Table II. Activities of Dimethylaniline (DMA) N-Demethylation, Aminopyrine (AM) N-Demethylation and Aniline (AN) Hydroxylation in Human Term Placenta

Measurement	Enzyme source		
	Whole homogenate		9000×*g* sup.
	(I)[a]	(II)[a]	(II)[a]
DMA N-demethylation (mμmole/g/30 min)	11.1	41.0	61.1
AM N-demethylation (mμmole/g/30 min)	33.5	51.3	53.9
AN hydroxylation (mμmole/g/30 min)	4.5	4.7	2.7

a) Numbers in parentheses represent sample No. employed.

reaction, whereas other drugs may undergo demethylation reaction at the placental membrane. Another explanation to account for the fact that significant aniline hydroxylase activity is detected in the fetal liver, is that aniline hydroxylase is inducible in the fetal livers and the other enzymes are not. But the authors could not examine this speculation that aniline hydroxylase is inducible in the fetal liver since there have been no practical methods to support this speculation. Moreover, it is well established that hydroxylation of 3,4-benzpyrene, which exhibits a type II difference spectrum, is measurable in human placenta, particularly if the pregnant female has been exposed to inducing agents such as tabacco.[11,13] Meigs, *et al.*[17] have reported the existence of cytochrome P-450 in human placenta, however, the authors could not find any cytochrome P-450 peak probably because the authors could not remove blood completely from the placental tissues. Further investigations are needed to resolve such questions described above.

Acknowledgement We wish to express our appreciation to Dr. Koshiro Itahashi, Kawasaki Seietsu Hospital, Chiba for kind offer of human term placentas and fetal livers.

17) R.A. Meigs and K.J. Ryan, *Biochim. Biophys. Acta*, **165**, 476 (1968).

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Stereochemical Studies. XXVIII.[1] Some Aspects of the Asymmetric Synthesis of (*R*)-(+)-4-Methyl-4-phenyl-2-cyclohexenone *via* an Enamine

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Previously, the authors reported the new asymmetric synthesis of (*R*)-(+)-4-methyl-4-phenyl-2-cyclohexenone ((*R*)-(+)-I) which featured the alkylation of the enamine (II) prepared from racemic 2-phenylpropanal (III) and L-proline derivative (IV) with methyl vinyl ketone, followed by hydrolysis and ring closure.[3]

1) Part XXVII: G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2130 (1973).
2) Location: *Hongo, Bunkyo-ku, Tokyo.*
3) *a*) S. Yamada and G. Otani, *Tetrahedron Letters*, **1969**, 4237; *b*) G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2112, 2119 (1973).

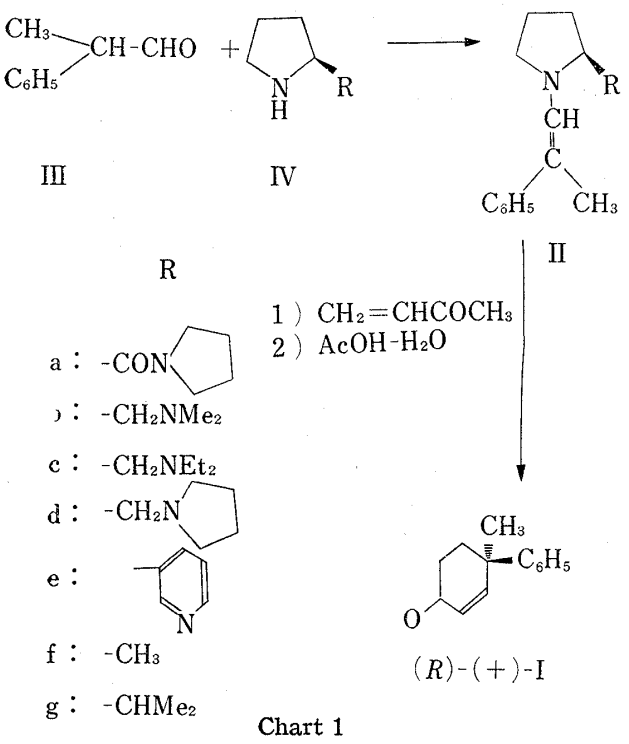

Chart 1

An unique versatility of this novel asymmetric synthesis was clearly established by a successful application to the total synthesis of (+)-mesembrine.[4] Owing to the original extensive studies,[3] it became obvious that the alkylation of L-proline pyrrolidide enamine (IIa) in anhyd. methanol or in a mixture of benzene–methanol (9: 1) afforded (*R*)-(+)-I with the highest asymmetric induction (36.5% or 49% optically pure) in moderate yields.

Aiming to find out more effective optically active pyrrolidine derivatives than L-proline pyrrolidide ((*S*)-(−)-IVa) which so far induced the highest asymmetric induction,[3] preparation of several optically active pyrrolidine derivatives (IVb—g) from L-proline other than those examined until now,[3] and application of these to the asymmetric synthesis were attempted.

Optically active pyrrolidines such as (*S*)-(+)-2-(dimethylamino)methylpyrrolidine ((*S*)-(+)-IVb),[5] (*S*)-(+)-2-(diethylamino)methylpyrrolidine ((*S*)-(+)-IVc) and (*S*)-(+)-2-(1-pyrrolidino)methylpyrrolidine((*S*)-(+)-IVd) were prepared by the reduction of the corresponding amides which were previously prepared from L-proline,[3] with lithium aluminium hydride. Free base of (*S*)-(−)-nornicotine ((*S*)-(−)-IVe) was obtained from its diperchlorate according to the usual manner. (*S*)-(−)-2-Methylpyrrolidine ((*S*)-(−)-IVf) was prepared from L-proline in a manner similar to that reported.[6] Preparation of (*S*)-(−)-2-isopropylpyrrolidine ((*S*)-(−)-IVg) was accomplished according to the reaction scheme shown in Chart 2. Treatment of benzyl 2-(1-hydroxy-1-methyl)ethylpyrrolidine-1-carboxylate (VI) prepared from N-benzyloxycarbonyl-L-proline ethyl ester (V) by Grignard reaction, with thionyl chloride,

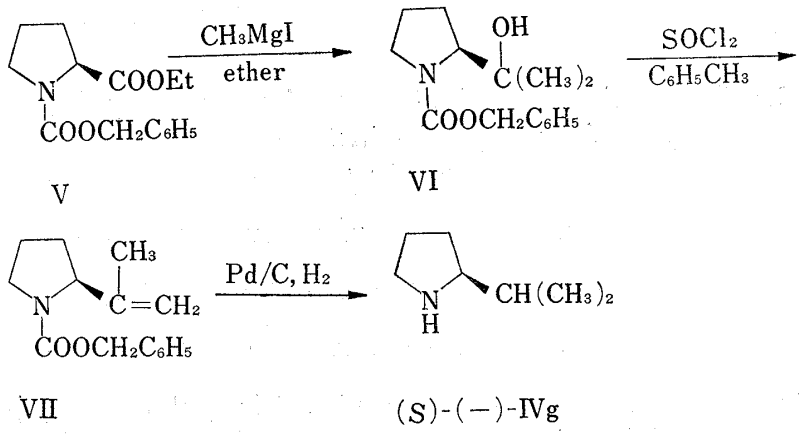

Chart 2

4) *a*) S. Yamada and G. Otani, *Tetrahedron Letters*, **1971**, 1133; *b*) G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2130 (1973).
5) I. Saito, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **18**, 1731 (1970).
6) *a*) P.G. Gassman and A. Fentiman, *J. Org. Chem.*, **32**, 2388 (1967); *b*) J.R. Piper and T.P. Johnston, *J. Org. Chem.*, **28**, 981 (1963); *c*) L.A. Paquette, J.P. Freeman, and S. Maiorana, *Tetrahedron*, **27**, 2599 (1971).

afforded benzyl 2-isopropenylpyrrolidine-1-carboxylate (VII), which was hydrogenated over 5% Pd on charcoal to give the desired (*S*)-(−)-2-isopropylpyrrolidine ((*S*)-(−)-IVg).

Reaction conditions for the enamine formation and the subsequent alkylation with methyl vinyl ketone, followed by acid-catalyzed hydrolysis and spontaneous ring closure, were identical with those already reported.[3] In all cases, (*R*)-(+)-I were obtained and were identified with the authentic sample[3] by comparing their spectral properties after purification.

Table I. Asymmetric Synthesis of (*R*)-(+)-4-Methyl-4-phenyl-2-cyclohexenone ((*R*)-(+)-I) using optically Active Pyrrolidines

Run	Pyrrolidines used for enamine formation	Reac. conditions for the alkylation			Formed (*R*)-(+)-4-methyl-4-phenyl-2-cyclohexenone ((*R*)-(+)-I)			
		Solvent	Temp. (°C)	Time (hr)	Yield[a] (%)	bp (°C)[b] (mmHg)	$[\alpha]_D^{20}$ [c] (*c*, EtOH)	Optical[d] yield
1	(*S*)-(+)-IVb	MeOH	15—20	20	55	119—120 (2)	+43.2° (0.866)	33
2	(*S*)-(+)-IVc	MeOH	15—20	20	54	124 (2—3)	+39.9° (1.234)	31
3	(*S*)-(+)-IVd	MeOH	15—20	20	82	125 (3)	+48.5° (1.116)	37
4	(*S*)-(+)-IVd	benzene–MeOH (9:1)	5	48	40	124 (3)	+58.5° (0.936)	45
5	(*S*)-(+)-IVd	toluene–MeOH (9:1)	−15	168	32	125 (3—4)	+66.5° (0.860)	51
6	(*S*)-(−)-IVe[e]	toluene–MeOH (9:1)	−15	168	28	126 (4)	+51.8° (0.736)	54
7	(*S*)-(−)-IVf	MeOH	15—20	20	29	125—126 (3—4)	+24.6° (0.456)	19
8	(*S*)-(−)-IVg	MeOH	15—20	20	27	120—122 (2—3)	+34.3° (0.426)	26

a) after purification by silica gel column chromatography
b) A sample purified by column chromatography was distilled.
c) Measured with a distilled sample.
d) (*R*)-(+)-I showing $[\alpha]_D^{20}$ +130° (EtOH)[3] was assumed to be 100% optically pure.
e) 75% optically pure

As shown in the Table, almost the same degrees of asymmetric induction as that achieved in the reaction with (*S*)-(−)-IVa (36.5% asymmetric induction) were observed in (*R*)-(+)-I prepared by the reactions of enemines (II), prepared using (*S*)-(+)-IVb, (*S*)-(+)-IVc and (*S*)-(+)-IVd, with methyl vinyl ketone in anhyd. methanol (see runs 1, 2 and 3). When (*S*)-(+)-IVd was employed as a pyrrolidine counterpart, the product yield of (*R*)-(+)-I was fairly increased as compared with that observed with (*S*)-(−)-IVa (48%). In the case of (*S*)-(+)-IVd, change of the reaction condition (lower temperature and less polar solvent) definitely improved the degree of the asymmetric induction by sacrificing the yield of (*R*)-(+)-I (see runs 3, 4 and 5). This was the same tendency as previously observed in the reaction with (*S*)-(−)-IVa.[3] Although the reaction with (*S*)-(−)-IVe at low temperature afforded (*R*)-(+)-I of the highest asymmetric induction among those observed until now, its product yield (28%) was clearly not enough for utilizing(*S*)-(−)-IVe for the preparative scale synthesis of (*R*)-(+)-I. On the other hand, when 2-alkylpyrrolidines such as (*S*)-(−)-2-methyl- and (*S*)-(−)-2-isopropylpyrrolidine (IVf, g) were employed as optically active pyrrolidines, chemical and optical yields for (*R*)-(+)-I were both decreased as compared with those observed for (*S*)-(+)-IVb, (*S*)-(+)-IVc and (*S*)-(+)-IVd. These results might be considered due to the decrease of steric bulkiness at the C_2-chiral center or the absence of tertiary amino group in the C_2-side chain. Further studies in order to improve the chemical and optical yields of (*R*)-(+)-I are still under progress.

Experimental[7]

Syntheses of optically Active Pyrrolidines

(*S*)-(+)-2-(Dimethylamino)methylpyrrolidine ((*S*)-(+)-IVb)——An anhyd. tetrahydrofuran solution (10 ml) of L-proline dimethylamide[3] (1.84 g, 0.013 mole) was gradually added to a stirred suspension of lithium aluminium hydride (0.74 g, 0.020 mole) in anhyd. tetrahydrofuran (20 ml) in an ice bath. After stirred under reflux for 18 hr, the whole reaction mixture was cooled in an ice bath, then was successively diluted with water (0.7 ml), 15% NaOH (0.7 ml) and water (1.5 ml).

The aqueous solution was refluxed for 0.5 hr after tetrahydrofuran (10 ml) was added. The whole was filtered after cooled, and dried over anhyd. K_2CO_3. Filtration and evaporation *in vacuo* gave an oily residue, which was purified by fractional distillation to give a pure (*S*)-(+)-IVb as a colorless oil (1.1 g, 69%), bp 90—95° (100 mmHg), $[\alpha]_D^{20°}$ +2.3° (*c*=4.24, EtOH) (Lit.,[5] $[\alpha]_D^{20°}$ +2.7° (*c*=0.817, EtOH)). IR ν_{max}^{cap} cm^{-1}: 3250 (NH). This infrared (IR) spectrum showed no absorption due to amide group. (*S*)-(+)-IVb thus obtained was further comfirmed as its dipicrate, mp 213—215° (Lit.,[5] mp 212—213°).

(*S*)-(+)-2-(Diethylamino)methylpyrrolidine ((*S*)-(+)-IVc)——Similar treatments of L-proline diethylamide[3] (1.02 g, 6.0 mmole) as in the case of (*S*)-(+)-IVb afforded which was purified by distillation to give a colorless oil (0.65 g, 70%), bp 103—105° (56 mmHg), $[\alpha]_D^{20}$ +13.4° (*c*=1.14, EtOH). IR ν_{max}^{cap} cm^{-1}: 3300 (NH). This IR spectrum clearly showed no absorption due to amide group. NMR (in $CDCl_3$): 0.90—2.00 (10H, multiplet, $2\times CH_3+2\times CH_2$), 2.04 (1H, singlet, NH), 2.80—3.80 (9H, multiplet, $4\times CH_2$ (adjacent to nitrogen)+CH).

(*S*)-(+)-2-(1-Pyrrolidino)methylpyrrolidine ((*S*)-(+)-IVd)——The same treatment of L-proline pyrrolidide[3] (10.1 g, 0.060 mole) as that of (*S*)-(+)-IVb gave pure (*S*)-(+)-IVd (7.6 g, 83%), bp 99—101° (12 mmHg) after fractional distillation. This sample showed $[\alpha]_D^{20}$ +8.5° (*c*=2.40, EtOH). IR ν_{max}^{cap} cm^{-1}: 3300 (NH). No absorption due to the amide carbonyl group was observed in this IR spectrum. NMR (in $CDCl_3$): 1.30×2.10 (8H, multiplet, $4\times CH_2$), 2.2—3.4 (9H, multiplet, $4\times CH_2$ (next to nitrogen)+CH), 3.80 (1H, singlet, NH). This oily base gave a dipicrate which showed mp 170° (recrystallized from EtOH). *Anal.* Calcd. for $C_{21}H_{24}O_{14}N_8$: C, 41.18; H, 3.95; N, 18.30. Found: C, 41.07; H, 4.06; N, 18.20.

(*S*)-(−)-Nornicotin ((*S*)-(−)-IVe)——(−)-Nornicotine diperchlorate (mp 180°) was converted to its free base according to the usual manner. Oily base thus obtained showed bp 115—117° (5 mmHg) (Lit.,[8] bp 124—125° (18 mmHg)), and $[\alpha]_D^{20}$ −66.8° (*l*=0.1, d^{20}=1.0737, neat) (Lit.,[8] $[\alpha]_D^{20}$ −88.8° (*l*=0.5, neat)). Based on the assumption that (*S*)-(−)-IVe showing $[\alpha]_D^{20}$ −88.8° (neat) was optically pure, (*S*)-(−)-IVe obtained here was calculated to be 75% optically pure.

(*S*)-(−)-2-Methylpyrrolidine ((*S*)-(−)-IVf)——Prepared according to the reported procedure.[6] (*S*)-(−)-IVf obtained as a colorless clear oil showed bp 87—93° (760 mmHg), $[\alpha]_D^{20}$ −11.7° (*c*=1.260, H_2O) (Lit.,[6c] bp 95° (760 mmHg), $[\alpha]_D^{24}$ −11.5° (*c*=2.5, H_2O)). IR ν_{max}^{cap}: 3300 (NH).

(*S*)-(−)-Benzyl 2-(1-Hydroxy-1-methyl)ethylpyrrolidine-1-carboxylate ((*S*)-(−)-(VI)——)To an ethereal solution of methylmagnesium iodide prepared by adding methyl iodide (71 g, 0.5 mole) in anhyd. ether (100 ml) to a suspension of magnesium (11 g, 0.45 g atom) in anhyd. ether (300 ml) was gradually added an anhyd. ethereal solution (150 ml) of N-benzyloxycarbonyl L-proline ethyl ester (V) (41.5 g, 0.15 mole) with stirring and cooling in an ice bath. After the addition was over, stirring was continued for 0.5 hr in an ice bath, then for 2 hr at room temperature. The reaction mixture was decomposed by adding 20% aqueous ammonium chloride (250 ml). The upper ether layer was separated and the aqueous layer was further extracted with ether. The combined ether extracts were washed with satd. NaCl, then dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave an oily residue, which was distilled to give pure (*S*)-(−)-VI as a pale yellow oil (38.5 g, 97.6%). bp 148—149° (0.1 mmHg). This oil showed $[\alpha]_D^{20}$ −62.9° (*c*=1.256, EtOH). IR ν_{max}^{cap} cm^{-1}: 3380 (OH), 1670 (NCOO). NMR (in CCl_4): 1.40, 1.12 (6H, singlet, $2\times CH_3$), 1.6×2.0 (4H, multiplet, $2\times CH_2$) 3.5—4.0 (2H, triplet, CH_2 (next to nitrogen)), 4.5 (1H, triplet, CH), 5.08 (2H, singlet, CH_2 (next to oxygen)), 6.5 (1H, singlet, OH), 7.25 (5H, singlet, C_6H_5). *Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.37; H, 8.24; N, 5.35.

(*S*)-(−)-Benzyl 2-Isopropenylpyrrolidine-1-carboxylate ((*S*)-(−)-VII)——Thionyl chloride (18 g, 0.15 mole) was added to a solution of (*S*)-(−)-VI (26.5 g, 0.1 mole) in anhyd. toluene (260 ml) with stirring and cooling in an ice bath over a period of 1 hr. Then the reaction mixture was stirred for 1 hr under cooling. Dilution of the whole reaction mixture with methanol (100 ml), followed by evaporation *in vacuo* gave a brown oily residue, which was submitted to a silica gel column chromatography (800 g, solvent benzene) to give (*S*)-(−)-VII (14 g, 57%) as a yellow oil. This oil showed $[\alpha]_D^{20}$ −27.5° (*c*=0.836, EtOH) after distillation

7) All melting and boiling points were uncorrected. Infrared (IR) spectra measurements were carried out using a spectrometer, Model IR-S, Japan Spectroscopic Co., Ltd. Optical activities were determined with a Yanagimoto Photo Derict Reading Polarimeter, Model OR-50. Nuclear magnetic resonance (NMR) spectra were measured with a spectrometer, Model 3H-60, Japan Electron Optics Lab., and all signals were expressed by ppm downfield from tetramethylsilane used as an internal standaerd.

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in vacuo, bp 124° (0.08 mmHg). IR ν_{max}^{cap} cm^{-1}: 1707 (NCOO), 1653, 895 (C=CH_2). NMR (in CCl_4): 1.67 (3H, singlet, C$\underline{H}_3$), 1.65—2.0 (4H, multiplet, 2×C$\underline{H}_2$), 3.3—3.5 (2H, triplet, C$\underline{H}_2$ (next to nitrogen)), 4.2 (1H, triplet, C$\underline{H}$), 4.68 (2H, singlet, C=C$\underline{H}_2$), 5.0 (2H, singlet, C$\underline{H}_2$ (next to oxygen)), 7.2 (5H, singlet, $C_6\underline{H}_5$). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.14; H, 7.60; N, 5.79.

(*S*)-(−)-2-Isopropylpyrrolidine ((*S*)-(−)-IVg)——Hydrogen gas was bubbled through a mixture of (*S*)-(−)-VII (4.9 g, 0.02 mole) and 5% Pd on charcoal (1 g) in EtOH (50 ml) for 4 hr. The suspension was filtrated, and the filtrate was evaporated *in vacuo* after adding 20% hydrogen chloride in EtOH (10 ml) to give a crystalline residue. Recrystallization from chloroform–ether afforded (*S*)-(+)-2-isopropylpyrrolidine hydrochloride ((*S*)-(+)-IVg-HCl) as colorless needles (1.7 g, 57%), mp 146°. $[\alpha]_D^{20}$ +3.4° (*c*=0.804, EtOH). *Anal.* Calcd. for $C_7H_{16}NCl$: C, 56.18; H, 10.77; N, 9.36. Found: C, 55.91; H, 10.82; N, 9.09. According to the usual manner, the hydrochloride (1.7 g) obtained above was converted into its free base, (*S*)-(−)-2-isopropylpyrrolidine ((*S*)-(−)-IVg), which was purified by distillation, bp 130—137° (1.02 g, 45%). $[\alpha]_D^{20}$ −14.4° (*c*=0.450, EtOH). IR ν_{max}^{cap} cm^{-1}: 3280 (NH), 1075 (CH(CH_3)$_2$). NMR (in $CDCl_3$): 0.7—1.0 (6H, doublet, 2×C$\underline{H}_3$), 1.0—2.0 (5H, multiplet, 2×C$\underline{H}_2$+C$\underline{H}$), 1.82 (1H, singlet, N$\underline{H}$), 2.4—3.1 (3H, multiplet, C$\underline{H}_2$+C$\underline{H}$ (next to nitrogen).

Asymmetric Synthesis of (*R*)-(+)-4-Methyl-4-phenyl-2-cyclohexenone ((*R*)-(+)-I)——General procedure of the asymmetric synthesis was identical with that previously reported.[3] Reaction condition for the alkylation and the physical data of (*R*)-(+)-I prepared were summarized in the Table. One experimental procedure was shown as an example.

Run 3——A mixture of III (0.67 g, 5.0 mmole) and (*S*)-(+)-IVd (0.77 g, 5.0 mmole) in anhyd. benzene (30 ml) was refluxed in the presence of Molecular sieves 4A[9] for 2 hr. Filtration followed by concentration *in vacuo* have crude enamine (II) as an orange oil (1.40 g, quantitive yield), IR ν_{max}^{cap} cm^{-1}: 1630 (C=C–N). Complete absence of the absorptions due to aldehyde and secondary amino groups was definitely observed in this IR spectrum. After methyl vinyl ketone (0.70 g, 0.010 mole, 2.0 eq.) was added to the methanolic solution (14 ml) of the crude enamine obtained above, the whole solution was stirred at room temperature (15—20°) for 20 hr, then was diluted with 33% acetic acid (5 ml). Reflux of the acidic mixture, followed by concentration *in vacuo*, afforded an oil, which was dissolved in benzene. Benzene solution was successively washed with satd. NaCl, 10% HCl, and satd. NaCl, and finally dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo*, followed by purification with silica gel column chromatography (80 g, solvent chloroform), gave pure (*R*)-(+)-I as a slightly-colorled oil (0.76 g, 82% based on III). This oil showed $[\alpha]_D^{20}$ +48.5° (*c*=1.116, EtOH) after distilled *in vacuo*, bp 125° (3 mmHg). IR spectrum of this oil measured in a capillary was superimposable with that of the authentic sample[3] in the same state. The degree of the asymmetric induction was calculated to be 37% when (*R*)-(+)-I showing $[\alpha]_D^{20}$ +130° (EtOH) was assumed to be optically pure.[3]

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