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An Efficient Synthesis of (S)-(+)-Manicone, an Alarm Pheromone of *Manica* Ants

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Abstract : Manicone [(4E,6S)-(+)-4,6-dimethyl-4-octen-3-one], an alarm pheromone component of *Manica* ants, was synthesized by a five-step sequence starting from 2-chloro-3-pentanone. The latter α-chloro ketone was converted into the corresponding N-isopropyl ketimine, which was sequentially alkylated via its 3-chloro-1-azaallylic anion with (S)-(+)-2-methyl-1-bromobutane. 1,2-Dehydrochlorination of the resulting chiral functionalized α-chloro ketimine, followed by acid hydrolysis and final Rh(III)-chloride-mediated isomerization afforded the pheromone (S)-(+)-manicone in enantiopure form.
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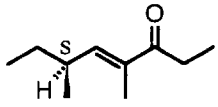
INTRODUCTION

Manicone **1**, the principal alarm pheromone of certain species of *Manica* ants, was isolated from the mandibular glands of *Manica mutica* and *Manica bradleyi* and identified as (E)-4,6-dimethyl-4-octen-3-one.[1] Its absolute configuration was determined as (6S)-(+) in *Manica rubida*.[2,3]



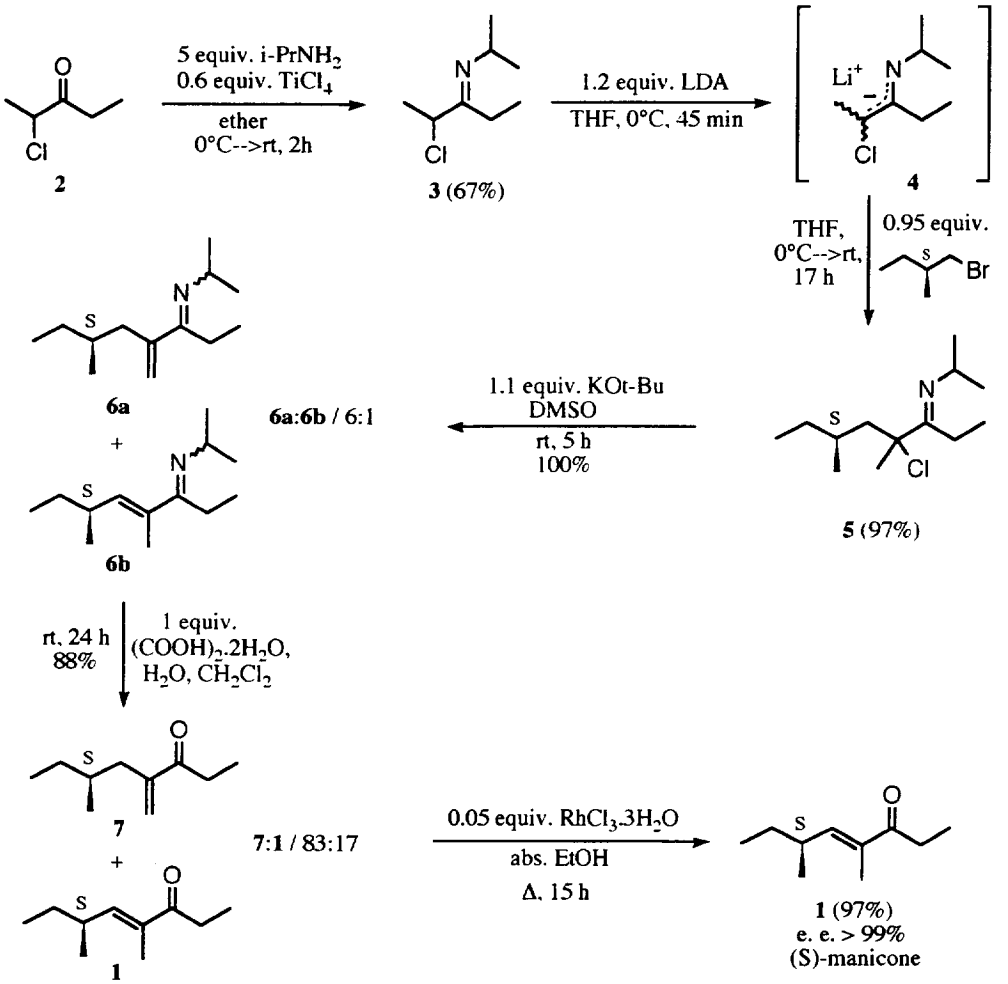
1 (S)-manicone

Considerable synthetic efforts have been reported for racemic (±)[4-8] and optically active[9-12] (+)-manicone **1**. However, most stereoselective syntheses consist of multistep sequences with low global yields[11,12] or have a moderate optical purity.[10] In this paper, a stereoselective five-step synthesis of (S)-(+)-manicone **1** is disclosed using the regiospecific alkylation of the α-chloro ketimine **3** as the key step.

RESULTS AND DISCUSSION

Because of their bifunctional properties α-chlorinated imines seem to be suitable substrates for the synthesis of α,β-unsaturated carbonyl compounds. The synthetic problem is therefore shifted to the synthesis of the appropriate functionalized α-chloro ketimine **5**. The starting α-chloro ketimine **3**, i.e. N-(2-chloro-3-pentylidene)isopropylamine, was synthesized by condensation of 2-chloro-3-pentanone **2** with isopropylamine

in the presence of stoichiometric amounts of titanium(IV) chloride.[13] Deprotonation of α-chloro ketimine **3** with lithium diisopropylamide (LDA) in THF at 0°C produced the intermediate 3-chloro-1-azaallylic anion **4**.[14] Although the ketimine **3** has hydrogen atoms at the α'-position the allylic anion **4** derived thereoff is relatively stable, in contrast to the corresponding oxygen analogues, i.e. α-chloro ketone enolates, which are very unstable species. The 3-chloro-1-azaallylic anion **4** was allowed to react with (S)-(+)-2-methyl-1-bromobutane to afford (S)-N-(4-chloro-4,6-dimethyl-3-octylidene)isopropylamine **5** in a regiospecific way and in a virtually quantitative yield (Scheme 1).



Scheme 1

1,2-Dehydrochlorination of the (S)-α-chloro ketimine **5** was accomplished by using potassium t-butoxide in DMSO at room temperature, leading to a 6:1 mixture of α,β-unsaturated imines **6a** en **6b**, which were not separated. Predominant formation of the less substituted elimination product **6a** occurs due to deprotonation by the bulky t-butoxide at the 4-methyl group. The use of a less sterically hindered base such as sodium methoxide in methanol increased the percentage of the desired more substituted α,β-unsaturated imine **6b** but also about 30% unidentified side products were formed.

The 6:1 mixture of α,β-unsaturated imines **6a** and **6b** was smoothly hydrolyzed in a two phase system of water/dichloromethane using oxalic acid as acid catalyst to afford a 83:17 mixture of the corresponding α,β-unsaturated ketones **7** and **1**, respectively. The final isomerization of the enone **7** to (S)-manicone **1** was first tried by using bases or acids as catalyst. Several combinations, such as LDA/THF, HCl(6N)/CH_2Cl_2, H_2SO_4 (6N)/CH_2Cl_2, pTosOH/benzene, were evaluated without success. Finally, the α,β-unsaturated ketone **7** was isomerized to the thermodynamically more stable isomer **1** ((S)-manicone) by reaction with a catalytic amount of rhodium(III) chloride hydrate in ethanol under reflux[15-17] (Scheme 1). This Rh(III) chloride-mediated isomerization has already been used as final step in a previous synthesis of (S)-manicone **1**.[11] However, in our hands, 15 hours of reaction under reflux with 0.05 equivalents of $RhCl_3.3H_2O$ were needed for completion of the reaction instead of the reported[11] reaction with 0.027 equivalents of catalyst during one hour.

Since it has been reported[11,12] that (S)-(E)-4,6-dimethyl-4-octen-3-one having $[\alpha]_D^{20}$ + 43.80 (c=5, Et_2O) has 97% ee, compound (S)-(E)-**1**, synthesized according to the above reported reaction sequence (2→3→5→6→7→1) and having $[\alpha]_D^{20}$ + 45.14 (c=4.94, Et_2O), had an optical purity of more than 99% ee. Noteworthy is the fact that the 1,2-dehydrochlorination of **5**, when performed with potassium t-butoxide in DMSO at higher temperatures (*e.g.* at 140°C), gave up to 85% of the more substituted α,β-unsaturated imine **6b**. However after hydrolysis of the mixture of **6a** and **6b** (ratio 15:85) and subsequent Rh(III)-catalyzed hydrolysis the e.e. diminished to 70%, indicating that racemization had taken place at higher temperature.

The present facility of operation of this synthetic route to (S)-(+)-manicone **1** contrasts dramatically with recent syntheses which utilized multistep routes and a whole array of organometallic reagents (Li, Cu, Zn, Pd, ...).[12]

EXPERIMENTAL PART

General methods. NMR spectra were recorded on a Jeol PMX60 si (60 MHz) and a JEOL JNM-EX 270 NMR spectrometer (270 MHz for ^{1}H-NMR, 68 MHz, for ^{13}C-NMR). IR spectra were obtained using a Perkin Elmer 1310 spectrophotometer. Mass spectra were recorded on a Varian MAT 112 mass spectrometer (70 eV) using GC-MS coupling. TLC was performed on silica gel plates Kieselgel $60F_{254}$ (layer thickness 0.25 mm). Column chromatography was carried out on a glass column with Merck Silicagel 60 (particle size 40-63 μm). The $[\alpha]_D$-value was measured at 20°C with an Optical Activity AA-10 polarimeter. The alkylation experiments were performed under a nitrogen atmosphere. Ether was dried and distilled from sodium

wire, while tetrahydrofuran (THF) was dried and distilled from sodium benzophenone ketyl. S-(+)-2-methyl-1-bromobutane was purchased from Fluka, chemical purity > 97% (GC), $[\alpha]_D^{20} = +4.1° \pm 0.5°$.

2-Chloro-3-pentanone (2). Through a solution of 86.1 g (1 mol) of 3-pentanone in 100 ml of a mixture H_2O/CH_2Cl_2 (1:1) was bubbled 64.0 g (0.9 mol) of chlorine (CAUTION : sometimes the reaction has to be initiated by heating before too much of chlorine is added). After completion of the reaction (2 h), the reaction mixture was extracted with CH_2Cl_2 (3x100 ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was carefully distilled through a 40 cm Vigreux column to afford 55.5 g (yield 46%) of compound **2** (bp. 74-75°C/64 mmHg). Chlorination of 3-pentanone with chlorine is preferred to chlorination with sulfuryl chloride which leads to very low yields (< 15%)[18,19] of 2-chloro-3-pentanone **2**.

N-(2-chloro-3-pentylidene)isopropylamine (3). To a stirred ice-cooled solution of 2-chloro-3-pentanone **2** (24.1 g, 200 mmol) in 150 ml of dry ether, isopropylamine (59.0 g, 1.0 mol) was added followed by the dropwise addition of a solution of titanium(IV) chloride (22.75 g, 120 mmol) in pentane (40 ml) [CAUTION! exothermic reaction].[13] After the addition is complete, the ice bath was removed and the heterogeneous mixture was stirred for another 2 h at room temperature. The mixture was then poured in aqueous 0.5 N sodium hydroxide (200 ml) and extracted with diethyl ether (3x100 ml). The combined extracts were dried (K_2CO_3) and concentrated under reduced pressure. The residual α-chloro ketimine **3** was distilled *in vacuo* to afford a colorless liquid (21.65 g, 67%, bp 65-69°C/19 mmHg). MS m/z (%) : 161/3 (M^+; 0.4); 146/8(1); 127(1); 110(1); 98(15); 90(2); 84(2); 56(100); 54(15); 43(19); 42(8); 41(23); 40(8). ^{1}H-NMR (CCl_4) : δ 1.06 (6H, d, J=7 Hz, $CH(C\underline{H}_3)_2$); 1.10 (3H, t, J=7.5 Hz, $C\underline{H}_3CH_2$); 1.57 (3H, d, J=7 Hz, $C\underline{H}_3CHCl$); 2.35 (2H, q, J=7.5 Hz, $CH_3C\underline{H}_2$); 3.66 (1H, septet, J=7 Hz, $C\underline{H}(CH_3)_2$); 4.41 (1H, q, J=7 Hz, C<u>H</u>Cl). ^{13}C-NMR ($CDCl_3$) : δ 12.81 ($\underline{C}H_3CH_2$); 20.76 (CH_2); 22.27 ($\underline{C}H_3CHCl$); 23.61 and 23.70 ($CH(\underline{C}H_3)_2$); 50.21 ($\underline{C}H(CH_3)_2$); 61.51 (CHCl); 168.00 (C=N). IR (NaCl) : 1660 cm^{-1} (C=N).

(S)-N-(4-chloro-4,6-dimethyl-3-octylidene)isopropylamine (5). To an ice-cooled solution of diisopropylamine (3.94 g, 39 mmol) in 150 ml of dry THF was subsequently added dropwise n-butyllithium (14.4 ml, 36 mmol; 2.5 M in hexane) and N-(2-chloro-3-pentylidene)isopropylamine **3** (5.33 g, 30 mmol), dissolved in dry THF (50 ml). After 1 h at 0°C, (S)-(+)-2-methyl-1-bromobutane (4.30 g, 28.5 mmol) in 20 ml THF was added and the reaction mixture was stirred for 17 h at room temperature and subsequently poured into 100 ml of aqueous sodium hydroxide (0.5 N). The (S)-imine **5** was extracted with diethyl ether (3x75 ml) and the combined extracts were dried (K_2CO_3). The solvent was evaporated to give 6.73 g (97%) of the crude α-chloro ketimine **5** which had a satisfactory purity (> 97%) to be used as such in the next step, although high vacuum distillation was possible (bp 28-33°C/0.04 mmHg). MS m/z (%) : 231/3 (M^+; 0.2); 196 (M^+-Cl; 2); 161/3(9); 146/8(1); 138/40(1); 126(10); 124(2); 110(1); 109(1); 98(26); 69(3); 68(3); 67(2); 58(2); 57(11); 56(100); 55(7); 54(2); 44(4); 43(13); 42(4); 41(14). ^{1}H-NMR ($CDCl_3$) (2 diastereoisomers; 55:45) : δ 0.83 and 0.86 (each 3H, each t, J=7.25 Hz, $C\underline{H}_3CH_2CH$); 0.85 and 0.93 (each 3H, each d, J=6.60 Hz, $C\underline{H}_3CHCH_2$); 1.07 and 1.12 (each 6H, each d, J=6.1 Hz, $CH(C\underline{H}_3)_2$); 1.16 (6H, t, J=7.5 Hz, $C\underline{H}_3CH_2C$=N); 1.20-1.55 (6H, m, $CH_3C\underline{H}_2C\underline{H}$); 1.70 (6H, s, $C\underline{H}_3CCl$); 1.70-2.10 (4H, m, $C\underline{H}_2CCl$); 2.41 and 2.43 (each 2H, each q, J=7.5 Hz, $C\underline{H}_2C$=N); 3.75 (2H, septet, J=6.1 Hz, $C\underline{H}(CH_3)_2$). ^{13}C-NMR

($CDCl_3$) : δ 11.36 and 11.41 ($\underline{C}H_3CH_2CH$); 13.57 and 13.66 ($\underline{C}H_3CH_2C=N$); 20.83 and 21.00 ($\underline{C}H_3CHCH_2$); 21.56 and 21.62 ($\underline{C}H_2C=N$); 23.34, 23.49 and 23.76 ($CH(\underline{C}H_3)_2$); 28.84 and 29.22 ($\underline{C}H_3CCl$); 30.92 and 31.14 ($CH_3\underline{C}H_2CH$); 31.57 and 31.75 ($CH_3CH_2\underline{C}H$); 49.29 and 49.36 ($\underline{C}H_2CCl$); 50.53 and 50.56 ($\underline{C}H(CH_3)_2$); 77.95 and 78.04 (CCl); 169.29 and 169.38 (C=N). IR (NaCl) : 1650 cm^{-1} (C=N).

(S)-N-(6-methyl-4-methylene-3-octylidene)isopropylamine (6a) and (S)-N-(4,6-dimethyl-4-octen-3-ylidene)isopropylamine (6b). A solution of 2.31 g (10 mmol) of α-chloro ketimine **5** in 20 ml DMSO was treated with 1.23 g (11 mmol) of potassium t-butoxide. The reaction mixture was stirred for 5 h at room temperature, poured into 100 ml of aqueous sodium hydroxide (0.5 N) and extracted with ether (3x50 ml). The combined extracts were washed with brine, dried (K_2CO_3) and concentrated to provide the mixture of α,β-unsaturated imines **6a** (E/Z : 5/1) and **6b** (ratio **6a/6b** > 6/1) (1.96 g, 100%; purity > 99%; GC). Spectroscopic data of the major product **(E)-6a** : MS m/z (%) : 195 (M^+; 23); 180(18); 166(33); 152(26); 138(38); 126(25); 125(18); 124(83); 110(74); 107(22); 98(12); 96(30); 95(11); 83(10); 82(14); 79(13); 69(21); 68(19); 63(19); 58(17); 57(17); 56(100); 55(35); 53(12); 44(21); 43(42); 42(15); 41(61). ^{1}H-NMR ($CDCl_3$) : δ 0.81 (3H, d, J=6.60 Hz, $C\underline{H}_3CHCH_2$); 0.87 (3H, t, J=7.4 Hz, $C\underline{H}_3CH_2CH$); 1.02 (3H, t, J=7.6 Hz, $C\underline{H}_3CH_2C=N$); 1.12 (6H, d, J=6.0 Hz, $CH(C\underline{H}_3)_2$); 1.00-1.55 (3H, m, $CH_3C\underline{H}_2C\underline{H}$); 2.00-2.55 (2H, m, $C\underline{H}_2C=C$); 2.41 (2H, q, J=7.6 Hz, $CH_2C=N$); 3.75 (1H, septet, J=6.0 Hz, $C\underline{H}(CH_3)_2$); 5.20 en 5.36 (each 1H, d, J=1.1 Hz, $=C\underline{H}_2$). ^{13}C-NMR ($CDCl_3$) : δ 11.55 ($\underline{C}H_3CH_2CH$); 12.60 ($\underline{C}H_3CH_2C=N$); 19.20 ($\underline{C}H_3CHCH_2$); 20.59 ($\underline{C}H_2C=N$); 23.97 and 24.00 ($CH(\underline{C}H_3)_2$); 29.59 ($CH_3\underline{C}H_2CH$); 33.64 ($CH_3\underline{C}HCH_2$); 40.61 ($\underline{C}H_2C=C$); 50.28 ($\underline{C}H(CH_3)_2$); 116.19 ($\underline{C}H_2=C$); 149.00 ($CH_2=\underline{C}$); 167.36 (C=N). IR (NaCl) : 1640, 1614 cm^{-1} (C=N, C=C).

(S)-(E)-4,6-dimethyl-4-octen-3-one (1) and (S)-6-methyl-4-methylene-3-octanone (7). A solution of 1.56 g (8 mmol) of the α,β-unsaturated imines **6a** and **6b** (ratio 6:1) in 15 ml of CH_2Cl_2 was stirred with 8 ml of a 1N aqueous solution of oxalic acid. The two-phase mixture was stirred for 24 h at room temperature and subsequently extracted with CH_2Cl_2 (3x20 ml). After drying ($MgSO_4$), filtration and evaporation of the solvent *in vacuo*, 1.08 g (88%) of the mixture of α,β-unsaturated ketones **1** and **7** was obtained (ratio **7:1/83:17**), sufficiently pure (> 98%; GC) to be used as such in the next step. The spectral data of compounds **1** and **7** matched in all aspects with the data previously reported.[11]

(S)-(+)-manicone (1). To a solution of a mixture of (S)-**1** and **7** (1.08 g, 7 mmol) in 20 ml of absolute ethanol was added $RhCl_3.3H_2O$ (90 mg, 0.35 mmol) and the mixture was refluxed under a nitrogen atmosphere for 15 h. The mixture was diluted with 50 ml of water and extracted with CH_2Cl_2 (3x30 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a light yellow oil (1.06 g, 97%, purity > 96%) which was purified by flash chromatography over silica gel (hexane:ethyl acetate/92:8) to afford pure (> 99%, GC) (S)-manicone **1** (0.55 g, 51%), e.e. > 99%.

REFERENCES

1. Fales, H.M.; Blum, M.S.; Crew, R.M.; Brand, J.M. *J. Insect Physiol.* **1972**, *18*, 1077-1081.
2. Bestmann, H.J.; Attygalle, A.B.; Glasbrenner, J.; Riemer, R.; Voskrowsky, O. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 784-785.
3. Bestmann, H.J.; Attygalle, A.B.; Glasbrenner, J.; Riemer, R.; Vostrowsky, O.; Constantino, M.E.; Melikian, G.; Morgan, E.D. *Liebigs Ann. Chem.* **1988**, 55-60.
4. Katzenellenbogen, J.A.; Utawanit, T. *J. Am. Chem. Soc.* **1974**, *96*, 6153-6158.
5. Kocienski, P.J.; Ansell, J.M.; Ostrow, R.W. *J. Org. Chem.* **1976**, *41*, 3625-3627.
6. Blanco, L.; Slougui, N.; Rousseau, G.; Conia, J.M. *Tetrahedron Lett.* **1981**, *22*, 645-648.
7. Alexakis, A.; Commerçon, A.; Coulentianos, C.; Normant, J.F. *Tetrahedron* **1984**, *40*, 715-731.
8. Yoneda, R.; Harusawa, S.; Kurihara, T. *J. Chem. Soc. Perkin Trans. I* **1988**, 3163-3168.
9. Banno, K.; Mukaiyama, T. *Chem. Lett.* **1976**, 279-282.
10. Mimura, T.; Kimura, Y.; Nakai, T. *Chem. Lett.* **1979**, 1361-1364.
11. Martischonok, V.; Melikyan, G.G.; Mineif, A.; Vostrowsky, O.; Bestmann, H.J. *Synthesis* **1991**, 560-564.
12. Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *40*, 8801-8824.
13. De Kimpe, N.; Sulmon, P.; Moëns, L.; Schamp, N.; Declercq, J.-P.; Van Meerssche, M. *J. Org. Chem.* **1986**, *51*, 3839-3848.
14. De Kimpe, N.; Sulmon, P.; Schamp, N. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 881-882.
15. Harrod, J.F.; Chalk, A.J. *J. Am. Chem. Soc.* **1964**, *86*, 1776-1779.
16. Grieco, P.A.; Nishizawa, M.; Marinovic, N.; Ehmann, W.J. *J. Am. Chem. Soc.* **1976**, *98*, 7102-7104.
17. Taber, D.F.; Gunn, B.P. *J. Org. Chem.* **1979**, *44*, 450-452.
18. Wyman, D.P.; Kaufman, P.R. *J. Org. Chem.* **1964**, *29*, 1956-1960.
19. Föhlisch, B.; Gehrlach, E.; Stezowski, J.J.; Kollat, P.; Martin, E.; Gottstein, W. *Chem. Ber.* **1986**, *119*, 1661-1682.

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