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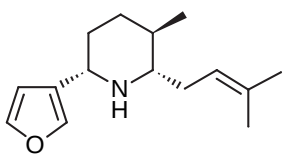
ENANTIOSPECIFIC TOTAL SYNTHESES OF NUPHAR PIPERIDINE ALKALOIDS, (-)-ANHYDRONUPHARAMINE, (-)-NUPHARAMINE, (-)-NUPHENINE AND (+)-3-EPI-NUPHARAMINE[1]

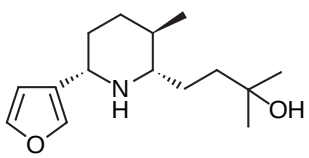
Toshio Honda*, Fumihiro Ishikawa, and Shin-ichi Yamane
Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

Abstract — A concise enantiospecific synthesis of nuphar piperidine alkaloids was achieved by employing a regioselective carbon-carbon bond cleavage reaction of the cyclopentane derivative, having a γ-chloro carbonyl system, as a key reaction.

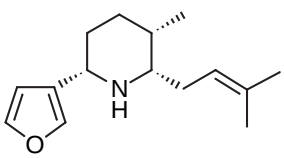
(-)-Anhydronupharamine (**1**)[2] and (-)-nupharamine (**2**),[3] isolated from the dried rhizome of *Nuphar japonicum* DC., are naturally occurring sesquiterpenoid alkaloids with three chiral centers on the piperidine ring. Their structures including absolute stereochemistry have been confirmed by chemical and spectroscopical studies[4,5] and also by syntheses.[6-8] (-)-Nuphenine (**3**)[9] and (+)-3-epinupharamine (**4**),[10,11] isolated from *Nuphar variegatum*, are other members of the family of nuphar piperidine alkaloids with the epimeric methyl group at the C-3 position and the absolute configuration of the latter



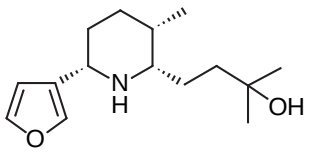
1 (-)-Anhydronupharamine



2 (-)-Nupharamine



3 (-)-Nuphenine



4 (+)-3-Epinupharamine

This paper is dedicated to Professor Teruaki Mukaiyama on the celebration of his 73rd birthday.

alkaloid (**4**) was recently determined to be 2*S*, 3*S*, 6*S* by its chiral synthesis.[6]

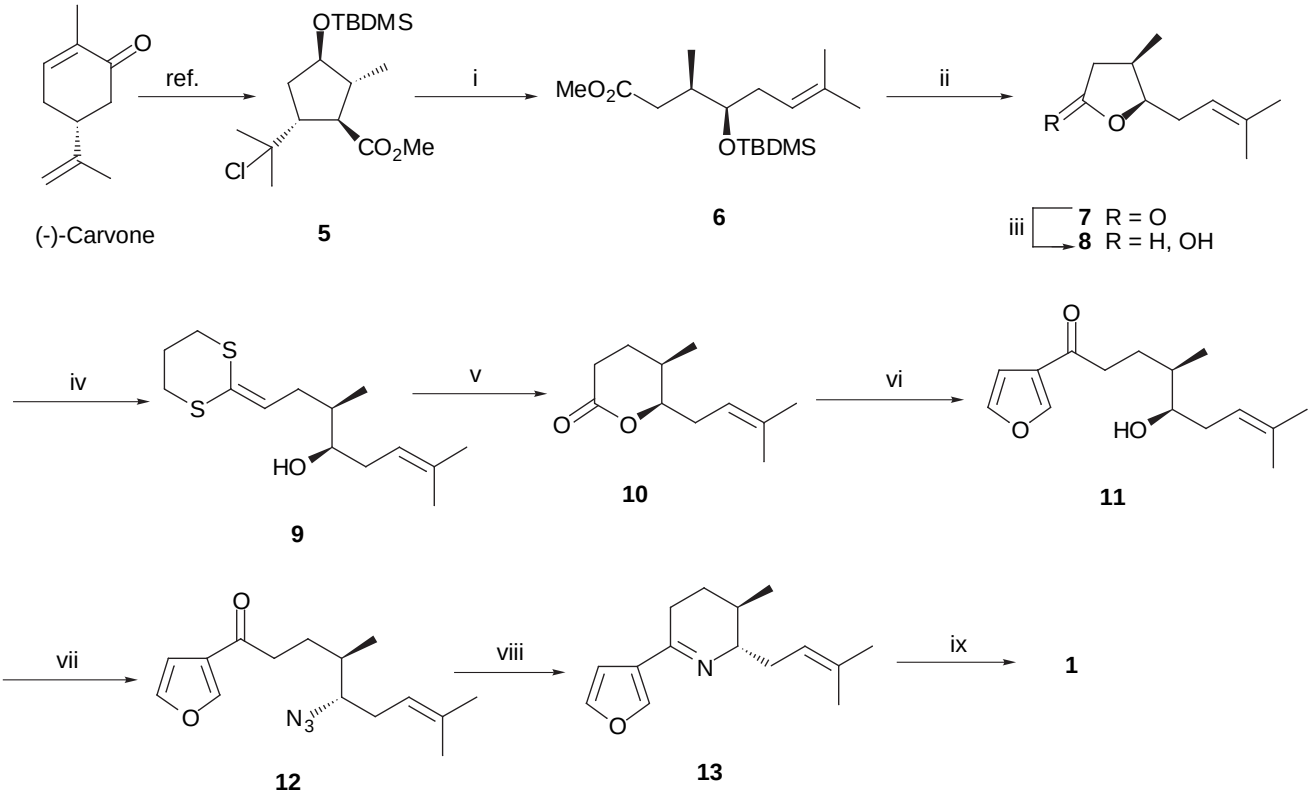
The ring systems and the stereochemical features presented in this group of alkaloids continue to challenge chemists interested in these alkaloids synthesis.[12]

In 1992, we developed[13] a novel carbon-carbon bond cleavage reaction of γ-halo carbonyl compounds using samarium iodide as a one-electron reducing agent, where fragmentation occurred between the α and β positions of the carbonyl group regioselectively. This fragmentation reaction has been successfully utilized in the syntheses of natural products including alkaloids, terpenes, and antibiotics.[14]

In continuation of our work on the synthesis of biologically active natural products using samarium iodide, we are interested in developing a novel synthetic route to nuphar piperidine alkaloids.

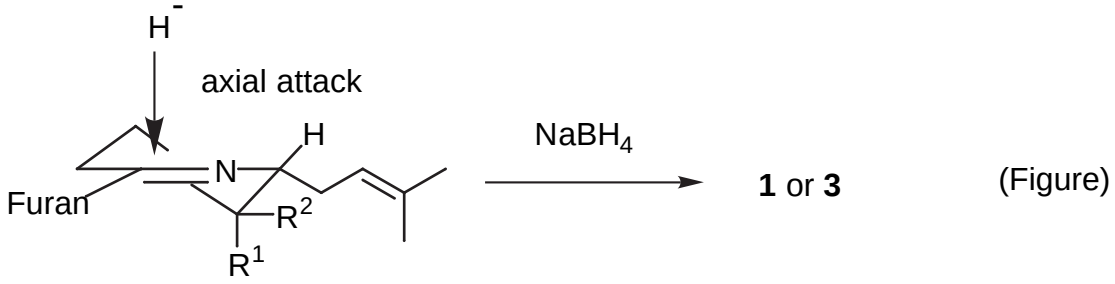
The basic features of our strategy towards these alkaloids involved the formation of an acyclic azide *via* a regioselective fragmentation reaction of a γ-halo carbonyl compound, followed by an intramolecular aza-Wittig reaction to provide a piperidine ring, as key reactions.

We initially investigated the synthesis of (-)-anhydronupharamine and (-)-nupharamine as follows. Treatment of the cyclopentane derivative (**5**) having a γ-halo ester system, readily accessible from (-)-carvone based on our earlier work,[13] with samarium iodide took place a regioselective fragmentation reaction to give the olefinic ester (**6**) in 86% yield. Deprotection of the silyl group of **6** with tetra-*n*-butylammonium fluoride gave the γ-lactone (**7**), which was further converted into the δ-lactone (**10**) by three steps involving a reduction of **7** with diisobutylaluminum hydride giving the lactol (**8**), treatment of the lactol (**8**) with 2-lithio-2-trimethylsilyl-1,3-dithiane,[15] prepared from 2-trimethylsilyl-1,3-dithiane and *n*-butyllithium, and hydrolysis of the resulting thioacetal (**9**) with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane, in 64% yield from **6**. Introduction of a furan ring was easily achieved by treatment of **10** with 3-lithiofuran, derived from 3-bromofuran and *n*-butyllithium, to give the adduct (**11**), in 92% yield, having all the carbon framework for the natural products. In order to accomplish the synthesis, the replacement of the hydroxy group by an amino function with inversion of the stereochemistry, and a formation of piperidine ring were required. Thus, the alcohol (**11**) was subjected to Lal's procedure[16] using diethyl azodicarboxylate (DEAD), triphenylphosphine, and diphenylphosphoryl azide (DPPA) to give the azide (**12**) with the desired stereochemistry, in 88% yield.



Scheme 1 *Reagents and conditions*: i, 3.7 eq. Sm, 3.5 eq. 1,2-diiodoethane, THF-HMPA (20:1), rt (85.5%); ii, Bu_4NF, THF, rt; iii, DIBAL, THF, -78°C (97.2% from **6**); iv, 2-trimethylsilyl-1,3-dithiane, *n*-BuLi, THF, -15°C; v, *p*-TsOH, CH_2Cl_2, rt (69.5% from **8**); vi, 3-bromofuran, *n*-BuLi, THF, -78°C (92.1%); vii, Ph_3P, DEAD, $(PhO)_2P(O)N_3$, THF, 0°C; viii, Ph_3P, THF, reflux; ix, $NaBH_4$, EtOH, rt (77.4% from **12**).

Finally, construction of a piperidine ring was achieved by employing an aza-Wittig reaction[7] of **12** with triphenylphosphine in refluxing THF to give the imine (**13**), which, on reduction with sodium borohydride in ethanol provided (-)-anhydronupharamine (**1**) as a single stereoisomer, in 77% yield from **12**.



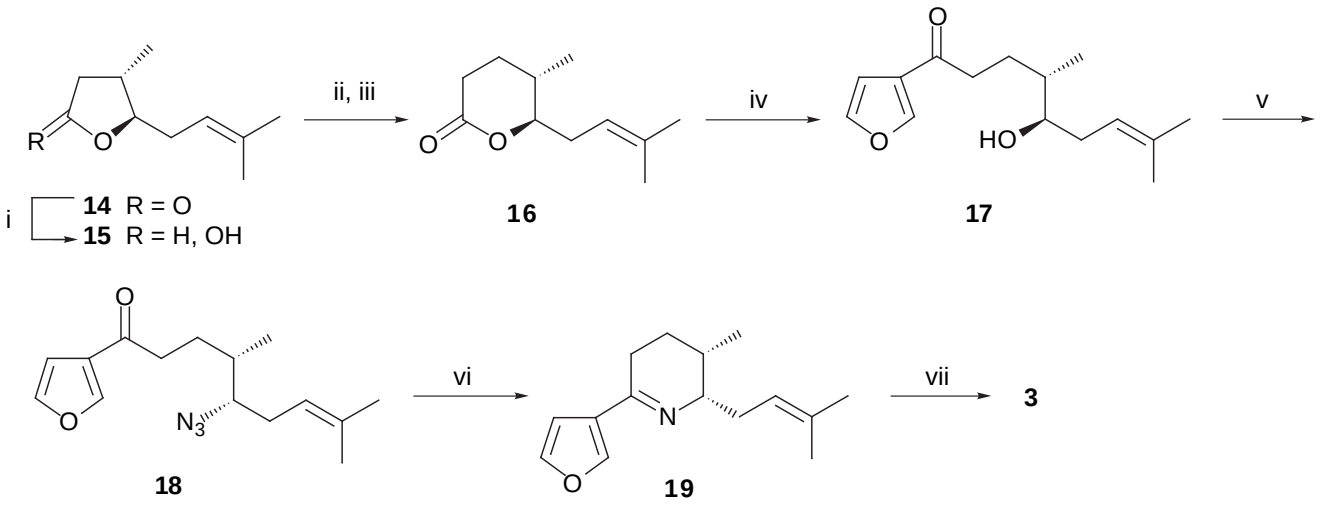
(Figure)

13 R^1 = H, R^2 = Me
19 R^1 = Me, R^2 = H

The stereoselectivity exhibited in the formation of **1** can be rationalized by assuming a stable conformation of the imine (**13**) as depicted in Figure, where the bulky substituent (3-methyl-2-butenyl group) occupies quasi-equatorial position and the hydride attack occurs from axial orientation.

The spectroscopic data of **1** including its specific optical rotation, $[\alpha]_D$ -64.9° (c=0.1, $CHCl_3$) {(lit.,[8] -62.5° (c=0.1, $CHCl_3$)}, were identical with those reported in the literature.[8] Since anhydronupharamine (**1**) was already converted into nupharamine (**2**) by treatment with hydrochloric acid,[8] this synthesis constitutes its formal chiral synthesis.

We next investigated the synthesis of (-)-nuphenine (**3**) and (+)-3-epinupharamine (**4**), both having the same configurations at the 2, 3, and 6-positions, by following the above synthetic scheme. (+)-Eldanolide (**14**),[13,17] easily derived from (+)-carvone by using the essentially same route as for the



Scheme 2 *Reagents and conditions*: i, DIBAL, THF, -78°C; ii, 2-trimethylsilyl-1,3-dithiane, *n*-BuLi, THF, -15°C; iii, *p*-TsOH, CH_2Cl_2, rt (90.5% from **15**); iv, 3-bromofuran, *n*-BuLi, THF, -78°C (98.0%); v, Ph_3P, DEAD, $(PhO)_2P(O)N_3$, THF,0°C (80.5%); vi, Ph_3P, THF, reflux; vii, $NaBH_4$, EtOH, rt (73.4% from **18**).

preparation of **7**, was subjected to ring expansion reaction with 2-lithio-2-trimethylsilyl-1,3-dithiane as above *via* the lactol (**15**) to furnish the δ-lactone (**16**), which on introduction of a furan ring gave the alcohol (**17**) in 89% yield from **15**. Introduction of an azido group with the inversion of the stereochemistry employing the Lal's procedure, followed by an intramolecular aza-Wittig reaction of **18**

afforded the imine (**19**). Finally the reduction of the imine (**19**) with sodium borohydride furnished (-)-nuphenine (**3**), $[\alpha]_{Hg(365\ nm)}$ -23.4° (MeOH) {lit.,[9] $[\alpha]_{Hg}$ -23° (MeOH)}, as the sole stereoisomer in 73% yield. Since the hydration of (-)-nuphenine (**3**) giving (+)-3-epinupharamine (**4**) has already been reported by Forrest and Ray,[10] this synthesis also constitutes its formal chiral synthesis.

In summary, we could develop efficient stereoselective syntheses of nuphar piperidine alkaloids starting from (-)- or (+)-carvone as chiral sources and this synthetic strategy should be applicable to the chiral synthesis of other naturally occurring nuphar alkaloids.

EXPERIMENTAL SECTION

IR spectra were recorded for thin films on a JASCO FT/IR-200 Fourier transform IR spectrophotometer. ^{1}H-NMR spectra were obtained for solution in $CDCl_3$ on a JEOL PMX-270 instrument, and chemical shifts are reported on the δ-scale from internal TMS. MS spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

Methyl (3*S*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-3,7-dimethyl-6-octenoate (6) ----- To a stirred suspension of samarium metal (18.58 g, 0.121 mol) and molecular sieves 4A (1 g) in THF (290 mL) was added a solution of 1,2-diiodoethane (23.11 g, 0.114 mol) in THF (290 mL) under argon at ambient temperature, and the solution was stirred for 30 min. After adding HMPA (73.5 mL), the resulting solution was stirred for 15 min at the same temperature. To this mixture was added a solution of the ester (**5**)(10.7 g, 30.7 mmol) in THF (107 mL). After stirring for 10 min, the mixture was treated with saturated sodium hydrogen carbonate solution, an excess of ether (400 mL), and Celite (100 g). Insoluble materials were filtered off and the filtrate was treated with water (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane-CH_2Cl_2 (5:2, v/v) as an eluent to give the esters (**6**)(8.24 g, 86%) as a colorless oil; IR 2860 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.03 (6H, s,

2×SiMe), 0.89 (9H, s, ^{t}Bu), 1.61 (3H, s, Me), 1.70 (3H, s, Me), 2.08-2.19 (4H, m, 2-H, 3-H, and 5-H_2), 2.41-2.51 (1H, m, 2-H), 3.57-3.66 (4H, m, 4-H and OMe), 5.06-5.12 (1H, m, 6-H); HRMS calcd for $C_{15}H_{29}O_3Si$ (M^+-Et) 285.1884. Found (M^+-Et) 285.1884.

(4*R*,5*R*)-5-(3-Methyl-2-butenyl)-4-methyl-2-hydroxytetrahydrofuran (8) ----- To a stirred solution of the ester (**6**) (8.12 g, 27.1 mmol) in THF (50 mL) were added tetra-*n*-butylammonium fluoride (54.2 mL, 54.2 mmol) at rt and the resulting mixture was stirred for further 10 min at the same temperature. After adding saturated ammonium chloride solution, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give a lactone (**7**)(4.34 g, quant.) as a colorless oil; IR 2960 and 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (3H, d, J=7.3 Hz, 3-Me), 1.64 (3H, s, Me), 1.72 (3H, s, Me), 2.17-2.45 (3H, m, C*H*HCH=C and 3-H_2), 2.57-2.77 (2H, m, 3-H and C*H*HCH=C), 4.44 (1H, dt, J=6.1 and 7.9 Hz, 2-H), 5.13 (1H, t, J=7.3 Hz, olefinic proton), which, without further purification, was subjected to next reaction, because of its high volatility. To a stirred solution of the lactone (**7**) in THF (120 mL) was added dropwise DIBAL (28.8 mL, 28.5 mmol) at -78°C under argon, and the resulting solution was stirred for further 2.5 h at the same temperature. After adding saturated ammonium chloride solution, the mixture was filtered through a pad of Celite to remove the insoluble material and the filtrate was then concentrated to leave an aqueous layer. The aqueous layer was extracted with ethyl acetate and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a lactol (**8**)(3.85 g, 97.2%) as a colorless oil; IR 2910 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3H, d, J=6.1 Hz, 4-Me), 1.63 (3H, s, Me), 1.71 (3H, s, Me), 1.74-1.86 (1H, m, 4-H), 1.95-2.44 (4H, m, 3-H_2 and CH_2CH=C), 4.03 (0.5H, dt, J=7.3 and 7.9 Hz, 2-H), 4.17 (0.5H, dt, J=7.3 and 7.9 Hz, 2-H), 5.12-5.19 (1H, m, 5-H), 5.44 (0.5H, dd, J=3.1 and 5.5 Hz, olefinic proton), 5.54 (0.5H, dd, J=3.1 and 5.5 Hz, olefinic proton); HRMS calcd for $C_{10}H_{18}O_2$ (M^+) 170.1305. Found (M^+) 170.1305. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66. Found: C, 70.06; H, 10.99.

(5*R*,6*R*)-6-(3-Methyl-2-butenyl)-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (10) ----
To a stirred solution of 2-lithio-2-trimethylsilyl-1,3-dithiane, prepared from 2-trimethylsilyl-1,3-dithiane

(13.2 mL, 68.8 mmol) and *n*-butyllithium (1.65 M solution in hexane, 38.5 mL, 63.5 mmol), in THF (90 mL) was added dropwise a solution of the lactol (**8**)(1.80 g, 10.6 mmol), obtained above, in THF (18 mL) at -78°C under argon, and the resulting solution was stirred for further 2 h at the same temperature. After adding saturated ammonium chloride solution, the mixture was extracted with ethyl acetate and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a thioacetal (**9**), which was dissolved in CH_2Cl_2 (50 mL). To this solution was added *p*-toluenesulfonic acid (100 mg) and the mixture was stirred for 2 h at rt. The solution was diluted with CH_2Cl_2 and washed with saturated sodium hydrogen carbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ether (10:1, v/v) gave the lactone (**10**)(1.34 g, 70%) as a colorless oil; $[\alpha]_D$ +31.1° (c 1.0, $CHCl_3$); IR 2935 and 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3H, d, J=6.7 Hz, 4-Me), 1.64 (3H, s, Me), 1.72 (3H, s, Me), 1.95-2.44 (5H, m, 4-H_2, 5-H, C*H*$_2$CH=C), 2.54 (2H, dd, J=6.1 and 7.9 Hz, 3-H_2), 4.28 (1H, dt, J=3.1 and 7.3 Hz, 6-H), 5.10-5.17 (1H, m, olefinic proton); MS *m/z* 182 (M^+). HRMS calcd for $C_{11}H_{18}O_2$ (M^+) 182.1306. Found (M^+) 182.1301.

(4*R*,5*R*)-4,8-Dimethyl-1-(3'-furyl)-5-hydroxy-6-nonen-1-one (11) ---- To a stirred solution of 3-bromofuran (1.58 mL, 4.25 mmol) in THF (16 ml) was added dropwise *n*-butyllithium (1.3 M solution in hexane, 3.16 mL, 4.25 mmol) at -78°C and the mixture was stirred for 4 min at the same temperature. A solution of the lactone (**10**)(645 mg, 3.54 mmol) in THF (6.5 mL) was added to the above solution and the mixture was stirred for further 15 min at the same temperature. After adding saturated ammonium chloride solution, the mixture was extracted with ethyl acetate and the extract was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-CH_2Cl_2 (2:1, v/v) gave the ketone (**11**) (816 mg, 92%) as a colorless oil; $[\alpha]_D$ +38.5° (c 0.8, $CHCl_3$); IR 2920 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3H, d, J=6.1 Hz, 4-Me), 1.64 (3H, s, Me), 1.73 (3H, s, Me), 1.56-2.24 (5H, m, 3-H_2, 4-H, and 6-H_2), 2.77-2.84 (2H, m, 2-H_2), 3.53 (1H, dt, J=4.3 and 7.9 Hz, 5-H), 5.15 (1H, t, J=7.9 Hz, 7-H),

6.77 (1H, s, furan proton), 7.43 (1H, s, furan proton), 8.04 (1H, s, furan proton); HRMS calcd for $C_{15}H_{22}O_3$ (M^+) 250.1567. Found (M^+) 250.1560.

(4*R*,5*S*)-5-Azido-4,8-dimethyl-1-(3'-furyl)-6-nonen-1-one (12) ----- To a stirred solution of the ketone (**11**)(50.0 mg, 0.2 mmol) and triphenylphosphine (78.6 mg, 0.3 mmol) in THF (1 mL) in the presence of molecular sieves 4A (100 mg) was added dropwise a solution of DEAD (52.2 mg, 0.3 mmol) in THF (0.5 mL) at 0°C. After stirring for 15 min, DPPA (64.4 mg, 0.28 mmol) was added to the mixture at 0°C and the resulting solution was stirred for further 3 h at the same temperature. Evaporation of the solvent gave a residue, which was treated with an excess of ether. After filtration of the mixture to remove insoluble materials, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-CH_2Cl_2 (1:1, v/v) gave the azide (**12**) (48.8 mg, 88%) as a colorless oil; $[\alpha]_D$ +41.4° (c 0.4, $CHCl_3$); IR 2900, 2100 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (3H, d, J=6.7 Hz, 4-Me), 1.65 (3H, s, Me), 1.73 (3H, s, Me), 1.42-1.77 (2H, m, 6-H_2), 1.88-2.01 (1H, m, 4-H), 2.28 (2H, t, J=6.7 Hz, 2-H_2), 2.64-2.89 (2H, m, 3-H_2), 3.25 (1H, dt, J=5.5 and 6.7 Hz, 5-H), 5.17 (1H, t, J=7.3 Hz, 7-H), 6.77 (1H, s, furan proton), 7.44 (1H, s, furan proton), 8.03 (1H, s, furan proton).

(-)-Anhydronupharamine (1) ----- A solution of the azide (**12**)(15.1 mg, 0.055 mmol) and triphenylphosphine (37.2 mg, 0.14 mmol) in THF (0.6 mL) was heated at reflux for 3 h. After evaporation of the solvent, the imine (**13**) formed was dissolved into EtOH (0.6 mL). To this solution was added portionwise sodium borohydride (6.5 mg, 0.19 mmol) at 0°C and the resulting mixture was stirred for further 1 h at the same temperature. After adding isopropanol (2 mL), the mixture was stirred for 15 min and the solution was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (20:1, v/v) gave (-)-anhydronupharamine (**1**) (9.9 mg, 77%) as a colorless oil; $[\alpha]_D$ -64.9° (c 0.1, $CHCl_3$); IR 2960 and 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (3H, d, J=6.7 Hz, 3-Me), 1.10-1.40 (1H, m, 3-H), 1.41-1.60 (2H, m, CH_2CH=C),

1.64 (3H, s, Me), 1.71 (3H, s, Me), 1.72-1.85 (2H, m, 4-H_2), 2.05 (1H, dt, J=9.2 and 11.6 Hz, 5-H), 2.24 (1H, dt, J=3.1 and 9.2 Hz, 5-H), 2.30-2.40 (1H, m, 2-H), 3.57 (1H, dd, J=2.4 and 11.6 Hz, 6-H), 5.12 (1H, t, J=7.3 Hz, olefinic proton), 6.39 (1H, s, furan proton), 7.34 (1H, s, furan proton), 7.35 (1H, s, furan proton).

(4*S*,5*R*)-5-(3-Methyl-2-butenyl)-4-methyl-2-hydroxytetrahydrofuran (15) ----- Reduction of (+)-eldanolide (**14**)(0.26 g, 0.83 mmol) with DIBAL (1.78 mL, 1.66 mmol) was carried out using the same procedure as for the preparation of **8** to give the lactol (**15**)(0.122 g, 86%) as a colorless oil; IR 2900 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (1.5H, d, J=6.7 Hz, 4-Me), 1.07 (1.5H, d, J=6.7 Hz, 4-Me), 1.40-1.90 (7H, m, 2×Me and 4-H), 2.02-2.43 (4H, m, 3-H_2 and CH_2CH=C), 2.80 (0.5H, s, OH), 3.00 (0.5H, s, OH), 3.50-3.58 (0.5H, m, 2-H), 3.69-3.79 0.5H, m, 2-H), 5.18-5.27 (1H, m, 5-H), 5.40-5.43 (0.5H, t, J=4.3 Hz, olefinic proton), 5.49-5.53 (0.5H, m, olefinic proton); HRMS calcd for $C_{10}H_{18}O_2$ (M^+) 170.1305. Found (M^+) 170.1309. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66. Found: C, 70.06; H, 10.99.

(5*S*,6*R*)-6-(3-Methyl-2-butenyl)-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (16) ---- Conversion of the lactol (**15**)(1.30 g) with 2-lithio-2-trimethylsilyl-1,3-dithiane (6.5 equiv.) was carried out using the same procedure as for the preparation of **10** to give the δ-lactone (**16**)(1.26 g, 91%) as a colorless oil; $[\alpha]_D$ +25.1° (c 1.2, $CHCl_3$); IR 2900 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.01 (3H, d, J=6.1 Hz, 5-Me), 1.46-1.95 (8H, m, 4-H_2 and 2×Me), 2.25-2.67 (5H, m, 5-H, 3-H_2 and CH_2CH=C), 3.96-4.03 (1H, m, 6-H), 5.21-5.28 (1H, m, olefinic proton); HRMS calcd for $C_{11}H_{18}O_2$ (M^+) 182.1307. Found (M^+) 182.1309. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.18; H, 10.17.

(4*S*,5*R*)-4,8-Dimethyl-1-(3'-furyl)-5-hydroxy-6-nonen-1-one (17) ---- Introduction of a furan ring into the lactone (**16**)(638 mg, 3.51 mmol) with 3-bromofuran (1.58 mL, 5.27 mmol) and *n*-butyllithium (1.2 equiv.) was carried out using the same procedure as for the preparation of **11** to give the ketone (17)(859 mg, 98%) as a colorless oil; $[\alpha]_D$ +6.5° (c 0.4, $CHCl_3$); IR 2900 and 1670 cm^{-1};

NMR ($CDCl_3$) δ 0.95 (3H, d, J=6.7 Hz, 4-Me), 1.55-1.74 (7H, m, 4-H and 2×Me), 1.88-2.31 (4H, m, 2-H_2 and 6-H_2), 2.68-2.92 (2H, m, 3-H_2), 3.39-3.46 (1H, m, 5-H), 5.14-5.21 (1H, m, 7-H), 6.77 (1H, s, furan proton), 7.43 (1H, s, furan proton), 8.04 (1H, s, furan proton); HRMS calcd for $C_{15}H_{22}O_3$ (M^+) 250.1567. Found (M^+) 250.1560.

(4*S*,5*S*)-5-Azido-4,8-dimethyl-1-(3'-furyl)-6-nonen-1-one (18) ----- Reaction of the alcohol (**17**)(184 mg, 0.736 mmol) with DPPA (260 mg, 1.15 mmol), triphenylphosphine (320 mg, 1.22 mmol) and DEAD (188 mg, 1.08 mmol) was carried out using the same procedure as for the preparation of **12** to give the azide (**18**)(163 mg, 81%) as a colorless oil; $[\alpha]_D$ +29.2° (c 0.2, $CHCl_3$); IR 2900, 2120 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (3H, d, J=6.7 Hz, 4-Me), 1.60-1.74 (8H, m, 6-H_2 and 2×Me), 1.81-1.95 (1H, m, 4-H), 2.18-2.40 (2H, m, 3-H_2), 2.70-2.84 (2H, m, 2-H_2), 3.29-3.70 (1H, m, 5-H), 5.11-5.16 (1H, m, 7-H), 6.77 (1H, s, furan proton), 7.44 (1H, s, furan proton), 8.03 (1H, s, furan proton).

(-)-Nuphenine (3) ----- The aza-Wittig reaction of the azide (**18**)(45.0 mg), followed by the reduction of the resulting imine was carried out using the same procedure as for the preparation of **1** to give (-)-nuphenine (**3**)(28.0 mg, 73%) as a colorless oil; $[\alpha]_{Hg(365\ nm)}$ -23.4° (MeOH); IR 2930 and 1635 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3H, d, J=6.7 Hz, 3-Me), 1.53-1.77 (11H, m, 3-H, 5-H_2, C*H*$_2$CH=C, and 2×Me), 1.95-2.12 (2H, m, 4-H_2), 2.76 (1H, dt, J=3.1 and 7.9 Hz, 2-H), 3.59 (1H, dd, J=3.7 and 9.2 Hz, 6-H), 5.08-5.13 (1H, m, olefinic proton), 6.39 (1H, s, furan proton), 7.34 (1H, s, furan proton), 7.35 (1H, s, furan proton).

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