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Reactivity of steroidal 1-azadienes toward enamines: an approach to novel chiral penta- and hexacyclic steroids†

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The chemical behavior of steroidal *N*-sulfonyl-1-azadienes toward carbonyl compounds, in the presence of pyrrolidine, is described. With aldehydes, these azadienes participate in hetero-Diels–Alder reactions with the *in situ* generated enamines. The stereoselectivity results from the approach of the dienophiles from the less hindered α-face of the steroid, with the pyrrolidine moiety *endo* and retention of the enamine *trans* geometry. This diastereoselective synthetic methodology led to a new class of chiral pentacyclic steroids. Interestingly, the studied steroidal scaffolds follow a different mechanistic pathway with cyclic ketones. They undergo a diastereoselective annulation reaction, under enamine catalysis, affording chiral hexacyclic steroids.

Introduction

Steroids are a class of compounds widely distributed in nature, exhibiting a wide spectrum of biological activities, namely as anti-cancer agents, enzyme inhibitors, antiestrogens and as neuroprotection agents.[1–5] The structural modification of the steroidal core is a strategy successfully used to modulate their biological properties.[6] In this context, one of the most promising transformations is the introduction of side chains/heterocycles or fused heterocycles at positions C16 and/or C17 of the D-ring.[7–12] Our own contribution in this field includes the synthesis of new chiral hexacyclic steroids derived from 16-dehydropregnenolone acetate (16-DPA) and other steroidal scaffolds through [8π + 2π] cycloaddition reactions with diazafulvenium methides.[13–15] These synthetic steroids and subsequent transformations afforded compounds with interesting anti-cancer activity against EL4 (murine T-lymphoma) and prostate cancer cell lines.[14,15] Interestingly, it was demonstrated that the new tetrahydropyrazolo[1,5-*a*]pyridine-fused steroids have the ability to suppress the expression of known androgen receptor targets, Nkx3.1 and PSA in two prostate cell lines, 22Rv1 and VCaP. Docking studies with the more promising molecule revealed binding to androgen receptor (PDB: 1T7T) similar to antiandrogen galeterone.[15]

1-Azadienes are largely used as building blocks in the synthesis of a wide range of cyclic and acyclic nitrogen-containing compounds.[16–18] Despite their participation in several transformations,[19–26] the most explored reactivity of these intermediates is their participation in hetero-Diels–Alder reactions.[27–32] Thus, electron-deficient 1-azadienes, which includes *N*-sulfonyl-1-azadienes, participate in inverse electron-demand hetero-Diels–Alder reactions with electron rich dienophiles.[33–35]

Interestingly, previous studies of our research group on the reactivity of steroidal *N*-sulfonyl-1-azadiene derived from 16-DPA toward ketones, under enamine catalysis, led to the development of a diastereoselective synthetic route to chiral penta- and hexacyclic steroids through an unexpected annulation reaction (Scheme 1a).[36]

Herein, reactions of steroidal 1-azadienes toward carbonyl compounds, in the presence of pyrrolidine, are further explored uncovering an interesting reactivity pattern (Scheme 1).

Results and discussion

Steroidal *N*-sulfonyl-1-azadienes **2** and **6** derived from 16-dehydropregnenolone acetate (16-DPA) and 16-dehydroprogesterone, respectively, were selected to carry out the reactivity study. Steroidal 1-azadiene **2** was obtained from commercial available 16-DPA, as described in our previous communication (Scheme 2).[36]

The synthetic route to steroidal *N*-sulfonyl-1-azadiene **6** is outlined in Scheme 3. 16-Dehydropregnenolone (16-DHP) was obtained from 16-DPA by acetate group's hydrolysis using sodium hydroxide in *tert*-butanol.[14] The oximation reaction of

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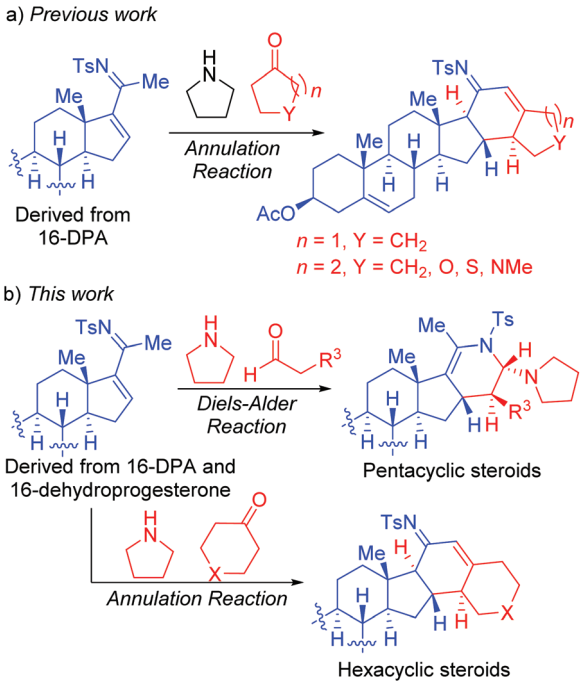
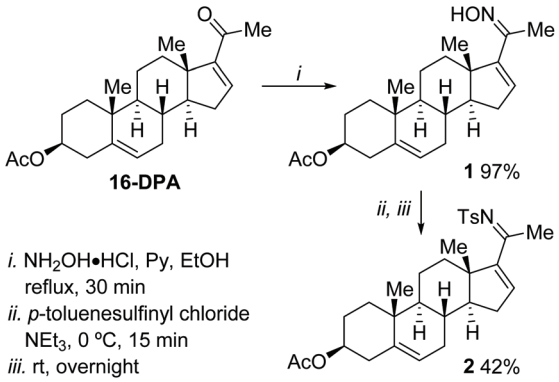


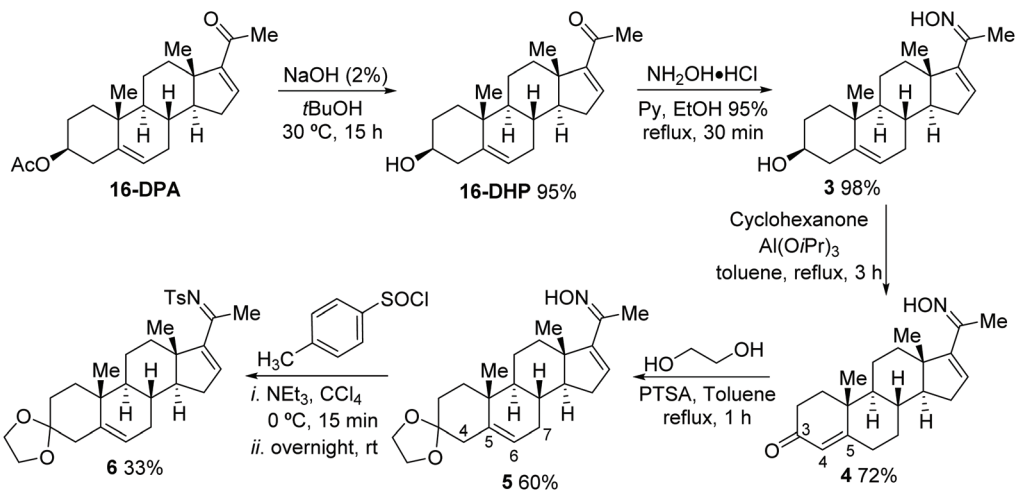
Scheme 1 Reactivity of steroidal 1-azadienes toward (a) ketones and (b) aldehydes in presence of pyrrolidine.



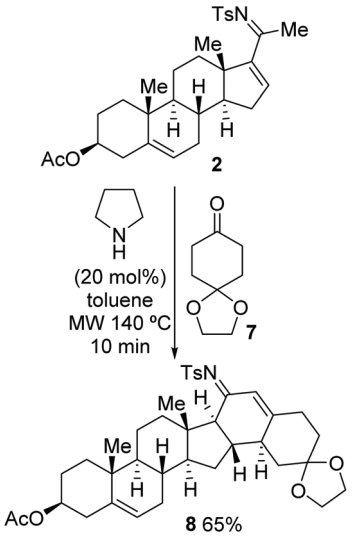
Scheme 2 Synthesis of steroidal *N*-sulfonyl-1-azadiene **2**.[36]

16-DHP, with hydroxylamine hydrochloride in the presence of pyridine, led to oxime derivative **3** in high yield (98%). Steroid **4** was synthesized in 72% yield by Oppenauer oxidation of oxime **3** using aluminium isopropoxide and cyclohexanone. To avoid any secondary reactions, the carbonyl group of steroid **4** was protected through the reaction with ethylene glycol in refluxing toluene, in the presence of *p*-toluenesulfonic acid (PTSA),[37] leading to compound **5** in 60% yield. Under these reaction conditions, the protection of the carbonyl group was accomplished together with the isomerization of the double bond to position 5, as described in the literature for other steroidal derivatives.[37–40] The structural assignment of compounds **4** and **5** was supported by NMR data. The ^{1}H NMR spectrum (400 MHz) of compound **4** shows the vinylic proton H-4 as a singlet at 5.64 ppm whereas in the case of compound **5**, a vinylic proton corresponding to proton H-6 is observed as a pseudo doublet (5.24 ppm). Furthermore, the COSY NMR spectrum (400 MHz) of compound **5** confirmed the coupling between protons H-6 and H-7 (see ESI†). Finally, steroid **5** was converted into the target steroidal azadiene **6** in moderate yield (33%) by treatment with *p*-toluenesulfinyl chloride in the presence of trimethylamine followed by a radical rearrangement.[36]

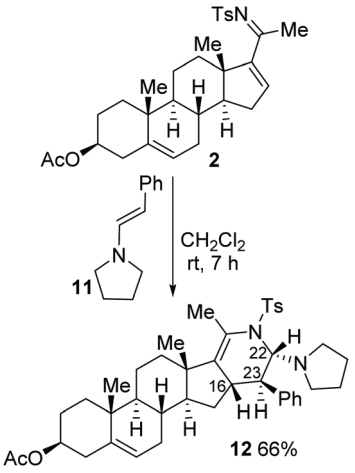
Initially, we decided to extend the study of the reactivity of 1-azadiene **2** to the reaction with 1,4-cyclohexanedione monoethylene acetal (**7**) which contains a protected carbonyl group. The presence of a protected carbonyl group in the target steroid would be an interesting structural feature, since it would open the possibility of further functionalization after deprotection. Thus, 1-azadiene **2** reacted with ketone **7** in the presence of catalytic amounts of pyrrolidine (20 mol%), under



Scheme 3 Synthesis of the steroidal azadiene **6**.



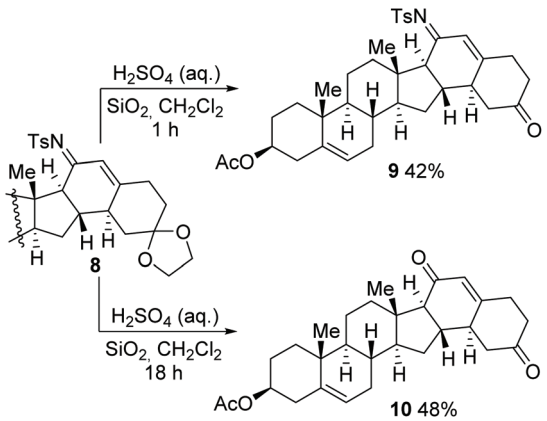
Scheme 4 Synthesis of hexacyclic steroid **8**.



Scheme 6 Reactivity of 1-azadiene **2** with enamine **11**.

microwave irradiation at 140 °C for 10 min, to give hexacyclic steroid **8** in 65% yield (Scheme 4).

Attempts to deprotect the carbonyl group of steroid **8** using conc. HCl in methanol,[41] pyridinium *p*-toluenesulphonate in acetone or ethanol at reflux[42] or aqueous dimethylsulfoxide at reflux[43] did not afford the desired compound. However, the synthesis of steroids **9** and **10** was achieved using wet silica gel[44] at room temperature (suspension of SiO_2 in aqueous H_2SO_4/dichloromethane). Depending on the reaction time it was possible to control the selective deprotection of the carbonyl group or to obtain the deprotection together with the hydrolysis of the imine moiety. Thus, the reaction carried out for 1 h afforded steroid **9** in 42% yield, while with a longer reaction time (18 h) steroid **10** was isolated in 48% yield (Scheme 5). Steroids **9** and **10** containing one and two carbonyl groups, respectively, are important scaffolds for subsequent functionalization.

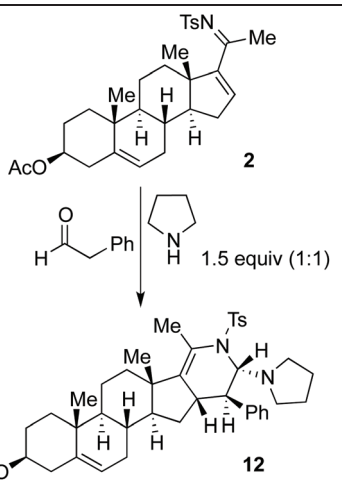


Scheme 5 Deprotection and hydrolysis reactions of hexacyclic steroid **8**.

In order to get further insight into the reactivity of steroidal *N*-sulfonyl-1-azadienes, we set out to study the chemical behavior of these azadienes in the presence of aldehydes and pyrrolidine. Initially, the reaction of 1-azadiene **2** with phenylacetaldehyde and catalytic amounts of pyrrolidine (20 mol%) was explored. Unfortunately, no product was detected from the reaction carried out either under microwave irradiation or under conventional heating.

This unsatisfactory result led us to explore the reaction of 1-azadiene **2** with enamine **11**, prepared in advance by reacting phenylacetaldehyde with pyrrolidine. Surprisingly, pentacyclic steroid **12**, containing a tetrahydropyridine ring and a pyrroli-

Table 1 Reactivity of 1-azadiene **2** towards phenylacetaldehyde in presence of pyrrolidine



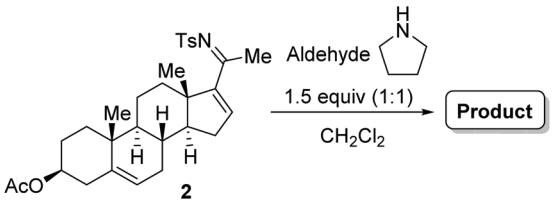
Entry	Solvent	Reaction conditions	**12**
1	DCM	Reflux, 24 h	35%
2	DCE	Reflux, 24 h	35%
3	DCM	MW, 50 °C, 10 min	75%
4	DCM	MW, 60 °C, 10 min	58%

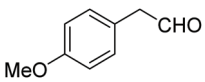
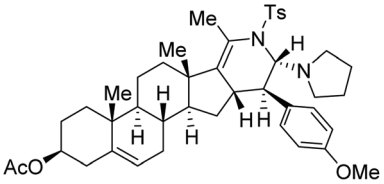
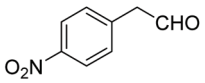
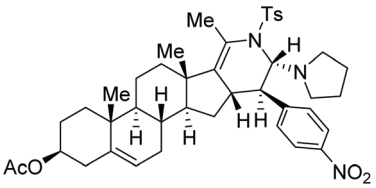
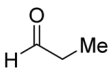
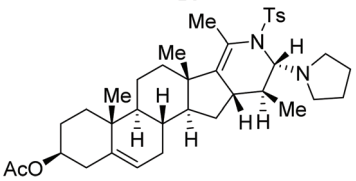
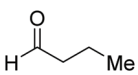
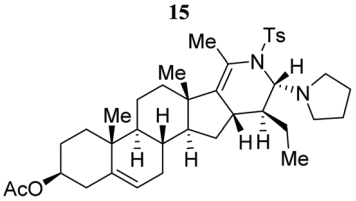
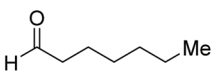
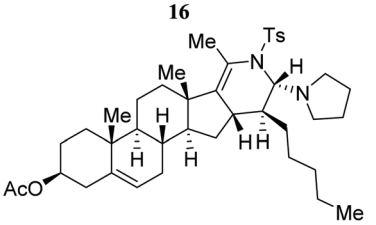
dine moiety, was obtained efficiently, carrying out the reaction at room temperature (66% yield). Steroid **12** was obtained in a diastereoselective fashion in a process involving the creation of three new chiral centers (Scheme 6).

The structural assignment of pentacyclic steroid **12** was supported by NMR data. In fact, the ^{1}H NMR spectrum (400 MHz) contain signals corresponding to protons of both pyrrolidine and phenyl groups. Moreover, the COSY spectrum (400 MHz) showed cross peaks between proton H-23 and protons H-22 and H-16.

This interesting result led us to explore the reactivity of 1-azadiene **2** with phenylacetaldehyde in the presence of equimolar amounts of pyrrolidine (Table 1). Thus, the reaction of steroidal 1-azadiene **2** with the enamine generated *in situ*, by the reaction of 1.5 equiv. of phenylacetaldehyde and pyrrolidine, in refluxing dichloromethane (DCM) gave the expected pentacyclic steroid **12** in moderate yield (35%) (entry 1). Using the same stoichiometry and carrying out the reaction in dichloroethane (DCE) at reflux a similar reaction outcome was observed (entry 2). Interestingly, preforming the reaction

Table 2 Synthesis of pentacyclic steroids *via* hetero-Diels–Alder reaction



Aldehyde	Reaction conditions	Isolated yield	Product
	MW, 50 °C, 10 min	62%	 **13**
	MW, 50 °C, 10 min	78%	 **14**
	MW, 50 °C, 10 min MW, 50 °C, 30 min MW, 60 °C, 30 min	32% 21% 27%	 **15**
	MW, 50 °C, 10 min MW, 60 °C, 10 min	39% 56%	 **16**
	MW, 50 °C, 10 min MW, 60 °C, 30 min	47% 62%	 **17**

under microwave irradiation at 50 °C for 10 min, using DCM as solvent, steroid **12** was isolated in 75% yield (entry 3). Pentacyclic steroid **12** was obtained in slightly lower yield (58%) when the reaction was carried out under microwave irradiation at 60 °C for 10 min (entry 4).

The study was extended to the reactivity of steroidal 1-azadiene **2** toward other aldehydes in the presence of pyrrolidine (Table 2). Using *p*-methoxyphenylacetaldehyde as enamine precursor, pentacyclic steroid **13** was obtained in 62%, under microwave irradiation at 50 °C for 10 min. The same reaction conditions were applied in the reaction of steroidal 1-azadiene **2** with another *N*-styrylpyrrolidine derivative, generated *in situ* from *p*-nitrophenylacetaldehyde/pyrrolidine, giving product **14** in 78% yield. Then, the reactivity of steroidal 1-azadiene **2** toward enamines where the aryl substituent was replaced by an alkyl group was explored. Pentacyclic steroid **15** was obtained in 32% yield, under microwave irradiation at 50 °C for 10 min, using propanal as enamine precursor. Increasing the reaction time to 30 min, the yield decreased to 21%. On the other hand, carrying out the reaction at 60 °C for 30 min, steroid **15** was isolated in 27% yield. Steroidal 1-azadiene **2** reacted also with butanal in the presence of pyrrolidine to give steroid **16** in moderate yield (39%), under microwave irradiation at 50 °C for 10 min. Interestingly, carrying out the reaction at 60 °C for 10 min afforded pentacyclic steroid **16** in 56% yield. The microwave-induced reaction of 1-azadiene **2** with heptanal in the presence of pyrrolidine, carried out at 50 °C and 60 °C for 10 min led to pentacyclic steroid **17** in 47% and 62% yield, respectively. It is noteworthy that all products were isolated as single diastereoisomers.

Attempts to carry out the reaction of steroidal 1-azadiene **2** with other *in situ* generated enamines or even with enamines prepared in advance from isobutyraldehyde, 2,2-diphenylacetaldehyde or cyclohexanecarbaldehyde and pyrrolidine were unsuccessful.

The stereochemistry assignment of the new chiral centers was supported by two dimensional NOESY spectrum (400 MHz) of the pentacyclic steroid **15**. Protons H-30 of the methyl group show cross peaks between the methyl group protons H-18 and with H-16, and proton H-16 is correlated with proton H-22 (Fig. 1).

The reactivity of steroidal 1-azadiene **6** toward cyclohexanone and phenylacetaldehyde in the presence of pyrrolidine was explored (Scheme 7). 1-Azadiene **6** reacted with cyclohexanone with a catalytic amount of pyrrolidine (20 mol%) under

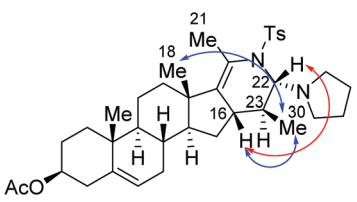
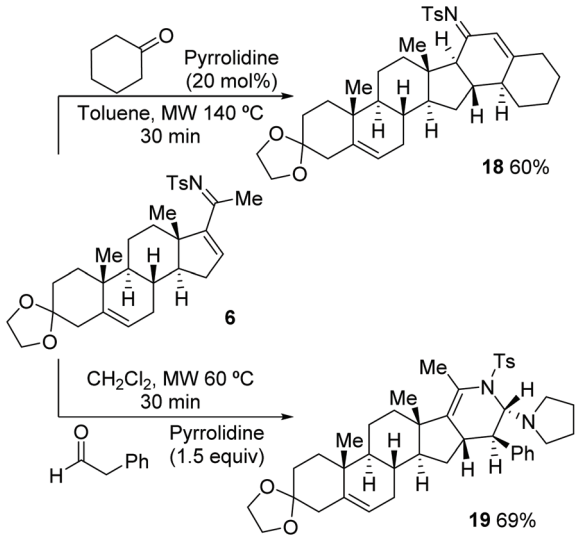


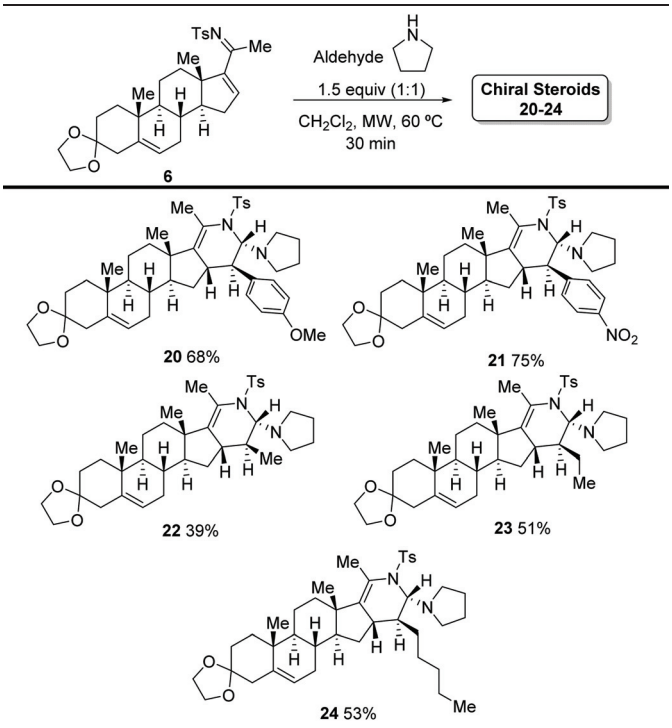
Fig. 1 Main correlations observed in the NOESY spectrum of compound **15**.

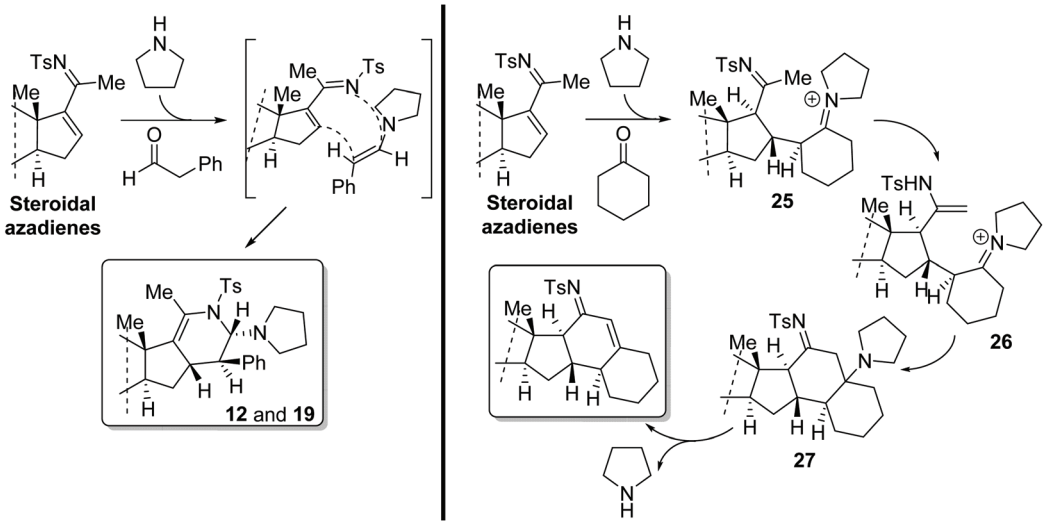


Scheme 7 Reactivity of steroidal 1-azadiene **6** toward cyclohexanone and phenylacetaldehyde in presence of pyrrolidine.

microwave irradiation at 140 °C for 30 min to give hexacyclic steroid **18** in 60% yield. On the other hand, the pentacyclic steroid **19** was isolated in 69% yield from the microwave-induced reaction of 1-azadiene **6** with phenylacetaldehyde in presence of 1.5 equiv. of pyrrolidine at 60 °C for 30 min.

Table 3 Synthesis of pentacyclic steroids *via* hetero-Diels–Alder reaction of azadiene **6** with aldehydes in presence of pyrrolidine





Scheme 8 Proposed Diels–Alder mechanism for the reaction of steroidal azadienes with aldehydes/pyrrolidine, illustrated with phenylacetaldehyde (on the left); proposed annulation mechanism for the reaction of steroidal azadienes with ketones/pyrrolidine, illustrated with cyclohexanone (on the right).

These results indicate that steroidal *N*-sulfonyl-1-azadienes **2** and **6** show the same reactivity pattern. These azadienes react with ketones in the presence of pyrrolidine *via* an annulation pathway whereas from the reaction with aldehydes hetero-Diels–Alder cycloadducts are obtained.

The hetero-Diels–Alder reaction of steroidal 1-azadiene **6** with other *in situ* generated enamines was also explored (Table 3). Carrying out the reaction with *N*-styrylpyrrolidines derived from *p*-methoxyphenylacetaldehyde and *p*-nitrophenylacetaldehyde, under microwave irradiation at 60 °C for 30 min, chiral steroids **20** and **21** were obtained in 68% and 75% yield, respectively. Chiral steroids **22**, **23** and **24**, were isolated in good yields (39–53%) using propanal, butanal and heptanal as enamine precursors.

The results regarding the reactivity of steroidal *N*-sulfonyl-1-azadienes towards aldehydes are consistent with hetero-Diels–Alder reactions of the azadienes with enamines generated *in situ* from the reaction of the appropriate aldehyde with pyrrolidine. It has been described that *trans*-enamines are preferentially formed starting from alkyl aldehydes, including phenylacetaldehyde.[45,46] Therefore, the proposed stereochemistry is in agreement with an approach of the dienophile from the less hindered α-face of the steroid,[13] with the pyrrolidine moiety *endo* and retention of the enamine *trans* geometry (Scheme 8a). On the other hand, the studied steroidal *N*-sulfonyl-1-azadienes follow a different mechanistic pathway in the presence of ketones and pyrrolidine (Scheme 8b). The observed reactivity can be rationalized considering an initial stereoselective conjugate addition of the *in situ* generated enamines to the 1-azadiene followed by an imine–enamine isomerization. Cyclization of intermediate **26** and subsequent elimination of pyrrolidine leads to the target chiral hexacyclic steroids.

Conclusion

The reactivity of steroidal *N*-sulfonyl-1-azadienes was explored, allowing the development of microwave-induced diastereoselective synthetic routes to chiral pentacyclic and hexacyclic steroids. An interesting reactivity pattern was uncovered in the reaction of carbonyl compounds in the presence of pyrrolidine. Azadienes derived from 16-dehydropregnenolone acetate and 16-dehydroprogesterone react with cyclic ketones in the presence of pyrrolidine *via* an annulation reaction whereas from the reaction with aldehydes/pyrrolidine hetero-Diels–Alder cycloadducts were obtained. The reported methodologies are simple and highly selective approaches to structurally diverse steroids with potential applications in medicinal chemistry.

Experimental section

General experimental methods

NMR spectra were recorded at the following frequencies: proton (^{1}H, 400 MHz) and carbon (^{13}C, 100 MHz) on a Bruker Avance III. The solvent was deuteriochloroform except where indicated otherwise. Chemical shifts are expressed in parts per million relative to TMS, and coupling constants (*J*) are given in hertz. Infrared spectra (IR) were recorded on an Agilent Technologies Carey 630 FTIR spectrometer with Attenuated Total Reflection (ATR). High-resolution mass spectroscopy (HRMS) was performed in a microTOF-Focus with electrospray ionization (ESI) and a time-of-flight (TOF) analyzer. Melting points were determined using a Falc R132467 Melting Point Device (open capillary method) and are uncorrected. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Analytical thin layer chromatography was per-

formed with silica gel plates (Merck, TLC silica gel 60 F254). Flash column chromatography was performed with silica gel 60A (Fluorochem 35–70 micron) 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. 3β-Acetoxy-5,16-pregnadien-20-tosylimine (**2**),[36] 16-dehydropregnenolone (16-DHP),[14] *p*-toluenesulfinyl chloride,[47] *N*-styrylpyrrolidine (**11**),[46] *p*-methoxyphenylacetaldehyde[48] and *p*-nitrophenylacetaldehyde[48,49] were prepared as described in the literature.

3β-Acetoxy-5,16-pregnadien-20-oxime (3). A mixture of 16-DHP (5.08 g, 16.2 mmol), hydroxylamine hydrochloride (2.02 g, 29.1 mmol) and pyridine (7 mL) in ethanol 95% (30 mL) was refluxed for 30 min. After this time, the reaction mixture was cooled in an ice bath and cool water was added to the mixture. The precipitated solid was filtered, washed with hot water and dried under vacuum. Compound **3** was obtained as a white solid (5.29 g, 98%). The NMR data are consistent with the literature.[50]

4,16-Pregnadien-3-one-20-oxime (4). Cyclohexanone (52 mL, 502.3 mmol) and aluminum isopropoxide (5.6 g, 27.3 mmol) were added to a solution of oxime **3** (2.63 g, 8.05 mmol) in dry toluene (100 mL). The reaction mixture was heated under reflux with a Dean–Stark trap for 1 h. After this time, the reaction mixture was allowed to cool to room temperature and ethyl acetate was added (60 mL), washed with H_2O (5 × 60 mL) and brine (30 mL), dried with Na_2SO_4 and the solvent evaporated off. Compound **4** was purified by crystallization with diethyl ether/hexane and obtained as a white solid (1.90 g, 72%). The NMR data are consistent with the literature.[50]

3-Ethylenedioxy-4,16-pregnadien-20-oxime (5). Ethylene glycol (6 mL, 110 mmol) and *p*-toluenesulphonic acid (0.58 g, 3.05 mmol) were added to a solution of oxime **4** (2.0 g, 6.11 mmol) in dry toluene (100 mL). The reaction mixture was heated under reflux with a Dean–Stark trap for 3 h. After this time, the reaction mixture was allowed to cool to room temperature, washed with H_2O (6 × 60 mL) and brine (30 mL), dried over Na_2SO_4 and the solvent evaporated off. Compound **5** was purified by crystallization with diethyl ether/hexane and obtained as a white solid (1.37 g, 60%). Mp > 140 °C with decomposition (from diethyl ether/hexane). $[\alpha]_D^{25}$ −10 (*c* 0.5 in THF); IR (ATR) ν 685, 947, 1092, 1365, 1602, 2895 and 3372 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.90 (s, 3H), 0.96–1.02 (m, 1H), 1.00 (s, 3H), 1.21–1.39 (m, 3H), 1.50–1.72 (m, 7H), 1.87 (s, 3H), 1.91–1.99 (m, 2H), 2.05 (dd, J = 14.0 and 2.4 Hz, 1H), 2.14–2.20 (m, 1H), 2.41–2.46 (m, 2H), 3.80–3.84 (m, 4H), 5.24 (pseudo d, J = 4.8 Hz 1H), 6.02–6.03 (m, 1H), 10.72 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 11.1, 15.7, 18.5, 20.3, 29.9, 30.7, 31.0, 31.1, 35.4, 35.6, 36.2, 41.2, 46.1, 49.7, 56.6, 63.5, 63.5, 108.6, 121.0, 130.7, 140.2, 151.2, 151.6. HRMS (ESI-TOF) *m*/*z* for $C_{23}H_{34}NO_3$ [M + H^+] calcd 372.2533, found 372.2522.

3-Ethylenedioxy-4,16-pregnadien-20-tosylimine (6). A solution of oxime **5** (1.27 g, 3.35 mmol) in CCl_4 (23.5 mL), at 0 °C and under N_2, was treated sequentially with triethylamine (0.56 mL, 4.02 mmol) and freshly prepared *p*-toluenesulfinyl chloride (0.64 g, 3.69 mmol). The reaction mixture was stirred at 0 °C for 15 minutes. After this time, the trimethylamine hydrochloride was filtered and washed with CCl_4 (50 mL). The resulting filtrate was stirred at room temperature overnight. The solvent was evaporated and the product purified by flash chromatography [ethyl acetate/hexane (1 : 4)]. Compound **6** was obtained as a white solid (0.563 g, 33%). Mp 155.6–156.6 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ +70 (*c* 0.5 in CH_2Cl_2). IR (ATR) ν 759, 798, 825, 1087, 1154, 1301, 1559, 2885 and 2939 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (s, 3H), 1.02 (s, 3H), 1.05–1.13 (m, 1H), 1.23–1.34 (m, 3H), 1.39–1.48 (m, 2H), 1.63–1.79 (m, 5H), 1.98–2.21 (m, 4H), 2.35 (ddd, J = 17.6, 6.4 and 3.4 Hz, 1H), 2.44 (s, 3H), 2.56 (pseudo dd, J = 14.0 and 2.0 Hz, 1H), 2.66 (s, 3H), 3.90–3.97 (m, 4H), 5.34 (pseudo d, J = 5.2 Hz, 1H), 6.83 (dd, J = 3.4 and 2.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 15.5, 18.8, 20.7, 21.0, 21.6, 30.2, 31.0, 31.3, 32.6, 34.6, 36.2, 36.7, 41.8, 46.8, 49.8, 56.6, 64.2, 64.4, 109.4, 121.5, 126.8, 129.3, 139.1, 140.7, 143.1, 147.0, 155.5, 176.6. HRMS (ESI-TOF) *m*/*z* for $C_{30}H_{40}NO_4S$ [M + H^+] calcd 510.2673, found 510.2671.

General procedure for the synthesis of hexacyclic steroids. A suspension of 1-azadiene **2** or **6** (0.3 mmol), the appropriate ketone (1.5 eq., 0.45 mmol) and pyrrolidine (5 μL, 20 mol%, 0.06 mmol) in toluene (1 mL) was irradiated in the microwave reactor at 140 °C for the time indicated in each case. After cooling, the solvent was evaporated off and the product purified by flash chromatography.

*Hexacyclic steroid **8**.* Obtained from the 1-azadiene **2** (0.15 g, 0.3 mmol) and 1,4-cyclohexanedione monoethylene acetal (**7**) (70 mg, 0.45 mmol) following the general procedure (irradiation time: 10 min). After purification by flash chromatography [ethyl acetate/hexane (1 : 3)] the hexacyclic steroid **8** was obtained as a white solid (0.126 g, 65%). Mp > 207 °C with decomposition (from ethyl acetate/hexane). $[\alpha]_D^{25}$ +60 (*c* 0.5 in CH_2Cl_2). IR (ATR) ν 742, 1031, 1090, 1152, 1244, 1560, 1599 and 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80 (s, 3H), 0.94–0.96 (m, 1H), 0.99 (s, 3H), 1.08–1.16 (m, 3H), 1.35–1.59 (m, 8H), 1.67–1.75 (m, 3H), 1.80–1.97 (m, 4H), 2.03 (s, 3H), 2.05–2.11 (m, 3H), 2.25–2.35 (m, 2H), 2.43 (s, 3H), 2.47–2.64 (m, 2H), 3.95–4.03 (m, 4H), 4.53–4.64 (m, 1H), 5.36 (pseudo d, J = 3.6 Hz, 1H), 7.00 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 11.9, 19.3, 20.3, 21.4, 21.6, 26.8, 27.7, 31.3, 31.6, 32.7, 34.0, 36.7, 36.9, 37.2, 38.1, 40.2, 41.5, 44.2, 44.4, 50.3, 55.6, 60.2, 64.5, 64.6, 73.8, 107.7, 120.7, 122.1, 126.7, 129.3, 139.3, 140.0, 143.0, 164.7, 170.6, 179.3. HRMS (ESI-TOF) *m*/*z* for $C_{38}H_{50}NO_6S$ [M + H^+] calcd 648.3353, found 648.3334.

*Hexacyclic steroid **18**.* Obtained from the 1-azadiene **6** (0.15 g, 0.3 mmol) and cyclohexanone (46.6 μL, 0.45 mmol) following the general procedure (irradiation time: 30 min). After purification by flash chromatography [ethyl acetate/hexane (1 : 4)] the hexacyclic steroid **18** was obtained as a white solid (0.100 g, 60%). Mp 209.0–209.8 °C with decomposition (from ethyl acetate/hexane). $[\alpha]_D^{25}$ +160 (*c* 0.5 in CH_2Cl_2). IR (ATR) ν 658, 717, 733, 760, 784, 810, 982, 1093, 1135, 1302, 1560 and 2936 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80 (s, 3H), 1.00 (s, 3H), 1.04–1.12 (m, 3H), 1.24–1.54 (m, 9H), 1.59–1.77 (m, 4H),

1.81–1.99 (m, 3H), 2.02–2.23 (m, 7H), 2.43 (s, 3H), 2.52–2.60 (m, 2H), 3.90–3.97 (m, 4H), 5.32–5.34 (m, 1H), 6.92 (s, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 11.9, 18.9, 20.3, 21.6, 25.2, 26.7, 26.9, 31.0, 31.4, 32.9, 35.7, 36.3, 36.7, 37.3, 41.4, 41.8, 44.1, 46.7, 50.0, 55.7, 60.1, 64.2, 64.4, 109.4, 120.2, 121.7, 126.7, 129.3, 139.5, 140.5, 142.8, 167.9, 180.0. HRMS (ESI-TOF) m/z for $C_{36}H_{48}NO_4S$ [M + H^+] calcd 590.3299, found 590.3295.

General procedure to deprotection and hydrolysis of hexacyclic steroid 8. A suspension of SiO_2 (1.2 g), dichloromethane (3.2 mL) and H_2SO_4 15% (0.12 mL) was stirred for 3 min and then steroid **8** (0.1 g, 0.154 mmol) was added. The reaction mixture was stirred at room temperature for the time indicated in each case. Upon completion, the reaction mixture was filtered, neutralized with saturated solution of $NaHCO_3$ and dichloromethane added (20 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), dried and the solvent evaporated off. The product was purified by flash chromatography [ethyl acetate/hexane (1 : 2)].

*Hexacyclic steroid **9**.* Reaction time: 1 h. After purification, hexacyclic steroid **9** was obtained as a white solid (39 mg, 42%). Mp 206.1–207.2 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ +30 (c 0.5 in CH_2Cl_2). IR (ATR) ν 742, 817, 1152, 1245, 1301, 1560, 1707, 1725, 1707 and 2917 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.81 (s, 3H), 0.93–0.97 (m, 1H), 0.99 (s, 3H), 1.06–1.17 (m, 3H), 1.45–1.63 (m, 7H), 1.79–1.86 (m, 2H), 1.92–1.96 (m, 1H), 2.02 (s, 3H), 2.04–2.11 (m, 2H), 2.13–2.31 (m, 4H), 2.44 (s, 3H), 2.47–2.60 (m, 2H), 2.63–2.71 (m, 2H), 2.77–2.95 (m, 2H), 4.54–4.62 (m, 1H), 5.35 (pseudo d, J = 4.8 Hz, 1H), 7.18 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.84–7.86 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 11.9, 19.3, 20.3, 21.4, 21.6, 26.7, 26.9, 27.7, 31.3, 31.5, 31.8, 36.7, 36.9, 37.1, 38.1, 38.6, 41.7, 44.1, 45.1, 45.5, 50.3, 55.6, 60.5, 73.8, 122.0, 122.0, 126.8, 129.4, 139.0, 140.0, 143.2, 161.8, 170.5, 208.4. HRMS (ESI-TOF) m/z for $C_{36}H_{46}NO_5S$ [M + H^+] calcd 604.3091, found 604.3071.

*Hexacyclic steroid **10**.* Reaction time: 18 h. After purification, hexacyclic steroid **10** was obtained as a white solid (33 mg, 48%). Mp 222.7–223.8 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −133 (c 0.075 in CH_2Cl_2). IR (ATR) ν 663, 813, 1030, 1237, 1667, 1702, 1728 and 2911 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.88 (s, 3H), 0.97–1.02 (m, 1H), 1.04 (s, 3H), 1.09–1.26 (m, 4H), 1.41–1.55 (m, 4H), 1.58–1.63 (m, 2H), 1.85–1.95 (m, 4H), 2.03 (s, 3H), 2.19–2.33 (m, 5H), 2.49–2.53 (m, 2H), 2.66–2.83 (m, 4H), 4.56–4.64 (m, 1H), 5.37 (pseudo d, J = 4.8 Hz, 1H), 5.91 (d, J = 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 12.3, 19.3, 20.2, 21.4, 26.9, 27.7, 31.0, 31.3, 31.6, 36.7, 37.0, 37.2, 38.1, 38.6, 41.1, 44.2, 44.7, 45.9, 50.4, 55.4, 63.5, 73.8, 122.0, 128.0, 140.1, 160.0, 170.6, 199.7, 209.0. HRMS (ESI-TOF) m/z for $C_{29}H_{39}O_4$ [M + H^+] calcd 451.2843, found 451.2831.

*Pentacyclic steroid **12**.* *N*-Styrylpyrrolidine (**11**) (0.26 g, 1.5 mmol) was added to a solution of 1-azadiene **2** (0.15 g, 0.30 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 7 h. After this time, the solvent was evaporated off and the product purified by flash chromatography [ethyl acetate/hexane (1 : 3)]. Pentacyclic steroid **12** was obtained as a white solid (0.140 g, 66%). Mp 110.1–111.8 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −250 (c 0.5 in CH_2Cl_2). IR (ATR) ν 669, 699, 929, 1031, 1163, 1238, 1337, 1730, 2857 and 2941 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.73 (s, 3H), 0.98 (s, 3H), 1.04–1.22 (m, 3H), 1.24–1.39 (m, 5H), 1.44–1.65 (m, 5H), 1.66–1.74 (m, 4H), 1.84–1.87 (m, 2H), 2.02 (s, 3H), 2.22 (d, J = 1.6 Hz, 3H), 2.25–2.28 (m, 3H), 2.44 (s, 3H), 2.48–2.50 (m, 2H), 2.66 (dd, J = 12.4 and 8.4 Hz, 1H), 2.89 (pseudo d, J = 6.0 Hz, 1H), 4.53–4.61 (m, 1H), 4.98 (d, J = 8.0 Hz, 1H), 5.25 (pseudo d, J = 4.4 Hz, 1H), 6.97 (d, J = 7.2 Hz, 2H), 7.19–7.23 (m, 1H), 7.25–7.27 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.3, 18.2, 19.2, 21.0, 21.4, 21.6, 23.5, 27.7, 31.1, 31.4, 36.5, 36.9, 38.0, 39.5, 44.8, 47.6, 49.7, 53.6, 54.7, 73.8, 80.6, 122.1, 124.5, 126.5, 127.5, 128.2, 128.3, 129.1, 137.0, 139.6, 142.9, 143.1, 150.1, 170.5. HRMS (ESI-TOF) m/z for $C_{42}H_{55}N_2O_4S$ [M + H^+] calcd 683.3877, found 683.3854.

General procedure for the hetero-Diels–Alder reactions. A suspension of 1-azadiene **2** or **6** (0.3 mmol), the appropriate aldehyde (0.45 mmol) and pyrrolidine (37.6 μL, 0.45 mmol) in dichloromethane (1 mL) was irradiated in the microwave reactor at the temperature and time indicated in each case. After cooling, the solvent was evaporated off and the product purified by flash chromatography.

*Pentacyclic steroid **12**.* Obtained from the 1-azadiene **2** (0.15 g, 0.3 mmol) and phenylacetaldehyde (52.6 μL, 0.45 mmol) following the general procedure (50 °C, 10 min). Pentacyclic steroid **12** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (0.150 g, 76%). Pentacyclic steroid **12** was identified by comparison with the specimen previously isolated (see above).

*Pentacyclic steroid **13**.* Obtained from the 1-azadiene **2** (0.15 g, 0.3 mmol) and *p*-methoxyphenylacetaldehyde (67.6 mg, 0.45 mmol) following the general procedure (50 °C, 10 min). Pentacyclic steroid **13** was purified by flash chromatography [ethyl acetate/hexane (1 : 4)] and obtained as a white solid (0.135 g, 62%). Mp 117.6–119.5 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −240 (c 0.5 in CH_2Cl_2). IR (ATR) ν 664, 813, 1032, 1161, 1241, 1333, 1511, 1730 and 2938 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.73 (s, 3H), 0.90–0.95 (m, 2H), 0.98 (s, 3H), 1.06–1.14 (m, 2H), 1.26–1.39 (m, 4H), 1.49–1.62 (m, 6H), 1.66–1.71 (m, 3H), 1.83–1.87 (m, 2H), 2.02 (s, 3H), 2.21 (d, J = 1.6 Hz, 3H), 2.24–2.28 (m, 2H), 2.44 (s, 3H), 2.47–2.50 (m, 2H), 2.60 (dd, J = 12.8 and 8.0 Hz, 1H), 2.87–2.89 (m, 2H), 3.80 (s, 3H), 4.53–4.61 (m, 1H), 4.93 (d, J = 8.0 Hz, 1H), 5.26 (pseudo d, J = 4.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.3, 18.2, 19.2, 21.0, 21.4, 21.6, 23.4, 27.7, 31.1, 31.4, 36.5, 36.9, 38.0, 39.7, 44.8, 47.6, 49.7, 53.6, 53.9, 55.2, 73.8, 80.8, 113.7, 122.1, 124.4, 127.5, 129.1, 135.0, 137.1, 139.6, 143.1, 150.2, 158.2, 170.6. HRMS (ESI-TOF) m/z for $C_{43}H_{57}N_2O_5S$ [M + H^+] calcd 713.3983, found 713.3988.

*Pentacyclic steroid **14**.* Obtained from the 1-azadiene **2** (0.15 g, 0.3 mmol) and *p*-nitrophenylacetaldehyde (74.3 mg, 0.45 mmol) following the general procedure (50 °C, 10 min). Pentacyclic steroid **14** was purified by flash chromatography

[ethyl acetate/hexane (1 : 4)] and obtained as a white solid (0.170 g, 78%). Mp 114.5–115.7 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −233 (*c* 0.6 in CH_2Cl_2). IR (ATR) ν 677, 927, 1031, 1090, 1161, 1239, 1342, 1520, 1729 and 2935 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.76 (s, 3H), 0.84–0.88 (m, 1H), 0.91–0.96 (m, 1H), 0.99 (s, 3H), 1.05–1.21 (m, 2H), 1.32–1.41 (m, 3H), 1.51–1.73 (m, 11H), 1.84–1.87 (m, 2H), 2.02 (s, 3H), 2.22 (d, *J* = 1.2 Hz, 3H), 2.26–2.28 (m, 3H), 2.44–2.45 (m, 1H), 2.47 (s, 3H), 2.79 (dd, *J* = 12.8 and 8.0 Hz, 1H), 2.87–2.90 (m, 2H), 4.53–4.61 (m, 1H), 4.88 (d, *J* = 8.0 Hz, 1H), 5.25 (pseudo d, *J* = 4.4 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.3, 18.2, 19.2, 20.9, 21.4, 21.6, 23.4, 27.7, 27.9, 31.0, 31.4, 36.5, 36.9, 38.0, 38.8, 44.8, 47.5, 49.7, 53.8, 54.4, 73.7, 79.8, 121.9, 123.6, 125.1, 126.8, 127.4, 128.9, 129.3, 136.9, 139.7, 143.6, 146.8, 149.6, 150.4, 170.5. HRMS (ESI-TOF) *m*/*z* for $C_{42}H_{54}N_3O_6S$ [M + H^+] calcd 728.3728, found 728.3727.

Pentacyclic steroid ***15***. Obtained from the 1-azadiene **2** (0.15 g, 0.3 mmol) and propanal (32.5 μL, 0.45 mmol) following the general procedure (50 °C, 10 min). Pentacyclic steroid **15** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (60 mg, 32%). Mp 169.4–170.8 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −98 (*c* 0.5 in CH_2Cl_2). IR (ATR) ν 666, 707, 810, 907, 950, 1030, 1153, 1235, 1335, 1731 and 2927 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.53 (pseudo t, *J* = 10.4 Hz, 1H), 0.69 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.99 (s, 3H), 1.03–1.14 (m, 2H), 1.19–1.28 (m, 2H), 1.37–1.64 (m, 8H), 1.67–1.72 (m, 4H), 1.83–1.91 (m, 3H), 2.03 (s, 3H), 2.14 (d, *J* = 2.0 Hz, 3H), 2.19–2.23 (m, 1H), 2.28–2.33 (m, 2H), 2.40 (s, 3H), 2.52–2.54 (m, 2H), 2.82 (d, *J* = 8.8 Hz, 2H), 4.54–4.59 (m, 1H), 4.61 (d, *J* = 7.2 Hz, 1H), 5.33 (pseudo d, *J* = 4.4 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.1, 18.2, 19.2, 20.4, 20.9, 21.4, 21.5, 23.3, 27.7, 27.8, 31.2, 31.5, 36.4, 36.5, 36.9, 38.0, 40.7, 43.3, 44.6, 47.9, 49.7, 53.6, 73.8, 80.4, 122.1, 127.3, 129.1, 139.7, 170.5. HRMS (ESI-TOF) *m*/*z* for $C_{37}H_{53}N_2O_4S$ [M + H^+] calcd 621.3721, found 621.3727.

Pentacyclic steroid ***16***. Obtained from the 1-azadiene **2** (0.15 g, 0.3 mmol) and butanal (40.6 μL, 0.45 mmol) following the general procedure (60 °C, 10 min). Pentacyclic steroid **16** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (0.107 g, 56%). Mp 174.7–175.8 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −110 (*c* 0.5 in CH_2Cl_2). IR (ATR) ν 667, 812, 926, 1032, 1164, 1238, 1335, 1730 and 2936 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.68 (s, 3H), 0.71–0.74 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.94–0.97 (m, 1H), 1.00 (s, 3H), 1.03–1.14 (m, 3H), 1.20–1.26 (m, 3H), 1.42–1.69 (m, 11H), 1.84–1.91 (m, 3H), 2.03 (s, 3H), 2.15 (d, *J* = 1.6 Hz, 3H), 2.20–2.22 (m, 1H), 2.26–2.33 (m, 2H), 2.40 (s, 3H), 2.48–2.55 (m, 2H), 2.77–2.88 (m, 2H), 4.54–4.62 (m, 1H), 4.78 (d, *J* = 7.2 Hz, 1H), 5.33 (pseudo d, *J* = 4.8 Hz), 7.20 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 10.5, 17.1, 18.1, 19.2, 21.0, 21.4, 21.5, 23.4, 25.9, 27.5, 27.7, 31.2, 31.5, 36.4, 36.5, 36.9, 38.0, 38.2, 44.5, 47.4, 48.3, 49.7, 53.8, 73.8, 77.9, 122.1, 124.0, 127.3, 128.9, 137.2, 139.7, 142.8, 150.2, 170.6. HRMS (ESI-TOF) *m*/*z* for $C_{38}H_{55}N_2O_4S$ [M + H^+] calcd 635.3877, found 635.3869.

Pentacyclic steroid ***17***. Obtained from the 1-azadiene **2** (0.15 g, 0.3 mmol) and heptanal (63.5 μL, 0.45 mmol) following the general procedure (60 °C, 30 min). Pentacyclic steroid **17** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (0.122 g, 60%). Mp 183.2–183.9 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −120 (*c* 0.5 in CH_2Cl_2). IR (ATR) ν 670, 1031, 1163, 1241, 1337, 1731 and 2931 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.69 (s, 3H), 0.83–0.87 (m, 1H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.99 (s, 3H), 1.06–1.10 (m, 2H), 1.16–1.24 (m, 5H), 1.25–1.33 (m, 4H), 1.35–1.41 (m, 2H), 1.44–1.50 (m, 3H), 1.56–1.63 (m, 4H), 1.69 (br s, 4H), 1.84–1.90 (m, 3H), 2.03 (s, 3H), 2.14 (d, *J* = 1.6 Hz, 3H), 2.19–2.20 (m, 1H), 2.28–2.33 (m, 2H), 2.39 (s, 3H), 2.46–2.57 (m, 2H), 2.76–2.88 (m, 2H), 4.54–4.62 (m, 1H), 4.77 (d, *J* = 6.8 Hz, 1H), 5.33 (pseudo d, *J* = 4.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.1, 17.1, 18.1, 19.2, 21.0, 21.4, 21.5, 22.7, 23.4, 25.7, 27.7, 27.8, 31.2, 31.5, 32.1, 33.9, 36.4, 36.5, 36.9, 38.0, 38.7, 44.5, 47.1, 47.3, 49.7, 53.8, 73.8, 78.4, 122.1, 124.1, 127.2, 129.0, 137.3, 139.7, 142.8, 150.1, 170.5. HRMS (ESI-TOF) *m*/*z* for $C_{41}H_{61}N_2O_4S$ [M + H^+] calcd 677.4347, found 677.4346.

Pentacyclic steroid ***19***. Obtained from the 1-azadiene **6** (0.15 g, 0.3 mmol) and phenylacetaldehyde (52.6 μL, 0.45 mmol) following the general procedure (60 °C, 30 min). Pentacyclic steroid **19** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white foam (0.141 g, 69%). $[\alpha]_D^{25}$ −166 (*c* 1.2 in CH_2Cl_2). IR (ATR) ν 670, 706, 1093, 1163, 1337, 1596 and 2946 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.73 (s, 3H), 0.82–0.88 (m, 1H), 0.91–0.95 (m, 1H), 0.99 (s, 3H), 1.02–1.09 (m, 1H), 1.14–1.22 (m, 1H), 1.26–1.37 (m, 3H), 1.42–1.55 (m, 3H), 1.67–1.81 (m, 9H), 2.07 (dd, *J* = 14.4 and 2.8 Hz, 1H), 2.22 (d, *J* = 1.6 Hz, 3H), 2.25–2.28 (m, 1H), 2.44 (s, 3H), 2.64 (dd, *J* = 13.2 and 8.0 Hz, 1H), 2.86–2.89 (m, 2H), 3.89–3.95 (m, 4H), 4.98 (d, *J* = 8.0 Hz, 1H), 5.21–5.23 (m, 1H), 6.96–6.98 (m, 2H), 7.19–7.23 (m, 1H), 7.25–7.27 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.3, 18.2, 18.8, 21.0, 21.6, 23.5, 27.7, 31.0, 31.1, 31.3, 36.2, 36.5, 36.6, 39.5, 41.7, 44.8, 47.6, 49.5, 53.7, 54.7, 64.2, 64.4, 80.6, 109.3, 121.6, 124.5, 126.5, 127.5, 128.2, 128.3, 129.1, 137.0, 140.1, 142.9, 143.1, 150.2. HRMS (ESI-TOF) *m*/*z* for $C_{42}H_{55}N_2O_4S$ [M + H^+] calcd 683.3877, found 683.3874.

Pentacyclic steroid ***20***. Obtained from the 1-azadiene **6** (0.15 g, 0.3 mmol) and *p*-methoxyphenylacetaldehyde (67.6 mg, 0.45 mmol) following the general procedure (60 °C, 30 min). Pentacyclic steroid **20** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (0.145 g, 68%). Mp 99.8–101.0 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −270 (*c* 0.5 in CH_2Cl_2). IR (ATR) ν 813, 1032, 1094, 1160, 1247, 1332, 1511 and 2936 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.73 (s, 3H), 0.82–0.85 (m, 1H), 0.91–0.96 (m, 1H), 0.98 (s, 3H), 1.02–1.09 (m, 1H), 1.13–1.19 (m, 1H), 1.26–1.31 (m, 3H), 1.43–1.54 (m, 3H), 1.64–1.80 (m, 9H), 2.05–2.09 (m, 1H), 2.20 (d, *J* = 1.2 Hz, 3H), 2.24–2.28 (m, 1H), 2.44 (s, 3H), 2.47–2.53 (m, 3H), 2.59 (dd, *J* = 12.8 and 8.0 Hz, 1H), 2.85–2.88 (m, 2H), 3.80 (s, 3H), 3.90–3.95 (m, 4H), 4.93 (d, *J* = 8.0 Hz, 1H), 5.22–5.23 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz,

2H), 7.29 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.3, 18.2, 18.8, 21.0, 21.6, 23.5, 27.7, 31.0, 31.1, 31.3, 36.2, 36.5, 36.6, 39.6, 41.7, 44.9, 47.6, 49.5, 53.7, 53.9, 55.2, 64.2, 64.4, 80.8, 109.3, 113.7, 121.6, 124.4, 126.5, 127.5, 129.1, 129.1, 129.7, 135.0, 137.1, 140.1, 143.1, 150.2, 158.2. HRMS (ESI-TOF) m/z for $C_{43}H_{57}N_2O_5S$ [M + H^+] calcd 713.3983, found 713.3980.

Pentacyclic steroid ***21***. Obtained from the 1-azadiene **6** (0.15 g, 0.3 mmol) and *p*-nitrophenylacetaldehyde (74.3 mg, 0.45 mmol) following the general procedure (60 °C, 30 min). Pentacyclic steroid **21** was purified by flash chromatography [ethyl acetate/hexane (1 : 4)] and obtained as a yellow solid (0.163 g, 75%). Mp 113.5–115.3 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −270 (c 0.5 in CH_2Cl_2). IR (ATR) ν 676, 928, 1093, 1161, 1343, 1521, 1597 and 2940 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.76 (s, 3H), 0.81–0.86 (m, 1H), 0.92–0.96 (m, 1H), 0.99 (s, 3H), 1.02–1.08 (m, 1H), 1.13–1.20 (m, 1H), 1.25–1.44 (m, 4H), 1.51–1.79 (m, 12H), 2.05–2.08 (m, 1H), 2.22 (s, 3H), 2.26–2.28 (m, 1H), 2.43–2.53 (m, 2H), 2.47 (s, 3H), 2.78 (dd, J = 12.4 and 8.4 Hz, 1H), 2.86–2.87 (m, 2H), 3.88–3.97 (m, 4H), 4.88 (d, J = 8.0 Hz, 1H), 5.21 (br s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.3, 18.2, 18.8, 21.0, 21.6, 23.4, 27.9, 31.0, 31.1, 31.3, 36.2, 36.5, 38.8, 41.7, 44.8, 47.5, 49.4, 53.8, 54.4, 64.2, 64.4, 79.8, 109.3, 121.4, 123.7, 125.1, 127.4, 128.9, 129.3, 136.9, 140.2, 143.6, 146.8, 149.6, 150.4. HRMS (ESI-TOF) m/z for $C_{42}H_{54}N_3O_6S$ [M + H^+] calcd 728.3728, found 728.3729.

Pentacyclic steroid ***22***. Obtained from the 1-azadiene **6** (0.15 g, 0.3 mmol) and propanal (32.3 μL, 0.45 mmol) following the general procedure (60 °C, 30 min). Pentacyclic steroid **22** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (72.6 mg, 39%). Mp 118.0–119.7 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −80 (c 0.5 in CH_2Cl_2). IR (ATR) ν 669, 813, 950, 1086, 1099, 1155, 1167, 1336, 1457 and 2940 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.53 (pseudo t, J = 10.4 Hz, 1H), 0.69 (s, 3H), 0.93 (d, J = 6.4 Hz, 3H), 1.00 (s, 3H), 1.03–1.10 (m, 2H), 1.18–1.23 (m, 1H), 1.26–1.53 (m, 6H), 1.55–1.79 (m, 9H), 1.84–1.92 (m, 1H), 2.10 (dd, J = 14.4 and 2.6 Hz, 1H), 2.14 (d, J = 1.6 Hz, 3H), 2.20 (dd, J = 8.0 and 2.6 Hz, 1H), 2.40 (s, 3H), 2.52–2.56 (m, 3H), 2.75–2.86 (m, 2H), 3.89–3.96 (m, 4H), 4.61 (d, J = 7.2 Hz, 1H), 5.29–5.30 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.1, 18.2, 18.8, 20.5, 21.0, 21.5, 23.3, 27.9, 31.0, 31.3, 31.4, 36.2, 36.4, 36.6, 40.7, 41.7, 43.3, 44.6, 47.8, 49.3, 53.7, 64.2, 64.4, 80.4, 109.3, 121.6, 124.3, 127.3, 129.1, 137.2, 140.2, 142.9, 150.1. HRMS (ESI-TOF) m/z for $C_{37}H_{53}N_2O_4S$ [M + H^+] calcd 621.3721, found 621.3720.

Pentacyclic steroid ***23***. Obtained from the 1-azadiene **6** (0.15 g, 0.3 mmol) and butanal (32.3 μL, 0.45 mmol) following the general procedure (60 °C, 30 min). Pentacyclic steroid **23** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (97.1 mg, 51%). Mp 109.3–110.9 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −93 (c 0.75 in CH_2Cl_2). IR (ATR) ν 669, 929, 1088, 1099, 1165, 1337, 1458 and 2937 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.68 (s, 3H), 0.72–0.74 (m, 1H), 0.80 (t, J = 7.4 Hz, 3H), 0.93–0.97 (m, 1H), 1.00 (s, 3H), 1.04–1.13 (m, 2H), 1.21–1.31 (m, 3H), 1.38–1.50 (m, 5H), 1.60–1.73 (m, 7H), 1.75–1.79 (m, 2H), 1.85–1.93 (m, 1H), 2.10 (dd, J = 14.0 and 2.4 Hz, 1H), 2.15 (d, J = 1.6 Hz, 3H), 2.20–2.22 (m, 1H), 2.39 (s, 3H), 2.52–2.56 (m, 3H), 2.80–2.81 (m, 2H), 3.91–3.96 (m, 4H), 4.78 (d, J = 7.2 Hz, 1H), 5.29–5.30 (m, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 10.4, 17.1, 18.0, 18.8, 21.0, 21.5, 23.4, 25.9, 27.5, 31.0, 31.2, 31.4, 36.2, 36.5, 36.6, 38.2, 41.7, 44.5, 47.4, 48.2, 49.4, 53.8, 64.2, 64.4, 77.8, 109.3, 121.6, 123.9, 127.3, 128.9, 137.2, 140.2, 142.8, 150.3. HRMS (ESI-TOF) m/z for $C_{38}H_{55}N_2O_4S$ [M + H^+] calcd 635.3877, found 635.3874.

Pentacyclic steroid ***24***. Obtained from the 1-azadiene **6** (0.15 g, 0.3 mmol) and heptanal (63.4 μL, 0.45 mmol) following the general procedure (60 °C, 30 min). Pentacyclic steroid **24** was purified by flash chromatography [ethyl acetate/hexane (1 : 3)] and obtained as a white solid (0.108 g, 53%). Mp 79.6–81.2 °C (from ethyl acetate/hexane). $[\alpha]_D^{25}$ −100 (c 0.75 in CH_2Cl_2). IR (ATR) ν 669, 955, 1019, 1087, 1163, 1337, 1458 and 2931 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.65–0.70 (m, 1H), 0.69 (s, 3H), 0.89 (t, J = 7.2 Hz, 3H), 0.94–0.97 (m, 1H), 1.00 (s, 3H), 1.04–1.08 (m, 2H), 1.15–1.22 (m, 5H), 1.26–1.33 (m, 5H), 1.43–1.50 (m, 3H), 1.58–1.72 (m, 8H), 1.74–1.80 (m, 2H), 1.86–1.93 (m, 1H), 2.10 (dd, J = 14.4 and 2.8 Hz, 1H), 2.14 (d, J = 2.0 Hz, 3H), 2.19–2.22 (m, 1H), 2.40 (s, 3H), 2.51–2.56 (m, 3H), 2.78–2.81 (m, 2H), 3.90–3.95 (m, 4H), 4.77 (d, J = 7.2 Hz, 1H), 5.29–5.31 (m, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.1, 17.1, 18.1, 18.8, 21.0, 21.5, 22.7, 23.4, 25.6, 27.8, 31.0, 31.2, 31.4, 32.0, 33.8, 36.2, 36.5, 36.6, 38.7, 41.7, 44.5, 47.0, 47.3, 49.4, 53.8, 64.2, 64.4, 78.4, 109.3, 121.6, 124.0, 127.2, 129.0, 137.3, 140.2, 142.8, 150.2. HRMS (ESI-TOF) m/z for $C_{41}H_{61}N_2O_4S$ [M + H^+] calcd 677.4347, found 677.4340.

Conflicts of interest

There are no conflicts to declare.

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