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Aldol Reactions of Conformationally Stable Axially Chiral Thiohydantoin Derivatives

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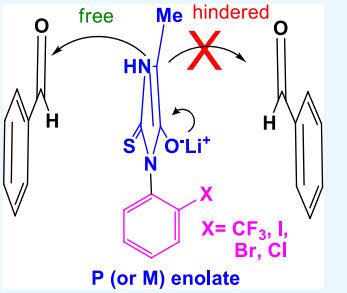
ABSTRACT: Two novel axially chiral *ortho*-trifluoromethylphenyl thiohydantoin derivatives have been prepared atroposelectively from the reaction of **R** and **S** alanine methyl ester HCl salts with *ortho*-trifluoromethylphenyl isothiocyanate in the presence of triethyl amine. It was found that after 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-*o*-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.[1,2] Thiohydantoins are cyclic amino acid derivatives which are considered "privileged scaffolds" in drug discovery and have been shown to have numerous pharmacological activities.[3,4] 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.[5] The Sparr group performed atroposelective arene-forming aldol reactions using proline-driven organocatalysts and further used them elegantly in some natural products[6−10] 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 developed previously by Curran,[12] Clayden,[13] and Simpkins[5] 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,[3] 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-substituted 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 CF_3 substituent, which is known to cause a high barrier to rotation from previous studies,[20,21] 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-ones[22] and oxazolidinediones[23] where starting compounds were racemic and therefore returned racemic products.

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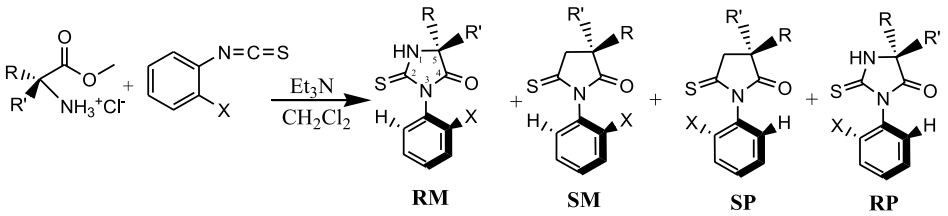
Table 1. Axially Chiral Thiohydantoin Compounds Studied (1−7), Their Synthesis, Reaction Time, and Yields[a]



comp.	X	R	R′	reaction time (h)	yield (%)
1	Br	CH_3	H	1	88
2[3]	Br	H	CH_3	1	63
3[3]	H	H	CH_3	1	59
4[3]	Cl	H	CH_3	1	64
5[3]	I	H	CH_3	4	75
6	CF_3	CH_3	H	1	79
7	CF_3	H	CH_3	1	77

[a]Compounds **1**, **6**, and **7** are novel, whereas **2**−**5** have been reported before.[3]

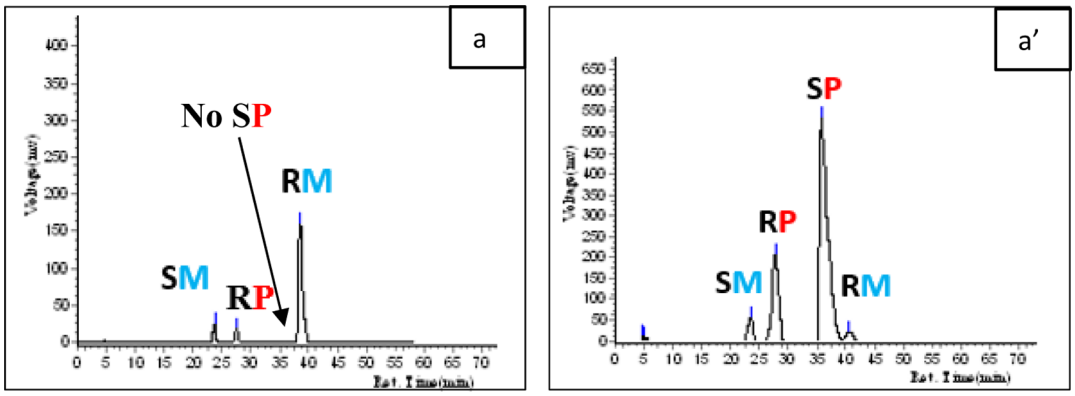
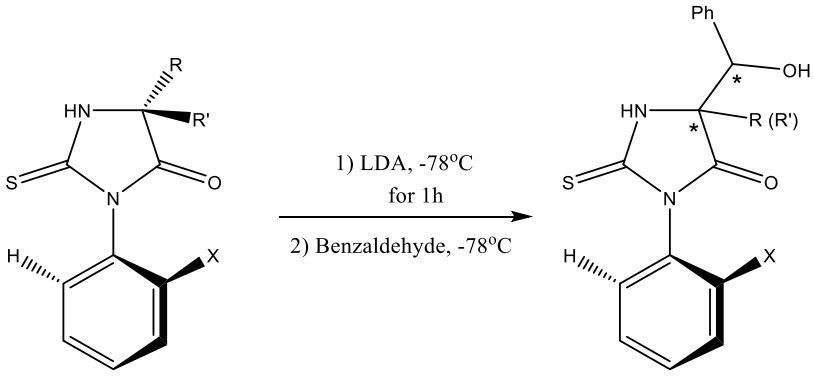


Figure 1. (a) HPLC chromatogram of compound **1** obtained after the immediate removal of the reaction solvent; (a′) HPLC chromatogram of compound **2** obtained after the immediate removal of the reaction solvent.

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



			Rxn time (h)	Yield%
2a) X = Br	R = H	R′ = CH_3	3	41
3a) X = H	R = H	R′ = CH_3	3	66
4a) X = Cl	R = H	R′ = CH_3	3	47
5a) X = I	R = H	R′ = CH_3	3	25
6a) X = CF_3	R = CH_3	R′ = H	3	35
7a) X = CF_3	R = H	R′ = CH_3	3	32

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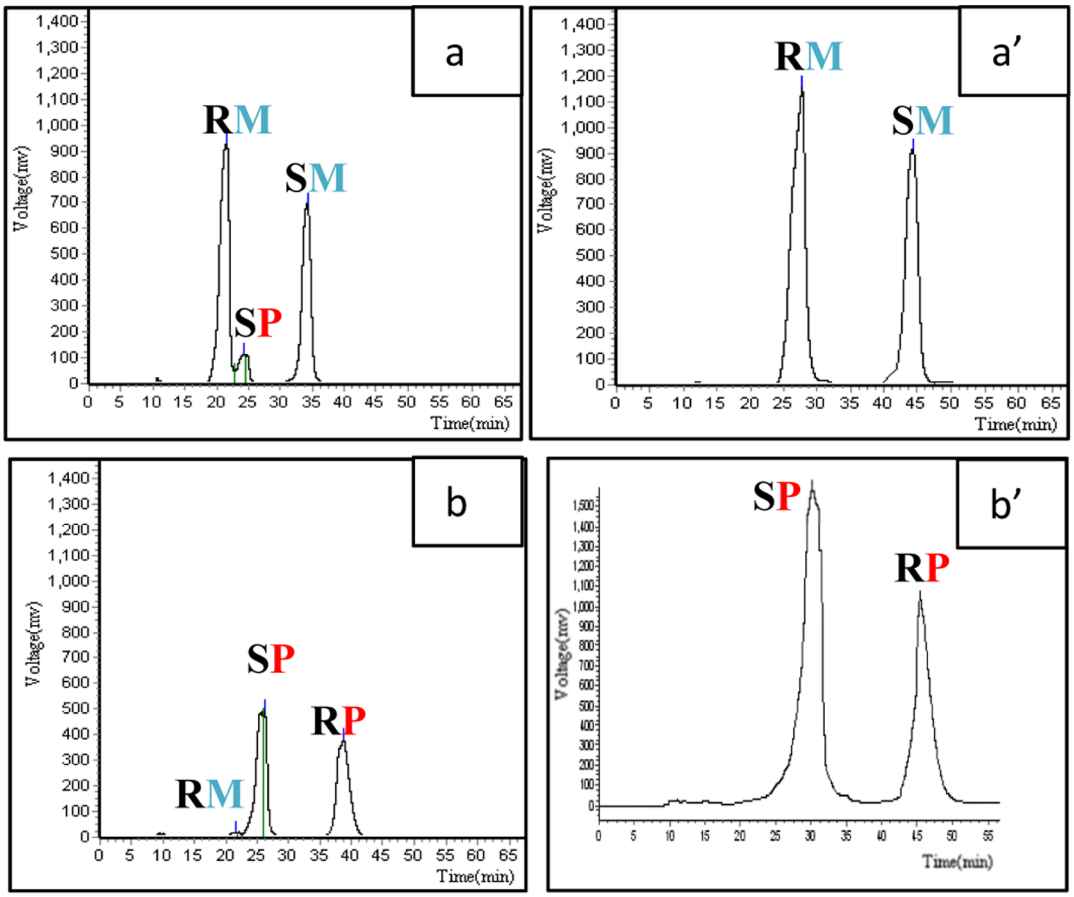

Figure 2. HPLC chromatograms (a) of compound **6** obtained after the immediate removal of the reaction solvent, (a′) of compound **6** after recrystallization from ethyl acetate/hexane, (b) of compound **7** obtained after the immediate removal of the reaction solvent, and (b′) of compound **7** after recrystallization from ethyl acetate/hexane.

RESULTS AND DISCUSSION

Axially chiral thiohydantoins have been synthesized by the previously utilized method[3] by treating the amino acid methyl ester HCl salts with *ortho*-phenyl isothiocyanates in the presence of triethyl amine in CH_2Cl_2 (Table 1). The axially chiral stereoisomers of the products have been identified by comparing their ^{1}H 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[3] (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**/**RP**/**SP**/**RM** with ratios 3:14:83:0.[3] 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 5*R*-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,[3] 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*-CF_3 derivatives (**6**,**7**) were planned with the hope of obtaining quantitatively **P** or quantitatively **M** conformers of thiohydantoins with this large substituent.[20,21] 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 ^{1}H 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[24] 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**

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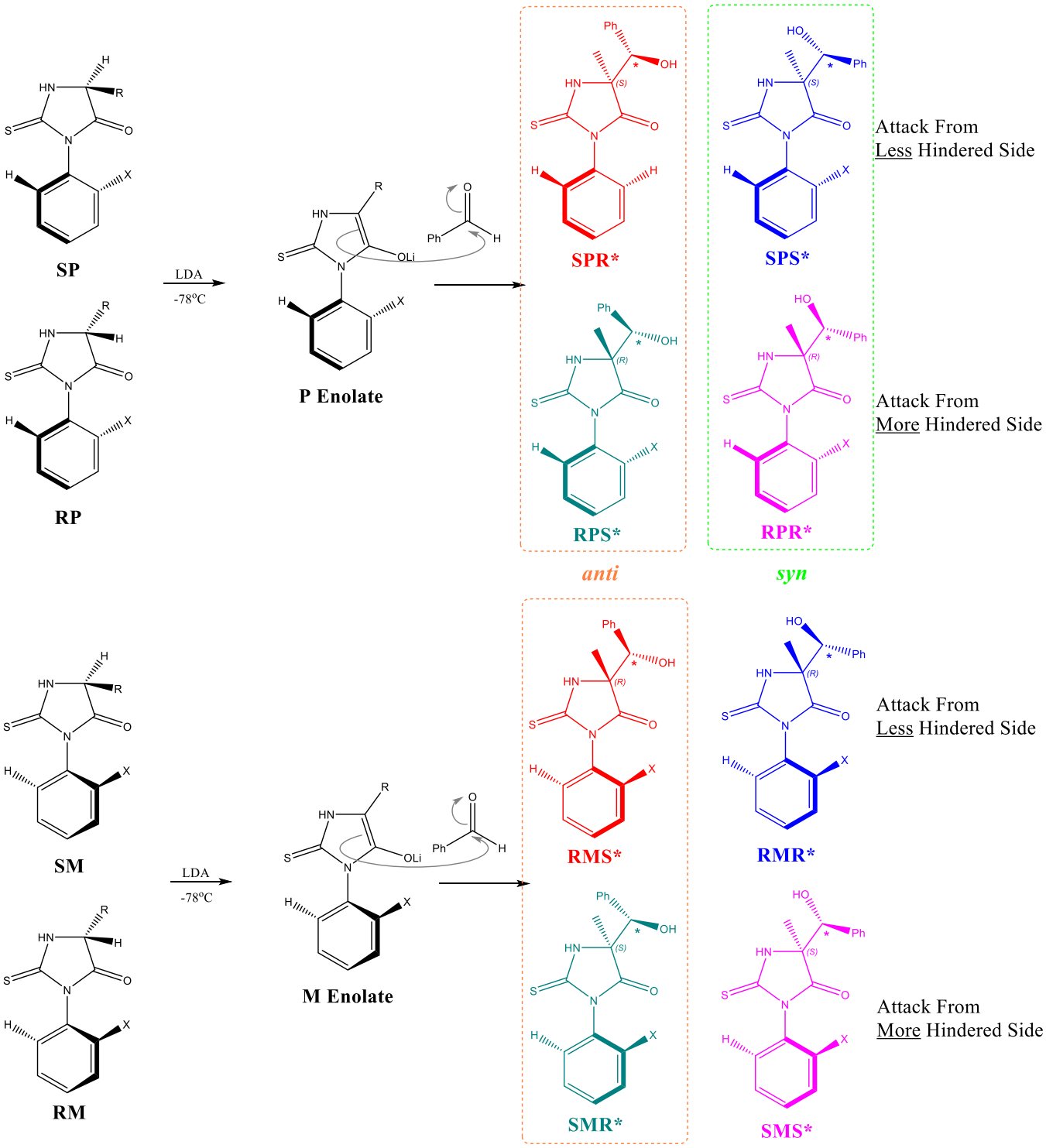

Figure 3. Enolization mechanism of the aldol reaction.

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**)[3] 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).[22,23]

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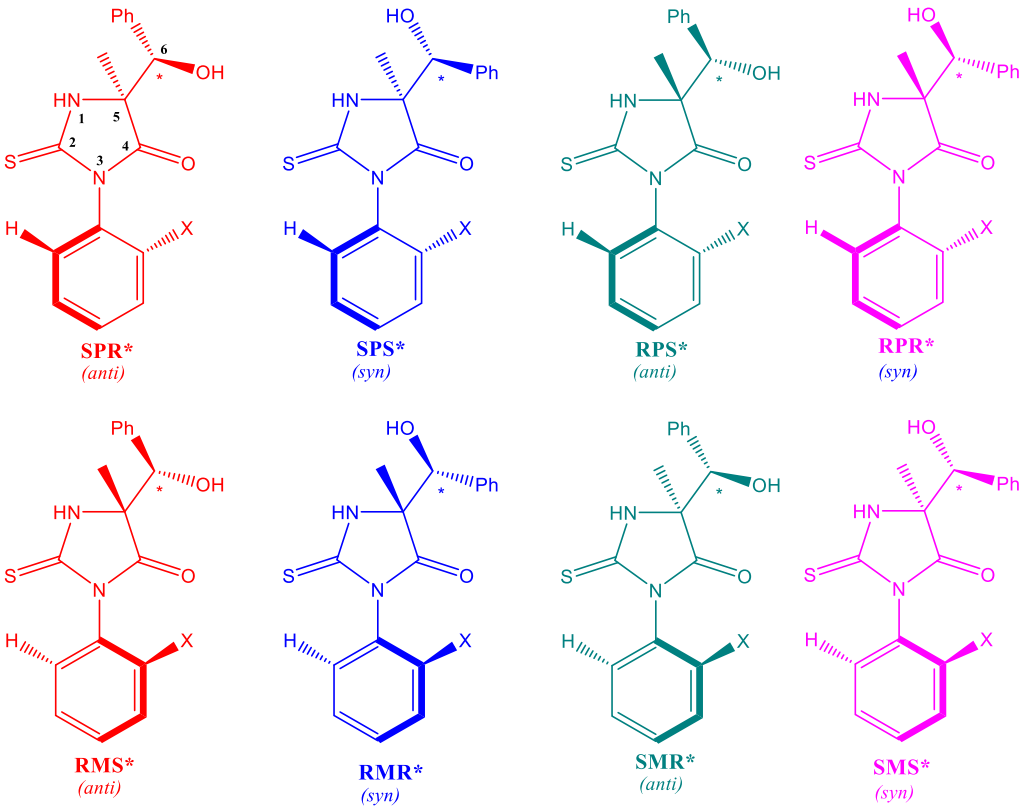

Figure 4. Possible isomers of the aldol adducts of 5-methyl-3-*o*-arylthiohydantoins.

The previously reported thiohydantoins (**2**−**5**) have been synthesized predominantly in **P** conformations (**P**/**M** ratios > 95%).[3] Starting with a 3:6:91:0 isomeric ratio of **SM**/**RP**/**SP**/**RM**[3] of **2** would be equivalent to starting with 97% **P** and 3% **M** because upon the formation of the intermediate enolate after reaction with LDA, the C5 would be planar and thus loose its chirality, whereas the chiral axis will persist. The attack of the enolate on benzaldehyde would reform the C5 chiral center stereoselectively. The stereoselectivity of the reaction would depend on the extent of the shielding effect of the **P** isomer's *ortho* substituent on the face of the enolate where it is present (Figure 3).

In the aldol adducts, because there are three chiral elements, which are the chiral center at C5 of the heterocyclic ring, the chiral axis (N_{sp^2}−C_{aryl} bond), and the newly formed chiral center which is denoted by *, eight isomers (**SPR***, **SPS***, **RPS***, **RPR***, **RMS***, **RMR***, **SMR***, and **SMS***) as four diastereomeric pairs are expected to form (Figure 4). *Syn*/*anti* assignments have been done by referring to the stereochemical studies carried out previously on related compounds.[4]

In order to make the assignments more easily, the aldol reaction was first tried with compound **3** which has no chiral axis. In this way, only two isomeric pairs **SR*** and **RS*** (*anti*) and **SS*** and **RR*** (*syn*) are expected to form because of the absence of the chiral axis (Figure 5).

The ^{1}H NMR spectrum of the aldol product **3a** taken in $CDCl_3$ 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.[4]

Based on the results obtained for compound **3a** in which the phenyl ring at C6 prefers to be on the equatorial position,[4] isomers of the axially chiral aldol products **2a**, **4a**, and **5a** were assigned by ^{1}H NMR taken in $CDCl_3$ 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[3] show that conformations of the axially chiral thiohydantoins will not change during the aldol reaction. In the ^{1}H 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*-bromo (Figure 7a) and 2:8:21:69 for the *o*-chloro (Figure 7b) derivatives. 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 **RMS*** and **RMR***, 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, **RMS*** and **RMR*** from the **M**, 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 ^{1}H NMR spectrum of the crude products, as seen for compounds **2a** and **4a**.

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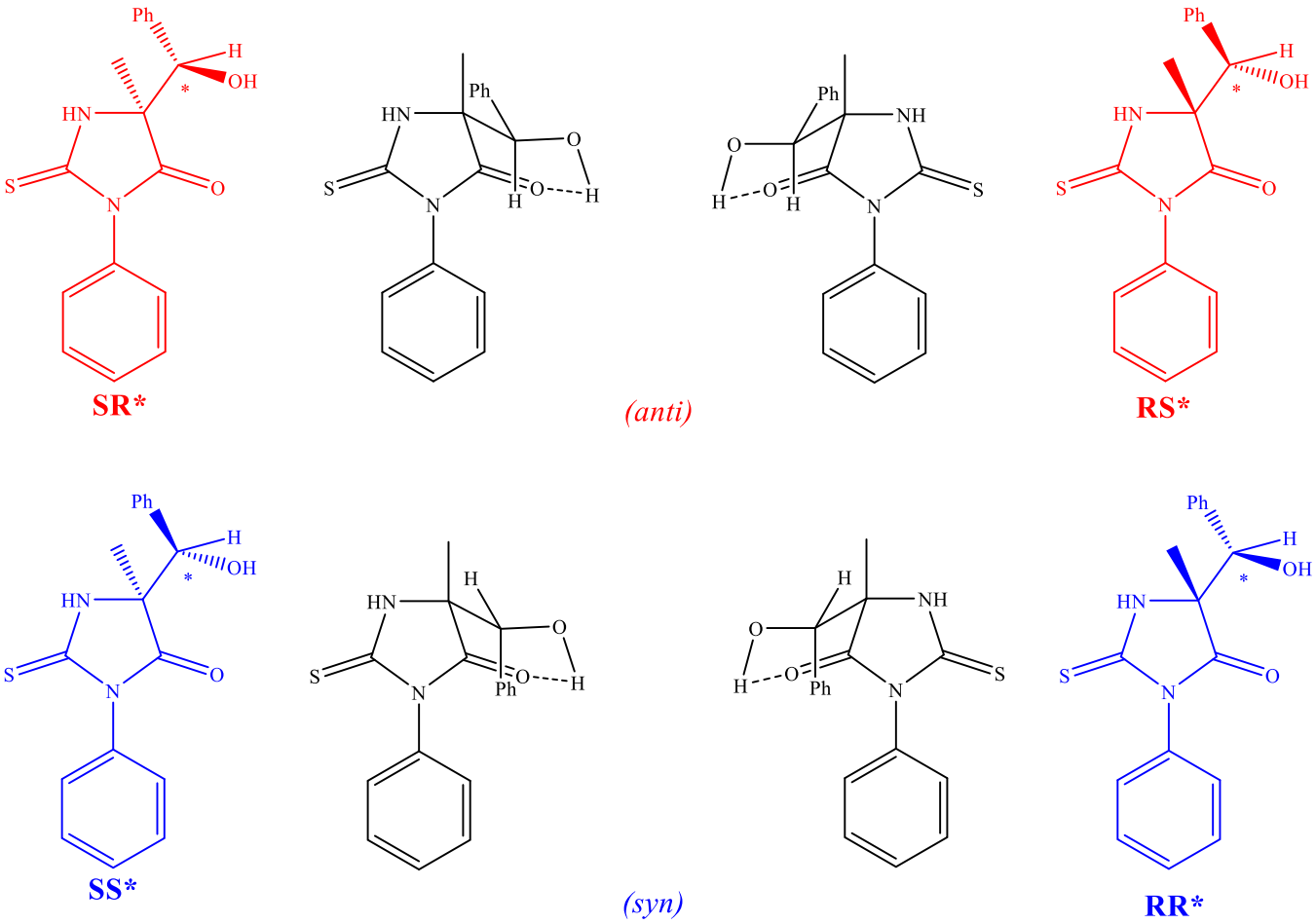

Figure 5. Structures of aldol products having no chiral axis (**3a**).

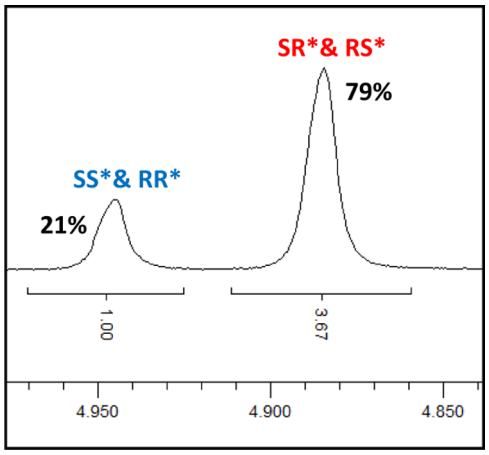

Figure 6. Partial ^{1}H NMR spectrum of compound **3a** in $CDCl_3$ without any purification.

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** where the large phenyl ring is preferentially in the equatorial position, the assignments in ^{1}H 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 ^{1}H NMR spectra of each crude compound (Figures 7 and 8 and Table 3) in $CDCl_3$. 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 to 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), ^{1}H NMR of the crude product (**6a**) in $CDCl_3$ showed the presence of two isomers with a ratio of 20:80 (Figure 7d). In ^{1}H NMR of the purified product, on the other hand, a single isomer was seen in $CDCl_3$ (Figure 8a), but two isomers with a ratio of 2:3 were seen in DMSO-d_6 and in DMF-d_7 (Figure 8a′). These results have been interpreted in the following way: during the aldol reaction, the *ortho* substituent CF_3 shielded the *Si* face of the intermediate enolate so that attack on the benzaldehyde

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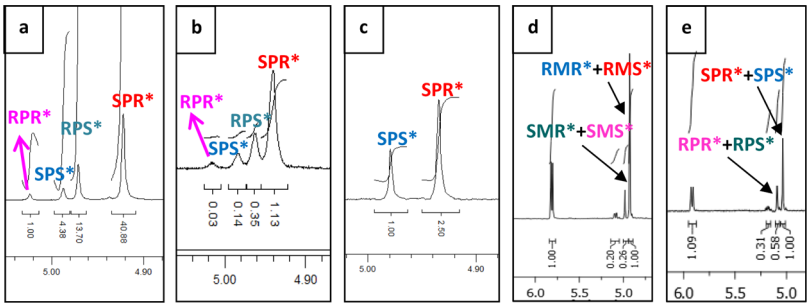

Figure 7. Partial ^{1}H NMR spectrum of crude compounds (a) **2a**, (b) **4a**, (c) **5a** (d) **6a**, and (e) **7a** in $CDCl_3$.

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

compounds	P/M[a]	isomer ratios before purification[b] (RPR*/RPS*):(SPS*/SPR*)	isomer ratios after purification (RPR*/RPS*):(SPS*/SPR*)
2a	97:3	(2:23):(7:68)	(3:31):(7:59)[c]
3a	racemic	21:79[e]	5:95
4a	97:3	(2:21):(8:69)	(0:40):(0:60)[c]
5a	95:5	(0:0):(29:71)	(0:0):(7:93)[c]
6a	0:100	(20):(80)[f]	(0):(100)[c,f] (0:0):(40:60)[d,f]
7a	100:0	(37):(63)	(0):(100)[c] (0:0):(40:60)[d]

[a]**P/M** ratio is the ratio of the (**SP** + **RP**):(**SM** + **RM**) of the starting thiohydantoin. [b]The isomer ratio was obtained from the integrations of the singlets observed for the hydrogen at the benzylic carbon around 5 ppm in the ^{1}H NMR spectrum taken in $CDCl_3$ after the reaction without any purification. [c]The isomer ratio was obtained from the integrations of the singlets observed for the hydrogen at the benzylic carbon around 5 ppm in the ^{1}H NMR spectrum taken in $CDCl_3$ after precipitation from diethyl ether/petroleum ether and ethyl acetate/hexane. [d]The isomer ratio was obtained from the integrations of the singlets observed for the hydrogen at the benzylic carbon around 5 ppm in the^{1}H NMR spectrum taken in DMSO-d_6 after precipitation from ethylacetate/hexane. [e]Because the product has no axial chirality, only the isomers **SR*&RS*** (major) and **SS*&RR*** (minor) exist. [f]Because the aldol reaction started with only **M** isomers, only **M** isomers were formed as products.

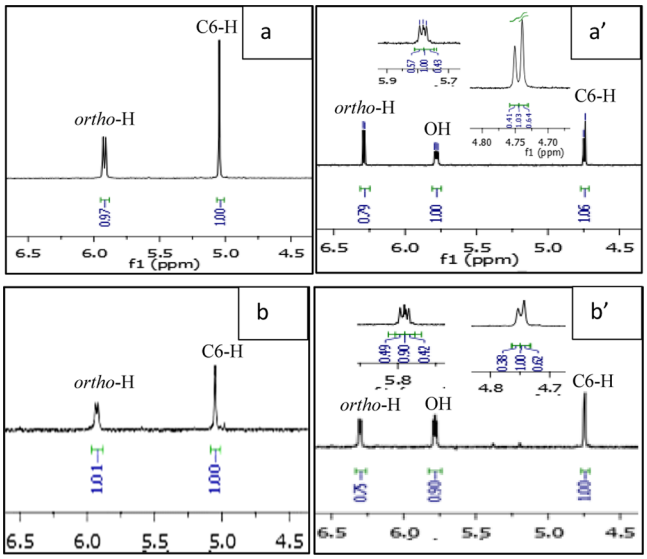

Figure 8. (a) Partial ^{1}H NMR spectrum of purified **6a** in $CDCl_3$; (a′) partial ^{1}H NMR spectrum of purified **6a** in DMSO-d_6; (b) partial ^{1}H NMR spectrum of purified **7a** in $CDCl_3$; and (b′) partial ^{1}H NMR spectrum of purified **7a** in DMSO-d_6.

occurred predominantly (ratio 20:80) from the *Re* face producing *R* configured aldol products at C5 of the thiohydantoin ring. Because the product isomers are diastereomers of each other, they principally should be separable, and, in fact, simple recrystallization eliminated the minor isomer. In $CDCl_3$, the *syn* and *anti* aldol products could not be discriminated (Figure 8a). However, in hydrogen-bonding solvents, they were. In DMSO-d_6 and DMF-d_7, two doublets were seen for the OH protons and two different broad singlets

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

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

[a]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 ^{1}H NMR spectrum taken in $CDCl_3$ before purification. [b]The syn/anti isomer ratio could not be determined because the isomers could not be separated. [c]The syn/anti isomer ratio was determined from the ^{1}H NMR spectrum taken in $CDCl_3$ after purification. [d]The syn/anti isomer ratio was determined from the ^{1}H NMR spectrum taken in DMSO-d_6 after purification.

for the hydrogen at C6 of the two isomers (Figure 8a′). The *ortho* hydrogen of CF_3-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). Because the aldol reaction started with **6** having only **M** axial chirality, the product's conformation should also be **M**.

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, CF_3, like iodine as an *ortho* substituent, enabled full protection during the aldol reactions of **6** and **7**.

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Thus, for the *o*-iodophenyl (**5a**) and the *o*-trifluoromethylphenyl 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*-CF_3 bearing axially chiral thiohydantoins **6** and **7** yielded solely **M** and **P** conformed products, 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-*o*-aryl thiohydantoins, **2**−**7**, the selectivity at C5 depended on the *ortho*-phenyl 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*-CF_3 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. ^{1}H and ^{13}C 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 mm^2) 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 (Et_3N) in CH_2Cl_2 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 $MgSO_4$ 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) Et_3N in 10 mL of CH_2Cl_2. Yield: 0.56 g (55%); white solid, mp 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.26 (m, 10H, aromatic ring and NH); 4.46 and 4.34 (two quartets, 2H, α-H at C-5); 1.66 and 1.58 (d, 6H, methyl signals at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.76, 173.19, 133.57, 133.52, 132.17, 131.35, 131.23, 131.04, 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 $C_{10}H_9BrN_2OSH^+$, 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 Et_3N in 10 mL of CH_2Cl_2. Yield: 0.59 g (60%); white solid, mp 238−239 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{11}H_9F_3N_2OSH^+$, 275.0466; found, 275.0467.

*5-Methyl-3-o-trifluoromethylphenylthiohydantoin (**7**).* 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 L-alanine methyl ester HCl salt and 0.5 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.41 g (43.5%); white solid, mp 238−239 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77−7.25 (m, 10H, aromatic ring and NH), 4.39 and 4.26 (two quartets, 2H, α-H at C-5), 1.55 and 1.54 (two doublets, H, methyl signals at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.30, 173.74, 133.12, 133.07, 132.05, 131.86, 130.38, 127.71, 127.77, 124.18, 121.63, 121.51, 55.90, 55.67, 17.18, 16.70 ppm. (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES$^+$): calcd for $C_{11}H_9F_3N_2OSH^+$, 275.0466; found, 275.0465.

General Procedure for the Aldol Reaction (2a−7a). The aldol reactions were carried out under nitrogen. To the solution of 5-methyl-3-*o*-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 NH_4Cl solution (2 equiv). The solution was extracted with diethyl ether three times and dried over anhydrous $CaCl_2$. 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 **2** 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, benzylic H), 1.91, 1.83, and 1.70 (s, 3H, CH_3 at α-C). ^{13}C NMR (100 MHz, $CDCl_3$): 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, 68.6, 20.3, 20.1 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES$^+$): calcd for $C_{17}H_{15}BrN_2O_2SH^+$, 391.0116; found, 391.0117.

*5-(Hydroxy(phenyl)methyl)-5-methyl-3-phenyl Thiohydantoin (**3a**).* The compound was synthesized according to the general procedure using 0.23 g (1.12 mmol) of compound **3** in 7.0 mL of THF, 1.3 mL (2.68 mmol) of LDA, and 0.23 mL (2.23 mmol) of benzaldehyde. Yield: 0.23 g (66%), mp 135−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H, NH); 7.45−7.25 (m, 8H, aromatic rings); 6.63 (m, 2H, aromatic proton); 5.07 and 5.01 (s, 1H, benzylic H); 1.83 (s, 6H, CH_3 at α-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 174.3, 137.2,

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132.3, 129.4, 129.2, 129.0, 128.7, 128.0, 127.2, 69.0, 20.0, 19.5 ppm. HRMS (TOF MS ES$^+$): calcd for $C_{17}H_{16}N_2O_2SH^+$, 313.1011; found, 313.1023.

*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 165−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (br s, 1H, NH), 7.46−7.16 (m, 9H, aromatic ring), 6.07 (dd, 1H, aromatic proton), 5.04 and 5.02 (s, 1H, benzylic H), 2.86 and 2.58 (br s, 1H, −OH), 1.83 and 1.73 (s, 3H, CH_3 at α-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8, 173.4, 137.2, 136.9, 133.4, 133.2, 131.1, 130.9, 130.8, 130.5, 130.3, 130.2, 130.0, 129.29, 129.26, 128.9, 128.6, 127.6, 127.5, 127.2, 69.3, 68.0, 20.1, 19.9 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES$^+$): calcd for $C_{17}H_{15}ClN_2O_2SH^+$, 347.0621; found, 347.0624.

*5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-iodophenyl Thiohydantoin (**5a**).* The compound was synthesized according to the general procedure using 0.25 g (0.75 mmol) of compound **5** in 4.7 mL of THF, 0.9 mL (1.81 mmol) of LDA, and 0.15 mL (1.51 mmol) of benzaldehyde. Yield: 0.084 g (25%), mp 176−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00−8.00 (m, 10H, NH and aromatic ring), 5.98 (d, 1H, aromatic proton), 5.05 and 5.01 (s, 1H, benzylic H), 2.68 (br s, 1H, −OH), 1.86 (s, 3H, CH_3 at α-C). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{15}IN_2O_2SH^+$, 438.9977; found, 438.9976.

*5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-trifluoromethylphenyl Thiohydantoin (**6a**).* The compound was synthesized according to the general procedure using 0.25 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 184−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.46 (m, 9H, aromatic ring and NH), 5.93 (d, 1H, aromatic H), 5.05 (s, 2H, at C6), 1.83 (s, 3H, CH_3 at α-C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H, NH), 7.77−7.27 (m, 8H, aromatic ring), 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, CH_3 at α-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.45, 173.72, 137.18, 132.83, 131.32, 130.06, 129.31, 128.63, 127.39, 127.31, 127.36, 76.98, 69.39, 20.00 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES$^+$): calcd for $C_{18}H_{15}F_3N_2O_2SH^+$, 381.0885; found, 381.0885.

*5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-trifluoromethylphenyl 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 207−209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93−7.45 (m, 9H, aromatic ring and NH), 5.94 (d, 1H, aromatic H), 5.05 (s, 1H, benzylic H), 1.84 (s, 3H, CH_3 at α-C). ^{1}H NMR (400 MHz, DMSO-d_6): 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), 4.74−4.75 (two singlets, 2H, benzylic H), 1.55 (s, 3H, CH_3 at α-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.59, 173.78, 137.23, 132.89, 131.37, 130.47, 130.11, 129.35, 128.67, 127.43, 127.07, 125.33, 69.45, 20.04 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES$^+$): calcd for $C_{18}H_{15}F_3N_2O_2SH^+$, 381.0885; found, 381.0885.

■ ASSOCIATED CONTENT

Supporting Information

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

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

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Notes

The authors declare no competing financial interest.

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