Asymmetric Synthesis of (*R*)-Muscone by Enantioselective Addition of Chiral Methyl Cuprate to (*E*)-2-Cyclopentadecen-1-one

Kazuhiko Tanaka,* Hideki Ushio, and Hitomi Suzuki

Department of Chemistry, Faculty of Science, Kyoto University, Sakyo, Kyoto 606, Japan

(*R*)-(−)-Muscone was prepared in 89% enantiomeric excess using newly devised chiral ligands such as (1*R*,2*R*,3*S*,4*S*)-3-[(1-methylpyrrolyl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol in conjugate addition of methyl cuprate to (*E*)-2-cyclopentadecen-1-one.

(*R*)-(−)-Muscone, (**2**), a principal odoriferous constituent isolated from the male musk-deer, *Moschus moschiferus*, was determined as (*R*)-(−)-3-methylcyclopentadecan-1-one by Ruzicka in 1926.[1] The importance of this unique 15-membered cyclic ketone as the ingredient of perfumes and its rare occurrence in nature† have prompted numerous searches for procedures and methods to prepare racemic[2] and optically active muscone.[3] In all asymmetric syntheses, however, the procedures require multi-step processes starting from chiral building blocks such as (*R*)-3-methyl-*N*-phenylglutamic acid[3e] and (*S*)-4-bromo-3-methylbutanenitrile.[3f]

The shortest route to (*R*)-muscone is enantioselective introduction of the methyl group to (*E*)-2-cyclopentadecen-1-one since this unsaturated 15-membered ketone is readily prepared from commercially available cyclopentadecanone,‡ but this approach has never been developed.[4] Recently the high enantioselective conjugate addition of chiral organocuprates to 2-cyclohexen-1-one [85—92% enantiomeric excess (e.e.)] and 2-cyclopenten-1-one (72—81% e.e.) has been achieved using (1*R*,2*S*)-2,3,6-trimethyl-1-phenyl-3,6-diazaheptanol[5] or (*S*)-2-(methoxymethyl)pyrrolidine[8] as a chiral ligand.

We now report the first enantioselective conjugate addition of methyl cuprate to a macrocyclic enone,[4] (*E*)-2-cyclopenta-

---

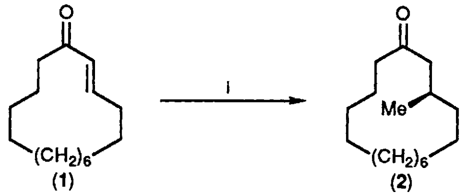
† Since habitat destruction and illegal poaching for the musk trade threaten the survival of this unusual deer species, they are protected by the Convention on International Trade in Endangered Species of Wild Fauna and Flora.

‡ Cyclopentadecanone is commercially available from Nippon Mining Co., Tokyo.

Table 1. Asymmetric synthesis of muscone (**2**) by conjugate addition of chiral lithium dimethylcuprate to (*E*)-2-cyclopentadecen-1-one (**1**).

Entry	Chiral Ligand		Muscone (**2**)			
		$[\alpha]_D$° (*T*/°C, *c*, $CHCl_3$)	Yield/%	$[\alpha]_D$° (*T*/°C, *c*, MeOH)	%e.e.[a]	Config.
1	*exo*-TATH[b] (**3a**)[c]	+34.4 (24, 2.16)	82	+5.74 (25, 5.02)	49	*S*
2	*endo*-TATH (**4a**)[d]	+14.4 (21, 2.00)	84	−10.09 (21, 5.06)	86	*R*
3	*exo*-FATH[e] (**3b**)[c]	+42.9 (23, 1.95)	86	+5.83 (24, 5.15)	50	*S*
4	*endo*-FATH (**4b**)[d]	+11.3 (23, 2.19)	90	−3.90 (25, 5.16)	33	*R*
5	*exo*-MPATH (**3c**)[c]	+36.4 (21, 2.12)	88	+6.69 (26, 5.17)	57	*S*
6	*endo*-MPATH (**4c**)[d]	+18.6 (26, 1.95)	81	−10.41 (22, 5.05)	89	*R*
7	*exo*-BATH[c] (**3d**)[c]	+22.4 (23, 2.03)	72	+4.54 (27, 5.25)	39	*S*
8	*endo*-BATH (**4d**)[d]	+27.9 (24, 2.03)	90	−7.52 (22, 5.09)	64	*R*
9	*endo*-MATH (**4e**)[d]		70	−4.54 (24, 5.36)	39	*R*
10	(**5**)[c]	+57.0 (23, 1.00)[g]	59	+1.70 (24, 5.15)	15	*S*

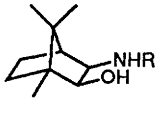
[a] $[\alpha]_D$ of optically pure (*R*)-muscone is −11.7° (*c* 0.80 in MeOH); see, Q. Branca and A. Fischli, *Helv. Chim. Acta*, 1977, **60**, 925. [b] TATH = 3-thenylamino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol. [c] Chiral amine (2 equiv.), methyl-lithium (4 equiv.), CuI (1.1 equiv.), methyl-lithium (2 equiv.), and (**1**) (1 equiv.) were used in toluene. [d] Chiral amine (2 equiv.), methyl-lithium (2 equiv.), CuI (1 equiv.), methyl-lithium (2 equiv.), and (**1**) (1 equiv.) were used in toluene. [e] FATH = 3-furfurylamino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol. [f] BATH = 3-benzylamino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol. [g] K. Soai, A. Okawara, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111.



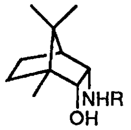
(**1**) (**2**)

Scheme 1. *Reagents and conditions*: i, chiral ligand, CuI, MeLi, toluene, −78 °C.

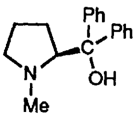
decen-1-one using the newly devised chiral ligands derived from inexpensive D-camphor, leading to the formation of (*R*)-muscone with high enantiomeric excess (Scheme 1). As indicated in Table 1, the stereochemistry of the product correlates to the configuration of the chiral ligand used. Thus, the reagent prepared from *exo*-ligand reacted with (**1**) in toluene at −78 °C and produced (*S*)-muscone, while using the *endo*-ligand provided (*R*)-muscone in higher optical yield. The reagent derived from (1*R*,2*R*,3*S*,4*S*)-3-[(1-methylpyrrolyl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol [*endo*-MPATH (**4c**)] was found to be most effective, giving (*R*)-muscone with 89% e.e. The chiral ligands used were easily recovered by silica gel chromatography without loss of optical purity.§



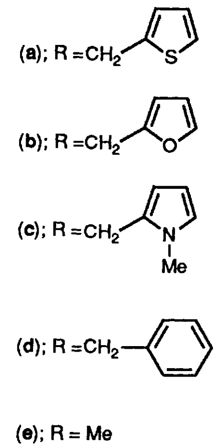
(**3a**—**d**)



(**4a**—**e**)



(**5**)



The enantioselectivity was found to be affected by the basicity of the ligand. The use of a more basic amine such as (1*R*,2*R*,3*S*,4*S*)-3-methylamino-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ol [*endo*-MATH (**4e**)] bearing the electron-donating methyl group provided (*R*)-muscone in 39% e.e., while less basic ligands[7] (**4a**—**d**) gave higher optical yields. It should be noted that the ligand (**5**), which had been successfully used in enantioselective addition of diethylzinc to aldehydes (up to 92% e.e.),[8] was ineffective in this reaction. Quinine was also ineffective. The use of toluene is important in obtaining high chemical and optical yields. The reaction of (**1**) with *endo*-MPATH (**4c**) in tetrahydrofuran under similar conditions resulted in recovery of the starting material (81%). No reaction was observed in hydrocarbon solvents such as hexane and cyclohexane. The stereochemistry was also dependent on the stoicheiometry of the cuprate to (**1**). The use of *endo*-(**4e**) (1 equiv.) resulted in reduced enantioselectivity (18% e.e.) relative to the ligand (2 equiv.) (entry 9, Table 1). Although a detailed mechanistic rationale for the observed enantioselectivity must await further research, the present operationally simple method, making use of readily available chemicals,[7] is especially attractive for large-scale synthesis of (*R*)-muscone.§

---

§ The following experimental procedure was used for the preparation of (*R*)-(−)-muscone in gram amounts. To a solution of (**4a**) (2.85 g, 10.74 mmol) in dry toluene (90 ml) at room temperature under argon was added methyl-lithium (1.00 M ether solution, 11 mmol). The solution was stirred at room temperature for 30 min and cooled to −20 °C. Cuprous iodide (1.023 g, 5.37 mmol) was added and the resulting suspension was allowed to stir for 2.5 h as it warmed to −5 °C. The dark grey suspension was cooled to −78 °C and methyl-lithium (10.8 mmol) was added dropwise. The suspension was stirred for 30 min at −78 °C, warmed to −25 °C during 1.5 h, and again cooled to −78 °C. A solution of (1) (1.086 g, 4.89 mmol) in dry toluene (7 ml) was added dropwise at −78 °C and the mixture was stirred overnight. After quenching at −78 °C by addition of 12 ml of 1 : 1 mixture of saturated ammonium chloride–30% ammonium hydroxide and extraction with ether, the organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica gel (hexane : ethyl acetate 45 : 1—2 : 1) afforded 0.98 g of (*R*)-muscone (84%) as a colourless oil giving a single peak by GLPC and 2.25 g of (**4a**) (79%) as a pale yellow solid. Distillation of the oil gave 0.95 g (81%) of pure (*R*)-muscone whose specific rotation is shown in Table 1. Recrystallization of the recovered (**4a**) gave 2.05 g (72%), m.p. 108—109 °C; $[\alpha]_D^{20}$ + 14.5° (*c* 2.00 in $CHCl_3$).

We thank Bio Research Center, Nippon Mining Co., Ltd, for a generous gift of cyclopentadecanone.

Received, 31st January 1990; Com. 0/00462F

References

1 L.Ruzicka, *Helv. Chim. Acta*, 1926, **9**, 715.

2 For recent syntheses of racemic muscone, see: H. Suginome and S. Yamada, *Tetrahedron Lett.*, 1987, **28**, 3963; R. W. Thies and K. P. Daruwala, *J. Org. Chem.*, 1987, **52**, 3798.

3 (a) Q. Branca and A. Fischli, *Helv. Chim. Acta*, 1977, **60**, 925; (b) K. Utimoto, M. Tanaka, M. Kitai, and H. Nozaki, *Tetrahedron Lett.*, 1978, 2301; (c) A. Abad, M. Arno, A. Pardo, J. R. Pedro, and E. Seoane, *Chem. Ind.*, 1985, 29; (d) K. A. Nelson and E. A. Mash, *J. Org. Chem.*, 1986, **51**, 2721; (e) D. Terunuma, M. Motegi, M. Tsuda, T. Sawada, H. Nozawa, and H. Nohira, *ibid.*, 1987, **52**, 1630; (f) Z.-F. Xie, H. Suemune, and M. Sakai, *J. Chem. Soc., Chem. Commun.*, 1988, 1638.

4 For a preparation of racemic muscone by conjugate addition of methylmagnesium bromide to 2-cyclopentadecen-l-one, see: B. D. Mookherjee, R. R. Patel, and W. O. Ledig, *J. Org. Chem.*, 1971, **36**, 4124.

5 E. J. Corey, R. Naef, and F. J. Hannon, *J. Am. Chem. Soc.*, 1986, **108**, 7114.

6 R. K. Dieter and M. Tokles, *J. Am. Chem. Soc.*, 1987, **109**, 2040.

7 These amines are purified by silica gel chromatography using hexane–ethyl acetate (1 : 1); see also: K. Tanaka, H. Ushio, and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1989, 1700.

8 K. Soai, A. Ookawa, K. Ogawa, and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467.