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NAD(P)$^+$-NAD(P)H Model. 63. Regioselective Reduction of Dienoic Ketones and Aldehydes with an NAD(P)H Model on Silica Gel

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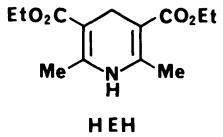
The Hantzsch ester reduces carbon–carbon double bonds in α,β-unsaturated ketones and aldehydes under the catalysis of silica gel. The 1,4-selectivity is satisfactorily high even in the reductions of polyenes conjugated to a carbonyl group. Methyl substituent at an olefinic position (α or β to the carbonyl group) retards the reduction. The reduction can be used as a useful tool in obtaining building blocks for the syntheses of terpenoids and their derivatives.

Quite a few reports have been published concerning to the mechanism of reduction with NADH, NADPH, and their analogs.[1] Stereochemistry for the reduction of carbonyl function in both biological and mimetic systems has been documented as well.[2] On the other hand, studies on synthetic application of the reduction with dihydropyridine derivatives has attracted little attention from organic chemists.[3] Namely, the mimetic reduction of carbon–carbon double bonds has been studied much less extensively than the reduction of carbon–oxygen double bonds, and reducible olefins in mimetic systems are limited to those that are substituted by a strongly electron-withdrawing substituent(s).[4] In some cases, photoirradiation is also effective for the reduction of olefins.[5] The reduction of carbon–carbon double bonds may have more value in synthetic organic chemistry than the reduction of carbon–oxygen double bonds and should be studied much more seriously.

Contrary to the mimetic systems, however, there are several biological systems that reduce carbon–carbon double bonds with the catalyses of NAD$^+$- or NADP$^+$-dependent dehydrogenases or reductases.[6] Since most NAD(P)H models so far studied have redox potentials comparable to that of NADH or NADPH[7] and these coenzymes reduce olefins in enzymatic systems, our effort should be concentrated on finding a suitable catalyst that behaves as a *mimetic enzyme* in order to undergo the organic reduction under mild conditions.

In previous papers of the series, we reported that silica gel is indeed a good catalyst for the reduction of carbon–carbon double bonds in α,β-unsaturated ketones and aldehydes,[8] and those in α-nitro olefins.[9] We now wish to report that the reduction with Hantzsch ester (HEH) in the presence of silica gel proceeds with very high chemoselectivity and regioselectivity under mild conditions, and that the reduction can be employed as a useful tool for wide variety of organic syntheses.



HEH

Experimental

Instruments. ^{1}H NMR spectra were measured at 100 and 400 MHz with a JEOL JNM-FX100 and a JEOL GX400 Fourier transform NMR spectrometers. IR spectra were recorded on a Hitachi EPI-S2 infrared spectrometer. Elemental analyses were performed with a Yanaco MT-3 elemental analyzer. Gas chromatographic data were recorded on a Yanaco G-1800 gas chromatograph (OV330, 1 m).

Materials. Hantzsch ester (HEH), and HEH-4,4-d_2 were prepared as reported in a previous paper.[10] The deuterium content in HEH-4,4-d_2 was confirmed to be 98% by 400 MHz ^{1}H NMR analysis. Citral (**3**), 2,4-nonadienal (**4c**), and β-ionone (**15**) are commercially available (Nakarai Chemicals Ltd.).

Other substrates were prepared according to literature methods.[11]

Silica gel (Nakarai Silica Gel 60, 35—70 mesh) was activated at about 80 °C in an oven for a few days. Anhydrous benzene was freshly distilled over calcium hydride immediately before the use.

Reduction of Benzylideneacetone (1a). In a 20 ml flask equipped with a magnetic stirrer and a reflux condenser, were placed 288 mg (2 mmol) of **1a**, 760 mg (3 mmol) of HEH, 2.0 g of silica gel, and 10 ml of anhydrous benzene. The mixture was heated to reflux for about 20 h under an argon atmosphere in the dark. The reaction mixture was cooled to room temperature, filtered, and washed with 30 ml of benzene. The filtrate was washed with 2 M†† hydrochloric acid (2×20 ml), water (2×20 ml), and 20 ml of brine, then dried on anhydrous sodium sulfate. Filtration and evaporation left a crude product, which was subjected to column chromatography on silica gel with benzene eluent to give 280 mg (96% yield) of the pure product, 4-phenyl-2-butanone (**2a**). The yield measured on gas chromatography was 100%.

†† 1 M=1 mol dm^{-3}.

^{1}H NMR ($CDCl_3$) δ=2.07 (s, 3H, CH_3CO), 2.74—2.81 (m, 4H, CH_2), 7.14—7.27 (m, 5H, Ph). IR (neat) 3000 (m) and 1717 (s) cm^{-1}. Found: C, 80.94; H, 8.31%. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.31%.

Reduction of Cinnamaldehyde (1b). Reduction of 264 mg (2 mmol) of **1b** with 760 mg (3 mmol) of HEH and 2.0 g of silica gel afforded 192 mg (72% yield) of 3-phenylpropanal (**2b**). The yield on gas chromatography was 100%.

^{1}H NMR ($CDCl_3$) δ=2.64—3.04 (m, 4H, CH_2), 7.04—7.35 (m, 5H, Ph), and 9.76 (t, 1H, CHO). IR (neat) 3000 (m) and 1730 (s) cm^{-1}. Found: C, 80.38; H, 7.62%. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51%.

Reduction of Ethyl Cinnamate (1c). Starting with 2 mmol of **1c**, 3 mmol of HEH, and 2.0 g of silica gel, no product was detected, and the starting materials were obtained from the reaction mixture in 100% recovery, respectively.

Reduction of β-Nitrostyrene (1d). A mixture of 151 mg (1 mmol) of **1d**, 280 mg (1.1 mmol) of HEH, and 1.0 g of silica gel in 5 ml of anhydrous benzene was heated to reflux for 5 h under an argon atmosphere in the dark. The reaction mixture was worked up as described above giving 129 mg (84% yield) of 2-phenyl-1-nitroethane, (**2d**).

^{1}H NMR ($CDCl_3$) δ=3.30 (t, 2H, J=7 Hz, $PhCH_2$), 4.58 (t, 2H, J=7 Hz, CH_2NO_2), and 7.11—7.33 (m, 5H, Ph). IR (neat) 3000 (m), 1530 (s), and 1380 (s) cm^{-1}. Found: C, 63.90; H, 6.10; N, 9.16%. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27%.

Reduction of Citral (3). Reduction of 152 mg (1 mmol) of **3** with 380 mg (1.5 mmol) of HEH and 1.0 g of silica gel under the same conditions as described above gave 103 mg (67% yield) of citronellal.

^{1}H NMR ($CDCl_3$) δ=0.97 (d, 3H, J=7 Hz, CH_3CH), 1.20—1.44 (m, 3H, $-CH_2CH(CH_3)-$), 1.60 (s, 3H, $(CH_3)_2C=$), 1.68 (s, 3H, $(CH_3)_2C=$), 2.00 (q, 2H, J=7 Hz, $-CH_2CH=$), 2.24—2.50 (m, 2H, CH_2CHO), 5.00—5.17 (m, 1H, C=CH), and 9.74 (t, 1H, J=1 Hz, CHO). IR (neat) 3000 (m) and 1740 (s) cm^{-1}. Found: C, 77.62; H, 11.74%. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.74%.

Reduction of (3*E*,5*E*)-6-Phenyl-3,5-hexadien-2-one (4a). After the reaction of 172 mg (1 mmol) of **4a** with 380 mg (1.5 mmol) of HEH and 1.0 g of silica gel in 10 ml of anhydrous benzene followed by usual work-up, column chromatography on silica gel with benzene eluent gave 153 mg (88% yield) of a mixture of two products, **5a** and **6a**. The ratio of **5a** to **6a** was determined by ^{1}H NMR analysis. The integration of signals for allylic C_α (C_3) protons (2H) in **6a** which appeared at δ 3.12 (d, J=5 Hz) and δ 3.25 (d, J=5 Hz)[12] was compared with that of signals for acetyl protons (3H) at δ 2.11 and the ratio was calculated as 73:27 (*E*:*Z* of **6a**=63:37).

^{1}H NMR ($CDCl_3$) δ=2.11 (s, CH_3CO-), 2.42—2.60 (m, CH_2 of **5a**), 3.12 (d, J=5 Hz, $-CH_2CO-$ of (*E*)-**6a**), 3.25 (d, J=5 Hz, $-CH_2CO-$ of (*Z*)-**6a**), 3.36 (d, J=5 Hz, $PhCH_2-$ of **6a**), 5.56—5.76 (m, H_β and H_γ of **6a**), 6.12 (dt, J=15, 6 Hz, H_γ of **5a**), 6.38 (d, J=15 Hz, H_δ of **5a**), and 7.04—7.41 (m, Ph). IR (neat) 3025 (m), 2925 (m), 1715 (s), and 1660 (w) cm^{-1}.

Reduction of 86 mg (0.5 mmol) of **4a** with 191 mg (0.75 mmol) of HEH-4,4-d_2 (98% purity in deuterium) and 0.5 g of silica gel afforded 75 mg of a mixture of the two products. The analysis of the 400 MHz ^{1}H NMR spectrum of the mixture revealed that the deuterium was incorporated in the 4-position of **5a** and in the 6-position of **6a**. The deuterium content in each product was 98%. The ratio of **5a**-4-*d*:**6a**-6-*d* was calculated to be 88:12.

400 MHz ^{1}H NMR ($CDCl_3$) δ=2.15 (s, CH_3CO-), 2.45 (q, J=6.8 Hz, $-CHD-$ of **5a**-4-*d*), 2.59 (d, J=7.3 Hz, $-CH_2CO-$ of **5a**-4-*d*), 3.14 (d, J=5.9 Hz, $-CH_2CO$ of (*E*)-**6a**-6-*d*), 3.28 (d, J=7.3 Hz, $-CH_2CO-$ of (*Z*)-**6a**-6-*d*), 3.36 (bs, $PhCHD-$ of **6a**-6-*d*), 5.60—5.72 (m, H_β and H_γ of **6a**-6-*d*), 6.18 (dd, J=16.1, 6.8 Hz, H_γ of **5a**-4-*d*), 6.40 (d, J=16.1 Hz, H_δ of **5a**-4-*d*), and 7.17—7.37 (m, Ph). IR (neat) 3030 (w), 2975 (s), 2170 (w), 1715 (s), and 1652 (w) cm^{-1}.

Reduction of (3*E*,5*E*)-3,5-Nonadien-2-one (4b). The reduction of 138 mg (1 mmol) of **4b** with 380 mg (1.5 mmol) of HEH and 1.0 g of silica gel gave 132 mg (94% yield) of a mixture of two compounds, **5b** and **6b**. The ratio of **5b**:**6b** was determined as 75:25 by comparing the integration for allylic C_α (C_3) protons (2H) at δ 3.16 (d, J=7 Hz) and 3.28 (d, J=8 Hz)[12] with the integration for the whole vinylic protons at δ 5.30—6.36 (m). The ratio thus determined was consistent with the ratio of the integration for vinylic protons of **5b** at δ 5.44—5.52 to that of vinylic protons of **6b** at δ 5.31—5.40.

IR (neat) 2925 (s), 1720 (s), and 1680 (m) cm^{-1}.

Reduction of (2*E*,4*E*)-2,4-Nonadienal (4c). The reduction of 158 mg (1.0 mmol) of **4c** with 380 mg (1.5 mmol) of HEH and 1.0 g of silica gel afforded 85 mg of **5c** and 21 mg of **6c** as pure compounds, respectively, after a routine column chromatography. The ratio of **5c**:**6c** was 80:20.

IR (neat) 2930 (s), 1715 (s), and 1660 (w) cm^{-1}.

Reduction of α-Methylcinnamaldehyde. The reduction of 14.6 mg (0.1 mmol) of α-methylcinnamaldehyde with 38.0 mg (0.15 mmol) of HEH, 150 mg of silica gel, and 2 ml of dry benzene gave the corresponding alcohol in 20% yield after 3 h and in 60% yield after 20 h.

Reduction of β-Methylcinnamaldehyde. The reduction of 14.6 mg (0.1 mmol) of β-methylcinnamaldehyde with 38.0 mg (0.15 mmol) of HEH was carried out under the same conditions as described above. The GLC analysis indicated that the chemical yields of the corresponding alcohol were 39% after 3 h and 79% after 20 h.

Reduction of 6-Phenyl-3,5-heptadien-2-one (7). The reduction of 186 mg (1 mmol) of **7** with 380 mg (1.5 mmol) of HEH and 1.0 g of silica gel afforded 175 mg (93% yield) of a mixture of two products, **9** and **10**. The ratio of **9**:**10** was calculated to be 92:8 from the ratio of integration for the allylic C_α (C_3) protons (2H) of **10** at δ 3.09 (d, J=6 Hz) to that for the trisubstituted vinylic proton (1H) of **9** at δ 5.32—5.76 (m).

^{1}H NMR ($CDCl_3$) δ=1.28 (d, J=8 Hz, CH_3CH of **10**), 2.00 (s, CH_3CH of **9**), 2.10 (s, CH_3CO- of **9** and **10**), 2.34—2.65 (m, CH_2 of **9**), 2.58—2.86 (m, $PhCH-$ of **10**), 3.09 (d, J=6 Hz, $-CH_2CO-$ of **10**), 5.32—5.76 (m, H_γ of **9**), 6.00—6.33 (m, H_β and H_γ of **10**), and 7.12—7.60 (m, Ph). IR (neat) 3050 (m), 2980 (s), 1715 (s), and 1680 (m) cm^{-1}.

Reduction of 6,10-Dimethyl-3,5,9-undecatrien-2-one (8). The reduction of 192 mg (1 mmol) of **8** with 380 mg (1.5 mmol) of HEH and 1.0 g of silica gel afforded 167 mg (86% yield) of a mixture of two products, **11** and **12**. The ratio of **11**:**12** was calculated to be 95:5 by examining the integration for the trisubstituted vinylic protons of **11** (2H) and **12** (1H) at δ 4.96—5.20 (m), and that for allylic C_α (C_3)

protons (2H) of **12** at δ 3.09 (d, *J*=6 Hz). The ratio was also confirmed by comparison of the integration for trisubstituted vinylic protons of **11** and **12** and that for disubstituted vinylic protons of **12** at δ 5.38—5.59 (m).

^{1}H NMR ($CDCl_3$) δ=0.98 (d, *J*=6 Hz, CH_3CH of **12**), 1.58 (s, $(CH_3)_2C$= of **11** or **12**, and CH_3C of **11**), 1.67 (s, $(CH_3)_2C$= of **12** or **11**), 1.92—2.08 (m, CH_2 of **11** and **12**, and CH_3CH of **12**), 2.11 (s, CH_3CO- of **11** and **12**), 2.12—2.36 (m, CH_2 of **11**), 3.09 (d, *J*=6 Hz, -CH_2CO- of **12**), 4.96—5.20 (m, C=CH- of **11** and **12**), and 5.38—5.59 (m, -CH=CH- of **12**). IR (neat) 2980 (s), 1740 (s), and 1670 (m) cm^{-1}. Found: C, 80.60; H, 11.53%. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41%.

Preparation of Farnesol (14). Geranylacetone (**11**) (194 mg, 1 mmol) was converted into 172 mg (65% yield) of the corresponding α,β-unsaturated ester, **13**, as shown in Eq. 7.

The E:Z ratio of the new olefinic double bond was confirmed to be larger than 20:1 by ^{1}H NMR analysis; the signals for the allylic methyl protons trans to the carboethoxy group appeared at δ 2.12, whereas those cis to the carboethoxy group could not be detected at higher field.

^{1}H NMR ($CDCl_3$) δ=1.28 (t, *J*=7 Hz, 3H), 1.59 (s, 6H), 1.67 (s, 3H), 1.80—2.40 (m, 4H), 2.12 (s, 3H), 2.40 (t, *J*=6 Hz, 2H), 4.14 (q, *J*=7 Hz, 2H), 4.96—5.20 (m, 2H), and 5.65 (s, 1H). IR (neat) 2980 (s), 1740 (s), and 1670 (m) cm^{-1}. Found: C, 77.48; H, 10.53%. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.68%.

The reduction of 150 mg (0.57 mmol) of **13** was carried out with 21.7 mg (0.28 mmol) of lithium aluminium hydride to give 111 mg (88% yield) of farnesol (**14**).

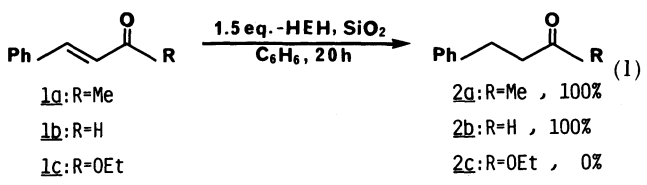
^{1}H NMR ($CDCl_3$) δ=1.60 (s, 9H), 1.68 (s, 3H), 1.82—2.36 (m, 8H), 4.15 (d, *J*=7 Hz, 2H), 4.97—5.24 (m, 2H), and 5.41 (t, *J*=7 Hz, 1H). IR (neat) 3355 (s), 2925 (s), and 1668 (m) cm^{-1}. Found: C, 81.11; H, 12.00%. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79%.

Reduction of β-Ionone (15). The reduction of 192 mg (1 mmol) of **15** with 380 mg (1.5 mmol) of HEH and 1.0 g of silica gel gave 136 mg of **16** as a sole product. The structure of **16** was confirmed by ^{13}C and ^{1}H NMR spectra.

^{1}H NMR ($CDCl_3$) δ=0.95 (s, 6H), 1.25—1.68 (m, 4H), 1.56 (s, 3H), 1.90 (t, *J*=6 Hz, 2H), 2.12—2.60 (m, 4H), and 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$) δ=19.54 (q), 19.72 (q), 22.41 (t), 28.49 (q), 29.72 (t), 32.82 (t), 35.10 (s), 39.90 (t), 44.56 (t), 127.83 (s), 136.14 (s), and 208.68 (s). IR (neat) 2960 (s), 1715 (s), and 1665 (s) cm^{-1}. Found: C, 80.12; H, 11.56%. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41%.

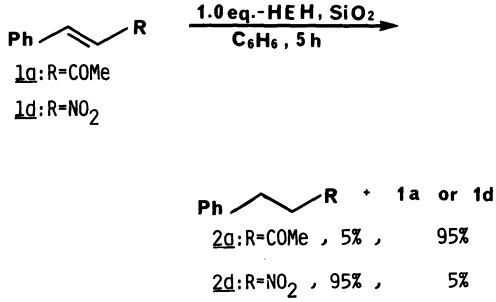
Results and Discussion

Chemoselectivity. Benzylideneacetone (**1a**) and cinnamaldehyde (**1b**) were reduced quantitatively into 4-phenyl-2-butanone (**2a**) and 1-phenylpropanal (**2b**), respectively, after 20 h at the temperature of refluxing benzene, whereas ethyl cinnamate (**1c**) remained entirely unchanged (Eq. 1). The result indicates that the reduction discriminates the carbon-carbon double



(1)

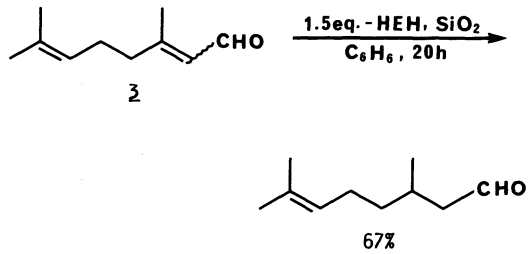
bond adjacent to a carbonyl group from that adjacent to an alkoxy-carbonyl group. The discrimination can also be seen between the double bonds adjacent to acetyl and nitro groups; under the conditions where 95% of β-nitrostyrene (**1d**) was reduced, only 5% of **1a** was converted into 4-phenyl-2-butanone (**2a**) (Eq. 2).



(2)

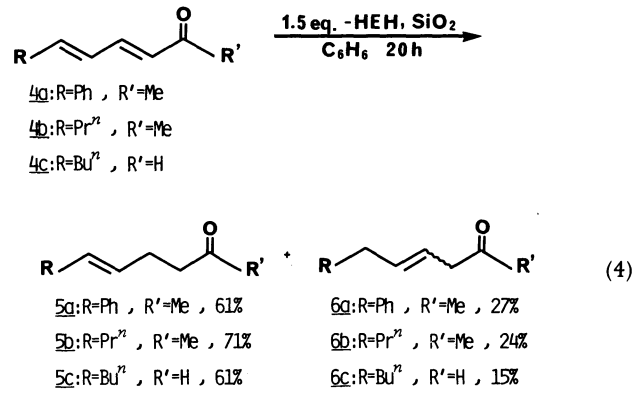
Under the same conditions, where **1b** afforded **2b** in quantitative yield, α- and β-methylcinnamaldehydes yielded the corresponding product alcohols in only 60 and 71% yields, respectively. Apparently, the methyl substituent at an olefinic position retards the reduction.

The isolated double bond is not affected by the reduction; only 1,4-reduction took place for citral (**3**) (Eq. 3).



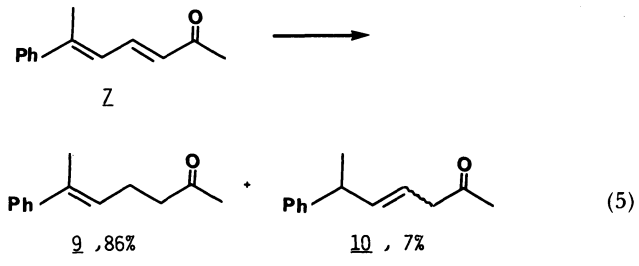
(3)

Reduction of Conjugated Dienones and Dienals. Reduction of conjugated dienoketones and aldehydes proceeded smoothly and afforded the products in good yields (Eq. 4). Although 1,4- and 1,6-type reductions are competitive here, the regioselectivity observed was reasonably satisfactory with the predominance of the 1,4-type reduction;[13] **5a**:**6a**=73:27, **5b**:**6b**=75:25, and **5c**:**6c**=80:20.



(4)

The ratio was determined by the ^1H NMR analysis comparing the sum of integration of signals for the vinylic protons with that for the allylic α-protons. The latter signal is inherent to the 1,6-reduction product, **6**, and usually appear at around δ 3.05—3.15 as a doublet. It should be noted that the predominance of the 1,4-reduction over the 1,6-reduction shows a sharp contrast to the predominant 1,6-selectivity exerted by the reduction with sodium dithionite under phase-transfer conditions[14] or with diisobutylaluminium hydride in the presence of methylcopper.[15] When the 6-position of conjugated carbon-carbon double bonds is substituted by a methyl group, the ratio of 1,4- vs. 1,6-reduction becomes much higher as a consequence of steric inhibition. For example, the reduction of 6-phenyl-3,5-heptadien-2-one (**7**) and 6,10-dimethyl-3,5,9-undecatrien-2-one (**8**) afforded **9** and **10** in 92:8 ratio and **11** and **12** in 95:5 ratio, respectively (Eqs. 5 and 6).



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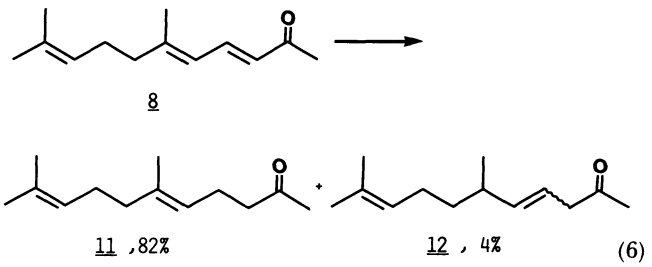
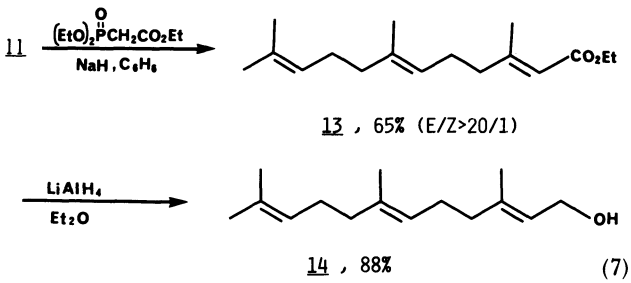


(6)

The reduction of **4a** with HEH-4,4-d_2 afforded **5a**-4-*d* and **6a**-6-*d*, which clearly demonstrated that a deuterium was directly incorporated into the 4- and 6-positions of the 1,4- and 1,6-reduction products, respectively.

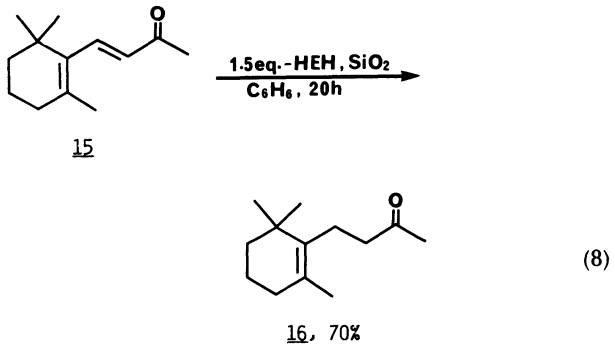
Application to Syntheses. Geranylacetone (**11**) thus obtained is an important component for the syntheses of terpenoids; a straightforward synthesis of farnesol (**14**) is one of examples (Eq. 7).[16]

The significance of the steric effect on the regioselectivity was clearly exaggerated by the reduction of β-ionone (**15**) which has three methyl groups on the cyclohexenyl moiety. In addition to the methyl



(7)

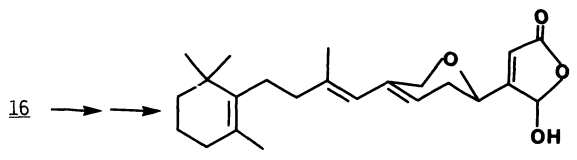
substituent on the endo-double bond, two methyl groups on the cyclohexenyl ring also plays a role to decrease the reactivity of this double bond, and the sole product obtained in this reduction is **16**, the 1,4-reduction product (Eq. 8). Recently, we came to the conclusion that the silica gel-catalyzed reduction with



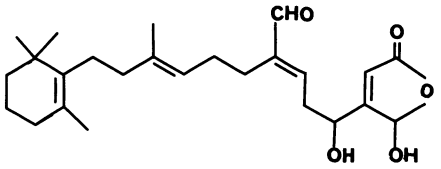
(8)

HEH proceeds with the HEH absorbed on silica gel instead of the intermediacy of a substrate-silica gel complex.[17] Consequently, the reacting HEH is sterically highly blocked by a huge silica-gel component, and a small difference in steric effects in the substrate may differentiate the reactivity of certain carbon–carbon double bond quite sensitively. A CPK molecular model shows that the axial methyl group at the 1-position of the cyclohexenyl ring of **15** prevents the (formal) hydride from attacking the endo-double bond from the axial side, whereas the attack from the equatorial side results in the 1,3-diaxial repulsion between 1- and 3-methyl groups in the product. Thus, this endo-double bond in **15** is sterically set unreactive remaining the exo-double bond as the sole reacting function.

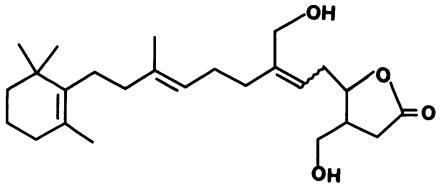
The product, **16**, is a component of natural products. For example, it is an important precursor of manoalides (Eq. 9), a series of natural marine products (e.g., 17—19) with strong biological activities.[18]



manoalide(17)



seco-manoalide(18)



(E)and(Z)-neomanoalide(19) (9)

In conclusion, HEH is a very mild reducing agent, which, in turn, can be employed as an efficient device to sharply differentiate the susceptibilities of functional groups in the reduction. Namely, it has been demonstrated that HEH on silica gel is a useful tool to synthesize γ,δ-unsaturated ketones and aldehydes that are important building blocks for the syntheses of terpenoids and other natural products.

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