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## Toward Palau'amine: Hg(OTf)<sub>2</sub>-Catalyzed Allyl Alcohol Cyclization of Acylhydrazide to Construct the Cyclopentane Core

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### Keywords

Palau' amine; Mercuric Triflate; Allyl Alcohol Cyclization; Acylhydrazide; Quaternary Carbon Center

The pyrrole-imidazole alkaloids, which comprise a large family of natural products,<sup>1</sup> have received a great deal of attention due to their potent biological activities and tremendous structural diversity. Palau'amine (**1a**) was originally isolated from a sponge, *Stylorella agminata*, in 1993 by Scheuer as a novel class of the pyrrole-imidazole alkaloid.<sup>2</sup> Since the initial disclosure of its proposed structure (**1a**), palau'amine (**1**) has been an attractive synthetic target because of its intriguing molecular architecture and significant biological properties such as antifungal, antitumor, and immunosuppressive activities. However, according to several groups, the originally proposed structure **1a** was recently revised as **1b**, which possesses the indicated the *trans*-D/E ring junction and the β-chlorine substituent.<sup>3, 5e, 5g</sup>

The noteworthy structural features of palau'amine include: two guanidine moieties, fused polycyclic system with a spiro cycle, complex all carbon substituted cyclopentane ring, nitrogen-substituted quaternary carbon center, and eight contiguous stereogenic centers. Not surprisingly, many attempts to synthesize palau'amine and related natural products have been reported so far,<sup>4, 5</sup> and the first total synthesis of the related natural products axinellamines A and B (**2**) was recently accomplished.<sup>6</sup> However, a total synthesis of palau'amine itself has not yet been reported. Efficient construction of the complex cyclopentane core with the correct stereochemistry at each carbon center, including a quaternary carbon center, is definitely one of the most difficult synthetic challenges for the synthesis of palau'amine. Herein, we describe an efficient synthesis of the cyclopentane core of palau'amine by the application of a highly efficient novel Hg(OTf)<sub>2</sub>-catalyzed reaction developed in our laboratory.<sup>7</sup> In 2008, the Hg(OTf)<sub>2</sub>-catalyzed alkyne cyclization reactions were expanded to the alkene cyclization reactions by using allylic alcohol or vinyl methyl ether substrates that, after cyclization, undergo a smooth proto-demercuration to give the cyclized products and the regenerated Hg

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(OTf)<sub>2</sub> catalyst.<sup>8</sup> For instance, Hg(OTf)<sub>2</sub>-catalyzed cyclization of *N*-tosylanilino allylic alcohol **3** provided 2-vinylindolines **4** in high yield (Scheme 1).<sup>8b</sup> Thus, the cyclization of cyclopentylidene alcohol **5** is expected to give **6** by constructing a quaternary carbon center that corresponds to the C16 of palau'amine. However, the catalytic cyclization of amide **5** is also possible to give the *O*-cyclized product **7** in preference to the *N*-cyclized product **6**. Indeed, we confirmed this was the case. The conventional methods for *N*-selective cyclization are limited by the cumbersome substrate modifications, the addition of strong Lewis acids and/or strong base, or the formation of *N*-radical.<sup>9</sup> Moreover, the catalytic conditions for generating such a quaternary carbon center have not yet to be determined. Therefore, we designed an acylhydrazide **8** as a simple modification of primary amides for Hg(OTf)<sub>2</sub>-catalyzed cyclization. The vinyl lactum **9**, prepared by the Hg(OTf)<sub>2</sub>-catalyzed cyclization of **8**, could be an excellent precursor to construct cyclopentane core **10** by introducing two CH<sub>2</sub>-N groups (Scheme 1).

Commercially available 2-cyclopentene-1-one **10** was employed as the starting material. A Morita-Baylis-Hillman reaction of **10** with a commercial preparation of (*tert*-butyldimethylsilyloxy)-acetaldehyde afforded **11** in 70% yield. **11** was subsequently converted to **13** by a sequential operation of acetylation, a Luche reduction,<sup>10</sup> and a TBS protection. The acetate **13** were then obtained as a 2: 1 diastereomeric mixture, setting the stage for an Ireland-Claisen rearrangement.<sup>11, 12</sup> After the treatment of **13** with LHMDS/TBSCl/HMPA in THF at -78 °C, refluxing in toluene induced the desired Ireland-Claisen rearrangement to afford the cyclopentylidene carboxylic acid **15** via **14** in good yield. Next, we attempted to prepare an acylhydrazide by the coupling of **15** with *N*-tosylhydrazide by the combined action of EDCI and DMAP in dichloromethane. Surprisingly, the nitrogen masked with a tosyl group participated in the condensation to give a 2: 1 diastereomeric mixture of **16** in 68% overall yield after four steps from **13**. Presumably, the nucleophilicity of the more basic primary amine was attenuated by protonation with the HCl derived from the used EDCI-HCl salt.<sup>13</sup> The double bond geometry of **15** was determined to be *Z* by the NOE experiment of its amide derivative (Scheme 2). The TBS groups were cleaved under mild acidic conditions to give diol **17**.

Reaction of **17** with 2 mol % of Hg(OTf)<sub>2</sub> took place smoothly in nitromethane at room temperature to afford **18a** and **18b** in 84% yield as a separable 1:2 diastereomeric mixture. The lactone **19** was not detected (Scheme 3). Stereochemical outcome at the ring junction was completely controlled to *cis* regardless of the stereocenter of the secondary alcohol at C17. The structures of **18a** and **18b** were unambiguously confirmed by an X-ray diffraction study and NOE studies (see supporting information).<sup>14</sup> We thus established that the Hg(OTf)<sub>2</sub>-catalyzed protocol efficiently mediates *N*-selective cyclizations of amide carbonyl moieties, which is very difficult to achieve using conventional methodologies.<sup>15</sup>

Having prepared a sufficient amount of *N*-cyclized product **18**, we attempted to construct the cyclopentane core of palau'amine. The SO<sub>3</sub>-pyridine oxidation of the mixture of **18a** and **18b** gave a single ketone **20** in quantitative yield.<sup>16</sup> Direct oxidation of **20** to enone **22**, using IBX,<sup>17</sup> and selenium dioxide, or enolate oxidation using selenium halide, sulfinimidoyl chloride,<sup>18</sup> and NBS, were unsuccessful. Although the preparation of the silyl enol ether was not straightforward, a combination of TMSI and hexamethyldisilazane in dichloromethane was found to give trimethylsilylenolether **21** in quantitative yield.<sup>19, 20</sup> Saegusa-Ito oxidation of **21** provided enone **22** in good yield.<sup>21</sup> Morita-Baylis-Hillman reaction of **22** with formaldehyde gave alcohol **23** in excellent yield. Subsequent 1, 4-addition of nitromethane in the presence of a catalytic amount of a 1, 1, 3, 3-tetramethylguanidine (TMG) afforded the desired 1, 4-adduct **24**.<sup>22</sup> We found that **24** was readily converted to the exomethylene product by dehydration during a column chromatography purification on silica gel. Therefore, the crude **24** was directly subjected to reduction with NaBH<sub>4</sub> to give **25**. The stereochemistry of **25** was confirmed to be as we planned for our palau'amine synthesis by an NOE experiment. Finally,

the primary alcohol of **25** was converted to azide **26** that is the targeted cyclopentene core of palau' amine. The structure of **26** was unequivocally established by an X-ray diffraction study (Scheme 6 and supporting information).<sup>23</sup>

In summary, we have established an efficient route to the cyclopentane **26**, which corresponds to our E ring synthetic intermediate of palau' amine by the application of novel Hg(OTf)<sub>2</sub>-catalyzed cyclization. Furthermore, a selective *N*-cyclization protocol of acylhydrazide for catalytic construction of a quaternary carbon center was also developed. Throughout this investigation, Hg(OTf)<sub>2</sub> was shown to be a powerful catalyst for the construction of complex carbon frameworks of the type found in natural products. Total synthesis of palau' amine, one of the most challenging synthetic targets in the last decade, is currently underway in our laboratory.

## Experimental Section

Experimental details, full data, <sup>1</sup>H and <sup>13</sup>C NMR spectra of each intermediate from **11** to **26**, and data of X-ray analysis are available in Supporting Information.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

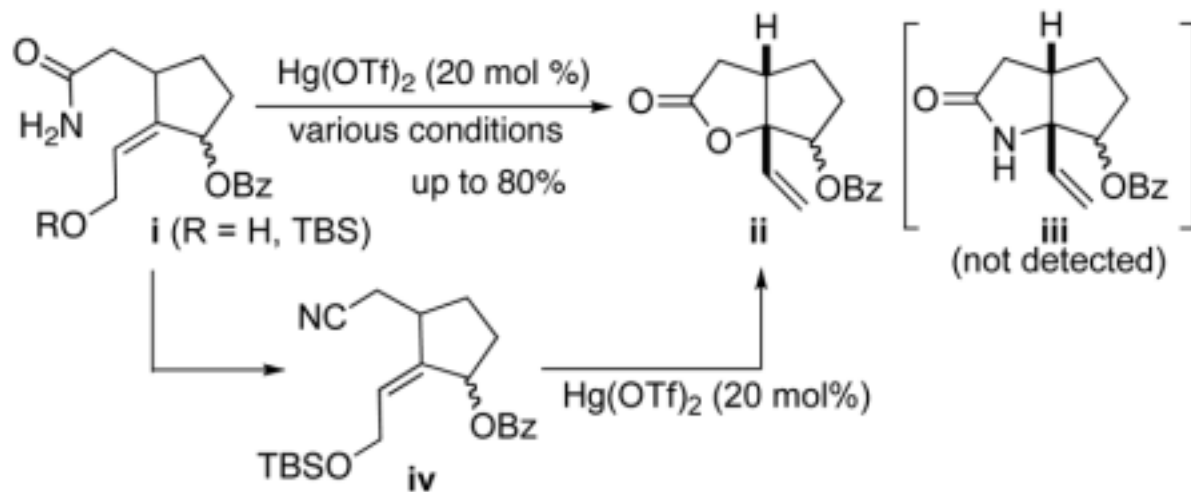
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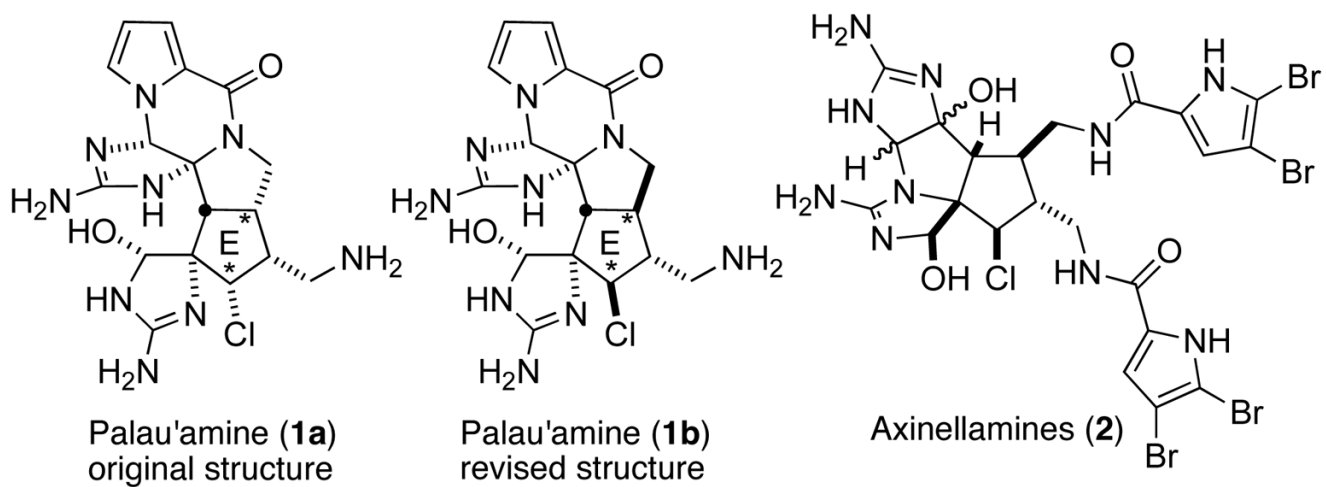
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15. The Hg(OTf)<sub>2</sub>-catalyzed cyclization of the primary amides **i** afforded only lactone **ii**, and lactum **iii** was not detected at all under a variety of reaction conditions (solvent effect or addition of Lewis acids). Even the reaction of

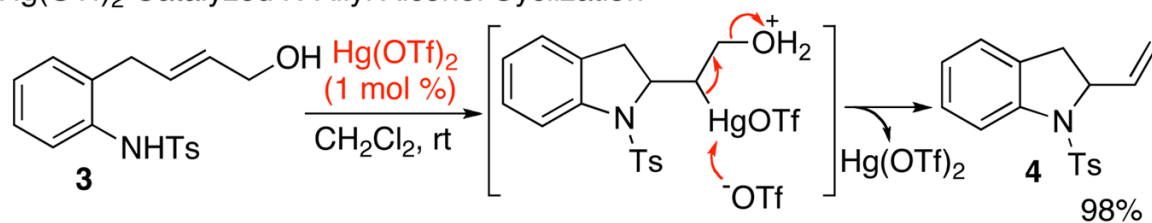


nitrile **iv** did not afford lactum **iii**.

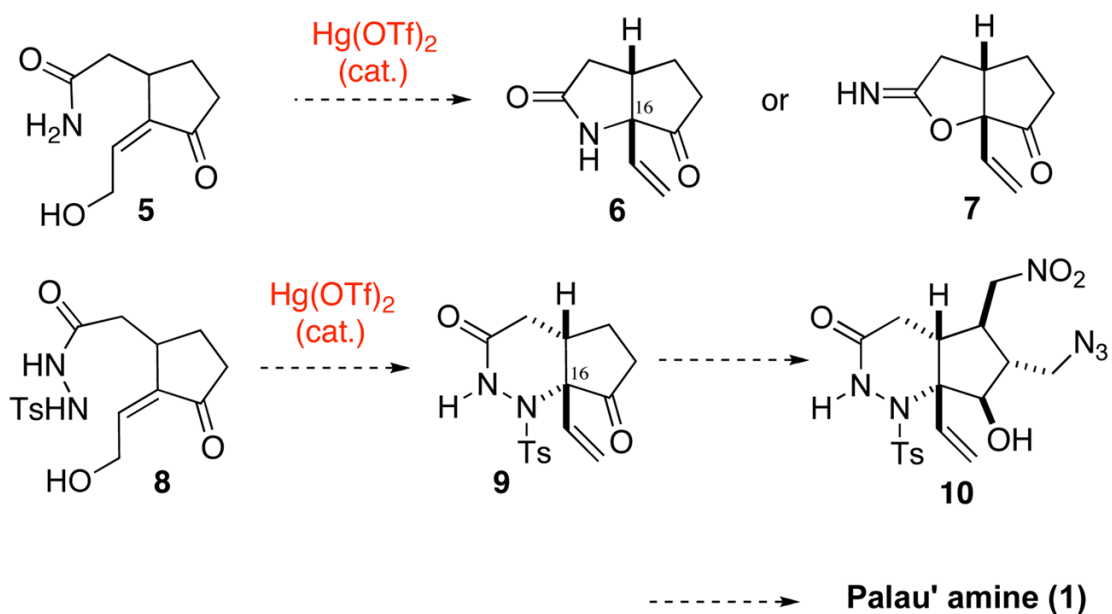
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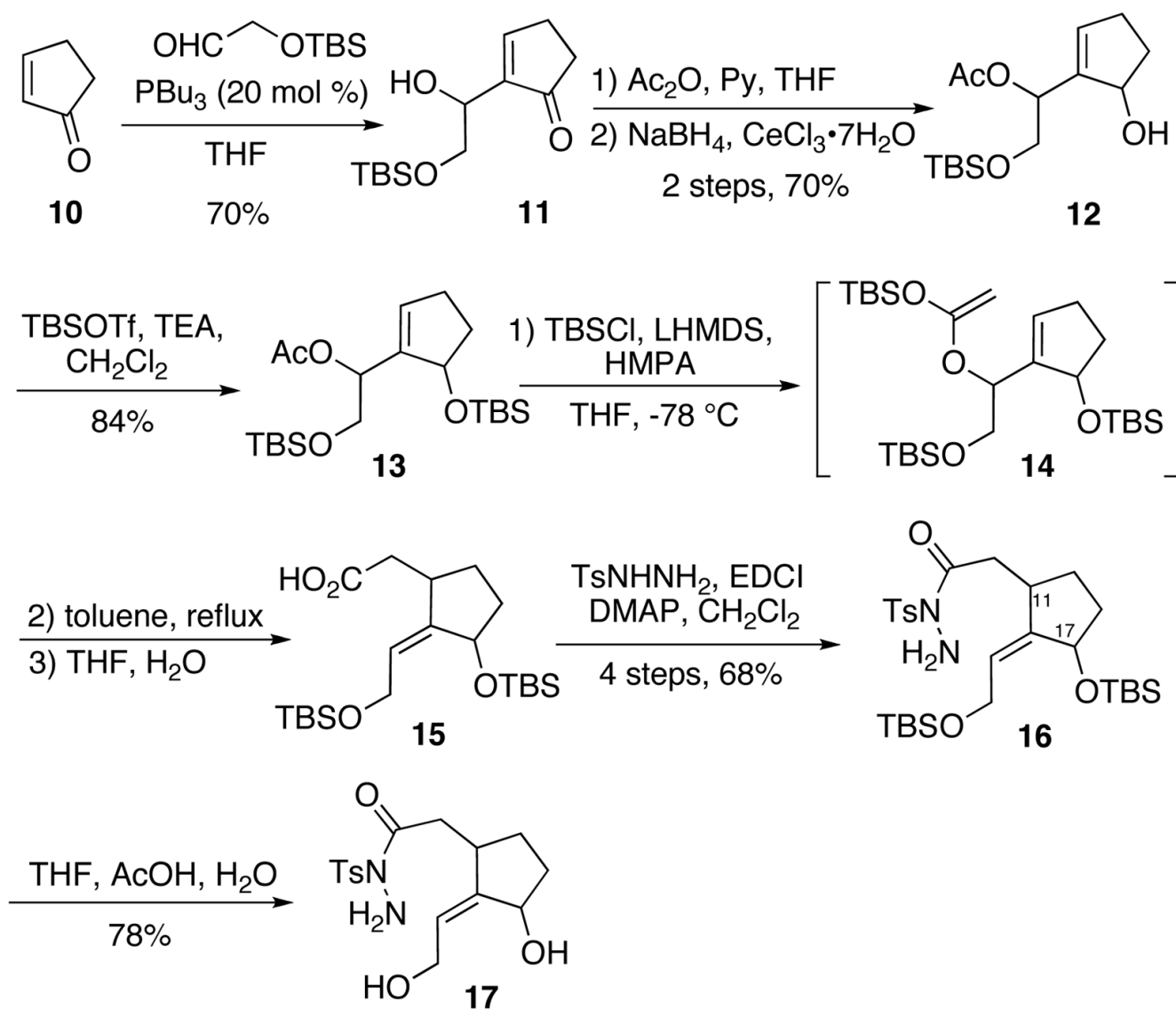
**Figure 1.**  
Structure of Palau'amine (Original and Revised Structures) and Axinellamines (2).

Hg(OTf)<sub>2</sub>-Catalyzed N-Allyl Alcohol Cyclization

## Retrosynthesis of the Cyclopentane Core of Palau'amine

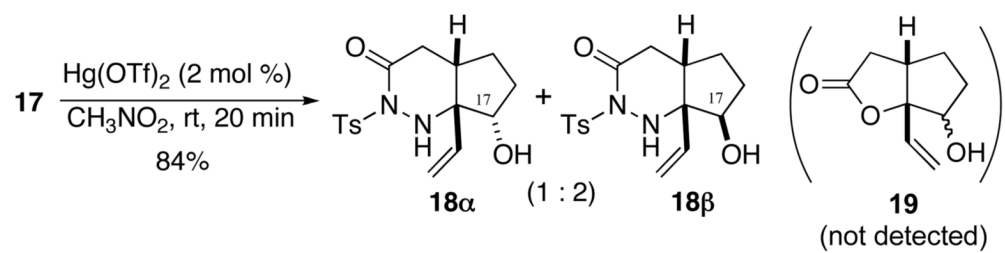
**Scheme 1.**

Hg(OTf)<sub>2</sub>-Catalyzed Cyclization of Allylic Alcohol and Synthetic Design of Palau'amine Cyclopentane Core **10**.

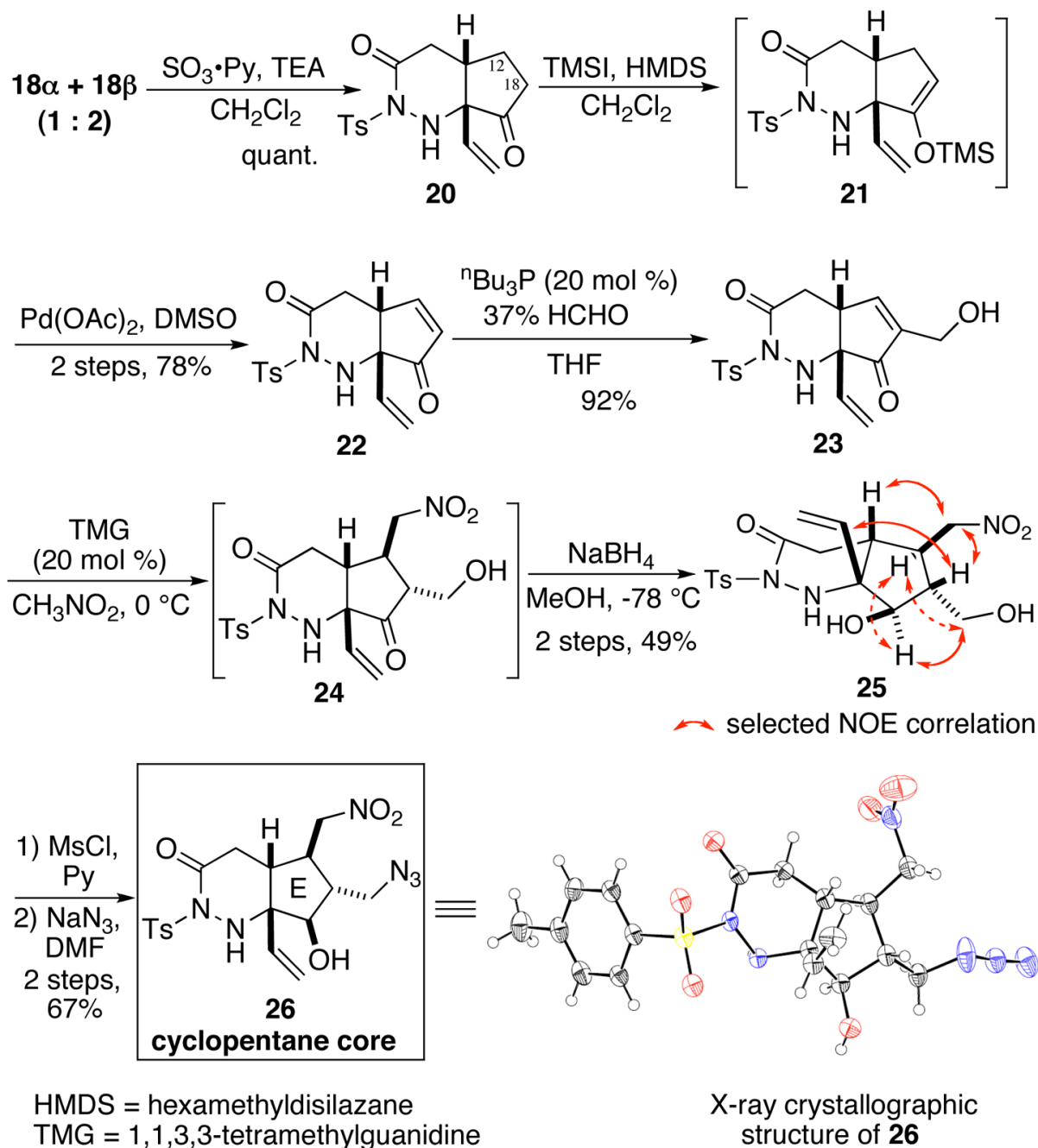


**Scheme 2.**  
Synthesis of Hydrazide **17**





**Scheme 3.**  
Hg(OTf)<sub>2</sub>-Catalyzed Allyl Alcohol Cyclization of Acylhydrazide.



**Scheme 4.**  
 Synthesis and X-ray crystallographic structure of **26**.