Syntheses of Apogalanthamine Analogs as α-Adrenergic Blocking Agents. IX [1]. Syntheses of Optically Active 8-Hydroxy-6-methyl-5,6,7,8-tetrahydrodibenz[c,e]azocines

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(8*R*)- and (8*S*)-Hydroxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocines (*R*- and *S*-**1**) were synthesized by oxidative kinetic resolution of *N*-(2-iodobenzyl)-β-(2-iodophenyl)ethanolamine (**8**), followed by cyclization of the optically active acetates (*R*- and *S*-**6**) of *R*- and *S*-**8** with zero-valent nickel to (8*R*)- and (8*S*)-acetoxyazocines (*R*- and *S*-**7**), and by hydrolysis of the acetates (**R**- and *S*-**7**).

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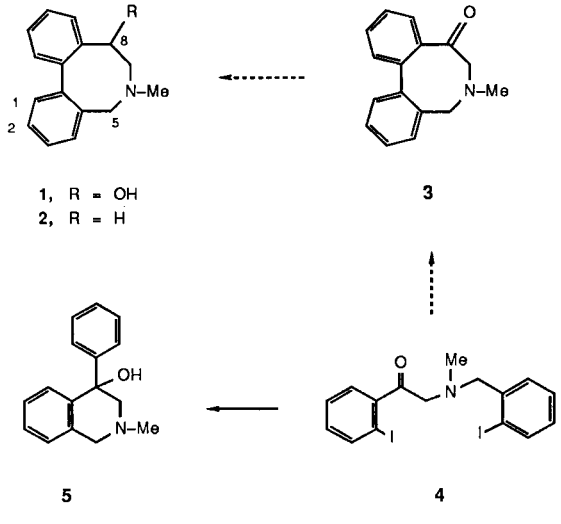
Previously we reported the syntheses of apogalanthamine analogs, 5,6,7,8-tetrahydrodibenz[*c,e*]azocine derivatives, as α-adrenergic blocking agents [2] by cyclization [3] of biphenyl derivatives and by photochemical cyclization [4] of halogeno-*N*-benzyl-β-phenethylamine derivatives.

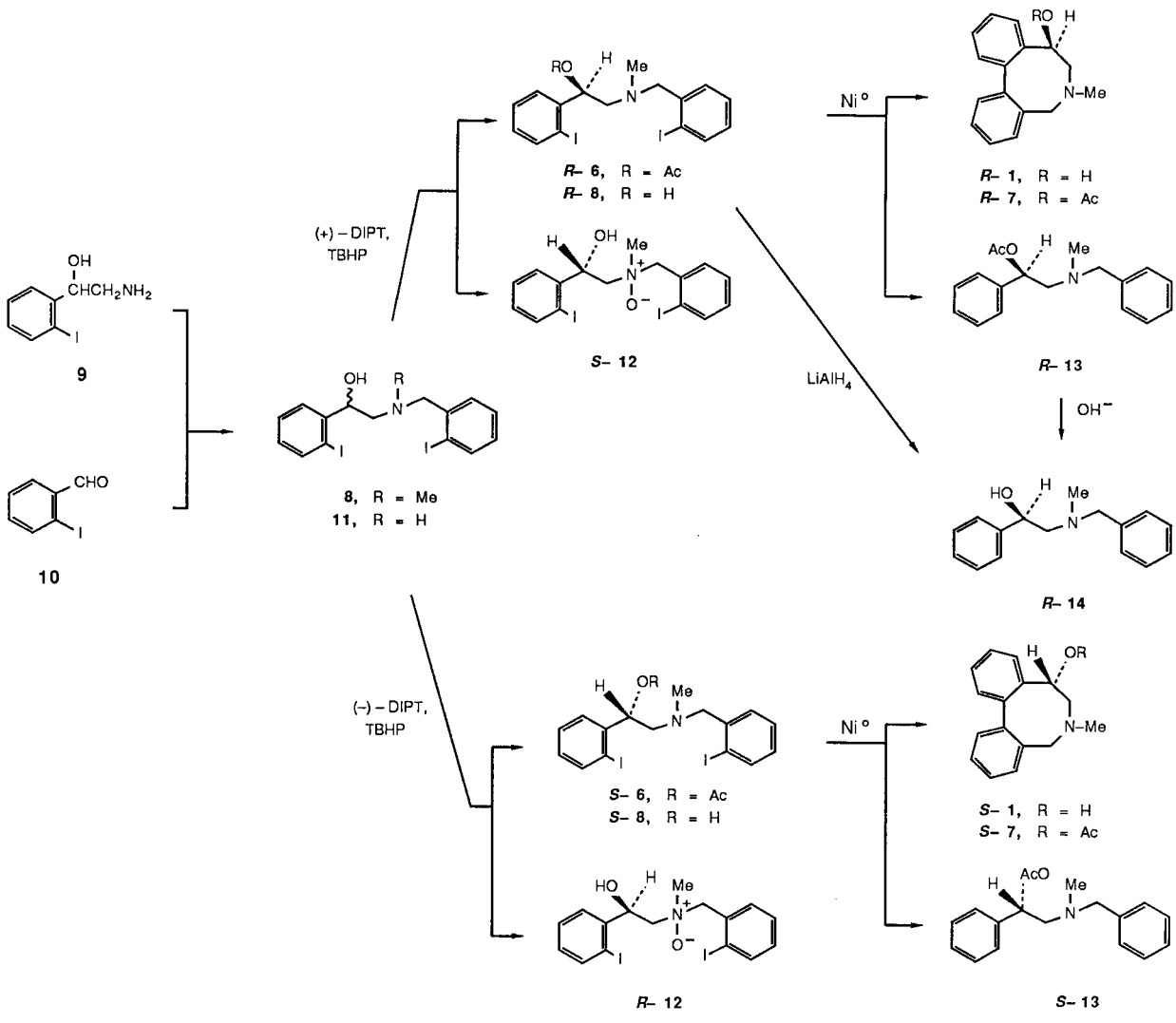
8-Hydroxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (**1**) was interesting from the pharmacological point of view, since a 6-methylazocine derivative **2** was found to have α_1-selective blocking activity [5] and the 8-hydroxyazocine derivative **1** has a partial structure of β-phenylethanolamine [6]. Recently, we reported [1] that an attempt to prepare a carbonyl analog **3** as a precursor of **1** by cyclization of *N*-(2-iodobenzyl)-*N*-methyl-2-iodophenacylamine (**4**) with zero-valent nickel was unsuccessful. But unexpectedly, we found that the resulting product was a tetrahydroisoquinolin-4-ol **5**, a new potentiator of noradrenaline [7] (Scheme 1). This paper describes the syntheses of optically active 8-hydroxyazocines (*R*- and *S*-**1**) by cyclization of (*R*)- and (*S*)-β-phenylethanolamine acetates (*R*- and *S*-**6**) with zero-valent nickel, followed by hydrolysis of the 8-acetoxyazocine derivatives (*R*- and *S*-**7**) shown in Scheme 2.

Scheme 1



First, we tried to synthesize the racemic 8-hydroxyazocine **1** *via* a key intermediate, a racemic *N*-benzyl-β-phenylethanolamine **8**. The amine **8** was prepared by condensation of a β-phenylethanolamine **9** with *o*-iodobenzaldehyde (**10**), followed by *N*-methylation of the resulting secondary amine **11**. The racemic acetate **6** prepared by acetylation of **8** was treated with zero-valent nickel generated *in situ* [8] to give the racemic 8-acetoxyazocine **7** in 84% yield. Hydrolysis of **7** with 7% aqueous potassium carbonate-ethanol afforded the racemic 8-hydroxyazocine **1** in 77% yield. On the basis of these results, the optically active 8-hydroxyazocines (*R*- and *S*-**1**) were synthesized as follows. The racemic **8** was kinetically resolved by use of *t*-butyl hydroperoxide and a titanium-(+)-tartrate complex [9] to give the (*R*)-ethanolamine *R*-**8** ($[\alpha]_D$ −89.6°, 15% yield) along with (*S*)-*N*-oxide *S*-**12** ($[\alpha]_D$ +16.2°, 79% yield). The configuration of the benzylic carbon atom in the amine *R*-**8** was confirmed by the fact that lithium aluminium hydride reduction of *R*-**8** gave a known (*R*)-ethanolamine *R*-**14** ($[\alpha]_D$ −25.8°) [9]. The (*S*)-*N*-oxide *S*-**12** was reduced with sulfur dioxide in methanol to an optically impure (*S*)-ethanolamine *S*-**8** ($[\alpha]_D$ +17.9°), which was purified with *t*-butyl hydroperoxide and a titanium-(-)-tartrate complex to afford the (*S*)-ethanolamine *S*-**8** ($[\alpha]_D$ +105.8°, 26% yield). Acetylation of *R*- and *S*-**8** gave the acetates (*R*- and *S*-**6**). The enantiomeric excesses (76.8 and 83.8% ee) of *R*- and *S*-**6** were determined by their ^{1}H nmr analysis using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europeium(III) as a chiral shift reagent [9]. The acetates *R*- and *S*-**6** were treated with zero-valent nickel to give the 8-acetoxyazocines *R*- and *S*-**7** in 80 and 65% yields, respectively, along with deiodinated by-products *R*- and *S*-**13**. The former by-product was found to be *R*-**13**, since it was hydrolyzed to give the known ethanolamine *R*-**14** described above. Hydrolysis of the 8-acetoxyazocines *R*- and *S*-**7** afforded the optically active 8-hydroxyazocines *R*- and *S*-**1** ($[\alpha]_D$ +5.6° and $[\alpha]_D$ −6.0°) in 65 and 67% yields. The structures of these compounds *R*- and *S*- were confirmed by their physical and spectral data (see Experimental). The ir and ^{1}H nmr spec-

Scheme 2



tra of *R*-**1** were identical with those of *S*- and racemic **1**. The ORD curve of *R*-**1** having a negative Cotton effect was similar to that of *R*-**7**. This result and the *R*-configuration of the deiodinated acetate *R*-**13** showed that the *R*-configuration at the benzylic carbon atom in *R*-**1** was not changed during the conversion of *R*-**8** to *R*-**1**. This conclusion was supported by the fact that the ORD curves of (*R*)-series compounds, *R*-**8**, *R*-**6**, *R*-**13**, and *R*-**7** and *R*-**1** were antipodal to those of the corresponding (*S*)-series compounds.

The α-adrenergic blocking activities of these azocine derivatives *R*- and *S*-**1** will be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. The spectrophotometers used were a Hitachi IR-215 for ir spectra(in potassium bromide unless otherwise indicated), a JEOL JMS-D 300 for mass spectra(ms), a Union PM-201 for optical rotations, a JASCO ORD/UV-5 spectrometer for optical rotatoray dispersion(ORD) and a JEOL-PS-100 or a JEOL JNM FX-200 for ^{1}H nmr spectra (in deuteriochloroform) with tetramethylsilane (TMS) as an internal standard. The plates used for preparative tlc were coated with silica gel (Kieselgel, PF_{254} Merck). The following solvent systems were used: 1) chloroform-methanol (50:1), 2) chloroform-methanol (10:1).

β-(2-Iodophenyl)ethanolamine (**9**).

According to the method of Anhoury *et al.* [10], the ethanolamine **9** was prepared. To a solution of **10** (5.00 g) in 2*M*-sodium hydrogen sulfite solution (50 ml) was added a solution of potassium cyanide (5.6 g) in water (11 ml) under ice-cooling. The mixture was stirred for 5 minutes. Work-up in the usual way gave 2-iodobenzaldehyde cyanohydrin as colorless needles (5.20 g, 93%), mp 92-93.5° from ether-petroleum ether; ir: 3400 (OH), 2250 cm^{-1} (CN); ^{1}H nmr: δ 7.89-6.87 (4H, m, ArH), 5.70 (1H, s, CH).

Anal. Calcd. for C_8H_6INO: C, 37.09; H, 2.34; N, 5.41. Found: C, 37.41; H, 2.16; N, 5.42.

A solution of the cyanohydrin (3.35 g) thus obtained in anhydrous tetrahydrofuran (15 ml) was slowly added to 1*M*-diborane in tetrahydrofuran (26 ml) and the mixture was refluxed for 1.5 hours. The mixture

was kept overnight at room temperature and then ethanol (8.4 ml) was added under ice-cooling. A stream of hydrogen chloride was passed through the mixture to give a precipitate. Recrystallization of the precipitate from methanol gave the hydrochloride of **9** as colorless plates (2.95 g, 81%), mp 244-247° dec; ir: 3100-2700 cm^{-1} ($^+NH_3$); ^1H nmr (free base): δ 7.70 (1H, d, J = 8 Hz, H-3'), 4.74 (1H, dd, J = 8 and 4 Hz, H-β), 3.00 (1H, dd, J = 12 and 4 Hz, H-α), 2.58 (1H, dd, J = 12 and 8 Hz, H-α), 2.36 (3H, brs, NH_2 and OH).

Anal. Calcd. for $C_6H_{10}INO \cdot HCl$: C, 32.07; H, 3.70; N, 4.68. Found: C, 32.25; H, 3.57; N, 4.70.

N-(2-Iodobenzyl)-β-(2-iodophenyl)ethanolamine (**11**).

A mixture of the hydrochloride (2.00 g) of **9**, the benzaldehyde **10** (1.70 g) and sodium hydrogen carbonate (2.01 g) in ethanol (200 ml) was refluxed under nitrogen for 2 hours. To this mixture was gradually added sodium borohydride (2.04 g) under ice-cooling. The mixture was refluxed for 2 hours. Work-up in the usual way gave colorless needles (2.57 g, 80%) of **11**, mp 137.5-139° from benzene; ir: 3260 cm^{-1} (NH); ^1H nmr: δ 7.85 and 7.77 (each 1H, d, J = 8 Hz, H-3 and H-3'), 4.91 (1H, dd, J = 8 and 3 Hz, H-β), 3.90 (2H, s, $ArCH_2N$), 3.08 (1H, dd, J = 12 and 3 Hz, H-α), 2.55 (1H, dd, J = 12 and 8 Hz, H-α), 2.49 (2H, brs, NH and OH).

Anal. Calcd. for $C_{15}H_{15}I_2NO$: C, 37.59; H, 3.16; N, 2.92. Found: C, 37.89; H, 2.99; N, 2.96.

Racemic *N*-(Iodobenzyl)-*N*-methyl-β-(2-iodophenyl)ethanolamine (**8**).

A mixture of **11** (106.8 mg), boric acid (90 mg) and formalin (0.8 ml) in methanol (16 ml) was stirred for 5 minutes at room temperature. Sodium borohydride (90 mg) was added, and the mixture was stirred for 30 minutes. Work-up in the usual way gave a crude oil (111.8 mg). The oil was subjected to preparative tlc (benzene, three developments) to give two fractions (Rf 0.43-0.54 and Rf 0.64-0.72). The former fraction gave **8** as an oil (53.0 mg, 48%); ^1H nmr: δ 7.89 and 7.78 (each 1H, dd, J = 8 and 2 Hz, H-3 and H-3'), 4.96 (1H, dd, J = 11 and 3 Hz, H-β), 3.58 and 3.78 (each 1H, d, J = 13 Hz, AB-type of $ArCH_2N$), 3.00 (1H, brs, OH), 2.81 (1H, dd, J = 12 and 3 Hz, CH-α), 2.35 (1H, dd, J = 12 and 11 Hz, CH-α), 2.39 (3H, s, NCH_3); ms: m/z M-1, 491.9326. $C_{16}H_{16}I_2NO$ requires M-1, 491.9326.

Anal. Calcd. for $C_{16}H_{17}I_2NO$: C, 38.97; H, 3.48; N, 2.84. Found: C, 39.36; H, 3.49; N, 2.77.

The latter fraction gave 3-(2''-iodobenzyl)-5-(2'-iodophenyl)oxazolidine as an oil (25.1 mg, 23%); ^1H nmr: δ 7.69 (2H, dd, J = 8 and 3 Hz, H-3' and H-3''), 5.08 (1H, t, J = 7 Hz, H-5), 4.57 (2H, s, CH_2-2), 3.80 (2H, s, $ArCH_2N$), 3.68 and 2.66 (each 1H, dd, J = 11 and 7 Hz, CH_2-4); ms: m/z, M^+, 490.9276. $C_{16}H_{15}I_2NO$ requires M^+, 490.9246.

Anal. Calcd. for $C_{16}H_{15}I_2NO$: C, 39.13; H, 3.08; N, 2.85. Found: C, 39.50; H, 3.23; N, 2.68.

Oxidative Kinetic Resolution of Racemic **8** to (*R*)-*N*-(2-Iodobenzyl)-*N*-methyl-β-(2-iodophenyl)ethanolamine (*R*-**8**).

(+)-Diisopropyl tartrate (224.6 mg, 0.96 mmole) was placed in a two neck flask fitted with a septum cap and the flask was flushed with nitrogen. A solution of racemic **8** (385.7 mg, 0.78 mmole) in dry methylene chloride (5 ml) and titanium tetraisopropoxide (0.49 ml, 468 ml, 1.65 mmoles) were added by syringe and the mixture was stirred at room temperature for 30 minutes. To the solution was added 3*M*-*t*-butyl hydroperoxide in toluene (0.16 ml, 0.48 mmole) at −24°. The mixture was stirred for 2 hours in a cooling bath. Ether (8 ml), water (0.4 ml) and 40% aqueous sodium hydroxide (0.4 ml) were added. The mixture was vigorously stirred at room temperature for 19.5 hours and then was filtered through a pad of Celite and washed with methylene chloride (100 ml). The combined filtrate was concentrated to give an oily residue, which was azeotropically dried with benzene to leave a yellow oil (386 mg). This was subjected to preparative tlc (solvent 1) to give two fractions (Rf 0.71-0.77 and Rf 0.07-0.16). The former fraction gave *R*-**8** as an oil (58.9 mg, 15%), $[\alpha]_D^{20}$ −89.6° (c = 2.95, chloroform); ORD (c = 0.015, ethanol): M^{20} (nm), −1920° (300), −6800° (260), −15450° (240), −24030° (230).

Anal. Calcd. for $C_{16}H_{17}I_2NO$: C, 38.97; H, 3.48; N, 2.84. Found: C, 39.33; H, 3.40; N, 2.81.

The latter fraction gave optically impure (*S*)-*N*-oxide *S*-**12** as amorphous material (291.7 mg, 79%); $[\alpha]_D^{20}$ +16.2° (c = 2.29, ethanol); ^1H nmr: 5.49 (1H, dd, J = 10 and 1.5 Hz, H-β), 4.60 (2H, s, $ArCH_2N$), 3.60 (1H, dd, J = 12.5 and 1.5 Hz, H-α), 3.37 (3H, s, NCH_3), 2.98 (1H, dd, J = 12.5 and 10 Hz, H-α); ms: m/z, M+1, 509.9503. $C_{16}H_{18}I_2NO_2$ requires M+1, 509.9453.

Anal. Calcd. for $C_{16}H_{17}I_2NO_2 \cdot 1/2H_2O$: C, 37.09; H, 3.50; N, 2.70. Found: C, 37.35; H, 3.44; N, 2.75.

(*R*)-*N*-Benzyl-*N*-methyl-β-phenylethanolamine (*R*-**14**).

i) By Reduction of *R*-**8** with Lithium Aluminum Hydride.

To a suspension of lithium aluminum hydride (250 mg) in dry ether (5 ml) was added a solution of *R*-**8** (39.1 mg) in dry ether (2 ml) and the mixture was stirred for 2 hours. Ether (50 ml) and 10% aqueous potassium hydroxide (1 ml) were added and the mixture was filtered. The filtrate was washed with water, dried and evaporated to give a deiodinated ethanolamine (*R*-**14**) [9] as a colorless oil (6.8 mg); $[\alpha]_D^{20}$ −25.8° (c = 0.34, ethanol) [lit [9] $[\alpha]_D$ −41.0° (c = 2.19, ethanol)]; ^1H nmr: δ 7.32 (10H, m, ArH), 4.74 (1H, dd, J = 8.5 and 5 Hz, H-β), 3.77 and 3.44 (each 1H, d, J = 13.5 Hz, AB-type of $ArCH_2N$), 2.65 (1H, dd, J = 14.5 and 8.5 Hz, H-α), 2.49 (1H, dd, J = 14.5 and 5 Hz, H-α), 2.33 (3H, s, NCH_3); ORD (c = 0.0051, ethanol): M^{20}(nm), −940° (300), −2830°(260), −5670° (240), −8500° (230).

ii) By Hydrolysis of the Acetate (*R*-**13**).

A mixture of *R*-**13** (6.0 mg), which was obtained by treatment of *R*-**6** with zero-valent nickel as described below, 7% aqueous potassium carbonate (0.5 ml) and ethanol (0.5 ml) was stirred for 38 hours at room temperature. Work-up in the usual way gave the ethanolamine (*R*-**14**) as an oil (5.1 mg); $[\alpha]_D^{20}$ −31.4° (c = 0.26, ethanol). The ^1H nmr spectra of *R*-**14** obtained by methods i) and ii) were identical.

Reduction of *N*-Oxide (*S*-**12**) with Sulfur Dioxide.

Sulfur dioxide was passed through a solution of the *N*-oxide (*S*-**12**) (291 mg) obtained above in methanol (15 ml) under stirring for 10 minutes. The mixture was kept at room temperature for 30 minutes and the solvent was evaporated. The oily residue (245 mg) was purified by preparative tlc (solvent 2) to give *S*-**8** as an oil (211 mg); $[\alpha]_D^{20}$ +17.9° (c = 2.40, chloroform).

(*S*)-*N*-(2-Iodobenzyl)-*N*-methyl-β-(2-iodophenyl)ethanolamine (*S*-**8**).

The optically impure *S*-**8** (190 mg, 0.385 mmole) obtained above was treated with (-)-diisopropyl tartrate (108 mg, 0.463 mmole), titanium tetraisopropoxide (0.240 mg, 0.808 mmole) and *t*-butyl hydroperoxide (0.070 ml, 0.212 mmole) in methylene chloride (4 ml) in the same way as *R*-**8**. The oily product (213 mg) was subjected to preparative tlc (solvent 2) to give *S*-**8** as an oil (49.8 mg, 26%, from the fraction of Rf 0.87-0.96); $[\alpha]_D^{20}$ +105.8° (c = 2.07, chloroform); ORD (c = 0.012, ethanol): M^{20}(nm), +2510° (300), +8380° (260), +20950° (240), +38550° (230).

Anal. Calcd. for $C_{16}H_{17}I_2NO$: C, 38.97; H, 3.48; N, 2.84. Found: C, 39.32; H, 3.60; N, 2.73.

The fraction of Rf 0.52-0.58 gave (*R*)-*N*-oxide (*R*-**12**) as amorphous material (126.6 mg, 65%); $[\alpha]_D^{20}$ −12.3° (c = 3.17, chloroform).

Anal. Calcd. for $C_{16}H_{17}I_2NO_2$: C, 37.74; H, 3.37; N, 2.75. Found: C, 38.10; H, 3.20; N, 2.96.

The ^1H nmr spectra of these compounds *S*-**8** and *R*-**12** were identical with those of *R*- and racemic **8**, and *S*-**12**.

Racemic *O*-Acetyl-*N*-(2-iodobenzyl)-*N*-methyl-β-(2-iodophenyl)ethanolamine (**6**).

A mixture of **8** (208.8 mg), pyridine (8 ml) and acetic anhydride (8 ml) was stirred for 2 days at room temperature. The mixture was concentrated *in vacuo* and the chloroform extract of the residue was washed with water, dried and evaporated to give **6** as an oil (221 mg, 98%); ir

(neat): 1740 cm^{-1} (C=O); ^1H nmr: δ 7.80 (2H, d, J = 8 Hz, H-3 and H-3'), 6.19 (1H, dd, J = 8 and 4 Hz, H-β), 3.74 and 3.52 (each 1H, d, J = 14 Hz, AB-type of $ArCH_2N$), 2.82 (1H, dd, J = 14 and 8 Hz, H-α), 2.68 (1H, dd, J = 14 and 4 Hz, H-α), 2.48 (3H, s, NCH_3), 2.06 (3H, s, $OCOCH_3$); ms: m/z M^+, 534.9510. $C_{18}H_{19}I_2NO$ requires M^+, 534.9510.

Anal. Calcd. for $C_{18}H_{19}I_2NO_2$: C, 40.39; H, 3.58; N, 2.62. Found: C, 40.38; H, 3.70; N, 2.73.

(*R*)-*O*-Acetyl-*N*-(2-iodobenzyl)-*N*-methyl-β-(2-iodophenyl)ethanolamine (*R*-**6**).

The ethanolamine *R*-**8** (155.2 mg) was acetylated in the same way as racemic **8** to give *R*-**6** as an oil (127.1 mg, 76%); $[\alpha]_D^{20}$ −39.6° (c = 2.05, ethanol); ORD (c = 0.0026, ethanol): M^{20}(nm), −2060° (300), −5140° (260), −11180° (240), −15250° (230).

Anal. Calcd. for $C_{18}H_{19}I_2NO_2$: C, 40.39; H, 3.58; N, 2.62. Found: C, 40.75; H, 3.79; N, 2.55.

(*R*)-*O*-Acetyl-*N*-(2-iodobenzyl)-*N*-methyl-β-(2-iodophenyl)ethanolamine (*S*-**6**).

The ethanolamine *S*-**8** (165 mg) was acetylated in the same way as racemic **8** to give *S*-**6** as an oil (150 mg, 84%); $[\alpha]_D^{28}$ +49.1° (c = 2.05, ethanol); ORD (c = 0.018, ethanol): M^{28}(nm), +1500° (300), +4800° (270), +11390° (240), +16780° (230).

Anal. Calcd. for $C_{18}H_{19}I_2NO_2$: C, 40.39; H, 3.58; N, 2.62. Found: C, 40.49; H, 3.56; N, 2.61.

The ^1H nmr spectra of *R*- and *S*-**6** were identical with that of the racemic **6**.

Racemic 8-Acetoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (**7**).

Triphenylphosphine (724.6 mg, 2.77 mmoles), triphenylphosphine-nickel dichloride (904.2 mg, 1.38 mmoles), zinc powder (91.3 mg, 1.38 mmoles) and potassium iodide (237.2 mg, 1.43 mmoles) were placed to a two neck flask. The flask was evacuated and filled with nitrogen. Dry, oxygen-free dimethylformamide (14 ml) was added by syringe. The mixture was stirred at 55° for 30 minutes to give a red-brown solution of zero-valent nickel a solution of racemic **6** (335.9 mg, 0.63 mmole) in dry, oxygen free dimethylformamide (1.4 ml) was added to the mixture and stirred at 55° for 9.5 hours. Then, 2% hydrochloric acid (80 ml) was added and the aqueous layer was washed with ether. The aqueous layer was made basic with sodium carbonate and extracted with chloroform. The extract was washed with water, dried and evaporated *in vacuo* to give an oil (203 mg). This was subjected to preparative tlc (solvent 1). The fraction of Rf 0.20-0.35 gave racemic **7** as an oil (148.7 mg, 84%); ir (neat): 1740 cm^{-1} (C=O); ^1H nmr: δ 5.42 (1H, dd, J = 8 and 2 Hz, H-8), 3.68 and 3.22 (each 1H, d, J = 14 Hz, AB-type of CH_2-5), 3.15 (1H, dd, J = 13 and 2 Hz, H-7), 2.95 (1H, dd, J = 13 and 8 Hz, H-7), 2.48 (3H, s, NCH_3), 2.02 (3H, s, $OCOCH_3$); ms: m/z M^+, 281.1400. $C_{18}H_{19}NO_2$ requires M^+, 281.1413.

Anal. Calcd for $C_{18}H_{19}NO_2 \cdot 1/4\ H_2O$: C, 75.63; H, 6.87; N, 4.90. Found: C, 75.99; H, 6.99; N, 4.53.

The fraction of Rf 0.40-0.46 gave racemic **13** as an oil (30 mg, 17%); ir (neat): 1740 cm^{-1} (C=O); ^1H nmr: δ 7.24-7.30 (10H, m, ArH), 5.95 (1H, dd, J = 8 and 5 Hz, H-β), 3.56 (2H, s, $ArCH_2N$), 2.96 (1H, dd, J = 13.5 and 8 Hz, H-α), 2.62 (1H, dd, J = 13.5 and 5 Hz, H-α), 2.30 (3H, s, NCH_3), 2.08 (3H, s, $OCOCH_3$); ms: m/z M-1, 282.1483. $C_{18}H_{20}NO_2$ requires M-1, 282.1491.

Anal. Calcd. for $C_{18}H_{21}NO_2 \cdot 1/4\ H_2O$: C, 75.10; H, 7.53; N, 4.87. Found: C, 75.23; H, 7.52; N, 4.56.

(8*R*)-Acetoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (*R*-**7**).

The acetate *R*-**6** (116.8 mg) was treated with zero-valent nickel in the same way as racemic **6** to give a crude product (98.1 mg). This was subjected to preparative tlc (solvent 1). The fraction of Rf 0.16-0.35 gave *R*-**7** as an oil (48.6 mg, 80%); $[\alpha]_D^{20}$ −4.9° (c = 2.43, ethanol); ORD (c = 0.00085, ethanol): M^{20} (nm), −6630° (300), −13260° (270), −31500° (260), −71290° (252) (trough), 0° (238), +46420° (232) (peak), +33160° (228).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.45; H, 6.55; N, 4.67.

The fraction of Rf 0.42-0.52 gave the deiodinated acetate *R*-**13** as an oil (6.9 mg, 11%); $[\alpha]_D^{20}$ −87.0° (c = 0.35, ethanol); ORD (c = 0.0032, ethanol): M^{20} (nm), −590° (300), −1580° (260), −5310° (240), −9800° (230). This compound *R*-**13** was hydrolyzed to *R*-**14** described above.

(8*S*)-Acetoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (*S*-**7**).

The acetate *S*-**6** (106.7 mg) was treated with zero-valent nickel in the same way as racemic **6** to give a crude product (56.6 mg). This was subjected to preparative tlc (solvent 1) to give two fractions (Rf 0.17-0.27 and Rf 0.40-0.51). The former fraction gave *S*-**7** as an oil (36.5 mg, 65%); $[\alpha]_D^{28}$ +9.3° (c = 1.72, ethanol); ORD (c = 0.0023, ethanol): M^{28} (nm), +7250° (300), +16310° (270), +29000° (260), +50750° (252) (peak), 0° (238), −29000° (230) (trough), −19940° (225).

Anal. Calcd. for $C_{18}H_{19}NO_2 \cdot 1/4\ H_2O$: C, 75.63; H, 6.87; N, 4.90. Found: C, 75.97; H, 6.84; N, 4.53.

The latter fraction gave *S*-**13** as an oil (7.0 mg, 13%); $[\alpha]_D^{28}$ +76.3° (c = 0.41, ethanol); ORD (c = 0.018, ethanol): M^{28} (nm), +1420° (300), +2690° (260), +4920° (240), +8890° (230).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.62; H, 7.77; N, 4.86.

The ^1H nmr spectra of *S*-**7** and *S*-**13** were identical with those of *R*- and racemic **7**, and **13**.

Racemic 8-Hydroxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (**1**).

A mixture of racemic **7** (70.9 mg), 7% aqueous potassium carbonate (5 ml) and ethanol (5 ml) was stirred at room temperature for 26.5 hours. To the mixture was added water (50 ml) and the solvent was evaporated. The residue was extracted with chloroform. The extract was washed with water, dried and evaporated to give crude crystals (53.7 mg). These were recrystallized from chloroform to give racemic **1** as colorless needles (46.4 mg, 77%), mp 134-135.5°; ir: 3100 cm^{-1} (OH); ^1H nmr: δ 7.68 (1H, dd, J = 8 and 2 Hz, H-9), 4.35 (1H, dd, J = 9 and 1 Hz, H-8), 3.50 and 3.01 (each 1H, d, J = 14 Hz, AB-type of CH_2-5), 3.01 (1H, dd, J = 12 and 1 Hz, H-7), 2.66 (1H, dd, J = 12 and 9 Hz, H-7), 2.49 (1H, brs, OH), 2.41 (3H, s, NCH_3); ms: m/z M^+, 239.1295. $C_{16}H_{17}NO$ requires M^+, 239.1308.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.01; H, 7.14; N, 5.60.

(8*R*)-Hydroxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (*R*-**1**).

The acetate *R*-**7** (40 mg) was hydrolyzed in the same way as racemic **7** to give *R*-**1** as colorless needles (22.1 mg, 65%), mp 112-114° (from chloroform-ether); $[\alpha]_D^{20}$ + 5.6° (c = 0.71, ethanol); ORD (c = 0.0015, ethanol); M^{20} (nm), −3110° (300), −9320° (280), −35730° (260), −62140° (250) (trough), 0° (237), +55930° (229) (peak), +40390° (222).

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 79.91; H, 7.15; N, 5.45.

(8*S*)-Hydroxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (*S*-**1**).

The acetate *S*-**7** (31 mg) was hydrolyzed in the same way as racemic **7** to give *S*-**1** as colorless prisms (17.7 mg, 67%), mp 114-116° (from ether-petroleum ether); $[\alpha]_D^{28}$ −6.0° (c = 0.67, ethanol); ORD (c = 0.023, ethanol): M^{28} (nm), +4110° (300), +14420° (270), +30420° (260), +44190° (250) (peak), 0° (237), −37000° (230) (trough), −10280° (228).

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 79.95; H, 7.14; N, 5.82.

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