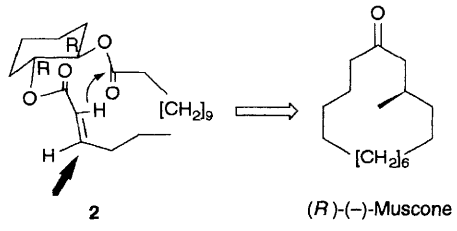
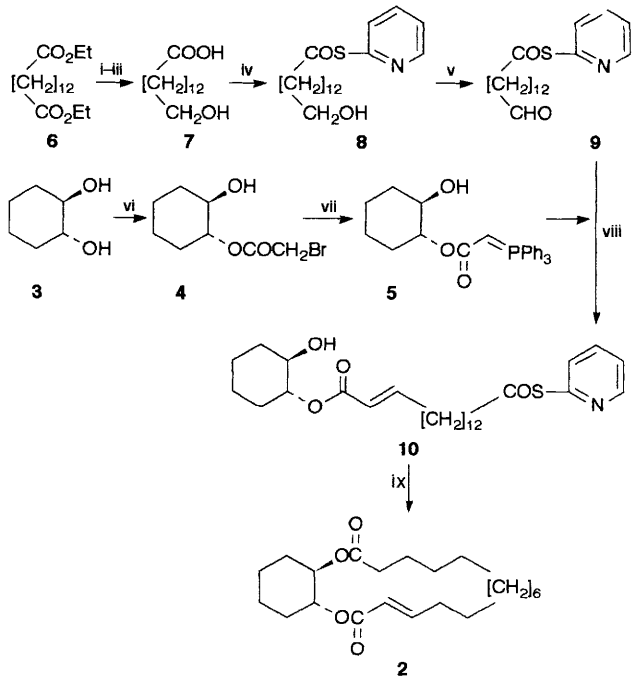
(*R*)-(−)-Muscone was synthesized in a stereocontrolled manner *via* the diastereoselective conjugate addition to a cyclic α,β-unsaturated ester of (*R,R*)-cyclohexane-1,2-diol accompanied by spontaneous Dieckmann condensation.

(*R*)-(−)-Muscone is a principal odoriferous constituent isolated from the male musk deer, *Moschus moschiferus*.[1] The limited supply of this compound from nature requires new synthetic methods,[2,3] and we now describe a new approach. We have already reported that the conjugate addition of organocuprate reagents to α,β-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.[4] 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 α,β-unsaturated ester in the 20-membered ring conformationally favours the s-*trans* form; (*ii*) reagents attack, in a diastereoselective manner, the α,β-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 β-ketoester is converted to (*R*)-(−)-muscone (Scheme 1) under decarboxylation conditions, with recovery of the chiral (*R,R*)-cyclohexane-1,2-diol.



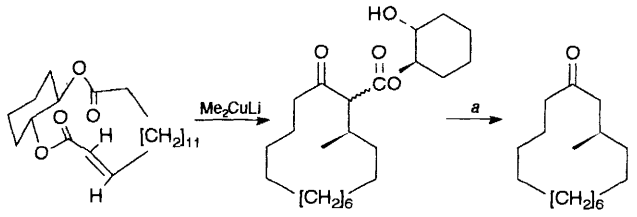
2 (*R*)-(−)-Muscone

Scheme 1



Scheme 2 *Reagents and conditions*: i, KOH (1 equiv.), MeOH–H_2O, 30%; ii, BH_3–Me_2S, tetrahydrofuran (THF), 89%; iii, KOH, MeOH–H_2O, 88%; iv, di-2-pyridyl disulphide, PPh_3, THF, 79%; v, Swern oxidation, 70%; vi, $BrCH_2COCl$, CH_2Cl_2, reflux, 4 h, 64%; vii, PPh_3, C_6H_6, reflux, 66%, then $KHCO_3$, 92%; viii, toluene, 71%; ix, xylene, reflux, 24 h, 57%

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



2 **1** (*R*)-(−)-Muscone

Entry	Solvent	*T*/°C	Yield (%) (**1** from **2**)	Muscone $[\alpha]_D^{23}$ (MeOH)	E.e. (%)[b]	Yield (%) (from **1**)
1	Et_2O	−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**			

[a] $LiAlH_4$; Jones oxidation; then 50 °C. [b] E.e. = enantiomeric excess.

Compound **2** was prepared by the reactions in Scheme 2. (*R,R*)-Cyclohexane-1,2-diol[5] was converted to its monobromoacetate **4**, and treatment with PPh_3 afforded the phosphonium salt which was converted to the ylide **5** with 5% aqueous $KHCO_3$. 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[6] 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 $LiAlH_4$, and subsequent Jones oxidation followed by decarboxylation (50 °C) afforded (*R*)-(−)-muscone (49–55% yield from **1**),† whose spectroscopic data were identical with the reported values.[3d] 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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† The optical yield of (*R*)-(−)-muscone was determined from its 270 MHz ^{13}C NMR spectra, after conversion to the acetal with chiral (*R,R*)-butanediol. Although muscone ($[\alpha]_D$ −11.4°) in entry 2 shows high optical purity corresponding to that of the natural compound ($[\alpha]_D$ −11.7°), the ^{13}C NMR spectrum of the chiral acetal showed 85% e.e.

Selected spectral data of main products. **10**: IR (neat) ν/cm^{-1} 3400, 1710, 1650, 1570, 850 and 720; ^1H NMR ($CDCl_3$) 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^+), 364, 345, 267, 111 and 98. **2**: $[\alpha]_D^{22}$ −10.4° ($CHCl_3$, *c* 1.55); IR (neat) ν/cm^{-1} 2830, 1720, 1650 and 1210; ^1H NMR ($CDCl_3$) 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^+), 267, 250 and 98. **1**: IR (neat) ν/cm^{-1} 3450, 2930, 1730 and 1190; ^1H NMR ($CDCl_3$) 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^+), 362, 282 and 265.