Preparation of (*R*)- and (*S*)-α-Methyldopa from a Chiral Hydantoin Containing the α-Phenylethyl Group

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ABSTRACT Chiral hydantoin (*S*)-**1** was prepared in good yield from phenyl isocyanate and N-[(*S*)-α-phenylethyl]glycinate, (*S*)-**3**. Enolate (*S*)-**1**-Li was methylated in high yield and good diastereoselectivity. In contrast, a second alkylation reaction of methylated enolate (*S*)-**4**-Li proceeded with essentially no diastereoselectivity. Nevertheless, dialkylated hydantoins, (*S*,*S*)-**7** and (*S*,*R*)-**7**, could be readily separated by flash chromatography and subsequent hydrolysis of either derivative afforded the desired (*S*)-L-α-methyldopa or (*R*)-D-α-methyldopa in good yield. *Chirality 14:144–150, 2002.*

KEY WORDS: alkylation; stereoselective; diastereoselective; enantioselective; lithium enolates; amino acids and derivatives

In recent years, the preparation of enantiopure α,α-dialkylated amino acids has received substantial attention owing to the important chemical and biological properties exhibited by these compounds.[1–3] Among the various methods developed for the preparation of enantioenriched α-substituted α-amino acids, those employing chiral glycine derivatives[4–15] (Fig. 1) have been particularly successful.

Motivated by the demonstrated efficiency of (*R*)- and (*S*)-α-phenylethylamine in the preparation of enantiopure compounds,[16,17] we decided to undertake the synthesis of novel hydantoin (*S*)-**1** in order to explore its potential for the asymmetric synthesis of α,α-disubstituted α-amino acids. In this regard, 1,3-stereoinduction in derived enolate (*S*)-**1**-Li was anticipated to be higher than the 1,4-stereoinduction achieved several years ago by Schoellkopf[4] in the related substrate **M** (Chart 1).

In particular, in this article we report the double alkylation of (*S*)-**1** to afford suitable precursors of both (*R*)- and (*S*)-α-methyldopa [(*R*)- and (*S*)-**2**]. (*S*)-α-Methyldopa is a well-known antihypertensive drug, whereas the (*R*)-enantiomer is totally inactive.[18–20]

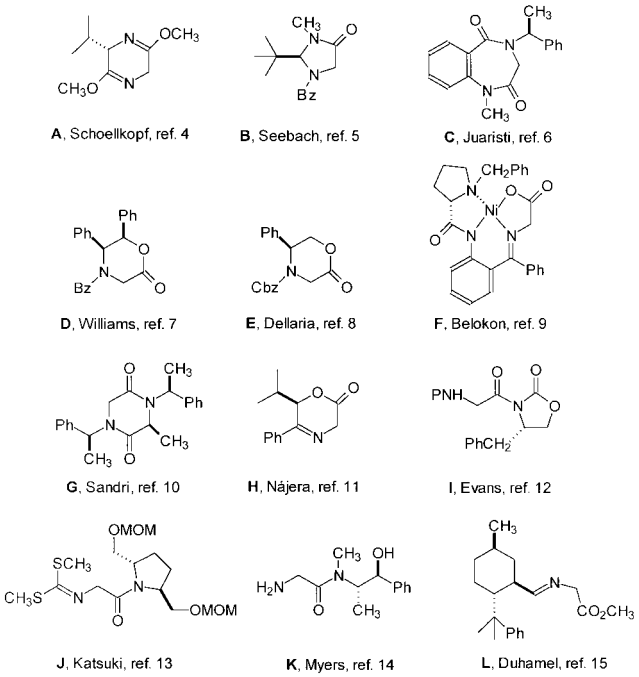

Fig. 1. Some chiral glycine derivatives developed for the synthesis of enantioenriched α-substituted α-amino acids. P = protecting group; MOM = methoxymethyl

MATERIALS AND METHODS

(–)-(*S*)-α-Phenylethylamine (Aldrich Chemical Co., Milwaukee, WI; 98%); phenyl isocyanate (Aldrich; 98+%); methyl 2-bromopropionate (Aldrich; 98%); hydriodic acid, 57% wt. in water (Aldrich; 99+%). Solvents: anhydrous tetrahydrofuran (THF; Aldrich; 99.9%). Melting points (Electrothermal apparatus) are uncorrected. TLC: Merck-DCF_{254} plates, detection by UV light at 254 nm. Flash column chromatography:[21] Merck silica gel (230–400 mesh). ^1H and ^{13}C NMR: Jeol Eclipse-400 (400 and 100 MHz, respectively). Bruker Ultra Shield (300 and 75 MHz, respectively), and Jeol GSX-270 (270 and 67.5 MHz, respectively). All chemical shifts are reported in ppm with TMS as internal reference. $[\alpha]_D$: Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN).

Dedicated to Professor Ernest L. Eliel—one of the most influential chemists in modern times—with gratitude for his constant and caring friendship.
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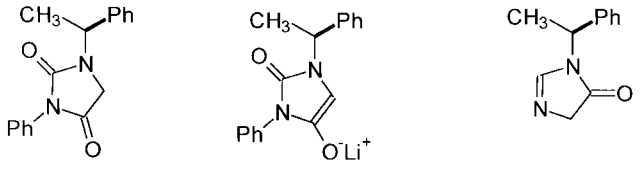


Chart 1. Chiral hydantoin (*S*)-**1**, its lithium enolate (*S*)-**1**-Li, and Schoellokopf's imidazolidinone **M**.

Ethyl N-[(S)-α-phenylethyl]glycinate, (S)-3

(*S*)-Phenylethylamine reacted with ethyl bromoacetate according to the literature procedure.[22] $[\alpha]_D^{28}$ = −63.2 (c = 2.1, $CHCl_3$). Lit.[22] $[\alpha]_D^{28}$ = −64.1 (c = 1, $CHCl_3$).

1-N-[(S)-Phenylethyl]-3-N′-phenyl-1,3-imidazolidin-2,4-dione, (S)-1

In a 250-mL round-bottomed flask fitted with magnetic stirrer was placed 11.0 g (50.0 mmol) of (*S*)-**3**, 8.7 mL (9.5 g, 50.0 mmol) of phenyl isocyanate, and 20 mL of toluene. The resulting mixture was stirred and heated to reflux until complete consumption of the starting materials (tlc analysis). The reaction mixture was allowed to cool to room temperature, concentrated, and crystallized from toluene to give 11.3 g (81% yield) of the desired hydantoin, mp = 94−95°C. $[\alpha]_D^{28}$ = −101.4 (c = 1.3, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (d, J = 7.3, 3H), 3.65 (d, J = 17.5, 1H), 3.95 (d, J = 17.5, 1H), 5.58 (q, J = 7.0, 1H), 7.34−7.44 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 45.5, 50.2, 126.1, 127.1, 128.1, 128.3, 129.0, 129.1, 139.1, 155.1, 168.9.

Anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.85; H, 5.71. Found: C, 73.00; H, 5.81.

1-N-[(S)-α-Phenylethyl]-3-N′-phenyl-(5R)- and 1-N-[(S)-α-Phenylethyl]-3-N′-phenyl-(5S)-methyl-1,3-imidazolidin-2,4-dione, (S,R)- and (S,S)-4

In a 25-mL round-bottomed flask fitted with a magnetic stirrer was placed 10 mL of dry THF, 0.26 mL (0.20 g, 1.94 mmol) of diisopropylamine, and 0.85 mL (2.04 mmol) of 2.4 M *n*-BuLi, and the resulting solution was stirred under nitrogen for 1 h at 0°C. The temperature was lowered to −78°C before the addition of 0.50 g (1.78 mmol) of hydantoin (*S*)-**1** in 2.0 mL of THF. The resulting mixture was stirred at −78°C for 1 h and then 0.16 mL (0.36 g, 2.53 mmol) of iodomethane was added. Stirring was continued at −78°C until complete disappearance of the substrate (tlc analysis). The reaction was quenched with 0.8 mL of ammonium chloride, the crude product was extracted with CH_2Cl_2, and the combined organic extracts washed with brine solution. Concentration at reduced pressure afforded 0.39 g (75% yield) of the methylated products as a 93:7 diastereomeric mixture of (*S,S*)- and (*S,R*)-**4**, respectively, on the basis of ^{1}H NMR analysis. Separation of the diastereoisomers was accomplished by flash chromatography (hexane:EtOAc, 95:5). (*S,S*)-**4**: 0.32 g of white solid, mp = 100−101°C. $[\alpha]_D^{28}$ = −114.8 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 6.9, 3H), 1.78 (d, J = 7.2, 3H), 3.78 (q, J = 6.9 Hz, 1H), 5.56 (q, J = 7.3, 1H), 7.27−7.58 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.2, 51.9, 54.8, 126.4, 127.8, 128.4, 128.6, 129.4, 132.2, 138.9, 155.5, 173.0.

Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.43; H, 6.17; N, 9.51. Found: C, 73.39; H, 6.15; N, 9.56.

(*S,R*)-4. 21 mg of white solid, mp = 106−107°C. $[\alpha]_D^{28}$ = −88.6 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 7.0, 3H), 1.80 (d, J = 7.3, 3H), 4.17 (q, J = 7.0, 1H), 5.41 (q, J = 7.3, 1H), 7.35-7.49 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 17.6, 51.2, 54.6, 126.4, 127.5, 128.3, 128.4, 129.1, 129.4, 132.2, 155.5, 173.0.

Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.43; H, 6.17. Found: C, 73.16; H, 6.34.

Methyl N-[(S)-α-phenylethyl]-(2R)- and Methyl N-[(S)-α-phenylethyl]-(2S)-amino propionate, (S,R)- and (S,S)-5

In a 250-mL round-bottomed flask fitted with a magnetic stirrer was placed 15.0 mL (22.5 g, 0.13 mol) of racemic methyl 2-bromopropionate, 19.1 mL (17.9 g, 0.15 mol) of (*S*)-α-phenylethylamine, 18.7 mL (13.6 g, 0.13 mol) of triethylamine, and 40 mL of methanol, and the resulting solution was stirred under reflux for 45 min. The crude product was extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated at reduced pressure to give 28.4 g (93% yield) of the desired product as a 50:50 mixture of diastereoisomers. Separation was accomplished by flash column chromatography (hexane:EtOAc, 95:5).

(*S,S*)-5. colorless oil. $[\alpha]_D^{28}$ = −188.4 (c = 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 7.1, 3H), 1.31 (d, J = 7.0, 3H), 1.85 (s, 1H), 3.11 (q, J = 7.1, 1H), 3.66 (s, 3H), 3.70 (q, J = 7.0, 1H), 7.27−7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 25.3, 51.6, 54.2, 56.6, 126.8, 127.0, 128.4, 145.0, 176.8.

(*S,R*)-5. colorless oil, $[\alpha]_D^{28}$ = −25.0 (c = 0.3, CH_2Cl_2). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (d, J = 7.2, 3H), 1.33 (d, J = 7.0, 3H), 1.97 (s, 1H), 3.34 (q, J = 7.0, 1H), 3.57 (q, J = 7.2, 1H), 7.20−7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 23.3, 51.7, 54.0, 55.9, 126.7, 127.1, 128.5, 145.0, 175.9.

(R)-Alanine, (R)-6

In a hydrogenation flask was placed 0.3 g (1.4 mmol) of (*S,R*)-**5** (more polar diastereomeric product in the previous reaction), 0.22 g (1.6 mmol) of $Pd(OH)_2$, and 5 mL of methanol. The reaction flask was pressurized with hydrogen to 4 atm and the reaction mixture was shaken until complete disappearance of the substrate (tlc analysis). The crude product was filtered and concentrated at reduced pressure to afford the desired amino acid as a white solid, mp = 288−291°C (decomposes) [lit.[23] mp = 291°C (decomposes)]. $[\alpha]_D^{28}$ = −13.5 (c = 1, 1 N HCl), lit.[23] $[\alpha]_D$ = −14.2 (c = 6, 1N HCl).

1-N-[(S)-α-Phenylethyl]-3-N′-phenyl-(4R)- and 1-N-[(S)-α-phenylethyl]-3-N′-phenyl-(4S)-(3,4-dimethoxy)benzyl-4-methyl-1,3-imidazolidin-2,4-dione, (S,R)- and (S,S)-7

In a 25-mL round-bottomed flask fitted with a magnetic stirrer was placed 13 mL of dry THF, 0.37 mL (2.70 mmol) of diisopropylamine, and 1.13 mL (2.70 mmol) of 2.4 M *n*-BuLi and the resulting solution was stirred under nitrogen for 1 h at 0°C. The temperature was then lowered to −78°C (dry ice/acetone bath) before the addition of methylated hydantoin (*S*,*S*)-**4** (0.80 g, 2.70 mmol) in 2 mL of THF. The resulting mixture was stirred at −78°C for 1 h and then 0.50 g (2.68 mmol) of (3,4-dimethoxy)benzyl chloride in 2 mL of THF was added. Stirring was continued at −78°C until the complete disappearance of the substrate (tlc analysis). The reaction was quenched with 0.8 mL of ammonium chloride, the crude product was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine solution. Concentration at reduced pressure afforded 1.14 g (95% yield) of the dialkylated product, shown by ^{1}H NMR spectroscopy to consist of a 51:49 mixture of diastereoisomers. Separation of these diastereoisomers was achieved by flash chromatography (hexane:EtOAc, 95:5 → 92:8).

(*S*,*S*)-7. 0.58 g (48% yield) of white solid, mp = 137−138.5°C. $[\alpha]_D^{28}$ = +76.0 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.90 (d, J = 7.2, 3H), 2.99 (d, J = 14.1, 1H), 3.04 (d, J = 14.1, 1H), 3.30 (s, 3H), 3.75 (s, 3H), 4.57 (q, J = 7.2, 1H), 6.14 (dd, J^1 = 8.2, J^2 = 2.0, 1H), 6.24 (d, J = 2.0, 1H), 6.49 (d, J = 8.2, 1H), 6.86 (d, J = 6.7, 1H), 7.21−7.49 (m, 8H). 7.71 (d, J = 6.4, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 22.2, 41.9, 54.2, 55.6, 55.9, 67.8, 110.8, 112.6, 122.7, 126.4, 126.6, 128.0, 128.2, 128.7, 128.9, 129.0, 131.4, 141.6, 148.2, 148.5, 154.4, 174.0.

Anal. calcd for $C_{27}H_{28}N_2O_4$: C, 72.97; H, 6.31. Found: C, 72.67; H, 6.41.

(*S*,*R*)-7. 0.49 g (41% yield) of colorless oil. $[\alpha]_D^{28}$ = +20.0 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.93 (d, J = 7.2, 3H), 3.08 (d, J = 14.4, 1H), 3.26 (d, J = 14.1, 1H), 3.72 (s, 3H), 3.90 (s, 3H), 4.53 (q, J = 7.2, 1H), 6.74 (s, 1H), 6.82−7.52 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.9, 42.1, 54.9, 56.2, 56.3, 68.3, 111.4, 112.9, 122.7, 126.8, 127.1, 127.3, 128.0, 128.5, 129.2, 129.3, 131.9, 144.4, 148.9, 149.2, 155.0, 174.8.

General Procedure for the Hydrolysis of Dialkylated Hydantoins 7

A suspension of 1.0 mmol of **7** in 5 mL of 57% HI was heated to 110−120°C in a sealed ampule for 48 h. The reaction mixture was allowed to cool to ambient temperature and it was then extracted with four portions of ethyl acetate. The aqueous phase was concentrated at reduced pressure to give the amino acid hydroiodide, which was dissolved in 2 mL of water and adsorbed to acidic ion exchange resin Dowex 50W × 4. The resin was washed with distilled water until the washings came out neutral, then the free amino acid was recovered with 1 N NH_3. Evaporation then afforded the free amino acid.

(S)-α-Methyldopa, (S)-2

Dialkylated hydantoin (*S*,*S*)-**7** (0.50 g, 1.13 mmol) was hydrolyzed according to the general procedure to afford 0.21 g (89% yield) of pure, free amino acid (*S*)-**2**, $[\alpha]_D^{28}$ = −3.3 (c = 1, 6N HCl), lit.[24] $[\alpha]_D^{23}$ = −4.0 ± 0.5 (c = 1, 0.1 N HCl). ^{1}H NMR (270 MHz, D_2O) δ 1.55 (s, 3H), 2.91 (AB, J = 13.5, 2H), 6.60 (d, J = 8.8, 1H), 6.62 (s, 1H), 6.78 (d, J = 8.8, 1H). ^{13}C NMR (67.5 MHz, D_2O) δ 21.7, 41.7, 60.9, 116.7, 117.8, 122.7, 125.6, 144.0, 144.3, 173.7.

(R)-α-Methyldopa, (R)-2

Dialkylated hydantoin (*S*,*R*)-**7** (0.40 g, 0.90 mmol) was hydrolyzed according to the general procedure to afford 0.17 g (91% yield) of pure, free amino acid (*R*)-**2**, $[\alpha]_D^{28}$ = +3.2 (c = 1, 6N HCl), lit[24] $[\alpha]_D^{23}$ = −4.0 ± 0.5 (c = 1, 0.1 N HCl) for the (*S*) enantiomer. ^{1}H and ^{13}C NMR spectra are similar to those described for (*S*)-**2**.

RESULTS AND DISCUSSION

Preparation of the Chiral Hydantoin (S)-1

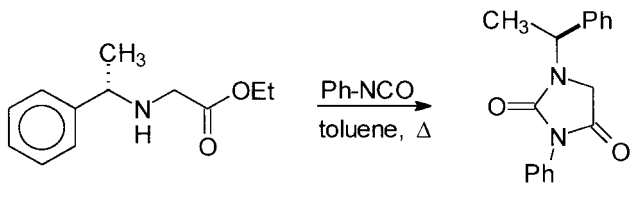
The desired hydantoin (*S*)-**1** was prepared in good yield from the reaction of phenyl isocyanate with known[22] chiral amino ester (*S*)-**3** (Scheme 1). (*Racemic* **1** was recently prepared by Lee et al.[25] from resin-bound ketimines.)

Conformational Analysis of (S)-1

With the aim of predicting the stereodirecting effect of the α-phenylethyl chiral auxiliary in hydantoin (*S*)-**1**, a series of theoretical modeling studies were carried out.

Initial geometry for (*S*)-**1** was calculated by means of the semiempirical PM3 method, accessible in the *Gaussian 94* package of programs.[26] The structure of lowest energy selected from the semiempirical calculations was then optimized at ab initio HF/3-21 G level,[27] as available in *Gaussian 94*.[26]

Figure 2 presents the geometry of the lowest energy conformer obtained at the ab initio level. The most interesting observation is that this calculated structure is consistent with expectation based on the concept of allylic 1,3-strain ($A^{1,3}$ strain),[28] that is, the C−H bond at the α-phenylethyl moiety eclipses the vicinal carbonyl double bond. (By comparison, the conformation with C−H antiperiplanar to the carbonyl group is estimated to be nearly 3.0 kcal/mol higher in energy; Fig. 2.)



(*S*)-**3** (*S*)-**1**, 82% yield

Scheme 1. Preparation of chiral hydantoin (*S*)-**1**.

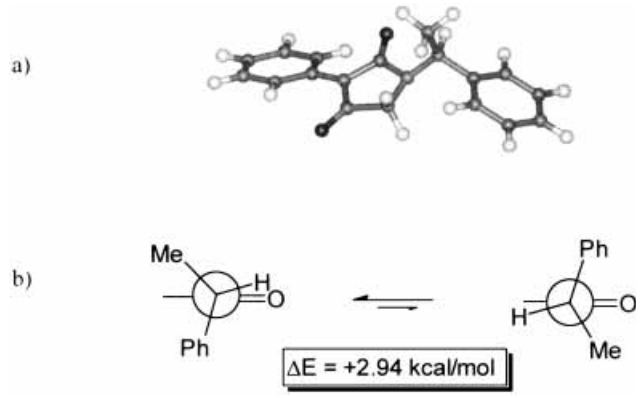
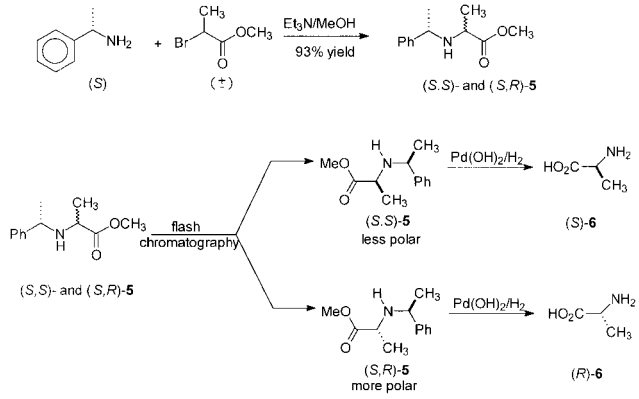


Fig. 2. Strucutre and conformation of hydantoin (*S*)-**1**, calculated at the ab initio HF/3-21G level.[26]

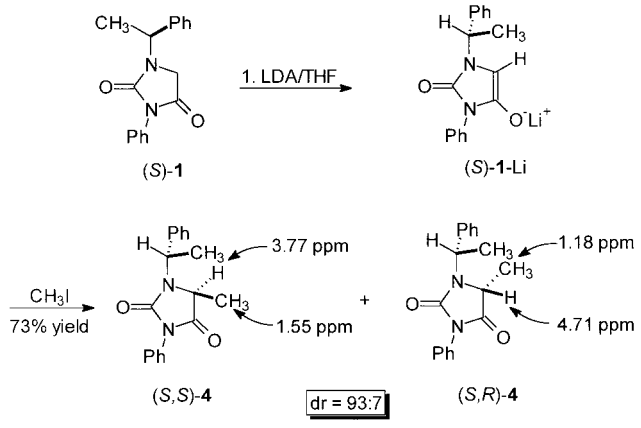


Scheme 3. Chemical correlation of diastereomeric amino esters **5** with (*R*)- and (*S*)-alanine.

Analysis of the calculated conformation of (*S*)-**1** (Fig. 2) leads to the conclusion that the methyl and phenyl groups must differentiate the diastereotopic faces of the C=C bond in the transition state for reaction of derived enolate (*S*)-**1**-Li, since factors that influence reactant conformational energies will also influence transition state conformational energies.[29]

Diastereoselectivity of Methylation of Enolate (S)-1-Li

As anticipated from the molecular modeling studies discussed in the previous section, reaction of enolate (*S*)-**1**-Li with methyl iodide proceeded with good prochiral face stereodifferentiation; the diastereomeric ratio of products (dr) being 93:7. The configuration of the newly created stereogenic center in the major product was assigned by observation of a shielding effect on H(5) in the ^{1}H NMR spectrum. Similarly, the chemical shift for the C(5)-CH_3 methyl group in the major product appears at lower field, relative to the corresponding signal in the minor product, which actually reflects a shielding of the methyl group by the phenyl in the vicinal *N*-α-phenylethyl group. These observations allow assignment of the configuration of the major product as (*S,S*) – H(5) being shielded by the *syn* phenyl ring[30] (Scheme 2).

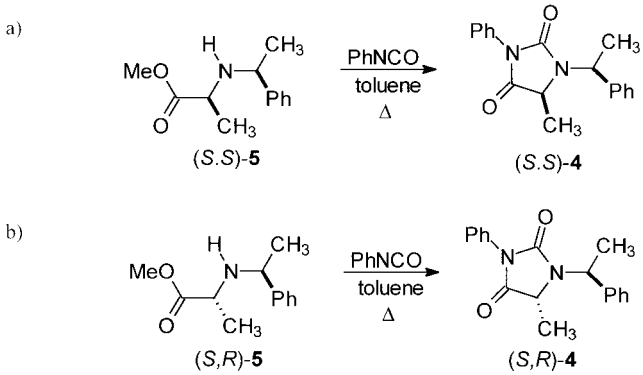


Scheme 2. Diastereoselectivity of methylation of enolate (*S*)-**1**-Li. The Chemical shifts for H(5) and C(5)-CH_3 allow the determination of configuration at C(5).

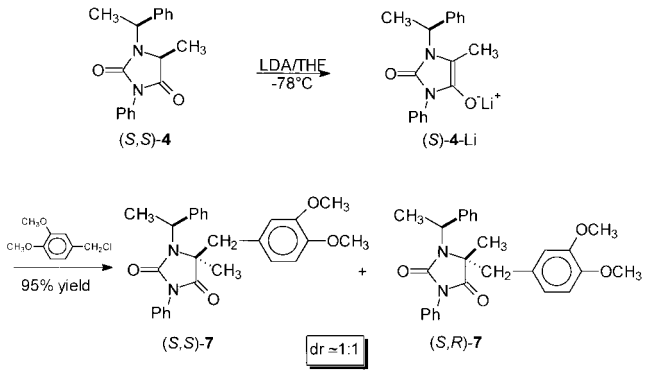
Assignment of Configuration in (S,S)-4 and (S,R)-4 by Chemical Correlation

The tentative assignment of configuration of methylated products **4**, based on analysis of ^{1}H NMR chemical shifts (above paragraph), could be confirmed by chemical correlation. First, (*S*)-phenylethylamine reacted with racemic methyl 2-bromopropionate to give a mixture of diastereomeric amino esters **5**, which were separated by flash chromatography. Hydrogenolysis [H_2/$Pd(OH)_2$] of the less polar isomer afforded (*S*)-alanine (Scheme 3), allowing assignment of the (*S*)-configuration at C(2). Similarly, hydrogenolysis of the more polar isomer gave (*R*)-alanine; thus, the starting amino ester was identified as (*S,R*)-**5**. (Scheme 3).

Once the configuration of (*S,S*)-**5** and (*S,R*)-**5** was securely determined, each of these diastereomeric amino esters was separately treated with phenylisocyanate to produce the enantiomerically pure methylated hydantoins (*S,S*)- and (*S,R*)-**4** (Scheme 4). Comparison with the samples obtained by methylation of (*S*)-**1** confirmed the



Scheme 4. Preparation of enantiopure samples of methylated hydantoins (*S,S*)-**4** and (*S,R*)-**4**.



Scheme 5. Lack of diasteroselectivity in the second alkylation of (*S,S*)-**4** via the corresponding lithium enolate.

configurational assignments that had been based on ^{1}H NMR chemical shifts.

Diastereoselectivity of Alkylation of Methylated Hydantoin (S,S)-4

In contrast with the high diastereoselectivity observed in the methylation of starting hydantoin (*S*)-**1** (see above), the reaction of methylated (*S,S*)-**4** with (3,4-dimethoxy)benzyl chloride proceeded with essentially zero diastereoselectivity (Scheme 5).

Separation of the diastereomeric, dialkylated products (*S,S*)- and (*S,R*)-**7** was accomplished by flash chromatography. One of these two diastereomers turned out to be a viscous oil, but the other could be crystallized into suitable material for X-ray crystallographic analysis (Fig. 3). Salient features of this crystallographic structure are 1) the *like*[31,32] relative configuration of the stereogenic centers [therefore, the absolute configuration at the newly created stereogenic center is (*S*)]; and 2) the antiperiplanar arrangement between the C–H bond at the α-phenylethyl substituent and the vicinal C=O carbonyl bond. This orientation of the α-phenylethyl group is not the one usually expected from A^{1,3} strain considerations,[28] but can be readily rationalized when considering the overriding steric hindrance between alkyl substituents in a conformation presenting a coplanar arrangement between C–H (α-phenylethyl group) and the vicinal C=O function.

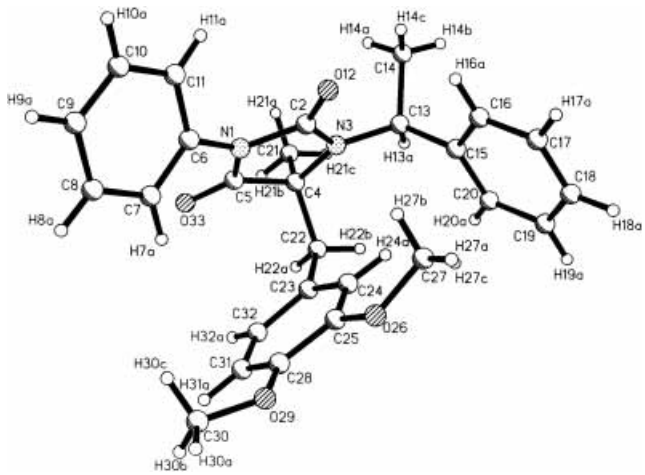


Fig. 3. Struture and solid-state conformation of dialkylated hydantoin (*S,S*)-**7**.

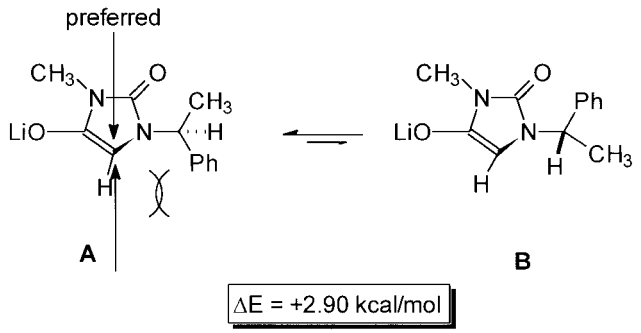
Indeed, semiempirical PM3 calculations do reproduce the solid-state conformation of dialkylated hydantoin (*S,S*)-**7**, whereas the conformer with coplanar C–H/C=O segments is estimated to be 2.25 kcal/mol higher in energy.

Molecular Modeling of Lithium Enolates (S)-1-Li and (S)-4-Li

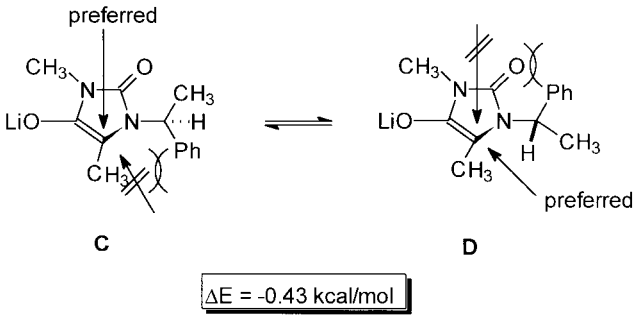
Why is the alkylation of the starting hydantoin, (*S*)-**1**, highly diastereoselective, whereas the alkylation of the enolate derived from methylated (*S,S*)-**4** non-diastereoselective? In order to respond to this question, we undertook a theoretical study of the lithium enolates involved in these alkylation reactions. The level of theory used for the molecular modeling was ab initio, within the framework of density functional theory, using the hybrid functional B3LYP with a 6-311G(d,p) basis set.[26] Nevertheless, this study does not take into account possible consequences of enolate aggregation effects[33] or solvation impact on reactivity.[34] Finally, in order to simplify the system to be studied at the high level of theory chosen, the *N*-phenyl substitutent at the remote ring nitrogen was replaced by a methyl group.

Two conformations of lowest energy were identified for the lithium enolate derived from starting hydantoin (S)-**1**-Li. As summarized in Scheme 6, conformer A, which fulfills the requirements dictated by the concept of A^{1,3} strain, is estimated to be 2.90 kcal/mol more stable than conformer B. According to this calculated ΔE value, conformer A must be highly predominant (≥99%), so that reaction taking place on the enolate face *syn* to the phenethyl's methyl group should be the preferred pathway for C–C bond formation, as experimentally observed.

In contrast, the conformational free energy difference for equilibrium C ⇌ 2; D in C(5)-methyl substituted enolate (*S*)-**4**-Li (Scheme 7) is rather small, ΔE = −0.43 kcal/

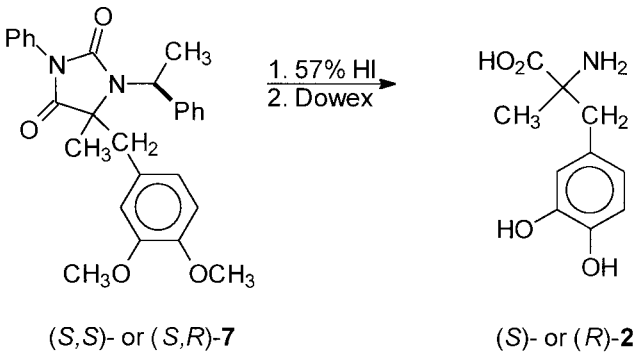


Scheme 6. Calculated (b31yp 6-311g(d,p)//3-21g*) energy difference between the conformers of lowest energy for enolate (*S*)-**1**-Li. Addition of the electrophile on the prochiral face *syn* to the phenethyl's methyl group should be preferred over addition on the opposite enolates's face.[17]



Scheme 7. Calculated (b31yp 6-31g(d,p)//3-21g*) energy difference between the conformers of lowest energy for enolate (*S*)-**1**-Li. The small energy between rotamers **C** and **D** implies that both enolates compete for electrophilic attack, and because each rotameric enolate directs addition on opposite diastereotopic faces, the reaction is non-stereoselective.

mol. This result suggests that both enolate rotamers have opportunity to effectively participate in the alkylation reaction. Because C and D favor electrophile addition on opposite faces, the experimentally found lack of diastereoselectivity (previous section) is not surprising.



Scheme 8. Hydrolysis of dialkylated hydantoins **7** to afford enantipure (*S*)- and (*R*)-α-methyldopa.

Hydrolysis of Dialkylated Hydantoins (S,S)-7 and (S,R)-7 to Afford (S)- and (R)-α-Methyldopa

Acid hydrolysis of dialkylated precursors **7** was best achieved with 57% HI.[6,10] Under these conditions, both "amide" groups were cleaved and the phenethyl group was removed to give the desired amino acids, (*S*)- and (*R*)-**2**, in good yields (89–91% yield) of the free amino acid after ion-exchange purification (Scheme 8).

CONCLUSION

Chiral hydantoin (*S*)-**1** was methylated with high diastereoselectivity to give derivative (*S*,*S*)-**4**, which was then alkylated in a non-diastereoselective reaction to give a 50:50 mixture of dialkylated hydantoins (*S*,*S*)- and (*S*,*R*)-**7**. These diastereomeric derivatives are readily separated and hydrolyzed to afford (*S*)- and (*R*)-α-methyldopa in good yield.

Molecular modeling (ab initio B3LYP 6-311(d,p)//3-2g*) offers a reasonable explanation of the experimental results, in terms of a highly predominant conformer of enolate (*S*)-**1**-Li where stereodifferentiation by the *N*-α-phenylethyl group is efficient, but a conformational equilibrium with little energetic difference between the reactive enolates in (*S*)-**4**-Li, so that competitive alkylation reaction pathways give rise to comparable diastereomeric ratios of dialkylated products, (*S*,*S*)-**7** and (*S*,*R*)-**7**.

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