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Activated sulfahydantoin as Boc-glycine enolate equivalent: highly diastereoselective α-hydroxyalkylation and application to the synthesis of aldopentonate analogues

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ABSTRACT

N-Boc-activated sulfahydantoin can be seen as glycine enolate equivalent. It appeared as a convenient starting material for the stereocontrolled preparation of threonine homologues through an alkaline *syn* aldolization involving a Boc migration. The methodology allowed the *one-pot* preparation of constrained analogues of polyoxamic acid.

Sulfahydantoins (3-oxo-1,2,5-thiadiazole-1,1-dioxides) **1** (Fig. 1) constitute as an emergent class of heterocycles, claimed as protease inhibitors (especially matrix proteinases) and ligand of MHC class II,[1–4] aglygones in pseudonucleoside analogues,[5] phosphate mimetic,[6] or substructure in the constrained peptides.[7]

The synthesis of sulfahydantoins (in racemic and optically active series) has been described starting from aldehydes, via a Bucherer–Berg reaction,[8] or by sulfamoylation and ring-closure of α-amino acid esters.[5,9] A huge diversity of sulfahydantoins was thus obtained in solution or on solid support.[10–12] We report, herein, a new and efficient method for the preparation of 2-N-substituted sulfahydantoins in three steps. The first step is a transsulfamoylation[13–15] ring-closure reaction, achieved in the presence of chlorosulfonyl isocyanate (CSI), an amino acid such as glycine methylester (H-Gly-OMe), and chloroethanol, to afford the corresponding oxazolidinone-sulfonyl-amino acid esters **2** (Scheme 1). In this particular system, the oxazolidinone moiety behaves as a good leaving group under the action of a nucleophile. In the presence of benzylamine or (*S*)-(−)-α-methylbenzylamine, the corresponding sulfahydantoin skeleton has been obtained, and the protection at the 5-N-position was easily carried out with Boc_2O in the presence of DMAP, to afford activated sulfahydantoins **3**[16] and the optically active (*S*)-**4**[17] in a satisfactory 50% overall yield starting from CSI (Scheme 1).

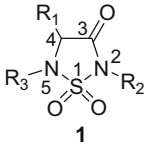

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Figure 1. General structure for sulfahydantoins.

Orthogonal groups such as benzyl or BOC can be selectively removed in appropriate conditions (hydrogenolysis and acidic treatment, respectively) to afford 2-N or 5-N-deprotected sulfahydantoins, for further derivatisation. Sulfahydantoins can be considered as glycine equivalents for stereocontrolled synthesis of modified α-aminoacids. In this respect, the Boc-glycine heterocyclic derivative **3**[16] was chosen as a convenient starting

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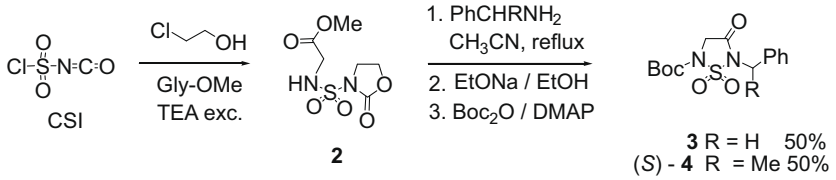


Scheme 1. Improved synthesis of Boc-activated sulfahydantoins.

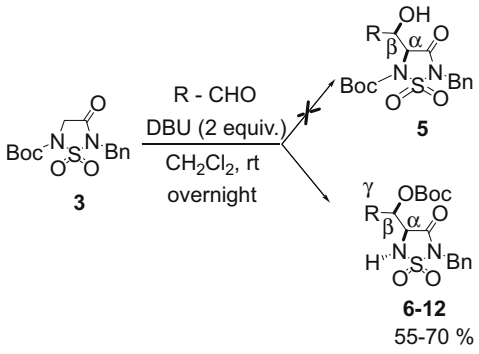
material to explore C–C condensation reactions. No examples are reported on the synthesis of *C*-4-substituted sulfahydantoins via an ionic condensation reaction involving the nucleophilic character of glycine enolate equivalent. Various reaction conditions were explored with the aim to achieve a C–C condensation reaction on the *C*-4 position of the sulfahydantoin ring (e.g., alkylation, α-and β-hydroxyalkylation, acylation, and Michael reaction). We also investigated the reaction by changing the nature of the group on the 5-N position of the heterocyclic system. When a silyl group such as TBDMS was introduced, the enolate formation in the same alkaline conditions was not allowed. The aldolization reaction was successful when the 5-N position was substituted with an activating electron-withdrawing group such as Boc, in the presence of DBU (2.0 equiv) as a base and in dichloromethane as solvent (from 0 °C to room temperature). The scope of the reaction was investigated using different achiral and chiral aldehydes with a stereocenter at the α-position, in order to explore their possible effect on the stereochemical course of the reaction, as reported in Scheme 2. In our hands, no alkylidenation-deacylation (Perkin–Sasaki-like reaction)[18–22] reaction was observed, in contrast with the previously described reactions having *N*-acyl or *N*-Boc diketopiperazines (DKPs) as substrates. Interestingly, the expected aldolization products **5** were not detected in the crude, but recovered in the form of stable products **6**–**12** (Scheme 2).

The presence of compounds of type **5** was excluded because the H_α-proton appeared as a doublet of doublets (in the range of 4.14–5.95 ppm for all the compounds in the series), characterized by two coupling constants, suggesting that a supplementary adjacent nucleus should be present. The possibility of a coupling through four bonds with the OH-proton was not probable, and a vicinal coupling would have been possible only if the adjacent nitrogen atom would be deprotected. Therefore, we speculated on the *N*–*O* acyl migration of the protecting group from the 5-N-position to the OH-function, as already described.[23,24]

This hypothesis may account the fact that the β-elimination reaction leading to crotonization products (Perkin–Sasaki-like reaction)[19–22] is defavored, since the heterocycle is deactivated. After Boc migration, the most acidic proton is the 5-N-hydrogen and not more than one at the α-position, which would have been pulled out by the base only if the Boc group was still present on the 5-N-position. The reaction is irreversible by virtue of the different roles played by the Boc residue: it behaves as an activating system at the beginning of the reaction (*N*-Boc), and as a protecting group (*O*-carbonate) after its migration. The mechanism is tentatively presented below (Scheme 3). The process might be initiated from intermediate **A** by the concerted aldolization/intramolecular attack of the formed alkoxide onto the *N*-Boc-carbonyl moiety. The unstable cyclic entity **B** might then rapidly evolve through cleavage of the C–N and formation of C–O bond to form a stable carbonate **C.**

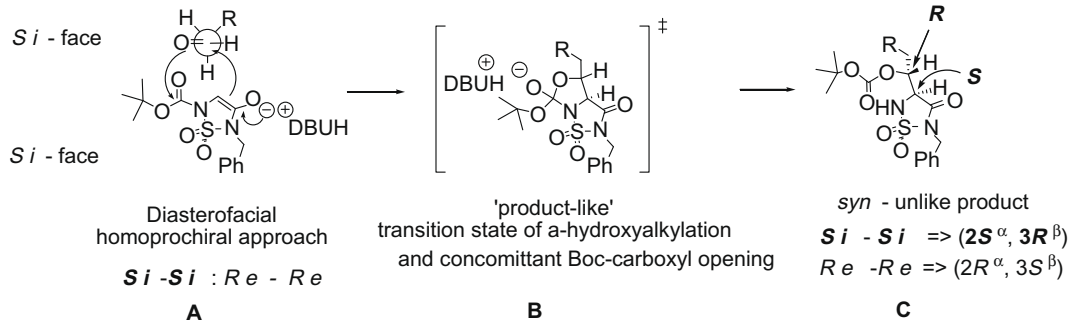
It is noteworthy that the rearrangement involved the transition from N-sp^2 to a N-sp^3 hybridization state, with a *cis* H^α–C^α–N–H configuration, as shown by NMR data. In all cases and relatively to CH_α–CH_β mutual relationship, the major (or exclusive) diastereoisomer was the *syn* aldol,[25] established on the basis of ^3J CH_α–CH_β values (1.46–2.90 Hz) and consistent with the small values already reported in the literature for similar systems[26–29] (Fig. 2).

In the aldol reaction, it is usually assumed that the transition states are rather '*reactant-like*', however in our case the reaction went through a '*product-like*' non-chelated transition state. Three contiguous chiral centers were formed starting from a prochiral *E*-enolate to afford the *syn*-unlike products **6**–**12**, conformationally similar to the transition state, according to a diastereofacial homoprochiral approach (*Si*–*Si*/*Re*–*Re*) conditioned by steric factors. In the case of propanal (compound **6**, *syn*/*anti* 9:1, referred to CH_α–CH_β relationship), variation of the reaction temperature, reaction time or by introducing an asymmetric element on the 2-N position of sulfahydantoin nucleus as in **4** did not provide



6 R = Et
7 R = *i* - P r
8 R = Cyclohexyl
9 R = Ph
10 R = 2 - Thiophenyl
11 R = (*R*) - (+) - 2,2-dimethyl - 1,3 - dioxolane - 4 - yl
12 R = (*R*) - (+) - 3 - Boc - 2,2 - dimethyloxazolidine - 4 - yl

Scheme 2. Synthesis of selected threonine-like sulfahydantoin derivatives.



Scheme 3. Mechanism for α-hydroxyalkylation/Boc-migration reaction.

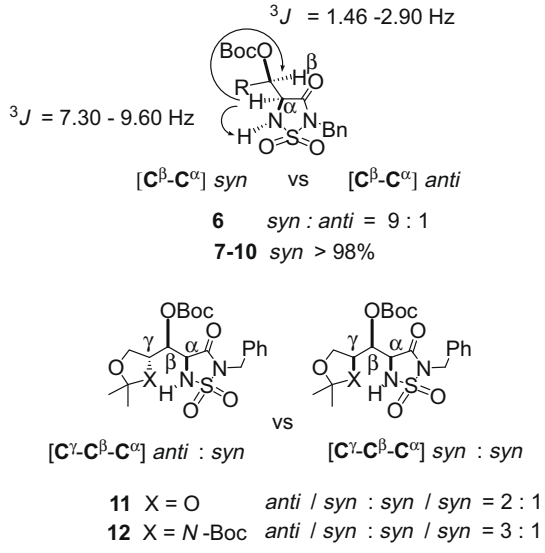


Figure 2. Stereostructures for aldol products **6**–**12**.

any improvement of the *syn*/*anti* diastereoselectivity observed in the subsequent aldolization,[30] which maybe due to the far distance of the chiral center and no asymmetric induction was observed, since a mixture of two epimers (with a ratio 55/45) was recovered. On the other hand, in the same reaction conditions as for the synthesis of product **6**, but by only changing the nature of aldehyde, an excellent preference for the *syn* adduct was always observed (compounds **7**–**10**, *syn*/*anti* 98:2). In the presence of a chiral aldehyde, three chiral centers were created after the aldolization reaction. Products **11** and **12** were recovered as a mixture of epimers at C^{γ}-position in a [C^{γ}–C^{β}–C^{α}] *anti*/*syn* versus [C^{γ}–C^{β}–C^{α}] *syn*/*syn*, respectively, of 2:1 (for compound **11**) and 3:1 (for compound **12**), showing a preference for the *anti* adduct in the [C^{γ}–C^{β}] mutual relationship. The validation of the sequential deprotection approach was then given from the successive acidic treatment (20% TFA in dichloromethane) followed by hydrogenolysis (H_2, Pd–C 5% in ethanol), providing **13**[31] and **14**,[32] respectively, starting from **7** (only this example is reported here, Scheme 4).

The isosteric similarity between the free sulfahydantoin moiety and the carboxylate group is noteworthy in such last compound.

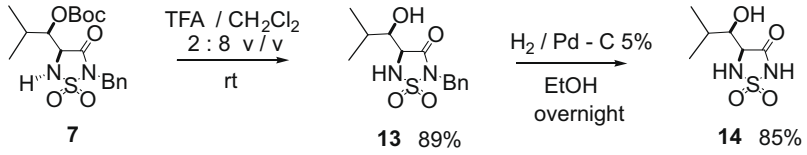
The putative mechanism of the stereocontrolled non-chelated α-hydroxyalkylation, involving an opposite position of R group of aldehyde and the bulky 5-*N*-Boc group leading to a *syn* diastereofacial preference observed under thermodynamic control conditions, can be exemplified on compound **12** obtained from Garner's (*R*)-(+)-3-Boc-2,2-dimethyloxazolidine-4-carboxyaldehyde, and justified to the Felkin–Ahn type model **I** and **II** (Fig. 3).

It would appear that the combination of a prochiral enolate and a chiral aldehyde leads to a facial discrimination for the aldolization reaction, in favor of a *Si*–*Si* or *Re*–*Re* approach for the two reaction partners, to afford only a single product (1*R*,2*S*,3*R*,4*R*)-**12** and (1*S*,2*R*,3*S*,4*S*)-**12** as a racemic mixture, instead of the predicted eight compounds. The racemization reaction involving the Garner's (*R*)-(+)-3-Boc-2,2-dimethyloxazolidine-4-carboxyaldehyde was due to the presence of 2 equiv of base, and it took place just before the attack of the prochiral enolate. The preferred diastereoisomer derived from a *matched*-pair; the totally *mismatched*-pair is energetically not favored, being the bulky Boc groups in a sterically demanding environment, for the *exo*-approach of aldehyde.

In order to confirm our hypothesis and to definitely assign the configuration of the stereocenters, compound **12** was crystallized at room temperature in a mixture *i*-PrOH/$(i\text{-Pr})_2$O and investigated by X-ray structural analysis. X-ray structure of (1*S*,2*R*,3*S*,4*S*)-**12** proved the favourite transition state model for a *syn*-unlike product *O*-Boc-protected (Fig. 4).

Measured vicinal coupling constants are compatible with dihedral angles in the X-ray structure: according to Karplus' equation, an angle ϕ[H^2–N^2–C^{α}–H^{α}] of 3.3° is consistent with a coupling constant of 9.6 Hz.

In conclusion, we have developed a rapid, highly diastereocontrolled matched synthesis of a series of *syn*-unlike products **6**–**12** in only one step, starting from sulfahydantoin **3** and via a concerted α-hydroxyalkylation/Boc-migration reaction. Compounds **6**–**12** can be considered as protected precursors of constrained analogues of polyoxamic acid derivatives, that for their intrinsic structure, result stable and not subjected to any lactonization reaction. Molecules **6**–**12** contain two or three chiral centers (depending on



Scheme 4. Sequential deprotection of Boc and Benzyl protecting groups on **7**.

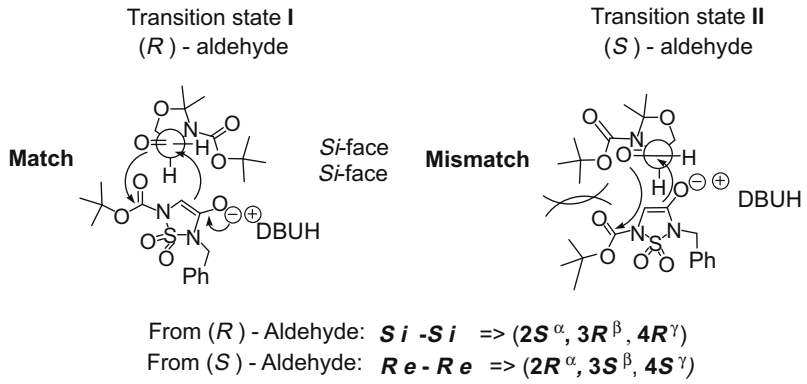


Figure 3. Comparison of transition states **I** and **II**: formation of the preferential diastereomeric adduct.

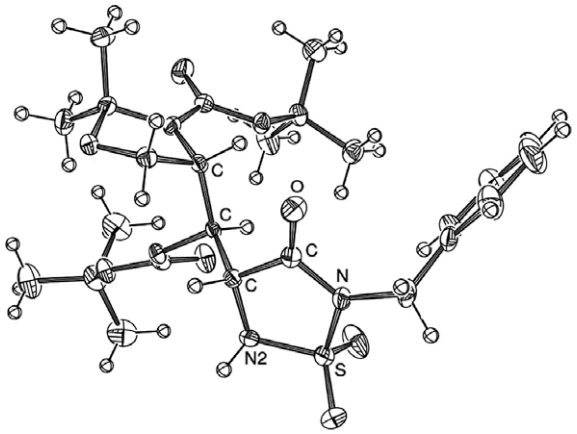


Figure 4. X-ray structure of (C^{α}-*R*, C^{β}-*S*, C^{γ}-*S*)-**12**.

the nature of starting aldehyde), available only in one step. More particularly, they can also be considered as useful chiral synthons for the synthesis of optically active constrained analogues of β-hydroxy α-aminoacids that are potentially endowed with antibacterial activity[18] or as functionalized 1,2 or 1,2,3 polyhydroxylated analogues of arabinonate, known to be potent phosphoglucoisomerase inhibitors.[33,34]

We are currently investigating the scope of this process and applying it to the synthesis of other analogues of (+)-polyhydroxyamino acids, constituting the side chain moiety of antifungal polyoxin antibiotics, endowed with biological activity.[35] Relating results will be reported in a next communication.

Acknowledgment

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16. *Compound* **3**: Yield (N-carboxylation) 96%; Mp 85–87 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.32 (m, 5H, Ar-H); 4.83 (s, 2H, CH_2–CO); 4.41 (s, 2H, CH_2-Ar); 1.50 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 159.95, 147.45, 133.32, 129.08, 128.80, 128.73, 86.64, 49.65, 44.33, 27.92. HRMS ESI(+): 326.0926 (calcd), 326.0961 (found).
17. *Compound 4*: Mp 53 °C. $[\alpha]_D^{20}$ −27 (*c* = 1, dichloromethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.60–7.30 (m, 5H, Ar-H), 5.42 (q, 1H, CH-Ar), 4.31 (dd, 2H, AB System, CH_2–CO), 1.94 (d, 3H, CH_3), 1.52 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 159.66, 147.46, 137.0, 128.62, 128.59, 127.81, 86.66, 54.55, 49.11, 27.93, 17.12.
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25. Selected data: *Compound* **6**: HPLC and NMR data on the crude showed two diastereoisomers, in a 9/1 ratio; overall yield 58% (not separated). Data for major product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30 (m, 5H, Ar-H), 5.15 (m, 1H, CH_β), 5.00 (d, 1H, NH, $^3J_{(H\alpha\text{-}NH)}$ = 8.0 Hz), 4.15 (dd, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 8.0 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 2.9 Hz, CH_α), 4.70 (d, 2H, ^2J = 15.2 Hz, CH_2-Ar), 1.70 (m, 2H, CH_2–CH_3), 1.40 (s, 9H, Boc), 0.90 (t, 3H, CH_2–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 166.36, 152.04, 133.88, 128.60, 128.38, 83.51, 73.83, 62.24, 44.87, 27.56, 24.90, 19.47. *Compound* **7**: Yield 65%; Mp 125–126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30 (m, 5H, ArH), 5.08 (m, 1H, CH_β), 4.94 (d, 1H, NH, $^3J_{(H\alpha\text{-}NH)}$ = 8.1 Hz), 4.65 (dd, 2H, ^2J = 15.4 Hz, CH_2-Ar), 4.25 (dd, $^3J_{(H\alpha\text{-}NH)}$ = 8.1 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 2.3 Hz, CH_α), 1.40 (s, 9H, Boc), 0.95 (dd, 6H, ^3J = 6.7 Hz, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 166.95, 152.10, 133.97, 128.69, 128.38, 122.67, 83.46, 66.20, 53.43, 44.87, 30.55, 27.51, 18.41, 18,11. *Compound* **8**: Yield 58%; Mp 140–142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.24 (m, 5H, Ar-H), 5.95 (d, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 8.2 Hz, NH), 5.13 (dd, 1H, $^3J_{(H\beta\text{-}H\gamma)}$ = 8.1 Hz, CH_β), 4.76 (dd, 2H, CH_2-Ar), 4.30 (dd, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 8.2 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 2.1 Hz, CH_α), 1.90–1.45 (m, 11H, *c*-Hex), 1.40 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 167.1, 152.09, 134.0, 128.70, 128.33, 126.47, 83.40, 61.02, 44.85, 39.61, 28.57, 28.40, 27.53, 25.80, 25.61, 25.50. *Compound* **9**: Yield 70%; Mp 144–146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.4–7.2 (m, 10H, 2 Ar-H), 6.15 (d, 1H, $^3J_{(H\alpha\text{-}H\beta)}$ = 2.4 Hz, CH_β), 4.95 (d, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 7.3 Hz, NH), 4.60 (dd, 2H, CH_2-Ar), 4.41 (dd, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 7.3 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 2.4 Hz, CH_α), 1.40 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 165.20, 159.94, 135.38, 133.74, 129.22, 128.73, 128.54, 125.81, 83.84, 73.79, 64.64, 44.85, 29.71, 27.93, 27.58. *Compound* **10**: Yield 54%; Mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.50–7.30 (m, 6H, Ar-H, and 1H, C_4H-Het), 7.25 (d, 2H, C_2H-Het), 7.05 (d, 1H,

C_3H-Het), 6.51 (m, 1H, CH_β), 5.24 (d, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 7.7 Hz, NH), 4.80 (dd, 2H, ^2J = 15.5 Hz, CH_2-Ar), 4.75 (d, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 7.7 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 2.5 Hz, CH_α), 1.43 (s, 9H, Boc). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 164.95, 151.32, 137.22, 133.69, 128.44, 128.59, 128.75, 127.20, 127.07, 84.13, 70.09, 64.31, 44.93, 27.59. *Compound* **11**: HPLC and NMR data on the crude showed two diastereoisomers, in a 2/1 ratio; overall yield 47% (not separated). Data for major product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40 (m, 5H, Ar-H), 5.28 (d_{br}, 1H, $^3J_{(H\beta\text{-}NH)}$ = 7.20 Hz, NH), 5.13 (dd, 1H, $^3J_{(H\beta\text{-}H\gamma)}$ = 7.5 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 1.60 Hz, CH_β), 4.75 (d, 1H, ^2J = 15.5 Hz, CH_2-Ar), 4.58 (dd, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 7.2 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 1.6 Hz, CH_α), 4.25 (ddd, 1H, $^3J_{(H\gamma\text{-}H\beta)}$ = 7.5 Hz, CH_γ), 4.13 (dd, 1H, $^3J_{(H\delta\ H\gamma)}$ = 4.6 Hz, $^3J_{(H\delta'\text{-}H\delta'')}$ = 9.10 Hz, $CH_{\delta'}$), 3.93 (dd, 1H, $CH_{\delta''}$), 1.48 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.35 (s, 9H, Boc), 1.30 (s, 3H, Boc); *Compound* **12**: (equimolar mixture of two enantiomers) Yield 50%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.35 (m, 2H, Ar-H), 7.25 (m, 3H, Ar-H), 6.5 (s_{br}, 1H, NH), 5.07 (d_{br}, 1H, $^3J_{(H\beta\text{-}H\gamma)}$ = 9.6 Hz, CH_β), 4.68 (d, 1H, ^2J = 15.3 Hz, CH_2-Ar), 4.63 (d, 1H, ^2J = 15.3 Hz, CH_2-Ar), 4.28 (dd, 1H, $^3J_{(H\alpha\text{-}NH)}$ = 6.7 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 1.46 Hz, CH_α), 4.75 (dd, 1H, $^3J_{(H\gamma\text{-}H\beta)}$ = 9.71 Hz, $^3J_{(H\gamma\text{-}H\delta)}$ = 4.51 Hz, CH_γ), 3.86 (dd, 1H, $^3J_{(H\delta\text{-}H\gamma)}$ = 9.71 Hz, $^3J_{(H\delta'\text{-}H\delta'')}$ = 4.83 Hz, $CH_{\delta'}$), 3.83 (dd, 1H, $CH_{\delta''}$), 1.55 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.40 (s, 9H, Boc), 1.30 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm): 163.80, 153.2, 151.29, 132.89, 127.88, 127.66, 127.30, 93.82, 82.59, 81.39, 71.26, 64.83, 63.48, 60.05, 55.98, 43.48, 29.30, 28.68, 27.28, 26.75, 26.50, 23.01. $C_{25}H_{37}N_3O_9S$, M_r = 555.64, Monoclinic $P21/n$, a = 9.8020(10), b = 21.506(3), c = 13.863(2) Å, V = 2835.7(6) Å^3, Z = 4, Dx = 1.302 Mg m^{-3}, λ(Mo Kα) = 0.71069 Å, μ = 0.168 mm^{-1}, $F(000)$ = 1184.0, T = 120(2) K. Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC No. 705481. Copies of the data can be obtained free of charge, on application to the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223/336 033 or by e-mail: deposit@ccdc.cam.ac.uk.

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30. HPLC and NMR measurements showed a mixture of both *syn* diastereoisomers in equimolar quantities starting from this chiral sulfahydantoin **4** and propanal, isobutanal or benzaldehyde.
31. *Compound* **13**: Yield 89%; Mp 105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40–7.20 (m, 6H, Ar-H and OH), 5.12 (d, 1H, $^3J_{(NH\text{-}H\alpha)}$ = 8.2 Hz, NH), 4.61 (dd, 2H, ^2J = 15.4 Hz, CH_2-Ar), 4.15 (m, 1H, CH_β), 4.02 (d, 1H, $^3J_{(NH\text{-}H\alpha)}$ = 8.2 Hz, $^3J_{(H\alpha\text{-}H\beta)}$ = 1.6 Hz, CH_α), 1.73 (m, 1H, CH_γ), 0.85 (s, 6H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 168.63, 133.96, 128.76, 128.54, 128.40, 73.47, 62.57, 44.91, 31.66, 18.63, 17.57.
32. *Compound* **14**: Yield 85%; Mp 113 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.80 (s, 1H, N^2H), 4.31 (m, 1H, CH_β), 3.62 (s, 1H, OH), 3.53 (d, 1H, $^3J_{(H\alpha\text{-}N^2H)}$ = 8.8 Hz, CH_α), 1.70 (m, 1H, CH_γ), 0.85 (d, 3H, CH_3), 0.62 (d, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 170.94, 74.22, 64.25, 30.75, 19.14, 18.77.
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