Efficient Synthesis of (−)-(*R*)-Muscone by Enantioselective Protonation

by **Charles Fehr***, **José Galindo**, **Iris Farris**, and **Ana Cuenca**^{1})

Firmenich SA, Corporate R&D, P.O. Box 239, CH-1211 Geneva 8
(phone: +41 22 780 36 38; fax: +41 22 780 33 34; e-mail: charles.fehr@firmenich.com)

Dedicated to Dr. *Günther Ohloff* on the occasion of his 80th birthday

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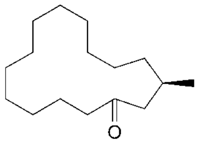
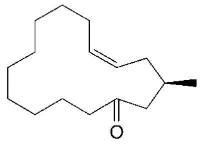
A new synthesis of (−)-(*R*)-muscone ((*R*)-**1**) by means of enantioselective protonation of a bicyclic ketone enolate as the key step (see **6** → (*S*)-**4** in *Scheme 2*) is presented. The C$_{15}$ macrocyclic system is obtained by ozonolysis (*Scheme 7*).

Introduction. – In recent years, macrocyclic musks [1][2] have gained renewed interest for their excellent odor qualities (warm, sensual, animal, natural), and for their better biodegradability as compared to benzenoid musks [2][3]. It is well-known that (−)-(*R*)-muscone ((*R*)-**1**), the principal odorous constituent of the male musk deer, exhibits a much more pronounced musk character than the unnatural (+)-(*S*)-muscone [4], and, similarly, we recently established that (+)-(*R*,*Z*)-5-muscenone ((*R*)-**2**) is an outstanding musk odorant, whereas its enantiomer is only weakly musky [4]. Recently measured threshold values (in the vapor phase; 35 panelists) [4] are: (*R*)-**1** (98% ee), $4.3 \cdot 10^{-4}$ µg/l air; (*S*)-**1** (98% ee), $9.5 \cdot 10^{-3}$ µg/l air; (*R*)-**2** (98% ee), $2.7 \cdot 10^{-5}$ µg/l air; (*S*)-**2** (98% ee), $3.0 \cdot 10^{-3}$ µg/l air.



(-)-(*R*)-muscone

(*R*)-**1**



(+)-(*R*,*Z*)-5-muscenone

(*R*)-**2**

The synthesis of (+)-(*R*,*Z*)-5-muscenone ((*R*)-**2**) [4] was based on a highly selective kinetic resolution (*Corey–Bakshi–Shibata* (CBS) reduction), and (−)-(*R*)-muscone ((*R*)-**1**) was obtained by hydrogenation of (*R*)-**2** and by an original transformation of the undesired enantiomer of the kinetic-resolution process (enantioconvergent transformation). Whereas this approach is concise and very efficient for (*R*)-**2**, we were interested to find a more-direct approach for (−)-(*R*)-muscone ((*R*)-**1**) [5].

In 1967, *Eschenmoser*, *Felix*, and *Ohloff* [6] published the syntheses of *Exaltone*® (=cyclopentadecanone; **3**) and (±)-muscone ((±)-**1**) by fragmentation of epoxy-

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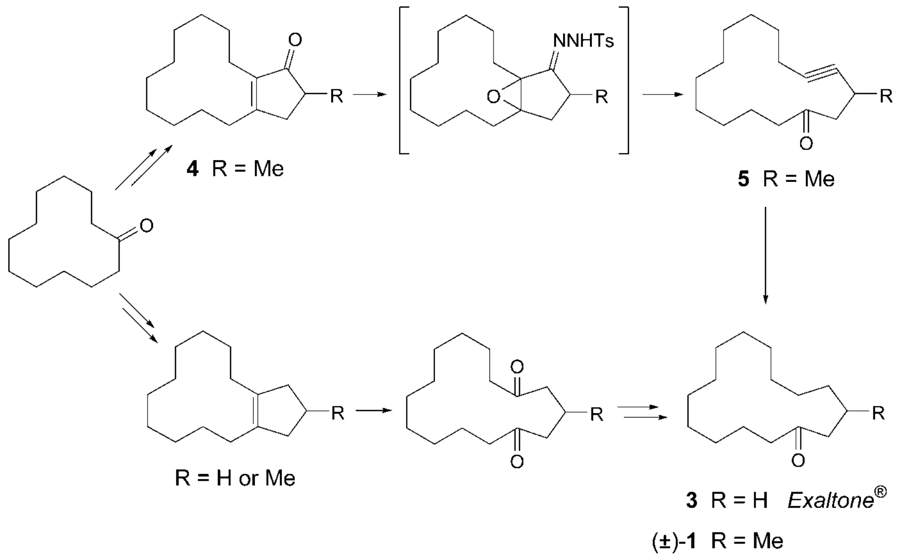
^{1}) Postdoctoral fellow at *Firmenich SA* (November 2001–January 2002).

hydrazones (*Scheme 1*). This and the ozonolysis route described by *Ohloff*, *Becker*, and *Schulte-Elte* [7] (*Scheme 1*) represent the first examples of a C_3-ring-expansion sequence by using cyclododecanone as an inexpensive starting material. Both processes have allowed the high-tonnage production of *Exaltone*® and muscone. The *N*-bromosuccinimide (NBS)-mediated fragmentation of enone hydrazones published in 1979 [8] provided a further improvement of these syntheses (*Scheme 1*).

Scheme 1



If α-methyl ketone **4** could be prepared in enantiomerically enriched form, application of the *Eschenmoser* fragmentation or the NBS-mediated fragmentation should give access to the enantiomerically enriched macrocyclic ketone **5** and thus muscone **1**. We therefore decided to study the enantioselective protonation of enolate **6** derived from the racemic ketone **4**[2]).

Results and Discussion. – In a first experiment, (±)-**4** was deprotonated with lithium diisopropylamide (LDA), and the resulting enolate **6** was protonated with (–)-*N*-isopropylephedrine **7**, which had already been used with success in various other enolate protonations [10][11][2]) (*Scheme 2*). To minimize the risk of racemization, enolate **6** was added to a solution of **7** at – 78°. After complete addition, excess Me_3SiCl was added to silylate any remaining enolate. A sample of the ketone was reduced ($LiAlH_4$, Et_2O), and the resulting diastereoisomeric alcohols (or trimethylsilyl ethers) could be separated by chiral GC (73% ee). The absolute configuration of **4** was subsequently determined to be (*S*) by conversion into (*R*)-muscone (*Scheme 2*, *Entry 1*).

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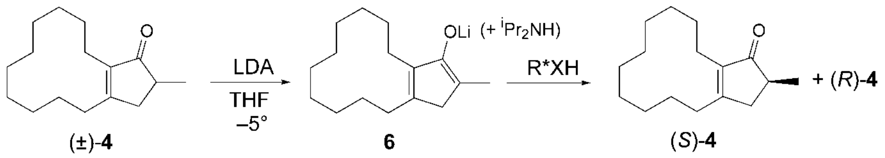
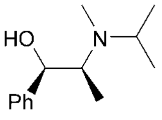
[2]) For reviews on enantioselective protonations, see [9].

Scheme 2



Entry	LDA [equiv.]	R*XH [equiv.]	Temp. [°]	**4** [% ee]
1	2.15	**7** (2.50)[a])	– 78	73 (*S*)
2	1.20	**7** (1.40)	– 78	70 (*S*)
3	1.20	**7** (1.40)	– 100	79 (*S*)
4	1.20	**7** (0.5)[b])	– 78	60 (*S*)
5	2.15	**8** (2.50) [a])	– 100	16 (*R*)
6	2.50	**9** (2.50) [a])	– 100	20 (*R*)
7	2.15	**10** (3.00) [a])	– 100	60 (*R*)
8	2.15	**11** (3.00) [a])	– 100	42 (*R*)

[a]) Inverse addition (**6** onto R*XH). [b]) Followed by the addition of 1-phenylpropan-2-one at – 100°.



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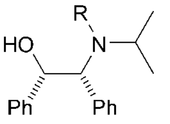
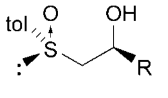
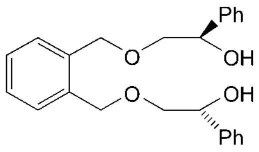


8 R = H
9 R = Me



10 R = ^{i}Pr
11 R = Ph
12 R = CF$_3$



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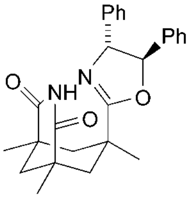

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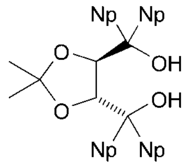
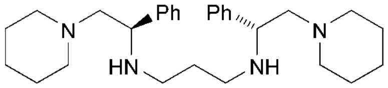


15 Np = naphthalen-1-yl



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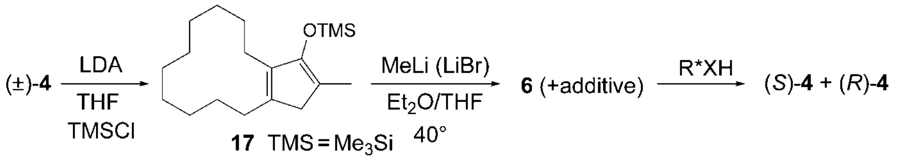
The quantity of LDA and proton donor could be diminished to almost equimolar amounts: protonation at – 78° gave (*S*)-**4** with 70% ee (*Scheme 2*, *Entry 2*). Protonation of the enolate at – 100° afforded (*S*)-**4** with 79% ee (*Entry 3*). We also demonstrated that protonation was complete immediately after addition of **6**, as prolonged protonation times did not alter the result. Finally, we showed that the protonation of enolate **6** could also be performed with sub-stoichiometric amounts of chiral proton donor (0.5 equiv. of **7**; *Entry 4*). Completing the protonation with 1-phenylpropan-2-one still afforded (*S*)-**4** with 60% ee; this catalytic reaction was discovered in our laboratory in 1994 [11].

We next decided to extend this study to the application of other chiral reagents and protonation conditions. Indeed, a wealth of chiral proton donors have been investigated, but comparisons of chiral reagents for a specific enolate are rare. When the protonation of **6** was performed with amino alcohols **8** or **9** [12], structurally related to **7**, (*R*)-**4** was isolated with only 16 and 20% ee, respectively (*Scheme 2*, *Entries 5* and *6*). Protonation with the sulfinyl-substituted alcohols **10** and **11**, successfully used by *Asensio*'s group [13], afforded (*R*)-**4** with 60 and 42% ee, respectively (*Entries 7* and *8*).

In addition, we also studied the protonation of amine-free enolate **6**, obtained from silyl enol ether **17** and methyllithium (*Scheme 3*). Protonation of amine-free **6** with (−)-*N*-isopropylephedrine **7** proved to be less effective than the first version and afforded (*S*)-**4** with only 51% ee (*Scheme 3*, *Entry 1*).

Scheme 3



Entry	MeLi or MeLi · LiBr [equiv.]	Additive [equiv.]	R*XH [equiv.]	Temp. [°]	**4** [% ee]
1	MeLi (1.12)		**7** (1.3)[a]	-78	51 (*S*)
2	MeLi (1.12)	$^{\mathrm{i}}\mathrm{Pr_2NH}$ (1.12)	**7** (1.3) [a]	-78	71 (*S*)
3	MeLi · LiBr (1.20)	$^{\mathrm{i}}\mathrm{Pr_2NH}$ (1.12)	**7** (1.3) [a]	-100	55 (*S*)
4	MeLi · LiBr (1.20)		**10** (3.0) [a]	-100	70 (*R*)
5	MeLi · LiBr (1.20)	LiBr (5.0)	**10** (3.0) [a]	-100	79 (*R*)
6	MeLi · LiBr (1.20)		**12** (3.0) [a]	-100	5 (*R*)
7	MeLi · LiBr (1.20)		**13** (2.0) [a]	-100	60 (*R*)
8	MeLi · LiBr (1.10)		**14** (1.1)	-78	55 (*S*)
9	MeLi · LiBr (1.20)		**15** (1.3) [a]	-78	44 (*S*)
10	MeLi · LiBr[b] (1.20)		**16** (1.2), then citric acid (excess)	-78	12 (*R*)

[a] Inverse addition (**6** onto R*XH). [b] Toluene/THF.

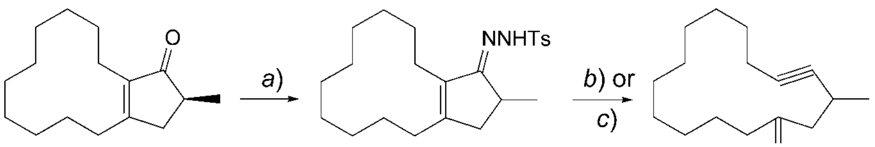
Indeed, when **6** was treated with diisopropylamine ($^{\mathrm{i}}\mathrm{Pr_2NH}$) prior to treatment with **7**, an ee of 71% was measured (*Scheme 3*, *Entry 2*), as would be expected from the experiments described in *Scheme 2* (there *Entries 1–3*). As replacement of MeLi by LiBr-complexed MeLi in the presence of $^{\mathrm{i}}\mathrm{Pr_2NH}$ had a negative effect (*Scheme 3*, *Entry 3*; 55% ee), MeLi · LiBr in the absence of $^{\mathrm{i}}\mathrm{Pr_2NH}$ was not tested. For the investigation of the chiral reagents **10** and **12**–**15**, enolate **6** contained always at least 1 equiv. of LiBr, in accordance with the literature reports. Protonation of **6** · LiBr with excess sulfinyl alcohol **10** [12] at $-100°$ furnished (*R*)-**4** with 70% ee (*Entry 4*). When enol ether **17** was treated with 5 equiv. of dried LiBr and then treated with MeLi · LiBr, protonation with **10** led to an improved ee of 79% (*Entry 5*). On the other hand, the (trifluoromethyl)-substituted sulfinyl alcohol **12** [13] was inappropriate for this substrate, perhaps due to its increased acidity (*Entry 6*; 5% ee). Application of *Takeuchi*'s reagent **13** [14] gave 60% ee (*Entry 7*), application of *Yamamoto*'s reagent **14** [15] 55% ee (*Entry 8*), and TADDOL derivative **15** [16] afforded 44% ee (*Entry 9*). Finally, we also tested *Koga*'s tetramine ligand **16** by using excess 10% aqueous citric acid for the protonation of the chiral enolate complex [17]. This procedure gave excellent results for 2-methyl-1-tetralone, but only 12% ee in our case (*Entry 10*). As Li enolate **6** was not soluble in toluene, we added some THF, which, in turn, may well have changed the aggregation of the enolate complex.

In conclusion, the most-efficient conditions in terms of selectivity, simplicity, recovery of the reagent, and availability of both enantiomers of the reagent, are those of *Scheme 2*, *Entry 3*. The racemic ketone **4** is deprotonated with 1.2 equiv. of LDA and protonated at – 100° with **7** (1.4 equiv.), thus affording (*S*)-**4** with 79% ee. The recovery of **7** is carried out by an acid-base extractive workup.

We next examined whether hydrazone formation and fragmentation would occur without racemization. As shown in *Scheme 4*, (*S*)-**4** racemized during formation of the hydrazone, and the fragmentation product **5** was racemic, as established by chiral GC of the corresponding diastereomeric alcohols. We do not know whether hydrazone **18** is partially or completely racemized.

Whereas nonracemic ketone **4** does not racemize under neutral conditions (extraction, distillation, chromatography), it is prone to racemization under acidic and basic conditions (*e.g.*, under conditions of enolate protonation at 0°).

Scheme 4



(*S*)-**4** (51% ee)

18 (unknown ee)
(+ (*S*)-**4** (33% ee))

5 (0% ee)

a) H_2NNHTs, mol.-sieves 4 Å, EtOH, reflux, 15 h. *b*) 1. NBS (2.2 equiv.), acetone, THF, $HO(CH_2)_2OH$, – 10°, 3 min; 2. aq. $NaHCO_3$ soln., 50°, 30 min. *c*) *m*-CPBA (1.2 equiv.), CH_2Cl_2, reflux, 1 h.

To minimize any risk of racemization, we reduced (*S*)-**4** diastereoselectively to (*S,S*)-**19** with diisobutylaluminium hydride (DIBAH) [18] in THF at – 75° (diastereoselectivity 89 : 11) (*Scheme 5*) or with *Superhydride*® (lithium triethylborohydride) in THF at – 75° (diastereoselectivity 94 : 6).When (*S*)-**4** (70% ee) was reduced with DIBAH, distilled (*S,S*)-**19** (containing 11% of diastereoisomer) was obtained in 96% yield. Crystallization from heptane afforded pure (*S,S*)-**19** (98% ee) in 58% yield and mother liquors (mixture of diastereoisomers and enantiomers; 29%). These could be recycled to **4** by *Jones* oxidation (92%), thus improving the overall yield of the process³). As the ee of (*S,S*)-**19** can be easily increased by crystallization, we conveniently prepared (*S*)-**4** according *to Scheme 2*, *Entry 2*, in 70% ee, reduced with

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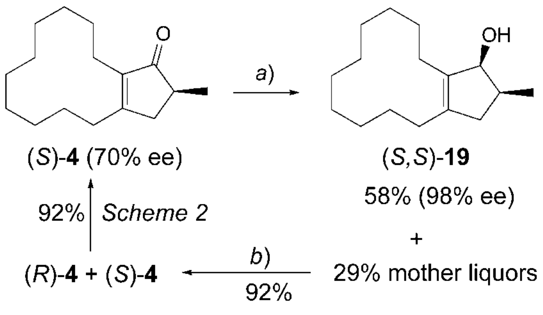
³) Alternatively, the ee of (*S*)-**4** (79% ee) could be increased by low-temperature crystallizations.

Scheme 5

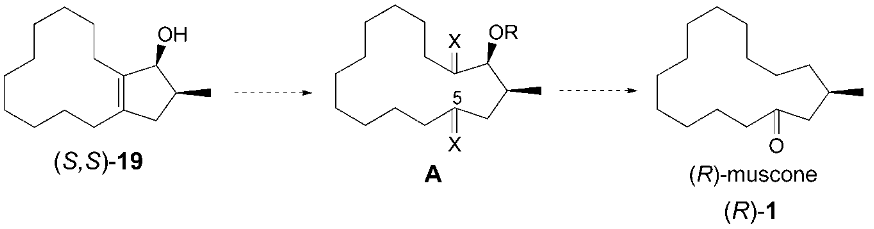


a) DIBAH (1.05 equiv), –78°, THF. b) *Jones* reagent, acetone, 10°.

DIBAH (more convenient than *Superhydride*®, which requires an oxidative workup followed by extraction), and crystallized the resulting (*S*,*S*)-**19**.

Transformation of (*S*,*S*)-**19** into (*R*)-muscone requires an oxidative ring cleavage, followed by functional-group modification of **A** in such a way that the C(5)=X group becomes the keto function of muscone (*Scheme 6*).

Scheme 6

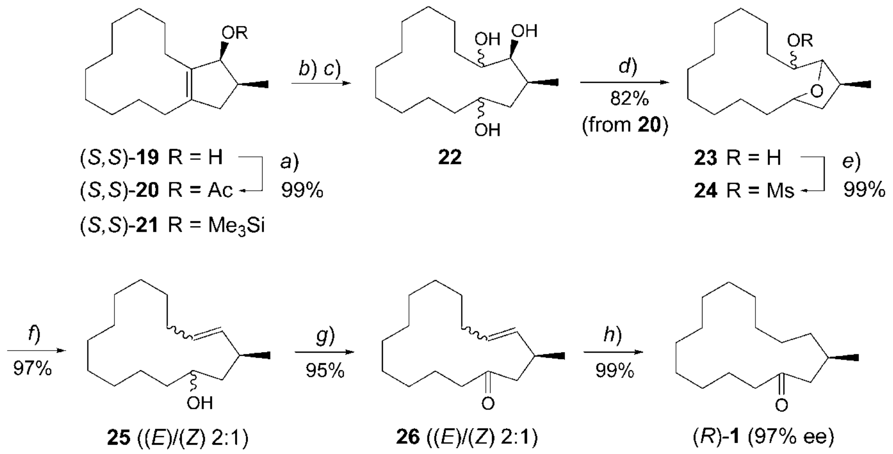


Preliminary ozonolyses performed on (*S*,*S*)-**19** and the corresponding acetate (*S*,*S*)-**20** and silyl ether (*S*,*S*)-**21** revealed that the formed ozonides are quite stable and difficult to reduce (H_2, Pd or Me_2S or $NaBH_4$; ^{13}C-NMR: 2*s* at *ca.* 110 ppm). Finally, the simplest and most-efficient procedure turned out to be the ozonolysis of acetate (*S*,*S*)-**20** (obtained in 99% yield), followed by $LiAlH_4$ reduction to triol **22** (diastereomer mixture; 86% yield) (*Scheme 7*).

All attempts to convert the vicinal-diol functionality into an olefin failed. Neither the *Corey–Winter* method (*via* a thiocarbonate) [19] nor the *Eastwood* procedure (*via* an orthoester) [20] was effective. A modification of the latter (by using Me_2N-$CH(OMe)_2$) [21] was also unsuccessful. We, therefore, followed another route, based on a reductive elimination as the key step.

Thus, unpurified triol **22** (100% yield) was cyclized under acidic conditions, and the resulting furanyl alcohol **23** (82% yield) was converted to mesylate **24** (99% yield), which underwent smooth reductive elimination in the presence of LDBB (=4,4′-di(*tert*-butyl)[1,1′-biphenyl]yllithium) in THF at –78° [22] (*Scheme 7*). The olefinic alcohol **25** was obtained in 97% yield as a mixture of four isomers (*E*)/(*Z*) *ca.* 2:1). *Jones*

Scheme 7



a) Ac_2O (1.2 equiv.), pyridine, cat. *N,N*-dimethylpyridin-4-amine (DMAP), 5°. *b*) O_3, CH_2Cl_2, $-78°$, then aq. $NaHCO_3$ soln. *c*) $LiAlH_4$ (5.0 equiv.), Et_2O, 35°, then H_2O, then 10% HCl soln. *d*) Cat. $TsOH \cdot H_2O$, toluene, 110° (*Dean–Stark*). *e*) MsCl (1.2 equiv.), Et_3N (1.6 equiv.), CH_2Cl_2, 0°. *f*) LDBB (3.3 equiv.), THF, $-78°$. *g*) *Jones* reagent (1.2 equiv.), acetone, 0°. *h*) $[Ir(cod)(py)(PCy_3)][PF_6]$ (*Crabtree*'s catalyst), H_2, CH_2Cl_2.

oxidation of **25** afforded muscenone **26** (*E*)/(*Z*) *ca.* 2 : 1), exhibiting a musky odor, in 95% yield.

The conversion of **26** into (−)-(*R*)-muscone ((*R*)-**1**) had already been accomplished by hydrogenation (Pd/C, MeOH) [5b], but the authors had not realized that this step led to 13% loss of enantiomer excess! (*Table*, *Entry 1*). Pd/C in AcOEt gave a better result (*Entry 2*), and *Lindlar* catalyst resulted in only *ca.* 2% of racemization, but the reaction was very slow (*Entry 3*). The Pt-catalyzed hydrogenations, including Pt/Al_2O_3 in *t*BuOH [23], also led to racemization (*Entries 4–6*), as did Rh/Al_2O_3 in EtOH [24] (*Entry 7*). The Ru-catalyzed homogeneous hydrogenation in the presence of a Ru^{II} catalyst, obtained from $[Ru(1,2{:}5,6\text{-}\eta\text{-cod})(\eta^3\text{-2-methylprop-2-enyl})_2]$ (cod = cycloocta-1,5-diene), 1,2-phenylenebis(diphenylphosphine) and HBF_4 in CH_2Cl_2 [25], was more successful (*ca.* 3% racemization; *Entry 8*). Whereas *Raney*-Ni in EtOH gave 5% racemization (*Entry 9*), the same catalyst doped with methanesulfonic acid (MsOH) led to only marginal racemization (0–2%; *Entry 10*), but some over-reduction was also observed (12% of corresponding diastereoisomeric alcohols), which necessitated partial re-oxidation of the reaction product [4][4]. Finally, Ir-catalysts, known for their reluctance towards isomerization [26], gave very good results. Ir/C showed weak reactivity, but led to minimal racemization (2%; *Entry 11*), and $[Ir(cod)(py)(PCy_3)]$ $[PF_6]$ (*Crabtree*'s catalyst; py = pyridine, Cy = cyclohexyl) [27] was selective in all respects (0–2% racemization, no over-reduction; 99% yield;

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[4] Alternatively, (−)-(*R*)-muscone ((*R*)-**1**) of 97% ee could be obtained from the muscenol diastereoisomers **25** (98% ee) by hydrogenation in the presence of *Raney*-Ni and catalytic amounts of MsOH in EtOH (92%), followed by *Jones* oxidation (87%).

Table. *Hydrogenation of* **26** ((*E*)/(*Z*) 2 : 1; 98% ee)

Entry	Reaction conditions	% ee (*R*)-**1**	Comments
1	H_2, Pd/C, MeOH	85	[5b]
2	H_2, Pd/C, EtOAc	93	
3	H_2, *Lindlar* catalyst, AcOEt	96	very slow
4	H_2, PtO_2, EtOH	92	
5	H_2, PtO_2, AcOH	94	over-reduction
6	H_2, Pt/Al_2O_3, *t*BuOH	88	[23]
7	H_2, Rh/Al_2O_3, EtOH	90	[24]
8	H_2, Ru^{II} catalyst [25], CH_2Cl_2, 90 bar	95	[25]
9	H_2, *Raney*-Ni[a]), EtOH	93	
10	H_2, *Raney*-Ni[a]), EtOH, cat. MsOH	97	12% over-reduction
11	H_2, Ir/C[b]), AcOEt	96	slow [26]
12	H_2, Ir^I catalayst [27], CH_2Cl_2	97	[27]

[a]) Washed with H_2O, then EtOH. [b]) L 1082 BB/W 5% (*Degussa*).

Entry 12) [4]. The overall yield for the synthesis of (−)-(*R*)-muscone ((*R*)-**1**) from bicyclic alcohol (*S,S*)-**19** is excellent (73%).

Conclusions. – A new and efficient synthesis of (−)-(*R*)-muscone ((*R*)-**1**; 97% ee), based on an enantioselective enolate protonation with (−)-*N*-isopropylephedrine **7**, was accomplished. The protonation with sub-stoichiometric amounts of **7** was also effective. In addition, a protocol for almost racemization-free hydrogenation of the 4-muscenone isomers **26** was elaborated (*Raney*-Ni and cat. MsOH in EtOH or *Crabtree*'s Ir^I catalyst in CH_2Cl_2).

We greatly acknowledge the help of Dr. *L. Saudan* for effecting the high-pressure hydrogenations and Dr. *M. Gambotti* (*Degussa AG*) for the generous gift of Ir/C.

Experimental Part

General. Bulb-to-bulb distillation: *Büchi-GKR-51* glass-oven; b.p. correspond to the oven temp. TLC: silica gel *F-254* plates (*Merck*); detection with EtOH/anisaldehyde/H_2SO_4 18 : 1 : 1. Column flash chromatography (FC): silica gel *60* (*Merck*; 0.063 – 0.2 mm, 70 – 230 mesh, ASTM). GC: *Varian* instrument, model *3500*; cap. columns: *DB1 30W* (15 m × 0.319 mm), *DB-WAX 15W* (15 m × 0.32 mm); chiral cap. column: *CP-Chirasil-DEX CB* (25 m × 0.25 mm; *Chrompack*); carrier gas He at 0.63 bar. Optical rotations: 1-ml cell; *Perkin-Elmer-241* polarimeter. ^1H- and ^{13}C-NMR: *Bruker WH-400* (400 MHz). MS: *Hewlett-Packard-MSD-5972* automated GC/MS instrument; electron energy 70 eV.

*(14*S*)-14-Methylbicyclo[10.3.0]pentadec-1(12)-en-13-one* ((*S*)-**4**). A soln. of (±)-**4** (5.00 g, 21.4 mmol) in THF (20 ml) was added between − 10 and − 5° to a soln. of LDA (25.7 mmol; prepared from 1.43M BuLi in hexane and $^iPr_2NH$) in THF (50 ml). The enolate soln. was stirred for 30 min and treated at − 78° within 1 h with a soln. of freshly distilled (−)-isopropylephedrine **7** (6.20 g, 30.0 mmol) in THF (50 ml). The cold mixture was treated rapidly with sat. aq. NH_4Cl soln. (80 ml) and extracted twice with Et_2O. The org. phase was then washed with 5% HCl soln., H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation (110°/0.01 Torr) afforded 4.61 g (92%; 70% *ee*) of (*S*)-**4**.

The acidic aq. phase was basified with 10% aq. KOH soln. and extracted with Et_2O, and the extract distilled to afford recovered **7** (6.08 g, 98%).

For the determination of $[\alpha]_D$ of (*S*)-**4**, a sample of (*S,S*)-**19** (99% ee) was oxidized with *Jones* reagent at 5 – 10° and the obtained (*S*)-**4** crystallized at low temperature (pentane). $[\alpha]_D^{20} = +20.3$ ($CHCl_3$, $c = 1.1$; 99% ee).

The ee was determined by chiral GC of the corresponding diastereoisomeric alcohols ($LiAlH_4$, Et_2O), or, more precisely, by injection of the corresponding stable trimethylsilyl ethers (*N,O*-bis(trimethylsilyl)acetamide, toluene, reflux).

Protonation with Sub-Stoichiometric Amounts of **7**. A soln. of (±)-**4** (468 mg, 2.00 mmol) in THF (4.2 ml) was added between 0 and 10° to a soln. of LDA (2.40 mmol; prepared from 1.47M BuLi in hexane and $^iPr_2NH$) in THF (10 ml). The enolate soln. was stirred for 30 min, cooled at −78°, and treated dropwise with a soln. of freshly distilled (−)-isopropylephedrine **7** (207 mg, 1.00 mmol) in THF (3.5 ml), followed by the dropwise addition within 35 min of 1-phenylpropan-2-one (252 mg, 1.88 mmol) in THF (3.5 ml) at −100 to −105°. The cold mixture was treated with sat. aq. NH_4Cl soln., followed by addition of Et_2O and 5% HCl soln. The neutral parts were extracted twice with Et_2O, and the org. extract was washed with H_2O, sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation at 100°/12 Torr afforded 1-phenylpropan-2-one (90% pure; 261 mg, 88%) and at 110°/0.01 Torr (*S*)-**4** (455 mg, 97%; 60% ee).

(13S,14S)-14-Methylbicyclo[10.3.0]pentadec-1(12)-en-13-ol ((*S,S*)-**19**). A soln. of (*S*)-**4** (4.23 g, 18.1 mmol; 70% ee) in THF (40 ml) was cooled at −78° and treated dropwise with 1M DIBAH in toluene (19.0 ml, 19.0 mmol). After complete addition (30 min), the mixture was stirred for another hour, then MeOH (40 ml) was added dropwise (10 min), whereupon a white precipitate formed. Filtration over *Celite*, evaporation, and bulb-to-bulb distillation afforded 4.10 g (96%) of (*S,S*)-**19** (70% ee). Recrystallization from hot heptane gave 2.48 g (58%) of (*S,S*)-**19** (98% ee) and 1.24 g of mother liquors (29%). $[\alpha]_D^{20} = -4.7$ ($CHCl_3$, $c = 1.71$). M.p. 107–108.5°.

(13S,14S)-14-Methylbicyclo[10.3.0]pentadec-1(12)-en-13-yl Acetate ((*S,S*)-**20**). A soln. of (*S,S*)-**19** (4.00 g, 16.9 mmol; 98% ee), pyridine (20 ml), and *N,N*-dimethylpyridin-4-amine (110 mg) was cooled at 5° and treated with Ac_2O (2.07 g 1.91 ml, 20.3 mmol). After 3 h at 5°, Et_2O and H_2O were added, and the product was extracted and the org. phase washed with 5% HCl soln. (6 ×), sat. aq. $NaHCO_3$ soln. (2 ×), and sat. aq. NaCl soln. (2 ×), dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation (150°/0.02 Torr) afforded 4.64 g (99%) of (*S,S*)-**20**. ^1H-NMR: 0.93 (*d*, *J* = 7, 3 H); 1.10–1.55 (*m*, 16 H); 1.85–2.02 (*m*, 3 H); 2.06 (*s*, 3 H); 2.20–2.50 (*m*, 4 H); 5.74 (*d*, *J* = 7, 1 H). ^{13}C-NMR: 171.4 (*s*); 143.7 (*s*); 134.1 (*s*); 82.1 (*d*); 41.4 (*t*); 34.6 (*d*); 25.4–22.1 (10*t*); 21.1 (*q*); 14.5 (*q*). MS: 236 (2), 218 (97), 203 (25), 175 (12), 161 (30), 147 (45), 133 (35), 119 (38), 107 (48), 94 (100), 91 (41).

(1S,2RS,13RS,15S)-15-Methyl-16-oxabicyclo[11.2.1]hexadecan-2-ol (**23**). A soln. of (*S,S*)-**20** (4.54 g, 16.3 mmol) in CH_2Cl_2 (200 ml) was introduced into a 1-l reactor connected *via* a sintered-glass inlet tube to a *Sorbios* ozone generator and cooled at −78°. Ozone (in O_2; flow *ca.* 3 g O_3/h) was bubbled through the soln., until it remained blue (40 min). Then the ozone generator was switched off, and the system was purged with O_2 for 20 min. The colorless soln. was allowed to reach r.t. and poured into a 10% aq. $NaHSO_3$ soln. (200 ml). After stirring for 20 min, the product (still containing ozonides; ^{13}C-NMR: *s* at *ca.* 110) was extracted with Et_2O (800 ml) and the org. phase washed with sat. aq. NaCl soln. (3 ×), dried (Na_2SO_4), and evaporated. The solid (5.25 g) was dissolved in Et_2O (70 ml) and the soln. introduced into a suspension of $LiAlH_4$ (3.10 g, 81.8 mmol) in Et_2O (30 ml) at a rate that maintained a gentle reflux. After complete addition (20 min), the mixture was heated under reflux for 1 h, then cooled to 5°, and treated carefully with H_2O (15 ml) (strong H_2 evolution!), then 10% HCl soln. (300 ml) (→ homogeneous). The triol **22** was extracted twice with AcOEt and the org. extract washed with H_2O, sat. aq. $NaHCO_3$ soln. (2 ×), and sat. aq. NaCl soln. (2 ×), dried (Na_2SO_4), and evaporated. The crude solid **22** (4.60 g) was dissolved in hot toluene (100 ml), treated with $TsOH \cdot H_2O$ (250 mg), and heated in a *Dean–Stark* apparatus under reflux for 90 min. Alcohol **23** was extracted twice with Et_2O and sat. aq. $NaHCO_3$ soln. The org. phase was washed with sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. The oil (4.41 g) was bulb-to-bulb distilled (130°/0.02 Torr): 3.75 g (82% from **20**) of **23** (91% pure; two major diastereoisomers: 57% and 28%). ^1H-NMR: 0.98–1.16 (*d*, *J* = 7, 3 H, all Me); 1.16 (*d*, *J* = 7, 3 H of major diast.); 1.15–1.93 (*m*, 22 H); 2.10–2.30 (*m*, 2 H); 3.25–4.08 (*m*, 3 H). ^{13}C-NMR (major diast.): 86.7 (*d*); 76.8 (*d*); 74.6 (*d*); 42.6 (*t*); 39.1 (*d*); 33.9 (*t*); 33.3 (*t*); 24.5–26.8 (7*t*); 22.3 (*t*); 20.1 (*q*). MS: 254 (52, $M^{+\cdot}$), 178 (10), 109 (15), 95 (30), 85 (68), 58 (100).

(1S,2RS,13RS,15S)-15-Methyl-16-oxabicyclo[11.2.1]hexadec-2-yl Methanesulfonate (**24**). A soln. of **23** (3.75 g, 13.4 mmol; 91% pure) in CH_2Cl_2 (100 ml) was treated with Et_3N (3.00 ml, 2.16 g, 21.4 mmol) and cooled at 0°. The suspension (some **23** crystallized) was treated dropwise with MsCl (1.26 ml, 1.87 g, 16.3 mmol). The temp. rose temporarily to 9°, and all the product went into soln. After stirring at 0° for 20 min, 5% HCl soln. (20 ml) was added and the crude product extracted. Successive washing with H_2O (2 ×), sat. aq. $NaHCO_3$ soln. (2 ×), and sat. aq. NaCl (2 ×), drying (Na_2SO_4), and evaporation afforded a yellow oil, which decomposed on the GC and whose purity was estimated at 91% (same as **23**). The crude mesylate **24** (4.85 g, 99%; 91% pure) was used without purification. ^1H-NMR (characteristic signals): 3.03 (*s*, 3 H); 3.53 (*m*, 1 H); 3.85–4.05

(*m*, 1 H); 4.62 (*m*, 1 H). ^{13}C-NMR (characteristic signals of major diast.): 84.7 (*d*); 83.8 (*d*); 77.9 (*d*); 42.5 (*t*); 39.0 (*d*). MS: 332 (2, $M^{+\bullet}$), 253 (100), 235 (95), 149 (10), 135 (28), 121 (23), 109 (53), 95 (92), 81 (82), 55 (65).

(1RS,3S,4EZ)-3-Methylcyclopentadec-4-en-1-ol (**25**). A soln. of 4,4′-di(*tert*-butyl)-1,1′-biphenyl (DBB) (11.66 g, 43.8 mmol) in THF (100 ml) was treated with Li granules (338 mg, 48.3 mmol) and stirred at r.t. for 2 h 30 min. The dark green mixture was cooled at −75° and treated dropwise within 15 min with a soln. of **25** (4.85 g, 13.3 mmol; 91% pure) in THF (20 ml) while the temp. was maintained between −70 and −75°. After stirring at −75° for 30 min, the dark green mixture was poured under stirring into sat. aq. NH_4Cl soln. Extraction with Et_2O and successive washing with sat. aq. $NaHCO_3$ soln. (2 ×) and sat. aq. NaCl soln., drying (Na_2SO_4), and evaporation afforded **25**/DBB (15.3 g). FC (SiO_2, cyclohexane/AcOEt 92 : 8) allowed to recover DBB (11.6 g) in the first fractions and subsequently **25** (3.24 g, 97%; four diast.; 95% pure). ^{1}H-NMR (characteristic signals): 3.65 (*m*, 1 H); 5.14–5.42 (*m*, 2 H). ^{13}C-NMR (characteristic signals of major diast.): 135.9 (*d*); 130.3 (*d*); 69.2 (*d*); 45.7 (*t*). MS: 338 (18, $M^{+\bullet}$), 223 (27), 220 (26), 149 (16), 135 (26), 125 (32), 109 (33), 97 (85), 81 (82), 69 (93), 55 (100), 41 (74).

(3S,4EZ)-3-Methylcyclopentadec-4-en-1-one (= *(S,EZ)-4-Muscenone*; **26**). A soln. of **25** (3.24 g, 12.9 mmol; 95% pure) in acetone (60 ml) was cooled at 0° and treated dropwise with a soln. of 2.5M *Jones* reagent (6.4 ml, 16.0 mmol). After stirring at 0° for 20 min, the green mixture was treated with 5% aq. NaOH soln. The product was extracted with pentane (3 ×), the extract washed successively with sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln. (2 ×), dried (Na_2SO_4), and evaporated to afford 3.26 g of a clear oil. FC (SiO_2, cyclohexane/AcOEt 96 : 4) furnished pure **26** (*E*)/(*Z*) 2 : 1; 2.90 g, 95%; 98% ee). The ee was determined by chiral GC, as the (4*E*)-enantiomers have different t_R. Analytical data: in accord with those reported in [4][5b]. ^{1}H-NMR (characteristic signals): 1.01, 1.03 (2*d*, *J* = 7, 3 H (*Z*)/(*E*)); 2.67, 2.97 (2*m*, 1 H (*E*)/(*Z*)); 5.20–5.30, 5.30–5.42 (2*m*, 2 H (*Z*)/(*E*)). ^{13}C-NMR (characteristic signals): 211.1, 211.0 (2*s* (*Z*)/(*E*)); 134.9, 134.7 (2*d* (*E*)/(*Z*)); 130.2, 129.6 (2*d* (*E*)/(*Z*)).

(−)-(R)-Muscone ((*R*)-**1**). The mixture **26** (500 mg, 2.12 mmol; (*E*)/(*Z*) 2 : 1; 98% ee) was dissolved in CH_2Cl_2 (20 ml), and the system was purged with Ar (2 min) and H_2 (2 min). (Cycloocta-1,5-diene)-(pyridine)(tricyclohexylphosphine)iridium(1+) hexafluorophosphate [Ir(cod)(py)(PCy_3)] [PF_6] (*Crabtree*'s catalyst; *Aldrich*; 9.5 mg) was added, and the colorless soln. was hydrogenated (4 h). Evaporation and bulb-to-bulb distillation (100°/0.08 Torr) afforded (*R*)-**1** (497 mg, 99%; 97% ee). The ee was determined by reduction of (*R*)-**1** to the corresponding diastereoisomeric alcohols ($LiAlH_4$, Et_2O) and chiral GC (excellent separation of the major diast.).

Alternatively, **26** (250 mg, 1.06 mmol; (*E*)/(*Z*) 2 : 1, 98% ee) was dissolved in EtOH (20 ml) containing 150 mg of 2.5% MsOH soln. in EtOH and hydrogenated with *Raney*-Ni (500 mg of suspension (not optimized); washed successively with H_2O and EtOH). The reaction was complete after 2 h. Filtration, evaporation, and bulb-to-bulb distillation (100°/0.08 Torr) afforded (*R*)-**1** (232 mg, 81%; 88% pure, containing 12% of the corresponding diastereoisomeric alcohols; 97% ee).

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