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Natural Products

Total Synthesis of (−)-Allosecurinine**

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In memory of Jennifer Robertson (Dresch)

The *Securinega* alkaloids are a small family of molecules isolated from plants of the *Euphorbiaceae* family (Figure 1).[1] One of the most obvious characteristic features of this family is an azabicyclo [3.2.1] ring system that is common to most members. Securinine (**1**) was first isolated in 1956 from the leaves of *Securinega suffruticosa*.[2] However, its structure was not determined until 1962 when it was isolated once again and studied further.[3] Along with securinine, a small amount of another compound was isolated and was found to be epimeric at the C2 position.[3a] This new compound was named allosecurinine. Further work by other research groups has since led to the discovery of several other securinega alkaloids including the enantiomeric forms of both **1** and **2**, virosecurinine (**3**) and viroallosecurinine (**4**), respectively.[4] The family is currently composed of 20 or more members.

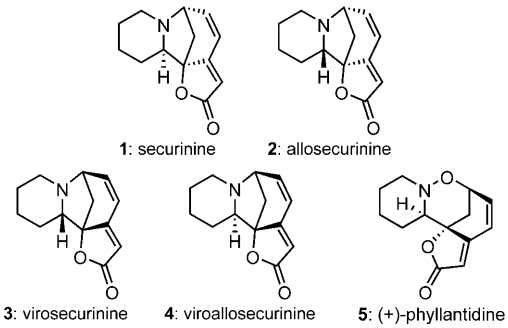
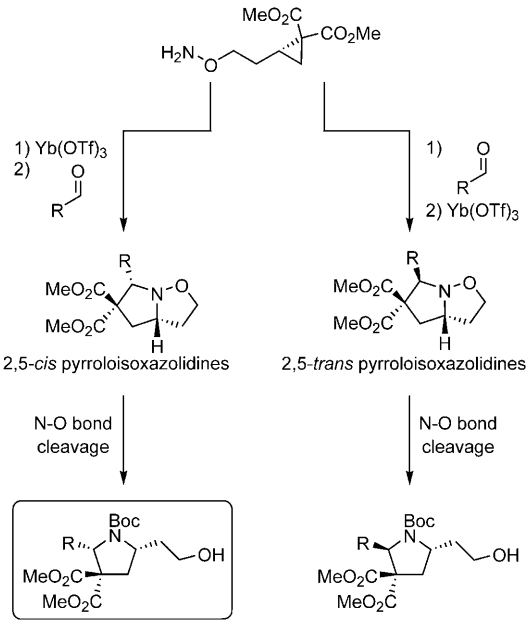


Figure 1. Representative members of the *Securinega* alkaloids.

There is great interest in this family of alkaloids in the synthetic chemistry community,[5] both for the synthetic challenge represented by their complex ring system and because of the known biological activities of some family members. Securinine, for instance, has been shown to be a γ-aminobutyric acid (GABA) receptor antagonist,[6] and many of the plants that produce *Securinega* alkaloids have been used in traditional folk medicine. Further biological research has shown some members to have antimalarial,[7] antibiotic,[8] and antifungal[9] activities to name but a few. Our interest in the *Securinega* alkaloids began several years ago with the total synthesis of (+)-phyllantidine **5**,[10] a recently isolated natural product containing a tetrahydro-1,2-oxazine ring system.[11] Our focus then fell upon allosecurinine, which, though isolated in 1962 has not been prepared by chemical synthesis, although there is a single synthesis reported for its enantiomer (also naturally occurring), viroallosecurinine.[5c] Recently, we have reported a methodology that allows easy access to both 2,5-*trans*- and 2,5-*cis*-substituted pyrrolidines (Scheme 1), and it was decided that its first application would be the synthesis of allosecurinine.[12]



Scheme 1. A facile approach to 2,5-*trans* and 2,5-*cis* pyrrolidines. OTf = trifluoromethanesulfonate, Boc = *tert*-butoxycarbonyl.

Our initial retrosynthesis (Scheme 2) began with a disconnection of the piperidine ring and removal of the butenolide to give pyrrolidine **7**. Further disconnections resulted in bisalkene **8**. The formation of compound **8** was envisioned to occur from α-oxygenation of an ester followed by oxidation-state manipulation and a Grignard addition to **9**. Ester **9** could then be simplified to diester **10** by a proposed dehydration and Krapcho decarboxylation. Pyrrolidine **10** is then a direct product from the unmasking of pyrroloisoxazolidine **11** by reductive N–O bond cleavage. This compound

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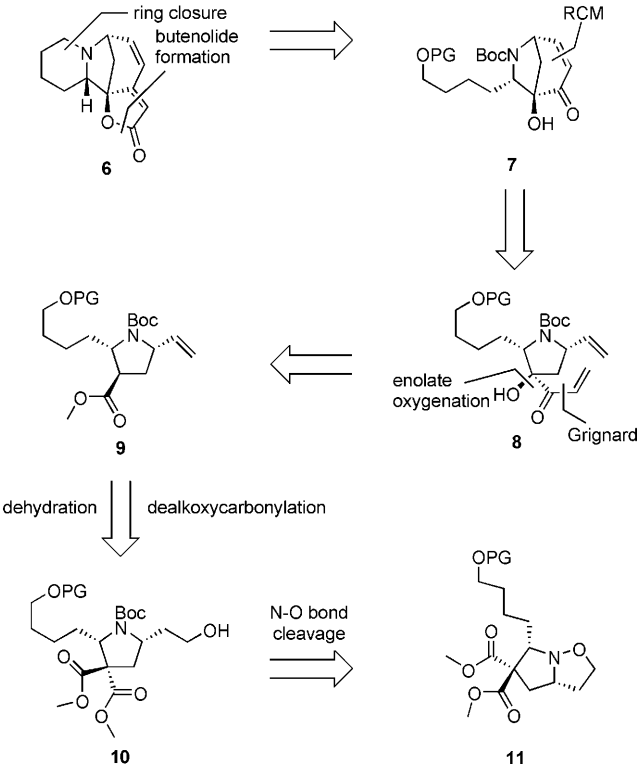
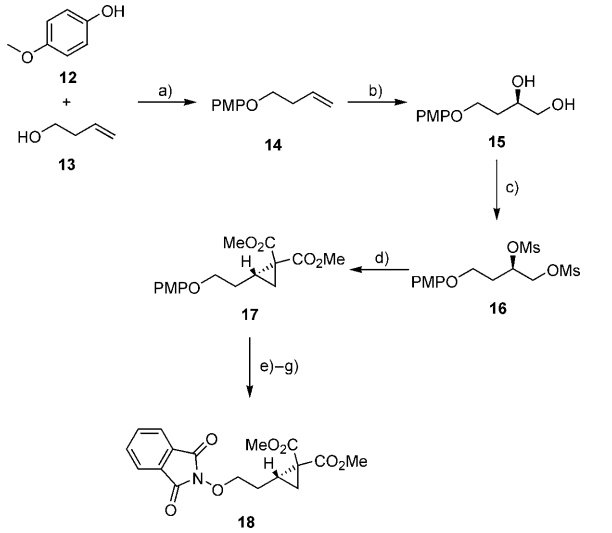


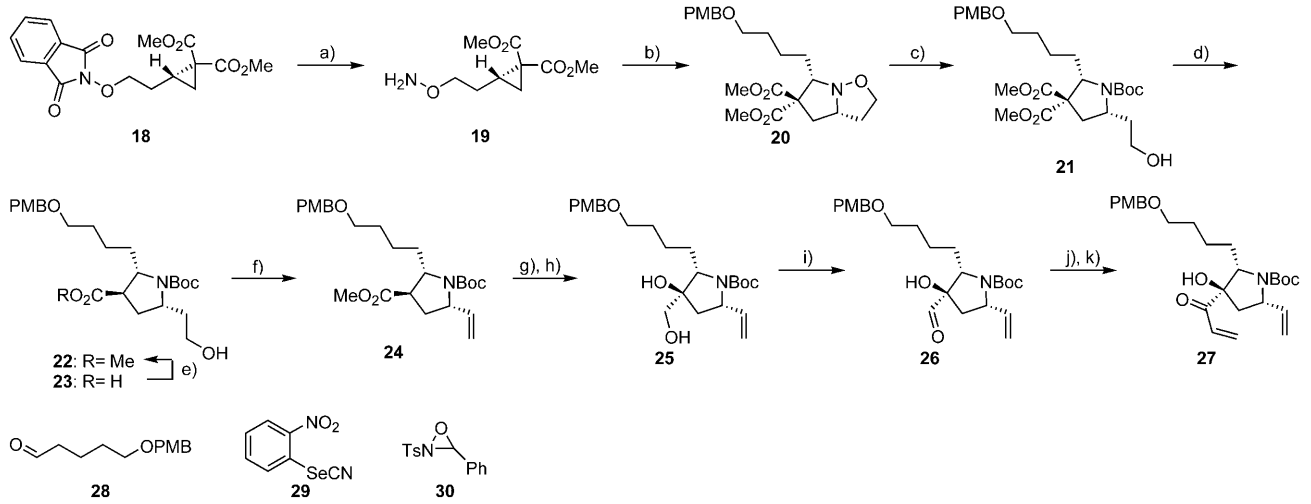
Scheme 2. A retrosynthesis for (−)-allosecurinine. RCM = ring-closing metathesis.



Scheme 3. Synthesis of the required *R* cyclopropane. a) PPh_3, DIAD, THF, 0 °C then reflux (95 %); b) $K_3[Fe(CN)_6]$, K_2CO_3, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, 1:1 *t*BuOH/H_2O, 0 °C (67 %); c) MsCl, NEt_3, CH_2Cl_2 (quant.); d) dimethylmalonate, NaH, THF, 0 °C then bismesylate, reflux (45 %); e) CAN, 4:1 AcCN/H_2O (93 %); f) TsCl, DABCO, CH_2Cl_2, 0 °C to RT; g) *N*-hydroxyphthalimide, DBU, DMF (69 % (2 steps), ≥ 99 % *ee*). DIAD = diisopropyl azodicarboxylate, $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, Ms = methanesulfonyl, CAN = ceric ammonium nitrate, Ts = *p*-toluenesulfonyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

can then lead back to an appropriate alkoxyamine cyclopropane and aldehyde as previously described.

With our retrosynthesis complete, the synthesis commenced with the production of the required enantiopure cyclopropane **18** (Scheme 3). Protection of homoallylic alcohol **13** as a *p*-methoxyphenyl ether by Mitsunobu displacement provided a substrate (**14**), which was previously utilized by Corey et al. in an asymmetric dihydroxylation reaction, and yielded the required enantiomer of diol **15** for our purposes.[13] Diol **15** could then be bismesylated to produce



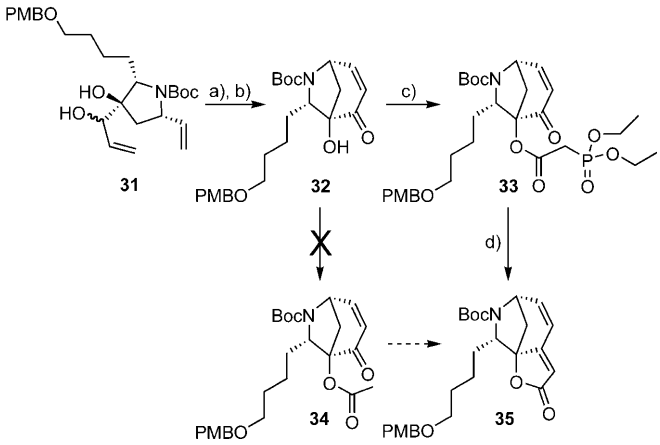
Scheme 4. Pyrrolidine synthesis and elaboration. a) hydrazine hydrate, 3:1 EtOH/CH_2Cl_2; b) ytterbium(III) trifluoromethanesulfonate hydrate (5 mol %), CH_2Cl_2, 30 min, then aldehyde **28** (88 %); c) $Pd(OH)_2/C$ (30 wt %), Boc_2O, H_2, MeOH (85 %); d) NaCN, wet DMSO, 140 °C, 12 min.; e) $TMSCHN_2$, 2:1 benzene/MeOH (86 % from **21** and re-esterified **23**); f) Bu_3P, *o*-nitrophenylselenocyanate (**29**), THF then H_2O_2, THF (94 %, 2 steps); g) KHMDS, THF, −78 °C, 1.5 h then Davis oxaziridine **30**, −78 °C; h) $CaCl_2$, $NaBH_4$, 1:1 THF/EtOH (73 %, 2 steps); i) IBX, DMSO (86 %); j) vinylmagnesium bromide, THF, 0 °C → RT (76 %); k) IBX, DMSO (69 %). TMS = trimethylsilyl, PMB = *p*-methoxybenzyl, KHMDS = potassium bis(trimethylsilyl)amide, IBX = *o*-iodoxybenzoic acid.

16, which then underwent a double displacement with dimethyl malonate to produce cyclopropane **17** in low yield; however, the only other materials present after displacement were the starting bismesylate and malonate. The starting material could thus be recycled, which greatly increased the amount of material obtained after several iterations. It is worthy of note that, regardless of the amount of malonate and base, this reaction failed to proceeded in higher than 50% yield. Deprotection of the PMP ether with CAN afforded a substrate which could then be tosylated and subjected to displacement with *N*-hydroxyphthalimide to yield cyclopropane **18** which was recrystallized to a minimum of 99% *ee*.

Deprotection of cyclopropane **18** with ethanolic hydrazine yielded free cyclopropane **19**, which underwent cyclization in the presence of $Yb(OTf)_3$. Treatment with protected aldehyde **28** provided 2,5-*cis* pyrroloisoxazolidine **20** in excellent yield (Scheme 4). Unmasking of the pyrrolidine proceeded smoothly under a hydrogen atmosphere in the presence of Pearlman's catalyst and di-*tert*-butyldicarbonate to provide **21** in 85% yield. At this point HPLC analysis on a chiral stationary phase showed that the cycloaddition had not eroded the stereochemical integrity of the cyclopropane as compound **21** was obtained in greater than 95% *ee*.

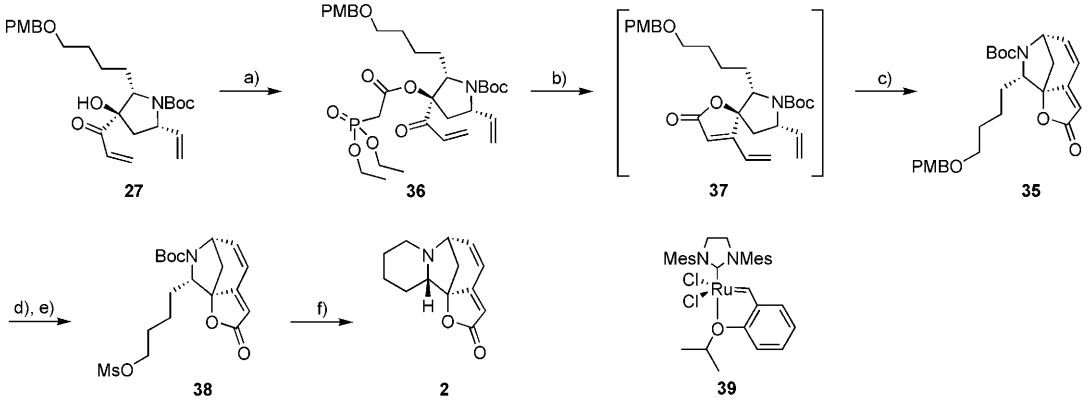
Krapcho decarboxylation[14] of the geminal diesters was carried out under microwave irradiation and produced the required monoester **22** in reasonable yield, along with a significant amount of monoacid **23**. This acid was easily isolated by acidification and extraction, and was transformed into the required ester **22** by treatment with $TMSCHN_2$. Dehydration of the primary alcohol in **22** by mesylation and elimination was attempted with a number of bases, but the alcohol proved extremely resistant to elimination. Thankfully, the Grieco procedure that utilizes *o*-nitrophenylselenocyanate and Bu_3P followed by oxidation furnished the required alkene **24** in excellent yield.[15] With pyrrolidine **24** in hand, the next step was α-hydroxylation of the ester. Deprotonation with KHMDS at −78 °C followed by treatment with the Davis oxaziridine produced the required α-hydroxy ester,[16] which was immediately reduced with $NaBH_4$ in the presence of $CaCl_2$ to provide diol **25**. Oxidation of **25** with IBX provided aldehyde **26**, which underwent smooth Grignard addition yielding a mixture of diastereomeric allylic alcohols, these were then oxidized with IBX in DMSO to yield α,β-unsaturated ketone **27**. The synthesis of aldehyde **26** also provided the first opportunity to perform an nuclear Overhauser effect (NOE) experiment which confirmed our predicted relative stereochemistry.

Attempted metathesis of **27** proceeded in low and variable yields; however, metathesis of allylic alcohol **31**, followed by oxidation with IBX yielded α,β-unsaturated ketone **32** albeit in a low yield of 45% (Scheme 5).



Scheme 5. First attempts at completing the synthesis of allosecurinine. a) Hoveyda–Grubbs 2nd generation catalyst (**39**), THF, reflux; b) IBX, DMSO (45%, 2 steps); c) DCC, diethylphosphonoacetic acid, CH_2Cl_2; d) LiBr, NEt_3, THF. DCC = dicyclohexyl carbodiimide.

Compound **32** could then be further derivatized utilizing large excesses of DCC and diethylphosphonoacetic acid to provide Horner–Emmons substrate **33**. Compound **33** was treated with several bases in an attempt to form the butenolide, but many of these conditions led solely to decomposition. The use of NEt_3 in the presence of LiBr produced the butenolide **35**, but in an unacceptable yield of approximately 20%, and once again the product was contaminated with large amounts of urea. An attempt was then



Scheme 6. Completion of the synthesis of allosecurinine. a) DCC, diethylphosphonoacetic acid, CH_2Cl_2 (90%); b) LiBr, NEt_3, THF; c) Hoveyda–Grubbs 2nd generation catalyst (**39**), THF, reflux (40%, 2 steps); d) DDQ, 9:1 CH_2Cl_2/H_2O; e) MsCl, NEt_3, THF (83%, 2 steps); f) TFA/CH_2Cl_2 then silica gel/acetone (65%). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. TFA = trifluoroacetic acid.

made to prepare acetate **34**, however no conditions were found to successfully produce this ester and only starting material was recovered in most cases. Our plan was thus subsequently altered to allow formation of the butenolide prior to metathesis.

Treatment of **27** with diethylphosphonoacetic acid and DCC led to the phosphonate **36** required for an intramolecular Horner–Emmons reaction (Scheme 6). Treatment of **36** with LiBr and NEt_3 provided butenolide **37**, which was found to decompose upon column chromatography. To obviate this difficulty, crude **37** was immediately taken up in THF and treated with the Hoveyda–Grubbs 2nd generation catalyst (**39**) at reflux. The resulting α,β,γ,δ-unsaturated ester **35** was obtained in a reasonable yield of 40%. This compound could then be deprotected with DDQ and mesylated in 83% yield to produce the penultimate compound **38**. Compound **38** was then treated with TFA in DCM to deprotect the pyrrolidine nitrogen. Upon neutralization and stirring with silica gel in acetone, allosecurinine (**2**) was obtained in 65% yield.

In summary, we have successfully completed the total synthesis of (−)-allosecurinine in 15 steps from homochiral cyclopropane **18** in an overall yield of 5%. Chiral shift analysis gave no indication of the enantiomeric viroallosecurinine in the sample. The possibility of adapting this methodology to the synthesis of other *Securinega* alkaloids is currently under investigation.

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