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Synthesis and reactivity of 5-methylenehydantoins

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ABSTRACT

5-Methylenehydantoin, as well as the *N*-mono- and *N*,*N*-di-protected derivatives, can be obtained by different synthetic routes. These compounds can undergo a large variety of reactions, such as Diels–Alder, epoxidation, methanol addition and conjugate addition reactions of different types of nucleophiles, including carbon (cyanide), nitrogen (piperidine) and sulfur (thiols, thioacetate) nucleophiles. The reactivity with electrophilic reagents, such as *m*-CPBA or methanol in acidic medium, and the need for Lewis acids to promote the conjugate addition reactions indicate that hydantoin is a poor electron-withdrawing group.

1. Introduction

The hydantoin unit is highly important in pharmaceutical chemistry for several reasons. On the one hand hydantoins, and in particular 5-substituted hydantoins, are present in a large variety of pharmaceuticals, both from natural and synthetic origin. Different biological properties, such as anticonvulsive,[1] antidepressant,[2] antiviral,[3] or anticoagulant,[4] are associated to the presence of hydantoins. Spirohydantoins have been described for treatment of chronic diabetes problems.[5] Phenytoin (5,5-diphenylhydantoin) has been used in the treatment of epilepsy,[6] nilutamide (5,5-dimethylhydantoin) was approved for treatment of prostate cancer.[7] The structure of 5-alkylidenehydantoin is present in several natural products, such as aplysinopsines,[8] axinohydantoins,[9] and mukanadin B.[10]

On the other hand, 5-substituted hydantoins are important from a synthetic point of view, as they are intermediates in the industrial synthesis of aminoacids.[11] Among them 5-aryl-hydantoins play a crucial role in the synthesis of semisynthetic antibiotics.[12] As an example 5-(4-hydroxyphenyl)-hydantoin can be prepared by direct condensation of phenol, urea, and either glyoxylic acid[13] or methyl 2-hydroxy-2-methoxyacetate,[14,15] reaction of phenol with allantoin,[15,16] or reaction of *p*-hydroxymandelic acid and urea,[17] in all cases with homogeneous or heterogeneous acids. Heterogeneous Lewis acids can be used as catalysts to obtain 5-aryl-hydantoins from 5-bromohydantoin and aromatics.[18]

Therefore the development of new synthetic approaches for the preparation of new hydantoins is an area of practical interest. One synthetic alternative for preparation of structurally complex hydantoins would be the use of 5-ylidenehydantoins as synthetic intermediates. Thus a research program was started with the objective of generating a library, as large as possible, of hydantoin derivatives with potential pharmaceutical interest. In this paper we describe the synthesis of 5-ylidenehydantoins, with particular emphasis on 5-methylenehydantoins, with and without protection in the nitrogen atoms, and the evaluation of the latest as synthetic intermediates in different types of reactions, such as Diels–Alder, epoxidation and conjugate additions.

2. Results and discussion

2.1. Synthesis of 5-ylidenehydantoins

2.1.1. Synthesis from hydantoin. A first alternative is the functionalization of position 5 of the hydantoin ring. One option is the condensation of formaldehyde with a phosphorous derivative of hydantoin (Scheme 1). In the Wittig variation it is necessary to prepare a phosphonium salt (**2**). This was possible by bromination of hydantoin[18] in dioxane under reflux and in situ reaction with triphenylphosphine at 55 °C.[19] The Wittig reaction was first tested with benzaldehyde, using different organic bases (triethylamine, aminoethanol, *N*,*N*-dimethylaminoethanol) with no success. The

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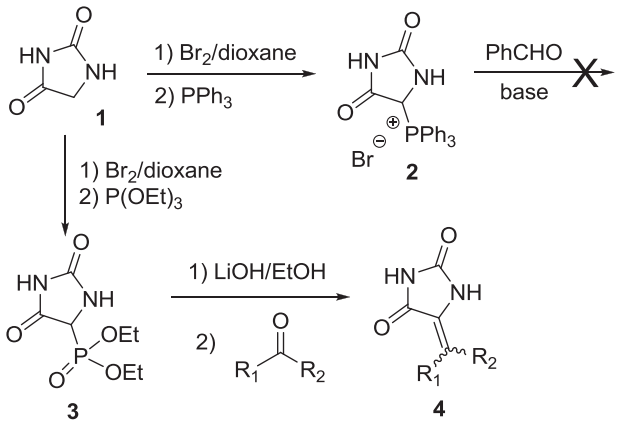
insolubility of the phosphonium salt (**2**) in any organic solvents may be the origin for this lack of reactivity.



Scheme 1.

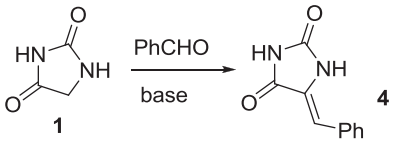
The Horner–Wadsworth–Emmons variation (Scheme 1) was more efficient, as the phosphonate[19] **3**, also in situ generated from hydantoin, was much more soluble in organic solvents. NaH and LiOH[19] were tested as bases for the reaction with benzaldehyde. The best yield was obtained with LiOH, that was used in the reaction with different aliphatic and aromatic aldehydes, as well as aliphatic ketones (Table 1), leading to several 5-alkylidene- and 5-arylidenehydantoins (**4**) as *Z*/*E* mixtures. However, the reaction failed with formaldehyde and aromatic ketones.

Table 1
Results of the reaction between phosphonate substituted hydantoin (**3**) and different aldehydes and ketones[a]

R_1	R_2	Yield (%)	*Z*/*E*
n-C_3H_7–	H–	32	63:37
i-C_3H_7–	H–	58	38:62
n-C_6H_{13}–	H–	98	50:50
Ph–	H–	72	67:33
p-MePh–	H–	74	67:33
2-Furyl–	H–	96	77:23
p-MeOPh–	H–	54	72:28
p-ClPh–	H–	51	54:46
p-NO_2Ph–	H–	28	75:25
p-CHOPh–	H–	42[b]	n.d.[c]
o-CHOPh–	H–	78[b]	n.d.[c]
H–	H–	0	—
Me–	Me–	28	—
–C_5H_{10}–		60	—
–C_4H_8–		25	—
Ph–	Me–	0	—
Ph–	Ph–	0	—

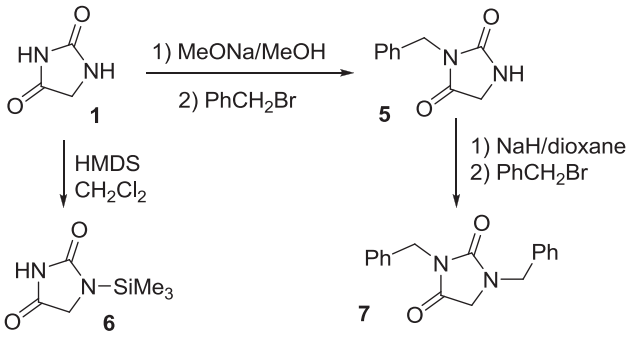
[a] Conditions: 2 mmol 16, 2 mmol LiOH, 2 mmol carbonyl compound, 20 ml ethanol, rt 24 h.
[b] Yield of condensation by both aldehydes.
[c] Mixture of *ZZ*, *ZE* and *EE* products. The ratio could not be determined.

The other possibility is the direct condensation of hydantoin with formaldehyde in basic medium. This method had been described for aromatic aldehydes,[20] and also for aliphatic aldehydes[21] including carbohydrates.[22] Reaction with benzaldehyde using aminoethanol as a base in water led to better results (94% yield of *Z* isomer **4**, Scheme 2) than the Horner–Wadsworth–Emmons reaction. Moreover the selectivity was much better, with only *Z* isomer being detectable by ^{1}H NMR. However only 16% yield was obtained with acetone, and the reaction with formaldehyde led to a complex mixture, which ^{1}H NMR spectrum showed the disappearance of NH groups and several signals at 3.8–4.2 ppm compatible with the presence of N–CH_2–O groups. Neither the change of solvent by other with different properties and hence different hydantoin solubility (1,4-dioxane, THF, dichloromethane, water) nor that of base (piperidine, triethylamine) allowed improving these results.



Scheme 2.

Hydantoin (**1**) is insoluble in most of organic solvents and NH groups may interfere in different reactions, as seen above. In order to solve both problems, it is possible to selectively protect one or both NH groups with benzyl or trimethylsilyl moieties (Scheme 3).



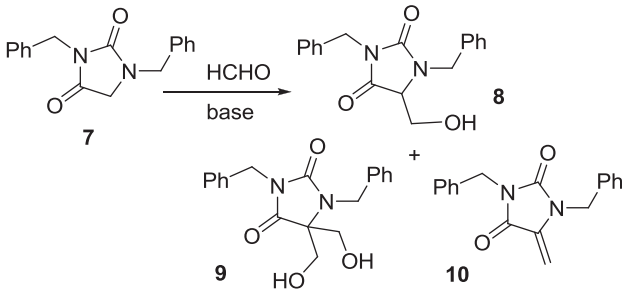
Scheme 3.

Treatment of hydantoin with sodium methoxide in methanol allows the selective protection of the most acidic NH in position 3. Reaction with benzyl bromide led to 3-benzylhydantoin (**5**) with 65% yield. The use of an excess of sodium methoxide and benzyl bromide did not produce the dibenzylation, showing that a stronger base was needed in order to abstract the NH in position 1. 1,3-Dibenzylhydantoin (**7**) can be prepared by two alternative methods. On the one hand, treatment of **5** with NaH in dioxane and benzyl bromide led to **7** with 90% yield. It is also possible the direct dibenzylation from hydantoin using LDA/THF or K_2CO_3/DMF as a base. In the first case by-products derived from diisopropylamine made difficult the purification of **7**. In the second one the final yield was only 20%. In view of these problems the synthesis of **7** was carried out in two steps.

The selective protection of NH in position 1 was achieved by silylation with hexamethyldisilazane (Me_3Si–NH–$SiMe_3$, HMDS) to obtain 1-trimethylsilylhydantoin (**6**, Scheme 3). Disilylation was not possible either by using harder conditions or by treatment with base. In this case the reactivity of position 1 seems to indicate that *N* is acting as a nucleophile, and *N* in position 3 is not nucleophilic enough to react with HMDS.

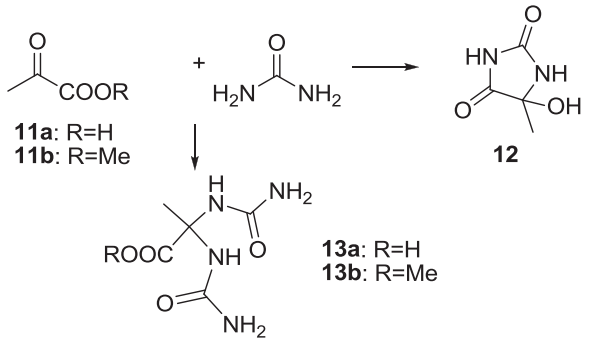
Thus the condensation reaction was carried out with 1,3-dibenzylhydantoin (**7**) using aminoethanol as a base in THF. A mixture of 1,3-dibenzyl-5-hydroxymethylhydantoin (**8**), 1,3-dibenzyl-5,5-bis(hydroxymethyl)hydantoin (**9**) and 1,3-dibenzyl-5-methylene-hydantoin (**10**) was obtained (Scheme 4). Attempts to minimize the formation of the dihydroxyalkylated product **9** by lowering reaction temperature and time, amount of formaldehyde led to very low conversion. On the contrary the substitution of THF by dioxane and the increase in reaction temperature even enhanced the formation of **9**. It seems that once the hydroxymethylhydantoin

8 is formed, it favourably and unavoidably competes with **7** for hydroxyalkylation. Conversion of **8** into **10**, was accomplished by heating the crude in the presence of $MgSO_4$, leading to 40% yield of the desired product.



Scheme 4.

2.1.2. Simultaneous synthesis of the hydantoin ring. The condensation of pyruvic acid with acetamide leads to *N*-acetamidoacrylic acid.[23] Analogously the condensation of pyruvic acid with urea should give the corresponding ureide, and then the hydantoin by cyclization (Scheme 5). In fact 5-bromomethylenehydantoins have been synthesized from 3-bromopyruvic acid and ureas, catalyzed by BF_3.[24]

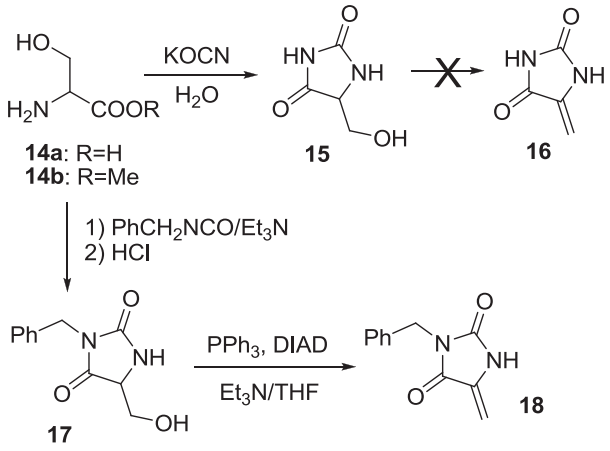


Scheme 5.

Starting from pyruvic acid or methyl pyruvate in excess with continuous water elimination using a Dean–Stark, the reaction led to 5-hydroxy-5-methylhydantoin (**12**), either in the absence or in the presence of an acid catalyst. The use of stoichiometric amounts of both reagents produced the double reaction of the carbonyl group of the pyruvic derivative to obtain the corresponding diureide **13**, showing that nucleophilic attack of urea on the carbonyl group is the first step whereas cyclization is the second one. The intermediate hydroxyureide easily reacts with a second molecule of urea, unless the concentration of pyruvic/pyruvate is much higher.

All the attempts to eliminate the hydroxyl group of **12** were unsuccessful. One possibility was the conversion into a good leaving group by sulfonation. However **12** was unable to react with *p*-toluenesulfonyl chloride/BuLi/DMF and methanesulfonyl chloride/Et_3N/THF, probably due to the steric hindrance around the tertiary alcohol together with the poor solubility of **12** in organic solvents and the acidity of the free NH groups. Treatment with acids (neat acetic, neat phosphoric, hydrochloric/benzene, neat formic/acetic anhydride) under heating led to complex mixtures of unidentified compounds, with only traces of 5-methylenehydantoin. The instability of the carbonium ion in position 5 of hydantoin, due to the electron-withdrawing character of the neighbour carbonyl and the presence of other basic centres in the molecule, may account for this behaviour.

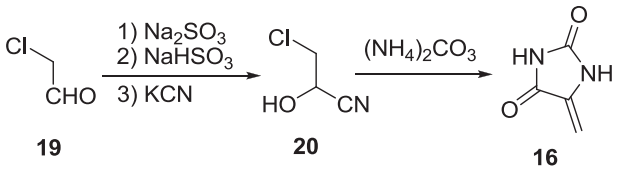
The elimination should be easier in the case of 5-hydroxymethylhydantoin (**15**). It can be prepared in quantitative yield from serine (**14a**) by reaction with KOCN (Scheme 6).[25] However, reactions with sulfonyl chlorides were again unsuccessful, probably due to the low solubility of **15** in most organic solvents. In the case of reaction with acids, conversion was observed at high temperature and long reaction time, but only unidentified products were obtained.



Scheme 6.

Protection of hydantoin should help to overcome the solubility problems. 3-Benzyl-5-hydroxymethylhydantoin (**17**) was prepared from serine methyl ester (**14b**) and benzyl isocyanate in two steps, first a condensation in basic medium to give the ureide, and then cyclization in acidic medium with 83% overall yield (Scheme 6). Elimination was possible with PPh_3/diethyl azadicarboxylate (DIAD)/Et_3N/THF[26] to produce 3-benzyl-5-methylenehydantoin (**18**). The lack of reactivity of **15** under the same conditions seems to confirm the solubility issue with this reagent.

Another option would be the preparation of 5-methylenehydantoin (**16**) by elimination of 5-chloromethylhydantoin. This route (Scheme 7) started with the preparation of 3-chloro-2-hydroxypropionitrile (**20**) from chloroacetaldehyde (**19**) and subsequent formation of hydantoin with simultaneous elimination. The need for purification of the intermediate cyanohydrin by extraction in ether, together with its quite high solubility in water and its high volatility, make yield remain very low (15%).



Scheme 7.

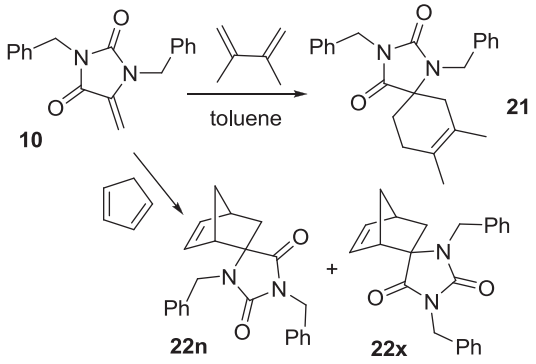
2.2. Reactivity

In this work the objective was to test the reactivity of methylenehydantoins as either electron-deficient alkenes, due to the presence of the carbonyl as electron-withdrawing group, and the limitations due to the slightly donor character of the nitrogen. As the idea was the preparation of a large number of molecules, the synthetic methods were not optimized. Most of methods were tested with the more soluble 1,3-dibenzyl-5-methylenehydantoin

(**10**) and only some of them were tried with the unprotected 5-methylenehydantoin (**16**).

2.2.1. Diels–Alder reactions. One example of Diels–Alder reaction with a chirally 1,3-disubstituted-5-methylenehydantoin had been described in the literature,[27] as well as some 1,3-dipolar cycloadditions,[28] and the use of 5-methylene-4-thiohydantoins as heterodienes.[29]

In a first reaction, 1,3-dibenzyl-5-methylenehydantoin (**10**) was made react with 2,3-dimethylbuta-1,3-diene (Scheme 8). Under thermal conditions (toluene under reflux) the reaction did not take place, but the corresponding spirohydantoin **21** was obtained using ZnI_2 (50% mol) at 80 °C.

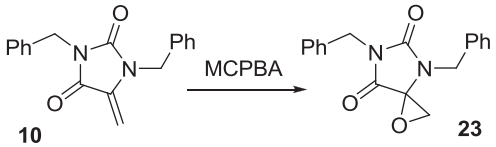


Scheme 8.

The reaction with cyclopentadiene (Scheme 8) was carried out at rt with Et_2AlCl (100% mol). Both possible spirohydantoin isomers, **22n** and **22x**, in 75:25 ratio were obtained, being major the one with the nitrogen in *endo* position (**22n**), in agreement with the result obtained with *N*-acetyl-dehydroalaninates.[30]

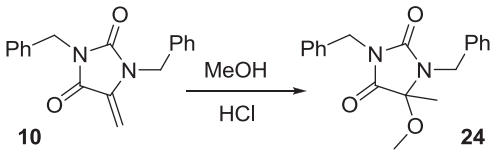
2.2.2. Epoxidation. The epoxidation of 5-methylenehydantoins would lead to oxiranic spirohydantoins, which may be interesting synthetic intermediates. All the attempts to epoxidize 1,3-dibenzyl-5-methylenehydantoin in basic medium, either with hydrogen peroxide, using K_2CO_3 or hydrotalcite[31] as a base, or *tert*-butyl hydroperoxide, using KF/alumina as a base,[32] were unsuccessful, probably due to the poor electron-withdrawing character of the hydantoin group.

Thus the epoxide **23** was obtained in quantitative yield by direct epoxidation with a typical electrophilic oxidant, such as *m*-chloroperbenzoic acid in CH_2Cl_2 at rt (Scheme 9). This result opens the way to the possible use of catalytic epoxidations with alkyl hydroperoxides.



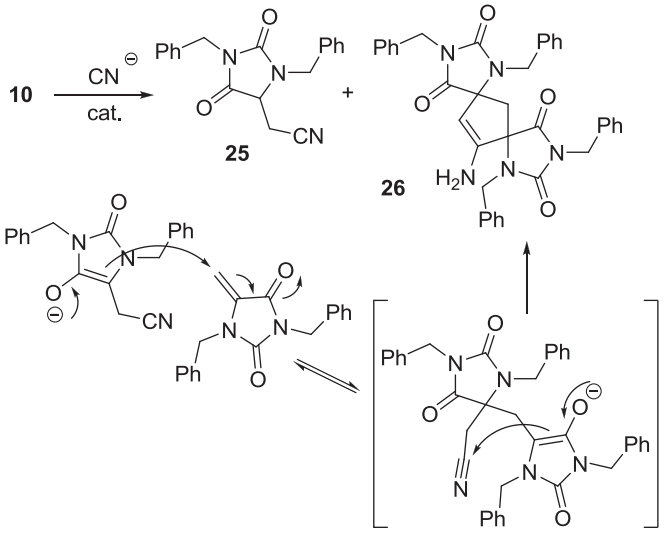
Scheme 9.

2.2.3. Reaction with methanol. The addition of oxygen nucleophiles would allow obtaining hydantoin precursors of serine analogues, and methanol was chosen as model compound. 1,3-Dibenzyl-5-methylenehydantoin (**10**) was shown to be inert against MeONa/MeOH/THF, NaOH/MeOH/THF, MeOH/CH_3CN/water/$Cu(OTf)_2$, or MeOH under reflux.[33] Only the reaction of methanol in acidic medium led to reaction, but in this case methoxide was added to carbon 5 of hydantoin ring, leading to 1,3-dibenzyl-5-methoxy-5-methylhydantoin **24** (Scheme 10). Again the poor withdrawing character of hydantoin seems to be the origin of this behaviour, allowing the formation of the tertiary carbonium cation in position 5 of the hydantoin ring.



Scheme 10.

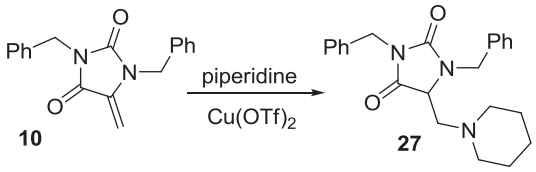
2.2.4. Conjugate addition of cyanide. The addition of a C1 synthon would open the way to hydantoin precursors of aspartic analogues. Cyanide was chosen as simple but versatile C1 nucleophile. A Lewis acid was necessary to promote the reaction, in this case $Cu(OTf)_2$ (15% mol),[34] confirming the poor electrophilic character of the alkene. Reaction of 1,3-dibenzyl-5-methylenehydantoin with NaCN in the presence of the Lewis acid in acetonitrile/water at 40 °C, led to quantitative conversion to the expected 5-cyanomethylhydantoin **25** and another product. Purification and analysis showed that this product was a spirobis(hydantoin) **26**, that should come from the addition of the enolate of **25** to a second molecule of methylenehydantoin and subsequent cyclization of the intermediate enolate (Scheme 11). The spirobis(hydantoin) **26** can be obtained as the only product when using only a slight excess of NaCN (NaCN/**10**=1.5) after 14 h, whereas total selectivity to the cyanomethylhydantoin **25** can be obtained at low conversion (50%) by using a larger excess of NaCN (NaCN/**10**=15) at rt. Longer reaction times and/or higher temperature (40 °C) always lead to a **25**/**26** selectivity of 77/23. An intramolecular attack of the intermediate enolate to a nitrile had been described in the conjugate addition of malononitrile enolate to 5-arylidene-2-thiohydantoins,[29] but to the best of our knowledge this is the first intermolecular addition described for this kind of systems.



Scheme 11.

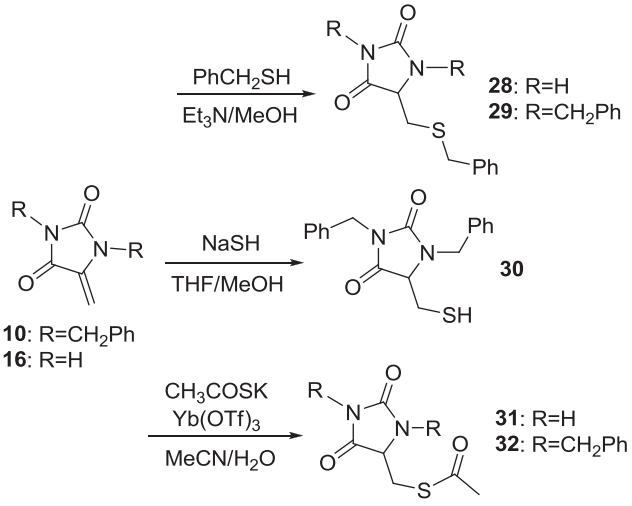
2.2.5. Conjugate addition of piperidine. Piperidine was chosen as an example of nitrogen nucleophile (Scheme 12). Quantitative yield of compound **27** was obtained by addition of piperidine to 1,3-dibenzyl-5-methylenehydantoin (**10**) at 40 °C using only 3 equiv of piperidine in the presence of $Cu(OTf)_2$ (15% mol).[34] The lack of

by-products of the same type as **26** may be due to the change from a charged nucleophiles (cyanide) to a neutral one (piperidine).



Scheme 12.

2.2.6. Conjugate addition of sulfur compounds. Due to the interest of hydantoin precursors of cysteine analogues, several types of sulfur compounds were tested as nucleophiles (Scheme 13).



Scheme 13.

Reaction with phenylmethanethiol was accomplished in methanol with triethylamine as a base, the same conditions used for dehydroalaninates.[35] Yields were quantitative with 5-methylenehydantoins, even with the poorly soluble unprotected **16**.

Reaction with sodium hydrosulfide was not possible with **16**, probably due to the acidic character of the NH groups. On the contrary, reaction with **10** in methanol/THF (1:1) took place with 100% conversion to produce **30** (Scheme 13).

Potassium thioacetate is less basic and nucleophilic than sodium hydrosulfide. Reaction did not take place (<5% yield) in water/acetonitrile in the absence of catalyst. However different Lewis acids ($CuCl_2$, $Cu(OTf)_2$, $YbCl_3$, $Yb(OTf)_3$) were able to promote the reaction. After an optimization process, including thioacetate/hydantoin ratio, type and amount of Lewis acid, and reaction temperature, 100% yield of either **31** or **32** was obtained with 10 equiv of thioacetate and 60% mol $Yb(OTf)_3$ at 90 °C.

In this case the lack of bis-hydantoin by-products cannot be ascribed to the use of neutral nucleophiles. A more likely reason would be the absence of an electrophilic centre (such as nitrile in the case of the bis-hydantoin enolate intermediate to **26**) able to shift the equilibrium towards a stable bis-hydantoin product.

3. Conclusions

5-Methylenehydantoins, including unprotected, 1- and 3-monoprotected and 1,3-diprotected ones, can be prepared by different methods, although in low yield. 1,3-Dibenzyl-5-methylenehydantoin and, in lower degree, 5-methylenehydantoin have shown to be valuable intermediates for a wide variety of reactions, including Diels–Alder cycloadditions, epoxidation and conjugate additions of thiols (phenylmethanethiol, sodium hydrosulfide, potassium thioacetate), amines (piperidine) and cyanide. Hydantoin precursors of cysteine or aspartic acid can be then prepared, as well as different types of spirohydantoins. In contrast with the expected behaviour, methylenehydantoins are poorly electrophilic, due to the low electron-withdrawing character of the hydantoin ring, and efficiently react as nucleophiles. Electrophilicity can be improved by the use of Lewis acids. These results open the way for future developments in the field.

4. Experimental section

4.1. General procedure for 5-alkylidenehydantoins (4)

To a solution of hydantoin (956 mg, 5 mmol) in anhydrous dioxane (2 ml) heated at 105 °C under inert atmosphere was slowly added bromine (800 mg, 5 mmol) and the resulting solution was stirred at the same temperature for 45 min. After cooling at rt, triethyl phosphite (830 mg, 5 mmol) was slowly added, always keeping reaction temperature below 45 °C. The mixture was stirred for 90 min and the solvent was removed under reduced pressure. The crude was washed with hexane, filtered and dried to obtain 5-diethylphosphonatehydantoin (**3**) (1.44 g, 92% yield). ^{1}H NMR (DMSO-d_6, δ ppm): 8.89 (s, 1H), 7.33–7.25 (m, 5H), 4.94 (d, 1H, J=14.8 Hz), 4.58 (dd, 1H, J=14.9 Hz), 4.52 (d, 1H, J=14.9 Hz), 4.07 (c, 4H, J=7.0 Hz), 1.21 (t, 6H, J=7.0 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 167.6, 136.2, 128.3, 127.5, 127.3, 127.1, 55.7, 54.2, 41.2, 16.1. ^{31}P NMR (DMSO-d_6, δ ppm): 12.8.

A solution of 5-diethylphosphonatehydantoin (**3**) (2 mmol), the carbonyl compound (2 mmol) and LiOH (48 mg, 2 mmol) in ethanol (20 ml) was stirred at rt for 24 h. The solid product was filtered, washed with ethanol and dried.

5-*Benzylidenehydantoin* (273 mg, 72% yield, *Z*/*E* ratio 67/33): Elemental analysis ($C_{10}H_8N_2O_2$): theoretical C 63.82, H 4.28, N 14.89; experimental: C 63.73, H 4.41, N 14.77. *Z* isomer: ^{1}H NMR (DMSO-d_6, δ ppm): 11.24 (s, 1H), 10.54 (s, 1H), 7.62–7.31 (m, 5H), 6.41 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 165.5, 156.7, 132.9, 129.3, 128.7, 128.3, 127.9, 108.3. *E* isomer: ^{1}H NMR (DMSO-d_6, δ ppm): 11.15 (s, 1H), 10.30 (s, 1H), 7.62–7.31 (m, 5H), 6.33 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 163.5, 153.8, 129.8, 128.7, 128.6, 128.2, 128.0, 115.5.

5-(2-*Methylpropylene*)*hydantoin* (179 mg, 58% yield, *Z*/*E* ratio 38/62): Elemental analysis ($C_7H_{10}N_2O_2$): theoretical C 54.54, H 6.49, N 18.18; experimental: C 54.47, H 6.61, N 18.27. *Z* isomer: ^{1}H NMR (DMSO-d_6, δ ppm): 10.93 (s, 1H), 10.14 (s, 1H), 5.35 (d, 1H, J=10.1 Hz), 2.63 (m, 1H), 0.99 (d, 3H, J=6.6 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 164.7, 154.8, 128.6, 118.2, 25.7, 22.1. *E* isomer: ^{1}H NMR (DMSO-d_6, δ ppm): 10.93 (s, 1H), 9.92 (s, 1H), 5.23 (d, 1H, J=10.1 Hz), 3.55 (m, 1H), 0.97 (d, 3H, J=6.6 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 164.5, 153.9, 127.8, 123.8, 24.4, 22.9.

5-*Isopropylidenehydantoin* (80 mg, 28% yield): Elemental analysis ($C_6H_8N_2O_2$): theoretical C 51.42, H 5.75, N 19.99; experimental: C 51.33, H 5.91, N 20.07. ^{1}H NMR (DMSO-d_6, δ ppm): 10.85 (s, 1H), 9.77 (s, 1H), 2.11 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (DMSO-d_6, δ ppm): 164.7, 153.9, 124.9, 123.9, 20.6, 17.9.

4.2. Synthesis of 3-benzylhydantoin (5)

A solution of hydantoin (6.00 g, 60 mmol) and sodium methoxide (3.66 g, 68 mmol) in anhydrous methanol (60 ml) was heated at 60 °C for 1 h under inert atmosphere. Benzyl bromide (12.24 g, 72 mmol) was then added and the mixture was stirred at the same temperature for 14 h. After cooling at rt, the solvent was eliminated

under reduced pressure, and the obtained solid was stirred with water (100 ml) for 12 h, filtered and dried under vacuum. 3-Benzylhydantoin (7.5 g, 65% yield) was obtained as a white solid. Elemental analysis ($C_{10}H_{10}N_2O_2$): theoretical C 63.15, H 5.30, N 14.73; experimental: C 63.26, H 5.24, N 14.59. ^{1}H NMR (DMSO-d_6, δ ppm): 8.12 (s, 1H), 7.32–7.26 (m, 5H), 4.53 (s, 2H), 3.98 (s, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 171.8, 157.3, 136.7, 128.3, 127.3, 127.2, 45.9, 40.9.

4.3. Synthesis of 1,3-dibenzylhydantoin (7)

A solution of 3-benzylhydantoin (**5**, 6.80 g, 35.8 mmol) and sodium hydride (0.974 g, 40 mmol) in anhydrous dioxane (50 ml) was heated at 90 °C for 90 min under inert atmosphere. Benzyl bromide (7.31 g, 43 mmol) was then added and the mixture was stirred at 110 °C for 14 h. After cooling at rt, the solvent was eliminated under reduced pressure. Dichloromethane (50 ml) was added, the solid was filtered off, and the solution was concentrated under reduced pressure. The oil was crystallized in hexane to obtain 1,3-dibenzylhydantoin (9.02 g, 90% yield) as a white solid. Elemental analysis ($C_{17}H_{16}N_2O_2$): theoretical C 72.84, H 5.75, N 9.99; experimental: C 72.75, H 5.62, N 10.05. ^{1}H NMR ($CDCl_3$, δ ppm): 7.34–7.16 (m, 10H), 4.61 (s, 2H), 4.47 (s, 2H), 3.64 (s, 2H). ^{13}C NMR ($CDCl_3$, δ ppm): 169.2, 156.2, 135.7, 135.0, 128.7, 128.4, 128.3, 127.9, 127.8, 127.6, 48.8, 46.4, 42.3.

4.4. Synthesis of 1-trimethylsilylhydantoin (6)

A mixture of hydantoin (1.0 g, 10 mmol), hexamethyldisilazane (3.22 g, 20 mmol) and dichloromethane (5 ml) was heated under reflux for 72 h under inert atmosphere. After cooling at rt, the solvent was eliminated under reduced pressure to obtain 1-trimethylsilylhydantoin (1.66 g, 96% yield). ^{1}H NMR (DMSO-d_6, δ ppm): 10.60 (s, 1H), 3.92 (s, 2H), 0.23 (s, 9H). ^{13}C NMR (DMSO-d_6, δ ppm): 174.3, 160.6, 50.2, −1.3.

4.5. Synthesis of 1,3-dibenzyl-5-methylenehydantoin (10)

A mixture of 1,3-dibenzylhydantoin (1.4 g, 5 mmol), ethanolamine (0.25 ml), THF (2.5 ml) and formaldehyde (15 ml of 37% aq solution) was heated in a closed vessel at 80 °C for 24 h. After cooling at rt the solvent was removed under reduced pressure. The crude was dissolved using dichloromethane (150 ml) and water (150 ml). After decantation, the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The oily residue was purified by column chromatography on silica gel using dichloromethane as an eluent. 1,3-Dibenzyl-5-methylenehydantoin (350 mg, 24% yield) was obtained as a white solid. Elemental analysis ($C_{18}H_{16}N_2O_2$): theoretical C 73.95, H 5.52, N 9.58; experimental: C 74.07, H 5.61, N 9.67. ^{1}H NMR ($CDCl_3$, δ ppm): 7.37–7.15 (m, 10H), 5.28 (d, 2H; J=2.4 Hz), 4.70 (s, 2H), 4.69 (s, 2H), 4.60 (d, 2H; J=2.4 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 162.2, 154.2, 135.8, 135.6, 135.0, 128.9, 128.8, 128.7, 128.1, 128.0, 127.3, 95.6, 44.2, 44.6.

4.6. Synthesis of 5-hydroxy-5-methylhydantoin (12)

To a solution of pyruvic acid (8.8 g, 100 mmol) in anhydrous benzene (56 ml) heated under reflux in a Dean–Stark apparatus, urea (2.5 g, 40 mmol) was added and the resulting solution was refluxed for 5 h. After cooling at rt, the solid was filtered off, washed with methanol and dried. 5-Hydroxy-5-methylhydantoin (1.24 g, 27% yield) was obtained as a white solid. Elemental analysis ($C_4H_6N_2O_3$): theoretical C 36.93, H 4.65, N 21.53; experimental: C 36.82, H 4.57, N 21.42. ^{1}H NMR (DMSO-d_6, δ ppm): 10.35 (s, 1H), 7.93 (s, 1H), 6.78 (s, 1H), 1.32 (s, 3H). ^{13}C NMR (DMSO-d_6, δ ppm): 175.7, 156.1, 68.7, 24.3.

4.7. Synthesis of 2,2-diureidepropanoic acid (13a)

To a solution of pyruvic acid (3.5 g, 40 mmol) in anhydrous benzene (56 ml) heated under reflux in a Dean–Stark apparatus, urea (2.5 g, 40 mmol) was added and the resulting solution was refluxed for 7 h. After cooling at rt, the solid was filtered off, washed with methanol and dried. 2,2-Diureidepropanoic acid (1.9 g, 25% yield) was obtained as a white solid. Elemental analysis ($C_5H_{10}N_4O_4$): theoretical C 31.58, H 5.26, N 29.47; experimental: C 31.45, H 5.21, N 29.63. ^{1}H NMR (DMSO-d_6, δ ppm): 12.62 (s, 1H), 6.63 (s, 2H), 5.70 (s, 4H), 1.58 (s, 3H). ^{13}C NMR (DMSO-d_6, δ ppm): 165.8, 156.0, 102.3, 33.2.

4.8. Synthesis of methyl 2,2-diureidepropanoate (13b)

To a solution of methyl pyruvate (11.4 g, 100 mmol) in anhydrous benzene (70 ml) heated under reflux in a Dean–Stark apparatus, urea (2.5 g, 40 mmol) was added and the resulting solution was refluxed for 20 h. After cooling at rt, the solvent and the excess of pyruvate were eliminated at reduced pressure. The yellowish solid was filtered off, washed with acetone and dried. Methyl 2,2-diureidepropanoate (3.3 g, 81% yield) was obtained as a white solid. Elemental analysis ($C_6H_{12}N_4O_4$): theoretical C 35.29, H 5.26, N 27.45; experimental: C 35.41, H 5.11, N 27.52. ^{1}H NMR (DMSO-d_6, δ ppm): 6.82 (s, 2H), 5.71 (s, 4H), 3.61 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (DMSO-d_6, δ ppm): 172.5, 157.3, 66.3, 52.4, 24.6.

4.9. Synthesis of 5-hydroxymethylhydantoin (15)

A solution of potassium cyanate (4.0 g, 49.4 mmol) and serine (4.0 g, 38.1 mmol) in water (50 ml) was heated under reflux for 90 min. After cooling at rt, hydrochloric acid (15 ml, 35% aq solution) was added and the mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure, and the resulting solid was washed with methanol and dried, leading to 5-hydroxymethylhydantoin (5.1 g, 99% yield) as a white solid. Elemental analysis ($C_4H_6N_2O_3$): theoretical C 36.93, H 4.65, N 21.53; experimental: C 37.05, H 4.52, N 21.41. ^{1}H NMR (DMSO-d_6, δ ppm): 10.51 (s, 1H), 7.77 (s, 1H), 5.06 (m, 1H), 3.98 (m, 1H), 3.57 (m, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 109.0, 164.2, 66.7, 66.2.

4.10. Synthesis of 3-benzyl-5-hydroxymethylhydantoin (17)

Benzyl isocyanate (4.51 g, 33.9 mmol) was added to a solution of serine methyl ester (5.25 g, 33.9 mmol) and triethylamine (3.42 g, 33.9 mmol) in anhydrous acetonitrile (30 ml) under inert atmosphere, and the mixture was heated at 80 °C for 24 h. The solvent was removed under reduced pressure; the crude was dissolved with water (200 ml) and then extracted with dichloromethane (4×200 ml). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was washed with diethyl ether (200 ml), filtered, washed, and dried leading to methyl 2-(3-benzylureide)-3-hydroxypropanoate (7.1 g, 83% yield). Elemental analysis ($C_{12}H_{16}N_2O_4$): theoretical C 57.13, H 6.39, N 11.10; experimental: C 57.25, H 6.51, N 11.01. ^{1}H NMR (DMSO-d_6, δ ppm): 7.34–7.19 (m, 5H), 6.75 (t, 1H; J=5.4 Hz), 6.34 (d, 1H; J=7.4 Hz), 5.11 (t, 1H; J=5.1 Hz), 4.24 (m, 1H), 4.21 (d, 2H; J=6.0 Hz), 3.78–3.71 (m, 1H), 3.63 (s, 3H), 3.61–3.54 (m, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 172.2, 157.6, 140.6, 128.2, 126.9, 126.5, 61.9, 55.0, 51.7, 42.7.

Hydrochloric acid (2.5 ml of 35% aq solution) was added to a solution of methyl 2-(3-benzylureide)-3-hydroxypropanoate (7.1 g, 28.2 mmol) in methanol (200 ml), and the mixture was

heated at 80 °C for 24 h. The solvent was removed under reduced pressure and the resulting solid was washed with diethyl ether (200 ml), filtered, and dried, leading to 3-benzyl-5-hydroxymethylhydantoin (6.2 g, 99% yield) as a white solid. Elemental analysis ($C_{11}H_{12}N_2O_3$): theoretical C 59.99, H 5.49, N 12.72; experimental: C 59.87, H 5.61, N 12.57. ^{1}H NMR (DMSO-d_6, δ ppm): 8.19 (s, 1H), 7.30–7.24 (m, 5H), 5.16 (t, 1H; J=5.1 Hz), 4.56 (d, 1H; J=15.6 Hz), 4.48 (d, 2H; J=15.6 Hz), 4.15 (t, 1H, J=2.3 Hz), 3.65 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 173.0, 157.1, 136.8, 128.4, 127.2, 127.0, 59.8, 59.2, 40.9.

4.11. Synthesis of 3-benzyl-5-methylenehydantoin (18)

To a solution of 3-benzyl-5-hydroxymethylhydantoin (3.27 g, 14.8 mmol) and triphenylphosphine (4.32 g, 16.5 mmol) in anhydrous THF (40 ml) cooled at 0 °C under inert atmosphere, diisopropyl azadicarboxylate (3.25 ml, 16.5 mmol) was slowly added. The mixture was stirred at rt for 10 min, triethylamine (1.51 g, 15 mmol) was added and the resulting solution was stirred for 14 h. The solvent was removed under reduced pressure. The resulting oil was purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) as an eluent, leading to 3-benzyl-5-methylenehydantoin (2.95 g, 95% yield). Elemental analysis ($C_{11}H_{10}N_2O_2$): theoretical C 65.34, H 4.95, N 13.86; experimental: C 65.43, H 4.82, N 13.77. ^{1}H NMR (DMSO-d_6, δ ppm): 8.88 (s, 1H), 7.36–7.24 (m, 5H), 5.18 (d, 1H, J=2.1 Hz), 4.87 (d, 1H, J=2.1 Hz), 4.60 (s, 2H). ^{13}C NMR ($CDCl_3$, δ ppm): 163.0, 154.3, 135.9, 134.7, 133.0, 131.6, 127.9, 95.9, 42.1.

4.12. Synthesis of 5-methylenehydantoin (16)

Chloroacetaldehyde diethyl acetal (15.2 g, 100 mmol) was dissolved in an aqueous solution of HCl (30 ml, 5.5 M) and the solution was stirred at rt for 24 h. After cooling at 0 °C, Na_2SO_3 (18.9 g, 150 mmol) and $NaHSO_3$ (39 g of a 40% aq solution, 150 mmol) were added. After 10 min stirring at 0 °C, the solution was warmed at rt, KCN (75 ml of 2 M aq solution) was added dropwise (20 min), the resulting mixture was stirred for 2 h, and then extracted with diethyl ether (4×50 ml). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. A solution of $(NH_4)_2CO_3$ (180 mmol) in water/methanol (3/2, 200 ml) was added to the residue, and the mixture was stirred at rt for 14 h. The methanol was evaporated under reduced pressure and the aqueous solution was extracted with ethyl acetate (6×50 ml). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was washed with a small amount of water and dried, leading to 5-methylenehydantoin (1.0 g, 9% yield) as a white solid. Elemental analysis ($C_4H_4N_2O_2$): theoretical C 42.86, H 3.60, N 24.99; experimental: C 42.80, H 3.72, N 24.85. ^{1}H NMR (DMSO-d_6, δ ppm): 11.07 (s, 1H), 10.27 (s, 1H), 5.01 (d, 1H, J=3.3 Hz), 4.72 (d, 1H, J=3.3 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 164.1, 154.3, 136.4, 92.7.

4.13. Diels–Alder reaction with 2,3-dimethylbuta-1,3-diene

To a solution of 1,3-dibenzyl-5-methylenehydantoin (87.6 mg. 0.3 mmol) and ZnI_2 (32 mg, 0.15 mmol, pre-dried for 24 h at 140 °C under vacuum) in anhydrous toluene (5 ml) under inert atmosphere was added 2,3-dimethylbuta-1,3-diene (738 mg, 9 mmol) and the mixture was stirred at 80 °C for 40 h. The reaction was cooled at rt and the solvent was eliminated under reduced pressure. The crude was fractioned with CH_2Cl_2 (15 ml) and water (15 ml). Once separated, the organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The resulting solid was washed with methanol (10 ml) leading to 1,3-dibenzyl-7,8-dimethyl-1,3-diazaspiro[4.5]dec-7-en-2,4-dione (**21**) (102 mg, 91% yield). Elemental analysis ($C_{24}H_{26}N_2O_2$): theoretical C 76.98, H 7.00, N 7.48; experimental: C 77.13, H 7.07, N 7.35. ^{1}H NMR ($CDCl_3$, δ ppm): 7.34–7.11 (m, 10H), 4.64 (s, 2H), 4.51 (d, 1H, J=15.6 Hz), 4.42 (d, 1H, J=15.6), 2.26 (m, 1H), 2.13 (m, 1H), 1.85(m, 1H), 1.81 (m, 2H), 1.65 (m, 1H), 1.55 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 175.8, 156.5, 138.4, 136.4, 128.7, 128.5, 128.4, 127.8, 127.4, 127.1, 125.4, 122.0, 63.4, 44.3, 42.5, 36.7, 30.1, 28.2, 18.8, 18.7.

4.14. Diels–Alder reaction with cyclopentadiene

(a) Thermal reaction: A solution of 1,3-dibenzyl-5-methylenehydantoin (146 mg. 0.5 mmol) and freshly distilled cyclopentadiene (660 mg, 10 mmol) in toluene (12 ml) was stirred at 100 °C for 24 h. The reaction was cooled at rt and the solvent was eliminated under reduced pressure. The crude oil was crystallized in hexane, leading to product **22n** (170 mg, 95% yield). ^{1}H NMR ($CDCl_3$, δ ppm): 7.37–7.00 (m, 10H), 6.41 (dd, 1H, J=5.7, 3.6 Hz), 5.74 (dd, 1H, J=5.7, 3.6 Hz), 4.75 (s, 2H), 4.66 (d, 1H, J=12.0 Hz), 4.32 (d, 1H, J=12.0 Hz), 2.92 (dd, 1H, J=3.6, 3.6 Hz), 2.91 (d, 1H, J=3.6 Hz), 2.53 (d, 1H, J=5.7 Hz), 2.15 (dd, 1H, J=12.3, 3.6 Hz), 1.35 (d, 1H, J=12.3 Hz), 1.26 (d, 1H, J=5.7 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 176.0, 155.8, 139.5, 136.7, 135.4, 132.8, 127.9, 127.6, 127.4, 126.7, 126.0, 125.3, 68.6, 52.7, 47.1, 43.7, 41.6, 40.8, 34.0.

(b) Catalytic reaction: A solution of 1,3-dibenzyl-5-methylenehydantoin (292 mg, 1 mmol) and $EtAlCl_2$ (1 mmol) in anhydrous CH_2Cl_2 (5 ml) was stirred under inert atmosphere for 1 h at rt. Then freshly distilled cyclopentadiene (1320 mg, 20 mmol) was added and the reaction was stirred at rt for 12 h. The solvent was eliminated under reduced pressure and the crude oil was crystallized in hexane, leading to a mixture of **22n** and **22x** in 75/25 ratio (350 mg, 98% yield).

Spectra of **22x** (from the mixture). ^{1}H NMR ($CDCl_3$, δ ppm): 7.37–7.00 (m, 10H), 6.31 (dd, 1H, J=5.5, 2.9 Hz), 6.09 (dd, 1H, J=5.5, 3.3 Hz), 4.88 (d, 1H, J=16.5 Hz), 4.7 (s, 2H), 4.49 (d, 1H, J=16.5 Hz), 2.94 (m, 2H), 2.66 (m, 1H), 1.83 (m, 1H), 1.81 (m, 1H), 1.59 (m, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 174.4, 155.3, 138.6, 136.7, 134.5, 132.7, 127.8, 127.6, 127.5, 127.0, 126.2, 125.8, 69.4, 51.1, 48.0, 43.2, 41.9, 41.8, 35.8.

4.15. Epoxidation

A solution of 1,3-dibenzyl-5-methylenehydantoin (87.6 mg. 0.3 mmol) and *m*-chloroperbenzoic acid (309 mg, 0.9 mmol) in CH_2Cl_2 (10 ml) was stirred for 40 h at rt. CH_2Cl_2 (20 ml) and aqueous NaOH solution (30 ml, 0.085 M) were added. Once separated, the organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum, leading to 4,6-dibenzyl-1-oxo-4,6-diazaspiro[2.4]heptane-5,7-dione (**23**) (87 mg, 94% yield). ^{1}H NMR ($CDCl_3$, δ ppm): 7.51–7.02 (m, 10H), 4.71 (d, 1H, J=15.6 Hz), 4.62 (d, 1H, J=14.8 Hz), 4.57 (d, 1H, J=14.8 Hz), 4.37 (d, 1H, J=11.6 Hz), 4.31 (d, 1H, J=15.6 Hz), 4.21 (d, 1H, J=11.6 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 169.7, 156.5, 136.2, 135.6, 128.7, 128.6, 128.2, 128.0, 127.9, 127.7, 87.9, 60.5, 43.3, 43.0.

4.16. Synthesis of 1,3-dibenzyl-5-methoxy-5-methylhydantoin (24)

To a solution of 1,3-dibenzyl-5-methylenehydantoin (29.2 mg. 0.1 mmol) in methanol (5 ml) was added an aqueous solution of HCl (35%, 0.2 ml) and the resulting mixture was heated at 80 °C for 24 h. After cooling at rt the solvent was eliminated under reduced pressure to obtain 1,3-dibenzyl-5-methoxy-5-methylhydantoin in quantitative yield. Elemental analysis ($C_{19}H_{20}N_2O_3$): theoretical C 70.35, H 6.21, N 8.64; experimental: C 70.19, H 6.27, N 8.52. ^{1}H NMR ($CDCl_3$, δ ppm): 7.37–7.20 (m, 10H), 4.68 (d, 1H, J=14.6 Hz), 4.64 (d,

1H, *J*=14.6 Hz), 4.57 (d, 1H, *J*=15.2 Hz), 4.27 (d, 1H, *J*=15.2 Hz), 2.78 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 171.2, 155.5, 137.2, 136.1, 128.8, 128.7, 128.6, 128.5, 128.0, 127.8, 89.5, 51.2, 42.5 (2×s), 21.8.

4.17. Addition of sodium cyanide

A solution of 1,3-dibenzyl-5-methylenehydantoin (29.2 mg. 0.1 mmol), sodium cyanide (74 mg, 1.5 mmol) and $Cu(OTf)_2$ (5.5 mg, 0.015 mmol) in an acetonitrile/water mixture (2 ml, 50:50 v/v) was heated at 40 °C for 4 h. CH_2Cl_2 (15 ml) and water (15 ml) were added to the mixture. Once separated, the organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum, leading a mixture of **25** and **26** in molar ratio 77:23 with 100% conversion.

(1,3-*Dibenzyl*-2,5-*dioxoimidazolidin*-4-*yl*)*acetonitrile* (**25**): ^{1}H NMR ($CDCl_3$, δ ppm): 7.50–7.15 (m, 10H), 4.91 (d, 1H, *J*=15.4 Hz), 4.70 (d, 1H, *J*=15.8 Hz), 4.60 (d, 1H, *J*=15.8 Hz), 4.30 (d, 1H, *J*=15.4 Hz), 3.87 (t, 1H, *J*=4.8 Hz), 2.67 (t, 2H, *J*=4.8 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 169.5, 156.1, 137.7, 136.7, 128.3, 127.8, 127.6, 127.4, 127.3, 127.1, 114.8, 55.1, 45.7, 43.1, 19.3.

12-*Amino*-1,3,8,10-*tetrabenzyl*-1,3,8,10-*tetraazadispiro*-[4.1.4.2] *tridec*-12-*en*-2,4,9,11-*tetraone* (**26**): ^{1}H NMR ($CDCl_3$, δ ppm): 7.56–7.20 (m, 20H), 4.80 (d, 1H, *J*=15.4 Hz), 4.78 (d, 1H, *J*=15.1 Hz), 4.74 (s, 4H), 4.63 (d, 1H, *J*=15.4 Hz), 4.58 (d, 1H, *J*=15.1 Hz), 4.07 (s, 1H), 2.72 (s, 2H), 2.52 (d, 1H, *J*=15.4 Hz), 2.48 (d, 1H, *J*=15.4 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 175.3, 173.0, 155.8, 155.5, 146.5, 129.1, 128.9, 128.8, 128.7 (2×s), 128.6, 128.5, 128.4 (2×s), 128.3, 128.1, 127.9, 127.8, 127.3, 127.2, 103.2, 74.3, 73.2, 42.9 (2×s), 42.7 (2×s), 39.0.

4.18. Synthesis of 1,3-dibenzyl-5-(piperdin-1-ylmethyl) hydantoin (27)

A solution of 1,3-dibenzyl-5-methylenehydantoin (116.8 mg, 0.4 mmol), piperidine (122 mg, 1.4 mmol) and $Cu(OTf)_2$ (22 mg, 0.06 mmol) in an acetonitrile/water mixture (4 ml, 50:50 v/v) was heated at 40 °C for 40 h. CH_2Cl_2 (30 ml) and water (30 ml) were added to the mixture. Once separated, the organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum, leading 1,3-dibenzyl-5-(piperdin-1-ylmethyl)hydantoin (68 mg, 90% yield). Elemental analysis ($C_{23}H_{27}N_3O_2$): theoretical C 73.18, H 7.21, N 11.13; experimental: C 73.31, H 7.05, N 11.20. ^{1}H NMR ($CDCl_3$, δ ppm): 7.36–7.17 (m, 10H), 5.04 (d, 1H, *J*=14.8 Hz), 4.66 (d, 1H, *J*=14.8 Hz), 4.58 (d, 1H, *J*=14.8 Hz), 4.27 (d, 1H, *J*=14.8 Hz), 3.74 (dd, 1H, *J*=3.3, 6.8 Hz), 2.68 (dd, 1H, *J*=3.3, 13.9 Hz), 2.59 (dd, 1H, *J*=6.8, 13.9 Hz), 2.31 (m, 2H), 2.29 (m, 2H), 1.37 (m, 4H), 1.29 (m, 2H). ^{13}C NMR ($CDCl_3$, δ ppm): 172.0, 156.8, 136.4, 136.2, 128.8, 128.6, 128.5, 128.2, 127.9, 127.7, 59.0, 57.5, 55.4, 45.2, 42.5, 26.0, 24.0.

4.19. Addition of phenylmethanethiol

A solution of 5-methylenehydantoin or 1,3-dibenzyl-5-methylenehydantoin (1 mmol), phenylmethanethiol (124 mg, 1 mmol) and triethylamine (20.2 mg, 0.2 mmol) in methanol (7 ml) was stirred at rt for 24 h. The resulting solution was washed with hexane (3×7 ml) and the solvent was eliminated under reduced pressure to obtain the corresponding product.

5-*Benzylsulfanylmethylhydantoin* (**28**, 217 mg, 92% yield). ^{1}H NMR (DMSO-d_6, δ ppm): 10.74 (s, 1H), 8.01 (s, 1H), 7.32–7.31 (m, 5H), 4.31 (m, 1H), 3.77 (s, 2H), 2.72 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 174.9, 157.6, 138.3, 129.0, 128.4, 127.0, 57.7, 35.9, 32.0.

1,3-*Dibenzyl*-5-*benzylsulfanylmethylhydantoin* (**29**, 395 mg, 95% yield). ^{1}H NMR ($CDCl_3$, δ ppm): 7.41–7.09 (m, 15H), 5.00 (d, 1H, *J*=15.2 Hz), 4.67 (s, 2H), 3.91 (d, 1H, *J*=15.2 Hz), 3.86 (t, 1H, *J*=3.3 Hz), 3.43 (s, 2H), 2.79 (dd, 1H, *J*=3.3, 14.1 Hz), 2.72 (dd, 1H, *J*=3.3, 14.1 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 171.5, 156.6, 137.5, 129.0, 128.6, 128.5 (3×s), 128.2 (2×s), 58.3, 44.8, 42.8, 36.8, 29.8.

4.20. Synthesis of 1,3-dibenzyl-5-sulfanylmethylhydantoin (30)

To a solution of 1,3-dibenzyl-5-methylenehydantoin (58.4 mg, 0.2 mmol) in a mixture of methanol and THF (4 ml, 50:50 v/v) was added a solution of sodium hydrogenosulfide (17 mg, 0.3 mmol) in methanol (6 ml). The resulting solution was stirred at rt for 24 h and the solvent was eliminated under reduced pressure. The crude oil was partitioned between with CH_2Cl_2 (10 ml) and a saturated aqueous solution of NH_4Cl (10 ml). The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum, leading 1,3-dibenzyl-5-sulfanylmethylhydantoin (52 mg, 80% yield). ^{1}H NMR ($CDCl_3$, δ ppm): 7.37–7.19 (m, 10H), 4.85 (d, 1H, *J*=15.6 Hz), 4.68 (d, 1H, *J*=14.8 Hz), 4.62 (d, 1H, *J*=14.8 Hz), 4.14 (d, 1H, *J*=15.6 Hz), 3.95 (t, 1H, *J*=3.6 Hz), 2.90 (m, 1H), 2.71 (m, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 171.0, 156.9, 135.9, 135.4, 129.1, 128.6, 128.5, 128.4, 128.3, 128.0, 59.9, 45.2, 42.8, 23.4.

4.21. Synthesis of *S*-(2,5-dioxoimidazolidin-4-yl)methyl thioacetate (31)

A solution of 5-methylenehydantoin (33.1 mg, 0.3 mmol), potassium thioacetate (339 mg, 3 mmol) and $Yb(OTf)_3$ (102 mg, 0.18 mmol) in an acetonitrile/water mixture (12 ml, 50:50 v/v) was heated at 90 °C for 14 h. After cooling, CH_2Cl_2 (10 ml) and water (10 ml) were added to the mixture. Once separated, the organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum, leading *S*-(2,5-dioxoimidazolidin-4-yl)methyl thioacetate (56.3 mg, 99% yield). ^{1}H NMR (DMSO-d_6, δ ppm): 4.87 (dd, 1H, *J*=2.9, 4.4 Hz), 3.87 (dd, 1H, *J*=4.4, 14.5 Hz), 3.38 (dd, 1H, *J*=2.9, 14.5 Hz), 2.32 (s, 3H). ^{13}C NMR (DMSO-d_6, δ ppm): 193.4, 169.0, 152.4, 59.1, 29.6, 27.7.

4.22. Synthesis of *S*-(1,3-dibenzyl-2,5-dioxoimidazolidin-4-yl) methyl thioacetate (32)

From 1,3-dibenzyl-5-methylenehydantoin (29.2 mg, 0.1 mmol), using the same method described above to obtain 32 mg (87% yield). Elemental analysis ($C_{20}H_{20}N_2O_3S$): theoretical C 65.20, H 5.47, N 7.60, S 8.70; experimental: C 65.08, H 5.51, N 7.49, S 8.58. ^{1}H NMR ($CDCl_3$, δ ppm): 7.34–7.18 (m, 10H), 4.97 (d, 1H, *J*=15.2 Hz), 4.65 (d, 1H, *J*=14.4 Hz), 4.55 (d, 1H, *J*=14.4 Hz), 4.01 (d, 1H, *J*=15.2 Hz), 3.95 (dd, 1H, *J*=3.0, 4.4 Hz), 3.36 (dd, 1H, *J*=4.4, 14.4 Hz), 2.82 (dd, 1H, *J*=3.0, 14.4 Hz), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 193.9, 170.9, 156.5, 135.9, 135.4, 129.1, 128.7 (2×s), 128.6 (2×s), 128.4, 128.3, 127.9, 57.6, 44.7, 42.8, 30.6, 27.8.

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Supplementary data

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