Enantioselective Routes to (–)-(*R*)-Muscone

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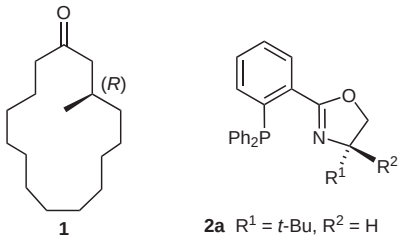
Abstract: The macrocyclic ring of muscone was prepared by Pd-catalyzed cyclization of hexadeca-1,15-diyne, which was converted to cyclopentadec-2-enone. The stereogenic center was introduced by enantioselective Cu-catalyzed conjugate addition of dimethylzinc. Because the ee in this step was only moderate, a new route via cyclopentadeca-2,14-dienone was developed. Enantioselective conjugate addition to this substrate led to 14-methylcylodec-2-enone, which was hydrogenated to give (–)-(*R*)-muscone in high overall yield with up to 98% ee.

Key words: macrocycles, copper, palladium, asymmetric catalysis, muscone

(–)-(*R*)-Muscone, the principal odorous component of the male musk deer, is an important ingredient of perfumes.[1,2] In contrast to the natural *R*-enantiomer, the *S*-enantiomer has a much weaker, less pronounced musk odor.[2,3] Therefore, great efforts have been made to develop industrially feasible enantioselective routes to (*R*)-muscone.[4] Although numerous enantioselective syntheses have been reported, none of them meets the stringent requirements of a commercial process.



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2a R^1 = *t*-Bu, R^2 = H
2b R^1 = Me, R^2 = Me

Figure 1

We have recently found that palladium complexes with phosphinooxazoline ligands such as **2a** or **2b** (Figure 1) are efficient catalysts for the homo- and heterocoupling of alkynes to enynes.[5] This method was applied to the intramolecular coupling of hexadeca-1,15-diyne **4** to give the macrocyclic enyne **5**, which we thought would be an attractive precursor for the synthesis of muscone (Scheme 1).

The starting diyne **4** was readily prepared from 1,12-dibromododecane and the Li-acetylide-1,2-ethylenediamine complex. When a 0.1 M solution of diyne **4** in toluene was slowly added to a 0.25 mM solution of 5 mol% of ligand **2a** and 2.5 mol% of $Pd(OAc)_2$ in toluene at 80 °C over 24 hours using a syringe pump, the desired enyne **5** was isolated in 70% yield after a reaction time of three days. Even better results were obtained in cyclohexane with faster rates and yields of up to 85% after 12 hours. Ligand **2b** gave somewhat lower yields (61% in toluene).

The macrocyclic enyne **5** possesses the proper carbon skeleton of muscone and a reactive enyne system, offering several options for converting this precursor to the target molecule (*R*)-**1**. The most direct way would be water addition to the triple bond with concomitant isomerization to the enone **8**. Enantioselective hydrogenation of this compound with 98% ee has recently been reported.[6] As expected, conversion of enyne **5** to the corresponding β-methyl-substituted enone **8** proved to be difficult. Under acidic conditions, the α-methyl-substituted isomer **9** was formed as the main product via a Rupe rearrangement (Scheme 1), whereas with $HgSO_4/H_2SO_4$ the α-methylene ketone **10** was obtained (Scheme 2).

Therefore alternative routes were investigated. Monoepoxidation of the methylene group of enyne **5** with MCPBA and subsequent reductive epoxide opening with $LiBH(Et)_2$ led to the corresponding tertiary alcohol in high yield. However, attempts to rearrange the alcohol to the desired enone gave unsatisfactory results [30% **8** in addition to 30% **12** with $Mo(acac)_2$]. Hydroboration of the enyne **5** with subsequent oxidation produced the unsaturated enones **8** and **11** in 60% total yield with enyne **12** as a side product (Scheme 2). However, enones **8** and **11** were formed as *E*/*Z*-mixtures, which were difficult to separate, making this route unpractical. Therefore, the reaction sequence via enone **7**, shown in Scheme 1, was chosen.

Selective oxidative cleavage of the methylene group in **5** was achieved by ozonolysis in 57% yield. Trimethyl phosphite as reducing agent proved to be superior to dimethylsulfide (53% yield).[7] Oxidation with sodium periodate in the presence of catalytic amounts of ruthenium(III) chloride[8] gave unsatisfactory yields (39%). Treatment of ynone **6** with an aqueous solution of chromium(II) sulfate in DMF[9] led to the desired *trans*-enone **7** in 84% yield. The *trans* geometry was assigned by ^{1}H NMR spectroscopy, based on the chemical shift of the olefinic β-CH signal at δ = 6.78 ppm ($CDCl_3$; *cis* isomer δ = 6.20 ppm).[10]

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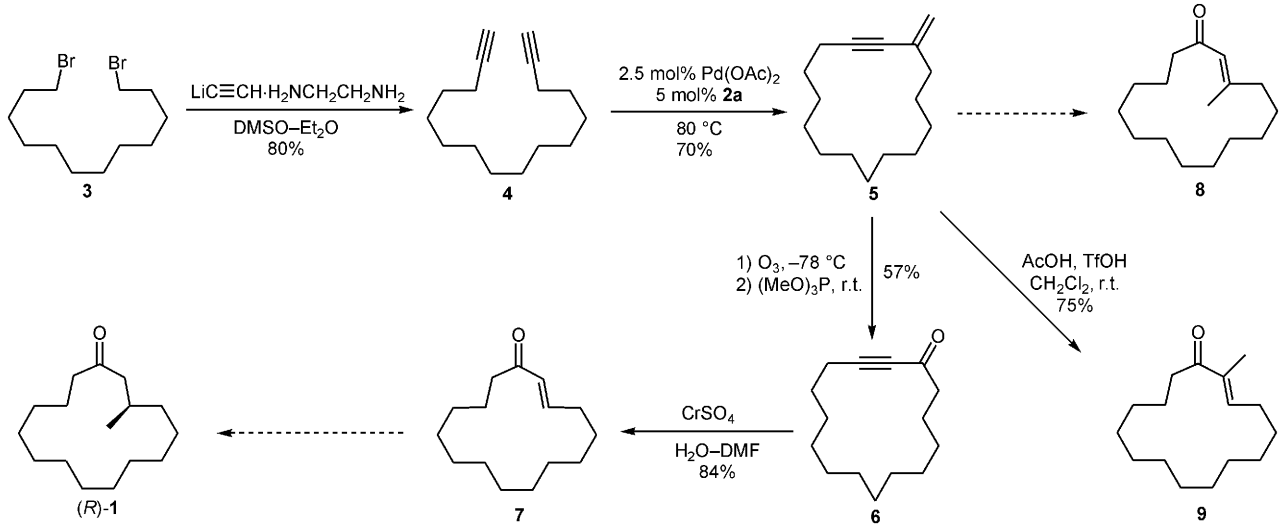
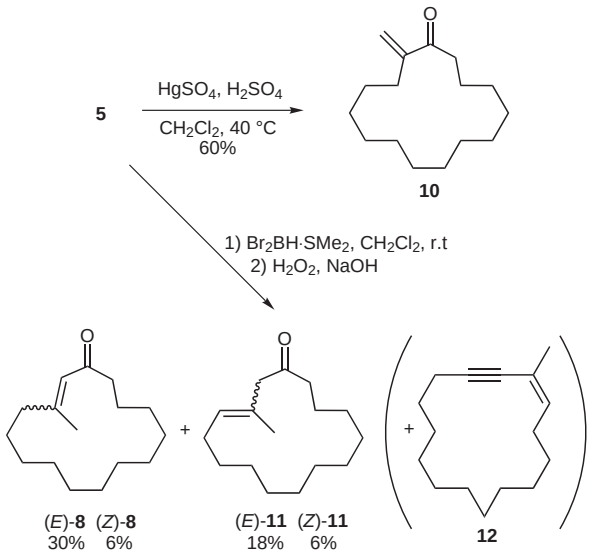


Scheme 1

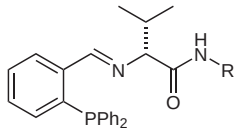
Several methods have been reported for the conversion of enone **7** to (*R*)-muscone by enantioselective 1,4-addition.[4a,11] The highest ee so far was achieved by Tanaka et al. using MeLi and a copper complex with a chiral amino alcohol (96% ee).[12] However, more than 0.3 equivalents of the copper complex had to be used, making this method unpractical for large-scale reactions. Higher turnover numbers were observed with dimethylzinc and copper catalysts derived from chiral phosphites or phosphoramidites, but the enantioselectivities did not exceed 85% ee.[4a,11]

We also tested various other chiral ligands for this transformation, including binaphthol-derived phosphite-oxazolines, which are efficient ligands for the 1,4-addition of dialkylzinc reagents to five-, six-, and seven-membered ring cycloalkenones.[13] However, only moderate yields and enantioselectivities of up to 63% ee were achieved.



Scheme 2

Similar results were obtained with valine-derived phosphine-imine ligands of type **13**.[14] The catalysts were prepared from [Cu(II)$(OTf)_2$] and one equivalent of **13** in dichloromethane and isolated as green solids by precipitation with pentane. With the catalyst derived from **13a** 58% ee was obtained at 23 °C. A major problem was the low reactivity of the enone, resulting in only 60% conversion at ambient temperature. At 50 °C, conversion was high, but addition of the resulting zinc enolate to the starting enone was observed as a side reaction, which lowered the yield considerably. The corresponding (*Z*)-cyclopentadecenone was found to be more reactive. However, the enantioselectivities were also modest (50% ee at 23 °C and 58% ee at 0 °C with **13a**, Figure 2).

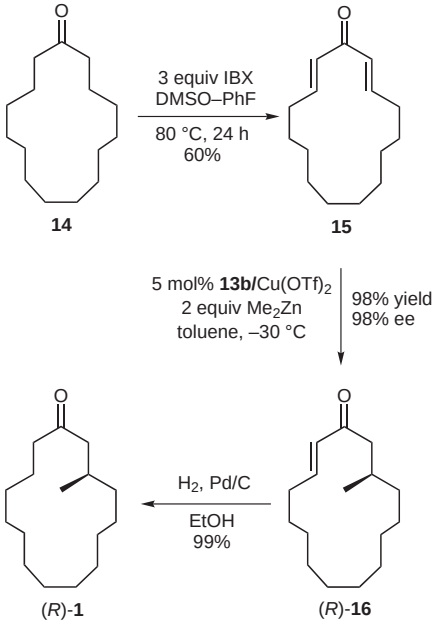


13a R = *t*-Bu; **13b** R = 1-Adamantyl

Figure 2

We thought that the lower enantioselectivity of enone **7** compared to cyclohexenone might be attributable to the greater flexibility of the large ring and the presence of both the *s-cis* and the *s-trans* isomer, which are expected to react with different enantioselectivity. Therefore, we decided to examine the corresponding cyclopentadeca-2,14-dienone (**15**) as substrate, because we expected this compound to be conformationally more rigid due to the additional C=C bond and more reactive than enone **7**, allowing lower reaction temperatures with fewer side reactions.

Starting from commercially available cyclopentadecanone (**14**), double dehydrogenation with IBX [1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide] following a



Scheme 3

procedure by Nicolaou et al.[15] gave the desired cyclopentadeca-2,14-dienone (**15**) in 60% yield (Scheme 3).[16] At 80 °C, ketone **14** was completely consumed. As a major by-product the mono-unsaturated cyclopentadec-2-enone (**7**) was formed, which could be separated by chromatography on silica gel and reused. Yields were found to depend on the reaction temperature, substrate concentration, and solvent.

Enantioselective copper-catalyzed conjugate addition to dienone **15** was conducted with 5 mol% of [Cu(**13**)](OTf)$_2$ as catalyst and 2 equivalents of dimethylzinc.[17] As expected the reaction was much faster than with enone **7** and went to completion even at –30 °C. No trace of 3,14-dimethyl-cyclopentadecanone, resulting from a second addition of dimethylzinc, was detected by gas chromatography. Apparently, conjugate addition leads to a stable zinc dienolate, which does not react further with dimethylzinc. However, at ambient temperature addition of the dienolate to the starting dienone was observed as a side reaction, resulting in somewhat lower yields than at –30 °C (Table 1, entry 1).

A temperature of –30 °C was found optimal with respect to both yield and enantioselectivity. Using the adamantyl-substituted ligand **13b**, a very high ee of 98% was obtained, slightly higher than the value recorded for the *tert*-butyl derivative **13a** (95% ee). Hydrogenation of product (*R*)-**16** over Pd/C led to (*R*)-muscone **1** in essentially quantitative yield.

In summary, we have shown that the macrocyclic ring system of muscone is readily prepared by Pd-catalyzed cyclization of hexadeca-1,15-diyne. The cyclization product could also be of interest for the synthesis of macrocyclic products other than muscone, as the reactive enyne system should allow transformation to a variety of functionalized products. The second route to (*R*)-muscone via conjugate addition to dienone **15** as the key step gives access to this important perfume ingredient in very high enantiomeric purity.

Acknowledgment

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Table 1 Cu-Catalyzed 1,4-Addition of Dimethylzinc to Dienone **15**[a]

Entry	Ligand	Temp (°C)	Time (h)	Conversion (%)[b]	Yield (%)[c]	ee of **16** (%)[d]
1	**13a**	25	16	99	85	70 (*R*)
2	**13a**	–30	48	98	97	95 (*R*)
3	**13b**	–30	48	98	98	98 (*R*)

[a] Reactions were carried out under argon using 5 mol% of [Cu(**13**)](OTf)$_2$ in toluene.
[b] Determined by GC using tridecane as internal standard.
[c] Yields of purified products.
[d] Determined by HPLC (Daicel AS).

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(16) **Synthesis of Cyclopentadeca-2,14-dienone (15).** Cyclopentadecanone (1.8 g, 8.0 mmol) was treated with IBX (6.7 g, 24.0 mmol) in 30 mL of DMSO and 10 mL of fluorobenzene at 80 °C for 24 h (formation of a white precipitate was observed). The reaction was quenched by slow addition of 100 ml of 5% aq $NaHCO_3$ solution at 0 °C, followed by filtration over a Celite® pad (7 × 3 cm) eluting with CH_2Cl_2 (150 mL). The organic phase was collected and the aqueous phase extracted with CH_2Cl_2 (2 × 150 mL) and Et_2O (150 mL). The organic phases were combined and the solvents removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc, 9:1) affording 1.1 g (60%) of **15** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.35 (m, 12 H), 1.51 (m, 4 H), 2.23 (m, 4 H), 6.20 (dt, 2 H, *J* = 1.6, 15.6 Hz), 6.63 (dt, 2 H, *J* = 8.0, 15.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 27.3, 27.6, 27.8, 32.2, 130.2, 148.7, 193.4. MS (EI): *m/z* (%) = 220 (7.5) [M^+], 205 (1), 191 (2), 179 (11), 163 (7), 149 (13), 135 (14), 109 (19), 95 (55), 81 (67), 67 (54), 55 (81), 41 (100). R_f = 0.45 (hexane–EtOAc, 9:1).
(17) **Synthesis of 14-Methyl-cyclopentadec-2-enone (16).** The copper complex of ligand **13b** (17.6 mg, 0.02 mmol, 5 mol%) was placed under argon in an ampoule equipped with a magnetic stirring bar and a Young® valve, and dissolved in 3 mL of degassed toluene. The ampoule was sealed under argon and the mixture stirred for 30 min at –30 °C. To this green solution 2 equiv of 1.0 M dimethylzinc solution in heptane (0.8 mL, 0.8 mmol) were added dropwise under an argon stream (color change to yellow), followed by cyclopentadeca-2,14-dienone (88 mg, 0.4 mmol). After stirring at –30 °C for 48 h, the reaction was quenched with 3 mL of sat. aq NH_4Cl solution. After addition of 5 µL of *n*-tridecane as internal standard and extraction with 5 mL of Et_2O, the organic layer was filtered and analyzed by GC and GCMS. The solvents were evaporated and the reaction mixture purified by column chromatography on silica gel eluting with hexane–EtOAc 9:1 to give **16** as a colorless oil (93.7 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.8, 3 H), 1.10–1.30 (m, 18 H), 2.00–2.15 (m, 1 H), 2.20–2.35 (m, 2 H), 2.35 (d, 2 H, *J* = 10.0 Hz), 6.11 (dt, 1 H, 1.6, 15.6 Hz), 6.74 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 24.5, 26.9, 27.0, 27.1, 27.2, 27.3, 27.5, 30.6, 31.7, 34.3, 49.2, 131.4, 148.2, 201.3. MS (EI): *m/z* (%) = 236 (22) [M^+], 221 (6.5), 178 (6), 151 (4), 135 (8), 123 (14), 109 (29), 81 (57), 67 (41), 55 (100), 41 (98). R_f = 0.55 (hexane–EtOAc, 9:1). HPLC (250 mm × 4.6 mm, Daicel, Chiracel AS, detection at 223 nm, hexane–*i*-PrOH 98.5:1.5, 0.5 mL/min, 293K): 21.1 min (*R*), 24.1 min (*S*).