Tetrahedron Vol. 49, No. 5, pp. 1017-1024, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

DIASTEREOSELECTIVE SYNTHESIS AND OPTICAL RESOLUTION OF 3,4-SUBSTITUTED TETRAHYDROISOQUINOLIN-4-OLS

Masaru Kihara,* Motoki Ikeuchi, Kaori Jinno, Minoru Kashimoto, Yoshimaro Kobayashi, and Yoshimitsu Nagao

Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770, Japan

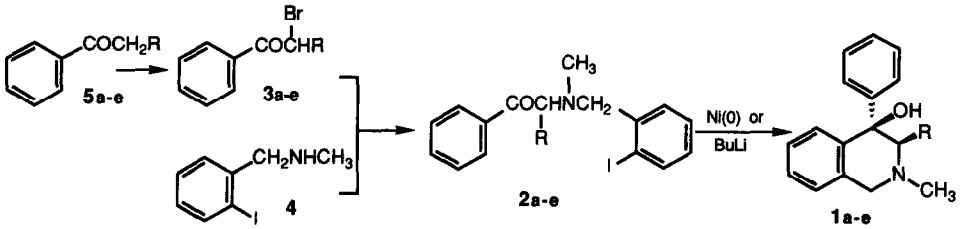
(*Received in Japan* 20 *October* 1992)

Key Words: tetrahydroisoquinolin-4-ol; diastereoselective synthesis; optical resolution; butyllithium; zerovalent nickel

Abstracts: Trans-3,4-substituted 1,2,3,4-tetrahydroisoquinolin-4-ols were prepared diastereoselectively by an insertion reaction with zerovalent nickel and by Barbier reaction with butyllithium of N-(2-iodobenzyl)phenacylamines. The isoquinolin-4-ols were resolved by means of HPLC method and the absolute configurations were determined.

In the course of our study on the synthesis of biologically active compounds, we prepared 4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(PI-OH)(**1a**) as a strong and selective noradrenaline(NA) potentiator.[1] PI-OH was also found to have a high enantioselectivity since R-(+)-PI-OH showed a strong NA potentiating activity but S-(-)-PI-OH did not show any potentiating and inhibiting activity.[2] Salman and co-workers reported the enantioselectivity of centchroman, which is a derivative of trans-3,4-diphenylchroman, for cytosol estrogen receptor affinity.[3] From these findings, 3,4-substituted tetrahydroisoquinolin-4-ols are interesting compounds for studying the structure-activity relationships and the enantioselectivity for NA potentiating activity. We now report the first diastereoselective synthesis and the optical resolution of 3,4-substituted 1,2,3,4-tetrahydroisoquinolin-4-ols(**1b-e**).

In the previous papers, we reported the convenient synthesis of PI-OH derivatives(**1**) by an intramolecular insertion reaction of the corresponding N-(2-iodobenzyl)phenacylamines(**2**) with zerovalent nickel[Ni(0)] although in low yields.[4] Recently, the convenient and efficient synthesis of PI-OH derivatives was performed by an intramolecular Barbier



a: R=H ; b: R=CH_3 ; c: R=CH_2CH_3 ; d: R=$CH(CH_3)_2$; e: R=C_6H_5

Scheme 1

Table I. Yields of Isoquinolin-4-ols(**1b-e**) from N-Benzylphenacylamines (**2b-e**) with BuLi and Zerovalent Nickel

Starting material	Product	Yield(%) With BuLi	Yield(%) With Ni(0)
2b	**1b**	73	80
2c	**1c**	62	71
2d	**1d**	31	13
2e	**1e**	57	47

reaction of phenacylamines(**2**) with BuLi.[5] On the basis of these facts, we carried out the synthesis of 3,4-substituted isoquinolin-4-ols(**1b-e**) by Barbier reaction of phenacylamines(**2b-e**) as well as by an insertion reaction in order to clarify the efficacy for the cyclization reaction of **2b-e**. The phenacylamines(**2b-e**) as key intermediates were prepared from the corresponding phenacyl bromides(**3b-e**) and 2-iodo-N-methylbenzylamine(**4**) in good yields(Scheme 1). The phenacyl bromides(**3b-e**) were obtained by bromination of alkyl phenyl ketones(**5b-e**) with benzyltrimethylammonium tribromide(BTMA Br_3).[6]

Cyclization of phenacylamines(**2b,c** and **2e**) with BuLi gave the isoquinolin-4-ols(**1b,c** and **1e**) in 57-73% yields(Table I). An insertion reaction of **2b,c** and **2e** with Ni(0) also afforded the isoquinolin-4-ols(**1b,c** and **1e**) in 47-80% yields. It is interesting to note that the yields of **1b,c** with zerovalent nickel are higher than those with BuLi as the yields of N-methyl derivatives of isoquinolin-4-ols so far prepared with Ni(0) were lower than 45%.[4] The low yields of **1d** by both methods seems to be due to the steric hindrance between the isopropyl and the phenyl substituents.

The isoquinolin-4-ol(**1b**) can exist in either 3,4-trans[7] or 3,4-cis diastereomers. Inspection of **1b** with Driding model indicates that each diastereomer has two half-chair conformations[8] A, B and C, D as shown in Fig. 1. ^{1}H-NMR spectrum of **1b** thus obtained by both methods showed a single diastereomer. The nuclear Overhauser effect(NOE) increments between 1-H_{ax} and 3-H_{ax}, and between 3-H_{ax} and an aromatic proton in the 4-phenyl group were observed as 4.4% and 12.9%, respectively. These facts show that **1b** has a trans-form

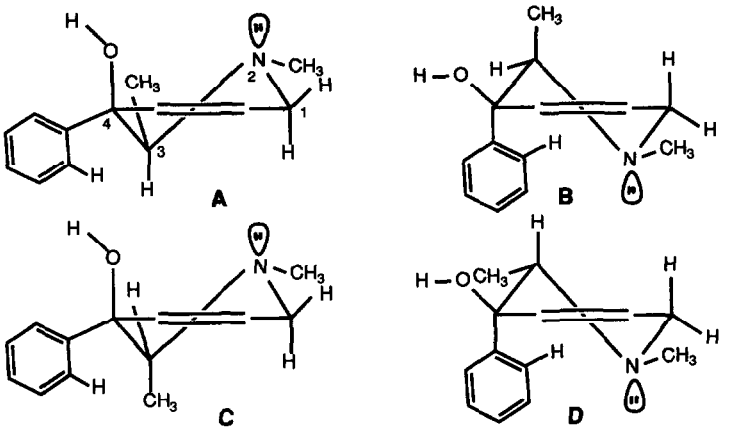


Fig. 1. Conformations of **1b**

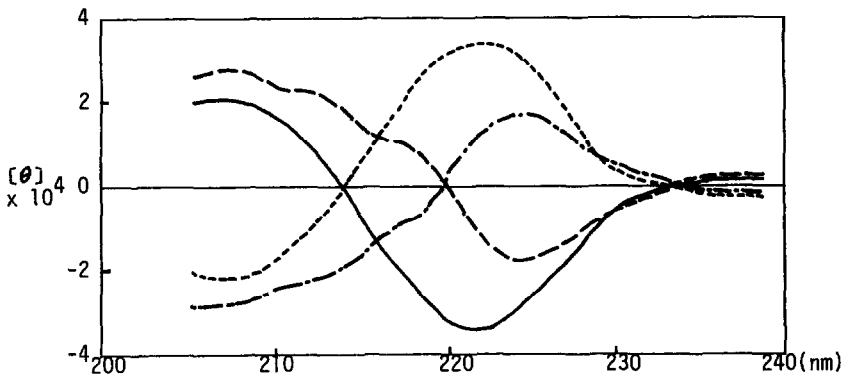


Fig. 2. CD spectra of optically active **1b** and **1e** in MeOH : (———) R,R-(+)-**1b** ; (------) S,S-(-)-**1b** ; (— — —) R,R-(+)-**1e** ; (—·—·—) S,S-(-)-**1e**.

and a conformation A. Similarly, ^{1}H-NMR spectra and NOE experiments of other isoquinolin-4-ols(**1c-e**) indicated the stereochemistry to be trans-forms possessing conformation A. Thus, the cyclization of **2b-e** with BuLi and Ni(0) is concluded to give diastereoselectively trans-3,4-substituted isoquinolin-4-ols(**1b-e**).[10]

Optical resolution of the isoquinolin-4-ols(**1b** and **1e**) was performed by HPLC with a chiral stationary phase(Daicel Chiralcel OJ)[2,11] using hexane-2-propanol as an eluent. Resolution of **1b** gave a couple of enantiomers, (+)-**1b**;$[\alpha]_D$ +15.7° and (-)-**1b**;$[\alpha]_D$ -16.7°. HPLC chromatogram of **1e** showed completely separated two fractions(retention times 8.5 and 16.8 min) and resolution of **1e** gave the enantiomers, (+)-**1e**; $[\alpha]_D$ +11.5° and (-)-**1e**;$[\alpha]_D$ -11.5°.

The absolute configurations of (+)- and (-)-**1b**, and (+)- and (-)-**1e** were determined by exciton chirality method.[12] CD spectra(Fig. 2) of the (+) and (-) enantiomers of **1b** showed typical split Cotton curves with $[\theta]_{222}$ -33000, $[\theta]_{207}$ +21100 and $[\theta]_{222}$ +34600,

$[\theta]_{207}$ -22100, respectively. The negative exciton chirality[12] of the (+) enantiomer suggests the stereochemistry at C4 to be R-configuration. This configuration was supported by comparison of the CD spectrum of (+)-**1b** with that of R-(+)-PI-OH, configuration of which was also determined by x-ray crystallographic analysis.[2] Therefore, the stereochemistry in (+)-**1b** is 3R,4R configuration. As **1e** bears three phenyl groups as an almost equivalent chromophore, 3R,4R-**1e** must have a totally negative chirality by addition[13] of chiralities among the three chromophores. CD spectrum of (+)-**1e** indicated a negative exciton chirality as shown in Fig. 2. These facts show that the absolute configuration of (+)-**1e** is 3R,4R and (-)-**1e** has a 3S,4S configuration.

In conclusion, reaction of the phenacylamines(**2b-e**) with BuLi and Ni(O) gave diastereoselectively trans-3,4-substituted isoquinolin-4-ols(**1b-e**) and the racemic **1b** and **1e** were easily resolved to 3R,4R-(+)- and 3S,4S-(-)-**1b**, and 3R,4R-(+)- and 3S,4S-(-)-**1e**, respectively.

EXPERIMENTAL

All melting points are given as uncorrected values. Infrared(IR) spectra were taken with a Perkin-Elmer 1720 infrared fourier transform spectrometer and are given in cm^{-1}. High-resolution mass(MS) spectra were recorded on a JEOL JMS-D 300 spectrometer. Proton nuclear magnetic resonance(^{1}H-NMR) spectra were recorded on a JEOL JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as a standard and are given in δ values. Optical rotations were determined with a Union PM-201 polarimeter. CD spectra were recorded on a JASCO J-600 spectropolarimeter. HPLC was run on a Shimazu LC-6A liquid chromatograph equipped with a chiral stationary phase column(Daicel Chiralcel OJ, 1.0 cm i.d. x 25 cm).

α-Methylphenacyl Bromide(**3b**) BTMA Br_3(4.921 g, 11.0 mmol) was added to a solution of ethyl phenyl ketone(**5b**)(1.086 g, 8.09 mmol) in CH_2Cl_2-MeOH(5:2) (112 ml) and the mixture was refluxed for 20 h at 50-60°C. The mixture was evaporated *in vacuo* and H_2O(40 ml) was added to the residue. The mixture was extracted with ether(120 ml x 3). The extract was washed with saturated solution of $Na_2S_2O_3$ in H_2O and brine, and dried over $MgSO_4$ and evaporated to give **3b** as a pale yellow oil(1.70 g, 99%). ^{1}H-NMR: 8.04(2H,dd,J=8.5 and 1.5 Hz), 7.65-7.45(3H,m), 5.30(1H,q,J=6.6Hz), 1.91(3H,d,J=6.6Hz). IR(film):1683(C=O). FABMS (m/z)(M+H):Calcd for C_9H_9BrO:212.9915. Found:212.9933.

*The phenacyl bromides(**3c-e**) were prepared in the same way as **3b**.*

α-Ethylphenacyl Bromide(**3c**) Reaction of butyrophenone(**5c**)(2.02 g, 13.6 mmol) with BTMA Br_3(5.84 g, 15.0 mmol) in CH_2Cl_2-MeOH(5:2)(56 ml) gave **3c** as a pale yellow oil(2.88 g, 93 %). ^{1}H-NMR: 8.02(2H,dd,J=8.5 and 1.7Hz), 7.64-7.26(3H,m), 5.08(1H,t,J=6.3Hz), 2.29-2.10 (2H, m), 1.09(3H,t,J=7.3Hz). IR(KBr):1686(C=O). FABMS(m/z)(M+H):Calcd for $C_{10}H_{12}BrO$: 227.0071. Found:227.0054.

α-i-Propylphenacyl Bromide(**3d**) A mixture of isovaleroyl chloride(12.42 g, 0.1 mol), benzene(35.6 g, 0.45 mol) and $AlCl_3$(16.04 g, 0.12 mol) was refluxed for 30 min. The

mixture was poured into ice-water(100 ml) and extracted with $CHCl_3$(100 ml x 3). The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give 2-methylpropyl phenyl ketone(**5d**) as an oil(16.20 g, 94%). ^{1}H-NMR: 8.00(2H,dd,J=8.5 and 1.5Hz), 7.60-7.23 (3H,m), 2.84(2H,d, J=6.8Hz), 2.40-2.08(1H,m), 1.00(6H,d,J=6.6Hz). IR(KBr): 1686(C=O). MS (m/z)(M^+):Calcd for $C_{11}H_{14}O$: 162.1042. Found:162.1042.

Reaction of 2-methylpropyl phenyl ketone(**5d**)(2.00 g, 12.3 mmol) obtained as above with BTMA Br_3(7.21 g, 18.5 mmol) in CH_2Cl_2-MeOH(5:2)(56 ml) gave **3d** as an oil(1.95 g, 66 %). ^{1}H-NMR: 8.00(2H,dd,J=8.5 and 1.5Hz), 7.65-7.26(3H,m), 4.94(1H,d,J=8.5Hz), 2.57-2.36 (1H, m), 1.22, 1.03(each 3H,d,J=6.6Hz). IR(KBr): 1679(C=O). MS(m/z)(M^+): Calcd for $C_{11}H_{13}BrO$:240.0148. Found:240.0118.

α-Phenylphenacyl Bromide(**3e**) Reaction of deoxybenzoin(**5e**)(5.32 g, 27.1 mmol) with BTMA Br_3(15.85 g, 40.7 mmol) in CH_2Cl_2-MeOH(5:2)(84 ml) gave **3e** as an oil(6.41 g, 98%). ^{1}H-NMR: 7.99(2H,dd,J=8.5 and 1.5Hz), 7.66-7.26(8H,m), 6.38(1H,s). IR(KBr):1687(C=O). FABMS(m/z) (M+H):Calcd for $C_{14}H_{12}BrO$:275.0072. Found:275.0069.

N-(2-Iodobenzyl)-α,N-dimethylphenacylamine(**2b**) A solution of the phenacyl bromide(**3b**) (1.70 g, 7.98 mmol) in dioxane(25 ml) was added to a solution of the benzylamine(**4**)(4.17 g, 16.9 mmol) in dioxane(25 ml). The mixture was stirred for 18 h at 55-60°C. The precipitates formed were filtered and the filtrate was evaporated to give a crude oil(4.60 g). This was subjected to flash chromatography on SiO_2 with benzene-hexane(1:1) to give **2b** as a pale yellow oil(2.51 g, 82%). ^{1}H-NMR: 7.92(2H,dd,J=8.5 and 1.5Hz), 7.82(1H,d,J=7.6Hz), 7.54-7.24(5H,m), 6.94(1H,m), 4.35 (1H,q,J=6.6Hz), 3.71(2H,s), 2.27(3H,s), 1.36(3H,d,J=6.6 Hz). IR(KBr):1700(C=O). MS(m/z):Calcd for $C_{17}H_{18}INO$:378.0356(M-1); 380.0513(M+1). Found: 378.0310(M-1); 380.0472(M+1).

Other phenacylamines(**2c-e**) were prepared in the same way as **2b**.

α-Ethyl-N-(2-iodobenzyl)-N-methylphenacylamine(**2c**) Reaction of **4**(1.153 g, 4.67 mmol) in dioxane(13 ml) with **3c**(353 mg, 1.56 mmol) in dioxane(13 ml) gave **2c** as a pale yellow oil (430 mg, 78%). ^{1}H-NMR: 7.88(2H,dd,J=8.5 and 1.5Hz), 7.81(1H,d,J=7.6Hz), 7.60-7.23(6H,m), 4.12(1H,dd,J=8.8 and 5.6Hz), 3.73(2H,s), 2.31(3H,s), 2.17-1.76(2H,m), 0.94(3H,t,J=7.3Hz). IR(KBr):1683(C=O). MS(m/z)(M-1): Calcd for $C_{18}H_{20}INO$:392.0513. Found:392.0515.

N-(2-Iodobenzyl)-α-isopropyl-N-methylphenacylamine(**2d**) Reaction of **4**(1.01 g, 4.10 mmol) in dioxane(7 ml) with **3d**(463 mg, 1.92 mmol) in dioxane(7 ml) gave **2d** as a pale yellow oil (326 mg, 42%). ^{1}H-NMR: 7.95(2H,dd,J=8.5 and 1.5Hz), 7.83(1H,dd,J=7.6 and 1.7Hz), 7.71-7.35(6H,m), 4.89(1H,d,J=8.6Hz), 3.70, 3.56(each 1H,d,J=18.9Hz), 2.52-2.34(1H,m), 2.25 (3H,s), 1.16, 0.98(each 3H,d,J=6.6Hz). IR(KBr): 1697(C=O). MS(m/z)(M^+): Calcd for $C_{19}H_{22}INO$:407.0746. Found:407.0746.

N-(2-Iodobenzyl)-N-methyl-α-phenylphenacylamine(**2e**) Reaction of **4**(1.06 g, 4.29 mmol) in dioxane(13 ml) with **3e**(346 mg, 1.43 mmol) in dioxane(13 ml) gave **2e** as a pale yellow oil (609 mg, 96%). ^{1}H-NMR: 7.95(2H,dd,J=8.1 and 1.2Hz), 7.80(1H,dd,J=7.8 and 1.2Hz), 7.58-7.25(11H,m), 6.93(1H,ddd,J=8.6, 8.6 and 1.7Hz), 5.41(1H,s), 3.80, 3.70(each 1H,d, J=14.4Hz), 2.32(3H,s). IR(KBr): 1687(C=O). MS(m/z)(M-1): Calcd for $C_{22}H_{20}INO$: 440.0511. Found:440.0471.

2,3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(**1b**) With Ni(0): Ph_3P(3.466 g, 13.2 mmol), $NiCl_2$(1.713 mg, 13.2 mmol), and Zn(864 mg, 13.2 mmol) were placed in a two necked flask. The flask was evacuated and filled with N_2. Dry oxygen-free DMF(30 ml) was added through a syringe. The mixture was stirred at 55°C for 5 min. A solution of **2b** (2.507 g, 6.61 mmol) in dry oxygen-free DMF(10 ml) was added and the mixture was stirred for 3 h at 55°C. Then, the mixture was acidified with 2% HCl and washed with ether. The aqueous layer was basified with NH_4OH and extracted with $CHCl_3$(70 ml x 4). The extract was dried over $MgSO_4$ and evaporated to give a crude product(2.466 g). This was subjected to flash chromatography on SiO_2 with $CHCl_3$-acetone(5:1) to give the isoquinolin-4-ol (**1b**) as colorless leaves(1.346 g, 80%)(from EtOH), mp 166-167°C. ^{1}H-NMR: 7.39-7.01(8H,m), 6.78 (1H,d, J=7.8Hz), 3.82, 3.61(each 1H,d, J=15Hz), 2.74(1H,q, J=6.6Hz), 2.41(3H, s), 0.92 (3H,d,J=6.6Hz). IR(KBr): 3400(OH). MS(m/z)(M^+):Calcd for $C_{17}H_{19}NO$: 253.1468. Found: 253.1472. Anal.Calcd for $C_{17}H_{19}NO$:C,80.60;H,7.56;N,5.53. Found:C,80.30;H,7.61;N,5.52.
With BuLi: BuLi(1.6 M sol. in hexane, 0.46 ml, 0.74 mmol) was added to a solution of the phenacylamine(**2b**)(215 mg, 0.56 mmol) in dry THF (4 ml) by a syringe at -78°C under N_2 and the mixture was stirred for 10 min at -78°C. H_2O(10 ml) was added and the mixture was extracted with ether(30 ml x 3). The extract was dried over $MgSO_4$ and evaporated to give an oil(210 mg). This was subjected to preparative TLC on SiO_2 with $CHCl_3$-acetone(5:1). The fraction of Rf 0.13-0.25 gave **1b** as colorless leaves(105 mg, 73%). This product(**1b**) was identical with a sample of **1b** prepared with Ni(0) as above by comparisons of their ^{1}H-NMR and IR spectra.

Other isoquinolin-4-ols(**1c-e**) were prepared by both methods using Ni(0) and BuLi in the same way as **1b** and the structures of **1c-e** prepared by both methods were identified by comparisons of their ^{1}H-NMR spectra and the TLC behaviours, respectively.
3-Ethyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(**1c**) With Ni(0): Reaction of **2c**(417 mg, 1.06 mmol) in dry oxygen-free DMF(3 ml) with Ni(0) [prepared from Ph_3P (1.193 g, 4.55 mmol), $NiCl_2$(304 mg, 2.34 mmol) and Zn(144 mg, 2.27 mmol) in dry oxygen-free DMF (10 ml)] gave crude crystals(283 mg). This was purified by preparative TLC on Al_2O_3 with benzene-$CHCl_3$(10:1) gave **1c** as pale yellow crystals(201 mg, 71%). Recrystallization from EtOH afforded colorless needles, mp 117-118°C. ^{1}H-NMR: 7.42-7.02(8H,m), 6.76(1H,m), 3.89, 3.73(each 1H,d,J=15.6Hz), 2.62(1H,t,J=2.9Hz), 2.52(3H,s), 1.66-1.40 (2H,m), 1.26(1H,br s), 0.80(3H,t,J=7.3Hz). IR(KBr): 3153(OH). Anal. Calcd for $C_{18}H_{21}NO$: C,80.86;H,7.92; N, 5.24. Found:C,80.48;H,7.96;N,4.97.
With BuLi: Reaction of **2c**(430 mg, 1.09 mmol) in dry THF(5 ml) with BuLi(1.6 M sol. in hexane, 1.1 ml, 1.8 mmol) gave a crude product(323 mg). This was purified in the same way as above gave **1c** as pale brown crystals(181 mg, 62%).
3-Isopropyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(**1d**) With Ni(0): Reaction of **2d**(66 mg, 0.16 mmol) in dry oxygen-free DMF(3 ml) with Ni(0) [prepared from Ph_3P(200 mg, 0.76 mmol), $NiCl_2$(52 mg, 0.40 mmol) and Zn(28 mg, 0.40 mmol) in dry oxygen-free DMF(5 ml)] gave a crude product(11 mg). This was purified by preparative TLC on Al_2O_3 with hexane-acetone(1:1) gave **1d** as a pale yellow oil(5.7 mg, 13%). ^{1}H-NMR: 7.50-

7.03(9H, m), 3.96 and 3.86(each 1H,d,J=15.6Hz), 2.86(1H,d,J=3.9Hz), 2.74(1H,br s), 2.51 (3H,s), 2.16-2.10(1H,m), 0.94, 0.87(each 3H,d,J=7.1Hz). IR(KBr): 3367(OH). MS(m/z)(M^+): Calcd for $C_{19}H_{23}NO$:281.1779. Found:281.1761.

With BuLi: Reaction of **2d**(91 mg, 0.22 mmol) in dry THF(2 ml) with BuLi(1.6 M sol. in hexane, 0.23 ml, 0.35 mmol) gave a crude product(50 mg). This was purified in the same way as above gave **1d** as a pale yellow oil(19.4 mg, 31%).

2-Methyl-3,4-diphenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(**1e**) With Ni(0): Reaction of **2e**(399 mg, 0.90 mmol) in dry oxygen-free DMF(4 ml) with Ni(0) [prepared from Ph_3P(948 mg, 3.62 mmol), $NiCl_2$(234 mg, 1.81 mmol) and Zn(115 mg, 1.81 mmol) in dry oxygen-free DMF(10 ml)] gave a crude product(197 mg). This was purified by flash chromatography on SiO_2 with CH_2Cl_2-AcOEt(10:1) to give **1e** as white crystals(135 mg, 47%). Recrystallization from EtOH afforded colorless prisms, mp 184.5-185.5°C. ^{1}H-NMR: 7.29-6.91(14H,m), 4.09, 3.76(each 1H,d,J=15.5Hz), 3.66(1H,s), 3.57(1H,br s), 2.21(3H,s). IR(KBr): 3307(OH). MS(m/z)(M^+): Calcd for $C_{22}H_{21}NO$: 315.1623. Found:315.1646. Anal. Calcd for $C_{22}H_{21}NO$:C,83.77;H,6.71; N,4.44. Found:C,83.51;H,6.72;N,4.41.

With BuLi: Reaction of **2e**(6.472 g, 14.7 mmol) in dry THF(15 ml) with BuLi(1.6 M sol. in hexane, 14.7 ml, 23.5 mmol) gave pale brown crystals. This was purified in the same way as above gave **1e** as pale yellow crystals(2.641 g, 57%).

Resolution of (±)-2,3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(**1b**)

(±)-**1b**(40 mg) was submitted to semipreparative HPLC with a hexane-2-propanol(100:1) mixture at a flow rate of 4 ml/min and detected at 220 nm to give two fractions. The first fraction at 10.7 min retention time afforded the (+) enantiomer as a white solid (13.4 mg), mp 115-116°C. $[\alpha]_D^{23}$ +15.7°(c 0.21, MeOH), CD(c 0.00108, MeOH) $[\theta]^{23}$ (nm) 0(233), -33000(222), 0(214), +21100(207).

The second fraction at retention time 13.5 min gave the (-) enantiomer as a white solid(16.8 mg), mp 114-115°C. $[\alpha]_D^{23}$ -16.7°(c 0.21,MeOH), CD(c 0.00102, MeOH) $[\theta]^{23}$ (nm) 0(233), +34600(222), 0(214), -22100(207).

Resolution of (±)-2-Methyl-3,4-diphenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(**1e**)

(±)-**1e**(100 mg) was submitted to semipreparative HPLC with a hexane-2-propanol(15:1) mixture at a flow rate of 4 ml/min to give two fractions. The first fraction at 8.5 min retention time afforded the (+) enantiomer as a white solid(44.6 mg), mp 117-118°C. $[\alpha]_D^{20}$ +11.5°(c 1.05, MeOH), CD(c 0.00102, MeOH) $[\theta]^{20}$ (nm) 0(234), -17700(224), 0(220), +25700 (207).

The second fraction at retention time 16.8 min gave the (-) enantiomer as a white solid(44.1 mg), mp 117°C. $[\alpha]_D^{20}$ -11.5°(c 1.05, MeOH), CD(c 0.00108, MeOH) $[\theta]^{20}$ (nm) 0(234), +17700(224), 0(220), -25700(207).

^{1}H-NMR spectra of the optically active **1b** and **1e** resolved as above were identical with those of the racemic **1b** and **1e**, respectively.

REFERENCES AND NOTES

1. Ishida.Y.; Koga,N.; Nanbu,T.; Kihara,M.; Kobayashi.S. Br.J.Pharmacol. **1988**,94,19-26.
2. Kihara,M.; Kashimoto,M.; Kobayashi,S.; Ishida,Y.; Moritoki,H.; Taira,Z. J.Med.Chem. **1990**,33,2283-2286.
3. Salman,M.; Ray,S.; Anand,N.; Agarwal,A.K.; Singh,M.M.; Setty,B.S.; Kamboj,V.P. J.Med.Chem. **1986**,29,1801-1803.
4. a) Kihara,M.; Nakanishi,A.; Kobayashi,S. Heterocycles **1989**,29,957-965; b) Kihara,M.; Ishida,Y.; Kobayashi,S. J.Chem.Research(S) **1987**,236-237.
5. a) Kihara,M.; Kashimoto,M.; Kobayashi,Y. Tetrahedron **1992**,48,67-78; b) Kihara,M.; Kashimoto,M.; Kobayashi,Y.; Kobayashi,S. Tetrahedron Lett. **1990**,31,5347-5348.
6. Kajigaeshi,S.; Kakinami,T.; Tokiyama,H.; Hirakawa,T.; Okamoto,T. Bull.Chem.Soc.Jpn. **1987**,60,2667-2668.
7. Trans means the stereochemical correlation between the substituent at C3 and the 4-phenyl group.
8. The boat conformers of **1b-e** are excluded from further consideration since it was apparent that the boat conformers of 1- and 4-phenyl-1,2,3,4-tetrahydroisoquinolines were not stable(ref. 9).
9. Charifson,P.S.; Bowen,J.P.; Wyrick,S.D.; Hoffman,A.J.; Cory,M.; McPhail,A.T.; Mailman,R.B. J.Med.Chem. **1989**,32,2050-2058.
10. Examinations of NA potentiating activities of the isoquinolin-4-ols(**1b-e**) and the optically active **1b** and **1e** are in progress.
11. Camilleri,P.; Dyke,C.A.; Paknoham,S.J.; Senior,L.A. J.Chromatogr. **1990**,498,414-416.
12. Harada,N.; Nakanishi,K. Acc.Chem.Res. **1972**,5,257-263.
13. Harada,N.; Sato,H.; Nakanishi,K. J.Chem.Soc.,Chem.Commun. **1970**,1691-1693.