Aldol Reactions of Conformationally Stable Axially Chiral Thiohydantoin Derivatives

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ABSTRACT: Two novel axially chiral ortho-trifluoromethylphenyl thiohydantoin derivatives have been prepared atroposelectively from the reaction of R and S alanine methyl ester HCl salts with ortho-trifluoromethylphenyl isothiocyanate in the presence of triethyl amine. It was found that after purification of the crude product by simple recrystallization, the R amino acid esters yielded thiohydantoins having solely M axial chirality whereas the S ones returned the P isomers only. This result prompted us to perform stERICALLY controlled aldol reactions on M and P thiohydantoin atropisomers. It was found that during the aldol reaction of 3-ortho-trifluoromethyl-5-methylthiohydantoins, the o-trifluoromethyl group of the M isomers efficiently shielded the Si face of the intermediate and in this way, enabled the selective formation of only the R configured aldol products at C5 of the heterocyclic ring. The P thiohydantoins, on the other hand, yielded only the S C5 configured aldol products as a result of the Re face shielding of the ortho-trifluoromethyl group of intermediate enolates. A noteworthy face selectivity of the benzaldehyde molecule was not observed (anti/syn only 3/2) during the aldolization of trifluoromethylphenyl derivatives of thiohydantoins. Aldol reactions were also done using the previously synthesized axially chiral thiohydantoins with ortho-Cl, Br, and I phenyl substituents which had predominantly P conformations (P/M ratios > 95%), and the stereochemical outcomes were compared with those of the ortho-trifluoromethyl substituted ones. 80–90% face selectivity of the benzaldehyde molecule was observed for the axially chiral o-halophenyl substituted thiohydantoins. The syntheses done with axially chiral 3-ortho-trifluoromethylphenyl- and 3-ortho-iodophenyl-5-methyl thiohydantoins enabled stereoselective formation of quaternized chiral carbon centers at C5 of the thiohydantoin ring.

INTRODUCTION

Axially chiral compounds are important in various different fields such as catalysis, medicine, and materials science.5,6 Thiohydantoins are cyclic amino acid derivatives which are considered “privileged scaffolds” in drug discovery and have been shown to have numerous pharmacological activities.5,4 Aldol reactions are very well known and widely studied C–C bond-forming reactions. However, although the enantioselective and diastereoselective aldol reactions have been developed significantly, the atroposelective versions of them are rare.7 The Sparr group performed atroposelective aren e-forming aldol reactions using proline-driven organocatalysts and further used them elegantly in some natural products6–10 and axially chiral amide syntheses.11 Here, we report atroposelective aldol reactions of axially chiral thiohydantoin derivatives using a different approach. The methodology has been de veloped previously by Curran,12 Clayden,13 and Simpkins14 for some addition and cycloaddition reactions of sterically congested ortho-aryl-substituted axially chiral imide and amide derivatives where the bulky ortho-substituent protected one face of the molecule so that the reaction took place from the other face. The synthesis became asymmetric if optically active starting compounds were used.14–19 We had previously reported the atroposelective synthesis of axially chiral thiohydantoin derivatives,8 in which highly P conformations were obtained. The present work aims to perform stERICALLY controlled atroposelective aldol addition reactions of them and of the newly synthesized novel ortho-trifluoromethylphenyl-sub stituted thiohydantoin derivatives. The novel ortho-trifluoromethylphenyl thiohydantoin derivatives which were used as starting compounds for the atroposelective aldol reactions could be obtained in only one type of axially chiral form: either P or M depending on whether the starting amino acid was S or R at it’s α carbon. S amino acids returned P thiohydantoins, whereas R returned M. We presumed that the CF3 substituent, which is known to cause a high barrier to rotation from previous studies20,21 or the halo substituents Cl, Br, or I will efficiently hinder the enolate attack on the aldehyde from the side where it stands, so that the attack will take place from the other side, and in this way, render an asymmetric synthesis. We had previously reported the aldol reactions of axially chiral 3-(o-aryl)- thiazolidine-4-ones22 and oxazolidinediones23 where starting compounds were racemic and therefore returned racemic products.

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Table 1. Axially Chiral Thiohydantoin Compounds Studied (1–7), Their Synthesis, Reaction Time, and Yields

| comp. | X  | R   | R'  | reaction time (h) | yield (%) |
|-------|----|-----|-----|-------------------|-----------|
| 1     | Br | CH₃ | H   | 1                 | 88        |
| 2     | Br | H   | CH₃ | 1                 | 63        |
| 3     | H  | H   | CH₃ | 1                 | 59        |
| 4     | Cl | H   | CH₃ | 1                 | 64        |
| 5     | I  | H   | CH₃ | 4                 | 75        |
| 6     | CF₃| CH₃ | H   | 1                 | 79        |
| 7     | CF₃| H   | CH₃ | 1                 | 77        |

a Compounds 1, 6, and 7 are novel, whereas 2–5 have been reported before.

Figure 1. (a) HPLC chromatogram of compound 1 obtained after the immediate removal of the reaction solvent; (a') HPLC chromatogram of compound 2 obtained after the immediate removal of the reaction solvent.

Scheme 1. Synthesis of the Aldol Products (2a−7a); the Reaction Has Been Shown on the M Isomer

Rxn time (h) Yield% 

|       | X  | R   | R'  |       |
|-------|----|-----|-----|-------|
| 2a)   | Br | H   | CH₃ | 3     |
| 3a)   | H  | H   | CH₃ | 3     |
| 4a)   | X  | H   | CH₃ | 3     |
| 5a)   | X  | H   | CH₃ | 3     |
| 6a)   | CF₃| CH₃ | H   | 3     |
| 7a)   | CF₃| H   | CH₃ | 3     |
RESULTS AND DISCUSSION

Axially chiral thiohydantoins have been synthesized by the previously utilized method by treating the amino acid methyl ester HCl salts with ortho-phenyl isothiocyanates in the presence of triethyl amine in CH₂Cl₂ (Table 1). The axially chiral stereoisomers of the products have been identified by comparing their ¹H NMR spectra with their high-performance liquid chromatography (HPLC) chromatograms obtained on optically active sorbents. To confirm the isomeric assignments, we started this work by synthesizing (R)-3-(o-bromophenyl)-5-methylthiohydantoin (1) and compared its HPLC chromatogram with that of (S)-3-(o-bromophenyl)-5-methylthiohydantoin (2), which was studied before (Figure 1). For (S)-3-(o-bromophenyl)-5-methylthiohydantoin, the elution order of the isomeric peaks in the HPLC chromatogram was assigned as (from the first-appearing peak to the last) SM/SP/RM/RP with ratios 3:14:83:0. We presumed that starting the same synthesis with the R-alanine methyl ester would yield the RM isomer of the axially chiral thiohydantoin because RM is also transoid like SP (considering the methyl group at C-5 and the o-bromo substituent). As a matter of fact, the HPLC chromatogram of the thiohydantoin obtained from the R-alanine methyl ester, namely the 5R-5-methyl-N-o-bromophenylthiohydantoin (1a), showed the same retention time of the isomer previously assigned to RM, and the corresponding isomeric ratio was obtained as 8:4:0:88, with the last peak (RM) having the highest intensity (Figure 1). Because within these molecules the C5 and the o-phenyl substituents prefer to stay transoid with respect to each other, on starting the thiohydantoin synthesis with S alanine, SP was the major product, whereas on starting with R alanine, the last peak on the chromatogram which had been assigned to RM turned out to be the major product.

Having shown that isomeric assignments can be done via HPLC analyses, the synthesis of the o-CF₃ derivatives (6,7) were planned with the hope of obtaining quantitatively P or quantitatively M conformers of thiohydantoins with this large substituent. With this aim, first, (R)-5-methyl-3-o-trifluoromethylphenylthiohydantoin (6) was synthesized (Scheme 1), and the isomeric ratio of the crude product was determined by comparing ¹H NMR with HPLC on CHIRALPAK IC, as RM/SP/SM/RP 53:9:38:0 (Figure 2a). After recrystallization from ethyl acetate/hexane, the product was indeed obtained as a 57:43 mixture of RM and SM isomers only (Figure 2a′). The (S)-5-methyl-3-o-trifluoromethylphenylthiohydantoin (7), on the other hand, yielded RM/SP/SM/RP 1.4:52.4:0:46.2 at first, and after recrystallization, the P isomers this time were obtained as a 54.2:45.8 (SP/RP) mixture (Figure 2b,b′). Apparently, racemization has taken place at C5 of 6 and 7. When the RM isomer was resolved micropreparatively by HPLC on a chiral column and the collected isomer was reinjected into HPLC for analysis, it was found that it converted to SM to give a 59:41 mixture of RM and SM isomers. The mechanism of racemization is under investigation. However, the important result for us was that on starting with R alanine, the product was obtained as the M conformer, whereas on starting with S alanine, the axially chiral thiohydantoin was synthesized only as P. The S and R

![Figure 2. HPLC chromatograms (a) of compound 6 obtained after the immediate removal of the reaction solvent, (a’) of compound 6 after recrystallization from ethyl acetate/hexane, (b) of compound 7 obtained after the immediate removal of the reaction solvent, and (b’) of compound 7 after recrystallization from ethyl acetate/hexane.](https://doi.org/10.1021/acsomega.1c03452)
Configurations will be lost upon enolate formation in the aldol reaction, and the P and M axial chirality obtained from S- and R-alanine, respectively, will control the selectivity of the aldol reaction.

The M conformation of thiohydantoin 6 did not change upon staying in toluene at 25 °C for 48 h. The barrier to rotation around the chiral axis was determined as 117 kJ/mol by thermal racemization at 60 °C following the conversion of RM to RP and SM to SP by HPLC on a chiral column (see Supporting Information). In this way, it was shown that any rotation will not take place at room temperature and below.

We then focused our attention to doing aldol reactions on the previously studied (2−5) and newly synthesized thiohydantoins (6,7) with benzaldehyde. The synthesis has been done at −78 °C in tetrahydrofuran (THF). First, the thiohydantoin was treated with LDA (lithium diisopropylamide) for 1 h to form the enolate by the abstraction of hydrogen at C-5 of the heterocyclic ring and then, benzaldehyde was added and the reaction was continued for 3 h (Scheme 1).

Figure 3. Enolization mechanism of the aldol reaction.
The previously reported thiohydantoins (2–5) have been synthesized predominantly in P conformations (P/M ratios > 95%). Starting with a 3:6:9:1:0 isomeric ratio of synthesized predominantly in Figure 4.

The 1H NMR spectrum of the aldol product 3a taken in CDCl3 without any purification showed two singlets at 4.94 and 4.88 ppm, which correspond to the signal of the hydrogen at the newly formed chiral center for the minor and the major isomeric pairs with the ratio of 21:79 by per cent (Figure 6). This syn/anti selectivity has also been observed for the structurally related aldol adducts.

Based on the results obtained for compound 3a in which the phenyl ring at C6 prefers to be on the equatorial position,3 isomers of the axially chiral aldol products 2a, 4a, and 5a were assigned by 1H NMR taken in CDCl3 without any purification. The barriers to rotation reported earlier as 116.2, 109.8, and 118.4 kJ/mol for 2, 4, and 5, respectively, at 60 °C show that conformations of the axially chiral thiohydantoins will not change during the aldol reaction. In the 1H NMR spectrum of the products, for 2a and 4a, four singlets which belong to the hydrogen attached to the newly formed chiral center around 5 ppm were seen. This indicates the formation of all isomers with the ratio of 2:7:23:68 for the o-arylthiohydantoins. However, for compound 5a which bears an o-iodo substituent, only two singlets appeared in the corresponding region with a diastereomeric ratio of 29:71 (Figure 7c). These ratios summarized in Table 2 show that the protection of o-Br and o-Cl is less than 100% while o-I fully protects the side where it is.

The formation of the aldol products can be explained by the enolization mechanism (Figure 3) in which the major isomers are formed due to the attack from the less hindered side of the P and M enolates, forming SPR* and SPS* and their enantiomers RMR* and RPS*, and the minor ones are formed because of the attack from the more hindered side, producing RPS* and RPR* and their mirror images SMR* and SMS*. If the formed enolate is 100% protected from the side where the o-aryl substituent is present toward the electrophilic attack of benzaldehyde, only the isomers SPR* and SPS* from the P and their enantiomers, RMR* and RPS*, are expected to form, as obtained for 5a, 6a, and 7a. However, if the protection is less than 100%, all of the isomers should be seen in the 1H NMR spectrum of the crude products, as seen for compounds 2a and 4a.

![Figure 4. Possible isomers of the aldol adducts of 5-methyl-3-o-aryltiohydantoins.](https://doi.org/10.1021/acsomega.1c03452)
In order to make the assignments correctly, it was thought that the ratio of SPR*/SPS* should be similar to the one of RPS*/RPR* because if benzaldehyde is attached selectively while forming SPR* and SPS*, it may be assumed to have the similar selectivity for producing RPS* and RPR*. Based on this idea and the results obtained for compound 3a, the assignments in 1H NMR were done for the axially chiral aldol isomers (2a−7a). When the singlets from the most upfield to the most downfield are assigned as SPR*, RPS*, SPS*, and RPR* for the 2a−5a diastereomers (and also their enantiomers), respectively (Figure 7a−c), similar ratios between SPR*:SPS* and RPS*:RPR* were found, which are 75:25 and 78:22 for 2a, 90:10 and 91:9 for 4a, and 71:29 (SPR*:SPS*) for 5a (no RPR* and RPS* were produced).

The degree of protection by the o-substituent was determined by the per cent ratio of the sum of SPR* and SPS*, formed due to the attack from the less hindered side, over the sum of RPS* and RPR*, produced by the attack from the more hindered side (Figure 3). 75:25 for 2a, 77:23 for 4a, and 100% for 5a, 6a, and 7a were found from the integrations of the singlets around 5 ppm in 1H NMR spectra of each crude compound (Figures 7 and 8 and Table 3) in CDCl3. These ratios show that there is no difference between bromo and chloro derivatives in terms of face selectivity of the electrophilic attack of benzaldehyde. However, the protection of o-halogen reaches a maximum for the biggest halogen, iodo, in which full protection was seen.

When the aldol reaction of 6 (starting with RM and SM isomers only) was done with benzaldehyde (Scheme 1), 1H NMR of the crude product (6a) in CDCl3 showed the presence of two isomers with a ratio of 20:80 (Figure 7d). In 1H NMR of the purified product, on the other hand, a single isomer was seen in CDCl3 (Figure 8a), but two isomers with a ratio of 2:3 were seen in DMSO-d6 and in DMF-d7 (Figure 8a′). These results have been interpreted in the following way: during the aldol reaction, the ortho substituent CF3 shielded the Si face of the intermediate enolate so that attack on the benzaldehyde...
were seen for the OH protons and two diastereoisomers of each other, they principally should be separable, and, doing the same reaction starting with isomers of 7, SP, and RP yielded, after purification, only the SPR* (anti) and SPS* (syn) aldol products (7a) with a 3:2 ratio (Figure 8b). Thus, CF3 like iodine as an ortho substituent, enabled full protection during the aldol reactions of 6 and 7.

**Figure 7.** Partial 1H NMR spectrum of crude compounds (a) 2a, (b) 4a, (c) 5a (d) 6a, and (e) 7a in CDCl3.

**Figure 8.** (a) Partial 1H NMR spectrum of purified 6a in CDCl3; (a’) partial 1H NMR spectrum of purified 6a in DMSO-d6; (b) partial 1H NMR spectrum of purified 7a in CDCl3; and (b’) partial 1H NMR spectrum of purified 7a in DMSO-d6.

**Table 2. Isomeric Ratios of the Aldol Reaction of the Compounds 2a−7a**

| compounds | P/M | isomer ratios before purification | isomer ratios after purification |
|-----------|-----|---------------------------------|---------------------------------|
| 2a        | 97:3 | (2:23):(7:68)                  | (3:31):(7:59)                  |
| 3a        | racemic | 21:79                            | 5:95                        |
| 4a        | 97:3 | (2:21):(8:69)                  | (0:40):(0:60)                  |
| 5a        | 95:5 | (0:00):(29:71)                  | (0:00):(7:93)                  |
| 6a        | 0:100 | (20:80)                          | (0:100):(40:60)                |
| 7a        | 100:0 | (37:63)                          | (0:100):(0:40:60)              |

*P/M ratio is the ratio of the (SP + RP)/(SM + RM) of the starting thiohydantoin. The isomer ratio was obtained from the integrations of the singlets observed for the hydrogen at C6 of the two isomers (Figure 8b) before precipitation from ethylacetate/hexane.*

**Table 3. Isomer Ratios of the Starting Thiodyantoin (2−7) and the Corresponding Aldol Products (2a−7a)**

| starting thiodyantoin | aldol product | S/R at C5 | syn/anti | syn/anti |
|-----------------------|---------------|-----------|----------|----------|
| 2 (P/M 97:3)          | 2a            | 75:25     | 9:91     | 10:90    |
| 3 (racemic)           | 3a            | 79:21     | 21:79    | 5:95    |
| 4 (P/M 97:3)          | 4a            | 77:23     | 10:90    | 0:100    |
| 5 (P/M 95:5)          | 5a            | 100:0     | 29:71    | 7:93     |
| 6 (P/M 0:100)         | 6a            | 20:80     |  b       | 40:60    |
| 7 (P/M 100:0)         | 7a            | 63:37     | b        | 40:60    |

*syn/anti isomer ratio was determined from the ratio of (RPR + SPS):(RPS + SPR) isomers obtained from the integrations of the singlets observed in the 1H NMR spectrum taken in CDCl3 after purification. The syn/anti isomer ratio could not be determined because the isomers could not be separated. The syn/anti isomer ratio was determined from the 1H NMR spectrum taken in DMSO-d6 after purification.

The isomer ratio was obtained from the integrations of the singlets observed for the hydrogen at C6 of the two isomers (Figure 8a). The ortho hydrogen of CF3-phenyl appeared at about 6 ppm because of the shielding effect of the phenyl group bonded to C6 (Figure 8a,b). The two isomeric aldol products were designated as RMS* (anti) and RMR* (syn), R being the chiral center at C5 and R* and S* being the newly formed chiral centers at C6 (Scheme 1 and Figure 3). The syn/anti isomer ratio was determined from the 1H NMR spectrum taken in DMSO-d6 after purification.

Because the product has no axial chirality, only the isomers RR* & RR* (major) and SS* & RR* (minor) exist. Because the aldol reaction started with only M isomers, only M isomers were formed as products.
Thus, for the o-iodophenyl (5a) and the o-trifluoromethyl-phenyl thiohydantoin derivatives (6a, 7a), a complete atroposelectivity was observed for forming the chiral center at C-5. For the smaller sized ortho substituent bearing derivatives 2 and 4, lower atroposelectivities were observed.

**CONCLUSIONS**

The synthesis of the novel o-CF3 bearing axially chiral thiohydantoins 6 and 7 yielded solely M and P conformers, respectively. Starting with R alanine, the product was obtained as the M conformer. On the other hand, starting with S yielded only the P conformer.

The aldol reactions of the compounds (2–7) followed an enolization mechanism in which the P or M enolate formed from the reaction of LDA with the corresponding thiohydantoin produced the aldol adducts (2a–7a). Among the aldol products 2a–7a of 5-methyl-3-aryl thiohydantoins, 2–7, the selectivity at C5 depended on the ortho substituent at N3, resulting from the enolate attack occurring dominantly from the less hindered side of the ortho-substituted compound. The largest substituents o-iodo and o-CF3 yielded 100% selectivity. In addition, a 70:30 to 91:9 face selectivity was observed upon the formation of 2a–5a for the attachment of benzaldehyde in favor of the anti adduct whereas no appreciable face selectivity was observed upon the formation of 6a and 7a.

**EXPERIMENTAL PROCEDURE**

**Materials and Methods.** 1H and 13C nuclear magnetic resonance (NMR) spectra of all compounds were recorded on a Varian Mercury VX-400 MHz-BB. Liquid chromatography analyses with an ultraviolet (UV) detector (λ = 254 nm) were performed using CHIRALPAK IC columns (particle size, 5 µm; column size, 250 × 4.6 mm2) as the stationary phase. Melting points were determined on an Electrothermal 9100 melting point apparatus. All reagents and solvents were obtained commercially (Aldrich, Merck) and used without further purification.

**General Procedure for Thiohydantoin Derivatives (1 and 6–9).** Compounds 1, 6, and 7 were synthesized by treating the amino acid methyl ester HCl salts with ortho-phenyl isothiocyanates in the presence of triethyl amine (Et3N) in CH2Cl2 under reflux for 1 h. For the synthesis of compounds, R and S alanine and phenyl alanine methyl ester HCl salts were used as starting amino acids. The crude product was washed with distilled water and saturated salt solution. Finally, the solution was dried over MgSO4 and filtered. The solvent was removed. The crude product recrystallized from ethyl acetate/hexane.

**5-Methyl-3-o-bromophenylthiohydantoin (1).** The compound was synthesized according to the general procedure. 0.48 mL (3.58 mmol) of o-bromophenyl isothiocyanate was added to a solution of 0.5 g (3.58 mmol) of d-alanine methyl ester HCl salt and 0.5 mL of (3.58 mmol) Et3N in 10 mL of CH2Cl2. Yield: 0.56 g (55%); white solid, mp 220 °C. 1H NMR (400 MHz, CDCl3): δ 7.74–7.26 (m, 10H, aromatic ring and NH); 4.46 and 4.39 (two quartets, 2H, α-H at C-5), 1.66 and 1.58 (d, 6H, methyl signals at C-5). 13C NMR (100 MHz, CDCl3): δ 182.76, 173.19, 133.57, 133.52, 132.17, 131.35, 131.23, 130.04, 128.52, 128.44, 123.38, 55.87, 55.74, 17.46, 16.90 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES+): calcd for C17H15BrN2O2SH+, 284.9697; found, 284.9697.

**5-Methyl-3-o-trifluoromethylphenylthiohydantoin (6).** The compound was synthesized according to the general procedure. 0.54 mL (3.58 mmol) of 2-(trifluoromethyl) phenyl isothiocyanate was added to a solution of 0.5 g (3.58 mmol) of d-alanine methyl ester HCl salt and 0.5 mL (3.58 mmol) of Et3N in 10 mL of CH2Cl2. Yield: 0.59 g (60%); white solid, mp 238–239 °C. 1H NMR (400 MHz, CDCl3): δ 7.77–7.12 (m, 10H, aromatic ring and NH), 4.39 and 4.27 (two quartets, 2H, α-H at C-5), 1.55 and 1.53 (two doublets, H, methyl signals at C-5). 13C NMR (100 MHz, CDCl3): δ 183.40, 183.30, 173.90, 173.85, 133.14, 132.18, 131.75, 130.74, 130.40, 129.20, 128.89, 127.71, 124.15, 121.60, 55.98, 55.75, 17.07, 16.60 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES+): calcd for C11H9F3N2OSH+, 275.0466; found, 275.0467.

**General Procedure for the Aldol Reaction (2a–7a).** The aldol reactions were carried out under nitrogen. To the solution of 5-methyl-3-aryl thiohydantoins (0.16 M) in THF at −78 °C was added LDA (2 M, 2.4 equiv). The mixture was stirred for 1 h for enolate formation and then benzaldehyde (2 equiv) was added. The reaction mixture was stirred for 2–3 h at −78 °C and quenched with saturated NH4Cl solution (2 equiv). The solution was extracted with diethyl ether three times and dried over anhydrous CaCl2. The ether was evaporated, and the crude product was precipitated from diethyl ether/petroleum ether and ethyl acetate/hexane.

**5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-bromophenyl Thiohydantoin (2a).** The compound was synthesized according to the general procedure using 0.25 g (0.88 mmol) of compound 5 in 5.5 mL of THF, 1.05 mL (2.10 mmol) of LDA, and 0.18 mL (1.75 mmol) of benzaldehyde. Yield: 0.14 g (41%), mp 158–160 °C. 1H NMR (400 MHz, CDCl3): δ 7.76 (br s, 1H, NH), 7.74–7.00 (m, 9H, aromatic ring), 6.05 (m, 1H, aromatic proton), 5.11, 5.08, 5.06, and 5.01 (s, 1H, benzyl H), 1.91, 1.83, and 1.70 (s, 3H, CH3 at α-C). 13C NMR (100 MHz, CDCl3): δ 181.6, 173.3, 137.3, 137.2, 133.5, 133.4, 133.2, 131.8, 131.3, 131.2, 131.1, 130.5, 129.3, 129.23, 129.19, 129.17, 128.99, 128.93, 128.6, 128.5, 128.3, 127.7, 127.24, 127.21, 127.0, 123.5, 123.3, 69.5, 66.8, 20.3, 20.1 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES+): calcd for C18H13BrN2O3SH+, 391.0116; found, 391.0117.
5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-chlorophenyl Thiohydantoin (4a). The compound was synthesized according to the general procedure using 0.50 g (2.08 mmol) of compound 4 in 13 mL of THF, 2.5 mL (4.99 mmol) of LDA, and 0.42 mL (4.16 mmol) of benzaldehyde. Yield: 0.34 g (47%), mp 165 °C (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES⁺): calcd for C17H15IN2O2SH+, 438.9977; found, 438.9976.

5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-iodophenyl Thiohydantoin (5a). The compound was synthesized according to the general procedure using 0.25 g (0.9 mmol) of compound 5 in 4.7 mL of THF, 0.9 mL (1.81 mmol) of LDA, and 0.60 mL (1.51 mmol) of benzaldehyde. Yield: 0.084 g (25%), mp 176 °C (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES⁺): calcd for C17H15IN2O2SH+, 438.9977; found, 438.9976.

5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-trifluoromethyl-phenyl Thiohydantoin (6a). The compound was synthesized according to the general procedure using 0.5 g (0.9 mmol) of compound 6 in 5.7 mL of THF, 1.09 mL (2.18 mmol) of LDA, and 0.60 mL (1.82 mmol) of benzaldehyde. Yield: 0.12 g (35%), mp 186 °C. 1H NMR (400 MHz, CDCl3): δ 7.76–7.46 (m, 9H, aromatic ring and NH), 7.27 (m, 8H, aromatic H), 6.29 (d, J = 7.6 Hz, 1H, aromatic H), 5.80 and 5.76 (two doublets, 1H, –OH), 4.74–4.75 (two singlets, 2H, at C6), 1.83 (s, 3H, CH3 at α-C). 13C NMR (100 MHz, CDCl3): δ 181.5, 173.1, 139.7, 139.5, 137.2, 135.3, 131.3, 130.5, 129.8, 129.5, 129.4, 129.2, 129.0, 128.6, 127.3, 127.0, 99.2, 98.9, 69.5, 68.6, 20.3, 20.2 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES⁺): calcd for C17H15F3N2O2SH+, 381.0885; found, 381.0885.

5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-trifluoromethyl-phenyl Thiohydantoin (7a). The compound was synthesized according to the general procedure using 0.5 g (1.82 mmol) of compound 7 in 11.4 mL of THF, 2.17 mL (4.37 mmol) of LDA, and 1.2 mL (3.64 mmol) of benzaldehyde. Yield: 0.22 g (32%), mp 192 °C. 1H NMR (400 MHz, CDCl3): δ 7.86–7.16 (m, 9H, aromatic ring and NH), 7.65 (d, 1H, aromatic H), 5.03 (s, 1H, benzyl H). 1H NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1H, NH), 7.77–7.26 (m, 8H, aromatic ring), 6.30 (d, 1H, aromatic H), 5.79 and 5.75 (two doublets, 1H, –OH), 4.47–4.50 (two singlets, 2H, benzyl H), 1.55 (s, 3H, CH3 at α-C). 13C NMR (100 MHz, CDCl3): δ 184.59, 173.78, 173.23, 132.89, 131.37, 130.47, 130.11, 129.35, 128.67, 127.43, 127.07, 125.33, 69.45, 20.04 ppm (diastereomers give different carbon signals). HRMS (TOF MS ES⁺): calcd for C18H13F3N2O2SH+, 381.0885; found, 381.0885.

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**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03452.

Copies of 1H and 13C NMR spectra for all new compounds and the chromatograms of the thermal interconversion study (PDF)

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**Notes**

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