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A novel intramolecular Diels–Alder approach to securinega alkaloids: formal synthesis of securinine

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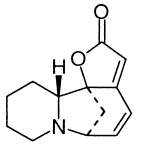
Abstract

A formal total synthesis of securinine (**1**) was achieved by employing an intramolecular Diels–Alder reaction of the enol ester, derived from 2-acetylpyridine and sorbic anhydride, as a key step.

Keywords: securinine; Diels–Alder reaction; $GABA_A$ receptor antagonist; enol ester.

Securinine (**1**; Fig. 1),[1] originally isolated from *Securinega suffruticasa* RHED.[2] is a tetracyclic indolizidine alkaloid with an α,β-unsaturated-γ-lactone unit, and its structure, including the absolute configuration, was determined by chemical and spectroscopical studies,[3,4] and also by X-ray crystallographic study.[5] The first total synthesis of securinine was accomplished by Horii and co-workers in 1967.[6] Since then, several synthetic approaches to this alkaloid were reported with little success,[7] although a number of syntheses of norsecurinine were reported.[8] Securinine has been shown to be a stereospecific $GABA_A$ receptor antagonist. Since it would appear to be a fairly inflexible molecule with a well-defined geometry, securinine offers the hope that it might aid in understanding the shape of the $GABA_A$ receptor site.[9]



securinine **1**

Figure 1.

Our own interest in the synthesis of **1**, due to its interesting biological activity and unique structural features, grew out of a desire to find a new route for the synthesis of securinine and its

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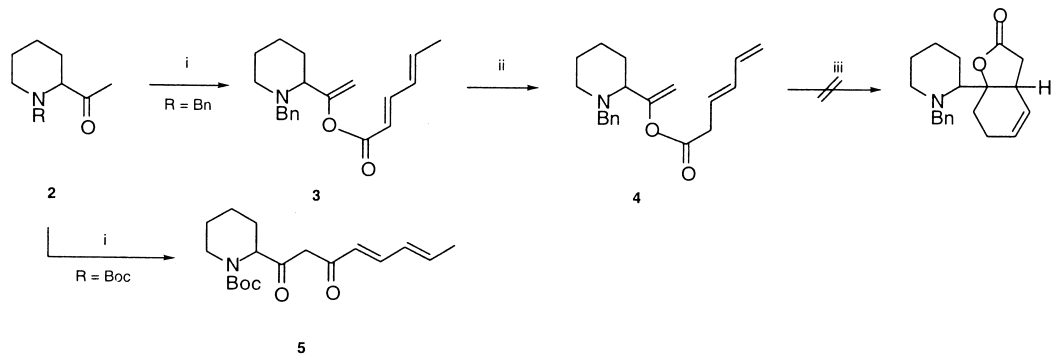
congeners. Thus, we decided to employ an intramolecular [4+2]cycloaddition reaction of an enol ester derivative, since this approach[10] should be potentially general, and thus widely applicable to the synthesis of securinega alkaloids with polycyclic, fused-ring systems, especially those containing lactone rings.

First, we attempted a cycloaddition reaction of the enol ester **4**, which was derived from 1-benzyl-2-acetylpiperidine (**2**; R = Bn) and sorbic anhydride in the presence of LiHMDS, followed by deconjugation of the diene system **3**;[11] however, unfortunately none of the desired cycloaddition products could be isolated under various reaction conditions. On the other hand, the acylation of **2** (R = Boc) afforded only *C*-acylated compound **5** instead of the desired *O*-acylation product (Scheme 1).

We therefore turned our attention to the cycloaddition of a pyridine derivative (**8**), although a stereoselective reduction of the pyridine ring of the cycloadduct to the corresponding piperidine

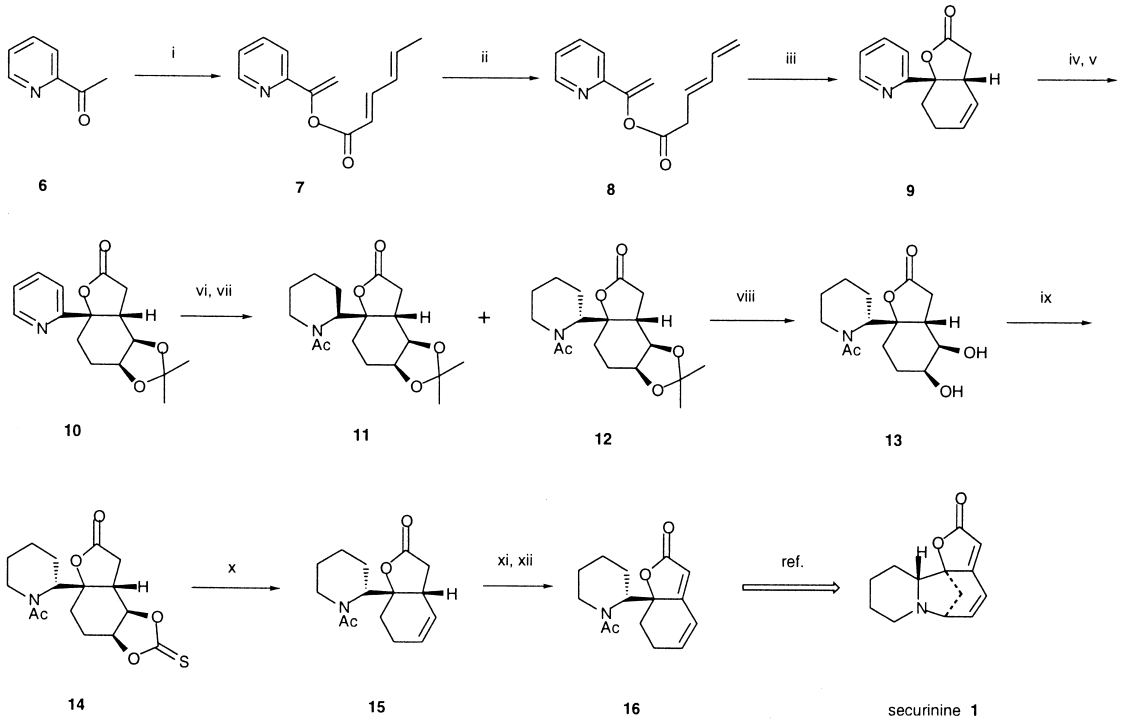


Scheme 1. *Reagents and conditions*: (i) $LiN(TMS)_2$, sorbic anhydride, THF, –78°C; (ii) $LiN(TMS)_2$, THF, –78°C, then aq. AcOH; (iii) heat or Lewis acid

ring would be required at a later stage of this synthesis (Scheme 2).

Thus, 2-acetylpyridine (**6**) was treated with sorbic anhydride in the presence of LiHMDS to give the enol ester **7** which, on treatment with LiHMDS in dry THF and HMPA followed by quenching with aqueous acetic acid,[11] afforded the deconjugated diene **8** in 42% yield from **6**. Heating of a solution of **8** in toluene at 180°C in a sealed tube provided the cycloaddition product **9**, mp 66–67.5°C, and its stereoisomer in 70 and 8% yields, respectively. The stereochemistry of the major product (**9**) was assumed to be *cis* based upon examination of molecular models of the transition states as depicted in Fig. 2, where the *exo* transition state (*exo*-TS) was preferred to the *endo* transition state (*endo*-TS) in terms of steric repulsion.

With the desired compound in hand, we investigated reduction of the pyridine ring in order to accomplish the synthesis of securinine. After protection of the olefin of **9** as the acetonide by dihydroxylation with osmium tetroxide, followed by acetonization with 2,2-dimethoxypropane in 96% two-step yield, compound **10** was hydrogenated over platinum oxide under an atmosphere of hydrogen to give the piperidine derivatives which, on acetylation with acetic anhydride, furnished the corresponding acetates **11** and **12** in a ratio of 2:3, respectively, in 91% yield from **10**. The stereochemistry of the major product was unambiguously determined by X-ray crystallography for the diol **13** (Fig. 3),[12] derived from **12** by acid treatment in 91% yield, although unfortunately the expected high stereoselectivity could not be obtained.



Scheme 2. *Reagents and conditions*: (i) $LiN(TMS)_2$, sorbic anhydride, THF, –78°C; (ii) $LiN(TMS)_2$, THF, –78°C, then aq. AcOH; (iii) toluene, 180°C; (iv) OsO_4, NMO, $^tBuOH–H_2O$, rt; (v) 2,2-dimethoxypropane, CSA, DMF, rt; (vi) PtO_2, AcOH, H_2, rt; (vii) acetic anhydride, DMAP, pyridine, rt; (viii) 1N HCl, THF, rt; (ix) 1,1-thiocarbonyldiimidazole, toluene, 110°C; (x) $Ni(COD)_2$, DMF, 60°C; (xi) LDA, PhSeCl, THF, –78°C; (xii) 30% H_2O_2, pyridine, CH_2Cl_2, 0°C

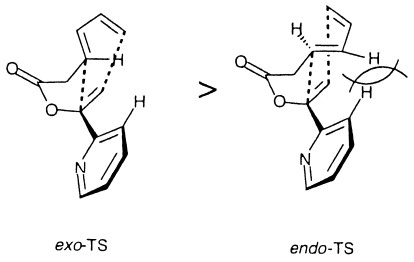


Figure 2.

Regeneration of the olefin from **13** was achieved in two steps involving thionocabonate formation with thiocarbonyldiimidazole and subsequent elimination of the thionocarbonate group of **14** with bis(1,5-cyclooctadiene)-nickel(0) [$Ni(COD)_2$],[13] to give the olefin **15**, mp 138°C, in 80% overall yield. Finally, the introduction of the diene system for **15** was successfully carried out via phenylselenylation and oxidative elimination of the selenide to give the diene **16** in 40% yield. Since the diene **16** was already converted into securinine,[6] this synthesis constitutes its formal total synthesis.

In summary, we have disclosed a formal synthesis of **1** by employing an intramolecular Diels–Alder reaction as a key reaction. However, the conversion of **16** into securinine was achieved in quite

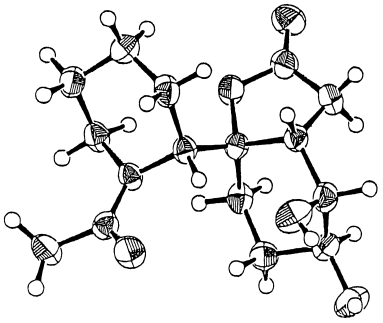


Figure 3. ORTEP drawing of compound **13**

low yield;[6] therefore, it is desirable to find an alternative synthetic path by changing the protecting group on the amino group of compound **16**.

Acknowledgements

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