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A Highly Chemoselective Reduction of Conjugated Nitro Olefins with Hantzsch Ester in the Presence of Silica Gel

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An effective system to reduce conjugated nitro olefins into the corresponding nitroalkanes is described. The system composed of Hantzsch ester (HEH) and silica gel in benzene exerts high yield and excellent chemoselectivity under almost neutral conditions. Facile applications of the system to the syntheses of natural products are also described.

The importance of aliphatic nitro compounds has remarkably increased in synthetic organic chemistry.[1] They are very useful tools for carbon–carbon bond formation because the strongly electron-withdrawing property of nitro group makes it possible to generate an α-carbanion adjacent to the group and to react with various electrophiles under mild reaction conditions. Moreover, nitro group itself can be converted into other functions such as carbonyl,[2] amino,[3] oxime,[4] hydrogen,[5] and so on. Namely the preparation[6] and reaction[7] of conjugated nitro olefins have been studied extensively and the compounds of this class have been widely accepted as intermediates to nitroalkanes via reductive hydrogenation.[8–12] Although a number of reducing reagents to convert a nitro olefin into the corresponding nitroalkane have been reported, there still remain several problems to be improved. For example, catalytic hydrogenation also reduces non-conjugated carbon–carbon double bonds,[9] and sodium borohydride cannot be employed for the reduction of compounds with a carbonyl function.[10]

On the other hand, reduction with NAD(P)H or its analogs received a wide interest in the recent decade. Particularly, the discussion on the mechanism of reduction has involved a lot of researchers not only in organic chemistry but also physical, analytical, and biochemistries.[13] It is suspected that 1,4-dihydropyridine derivatives might be characterized as a remarkable reducing reagent because the compounds in this category have too low potentials to reduce most of various functional groups, which, in turn, may exert interesting selectivity (chemo-, regio-, stereo-, or some other), especially for substrates with a variety of functional groups, under certain reaction conditions. However, unfortunately, studies on 1,4-dihydropyridine derivatives as tools in synthetic chemistry have enjoyed little attention and only few reports have been published concerning to this subject.[14,15] Namely, we found that silica gel catalyzes the reduction of certain functional groups while others remain unaffected.[14,16,17]

As a part of our research to find a selective organic reaction, it was elucidated that 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester, HEH) is indeed a useful reagent to reduce certain functional groups selectively. In this report, the author wishes to describe a convenient method for the reduction of nitro olefins with HEH, in the presence of silica gel, with high chemoselectivity and in high yield under mild reaction conditions.[18]

Experimental

Instruments. ^{1}H NMR spectra were measured at 100 MHz with a JOEL JUN-FX 100 Fourier transform NMR spectrometer and at 400 MHz with a JOEL GX400 Fourier transform NMR spectrometer. 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 (OV 330). GC mass data were recorded on a Hitachi M-80A GC Mass analyzer.

Materials. Hantzsch ester (HEH) and its 4,4-dideuteriated analog (HEH-4,4-d_2) were prepared as reported in a previous paper.[19] The deuterium content in HEH-4,4-d_2 was confirmed to be 98% by 400 MHz ^{1}H NMR analysis. Solvents were freshly distilled before the use. Silica gel (Nakarai Silica Gel 60, 35—70 mesh) was dried in an oven at 80 °C for a few days.

Preparation of Nitro Olefins. 1-Nitro-4-methyl-1-pentene (1a): A mixture of 8.6 g of 3-methylbutanal, 9.2 g of nitromethane, and 2.0 g of triethylamine was stirred at room temperature for 17 h, then quenched by addition of 50 ml of 2 M (1 M=1 mol·dm^{-3}) hydrochloric acid. The resulting solution was washed with water (2×50 ml) and 50 ml of brine, and dried on anhydrous sodium sulfate. After removal of the solvent, the residue was purified by a column chromatography on silica gel with benzene eluent to give 11.4 g (78%) of 1-nitro-4-methyl-2-pentanol. The β-nitro alcohol was then added into a mixture of 16 g of acetic anhydride and 18.4 g of pyridine and the solution was stirred at room temperature for 2 h. The reaction mixture was poured into 50 ml of 2 M hydrochloric acid and extracted with ether (3×30 ml). The organic layer was washed with water (3×30 ml) and brine (1×30 ml) and then dried on anhydrous sodium sulfate. After removal of the solvent the residue was purified by column chromatography on silica gel with hexane–benzene (1:1) as an eluent to give 14.4 g (98%) of the acetate. 14.4 g of the acetate was dissolved in 100 ml of benzene and the resulting solution was refluxed with 32 g of sodium carbonate for 5 h. The reaction mixture was filtered and the filtrate was washed with water (2×50 ml)

and brine (1×50 ml). The organic layer was dried and the solvent was evaporated under reduced pressure. Distillation of the residue with a Kugelrohr distillator gave 5.7 g (58%) of **1a**: bp 100 °C (2.7×10^3 Pa). ^{1}H NMR ($CDCl_3$) δ=0.98 (d, 6H, J=6 Hz), 1.65—2.04 (m, 1H), 2.18 (t, 2H, J=6 Hz), 6.95 (d, 1H, J=14 Hz) and 7.25 (dt, 1H, J=14, 6 Hz). IR (neat) 3000 (m), 1655 (s), 1530, and 1383 cm^{-1} (s).

Other nitro olefins except **1i** were prepared with the same method as described for **1a**.

1-Nitro-1-nonene (1b): Yield 43%. ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H, J=6 Hz), 1.20—1.63 (m, 10H), 2.26 (q, 2H, J=6 Hz), 6.94 (d, 1H, J=14 Hz), and 7.25 (dt, 1H, J=14, 6 Hz). IR (neat) 3000 (m), 1656 (m), 1532, and 1357 cm^{-1} (s).

Methyl 4-Nitro-4-heptenoate (1c): Yield 67%. ^{1}H NMR ($CDCl_3$) δ=1.14 (t, 3H, J=7 Hz), 2.16—2.48 (m, 2H), 2.78—3.01 (m, 4H), 3.68 (s, 3H), and 7.06 (t, 1H, J=7 Hz). IR (neat) 3000 (m), 1750 (s), 1644(m), 1530, and 1375 cm^{-1} (s).

5-Nitro-5-octen-2-one (1d): Yield 51%. ^{1}H NMR ($CDCl_3$) δ=1.13(t, 3H, J=7 Hz), 2.16—2.48 (m, 2H), 2.63—2.96 (m, 4H), and 7.11 (t, 1H, J=7 Hz). IR (neat) 3000 (m), 1725 (s), 1644 (m), 1530, and 1370 cm^{-1} (s).

3,6-Dimethyl-9-nitro-2,8-undecadiene (1e): Yield 60%. Bp 80—90 °C (9.3×10 Pa) (by Kugelrohr distillation). ^{1}H NMR ($CDCl_3$) δ=0.95 (d, 3H, J=6 Hz), 1.10 (t, 3H, J=7 Hz), 1.07—1.44 (m, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.91—2.27 (m, 4H), 2.61 (q, 2H, J=7 Hz), 5.07 (m, 1H), and 7.06 (t, 1H, J=8 Hz). IR (neat) 3000 (m), 1670 (m), 1527, and 1380 cm^{-1} (s).

4,8-Dimethyl-1-nitro-1,7-nonadiene (1f): Yield 63%. Bp 100—120 °C (3.3×10 Pa) (by Kugelrohr distillation). ^{1}H NMR ($CDCl_3$) δ=0.95 (d, 3H, J=6 Hz), 1.10—1.44 (m, 3H), 1.60 (m, 3H), 1.68 (m, 3H), 1.93—2.44 (m, 4H), 5.07 (m, 1H), 6.95 (d, 1H, J=14 Hz), and 7.25 (dt, 1H, J=14, 8 Hz). IR (neat) 3000 (m), 1650 (m), 1530, and 1380 cm^{-1} (s).

β-Nitrostyrene (1j): Yield 60%. Mp 58 °C. ^{1}H NMR ($CDCl_3$) δ=7.36—7.50 (m, 5H), 7.53 (d, 1H, J=14 Hz), and 7.96 (d, 1H, J=14 Hz). IR (Nujol) 3000 (m), 1630 (m), 1515, and 1385 cm^{-1} (s).

o-Methoxy-β-nitrostyrene (1k): Yield 78%. Mp 81.5—82 °C. ^{1}H NMR ($CDCl_3$) δ=3.91 (s, 3H), 6.90—7.05 (m, 2H), 7.35—7.52 (m, 2H), 7.80 (d, 2H, J=14 Hz), and 8.06 (d, 2H, J=14 Hz). IR (Nujol) 3000 (m), 1628 (m), 1538, and 1375 cm^{-1} (s).

p-Methoxy-β-nitrostyrene (1l): Yield 74%. Mp 85.5—86.5 °C. ^{1}H NMR ($CDCl_3$) δ=3.85 (s, 3H), 6.85—7.00 (m, 2H), 7.41—7.56 (m, 2H), 7.48 (d, 1H, J=14 Hz), and 7.95 (d, 1H, J=14 Hz). IR (Nujol) 3000 (m), 1608 (m), 1608 (m), 1513, and 1375 cm^{-1} (s).

β-Methyl-β-nitrostyrene (1m): Yield 82%. Mp 64 °C. ^{1}H NMR ($CDCl_3$) δ=2.42 (s. 3H), 7.39 (m, 5H), and 8.02 (m, 1H). IR (Nujol) 3000 (m), 1650 (m), 1530, and 1378 cm^{-1} (s).

p-Methoxy-β-methyl-β-nitrostyrene (1n): Yield 50%. Mp 46.5—47 °C. ^{1}H NMR ($CDCl_3$) δ=2.45 (s, 3H), 3.84 (s, 3H), 6.86—7.01 (m, 2H), 7.31—7.44 (m, 2H), and 8.02 (m, 1H). IR (Nujol) 3000 (m), 1605(m), 1515, and 1380 (s).

2-(2-Furyl)-1-nitroethene (1o): Yield 32%. Mp 72 °C. ^{1}H NMR ($CDCl_3$) δ=6.51—6.58 (m, 1H), 6.84—6.88 (m, 2H), 7.49 (d, 1H, 14 Hz), and 7.69 (d, 1H, J=14 Hz). IR (Nujol) 3000 (m), 1635 (m), 1500, and 1375 cm^{-1} (s).

2-(2-Thienyl)-1-nitroethene (1p): Yield 66%. Mp 79—80 °C. ^{1}H NMR ($CDCl_3$) δ=7.07—7.16 (m, 1H), 7.21—7.56 (m, 2H), 7.43 (d, 1H, J=13 Hz), and 8.12 (d, 1H, J=13 Hz). IR (Nujol) 3000 (m), 1622(m), 1525, and 1380 cm^{-1} (s).

Ethyl 3-Methyl-2-nitro-2-butenoate (1g): A mixture of 7.6 ml of 90% fuming nitric acid and 1.1 ml of water was cooled to 0 °C, and 2.56 g of ethyl 3-methyl-2-butenoate was added to this mixture over 1.25 h with vigorous stirring. The solution was stirred for 1.5 h at 0 °C and 1 h at room temperature, and then poured onto 50 ml of crushed ice and extracted three times with 30 ml of chloroform. The extracts were combined and washed three times with 50 ml of water, six times with 30 ml of saturated aqueous sodium hydrogencarbonate and twice with 30 ml of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual oil was distilled to give 3.14 g (91%) of **1i** as colorless oil. Bp 87.5 °C (3.1×10^2 Pa). ^{1}H NMR ($CDCl_3$) δ=1.29 (t, 3H, J=7 Hz), 1.97 (s, 3H), 2.25 (s, 3H), and 4.27 (q, 2H, J=7 Hz). IR (neat) 3000 (m), 1725 (s), 1650 (m), 1540, and 1375 cm^{-1} (s).

2-Methyl-2-(2-nitroethenyl)cyclohexanone (**1h**) and 1-(2-nitroethenyl)cyclohexanecarbaldehyde (**1i**) were supplied by Prof. K. Fuji of Institute for Chemical Research, Kyoto University.

Reduction of Nitro Olefins. 1-Nitro-4-methylpentane (2a): In a 30 ml round-bottom flask equipped with a magnetic stirrer and a reflux condenser were placed 258 mg (2.0 mmol) of **1a**, 560 mg (2.2 mmol) of HEH, 2.0 g of silica gel (Nakarai Silica Gel 60, 35—70 mesh), and 10 ml of anhydrous benzene. The reaction mixture was heated to reflux for 30 minutes under an argon atmosphere. The reaction mixture was cooled to room temperature, filtered, and the precipitate was washed with 30 ml of benzene. The combined organic solution was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel with hexane-benzene (1:1) as an eluent. As a pure product, 202 mg (78%) of **2a** was obtained. ^{1}H NMR ($CDCl_3$) δ=0.91 (d, 6H, J=6 Hz), 1.14—1.36 (m, 2H), 1.42—1.74 (m, 1H), 1.86—2.08 (m, 2H), and 4.34 (t, 2H, J=7 Hz). IR (neat) 3000 (m), 1555, and 1390 cm^{-1} (s).

Reductions of the other nitro olefins were carrried out following the general procedure described above.

1-Nitrononane (2b): Yield 91%. ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H, J=6 Hz), 1.20—1.40 (m, 12H), 2.00 (m, 2H), and 4.36 (t, 2H, J= 7 Hz). IR (neat) 3000 (m), 1558, and 1385 cm^{-1} (s).

Methyl 4-Nitroheptanoate (2c): Yield 87%. ^{1}H NMR ($CDCl_3$) δ=0.95 (t, 3H, J=6 Hz), 1.20—1.53 (m, 2H), 2.00—2.46 (m, 6H), 3.70(s, 3H), and 4.42—4.69 (m, 1H). IR (neat) 3000 (m), 1743 (s), 1550, and 1380 cm^{-1} (s).

5-Nitro-2-octanone (2d): Yield 86%. ^{1}H NMR ($CDCl_3$) δ=0.95 (t, 3H, J=6 Hz), 1.20—1.53 (m, 6H), 2.08 (s, 3H), and 4.44—4.71 (m, 1H). IR (neat) 3000 (m), 1715 (s), 1550, and 1370 cm^{-1} (s).

3,6-Dimethyl-9-nitro-2-undecene (2e): Yield 88%. ^{1}H NMR ($CDCl_3$) δ=0.87 (d, 3H, J=6 Hz), 0.95 (t, 3H, J=7 Hz), 1.08—1.48 (m, 6H), 1.59 (s, 3H), 1.75—2.08 (m, 5H), 4.21—4.48 (m, 1H), and 4.97—5.16 (m, 1H). IR (neat) 3000 (m), 1560, and 1380 cm^{-1} (s).

2,6-Dimethyl-9-nitro-2-nonene (2f): Yield 83%. ^{1}H NMR ($CDCl_3$) δ=0.91, (d, 3H, J=6 Hz), 1.12—1.44 (m, 5H), 1.60 (s, 3H), 1.68 (s, 3H), 1.97 (q, 2H, J=7 Hz), 2.03 (t, 2H, J=7 Hz), 4.35 (t, 2H, J=7 Hz), and 4.98—5.16 (m, 1H). IR (neat) 3000 (m), 1563, and 1390 cm^{-1} (s).

Ethyl 3-Methyl-2-nitrobutanoate (2g): Yield 71%. ^{1}H

NMR ($CDCl_3$) δ=1.13 (d, 6H, J=7 Hz), 1.35 (t, 3H, J=7 Hz), 2.47—2.96 (m, 1H, J=7 Hz), 4.34 (q, 2H, J=7 Hz), and 5.93 (d, 1H, J=8 Hz). IR (neat) 3000 (m), 1760 (s), 1570, and 1380 cm^{-1} (s).

2-Methyl-2-(2-nitroethyl)cyclohexan-1-one (2h): Yield 90%. ^1H NMR ($CDCl_3$) δ=1.20 (s, 3H), 1.68—1.90 (m, 6H), 2.04—2.46 (m, 4H), and 4.43 (t, 2H, J=7 Hz). IR (neat) 3000 (m), 1715 (s), 1560, and 1390 cm^{-1} (s).

1-(2-Nitroethyl)cyclohexanecarbaldehyde (2i): Yield 45%. ^1H NMR ($CDCl_3$) δ=1.27—1.98 (m, 10H), 2.22 (t, 2H, J=7 Hz), 4.32 (t, 2H, J=8 Hz), and 9.23 (s, 1H). IR (neat): 3000 (m), 1710 (s), 1561, and 1390 cm^{-1} (s).

(2-Nitroethyl)benzene (2j): Yield 84%. ^1H NMR ($CDCl_3$) δ=3.30 (t, 2H, J=7 Hz), 4.58 (t, 2H, J=7 Hz), and 7.11—7.33 (m, 5H). IR (neat) 3000 (m), 1530, and 1380 cm^{-1} (s).

1-Methoxy-2-(2-nitroethyl)benzene (2k): Yield 84%. ^1H NMR ($CDCl_3$) δ=3.31 (t, 2H, J=7 Hz), 3.81 (s, 3H), 4.59 (t, 2H, J=7 Hz), and 6.81—7.35 (m, 4H). IR (neat) 3000 (m), 1556, and 1383 cm^{-1} (s).

1-Methoxy-4-(2-nitroethyl)benzene (2l): Yield 65%. ^1H NMR ($CDCl_3$) δ=3.27 (t, 2H, J=7 Hz), 3.91 (s, 3H), 4.58 (t, 2H, J=7 Hz), and 6.80—7.17 (m, 4H). IR (neat) 3000 (m), 1550, and 1380 cm^{-1} (s).

2-Nitropropylbenzene (2m): Yield 87%. ^1H NMR ($CDCl_3$) δ=1.51 (d, 3H, J=6 Hz), 2.86—3.40 (m, 2H), 4.57—4.92 (m, 1H), and 7.07—7.30 (m, 5H). IR (neat) 3000 (m), 1550, and 1390 cm^{-1} (s).

1-Methoxy-4-(2-nitropropyl)benzene (2n): Yield 100%. ^1H NMR ($CDCl_3$) δ=1.50 (d, 3H, J=6 Hz), 2.80—3.32 (m, 2H), 3.74 (s, 3H), 4.52—4.87 (m, 1H), and 6.74—7.08 (m, 4H). IR (neat) 3000 (m), 1545, and 1385 cm^{-1} (s).

2-(2-Furyl)-1-nitroethane (2o): Yield 62%. ^1H NMR ($CDCl_3$) δ=3.34 (t, 2H, J=7 Hz), 4.62 (t, 2H, J=7 Hz), 6.08—6.14 (m, 1H), 6.26—6.32 (m, 1H), and 7.30—7.33 (m, 1H). IR (neat) 3000 (m), 1555, and 1380 cm^{-1} (s)

2-(2-Thienyl)-1-nitroethane (2p): Yield 83%. ^1H NMR ($CDCl_3$) δ=3.49 (t, 2H, J=7 Hz), 4.57 (t, 2H, J=7 Hz), 6.02—6.95 (m, 2H), and 7.03—7.18 (m, 1H). IR (neat) 3000 (m), 1550, and 1382 cm^{-1} (s).

Reduction of 1j with HEH-4,4-d_2: A mixture of 75 mg (0.5 mmol) of **1j**, 280 mg (1.1 mmol) of HEH-4,4-d_2 (98% purity in deuterium) and 500 mg of silica gel in 5 ml of anhydrous benzene was refluxed for 30 minutes under a nitrogen atmosphere. The reaction mixture was worked up as described above giving 71 mg (93%) of **2j**-d_1. The analysis of the 400 MHz ^1H NMR spectrum revealed that the deuterium was incorporated into the 2-position of **2j** quantitatively.

400 MHz ^1H NMR ($CDCl_3$) δ=3.24 (tt, 1H, J=2, 8 Hz), 4.53 (d, 2H, J=8 Hz), 7.19—7.35 (m, 5H). GC-MS: m/z 152 (M^+).

Synthesis of 3,7,11-Trimethyl-1-dodecanol (8). The nitro olefin, **4**, was prepared starting from 7.8 g of 3,7-dimethyloctanal (**3**) and 6.1 g of nitromethane in 81% yield following the procedure described above for **1a**.

^1H NMR ($CDCl_3$), δ=0.83 (d, 6H, J=7 Hz), 0.90 (d, 3H, J=7 Hz), 1.03—1.78 (m, 8H), 2.23 (t, 2H, J=6 Hz), 6.93 (d, 1H, J=14 Hz), and 7.22 (dt, 1H, J=14, 6 Hz). IR (neat) 3000 (m), 1663 (m), 1530, and 1350 cm^{-1} (s).

Reduction of 1.99 g of **4** with 2.80 g of HEH and 10 g of silica gel was carried out as described for **1a** to give 1.95 g (97%) of 4,8-dimethyl-1-nitrononane (**5**).

^1H NMR ($CDCl_3$) δ=0.86 (d, 6H, J=7 Hz), 0.88 (d, 3H, J=7 Hz), 1.03—1.56 (m, 10H), 1.83—2.12 (m, 2H), and 4.33 (t, 2H, J=6 Hz). IR (neat) 2950 (m), 1576, and 1380 cm^{-1} (s). Found: C, 65.89; H, 11.34; N, 6.88%. Calcd for $C_{11}H_{23}NO_2$: C, 65.61; H, 11.52; N, 6.96%.

A mixture of 1.0 g of **5**, 0.57 g of ethyl crotonate, 0.8 g of DBU and 5 ml of DMF was stirred at room temperature for 20 h. The reaction mixture was worked up as an usual way to give 0.87 g (55%) of ethyl 3,7,11-trimethyl-4-nitrododecanoate (**6**).

^1H NMR ($CDCl_3$) δ=0.82 (d, 9H, J=7 Hz), 0.95—2.51 (m, 21H), 4.05—4.18 (m, 2H), and 4.32—4.49 (m, 1H). IR (neat) 3000 (m), 1750 (s), 1575, and 1380 cm^{-1} (s). Found: C, 65.08; H, 10.53; N, 4.37%. Calcd for $C_{17}H_{33}NO_4$: C, 64.71; H, 10.55; N, 4.44%.

A mixture of 630 mg (2.0 mmol) of **6**, 700 mg (2.4 mmol) of tributyltin hydride, and 100 mg (0.6 mmol) of AIBN in 5 ml of benzene was heated to reflux for 5 h. The reaction mixture was chromatographed on silica gel using benzene/hexane (1/1) as an eluent to give 351 mg (65%) of ethyl 3,7,11-trimethyldodecanoate (**7**).

^1H NMR ($CDCl_3$) δ=0.82 (d, 6H, J=7 Hz), 0.86 (d, 6H, J=7 Hz), 0.95—1.61 (m, 11H), 2.24 (d, 2H, J=6 Hz), and 4.12 (q, 2H, J=6 Hz). IR (neat) 3000 (m) and 1745 cm^{-1} (s). Found: C, 75.86; H, 12.55%. Calcd for $C_{17}H_{34}O_2$: C, 75.48; H, 12.68%.

The ester **7** was reduced with $LiAlH_4$ in ether at 0 °C to give the aimed alcohol **8** in 90% yield.

^1H NMR ($CDCl_3$) δ=1.78—1.88 (m, 12H), 1.95—1.62 (m, 17H), 3.20 (bs, 1H), and 3.58 (t, 2H, J=6 Hz). IR (neat) 3580 (s), and 2975 cm^{-1}.

Synthesis of Dendrolasin: To a solution of 6.1 g of nitromethane and 9.6 g of 3-furancarbaldehyde (**9**) in 100 ml of ethanol was added 10 ml of 10 M KOH over 30 minutes at 0 °C with vigorous stirring. The reaction mixture was stirred for 30 minutes and poured onto 100 ml of ice water. The precipitate was filtered and recrystallized from hot ethanol to give 12.0 g (86%) of 1-(3-furyl)-2-nitroethene (**10**) as yellow needles. Mp 68—70 °C.

^1H NMR ($CDCl_3$) δ=6.60 (dd, 1H, J=6, 1 Hz), 6.93 (d, 1H, J=6 Hz), 7.54 (d, 1H, J=14 Hz), 7.60 (m, 1H), and 7.79 (d, 1H, J=14 Hz). IR (KBr) 3010 (m), 1640 (m), 1500, and 1375 cm^{-1} (s).

A mixture of 1.39 g of **10**, 3.08 g of HEH, 10.0 g of silica gel and 50 ml of benzene was heated to reflux under a nitrogen atmosphere for 30 minutes. Silica gel was filtered off and the filtrate was chromatographed on silica gel using benzene as an eluent to give 1.33 g (94%) of 1-(3-furyl)-2-nitroethane (**11**) as yellowish oil.

^1H NMR ($CDCl_3$) δ=3.34 (t, 2H, J=7 Hz), 4.62 (t, 2H, J=7 Hz), 6.13 (m, 1H), 6.31 (m, 1H), and 7.35 (m, 1H). IR (neat) 3000 (s), 1550, and 1375 cm^{-1} (s).

To a solution of 705 mg (5 mmol) of **11** and 700 mg of 2,6-dimethyl-5-heptenal in 10 ml of toluene was added 132 mg (1.5 mmol) of *N,N*-dimethylethylenediamine. The mixture was heated to reflux for 24 h. The reaction mixture was diluted with 20 ml of 2 M hydrochrolic acid and extracted with ethyl acetate. The extract was condensed and chromatographed on silica gel to give two isomeric products, 46% of **12** and 25% of **13**. The nitro olefin **13** was easily isomerized into allylic nitro compound **12** in quantitative yield by refluxing it in benzene in the presence of 0.1 equivalent amount of triethylamine for 5 h.

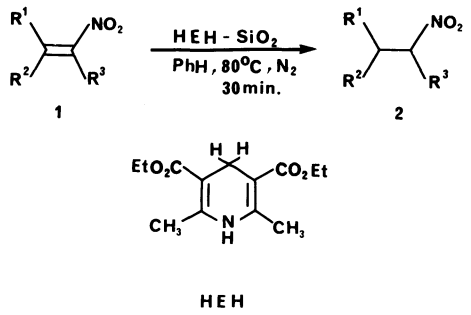
^{1}H NMR ($CDCl_3$) δ=1.61 (s, 6H), 1.86 (s, 3H), 2.20—2.61 (m, 5H), 5.08 (q, 1H, J=7 Hz), 5.23—5.64 (m, 2H), 6.31 (s, 1H), 7.21 (s, 1H), and 7.41 (t, 1H, J=2 Hz). IR (neat) 2950 (s), 1625 (m), 1560, and 1375 cm^{-1} (m).

A mixture of 526 mg (2.0 mmol) of **12**, 1.75 g (6.0 mmol) of tributyltin hydride 98 mg of AIBN, and 10 ml of benzene was refluxed for 5 h and then washed with water and brine. The solution was condensed under reduced pressure and chromatographed on silica gel using benzene as an eluent to give 187 mg (43%) of dendrolasin (**14**).

^{1}H NMR ($CDCl_3$) δ=1.59 (s, 6H), 1.85 (s, 3H), 2.23—2.58 (m, 8H), 5.18—5.43 (m, 2H), 6.30 (s, 1H), 7.22 (s, 1H), and 7.36 (t, 1H, J=2 Hz). IR (neat) 2950 (s), and 1620 cm^{-1} (m). GC-Ms m/z 218 (M^+).

Results and Discussion

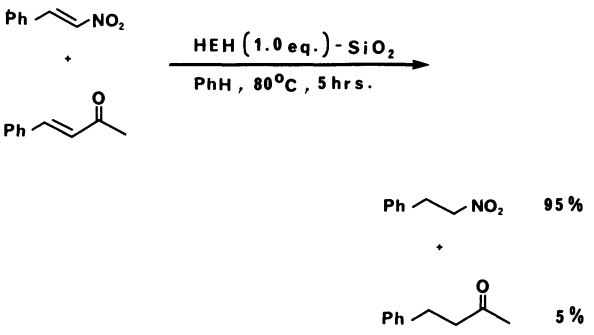
Reduction of Nitro Olefins: It was reported that silica gel activates HEH in benzene effectively and α,β-unsaturated carbonyl compounds are reduced with this system in satisfactory yields and with high chemo- and regioselectivities.[20] The reduction of carbon-carbon double bonds in α,β-conjugated nitro olefins also proceeds with the same reducing system; as shown in Scheme 1, a mixture of a nitro olefin, 1.1 equivalent amount of HEH, and silica gel in refluxing benzene



Scheme 1.

affords the corresponding nitroalkane quite smoothly. The results are summerized in Table 1. Both aromatic and aliphatic nitro olefins are reduced in excellent to good yields. It is worth while to note that the carbon-carbon double bonds in nitro olefins that bear carbonyl functional groups can be reduced with the present system without affecting any influence on the carbonyl functions.

The carbon-carbon double bond in an α,β-unsaturated ketone is a function which is reduced with the HEH-silica gel system. However, when an α,β-unsaturated carbonyl compound was subjected to the reduction competitively with an equivalent amount of nitro olefin, 95% of the latter was reduced after 5 h whereas 95% of the former was found unreacted (Scheme 2).



Scheme 2.

When 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine-4,4-d_2 (HEH-4,4-d_2) was subjected to the reduction of β-nitrostyrene and 1-nitro-2-phenylethane produced was analyzed on 400 MHz ^{1}H NMR spectrometer, it was found that more than 98% of the deuterium was incorporated into the 2-position, which indicates that the hydrogen on the 4-position of HEH migrates onto the substrate without exchanging with hydrogens in the solvent.

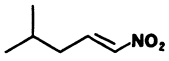
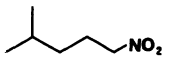
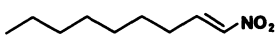
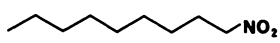
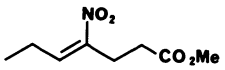
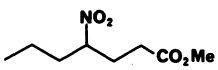
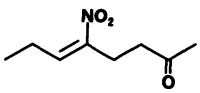
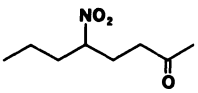
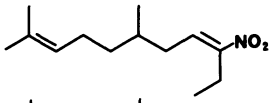
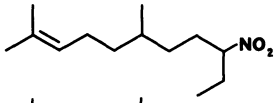
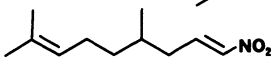
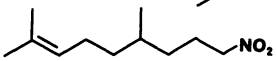
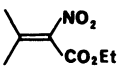
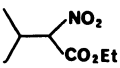
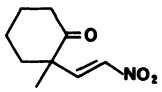
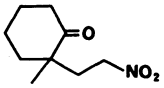
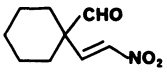
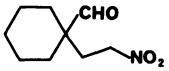
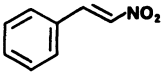
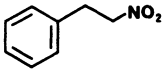
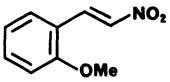
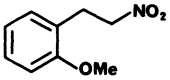
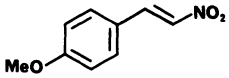
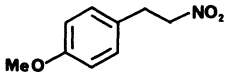
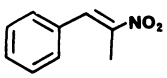
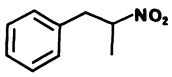
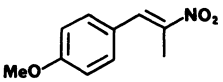
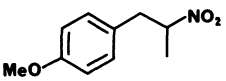
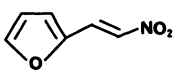
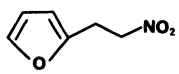
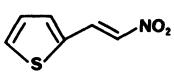
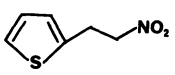
The reduction of nitro olefin is accompanied by the formation of dimeric products.[10] No dimer was detected, however, in the products from the present reduction system. In previous papers of the series, it was reported that silica gel plays not only a role of a Lewis acid catalyst to activate HEH but also a role of a proton donner with the silanol group on its surface.[17] Here again, it seems reasonable to expect that a carbanion formed from the substrate nitro olefin by accepting a (net) hydride from HEH is immediately protonated on the surface of silica gel to afford a stable product.

Although stereoselective reduction has not been examined yet, the author believes that the present reduction system can provide a versatile method in organic synthesis with its high yield, excellent chemoselectivity, and facility of the procedure, and the method has been applied to the syntheses of natural products as will be described in the following section.

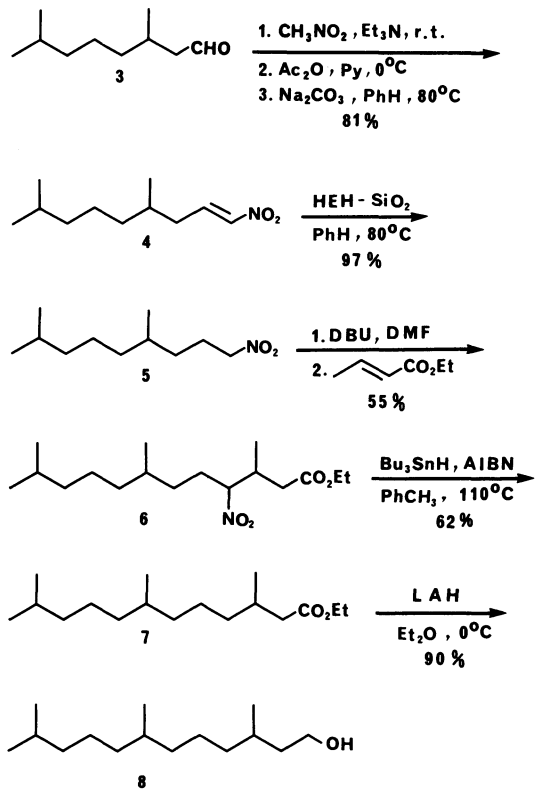
Syntheses of Natural Product. Synthesis of 3,7,11-Trimethyl-1-dodecanol: A sesquiterpene alcohol, 3,7,11-trimethyl-1-dodecanol (**8**), has been widely accepted as a key intermediate in the synthesis of α-Tocopherol (Vitamin E).[21] The present reduction system can usefully be applied to the synthesis of this alcohol. The whole reaction scheme is shown in Scheme 3.

3,7-Dimethyloctanal (**3**) was condensed with nitromethane to give a β-nitro alcohol in the presence of triethylamine as a catalyst. The nitro alcohol was then converted into conjugated nitro olefin, **4**, via acetylation and elimination of acetic acid. The nitro olefin **4** was reduced with 1.1 equivalent amount of HEH into the corresponding nitroalkane **5** in 97% yield. Michael-type addition of **5** to ethyl crotonate in the presence of DBU[22] gave the γ-nitro ester **6**, which was subjected to the reaction with tributyltin hydride and AIBN as a free radical initiator, to substitute the

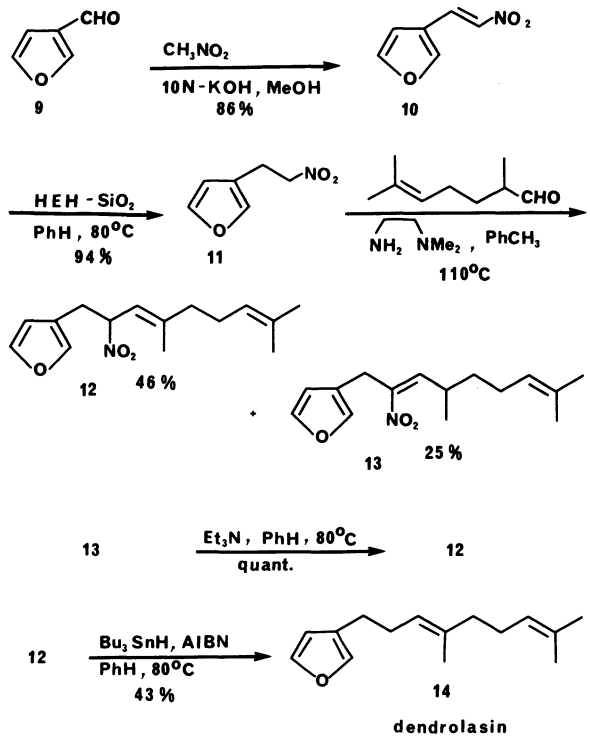
Table 1. Reduction of Conjugated Nitroolefins with HEH-SiO_2

	Substrate **1**	Product **2**	Yield[a]/%
a			78
b			91
c			87
d			86
e			88
f			83
g			71
h			90
i			45
j			84
k			84
l			65
m			87
n			100
o			62
p			83

a) Isolated yield.



Scheme 3.



Scheme 4.

nitro group by a hydrogen.[5] The resulting ester **7** was converted into the alcohol **8** by the reduction with lithium aluminum hydride in 90% yield. The overall yield of **8** based on the aldehyde **3** was 24%.

Synthesis of Dendrolasin: A furanoterpenoid, dendrolasin (**14**) was isolated from *Lasius (Dendrolasius) fuliginosus*, an ant, as an alarm pheromone[23] and synthesized by several groups.[24] It is found that the application of the present reduction system provides a very short (4 steps, 25% overall yield) process for **14** as shown in Scheme 4.

Condensation of furan-3-carbaldehyde (**9**) with nitromethane in 10 M KOH–MeOH gave 1-(3-furyl)-2-nitroethene (**10**) in 86% yield. The nitro olefin **10** was reduced into the corresponding saturated nitro compound **11** in 94% yield, which was condensed with 2,6-dimethyl-5-heptenal in the presence of *N,N*-dimethylethylenediamine under reflux in toluene[25] to yield the allylic nitro compound **12** (46% yield) together with the conjugated nitro olefin **13** (25% yield). The latter can be isomerized into the former quantitatively under reflux in benzene with triethylamine. Substitution of the nitro group in **13** by a hydrogen can be achieved in 43% yield by treating **13** with tributyltin hydride in the presence of AIBN to give dendrolasin (**14**).

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