Stereoselective Synthesis of β-Sinensal *via* a π-Allylnickel(II) Complex †

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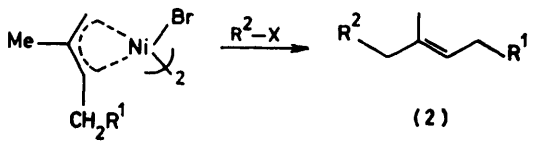
A new π-allylnickel(II) complex, di-μ-bromo-bis(1—3-η-2-methyl-6-methyleneocta-2,7-dienyl)dinickel (5) was prepared by the reaction of bromomyrcene (7a) and (8a) with nickel tetracarbonyl in benzene. The reaction of the complex (5) with iodobenzene in dimethylformamide afforded 8-phenylmyrcene (10) in a high degree of stereoselectivity (*E*/*Z* = 85/15). The complex (5) reacted with the chloro-acetal (14), derived in three steps from isoprene, to give the acetal (15) which upon hydrolysis afforded β-sinensal (1) in high stereoselectivity (93% *E*).

β-SINENSAL (1) is one of the two sesquiterpene aldehydes which make critical contributions to the order and taste of Chinese orange oil (*Citrus sinensis* L.).[1] Stereoselective and non-stereoselective syntheses of β-sinensal (1) [2] were reported several years ago, but most of the existing methods consist of multi-step extensions of a carbon skeleton to built up the sesquiterpene framework.

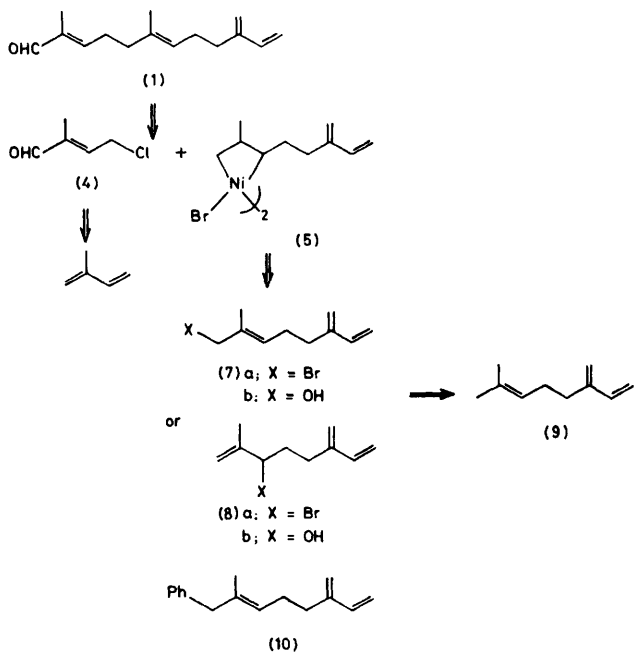
As part of our investigations on the stereoselective syntheses of trisubstituted olefins (2) using 1,2-disubstituted π-allylnickel(II) bromides (3),[3] we now report a successful application of this procedure to a stereoselective synthesis of β-sinensal (1).



(3) (2)

Coupling reactions between π-allylnickel(II) complexes [4] and organic halides are useful for synthesis in that they can be performed under strictly neutral conditions, and do not require activating groups which must otherwise be removed or converted into other functional groups after the carbon–carbon bond-forming reaction. Scheme 1 outlines the retrosynthetic strategy of (1), which consists of a single carbon–carbon bond-forming step, starting from readily available isoprene (6) and myrcene (9).

First we examined the synthesis and stereoselective reaction of a new nickel(II) complex, 1—3-η-2-methyl-6-methyleneocta-2,7-dienylnickel(II) bromide (5), derived from 8-bromo-7-methyl-3-methyleneocta-1,6-diene (7a) or 3-bromo-2-methyl-6-methyleneocta-1,7-diene (8a). These bromides (7a) or (8a) could be obtained from the corresponding alcohol (7b), formed by selenium dioxide oxidation of (9),[2b,5] or from the isomeric secondary alcohol (8b), formed by base-induced isomerization of epoxymyrcene [6] or photosensitized oxygenation of (9) [7] as a mixture with the isomeric tertiary alcohol. We chose the sensitized oxygenation to functionalize (9) because of its simplicity, moderate overall yield, and ease of operation on a large scale. The action of phosphorus tribromide on (7b) afforded a 1 : 1 mixture (n.m.r.) of the primary bromide (7a) and the secondary bromide (8a), which was then treated with nickel tetracarbonyl in benzene at 40 °C to produce the nickel(II) complex (5). The crude complex (5), obtained by removal of the benzene at reduced pressure, was treated



SCHEME 1

with iodobenzene in dimethylformamide at 40 °C to afford 7-methyl-3-methylene-8-phenylocta-1,6-diene (10) in 51% yield as a mixture of the 6*E* (85%) and 6*Z* (15%) isomers.

We next turned our attention to the preparation of a key C_5 intermediate such as (4). We initially desired the acetal (13) of the bromo-analogue of (4), as the majority of coupling reactions dealing with π-allylnickel(II) bromides had been performed with various organic bromides which are obviously more reactive toward nickel complexes than the corresponding chlorides.[4b] Scheme 2 illustrates the attempted synthesis of (13) from the readily accessible keto-acetal (11).

Thus the hydroxy-acetal (12) was obtained, by condensation of the keto-acetal (11) with the phosphonate derived from ethyl bromoacetate followed by reduction with lithium aluminium hydride, in fewer steps and

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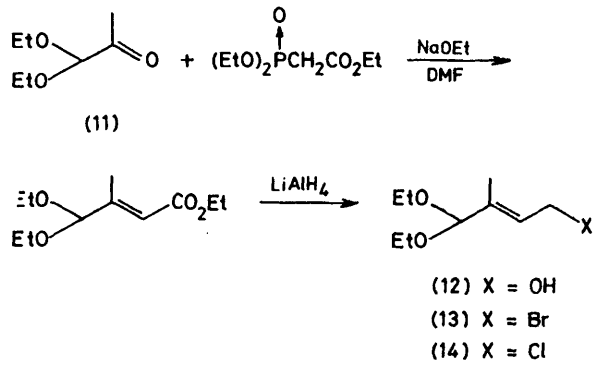
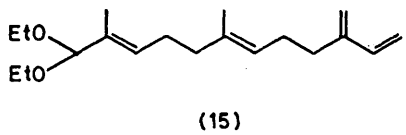
better overall yields than by the reported method.[8] The conversion of (12) into the bromo-acetal (13), however, proved unsuccessful using several conventional methods including the treatment of the alcohol (12) with triphenylphosphine and tetrabromomethane in acetonitrile.[9] During this investigation a convenient two-step synthesis of the chloro-acetal (4) from isoprene was



SCHEME 2

reported by Re *et al.*[10] This chloro-acetal then seemed to be a preferred substrate for the coupling reaction with π-allylnickel(II) complexes provided it had sufficient reactivity: this proved to be the case.

The aldehyde (4) was converted into the acetal (14) using triethyl orthoformate, and (14) was treated with the complex (5) in dimethylformamide at 40 °C for 20 h to yield, after acidic treatment, β-sinensal (1) as an oil in 50% yield. The product was shown to consist of all-*trans*-(1) (93%) and a minor amount of two mono-*cis*-isomers (5 and 2%) by g.l.c. analysis, indicating again the high stereoselectivity of the reaction with (5). Chromatography on neutral alumina yielded, along with (1), two by-products (16) and (17) as the most and least mobile components, respectively, which were obviously derived from (5) and (14) by a homo-coupling reaction.



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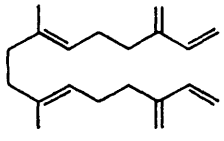
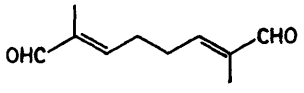


(16)



(17)

The primary product of the coupling reaction, the acetal (15), was isolated by treatment of the reaction mixture with alkali followed by chromatography of the crude product on neutral alumina (activity grade III), partial hydrolysis of the acetal occurring on the column. The use of tetrahydrofuran as a solvent for the coupling reaction between (14) and (5) resulted in a lower yield (23%) of the product (1), but gave a higher stereoselectivity (98%).

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded for solutions in CCl_4 or $CDCl_3$ with a JEOL C-60 spectrometer using tetramethylsilane as an internal standard. I.r. spectra were taken for neat films on a Hitachi model 215 spectrophotometer; mass spectra were determined on a Hitachi RMU-6E spectrometer. G.l.c. analyses were performed with Shimazu GC-4A or GC-3B instruments using a column (3 m × 3 mm) of 20% silicone DC 200 on 60—80 mesh Celite 545. Column chromatography was carried out on Wakogel C-200 (silica gel) or Woelm neutral alumina. Tetrahydrofuran was dried by distillation from lithium aluminium hydride; *NN*-dimethylformamide (DMF) was dried by distillation from calcium hydride under reduced pressure. Experiments dealing with highly toxic nickel tetracarbonyl (Matheson) were conducted in a well-ventilated hood,[11] and reactions involving π-allylnickel complexes were carried out under an argon atmosphere.

2-Methyl-6-methyleneocta-1,7-dien-3-ol (8b) was obtained by the sensitized photo-oxygenation of myrcene [12] followed by column chromatography of the alcoholic product on silica gel (30 g per g) using isopropyl ether–hexane (1 : 9 v/v) as eluant to effect separation of the isomeric tertiary alcohol.

8-*Bromo*-7-*methyl*-3-*methyleneocta*-1,6-*diene* (7a) and 3-*Bromo*-2-*methyl*-6-*methyleneocta*-1,7-*diene* (8a).—To a stirred solution of the alcohol (8b) (4.0 g, 26 mmol) and pyridine (0.2 ml) in n-hexane (45 ml) was added a solution of phosphorus tribromide (3.5 g, 13 mmol) in n-hexane (15 ml) at −10 °C over 1 h. After the mixture had been stirred at −10 °C for 8 h, it was poured into ice–water and extracted with n-hexane. The extract was washed (aqueous $NaHCO_3$, H_2O, and aqueous NaCl), dried ($MgSO_4$), and concentrated *in vacuo* to leave a mixture of the bromides (7a) and (8a) (*ca.* 1 : 1) as a pale yellow oil (3.9 g, 68%), homogeneous on t.l.c. (hexane, R_F 0.6); $\nu_{max.}$ 1 640, 1 600, 1 210, and 900 cm^{-1}; δ (CCl_4) 1.73 (s), 1.84 (d), 1.6—1.9 (m), 2.0—2.4 (m), 3.86 (s), 4.40 (t), 4.80—5.70 (m), and 6.28 (dd). This material was used without further purification.

7-*Methyl*-3-*methylene*-8-*phenylocta*-1,6-*diene* (10.)—A solution of the above bromide (4.1 g, 19 mmol) in dry benzene (30 ml) was slowly added to a stirred solution of nickel tetracarbonyl (4.9 g, 29 mmol) in benzene (13 ml) at 40 °C over 2 h. After the mixture had been stirred at 40 °C for 2 h, the excess of nickel carbonyl and the solvent were removed under reduced pressure below 20 °C to give the complex (5) as a dark red residue. The crude complex (5) was dissolved in DMF (30 ml) and a solution of iodobenzene (2.6 g, 13 mmol) in DMF (10 ml) was added to the solution at 40 °C. After the mixture had been stirred at 40 °C for 16 h, the green reaction mixture was poured into ice-cooled dilute hydrochloric acid, extracted with ether–n-hexane, washed (aqueous $NaHCO_3$, H_2O, and aqueous NaCl), and dried ($MgSO_4$). Distillation under reduced pressure gave the *coupling product* (10) (1.4 g, 51%), b.p. 83—85 °C at 0.15 mmHg; $\nu_{max.}$ 1 640, 1 500, and 900 cm^{-1}; δ (CCl_4) 1.52 and 1.60 (total 3 H, each s, *trans*- and *cis*-CH_3), 2.20 (4 H, m, CH_2CH_2), 3.20 and 3.31 (total 2 H, each s, *trans*- and *cis*-CH_2Ph), 4.9 (2 H, s, CH_2=), 4.95—5.30 (3 H, m, CH_2= and CH=), 6.31 (1 H, dd, *J* 10 and 18 Hz, CH=), and 7.09 (5 H, s, C_6H_5) (Found: C, 90.8; H, 9.65. $C_{16}H_{20}$ requires C,

90.5; H, 9.5%). The stereoisomeric ratio of the product was 85% *E* and 15% *Z* based on g.l.c. and n.m.r.

Ethyl 4,4-Diethoxy-3-methylbut-2-enoate.—To a solution of methylglyoxal diethyl acetal [13] (12.0 g, 82 mmol) and ethyl diethylphosphonoacetate [14] (22.0 g, 98 mmol) in anhydrous DMF (135 ml) was added, at room temperature over 50 min, an alcoholic solution of sodium ethoxide prepared by adding sodium (2.3 g, 100 mmol) in anhydrous ethanol (66 ml). After the mixture had been stirred at room temperature for 3 h, water (300 ml) was added to the reaction mixture, and it was extracted with ether, washed (H_2O), and dried ($MgSO_4$). Distillation under reduced pressure afforded the ester (15.2 g, 82%), b.p. 105—120 °C at 8 mmHg; $\nu_{max.}$ 1 720, 1 230, 1 160, 1 115, and 1 070 cm^{-1}; δ (CCl_4) 1.20 (6 H, t, *J* 7 Hz, acetal CH_3), 1.27 (3 H, t, *J* 7 Hz, ester CH_3), 1.84 and 2.07 (total 3 H, ratio 1 : 4, each s, *cis*- and *trans*-CH_3), 3.25—3.70 (4 H, m, acetal CH_2), 4.08 (2 H, q, *J* 7 Hz, ester CH_2), 4.64 (1 H, s, CH), and 5.87 and 6.02 (total 1 H, ratio 4 : 1, each s, CH=).

4,4-Diethoxy-3-methylbut-2-en-1-ol (12).—A solution of the above ester (5.0 g, 23 mmol) in ether (20 ml) was added to a mixture of lithium aluminium hydride (0.6 g, 13 mmol) in ether (30 ml) at 0 °C over 1 h. After the mixture had been stirred under reflux for 2 h, aqueous sodium hydroxide (15%, 0.6 mol), and then water (1.8 ml) were added to the reaction mixture under ice-cooling. The mixture was filtered and dried ($MgSO_4$). Distillation under reduced pressure gave the alcohol (12) (3.9 g, quantitative), b.p. 70—78 °C at 0.2 mmHg (lit.,[8] 67—70 °C at 0.1 mmHg); $\nu_{max.}$ 3 350, 1 110, and 1 060 cm^{-1}; δ ($CDCl_3$) 1.22 (6 H, t, *J* 7 Hz, CH_3), 1.67 and 1.76 (total 3 H, ratio 4 : 1, each s, CH_3C=), 2.26br (1 H, s, OH), 3.28—3.77 (4 H, m, acetal CH_2), 4.22 (2 H, d, *J* 7 Hz, CH_2O), 4.64 (1 H, s, acetal CH), and 5.78 (1 H, t, *J* 7 Hz, CH=).

(E)-4-*Chloro*-1,1-*diethoxy*-2-*methylbut*-2-*ene* (14).—To a mixture of the chloro-aldehyde (4) [10] (3.6 g, 30 mmol) and ethyl orthoformate (6.7 g, 45 mmol) was added a hot solution of ammonium nitrate (200 mg) in anhydrous ethanol (3 ml). After the mixture had stood at 60 °C for 6 h, it was filtered and concentrated *in vacuo* in the presence of anhydrous sodium carbonate (300 mg). Distillation under reduced pressure afforded the *acetal* (14) (3.5 g, 60%), b.p. 58—64 °C at 0.35 mmHg; $\nu_{max.}$ 1 260, 1 110, and 1 060 cm^{-1}; δ (CCl_4) 1.20 (6 H, t, *J* 7 Hz, acetal CH_3), 1.70 (3 H, s, CH_3C=), 3.2—3.7 (4 H, m, CH_2O), 4.02 (2 H, d, *J* 7 Hz, CH_2Cl), 4.55 (1 H, s, CH), and 5.74 (1 H, t, *J* 7 Hz, CH=) (Found: C, 56.35; H, 9.1. $C_9H_{17}ClO_2$ requires C, 56.1; H, 8.9%).

β-*Sinensal* (1).—The complex (5) was prepared from the bromide (7a) and (8a) (3.3 g, 15 mmol) and nickel tetracarbonyl (5.1 g, 30 mmol) by the procedure described in the preparation of the diene (10). The complex (5) was dissolved in DMF (80 ml) at 5 °C and to this solution was added a solution of the acetal (14) (2.5 g, 13 mmol) in DMF (80 ml) at 40 °C over 40 min. After the mixture had been stirred at 40 °C for 20 h, it was poured into dilute hydrochloric acid, extracted with ether–n-hexane, washed (aqueous $NaHCO_3$, H_2O, and aqueous NaCl), dried ($MgSO_4$), and concentrated *in vacuo* to leave a light yellow liquid (3.0 g). Chromatography on neutral alumina (activity III, 50 g per g) using n-hexane–dichloromethane as eluant afforded β-sinensal (1) (1.4 g, 50%) as an oil, identical (i.r. and n.m.r. spectra) with authentic β-sinensal.[1] The 2,4-dinitrophenylhydrazone had m.p. 85—87 °C (lit., 87—88,[1] 84.5—85.5,[2c] 80—81 °C [2a]). G.l.c. (200 °C) showed a major peak at t_R 3.7 min (93%), accompanied by two minor peaks at t_R 2.8 min (5%) and 4.0 min (2%), which were presumed to be mono-*cis*-β-sinensals.

The two by-products were isolated from the above reaction by column chromatography: the *hydrocarbon* (16) (0.46 g, 26%) was the most mobile component, homogeneous on t.l.c. (hexane, R_F 0.75); $\nu_{max.}$ 2 920, 1 600, 1 440, 985, and 890 cm^{-1}; δ (CCl_4) 1.60 (6 H, s, CH_3), 2.03—2.20 (12 H, m, CH_2CH_2), 4.94—5.30 (10 H, m, HC= and H_2C=), and 6.30 (2 H, dd, *J* 10.5 and 17 Hz, vinylic HC=); *m/e* 270 (M^+) (Found: C, 88.6; H, 11.5. $C_{20}H_{30}$ requires C, 88.8; H, 11.2%); and the dialdehyde (17) (0.22 g, 20%) was the least mobile component, homogeneous on t.l.c. (hexane–ethyl acetate 1 : 1 v/v, R_F 0.4); $\nu_{max.}$ 2 920, 2 700, and 1 680 cm^{-1}; δ (CCl_4) 1.74 (6 H, s, CH_3), 2.20—2.33 (8 H, m, CH_2), 6.50 (2 H, m, HC=), and 9.40 (2 H, s, CHO); *m/e* 166 (M^+) (Found: C, 72.55; H, 8.35. $C_{10}H_{14}O_2$ requires C, 72.25; H, 8.5%).

β-*Sinensal Diethyl Acetal* (15).—The reaction of the acetal (14) (1.93 g, 10 mmol) and the complex (5), prepared from the bromide (7a) and (8a) (3.44 g, 16 mmol), was conducted at 40 °C in DMF as described above. The reaction mixture was poured into 3M-NH_4OH (200 ml) containing NH_4Cl (10 g), stirred well until it turned blue, and extracted with hexane–ether, washed (1M-NH_4OH containing 10% NaCl), and dried ($MgSO_4$). The crude product was chromatographed on neutral alumina (activity III) using dichloromethane–hexane as eluant to afford the acetal (15) (0.78 g, 27%), $\nu_{max.}$ 2 980, 2 930, 1 440, 1 060, and 900 cm^{-1}; δ (CCl_4) 1.16 (6 H, t, *J* 7 Hz, CH_3), 1.61 (6 H, s, CH_3), 2.03—2.21 (8 H, m, CH_2CH_2), 3.15—3.66 (4 H, m, CH_2O), 4.47 (1 H, s, acetal CH), 4.93—5.30 (6 H, m, CH_2= and CH=), and 6.30 (1 H, dd, *J* 10.5 and 18 Hz, vinyl H); *m/e* 247 ($M^+ - C_2H_5O$) (Found: C, 79.4; H, 9.55. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%). Further elution with dichloromethane–hexane gave a transient fraction containing the acetal (15) and β-sinensal (1) (230 mg, *ca.* 9%), followed by β-sinensal (1) (280 mg, 13%).

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