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Atroposelective Synthesis of Axially Chiral Thiohydantoin Derivatives

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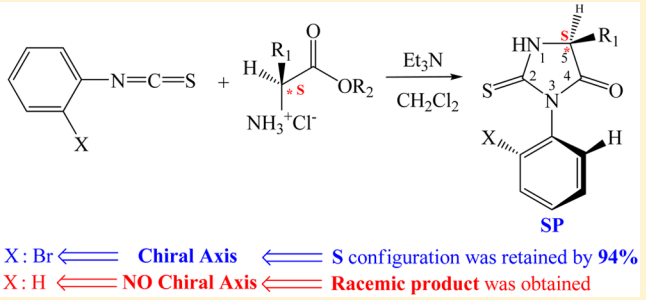
Supporting Information

ABSTRACT: Nonracemic axially chiral thiohydantoins were synthesized atroposelectively by the reaction of *o*-aryl isothiocyanates with amino acid ester salts in the presence of triethylamine (TEA). The synthesis of the nonaxially chiral derivatives, however, gave thiohydantoins racemized at C-5 of the heterocyclic ring. The micropreparatively resolved enantiomers of the nonaxially chiral derivatives from the racemic products were found to be optically stable under neutral conditions. On formation of the 5-methyl-3-arylthiohydantoin ring, bulky *o*-aryl substituents at N3 were found to suppress the C-5 racemization and in this way enabled the transfer of chirality from the *α*-amino acid to the products. The corresponding 5-isopropylthiohydantoins turned out to be more prone to racemization at C-5 during the ring formation. The isomer compositions of the synthesized axially chiral thiohydantoins have been determined through HPLC analyses with chiral stationary phases. In most cases a high prevalence of the **P** isomers over the **M** isomers has been obtained. The barriers to rotation determined around the N_{sp^2}–C_{aryl} chiral axis were found to be dependent upon the size of the *o*-halo aryl substituents.



INTRODUCTION

Hydantoins and thiohydantoins are cyclic amino acid derivatives which are considered by some groups to be among the "privileged scaffolds" in drug discovery[1] and have been shown to have various pharmacological activities.[2−4] Kawabata et al. recently developed a method for asymmetric synthesis of chiral hydantoins which involved a Clayden rearrangement of chiral enolates generated from *α*-amino acid esters via the protocol of memory of chirality.[5] Axially chiral thiohydantoins are among the very first studied class of axially chiral heterocyclic analogues of biaryl derivatives.[6,7] Compounds **1**−**4** and **6** were synthesized decades ago; barriers to hindered rotation around the N_{sp^2}–C_{aryl} bond have been reported through NMR analyses, and results with attributes to stereochemistry were presented.[6,8] However, in these papers the chirality transfer issue from the amino acid to the thiohydantoin ring has not been addressed. We set out to synthesize axially chiral (5*S*)-methyl- and (5*S*)-isopropyl-3-*o*-aryl-2-thiohydantoins **1**−**6** and **8**−**12**, diastereoselectively preserving the asymmetric center at C-5 for further exploitation of the compounds in several sterically controlled (atroposelective) reactions. During the syntheses, however, we found out that the cyclization to the heterocyclic ring occurred with variable extents of racemization at C-5, depending on the electronic nature and the bulkiness of the ortho substituent together with the substituent at C-5. The nonaxially chiral derivatives were isolated as racemates. We therefore found it necessary to reinvestigate this important class of compounds, focusing on the optical stabilities at C-5 of the heterocyclic ring, to find out their potential to be used in asymmetric syntheses via the chiral pool strategy. In addition, we undertook the synthesis of highly **P** or **M** enriched axially chiral thiohydantoins for further use as scaffolds in the preparation of asymmetric amino acid derivatives through atroposelective enolate reactions. This paper describes the syntheses of axially chiral thiohydantoins **1**−**6** from L-alanine methyl ester and **8**−**13** from L-valine ethyl ester atroposelectively, isomeric assignments of the products, and determinations of the barriers to hindered rotation via HPLC analyses on chiral stationary phases.

RESULTS AND DISCUSSION

Axially chiral 5-methyl- (**1**−**6**) and 5-isopropyl-3-(*o*-aryl)-2-thiohydantoin (**8**−**13**) derivatives were synthesized as nonracemic diastereomeric pairs of atropisomers as determined by HPLC analyses with a chiral stationary phase and by ^{1}H NMR. The synthesis of 5-methyl-3-phenyl-2-thiohydantoin (**7**) and 5-isopropyl-3-phenyl-2-thiohydantoin (**14**), which lack chiral axes, gave racemic mixtures. The reaction of the corresponding aryl isothiocyanates with L-alanine methyl ester HCl salt (**1**−**7**) or L-valine ethyl ester HCl salt (**8**−**14**) in the presence of triethylamine (TEA) under reflux in CH_2Cl_2 (Scheme 1) by a modified procedure of Burgess et al.[9] yielded **1**−**14**. The reaction times have been optimized by following the reaction progress by HPLC.

The axially chiral **1**−**6** and **8**−**13** may exist in **SP**, **RM**, **SM**, and **RP** isomeric forms (Scheme 1). **SP**/**RM** is transoid, whereas is **SM**/**RP** is cisoid with respect to the substituent at C5 and the *o*-aryl substituent. For all of these compounds,

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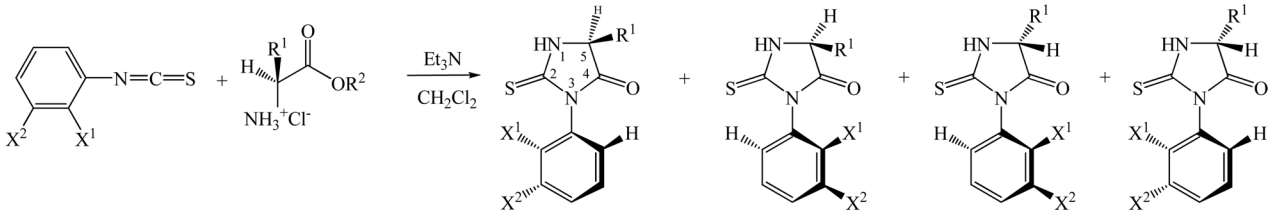
Scheme 1. Synthesis of Compounds 1−14



Comp.			R^1	R^2	Rxn Time (h)	Yield (%)
1	X^1= CH_3	X^2= H	CH_3	CH_3	1	66
2	X^1= F	X^2= H	CH_3	CH_3	1	46
3	X^1= Cl	X^2= H	CH_3	CH_3	1	64
4	X^1= Br	X^2= H	CH_3	CH_3	1	63
5	X^1= I	X^2= H	CH_3	CH_3	4	75
6	X^1= X^2= Benzo		CH_3	CH_3	1	55
7	X^1= H	X^2= H	CH_3	CH_3	1	59
8	X^1= CH_3	X^2= H	isopropyl	C_2H_5	1	58
9	X^1= F	X^2= H	isopropyl	C_2H_5	1	74
10	X^1= Cl	X^2= H	isopropyl	C_2H_5	1	44
11	X^1= Br	X^2= H	isopropyl	C_2H_5	4	46
12	X^1= I	X^2= H	isopropyl	C_2H_5	4	91
13	X^1= X^2= Benzo		isopropyl	C_2H_5	1	69
14	X^1= H	X^2= H	isopropyl	C_2H_5	1	39

except for **2** and **9**, the isomers were resolvable to their four isomers by HPLC on chiral stationary phases. Recrystallization of the products changed the transoid/cisoid ratios noticeably (Table 1). Compounds **7** and **14** are not axially chiral and were shown to be racemic through NMR studies with (*S*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((*S*)-TFAE) together with HPLC analyses.When the enantiomers of **7** and **14** were resolved micropreparatively and subjected to a thermal racemization experiment under neutral conditions, they were found to be optically stable (under basic conditions racemization of the resolved enantiomer of **7** was observed within 15 min).

Table 1. Relative Proportions of the Isomers Determined by HPLC with a Chiral Stationary Phase

	SM:RP:SP:RM	
compd	crude	after recrystallization
1[f]	7:49:43:1	10:50:40:0[a]
2	N.D.[c]	10:36:34:20[b]
3[f]	4:7: 89:0	3:6: 91:0
4[f]	3:14:83:0	3:6: 91:0[d]
5[g]	4:12:84:0	5:10:85:0
6[h]	9:73:17:1	10:74:16:0[e]
8[f]	8:28:57:7	4:33:49:14
9	N.D.[c]	17:20:32:31[b]
10[f]	2:51:43:4	2:52:42:4
11[f]	3:63:33:1	3:73:22:2
12[g]	3:41:53:3	0:85:14:1[d]
13[f]	22:28:42:8	32:41:20:7

[a]Compounds were recrystallized from ethyl acetate/hexane. [b]The er and dr of **2** were found by ^{1}H NMR in the presence of (*S*)-TFAE. [c]N.D. denotes not determined. [d]**4** and **12** were recrystallized from methanol/water. [e]**6** was recrystallized from ethyl acetate. [f]Conditions: ChiralPak IC as the stationary phase, 95/5 Hex/EtOH as the eluent, flow rate 0.6 mL/min [g]Conditions: ChiralPak IB as the stationary phase, 95/5 Hex/EtOH as the eluent, flow rate 1.0 mL/min [h]Conditions: ChiralPak IC as the stationary phase, 95/5 Hex/EtOH as the eluent, flow rate 1.0 mL/min.

We started with compound **4**, 5-methyl-3-(*o*-bromophenyl)-2-thiohydantoin, because X-ray and ^{1}H NMR data for this product had been reported in the literature.[6] X-ray data for **4** showed that the structure of the compound was **SP**, where the bromine atom was transoid with respect to the C-5 methyl.[6] The ^{1}H NMR of **4** synthesized in this work also showed a transoid relationship between the *o*-Br and the C5 methyl groups, as shown in Figure 1. ^{1}H NMR shows that compound **4** is present as an unequal composition of two diastereomers. The major diastereomer has its quartet at a higher field but its doublet at a lower field than the minor isomer. This is because, when Br is transoid with respect to C5 methyl, it lies on the same side as C5−H (Scheme 1) and the anisotropy of Br will cause the C5−H of this stereoisomer to appear at a higher field.[10] Thus, the major diastereomer is either **SP** or its enantiomer **RM**. In order to decide whether the species is **SP** or **RM**, the reaction was followed by HPLC on a chiral stationary phase. In the chromatogram of the sample taken from the reaction mixture after 15 min from the start of the experiment at room temperature, three peaks at 27, 31, and 39 min were observed, the highest intensity peak having a 39 min retention time. This peak was also the highest one in the chromatogram obtained after refluxing the reaction mixture (40 °C) for 1 h for completion of the reaction (see Figure S8 in the Supporting Information). On this basis, the highest intensity peak in the chromatogram has been assigned to **SP**, since it was considered unlikely for L-alanine to racemize to such an extent within 15 min to be able to give **RM**, on the basis of the fact that the resolved

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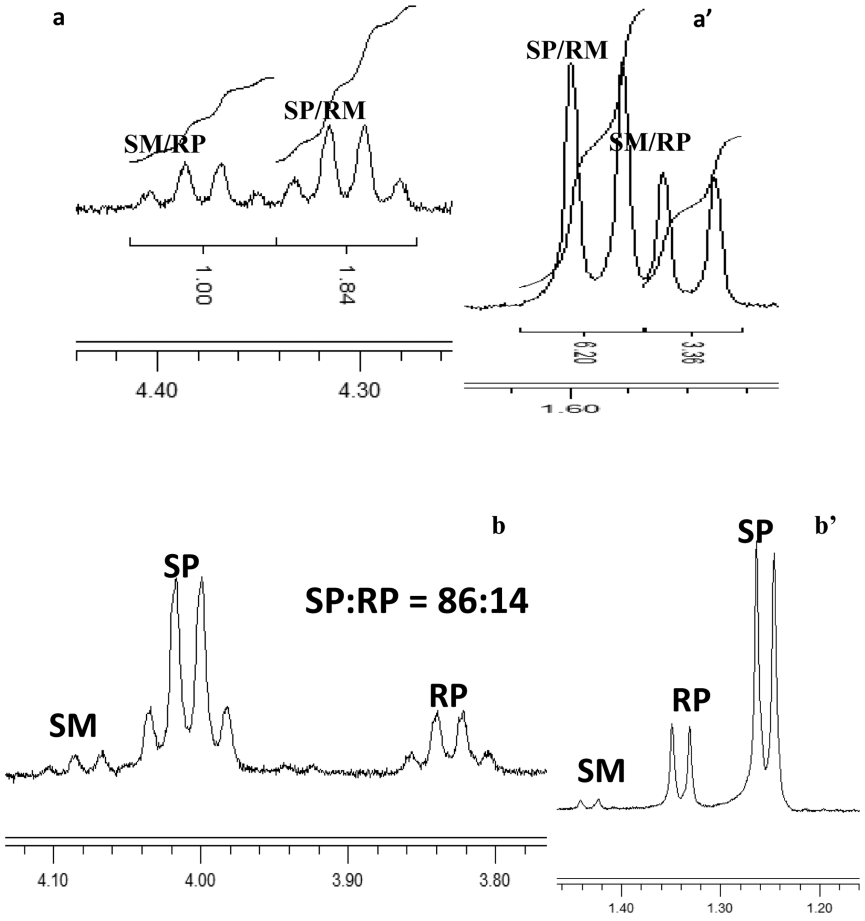

Figure 1. Partial ^{1}H NMR spectrum of compound **4** in $CDCl_3$: (a) quartets and (a′) doublets without (*S*)-TFAE; (b) quartets in the presence of 6 equiv of *S*-TFAE; (b′) doublets in the presence of 6 equiv of (*S*)-TFAE.

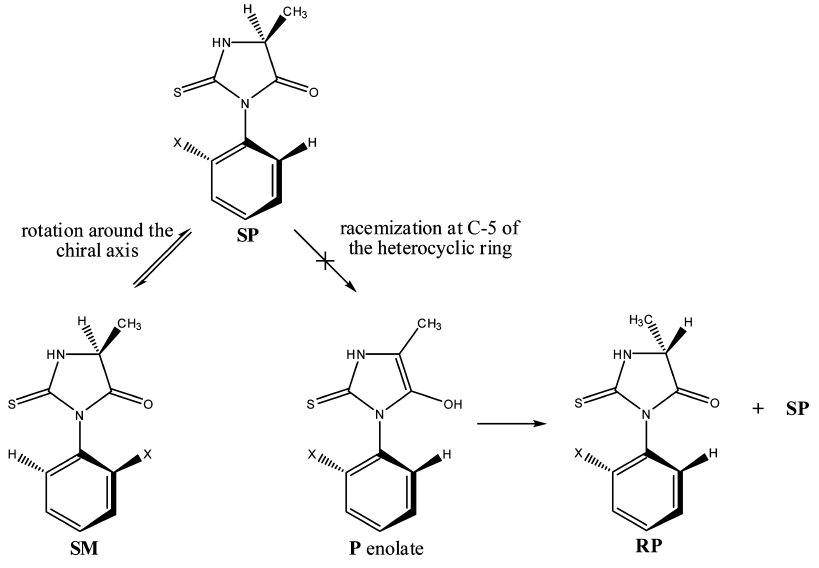

Figure 2. Possible interconversions for the studied compounds shown for the **SP** isomer.

enantiomers of **7** did not racemize even over a period of 7.5 h at 40 °C. The two major peaks on the chromatogram were found to be separable by recrystallization; thus, they should be diastereomeric isomers. For this reason the next higher intensity peak on the chromatogram has been assigned to **RP**, not to **SM**, on the basis of the fact that **SP** did not interconvert to this peak during the thermal interconversion experiment, as will be explained later in the text. The enantiomer assignments were done by comparing the ^{1}H NMR spectra in the presence of (*S*)-TFAE (Figure 1) with the HPLC chromatogram.

^{1}H NMR spectrum of **4** with (*S*)-TFAE was taken to make the enantiomers visible. Diastereomeric complexes are expected to form through supramolecular interactions, such

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as H bonding and π stacking[11] between (*S*)-TFAE and enantiomeric stereoisomers of **4**. The ^{1}H NMR spectrum of **4** with (*S*)-TFAE indicated a partial racemization at C-5 of the heterocyclic ring (Figure 1b). By comparison of the ^{1}H NMR of **4** taken with (*S*)-TFAE and the chromatograms mentioned above, the first peak on the chromatogram was assigned to **SM**. The **RM** did not form during the synthesis but it was produced to a slight extent during the thermal interconversion studies at 60 °C (Figure 2).

Isomeric assignments done in this way for the axially chiral **1**−**6** and **8**−**13** through HPLC-NMR analyses and the isomeric ratios are given in Table 1. It has been shown that the isomeric compositions obtained at the end of the reaction vary depending on the type of the ortho substituent and the substituent on C-5. Table 1 also shows the relative proportions of the isomers obtained after purification of the crude product by recrsytallization. As can be inferred from the table, recrystallization for some derivatives dramatically increased the diastereomeric ratio (transoid/cisoid ratio) of the products. This result is important because it shows that **R** thiohydantoin can easily be separated from the **S** species by means of axial chirality, in the same way as enantiomers are separated from each other via formation of diastereomeric pairs.[12] From the **SP**/**RP** ratios, which indicate the degree of racemization at C-5, it can be seen for 5-methyl derivatives that, when the *o*-halogen is changed from F to Cl, the **SP**/**RP** ratio increased, which means that the degree of racemization at the chirality center decreased. It figures that bulkier ortho substituents suppress the racemization at C-5 of the thiohydantoin ring, enabling the transfer of chirality of the α-amino acids to the products. On comparison of the **SP**/**RP** ratios of **1** and **3**, on the other hand, the role of the electronic effects seems to be also an important factor in determining the extent of racemization. The observed influence of the *o*-chloro substituent, however, is probably through space rather than being through bond as has been proposed before.[13] The α-naphthyl group of **6** gave rise to an interesting type of atroposelectivity where a reversal of the **SP**/**RP** ratio has been observed. The higher concentration of **RP** + **SM** is also manifested in its ^{1}H NMR spectrum. When the naphthyl group is cisoid with C-5 methyl, namely the **RP** (and **SM**) species, it has a shielding anisotropy effect on the ^{1}H NMR signal of CH_3. When, on the other hand, the naphthyl is on the C-5 H side (**RM** and **SP**), the C-5 H signal is shielded. Thus, the lower intensity quartets and doublets belong to **RM** + **SP** and the higher intensity peaks belong to **RP** + **SM**, in parallel with the HPLC experiment. It should be noted that for compounds **4** and **5** the major isomers are **RM**/**SP**, appearing more shielded due to the anisotropy effect of the bromine and the iodine this time. The related NMR spectra and the HPLC chromatograms can be seen in the Supporting Information.

It figures from Table 1 that the valine ester is more prone to racemization in forming the C-5 isopropyl substituted thiohydantoin ring. The **SP**/**RP** ratio of **10** is close to 1, and that of **11** is less than 1. This result for **11** may be due to the longer reaction time required for the completion of the reaction. However, compounds **8** and **10**, although subjected to the same reaction times as **3**−**5**, showed **SP**/**RP** ratios lower than those of the latter.

Then, with the purpose of doing a time course experiment to confirm that racemization at C-5 (Figure 2) is not occurring, the **RP** and **SP** isomers of **4** were resolved micropreparatively by HPLC on Chiralpak IC. The resolved isomers were kept separately in toluene in a constant temperature bath at 30 °C and injected to HPLC at certain time intervals for analysis. It has been observed that **RP** converted to **RM** with time and **SP** did not appear at all during the time span of the experiment (Figure 3a). This fact

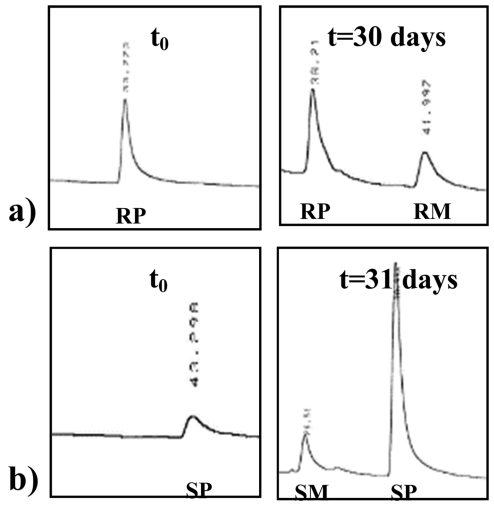

Figure 3. (a) Thermal interconversion of micropreperatively resolved **RP** to **RM** of **4** through rotation, in toluene at 30 °C by HPLC on ChiralPak IC. (b) Thermal interconversion of micropreperatively resolved **SP** to **SM** of **4** through rotation, in toluene at 30 °C by HPLC on ChiralPak IC.

indicated that **RP** did *not* racemize at C-5, to give any **SP**. When the experiment was repeated with the resolved **SP**, it was found to convert to **SM** with time, without formation of any other isomer (Figure 3b).

Next, isomers of compound **1** were resolved micropreparatively and the resolved **SP** and **RP** were subjected to thermal interconversion experiments. Chromatograms (see the Supporting Information) indicate that the conversions occurred only between **SP** and **SM** and between **RP** and **RM**. **SP** did not convert to **RP**. This result, similar to that of **4**, points to the fact that **RP** was produced during the formation of the heterocycle and not by a racemization of the ring via enolization followed by reprotonation. To further prove that enolization is not taking place, deuteration experiments were done on **1** in methanol-d_4 at 30 °C using ^{1}H NMR, where there was a possibility to follow the deuteration by comparing the *o*-methyl signals with the C-5 hydrogen signal. This experiment did not show any sign of deuteration, also in the presence of a few drops of D_2O. Therefore, it was concluded that racemization is not taking place under neutral conditions.

Having found out that the only occurring dynamic process was between the rotational isomers, the barrier to hindered rotation around the $N_{sp^2}-C_{aryl}$ chiral axis has been determined. A nonequilibrium mixture of isomers of **4** was kept in toluene at 60 °C and analyzed by HPLC on Chiralpak IC versus time. During this thermal process the peaks of **SM** and **RM** increased with time (Figure 4), while those of the other two decreased. A plot of $\ln[(M_0 - M_{eq})/(M_t - M_{eq})]$ vs time[14] (Figure 5), where M_0 is the initial concentration of the isomer, M_{eq} is the equilibrium concentration, and M_t is the concentration at time *t*, gave the first-order rate constants

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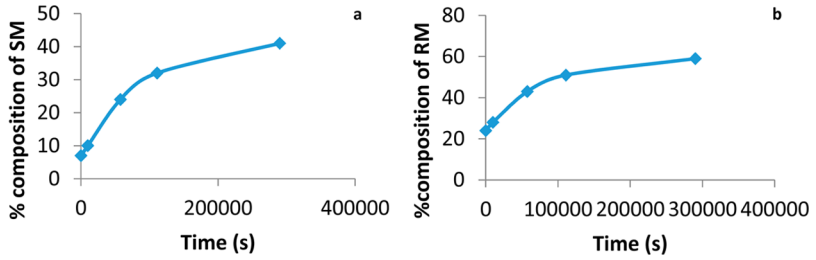

Figure 4. (a) Percent composition of **SM** vs time graph for the **SP** → **SM** conversion. (b) Percent composition of **RM** vs time graph for the **RP** → **RM** conversion.

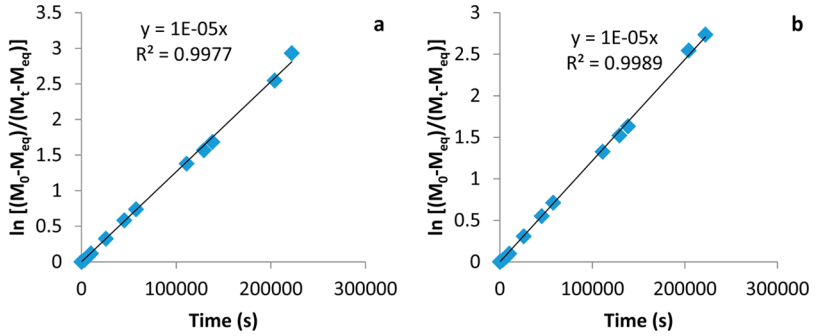

Figure 5. $\ln[(M_0 - M_{eq})/(M_t - M_{eq})]$ vs time graph: (a) for the conversion of **RP** to **RM** from the mixture of all isomers of **4**; (b) for the conversion of **SP** to **SM** from the mixture of all isomers of **4**.

Table 2. Rotational Barriers of Compounds 1−6 and 8−13

		SP ⇄ SM					RP ⇄ RM				
compd	temp (K)	K	k_f (s^{-1})	ΔG_f (kJ/mol)	k_r (s^{-1})	ΔG_r (kJ/mol)	K	k_f (s^{-1})	ΔG_f (kJ/mol)	k_r (s^{-1})	ΔG_r (kJ/mol)
1	303	0.7	3.0×10^{-5}	100.5 ± 0.7	2.0×10^{-5}	101.5 ± 0.7	1.3	1.7×10^{-5}	101.9 ± 0.7	2.3×10^{-5}	101.3 ± 0.7
2[14]	359	1.1	7.6	82.4							
3	333	0.7	4.2×10^{-5}	109.8 ± 0.7	5.8×10^{-5}	108.9 ± 0.7	1.3	5.6×10^{-5}	109.0 ± 0.7	4.4×10^{-5}	109.7 ± 0.7
4	333	0.7	4.1×10^{-6}	116.2 ± 0.7	6.0×10^{-6}	115.2 ± 0.7	1.5	5.9×10^{-6}	115.2 ± 0.7	4.1×10^{-6}	116.2 ± 0.7
5	333	0.9	1.9×10^{-6}	118.4 ± 0.7	2.1×10^{-6}	118.0 ± 0.7			N.D.		
	383	0.8	1.7×10^{-4}	122.2 ± 0.7	2.3×10^{-4}	121.3 ± 0.7			N.D.		
6	303			N.D.			1.0	1.5×10^{-6}	108.0 ± 0.7	1.5×10^{-6}	108.0 ± 0.7
	333	1.2	1.1×10^{-4}	107.1 ± 0.7	9.1×10^{-5}	107.6 ± 0.7	1.1	1.1×10^{-4}	107.2 ± 0.7	9.4×10^{-5}	107.5 ± 0.7
8	303	1.0	1.0×10^{-5}	103.3 ± 0.7	1.0×10^{-5}	103.2 ± 0.7	1.0	9.9×10^{-6}	103.3 ± 0.7	1.0×10^{-5}	103.2 ± 0.7
9	358[a]		5.3	83.2							
	378[b]		8.0	86.8							
10	333	0.9	9.3×10^{-5}	107.6 ± 0.7	1.1×10^{-4}	107.2 ± 0.7	1.1	1.1×10^{-4}	107.2 ± 0.7	9.4×10^{-5}	107.5 ± 0.7
11	333	1.0	5.1×10^{-6}	115.6 ± 0.7	4.9×10^{-6}	115.7 ± 0.7	1.0	5.0×10^{-6}	115.7 ± 0.7	5.1×10^{-6}	115.6 ± 0.7
12	333	1.3	2.3×10^{-6}	117.8 ± 0.7	1.7×10^{-6}	118.6 ± 0.7	0.7	1.7×10^{-6}	118.7 ± 0.7	2.3×10^{-6}	117.8 ± 0.7
13	333			N.D.			0.9	9.6×10^{-5}	107.5 ± 0.7	1.0×10^{-4}	107.3 ± 0.7

[a]The rotational barrier of **9** was determined by dynamic NMR. The coalescence temperature and coalescence rate constant were calculated from the coalescence of two methyl signals, which are doublets. [b]The rotational barrier of **9** was determined by dynamic NMR. The coalescence temperature and coalescence rate constant were calculated from the coalescence of α-hydrogen at C-5, which is a doublet.

for the hindered rotation around the $N_{sp^2}-C_{aryl}$ chiral axis and the corresponding barriers from the Eyring equation $\Delta G^{\ddagger} = RT \ln[k_b T/kh]$.[15]

The rotational barriers for the forward and the reverse directions for **1−6** and **8−13** are given in Table 2. The $\Delta G^{\ddagger}$ value we found for the **SP** to **SM** conversion of **4** at 60 °C, 116.2 kJ/mol (27.8 kcal/mol), is larger than the $\Delta G^{\ddagger}$ value reported by Colebrook et al. (25.2 kcal/mol) for the rotational barrier of the same compound for hindered rotation.[8] The difference, in addition to the different methods used, may also be due to the different temperatures and solvents used (toluene vs pyridine, 60 °C vs 25 °C). The barriers for **2−5** and **9−12** indicate that $\Delta G^{\ddagger}$ values increase with the size of the ortho substituent on the aryl ring. On comparison of the barriers to rotation of **1** and **3** and of **8** and **10**, however, chlorine was found to exert a greater steric effect than methyl, as has been observed before.[13] The barrier determined in an earlier work for 3-*o*-chlorophenyl-5-methylthiohydantoin (25.7 kcal/mol) was found to be slightly higher than that of the corresponding *o*-bromo derivative (25.2 kcal/mol).[16] This unexpected result may be due to the different temperatures used in the two experiments. We showed in this work that, if analyses are done at the same temperature, the barrier of the *o*-bromo derivative turns out to be higher than that of the *o*-chloro derivative (Table 2).

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CONCLUSION

In conclusion, we have shown the atroposelective syntheses of axially chiral thiohydantoins **1**−**6** and **8**−**12**. Diastereomeric ratios were found to increase by recrystallization up to 94%. The thiohydantoin isomers converted to one another via rotation, and the barrier heights, determined by HPLC with chiral stationary phases, were found to increase in the halogen series with the size of the ortho substituents. The syntheses of **3**−**5** proceeded with almost complete enantioselectivities with respect to the formation of **SP**. Bulky *o*-aryl substituents of 5-methyl-3-aryl-thiohydantoin derivatives were found to help in the transfer of chirality of the amino acid to the thiohydantoin ring. For compounds **3**−**8** and **10**−**12**, a high prevalence of the **P** isomers over the **M** isomers was determined, which would make these compounds good candidates for future atroposelective reactions at C-5 that will be carried out over the corresponding enolates.

EXPERIMENTAL SECTION

Synthesis of Compounds. *General Procedure for the Preparation of Thiohydantoin Derivatives **1**−**14**.* Compounds **1**−**7** were synthesized by the reaction of the corresponding isothiocyanate and L-alanine methyl ester HCl salt in the presence of triethylamine (Et_3N) and CH_2Cl_2 under reflux for 1 h. For the compounds **8**−**14**, L-valine ethyl ester HCl salt was used under the same conditions. At the end of the reaction, the crude product was extracted with distilled water and saturated brine solution. Finally the solution was dried over $MgSO_4$ and filtered and the solvent removed immediately. The crude products were recrystallized from ethyl acetate/hexane, ethyl acetate, or methanol/water, as shown in Table 1.

*5-Methyl-3-o-tolylthiohydantoin (**1**).*[13] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.43 mL portion (3.58 mmol) of *o*-tolyl 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: 0.52 g (66%); white solid. Mp: 215−218 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (bs, 1H, NH), 7.41−7.12 (m, 8H, aromatic ring), 4.37 and 4.35 (two quartets, J = 7.2 Hz and J = 6.8 Hz, 2H, α-H), 2.20 and 2.17 (two singlets, 6H, methyl attached to the aromatic ring), 1.61−1.59 (two doublets, J = 7.2 Hz, 6H, methyl signals at C-5 coincided). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.8, 183.7, 174.1, 174.1, 136.8, 136.6, 132.0, 131.9, 131.4, 131.3, 130.2, 129.4, 129.2, 127.3, 127.2, 55.8, 55.7, 18.0, 17.7, 17.6, 17.4 ppm (diastereomeric isomers gave different carbon signals). Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.71; H, 5.40; N, 12.50.

*5-Methyl-3-o-fluorophenylthiohydantoin (**2**).*[16] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.44 mL portion (3.58 mmol) of *o*-fluorophenyl 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: 0.37 g (46%); white solid. Mp: 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (bs, 1H, NH), 7.50−7.22 (m, 8H, aromatic ring), 4.41 and 4.36 (two quartets, J = 7.2 Hz and J = 6.4 Hz, 2H, α-H at C-5 coincided), 1.61 and 1.60 (two doublets, J = 6.8 Hz, 6H, methyl signals at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.0, 182.9, 173.6, 173.4, 158.0, 157.9 ($^1J_{C-F}$ = 254 Hz), 131.6, 131.6, 130.8, 130.7, 124.7, 124.62, 124.61, 124.6, 120.6, 120.48, 120.45, 120.4, 116.9, 116.8, 116.7, 116.6, 55.8, 55.7, 17.2, 16.9 ppm (diastereomeric isomers gave different carbon signals). Anal. Calcd for $C_{10}H_9FN_2OS$: C, 53.56; H, 4.05; N, 12.49. Found: C, 53.28; H, 3.85; N, 12.45.

*5-Methyl-3-o-chlorophenylthiohydantoin (**3**).*[13] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.47 mL portion (3.58 mmol) of *o*-chlorophenyl 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: 0.55 g (64%); white solid. Mp: 198−200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.30 (m, 10H, aromatic ring and NH), 4.43 and 4.36 (two quartets, J = 6.8 Hz and J = 7.2 Hz, 2H, α-H at C-5), 1.64−1.59 (two methyl signals coincided with the solvent signal, 6H, methyls at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.9, 182.8, 173.4, 173.4, 133.3, 133.2, 131.2, 131.2, 131.0, 130.7, 130.6, 130.41, 130.35, 127.8, 127.7, 55.8, 55.7, 17.7, 16.9 ppm (diastereomeric isomers gave different carbon signals). Anal. Calcd for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; N, 11.64. Found: C, 49.56; H, 3.57; N, 11.44.

*5-Methyl-3-o-bromophenylthiohydantoin (**4**).*[6] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.48 mL portion (3.58 mmol) of *o*-bromophenyl 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: 0.65 g (63%); white solid. Mp: 224−225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.14 (m, 10H, aromatic ring and NH), 4.38 and 4.31 (two quartets, J = 7.2 Hz and J = 6.8 Hz, 2H, α-H at C-5), 1.59 and 1.56 (d, J = 7.2 Hz and J = 6.8 Hz, 6H, methyl signals at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 173.2, 133.6, 133.5, 132.2, 131.4, 131.2, 131.1, 128.5, 128.5, 123.4, 123.4, 55.9, 55.8, 17.4, 16.9 ppm (diastereomeric isomers gave different carbon signals). Anal. Calcd for $C_{10}H_9BrN_2OS$: C, 42.12; H, 3.18; N, 9.82. Found: C, 42.12; H, 3.04; N, 9.64.

*5-Methyl-3-o-iodophenylthiohydantoin (**5**).* This compound was synthesized according to the general procedure, the reflux time being 4 h. A 1.00 g portion (3.83 mmol) of *o*-iodophenyl isothiocyanate was added to a solution of 0.53 g (3.83 mmol) of L-alanine methyl ester HCl salt and 0.53 mL (3.83 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.95 g (75%); white solid. Mp: 222−224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.12 (m, 10H, aromatic ring and NH), 4.38 and 4.30 (two quartets, J = 7.2 Hz, 2H, α-H at C-5), 1.62 and 1.56 (two doublets, J = 7.2 Hz, H, methyl signals at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.5, 173.1, 139.9, 135.6, 131.3, 130.6, 129.5, 99.0, 56.0, 17.4 ppm. Anal. Calcd for $C_{10}H_9IN_2OS$: C, 36.16; H, 2.73; N, 8.43. Found: C, 36.12; H, 2.62; N, 8.06.

*5-Methyl-3-α-naphthylthiohydantoin (**6**).*[6] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.66 g portion (3.58 mmol) of 1-naphthyl isothiocyanate was added to the 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: 0.51 g (55%); white solid. Mp: 238−240 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94−7.33 (m, 16H, NH and aromatic ring), 4.46 and 4.38 (two quartets, J = 7.2 Hz, 2H, α-H at C-5), 1.65−1.59 (two doublets, J = 7.2 Hz, 6H, methyl signals at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.1, 184.0, 174.4, 174.3, 134.38, 134.36, 130.5, 130.4, 130.0, 129.9, 129.3, 128.8, 128.7, 127.7, 127.5, 127.4, 127.3, 126.6, 125.4, 125.3, 122.0, 121.6, 55.8, 55.7, 17.8, 17.2 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES+): calcd for $C_{14}H_{12}N_2OSH^+$ 257.0749, found 257.0755.

*5-Methyl-3-phenylthiohydantoin (**7**).*[16] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.43 g portion (3.58 mmol) of phenyl isothiocyanate was added to a solution of 0.50 g (3.58 mmol) of L-alanine methyl ester HCl salt and 0.50 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.43 g (59%); white solid. Mp: 184−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48−7.24 (m, 5H, aromatic ring and NH), 4.28 (one quartet, J = 7.2 Hz, 1H, α-H at C-5), 1.53 (one doublet, J = 7.2 Hz, 3H, methyl signal at C-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.6, 174.1, 132.6, 129.3, 129.2, 128.2, 55.5, 17.0 ppm. HRMS (TOF MS ES+): calcd for $C_{10}H_{10}N_2OSH^+$ 207.0592, found 207.0599.

*5-Isopropyl-3-o-tolylthiohydantoin (**8**).* This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.48 mL portion (3.58 mmol) of *o*-tolylphenyl isothiocyanate was added to a solution of 0.65 g (3.58 mmol) of L-valine ethyl ester HCl salt and 0.5 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.51 g (58%); white solid. Mp: 162−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (bs, 1H, NH), 7.40−7.05 (m,

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J. Org. Chem. 2016, 81, 5895−5902

8H, aromatic ring), 4.22−4.19 (m, 2H, α-H's at C-5 coincided), 2.43−2.35 (m, 2H, β-H's coincided), 2.20 (s, two *o*-methyl signals coincided), 1.15 and 1.14 (two doublets, J = 7.2 Hz, 6H, methyls at β-C), 1.07 (two doublets, J = 6.8 Hz, 6H, two methyl signals coincided at β-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.4, 172.99, 172.97, 137.0, 136.8, 132.1, 131.4, 130.2, 130.2, 129.4, 129.1, 127.3, 127.2, 65.6, 65.2, 31.4, 30.9, 19.2, 19.0, 18.3, 18.0, 16.9, 16.4 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES+): calcd for $C_{13}H_{16}N_2OSH^+$ 249.1062, found 249.1069.

5-Isopropyl-3-o-fluorophenylthiohydantoin (**9**). This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.44 mL portion (3.58 mmol) of *o*-fluorophenyl isothiocyanate was added to a solution of 0.65 g (3.58 mmol) of L-valine ethyl ester HCl salt and 0.5 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.67 g (74%); white solid. Mp: 158−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.21 (m, 10H, aromatic ring and NH), 4.23 and 4.19 (two doublets, J = 4.0 Hz, 2H, α-H at C-5), 2.42−2.34 (m, 2H, β-H), 1.14 (d, J = 7.2 Hz, 6H, one of the diastereotopic methyl signals at β-C), 1.05 (two methyl signals coincided, J = 6.8 Hz, 6H, other diastereotopic methyl signals at β-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 183.8, 172.6, 172.5, 159.5, 158.1 ($^1J_{C-F}$ = 251.6 Hz), 131.8, 131.75, 131.1, 130.8, 124.83, 124.80, 120.7, 120.6, 117.0, 116.9, 65.6, 65.4, 31.4, 31.3, 18.99, 18.95, 16.5, 16.2 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES+): calcd for $C_{12}H_{13}FN_2OSH^+$ 253.0811, found 253.0816.

5-Isopropyl-3-o-chlorophenylthiohydantoin (**10**).[17] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.43 mL portion (3.58 mmol) of *o*-chlorophenyl isothiocyanate was added to a solution of 0.65 g (3.58 mmol) of L-valine ethyl ester HCl salt and 0.5 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.42 g (44%); white solid. Mp: 176−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (bs, 1H, NH), 7.58−7.23 (m, 8H, aromatic ring), 4.26 and 4.20 (two doublets, J = 4.0 Hz, 2H, α-H at C-5), 2.45−2.35 (m, 2H, β-H's coincided), 1.16 (two doublets, J = 7.2, 6H, two methyl signals at β-C coincided), 1.11 and 1.06 (d, J = 6.8, 6H, methyl signals at β-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.61, 183.60, 172.5, 172.3, 133.6, 133.43, 131.38, 131.3, 131.1, 130.9, 130.8, 130.7, 128.0, 127.97, 65.8, 65.5, 31.3, 31.1, 19.4, 19.0, 17.0, 16.5 ppm (diastereomeric isomers gave different carbon signals). HRMS (TOF MS ES+): calcd for $C_{12}H_{13}ClN_2OSH^+$ 269.0515, found 269.0516.

5-Isopropyl-3-o-bromophenylthiohydantoin (**11**).[18] This compound was synthesized according to the general procedure, the reflux time being 4 h. A 0.48 mL portion (3.58 mmol) of *o*-bromophenyl isothiocyanate was added to a solution of 0.65 g (3.58 mmol) of L-valine ethyl ester HCl salt and 0.5 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.51 g (46%); white solid. Mp: 170−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (bs, 1H, NH), 7.74−7.23 (m, 8H, aromatic ring), 4.26 and 4.19 (two doublets, J = 4.0 Hz and J = 4.4, 2H, α-H at C-5), 2.41−2.37 (m, 2H, β-H), 1.18 and 1.14 (d, J = 7.2 Hz, 6H, two methyl signals at β-C), 1.15 and 1.07 (d, J = 6.8 Hz, 6H, two methyl signals at β-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.3, 183.2, 172.1, 172.0, 133.7, 133.6, 132.4, 131.32, 131.26, 131.2, 131.0, 128.50, 128.46, 123.5, 123.2, 65.6, 65.3, 31.0, 30.9, 19.2, 18.7, 17.3, 16.3 ppm (diastereomeric isomers gave different carbon signals). Anal. Calcd for $C_{12}H_{13}BrN_2OS$: C, 46.02; H, 4.18; N, 8.94. Found: C, 46.38; H, 3.78; N, 9.08.

5-Isopropyl-3-o-iodophenylthiohydantoin (**12**). This compound was synthesized according to the general procedure, the reflux time being 4 h. A 1.00 g portion (3.83 mmol) of *o*-iodophenyl isothiocyanate was added to a solution of 0.70 g (3.83 mmol) of L-valine ethyl ester HCl salt and 0.53 mL (3.83 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 1.25 g (91%); white solid. Mp: 177−180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97−7.17 (m, 5H, NH and aromatic ring), 4.26 and 4.14 (d, J = 4.0 Hz and J = 4.8 Hz, 2H, α-H at C-5), 2.43−2.36 (m, 2H, β-H), 1.20 (two doublets, J = 7.2 and J = 6.8 Hz, 6H, two methyl signals at β-C), 1.15 and 1.06 (two doublets, J = 7.2 Hz and J = 6.8 Hz, 6H, two methyl signals at β-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.1, 172.0, 139.9, 135.9, 131.3, 130.3, 129.5, 99.3, 65.5, 31.0, 18.8, 16.3 ppm. Anal. Calcd for $C_{12}H_{13}IN_2OS$: C, 40.01; H, 3.64; N, 7.78. Found: C, 40.27; H, 3.21; N, 7.50.

5-Isopropyl-α-naphthylthiohydantoin (**13**). This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.66 g portion (3.58 mmol) of 1-naphthyl isothiocyanate was added to a solution of 0.65 g (3.58 mmol) of L-valine ethyl ester HCl salt and 0.5 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.70 g (69%); white solid. Mp: 199−201 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (bs, 1H, NH), 8.00−7.33 (m, 14H, aromatic ring), 4.32 and 4.25 (two doublets, J = 3.6 Hz, 2H, α-H at C-5), 2.49−2.36 (m, 2H, β-H), 1.18 and 1.17 (d, J = 7.2 Hz and J = 6.8 Hz, 6H, methyl signals at β-C), 1.14 and 1.09 (d, J = 6.8 Hz, 6H, methyl signals at β-C). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7, 173.7, 134.54, 130.53, 130.3, 129.7, 128.86, 127.89, 127.5, 126.8, 125.5, 122.4, 65.5, 46.0, 31.5, 18.9, 16.5 ppm. HRMS (TOF MS ES+): calcd for $C_{16}H_{16}N_2OSH^+$ 285.1062, found 285.1063.

5-Isopropyl-3-phenylthiohydantoin (**14**).[19] This compound was synthesized according to the general procedure, the reflux time being 1 h. A 0.43 mL portion (3.58 mmol) of phenyl isothiocyanate was added to a solution of 0.65 g (3.58 mmol) of L-valine ethyl ester HCl salt and 0.5 mL (3.58 mmol) of Et_3N in 10 mL of CH_2Cl_2. Yield: 0.33g (39%); white solid. Mp: 210−212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (bs, 1H, NH), 7.47−7.21 (m, 5H, aromatic ring), 4.11 (d, J = 1.2 Hz, 1H, α-H), 2.37−2.28 (m, 1H, β-H), 1.08 (d, J = 7.2 Hz, 3H, methyl signal at β-C), 0.98 (d, J = 6.8 Hz, 3H, methyl signals at β-C)^{13}C NMR (100 MHz, $CDCl_3$): δ 184.5, 173.2, 132.8, 129.5, 129.4, 128.5, 65.2, 31.4, 19.0, 16.4 ppm. HRMS (TOF MS ES+): calcd for $C_{12}H_{14}N_2OSH^+$ 235.0905, found 235.0913.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00696.

All NMR spectra, HPLC chromatograms, and graphs obtained for the determination of the rotational barriers (PDF)

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Notes

The authors declare no competing financial interest.

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