Organic Process Research & Development **2007,** *11,* 1043–1050

A Practical Synthesis of Enantiopure 7-Alkoxy-4-aryl-tetrahydroisoquinoline, a Dual Serotonin Reuptake Inhibitor/Histamine H_3 Antagonist

Xiaohu Deng,* Jimmy T. Liang, Jing Liu, Heather McAllister, Carsten Schubert,† and Neelakandha S. Mani

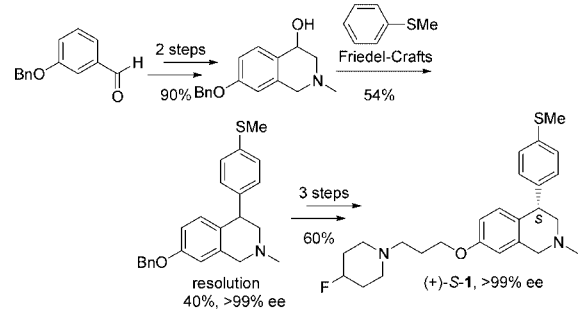
Johnson & Johnson Pharmaceutical Research & Development, LLC., 3210 Merryfield Row, San Diego, California 92121, U.S.A.

Abstract:

An efficient synthesis of compound 1 featuring a novel sequential Friedel–Crafts alkylation strategy to construct the 4-aryl-tetrahydroisoquinoline core structure has been developed. Resolution with (D/L)-di-*p*-toluoyl-tartaric acid is utilized to provide the enantiomerically pure material. Overall, the route is concise and amenable for large-scale synthesis.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) represent a very important class of antidepressant drugs; for example, Prozac and Zoloft, both SSRIs, are among the most commonly prescribed drugs for depression. However, SSRIs do not treat some of common symptoms associated with depression such as cognitive impairment and fatigue, even as mood improves.[1] Histamine H_3 inhibitors, in contrast, have been shown to improve cognition and increase wakefulness in preclinical pharmacology experiments.[2] With the expectation that a serotonin reuptake inhibitor with histamine H_3 activity may improve efficacy for the treatment of depression, a series of dual serotonin reuptake inhibitors/histamine H_3 antagonists were designed in our laboratories.[3] These compounds share the common structural feature of a 4-aryl-tetrahydroisoquinoline core tethered with a H_3 pharmacophore side chain. Among the analogs prepared, compound **1** has high affinity for both the histamine H_3 receptor and the serotonin reuptake transporter; good selectivity against a panel of over 50 receptors, ion channels and transporters; and favorable pharmacokinetic properties including good oral bioavailability and high exposure and receptor occupancy in the rat brain. A practical synthesis to provide multigram quantities of **1** was needed for further pharmacological evaluation. The initial discovery route (Scheme 1), which involves two low-yielding steps and multiple chromatographic purifications including one chiral HPLC separation, is not suitable for large-scale synthesis.[3b] For scale-up purposes, a novel sequential Friedel–Crafts alkylation strategy was devised to rapidly construct the 4-aryl-tetrahydroisoquinoline core structure, followed by a practical resolution to provide the enantiomerically pure material. We expect this sequence be applicable to the syntheses of similar 4-aryl-tetrahydroisoquinoline compounds.



Results and Discussion

The first challenge we faced in this project was to set the stereogenic center of compound **1** without resorting to chiral HPLC separation. Enantioselective syntheses of tetrahydroisoquinoline alkaloids have been extensively studied in the literature,[4] mostly involving the use of chiral auxiliaries.[5] Other successful strategies include stereoselective intramolecular cyclization of chiral precursors[6] and deracemization of diarylmethane derivatives.[7] From a practical and economical standpoint, however, we reasoned that a classic resolution would be our best choice.[8] Ideally, chiral resolution should be performed at the earliest possible stage to avoid wastage of the precious advanced intermediates. Hence, compound **4** was considered a suitable candidate. The first four steps of the discovery route

* To whom correspondence should be addressed. E-mail: xdeng@prdus.jnj.com.

† Johnson & Johnson, 665 Stockton Drive, Exton, PA 19341, U.S.A.

(1) (a) Nierenberg, A. A.; Keepe, B. R.; Leslie, V. C.; Alpert, J. E.; Pava, J. A.; Worthington, J. J.; Rosenbaum, J. F.; Fava, M. *J. Clin. Psychiatry* **1999**, *60*, 221–225. (b) Fava, G. A.; Fabbri, S.; Sonino, N. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2002**, *26*, 1019–1037.

(2) Letavic, M. A.; Barbier, A. J.; Dvorak, C. A.; Carruthers, N. I. *Prog. Med. Chem.* **2006**, *44*, 181–206.

(3) (a) Keith, J. M.; Gomez, L. A.; Letavic, M, A.; Ly, K. S.; Jablonowski, J. A.; Seierstad, M.; Barbier, A. J.; Wilson, S. J.; Boggs, J. D.; Fraser, I. C.; Mazur, C.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 702–706. (b) Letavic, M. A.; Keith, J. M.; Jablonowski, J. A.; Stocking, E. M.; Gomez, L. A.; Ly, K. S.; Miller, J. M.; Barbier, A. J.; Bonaventure, P.; Boggs, J.; Wilson, S. J.; Miller, K.; Lord, B.; McAllister, H. M.; Tognarelli, D. J.; Wu, J.; Abad, M. C.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1047–1051.

(4) (a) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903–931. (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341–3370.

(5) (a) Anan, H.; Tanaka, A.; Tsuzuki, R.; Yokota, M.; Yatsu, T.; Honda, K.; Asano, M.; Fujita, S.; Furuya, T.; Fujikura, T. *Chem. Pharm. Bull.* **1991**, *39*, 2910–2914. (b) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086–7087. (c) Philippe, N.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Org. Lett.* **2000**, *2*, 2185–2187. (d) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Biomol. Chem.* **2003**, *1*, 1701–1706. (e) Asami, M.; Taketoshi, A.; Miyoshi, K.; Hoshino, H.; Sakakibara, K. *Chem. Lett.* **2007**, *36*, 64–65.

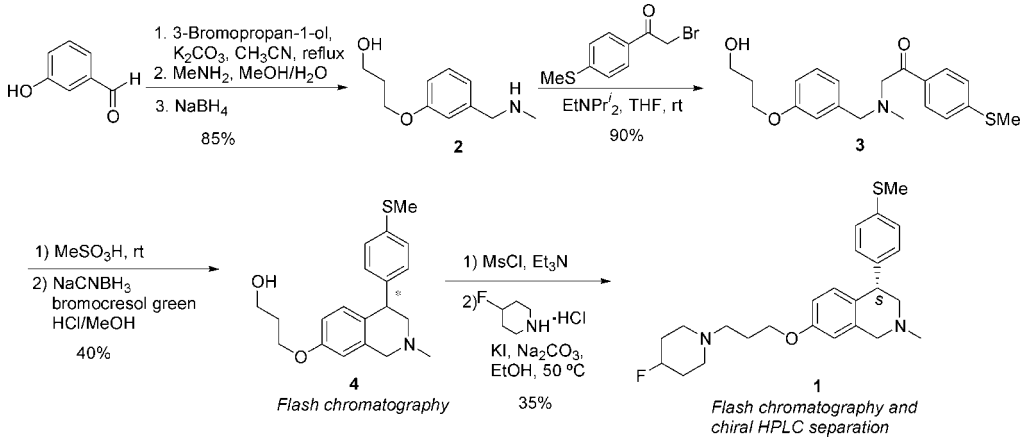
(6) Philippe, N.; Denivet, F.; Vasse, J-L; Santos, J. S. O.; Levacher, V.; Dapas, G. *Tetrahedron* **2003**, *59*, 8049–8056.

(7) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509–2516.

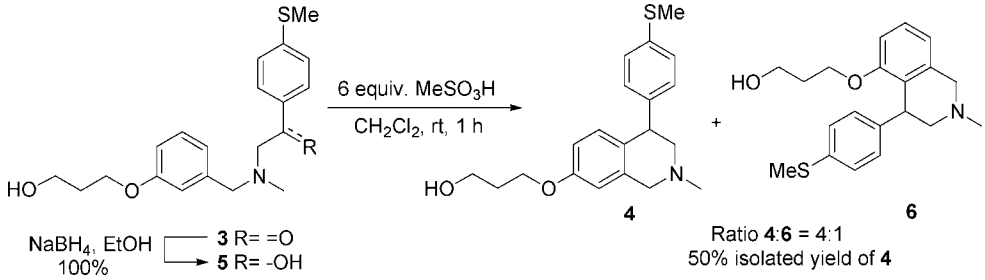
(8) (a) Den Hollander, C. W.; Leimgruber, W.; Mohacsi, E. U.S. Patent 1975/3904632. (b) Rheiner, A., Jr. SWXXAS CH 1973/53847.

10.1021/op700183q CCC: $37.00 © 2007 American Chemical Society
Published on Web 11/16/2007

Scheme 1. **Discovery synthesis of 1, a dual serotonin reuptake inhibitor/histamine H_3 antagonist**



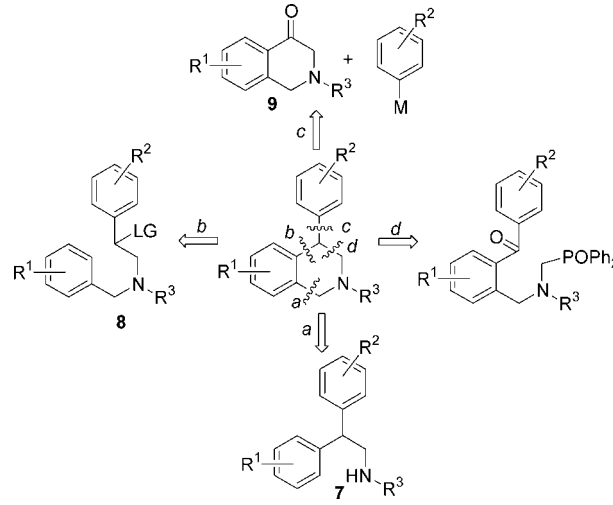
Scheme 2. **Acid-mediated cyclization of alcohol 5**



(Scheme 1) were readily scalable to provide compound **3** in 160-g scale. However, the subsequent acid-catalyzed cyclization and reduction steps afforded a low yield of 4-aryl-tetrahydroisoquinoline **4** (40%). To solve this problem, alcohol **5**, which literature precedents suggested to be more reactive towards the acid-mediated cyclization reaction,[9] was prepared by the reduction of **3** with $NaBH_4$ in EtOH in quantitative yield. The cyclization reaction of alcohol **5** could be catalyzed with various acids such as $MeSO_3H$, H_2SO_4, $AlCl_3$, $BF_3 \cdot Et_2O$, $FeCl_3$ and $SnCl_4$. Conversion was usually excellent; however, a mixture of the two possible regioisomers (Scheme 2) was invariably observed. After screening numerous reaction conditions, 6 equiv of $MeSO_3H$ in CH_2Cl_2 was found to give the best regioselectivity at 4:1 ratio favoring the desired product **4**. Fortunately, the undesired regioisomer **6** was easily removed by recrystallization from hot EtOAc. Using this method, 100 g batches of compound **4** were readily prepared without any column chromatography purification.

With racemic compound **4** in hand, resolution via diastereomeric salt formation was investigated. A panel of commercially available optically pure acids[10] was explored in several common solvents such as EtOH, IPA, CH_3CN and EtOAc. Unfortunately, all of the experiments failed to afford any crystalline salts. Attempts to resolve compound **1** were also unsuccessful. We speculated that the flexible alkoxy side chain might have impeded the crystallization process. Thus, replacement of the side chain with a more rigid group that is easily removable for future manipulation, such as a benzyl group, should greatly enhance the possibility of a successful resolution. Based on these considerations as well as the need of addressing the inherent regioselectivity problem of the acid-mediated cyclization step to prepare compound **4**, we decided to explore a more efficient route to the 4-aryl-tetrahydroisoquinoline core.

Scheme 3. **Common disconnections for the construction of the 4-aryl-tetrahydroisoquinoline core**



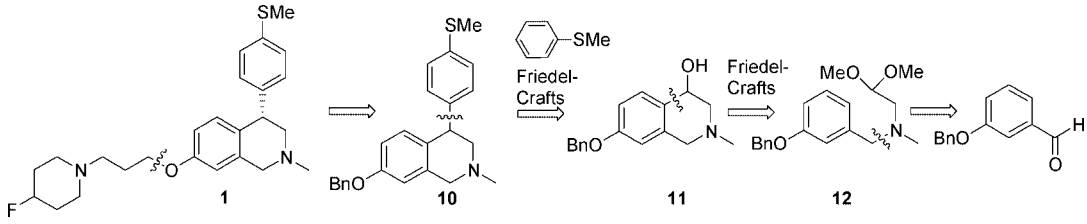
Following the isolation of Cherylline, a rare type of natural phenolic alkaloid, by Brossi and co-workers in 1970,[11] synthesis of 4-aryl-tetrahydroisoquinoline has attracted considerable at-

(9) Hara, H.; Shirai, R.; Hoshino, O.; Umezawa, B. *Chem. Pharm. Bull.* **1985**, *33*, 3107–3112.

(10) L-Tartaric acid, L-malic acid, dibenzoyl-L-tartaric acid, di-*p*-toluoyl-D-tartaric acid, (*S*)-(−)-2-pyrrolidone-5-carboxylic acid, (*R*)-(−)-10-camphorsulfonic acid, (*S*)-(+)-mandelic acid, (*S*)-(+)-6-methoxy-α-methyl-2-naphthalene acetic acid, di-*O*-isopropylidene-2-keto-L-gulonic acid, deoxycholic acid, L-glutamic acid, (*R*)-(−)-thiazolidine-4-carboxylic acid, D-quinic acid, L-aspartic acid, D-isoascorbic acid, (1*R*,3*S*)-(+)-camphoric acid, D-lactobionic acid, (*S*)-(−)-2-(phenylcarbamoyloxy)propionic acid, D-glucuroic acid.

(11) Brossi, A.; Grethe, G.; Teitel, S.; Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1970**, *35*, 1100–1104.

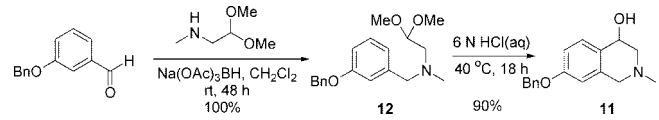
Scheme 4. **Retrosynthetic analysis**



tention due to its potential applications for the treatment of depression,[12] estrogen-related disorders,[13] Alzheimer's disease and Parkinson's disease.[14] In the literature, four distinct disconnections are most commonly employed for the construction of the 4-aryl-tetrahydroisoquinoline core, as shown in Scheme 3: (a) Pictet–Spengler cyclization of **7** with formaldehyde;[15] (b) acid-catalyzed intramolecular cyclization of compound **8** (usually a ketone or alcohol),[16] which was adopted in the discovery synthesis of compound **1**; an interesting variation of this strategy involving a Pd-catalyzed intramolecular cross-coupling reaction has also been recently reported;[17] (c) nucleophilic addition of a metal species to ketone **9**;[11,18] (d) intramolecular olefination followed by a reduction.[19]

The type c disconnection was particularly appealing to us because of the better control of regioselectivity. However, the literature methods involved the use of expensive organometallic nucleophiles. Furthermore, two subsequent steps after the nucleophilic addition were required to furnish the 4-aryl-tetrahydroisoquinoline core (dehydration of the alcohol addition product followed by reduction of the olefin). We reasoned that a direct alkylation at the benzylic position of a suitable tetrahydroisoquinoline precursor with electron-rich thioanisole would provide a shorter overall sequence and easy access to the required precursors. Therefore, a new strategy featuring sequential Friedel–Crafts alkylations was devised, as depicted in Scheme 4.

Scheme 5. **Synthesis of compound 11**



The requisite precursor **11** was easily prepared in a two-step sequence.[20] Reductive amination of 3-benzyloxybenzaldehyde with commercially available (2,2-dimethoxy-ethyl)-methylamine followed by a Friedel–Crafts cyclization in a 6 N aqueous HCl solution provided **11** in excellent yield on 50-g scales (Scheme 5). Notably, the Friedel–Crafts cyclization took place regioselectively at the *para* position of the benzyloxy group. No *ortho* regioisomer was observed.

The key transformation, alkylation of compound **11** with thioanisole, was then investigated. Direct Friedel–Crafts alkylation on benzyl alcohols is rarely found in the literature,[6,21] presumably because benzylic carbocations (the active species in the Friedel–Crafts alkylation) tend to decompose to the corresponding olefins. Indeed, our initial attempt by adding 1 equiv of triflic anhydride to a solution of compound **11** with 10 equiv of thioanisole in CH_2Cl_2 yielded only 15% of compound **10**. Nevertheless, a variety of Brönsted and Lewis acids were screened as the catalysts (Table 1). $MeSO_3H$ and H_2SO_4 led to primarily decomposition (entries 2 and 3). The Lewis acids $FeCl_3$ and $AlCl_3$ afforded no reaction (entries 4 and 5), and $TiCl_4$ caused decomposition (entry 6). $SnCl_4$ furnished desired product **10** in 34% yield, but the reaction was messy (entry 7). Switching to $BF_3 \cdot Et_2O$ afforded much cleaner reactions. Two equivalents of $BF_3 \cdot Et_2O$ were required for the reaction to go to completion, presumably because the eliminated H_2O consumes 1 equiv of the Lewis acid (entries 9–11); 54% isolated yield was obtained.[22] Further increasing to 4 equiv of $BF_3 \cdot Et_2O$ did not improve the yield (entry 12). CH_2Cl_2 was the preferred solvent; changing to *tert*-butyl methyl ether (MTBE) led to no reaction or diminished yield (entries 8 and 13). It is important to note that the $BF_3 \cdot Et_2O$-mediated Friedel–Crafts reaction took place exclusively at the *para* position of thioanisole, and no detectable *ortho* substitution product was observed. The attempts to promote this reaction with catalytic amounts of water-stable Lewis acids such as $La(OTf)_3$ and $Yb(OT)_3$ were not successful (entries 14–16),

(12) (a) Jacob, J. N.; Nichols, D. E. *J. Med. Chem.* **1981**, *24*, 1013–1015. (b) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433–1454.

(13) Chesworth, R.; Zawistoski, M. P.; Lefker, B. A.; Cameron, K. O.; Day, R. F.; Mangano, F. M.; Rosati, R. L.; Colella, S.; Petersen, D. N.; Brault, A.; Lu, B.; Pan, L. C.; Perry, P.; Ng, O.; Castleberry, T. A.; Owen, T. A.; Brown, T. A.; Thompson, D. D.; Dasilva-Jardine, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2729–2733.

(14) Wanner, K. T.; Beer, H.; Hoefner, G.; Ludwig, M. *Eur. J. Org. Chem.* **1998**, *9*, 2019–2029.

(15) (a) Bates, H. A. *J. Org. Chem.* **1981**, *46*, 4931–4935. (b) Bates, H. A. *J. Org. Chem.* **1983**, *48*, 1932–1934. (c) Bates, H. A.; Bagheri, K.; Vertino, P. M. *J. Org. Chem.* **1986**, *51*, 3061–3063. (d) Katakawa, J.; Yoshimatsu, H.; Yoshida, M.; Zhang, Y.; Irie, H.; Yajima, H. *Chem. Pharm. Bull.* **1988**, *36*, 3928–3932. (e) Ruchirawat, S.; Tontoolarug, S.; Sahakitpichan, P. *Heterocycles* **2001**, *55*, 635–640.

(16) (a) Hara, H.; Shirai, R.; Hoshino, O.; Umezawa, B. *Heterocycles* **1983**, *20*, 1945–1950. (b) Zara-Kaczian, E.; Deak, G.; Szollosy, A.; Brlik, J. *Acta Chim. Hung.* **1990**, *127*, 743–755. (c) Toda, J.; Sonobe, A.; Ichikawa, T.; Saitoh, T.; Horiguchi, Y.; Sano, T. *ARKIVOC* **2000**, *1*, 165–180.

(17) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631–633.

(18) Renaud, J.; Bischoff, S. F.; Buhl, T.; Floersheim, P.; Fournier, B.; Halleux, C.; Kallen, J.; Keller, H.; Schlaeppi, J. M.; Stark, W. *J. Med. Chem.* **2003**, *46*, 2945–2957.

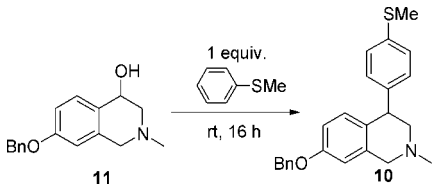
(19) Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 789–794.

(20) Dyke, S. F.; Bather, P. A.; Garry, A. B.; Wiggins, D. W. *Tetrahedron* **1973**, *29*, 3881–3888.

(21) (a) Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* **1991**, *56*, 183–187. (b) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, *68*, 9340–9347. (c) Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, *43*, 351–353.

(22) After the reaction was complete, only product **10** and unreacted thioanisole were observed on HPLC and TLC analysis. Decomposition of starting material **11** might have occurred, which led to weakly or non-chromophoric side products.

Table 1. **Acid-mediated Friedel–Crafts alkylation of compound 11**



entry	acid	solvent	result
1	1.0 equiv Tf_2O	CH_2Cl_2	15%[a]
2	2 equiv $MeSO_3H$	CH_2Cl_2	decomposition
3	1.5 equiv H_2SO_4	CH_2Cl_2	decomposition
4	1.1 equiv $FeCl_3$	CH_2Cl_2	SM
5	3.0 equiv $AlCl_3$	CH_2Cl_2	SM
6	1.1 equiv $TiCl_4$	CH_2Cl_2	decomposition
7	1.1 equiv $SnCl_4$	CH_2Cl_2	34%
8	1.1 equiv $SnCl_4$	MTBE	decomposition
9	0.5 equiv $BF_3 \cdot Et_2O$	CH_2Cl_2	SM
10	1.2 equiv $BF_3 \cdot Et_2O$	CH_2Cl_2	incomplete
11	2.0 equiv $BF_3 \cdot Et_2O$	CH_2Cl_2	54%
12	4.0 equiv $BF_3 \cdot Et_2O$	CH_2Cl_2	51%
13	2.0 equiv $BF_3 \cdot Et_2O$	MTBE	SM
14	0.1 equiv $La(OTf)_3$	CH_2Cl_2	SM[b]
15	0.1 equiv $Yb(OTf)_3$	CH_2Cl_2	SM[b]
16	0.1 equiv $La(OTf)_3$	CH_3NO_2	SM[b]

[a] Ten equivalents of thioanisole were used. [b] No desired reaction was observed even at reflux temperature overnight.

probably because the Lewis acids coordinate to the basic tertiary amine. Nonetheless, to the best of our knowledge, this sequence represented the first example of construction of a 4-aryl-tetrahydroisoquinoline core structure through sequential Friedel–Crafts reactions.

With gram quantities of racemic **10** in hand, we screened a panel of commercially available optically pure acids[10] and di-*p*-toluoyl-tartaric acid stood out as the acid of choice. With 0.5 equiv of D-di-*p*-toluoyl-tartaric acid, the *R* enantiomer was preferably precipitated from EtOH/CH_3CN as a crystalline diastereomeric hemi-tartrate salt **13** in >99% ee in 33% recovery. Recrystallization of the mother liquor afforded another crop of **13** in >99% ee to give an overall 40% recovery. A single crystal X-ray structure of **13** was obtained to assign the absolute stereochemistry (Figure 1). Basification of the diastereomeric salt **13** with aqueous Na_2CO_3 solution afforded enantiopure free base (–)-(*R*)-**10**, which was derivatized to compound **4**. In comparison with enantiopure sample **4** previously separated by chiral HPLC, the desired enantiomer was found to be the *S* configuration. The same chiral resolution was then performed with L-di-*p*-toluoyl-tartaric acid to provide (+)-(*S*)-**10** in identical results.[23]

Debenzylation of (+)-(*S*)-**10** followed by alkylation with 3-bromopropan-1-ol furnished (+)-(*S*)-**4** in 80% yield for two steps (Scheme 6).

The final stage of synthesis of **1** is the introduction of the 4-fluoropiperidine moiety. The discovery conditions (Scheme 1) provided the desired compound **1** in only 35% yield even with 4 equiv of expensive 4-fluoropiperidine hydrochloride. Whereas the mesylation of alcohol **4** went smoothly in quantitative yield, we identified that the problem of the low yield resided on the weak nucleophilicity of 4-fluoropiperidine. The chloride ions present in the starting material were competing with 4-fluoropiperidine in the displacement of the mesylate (Scheme 7), resulting in byproduct **15**. Once chloride **15** was formed, displacement of **15** with 4-fluoropiperidine only took place at a much higher temperature (ca. 200 °C). To solve this problem, the 4-fluoropiperidine free base was freshly prepared from the commercially available hydrochloride salt by partitioning between water-immiscible *tert*-amyl alcohol and aqueous NaOH solution. The *tert*-amyl alcohol solution of the 4-fluoropiperidine free base[24] was then used directly in the displacement reaction of the mesylate at 100 °C to afford **1** in excellent yield. After recrystallization from hot EtOH, pure (+)-(*S*)-**1** was obtained in 75% isolated yield. HPLC analysis indicated no racemization occurred during the whole synthesis.

Conclusions

In conclusion, a practical synthesis of enantiomerically pure (+)-(*S*)-**1** was developed (Scheme 8). This route features a novel sequential Friedel–Crafts reaction strategy to construct the 4-aryl-tetrahydroisoquinoline core structure. A classic resolution using D-di-*p*-toluoyl-tartaric acid was successfully performed to provide enantiomerically pure material. Overall, this route is concise, high-yielding and amenable for large-scale synthesis.

Experimental Section

General. All reagents and solvents were purchased from commercial sources and used without further purification. ^1H and ^{13}C NMR spectra were recorded on Bruker 500 (^1H, 500 MHz; ^{13}C, 125 MHz) or 400 (^1H, 400 MHz; ^{13}C, 100 MHz) NMR spectrometers. Flash column chromatography was performed using Merck silica gel 60. Reaction was monitored by HPLC analysis (HP 1100, Agilent ZORBAX Eclipse XDB-C8 column, 5 μm, 4.6 mm × 150 mm, flow rate 0.75 mL/min, gradient (acetonitrile/water containing 0.05% trifluoroacetic acid) of 1% acetonitrile/99% water to 99% acetonitrile/1% water ramp over 8 min, then hold at 99% acetonitrile/1% water). HRMS (ESI) was performed on a Bruker μTof. Analytical chiral analysis was performed on a Hewlett Packard 1100 HPLC or a Jasco 1580 series SFC. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected.

3-(3-Methylaminomethylphenoxy)propan-1-ol (2). To a solution of 3-hydroxy-benzaldehyde (68 g, 0.56 mol, 1.0 equiv) in CH_3CN (1 L) were added K_2CO_3 (115 g, 0.83 mol, 1.5 equiv) and 3-bromopropan-1-ol (93 g, 0.67 mol, 1.2 equiv) sequentially at room temperature. The reaction mixture was stirred at reflux temperature for 3 h and then cooled to room temperature. EtOAc (500 mL) and H_2O (500 mL) were added. The organic layer was washed with water (500 mL × 2), brine (500 mL) and dried over $MgSO_4$. Evaporation of the solvents afforded 3-(3-hydroxy-propoxy)-benzaldehyde as a colorless oil (HPLC retention time: 7.32 min, 101 g, 0.56 mol, 100%), which was used directly in the next reaction. The crude 3-(3-hydroxy-propoxy)-benzaldehyde was dissolved in EtOH (700 mL).

(23) Attempts to racemize the undesired (–)-(*R*)-**10** under strong basic conditions or Pd-catalyzed hydrogenation conditions were not successful.

(24) Neat 4-fluoropiperidine free base is highly volatile and difficult to handle.

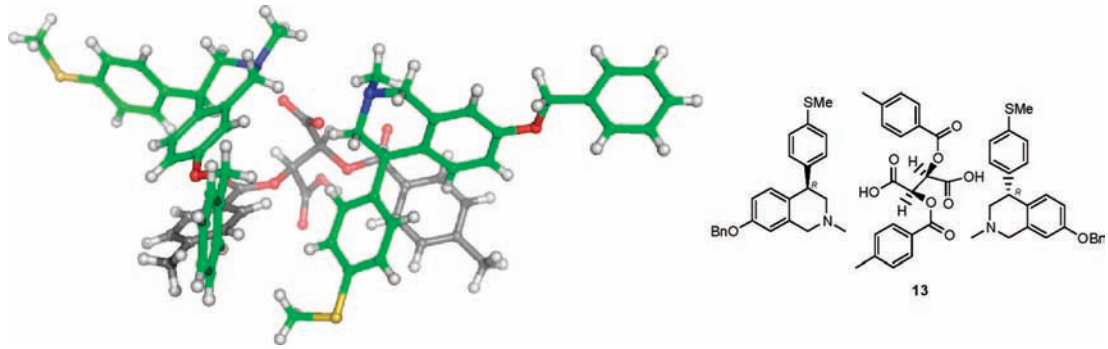
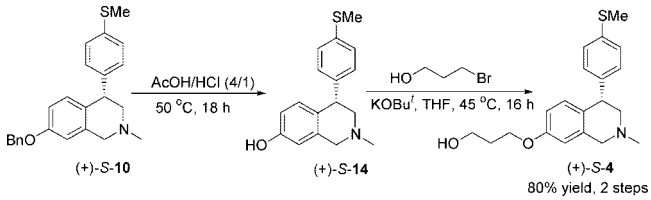
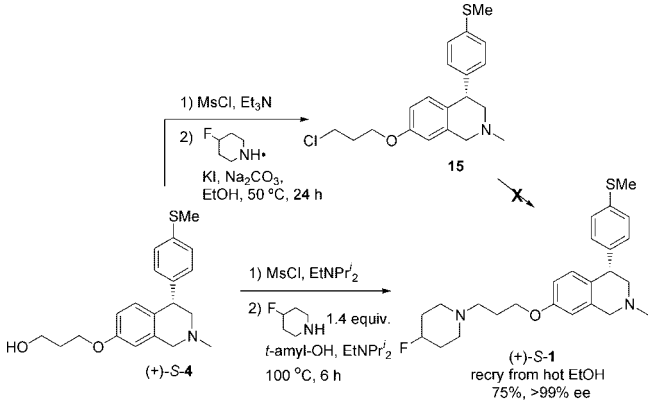


Figure 1. **X-ray structure of compound 13.**

Scheme 6. **Synthesis of compound 4**



Scheme 7. **Displacement of compound 4**



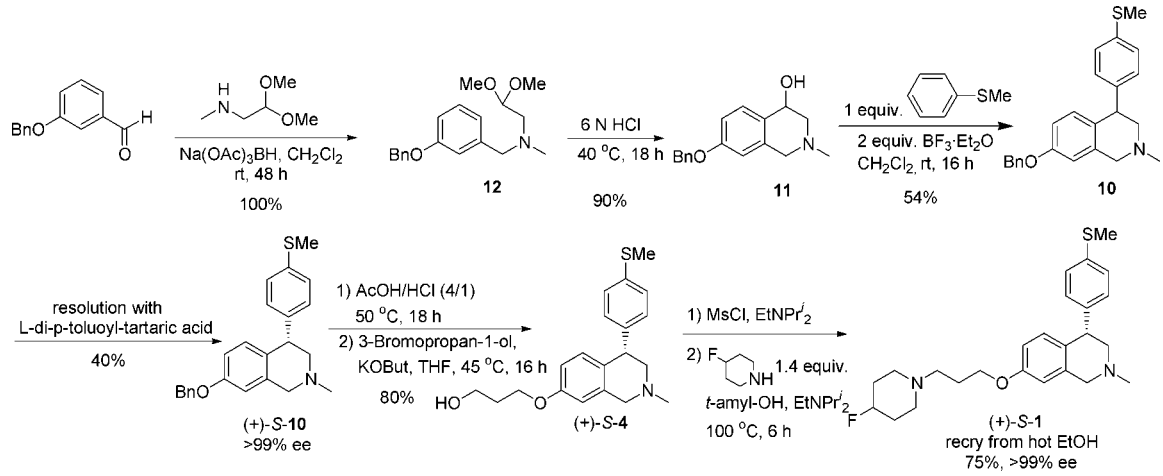
$MeNH_2$ (40 wt % in water, 58 mL, 0.67 mol, 1.2 equiv) was added over 20 min at 0 °C. After 10 min, $NaBH_4$ (10.6 g, 0.28 mol, 0.5 equiv) was carefully added as solid. The reaction mixture was stirred at 0 °C for 3 h. Aqueous 2.0 mol/L HCl solution was slowly added until pH = 2.0 to quench the unreacted $NaBH_4$. EtOH was evaporated, and the residue was dissolved in H_2O (700 mL). After being washed with EtOAc (300 mL), the aqueous layer was basified with NaOH pellet to pH = 12 and then extracted with CH_2Cl_2 (300 mL × 3). The combined organic layers were dried over $MgSO_4$ and concentrated to afford **2** as a colorless oil (92 g, 0.48 mol, 85%). No further purification was performed. HPLC retention time: 5.04 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.23 (t, J = 7.9 Hz, 1H), 6.94 (t, J = 1.8 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.81 (dd, J = 8.2, 2.4 Hz, 1H), 4.13 (t, J = 6.0 Hz, 2H), 3.83 (t, J = 5.9 Hz, 2H), 3.74 (s, 2H), 2.44 (s, 3H), 2.02 (penta, J = 6.0 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 159.1, 140.3, 129.5, 120.9, 114.3, 113.7, 65.7, 60.2, 55.5, 35.4, 32.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{11}H_{18}NO_2$ 196.1332, found 196.1328.

2-{[3-(3-Hydroxypropoxy)benzyl]-methylamino}-1-(4-methylsulfanylphenyl)ethanone (3). To a solution of **2** (100 g, 0.51 mol, 1.0 equiv) and EtNPr$^i_2$ (80 g, 0.62 mol, 1.2 equiv) in THF (1 L) was added 2-bromo-1-(4-methylsulfanyl-phenyl)-ethanone (125 g, 0.51 mol, 1.0 equiv) in portions over 20 min. The reaction mixture was stirred at room temperature for 1 h. After removal of the solvent via evaporation, the residue was partitioned between EtOAc (1 L), saturated $NaHCO_3$ aqueous solution (500 mL) and water (500 mL). The aqueous layer was further extracted with EtOAc (500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford **3** as a colorless oil (165 g, 0.46 mol, 90%). No further purification was performed. HPLC retention time: 7.00 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.87 (dt, J = 8.6, 1.9 Hz, 2H), 7.25–7.18 (m, 3H), 4.94–6.87 (m, 2H), 6.82–6.77 (m, 1H), 4.08 (t, J = 6.0 Hz, 2H), 3.83 (t, J = 6.0 Hz, 2H), 3.72 (s, 2H), 3.61 (s, 2H), 2.50 (s, 3H), 2.35 (s, 3H), 2.02 (penta, J = 6.0 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 197.0, 158.9, 145.9, 139.9, 132.3, 129.3, 128.8, 124.8, 121.6, 115.0, 113.7, 65.6, 63.1, 62.0, 60.2, 42.9, 32.1, 14.7. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{20}H_{26}NO_3S$ 360.1628, found 360.1627.

3-[3-({[2-Hydroxy-2-(4-methylsulfanylphenyl)ethyl]-methylamino}-methyl)-phenoxy]-propan-1-ol (5). To a solution of **3** in MeOH (1 L) was added a solution of $NaBH_4$ (9.7 g, 0.26 mol, 0.5 equiv) in H_2O (70 mL) drop wise at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Aqueous 2 mol/L HCl solution was then added cautiously to quench the unreacted $NaBH_4$. After removal of MeOH via evaporation, the residue was partitioned between EtOAc (1.2 L), saturated $NaHCO_3$ (600 mL) and water (600 mL). The aqueous layer was further extracted with EtOAc (600 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford **5** as a colorless oil (167 g, 0.46 mol, 100%). No further purification was performed. HPLC retention time: 6.85 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.30–7.20 (m, 5H), 6.92–6.86 (m, 2H), 6.84–6.80 (m, 1H), 4.71 (dd, J = 10.4, 3.5 Hz, 1H), 4.13 (t, J = 6.0 Hz, 2H), 3.86 (t, J = 5.9 Hz, 2H), 3.70 (d, J = 13.1 Hz, 1H), 3.48 (d, J = 13.1 Hz, 1H), 2.62–2.46 (m, 2H), 2.46 (s, 3H), 2.32 (s, 3H), 2.04 (penta, J = 6.0 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 159.0, 139.9, 139.2, 137.4, 129.4, 126.8, 126.5, 121.5, 115.1, 113.4, 69.1, 65.7, 65.4, 62.3, 60.4, 41.9, 32.0, 16.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{20}H_{28}NO_3S$ 362.1784, found 362.1777.

3-[2-Methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinolin-7-yloxy]propan-1-ol (4). To a solution of **5** (185 g, 0.51 mol, 1.0 equiv) in CH_2Cl_2 (4 L) in an ice bath was added methanesulfonic acid (296 g, 3.08 mol, 6.0 equiv) drop wise under N_2 (the internal temperature was kept below 20 °C). After the addition, the ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h.

Scheme 8. **A practical synthesis of (+)-*S*-1**



Aqueous NaOH solution was then added cautiously to quench the reaction until pH = 12. The aqueous layer was further extracted with CH_2Cl_2 (1 L). The combined organic layers were dried over $MgSO_4$ and concentrated to yield crude product as a thick oil. EtOAc (~2 mL/g) was added, and the solution was heated to 70 °C to form a homogeneous solution. Upon cooling, the desired regioisomer **4** precipitated as a white solid (~75 g). The mother liquor was concentrated, and the above procedure was repeated to give another crop of pure material (~12 g). The combined yield was 50% (87 g, 0.25 mol). HPLC retention time: 7.02 min. R_f = 0.37 (10% MeOH in EtOAc). Mp: 49–52 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.24–7.16 (m, 2H), 7.14–7.08 (m, 2H), 6.80–6.74 (m, 1H), 6.68–6.60 (m, 2H), 4.24–4.12 (m, 1H), 4.08 (t, J = 6.0 Hz, 2H), 3.84 (t, J = 6.0 Hz, 2H), 3.69 (d, J = 14.9 Hz, 1H), 3.58 (d, J = 14.9 Hz, 1H), 3.03–2.95 (m, 1H), 2.56–2.46 (m, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.02 (penta, J = 6.0 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 157.0, 142.0, 136.4, 136.1, 130.4, 129.5, 129.4, 126.9, 113.2, 111.4, 65.8, 61.9, 60.6, 58.6, 45.9, 44.7, 32.0, 16.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{20}H_{26}NO_2S$ 344.1679, found 344.1687. The chiral HPLC retention times (Chiralcel OJ-H column, 80/20 hexanes/EtOH, 0.9 mL/min, 25 °C) are 11.18 min for the desired (+)-(*S*)-enantiomer and 16.67 min for undesired (−)-(*R*)-enantiomer, respectively. Optical rotation of the (+)-(*S*)-enantiomer: observed $[\alpha]^{20}_D$ = +30.0° (c 1.0, EtOH).

3-[2-Methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinolin-5-yloxy]-propan-1-ol (6). The undesired regioisomer was isolated via flash chromatography with MeOH/EtOAc as the eluents. R_f = 0.6 (10% MeOH in EtOAc). HPLC retention time: 6.77 min. Mp: 67–71 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.18–7.12 (m, 3H), 7.07–7.02 (m, 2H), 6.74 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 4.18 (t, J = 4.2 Hz, 1H), 3.98–3.92 (m, 1H), 3.84 (d, J = 15.0 Hz, 1H), 3.80–3.72 (m, 1H), 3.45–3.30 (m, 3H), 2.74 (d, J = 4.4 Hz, 2H), 2.44 (s, 3H), 2.32 (s, 3H), 1.80–1.60 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 156.6, 143.8, 137.2, 135.0, 128.6, 127.2, 126.8, 124.7, 118.7, 109.0, 65.1, 61.4, 60.0, 58.3, 46.2, 40.5, 31.7, 16.4. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{20}H_{26}NO_2S$ 344.1679, found 344.1671.

(3-Benzyloxybenzyl)-(2,2-dimethoxyethyl)-methylamine (12). In a 1-L three-neck round-bottom flask cooled in a room temperature water bath, (2,2-dimethoxy-ethyl)-methyl-amine (12.1 mL, 94.2 mmol, 1.0 equiv) was added to a solution of 3-benzyloxy-benzaldehyde (20.0 g, 94.2 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL). $NaBH(OAc)_3$ (24.0 g, 113 mmol, 1.2 equiv) was added in portions. The reaction mixture was stirred at room temperature for 18 h. Saturated aqueous $NaHCO_3$ solution (300 mL) was added, and the mixture was stirred for 2 h. The organic layer was separated, dried over Na_2SO_4, and evaporated to afford **12** as a colorless oil (29.2 g, 92.3 mmol, 98%). HPLC retention time: 7.88 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.47 (pseudo d, J = 7.4 Hz, 2H), 7.41 (pseudo t, J = 7.2 Hz, 2H), 7.35 (tt, J = 7.3, 1.3 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 7.04 (pseudo s, 1H), 6.96 (d, J = 7.7 Hz, 1H), 6.90 (dd, J = 8.2, 2.0 Hz, 1H), 5.09 (s, 2H), 4.55 (t, J = 5.3 Hz, 1H), 3.58 (s, 2H), 3.36 (s, 6H), 2.59 (d, J = 5.3 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 158.9, 140.6, 137.2, 129.2, 128.6, 127.9, 127.5, 121.7, 115.4, 113.6, 103.0, 69.9, 62.9, 58.4, 53.3, 43.3. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{19}H_{25}NO_3$ 316.1907, found 316.1911.

7-Benzyloxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (11). In a 3-L one-neck round-bottom flask equipped with a magnetic stir bar, **12** (100 g, 0.32 mol, 1.0 equiv) was diluted in 6 mol/L aqueous HCl solution (600 mL). The reaction mixture was stirred at 40 °C for 18 h and then cooled to 0 °C. With vigorous stirring, NaOH pellets were slowly added until pH = 13. The basic aqueous solution was extracted with EtOAc (200 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to afford a slightly yellow oil. The crude oil was purified on a plug of silica gel (20 cm OD, 4 in. height) with 95/5 EtOAc/MeOH as the eluents to afford **11** as a yellow solid (77 g, 0.28 mol, 90%). HPLC retention time: 6.87 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.45–7.43 (m, 2H), 7.41–7.38 (m, 2H), 7.36–7.34 (m, 2H), 6.90 (dd, J = 8.4, 2.6 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 5.07 (d, J = 2.3 Hz, 2H), 4.57 (pseudo s, 1H), 3.50 (br s, 1H), 3.48 (d, J = 15.0 Hz, 1H), 3.18 (d, J = 15.0 Hz, 1H), 2.98 (ddd, J = 11.7, 2.8, 1.2 Hz, 1H), 2.50 (dd, J = 11.7, 2.7 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 158.1, 137.0, 136.3, 130.6, 129.1, 128.6, 128.0, 127.4, 113.9, 111.9, 70.0, 66.6, 60.7, 57.8,

46.0. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{17}H_{19}NO_2$ 270.1489, found 270.1484.

7-Benzyloxy-2-methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinoline (10). In a 500-mL 1-neck round-bottom flask equipped with a magnetic stir bar, **11** (33.9 g, 0.12 mol, 1.0 equiv) and thioanisole (14.8 mL, 0.12 mol, 1.0 equiv) were dissolved in CH_2Cl_2 (200 mL). $BF_3 \cdot Et_2O$ (32 mL, 0.25 mol, 2.0 equiv) was added drop wise at 0 °C. After stirring at 0 °C for 2 h and then at room temperature overnight, the reaction was quenched cautiously with 2 mol/L KOH aqueous solution until pH = 13. CH_2Cl_2 (200 mL) was added, and the insoluble white solids were removed by filtration. The aqueous layer was further extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated to afford a dark oil. The crude oil was purified on a plug of silica gel (20 cm o.d., ca. 4 in. height) with EtOAc as the eluent to afford 10 as a colorless oil (25.4 g, 67 mmol, 54%). HPLC retention time: 8.75 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.48–7.31 (m, 5H), 7.19 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 6.78 (J = 8.4 Hz, 1H), 6.72 (dd, J = 6.0, 2.5 Hz, 1H), 6.69 (d, J = 2.2 Hz, 1H), 5.02 (s, 2H), 4.17 (t, J = 7.0 Hz, 1H), 3.69 (d, J = 14.9 Hz, 1H), 3.58 (d, J = 14.9 Hz, 1H), 2.98 (dd, J = 5.8, 5.6 Hz, 1H), 2.51 (dd, J = 8.6, 2.8 Hz, 1H), 2.47 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 157.0, 142.1, 137.1, 136.4, 136.0, 130.3, 129.48, 129.45, 128.5, 127.9, 127.4, 126.8, 113.5, 111.8, 70.0, 61.9, 58.6, 45.9, 44.7, 16.1. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{24}H_{26}NOS$ 376.1730, found 376.1746. The chiral HPLC retention times (Chiralcel OD-H 250 mm × 4.6 mm column, 9/1 hexane/EtOH, 1.0 mL/min, 43 bar, 25 °C) are 8.04 min for the desired (+)-(*S*)-enantiomer and 7.14 min for the undesired (−)-(*R*)-enantiomer, respectively. Optical rotation of the (+)-(*S*)-enantiomer: observed $[\alpha]^{20}_D$ = +23.9° (*c* 1.0, EtOH).

Bis-7-benzyloxy-2-methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinoline, (D)-Di-*p*-toluolyltartaric Acid (13). In a 1-L Erlenmeyer flask, **10** (24.6 g, 65 mmol, 1.0 equiv) and (D)-di-*p*-toluoyl-tartaric acid (12.6 g, 33 mmol, 0.5 equiv) were combined in EtOH (500 mL) and CH_3CN (200 mL). The mixture was heated until all solids dissolved. A small amount of diastereomeric pure **13** (1–2 wt %) was added as seeds.[25] The mixture was allowed to cool to room temperature and stand for 5 h. The precipitated crystals were collected by filtration and washed with EtOH to afford **13** (12.5 g) in >99% ee based on HPLC analysis.[26] The mother liquor was concentrated and recrystallized twice with seeding to afford another 2.6 g of **13** in >99% ee. The combined recovery was 15.1 g in 40% yield. A single crystal X-ray structure was obtained to assign the absolute stereochemistry of **13** as the *R* configuration. Mp: 136–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.94 (d, J = 8.1 Hz, 4H), 7.41–7.31 (m, 10H), 7.16 (d, J = 8.3 Hz, 4H), 7.11 (d, J = 8.0 Hz, 4H), 7.03 (d, J = 8.3 Hz, 4H), 6.73–6.68 (m, 4H), 6.60 (d, J = 1.7 Hz, 2H), 5.88 (s, 2H), 4.98 (s, 4H), 4.30 (dd, J = 5.6, 4.8 Hz, 2H), 4.04 (d, J = 15.3 Hz, 2H), 3.92 (d, J = 14.3 Hz, 2H), 3.36 (dd, J = 6.6, 5.6 Hz, 2H), 2.77 (t, J = 23.3 Hz, 2H), 2.61 (s, 6H), 2.46 (s, 6H), 2.33 (s, 6H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 171.5, 165.8, 157.5, 143.3, 138.7, 137.2, 136.8, 131.3, 130.3, 130.1, 129.5, 128.9, 128.6, 128.0, 127.7, 127.5, 127.4, 126.9, 114.8, 111.6, 73.7, 70.0, 58.4, 55.2, 42.5, 41.3, 21.6, 15.8. Optical rotation: observed $[\alpha]^{20}_D$ = –0.8° (*c* 1.0, CH_2Cl_2).

The same resolution was performed with (L)-di-*p*-toluolyl-tartaric acid to provide the diastereomeric pure salt (*S*)-**13** in a similar yield. Basification of (*S*)-**13** with aqueous Na_2CO_3 solution afforded enantiopure free base (+)-(*S*)-**10**. Analytic data were identical to the sample previously isolated with chiral HPLC.

(+)-(*S*)-2-Methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinolin-7-ol [(+)-(*S*)-14]. In a 250-mL one-neck round-bottom flask equipped with a magnetic stir bar, (+)-(*S*)-**10** (3.32 g, 8.8 mmol, 1.0 equiv) was diluted in a mixed solvent of AcOH (23 mL) and aqueous HCl solution (37 wt %, 8 mL). The mixture was heated at 60 °C for 8 h and then cooled to room temperature. The solvents were evaporated, and the residue was partitioned between EtOAc (60 mL) and cold saturated Na_2CO_3 solution (60 mL). The aqueous layer was further extracted with EtOAc (25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford **14** as an off-white solid (2.42 g, 8.5 mmol, 96%). No further purification was performed. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.18 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.3 Hz, 2H), 6.66 (d, J = 8.4 Hz, 1H), 6.50 (dd, J = 5.8, 2.6 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H), 4.17 (dd, J = 5.8, 3.1 Hz, 1H), 3.65 (d, J = 14.9 Hz, 1H), 3.52 (d, J = 14.9 Hz, 1H), 3.02 (m, 1H), 2.50 (dd, J = 9.2, 2.3 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 154.8, 141.3, 136.3, 135.4, 130.4, 129.4, 128.1, 126.8, 114.8, 112.7, 61.8, 58.1, 45.5, 44.1, 16.0. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{17}H_{20}NOS$: 286.1260, found: 286.1268. The chiral HPLC retention times (Chiralcel OJ-H 250 mm × 4.6 mm column, 85/15 hexane/EtOH, 1.0 mL/min, 47 bar, 25 °C) are 9.52 min for the desired (+)-(*S*)-enantiomer and 14.0 min for the undesired (−)-(*R*)-enantiomer, respectively. Optical rotation of the (+)-(*S*)-enantiomer: observed $[\alpha]^{20}_D$ = +25.6° (*c* 1.0, EtOH).

(+)-(*S*)-3-[2-Methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinolin-7-yloxy]-propan-1-ol [(+)-(*S*)-4]. To a solution of (+)-(*S*)-**14** (1.54 g, 5.4 mmol, 1.0 equiv) in THF (20 mL) was added $KOBu^t$ (0.73 g, 6.5 mmol, 1.2 equiv) was added at room temperature. After 10 min, 3-bromo-propanol (0.90 g, 6.5 mmol, 1.2 equiv) was added. The reaction mixture was stirred at 45 °C for 18 h and then cooled to room temperature. H_2O (20 mL) and EtOAc (20 mL) were added. The organic layer was separated, dried with Na_2SO_4, and concentrated to afford a thick oil. The crude oil was stirred in Et_2O (7 mL) and hexane (3 mL) for 48 h.[27] The precipitated solid was collected by filtration to give pure **4** (1.38 g, 4.0 mmol, 75%). The analytical data are identical to the sample previously prepared.

(*S*)-7-[3-(4-Fluoro-piperidin-1-yl)-propoxy]-2-methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinoline [(+)-(*S*)-1]. To the solution of (+)-(*S*)-**4** (22.5 g, 65.6 mmol, 1.0 equiv) and $EtNPr^i_2$ (12.7 g, 99 mmol, 1.5 equiv) in CH_2Cl_2 (200 mL) was added MsCl (8.25 g, 72 mmol, 1.1 equiv) was added via

(25) Without seeding, the ee of the precipitated crystal was ca. 60%.
(26) Diastereomeric salt **13** was basified with aqueous Na_2CO_3 solution to free base **10**. The ee was measured on **10**.
(27) Too much solvent prevented the precipitation of the product.

syringe under N_2. After stirring at room temperature for 1.5 h, the reaction was complete. The organic layer was washed with saturated $NaHCO_3$ (100 mL), dried over $MgSO_4$, and concentrated to afford the corresponding mesylate (HPLC retention time: 7.78 min), which was used in the next reaction right away. Commercial starting material 4-fluoropiperidine hydrochloride (12.8 g, 92 mmol, 1.4 equiv) was dissolved in 2 mol/L NaOH aqueous solution (200 mL), which was extracted with *tert*-amyl alcohol (200 mL). The *tert*-amyl alcohol layer was dried over $MgSO_4$ and filtered directly into the reaction vessel. The mesylate previously prepared and $EtNPr^i_2$ (34 g, 264 mmol, 4.0 equiv) were added sequentially. The reaction solution was stirred at reflux temperature under N_2 for 8 h and then cooled to room temperature. The solvents were evaporated, and the residue was dissolved in CH_2Cl_2 (500 mL). The organic layer was washed with saturated $NaHCO_3$ (200 mL), dried over Na_2SO_4, and concentrated. Recrystallization of the crude product from hot EtOH afforded pure **1** as a white solid (21 g, 49 mmol, 75%). HPLC retention time: 6.55 min. Mp: 97–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.18 (dt, J = 8.3, 1.8 Hz, 2H), 7.10 (dt, J = 8.3, 1.8 Hz, 2H), 6.76 (d, J = 8.5 Hz, 1H), 6.66–6.58 (m, 2H), 4.76–4.56 (m, 1H), 4.15 (dd, J = 7.8, 6.0 Hz, 1H), 3.97 (t, J = 6.3 Hz, 2H), 3.68 (d, J = 15.2 Hz, 1H), 3.58 (d, J = 14.8 Hz, 1H), 2.97 (ddd, J = 11.3, 5.5, 0.8 Hz, 1H), 2.65–2.48 (m, 5H), 2.46 (s, 3H), 2.40 (s, 3H), 2.42–2.32 (m, 2H), 2.00–1.80 (m, 6H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 157.2, 142.2, 136.4, 136.1, 130.3, 129.5, 129.1, 126.9, 113.3, 111.4, 89.34, 89.32, 88.0, 66.2, 62.0, 58.6, 55.1, 49.70, 49.66, 45.9, 44.7, 31.6, 31.4, 27.1, 16.1. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{34}FN_2OS$ 429.2370, found 429.2362. The chiral SFC retention times (Chiralcel AD-H column, 30% IPA/0.2% Et_3N, 100 bar, 2 mL/min, 25 °C) are 10.5 min for the desired (+)-(*S*)-enantiomer and 5.9 min for the undesired (–)-(*R*)-enantiomer, respectively. Optical rotation of the (+)-(*S*)-enantiomer: observed $[\alpha]^{20}_D = +25.6°$ (*c* 1.0, EtOH).

7-(3-Chloropropoxy)-2-methyl-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroisoquinoline (15). Compound **15** was isolated as the major byproduct when 4-fluoro-piperidine hydrochloride was used directly in the alkylation reaction. HPLC retention time: 8.42 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.24–7.16 (m, 2H), 7.14–7.08 (m, 2H), 6.77 (d, J = 8.5 Hz, 1H), 6.67–6.60 (m, 2H), 4.21–4.14 (m, 1H), 4.07 (t, J = 5.8 Hz, 2H), 3.74 (t, J = 6.4 Hz, 2H), 3.70 (d, J = 14.8 Hz, 1H), 3.59 (d, J = 14.8 Hz, 1H), 3.02–2.95 (m, 1H), 2.56–2.46 (m, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.26–2.16 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 156.9, 142.0, 136.3, 136.1, 130.4, 129.5, 129.4, 126.9, 113.3, 111.4, 64.2, 61.8, 58.5, 45.9, 44.7, 41.5, 32.3, 16.1. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{25}ClNOS$ 362.1340, found 362.1333.

Acknowledgment

We wish to thank Mr. Jozef Proost in Johnson & Johnson PRD BEERSE, Belgium, for conducting chiral HPLC separation of compound **4**, and Dr. Jiejun Wu for analytical support.

Supporting Information Available

^{1}H and ^{13}C spectra of compounds **1**–**6** and **10**–**15** and X-ray data of compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review August 10, 2007.

OP700183Q