

Determination of Ring Conformation in 1-Benzyl-1,2,3,4-tetrahydroisoquinolines and a New Synthesis of the Chiral Compounds

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Received September 16, 1997; accepted October 22, 1997

The conformation of the piperidine ring in 1-benzyl-1,2,3,4-tetrahydroisoquinolines was determined as ²H₃ form with a pseudoaxial position of the 1-benzyl group by circular dichroism (CD) spectral comparison with 1-methyl-1,2,3,4-tetrahydroisoquinolines. The chiral center at C-1 of 1,2,3,4-tetrahydroisoquinoline (TIQ) was constructed in an unambiguous manner by applying a new method of TIQ synthesis utilizing the Pummerer reaction as a key step. Enantiomerically pure (*R*)- and (*S*)-1-methyl- and 1-benzyltetrahydroisoquinolines (**1**) were prepared starting from readily available chiral amines (**2**) in good overall yields.

Key words 1-benzyl-1,2,3,4-tetrahydroisoquinoline; conformation; circular dichroism spectrum; Pummerer reaction; 1-methyl-1,2,3,4-tetrahydroisoquinoline

1-Methyl- and 1-benzyl-1,2,3,4-tetrahydroisoquinolines (1-MeTIQ and 1-BnTIQ) (**1**) are known to occur in the human brain and to participate in the pathogenesis of Parkinson's disease. In animal experiments it was found that 1-MeTIQ protects against the onset of parkinsonism,¹⁾ while 1-BnTIQ induces the syndrome.²⁾ Generally speaking, elucidation of the stereostructure of biologically active compounds is essential for the interpretation of related biological phenomena. We speculated that this difference in biological activity between these TIQs might be attributable to a conformational difference in the TIQ ring. Although the ring conformation in 1-MeTIQ was unambiguously determined by Craig *et al.*,³⁾ that of 1-BnTIQ has not been reported.

In order to prepare enantiomerically pure 1-MeTIQ and 1-BnTIQ in an unambiguous manner we adopted a new method of TIQ synthesis utilizing the Pummerer reaction. Application of the Pummerer reaction to the synthesis of TIQ was first reported by Takano and co-workers.⁴⁾ Recently, we have modified this method and achieved a highly efficient TIQ synthesis starting from aromatic aldehydes⁵⁾ and aromatic ketones.⁶⁾ In particular, we demonstrated that the intramolecular cyclization *via* the Pummerer reaction quantitatively occurs under mild conditions even when the nucleophilic benzene ring of the sulfoxide [(±)-**5**] is not activated by an electron-donating substituent (Chart 1). In this paper, we describe a new synthesis of chiral 1-MeTIQ and 1-BnTIQ in both enantiomeric forms, starting from chiral 1-phenylethylamine and 1,2-diphenylethylamine, and deduce the conformation of 1-BnTIQ by applying the quadrant rule introduced by Craig *et al.*³⁾

Results and Discussion

The sulfoxide, (*R*)-*N*-(1-phenylethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**5a**), was prepared in three steps from commercially available (*R*)-1-phenylethylamine (**2a**). The optical purity of **2a** was confirmed to be over 99% by chiral HPLC analysis. Treatment of **2a** with 2-phenylthioethyl chloride in refluxing toluene in the presence of

a phase-transfer catalyst caused monoalkylation to give (*R*)-*N*-(1-phenylethyl)-2-(phenylthio)ethylamine (**3a**) in 79% yield. The product was proved to be enantiomerically pure by chiral HPLC analysis. Formylation of **3a** with formic acid–acetic anhydride followed by oxidation of the resulting formamide (**4a**) with NaIO₄ in aqueous MeOH gave the sulfoxide (**5a**) in 86% yield. This oxidation also gave the sulfone (**6a**) as a by-product in 8% yield. The HPLC analysis of **5a** indicated that the sulfoxide was a 1 : 1 mixture of diastereomers. Thus, the (*R*)-sulfoxide (**5a**) was prepared from **2a** in 68% overall yield.

The intramolecular cyclization of **5a** proceeded quantitatively on sequential treatment with trifluoroacetic anhydride (TFAA) and BF₃·Et₂O in benzene at room temperature, as in the case of the racemate⁶⁾ to give a TIQ derivative (**7a**) as a mixture of diastereomers in 97% yield. Reductive desulfurization of **7a** with NaBH₄ in the presence of NiCl₂ gave (*R*)-*N*-formyl-1-MeTIQ (**8a**) in 79% yield, although (*R*)-*N*-formyl-1,2-dihydroisoquinoline (**9a**) was also formed as a by-product in 5% yield. Hydrolysis of **8a** with 10% NaOH in EtOH gave **1a** in 94% yield. Reduction of **8a** with LiAlH₄ gave **10a** in 95% yield. Thus, (*R*)-1-MeTIQ (**1a**) and (*R*)-1,2-diMeTIQ (**10a**) were prepared from **2a** in 49% and 50% overall yields, respectively.

The enantiomeric amine (**2b**) gave (*S*)-1-MeTIQ (**1b**) and (*S*)-1,2-diMeTIQ (**10b**) in similar overall yields (51% for **1b** and 47% for **10b**).

(*R*)-1-BnTIQ (**1c**) and the *N*-methyl derivative (**10c**) were synthesized *via* exactly the same steps from (*R*)-1,2-

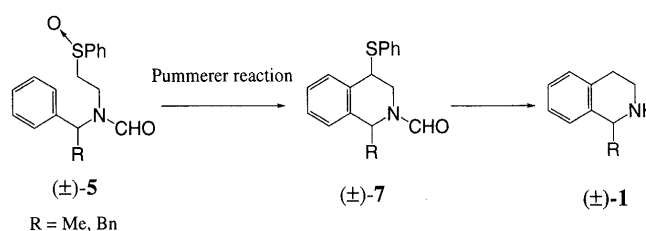


Chart 1

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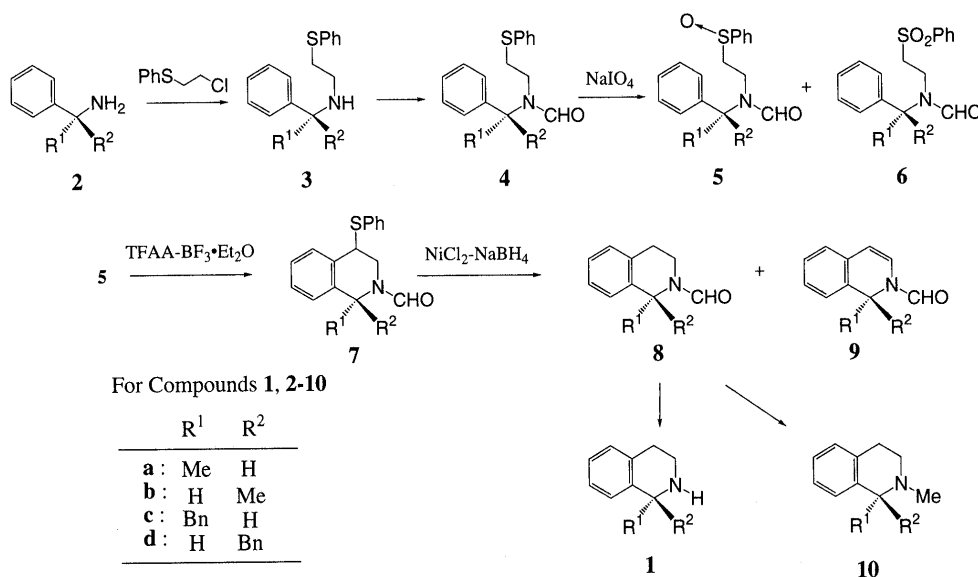


Chart 2

diphenylethylamine (**2c**). The chiral amine (**2c**) was obtained by optical resolution of the *d*-tartaric acid salt. The optical purity of the (*R*)-isomer was confirmed to be over 99% by chiral HPLC analysis. Monoalkylation of **2c** with 2-phenylthioethyl chloride slowly proceeded in the presence of a phase-transfer catalyst under refluxing dioxane to give (*R*)-*N*-(1,2-diphenylethyl)-2-(phenylthio)ethylamine (**3c**) in 61% yield. The compound was proved to be enantiomerically pure by chiral HPLC analysis. Formylation of **3c** followed by oxidation with NaIO₄ yielded the sulfoxide (**5c**) as a mixture of diastereomers in 95% yield. Pummerer cyclization of **5c** followed by reductive desulfurization gave (*R*)-*N*-formyl-1-BnTIQ (**8c**) in 69% yield, and this product was converted into **1c** and **10c** by conventional methods. Thus, (*R*)-1-BnTIQ (**1c**) and (*R*)-1-Bn-2-MeTIQ (**10c**) were prepared from **2c** in 34% and 32% overall yields, respectively.

The enantiomers, (*S*)-1-BnTIQ (**1d**) and (*S*)-1-Bn-2-MeTIQ (**10d**), were synthesized from the enantiomeric amine (**2d**) in similar overall yields (each 35% for **1d** and **10d**).

1-MeTIQs (**1a, b**) and 1-BnTIQs (**1c, d**) thus prepared were confirmed to be enantiomerically pure by chiral HPLC analyses,⁷⁾ demonstrating that epimerization at the chiral carbon did not occur at any step. The CD spectra of **1a—d**, the *N*-methyl derivatives **10a—d**, and the *N*-formyl derivatives **8a—d** clearly showed that each of the pairs are enantiomeric, as shown in Fig. 1.

The chiral moiety (piperidine ring) of 1-substituted TIQ may assume two conformations A and B (only the *R*-isomer is depicted in Fig. 2) with an opposite sense of helicity relative to the benzene ring and the CD spectra of 1-MeTIQ exhibited two Cotton effects at around 220 nm (¹L_a band) and 270 nm (¹L_b band).³⁾ The semiempirical quadrant rule based on one-electron theory developed by Craig *et al.*³⁾ states that conformation A (²H₃ form) shows a negative Cotton effect at the ¹L_b CD band, while conformation B (³H₂ form) shows a positive Cotton effect at the ¹L_b CD band. By applying this rule, 1-MeTIQ was concluded to adopt a half chair conformation (A) with

1-Me in a pseudoaxial position, rather than a half chair conformation (B) with 1-Me in a pseudoequatorial position, as shown in Fig. 2. (*R*)-1-BnTIQ (**1c**) and (*S*)-1-BnTIQ (**1d**) exhibited a negative and a positive Cotton effect at the ¹L_b CD band (266 nm), respectively (Fig. 1a). This observed sign is identical with that of the corresponding 1-MeTIQ, although the intensity is rather different. If the quadrant rule is assumed to be applicable to 1-BnTIQ, the above result would indicate that the piperidine ring in 1-BnTIQ has the same conformation to that of 1-MeTIQ. This assumption seems reasonable, since the benzyl group is independent of the helicity of the tetrahydroisoquinoline ring. Thus, the piperidine ring in 1-BnTIQ was concluded to adopt the ²H₃ conformation A with a pseudoaxial position of the 1-benzyl group, rather than the ³H₂ conformation B with the pseudoequatorial one, as shown in Fig. 2.

The CD spectra of *N*-methyl-1-BnTIQ also showed the Cotton effect with same sign as that of *N*-methyl-1-MeTIQ, as shown in Fig. 1b, indicating that the *N*-methyl-1-BnTIQ adopts conformation A. Interestingly, the *N*-formyl derivatives (**8a—d**) showed the same signal at the ¹L_b band in both 1-MeTIQs and 1-BnTIQs, where the (*R*)-isomers showed a negative Cotton effect and the (*S*)-isomers showed a positive one (Fig. 1c). This observation again suggested that the piperidine ring in the *N*-formyl TIQs also adopts conformation A.

The results demonstrated that the quadrant rule which has been applied to determine the conformation of 1-MeTIQ derivatives is also applicable to the 1-BnTIQ derivatives, since all (*R*)-1-substituted TIQs show a negative Cotton effect at the ¹L_b band, while the (*S*)-derivatives give a positive one, although the ¹L_a band observed at around 230 nm is different, especially in the intensity. Thus, it is concluded that the piperidine ring in 1-substituted TIQs has a ²H₃ conformation with a pseudoaxial position of the 1-substituent, irrespective of the *N*-substituent. The speculation that the difference in biological behavior between these TIQs might originate from a difference in their TIQ ring conformation seems

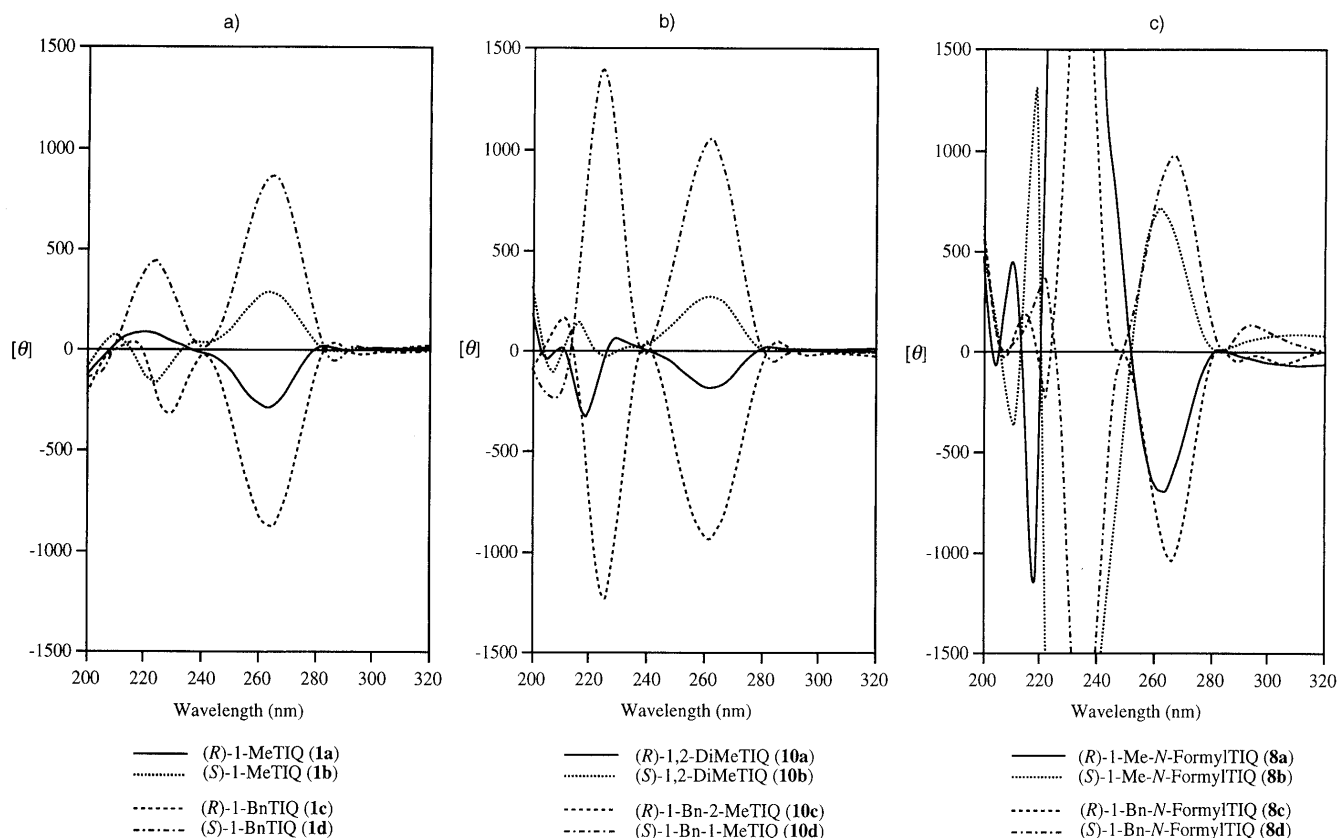


Fig. 1. CD Spectra of 1-MeTIQs and 1-BnTIQs in MeOH

a) 1-Me- and 1-BnTIQs (**1**), b) *N*-methylTIQs (**10**), c) *N*-formylTIQs (**8**).

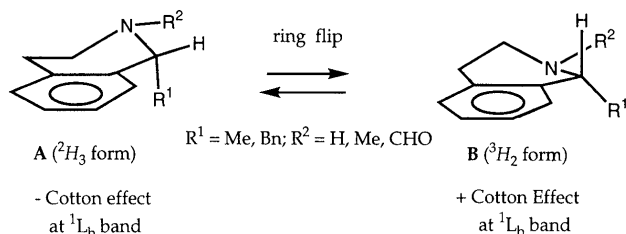


Fig. 2. Possible Conformations of (*R*)-1-Substituted TIQ

to be excluded. However, the finding that the TIQs have an identical ring conformation seems to suggest that the biological activity related to Parkinson's disease is not attributable to their interaction with an intrinsic receptor, although the presence of such a receptor has not yet been established in any case.

At the same time, the preparation of the chiral TIQs *via* this route was easily carried out on a large scale, demonstrating that this synthesis has a practical value, at least in laboratories. Moreover, this route should provide an efficient chiral synthesis applicable not only to 1-substituted TIQs,⁸⁾ but also to structurally related alkaloids⁹⁾ since the chiral arylmethanamines required as starting materials are readily obtainable by enantioselective reduction of imines.¹⁰⁾

Experimental

Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. 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 F₂₅₄ plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200). The HPLC analyses of **2** and **3** 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) and the HPLC analysis of **1** on a chiral column of Chiral-CBH (10 cm × 4 mm i.d.; room temperature; mobile phase, 10 mM phosphate buffer (pH 5.0) containing 50 mM EDTA disodium salt–acetonitrile (975:25); flow rate, 0.5 ml/min). The starting materials (*R*)-(+)-**2a** [$[\alpha]_D^{27} + 32.7^\circ$ ($c = 0.99$, CHCl₃)] and (*S*)-(–)-phenylethylamine (**2b**) [$[\alpha]_D^{27} - 34.2^\circ$ ($c = 0.95$, CHCl₃)] were obtained from Tokyo Chemical Industry Co. Ltd. and used without further purification. The spectral data for compounds **1**, **3**–**10** (except **5** and **7**) were identical with those of the corresponding racemates.⁶⁾

Optical Resolution of 1,2-Diphenylethylamine A solution of 1,2-diphenylethylamine (30 g) and L-(+)-tartaric acid (22.8 g, 1 mol eq) in MeOH (500 ml) was allowed to stand overnight at room temperature. The crystalline solid was repeatedly recrystallized from MeOH to give the (*R*)-1,2-diphenylethylamine (+)-tartaric acid salt (yield: 17.9 g, 33.8%, mp 214–217 °C). The mother liquor was concentrated *in vacuo*, and the residue was recrystallized from MeOH–EtOH to give (*S*)-1,2-diphenylethylamine (+)-tartaric acid salt (yield: 11.1 g, 20.9%, mp 193–196 °C). Treatment of each salt with 5% NaOH, followed by extraction with CHCl₃, afforded the free amine (**2c**) [$[\alpha]_D^{28} - 11.1^\circ$ ($c = 1.03$, CHCl₃)] and **2d** [$[\alpha]_D^{29} + 10.7^\circ$ ($c = 1.05$, CHCl₃)]. The optical purity of each of **2c** and **2d** was confirmed to be over 99% by chiral HPLC analysis (**2c**, 10.5 min; **2d**, 11.1 min).

Alkylation of 3 with 2-Phenylthioethyl Chloride A solution of **2a**–**d** (5–10 g), 2-phenylthioethyl chloride (1.2 mol eq), Na₂CO₃ (1.5 mol eq), NaI (0.5 mol eq), and a phase-transfer catalyst (0.1 mol eq, tetrabutylammonium bromide for **2a**, **b**, and tetraethylammonium bromide for **2c**, **d**) in dry toluene for **2a**, **b**, and in dry dioxane for **2c**, **d** (100–150 ml) was refluxed for 24 h (**2a**, **b**) or 120 h (**2c**, **d**). After removal of precipitated materials by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in Et₂O and extracted with 5% HCl. The insoluble solid and the aqueous phase were combined, basified with 10% NaOH, and extracted with CHCl₃. The products (**3a**–**d**) were purified by column

chromatography eluted with hexane–AcOEt (2:1) for **3a, b** and hexane–AcOEt (3:1) for **3c, d**.

N-(1-Phenylethyl)-2-(phenylthio)ethylamines: (*R*)-(+)-(**3a**): yield 79%, colorless oil, chiral HPLC: 18.7 min, $[\alpha]_D^{28} + 64.2^\circ$ ($c=1.04$, CHCl_3). and (*S*)-(–)-(**3b**): yield 75%, colorless oil, chiral HPLC: 11.7 min, $[\alpha]_D^{28} - 64.4^\circ$ ($c=1.00$, CHCl_3).

N-(1,2-Diphenylethyl)-2-(phenylthio)ethylamines: (*R*)-(–)-(**3c**): yield 61%, colorless needles from hexane–Et₂O, mp 78–80 °C, chiral HPLC: 10.5 min, $[\alpha]_D^{28} + 1.3^\circ$ ($c=1.01$, CHCl_3). (*S*)-(+)-(**3d**): yield 58%, colorless needles from hexane–Et₂O, mp 81–83 °C, chiral HPLC: 11.1 min, $[\alpha]_D^{29} - 2.1^\circ$ ($c=1.00$, CHCl_3).

Formylation of Amines (3) A mixture of **3a–d** (4.5–7.7 g), 98–100% formic acid (30 mol eq) and acetic anhydride (10 mol eq) was heated at 70 °C for 1 h, then concentrated *in vacuo*. The residue was diluted with water, basified with 10% NaOH, and extracted with CHCl_3 . The products (**4a–d**) were purified by column chromatography eluted with AcOEt–hexane (1:1) for **4a, b** and hexane–AcOEt (3:1) for **4c, d**.

N-(1-Phenylethyl)-*N*-[2-(phenylthio)ethyl]formamides: (*R*)-(+)-(**4a**): yield 97%, colorless oil, $[\alpha]_D^{29} + 43.2^\circ$ ($c=1.05$, CHCl_3). (*S*)-(–)-(**4b**): yield 96%, colorless oil, $[\alpha]_D^{28} - 42.5^\circ$ ($c=1.05$, CHCl_3).

N-(1,2-Diphenylethyl)-*N*-[2-(phenylthio)ethyl]formamides: (*R*)-(+)-(**4c**): yield 99%, colorless gum, $[\alpha]_D^{28} + 112.1^\circ$ ($c=1.10$, CHCl_3). (*S*)-(–)-(**4d**): yield 99%, colorless gum, $[\alpha]_D^{28} - 112.5^\circ$ ($c=0.96$, CHCl_3).

Oxidation of 5 with NaIO_4 A solution of NaIO_4 (1.5 mol eq) in H_2O (40–80 ml) was added to a solution of **4a–d** (4.5–17.4 g) in MeOH (200–350 ml), and the mixture was stirred at room temperature for 15–20 h. After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The main products (**5a–d**) and the by-products (**6a–d**) were separated by column chromatography eluted with AcOEt (for **5a, b** and **6a, b**) and AcOEt–hexane (2:1) (for **5c, d** and **6c, d**). Yield of sulfoxides (**5**): 89% (**5a**, colorless gum), 91% (**5b**, colorless gum), 96% (**5c**, colorless gum), and 97% (**5d**, colorless gum). Yield of sulfones (**6**): 7.8% (**6a**, colorless gum), 6.3% (**6b**, colorless gum), 3.6% (**6c**, colorless gum), and 2.3% (**6d**, colorless gum).

Pummerer Cyclization of Sulfoxides (5) TFAA (5 mol eq) was added to a solution of **5a–d** (4.0–7.85 g) in dry benzene (100–150 ml) at room temperature, and then the mixture was stirred for 1 h. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3 mol eq) was added and stirring was continued at the same temperature for 1 h. The reaction mixture was washed with 5% NaOH. The products (**7a–d**) were purified by column chromatography eluted with AcOEt–hexane (1:1) for **7a, b** and hexane–AcOEt (2:1) for **7c, d**. Yields of *N*-formyl-4-PhSTIQs (**7**): 97% (**7a**, colorless gum), 98% (**7b**, colorless gum), 99% (**7c**, pale yellow gum), and 99% (**7d**, pale yellow gum).

Reductive Desulfurization of 4-PhSTIQs (7) NaBH_4 (10.5 mol eq) was added in small portions to a stirred solution of **7a–d** (3.65–7.64 g) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (3.5 mol eq) in MeOH–THF (3:1) (200–450 ml) under ice-cooling. The reaction mixture was further stirred at room temperature for 30 min, then the precipitates were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was suspended in water, acidified with 5% HCl, and extracted with CHCl_3 . The products (**8a–d**) and the by-products (**9a–d**) were separated by column chromatography eluted with AcOEt–hexane (1:1) for **8a, b** and **9a, b**, and hexane–AcOEt (2:1) for **8c, d** and **9c, d**. Yield of *N*-formyl-1,2-dihydroisquinolines (**9**): 4.8% (**9a**, pale yellow oil), 3.6% (**9b**, pale yellow oil), 7.1% (**9c**, pale yellow gum), and 5.1% (**9d**, pale yellow gum).

N-FormylTIQs (**8**): (*R*)-(–)-(**8a**): yield 79%, colorless oil, $[\alpha]_D^{26} - 171.6^\circ$ ($c=0.99$, CHCl_3). CD ($c=2.93 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: +12700 (230), –700 (264). (*S*)-(+)-(**8b**): yield 85%, colorless oil, $[\alpha]_D^{27} + 163.6^\circ$ ($c=0.97$, CHCl_3). CD ($c=3.14 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: –12050 (230), +700 (264). (*R*)-(–)-(**8c**): yield 70%, colorless gum, $[\alpha]_D^{28} - 65.3^\circ$ ($c=0.97$, CHCl_3). CD ($c=2.18 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: +2250 (234), –1020 (268). (*S*)-(+)-(**8d**): yield 73%, colorless gum, $[\alpha]_D^{28} + 60.4^\circ$ ($c=0.97$, CHCl_3). CD ($c=2.05 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: –2090 (234), +990 (268).

Hydrolysis of *N*-FormylTIQs (8) A solution of **8a–d** (0.93–2.50 g) in EtOH (40 ml) and 10% NaOH (4–8 ml) (for **8a, b**) or 10% HCl (4–8 ml) (for **8c, d**) was refluxed for 10 h (for **8a, b**) or 30 h (for **8c, d**). The reaction mixture was concentrated *in vacuo*, then the residue was basified with 10% NaOH, and extracted with CHCl_3 . The products

(**1a–d**) were purified by column chromatography eluted with CHCl_3 –MeOH (9:2) for **1a, b** and CHCl_3 –MeOH (9:1) for **1c, d**.

1-MeTIQs: (*R*)-(+)-(**1a**): yield 94%, colorless oil, [HCl salt: colorless needles from EtOH–Et₂O, mp 222–223 °C], chiral HPLC: 3.05 min, $[\alpha]_D^{29} + 75.0^\circ$ (free base, $c=1.01$, CHCl_3) [lit.,¹¹] +42° (HCl salt, $c=1.13$, EtOH)]. CD (HCl salt, $c=2.76 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: –290 (266) [lit.,³] –360 (272) in 95% EtOH]. (*S*)-(–)-(**1b**): yield 93%, colorless oil [HCl salt: colorless needles from EtOH–Et₂O, mp 222–225 °C], chiral HPLC: 2.51 min, $[\alpha]_D^{29} - 77.5^\circ$ (free base, $c=0.98$, CHCl_3) [lit.,¹²] –71.3° (free base, $c=0.64$, THF)]. CD (HCl salt, $c=2.72 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: +280 (266).

1-BnTIQs: (*R*)-(+)-(**1c**): yield 86%, colorless gum [HCl salt: colorless needles from EtOH–Et₂O, mp 193–194 °C], chiral HPLC: 3.86 min, $[\alpha]_D^{29} + 54.4^\circ$ (free base, $c=1.01$, CHCl_3) [lit.,¹¹] +62.6° (free base, $c=0.92$, THF)]. CD (HCl salt, $c=1.93 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: –880 (266). (*S*)-(–)-(**1d**): yield 88%, colorless gum [HCl salt: colorless needles from EtOH–Et₂O, mp 192–194 °C], chiral HPLC: 3.33 min, $[\alpha]_D^{29} - 57.3^\circ$ (free base, $c=0.99$, CHCl_3) [lit.,¹²] –62.2° (free base, $c=1.24$, THF)]. CD (HCl salt, $c=1.95 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: +870 (266).

LiAlH_4 Reduction of *N*-FormylTIQs (8) LiAlH_4 (2 mol eq) was added to a solution of **8a–d** (0.72–1.0 g) in dry THF (40 ml) under ice-cooling, and the mixture was refluxed for 2 h. Et₂O, saturated with water, was added to the reaction mixture and insoluble material was removed by filtration. The products (**10a–d**) were purified by column chromatography eluted with CHCl_3 –MeOH (9:1) for **10a, b** and AcOEt–MeOH (9:1) for **10c, d**.

1,2-DiMeTIQs: (*R*)-(+)-(**10a**): yield 95%, colorless oil, $[\alpha]_D^{28} + 56.1^\circ$ ($c=0.96$, CHCl_3). CD (HCl salt, $c=2.64 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: –190 (266). (*S*)-(+)-(**10b**): yield 87%, colorless oil, $[\alpha]_D^{29} - 57.6^\circ$ ($c=0.96$, CHCl_3) [lit.,³] –51° (EtOH)]. CD (HCl salt, $c=2.56 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: +230 (267) [lit.,³] +320 (272) in 95% EtOH].

1-Bn-2-MeTIQs: (*R*)-(–)-(**10c**): yield 79%, colorless oil, $[\alpha]_D^{29} - 26.5^\circ$ ($c=0.99$, CHCl_3). CD (HCl salt, $c=1.88 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: –1240 (225), –940 (264). (*S*)-(+)-(**10d**): yield 87%, colorless oil, $[\alpha]_D^{29} + 29.7^\circ$ ($c=1.03$, CHCl_3). CD (HCl salt, $c=1.85 \times 10^{-3}$ M in MeOH) $[\theta]^{25}(\text{nm})$: +1440 (225), +1040 (264).

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