5. K. Graham, E.A. Graham, and G.H.N. Towers, *Can. J. Zool.*, **58**, 1955 (1980).
6. T. Arnason, G.F.Q. Chan, C.K. Wat, K. Downum, and G.H.N. Towers, *Photochem. Photobiol.*, **33**, 821 (1981).
7. T. Arnason, J.R. Stein, E.A. Graham, C.K. Wat, G.H.N. Towers, and J. Lam, *Can. J. Bot.*, **59**, 54 (1981).
8. C.K. Wat, S.K. Prasad, E.A. Grapham, S. Partington, T. Arnason, G.H.N. Towers, and J. Lam, *Biochem. Syst. Ecol.*, **9**, 59 (1981).
9. T. Arnason, T. Swain, C.K. Wat, E.A. Grapham, S. Partington. G.H.N. Towers, and J. Lam, *Biochem. Systm. Ecol.*, **9**, 63 (1981).
10. J.B. Hudson, E.A. Graham, and G.H.N. Towers, *Photochem. Photobiol.*, **36**, 181 (1982).
11. J.B. Hudson, E.A. Graham, and G.H.N. Towers, *Photochem. Photobiol.*, **43**, 27 (1986).
12. D. Weir, J.C. Sciano, J.T. Arnason, and C. Evans, *Photochem. Photobiol.*, **42**, 223 (1985).
13. S. Kita and K. Fukui, *Bull. Chem. Soc. Jpn.*, **42**, 66 (1969).
14. Unpublished results of our laboratory.
15. E.J. Corey and J.O. Albright, *J. Org. Chem.*, **48**, 2114 (1983).
16. D.D. Perrin,W.L.F. Armarego, and B.R. Perrin, "Purification of Laboratory Chemicals", Pergamon Press, Oxford, 1980.
17. G. Englington and W. McCrae, *J. Chem. Soc.*, 2295 (1963).

A Chiral Synthesis of a Mosquito Oviposition Pheromone

Suk-Ku Kang* and Dong-Soo Shin

Department of Chemistry, Sung Kyun Kwan University Natural Science Campus, Suwon 170

Received May 21, 1986.

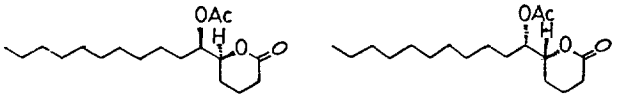
(+)-(5S,6R)-Erythro-6-acetoxy-5-hexadecanolide, an optically active form of them ajor component of an oviposition attractant pheromone of a mosquito **Culex pipiens fatigans**, was synthesized enantiospecifically from (-)-2-deoxy-D-ribose.

Introduction

Recently great advances have been made in total synthesis of optically active natural products from readily available chiral precursors such as carbohydrates, amino acids, hydroxy acids, and terpenes.[1]

Since the absolute stereochemistry of pheromones is important in pheromone activity, a number of chiral pheromones have been synthesized from chiral pools.[2] As a part of our research program directed toward the synthesis of chiral pheromones, we wish to describe a chiral synthesis of (+)-(5S,6R)-erythro-6-acetoxy-5-hexadecanolide, an optically active form of the major component of a mosquito oviposition attractant pheromone.

The oviposition attractant pheromone of the mosquito **Culex pipiens fatigans** was isolated from the optical droplet of the mosquito eggs and identified erythro-6-acetoxy-5-hexadecanolide by Laurence and Pickett.[3]The synthetic racemate(*la*→*lb*) (Figure 1) was reported as active as the natural pheromone. K. Machiya[4] tested the bioassay of the four erythro-and threo-isomers and reported that(-)-(5R,6S)-erytro-6-acetoxy-5-hexadecanolide was the most effective as an attractant. Recently B.R. Laurence and K. Mori[5] reported that (-)-(5R,6S)-(lb) enantioner is the vioposition attractant pheromone and the more biologically active enantiomer.



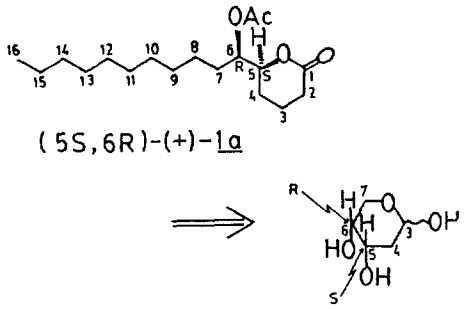
1a 1b

Several syntheses of erythro-6-acetoxy-5-hexadecanolide have been reported in the literature. C. Fuganti,[6] K. Mori,[7] and T. Fujisawa[8] have reported the synthesis of both enantiomers. One enantiomer(**la**) was synthesized from (+)-diethyl tartrate by Y. Masaki.[9] L. Gue-qiang[10] and K. Machiya[4] reported the synthesis of the four optical isomers of the mosquito oviposition attractant pheromone.

Results and Discussion

By retrosynthetic analysis, 2-deoxy-D-ribose(**2**) can be manipulated to (5S,6R)-erythro-6-acetoxy-5-hexadecanolide (**la**), in which the original chiral centers(5S,6R) of 2-deoxy-D-ribose is preserved without racemization (Scheme 1).

The C(3)-C(7) segment for the establishment of **la** is 2-deoxy-D-ribose.[11] The segment C(1)-C(2) can be constructed by the Wittig coupling of 2-deoxy-D-ribose with [(ethoxycarbonyl)methylene]triphenylphosphorane. One the other hand, the fragment C(8)-C(16) can be also constructed

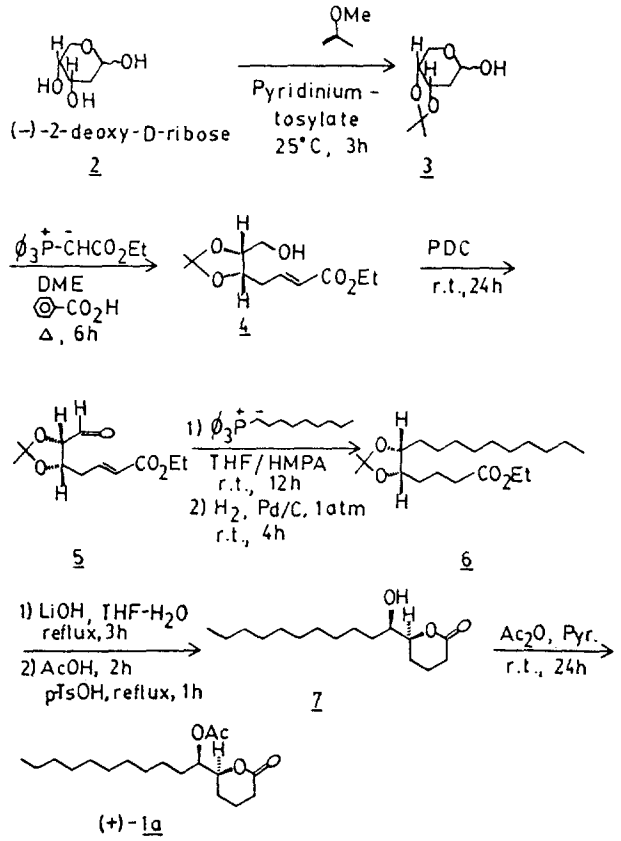


Scheme 1

by the Wittig coupling of nonylidenetriphenylphosphonium ylid with C(7) aldehyde.

Reaction of 2-deoxy-D-ribose(**2**) with 2-methoxypropene and a catalytic amount of pyridinium tosylate[11a] in ethyl acetate at 25°C for 3h furnished 60% of the deoxyribopyranose-3,4-acetonide(**3**). Treatment of **3** with 1.1 eqiv. of [(ethoxycarbonyl) methylene] triphenylphosphorane in dimethoxyethane(DME) containing a trace of benzoic acid[12] at refulx for 6h effected Wittig olefination to and α, β-unsaturated ester(**4**) (95% from **3**). Oxidation of **4** with pyridinium dichromate (PDC)[13] at room temperature for 24h gave an aldehyde ester(**5**) (78% from **4**).

structed by the Wittig coupling of 2-deoxy-D-ribose with [(ethoxycarbonyl) methylene] triphenylphosphorane. On the other hand, the fragment C(8)-C(16) can be also constructed by the Wittig coupling of nonylidenetriphenylphosphonium ylide with C(7) aldehyde.



Scheme 2

The C(8)-C(16) segment for the synthesis of **1a** was prepared by Wittig coupling followed by hydrogenation. Wittig reaction[14] of **5** with 1.5 eqiv. of nonylidenetriphenylphosphonium ylide in tetrahydrofuran(THF)/hexamethylphosphoric triamide (HMPA) at -50°C → rt for 12h occurred to give the cis olefin which upon hydrogenation (1 atm) in ethanol at 25°C for 4h over 10% palladium-on-charcoal catalyst afforded the ester acetonide(**6**) in 98% yield.

The conversion of the ester acetonide(**6**) into the final product has been already reported.[3,5,15] Ester hydrolysis[16] with 1.5 equiv. of LiOH in THF-H_2O (3:1) for 3h followed by deprotection of the acetonide with aq. AcOH solution for 2hr (between 75 and 80°C) yielded the 6-hydroxy-5-hexadecanolide(**7**). The lactionization was performed as the procedure of Laurence and Pickett[3] and K. Machiya[4] and C. Fuganti[6] afforded the (5S,6R)-erythro-6-acetoxy-5-hexadecanolide(**1a**) (Scheme 2).

Synthesis of (5R,6S)-erythro-6-acetoxy-5-hexadecanolide (**1b**) is in progress using 2-deoxy-D-ribose.

Experimental

H-NMR Spectra were measured in chloroform-d_1 solution at 80 MHz on a BRUKER WP 80 SY instrument. Chemical shifts are reported in ppm δ relative to internal tetramethylsilane. Infrared spectra were recorded on a Shimadzu IR-440 Spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Optical rotations were measured on a JASCO DIP-360 polarimeter. All solvents were distilled before use. Preparative thin layer chromatography (PTLC) was performed by using 20 × 20cm plates coated with 0.25 or 2mm thickness of silica gel containing GF 254 indicator (Merck). Column chromotography was performed using Merck silica gel 60 (70-230 mesh). All chromatography solvent were distilled prior to use.

Deoxyribopyranose-3,4-acetonide (3).

To a suspension of 2-deoxy-D-ribose (4.02g, 30 mmol) and pyridinium tosylate (150mg, 0.6 mmol) in dry ethyl acetate (60 m*l*) was added 2-methoxypropene (2.81g, 39 mmol) at 25°C. The mixture was strired at 25°C for 3hr, and quenched by stirring with a pH 5.5 phosphate buffer(15 m*l*) at 25°c for 10 min. The organic layer was separated and aqueous layer was extracted with two 20 m*l* portions of methylene chloride. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was chromatographed on silica gel (ether-hexane, 1:1) to give 3.14g (60%) of deoxyribopyranose-3,4-acetonide (**3**) as a colorless oil: TLC Rf 0.46(ether); $[\alpha]_D^{20}$ -20.89° (c=1.0, $CHCl_3$);IR(neat) 3400 cm^{-1}; ^{1}H-NMR δ 1.34(3H,s), 1.49(3H,s), 1.6-2.4(2H,m), 3.3-4.6(4H,m), 4.9-5.3(1H,m).

(5S,6R)-5,6-Isopropylidenedioxy-7-hydroxy-2-heptenoic acid ethyl ester(4).

To a solution of the acetonide (**3**) (2.8g, 16 mmol) in dimethoxyethane (20 m*l*) was added ethoxycarbonylmethylenetriphenylphosphorane (6.13g, 17.6 mmol) and benzoic acid (20mg). The mixture was gently refluxed for 6hr. The solvent was evaporated to afford an oil which was purified on silica gel (ether) to give 3.55g (91%) of an acetonide as a colorless oil (mixture of E-and Z-isomer in a ratio of 9:1): TLC Rf 0.67 (ether) $[\alpha]_D^{20}$ -25.03° (c=1.0, $CHCl_3$); IR(neat) 3500, 1720, 1655 cm^{-1}: ^{1}H-NMR δ 1.25(3H, t), 1.36(3H, s), 1.47(3H,s)

2.48(2H, m), 3.71-3.73(2H,m), 4.0-4.45(4H,m), 5.92(1H, dt), 6.99(1H, dt).

(5S, 6R)-5,6-Isopropylidenedioxy-7-oxo-2-heptenoic acid ethyl ester(5).

To a stirred solution of pyridinium dichromate (PDC) (3.45g, 9.21 mmol) in dry CH_2Cl_2 (9 m*l*) was added dropwise the hydroxy ester(**4**) (1.5g 6.14 mmol) at room temperature. The mixture was stirred at room temperature for 20hr, and diluted with ether, filtered on a pad of celite and evaporated to afford an oil which was purified on silica gel (ether) to give 1.16g (78%) of the ester aldehyde (**5**): TLC Rf 0.57 (ether); IR(neat) 2750, 1720 cm^{-1}; ^{1}H-NMR δ 1.25(3H,t), 1.36(3H,s), 1.47(3H,s), 3.71-3.73(2H,m), 4.0-4.45(4H,m), 5.92(1H,dt), 6.99(1H,dt), 9.75(1H,d); ^{13}C-NMRδ 14.08, 25.07, 25.28, 25.31, 32.47, 60.24, 81.51, 110.84, 124.17, 143.03, 165.91, 201.83.

(5S,6R)-5,6-Isopropylidenedixoy-hexadeca-2,7-dienoic acid ethyl ester and (5S,6R)-5,6-0-Isopropylidenedioxy-bexadecanoic acid ethyl ester (6).

A suspension of nonyltriphenylphosphonium bromide (2.34g, 4.98 mmol, 1.5 equiv) in 9 m*l* of dry tetrahydrofuran was stirred until the salt dissolved at room temperature. The mixture was cooled to -5°C and n-BuLi (3.06 m*l*) was added dropwise at such a rate as to keep the temperature below $+5$°C. After addition of the n-BuLi, the mixture was held at 0°C for 1hr. The unsaturated ester aldehyde (**5**) (0.812g, 3.32 mmol. 1.0 equiv) was dissolved in a mixture of the tetrahydrofuran (THF, 3.74 m*l*) and hexamethylphosphoramide (HMPA, 3.74 m*l*). The aldehyde solvent mixture was cooled to -50°C and ylide was transferred to the dropping funnel with N_2 and added dropwise to the aldehyde HMPA mixture at or below -35°C until the red color of the ylide persisted in the mixture. The reaction mixture was allowed to rise at room temperature overnight. The reaction was worked up by dilution with ice and water and extraction with ether several times. The ether extracts were washed with water saturated NaCl solution, and dried over Na_2SO_4. The crude product was chromatographed on silica gel (ether-hexane, 1:9) to give 485 mg (41%) of the pure dienoic acid ethyl ester acetionide: $[\alpha]_D^{20}$-17.4 (c=1, $CHCl_3$); IR(neat) 3000, 1720, 1655 cm^{-1}; ^{1}H-NMR δ 0.85 (3H,t), 1.21(3H,t), 1.25(14H,br.s), 1.29(3H,s), 1.40(3H,s), 1.50-2.21(2H,m), 4.05-4.17 (4H,m), 5.45(2H,m), 5.92(1H,dt), 6.99(1H,dt).

The mixture of the dienoic acid ethyl ester (485 mg, 1.37 mmol) in ethyl acetate (2 m*l*) containing 97 mg of 10% palladium on charcoal was hydrogenated at 25°C under 1 atm of hydrogen. After the completion of hydrogen absorption (about 4hr), the solution was filtered through celite and the filtrate was evaporated to afford 478 mg (98%) of the saturated ester(**6**); IR(neat) 3000, 1720 cm^{-1}; ^{1}H-NMR δ 0.85(3H,t), 1.25(18H,s), 1.21(3H,t), 1.29(3H,s), 1.40(3H,s), 1.50-2.21 (4H,m), 2.39(2H,m) 4.05(4H, m).

(5S,6R)-(-)-5,6-0-Isopropylidenedioxyhexadecanoic acid and (5S,6R)-(+)-6-hydroxy-5-hexadecanolide (7).

To a solution of the saturated ester (**6**) (123 mg, 0.35 mmol, 1.0 equiv) in THF (1 m*l*)-H_20 (0.3 m*l*) was added LiOH (21.3 mg, 0.52 mmol, 1.5 equiv) and the mixture was refluxed for 3hr. The resulting mixture was cooled and poured into ice-cooled dil. HCl and extracted with ether. The ether solution washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified on silica gel (ether-hexane, 1:2) to afford 95 mg of the hexadecanoic acid acetonide (oil, 84%); IR(neat) 3000, 2840, 1700, 1360 cm^{-1}; ^{1}H-NMR δ 0.85 (3H,t), 1.25(18H,br.s), 1.29(3H,s), 1.40(3H,s), 1.5-2.10(4H,m), 2.39(2H,t), 4.02(2H,m), 10.41(1H, br. s). A mixture of the hexadecanoic acid acetonide (57mg, 0.17 mmol) in aqueous AcOH (2.75m*l*) was heated for 2hr between 75 and 80°C. After removing the solvents by azeotropic distillation, the residue was dissolved in benzene and to this mixture was added a catalytic amount of p-TsOH, followed by heating under reflux for 1hr. The mixture was poured into water and extracted with AcOEt. The combined organic layer was washed with sat. $NaHCO_3$ and brine, and then dried over Na_2SO_4. After evaporating the solvent, the residue was purified on silica gel (ether-hexane, 10:1) to afford 39 mg of the pure lactone (**7**) (yield, 84%); $[\alpha]_D^{20}+9.1$ (c=1, $CHCl_3$); IR(neat) 3400, 2900, 2850, 1710 cm^{-1}; ^{1}H-NMR δ 0,85(3H,t), 1.26(16H,br.s), 1.35-1.6(2H,m), 1.76-2.0(4H,m), 2.1(1H, br. s), 2.43-2.64(m), 3.84(1H, m), 4.15-4.35(1H, m).

(5S,6R)-(+)-6-Acetoxy-5-hexadecanolide (Ia).

To a stirred solution of the lactone(**7**) (39mg, 0.14 mmol) in dry pyridine (0.17g, 2.1 mmol) was added acetic anhydride (22mg, 0.21 mmol) and the mixture was stirred for 1 day at room temperature. The resulting mixture was poured into ice cooled dil. HCl and extracted with AcOEt. The extract was washed with sat. $NaHCO_3$ and sat. NaCl, and then dried over Na_2SO_4. After evaporating the solvent, the residue was purified on silica gel (AcOEt-benzene, 1:5) to afford 38 mg of the hexadecanolide (**Ia**) as a colorless oil (yield, 87%); $[\alpha]_D^{20}+34.5$° (c=1.0, $CHCl_3$); [lit.,[4] $+38.8$°(c=1.5, $CHCl_3$)]; IR(neat) 2900, 2830, 1730 cm^{-1}; ^{1}H-NMR 0,85 (3H,t), 1.26(16H,br.s), 1.58-2.0(6H,m), 2.1(3H,s), 2.53(2H,m), 4.34(1H,m), 4.98(1H,m).

References

1. S. Hanessian, *Total Synthesis of Natural Products, The 'Chiron' Approach*, Ed. by pergamon press, Oxford (1983).
2. K. Mori, *The Total Synthesis of Natural Products* (Edited by J. ApSimon), Vol. 4, John Wiley, New York (1981), pp 1-183.
3. B.R. Laurence and J.A. Pickett, *J. Chem. Soc., Chem. Commun.*, 59 (1982).
4. K. Machiya, I. Ichimoto, M. Kirihata, and H. Ueda, *Agric. Biol. Chem.*, **49**, 643 (1985).
5. B.R. Laurence, K. Mori, T. Otsuka, J.A. Pickett, and L.J. Wad hams, *J. Chem. Ecol.*, **11**(5), 643 (1985).
6. C. Fuganti, P. Grasselli, and S. Servi, *J. Chem. Soc., Chem. Commun.*, 1285 (1982)
7. K. Mori and T. Otsuka, *Tetrahedron*, **39**, 3267 (1983).
8. T. Sato, M. Watanabe, N. Honda, and T. Fujisawa, *Chem. Lett.*, 1175 (1984).
9. Y. Masaki, K. Nagata, and K. Kaji, *Chem. Lett.*, 1835 (1983).
10. L. Guo-qiang, X. Hai-jian, W. Bi-chi, G. Guong-zhong, and Z. Wei-shan, *Tetrahedron Lett.*, **26**, 1233 (1985).
11. Recently 2-deoxy-D-ribose was used in the asymmetric synthesis of leukotrienes as chiral starting material; (a) E.J. Corey, A. Mariat, G. Goto, and F. Brion, *J. Am. Chem. Soc.*, **102**, 7985 (1980); (b) J. Rokach, R. Zamboni, C-K Lau and Y. Guindon, *Tetrahedron Lett.*, **22**, 2759 (1981); (c) J. Rokach, C-K Lau, R. Zamboni, and Y. Guindon, *Tetrahedron Lett.*, **22**, 2763 (1981).
12. E.J. Corey, D.A. Clark, G. Goto. A. Marfat, C. Mioskowski, B. Samuellsson, and S. Hammarstrom, *J. Am. Chem. Soc.*, **102**, 1436 (1980).
13. E.J. Corey and G. Schmidt, *Tetrahedron Lett.*, 399 (1979).

14. J.H. Tumlinson, M.G. Klein, R.E. Doolittle, and T.L. Ladd, Jr., *U.S. patent*, 4, 179, 446 (1979).
15. M. Yamaguchi and I. Hiro, *J. Chem. Soc., Chem. Commun.*, 202 (1984).
16. K.C. Nicolaou and S.E. Webber, *J. Am. Chem. Soc.*, **106** 5734 (1984).

Chemistry of the 3a,7a-Dihydro-1H-indole Esters. Aromatization by Bromine†

Chang Kiu Lee* and Yu Mi Ahn

Department of Chemistry, Kangweon National University, Chuncheon 200

In-Sook Han Lee

Department of Science Education, Kangweon National University, Chuncheon 200. *Received May 26, 1986*

A series of tetramethyl 1-substituted benzyl-3a,7a-dihydro-1H-indole-2,3,3a,4-tetracarboxylates were prepared and their reactions with bromine were examined. The initial reaction seemed to be the formation of the intermediate *N*-bromo quartnery ammonium bromide. This intermediate underwent aromatization with loss of the 3a-methoxycarbonyl group. Bromine replaced the *N*-substituent of the *p*-methoxybenzyl compound and addition of bromine occurred across the C_6-C_7 double bond of the indole ring. Bromination of the benzyl ring and aromatization occurred for the *m*-methoxybenzyl compound.

Although bromine has a strong potential as an oxidizing agent, it has not been employed for the process of aromatization of dihydrobenzenes (eg. 1,3-cyclohexadiene or 1,4-cyclohexadiene to benzene) because addition would take place rather than dehydrogenation. Indeed, there are only a few examples of using bromine for the purpose of aromatization of nitrogen containing heterocyclic compounds.[1,2] Iodine was used for the conversion of cyclohexenones into anisols.[3]

As a part of our continuing investigation on the chemistry of 3a,7a-dihydroindole esters (**2**) which were prepared from *N*-substituted pyrroles (**1**) and dimethyl acetylenedicarboxylate (DMAD)[4,5] we reexamined the aromatization reaction of **2** by bromine. We suggested previously the formation of *N*-bromo quarternary ammonium ion (**3**) in the process of aromatization of 2.[4] It could be justified by formation of the *N*-bromodihydroindole (**2i**) from the unsubstituted compound aromatization of *N*-substituted dihydroindole esters (**2**). The aromatization of *N*-substituted dihydroindole esters (**2**). The chemistry involved here may well reflect the reactivity of the tertiary amine with electrophilic reagents. The fate of **3** may give insight to the relative reactivity of the substituted benzyl groups.

Results and Discussion

At first, substituted benzylpyrroles (**1c-i**) were prepared by the reaction of 2,5-diethoxytetrahydrofuran and the corresponding benzylamines.[6] The 1:2 adducts (**2c-h**) were prepared by refluxing the pyrroles (**1c-h**) with DMAD in anhydrous ether for 40-90 h and the solid precipitates were isolated and recrystallized from methanol. Reaction time, yields and melting points of the compounds are listed in Table 1. Note the *p*-methoxybenzylpyrrole (**1g**) gave the highest yield (80%) while the *m*-methoxy compound (**1f**) gave the lowest yield (20%). *p*-Nitrobenzylpyrrole (**1i**) did not react.

When the 3a, 7a-dihydroindole esters (**2**) were treated with bromine in methanol at 0 °C, aromatization took place but the yield of **4** varied depending on the substituents as shown in the Table 1. Similarly, the *N*-methyl compound (**2b**)[7] underwent almost quantitative aromatization. However, with *N*-benzyl (**2c**) or substituted benzyl compounds (**2d-h**) the aromatization reaction was not complete even in the presence of three-fold excess of bromine. The UV spectra of the reaction mixtures and the TLC examination indicated that con-

Table 1. The Yields and Melting Points of 3a,7a-Dihydroindoles (2) and Indoles (4)

Compd	Reaction time, h	Yield, %	mp, °C
2a [a]	96	6	162-165
2b	41	80	145-147[b]
2c	40	68	133.5-135[c]
2d	47	78	141-142.5
2e	89	48	154-155
2f	89	20	60.5-61
2g	72	80	104-107
2h	96	53	136-138.5
4b		98	120-121.5
4c		70	114
4d		20	108
4e		50	142-144
4f		38	127-130
4g		23	157.5-159

[a]All values are from ref. 4. [b]Lit.[7] 146°C, [c]Lit.[7] 135°C.

†This paper is dedicated to professor Hak Sook Lyu of Yonsei University on his 60th birthday.