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Diels–Alder reactivity of 4-aryl-1-phthalimido-2-siloxy-1,3-butadienes

Esther Caballero,[a,*] Dulce Alonso,[a] Rafael Peláez,[a] Concepción Álvarez,[a] Pilar Puebla,[a] Francisca Sanz,[b] Manuel Medarde[a] and Fernando Tomé[a,*]

[a]*Laboratorio de Química Orgánica y Farmacéutica, Facultad de Farmacia, Campus Miguel de Unamuno, 37007 Salamanca, Spain*
[b]*Servicio difracción de Rayos X, Salamanca, Spain*

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Abstract—The reaction of (1*Z*,3*E*) and (1*E*,3*E*) 4-aryl-1-phthalimido-2-trialkylsiloxy-1,3-butadienes with maleimides and quinones has been studied. The observed *exo*-stereospecifity can be attributed to the simultaneous presence of the phthalimido and aryl groups, which produce strong hindrance during the *endo* approach.

1. Introduction

Trialkylsiloxy-1,3-butadienes have been used as versatile reagents for the synthesis of functionalized ring systems via the Diels–Alder cycloaddition reaction. The most well known is 1-methoxy-3-trimethylsiloxy-1,3-butadiene, Danishefsky's diene (**I**)[1] (Fig. 1), which shows high reactivity towards a large number of dienophiles. Some time ago we began a line of research aimed at the synthesis of new siloxydienes, analogues of Danishefsky's diene, that contain at position C-1 an aromatic ring (the siloxy moiety lying at position C-3) and are useful for the synthesis, via Diels–Alder reaction, of 3-arylcyclohexenone derivatives as intermediates for the synthesis of more complex polycyclic systems related to marine alkaloids. As aryl groups we used phenyl, carrying electron donor or withdrawing groups (OMe, NO_2),[2] or heterocyclic moieties[3] such as indole, pyrrole or thiophene, these dienes showing high reactivity with dienophiles such as maleimides or quinones. In all the Diels–Alder reactions carried out with this family of 1-(aryl or heteroaryl)-3-trialkylsiloxy-1,3-butadienes, the *endo* cycloadducts were obtained.

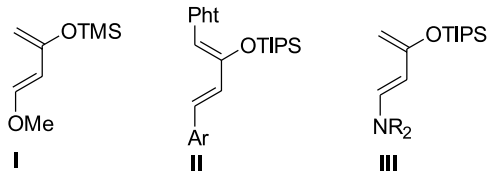

Figure 1.

Due to the presence of amino groups and derivatives in a large number of natural and synthetic products, we were interested in the development of new dienes that, in addition to these functional groups, would contain nitrogen groupings able to be transformed into the amino derivatives by simple transformations. To this end, 1-phthalimido-4-(aryl or heteroaryl)-2-trialkylsiloxy-1,3-butadienes (**II**) (Fig. 1) were designed. The incorporation of both siloxy and amino substituents into the diene structure has received little attention, although in recent years Rawal's group has been actively studying the chemistry of 1-amino-3-siloxy-1,3-butadienes (**III**) (Fig. 1).[4] These authors have shown that these dienes are highly reactive and that they undergo Diels–Alder reaction with complete regiocontrol and in some cases with exceptional diastereoselectivity. In our case, we are interested in the development of similar dienes, but changing the position between both groups. This change should lead to 1-amino-4-aryl-2-trialkylsiloxy-2-cyclohexenes that might be useful in the synthesis of different types of alkaloids.[5] The literature contains some references to studies on trialkylsilyl enol ethers aimed at introducing α-amino functionalization. Treatment with CAN/NaN_3 accompanied by hydrolysis of the siloxy group gives α-azidoketones,[6] whereas treatment with $(TsN)_2Se$ allows the enol function to be preserved and α-*N*-tosylaminosiloxyderivatives[7] to be obtained.

In our case, we are currently attempting to obtain 1-amino-

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* Corresponding authors. Tel.: +34 07923294528; fax: +34 07923294515 (E.C.); (F.T.); e-mail: escab@usal.es

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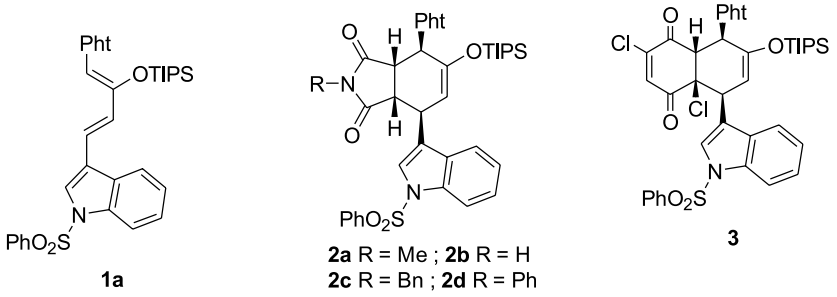
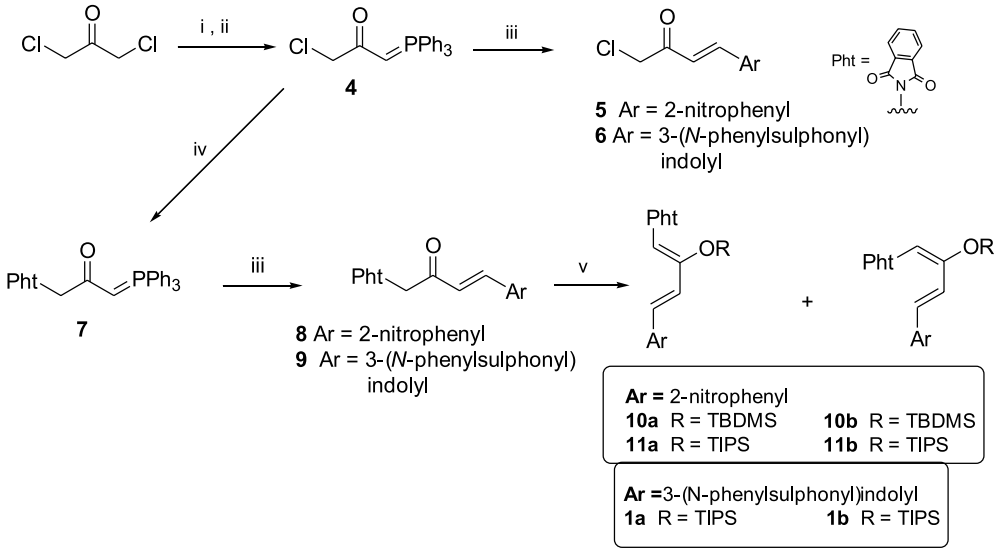


Figure 2.



Scheme 1. Reagents and conditions: (i) PPh_3/THF/reflux; (ii) Na_2CO_3/MeOH–H_2O, rt; (iii) Ar-CHO (1 equiv), C_6H_6, reflux; (iv) Potassium phthalimide, DMF, 100 °C; (v) TIPSOTf, or TBDMSOTf, Et_3N, CH_2Cl_2, 50 °C.

4-aryl-2-trialkylsiloxy-2-cyclohexenes through the Diels–Alder reaction by the use of conveniently functionalized dienes. First, we chose the phthalimido group as a precursor of the amino group. In this sense some preliminary studies have recently been published.[8] 1*Z*,3*E*-1-Phthalimido-4-(3-indolyl)-2-siloxy-1,3-butadiene (**1a**), prepared from 1,3-dichloroacetone, was assayed in the Diels–Alder reaction with maleimides and quinones as dienophiles. The reaction products **2** and **3** displayed the *exo* stereochemistry (Fig. 2), as deduced from NMR spectroscopy and X-ray diffraction studies, unlike the results obtained with related disubstituted dienes lacking the phthalimido substituent at C-1.[2a]

In this full paper we present further information from studies carried out with diene **1a**, its 1*E*,3*E* stereoisomer **1b** and related dienes carrying a 2-nitrophenyl group at C-4.

2. Results and discussion

Following a similar methodology to that previously described[8] (Scheme 1), intermediate **4** was prepared from 1,3-dichloroacetone and converted into the chloroenones **5** and **6**; very low yields were obtained. However, the nucleophilic substitution on **4** with potassium phthalimide took place conveniently to produce phosphorane **7**, which was coupled with 2-nitrobenzaldehyde, yielding the 2-nitroderivative **8**. From this synthetic intermediate, both stereoisomers **10a/10b** and **11a/11b** were obtained in a 3:1 ratio, by means of silylenolization in 2 h whereas from the 3-indole derivative **9** only **1a** was produced. In the latter case, longer reaction times (3 h or more) led to a mixture of **1a** and its stereoisomer **1b** in a 3:2 ratio.

The 3*E* configuration was established for all of these compounds by analysis of their ^{1}H NMR data, which showed a large coupling constant (15.6 Hz) between H-3 and H-4. The 1*Z* configuration in **10a** was deduced from the correlations observed between H-1 and H-4 protons in ROESY experiments (Fig. 3). Other correlations observed between the H-1 and H-3, H-4 and TBDMS could be explained in terms of the existence of an equilibrium between the *cisoid* and the *transoid* conformers of **10a**. Diene **10b** was more unstable than **10a**, as observed after

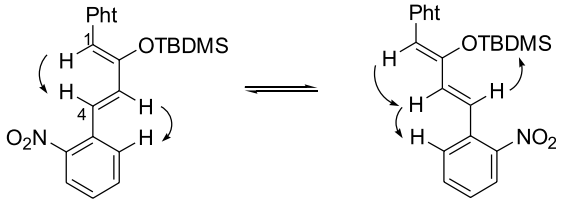
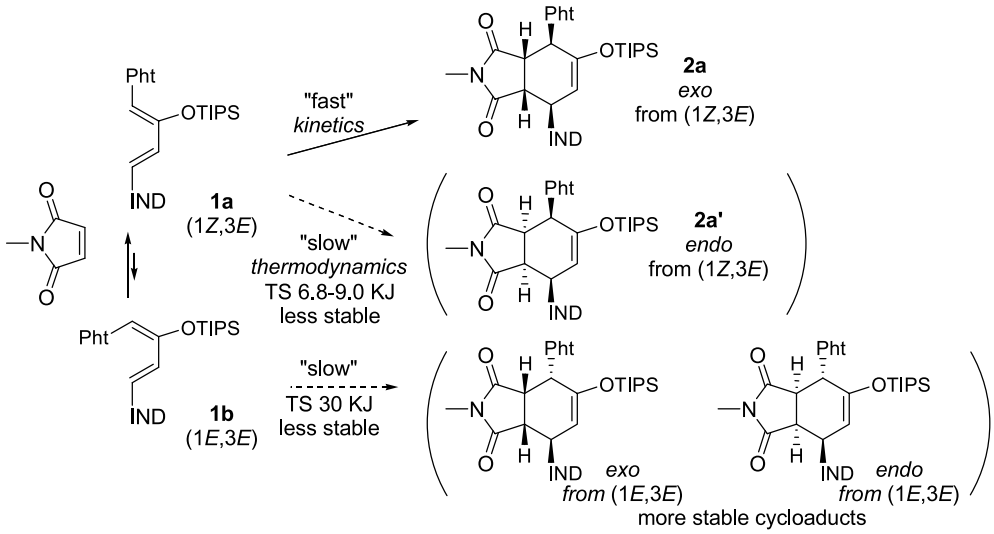


Figure 3. Selected ROESY correlations for **10a**.



Scheme 2. *endo*/*exo* Selectivity between **1a**+**1b** and *N*-methylmaleimide.

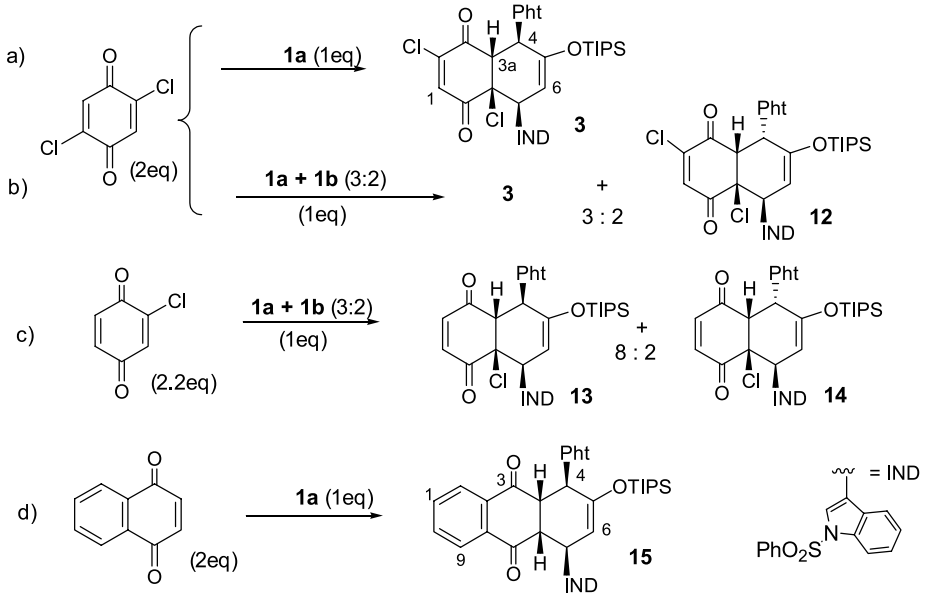
20 h in $CDCl_3$ solution, in which it isomerized to **10a**, accompanied by its transformation into enone **8**.

As reported, the different reaction time conditions allowed us to prepare **1a** (1*Z*,3*E*) or the **1a**+**1b** (1*Z*/*E*,3*E*) mixture, and hence we were able to use either the single stereoisomer or the mixture to study Diels–Alder reactivity.

In the first instance, we carried out the reaction between **1a** and maleimides (*N*-H, *N*-methyl, *N*-benzyl) and 2,5-dichloroquinone, which gave exclusively the *exo* adducts **2a**–**d** and **3**.

Following the same methodology, we performed the reaction between *N*-methylmaleimide and the mixture **1a**+**1b** (in 3:2 ratio), but only the *exo* cycloadduct **2a** was obtained with no reaction product derived from the *E*,*E* stereoisomer **1b** (Scheme 2). This implies a fast (as compared to the Diels–Alder reaction) equilibration of the dienes in solution, and either a higher reactivity of diene **1a** (kinetic control) or a higher stability of its adduct(s) (thermodynamic control). Molecular mechanics calculations (as implemented in the MM2 forcefield of Macromodel v.5.5) were carried out for representative *endo* and *exo* Diels–Alder transition states of the reaction between **1a** or **1b** and *N*-methylmaleimide and for the resulting cycloadducts. The stabilities of *exo* (**2a**) and *endo* (**2a**′) cycloadducts from **1a** (1*Z*,3*E*) were similar, but lower than those of cycloadducts that could be produced from **1b** (1*E*,3*E*).

Additionally, the *exo* transition state from **1a** was calculated to be 6.8–9.0 kJ/mol more stable than the *endo* one, and more than 30 kJ/mol more stable than those from **1b**. These observations suggest that the reaction would be controlled kinetically, yielding the less stable cycloadduct from the more reactive diene 1*Z*,3*E* through the more stable *exo* transition state. The interconversion of **1a** and **1b** under the



Scheme 3. Diels–Alder reactivity of **1a**, **1b** with quinones.

reaction conditions accounts for the formation of the cycloadducts derived only from the more reactive **1a** without the appearance of products derived from the less reactive **1b**. This interconversion was confirmed by refluxing pure **1a** in toluene, resulting in the formation of the equilibrium mixture **1a**+**1b** in a 3:2 ratio.

Next, we carried out several experiments with **1a** and differently substituted quinones (Scheme 3, entries a and d), and they gave the same stereochemical results as those observed with the maleimides. Thus, *exo* cycloadducts **3** and **15** were obtained. The structure of compound **3**, previously described, has now been confirmed by X-ray diffraction studies.[9] Figure 4 shows an ORTEP diagram in which the phthalimido and the chloro substituents occupy a pseudo-equatorial disposition and the indolyl an pseudo-axial disposition.

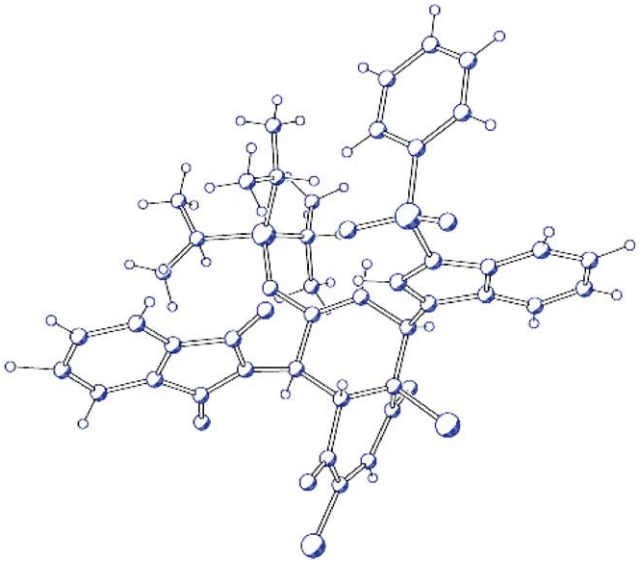


Figure 4. X-ray crystallographic analysis of **3**.

However, when mixtures of dienes **1a** and **1b** were reacted with an excess of quinones, mixtures of **3**+**12** and **13**+**14** were observed in the NMR spectra (Scheme 3, entries b and c). The main differences between them correspond to the H-2 of the indole (8.56 and 8.54 ppm) and H-3a (4.27 and 4.24 ppm) (values for **3**/**12**). In these cases, both dienes (1*Z*,3*E* and 1*E*,3*E*) afforded the corresponding adducts, contrary to the case of maleimides, where only adducts from diene **1a** were observed. The observed ratio between **3** and **12** was the same as that of the starting dienes, implying that both dienes have similar reactivities against the dichloroquinone and, since the reaction time (7 h) was similar to those of maleimides, that diene **1b** would be more reactive in this case than in the former one. When the reaction time required for the complete disappearance of diene was longer (20 h), as in the case of 2-chloroquinone, a higher ratio of the reaction product **13** derived from the 1*Z*,3*E* stereoisomer (**1a**) was observed. This indicates that in the equilibrium mixture diene **1a** is still more reactive than **1b**.

The dienes containing the 2-nitrophenyl moiety **10** and **11** were obtained as mixtures 1*Z*/1*E* (3:1) that were difficult to separate. We decided to use these mixtures in the Diels–Alder reaction with *N*-methylmaleimide and compare the results with those obtained from the **1a**+**1b** mixture. The reaction was carried out at a diene/dienophile 1:2 molar ratio in refluxing toluene, but no reaction was observed after 2 days. No evolution of the reaction was detected, even when $EtAlCl_2$ (20%) was added as catalyst and the reaction was heated to reflux. This lower reactivity could be explained in terms of the presence of two electron-withdrawing groups, the 2-nitrophenyl and the phthalimido moieties. We have previously shown that when only one of these electron-withdrawing groups is present, as is the case of 4-(2-nitrophenyl)-2-trialkylsiloxy-1,3-butadiene,[2b] the Diels–Alder reaction proceeds adequately.

In view of the good results obtained in the previous Diels–Alder reaction using the crude of the reaction produced in the synthesis of dienes (carrying the excess of triflate reagent), we decided to check the reactivity of dienes **10** and **11** again. The mixture **11a** and **11b** (3:1 ratio), without removing the excess of the triisopropyltriflate, was reacted with *N*-methylmaleimide and naphthoquinone, yielding **16** and **17** (Fig. 5) as the only reaction products after purification by chromatography and crystallization. In these products the *exo* stereochemistry was also proposed based on the ^{1}H NMR studies and it was confirmed by X-ray studies of **17**.[9] The formation of other stereoisomers from **11** was not detected by ^{1}H NMR of the reaction product.

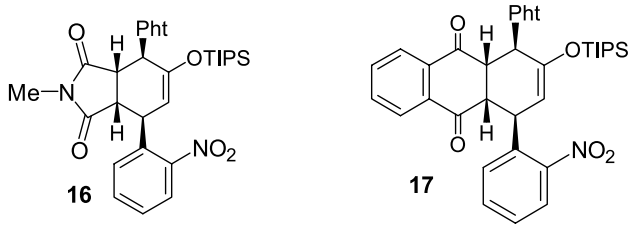
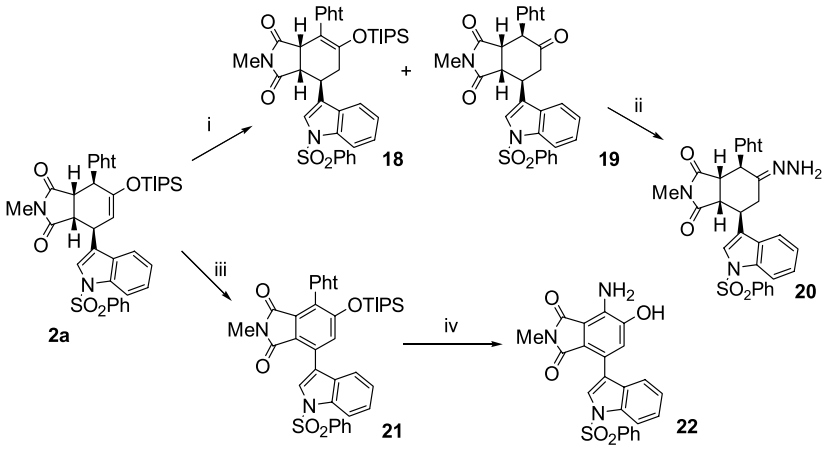


Figure 5.

From the above results, a noteworthy preference for the *exo* stereochemistry in the Diels–Alder reaction between the title dienes and maleimides or quinones can be deduced. Regardless of the nature of the C-4 aryl group, the presence of the phthalimido moiety on the C-1 of the diene produced a complete change of the preferred *endo*-stereochemistry of 4-aryl-2-siloxy-1,3-butadienes to the *exo*-stereochemistry now observed. This change would be due to the presence of a bulky *N*-substituent in the C-1 position of the diene and also to secondary interactions between the phthalimido and the aromatic ring with the dienophiles during the *exo* approach. In the case of 1-amino-3-siloxybutadienes, *endo*/*exo* mixtures, depending on the substituents of amino group have been observed. A combination of steric and electronic effects of dienes and dienophiles has been proposed to explain the factors influencing the stereoselectivity of these cycloadditions.[10] In any case, the high *exo*-stereoselectivity now observed by us has not been previously described.

After optimizing the Diels–Alder reaction, some transformations on the cycloadducts **2** were carried out to replace the



Scheme 4. Reagents and conditions: (i) HCl, CH_2Cl_2, rt; (ii) $NH_2NH_2 \cdot H_2O$, EtOH, reflux; (iii) DDQ, C_6H_6, reflux; (iv) $NH_2NH_2 \cdot H_2O$, THF, rt.

phthalimido by an amino group. These transformations are of interest in the application of this methodology to the synthesis of more elaborated polycyclic systems with fused heterocycles in their structures. Unfortunately, the usual deprotection of the phthalimido to the amino group by treatment with hydrazine[11] failed to produce any observable change. Other deprotection reactions such as treatment with methylamine,[12] also failed and thus we decided to check other transformations prior to the use of deprotecting agents.

When cycloadduct **2a** was treated with hydrochloric acid, two reaction products were isolated: compound **18** resulting from the double-bond migration, and the expected ketone **19** (Scheme 4). This migration has been observed for related cycloadducts carrying the double bond and the trialkylsiloxy substituent at the same position, producing compounds with the unsaturation closer to the ring system junction.[13] The preferred conformation of ketone **19** was similar to that of compound **2a**, as revealed by the large coupling constants between H-3a and H-4 or H-7 and H-7a in the ^{1}H NMR spectrum, in agreement with the pseudo-equatorial disposition of the phthalimido and indol-3-yl moieties. Ketone **19** gave hydrazone **20** by treatment with hydrazine but no product containing the amino function at the C-4 position was detected.

Another key step in the synthesis of fused polycyclic systems is the aromatization of the central cyclohexene ring to the corresponding benzene ring. In the present case, it is of interest to know whether this process takes place with or without elimination of the phthalimido moiety. Maintenance of the nitrogenated function is necessary for the construction of fused heterocycles, such as oxazoles. The aromatization of **2a** to **21** under DDQ standard conditions occurred in high yield, preserving the phthalimido moiety. Treatment of **21** with hydrazine afforded the expected deprotection of the amino group, thus obtaining the aminophenol derivative **22**.

3. Conclusions

We have efficiently prepared new trisubstituted dienes and studied their reactivity against different dienophiles. 1-Phthalimido-2-trialkylsiloxy-4-aryl-1,3-butadienes were highly reactive when the crude of the silylation enone reaction was used. The stereochemistry of the cycloadducts, regardless of the structure of the aromatic moiety, changed from the usually preferred *endo* when position C-4 was not substituted to the *exo*, when the bulky *N*-phthalimido was present in this position. The present methodology offers a way to obtain fused cyclohexene rings containing amino (under the protected phthalimido moiety) and an aromatic (heteroaromatic) groups as substituents. The resulting cycloadducts are versatile synthetic intermediates for the preparation of diverse heterocyclic systems.

4. Experimental

Melting points were determined on a Büchi 510 instrument and are uncorrected. NMR spectra were recorded on Bruker 400 MHz DRX spectrometer in $CDCl_3$ as solvent with TMS as internal standard. Mass spectra were obtained by EI or FAB methods on a VGTS-250 mass spectrometer. Microanalyses were carried out on Perkin-Elmer 2400 CHN. Flash chromatography was performed with Merck 60 silica gel (0.063–0.2 or 0.040–0.063 mm).

4.1. Preparation of (*E*)-*N*-[4-(aryl or 3-indolyl)-2-oxo-3-butenyl]phthalimide 8 and 9

To 1,3-dicholoroacetone (7.0 g, 55 mmol), a solution of triphenylphosphine (13.1 g, 50 mmol) in THF (33 mL) was added and the mixture was refluxed for 4 h. The monophosphonium chloride thus formed was isolated by filtration (15.6 g, 73%) and then treated with a solution of Na_2CO_3/MeOH–H_2O (1:1) at rt. After 30 min a precipitate appeared, **4**, and was filtered from the solution (12.2 g, 89%). To a suspension of **4** (3 mmol) in dry benzene, a solution of the 2-nitrobenzaldehyde (1 mmol) or *N*-(phenylsulphonyl)-3-indolylcarbaldehyde (1 mmol) was added. Compound **5** (54%) was obtained after reflux for 24 h, purification by chromatography and crystallization. In the case of **6**, the reaction was much slower and after 4 days at reflux it was isolated in 15% yield.

A solution of **4** (1.5 g, 4.25 mmol) in DMF (5 mL) was

added dropwise to a stirred suspension of potassium phthalimide (2.4 g, 12.7 mmol) in DMF (35 mL) and left to reflux for 45 min. After extraction with EtOAc, it was washed with water and brine, dried and evaporated in vacuo, and the residue was crystallized (ether/MeOH) to obtain **7** (1.1 g, 62%). To phosphorane **7** (1.5 mmol), under the same conditions described previously, the corresponding aldehyde (1 mmol) was added to give, after 2 h of reaction, **8** (78%). Phosphorane **7** (1 mmol) and *N*-(phenylsulphonyl)-3-indolylcarbaldehyde (2 mmol), under the conditions described previously, yielded **9** (79%) after 72 h of reaction.

4.1.1. Data for 4. White solid. Mp 180 °C (MeOH/H_2O); ^{1}H NMR (δ ppm) 7.8–7.2 (15H, m), 4.28 (1H, d, J=23.8 Hz), 4.02 (2H, s).

4.1.2. Data for 5. Yellow solid. ^{1}H NMR (δ ppm) 8.10 (1H, d, J=16.0 Hz), 8.06 (1H, d, J=8.4 Hz), 8.1–7.5 (3H, m), 6.82 (1H, d, J=16.0 Hz), 4.34 (2H, s).

4.1.3. Data for 6. Yellow solid. ^{1}H NMR (δ ppm) 8.0–7.3 (9H, m), 7.94 (1H, s), 7.84 (1H, d, J=15.8 Hz), 7.09 (1H, d, J=15.8 Hz), 4.28 (2H, s).

4.1.4. Data for 7. White solid. Mp 222 °C (ether/MeOH); ^{1}H NMR (δ ppm) 7.81 (2H, dd, J=5.0, 3.3 Hz), 7.7–7.5 (15H, m), 7.39 (2H, dd, J=5.3, 3.3 Hz), 4.46 (2H, s), 3.68 (1H, d, J=23.0 Hz).

4.1.5. Data for 8. Yellow solid. Mp 180 °C (ether); ^{1}H NMR (δ ppm) 8.18 (1H, d, J=16.4 Hz), 8.10 (1H, d, J=8.2 Hz), 7.90 (2H, dd, J=5.2, 3.2 Hz), 7.7–7.5 (3H, m), 7.76 (2H, dd, J=5.2, 3.2 Hz), 6.70 (1H, d, J=16.4 Hz), 4.85 (2H, s). Anal. Calcd for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.60; N, 8.33. Found: C, 64.46; H, 3.83; N, 8.15. HRMS *m/z* calcd for $C_{18}H_{12}N_2O_5$ 336.0746, found 336.0792.

4.1.6. Data for 9. Yellow solid. Mp 184 °C (ether); ^{1}H NMR (δ ppm) 8.02 (1H, dd, J=7.2, 2.0 Hz), 7.94 (1H, s), 7.9–7.3 (12H, m), 7.83 (1H, d, J=16.4 Hz), 6.93 (1H, d, J=16.4 Hz), 4.78 (2H, s). Anal. Calcd for $C_{26}H_{18}N_2O_5S$: C, 66.37; H, 3.86; N, 5.95; S, 6.82. Found: C, 66.08; H, 4.12; N, 6.03; S, 6.66. HRMS *m/z* calcd for $C_{26}H_{18}N_2O_5S$ 470.0936, found 470.0951.

4.2. General procedure for the preparation of 2-trialkylsiloxy-4-(2-nitrophenyl)-1-phthalimido-1,3-butadienes (10 and 11)

To a solution of enone **8** (1 mmol) in CH_2Cl_2 (20 mL) under Ar, Et_3N (5.4 mmol) and *tert*-butyldimethyl- or triisopropylsilyltriflate (4 mmol) were added dropwise. The reaction mixture was allowed to react at 50 °C for 2 h, and then Et_3N (1 mmol) was added. The mixture was diluted in CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and the solvent evaporated.

The corresponding reaction product was purified by flash chromatography on SiO_2 eluting with hexane/ether (1:1) to give **10a** (63%) and **10b** (21%).

4.2.1. Data for 10a. Yellow oil. ^{1}H NMR (δ ppm) 7.93 (1H, dd, J=8.4, 1.2 Hz, H-3Ar), 7.89 (2H, dd, J=5.2, 3.2 Hz, H-3, 6Pht), 7.75 (2H, dd, J=5.2, 3.2 Hz, H-4, 5Pht), 7.68 (1H, dd, J=7.6, 0.8 Hz, H-6Ar), 7.59 (1H, td, J=8.0, 0.8 Hz, H-5Ar), 7.45 (1H, d, J=15.6 Hz, H-4), 7.40 (1H, td, J=8.4, 0.8 Hz, H-4Ar), 6.73 (1H, d, J=15.6 Hz, H-3), 5.95 (1H, s, H-1), 0.90 (9H, TBDMS), 0.00 (6H, TBDMS). ^{13}C NMR (δ ppm) 166.3 (2-C), 149.8 (C), 148.2 (C), 134.4 (2-CH), 133.0 (CH), 132.3 (2-C), 131.7 (C), 129.3 (CH), 128.5 (CH), 128.1 (CH), 125.6 (CH), 124.8 (CH), 123.6 (2-CH), 105.2 (CH), 25.6 (3-CH_3), 18.2 (C), −4.2 (2-CH_3).

4.2.2. *Characteristic signals for* 10b. ^{1}H NMR (δ ppm) 7.34 (1H, d, J=15.3 Hz, H-4), 6.53 (1H, d, J=15.3 Hz, H-3), 5.80 (1H, s, H-1).

4.3. Diels–Alder reaction. General procedure

The corresponding diene (obtained without removing the excess of triisopropylsilyltriflate) (1 equiv) and dienophile (maleimides or quinones) (2–2.2 equiv) were dissolved in dry toluene and allowed to react at reflux for several hours under Ar atmosphere. The reaction products were purified by chromatography and crystallization to give compounds **3**, **13**–**17**.

4.3.1. (±)(1*R*,4*S*,4a*R*,8a*S*)-2-[4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-4a,7-dichloro-5,8-dioxo-2-triisopropylsiloxy-1,4,4a,5,8,8a-hexahydro-1-naphthyl]isoindole-1,3-dione (3). After 7 h reflux, **3** was isolated in 85% yield as a brown solid. Mp 242 °C (hexane/AcOEt). ^{1}H NMR (δ ppm) 8.56 (1H, s, H-2 Ind), 8.2–7.2 (13H, Ar), 7.17 (1H, s, H-1), 5.12 (1H, dd, J=6.0, 1.2 Hz, H-6), 5.04 (1H, dt, J=10.8, 1.2 Hz, H-4), 4.77 (1H, dd, J=6.0, 1.2 Hz, H-7), 4.27 (1H, d, J=10.8 Hz, H-3a), 1.0–0.9 (TIPS). ^{13}C NMR (δ ppm) 186.6 (C), 186.5 (C), 167.6 (C), 166.8 (C), 145.7 (C), 144.3 (C), 137.4 (C), 135.4 (C), 134.6 (2-CH), 133.9 (CH), 133.6 (CH), 131.8 (C), 131.4 (C), 131.1 (C), 129.1 (2-CH), 126.8 (2-CH), 124.7 (CH), 123.9 (CH), 123.8 (2-CH), 123.2 (CH), 121.8 (C), 120.1 (CH), 114.0 (CH), 104.7 (CH), 69.4 (C), 54.2 (CH), 49.1 (CH), 34.4 (CH), 17.6 (6-CH_3), 12.7 (3-CH). HRMS *m/z* Calcd for $C_{41}H_{40}Cl_2N_2O_7SSi$ 802.1703, found 802.1780.

Characteristic signals for **12**. ^{1}H NMR (δ ppm) 8.54 (1H, s, H-2 Ind), 4.24 (1H, d, J=10.8 Hz, H-3a).

4.3.2. (±)(1*R*,4*S*,4a*R*,8a*S*)-2-[4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-4a-chloro-5,8-dioxo-2-triisopropylsiloxy-1,4,4a,5,8,8a-hexahydro-1-naphthyl]isoindole-1,3-dione (13). After 20 h reflux, a mixture 8:2 ratio (in ^{1}H NMR) of **13** and **14** was isolated in 79% yield as a brown solid. Data for **13**: ^{1}H NMR (δ ppm) 8.58 (1H, s, H-2 Ind), 8.1–7.2 (13H, Ar), 6.91 (1H, d, J=10.4 Hz, H1), 6.67 (1H, dd, J=10.4, 2.0 Hz, H-2), 5.13 (1H, dd, J=6.0, 1.2 Hz, H-6), 5.06 (1H, dt, J=10.8, 1.2 Hz, H-4), 4.76 (1H, dd, J=6.0, 1.2 Hz, H-7), 4.13 (1H, dd, J=10.8, 2.0 Hz, H-3a), 1.0–0.9 (TIPS). ^{13}C NMR (δ ppm) 193.8 (C), 189.0 (C), 127.0 (2-C), 144.4 (C), 138.1 (C), 137.6 (C), 137.1 (C), 137.0 (CH), 134.5 (2-CH), 133.6 (CH), 131.9 (C), 131.5 (C), 131.2 (C), 129.0 (2-CH), 127.0 (2-CH), 124.6 (CH), 123.9 (2-CH), 123.6 (CH), 123.1 (CH), 122.1 (C), 120.2 (CH), 114.0 (CH), 104.5 (CH), 69.1 (C), 54.4 (CH), 49.3 (CH), 34.4 (CH), 16.6 (6-CH_3), 13.7 (3-CH). HRMS *m/z* calcd for $C_{41}H_{41}ClN_2O_7SSi$ 768.2092, found 768.2105.

Characteristic signals for **14**. ^{1}H NMR 8.53 (δ ppm) (1H, s, H-2 Ind), 4.11 (1H, dd, J=10.8, 2.0 Hz, H-3a).

4.3.3. (±)(1*R*,4*R*,4a*S*,9a*S*)-2-[4-(1-Benzenesulfonyl-1*H*-indol-3-yl-9,10-dioxo-2-triisopropylsiloxy-1,4,4a,9,9a,10-hexahydro-1-anthryl]isoindole-1,3-dione (15). After 13 h reflux, **15** was isolated in 90% as a white solid. Mp 225 °C (hexane/AcOEt). ^{1}H NMR (δ ppm) 8.11 (1H, s, H-2 Ind), 8.3–7.2 (17H, Ar), 5.25 (1H, dd, J=5.2, 1.6 Hz, H-6), 4.89 (1H, dd, J=11.2, 1.6 Hz, H-4), 4.80 (1H, d, J=5.2 Hz, H-7), 3.89 (1H, dd, J=11.2, 4.8 Hz, H-3a), 3.40 (1H, d, J=4.8 Hz, H-7a), 1.0–0.9 (TIPS). ^{13}C NMR (δ ppm) 195.1 (C), 194.7 (C), 167.8 (C), 167.6 (C), 145.7 (C), 137.9 (C), 135.8 (C), 134.8 (CH), 134.6 (2-CH), 134.3 (CH), 134.1 (CH), 134.1 (C), 133.6 (CH), 133.1 (C), 131.9 (2-C), 129.3 (C), 129.0 (2-CH), 127.4 (CH), 127.2 (2-CH), 127.0 (CH), 126.7 (CH), 124.8 (CH), 124.1 (C), 123.3 (2-CH), 118.5 (CH), 114.2 (CH), 103.5 (CH), 50.7 (CH), 48.3 (CH), 47.3 (CH), 28.7 (CH), 17.7 (6-CH_3), 12.4 (3-CH). HRMS *m*/*z* calcd for $C_{45}H_{44}N_2O_7SSi$ 784.2716, found 784.2726.

4.3.4. (±)(3a*S*,4*R*,7*R*,7a*S*)-2-Methyl-7-(2-nitrophenyl)-4-phthalimido-5-triisopropylsiloxy-3a,4,7,7a-tetrahydro isoindole-1,3-dione (16). After 7 h reflux, **16** was isolated in 87% yield as a yellow solid. ^{1}H NMR (δ ppm) 7.90 (1H, dd, J=7.8, 1.5 Hz, H-3Ar), 7.79 (1H, dd, J=7.8, 1.5 Hz, H-6Ar), 7.71 (1H, td, J=7.8, 1.5 Hz, 1H, H-5Ar), 7.45 (1H, dt, J=7.8, 1.5 Hz, H-4Ar), 7.7–8.0 (4H, m, Pht), 5.10 (1H, dt, J=8.0, 2.4 Hz, H-4), 4.91 (1H, t, J=2.4 Hz, H-6), 4.50 (1H, dt, J=8.0, 2.4 Hz, H-7), 3.82 (1H, t, J=8.0 Hz, H-3a), 3.27 (1H, t, J=8.0 Hz, H-7a), 2.99 (3H, s, N-Me), 1.1–0.8 (TIPS). ^{13}C NMR (δ ppm) 176.3 (2-C), 167.7 (2-C), 149.4 (C), 147.4 (C), 138.1 (C), 134.1 (2-CH), 133.5 (CH), 131.9 (2-C), 130.6 (CH), 128.0 (CH), 124.6 (CH), 123.4 (2-CH), 103.8 (CH), 46.1 (CH), 45.4 (CH), 42.8 (CH), 35.1 (CH), 24.8 (CH_3), 17.7 (6-CH_3), 12.4 (3-CH). HRMS *m*/*z* calcd for $C_{32}H_{37}N_3O_7Si$ 603.2401 found, 603.2479.

4.3.5. (±)(1*R*,4*R*,4a*S*,9a*S*)-2-[4-(2-Nitrophenyl-9,10-dioxo-2-triisopropylsiloxy-1,4,4a,9,9a,10-hexahydro-1-anthryl]isoindole-1,3-dione (17). After 7 h reflux, **17** was isolated in 84% yield as a brown solid. ^{1}H NMR (δ ppm) 8.41 (1H, dd, J=8.1, 1.2 Hz, H-6Ar), 8.17 (1H, dd, J=7.5, 1.2 Hz, H-9), 7.96 (1H, dd, J=7.5, 1.2 Hz, H-2), 7.92 (1H, dd, J=8.1, 1.2 Hz, H-3Ar), 7.76 (1H, td, J=8.0, 1.2 Hz, 1H, H-5Ar), 7.7–7.9 (6H, m, H-1, H-10, Pht), 7.46 (1H, dt, J=8.1, 1.2 Hz, H-4Ar), 5.08 (1H, d, J=5.2 Hz, H-7), 5.05 (1H, dd, J=5.2, 1.2 Hz, H-6), 4.95 (1H, dd, J=10.8, 1.2 Hz, H-4), 4.00 (1H, dd, J=10.8, 4.8 Hz, H-3a), 3.82 (1H, d, J=4.8 Hz, H-7a), 1.1–0.8 (TIPS). ^{13}C NMR (δ ppm) 195.2 (C), 193.6 (C), 167.6 (2C), 148.9 (C), 146.9 (C), 137.3 (C), 134.8 (CH), 134.6 (CH), 133.5 (C), 133.4 (CH), 132.8 (CH), 131.8 (2-CH), 131.7 (2-C), 130.3 (C), 128.0 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 123.3 (2-CH), 104.2 (CH), 51.9 (CH), 48.3 (CH), 47.5 (CH), 33.8 (CH), 17.3 (6-CH_3), 12.7 (3-CH). HRMS *m*/*z* calcd for $C_{37}H_{38}N_2O_7Si$ 650.2448, found 650.2526.

4.4. Hydrolysis of cycloadduct 2a (18 and 19)

Compound **2a** (75 mg, 0.10 mmol) dissolved in 4 mL of CH_2Cl_2 was treated with concentrated HCl (360 µl) and then stirred for 24 h. The reaction mixture was washed with saturated $NaHCO_3$ dried and evaporated. The reaction product was chromatographed on silica (hexane/EtOAc 7:3) to give **18** (38 mg, 50%) and **19** (22 mg, 36%).

4.4.1. (±)(3a*S*,4*R*,7a*S*)-4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-methyl-7-phthalimido-6-triisopropylsiloxy-3a,4,5,7a-tetrahydroisoindole-1,3-dione (18). White solid. Mp 252 °C (ether/MeOH). ^{1}H NMR (δ ppm) 8.04 (1H, d, J=8.2 Hz, H-7 Ind), 7.93 (1H, s, H-2 Ind), 7.56 (1H, d, J=7.2 Hz, H-4 Ind), 7.35 (1H, t, J=8.2 Hz, H-6 Ind), 7.3–8.2 (10H, m, Ar), 4.20 (1H, m, H-7), 4.04 (1H, dd, J=8.0, 2.4 Hz, H-3a), 3.42 (1H, t, J=8.0 Hz, H-7a), 3.02 (3H, s, N-Me), 2.86 (1H, ddd, J=16.8, 2.8, 1.2 Hz, H-6), 2.38 (1H, d, J=16.8 Hz, H-6), 1.0–0.8 (TIPS). ^{13}C NMR (δ ppm) 177.2 (C), 175.2 (C), 167.8 (C), 166.0 (C), 149.7 (C), 133.9 (CH), 133.8 (CH), 138.2 (C), 134.7 (C), 133.5 (CH), 132.5 (C), 132.2 (C), 129.5 (C), 129.1 (2-CH), 127.4 (2-CH), 124.9 (CH), 123.6 (CH), 123.5 (CH), 123.3 (CH), 123.1 (CH), 122.3 (C), 118.6 (CH), 113.7 (CH), 102.1 (C), 44.2 (CH), 41.3 (CH), 32.3 (CH_2), 28.1 (CH), 25.1 (CH_3), 16.9 (6-CH_3), 12.8 (3-CH). Anal. Calcd for $C_{40}H_{43}N_3O_7SSi$: C, 65.10; H, 5.87; N, 5.69; S, 4.35. Found: C, 65.34; H, 6.00; N, 5.91; S, 4.19.

4.4.2. (±)(3a*S*,4*R*,7*R*,7a*S*)-7-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-methyl-4-phthalimidotetrahydro isoindole-1,3,5-trione (19). White solid. Mp 196 °C (ether/MeOH). ^{1}H NMR (δ ppm) 7.98 (1H, d, J=8.2 Hz, H-7 Ind), 7.70 (1H, s, H-2 Ind), 7.55 (1H, d, J=7.3 Hz, H-4 Ind), 7.35 (1H, t, J=7.2 Hz, H-6 Ind), 7.2–8.0 (10H, m, Ar), 5.09 (1H, d, J=12.1 Hz, H-4), 4.17 (1H, dd, J=12.0, 9.4 Hz, H-3a), 3.93 (1H, td, J=11.0, 4.8 Hz, H-7), 3.73 (1H, dd, J=11.0, 9.4 Hz, H-7a), 2.98 (3H, s, N-Me), 2.93 (2H, m, H-6). ^{13}C NMR (δ ppm) 199.1 (C), 175.3 (2-C), 167.4 (2-C), 138.0 (C), 135.3 (C), 134.3 (2-CH), 133.8 (CH), 131.7 (2-C), 129.2 (2-CH), 126.9 (2-CH), 125.2 (CH), 124.1 (CH), 123.8 (2-CH), 123.4 (CH), 121.3 (C), 119.0 (CH), 117.4 (C), 114.1 (CH), 54.1 (CH), 43.9 (CH), 43.7 (CH_2), 39.0 (CH), 30.4 (CH), 25.1 (CH_3). Anal. Calcd for $C_{31}H_{23}N_3O_7S$: C, 64.02; H, 3.99; N, 7.22; S, 5.51. Found: C, 64.34; H, 4.020; N, 7.51; S, 5.19.

4.4.3. (±)(3a*S*,4*R*,7*R*,7a*S*)-7-(1-Benzenesulfonyl-1*H*-indol-3-yl)-5-hydrazono-2-methyl-4-phthalimido hexahydroisoindole-1,3-dione (20). One millimole of **19** in EtOH was treated with 3 mmol of hydrazine hydrate for 24 h at reflux. By crystallization, **20** was isolated in 90% yield as a yellow solid. Mp 239 °C (ether/MeOH). ^{1}H NMR (δ ppm) 7.96 (1H, d, J=8.2 Hz, H-7 Ind), 7.72 (1H, s, H-2 Ind), 7.52 (1H, d, J=7.3 Hz, H-4 Ind), 7.33 (1H, t, J=7.2 Hz, H-6 Ind), 7.2–8.0 (10H, m, Ar), 5.26 (1H, d, J=12.0 Hz, H-4), 4.38 (1H, dd, J=12.0, 9.2 Hz, H-3a), 3.68 (1H, td, J=9.0, 4.0 Hz, H-7), 3.59 (1H, t, J=9.2 Hz, H-7a), 2.94 (3H, s, N-Me), 2.93 (2H, m, H-6). ^{13}C NMR (δ ppm) 175.8 (2-C), 167.9 (2-C), 141.1 (C), 138.1 (C), 134.0 (2-CH), 135.3 (C), 132.0 (2-C), 133.7 (CH), 129.2 (2-CH), 126.9 (2-CH), 126.0 (CH), 125.8 (C), 124.1 (CH), 123.8 (2-CH), 123.5 (CH), 121.9 (C), 119.1 (CH), 114.1 (CH), 49.3 (CH), 43.5 (CH), 39.2 (CH), 31.7 (CH_2), 30.4 (CH), 24.9 (CH_3). Anal. Calcd for $C_{31}H_{24}N_4O_6$: C, 64.10; H, 4.17; N, 9.85; S, 5.52. Found: C, 63.90; H, 4.46; N, 9.88; S, 5.49.

4.4.4. 7-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-methyl-4-phthalimido-5-triisopropylsiloxyisoindole-1,3-dione

(21). To **2a** (50 mg, 0.07 mmol) dissolved in benzene (4 mL) was added DDQ (22 mg, 0.09 mmol), and the mixture was refluxed for 24 h. The crude reaction was diluted in AcOEt, washed with $NaHCO_3$ and brine, dried and evaporated to yield **21** (38 mg, 75%). Red solid. ^{1}H NMR (δ ppm) 8.20 (1H, s, H-2 Ind), 8.01 (1H, d, $J=7.0$ Hz, H-7 Ind), 7.3–8.1 (12H, m, Ar), 7.38 (1H, s, H-6), 3.07 (3H, s, N-Me), 1.1–0.9 (TIPS). ^{13}C NMR (δ ppm) 173.1 (C), 172.6 (C), 166.5 (C), 165.8 (C), 158.1 (C), 138.0 (C), 134.9 (C), 134.4 (2-CH), 134.0 (CH), 132.7 (2-C), 129.2 (2-CH), 128.0 (CH), 127.3 (2-CH), 126.5 (C), 125.0 (CH), 124.5 (C), 124.4 (CH), 123.6 (CH), 123.9 (2-CH), 121.0 (C), 120.1 (C), 119.6 (CH), 118.3 (C), 116.0 (C), 114.0 (CH), 24.0 (CH_3), 17.3 (6-CH_3), 12.7 (3-CH).

4.4.5. 4-Amino-7-(1-benzenesulfonyl-1*H*-indol-3-yl)-5-hydroxy-2-methylisoindole-1,3-dione (22). One millimole of **21** in THF was treated with an excess of hydrazine hydrate for 20 h at rt. The reaction product was submitted to chromatography to give **22** in 41% yield as a red solid. ^{1}H NMR (δ ppm) 8.02 (1H, dd, $J=7.2$, 1.6 Hz, H-7 Ind), 7.98 (1H, s, H-2 Ind), 7.4–8.0 (5H, m, Ar), 7.38 (1H, s, H-6), 7.28 (1H, t, $J=7.2$ Hz, H-6 Ind), 7.19 (1H, t, $J=7.2$ Hz, H-5 Ind), 6.98 (1H, s, H-6), 3.08 (3H, s, N-Me). ^{13}C NMR (δ ppm) 169.6 (C), 168.7 (C), 167.6 (C), 147.9 (C), 143.0 (C), 140.3 (C), 138.0 (C), 135.1 (C), 134.7 (C), 133.8 (CH), 129.2 (2-CH), 127.1 (2-CH), 126.6 (CH), 124.6 (CH), 123.3 (CH), 120.0 (CH), 118.9 (CH), 117.3 (C), 113.6 (CH), 102.6 (C), 23.5 (CH_3). HRMS *m/z* calcd for $C_{23}H_{17}N_3O_5S$ 447.0889, found 447.0892.

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