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1-Phthalimido-4-(3-indolyl)-2-siloxy-1,3-butadienes: synthesis and Diels–Alder reactivity

Esther Caballero,[a,*] Dulce Alonso,[a] Rafael Peláez,[a] Concepción Alvarez,[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—New 1-phthalimido-4-(3-indolyl)-2-trialkylsiloxy-1,3-butadienes were easily prepared from 1,3-dichloropropanone and their configurations were established from NMR data. Their Diels–Alder reactivity with different maleimides and quinones was studied, high yields of the *exo* cycloadducts being obtained, as confirmed by X-ray diffraction studies.

Several years ago, we started a research line directed at the synthesis of new siloxydienes and the study of their reactivity in the Diels–Alder reaction as a method to access different bioactive compounds. We reported the application of new 1-(methoxyphenyl)-3-siloxy-1,3-butadienes to the synthesis of some analogues of rebeccamycin.[1] We also applied this methodology to the total synthesis of the alkaloid arcyriaflavin-A from 1-(2-nitrophenyl)-3-*tert*-butyldimethylsiloxy-1,3-butadiene.[2] Recently, we reported the Diels–Alder reactivity of (*E*)-1-(3-indolyl)-3-*tert*-butyldimethylsiloxy-1,3-butadienes, which show good reactivity towards different dienophiles, such as maleimides, 4-phenyl-1,2,4-triazolidine-3,5-dione, acetylenedicarboxylate, and quinones.[3] The *endo* cycloadducts were always obtained in the aforementioned cases.

We have now designed new trisubstituted 1-amino-4-(aryl or heteroaryl)-2-trialkylsiloxy-1,3-butadienes in which the latent amino group can be introduced in different forms, such as phthalimido (Pht), formamido or azido groups, to be readily unmasked later under mild conditions. Several 1-amino-3-siloxy-1,3-butadienes and their applications in Diels–Alder reactions have been reported by Rawal's group[4] but, as far as we are aware, 1-amino-2-siloxy-1,3-butadienes have not yet been reported.

In this communication we describe the preparation and Diels–Alder reactivity of 1-phthalimido-4-[(*N*-phenylsulfonyl)-3-indolyl)]-2-triisopropylsiloxy-1,3-butadiene, designed for the synthesis of granulatimide, other natural products, and their analogues. Granulatimide (**1**) is a marine alkaloid isolated from extracts of the Brazilian ascidian *Didemnum granulatum*[5] and shows activity as a G2 checkpoint inhibitor.[6] Our approach to the synthesis of **1** and its analogue **2** is based on a retrosynthetic analysis that has 4-amino-7-(aryl or heteroaryl) perhydroisoindole-1,3,5-triones as key synthetic intermediates, as depicted in Scheme 1.

The preparation of these new dienes follows a straightforward route (Schemes 2 and 3). 1,3-Dichloropropanone was easily transformed into the phosphorane **4**,[7] and a Wittig reaction between **4** (1 equiv) and *N*-phenylsulfonylindole-3-carbaldehyde (1 equiv) yielded **5** (58%) in addition to undesired **6** (30%), which resulted from an intramolecular Wittig reaction. When an excess of the aldehyde (2 equiv) was added, only **5** (80%) was obtained. Wittig reactions of cyclic imides, including phthalimides, are known, although intramolecular examples are relatively rare.[8] Related reactions have also been described for the synthesis of 3-hydroxypyrroles[9] or 1*H*-pyrrolizine-3,6-(2*H*,5*H*)-dione.[10]

The title diene was prepared by enol silylation of the enone **5** with triisopropylsilyl triflate. The best conditions were found when 4 mol of triflate and 5.4 mol of Et_3N per mol of **5** were used in CH_2Cl_2 for 2 h at 50 °C. Under these conditions, only the 1*Z*,3*E* diene **7** (89%)

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* Corresponding author. Tel.: +34-923-294528; fax: +34-923-294515; e-mail: escab@usal.es

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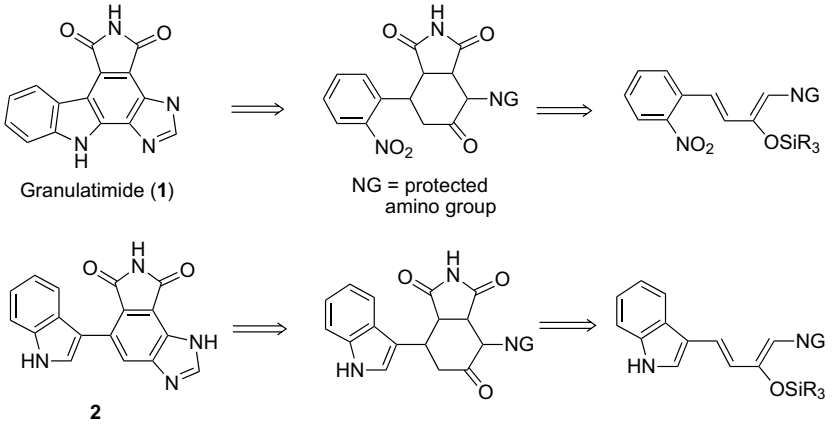
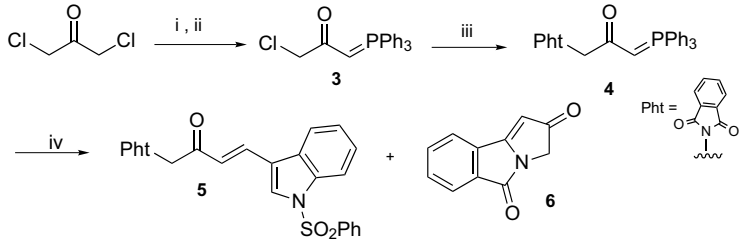
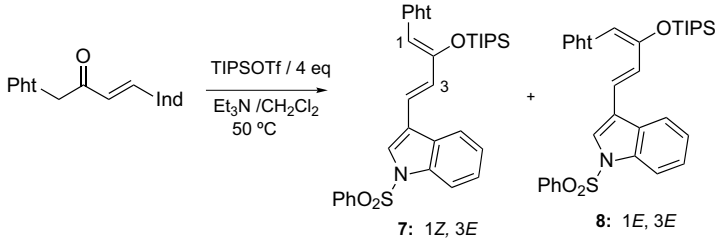


Scheme 1. Retrosynthetic analysis of granulatimide (**1**) and its analogue **2**.



Scheme 2. Synthesis of enone **5**. Reagents and conditions: (i) PPh_3/THF/reflux, 4 h, 73%; (ii) Na_2CO_3/MeOH–H_2O, rt, 30 min, 90%; (iii) Potassium phthalimide (3 equiv), DMF, 100 °C, 6 h, 62%; (iv) *N*-phenylsulfonylindole-3-carbaldehyde (1 equiv), toluene, reflux, 2 days, **5** (58%) and **6** (30%).



Scheme 3. Synthesis of dienes **7** and **8**.

was produced (Scheme 3). Longer reaction times (3 h or more) led to a mixture of **7** with its 1*E*,3*E* stereoisomer **8** in a 3:2 ratio.[11] The 1*Z*,3*E* stereochemistry for diene **7** was established by ROESY correlations (Fig. 1), which also revealed an extended *transoid* conformation of the C_2–C_3 single bond.

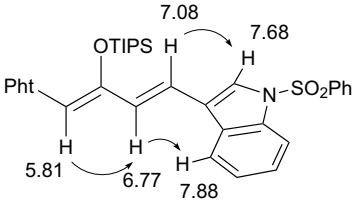
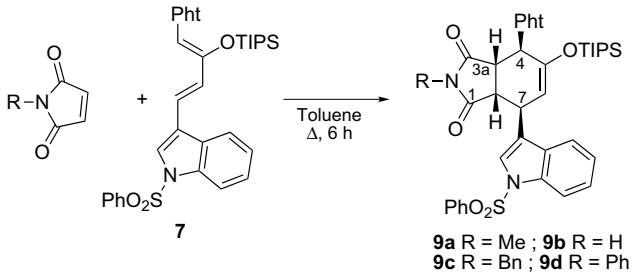


Figure 1. Selected ROESY correlations for **7**.

Once the preparation of **7** and **8** had been successfully achieved, the Diels–Alder reaction was examined. We used maleimides and quinones as dienophiles, in order to determine the scope of this methodology. Maleimide, *N*-methyl, *N*-phenyl, and *N*-benzyl-maleimides were chosen because they are building blocks required for the synthesis of granulatimide families and in view of their good reactivity with related dienes.

The reaction between *N*-methylmaleimide and purified **7** in toluene at reflux for 35 h gave exclusively the *exo* adduct **9a** (70%).[12] In order to improve the reaction, we used the diene obtained without removing the excess of the triisopropylsilyl triflate, which produced a reduction of the reaction time down to 6 h, and the increase of the yield up to 95% of **9a**. In both cases, the ^{1}H NMR spectra of the crude reaction product only showed signals corresponding to one cycloadduct, irrespective of the solvent (DMSO, CD_3OD) used (Scheme 4).[13]



Scheme 4. Diels–Alder reaction between **7** and different maleimides. All the products were characterized by NMR and mass spectrometry.

^{1}H NMR experiments (HMQC, HMBC, COSY) allowed us to assign unequivocally the spectroscopic data and the ROESY correlations between H-3a/H-7a/H-2Ind indicated that these groups are on the same face of the molecule. These correlations and that observed between H-6 and H-7 agree with the *exo* stereochemistry for **9a**, unlike the *endo* results obtained for the cycloaddition reactions of related 4-(3-indolyl)-2-siloxy-1,3-butadienes lacking the phthalimido residue at C-1.[1] The structure of **9a** was confirmed by X-ray diffraction studies.[14] As can be observed in the ORTEP drawing (Fig. 2), the phthalimido and indolyl moieties adopt pseudoequatorial dispositions, whereas their geminal hydrogen atoms H-4 and H-7 are in axial disposition and in *anti* arrangement with respect to H-3a and H-7a. This conformation in the solid state of the *exo* adduct is also the preferred one in solution.

The above stereochemical preference can be explained by a crowded transition state in which substituents at positions 1, 2, and 4 of the diene prevent the stabilization of the *endo* approach by secondary interactions with the dienophile. Moreover, the phthalimido and *N*-benzenesulfonylindol-3-yl moieties can interact favorably with *N*-methylmaleimide during the *exo* approach. This stereochemical outcome is also in agreement with modeling the transition states leading to the *exo* and *endo* cycloadducts, which were carried out by mean of a systematic Monte Carlo conformational search, followed by energy minimization using the MM2 force field with the parameters set for the Diels–Alder reaction derived by Houk and co-workers[15] For the reaction between **7** and *N*-methylmaleimide, the stabilities of *exo* and *endo* cycloadducts were similar but the *exo* transition state was more stable than the *endo* one (6.8–9.0 kJ/mol). When the phthalimido moiety is not present in this type of dienes,[1a] the *endo* stereoselectivity was observed, also in agreement with the calculated more stable transition state and with the absence of severe crowding for the *endo* approach. Although not for the synthesis of granulatimide and other planar analogues, the stereochemistry of the reaction is of great interest for the synthesis of folded analogues and other types of derivatives.

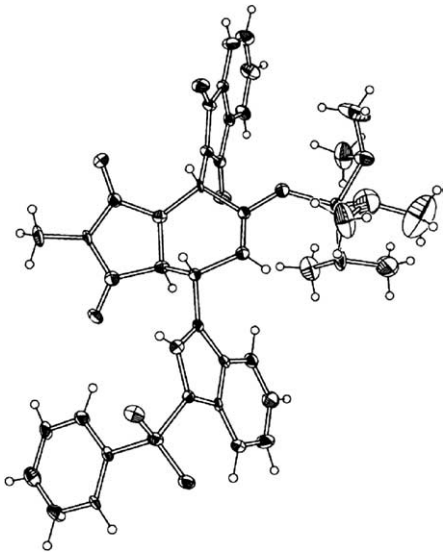
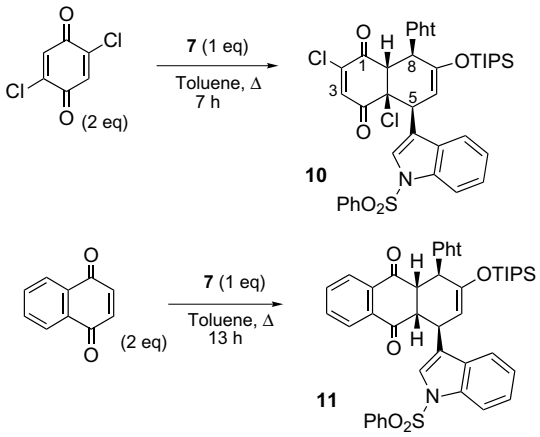


Figure 2. X-ray crystallographic analysis of **9a**.



Scheme 5. Diels–Alder reaction of **7** with quinones.

Compounds **9b**, **9c**, and **9d** were obtained under the conditions described for **9a**, in 95–80% yield and with the same stereochemical outcome described above.

In order to gauge the scope of the Diels–Alder reaction we carried out several experiments with diene **7** (under the same conditions described previously for maleimides) and differently substituted quinones (Scheme 5). The *exo* cycloadducts **10**[16] and **11** were obtained in high yield (85% and 90%, respectively). The proposed regiochemistry was deduced from the connectivities observed in HMBC experiments and corresponded to that produced with substituted chloroquinones and related siloxydienes.[17]

In conclusion, a straightforward method for the preparation of 1-phthalimido-4-(3-indolyl)-2-trialkylsiloxy-1,3-butadienes is described. The Diels–Alder reaction yields the *exo* adducts, opposite to the results obtained with related disubstituted dienes lacking the phthalimido substituents at C-1.

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11. Data for **7**: mp 198 °C (ether/MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) 8.01 (1H, d, $J = 7.2$ Hz, H-7Ind), 7.73 (1H, d, $J = 7.2$ Hz, H-4Ind), 7.9–7.5 (9H, Pht, $PhSO_2$), 7.68 (1H, s, H-2Ind), 7.37 (1H, dt, $J_1 = 7.2$, $J_2 = 1.0$ Hz, H-6Ind), 7.32 (1H, dt, $J_1 = 7.2$, $J_2 = 0.8$ Hz, H-5Ind), 7.08 (1H, d, $J = 16.0$ Hz, H-4), 6.77 (1H, d, $J = 16.0$ Hz, H-3), 5.81 (1H, s, H-1), 1.0–0.9 (TIPS). EA calculated for $C_{35}H_{38}N_2O_5SSi$: C 67.06, H 6.11, N 4.47, S 5.12. Found C 66.97, H 6.35, N 4.57, S 4.96.
12. Data for **9a**: mp 268 °C ($CHCl_3$/MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) 7.99–7.26 (14H, m, Ar), 5.02 (1H, d, $J = 2.4$ Hz, H-6), 4.98 (1H, m, H-4), 4.06 (1H, dt, $J_1 = 6.8$, $J_2 = 2.4$ Hz, H-7), 3.84 (1H, t, $J = 8.9$ Hz, H-3a), 3.30 (1H, dd, $J_1 = 8.9$, $J_2 = 6.8$ Hz, H-7a), 3.01 (3H, s, N–Me), 1.0–0.9 (TIPS). EA calculated for $C_{40}H_{43}N_3O_7SSi$: C 64.71, H 5.71, N 5.80, S 4.43. Found C 64.37, H 6.01, N 5.58, S 4.23. HRMS m/z calcd for $C_{40}H_{44}N_3O_7SSi$ 737.2591, found 737.2598.
13. During our work with related siloxydienes we have always observed only one stereoisomer. When the reactions were carried out at higher temperatures, the isomerization of the double bond was produced instead of the equilibration to the thermodynamic mixture of the *endo*/*exo* diastereoisomers. For more details see Ref. 1a.
14. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 200219. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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16. Data for **10**: mp 242 °C (Hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) 8.56 (1H, s, Ar), 8.2–7.2 (13H, m, Ar), 7.17 (1H, s, Ar), 5.12 (1H, dd, $J_1 = 6.0$, $J_2 = 1.2$ Hz, H-6), 5.04 (1H, dt, $J_1 = 10.8$, $J_2 = 1.2$ Hz, H-8), 4.77 (1H, dd, $J_1 = 6.0$, $J_2 = 1.2$ Hz, H-5), 4.27 (1H, d, $J = 10.8$ Hz, H-8a), 1.0–0.9 (TIPS). HRMS (FAB) m/z calcd for $C_{41}H_{41}N_2O_7SSiCl_2$ 802.1703, found 802.1780.
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