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Synthesis of β-Amino Diaryldienones Using the Mannich Reaction

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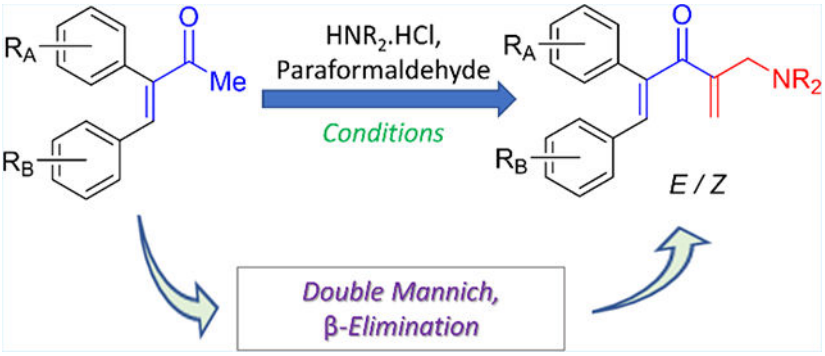
Abstract

The Mannich reaction has been used for decades to prepare many pharmaceutically important molecules. Here, using a "double-Mannich–β-elimination" synthetic sequence, we report the synthesis and the characterization details of a novel class of β-amino diaryldienones with prominent antiprostate cancer activity. Through these studies, we correct an erroneous structure in the current literature, present a discussion of the stereochemical outcome of a new reaction, and probe the mechanism(s) of byproduct formation through isotopic studies.

Graphical Abstract



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The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01195.

Experimental procedures and characterization for all new compounds along with 1D and 2D NMR data (PDF)

Accession Codes

CCDC 1896679–1896684 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Since its advent over a century ago, the venerable Mannich reaction has been a staple in synthetic organic chemistry.[1,2] Its robust utilization has spread across many different fields of research, including medicinal chemistry. Mannich bases (*β*-aminocarbonyl compounds) represent important pharmacophores in various pharmaceutical compounds.[3–6] Our own prostate cancer drug discovery program encountered a unique synthetic challenge that was ultimately solved by the utilization of the Mannich reaction. We found a hit compound (**NSC-89160**, Figure 1)[7] with potent antiprostate cancer effects in a high-throughput screening assay.[8–10]

The structure of **89160** given in the PubChem database was of a *β*-amino diarylenone derivative, with no known synthetic methodology available in the literature. The *Z*-alkene moiety in its structure provided a significant synthetic challenge in obtaining a stereochemically pure final compound via an in house synthesis. The shortest possible synthetic strategies through intermediate carbonyl species of type **i** (Figure 1) failed, because they tended to favor the cis-orientation of the aryl rings across the double bond (the *E*-isomer).

This led us to an alternative synthetic approach through a nitrile analogue. The Knoevenagel condensation of benzyl cyanide with 4-chlorobenzaldehyde yielded the substituted acrylonitrile *Z*-**1** (Scheme 1, panel A), preferentially in the *Z* conformation, which was then used as a key intermediate to access **89160**. Keeping the reaction temperatures at or below room temperature, devising efficient workup/purification procedures, and avoiding acidic conditions were essential for converting **1** to the desired product *Z*-**3**.[11,12] To our dismay, *Z*-**3**, in neither its hydrochloride nor its neutral form, was able to replicate the antiprostate cancer effects seen[8] with **89160**. At this point we also synthesized the compound in its *E* configuration (*E*-**3**, Scheme 1, panel B), using a strategic Mannich reaction performed under mild reaction conditions between enone **4** and the bis-aminomethyl Mannich reagent[13] **5**. A pre-NMR era preparation of compound *E*-**3** described in literature[14] was unsuccessful in providing pure *E*-**3** in good yield. Thus, the synthetic methods outlined here are the first reliable methods reported to obtain stereochemically pure **3** (*E* or *Z*) to the best of our knowledge. Unfortunately, *E*-**3** also failed to reproduce the biological effectiveness[8] of **89160**.

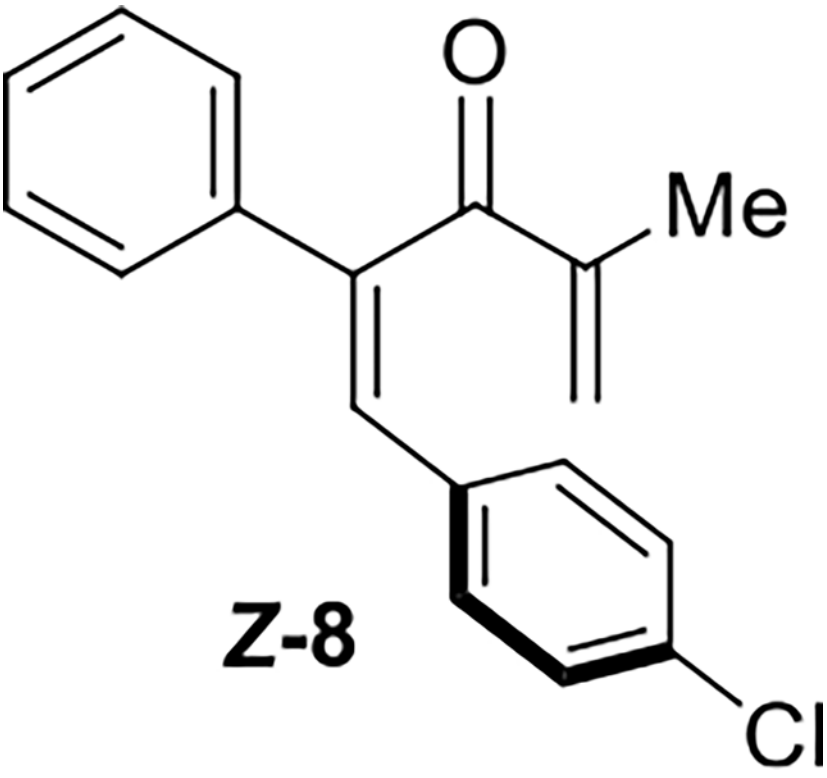
At this juncture, we suspected a misassignment of **89160** in the repository and performed a thorough structural analysis. ^{13}C and ^{1}H NMR spectroscopy revealed that there were only three sets of sp^3-type carbons/protons in **89160**. It is noteworthy here that the *α*- and the *β*-carbons (and their associated hydrogens) in *E*-**3** had accidental overlap in the ^{13}C and ^{1}H spectra, resulting in also only three aliphatic signals. In the conventional nonaromatic olefinic region of 5–7 ppm, only one proton signal (6.6 ppm) was visible in the ^{1}H spectra of **89160**. Although integration within the aromatic region appeared somewhat off, the presence of three aryl rings overlapping in this region made detailed interpretation difficult. The most compelling evidence for the determination of the correct structure came from 2D-NMR. An HSQC spectrum of **89160** clearly revealed that the olefinic proton signal at 6.6 ppm correlated to a methylene unit that had a second sp^2-type proton signal for the same carbon at 7.1 ppm. At this point, we deduced that the true structure of **89160** must have another

double bond α to the carbonyl group, leading to compound **6** (Figure 2). Based on what we knew at the time about this type of structure (i.e., NMR chemical shift of the enone proton in *E*/*Z* arrangement) and for steric reasons, we hypothesized (and later confirmed) that the stereochemistry across the diaryl substituted double bond would be *E*.

Despite its availability in a compound repository, there were no known synthetic methods to prepare **6**. Thus, we adapted the closest available methodology: the application of the Mannich reaction on acetophenone type substrates to synthesize the β-amino enone derivatives of structure **7** (Figure 3a). This type of reaction on acetophenone and the behavior of resultant β-amino enones **7** are well-known in literature.[15–18] The reaction typically proceeds at high temperature (120–140 °C), in DMF or acetic acid solvent, with an excess of paraformaldehyde and the corresponding amine hydrochloride or the corresponding Eschenmoser salt.

With **6** being ideally set up for Nazarov-type reactions, heating at high temperatures in acetic acid understandably gave no discernible product in our system (Figure 3b). While some nonreproducible minor product formation was observed in dimethylformamide, there were extensive complications, including the decomposition of the product (initiated by Nazarov-type processes and by an intramolecular hydride transfer process), and rapid isomerization of the *E* double bond.

A major unexpected byproduct isolated from this reaction was the dienone *Z*-**8** (stereochemistry further confirmed via an independent synthesis from *Z*-**1**).



In exploring the mechanism of *Z*-**8** formation, we hypothesized either possible reduction of **6** by dimethylformamide or formaldehyde or the involvement of an intramolecular hydride transfer process (Figure 4). Use of dimethylacetamide as the solvent still gave *Z*-**8**, eliminating the solvent as a major contributor for its formation. We thus proceeded to investigate the intramolecular hydride-transfer hypotheses using isotopically labeled[19] starting amine (Figure 4). Interestingly, **8** was observed in isolable amounts only for its *Z* isomeric form. Thus, we can assume first the formation of *Z*-**6**-d_2 from **4** as expected from a double-Mannich–*β*-elimination sequence followed by isomerization. Then the protonated species **9** would undergo an intramolecular hydride/deuteride shift leading to **10**.

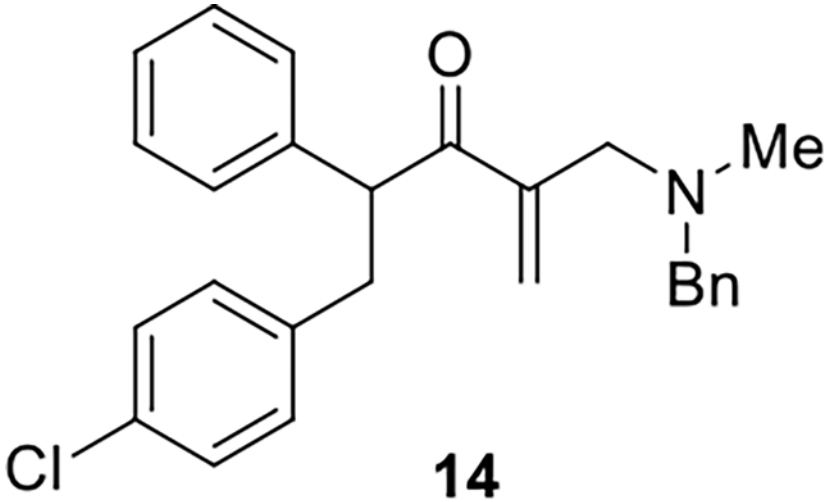
The iminium species **11** would then be eliminated to result in the new methylene group of *Z*-**8**-*d*. Since the deuteride transfer from the benzylic position would likely be preferred, the product mixture for *Z*-**8**-*d* has an excess of the deutero product despite the lower statistical transfer probability (i.e., two benzylic deuteriums vs three methyl hydrogens). Switching to the nonpolar solvent toluene helped to control this side reaction, boosting the desired product yield. A study done by heating *Z*-**6** in solvent for 4 h showed the presence of *Z*-**8** to be 10 times lower in toluene compared to reactions done in either DMF or DMA.

Thus, we chose toluene as the optimal reaction solvent and proceeded to optimize the reaction time, with a primary aim to control the isomerization of the *E*-double bond (Table 1). Initial reaction conditions utilized 2.2 equiv of the amine hydrochloride and 3.3 equiv of paraformaldehyde. In following the reaction progress by NMR, we realized that the highest conversion of ketone **4** was achieved at 1 h (Table 1, entry d), albeit with 32% of the product being isomerized to the *Z*-isomer. Observing the depletion of bis-amine adduct intermediate **5** after 1 h, we increased the amount of paraformaldehyde in the reaction mixture to 6.0 equiv from 2.2 equiv (Table 1, entries c, e, g, and i). This resulted in sustained generation of intermediate **5**, leading to faster reaction of starting ketone **4** and the intermediate species **3**. Optimal, reproducible conversion to product was observed at 1 h with the use of 6 equiv of paraformaldehyde (Table 1, entry e). Through optimized reaction and purification conditions, yields up to 62% of *E*-**6** had been achieved in excellent purity. We also noted that there were no discernible levels of *Z*-**3** in these reaction mixtures, indicating that the isomerization of the diaryl-substituted double bond under these conditions likely occurs after the formation of *E*-**6**.

By combining the knowledge gained from our NMR studies of the reaction intermediates, a plausible reaction mechanism is shown in Scheme 2. The in situ generated bis-amine adduct **5** facilitates the double-Mannich reaction under near-neutral pH conditions leading to the compound **12**, which then undergoes *β*-elimination to yield *E*-**6**. The lack of any discernible levels of isomerized (*Z*) species prior to *E*-*6* is likely the result of the rapid kinetics of these mechanistic steps and/or a strong preference of the starting ketone/intermediates to exist in the *E* stereochemistry (e.g., compound **4**). In large scale reactions, isolable levels of Nazarov type cyclized products (**13**) were also observed.

The substrate scope for the reaction can be found in the Supporting Information (p S32). In general, yields of 20–40% of the *E*-isomer (analogs of *E*-**6**) were achieved for the reaction across the various substituents evaluated. Given the tendencies of these substrates to undergo

isomerization and/or rearrangement/decomposition during the reaction, such reproducible yields of the stereopure products are arguably quite reasonable. Other amines apart from *N*-benzyl methylamine could be used in the reaction, with varying degrees of success. Reaction with dimethylamine hydrochloride (or with the Eschenmoser salt) did not produce isolable amounts of the *β*-amino diaryldienone, while the cyclic amines pyrrolidine (8%), piperidine (30%), and piperazine (34%) gave reasonable yields. The presence of electron-donating groups on the aryl rings is likely to be detrimental to this reaction, because it may positively contribute to isomerization and Nazarov type cyclization leading to byproducts. In agreement with this fact, when the 4-Cl substituent of compound **4** is replaced with a 4-methoxy group, the isomerization reaction predominates, leading only to the *Z*-*β*-amino diaryldienone (*Z*-**SI**-**17**, p S32) and the corresponding Nazarov cyclized product. If the enone double bond in compound **4** is not present, the reaction can be conducted in DMF to reproducibly obtain the resultant *β*-amino diarylenone **14** in yields up to 20%.



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NOE NMR data (see Supporting Information) clearly confirmed the stereochemistry of the *E* and the *Z* isomers of **6**. However, neither isomer was amenable for X-ray crystallography. Thus, we also studied the spectroscopic characteristics and X-ray crystal data of several closely related systems and summarized general trends between the stereochemistry of the diaryl-substituted enone versus the NMR chemical shift of the enone proton (see Supporting Information, Table SI–1, p S4). For compounds of structure **6**, a characteristic downfield shift is observed for this enone proton in the *E*-isomer than in the *Z*-isomer. This may be due to a deshielding magnetic anisotropic effect by the carbonyl group.

The *β*-amino diaryldienone compounds of structure *E*-**6** that we have synthesized through the chemistry outlined here have shown excellent *in vitro* and *in vivo* antiprostate cancer activity in androgen receptor (AR) positive tumors.[8–10] Functionally, they have shown potent activity as AR degraders and as inhibitors of the AR transactivation domain.[8] A complete disclosure of the biological activity of these compounds will be reported elsewhere. The *β*-amino enone functionality of *E*-**6** can also undergo further synthetic transformations (Scheme 3) to yield other compounds of medicinal chemistry interest.[20]

In summary, through this work we have established, for the first time, a method to reliably obtain β-amino diaryldienone compounds of structure **6** (and **3**) in excellent stereochemical (*E*/*Z*) purity. In the course of our studies, we have provided insights into the reaction mechanism, unveiled possible side reactions, studied the NMR characteristics versus the stereochemistry of the diaryl-substituted enone, and corrected an erroneously reported structure in current literature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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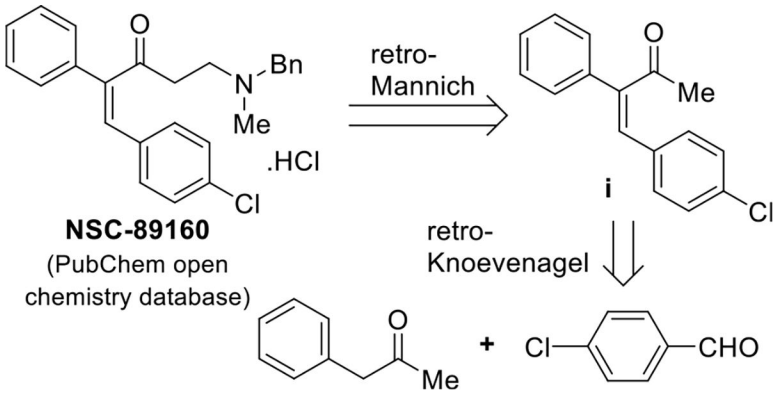


Figure 1.

Structure of the hit-compound **NSC-89160** and a possible shortest retrosynthetic disconnection.[7]

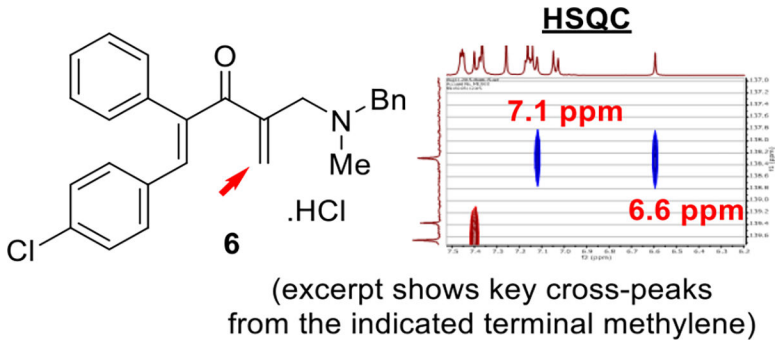


Figure 2.
Correct structure of the hit-compound **NSC-89160** (**6**).

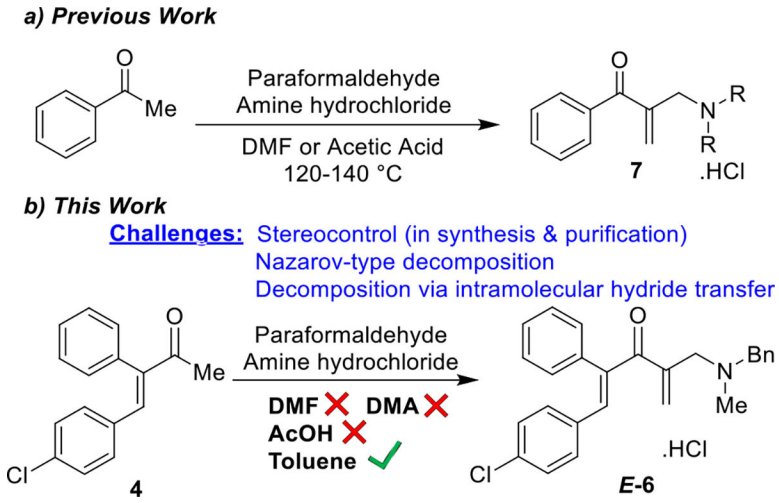


Figure 3.

Comparison of previous methodology to the current synthetic challenge. (a) Synthesis of β-amino enone derivative(s) **7** of acetophenone. (b) Synthetic approach for β-amino diaryldienone **6**.

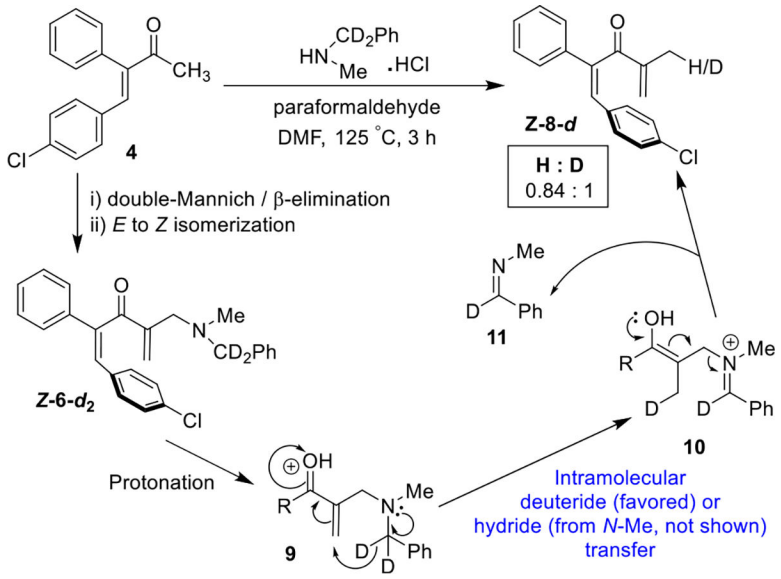
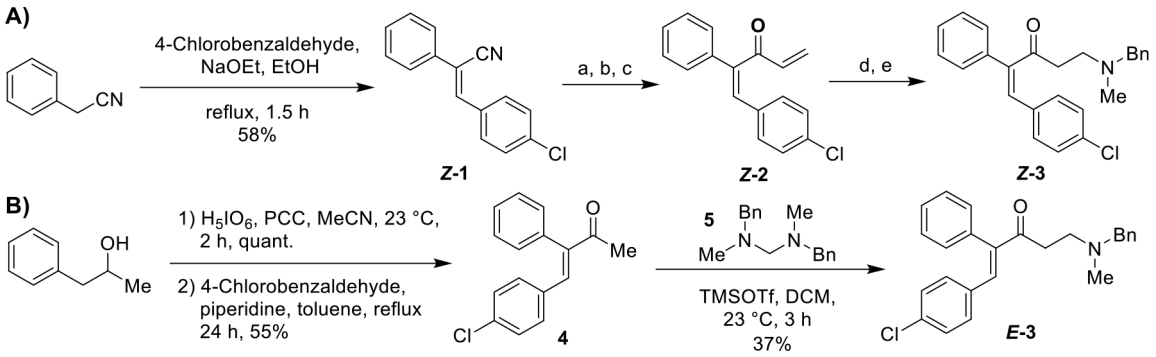


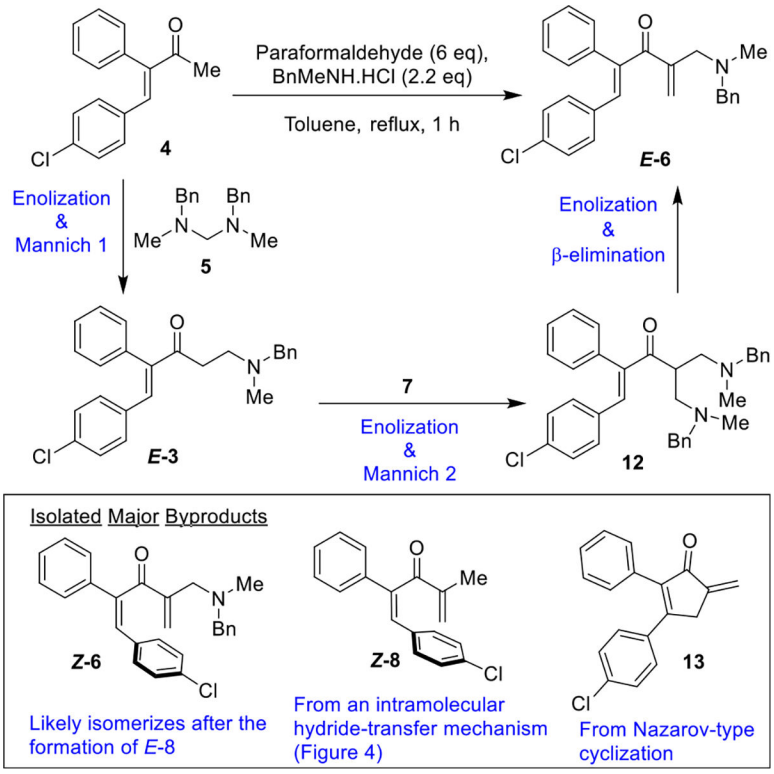
Figure 4.

Plausible mechanism for the intramolecular hydride-transfer mediated generation of **8** from **6**.



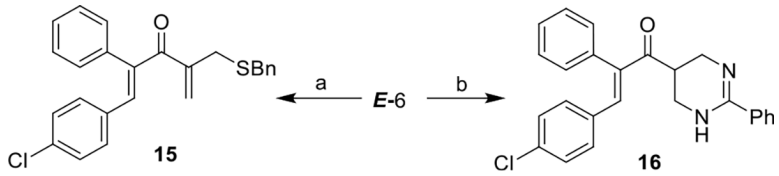
Scheme 1. Synthesis of the *Z*- (Panel A) and the *E*- (Panel B) *β*-Amino Diarylenone(s) 3[a]

[a](a) DIBAL-H, toluene, −78 °C, 2 h, 61%; (b) vinylmagnesium bromide, THF, −78 °C, 30 min, 76%; (c) DMP, DCM, 0 °C, 20 min, 56%; (d) HNBnMe, DCM, 23 °C, 3 h, 84%; (e) Na_2CO_3 (aq, 10%), DCM, 23 °C, quantitative.



Scheme 2.

Plausible Mechanism for the β-Amino Diaryldienone Synthesis

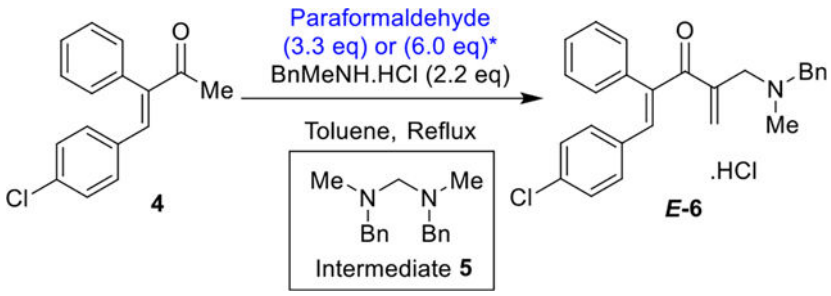


Scheme 3. Other Synthetic Transformations of *E*-6[a]

[a](a) BnSH, DCM 23 °C, overnight, 85%; (b) benzamidinium chloride, EtOH/H2O, Et3N, reflux, 30 min, 6%.

Table 1.

Optimization of Reaction Conditions for the Synthesis of *E*-6[a]



		equivalents in reaction mixture[a]				
					product 6	
	time	**4**	**5**	***E*-3**	***E***	***Z***
a	15 min	3.20	0.74	3.66	1.0	0.08
b	30 min	0.76	0.47	3.16	1.0	0.20
c	30 min[b]	0.20	0.75	1.14	1.0	0.08
d	1 h	0.30	0.06	3.04	1.0	0.48
e	**1 h** [b]	**none**	**0.41**	**neg.**	**1.0**	**0.28**
f	2 h	0.14	neg.	2.30	1.0	0.86
g	2 h[b]	none	none	none	1.0	0.70
h	3 h	neg.	none	1.60	1.0	0.98
i	3 h[b]	none	none	none	1.0	0.94

[a]Equivalents given in comparison to product *E*-**6**.

[b]6.0 equiv of paraformaldehyde.

neg. = negligible.