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Synthesis of chiral hexacyclic steroids *via* [8π + 2π] cycloaddition of diazafulvenium methides†

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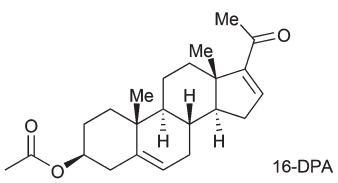
First examples of [8π + 2π] cycloaddition of 16-dehydropregnenolone (16-DPA) acetate with diazafulvenium methides leading to chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused steroids are reported. These hexacyclic steroids were obtained exclusively or selectively with the approach of the 1,7-dipole by the less hindered α-face of 16-DPA. Quantum chemical calculations at the DFT level were carried out, using the cycloaddition of 1-methyl- and 1-benzyl-diazafulvenium methides with *N*-phenylmaleimide as model reactions, in order to rationalize the stereochemistry outcome. The results indicate that *endo* cycloadditions of the more stable dipole conformation, having the 1-substituent pointing outward, are significantly more favorable than the alternative *exo* cycloaddition.

Introduction

Steroids are a widely important class of both naturally occurring and synthetic compounds with a great diversity of applications in human physiology and medicine.[1] Effectively, some steroids are important hormones, including cortisone, progesterone, estradiol and testosterone. Among the most used steroids in medicine are cortisone and progesterone and their various synthetic derivatives. On the other hand, synthetic steroids fused to heterocyclic compounds at positions 16 and 17 of the D-ring have unique biological properties. 16-Dehydropregnenolone acetate (16-DPA) is a commercial and particularly versatile building block, which has been used in the hemisynthesis of different steroidal drugs, including corticosteroids or soft corticosteroids, anabolic steroids, sex hormones and oral contraceptives.[2]



16-DPA

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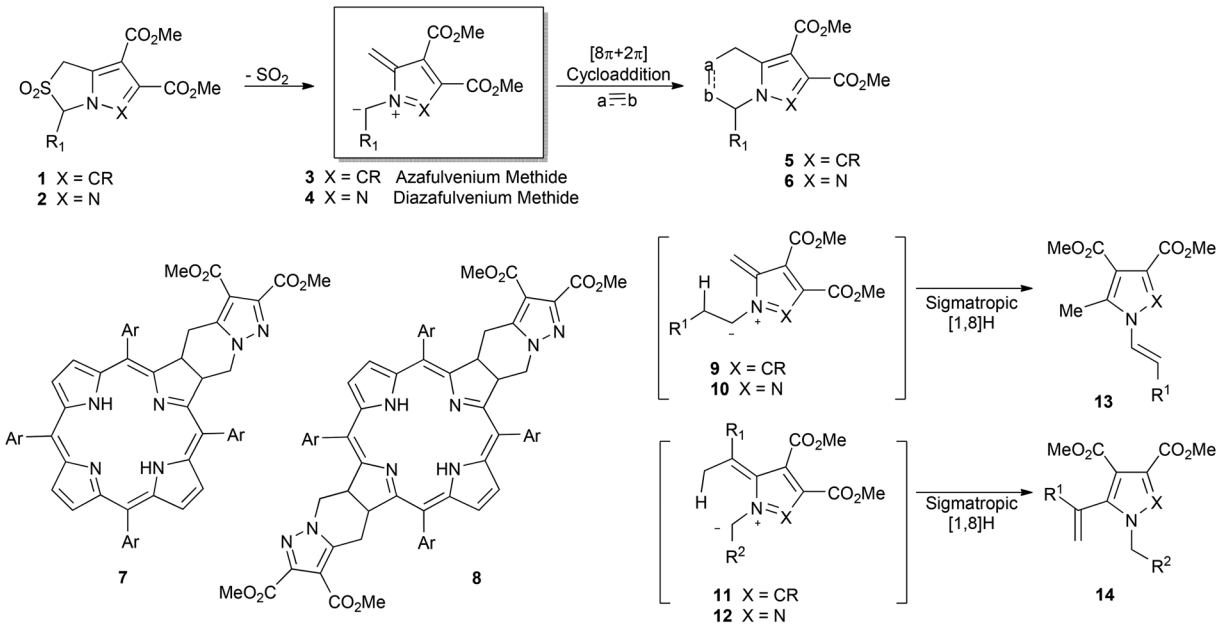
There are several synthetic strategies for the construction of penta- and hexacyclic steroids including the use of Diels–Alder reactions and 1,3-dipolar cycloadditions.[1] However, there are no reports on [8π + 2π] cycloadditions of 16-dehydropregnenolone with diazafulvenium methides which we anticipated could lead to a novel class of hexacyclic steroids.

The study of pericyclic reactions of aza- and diazafulvenium methide systems (*e.g.* **3** and **4**) as an approach to pyrroles and pyrazoles is one of our current research interests.[3–5] Aza- and diazafulvenium methides (*e.g.* **3** and **4**) are generated from 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxides and 1*H*,3*H*-pyrazolo[1,5-*c*]thiazole-2,2-dioxides, respectively, by thermal extrusion of sulfur dioxide. The 4,5-dimethoxycarbonyl-substituted aza- and diazafulvenium methides participate in dipolar cycloadditions acting exclusively as 8π 1,7-dipoles[3,5] whereas 5-(trifluoromethyl)-azafulvenium methides can act as 4π 1,3-dipoles or as 8π 1,7-dipoles.[4] Recently, the generation and reactivity of benzodiazafulvenium methides have also been described.[6] Aza- and diazafulvenium methides bearing methyl or benzyl groups at C-1 or C-7 undergo sigmatropic [1,8]H shifts giving vinyl-pyrroles and vinyl-pyrazoles, respectively. The 4,5-dimethoxycarbonyl derivatives participate exclusively in [8π + 2π] cycloadditions giving products resulting from the addition across the 1,7-positions.[3] These 1,7-cycloadducts include chlorin and bacteriochlorin type macrocycles (*e.g.* **7** and **8**), compounds with relevance in medicinal chemistry (Scheme 1).[5]

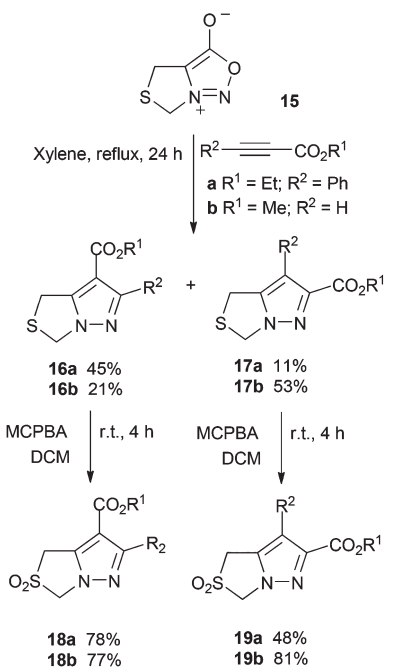
Herein, studies on a novel approach to chiral hexacyclic steroids based on [8π + 2π] cycloaddition of 16-DPA, used as a chiral steroidal scaffold, with diazafulvenium methides are described.



Scheme 1 Pericyclic reactions of 4,5-dimethoxycarbonyl aza- and diazafulvenium methides.

Results and discussion

The synthesis of 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazoles **18** and **19** is outlined in Scheme 2. Sydnone **15**, prepared from 1,2-thiazolidine-4-carboxylic acid *via* nitrosation followed by treatment with TFAA,[7] underwent 1,3-dipolar cycloaddition with ethyl phenylpropiolate and methyl propiolate to give the corresponding pyrazolo[1,5-*c*][1,3]thiazoles **16** and **17** in good overall yield. In both cases two regioisomers were obtained. Cycloaddition of sydnone **15** with ethyl phenylpropiolate gave 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate **16a** as the major product (45%) and regioisomer **17a** isolated in 11% yield. Interestingly, using methyl propiolate as the dipolarophile 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate **17b** was the major product obtained in 53% yield together with the synthesis of 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate **16b** in 21% yield. The assignment of the structure of compounds **16b** and **17b** was supported by two-dimensional COSY spectra (440 MHz). Coupling was observed between the protons H-1 and H-7 in the COSY spectrum of compound **17b**, whereas no such coupling was detected in the case of compound **16b**. The oxidation of pyrazolo[1,5-*c*][1,3]thiazoles **16** and **17** with MCPBA gave in good yield the target sulfones **18** and **19**, respectively.



Scheme 2 Synthesis of 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-c][1,3]thiazoles **18** and **19**.

The molecular structure of the compound 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate **18a** was established by X-ray crystallography (Fig. 1). This derivative crystallized as colourless blocks in the monoclinic system within the $P2_1/c$ space group, showing one molecule per asymmetric unit. Its molecular structure consists of a 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]-thiazole derivative with an ethyl carboxylate and a phenyl substituent at positions C7 and C6 of the fused ring, respectively. All distances and angles are within the expected values for similar compounds.[8]

Thiazolidine **20** was obtained from the condensation of L-cysteine with phenylacetaldehyde and converted into the corresponding sydnone **22**. Dipolar cycloaddition of 1,3-dipole **22** with DMAD afforded 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole **23** in 70% yield. The target sulfone **24** was obtained by oxidation of **23** with MCPBA (Scheme 3).

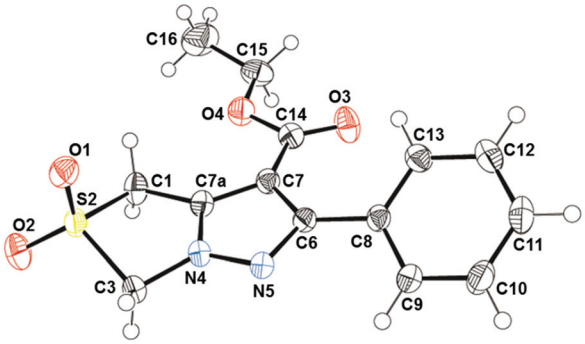
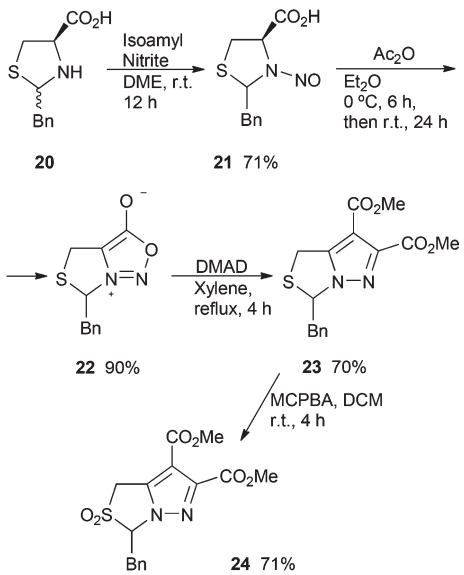


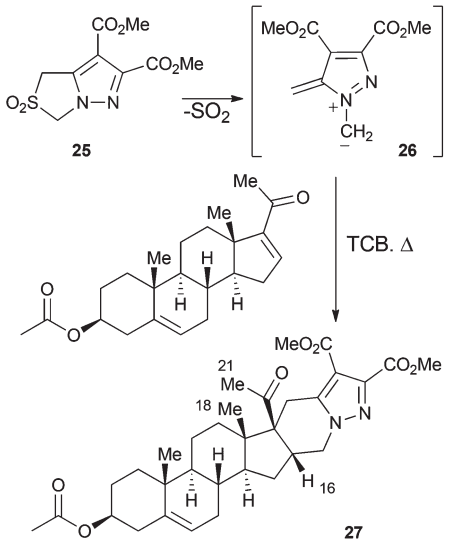
Fig. 1 ORTEP-3 diagram of compound **18a**, using 50% probability level ellipsoids.



Scheme 3 Synthesis of 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole **24**.

The reactivity of 16-dehydropregnenolone acetate towards diazafulvenium methide **26** was first explored (Table 1). This 1,7-dipole was generated *in situ* from 2,2-dioxo-1*H*,3*H*-pyrazolo-[1,5-*c*][1,3]thiazole **25**[9] under microwave irradiation and in refluxing 1,2,4-trichlorobenzene (TCB) leading to steroid derivative **27** as single regio- and stereoisomer. Carrying out the reaction under microwave irradiation at 250 °C for 10 min using 1 equivalent of sulfone **25**, compound **27** was isolated in 59% yield (entry 1). The cycloaddition was also carried out under the same reaction conditions but using an excess of sulfone, 1.5, 2.0 and 2.5 equivalents leading to the target compound in 68%, 67% and 73% yield, respectively (entries 4, 7 and 10). It was observed that a longer irradiation time (15 min and 20 min) did not lead to an improvement of the yield (entries 2, 3, 5, 6 and 8). On the other hand, irradiation of a TCB solution of 16-DPA and 1 equiv. of sulfone **25** and further irradiation for 10 min after the addition of 1 equiv. of **25**

Table 1 Cycloaddition of 16-dehydropregnenolone acetate with diazafulvenium methide **26**



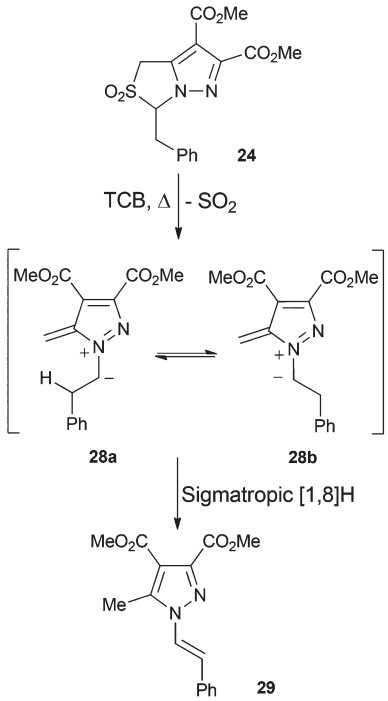
Entry	Sulfone	Reaction conditions	Isolated yield
1	1 equiv.	MW, 250 °C, 10 min	59%
2	1 equiv.	MW, 250 °C, 15 min	44%
3	1 equiv.	MW, 250 °C, 20 min	62%
4	1.5 equiv.	MW, 250 °C, 10 min	68%
5	1.5 equiv.	MW, 250 °C, 15 min	64%
6	1.5 equiv.	MW, 250 °C, 20 min	57%
7	2 equiv.	MW, 250 °C, 10 min	67%
8	2 equiv.	MW, 250 °C, 15 min	66%
9	1 + 1 equiv.	MW, 250 °C, 10 min + 10 min	60%
10	2.5 equiv.	MW, 250 °C, 10 min	73%
11	2 equiv.	Reflux, 3 h	76%

afforded compound **27** in 60% yield (entry 9). The [8π + 2π] cycloaddition of 16-DPA with diazafulvenium methide **26** under conventional thermolysis, refluxing TCB for 3 h, gave the hexacyclic steroid **27** in 76% yield in a regio- and stereoselective fashion (entry 11).

The assignment of the stereochemistry of compound **27** was made on the basis of two-dimensional NOESY spectra (400 MHz). Compound **27** showed cross peaks between protons H-18 (0.76 ppm) and protons H-21 (2.20 ppm), and the latter showed correlation with proton H-16 (3.69–3.73 ppm). The crystal structure of 16-dehydropregnenolone acetate is known[10] indicating that the approach of the dipole by the α-face is less hindered allowing the stereoselective synthesis of hexacyclic steroid **27**.

3-Benzyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole **24** was subjected to microwave induced thermolysis and flash vacuum pyrolysis (FVP) in the absence of 16-DPA (Table 2). As expected, *N*-styryl-1*H*-pyrazole **29** was obtained through an allowed suprafacial sigmatropic [1,8]H shift in the 8π 1,7-dipolar system of the *in situ* generated diazafulvenium methide **28**. Although this 1,7-dipole exists in equilibrium of at least two conformers, only conformer **28a** bears a hydrogen in the appropriate position to undergo the pericyclic reaction. Under

Table 2 Synthesis of *N*-styryl-1*H*-pyrazole **29**



Entry	Reaction conditions	Isolated yield
1	MW, 250 °C, 10 min	37%
2	MW, 250 °C, 15 min	77%
3	MW, 250 °C, 20 min	74%
4	MW, 230 °C, 20 min	75%
5	FVP, 500 °C, 3.3×10^{-5} mbar	54%
6	FVP, 600 °C, 5×10^{-5} mbar	41%
7	FVP, 700 °C, 1.3×10^{-5} mbar	35%

microwave irradiation, 1*H*-pyrazole **29** could be isolated in 77% yield by carrying out the reaction at 250 °C for 15 min (entry 2). The synthesis of this heterocyclic compound was also achieved by FVP. At 500 °C 1*H*-pyrazole **29** was isolated in 54% yield but flash vacuum pyrolysis at higher temperature was less efficient (entries 5–7).

The thermal reactivity of 3-benzyl-2,2-dioxo-1*H*,3*H*-pyrazolo-[1,5-*c*][1,3]thiazole **24** in the presence of 16-dehydropregnenolone acetate was then explored (Table 3). In this case, along with the desired 1,7-cycloadduct the competitive synthesis of *N*-styryl-1*H*-pyrazole **29** was to be expected. In fact, under the studied reaction conditions the new chiral hexacyclic steroid **30** was obtained together with the formation of pyrazole **29**. The optimized reaction conditions for the microwave-induced process led to both products in 70% overall yield (entry 5). Carrying out the reaction in refluxing TCB for 4 h afforded steroid **30** and pyrazole **29** in 34% and 18%, respectively (entry 8).

The structural assignment of compound **30** was supported by two-dimensional NMR spectra (400 MHz). The HMQC spectrum showed correlation of two doublets at 2.37 and 4.11 ppm with carbon C-32 (23.3 ppm) and correlation of the carbon with the chemical shift at 35.4 ppm (C-33) with the signals at 3.02 and 3.99–4.00 ppm allowing the assignment of the methylene groups H-32 and H-33. On the other hand, in the COSY spectrum the coupling of protons H-33 with proton H-24 (4.21 ppm) could be confirmed. The NOESY spectrum allowed the stereochemistry assignment since cross peaks were observed between protons H-18 and protons H-21 as well as between protons H-18 and proton H-16. In addition, the NOESY spectrum showed correlation of proton H-24 with proton H-16.

The novel hexacyclic steroid **30** was obtained regio- and stereoselectively. It should be noticed that the process involves an [8π + 2π] cycloaddition of a 1-substituted diazafulvenium methide, which leads to a product with an additional chiral center (C-24).

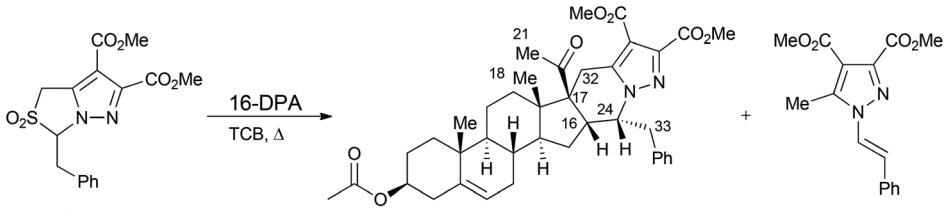
Diazafulvenium methide **32**, generated from sulfone **31**, reacted with 16-DPA *via* [8π + 2π] cycloaddition leading to a mixture of stereoisomers **34** and **35**. From these reactions *N*-vinylpyrazole **33** was also obtained (Table 4). The microwave-induced reaction was carried out setting the temperature at 250 °C using different stoichiometries and different reaction times. No significant differences were observed in the overall yield of the synthesis of 1,7-cycloadducts (29–37%). However, there were differences in the stereoisomeric ratio (entries 1–5). The *N*-vinylpyrazole **33** was isolated in yields ranging from 11% to 20%. Conventional heating led to a 98 : 2 mixture of stereoisomers **34** and **35** in 41% yield and to *N*-vinylpyrazole **33** isolated in 7% yield (entry 6).

Hexacyclic steroid **34** could be isolated in pure form allowing for full characterization. The mixture of stereoisomers crystallizes from ethyl acetate/hexane, leaving single stereoisomer **34** in the solution. The stereochemistry assignment of compound **34** was supported by the NOESY spectrum. Correlation was observed between protons H-21 (2.21 ppm) and protons H-24 and H-18 (0.75 ppm). On the other hand, cross peaks were observed between protons H-18 and proton H-16. The NOESY spectrum of the mixture of steroids **34** and **35** allowed the structural assignment of compound **35** since correlation between protons H-33 and proton H-16 could be observed.

The work was extended to the reactivity of 16-dehydropregnenolone acetate towards 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]-thiazole-7-carboxylates **18** under microwave irradiation and conventional heating (Table 5). The reaction of sulfone **18a** was more efficient when carrying out the microwave irradiation at 250 °C for 10 min, using 2.5 equiv., affording regio- and stereoselectively the target compound **36a** in 70% yield (entry 1). Under the same reaction conditions 16-DPA reacted with sulfone **18b** to give steroid **36b** as single regio- and stereoisomer in good yield, although in this case the best results were achieved but using 3 equiv. of the sulfone (entry 6). Conventional heating led to **36a** and **36b** in 36% and 54% yield, respectively (entries 3 and 7).

Attempts to carry out the reaction of 16-DPA with the diazafulvenium methide generated from ethyl 7-phenyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate **19a** were unsuccessful.

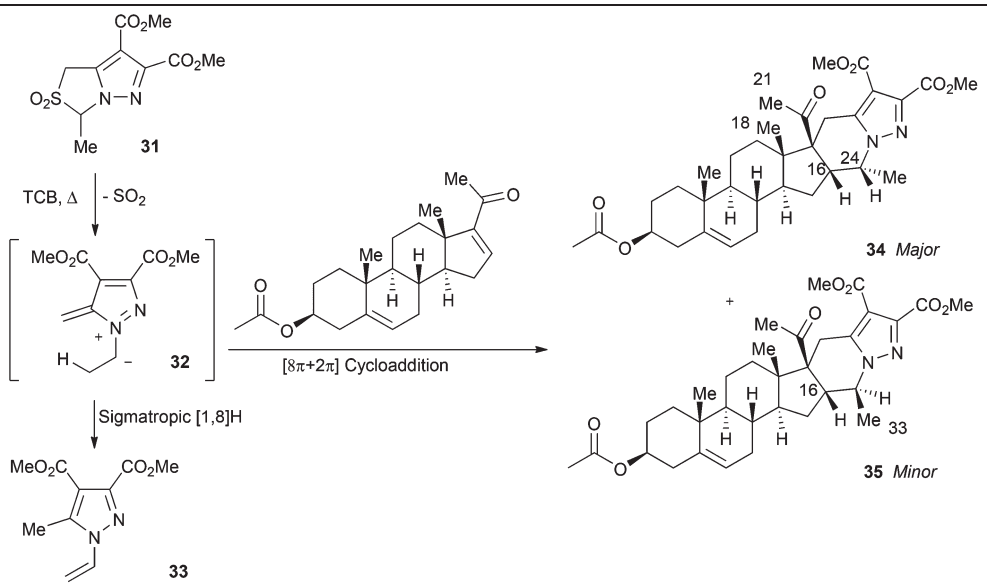
Table 3 Cycloaddition of 16-dehydropregnenolone acetate with diazafulvenium methide **28**



24 **30** **29**

Entry	Sulfone	Reaction conditions	Isolated yield **30**	Isolated yield **29**
1	1 equiv.	MW, 250 °C, 10 min	25%	12%
2	1 equiv.	MW, 250 °C, 15 min	30%	22%
3	1 equiv.	MW, 250 °C, 20 min	20%	32%
4	1.5 equiv.	MW, 250 °C, 10 min	28%	29%
5	1.5 equiv.	MW, 250 °C, 15 min	35%	35%
6	2 equiv.	MW, 250 °C, 15 min	32%	30%
7	3 equiv.	MW, 250 °C, 15 min	28%	36%
8	1.5 equiv.	Reflux, 4 h	34%	18%

Table 4 Cycloaddition of 16-dehydropregnenolone acetate with diazafulvenium methide **32**

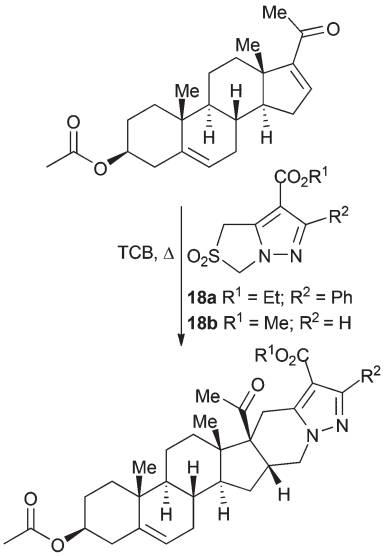


31 **32** **33** **34** *Major* **35** *Minor*

Entry	Sulfone	Reaction conditions	Isolated yield (**34** : **35**)	Isolated yield **33**
1	1 equiv.	MW, 250 °C, 10 min	37% (75 : 25)	11%
2	1 equiv.	MW, 250 °C, 15 min	34% (91 : 9)	13%
3	1.5 equiv.	MW, 250 °C, 15 min	29% (95 : 5)	19%
4	2 equiv.	MW, 250 °C, 10 min	32% (89 : 11)	19%
5	3 equiv.	MW, 250 °C, 10 min	31% (83 : 17)	20%
6	1 equiv.	Reflux, 4 h	41% (98 : 2)	7%

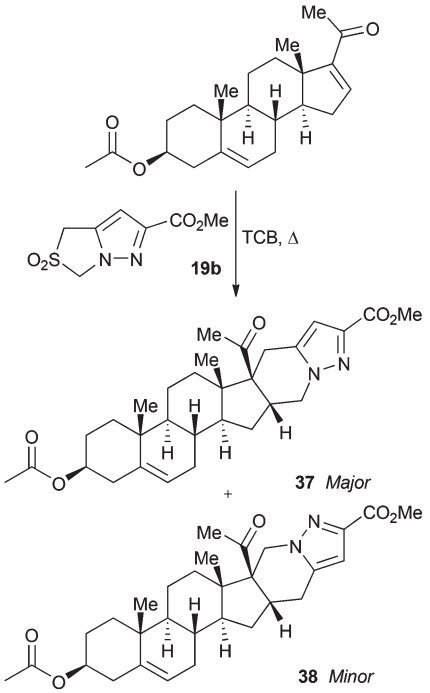
Finally, the thermolysis of sulfone **19b** in the presence of 16-DPA was explored (Table 6). In this case, the reaction was stereoselective but two regioisomers were obtained as an inseparable mixture, compound **37** being the major product. Microwave irradiation at 250 °C for 10 min and conventional heating, using 3 equiv. of sulfone **19b**, led to a regioisomeric mixture in 49% and 37% overall yield, respectively (entries 3 and 4). In both cases hexacyclic steroids were obtained in an 85 : 15 ratio.

Table 5 Synthesis of hexacyclic steroids **36** from 16-dehydropregnenolone acetate



Entry	Sulfone	Reaction conditions	Isolated yield
1	**18a**, 2.5 equiv.	MW, 250 °C, 10 min	**36a**, 70%
2	**18a**, 3 equiv.	MW, 250 °C, 10 min	**36a**, 60%
3	**18a**, 3 equiv.	Reflux, 4 h	**36a**, 36%
4	**18b**, 2 equiv.	MW, 250 °C, 10 min	**36b**, 53%
5	**18b**, 2.5 equiv.	MW, 250 °C, 10 min	**36b**, 53%
6	**18b**, 3 equiv.	MW, 250 °C, 10 min	**36b**, 69%
7	**18b**, 3 equiv.	Reflux, 4 h	**36b**, 54%

Table 6 Synthesis of hexacyclic steroids **37** and **38** from 16-dehydropregnenolone acetate



Entry	Sulfone	Reaction conditions	Isolated yield (**37** : **38**)
1	2 equiv.	MW, 250 °C, 10 min	33% (78 : 22)
2	2.5 equiv.	MW, 250 °C, 10 min	46% (76 : 24)
3	3 equiv.	MW, 250 °C, 10 min	49% (85 : 15)
4	3 equiv.	Reflux, 4 h	37% (85 : 15)

DFT calculations have been carried to determine the HOMO and LUMO energies of diazafulvenium methides **26**, **39**, **40** and **41** (Fig. 2). The dipole bearing two ester groups showed lower values than the mono-ester derivatives. On the other hand, dipole **39**, having the ester group at C-5, has FMO of lower energy than 4-carboxylate derivative **40**. Finally, the comparison of **40** and **41** allows us to conclude that the addition of a phenyl group at C-5 leads to an increase of the HOMO energy and a slight decrease of the LUMO energy. Considering the observed reactivity, the calculations indicate that in the [8π + 2π] cycloaddition of 16-DPA with diazafulvenium methides the $LUMO_{dipole}$–$HOMO_{dipolarophile}$ is the dominant interaction. In fact, the reaction of azafulvenium methide **40**, having a LUMO of higher energy, is significantly less efficient than the cycloaddition with 1,7-dipoles **26** and **39**. In the case of azafulvenium methide **41** no reaction was observed which indicates that steric factors must also be considered.

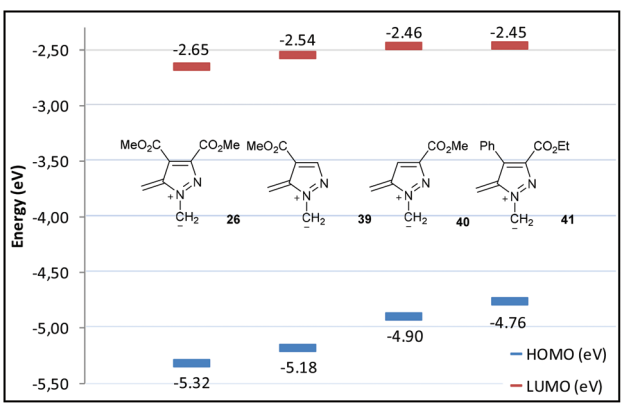
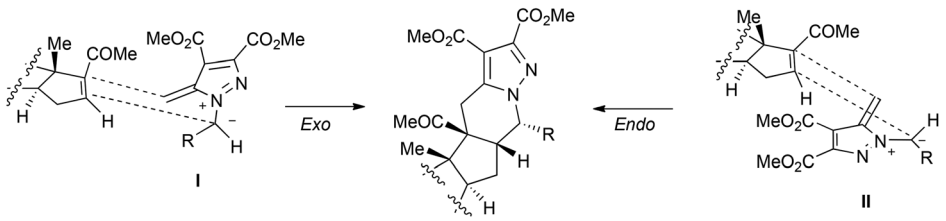


Fig. 2 HOMO–LUMO energies for diazafulvenium methides **26**, **39**, **40** and **41** calculated at the B3LYP/6-31G* level.

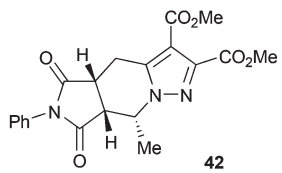
In order to be able to rationalize the stereoselectivity observed in the [8π + 2π] cycloadditions of 16-DPA towards 1-substituted diazafulvenium methides (**28** and **32**), quantum chemical calculations were carried out at the DFT level of theory (see ESI†). The cycloadducts, obtained exclusively or as the major product, could result from an *endo* cycloaddition of conformers **II** or alternatively could be formed *via* an *exo* cycloaddition of conformers **I**, which have the 1-substituent group pointing inward, considering the approach of the dipole by the less hindered α-face of the steroid (Scheme 4).

Cycloadditions of diazafulvenium methides **28** and **32** with *N*-phenylmaleimide (NPM) were selected as the model reac-

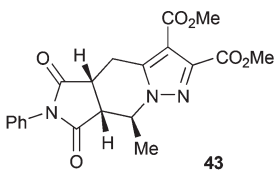


Scheme 4 *Exo* and *endo* [8π + 2π] cycloaddition of 16-DPA with 1-substituted diazafulvenium methides, considering the approach of the dipole by the α-face.

tions. The reaction of diazafulvenium methide **32** with NPM has been previously reported.[3c,e] Two racemic diastereoisomeric products were obtained: compound **42** isolated as the major product and compound **43**. The synthesis of these compounds was rationalized considering cycloadditions with *endo* selectivity but with the involvement of the two possible conformations of the 1-methyl-diazafulvenium methide. A microwave-induced reaction of 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*]-thiazole **24** in the presence of *N*-phenylmaleimide was carried out affording 1,7-cycloadduct **44** as a single product in 63% yield (Scheme 5).



42



43

The molecular structure of compound **44** was unambiguously established by X-ray crystallography (Fig. 3). This derivative crystallized as colorless plates in the triclinic system within the $P\bar{1}$ space group, showing two independent molecules per asymmetric unit. Three fused heterocyclic rings compose its molecular structure. There are three chiral centers (C4a, C7a, and C8a) in compound **44**, and its corresponding asymmetric unit cell is composed of a racemic mixture. The hydrogen atoms located at the C4A, C7A and C8 positions are *cis*, *i.e.* they are placed on the same faces of the fused rings. All distances and angles are within the expected values for similar compounds.[8]

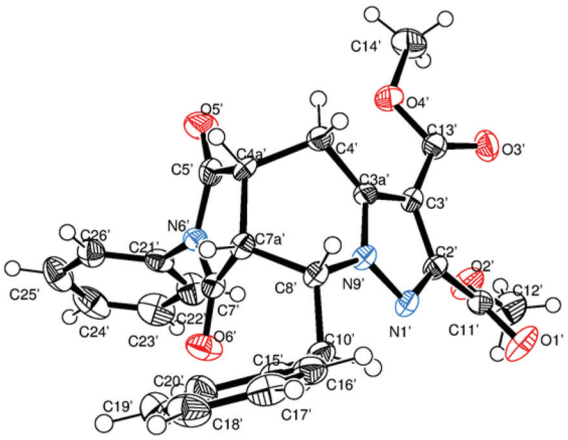
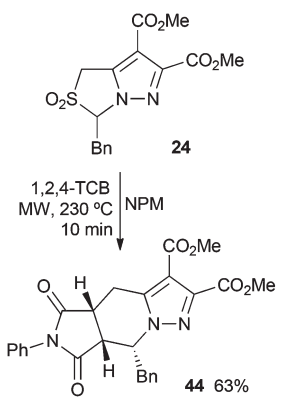


Fig. 3 ORTEP-3 diagram of compound **44**, using 50% probability level ellipsoids.



Scheme 5 Cycloaddition of diazafulvenium methide **28**, generated from 1*H*,3*H*-pyrazolo[1,5-*c*]thiazole-2,2-dioxide **24**, with *N*-phenylmaleimide.

The stereochemistry outcome of the [8π + 2π] cycloadditions of diazafulvenium methides **28** and **32** with NPM was the same as that observed in the reaction of these 1,7-dipoles with 16-DPA making the selected reactions for the theoretical study ideal models.

Therefore, quantum chemical calculations were carried out in order to investigate the reactivity of NPM and the 1-substituted diazafulvenium methides **28** and **32**. Calculations were performed using the Gamess[11] program package. Graphical representations were produced with Molden 5.0. All the calculations were conducted in the gas phase.

Since the cycloadducts, obtained as the major product, could result either from an *endo* cycloaddition of conformers **II** or *via* an *exo* cycloaddition of conformers **I**, the stability of the two conformations was explored through full optimization

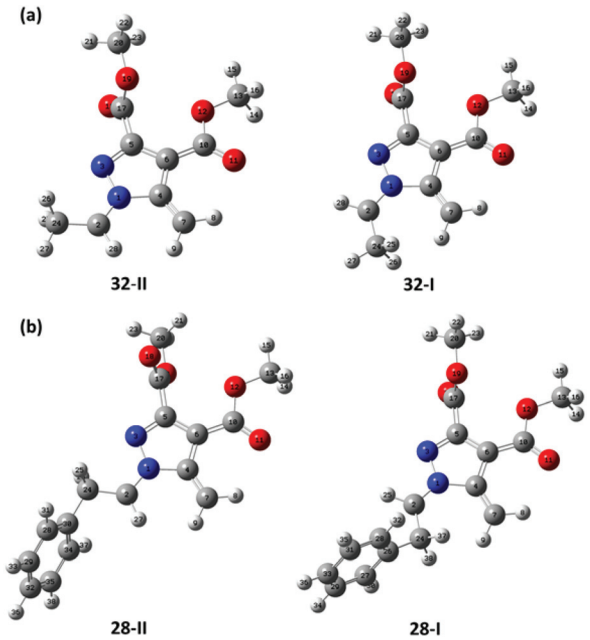


Fig. 4 Optimized geometries, at the DFT level, of the two conformers of the 1-substituted diazafulvenium methides **32** (panel a) and **28** (panel b). Color code: gray refers to carbon, red to oxygen, blue to nitrogen and white to hydrogen atoms.

at the DFT level of theory, using the B3LYP hybrid functional[12] and the standard 6-31G(d) basis set.

For compound **32** the conformer **II**, characterized by ϕ(C24–C2–N1–C4) = −179.8°, was found to be 14.6 kJ mol^{-1} more stable than conformer **I** with ϕ(C24–C2–N1–C4) = −0.2°. Similar results were found for compound **28**, for which the conformer **28b-II** with ϕ(C24–C2–N1–C4) = −179.3° is found to be 16.3 kJ mol^{-1} more stable than the counterpart **28a**-I with ϕ(C24–C2–N1–C4) = 0.6°. The final structures resulting from the DFT optimization are depicted in Fig. 4 for both compounds.

In this study, transition states resulting from the *endo*- and *exo*-cycloadditions of NPM, also optimized at the DFT level, with **32** and **28** were considered. In each case, full geometry optimizations of the transition structures were performed at the B3LYP/6-31G(d) level, followed by harmonic frequency calculations at the same level of theory, which confirmed the nature of the stationary points. The energy barriers corresponding to these transition states are reported in Table 7. The results include zero-point-energy (ZPE) and counterpoise basis set superposition error (BSSE) corrections. The optimized geometries of the more relevant transition structures for the referred cycloadditions are presented in Fig. 5. The results indicate that the barriers associated with the reactions involving the *exo* approach are, for both compounds, unfavorable by more than 20 kJ mol^{-1}, relative to the alternative approach.

Table 7 Energy barriers, ΔE of the transition states for the reaction of **32** and **28** with NPM, calculated at the B3LYP/6-31G(d) level of theory considering the lower energy conformer of each compound. Both ZPE and BSSE corrections were taken into account

Reaction	TS	ΔE (kJ mol^{-1})
32 + NPM	$TS1_{endo}$	30.6
	$TS2_{endo}$	33.2
	TS_{exo}	54.6
28 + NPM	TS_{endo}	28.4
	TS_{exo}	55.2

Conclusion

A strategy for the synthesis of a new class of chiral hexacyclic steroids has been reported. 16-Dehydropregnenolone acetate reacted with diazafulvenium methides *via* [8π + 2π] cycloaddition giving 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused steroids stereoselectively. 16-DPA acted as a chiral steroidal scaffold in the construction of the hexacyclic steroids *via* cycloaddition with substituted 1,7-dipoles.

Quantum chemical calculations at the DFT level, using the cycloaddition of 1-substituted diazafulvenium methides with *N*-phenylmaleimide as model reactions, indicate that diazafulvenium methides having the 1-substituent pointing outward are more stable than their counterpart with inward 1-substituent and that the barriers associated with the reactions involving the *exo* approach are unfavorable by more than 20 kJ mol^{-1}, relative to the alternative approach. Thus, cycloadducts obtained exclusively or as the major product are formed *via* an *endo* cycloaddition of the more stable dipole conformation, with the approach of the dipole by the less hindered α-face of the steroid.

Experimental section

General experimental methods

^{1}H NMR spectra were recorded on an instrument operating at 400 MHz. ^{13}C NMR spectra were recorded on an instrument operating at 100 MHz. The solvent is deuteriochloroform except where indicated otherwise. Chemical shifts are expressed in parts per million relative to internal standard TMS, and coupling constants (*J*) are in Hz. Infrared spectra (IR) were recorded on a Fourier transform spectrometer. High-resolution mass spectra (HRMS) were obtained on an electrospray (ESI) or electronic impact (EI) TOF mass spectrometer. Melting points were determined in open glass capillaries and are uncorrected. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Thin-layer chromatography (TLC) analyses were performed using precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase. Microwave reactions were carried out in a microwave reactor CEM Focused Synthesis System Discover S-Class using 10 mL microwave tubes. (4*R*)-2-Benzylthiazolidine-4-carboxylic acid (**20**),[13] dimethyl 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (**25**),[9] dimethyl 3-methyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (**31**)[3c] and 4*H*,6*H*-thiazolo[3,4-*c*][1,2,3]oxadiazol-7-ium-3-oxide (**15**)11 were prepared as described in the literature.

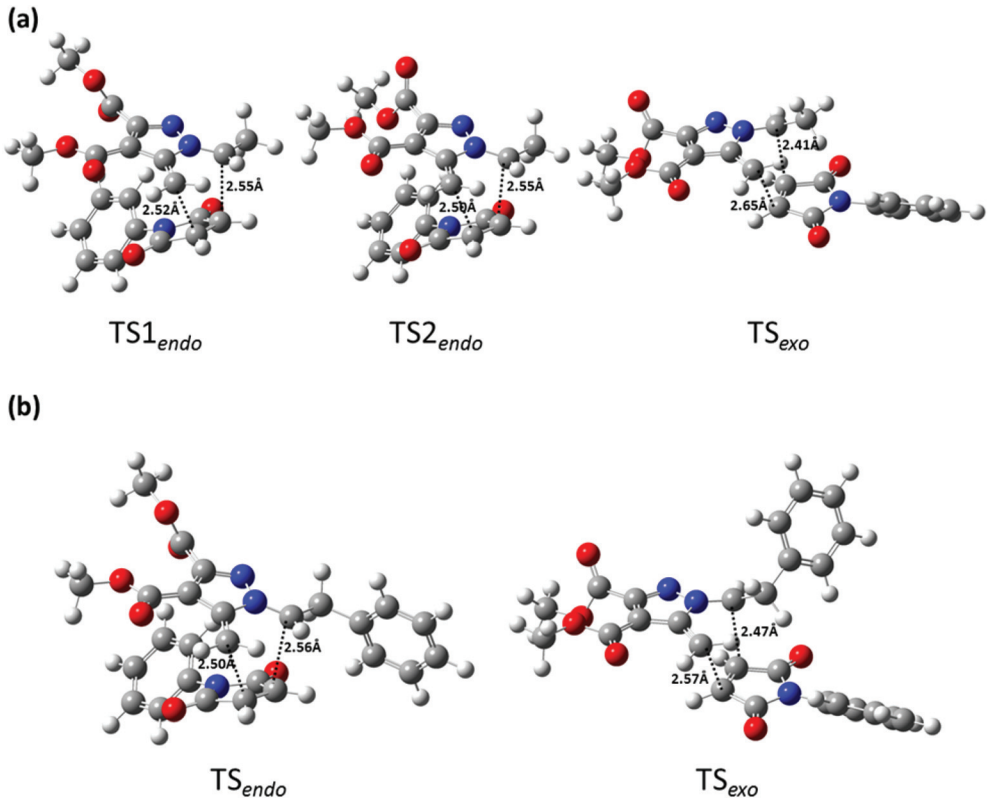


Fig. 5 Optimized geometries (B3LYP/6-31G(d) level) of the most relevant transition state structures found for the reaction (a) between **32** and NPM, and (b) between **28** and NPM. Color code: gray refers to carbon, red to oxygen, blue to nitrogen, and white to hydrogen atoms.

2-Benzyl-*N*-nitrosothiazolidine-4-carboxylic acid (21). To a stirred solution of (4*R*)-2-benzylthiazolidine-4-carboxylic acid (**20**) (10 g, 45 mmol) in DME (400 mL) is added isoamyl nitrite (9 mL, 67 mmol). The reaction mixture was stirred at room temperature for 16 h. After this time the solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate and was washed with 1 M HCl (3 × 10 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent was evaporated off. Purification of the crude product by flash chromatography [ethyl acetate–hexane (1 : 3), ethyl acetate–hexane (1 : 2) and ethyl acetate–hexane (1 : 2)] gave **21** as an orange oil (8.05 g, 71%): IR (film) ν 1234, 1438, 1452, 1737, 2940 and 3446 cm^{-1}. The ^1H NMR showed the presence of two conformational isomers (ratio 79 : 21): ^1H NMR: δ (*major isomer*) 2.79 (dd, 1H, J = 12.0 and 7.6 Hz), 2.98 (dd, 1H, J = 12.0 and 4.0 Hz), 3.45 (dd, 1H, J = 13.6 and 7.6 Hz), 3.73 (dd, 1H, J = 14.0 and 3.6 Hz), 4.89–4.93 (m, 1H), 5.93 (dd, 1H, J = 7.6 and 3.6 Hz), 7.19–7.34 (m, 5H). ^1H NMR: δ (*minor isomer*) 3.04 (dd, 1H, J = 13.6 and 2.4 Hz), 3.21–3.27 (m, 1H), 2.39 (dd, 1H, J = 7.2 and 5.2 Hz), 3.64 (dd, 1H, J = 14.0 and 6.4 Hz), 5.61–5.65 (m, 1H), 6.05 (dd, 1H, J = 8.8 and 6.4 Hz), 7.19–7.34 (m, 5H). HRMS (ESI-TOF) m/z for $C_{11}H_{13}N_2O_3S$ $[M + H]^+$ calcd 253.0641, found 253.0629.

6-Benzyl-4*H*,6*H*-thiazolo[3,4-*c*][1,2,3]oxadiazol-7-ium-3-oxide (22). Trifluoroacetic anhydride (3.1 mL, 21.65 mmol) was slowly added to a suspension of 2-benzyl-*N*-nitrosothiazolidine-4-carboxylic acid (**21**) (5.45 g, 21.65 mmol) in anhydrous diethyl ether (230 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h and then allowed to warm to room temperature. After stirring at room temperature for 24 h the solution was filtered and the solvent was evaporated off. Purification of the crude product by flash chromatography [ethyl acetate/hexane (1 : 2)] gave **22** as a yellow solid (4.56 g, 90%): mp 63.2–64.8 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −80 (c 0.25 in CH_2Cl_2). IR (KBr) ν 1026, 1309, 1512, 1523, 1728, 1739 and 1757 cm^{-1}. ^1H NMR: δ 3.39 (dd, 1H, J = 13.6 and 2.0 Hz), 3.48 (d, 2H, J = 5.2 Hz), 3.69 (d, 1H, J = 13.6 Hz), 5.96–5.99 (m, 1H), 7.20–7.21 (m, 2H), 7.31–7.33 (m, 3H). ^{13}C NMR: δ 24.6, 42.0, 68.1, 109.6, 128.3, 128.9, 129.8, 132.3, 163.1. HRMS (ESI-TOF) m/z for $C_{11}H_{11}N_2O_2S$ $[M + H]^+$ calcd 235.0536, found 235.0535.

General procedure for the synthesis of 1*H*,3*H*-pyrazolo[1,5-*c*]-[1,3]thiazole-carboxylates

The appropriate 4*H*,6*H*-thiazolo[3,4-*c*][1,2,3]oxadiazolium-3-oxide (6.94 mmol) and the dipolarophile (11.1 mmol) in xylene (10 mL) were heated at reflux under a N_2 atmosphere, for the time indicated in each case. The reaction was cooled to room temperature and the solvent was evaporated off.

Dimethyl 3-benzyl-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (23). Obtained from 6-benzyl-4*H*,6*H*-thiazolo-[3,4-*c*][1,2,3]oxadiazol-7-ium-3-oxide (**22**) (1.62 g, 6.94 mmol) and dimethyl acetylenedicarboxylate (1.36 mL, 11.1 mmol) as

described in the general procedure (reaction time: 3 h). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1 : 2) gave compound **23** as a yellow solid (1.61 g, 70%): mp 119.7–121.1 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −120 (*c* 1.0 in CH_2Cl_2). IR (KBr) ν 1074, 1142, 1228, 1321, 1437, 1556, 1693 and 1741 cm^{-1}. ^1H NMR: δ 3.36 (dd, 1H, *J* = 14.0 and 7.2 Hz), 3.54 (dd, 1H, *J* = 14.0 and 2.8 Hz), 3.70 (dd, 1H, *J* = 14.8 and 2.0 Hz), 3.80 (s, 3H), 3.99 (s, 3H), 4.03 (br s, 1H), 5.78–5.80 (m, 1H), 7.09–7.10 (m, 2H), 7.25–7.27 (m, 3H). ^{13}C NMR: δ 27.4, 42.6, 51.9, 52.7, 66.6, 108.2, 127.6, 128.5, 129.8, 134.0, 148.0, 149.3, 161.7, 161.8. HRMS (EI-TOF) *m*/*z* for $C_{16}H_{16}N_2O_4S$ $[M]^+$ calcd 332.0831, found 332.0833.

Ethyl 6-phenyl-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate (16a) and ethyl 7-phenyl-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate (17a). Obtained from 4*H*,6*H*-thiazolo[3,4-*c*]-[1,2,3]oxadiazol-7-ium-3-olate (**15**) (1 g, 6.94 mmol) and ethyl phenylpropiolate (1.83 mL, 11.1 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1 : 3) gave, in order of elution, **16a** as a white solid (0.86 g, 45%) and **17a** as a yellow solid (0.21 g, 11%).

Compound 16a: mp 80.0–81.4 °C (from ethyl acetate/hexane). IR (KBr) ν 1140, 1294, 1442, 1508 and 1712 cm^{-1}. ^1H NMR: δ 1.27 (t, 3H, *J* = 7.2 Hz), 4.24 (q, 2H, *J* = 7.2 Hz), 4.36 (s, 2H), 5.26 (s, 2H), 7.39–7.41 (m, 3H), 7.72–7.74 (m, 2H). ^{13}C NMR: δ 14.2, 29.3, 50.4, 60.2, 105.9, 127.8, 128.7, 129.2, 132.6, 149.4, 158.6, 162.7. HRMS (ESI-TOF) *m*/*z* for $C_{14}H_{15}N_2O_2S$ $[M + H]^+$ calcd 275.0849, found 275.0843.

Compound 17a: mp 73.7–74.4 °C (from ethyl acetate/hexane). IR (KBr) ν 1178, 1300, 1365, 1458 and 1724 cm^{-1}. ^1H NMR: δ 1.31 (t, 3H, *J* = 7.2 Hz), 4.11 (s, 2H), 4.33 (q, 2H, *J* = 7.2 Hz), 5.30 (s, 2H), 7.33–7.40 (m, 5H). ^{13}C NMR: δ 14.2, 26.9, 50.3, 61.0, 119.5, 127.5, 128.1, 129.3, 131.4, 143.2, 144.7, 162.2. HRMS (EI-TOF) *m*/*z* for $C_{14}H_{14}N_2O_2S$ $[M]^+$ calcd 274.0776, found 274.0777.

Methyl 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate (16b) and methyl 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate (17b). Obtained from 4*H*,6*H*-thiazolo[3,4-*c*][1,2,3]oxadiazol-7-ium-3-olate (**15**) (1 g, 6.94 mmol) and methyl propiolate (0.99 mL, 11.1 mmol) as described in the general procedure (reaction time: 4 h). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1 : 2) gave, in order of elution, **16b** as a white solid (0.27 g, 21%) and **17b** as a white solid (0.68 g, 53%).

Compound 16b: mp 111.2–112.0 °C (from ethyl acetate/hexane). IR (KBr) ν 1115, 1269, 1277, 1358, 1439, 1570 and 1697 cm^{-1}. ^1H NMR: δ 3.81 (s, 3H, H-9), 4.26 (br s, 2H, H-1), 5.19 (br s, 2H, H-3), 7.95 (s, 1H, H-6). ^{13}C NMR: δ 28.1 (C-1), 50.2 (C-3), 51.6 (C-9), 108.5 (C-7), 146.3 (C-6), 147.7 (C-7a), 163.2 (C-8). HRMS (EI-TOF) *m*/*z* for $C_7H_8N_2O_2S$ $[M]^+$ calcd 184.0306, found 184.0313.

Compound 17b: mp 100.1–100.7 °C (from ethyl acetate/hexane). IR (KBr) ν 1205, 1234, 1248, 1471, 1485 and 1712 cm^{-1}. ^1H NMR: δ 3.89 (s, 3H, H-9), 4.09 (br s, 2H, H-1), 5.20 (br s, 2H, H-3), 6.57 (br s, 1H, H-7). ^{13}C NMR: δ 26.9 (C-1), 49.9 (C-3), 52.2 (C-9), 102.8 (C-7), 144.6 (C-7a), 148.7 (C-6), 162.6 (C-8). HRMS (EI-TOF) *m*/*z* for $C_7H_8N_2O_2S$ $[M]^+$ calcd 184.0306, found 184.0301.

General procedure for the synthesis of 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-carboxylates

To a stirred ice-cold solution of the appropriate pyrazolo[1,5-*c*]-[1,3]thiazole-carboxylate (3.94 mmol) in dry dichloromethane (30 mL) was added portionwise 3-chloroperoxybenzoic acid (3 eq., 11.8 mmol) under dry nitrogen. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for the time indicated in each case, the reaction mixture was washed twice with 10% (w/v) aqueous sodium bisulfite solution (2 × 80 mL) and twice with 10% (w/v) aqueous sodium bicarbonate solution (2 × 80 mL). The organic fraction was then dried over anhydrous $NaSO_4$ and the solvent was evaporated off.

Dimethyl 3-benzyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (24). Obtained from dimethyl 3-benzyl-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (**23**) (1.31 g, 3.94 mmol) as described in the general procedure (reaction time: 4 h). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1 : 2) gave compound **24** as a white solid (1.02 g, 71%): mp 148.6–150.1 °C (from diethyl ether). $[\alpha]_D^{25}$ −10 (*c* 1.0 in CH_2Cl_2). IR (KBr) ν 1145, 1155, 1253, 1350, 1475, 1576, 1705 and 1728 cm^{-1}. ^1H NMR: δ 3.57 (dd, 1H, *J* = 14.8 and 8.0 Hz), 3.78 (dd, 1H, *J* = 14.8 and 2.4 Hz), 3.80 (s, 3H), 3.97 (d, 1H, *J* = 16.4 Hz), 4.01 (s, 3H), 4.47 (d, 1H, *J* = 16.4 Hz), 5.36 (dd, 1H, *J* = 8.0 and 2.8 Hz), 7.19–7.20 (m, 2H), 7.28–7.30 (m, 3H). ^{13}C NMR: δ 35.2, 52.1, 52.3, 53.0, 77.5, 111.7, 128.2, 128.9, 130.0, 131.5, 138.7, 146.2, 160.8, 161.4. HRMS (ESI-TOF) *m*/*z* for $C_{16}H_{17}N_2O_6S$ $[M + H]^+$ calcd 365.0802, found 365.0802.

Ethyl 6-phenyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate (18a). Obtained from ethyl 6-phenyl-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate (**16a**) (1.08 g, 3.94 mmol) as described in the general procedure (reaction time: 24 h). The product was obtained as a white solid which was recrystallised with ethyl ether (0.94 g, 78%): mp 139.7–140.1 °C (from diethyl ether). IR (KBr) ν 1109, 1133, 1169, 1346, 1475 and 1714 cm^{-1}. ^1H NMR: δ 1.28 (t, 3H, *J* = 7.2 Hz), 4.26 (q, 2H, *J* = 7.2 Hz), 4.72 (s, 2H), 5.25 (s, 2H), 7.43 (br s, 3H), 7.72 (br s, 2H). ^{13}C NMR: δ 14.2, 54.2, 60.8, 67.4, 109.3, 128.0, 129.3, 129.4, 131.2, 139.6, 156.3, 161.7. HRMS (ESI-TOF) *m*/*z* for $C_{14}H_{13}N_2O_4S$ $[M - H]^+$ calcd 305.0596, found 305.0599.

Ethyl 7-phenyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate (19a). Obtained from ethyl 7-phenyl-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate (**17a**) (1.08 g, 3.94 mmol) as described in the general procedure (reaction time: 24 h). The product was obtained as a white solid which was recrystallised with ethyl ether (0.58 g, 48%): mp 174.3–175.1 °C (from diethyl ether). IR (KBr) ν 1128, 1157, 1180, 1338 and 1734 cm^{-1}. ^1H NMR: δ 1.31 (t, 3H, *J* = 7.2 Hz), 4.35 (q, 2H, *J* = 7.2 Hz), 4.48 (s, 2H), 5.31 (s, 2H), 7.35–7.43 (m, 5H). ^{13}C NMR: δ 14.1, 52.2, 61.5, 67.7, 122.9, 128.3, 128.4, 129.3, 129.9, 133.7, 143.3, 161.3. HRMS (ESI-TOF) *m*/*z* for $C_{14}H_{14}N_2NaO_4S$ $[M + Na]^+$ calcd 329.0566, found 329.0565.

Methyl 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate (18b). Obtained from methyl 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]-thiazole-7-carboxylate (**16b**) (0.73 g, 3.94 mmol) as described in the general procedure (reaction time: 4 h). The product was obtained as a white solid which was recrystallised with ethyl ether (0.65 g, 77%): mp 160.2–160.5 °C (from diethyl ether). IR (KBr) ν 1034, 1107, 1138, 1215, 1255, 1334, 1381, 1483, 1572 and 1724 cm^{-1}. ^1H NMR: δ 3.85 (s, 3H), 4.66 (s, 2H), 5.21 (s, 2H), 8.07 (s, 1H). ^{13}C NMR: δ 52.1, 53.3, 67.5, 112.2, 137.8, 143.8, 162.2. HRMS (ESI-TOF) *m*/*z* for $C_7H_9N_2O_4S$ $[M + H]^+$ calcd 217.0278, found 217.0274.

Methyl 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6-carboxylate (19b). Obtained from methyl 1*H*,3*H*-pyrazolo[1,5-*c*][1,3]-thiazole-6-carboxylate (**17b**) (0.73 g, 3.94 mmol) as described in the general procedure (reaction time: 4 h). The product was obtained as a white solid which was recrystallised with ethyl ether (0.69 g, 81%): mp 200.9–201.7 °C (from diethyl ether). IR (KBr) ν 1144, 1198, 1248, 1350, 1450, 1481 and 1726 cm^{-1}. ^1H NMR: δ 3.95 (s, 3H), 4.51 (s, 2H), 5.25 (s, 2H), 6.86 (s, 1H). ^{13}C NMR: δ 52.4, 52.6, 67.4, 106.3, 135.2, 146.8, 161.8. HRMS (ESI-TOF) *m*/*z* for $C_7H_9N_2O_4S$ $[M + H]^+$ calcd 217.0278, found 217.0277.

General procedure for the [8π + 2π] cycloadditions of diazafulvenium methides with 16-DPA

Method A. A suspension of 16-DPA (0.28 mmol) and the appropriate sulfone (1–3 equiv.) in 1,2,4-trichlorobenzene (1 mL) was irradiated in the microwave reactor at 250 °C, for the time indicated in each case. After cooling to room temperature, the reaction mixture was purified by flash chromatography [hexane] to remove 1,2,4-trichlorobenzene followed by elution with ethyl acetate–hexane.

Method B. A suspension of 16-DPA (0.28 mmol) and the appropriate sulfone (1–3 equiv.) in 1,2,4-trichlorobenzene (1 mL) was heated at reflux under dry nitrogen, for the time indicated in each case. After cooling to room temperature, the mixture was purified by flash chromatography [hexane] to remove 1,2,4-trichlorobenzene followed by elution with ethyl acetate–hexane.

Dimethyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate fused to 16-dehydropregnenolone acetate (27). Obtained from dimethyl 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*]-[1,3]thiazole-6,7-dicarboxylate (**25**).[11] Purification of the crude product by flash chromatography [hexane, ethyl acetate/hexane (1 : 2)] gave compound **27** as a white solid (Method A: 116 mg, 73%; Method B: 120 mg, 76%): mp 258.1–260.2 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −30 (*c* 0.5 in CH_2Cl_2). IR (KBr) ν 1084, 1221, 1249, 1493, 1693, 1728 and 1740 cm^{-1}. ^1H NMR: δ 0.75 (s, 3H, H-18), 0.90–0.97 (m, 1H), 1.01 (s, 3H, H-19), 1.11–1.57 (m, 7H), 1.63–1.97 (m, 7H), 2.02 (s, 3H, H-23), 2.20 (s, 3H, H-21), 2.25–2.35 (m, 2H), 3.28 (d, 1H, *J* = 16.0 Hz, H-32), 3.34 (d, 1H, *J* = 16.0 Hz, H-32), 3.69–3.72 (m, 1H, H-16), 3.80 (dd, 1H, *J* = 13.2 and 5.6 Hz, H-24), 3.86 (s, 3H, H-27), 3.92 (s, 3H, H-30), 4.32 (dd, 1H, *J* = 13.2 and 6.4 Hz, H-24), 4.55–4.63 (m, 1H, H-3), 5.33 (d, 1H, *J* = 4.0 Hz, H-6). ^{13}C NMR: δ 16.6, 19.3, 20.7, 21.4, 24.8, 27.6, 27.7, 31.1, 31.8, 31.8, 33.0, 36.1, 36.5, 36.9, 38.0, 46.1, 49.3, 51.4, 51.8, 52.3, 52.5, 66.4, 73.7, 110.5, 121.9, 139.7, 142.4, 143.4, 162.3, 163.2, 170.5, 207.6. HRMS (ESI-TOF) *m*/*z* for $C_{32}H_{43}N_2O_7$ $[M + H]^+$ calcd 567.3065, found 567.3049.

Dimethyl (*S*)-7-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate fused to 16-dehydropregnenolone acetate (30) and dimethyl 5-methyl-1-styryl-1*H*-pyrazole-3,4-dicarboxylate (29). Obtained from dimethyl 3-benzyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (**24**). Purification of the crude product by flash chromatography [hexane, ethyl acetate/hexane (1 : 2) and (1 : 1)] gave, in order of elution, **29** as a white solid (Method A: 44 mg, 35%; Method B: 23.1 mg, 18%) and **30** as a white solid (Method A: 63.7 mg, 35%; Method B: 61.9 mg, 34%).

Compound 30: mp 113.7–115.4 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −50 (*c* 0.5 in CH_2Cl_2). IR (KBr) ν 1176, 1213, 1243, 1454, 1705 and 1732 cm^{-1}. ^1H NMR: δ 0.65 (s, 3H, H-18), 0.68–0.71 (m, 1H), 0.96 (s, 3H, H-19), 1.08–1.36 (m, 7H), 1.54–1.69 (m, 2H), 1.81–1.88 (m, 5H), 2.02 (s, 3H, H-23), 2.14 (s, 3H, H-21), 2.23–2.29 (m, 2H), 2.39 (d, 1H, *J* = 17.6 Hz, H-32), 3.04 (dd, 1H, *J* = 13.6 and 10.4 Hz, H-33), 3.36 (br d, 1H, *J* = 9.6 Hz, H-16), 3.89 (s, 3H, H-27), 3.96 (s, 3H, H-30), 4.01 (br d, 1H, *J* = 4.0 Hz, H-33), 4.12 (d, 1H, *J* = 16.8 Hz, H-32), 4.22 (br d, 1H, *J* = 7.2 Hz, H-24), 4.54–4.58 (m, 1H, H-3), 5.29 (br s, 1H, H-6), 7.28 (br d, 3H, *J* = 7.2 Hz), 7.34–7.37 (m, 2H). ^{13}C NMR: δ 16.6, 19.2, 20.7, 21.4, 23.3, 25.2, 27.4, 27.6, 31.7, 32.0, 32.7, 35.4, 36.4, 36.8, 37.9, 40.7, 46.6, 49.1, 51.8, 52.4, 52.6, 60.7, 65.5, 73.7, 110.0, 122.0, 126.9, 128.7, 129.1, 136.9, 139.5, 142.6, 144.3, 163.0, 163.4, 170.5, 208.0. HRMS (ESI-TOF) *m*/*z* for $C_{39}H_{49}N_2O_7$ $[M + H]^+$ calcd 657.3534, found 657.3519.

Compound 29: mp 126.0–127.9 °C (from ethyl acetate/hexane). IR (KBr) ν 1217, 1392, 1556, 1718 and 1739 cm^{-1}. ^1H NMR: δ 2.63 (s, 3H), 3.86 (s, 3H), 3.97 (s, 3H), 7.27–7.47 (m, 7H). ^{13}C NMR: δ 10.6, 51.9, 52.7, 112.9, 121.2, 123.1, 126.7, 128.5, 128.9, 134.2, 143.0, 144.5, 162.8, 163.1. HRMS (EI-TOF) *m*/*z* for $C_{16}H_{16}N_2O_4$ $[M]^+$ calcd 300.1110, found 300.1111.

Dimethyl (*S*)-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate fused to 16-dehydropregnenolone acetate (34), dimethyl (*R*)-7-methyl-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyridine-2,3-dicarboxylate fused to 16-dehydropregnenolone acetate (35) and dimethyl 5-methyl-1-vinyl-1*H*-pyrazole-3,4-dicarboxylate (33). Obtained from dimethyl 3-methyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (**31**).[3c] Purification of the crude product by flash chromatography [hexane, ethyl acetate/hexane (1 : 2) and (1 : 1)] gave, in order of elution, **33** [3c] as a white solid (Method A: 7.2 mg, 11%; Method B: 4.6 mg, 7%) and **34**/**35** as a mixture of diastereoisomers [Method A: 61.6 mg, 37% (75 : 25); Method B: 66.1 mg, 41% (98 : 2)].

Major component (**34**): $[\alpha]_D^{25}$ −30 (*c* 0.5 in CH_2Cl_2). IR (film) ν 1030, 1248, 1477, 1701, 1718, 1730 and 1741 cm^{-1}. ^1H NMR: δ 0.75 (s, 3H, H-18), 0.79–0.89 (m, 1H), 0.97 (s, 3H, H-19), 1.07–1.63 (m, 10H), 1.69 (d, 3H, *J* = 6.4 Hz, H-33), 1.75–1.93 (m, 4H), 2.01 (s, 3H, H-23), 2.21 (s, 3H, H-21), 2.25–2.28 (m, 2H), 2.45 (d, 1H, *J* = 16.8 Hz, H-32), 3.46 (br d, 1H, *J* = 10.8 Hz, H-16), 3.87 (s, 3H, H-27), 3.93 (s, 3H, H-30), 4.07–4.11 (m, 2H,

H-24 and H-32), 4.52–4.59 (m, 1H, H-3), 5.27 (br d, 1H, J = 3.6 Hz, H-6). ^{13}C NMR: δ 16.0, 16.7, 19.4, 20.9, 21.5, 23.5, 25.5, 27.6, 27.8, 31.8, 32.2, 32.9, 36.6, 36.9, 38.1, 43.8, 46.7, 49.2, 51.9, 52.5, 52.7, 55.3, 65.7, 73.8, 110.0, 122.2, 139.6, 142.7, 144.1, 163.1, 163.6, 170.6, 208.0. HRMS (ESI-TOF) m/z for $C_{33}H_{45}N_2O_7$ $[M + H]^+$ calcd 581.3221, found 581.3206.

Minor component (**35**): ^{1}H NMR: δ 0.72 (s, 3H, H-18′), 0.78–0.85 (m, 1H), 1.01 (s, 3H, H-19′), 1.06–1.59 (m, 10H), 1.67 (d, 3H, J = 6.4 Hz, H-33′), 1.74–1.92 (m, 4H), 2.02 (s, 3H, H-23′), 2.16 (s, 3H, H-21′), 2.24–2.31 (m, 2H), 2.96 (d, 1H, J = 15.2 Hz, H-32′), 3.32 (t, 1H, J = 18.0 Hz, H-24′), 3.65–3.68 (m, 1H, H-16′), 3.73 (d, 1H, J = 15.6 Hz, H-32′), 3.83 (s, 3H), 3.90 (s, 3H), 4.51–4.61 (m, 1H, H-3′), 5.35 (br d, 1H, J = 4.4 Hz, H-6′).

Ethyl 2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-3-carboxylate fused to 16-dehydropregnenolone acetate (36a). Obtained from ethyl 6-phenyl-2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*]-[1,3]thiazole-7-carboxylate (**18a**). Purification of the crude product by flash chromatography [hexane, ethyl acetate/hexane (1 : 4)] gave compound **36a** as a white solid (Method A: 117 mg, 70%; Method B: 60.3 mg, 36%): mp 110.1–111.9 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −50 (c 0.5 in CH_2Cl_2). IR (KBr) ν 1032, 1130, 1248, 1452, 1701, 1716 and 1729 cm^{-1}. ^{1}H NMR: δ 0.78 (s, 3H), 0.92–0.98 (m, 1H), 1.02 (s, 3H), 1.12–1.15 (m, 1H), 1.21 (t, 3H, J = 7.2 Hz), 1.26–1.54 (m, 6H), 1.62–1.79 (m, 2H), 1.86–1.94 (m, 5H), 2.03 (s, 3H), 2.23 (s, 3H), 2.29–2.32 (m, 2H), 3.38 (d, 1H, J = 16.4 Hz), 3.44 (d, 1H, J = 16.8 Hz), 3.70–3.72 (m, 1H), 3.84 (dd, 1H, J = 13.2 and 6.4 Hz), 4.22 (q, 2H, J = 7.2 Hz), 4.30 (dd, 1H, J = 13.2 and 6.4 Hz), 4.58–4.62 (m, 1H), 5.34 (d, 1H, J = 3.2 Hz), 7.35–7.37 (m, 3H), 7.59 (br d, 2H, J = 6.8 Hz). ^{13}C NMR: δ 14.1, 16.6, 19.3, 20.7, 21.4, 25.3, 27.7, 27.8, 31.2, 31.8, 31.9, 33.0, 36.3, 36.5, 36.9, 38.0, 46.2, 49.4, 51.0, 52.3, 59.9, 66.3, 73.7, 107.5, 122.0, 127.6, 128.1, 129.5, 133.1, 139.7, 143.7, 152.6, 163.9, 170.5, 208.2. HRMS (ESI-TOF) m/z for $C_{37}H_{47}N_2O_5$ $[M + H]^+$ calcd 599.3479, found 599.3471.

Methyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-3-carboxylate fused to 16-dehydropregnenolone acetate (36b). Obtained from methyl 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate (**18b**). Purification of the crude product by flash chromatography [hexane, ethyl acetate/hexane (1 : 2)] gave compound **36b** as a white solid (Method A: 98.2 mg, 69%; Method B: 76.8 mg, 54%): mp 219.5–220.3 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −30 (c 0.5 in CH_2Cl_2). IR (KBr) ν 1032, 1201, 1248, 1383, 1493, 1697, 1712 and 1728 cm^{-1}. ^{1}H NMR: δ 0.74 (s, 3H), 0.84–0.94 (m, 1H), 0.99 (s, 3H), 1.09–1.64 (m, 7H), 1.68–1.95 (m, 7H), 2.01 (s, 3H), 2.18 (s, 3H), 2.27–2.34 (m, 2H), 3.33 (s, 2H), 3.63–3.68 (m, 1H), 3.75–3.78 (m, 1H), 3.81 (s, 3H), 4.26 (dd, 1H, J = 13.2 and 6.4 Hz), 4.54–4.61 (m, 1H), 5.31 (br d, 1H, J = 3.6 Hz), 7.74 (s, 1H). ^{13}C NMR: δ 16.6, 19.3, 20.7, 21.4, 24.7, 27.6, 27.7, 31.2, 31.8, 31.8, 33.0, 36.4, 36.5, 36.9, 38.0, 46.1, 49.3, 51.0, 51.1, 52.3, 66.6, 73.7, 109.8, 121.9, 139.7, 140.2, 142.2, 164.0, 170.5, 208.1. HRMS (ESI-TOF) m/z for $C_{30}H_{41}N_2O_5$ $[M + H]^+$ calcd 509.3010, found 509.3007.

Methyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2-carboxylate fused to 16-dehydropregnenolone acetate (37/38). Obtained from methyl 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-7-carboxylate (**19b**). Purification of the crude product by flash chromatography [hexane, ethyl acetate/hexane (1 : 2)] gave compounds **37**/**38** as a mixture of regioisomers [Method A: 69.7 mg, 49% (85 : 15); Method B: 52.6 mg, 37% (85 : 15)].

Major component (**37**): IR (KBr) ν 1032, 1115, 1268, 1358, 1439, 1570 and 1697 cm^{-1}. ^{1}H NMR: δ 0.73 (s, 3H), 0.86–0.96 (m, 1H), 0.99 (s, 3H), 1.09–1.73 (m, 11H), 1.84–1.95 (m, 3H), 2.01 (s, 3H), 2.10 (s, 3H), 2.24–2.34 (m, 2H), 2.92 (d, 1H, J = 15.6 Hz), 3.07 (d, 1H, J = 15.6 Hz), 3.62–3.68 (m, 1H), 3.82–3.84 (m, 1H), 3.88 (s, 3H), 4.33 (dd, 1H, J = 13.2 and 6.4 Hz), 4.50–4.61 (m, 1H), 5.31 (d, 1H, J = 4.0 Hz), 6.56 (s, 1H). ^{13}C NMR: δ 16.6, 19.2, 20.6, 21.4, 25.5, 27.6, 27.9, 31.2, 31.78, 31.81, 33.0, 36.5, 36.7, 36.9, 37.9, 46.2, 49.3, 51.4, 51.9, 52.2, 66.7, 73.7, 105.4, 121.9, 139.0, 139.6, 142.1, 162.9, 170.5, 208.0. HRMS (ESI-TOF) m/z for $C_{30}H_{41}N_2O_5$ $[M + H]^+$ calcd 509.3010, found 509.3003.

Minor component (**38**): ^{1}H NMR: δ 0.72 (s, 3H), 0.86–0.96 (m, 1H), 1.00 (s, 3H), 1.09–1.73 (m, 11H), 1.84–1.95 (m, 3H), 2.02 (s, 3H), 2.17 (s, 3H), 2.24–2.34 (m, 2H), 2.36–2.40 (m, 1H), 3.12–3.16 (m, 1H), 3.43–3.50 (m, 1H), 3.87 (s, 3H), 4.23 (d, 1H, J = 14.0 Hz), 4.66 (d, 1H, J = 14.0 Hz), 5.34 (d, 1H, J = 4.4 Hz), 6.49 (s, 1H). ^{13}C NMR: δ 16.5, 19.2, 20.5, 21.4, 28.2, 28.3, 31.7, 31.8, 32.7, 33.8, 34.4, 36.6, 38.0, 45.7, 49.7, 51.8, 52.2, 69.3, 121.9, 139.7, 140.5, 142.4, 162.9, 207.4.

(4a*R*,7a*R*,8a*R*)-Dimethyl 8-benzyl-5,7-dioxo-6-phenyl-4a,5,6,7,7a,8-hexahydro-1H,3H-pyrazolo[1,5-*a*]pyrrolo[3,4-*d*]pyridine-2,3-dicarboxylate (44). A suspension of sulfone **24** (0.5 mmol) and *N*-phenylmaleimide (1 mmol) in 1,2,4-trichlorobenzene (1 mL) was irradiated in the microwave reactor at 230 °C, for 10 min. After cooling to room temperature, the mixture was purified by flash chromatography [hexane, ethyl acetate–hexane (1 : 2 and then (1 : 9)] to give compound **44** as a white solid (63%). mp 217.3–218.4 °C (from ethyl acetate/hexane). IR (KBr) ν 1221, 1392, 1489, 1712 and 1738 cm^{-1}. ^{1}H NMR: δ 3.21 (dd, 1H, J = 16.4 and 7.6 Hz), 3.47–3.80 (m, 2H), 3.83–3.86 (m, 1H), 3.85 (s, 3H), 3.93 (s, 3H), 4.64–4.69 (m, 1H), 7.04–7.07 (m, 2H), 7.27–7.46 (m, 8H). ^{13}C NMR: δ 22.7, 33.4, 38.3, 42.3, 52.0, 52.7, 59.3, 112.0, 126.3, 127.4, 128.9, 129.1, 129.3, 129.7, 131.1, 135.9, 141.5, 143.4, 162.3, 162.5, 173.3, 176.0. HRMS (EI-TOF) m/z for $C_{26}H_{23}N_3O_6$ $[M]^+$ calcd 473.1587, found 473.1584.

Procedure for the synthesis of dimethyl 5-methyl-1-styryl-1*H*-pyrazole-3,4-dicarboxylate (29)

A suspension of compound **24** (0.100 g, 0.27 mmol) in 1,2,4-trichlorobenzene (1 mL) was irradiated in the microwave reactor at 250 °C, for 15 min. After cooling to room temperature, the reaction mixture was purified by flash chromatography [hexane, ethyl acetate–hexane (1 : 2)] to give the styryl-1*H*-pyrazole-3,4-dicarboxylate **29** as a white solid (77%). Compound **29** was identified by comparison with the specimen previously isolated (see above).

X-ray diffraction

Crystals of compounds **18a** and **44** were selected, covered with polyfluoroether oil, and mounted on a nylon loop. Crystallographic data for this compound was collected at the IST using

graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) on a Bruker AXS-KAPPA APEX II diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat, at 150 K. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT on all observed reflections. Absorption corrections were applied using SADABS.[14] Structure solution and refinement were performed using direct methods with the programs SIR2004[15] or SIR2014[16] included in the package of programs WINGX-Version 2014.1[17] and SHELXL.[18] All hydrogen atoms were inserted in idealised positions and allowed to refine riding on the parent carbon atom, with C–H distances of 0.95 Å, 0.98 Å, 0.99 Å and 1.00 Å for aromatic, methyl, methylene and methine H atoms, respectively, and with $U_{iso}(H) = 1.2U_{eq}(C)$. The figures of the molecular structure were generated using ORTEP-III.[19]

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