NAD(P)$^+$-NAD(P)H Models. 71. A Convenient Route to the Synthesis of Juvabione

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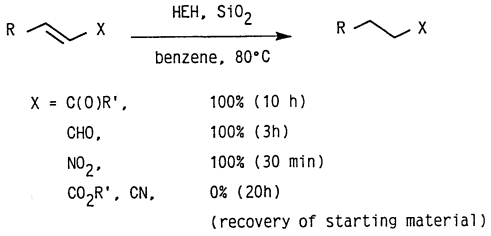
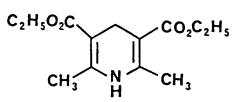
Synopsis. Synthesis of juvabione in short steps in a high overall yield has been achieved via the chemoselective reduction with Hantzsch ester (HEH) in the presence of silica gel as a key step.

Diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (Hantzsch ester, HEH), which has been studied extensively as a model of a coenzyme NAD(P)H,[1] was found to be a mild, therefore a selective reducing agent useful for organic syntheses.[2-7] Namely, under the catalysis of silica gel, HEH selectively hydrogenates the carbon-carbon double bonds conjugated with a nitro, a formyl, or a keto group in quantitative yield, whereas those conjugated with an alkoxycarbonyl or a cyano group as well as unconjugated ones are not affected at all (Scheme 1).

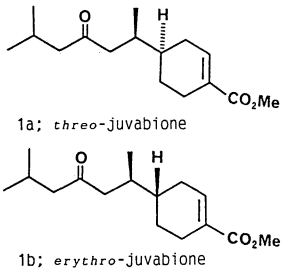


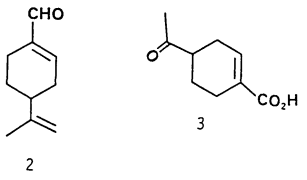


HEH

Scheme 1. Chemoselective reductions of activated olefins with HEH-SiO_2.

Juvabione was isolated from Balsam fir and identified as the methyl ester of todomatuic acid[8-10] by Bowers and his co-workers.[11] And it has attracted considerable biological interests as a sesquiterpene with a high juvenile hormone activity for a certain range of insect.[12] The compound has also received much attention of synthetic organic chemists and has been synthesized in a number of alternaitve pathways. Among many approaches to juvabione,[13] construction of methyl cyclohexenecarboxylate moiety was often the key stage of the strategies. Negishi et al.[14] established a short synthesis by using perillaldehyde (**2**) as a starting material. Drabkina et al.[15] employed 4-acetyl-1-cyclohexenecarboxylic acid (**3**) as a precursor. In this report, the author describes a short approach to juvabione via the reduction with HEH-SiO_2 of the precursor, methyl 4-(1,5-dimethyl-3-oxo-1-hexenyl)-1-cyclohexenecarboxylate (**9**) derived from methyl 4-acetyl-1-cyclohexenecaboxylate (**7**).





Results and Discussion

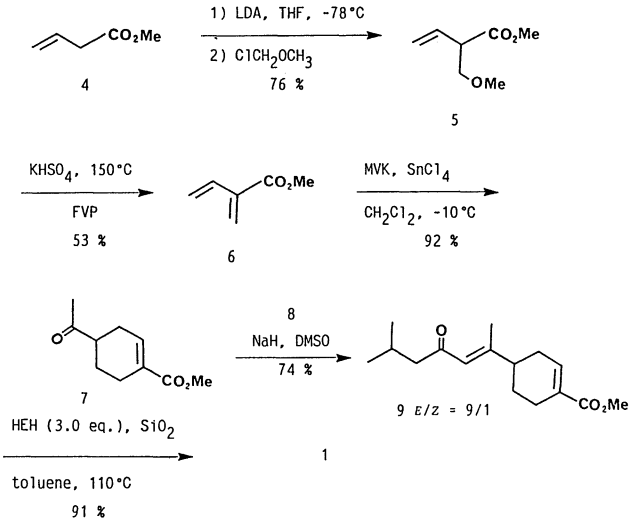
Methyl 2-methylene-3-butenoate (**6**) was obtained by flash vaccum pyrolysis of methyl 2-methoxymethyl-3-butenoate (**5**) at 150 °C on potassium hydrogensulfate[16] which was given by the alkylation of methyl 3-butenoate (**4**) with chloromethyl methyl ether.[17] The diene **6** was reacted with 3-buten-2-one below −10 °C in the presence of tin(IV) chloride to give para-adduct **7** as a sole product. The Wittig-Horner reaction[19] of **7** with dimethyl 4-methyl-2-

Table 1. Reduction of 9 with HEH-SiO_2

Entry	HEH/equiv	Solvent	Temperature/ °C	Yield[a]/%
a	1.5	Benzene	80	13
b	3.0	Benzene	80	19
c	1.5	Toluene	110	54
d	3.0	Toluene	110	91

a) Isolated yield.

oxopentylphosphonate (**8**) proceeded smoothly by the aid of sodium hydride in DMSO to afford **9** in 74% yield. The configuration at newly formed carbon-carbon double bond was determined to be E/Z=9/1 by means of ^{1}H NMR spectroscopy. Finally, the reduction of **9** with HEH under the catalysis of silica gel was investigated. As summarized in Table 1, when the reaction was run at 80 °C in refluxing benzene, the yield of the product was unsatisfactory even in the presence of **3** equivalent amounts of HEH. However, satisfactory results (92% yield) was obtained when the reaction with 3 equivalent amounts of HEH was run at 110 °C in refluxing toluene.



Scheme 2. Synthesis of juvabione (**1**).

Thus obtained product was characterized by satisfactory results from ^{1}H NMR, IR, GC-Mass, and elemental analyses,[13] and the ratio of its diastereomeric isomers was determined to be erythro form: threo form=14:86 by ^{13}C NMR analyses.[20] The total synthesis of **1** was completed in 27% overall yield.

Experimental

Instruments. ^{1}H NMR spectra were measured at 90 MHz with Hitachi R-90H FT-NMR spectrometer. IR spectra were recorded on JASCO IR-810 infrared spectrometer. GC-mass spectra were recorded on Hitachi M-80A GC-Mass spectrometer. Gas chromatography analyses were performed on Shimazu GC-9A gas chromatograph. Elemental analyses were performed with a Yanaco MT-3 elemental analyzer.

Chemicals. Solvents were dehydrated and distilled immediately prior to the use. Chloromethyl methyl ether, 3-butenoic acid, 3-buten-2-one, ethyl 3-methylbutanoate, dimethyl methylphosphonate, tin(IV) chloride, titanium(IV) chloride, and zinc(II) bromide were purchased from Wako Pure Chemical Industry Ltd. Wakogel C-200 was used for column chromatography and Nakarai Silica Gel 60 (35—70 mesh) was used as the catalyst for HEH reduction. Diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (HEH) was prepared as reported in a previous paper.[21]

Preparation of 7. To a solution composed of 2.24 g (20 mmol) of **6** and 1.40 g (20 mmol) of 3-buten-2-one in 50 ml of dichloromethane at −78 °C was added 5.2 g (20 mmol) of tin(IV) chloride over 30 min. The reaction mixture was warmed slowly to −10 °C with stirring and stirring was continued for 5 h at the same temperature. The whole mixture was poured into 50 ml of cold water, and the organic materials were extracted with dichloromethane (30 ml×3). The organic layer was washed with H_2O (50 ml×2) and brine (50 ml), dried on anhydrous magnesium sulfate, then condensed in vacuo after filtration. The crude product was purified by column chromatography on silica gel (hexane/benzene=1/1) to afford 3.35 g (92%) of **7** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.42—2.24 (m, 6H), 2.14 (s, 3H), 2.34—2.770 (m, 1H), 3.71 (s, 3H), and 6.84 (m, 1H); IR (neat) 1735 (s), 1720 (s), and 1650 (m); GC-Mass m/z 182 (M^+).

Wittig-Horner Reaction of 7 with 8. To a suspension of 580 mg of sodium hydride (abt. 60% in oil) in 10 ml of DMSO was added 1.92 g (10 mmol) of the phosphonate **8** dropwise via a syringe. The mixture was stirred at room temperature for 15 min and 1.82 g (10 mmol) of **7** was added to the mixture over 30 min at room temperature. The reaction mixture was stirred for 2 h at the same temperature and then heated to 65 °C for 15 min. The resulting solution was poured into 50 ml of 2 M HCl and the organic materials were extracted with ethyl acetate. The combined organic layer was dried on anhydrous magnesium sulfate and condensed in vacuo. Purification of the crude product on column chromatography (SiO_2-benzene) gave 1.95 g (74%) of **9**. The ratio of stereoisomers was determined to be approximately E/Z=9/1 from the integrated intensities of the methyl signals at 2.24 (E) and 1.92 (Z) ppm on ^{1}H NMR spectra; ^{1}H NMR ($CDCl_3$) δ=0.92 (d, J=7 Hz, 6H), 1.40—2.20 (m, 8H), 1.92 (s, E-isomer), 2.24 (s, Z-isomer, total 3H), 2.32 (d, J=7 Hz, 2H), 3.68 (s, 3H), 5.96 (bs, Z-isomer), 6.13 (bs, E-isomer, total 1H), and 6.96 (bs, 1H); IR (neat) 1735 (s), 1720 (s), 1660 (m), and 1655 (m) cm^{-1}; Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%. Found: C, 72.33; H, 9.04%.

Reduction of 9 with HEH-SiO_2. A mixture of 264 mg (1.0 mmol) of **9**, 756 mg (3.0 equiv) of HEH and 1.50 g of silica gel (Nakarai Silica Gel 60, 35—70 mesh) in 10 ml of absolute toluene was heated under reflux for 15 h. After the removal of silica gel by filtration, the organic solution was condensed and subjected to a column chromatography on silica gel using benzene as an eluent to give 242 mg (91%) of juvabione (**1**) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.88 (d, J=7 Hz, 3H), 0.92 (d, J=7Hz, 6H), 1.04—2.54 (m, 13H), 3.68 (s, 3H), and 6.94 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ=16.0 (q), 22.0 (q), 24.2 (d), 24.5 (d), 24.8 (t, threo C-5), 25.7 (t, erythro C-5), 27.9 (t, erythro C-3). 29.2 (t, threo C-3), 32.3 (d), 37.3 (d), 47.2 (d), 50.8 (q), 52.0 (t), 130.1 (s), 138.8 (d), 167.3 (s), 209.8 (s); IR (neat) 1725 (s), 1720 (s and 1660 (s) cm^{-1}; GC-Mass m/z 266 (M^+); Anal Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.08%. Found: C, 72.00; H, 9.54%.

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