phenylfuro[3,2-*c*][1,8]naphthyridin-4(2*H*)-one **14**. m.p.159-161°C (from EtOH); (Found C, 68.75; H, 5.49; N, 8.69. $C_{18}H_{16}N_2O_3$•1/2EtOH requires C, 68.86; H, 5.79; N, 8.46 %); $\delta_H$ 1.31 (3H, t, *J* 7.26, Me), 3.14 (1H, dd, *J* 2.97 and 17.15, 3-H), 3.41 (1H, dd, *J* 7.26 and 17.15, 3-H), 3.78 (1H, dq, *J* 7.26 and 9.24, $OCH_2$), 4.06 (dq, *J* 7.26 and 9.24, 1H, $OCH_2$), 6.08 (dd, *J* 2.97 and 7.26, 1H, 2-H), 7.15 (dd, *J* 4.6 and 7.92, 1H, 8-H), 7.26 (2H,.m, Ph), 7.44-7.58 (3H,.m, Ph), 8.09 (1H,.dd, *J* 1.65 and 7.92, 9-H), 8.47 (1H, dd, *J* 1.65 and 4.62, 7-H); $\nu_{max}/cm^{-1}$ 1667 (C=O); *m/z* (EI) 308 ($M^+$, 43.8), 263 [$(M\text{-}OEt)^+$, 100], 251 (64.5).

The less mobile fraction (9.5 mg, 19 %) was recovered starting material. The yields of **14** based on the converted cyclobutanol **8b** was 38 % .

***Photolysis of the Hypoiodite of Cyclobutanol* 9b.**——Cyclobutanol **9b** (50 mg, 0.16 mmol) was allowed to react for 2h in the same manner as mentioned above. After the same workup, a residue was subjected to PLC on silica gel [EtOAc/hexane ; 3/1] to give (±)-2-ethoxy-3,5-dihydro-5-phenylfuro [3,2*c*][1,8] naphthyridin - 4(2*H*)-one **14** (12.3 mg, 24.8 %) and recovered starting cyclobutanol **9b** (17.5 mg, 35 %). The yield of product **14** based on the converted cyclobutanol **9b** was 38 % .

***Photolysis of the Hypoiodite of Cyclobutanol* 8c *or* 9c.**——Cyclobutanol **8c** or **9c** (50 mg, 0.14 mmol) in benzene (8.5 $cm^3$) containing mercury(II) oxide (110.5 mg, 0.48 mmol) and iodine (129.4 mg, 0.48 mmol) was irradiated for 2h. After usual workup, the crude products were subjected to PLC on silica gel [EtOAc/hexane 2/1] to give two fractions. The more mobile fraction (25 mg, 31 %) was (±)-2-acetoxy-3,5-dihydro-2-methyl-5-phenylfuro[3,2-*c*][1,8]naphthyridin-4(2*H*)-one **15**. m.p. 183-184°C (from MeOH); (Found C, 67.66; H, 4.88; N, 8.24. $C_{19}H_{16}N_2O_4$ requires C, 67.84; H, 4.80; N, 8.33 %); $\delta_H$ 1.99 (s, 3H, Me), 2.10 (3H, s, MeCOO), 3.30 (1H, d, *J* 17.16, 3-H), 3.43 (1H, d, *J* 17.16, 3-H), 7.15 (1H, dd, *J* 4.62 and 7.59, 8-H), 7.24-7.26 (2H, m, Ph), 7.44-7.58 (3H, m, Ph), 8.08 (1H, dd, *J* 1.98 and 7.59, 9-H), 8.47 (1H, dd, *J* 1.98 and 4.62, 7-H); $\nu_{max}/cm^{-1}$ 1734 (OAc), 1675 (C=O); *m/z* (EI) 336 ($M^+$, 0.12), 294 (5.83), 275 (100), 251 (30.6).

The less mobile fraction (16.4 mg, 21 %) was (±)-2-acetoxy-3,9-dihydro-2-methyl-5-phenylfuro[2,1-*b*][1,8]aphthyridin-4(2*H*)-one **16**. m.p. 96-98°C (from EtOAc-Hexane); (Found: $M^+$, 336.1108. $C_{19}H_{16}N_2O_4$ requires M, 336.1110); $\delta_H$ 1.81 (3H, s, Me), 2.06 (3H, s, MeCOO), 3.34 (1H, d, *J* 15.84, 3-H), 3.48 (1H, d, *J* 15.84, 3-H), 7.32 (1H, dd, *J* 4.62 and 7.92, 6-H), 7.35 (2H, br. d, *J* 1.98, Ph), 7.53-7.59 (3H, m, Ph), 8.53 (1H, dd, *J* 1.98 and 4.62, 7-H), 8.74 (1H, dd, *J* 1.98 and 7.92, 5-H); $\nu_{max}/cm^{-1}$ 1720 (OAc), 1687, 1599 (aryl-CO-C=C-); *m/z* (EI) 336 ($M^+$, 0.34), 318 (0.19), 294 (2.6), 275 (100).

***Photolysis of the Hypoiodite of Cyclobutanol* 11.** ——Cyclobutanol **11** (50 mg, 0.14 mmol) in benzene (8.5 $cm^3$) containing mercury(II) oxide (110.5 mg, 0.51 mmol) and iodine (129.4 mg, 0.51 mmol) was irradiated for 2h. After usual workup, the crude products were subjected to PLC on silica gel [EtOAc/hexane 2/1] to give (6bα,10aα)-(±)-6b,7,8,9,10,10b-hexahydro-10a-methoxy-5-phenylbenzofuro[3,2-*c*][1,8]-naphthyridin-6(5*H*)-one **17** (30.3 mg, 61 %). m.p. 144-144.5°C (from MeOH); (Found C, 72.23; H, 5.87; N, 8.03. $C_{21}H_{20}N_2O_3$ requires C, 72.39; H, 5.80; N, 8.04 %); $\delta_H$ 1.42-1.58 (2H, m, 2H, $CH_2$ ), 1.66-1.79 (2H, m, $CH_2$),1.92-2.01 (1H, m, $CH_2$ ), 2.17-2.31 (2H, m, $CH_2$ ), 3.427 (1H, t, *J* 6.94, 6b-H), 3.432 (3H, s, OMe), 7.14 (1H, dd, *J* 4.6 and 7.76, 2-H), 7.26 (2H, br.d, *J* 1.65, Ph), 7.28-7.58 (3H, m, Ph), 8.11 (1H, dd, *J* 1.98

and 7.76, 1-H), 8.46 (1H, dd, *J* 1.98 and 4.62, 3-H); $\nu_{max}/cm^{-1}$ 1657 ; *m/z* (EI) 348 ($M^+$, 1.90), 333 [$(M-Me)^+$, 13.3], 315 (100).

***Dehalogenation of Iodide* 12b *with $Bu_3SnH$-AIBN*** .——To a solution of iodide **12b** (60.5 mg, 0.14 mmol) in benzene (7.4 $cm^3$) was added $Bu_3SnH$ (0.08 $cm^3$, 0.28 mmol) and AIBN (11.9 mg, 0.07 mmol). The solution was flushed with nitrogen and then irradiated for 0.5h with a 100 W high-pressure Hg arc through a Pyrex-filter at room temperature. The solvent was then removed by evaporation and to the residue were added diethyl ether (8 $cm^3$) and KF (17.6 mg, 0.28 mmol). The solution was stirred on overnight and was filtered through Celite. The organic layer was washed with water and then saturated brine. After dryness over anhydrous $Na_2SO_4$ and evaporation of the solvent, the crude products were subjected to PLC on silica gel [EtOAc/hexane ; 10/1 × 2] to give a dehalogenated product **12a** (27.7 mg, 65.5 %), which was identical with **12a**, obtained in the photolysis of the hypoiodite of cyclobutanol **8a**.

## REFERENCES


1. Part 158. Orito, K.; Sasaki,T.; Suginome, H; *J. Org. Chem.*,**1995,** *60,* 6208-6210.
2. For a review, see Suginome, H: Photochemistry of Alkyl Hypohalites. In *Handbook of Organic Photochemistry and Photobiology*; Horspool, W.H.; Song, P. -S. Eds.; CRC Press.: Boca Raton, FL., 1995; pp.1229-1253.
3. (a) Suginome, H.; Liu, C.F.; Seko,S.; Kobayashi, K.*J. Org.Chem.*, **1988,** *53,* 5952-5959. (b) Suginome, H.; Kobayashi, K.; Itoh, M.; Seko, S.; Furusaki, A. *J. Org.Chem.*,**1990,** *55,* 4933-4943. (c) Kobayashi, K.; Suzuki, M.; Suginome, H.*J. Org. Chem.*, **1992,** *57,* 599-606. (d) Suginome, H.; Kajizuka, Y.; Suzuki, M.; Senboku, H.; Kobayashi, K. *Heterocycles*, **1994,** *37,* 283-288.
4. (a) Blythin, D.J.; Watkins, R.W. US.4680297. (*Chem. Abstr.*, **1988**, *108,* 37817w). (b) Sherlock, M.H.; US.4596809. (*Chem. Abstr.*,**105**,153050c). (c) Sherlock, M.H.; Smith, S.R.; Siegel, M.I. Eur. Pat. Appl. EP 196024. (*Chem. Abstr.*,**1985,** *102,* 166726r). (e) Smith, S.R.; Siegel, M.I. PCT. Int. Appl. WO 9607537. (*Chem. Abstr.*,1987, **107,**183554d). (f) Blythin, D.J. Eur.Pat. Appl. EP.144996. (*Chem. Abstr.***1985,** *103,* 215271v).
5. Sherlock, M.H.; Kaminski, J.J.; Tom, W.C.; Lee, J.F.; Wong, S. -C.; Kreutner, W.; Bryant, R.W.; McPhail. A.T., *J. Med. Chem.*,**1988,** *31,* 2108-2121.
6. Wohl, R.T. *Synthesis*, **1974,** 38-39.
7. Corey, E.J.; Bass, J.D.; LeMahieu, R.; Mitra, R.B. *J. Am. Chem. Soc.*, **1964**, *86,* 5570-5583. Rubin, M.B.; Maymon, T.; Grover, D. *Isr. J. Chem.*, **1970,** *8,* 717-730.
8. For reviews. see (a) Baldwin, S.W: Synthetic Aspects of 2+2 Cycloadditions of α,β–Unsaturated Carbonyl Compounds. In *Organic Photochemistry*; Padwa, A: Ed.;Marcel Dekker.: New York, Vol.5, 1981, pp.123-225. (b) Weedon, A. C: Enone Photochemical Addition in Organic Synthesis. In *Synthetic Organic Photochemistry ;* Horspool, W M: Ed.; Plenum Press.: New York, 1984.; pp.61-143. (c) Schuster, D.I.; Lem, G.; Kaprinidis, N.A. *Chem. Rev.*, **1993,** *93,* 3-22. (c) Schuster, D.I:. [2+2]-Photoadditions of Cyclohexenones to Alkenes. In *Handbook of Organic Photochemistry and Photobiology* ; Horspool, W.M.; Song,P.-S. Eds.; CRC Press, Boca Raton, FL., 1995; pp.652-669.
9. Takahashi, H.; Itoh, M.; Suginome, H.; Masamune, T. *Chem. Lett.*, **1979,** 901-902.


(*Received in Japan* 24 *January* 1996; *accepted* 16 *February* 1996)

Pergamon

*Tetrahedron*, Vol. 52, No. 17, pp. 6139-6148, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00244-X

# ASYMMETRIC SYNTHESES OF PHEROMONES FOR *BACTROCERA NIGROTIBIALIS*, *ANDRENA WILKELLA*, AND *ANDRENA HAEMORRHOA* F FROM A CHIRAL NITRO ALCOHOL

**Takashi KITAYAMA**

Department of Agricultural Chemistry, Faculty of Agriculture, Kinki University, 3327-204, Naka-machi, Nara, 631, JAPAN

**Abstract:** The utility of a smallest chiral nitro alcohol, 1-nitro-2-propanol (**1**), in natural products syntheses was examined. Optically pure (+)-**1** was readily, prepared by the lipase-catalyzed stereoselective transesterification of (±)-**1**. The following Michael addition of TBDMS ether of (+)-**1** to methyl vinyl ether or acrylonitrile afforded important synthetic intermediates, **3a** and **b**. As a result, optically pure sex pheromones for *Bactrocera nigrotibialis*, *Andrena wilkella*, and *Andrena haemorrhoa* F were synthesized in short steps starting from **3a**. 

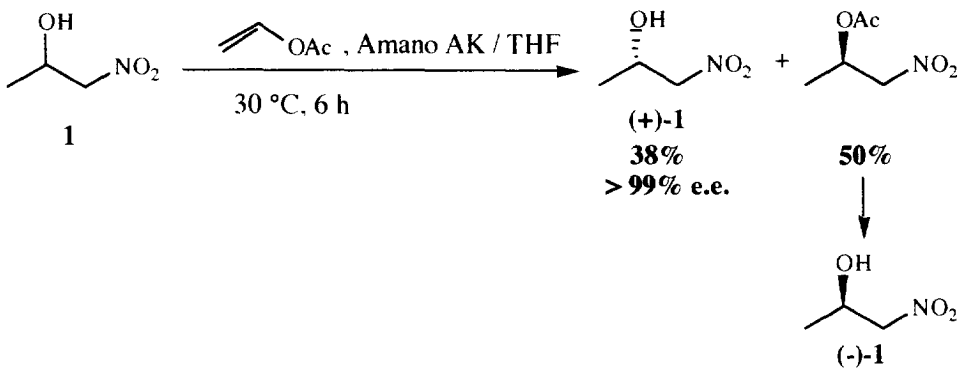
## Introduction

A spiroketal structure is a feature of an expanding variety of naturally occurring compounds, many of which important physiological activities as pheromones.[1,2] The sex pheromones having spiroketal structure for *Bactrocera nigrotibialis*[3-6], *Andrena wilkella*,[7,8] and *Andrena haemorrhoa* F[9-11] have been already synthesized. The synthetic methods, however, are not always satisfactory in terms of their long synthetic pathways and the low optical purities of the target compounds.

On the other hand, chiral nitro alcohols with a primary nitro group are potentially useful chiral building blocks in organic syntheses because they can be converted into many other useful chiral products *via* carbon-carbon bond formation at the α-position to the nitro group. However, chiral nitroalcohols have rarely been applied as building blocks because of the difficulties in the preparation of starting material. We have been previously reported the total synthesis of anticancer drugs and pheromones using (*S*)-4-nitro-2-butanol or (*S*)-5-nitro-2-pentanol derived from the corresponding ketones by Bakers' Yeast.[12,13] If optically active 1-nitro-2-propanol (**1**) could be synthesized as the smallest nitro alcohols, it would be effectively converted to various

valuable compounds. However, when 1-nitro-2-propanone was reduced by a microbe to obtain (+)-1-nitro-2-propanol ((+)-**1**), the retro aldol reaction predominated and the desirable compound was not obtained. On the contrary, (+)-**1** was obtained at high optical purity by the stereoselective transesterification of (±)-**1** with vinyl acetate under the catalysis of a lipase from *Pseudomonas* sp. (Amano AK) with enantiometric purity of over 99 % (Scheme 1).[14]

**Scheme 1**



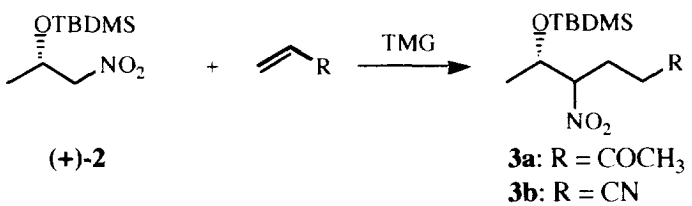

Since the absolute configuration of (+)-**1** has not yet been determined, it is necessary to determine this before using it as a chiral building block. In fact, the absolute configulation of (+)-**1** was determined to be (*S*)-form as described in the experimental section. Furthermore, the effect of solvent on stereoselectivity of biocatalytic reaction was investigated. The stereoselectivity of the reaction in a series of cyclic solvents was more sensitive than those of acyclic solvents. The best result was obtained when THF was the solvent (E = 47.7).[14]

We report here the total syntheses of optically pure sex and aggregation pheromones for *Bactrocera nigrotibialis*, *Andrena wilkella*, and *Andrena haemorrhoa* F in short steps starting from (+)-**1**.

## Results and Discussion

**Syntheses of Chiral 1-Nitro-2-propanol ((+)-1) and Its Michael Adduct.** Key steps for the syntheses of chiral spiroketal pheromones are the preparation of (+)-**1** and its Michael addition (Scheme 2).

**Scheme 2**



Kinetic resolution of (+)-**1** can be achieved by means of a lipase-catalyzed esterification.[13] The elongation of a carbon chain *via* the Michael addition of *O*-protected **1** ((+)-**2**) to an electron-deficient olefin proceeds smoothly in the presence of 1,1,3,3-tetramethylguanidine (TMG) as a catalyst. Although the Michael addition of the α-carbon of a primary nitro compound sometimes results in the formation of the 1:2-adduct,[12] the reaction of **2** with methyl vinyl ketone afforded mainly the 1:1-adduct, 6-(*t*-butyldimethylsilyloxy)-5-nitro-2-heptanone (**3a**) in THF. Thus **3a** was isolated from the reaction of (+)-**2** with methyl vinyl ketone in a 68% yield. On the other hand, the same reaction in acetonitrile afforded the 1:2-adduct even in the presence of excess **2**. Pure 1:1 adduct was obtained only in THF. When acrylonitrile was used as a Michael acceptor, however, the 1:1-adduct, 2-(*t*-butyldimethylsilyloxy)-5-cyano-3-nitropentane (**3b**), was the main product even in acetonitrile, affording a 67% yield of **3b** from (+)-**2**. It is estimated, therefore, that a delicate balance of basicity between the reactant carbanion stabilized by an α-nitro group and the resultant carbanion after the Michael addition plays a crucial role in the formation of the ratio of 1:1- *vs* 1:2-adduct (Table 1).

**Table 1. The Michael Addition of Carbanion from *O*-Protected 1-Nitro-2-propanol, 2**[a]

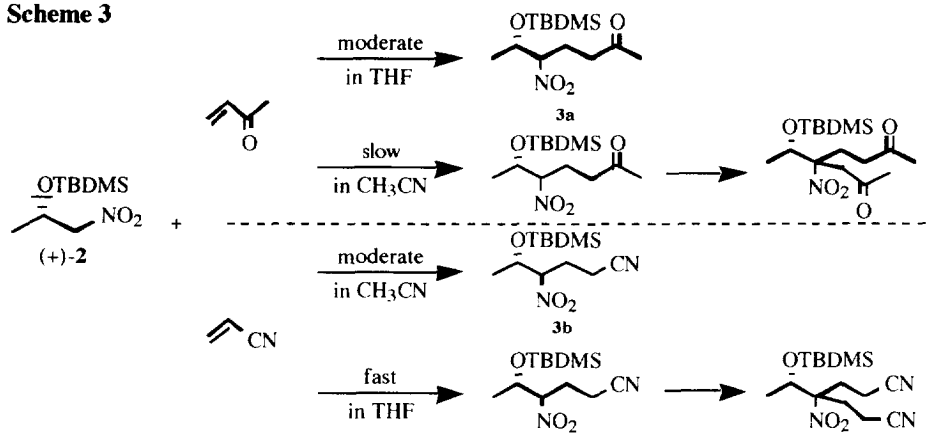
| 3 | R | Solvent | Yield(%) 1:1-Adduct | 1:2-Adduct |
|---|---|---|---|---|
| **a** | $COCH_3$ | THF | 68 | 5 |
| | | $CH_3CN$ | 43 | 20 |
| **b** | CN | $CH_3CN$ | 67 | 3 |
| | | THF | 47 | 14 |

a) Room temperature.

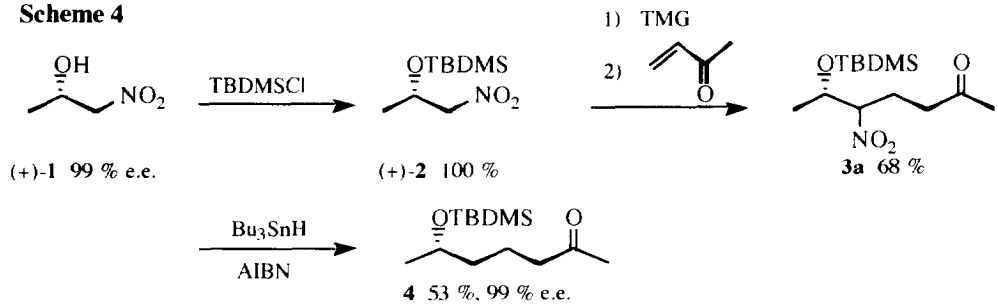
The anion-solvating tendency, acity ($A_1$), for acetonitrile and THF are 0.37 and 0.17, respectively,[14] indicating that acetonitrile has much larger ability to solvate the carbanion than THF. The more solvated anion should be less reactive than the less solvated type. In view of the reactivities of the Michael acceptors, acrylonitrile is more reactive than methyl vinyl ketone with σ values of cyano and keto groups being 0.66 and 0.50, respectively.[15] Therefore, when (+)-**2** reacts with a less reactive Michael acceptor in a highly reactive (i.e. less coordinative) solvent and with a more reactive Michael acceptor in a less reactive (i.e. more coordinative) solvent, the reaction affording a 1:2-adduct does not proceed, since the reaction yielding a 1:1-adduct proceeds with moderate velocity. On the contrary, when (+)-**2** reacts with a more reactive Michael acceptor in a more reactive solvent, a 1:2-adduct is afforded because of the increase in the reaction rate. Moreover, when (+)-**2** reacts with a less reactive Michael acceptor in a less reactive solvent, a 1:2-adduct is afforded because the long reaction period attributable to the decreased reaction rate (Scheme 3).

Reductive denitration of **3a** using the $Bu_3SnH$-AIBN system afforded **4** as the product in a 53% yield based on **3a** (Scheme 4). A reported synthesis of **4** starting from (*S*)-5-nitro-2-pentanol, which was obtained by the reduction of the corresponding γ-nitro ketone with bakers' yeast,[9] required the same number of steps.

**Scheme 3**



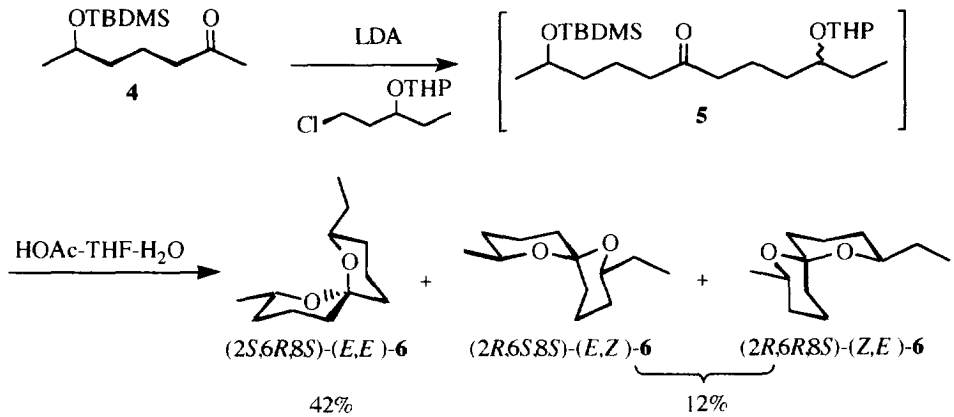

**Scheme 4**




**Syntheses of a Pheromone for *Bactrocera nigrotibialis*.** Synthesis of a bioactive enantiomer of this pheromone, (2*S*,6*R*,8*S*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane ((2*S*,6*R*,8*S*)-**6**), was originally reported by Perkins *et al.*,[3] who used (*S*)-(+)-lactate as a chiral starting material. The final product was synthesized by these authors after 8 steps.[3] In this study, the spiroketal, (2*S*,6*R*,8*S*)-**6**, was obtained at high enantiomeric purity *via* the intermediate **5** by the condensation of (+)-**4** with 1-chloro-3-tetrahydropyranyloxypentane followed by the intramolecular cyclization of the keto diol. $[\alpha]_D$ –72.9° (>99% e.e., confirmed by chiral GC using a perhexyl-α-cyclodextrin stationary phase, after 4 steps starting from (+)-**1**) (Scheme 5). The key compound in this procedure is 6-(*t*-butyldimethylsilyloxy)-2-heptanone (**4**).

Cyclization of **5** afforded the (2*S*,6*R*,8*S*)-isomer predominantly over the (2*S*,6*S*,8*S*)-isomer probably because of an anomeric effect in the initially formed oxane ring.[16] The main product, (2*S*,6*R*,8*S*)-isomer, was the most thermodynamically stable among the three posssible isomers. The minor products, (2*R*,6*S*,8*S*)- and (2*R*,6*R*,8*S*)-**6**, were isolated as a 1:1 mixture in addition to the major product of (2*S*,6*R*,8*S*))-isomer. The total yield of (2*S*,6*R*,8*S*)-**6** based on (+)-**1** was 15.1%. The yield was improved over the reported procedure in which the yield was 2.3% based on the (*S*)-lactate.[3]

**Scheme 5**

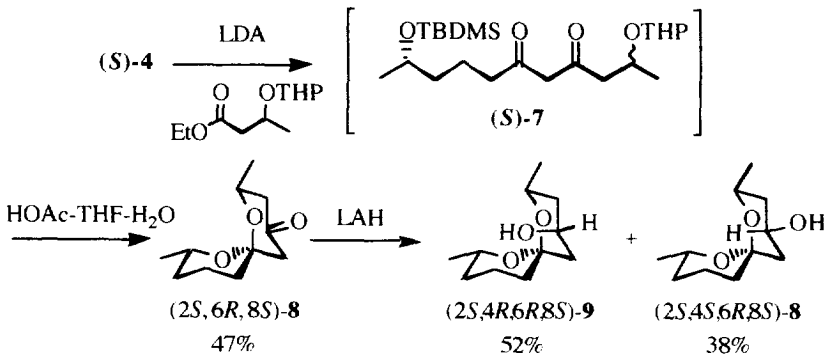



**Absolute Configuration of (+)-1**. Since the absolute configuration of (+)-**1** was unknown, it had to to be determined before using it as a chiral building block. The total synthesis of **6** addressed the issue. Compound (−)-**6** reportedly has the *S*-configuration,[3] and the absolute configuration of (+)-**1** can be assigned as *S* without ambiguity since (+)-**1** is converted to (−)-**6**. Consequently, the absolute configuration of compounds **3**, **4**, or **5** were also be assigned as the *S*-form.

**Synthesis of a Pheromone for *Andrena wilkella***. Syntheses of the biologically active enantiomer of this pheromone, (2*S*,4*R*,6*R*,8*S*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol ((2*S*,4*R*,6*R*,8*S*)-**9**),[8,17] and its (2*S*,4*S*,6*R*,8*S*)-isomer ((2*S*,4*S*,6*R*,8*S*)-**9**) have been reported.[17] The reported synthetic route required 8 steps. When (*S*)-**4** was used as the starting material for the synthesis of **9**, however, the product was obtained after only the two simple steps as shown in Scheme 6: lithium aluminum hydride reduction of (2*S*,6*R*,8*S*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-one (**8**), obtained by condensation of (*S*)-**4** with ethyl 3-tetrahydropyranyloxybutanoate followed by the intramolecular cyclization of the intermediate diketo diol.[17,18] We confirmed that each of isolated isomers (2*S*,4*R*,6*R*,8*S*)- and (2*S*,4*S*,6*R*,8*S*)-**9**, was a single product (e.e. > 99 %, by chiral GC using a hexakis(3-*O*-acetyl-2,6-di-*O*-pentyl)-α-cyclodextrin stationary phase. Moreover, the total yield of oxaketone, (2*S*,6*R*,8*S*)-(-)-**8**, based on (+)-**1** was 16.9%, which is better than the reported procedure by which the yield was 6.5% based on the (*S*)-3-hydroxybutyrate.[17,19]

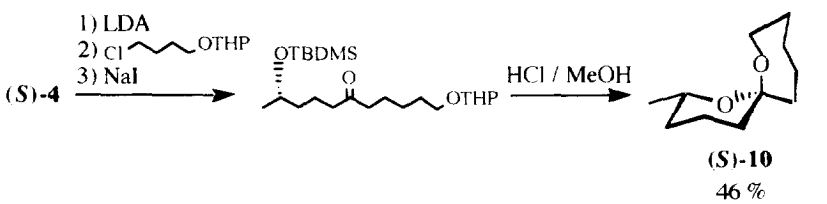
Thus, this procedure decreased the number of steps required for the asymmetric syntheses of (2*S*,4*R*,6*R*,8*S*)- and (2*S*,4*S*,6*R*,8*S*)-**9** to one half of those in the literature.[17]

**Scheme 6**




**Synthesis of a Pheromone for *Andrena haemorrhoa* F.**[10] This sex pheromone, which is involved in the volatile secretion from the mandibular gland of a male *A. haemorrhoa* F bee, to attract a female,[10] has been synthesized at over 99% e.e. after 5 steps starting from (*S*)-**1** (> 99% e.e.). Since the reported synthesis of this pheromone used 4-nitro-2-butanol, a γ-hydroxy nitroalkane, as the starting material, its skeleton had to be elongated by two carbons to afford the appropriate substrate. This is not necessary in the present procedure using (*S*)-**1** as the starting material, and the final product, **10**, was obtained from (*S*)-**4** according to established procedures (Scheme 7).[9] The optical purity of **10** thus obtained in a yield of 46% was over 99% according to a comparison of its optical rotation with that reported.[11]

**Scheme 7**




## Conclusion

Three pheromones with a spiroketal structure were synthesized at almost complete enantiomeric purity. The high purity of the product was based on the purity of the (*S*)-1-nitro-2-propanol, (*S*)-**1**, used in the synthesis being more than 99% in contrast to the 97% of that described in the literature. Thus, the use of (*S*)-**1**, obtained by the transesterification of the corresponding β-nitro alcohol,[13] as the starting material for asymmetric syntheses was superior to the use of other nitro alcohols in terms of enantiomeric purity. Consequently, (*S*)-**1** which has the least carbon atoms in this series was conveniently converted to various valuable compounds.

**Acknowledgment.** The author thanks professors Atsuyoshi Ohno of the Institute for Chemical Research, Kyoto University and Tadashi Okamoto of the Faculty of Agriculture, Kinki University for their helpful advice and discussion during this work.

## Experimental

**Instruments.** $^1$H NMR spectra were recorded on a Bruker AC-200P spectrometer in $CDCl_3$ or $D_2O$ with tetramethylsilane (TMS) or sodium 3-trimethylsilyl-1-propanesulfonate-1,1,2,2,-$d_4$ (DSS) as the internal reference, respectively. IR spectra were recorded on a HITACHI 270-30 infrared spectrometer. Optical rotation was measured with a HORIBA SEPA-200 polarimeter. Elemental analyses of alcohols protected by TBDMS were perfomed after deprotection because the TBDMS group has quite a high carbon-content and did not afford satisfactory results. Gas-chromatographic analyses were performed using a Shimadzu gas chromatograph Model GC-9A equipped with OV101, C-20M, or lipoden A columns. High performance liquid chromatographic analyses were performed using a Shimadzu liquid chromatograph Model LC-10 equipped with DAICEL CHIRALCEL OB.

**Materials.** Organic reagents and lipases were purchased from commercial sources unless otherwise indicated. Racemic 1-nitro-2-propanol ((±)-**1**) was synthesized as described.[20]

**(*S*)-1-Nitro-2-propanol ((*S*)-1) and (*R*)-1-Nitro-2-acetoxypropane ((*R*)-1-Ac).** A mixture of (±)-**1** (10.0 g, 95.2 mmol), vinyl acetate (49.9 g, 0.58 mol) and a lipase from *Psuedomonas* sp. (Amano AK) (6.66 g) in THF (170 ml) was stirred for 6 h at 30 °C. The resulting mixture was filtered and the filtrate was concentrated. The residue was applied to column chromatography over silica gel with a 10 : 1 mixture of hexane and ethyl acetate as an eluent, giving(*R*)-**1-Ac** in a 50 % yield and optically active **1** ($[\alpha]_D$ +40.7° (c = 1.00, $CHCl_3$)) in a 38 % yield. The recovered **1** which showed a positive optical rotation was chemically converted with AcCl/pyridine into (*S*)-**1-Ac**, and its e.e. was determined to be over 99 % by $^1$H NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent.

The (*S*)-**1** was reacted with *t*-butyldimethylsilyl chloride (TBDMSCl) to give (*S*)-(+)-1-nitro-2-(*t*-butyldimethylsilyloxy)propane ((*S*)-**2**) in a quantitative yield (6.30 g): $[\alpha]_D$ +22.1° (c= 1.77, $CHCl_3$).

$^1$H NMR ($CDCl_3$): δ ; -0.02 (s, 6H), 0.82 (s, 9H), 1.24 (d, 3H, J = 6.3 Hz), and 4.10 - 4.53 (m, 3H). IR (neat): 2936, 1556, and 1468 cm$^{-1}$.

**(*S*)-6-(*t*-Butyldimethylsilyloxy)-5-nitro-2-heptanone ((*S*)-3a).** A solution of (*S*)-**2** (0.50 g, 2.28 mmol) and tetramethylguanidine (0.13 g, 1.14 mmol) in 10 ml of dry THF was added dropwise to methyl vinyl ketone (0.19 g, 2.73 mmol) at room temperature. The solution was stirred for an additional 15 h at room temperature, then poured into 50 ml of water and the organic materials were extracted with ethyl acetate (50 ml x 3). The combined organic layer was washed with 0.9% NaCl (50 ml x 3), dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was applied to column chromatography over silica gel with a 30 : 1 mixture of hexane and ethyl acetate as an eluent to afford 6-(*t*-butyldimethylsilyloxy)-5-nitro-2-heptanone ((*S*)-**3a**) (0.45 g) in a 68 % yield: $[\alpha]_D$ +12.0° (c = 1.51, $CHCl_3$).

$^1$H NMR ($CDCl_3$): δ ; 0.00 - 0.10 (s, 6H), 0.73 - 0.92 (s, 9H), 1.14 - 1.27 (m, 3H), 1.88 - 2.77 (m, 4H),

2.14 (s, 3H), and 3.83 - 4.44 (m, 2H). IR (neat): 2932, 1716, and 1526 $cm^{-1}$. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00 %. Found: C, 48.07 ; H, 7.63 ; N, 8.01 %.

**(S)-2-(T-Butyldimethylsilyloxy)-5-cyano-3-nitropentane ((*S*)-3b).** A solution of (*S*)-**2** (0.50 g, 2.28 mmol) and tetramethylguanidine (0.13 g, 1.14 mmol) in 10 ml of dry acetonitrile was added dropwise to acrylonitrile (0.18 g, 3.42 mmol) at room temperature. The solution was stirred for 15 h at room temperature, then poured into 50 ml of water and the organic products were extracted with ethyl acetate (50 ml x 3). The combined organic layer was washed with 0.9% NaCl (50 ml x 3), dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was applied to column chromatography over silica gel with a 30 : 1 mixture of hexane and ethyl acetate as an eluent to afford (*S*)-2-(*t*-butyldimethylsilyloxy)-5-cyano-3-nitropentane ((*S*)-**3b**) (0.42 g) in a 67 % yield: $[\alpha]_D$ +10.7° (c = 1.04, $CHCl_3$).

$^1H$ NMR ($CDCl_3$): δ ; 0.00 - 0.12 (s, 6H), 0.85 - 0.97 (s, 9H), 1.18 - 1.30 (m, 3H), 2.07 - 2.90 (m, 4H), and 4.13 - 4.64 (m, 2H). IR (neat): 2941, 2472, 1546, and 1458 $cm^{-1}$. Calcd for $C_6H_{10}N_2O_5$: C, 45.57; H, 6.37; N, 17.71 %. Found: C, 45.49 ; H, 6.41 ; N, 17.75 %.

**(*S*)-6-(*t*-Butyldimethylsilyloxy)-2-heptanone ((*S*)-4).** A solution of **3a** (200 mg, 0.69 mmol), tributyl tin hydride (200 mg, 0.69 mmol), and AIBN (16.4 mg, 0.10 mmol) in dry benzene (20 ml) was refluxed for 4 h. The solution was concentrated *in vacuo* and the residue was chromatographed over a silica gel column using a 7 : 1 mixture of hexane and ethyl acetate as an eluent to afford (*S*)-6-(*t*-butyldimethylsilyloxy)-2-heptanone ((*S*)-(+)-**4**) (89.3 mg) in a 53 % yield: $[\alpha]_D$ +20.1° (c = 1.51, $CHCl_3$).

$^1H$ NMR ($CDCl_3$): δ ; 0.00 (s, 6H), 0.84 (s, 9H), 1.08 (d, 3H, J = 6.0 Hz), 1.33 - 1.63 (m, 4H), 2.09 (s, 3H), 2.39 (t, 2H, J = 7.0 Hz), and 3.71 - 3.80 (tq, 1H, J = 6.0 Hz). IR (neat): 2980, 1725, and 1255 $cm^{-1}$. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84 %. Found: C, 64.36; H, 10.83 %.

**(2*S*, 6*R*, 8*S*)-2-Ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane ((2*S*, 6*R*, 8*S*)-6).** Under a nitrogen atmosphere, **4** (30.1 mg, 0.123 mmol) was added dropwise to a solution of LDA (82.0 μl, 0.123 mmol) in THF (10 ml) at –78 °C, and the solution was stirred for 5 min. Into the solution, 1-chloro-3-tetrahydropyranyloxypentane (38.1 mg, 0.185 mmol) was added dropwise and the mixture was stirred for an additional hour at the same temperature. Sodium iodide (18.4 mg, 0.123 mmol) was added to the mixture and stirred for an additional hour at –78 °C, then poured into 50 ml of water. The organic materials were then extracted with ethyl acetate (50 ml x 3). The combined organic layer was washed with saturated aqueous sodium thiosulfate and 0.9% NaCl, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. A mixture of acetic acid, THF, and $H_2O$ (4 : 2 : 1, 3 ml) was added to the residue and the mixure was stirred for 2 days. The sulution was then made alkaline with 20 ml saturated aqueous sodium carbonate and the mixure was extracted with ether (50 ml x 3). The organic solution was washed with 0.9% NaCl, dried over sodium sulfate, and concentrated *in vacuo*. The residue was applied to column chromatographty over silica gel using hexane as an eluent to afford (2*S*,6*R*,8*S*)-**6** (10.2 mg, 42 %) of >99% optical purity and a mixure of (2*R*,6*S*,8*S*)- and (2*R*,6*R*,8*S*)-**6** (2.90 mg, 12 %).

(2*S*,6*R*,8*S*)-**6** : $[\alpha]_D$ –72.9° (c = 0.40, pentane) ; lit.[3] $[\alpha]_D$ –72.9° (pentane): $^1H$ NMR ($CDCl_3$): δ ; 0.75 (t,