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Use of 1,1,1,3,3,3-Hexamethyldisilazane and *N,O*-Bis-(trimethylsilyl)acetamide in Aromatic Claisen Rearrangement: An Efficient Method for Preventing Abnormal Claisen Rearrangement.

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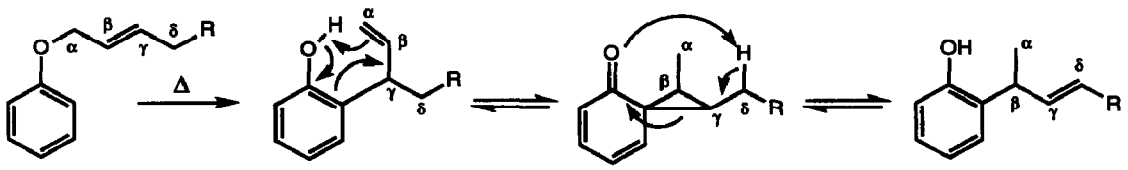
Abstract: *Both 1,1,1,3,3,3-hexamethyldisilazane and N,O-bis-(trimethylsilyl)acetamide have been shown to suppress the formation of abnormal aromatic Claisen rearrangement products by efficiently trapping the incipient normal products as their silyl ethers under mild conditions.*

The aromatic Claisen rearrangement is one of the most reliable and efficient methods for introducing alkyl groups to the *ortho* position of phenols.[1] While high yields are generally obtained for the Claisen rearrangement of simple allyl aryl ethers, a competition of the so-called abnormal Claisen rearrangement often becomes problematic when the substrates bearing γ- alkyl substituents on the allyl group are subjected to the thermal rearrangement. As illustrated in Scheme I, it has been demonstrated that the normal product **2** is transformed to the thermodynamically more favorable, abnormal product **4** via the spiro intermediate **3** through back-to-back sigmatropic rearrangements.[2] The abnormal Claisen rearrangement could, in theory, be blocked by protecting the incipient phenol **2** before it undergoes the 1,5-hydrogen shift. To the best of our knowledge, use of butyric[3] or acetic[4] anhydride is the only practical way of trapping the normal product.

Scheme I

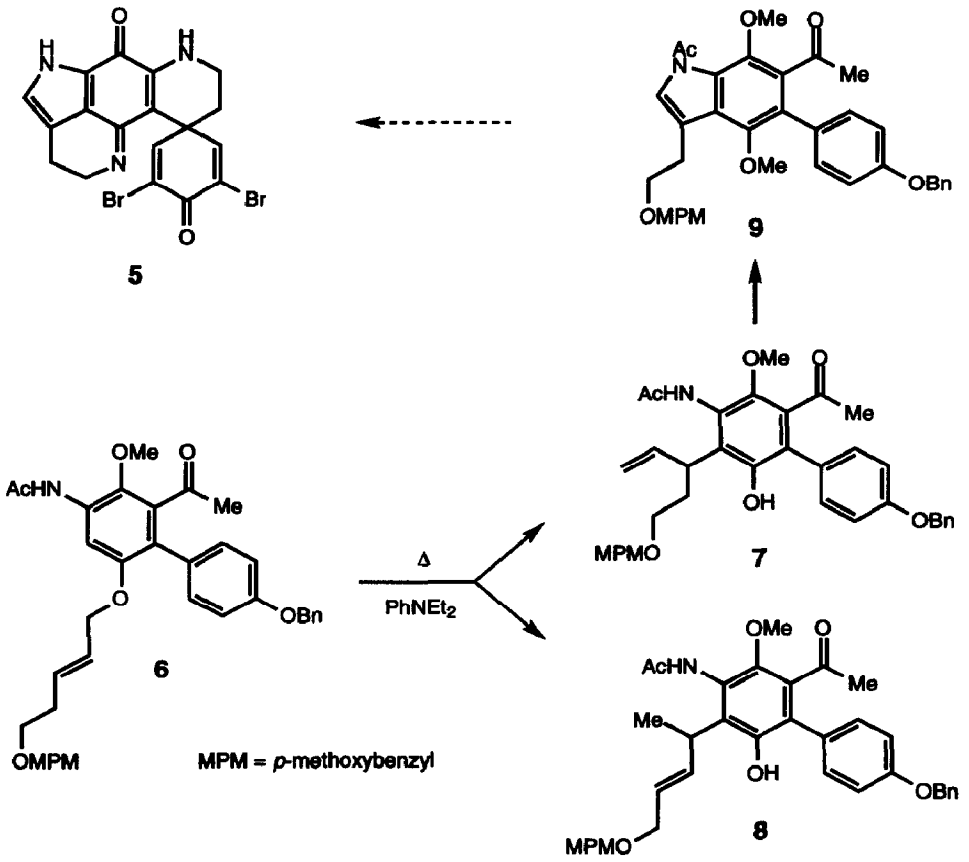


1 **2** **3** **4**

Normal **Abnormal**

During the course of our attempted total synthesis of discorhabdin C (**5**),[5] we needed to carry out the Claisen rearrangement of the highly functionalized allyl aryl ether **6** to form **7** which in turn was to be transformed to the indole **9** (Scheme II). To our great disappointment, heating **6** at 210 °C in *N,N*-diethylaniline resulted in the formation of a 1:1 mixture of the normal and abnormal rearrangement products, **7** and **8**. Use of acetic or butyric anhydride as a trapping agent caused extensive decomposition of the products. Therefore, attention was directed to milder trapping agents especially such silylating reagents as 1,1,1,3,3,3-hexamethyldisilazane and *N,O*-bis-(trimethylsilyl)acetamide. Gratifyingly, the Claisen rearrangement of **6** in *N,N*-diethylaniline in the presence of 10 equiv of hexamethyldisilazane proceeded smoothly at 210 °C to give, upon acidic workup, the normal product **7** in 72% yield without appreciable formation of the abnormal product **8**. In order to demonstrate the general applicability of our method, the compounds **10-14** were prepared and were subjected to the thermal rearrangement conditions in the presence of either 1,1,1,3,3,3-hexamethyldisilazane or *N,O*-bis-(trimethylsilyl)acetamide.[6] As summarized in Table I, these silylating agents have proven to be excellent blockers of the detrimental, abnormal Claisen rearrangement.

Scheme II



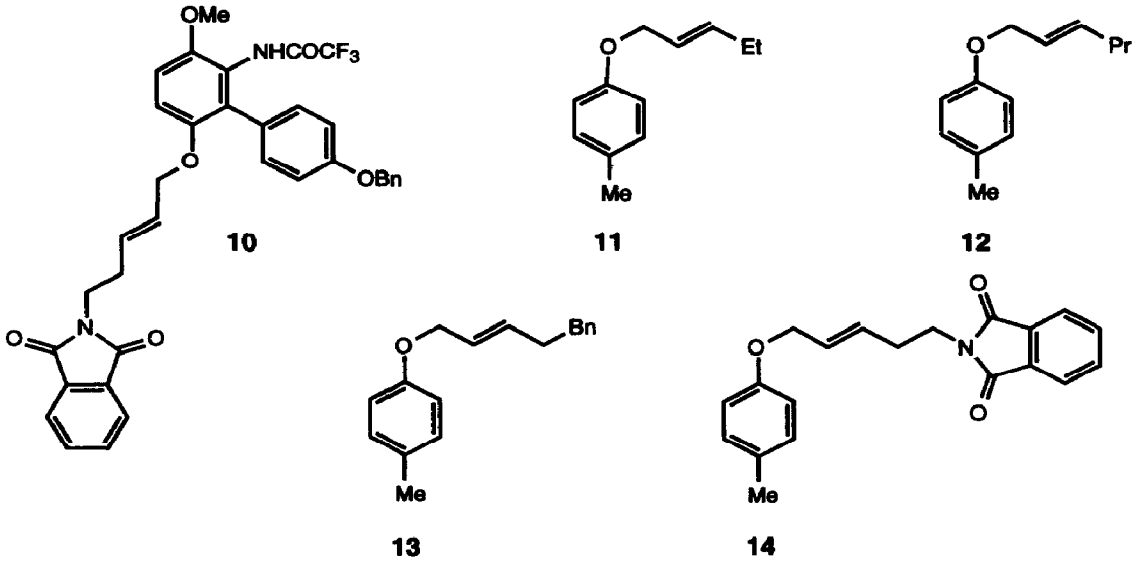


Table I. Aromatic Claisen Rearrangement in the Presence of Silylating Agents.

Compound	Trapping agent[a]	Equiv	Temp. (°C)	Time (h)	Ratio (Normal : Abnormal)[b]	Yield (%)[c]
6	A	10	210	8.0	>99 : <1	72
10	A	10	240	3.0	>99 : <1	95
11	none	0	230	5.5	58 : 42	63
11	A	10	230	8.0	>99 : <1	70
11	B	5	230	4.5	>99 : <1	81
12	none	0	230	6.0	37 : 63	86
12	A	10	230	7.5	>99 : <1	85
12	B	10	230	4.3	>99 : <1	85
13	none	0	230	4.0	59 : 41	67
13	A	10	230	5.0	>99 : <1	73
13	B	20	230	5.3	>99 : <1	70
14	none	0	230	4.8	82 : 18	76
14	A	10	230	8.3	>99 : <1	71
14	B	5	230	4.5	>99 : <1	74

[a] All reactions were carried out using *N,N*-diethylaniline as a solvent. A: 1,1,1,3,3,3-hexamethyldisilazane. B: *N,O*-bis-(trimethylsilyl)acetamide. [b] Determined by ^{1}H NMR. [c] Combined yield of normal and abnormal products.

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6. General procedure: A mixture of 50 mg of **12**, 0.6 ml (10 equiv) of hexamethyldisilazane, and 0.5 ml of *N, N*-diethylaniline was placed in a 10-ml culture tube. After argon was bubbled through the mixture for 5 min, the tightly capped culture tube was heated at 230 °C for 7.5 h in an oil bath. After cooling to room temperature, the mixture was partitioned between 20 ml of ether and 15 ml of 3 N HCl. The ethereal layer was evaporated to dryness under reduced pressure. The residue was dissolved in 5 ml of methanol, treated with 1 ml of 3 N HCl for 30 min at room temperature to complete the desilylation. The mixture was diluted with 20 ml of ether, washed with saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure. Separation on silica gel TLC using 30% ether in hexanes furnished 42.5 mg of the normal rearrangement product (85% yield).

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