A Chiral Synthesis of Four Stereoisomers of 1,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline, an Inducer of Parkinson-like Syndrome

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Four stereoisomers of 1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline, an inducer of Parkinson-like syndrome, were synthesized by applying a new method of 1,2,3,4-tetrahydroisoquinoline (TIQ) synthesis utilizing the Pummerer reaction as a key step. The chiral centers at C-1 and C-3 were constructed by two routes starting from alaninol (3) and 1-phenylethylamine (4) as a chiral source. Enantiomerically pure 1,3-dimethyl-TIQs (1*R*,3*S*)-(1), (1*S*,3*R*)-(ent-1), (1*S*,3*S*)-(2), and (1*R*,3*R*)-(ent-2) were prepared in a stereochemically unambiguous manner from 3 in 11 steps (route I) and from 4 in 6 steps (route II). The conformations of tetrahydroisoquinoline ring in 1-methyl, 3-methyl, and 1,3-dimethyl-TIQs were discussed on the basis of their CD, ^{1}H-NMR spectra, and steric energies.

Key words tetrahydroisoquinoline; 1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline; chiral synthesis; Pummerer reaction; parkinsonism

1,2,3,4-Tetrahydroisoquinoline (TIQ) and its derivatives (*R*)-salsolinol, 1-methyl-TIQ (1-MeTIQ), and 1-benzyl-TIQ (1-BnTIQ) are known to occur in human brain and to participate in the pathogenesis of Parkinson's disease.[1] In animal experiments it was found that 1-MeTIQ protects against the onset of parkinsonism,[2] while (*R*)-salsolinol,[3] TIQ,[4] and 1-BnTIQ[5] induce the syndrome. 1,3-Dimethyl-TIQ (1,3-DiMeTIQ) was detected in the brain of chronic ethanol-intoxicated rat which was subjected to repeated amphetamine administrations, and proved to cause behavior abnormalities similar to parkinsonism.[6] Furthermore, 1,3-DiMeTIQ was found to have weak phencyclidine-like effects.[7] However, the pharmacological experiments were carried out using a sample which consisted of a diastereomeric mixture. In this paper we describe a synthesis of four stereoisomers of 1,3-DiMeTIQ in an optically pure form, which may contribute to investigation of the biological field.

In order to prepare optically pure 1,3-DiMeTIQs in an unambiguous manner we adopted a method of TIQ synthesis utilizing the Pummerer reaction which we recently developed.[8] In the investigations, we demonstrated that the cyclization *via* the Pummerer reaction, if the amino group in the substrate of this reaction is protected as a formamide, quantitatively occurs under mild conditions even when the nucleophilic benzene ring of the substrate is not activated by an electron-donating substituent.[8a,b,d] Thus, we have found an efficient and convenient method of preparing chiral 1-MeTIQ and 1-BnTIQ as shown in Chart 2.[8c] The chiral center at C-1 was introduced by using simple chiral amines and the chirality was evidenced to be completely retained at any step of this synthesis. The 1,3-DiMeTIQ possessing two chiral centers at C-1 and C-3 will be constructed through a 4-phenylsulfanyl-1,3-DiMeTIQ (A) produced by the Pummerer reaction of a chiral sulfoxide (B).

We designed and constructed two chiral centers of 1,3-DiMeTIQ using two commercially available chiral materials, alaninol and 1-phenylethylamine (Chart 3). (*S*)-Alaninol (**3a**) will give two 1,3-DiMeTIQs (**1**, **2**) with absolute configurations of (1*R*,3*S*) and (1*S*,3*S*), and the (*R*)-enantiomer (**3b**) will give two 1,3-DiMeTIQs (ent-**1**, ent-**2**) with stereochemistries of (1*S*,3*R*) and (1*R*,3*R*) (route I). This route should produce the 1,3-DiMeTIQs with the confirmed stereochemistry at C-3 methyl group.

(*R*)-1-Phenylethylamine (**4a**) and the (*S*)-enantiomer (**4b**), on the other hand, will give 1,3-DiMeTIQs (**1**, ent-**2**) and the enantiomers (ent-**1**, **2**), respectively (route II). This route

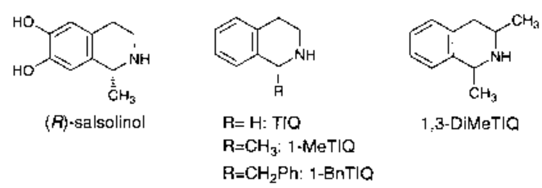

Chart 1

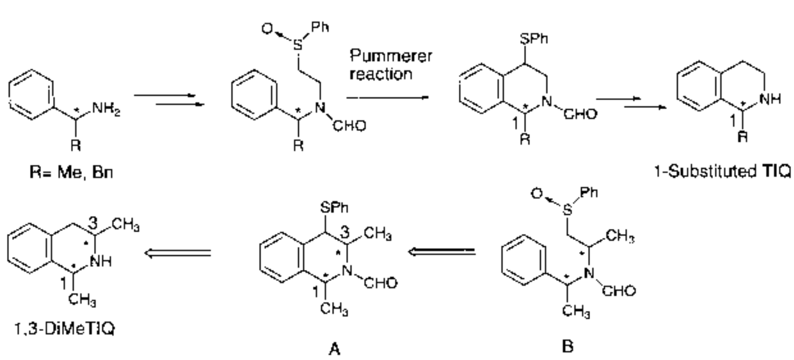

Chart 2

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should provide the 1,3-DiMeTIQs having the confirmed stereochemistry at C-1 methyl group. Thus, all four stereoisomers of 1,3-DiMeTIQ will be able to be synthesized in a stereochemically unambiguous manner, if the chiral center does not epimerize at any reaction involved in the two routes.

Results and Discussion

Synthesis of Chiral Sulfoxides, Substrates of Pummerer Reaction. i) Preparation of Chiral *N*-Benzyl-2-(1-methyl-2-phenylsulfanyl)-ethylamines (9) (*S*)-1-Methyl-2-phenylsulfanylethylamine (**8a**) and the (*R*)-enantiomer (**8b**), C-3 chiral moiety of the TIQ, were synthesized as follows. (*S*)-*N*-Benzyloxycarbonyl-*O*-tosyl-2-aminopropanol (**6a**) was prepared by selective *N*-benzyloxycarbonylation of (*S*)-alaninol (**3a**) followed by tosylation according to the known procedures.[9] Substitution of the tosylate (**6a**) with potassium thiophenol gave **7a** in 98% yield. Hydroylsis of **7a** with NaOH–EtOH furnished **8a** in 99% yield. Thus, the chiral synthon (**8a**) was prepared in 53% overall yield from **3a**. The (*R*)-enantiomer (**8b**) was prepared from (*R*)-alaninol (**3b**) in 55% overall yield in the same way.

Condensation of **8a** with benzaldehyde in EtOH–AcOH followed by reduction of the imino derivative with $NaBH_4$ gave (*S*)-*N*-benzyl derivative (**9a**) in 99% yield. Formylation of **9a** and then oxidation of the resulting (*S*)-*N*-formate (**10a**) with $NaIO_4$ in aqueous MeOH gave (*S*)-sulfoxide (**11a**) in good yield (87%), although sulfone (**12a**) accompanied it in 7% yield. Similarly, the (*R*)-sulfoxide (**11b**) was prepared from **8b** in 88% overall yield. Optical purity of the sulfides (**9a** and **9b**) was determined to be 100% by chiral HPLC analysis in which the corresponding enantiomer was not detected in any amount.

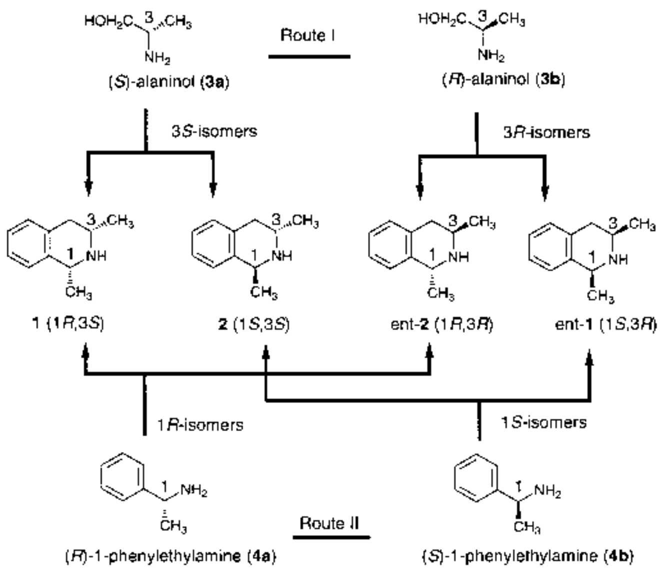

Chart 3

ii) Preparation of Chiral 1-Methyl-*N*-(1-phenylethyl)-2-phenylsulfanylethylamines (13, 14) and Their Enantiomers (ent-13, ent-14) Next, we prepared four stereoisomers of 1-methyl-*N*-(1-phenylethyl)-2-phenylsulfanylethylamine with two chiral centers *via* two routes starting from alaninol (**3**) (route I) and from 1-phenylethylamine (**4**) (route II) (Chart 5). Condensation of acetophenone with the (*S*)-amine (**8a**) proceeded smoothly when a mixture of the reactants was heated in the presence of titanium tetraisopropoxide without solvent at 80 °C for 4 h. After dilution with MeOH, the products without isolation were treated with $NaBH_4$ to yield a mixture of two diastereomeric sulfides. Separation of the mixture by MPLC gave the sulfides (**13**) and (**14**) in 70% and 30% yields, respectively.

The enantiomers (ent-**13**) and (ent-**14**) were prepared by the same procedures starting from the (*R*)-amine (**8b**) in similar yields. The specific optical rotations of these chiral sulfides indicated that the respective pairs (**13**, ent-**13**) and (**14**, ent-**14**) are enantiomeric with each other. The results suggested that the stereochemistry of the 3-methyl group was retained during the above transformations, thus establishing the C-3 absolute configuration. The stereochemistry of the 1-methyl group was identified by the synthesis of the same sulfides starting from (*R*)-1-phenylethylamine (**4a**) and the (*S*)-enantiomer (**4b**) described below.

Condensation of the (*R*)-amine (**4a**) with phenylsulfanylacetone[10] in titanium tetraisopropoxide followed by reduction with $NaBH_4$ gave two diastereomers (**13**, ent-**14**) in 56% and 30% yields, respectively. The (*S*)-enantiomer (**4b**) by the same procedures gave **14** and ent-**13** in 59% and 37% yields, respectively. The identities of the chiral sulfides obtained by the two routes were confirmed by chiral HPLC as shown in Fig 1. The HPLC clearly indicated that the optical purity of the chiral sulfides obtained by either route I or II was 100%. Thus, the stereochemistries of the chiral centers of **13** and ent-**13** were established as *cis*-1,3-dimethyl (1*R*,3*S*)[11] and (1*S*,3*R*), and those of **14** and ent-**14** as *trans*-1,3-dimethyl (1*S*,3*S*) and (1*R*,3*R*), respectively.

The sulfoxides, the substrates for the Pummerer reaction,

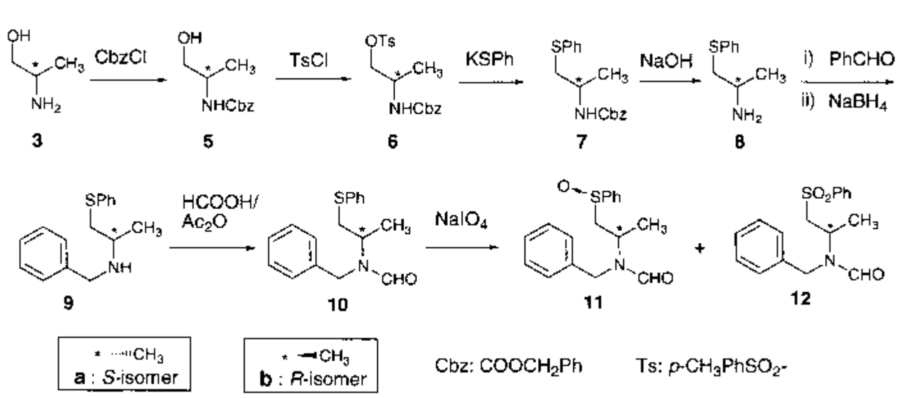

Chart 4

were prepared by *N*-formylation of the sulfides followed by oxidation with $NaIO_4$. Thus, the sulfides (**13**, ent-**13**, **14**, ent-**14**) gave the corresponding sulfoxides **17**, ent-**17**, **18**, and ent-**18** in 81%, 82%, 78%, and 76% yields, respectively (Chart 6).

Pummerer Reaction of Chiral Sulfoxides. i) Synthesis of Chiral 3-MeTIQ The possibility of epimerization at C-3 methyl group during the Pummerer reaction was examined by applying the reaction to the chiral sulfoxide (**11**) which produces a 3-MeTIQ derivative. Reaction of **11a** with trifluoroacetic anhydride (TFAA) in benzene at room temperature for 24 h did not cause the desired cyclization. Instead, the reaction gave the vinyl sulfide (**21**), an uncyclized product, in 31% yield. However, when a solution of **11a** in benzene was treated with TFAA for 4 h at room temperature, $BF_3 \cdot Et_2O$ was added and the mixture was allowed to react for a further 2 h; the reaction caused the cyclization to give 2-formyl-3-methyl-4-phenylsulfanylTIQ (**22a**) in 53% yield. In this case the vinyl sulfide (**21**) was not isolated, although it was detected on TLC in the reaction mixture. The ^{1}H-NMR spectrum of **22a** exhibited very complex signals. For example, those attributable to the 3-Me group appeared as four sets of doublets, indicating that **22a** consists of a mixture with respect to the stereochemistry of 4-PhS and also the rotational isomerism of the *N*-formyl group (Chart 7).

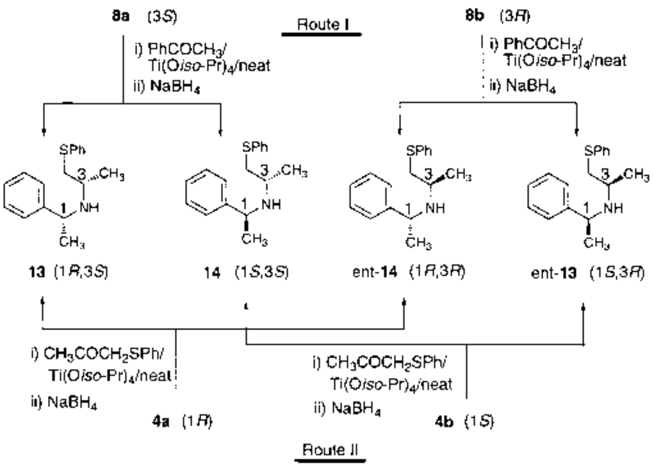

Chart 5

Reductive removal of the PhS group of **22a** with $NaBH_4$–$NiCl_2$ in MeOH–tetrahydrofuran (THF) gave 2-formyl-3-methyl-TIQ (**23a**) in 99% yield. This *N*-formate again exhibited the rotational isomerism of the formamide either in the ^{1}H-NMR spectrum or in its TLC behavior. Therefore, the chemical purity of **23a** could not be determined at this stage. The compound **23a** on deprotection of the formyl group by alkaline hydrolysis gave (*S*)-3-MeTIQ (**24a**) in 48% yield. Reduction of **23a** with $LiAlH_4$ gave the *N*-methyl derivative, (*S*)-2,3-DiMeTIQ (**25a**) in 54% yield. The TIQs were well characterized by their spectral and analytical data.

The enantiomers, (*R*)-3-MeTIQ (**24b**) and (*R*)-2,3-DiMeTIQ (**25b**) were synthesized from the enantiomeric sulfoxide (**11b**) in the same way. The enantiomeric property of the TIQs was clearly demonstrated by their circular dichroism (CD) spectra (Fig 2) and their optical rotations (Table 1). Although enantiomeric excess (ee.) of the TIQs could not be determined by chiral HPLC analysis since suitable conditions for separation of the enantiomers could not be found, they must have a high optical quality since their specific rotations have values similar to those reported[12] or larger[13] as shown in Table 1.

If the TIQ (**22**) was formed *via* the vinyl sulfide (**21**), the chirality at C-3 should be lost. This possibility was eliminated since the reaction of **21** with $BF_3 \cdot Et_2O$ or TFAA–$BF_3 \cdot Et_2O$ did not cause the cyclization to TIQ, although no characterizable products were obtained. This fact strongly suggested that the epimerization at the 3-Me group did not occur during the TIQ ring formation.

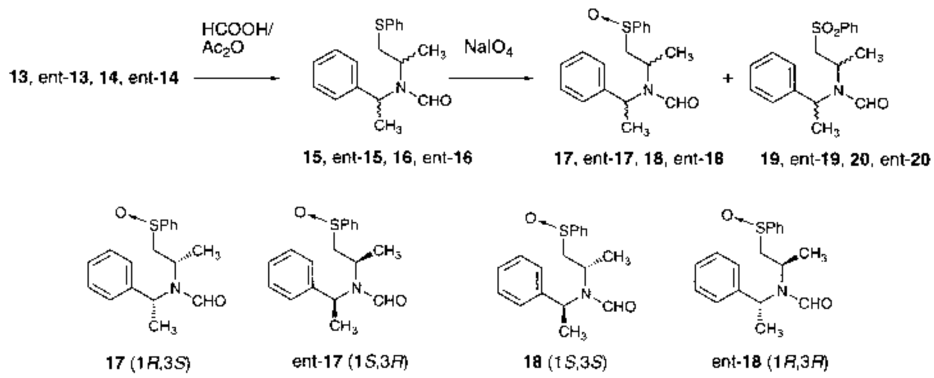

Chart 6

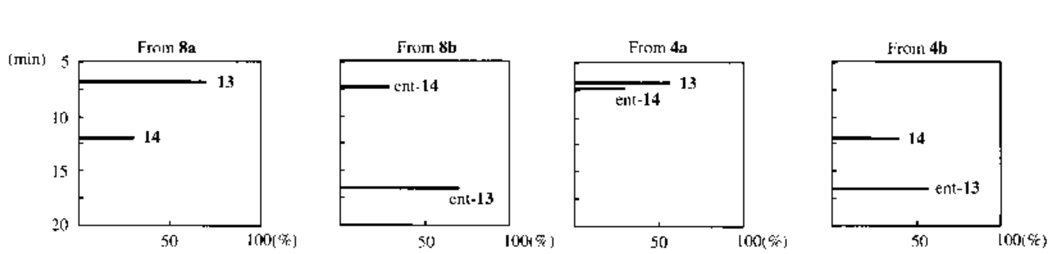

Fig. 1. Chiral HPLC of Chiral Sulfoxides **13**, **14**, ent-**13** and ent-**14**

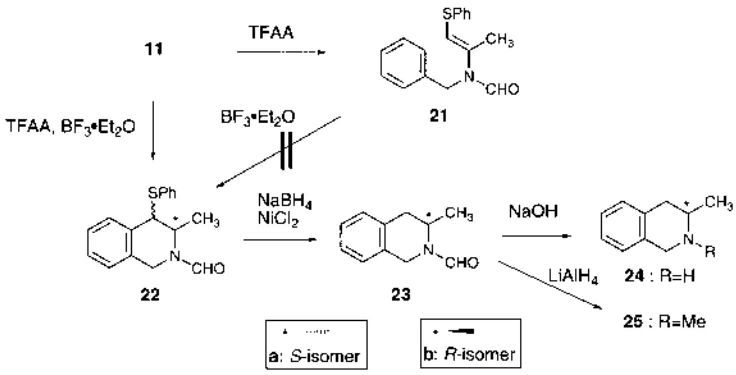

Chart 7

Table 1. Optical Rotations of TIQs and Absorptions of ^1L_b Band at the CD Spectra

	$[\alpha]_D$ (°)	$[\theta]$ (nm)
(*R*)-1-MeTIQ[a]	+75.0	−290 (266)
(*S*)-1-MeTIQ[a]	−77.5	+280 (266)
(*S*)-3-MeTIQ (**24a**)	+124.0[b,c]	+292 (270)
(*R*)-3-MeTIQ (**24b**)	−119.9[d]	−323 (270)
(1*R*,3*S*)-1,3-DiMeTIQ (**1**)	+47.0	+718 (265)
(1*S*,3*R*)-1,3-DiMeTIQ (ent-**1**)	−45.1	−689 (265)
(1*S*,3*S*)-1,3-DiMeTIQ (**2**)	+97.3	−671 (265)
(1*R*,3*R*)-1,3-DiMeTIQ (ent-**2**)	−96.9	+613 (265)

a) Ref. 8*d*. *b*) +118.9° (ref. 12). *c*) +78° (ref.13). *d*) −75° (ref. 13).

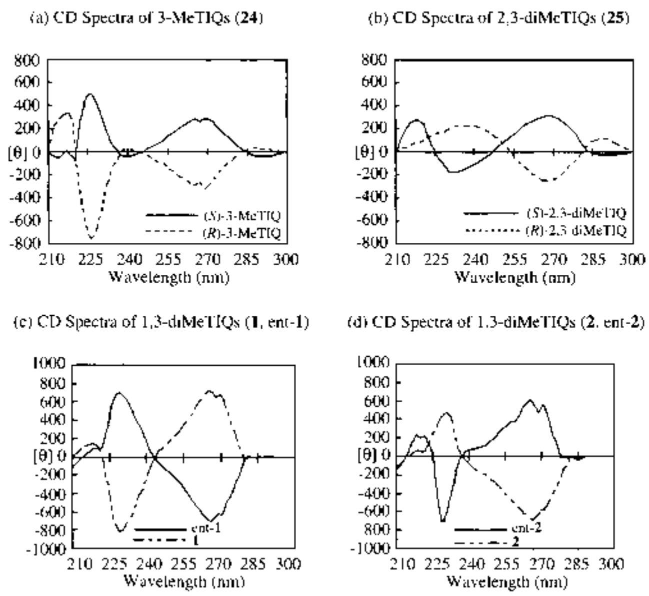

Fig. 2. CD Spectra of 3-MeTIQs and 1,3-DiMeTIQs

ii) Synthesis of Chiral 1,3-DiMeTIQ The Pummerer reaction of the chiral sulfoxides (**17**, ent-**17**, **18**, ent-**18**) was carried out as follows (Chart 8). A solution of ent-**17** in benzene was treated with TFAA for 2 h at room temperature, then $BF_3 \cdot Et_2O$ was added and the mixture was allowed to react for a further 2 h. The reaction formed three products, a 4-phenylsulfanylTIQ (ent-**26**), a vinyl sulfide (ent-**27**), and an aldehyde (ent-**28**) as a mixture. Desulfurization of crude ent-**26** with $NaBH_4$–$NiCl_2$ gave 2-formyl-1,3-DiMeTIQ (ent-**30**) in 16% yield (calculated from ent-**17**). Several attempts under other conditions with different amounts of reagents, reaction times and temperatures failed to improve the reaction.

Other 2-formyl-DiMeTIQs (**30**, **31**, ent-**31**) were obtained by the Pummerer reaction of the corresponding sulfoxide (**17**, **18**, ent-**18**) under the similar conditions in yields of 16%, 13%, and 19%, respectively.

Alkaline hydrolysis of the *N*-formates (**30**, ent-**30**, **31**, ent-**31**) gave the DiMeTIQs (**1**, ent-**1**, **2**, ent-**2**) in yields of 76%, 74%, 60%, and 65%, respectively. The pairs of the TIQs (**1**, ent-**1**) and (**2**, ent-**2**) in their CD spectra showed absorption with opposite signs (Fig 2), respectively. The optical rotations (Table 1) as well as the Cotton effects indicated that they are enantiomeric with each other. Although the optical purity of the TIQs could not be determined by chiral HPLC analysis, their optical qualities should be excellent since their ^{1}H- and ^{13}C-NMR spectra showed no contamination of other diastereomers which could be generated by the epimerization of the chiral centers. Thus, the absolute configurations of 1,3-dimethyl groups can be assigned as (1*R*,3*S*), (1*S*,3*R*), (1*S*,3*S*), and (1*R*,3*R*) for **1**, ent-**1**, **2**, and ent-**2**, respectively.

Ring Conformations of 1,3-DimethylTIQ Finally, we wish to discuss the conformation of the substituted TIQ ring. The chiral moiety (piperideine ring) of 1-, 3-, and 1,3-substituted TIQs may assume two conformations, A and B (only the 3*S*-isomers are depicted in Fig 3), with an opposite sense of helicity relative to the benzene ring. The semi-empirical quadrant rule of CD developed by Craige *et al.*[14] states that in the 1-substituted TIQ ring system the conformation A ($^2H_3$ form) shows a negative Cotton effect at ^1L_b band of a benzene transition (around 270 nm), while the conformation B ($^3H_2$ form) shows a positive Cotton effect at the same CD band. This rule seems well applicable to determining the ring conformation of the chiral 1-substituted TIQ derivatives.[8c,14] For example, (*R*)-1-MeTIQ which exhibited a negative Cotton effect is concluded to have conformation A with 1-pseudoaxial Me as a favored conformation.

(*S*)-3-MeTIQ (**24a**) showed a positive Cotton effect at the 270 nm CD band (Fig 2). If the quadrant rule is applicable to 3-MeTIQ, this sign of Cotton effect indicated that the 3-MeTIQ adopts a half chair conformation (B) ($^3H_2$ form) with 3-Me in an equatorial position. In the ^{1}H-NMR spectrum the signals of C-4 ring protons appeared as a double quartet at δ 2.49 (Hax, J=11, 16 Hz) and 2.77 (Heq, J=4, 16 Hz). The coupling constants (4, 11 Hz) between 3-H and 4-H indicated that the 3-Me group is in equatorial orientation if the ring has a half chair form. The CD and ^{1}H-NMR spectra of the *N*-

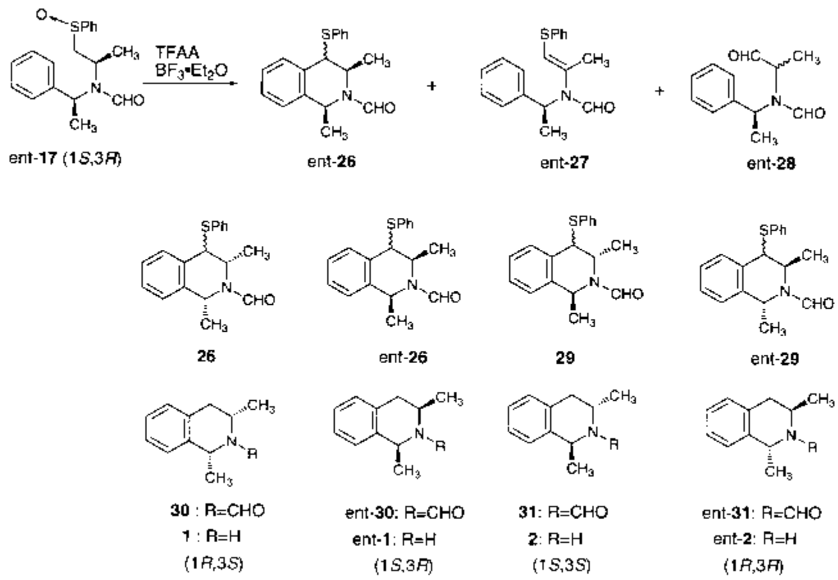

Chart 8

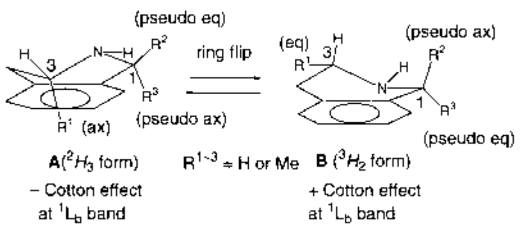

Fig. 3. Possible Conformations of (3*S*)-TIQs and the Sign of Cotton Effect Predicted by the Quadrant Rule

Table 2. Steric Energies (kcal/mol) for Conformations A and B Calculated by MM2, and a Favored Conformation Obtained by CD, ^{1}H-NMR, and MM2

TIQs	Steric energy		ΔE (A−B)	Favored conformation		
	A	B		CD	^{1}H-NMR	MM2
(*R*)-1-Me	1.21	1.67	−0.46	A[a]	—[b]	A
(*S*)-3-Me (**24a**)	1.45	−0.15	1.60	B	B	B
(1*R*,3*S*)-1,3-DiMe (**1**)	5.05	1.39	3.66	B	B	B
(1*S*,3*S*)-1,3-DiMe (**2**)	2.99	1.88	1.11	A	B	B

A: $^2H_3$ form. B: $^3H_2$ form. *a*) Ref. 8*c*. *b*) Inapplicable.

methyl derivative (**25a**) showed that it has the same ring conformation. Thus, the quadrant rule is concluded to be applicable to determine the ring conformation of 3-MeTIQ.

1,3-DiMeTIQ (**1**) with *cis*-dimethyl groups and the *trans*-isomer (**2**) showed a positive and a negative Cotton effect at around 265 nm, respectively (Fig 2). Application of the quadrant rule indicated that the *cis*-isomer (**1**) adopts the conformation B ($^3H_2$ form) with 3-equatorial Me and 1-pseudoequatorial Me, while the *trans*-isomer (**2**) adopts the conformation A ($^2H_3$ form) with 3-axial Me and 1-pseudoequatorial Me.

In the ^{1}H-NMR spectra the C-4 protons showed a similar signal pattern in both stereoisomers (**1**, **2**). The coupling constants between 3-H and 4-H have same values (4, 11 Hz), indicating that the 3-Me group of either isomer is positioned in an equatorial orientation. Thus, it can be concluded that the *cis*-isomer (**1**) adopts the conformation B with 3-equatorial Me and 1-pseudoequatorial Me, and the *trans*-isomer (**2**) also adopts the conformation B with 3-equatorial Me and 1-pseudoaxial Me. The assigned conformation of the *trans*-isomer (**2**) is in contradiction with the result obtained by the CD spectrum which suggested the conformation A.

In order to examine the validity of the quadrant rule applied to TIQ derivatives, steric energies of two conformations A and B in 1-Me, 3-Me, and two diastereomeric 1,3-DiMe-TIQs were calculated by MM2. The favored conformations assigned by CD, ^{1}H-NMR, and the steric energies are summarized in Table 2. The results of the calculation showed that 1-MeTIQ adopts the conformation A, while 3-MeTIQ (**24a**) adopts the conformation B as a favored one, respectively. These assignments are well coincident with those obtained by the quadrant rule. On the other hand, steric energies of 1,3-DiMeTIQs indicated that both the stereoisomers **1** and **2** adopt the conformation B as a favored one (ΔE=3.66 kcal/mol for **1** and 1.11 kcal/mol for **2**). As shown in Table 2 this conclusion is in accord with that obtained by their ^{1}H-NMR spectra, but conflicts with that of the quadrant rule.

Thus, the quadrant rule using the Cotton effect of ^1L_b band seems inapplicable to determine the ring conformation of 1,3-disubstituted TIQs. In other words, the Cotton effect of the transition may be affected not only by the helicity of the TIQ ring but also by some other electronic factors generated by interactions between the two methyl groups and the benzene ring.

In conclusion, the four chiral 1,3-DiMeTIQs, biologically important compounds, were synthesized by two routes using the Pummerer reaction as a key step. Route I starting from chiral alaninol (**3**) required 11 steps and gave the TIQs (**1**, **2**) and the enantiomers (ent-**1**, ent-**2**) in about 3% total yield, while route II from chiral 1-phenylethylamine (**4**) required 6 steps to give the same TIQs in about 6% total yield. This investigation at the same time clarified the conformation of substituted TIQ ring. Contrary to our expectations, the efficiency of the Pummerer reaction forming the TIQ ring was unsatisfactory. Nevertheless, this method may have practical value, at least, in laboratories, since all procedures, particularly in the synthesis *via* route II, are very convenient and can be carried out on a large scale.

Experimental

Unless otherwise noted, the following procedures were adopted. Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were obtained as films for oils and gums, and KBr disks for solids with JASCO FT/IR-5000, and are given in cm^{-1}. NMR spectra were measured on JEOL JNM-AL 300 (^1H: 300 MHz and ^{13}C: 75 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. Low resolution (LR)-MS and high resolution (HR)-MS were taken on a JEOL JMS-AX 505H spectrometer at 70 eV [electron ionization MS (EI-MS)] or at 270 eV [chemical ionization MS (CI-MS, reactant gas: isobutane)] using direct or GC/MS inlet systems, and figures in parentheses indicate the relative intensities. Optical rotations were determined using a JASCO DIP-1000 digital polarimeter. CD spectra were measured on a J-600 (JASCO) spectrometer in MeOH. TLC was performed on Merck precoated Silica gel 60 F_{254} plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200). Medium pressure liquid chromatography (MPLC) was performed on Kusano CIG prepacked column. The chiral HPLC analyses were performed on a chiral column of Sumichiral OA 4700 (25 cm×4 mm i.d.; room temperature, mobile phase, hexane–EtOH–trifluoroacetic acid (960 : 40 : 4); flow rate, 1.5 ml/min). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness. The known compounds were also characterized by MS, IR, and ^1H-NMR examinations.

Compounds **5** and **6** were prepared according to the known procedures.[9] **5a**: mp 67—69 °C, $[\alpha]_D^{26}=-6.7°$ (c=1.04, $CHCl_3$) [lit.,[15] mp 55—56 °C, $[\alpha]_D^{29}=-6.5°$ (c=1, $CHCl_3$) and lit.,[16] mp 67—68 °C, $[\alpha]_D^{29}=-7°$ (c=1.1, $CHCl_3$)]. **5b**: mp 67—70 °C, $[\alpha]_D^{26}=+7.4°$ (c=1.02, $CHCl_3$) [lit.,[9] mp 79—82.5 °C, $[\alpha]_D=+4.2°$ (c=2.5, MeOH)]. **6a**: mp 65—67 °C, $[\alpha]_D^{26}=-10.7°$ (c=1.04, $CHCl_3$). **6b**: mp 68—70 °C, $[\alpha]_D^{26}=+9.3°$ (c=1.05, $CHCl_3$) [lit.,[9] mp 66—69 °C, $[\alpha]_D=+17.5°$ (c=3.0, CH_2Cl_2)].

Preparation of (*S*)- and (*R*)-1-Methyl-2-phenylsulfanylethylamine (8). i) Substitution of *N*-Benzyloxycarbonyl-*O*-tosyl-2-aminopropanol (6) with Potassium Thiophenol Thiophenol (11.8 ml, 115 mmol) was added to a suspension of KOH (85%, 13.7 g, 208 mmol) in THF (450 ml) and the solution was stirred for 10 min at room temperature. To this solution **6a** (38 g, 104 mmol) in THF (50 ml) was slowly added, and the whole was stirred for 2.5 h at room temperature. After removal of insoluble precipitates by filtration, the filtrate was concentrated *in vacuo* to dryness. Recrystallization of the residue from AcOEt–hexane gave (*S*)-*N*-benzyloxycarbonyl-1-methyl-2-phenylsulfanylethylamine (**7a**) (30.2 g, 96%) as colorless needles, mp 70—71 °C (lit.,[17] mp 82—84 °C). IR: 1682 cm^{-1}. ^1H-NMR: 1.25 (3H, d, J=7 Hz, $-CHC\underline{H}_3$), 2.95, 3.18 (total 2H, dd, J=6, 13 Hz, $-CHC\underline{H}_2SPh$), 3.8—4.1 (1H, m, –CH–), 5.07 (2H, s, $-COOC\underline{H}_2Ph$), 6.9—7.5 (10H, m, PhH×2). ^{13}C-NMR: 19.7 (q), 40.1 (t), 46.6 (d), 66.5 (t), 126.1 (d×2), 127.9 (d×2), 128.4 (d×2), 128.9 (d×2), 129.3 (d×2), 135.9 (s), 136.4 (s), 155.5 (s). LR-MS m/z: 301 (M^+), 91 (base peak). $[\alpha]_D^{26}=+27.6°$ (c=1.01, $CHCl_3$) [lit.,[17] $[\alpha]_D=+26.3°$ (c=1.01, $CHCl_3$)].

Similarly, the (*R*)-isomer (**6b**) gave (*R*)-*N*-benzyloxycarbonyl-1-methyl-2-phenylsulfanylethylamine (**7b**) (93%) as colorless needles from AcOEt–hexane, mp 68—70 °C. LR-MS m/z: 301 (M^+), 91 (base peak). HR-MS m/z (M^+): Calcd for $C_{17}H_{19}NO_2S$: 301.1134. Found: 301.1112. $[\alpha]_D^{26}=-36.1°$ (c=0.97, $CHCl_3$).

ii) Hydrolysis of 7 with Potassium Hydroxide A solution of **7a** (10 g, 60 mmol) in EtOH (200 ml) and 20% KOH aq. (200 ml) was refluxed for 17 h. The reaction mixture was concentrated *in vacuo* and extracted with Et_2O. The residue was purified by column chromatography with AcOEt : hexane (1 : 1) to give (*S*)-1-methyl-2-phenylsulfanylethylamine (**8a**) (5.49 g, 99%) as a pale yellow oil. Chiral HPLC: 100% ee., retention time: 18.8 min). IR: No carbonyl absorption. ^1H-NMR: 1.16 (3H, d, J=6 Hz, $-CHC\underline{H}_3$), 1.54 (2H, s, $-NH_2$), 2.7—3.1 (3H, m, $-C\underline{H}C\underline{H}_2-$), 7.2—7.4 (5H, m, PhH). ^{13}C-NMR: 22.9 (q), 44.2 (t), 46.0 (d), 126.1 (d), 128.9 (d×2), 129.5 (d×2), 136.2 (s). LR-MS m/z: 167 (M^+), 44 (base peak). HR-MS m/z (M^+): Calcd for $C_9H_{13}NS$: 167.0766. Found: 167.0755. $[\alpha]_D^{26}=+42.7°$ (c=1.01, $CHCl_3$).

Similarly, the (*R*)-isomer (**7b**) gave (*R*)-1-methyl-2-phenylsulfanylethylamine (**8b**) (99%) as a pale yellow oil. Chiral HPLC: 100% ee., retention time: 19.3 min. LR-MS m/z: 167 (M^+), 44 (base peak). HR-MS m/z (M^+): Calcd for $C_9H_{13}NS$: 167.0768. Found: 167.0768. $[\alpha]_D^{26}=-45.8°$ (c=1.00, $CHCl_3$).

Preparation of (*S*)- and (*R*)-*N*-Benzyl-1-methyl-2-phenylsulfanyl-ethylamine (9) A solution of **8a** (5 g, 30 mmol), benzaldehyde (3.8 g, 36 mmol) and acetic acid (1.8 ml, 30 mmol) in EtOH (100 ml) was refluxed for 16 h. After the mixture was concentrated *in vacuo*, the residue was diluted with EtOH (100 ml) and treated with $NaBH_4$ at 0 °C for 30 min. After decomposition of excess hydride with water, the precipitates were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt : hexane (1 : 8) to give **9a** (7.61 g, 99%) as a colorless oil. Chiral HPLC: 100% ee., retention time: 13.3 min. IR: No carbonyl absorption. ^1H-NMR: 1.18 (3H, d, J=6 Hz, $-CHC\underline{H}_3$), 2.8—3.0 (3H, m, $-C\underline{H}C\underline{H}_2-$), 3.66, 3.84 (each 1H, d, J=13 Hz, $PhC\underline{H}_2NH-$), 7.1—7.4 (10H, m, PhH×2). ^{13}C-NMR: 20.0 (q), 41.1 (t), 51.2 (d), 64.9 (t), 126.1 (d), 126.8 (d), 128.0 (d×2), 128.3 (d×2), 128.8 (d×2), 129.7 (d×2), 136.3 (s), 140.2 (s). LR-MS m/z : 257 (M^+), 91 (base peak). HR-MS m/z (M^+): Calcd for $C_{16}H_{19}NS$: 257.1239. Found: 257.1246. $[\alpha]_D^{26}=+71.1°$ (c=1.00, $CHCl_3$).

Similarly, the (*R*)-isomer (**8b**) gave **9b** (99%) as a colorless oil. Chiral HPLC: 100% ee., Retention time: 15.2 min. LR-MS m/z: 257 (M^+), 91 (base peak). HR-MS m/z (M^+): Calcd for $C_{16}H_{19}NS$: 257.1239. Found: 257.1267. $[\alpha]_D^{26}=-64.3°$ (c=1.00, $CHCl_3$).

Formylation of 8 A mixed anhydride which was prepared from HCOOH (21 ml, 550 mmol) and Ac_2O (24 ml, 275 mmol) was added to the (*S*)-amine (**9a**) (7.07 g, 27.5 mmol), and the whole was heated at 60 °C for 1 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography with AcOEt : hexane (1 : 2) to give *N*-benzyl-*N*-[(*S*)-1-methyl-2-phenylsulfanylethyl]formamide (**10a**) (7.76 g, 99%) as a colorless oil. IR: 1671 (–NCHO). LR-MS m/z: 285 (M^+), 91 (base peak). HR-MS m/z (M^+): Calcd for $C_{17}H_{19}NOS$: 285.1286. Found: 285.1181.

Similarly, the (*R*)-isomer (**9b**) gave *N*-benzyl-*N*-[(*R*)-1-methyl-2-phenylsulfanylethyl]formamide (**10b**) (97%) as a colorless oil. LR-MS m/z: 285 (M^+), 91 (base peak). HR-MS m/z (M^+): Calcd for $C_{17}H_{19}NOS$: 285.1185. Found: 285.1165.

Oxidation of 10 with $NaIO_4$ A solution of sodium metaperiodate (6.73 g, 31.5 mmol) in H_2O (100 ml) was added to a solution of **10a** (5.85 g, 21 mmol) in MeOH (150 ml), and the mixture was stirred at room temperature for 17 h. After removal of inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. Chromatography of the residue with AcOEt : hexane (1 : 1) gave *N*-benzyl-*N*-[(*S*)-1-methyl-2-phenylsulfinylethyl]formamide (**11a**) (5.80 g, 91%) as a colorless oil. IR: 1671 (–NCHO), 1040 (S→O) cm^{-1} and *N*-benzyl-*N*-[(*S*)-1-methyl-2-phenylsulfonylethyl]formamide (**12a**) (0.45 g, 7%) as a colorless oil. IR: 1663 (–NCHO). LR-MS m/z : 317 (M^+), 288 (base peak).

Similarly, the (*R*)-isomer (**10b**) gave *N*-benzyl-*N*-[(*R*)-1-methyl-2-phenylsulfinylethyl]formamide (**11b**) (90%) as a colorless oil. IR: 1669 (–NCHO), 1040 (S→O), and *N*-benzyl-*N*-[(*R*)-1-methyl-2-phenylsulfonylethyl]formamide (**12b**) (9%) as a colorless oil. IR: 1669 (–NCHO) cm^{-1}. LR-MS m/z: 317 (M^+), 288 (base peak).

Preparation of 1-Methyl-*N*-(1-phenylethyl)-2-phenylsulfanylethylamines (13, ent-13, 14, ent-14) by Route I A mixture of **8a** (3.05 g, 18 mmol), acetophenone (2.5 ml, 21.6 mmol) and titanium tetraisopropoxide (8.4 ml, 27 mmol) was heated at 80 °C for 4 h under an argon atmosphere. After cooling, the reaction mixture was diluted with MeOH (30 ml), and treated with $NaBH_4$ (1.36 g, 36 mmol) at 0 °C for 2 h. After dilution of the mixture with H_2O (10 ml) and MeOH (20 ml), the precipitated inorganic materials were removed by filtration. The filtrate was concentrated *in vacuo* and extracted with Et_2O. The soluble part was purified by column chromatography with AcOEt : hexane (3 : 1) followed by MPLC with AcOEt : hexane (4 : 1) to give **13** (3.42 g, 70%) and **14** (1.45 g, 30%) as a colorless oil.

(1*S*)-1-Methyl-*N*-[(*R*)-1-phenylethyl]-2-phenylsulfanylethylamine (**13**): Chiral HPLC: 100% ee., retention time: 6.8 min. IR: No carbonyl absorption. ^1H-NMR: 1.07 (3H, d, J=6 Hz, $-NHCH(C\underline{H}_3)CH_2SPh$), 1.27 (3H, d, J=6 Hz, $PhCH(C\underline{H}_3)NH-$), 2.7—2.8 (1H, m, $-NHC\underline{H}(CH_3)CH_2SPh$), 2.94 (1H, dd, J=6, 13 Hz, $-NHCH(CH_3)C\underline{H}_2SPh$), 3.03 (1H, dd, J=5, 13 Hz, $-NHCH(CH_3)C\underline{H}_2SPh$), 3.82 (1H, q, J=7 Hz, $PhC\underline{H}(CH_3)NH-$), 7.1—7.4 (10H, m, PhH×2). ^{13}C-NMR: 21.1 (q), 24.7 (q), 40.3 (t), 49.7 (d), 55.4 (d), 125.9 (d), 126.5 (d×2), 126.9 (d), 128.4 (d×2), 128.9 (d×2), 129.4 (d×2), 136.8 (s), 145.8 (s). LR-MS m/z: 271 (M^+), 44 (base peak). HR-MS m/z (M^+): Calcd for $C_{17}H_{21}NS$: 271.1393. Found: 271.1371. $[\alpha]_D^{29}=-76.4°$ (c=1.05, $CHCl_3$).

(1*S*)-1-Methyl-*N*-[(*S*)-1-phenylethyl]-2-phenylsulfanylethylamine (**14**): Chiral HPLC: 100% ee., retention time: 12.0 min. IR: No carbonyl absorption. ^1H-NMR: 1.09 (3H, d, J=6 Hz, $NHCH(C\underline{H}_3)CH_2SPh$), 1.36 (3H, d, J=7 Hz, $PhCH(C\underline{H}_3)NH-$), 2.6—2.7 (1H, m, $-NHC\underline{H}(CH_3)CH_2SPh$), 2.84 (1H, dd, J=7, 13 Hz, $-NHCH(CH_3)C\underline{H}_2SPh$), 2.93 (1H, dd, J=5, 13 Hz, –NHCH-

$(CH_3)C\underline{H}_2SPh)$, 3.87 (1H, q, J=7 Hz, $PhC\underline{H}(CH_3)NH$–), 7.1—7.3 (10H, m, PhH×2). ^{13}C-NMR: 19.8 (q), 24.9 (q), 41.7 (t), 48.4 (d), 55.0 (d), 125.9 (d), 126.5 (d×2), 126.8 (d), 128.4 (d×2), 128.8 (d×2), 129.3 (d×2), 136.1 (s), 145.2 (s). LR-MS *m/z* : 271 (M^+), 105 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{17}H_{21}NS$: 271.1392. Found: 271.1377. $[\alpha]_D^{29}$=+60.1° (c=1.00, $CHCl_3$).

Similarly, the (R)-isomer (**8b**) (5 g, 30 mmol) gave ent-**13** (5.705 g, 70%) and ent-**14** (2.127 g, 26%) as a colorless oil.

(1R)-1-Methyl-N-[(S)-1-phenylethyl]-2-phenylsulfanylethylamine (ent-**13**): Chiral HPLC: 100% ee., retention time: 16.7 min. LR-MS *m/z*: 271 (M^+), 105 (base peak). HR-MS *m/z*: Calcd for $C_{17}H_{21}NS$. (M^+) : 271.1554. Found: 271.1374. $[\alpha]_D^{26}$=+77.1° (c=0.96, $CHCl_3$).

(1R)-1-Methyl-N-[(R)-1-phenylethyl]-2-phenylsulfanylethylamine (ent-**14**): Chiral HPLC: 100% ee., retention time: 7.4 min. LR-MS *m/z*: 271 (M^+), 105 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{17}H_{21}NS$: 271.1393. Found: 271.1373. $[\alpha]_D^{26}$=−70.9° (c=0.79, $CHCl_3$).

Preparation of 1-Methyl-*N*-(1-phenylethyl)-2-phenylsulfanylethylamines (13, ent-13, 14, ent-14) by Route II A mixture of (R)-1-phenylethylamine (**4a**) (280 μl, 2.2 mmol), phenylsulfanylacetone[10] (300 mg, 1.8 mmol) and titanium tetraisopropoxide (838 μl, 2.7 mmol) was heated at 80 °C for 4 h under an argon atmosphere. After cooling, the reaction mixture was diluted with MeOH (10 ml), and treated with $NaBH_4$ (136 mg, 3.6 mmol) at 0 °C for 30 min. After dilution with H_2O (5 ml), the precipitated inorganic materials were removed by filtration. The filtrate was concentrated *in vacuo* and extracted with Et_2O. The soluble part was purified by column chromatography with AcOEt : hexane (3 : 1) followed by MPLC with AcOEt : hexane (4 : 1) to give **13** (273 mg, 56%, Chiral HPLC: 100% ee., retention time: 6.7 min) and ent-**14** (146 mg, 30%, Chiral HPLC: 100% ee., retention time: 7.4 min) as a colorless oil.

Similarly, (S)-1-phenylethylamine (**4b**) (280 ml, 2.2 mmol) gave ent-**13** (287 mg, 59%, Chiral HPLC: 100% ee., retention time: 16.7 min) and **14** (178 mg, 37%, Chiral HPLC: 100% ee., retention time: 12.0 min) as a colorless oil.

Formylation of 13, ent-13, 14, and ent-14 A mixed anhydride which was prepared from HCOOH (13 ml, 340 mmol) and Ac_2O (15 ml, 170 mmol) was added to ent-**13** (4.5 g, 17 mmol), and the whole was heated at 60 °C for 2 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography with AcOEt : hexane (1 : 2) to give N-[(R)-1-methyl-2-phenylsulfanylethyl]-N-[(S)-1-phenylethyl]formamide (ent-**15**) (4.66 g, 94%) as a colorless oil. IR: 1668. LR-MS: *m/z*: 299 (M^+), 105 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{18}H_{21}NOS$: 299.1344. Found: 299.1375.

Similarly, formylations of **13**, **14**, and ent-**15** gave the formates **15**, **16**, and ent-**16**, respectively.

N-[(S)-1-Methyl-2-phenylsulfanylethyl]-N-[(R)-1-phenylethyl]formamide (**15**): Yield: 95%. Pale yellow oil. IR: 1668 cm^{-1}. LR-MS *m/z*: 299 (M^+), 150 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{18}H_{21}NOS$: 299.1344. Found: 299.1334.

N-[(S)-1-Methyl-2-phenylsulfanylethyl]-N-[(S)-1-phenylethyl]formamide (**16**): Yield: 99%. Colorless oil. IR: 1664 cm^{-1}. LR-MS *m/z*: 299 (M^+), 105 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{18}H_{21}NOS$: 299.1344. Found: 299.1347.

N-[(R)-1-Methyl-2-phenylsulfanylethyl]-N-[(R)-1-phenylethyl]formamide (ent-**16**): Yield: 93%. Colorless oil. IR: 1666 cm^{-1}. LR-MS *m/z*: 299 (M^+), 105 (base peak).

Oxidation of 15, ent-15, 16, and ent-16 with $NaIO_4$ A solution of sodium metaperiodate (3.5 g, 16.5 mmol) in H_2O (100 ml) was added to a solution of ent-**15** (3.5 g, 11.5 mmol) in MeOH (150 ml), and the mixture was stirred at room temperature for 17 h. After removal of inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. Chromatography of the residue with AcOEt : hexane (1:1) gave N-[(R)-1-methyl-2-phenylsulfinylethyl]-N-[(S)-1-phenylethyl]formamide (ent-**17**) (3.20 g, 87%) as a colorless oil [IR: 1664 (–NCHO), 1041 (S→O). CI-MS *m/z*: 316 (MH^+)], and N-[(R)-1-methyl-2-phenylsulfonylethyl]-N-[(S)-1-phenylethyl]formamide (ent-**19**) (0.35 g, 9%) as a colorless gum [IR: 1671 (–NCHO) cm^{-1}. LR-MS *m/z*: 331 (M^+), 105 (base peak)].

Similarly, oxidations of **15**, **16**, and ent-**16** gave the sulfoxides (**17**, **18**, ent-**18**) and the sulfones (**19**, **20**, ent-**20**), respectively.

N-[(S)-1-Methyl-2-phenylsulfinylethyl]-N-[(R)-1-phenylethyl]formamide (**17**): Yield: 86%. Colorless oil. IR: 1666 (–NCHO), 1041 (S→O) cm^{-1}. CI-MS *m/z*: 316 (MH^+), 316 (base peak).

N-[(S)-1-Methyl-2-phenylsulfinylethyl]-N-[(S)-1-phenylethyl]formamide (**18**): Yield: 79%. Colorless gum. IR: 1666 (–NCHO), 1041 (S→O) cm^{-1}. CI-MS *m/z*: 316 (MH^+), 316 (base peak).

N-[(R)-1-Methyl-2-phenylsulfinylethyl]-N-[(R)-1-phenylethyl]formamide (ent-**18**): Yield: 82%. Colorless gum. IR: 1675 (–NCHO), 1041 (S→O) cm^{-1}. CI-MS *m/z*: 316 (MH^+).

N-[(S)-1-Methyl-2-phenylsulfonylethyl]-N-[(R)-1-phenylethyl]formamide (**19**): Yield: 2%. Colorless gum. IR: 1656 (–NCHO) cm^{-1}. LR-MS *m/z*: 331 (M^+), 52 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{18}H_{21}NO_3S$: 331.1242, Found: 331.1243.

N-[(R)-1-Methyl-2-phenylsulfonylethyl]-N-[(R)-1-phenylethyl]formamide (ent-**20**): Yield: 2%. Colorless gum. IR: 1668 (–NCHO) cm^{-1}. LR-MS *m/z*: 331 (M^+), 105 (base peak).

N-[(S)-1-Methyl-2-phenylsulfonylethyl]-N-[(S)-1-phenylethyl]formamide (**20**): Yield: 7%. Colorless gum. IR: 1666 (–NCHO) cm^{-1}. LR-MS *m/z*: 331 (M^+), 52 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{18}H_{21}NO_3S$: 331.1243. Found: 331.1253.

Pummerer Reaction of *N*-Benzyl-*N*-(1-methyl-2-phenylsulfinylethyl)-formamides (11a, 11b). Synthesis of (*S*)- and (*R*)-3-MeTIQs i) TFAA (250 μl, 1.65 mmol) was added to a solution of **11a** (100 mg, 0.33 mmol) in benzene (10 ml) at room temperature, and the mixture was stirred for 24 h under an argon atmosphere. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography with AcOEt : hexane (1 : 1) to give N-(1-methyl-2-phenylsulfanylethenyl)-N-benzylformamide (**21**) (29 mg, 31%) as a yellow oil (crude). IR: 1671 (–NCHO). LR-MS *m/z*: 283 (M^+), 91 (base peak).

ii) TFAA (9.24 ml, 66.4 mmol) was added to a solution of **11a** (2 g, 6.64 mmol) in benzene (100 ml) under an argon atmosphere at room temperature. After the mixture was stirred for 4 h, $BF_3 \cdot Et_2O$ (5.04 ml, 33.2 mmol) was added, and the reaction mixture was further stirred at the same temperature for 2 h. The reaction mixture was extracted with $CHCl_3$, and washed with 5% NaOH. The residue was purified by column chromatography with AcOEt : hexane (1 : 2) to give (S)-2-formyl-3-methyl-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (**22a**) (996 mg, 53%) as a yellow oil (crude). IR: 1671 (–NCHO) cm^{-1}. LR-MS *m/z*: 283 (M^+), 102 (base peak).

Similarly, the (R)-isomer (**11b**) gave (R)-2-formyl-3-methyl-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (**22b**) (55%) as a yellow oil (crude). IR: 1671 (–NCHO) cm^{-1}. LR-MS *m/z*: 283 (M^+), 144 (base peak).

Reductive Desulfurization of 2-Formyl-4-phenylsulfanyl-3-MeTIQs (22) $NaBH_4$ (2.78 g, 73.5 mmol) was added in small portions to a stirred solution of **22a** (1 g, 3.5 mmol) and $NiCl_2 \cdot 6H_2O$ (5.85 g, 24.6 mmol) in MeOH–THF (3 : 1) (50 ml) under ice-cooling. The mixture was stirred at room temperature for 10 min, then filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt : hexane (4 : 1) to give (S)-2-formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (**23a**) (612 mg, 99%) as a yellow oil. IR: 1657 (–NCHO). LR-MS *m/z*: 175 (M^+), 91 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{11}H_{13}NO$: 175.0998. Found: 175.1026.

Similarly, the (R)-isomer (**22b**) gave (R)-2-formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (**23b**) (78%) as a yellow oil. IR: 1653 (–NCHO). LR-MS *m/z*: 175 (M^+), 91 (base peak). HR-MS *m/z* (M^+): Calcd for $C_{11}H_{13}NO$: 175.0994. Found: 175.0994.

Hydrolysis of 2-Formyl-3-MeTIQs (23) A solution of **23a** (150 mg, 0.85 mmol) in EtOH (10 ml) and 20% NaOH (10 ml) was refluxed for 17 h. The reaction mixture was diluted with water, and extracted with $CHCl_3$. The soluble part was purified by column chromatography with AcOEt to give (S)-3-methyl-1,2,3,4-tetrahydroisoquinoline (**24a**) (60 mg, 48%) as a pale yellow oil. IR: no carbonyl absorption. ^{1}H-NMR: 1.23 (3H, d, J=6 Hz, $-CH\underline{H}_3$), 2.49 (1H, dd, J=11, 16 Hz, C_4-H), 2.77 (1H, dd, J=4, 16 Hz, C_4-H), 3.0—3.1 (1H, m, C_3-H), 4.00, 4.10 (each 1H, d, J=16 Hz, C_1-H), 7.0—7.1 (4H, m, PhH). ^{13}C-NMR: 22.4 (q), 37.1 (t), 48.5 (t), 49.2 (d), 125.6 (d), 125.9 (d×2), 129.0 (d), 134.8 (s), 135.3 (s). CI-MS *m/z*: 148 (MH^+). $[\alpha]_D^{26}$=+124.0° (c=1.04, $CHCl_3$) [lit.[12]: +118.9° (c=0.2, EtOH) and lit.[13]: +78° (c=0.40, MeOH)]. CD (c=3.06×10^{-3} M in MeOH) $[\theta]^{25}$ (nm): +292 (270), +277 (264).

Similarly, the (R)-isomer (**23b**) gave (R)-3-methyl-1,2,3,4-tetrahydroisoquinoline (**24b**) (51%) as a pale yellow oil. CI-MS *m/z*: 148 (MH^+). $[\alpha]_D^{26}$=−119.9° (c=1.04, $CHCl_3$) [lit.[13]: −75° (c=0.40, MeOH)]. CD (c=3.43×10^{-3} M in MeOH) $[\theta]^{25}$ (nm): −323 (270), −291 (264).

Reduction of 2-Formyl-3-MeTIQs (23) with $LiAlH_4$ $LiAlH_4$ (46 mg, 1.2 mmol) was added to a solution of **23a** (103 mg, 0.59 mmol) in dry THF (20 ml) under ice-cooling, and the mixture was refluxed for 2 h. After decomposition of excess hydride with 10% NaOH (5 ml), the precipitates were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography over Al_2O_3 with AcOEt : hexane (4 : 1) to give (S)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**25a**) (51 mg, 54%) as a pale yellow oil. IR: no carbonyl absorption. ^{1}H-NMR: 1.17 (3H, d, J=6 Hz, $-CH\underline{H}_3$), 2.41 (3H, s, $-NCH_3$), 2.6—2.7 (2H, m, C_4-H), 2.8—2.9 (1H, m, C_3-H), 3.56, 3.81 (each 1H, d, J=15 Hz, C_1-H), 7.0—7.1 (4H, m, PhH). ^{13}C-NMR: 16.5 (q), 31.9 (t), 37.0 (q), 53.7 (t), 55.2 (d), 126.9 (d), 127.2 (d), 127.6 (s), 128.0 (d), 128.9 (d), 130.6 (s). $[\alpha]_D^{28}=+121.1°$ (c=1.68, $CHCl_3$) and +77.8° (c=1.16, MeOH) [lit.[12]: +86.3° (c=2.1, EtOH)]. CD ($c=3.15\times10^{-3}$ M in MeOH) $[\theta]^{25}$ (nm): +310 (268).

Similarly, the (R)-isomer (**23b**) gave (R)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**25b**) (52%) as a pale yellow oil. CI-MS m/z: 162 (MH^+). $[\alpha]_D^{28}=-148.5°$ (c=1.08, $CHCl_3$) and −77.4° (c=0.92, MeOH). CD ($c=2.92\times10^{-3}$ M in MeOH) $[\theta]^{25}$ (nm): −254 (266).

Pummerer Reaction of *N*-(1-Methyl-2-phenylsulfinylethyl)-*N*-(1-phenylethyl)formamides (17, ent-17, 18, ent-18). Synthesis of 1,3-DiMeTIQs TFAA (8.8 ml, 63.4 mmol) was added to a solution of ent-**17** (1 g, 3.17 mmol) in benzene (100 ml) under an argon atmosphere at room temperature. After the mixture was stirred for 2 h, $BF_3\cdot Et_2O$ (9.6 ml, 63.4 mmol) was added, and the reaction mixture was further stirred at the same temperature for 2 h. The reaction mixture was neutralized with 5% NaOH, and extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt : hexane (1 : 2) to give ent-**26**, ent-**27**, and ent-**28** as a crude material, respectively.

(1S,3R)-2-Formyl-1,3-dimethyl-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (ent-**26**): Yield: 46% (crude). Yellow oil. IR: 1668 (–NCHO) cm^{-1}. LR-MS m/z: 297 (M^+), 109 (base peak).

N-(1-Methyl-2-phenylsulfanyl)-*N*-[(S)-1-phenylethyl]formamide (ent-**27**): Yield: 2% (crude). Pale yellow oil. IR: 1656 (–NCHO) cm^{-1}.

N-(1-Methyl-2-oxoethyl)-*N*-[(S)-1-phenylethyl]formamide (ent-**28**): Yield: 10% (crude). Pale yellow oil. IR: 1731 (–CHO), 1656 (–NCHO) cm^{-1}.

Similarly, **17**, **18**, ent-**18** gave 2-formyl-4-phenylsulfanyl-1,3-DiMeTIQs (**26**, **29**, ent-**29**) as a crude material, respectively.

(1R,3S)-2-Formyl-1,3-dimethyl-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (**26**): Yield: 46% (crude). Yellow oil. IR: 1668 (–NCHO) cm^{-1}. LR-MS m/z: 297 (M^+), 188 (base peak). HR-MS m/z (M^+): Calcd for $C_{18}H_{19}NOS$: 297.1188. Found: 297.1203.

(1S,3S)-2-Formyl-1,3-dimethyl-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (**29**): Yield: 21% (crude). Yellow oil. IR: 1677 (–NCHO). LR-MS m/z: 297 (M^+), 130 (base peak). HR-MS m/z: (M^+): Calcd for $C_{18}H_{19}NOS$: 297.1188. Found: 297.1224.

(1R,3R)-2-Formyl-3-methyl-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (ent-**29**): Yield: 26% (crude). Yellow oil. IR: 1671 (–NCHO). LR-MS m/z: 297 (M^+), 109 (base peak). HR-MS m/z (M^+): Calcd for $C_{18}H_{19}NOS$: 297.1188. Found: 297.1218.

Reductive Desulfurization of 2-Formyl-4-phenylsulfanyl-1,3-DiMeTIQs (26, ent-26, 29, ent-29) $NaBH_4$ (795 mg, 21 mmol) was added in small portions to a stirred solution of ent-**26** (300 mg, 1 mmol) and $NiCl_2\cdot 6H_2O$ (1.16 g, 7 mmol) in MeOH : THF (3 : 1) (70 ml) under ice-cooling. The mixture was stirred at room temperature for 10 min, then filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt : hexane (1 : 2) followed by MPLC with AcOEt : hexane (1 : 2) to give (1S, 3R)-2-formyl-1,3-dimethyl-1,2,3,4-tetrahydrolisoquinoline (ent-**30**) as a colorless oil. Yield: 16% from ent-**17**. IR: 1671 (–NCHO) cm^{-1}.

Similarly, reduction of the isomers (**26**, **29**, ent-**29**) gave 2-formyl-1,3-DiMeTIQs (**30**, **31**, ent-**31**), respectively.

(1R,3S)-2-Formyl-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**30**): Yield: 16% from **17**. Colorless gum. IR: 1671 (–NCHO) cm^{-1}.

(1S,3S)-2-Formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (**31**): Yield: 13% from **18**. Colorless gum. IR: 1658 (–NCHO) cm^{-1}. LR-MS m/z: 189 (M^+), 146 (base peak).

(1R,3R)-2-Formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (ent-**31**): Yield: 19% from ent-**18**. Colorless gum. IR: 1658 (–NCHO) cm^{-1}. LR-MS m/z: 189 (M^+), 174 (base peak).

Hydrolysis of 2-Formyl-1,3-DiMeTIQs (30, ent-30, 31, ent-31) A solution of **30** (90 mg, 0.48 mmol) in EtOH (10 ml) and 20% NaOH (10 ml) was refluxed for 17 h under an argon atmosphere. The reaction mixture was diluted with water, and extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt to give **1** (58 mg, 76%) as a pale yellow oil.

Similarly, the isomers (ent-**30**, **31**, ent-**31**) gave 1,3-DiMeTIQs (ent-**1**, **2**, ent-**2**), respectively.

(1R,3S)-1,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline (**1**): A pale yellow oil. IR: no carbonyl absorption. ^{1}H-NMR: 1.21 (3H, d, J=7 Hz, C_3-Me), 1.45 (3H, d, J=7 Hz, C_1-Me), 2.46 (1H, dd, J=10, 16 Hz, C_4-Ha), 2.79 (1H, dd, J=4, 16 Hz, C_4-Hb), 3.28 (1H, m, C_3-H), 4.23 (1H, q, J=7 Hz, C_1-H), 7.0—7.2 (4H, m, PhH). ^{13}C-NMR: 22.4 (q), 24.2 (q), 37.5 (t), 42.7 (d), 50.8 (d), 125.6 (d), 125.9 (d), 126.7 (d), 129.1 (d), 134.4 (s), 134.0 (s). FAB-LR-MS m/z: 162 (MH^+, base peak). $[\alpha]_D^{29}=+47.0°$ (c=1.60, $CHCl_3$). CD ($c=3.11\times10^{-3}$ M in MeOH) $[\theta]^{25}$ (nm): +655 (270), +718 (265).

(1S,3R)-1,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline (ent-**1**): Yield: 74%. Pale yellow oil. FAB-LRMS m/z: 162 (MH^+), 162 (base peak). $[\alpha]_D^{29}=-45.1°$ (c=1.00, $CHCl_3$). CD ($c=2.48\times10^{-3}$ M in MeOH) $[\theta]^{25}$ (nm): −624 (271), −689 (265).

(1S,3S)-1,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline (**2**): Yield: 60%. Pale yellow oil. IR: no carbonyl absorption. ^{1}H-NMR: 1.25 (3H, d, J=6 Hz, C_3-Me), 1.48 (3H, d, J=7 Hz, C_1-Me), 2.57 (1H, dd, J=11, 16 Hz, C_4-H_a), 2.75 (1H, dd, J=4, 16 Hz, C_4-H_b), 3.0—3.1 (1H, m, C_3-H), 4.16 (1H, q, J=6 Hz, C_1-H), 7.1—7.2 (4H, m, PhH). ^{13}C-NMR: 22.3 (q), 22.6 (q), 38.3 (t), 49.0 (d), 52.6 (d), 125.2 (d), 125.9 (d), 125.9 (d), 128.9 (d), 135.1 (s), 139.9 (s). FAB-LR-MS m/z: 162 (MH^+), 162 (base peak). $[\alpha]_D^{29}=+97.3°$ (c=0.32, $CHCl_3$). CD ($c=4.97\times10^{-3}$ M in MeOH) $[\theta]^{25}$ (nm): −582 (271), −671 (26).

(1R,3R)-1,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline (ent-**2**): Yield: 65%. Pale yellow oil. FAB-LR-MS m/z: 162 (MH^+), 162 (base peak). $[\alpha]_D^{29}=-96.9°$ (c=0.87, $CHCl_3$). CD ($c=3.73\times10^{-3}$ M in MeOH) $[\theta]^{25}$ (nm): +554 (271), +613 (265).

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