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Formal Synthesis of (±)-Peduncularine: Use of the [3 + 2] Annulation of Allylic Silanes and Chlorosulfonyl Isocyanate

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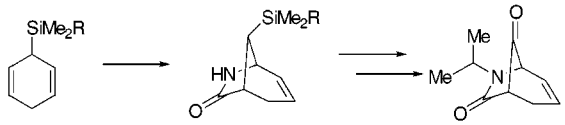
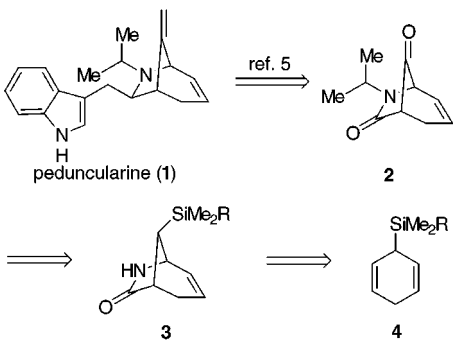
ABSTRACT



The formal synthesis of the alkaloid (±)-peduncularine (1) was accomplished through the use of a [3 + 2] allylic silane annulation. The annulation of cyclohexadienyl silane 6 with chlorosulfonyl isocyanate followed by an in situ reduction provided bicyclic lactam 7. Conversion of this intermediate to 2 in three steps completed the formal synthesis of (±)-peduncularine.

The alkaloid peduncularine (**1**) (Scheme 1), which was first isolated in 1971,[1,2] is the principal alkaloid of the Tasmanian shrub *Aristotelia peduncularis*.[3] It represents an interesting synthetic target due to its unusual 6-azabicyclo[3.2.1]octane core.[4] The natural product was synthesized once in an asymmetric total synthesis by Hiemstra and Speckamp,[5] and a racemic formal synthesis was also recently reported by Rigby.[6] Both approaches rely on the stereocontrolled synthesis of bicyclic lactam **2**. We recognized that our previously developed [3 + 2] annulation of allylic silanes and chlorosulfonyl isocyanate[7] (CSI) could lead to a concise and stereocontrolled synthesis of bicyclic lactams such as **2**. We proposed that the 6-azabicyclo[3.2.1]octane core could be accessed through the annulation of a cyclohexadienyl silane such as **4**. The annulation product **3** would possess the requisite handles for further elaboration to the formal synthesis target **2**. In this paper, we report the successful application of the strategy shown in Scheme 1. Our synthesis provides the alkaloid core in three synthetic steps and compound **2** in six steps from commercially available materials. This synthesis also represents the first use of the [3 + 2] annulation of allylic silanes in a natural product synthesis.

Scheme 1



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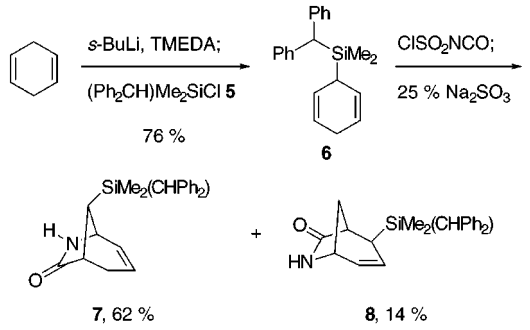
The 6-azabicyclo[3.2.1]octane core can be accessed stereoselectively in three steps with the use of our [3 + 2] annulation.[7] Alkylation of 1,4-cyclohexadiene with dimethylbenzhydrylsilyl chloride **5**, prepared in one step from diphenylmethane and dichlorodimethylsilane,[8] provided the requisite bisallylic silane **6** (Scheme 2) as the sole product.

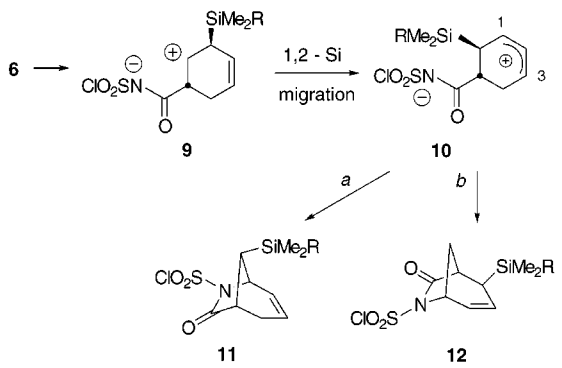
Scheme 2



The dimethylbenzhydrylsilyl group is currently being developed in our laboratories for general use in the [3 + 2] annulation of allylic silanes.[8] The thermally unstable cyclohexadienyl silane **6**, once prepared, was then submitted to the annulation conditions. Initial attempts using the procedure previously developed for acyclic allylic silanes[7] (CSI, $PhCH_3$; Red-Al) gave unsatisfying results due to a competing Hosomi−Sakurai pathway[9,10] and to the sensitivity of the bicyclic lactam to Red-Al. The optimized conditions for **6** required that the annulation took place at −40 °C in CH_2Cl_2 for 24 h. Additionally, the milder reduction conditions of 25% Na_2SO_3[11] were used to yield lactams **7** and **8** in a 82:18 ratio, each as single diastereomers. These modified conditions suppress the Hosomi−Sakurai reaction and provided the annulation products in 76% overall yield.

The appearance of both annulation products **7** and **8** can be understood by consideration of the annulation mechanism. Electrophilic attack of **6** by chlorosulfonyl isocyanate, antiperiplanar to the silyl group,[12] yields zwitterionic intermediate **9** (Scheme 3).[13] A 1,2-silyl migration[14] occurs to provide the more stable allylic cation **10**. Ring closure at

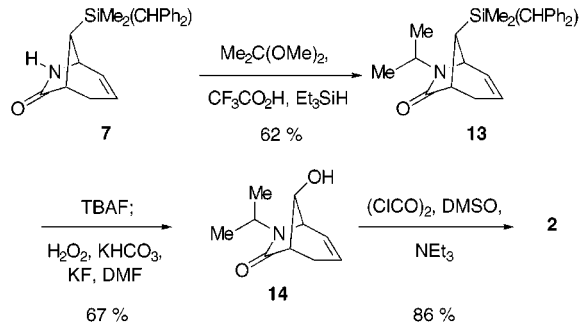
Scheme 3



C-1 of the allylic cation (route *a*) yields the desired *N*-chlorosulfonyl bicyclic lactam **11**, which is subsequently reduced to **7** by Na_2SO_3. Ring closure at C-3 (route *b*) yields the bicyclic lactam **12**, which is reduced to compound **8**. The ratio of **11** to **12**, approximately 5:1, could not be altered by solvent or temperature changes. For comparison, the ratio of the dimethylphenylsilyl analogues of **11** and **12** was 10:1. The dimethylphenylsilyl group, however, proved to be unsuitable in subsequent steps (vide infra). We believe that the lower selectivity observed for the dimethylbenzhydrylsilyl compounds is due to the developing steric interactions between the silyl group and the three-carbon bridge. Further investigations will be needed to determine conclusively the cause of the observed selectivities.

The completion of the formal synthesis required installation of the isopropyl group and oxidation of the carbon−silicon bond. A reductive *N*-alkylation[15] with 2,2-dimethoxypropane was performed on the mixture of lactams **7** and **8**, from which **13** could be isolated in 62% yield (Scheme 4).

Scheme 4



Displacement of the benzhydryl group of **13** with TBAF (1 M in THF)[16] followed by Tamao oxidation[17−19] provided alcohol **14**. Optimized Tamao oxidation conditions required heating to 65 °C in DMF for 17 h. Attempts to oxidize the dimethylphenylsilyl analogue of **13** failed due to both the acid[19] and base[20] sensitivity of the allylic amide. Use of the dimethylbenzhydrylsilyl group allowed us to obtain **14** in good yield under milder reaction conditions. Swern oxidation

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of **14** furnished **2**, completing the formal synthesis of (±)-peduncularine. The spectroscopic data of **2** were identical to those reported in the literature.[5]

A concise formal synthesis of peduncularine (**1**) has been developed using the [3 + 2] allylic silane annulation previously reported from our laboratories.[7] The synthesis of **2** has been accomplished in six steps from commercially available materials. All synthetic steps of this sequence proceeded in good yield, and the stereogenic centers formed from the annulation were established with high stereoselectivity. The use of a readily oxidized silyl group allowed for the installation of the required ketone of **2**. The formal synthesis of this natural product demonstrates the synthetic utility of the [3 + 2] annulation of allylic silanes with chlorosulfonyl isocyanate.

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Supporting Information Available: Full experimental and analytical data for all new compounds and compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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