Total Synthesis

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Total Synthesis of (+)-Phyllantidine**

*Cheryl A. Carson and Michael A. Kerr**

Dedicated to Professor K. C. Nicolaou on the occasion of his 60th birthday

There exists a small group of alkaloids isolated from the *Euporbiaceae* family of plants known as the securinega alkaloids (Figure 1).[1] These compounds have an indolizidine

[*] C. A. Carson, Dr. M. A. Kerr
Department of Chemistry
The University of Western Ontario
London, ON, N6A5B7 (Canada)
Fax: (+1) 519-661-3022
E-mail: makerr@uwo.ca

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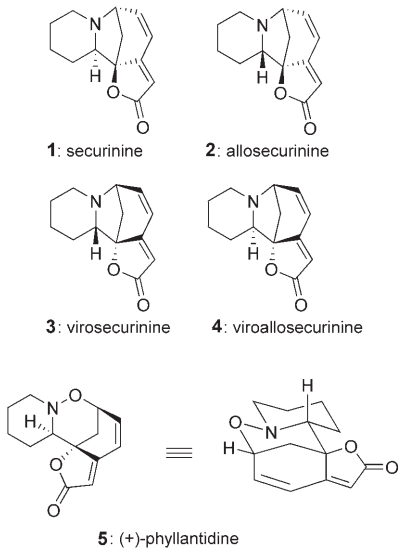
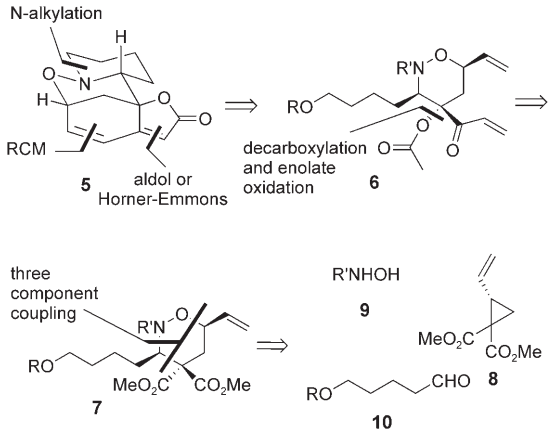


Figure 1. The securinega alkaloids including (+)-phyllantidine (**5**).

core imbedded within an azabicyclo [3.2.1] ring system. This is fused to a butenolide moiety forming a rather interesting and structurally complex molecular framework. Securinine (**1**) and its C2 epimer allosecurinine (**2**) are constituents of *Securinega suffruticosa*,[2] and the antipodal compounds virosecurinine (**3**) and viroallosecurinine (**4**) are found in *Securinega virosa*.[3] While these compounds show interesting activity in the central nervous system (CNS) in the form of antagonism of the γ-aminobutyric acid (GABA) receptor,[4] the synthetic chemist is drawn to the compact and complex architecture of the compounds. Indeed several syntheses of the securinine series of compounds have been reported.[5] Of interest to us are not the indolizidines **1**–**4** but a related and much rarer alkaloid phyllantidine **5** (isolated from *Phyllanthus discoides* and *Seurinega suffruticosa*)[6] and its enantiomer (from *Breynia coronata*).[7]

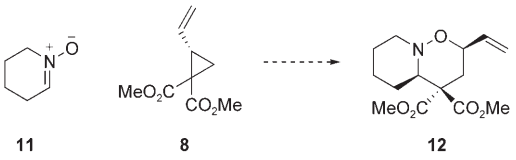
To date, no syntheses of phyllantidine (or *ent*-phyllantidine) have been reported, although phyllantidine is available through the peroxide (or peracid) oxidation of virosecurinine.[8] This proceeds via the *N*-oxide which undergoes a Meisenheimer rearrangement yielding phyllantidine. Since the synthetic routes to the securinine alkaloids are quite complex and lengthy, this route to phyllantidine is less than appealing. Herein, we present a convenient and direct synthesis of (+)-phyllantidine.

Perhaps the most significant structural feature of phyllantidine is the tetrahydro-1,2-oxazine ring. This heterocyclic motif is uncommon in natural products and is found in FR-900482 (and a few related compounds)[9]. This structural feature also makes phyllantidine an elusive target since there are few ways to directly prepare tetrahydro-1,2-oxazines. Recently, however, we reported that nitrones (either as isolated compounds or generated in situ) react smoothly with 1,1-cyclopropane diesters under the influence of Lewis acids to form tetrahydro-1,2-oxazines in what we have termed a "homo-1,3-dipolar cycloaddition".[10] The reactions are diastereoselective and yield only 3,6-*cis* adducts. Both the substitution pattern and relative stereochemistry of the adducts from this cycloaddition would fulfill the requirements of a practical synthetic route to phyllantidine (Scheme 1).



Scheme 1. Retrosynthesis of phyllantidine. RCM = ring-closing olefin metathesis.

Initially, we envisioned a cycloaddition between a cyclic nitrone **11** and cyclopropane **8** as a rapid access to an advanced bicyclic intermediate such as **12** [Eq. (1)]. However, we have not been able to obtain adducts from the cyclo-

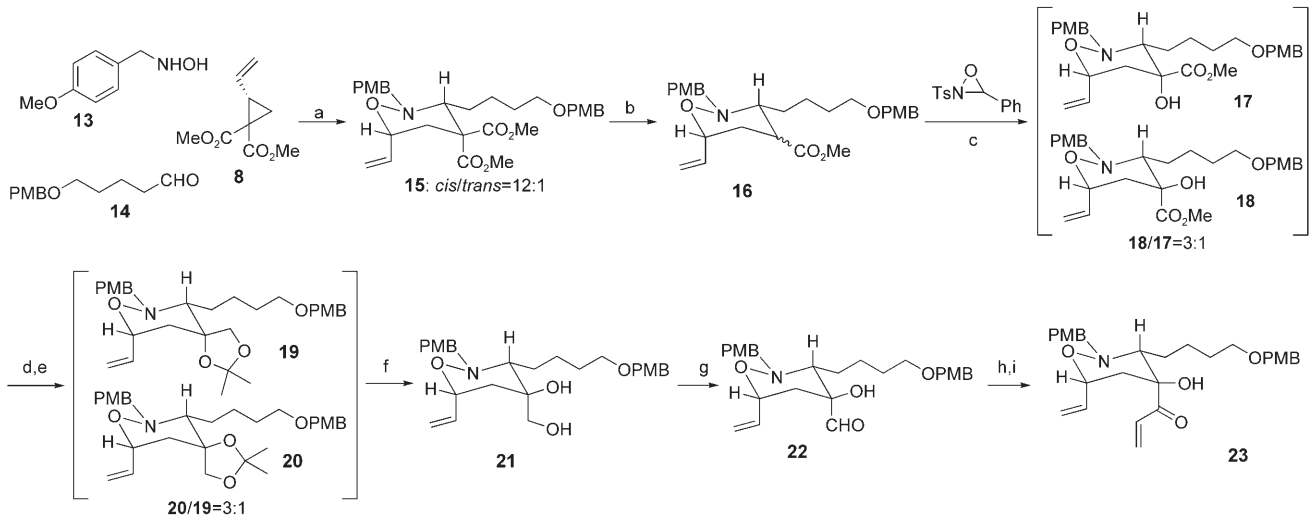


(1)

addition reaction using nitrones such as **11** as the substrate.

Our synthesis of phyllantidine commenced with the three-component coupling of hydroxylamine **13**, aldehyde **14**, and cyclopropane **8**[11] under the influence of catalytic ytterbium triflate hydrate to give the tetrahydro-1,2-oxazine **15** in 86% yield as a 12:1 mixture of diastereomers, in which the major product bore the required *cis* relationship between the oxazine vinyl substituent and the alkyl chain (Scheme 2). Interestingly, we occasionally saw this slight loss of diastereochemical integrity when the cycloaddition reaction mixture was heated to reflux. However, perhaps more interesting and surprising is that there was approximately 10% erosion of the absolute stereochemistry, with the *cis* adduct isolated as a 90:10 mixture of enantiomers. This has mechanistic implications and a detailed study of the stereochemistry of these cycloadditions is underway. Krapcho decarboxylation proceeded smoothly to produce **16** as a 1:1 mixture of diastereomers in 85% yield. Treatment of **16** (mixture of epimers) with KHMDS to generate the potassium enolate followed by treatment with the Davis oxaziridine[12] gave the hydroxy esters **17** and **18** as an inseparable mixture of diastereomers (1:3 in favor of the desired isomer; Scheme 2).

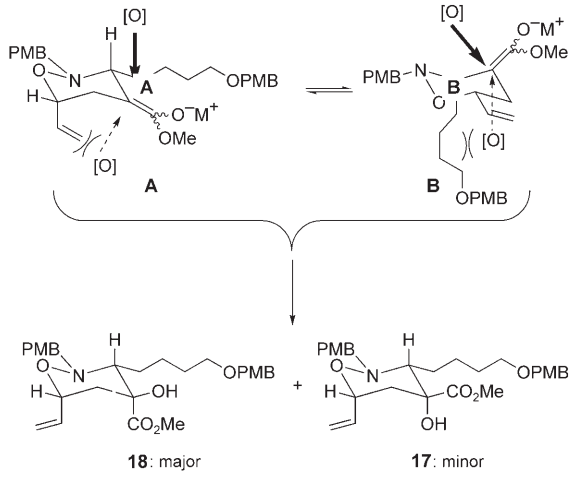
We were delighted to find that our expectations of a diastereoselective hydroxylation were born out, since this



Scheme 2. Synthesis of advanced intermediate **23**. a) Ytterbium(III) trifluoromethanesulfonate hydrate (5 mol%), MS (4 Å), toluene, heated at reflux (86%); b) LiCl (5 equiv), DMSO, H_2O, 160°C (85%); c) KHMDS, Davis oxaziridine, THF, −78°C (80% as a 3:1 diastereomeric mixture of **18** and **17**); d) LAH, THF, 0°C (97%); e) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, DMSO (74%); f) 6 N HCl, THF (93% based on **20**); g) IBX, DMSO (64%); h) CH_2=CHMgBr, THF, (76%); i) IBX, DMSO (79%). PMB = *p*-methoxybenzyl, Ts = toluene-4-sulfonyl, LAH = lithium aluminum hydride, KHMDS = potassium bis(trimethylsilyl)amide, IBX = *o*-iodoxybenzoic acid.

transformation was the greatest concern to us at the outset of the project. Our rationale for the predicted selectivity is shown in Scheme 3. The enolate derived from **16** may be envisaged as the chair conformers **A** or **B**. Whether one invokes **A** or **B**, approach of the electrophilic oxidant should be from the top face (bold arrow in Scheme 3) to avoid either a 1,3-diaxial interaction with the vinyl group in **A** or a 1,2-interaction with the alkyl chain in **B**. It is worth noting that in a simpler model system, in which both the substituents on the nitrogen atom and the alkyl chain were replaced by phenyl moieties, there was complete selectivity for the desired isomer.

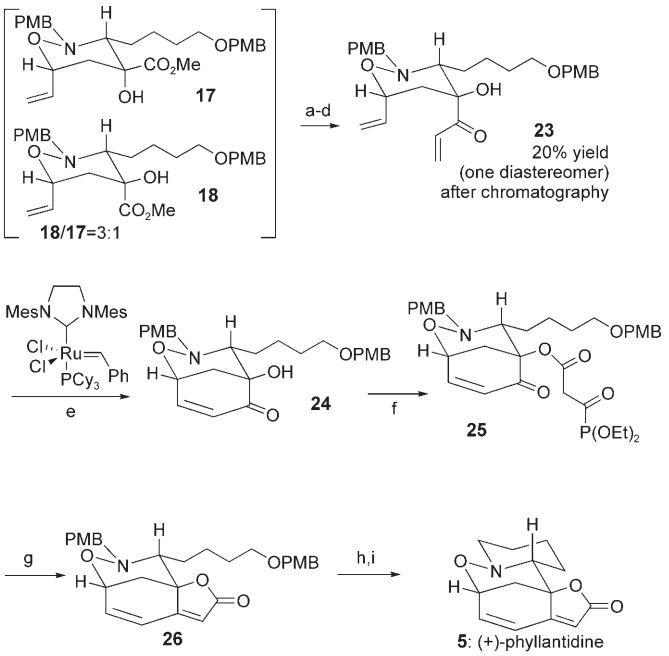
Reduction of this mixture with LAH afforded the diols (in 97% yield), which upon derivatization gave the acetonides **19** and **20** as a 1:3 mixture as expected (Scheme 3). This mixture was amenable to simple separation by flash column chromatography giving, after acetonide removal (in 93% yield), **21** as a single isomer. Oxidation of the primary hydroxy group gave an aldehyde **22** (in 64% yield), which was treated with vinylmagnesium bromide to give a diastereomeric mixture of the allylic alcohols in 76% yield. Oxidation gave the enone **23**, which we anticipated would be an appropriate substrate for RCM.



Scheme 3. Model for selective hydroxylation showing steric interactions between oxidant and vinyl group in **A** and between oxidant and alkyl chain in **B**.

While the sequence of reactions in Scheme 2 certainly produced **23** in a relatively efficient way, this sequence of protection through formation of acetonides, separation, and deprotection seemed rather clumsy. This procedure was necessary at the time to better understand the reaction sequence. In addition, separation of the diols resulting from the reduction of mixture **17**/**18** was not possible in a preparative manner.

In order to circumvent the tedious protection/deprotection sequence, the diastereomeric mixture of **17**/**18** (ratio 1:3) was subjected to a sequence of four reactions (Scheme 4), namely, reduction using LAH, oxidation of the primary alcohol to an aldehyde using IBX, addition of vinylmagnesium bromide, and finally oxidation of the allylic alcohol to give the vinyl ketone **23**. At this juncture, the unwanted diastereomer was readily removed by flash column chromatography. Enone **23** proved to be a suitable substrate for RCM with Grubbs second-generation catalyst. In the event, ring closure to give enone **24** proceeded in 74% yield. The O-acetyl derivative of **24** was explored as a substrate for aldol-type ring closure to form the butenolide, yet all attempts to affect this cyclization failed. Fortunately, an alternative acylation[13] using diethylphosphonoacetic acid afforded substrate **25** (in 71% yield), which after an intramolecular Horner–Emmons reaction, was converted into the desired **26** in quantitative yield.[14] The natural product **5** was ultimately



Scheme 4. Synthesis of (+)-phyllantidine. a) LAH, THF, 0°C; b) IBX, DMSO; c) CH_2=CHMgBr, THF; d) IBX, DMSO (20% overall yield of one diastereomer from a mixture of **17** and **18**); e) second-generation Grubbs catalyst (20 mol%), CH_2Cl_2, heated at reflux (74%); f) diethylphosphonoacetic acid, DCC, CH_2Cl_2 (71%); g) K_2CO_3, [18]crown-6, toluene (quant.); h) DDQ/CH_2Cl_2, H_2O (98%); i) Ph_3P, DIAD, toluene (98%). Mes = mesityl = 2,4,6-trimethylphenyl, DCC = 1,3-dicyclohexylcarbodiimide, DDQ = 2,3-dichloro-4,6-dicyano-1,4-benzoquinone, DIAD = diisopropylazodicarboxylate.

secured through oxidative removal of both the *p*-methoxybenzyl groups and ring closure under Mitsunobu conditions. This method of piperidine formation is unusual for C–N bond formation, and we were pleasantly surprised at its efficiency. However, there is ample precedent for such transformations.[15] The spectral data for synthetic (+)-phyllantidine correspond to those reported in the literature, including the sign of optical rotation. Analysis by HPLC on a chiral stationary phase indicated no trace of the (−) isomer.

In summary, we have succeeded in preparing for the first time the structurally unusual and demanding alkaloid phyllantidine using a homo [3+2] dipolar cycloaddition. The overall yield of the natural product is around 6% over 12 synthetic operations from the cycloaddition. Efforts to adapt this protocol (through N–O bond reduction and ring closure to form a pyrrolidine) to other *securinega* alkaloids are in progress.

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