Development of Methodology for Amide Oxidation and Its Application to Total Synthesis of *Securinega* Alkaloids

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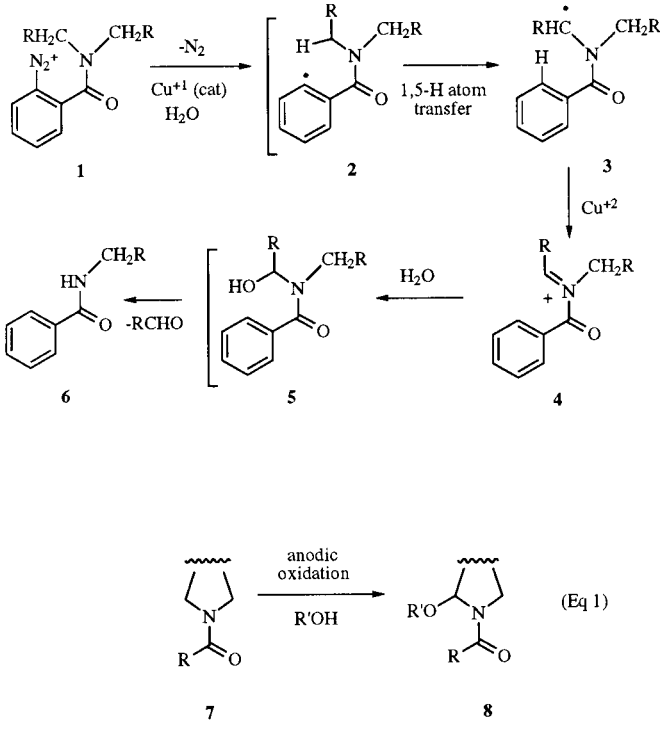
About forty years ago, Hey and Turpin observed that an *o*-diazo-*N,N*-dialkyl benzamide such as **1**, when treated with copper powder in aqueous solution, leads to formation of a dealkylation product **6** (Scheme 1) [1]. Subsequent mechanistic studies by Cohen and coworkers established that this process is more efficiently catalyzed by cuprous ion, and that the transformation involves free radical intermediates [2, 3]. Thus, diazonium salt **1** is first reduced by Cu^{+1}, providing an aryl radical **2**. 1,5-Hydrogen atom transfer from an *N*-alkyl group leads to radical **3**, which is then oxidized by Cu^{+2} to afford *N*-acyl iminium ion **4**. Addition of water to electrophilic species **4** yields an amido acetal derivative **5**, which loses an aldehyde molecule to give the dealkylated product **6**.

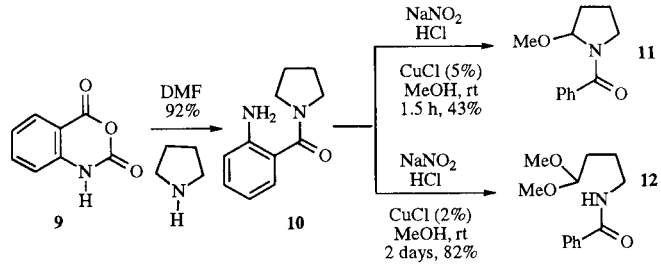
Scheme 1



Although this chemistry had not been investigated from a synthetic point of view, we believed it had potential as a convenient method for amide oxidation. In general, the preferred procedure for such a transformation has involved electrochemical anodic oxidation, which has been widely exploited by Shono [4] to prepare α-alkoxy amido compounds **8** using various types of substrates **7** (Eq. 1). The Shono group has also made nice use of many of these α-alkoxy amides in alkaloid total synthesis. However, we thought that considering the reluctance that synthetic chemists often display in adopting electrochemical techniques, it would be worthwhile to have available an efficient chemical alternative for amide oxidation. With this goal in mind, we set out to optimize reaction conditions for the process in Scheme 1 to make it generally attractive for synthetic purposes [5].

The starting *o*-diazobenzamides can be readily generated *in situ* from *o*-aminobenzamides like **10**, prepared in one step from secondary amines and isatoic anhydride (**9**) [6] (Scheme 2). In the case of the pyrrolidine-derived amide **10**, it was found that diazotization of the amine in anhydrous methanol in the presence of a catalytic amount of cuprous chloride led to the desired α-methoxy benzamide derivative **11** in moderate yield. The difficulty in this specific example is that the pyrrolidine ring has a tendency to open under these conditions. In fact, if the reaction is run for a longer time, acyclic amide acetal **12** is produced in good yield.

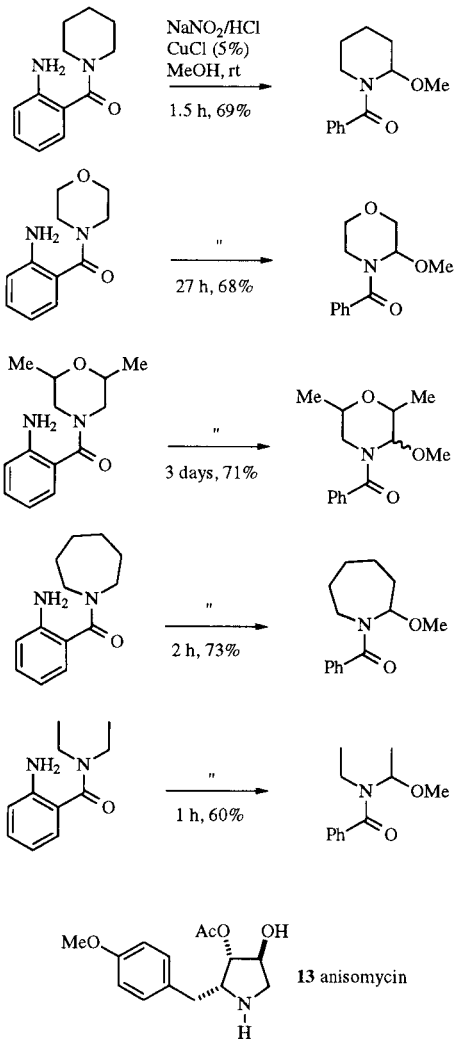
Scheme 2



The oxidation works quite well for the amides derived from symmetrical six- and seven-membered ring and acyclic amine systems as shown in Scheme 3. In these cases, ring opening is not a serious problem and the α-methoxybenzamides can all be isolated in good yields.

We decided to next explore the feasibility of utilizing this methodology in a short, enantioselective total synthesis of the interesting antibiotic (-)-anisomycin (**13**) [7,8]. The

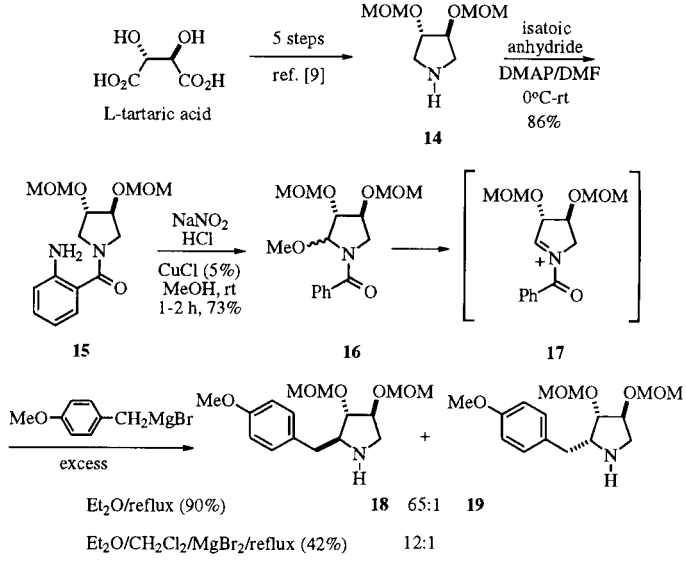
Scheme 3

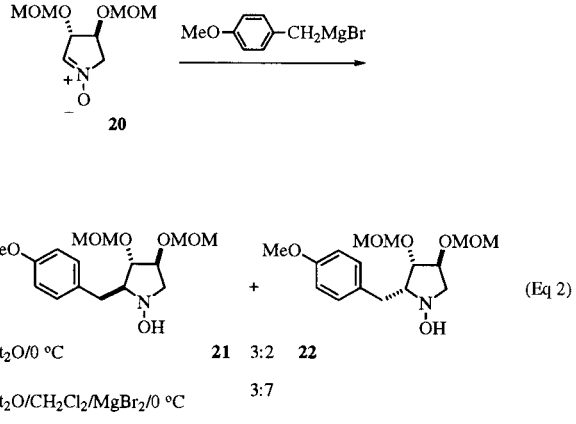


secondary amine needed for this approach is **14**, a known compound readily prepared enantiopure in five steps from L-tartaric acid [9] (Scheme 4). It might be noted that this amine has been used in a related nitrone-based strategy to anisomycin [9a] (*vide infra*). Treatment of **14** with isatoic anhydride led to *o*-aminobenzamide derivative **15**. Subsequent application of our oxidation conditions to **15** gave the desired α-methoxy amide **16** in good yield. It should be pointed out that due to the C_2-symmetry of the system, it is of no consequence which of the two α-positions of **15** is oxidized, since in any case the enantiomeric system leading to (-)-anisomycin would be produced.

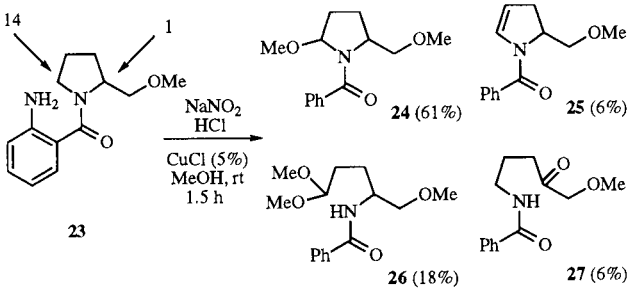
We next investigated the addition of *p*-methoxybenzylmagnesium bromide to methoxy amide **16** *via* *N*-acylimine **17**. However, treatment of **16** with a large excess of the Grignard reagent in refluxing ether to our disappointment gave the undesired *trans* stereoisomer amine **18** and only a trace of the *cis* compound **19** needed for the antibiotic. Using added magnesium bromide to try to induce a *syn* chelation-controlled addition did improve the ratio of **18/19** somewhat, but the total yield of alkylation products was substantially reduced. By comparison, Petrini and coworkers [9a] had found previously that nitrone **20** (Eq. 2) adds the same Grignard reagent in ether to give a 3:2 mixture of undesired *trans* isomer **21** to the requisite *cis* product **22**. However, in the presence of $MgBr_2$, the stereochemistry of addition is reversed to give *cis* **22** as the major stereoisomer. It is not immediately evident why we are seeing such different isomer ratios in our additions to *N*-acyl iminium ion **17**.

Scheme 4



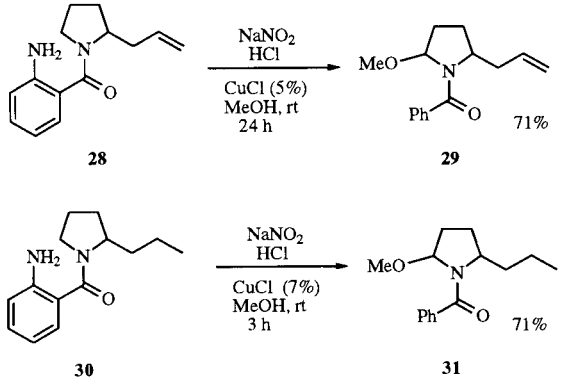


Scheme 5



All of the amide oxidations described above involved symmetrical secondary amine starting compounds. The obvious next stage of this project was to see if there is any regioselectivity when dealing with unsymetrical systems. The first case which was examined was the 2-substituted pyrrolidine amide **23** (Scheme 5), which when subjected to the standard diazotization conditions in the presence of cuprous chloride gave oxidation products **24-27** in the yields indicated. These results indicate a good methylene/methine regioselectivity of about 14/1.

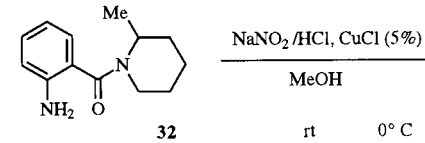
Scheme 6

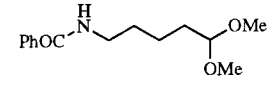
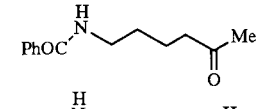
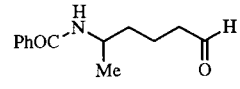
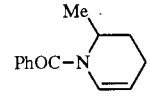
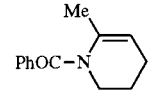


Two additional pyrrolidines **28** and **30** were also examined (Scheme 6). In both cases, only the products **29** and **31** resulting from methylene hydrogen atom abstraction were detected. Thus, with pyrrolidine-derived systems, the regioselectivity of the oxidation process is high.

In situations involving piperidines, regioselectivity has so far been mixed. Amide **32** from 2-methyl piperidine has been subjected to the oxidation conditions at a variety of temperatures giving the products indicated in Scheme 7. As can be seen, the ratio of methylene/methine hydrogen atom abstraction, which is basically temperature invariant (*vide infra*), is about 2.2/1.

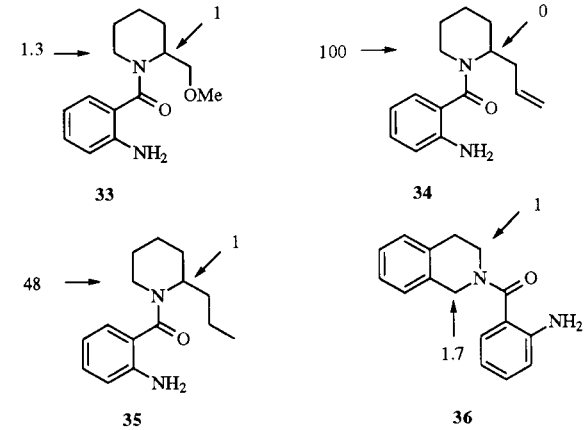
Scheme 7



	rt	0° C	-30° C	-78/-60° C
Reaction time	5 min	2 h	2 h	4 h / overnight
Ratio (methylene/methine)	2.22	2.42	2.28	2.11
	4%	0%	0%	0%
	22%	29%	17%	19%
	0%	12%	16%	9%
	51%	51%	40%	53%
	3%	7%	8%	10%
overall yield	81%	90%	81%	91%

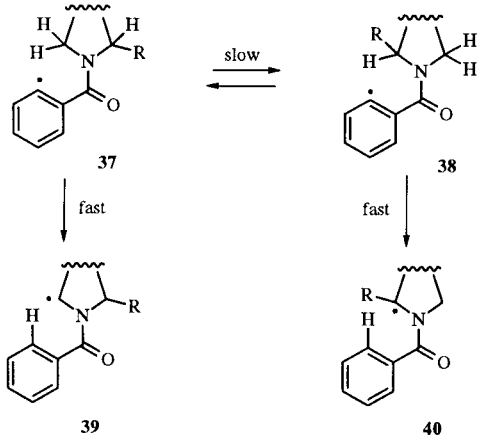
Some additional examples of these radical-based oxidations in unsymmetrical systems are shown in Figure 1. Whereas the methoxymethyl-substituted amide **33** did not show any significant selectivity, piperidine derivatives **34** and **35** bearing α-alkyl chains underwent the reaction with high regioselectivity. In the case of isoquinoline-derived amide **36**, there was only a slight preference for oxidation at the benzylic carbon.

Figure 1



Although data are at present rather limited for these radical oxidations of unsymmetrical systems, it would seem profitable to advance a tentative hypothesis to rationalize the results obtained to date. Mechanistic work by Cohen, *et al.* has established that amide rotation (eg **37** ↔ **38**) is slow relative to the rate of 1,5-hydrogen atom transfer to produce **39** and **40** (Scheme 8) [10]. Recent work by Snieckus, Curran and coworkers supports this conclusion [11]. Thus, the amide rotamer relative population determines the regioselectivity of the reaction. One might anticipate that for steric reasons rotamer **37** would be more highly populated than **38** as R gets larger. Thus, the predominant oxidation product should result from primary radical **39**. It might also be noted that the temperature independence of the reaction of the 2-methylpiperidine derivative (Scheme 7) is in accord with the observation that rotamer population in benzamides does not vary significantly between room temperature and -50°C [12].

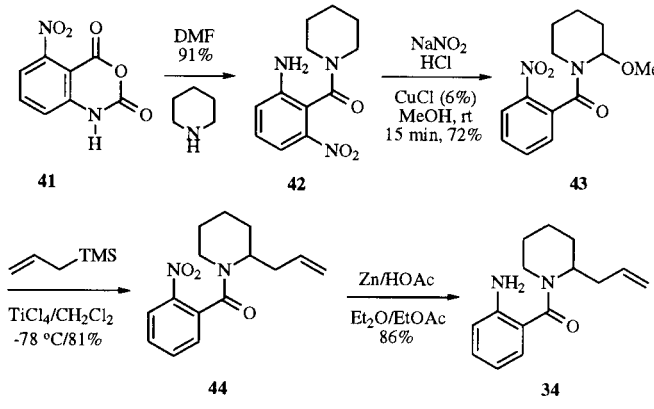
Scheme 8



In general, this postulate seems to qualitatively rationalize our observations with only the methoxymethyl piperidine derivative **33** being an apparent anomaly. Hopefully, with additional data in hand, a more firmly based and compelling case can eventually be made for the regiochemical results with unsymmetrical systems [13].

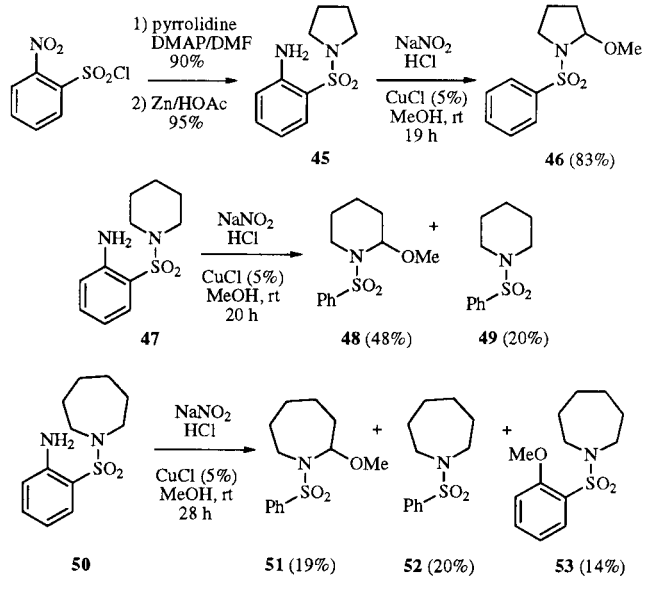
We have also investigated a simple extension of this general methodology that allows one to effect two consecutive oxidations. An example of this strategy is shown in Scheme 9. Commercially available 3-nitroisatoic anhydride (**41**) reacts with piperidine to afford 2-amino-6-nitrobenzamide derivative **42**. Oxidation of **42** under our usual conditions led to α-methoxyamide **43**. It was then possible to alkylate **43** with allyltrimethylsilane *via* the corresponding *N*-acyl iminium intermediate to afford **44**. Finally, reduction of the nitro group of **44** gave *o*-aminobenzamide **34** which has previously been shown to undergo regioselective amide oxidation (*cf.* Figure 1).

Scheme 9



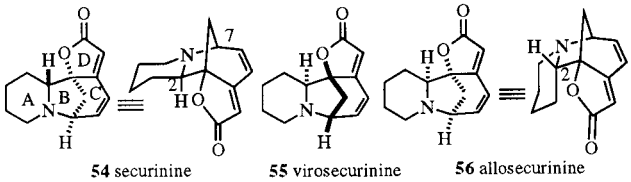
A further extension of this chemistry was attempted which utilizes *o*-aminobenzenesulfonamides [14]. Sulfonamide **45** was prepared in two steps from *o*-nitrobenzenesulfonyl chloride (Scheme 10). Subjection of **45** to the standard oxidation protocol gave α-methoxy benzenesulfonamide **46** in good yield. Unfortunately, however, the process did not work cleanly with other ring systems. For example, piperidine-derived sulfonamide **47** gave a mixture of α-methoxysulfonamide **48** and reduced product **49**. Similarly, the seven membered ring system **50** led to a mixture of three products **51-53**. Therefore, this sulfonamide variation does not seem sufficiently general to warrant further study.

Scheme 10

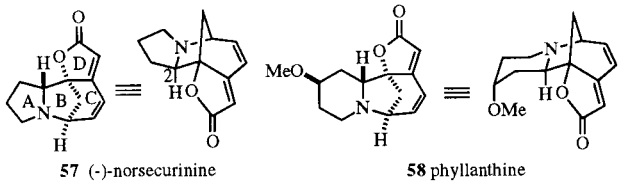


Recently we have moved towards applying this amide oxidation chemistry to a problem in alkaloid total synthesis. In particular, we have been involved in developing a new and general strategy for construction of the *Securinega* alkaloids. These alkaloids comprise a small group of compounds produced by plants of the *Euphorbiaceae* family [15]. Several representative alkaloids are shown in Figure 2. Securinine (**54**) is the most abundant member of this class. Interestingly, its enantiomer, virosecurinine (**55**), is also naturally occurring. An isomer of securinine which is epimeric at C-2, allosecurinine (**56**), is also known. (-)-Norsecurinine (**57**), which has a five-membered A-ring is common, and its (+)-enantiomer has been found in natural sources. Phyllanthine (**58**) is a minor alkaloid which has A-ring oxygen functionality.

Figure 2



54 securinine **55** virosecurinine **56** allosecurinine

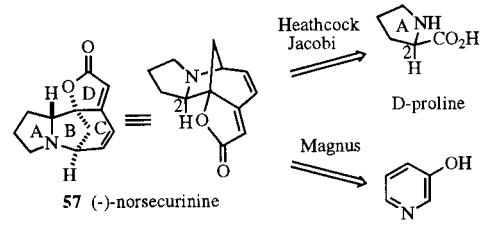


57 (-)-norsecurinine **58** phyllanthine

A number of these alkaloids display significant biological activity [15]. For instance, securinine (**54**) has a range of CNS activity and has been found to be a GABA antagonist. It has also found sporadic use clinically in treatment of amyotrophic lateral sclerosis (ALS), chronic aplastic anemia, poliomyelitis and Bell's palsy.

In 1966, Horii and coworkers reported a non-stereoselective total synthesis of securinine [16a]. A similar approach was also used in synthesis of the unnatural C-2 epimer of the enantiomer of phyllanthine (**58**) [16b]. More recently, three groups have been involved in synthetic approaches to norsecurinine (**57**). Heathcock and coworkers devised a strategy to the alkaloid from proline with the intent of using the chiral center of the amino acid as the source of C-2 and the pyrrolidine ring as the A-ring precursor (Scheme 11) [17]. Unfortunately, epimerization of an intermediate caused racemization and ultimately racemic norsecurinine was synthesized. Jacobi, *et al.* reported an elegant route to both (-) and (+)-norsecurinine from D- and L-proline, respectively [18]. Once again, proline was the source of the A-ring and C-2 chirality. Magnus, *et al.* have described a biogenetically-patterned synthesis of racemic norsecurinine starting from 3-hydroxypyridine [19].

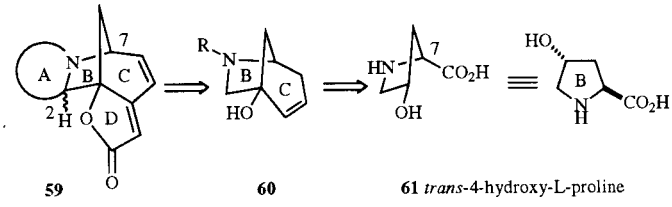
Scheme 11



57 (-)-norsecurinine

Our proposed approach to the *Securinega* alkaloids has a number of goals: (1) since the members of this family differ only in the A-ring size and functionality, as well as the C-2 configuration (*cf.* **54-58**), the strategy should be flexible enough to allow for the variations in this area of the molecules; (2) the approach should provide access to either enantiomeric series of alkaloids (*cf.* **54/55**). The basic strategy (Scheme 12) is to use commercially available *trans*-4-hydroxy-L-proline (**61**) (or its D-enantiomer) as a source of the alkaloid B-ring and the C-7 absolute chirality. The intent is to elaborate **61** into a B/C-ring fragment like **60**, followed by an annulation of an appropriate A-ring with the attendant C-2 configuration making use of our amide oxidation methodology (*vide infra*). Finally, the α,β-unsaturated lactone containing D-ring would be appended.

Scheme 12

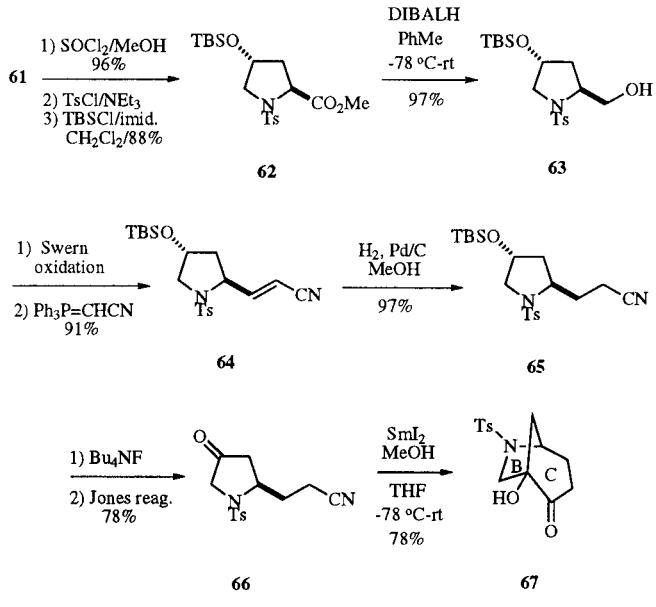


59 **60** **61** *trans*-4-hydroxy-L-proline

Thus, hydroxy proline **61** was converted in three straightforward steps to protected derivative **62** (Scheme 13). Reduction of the ester functionality afforded primary alcohol **63**, which upon Swern oxidation and Wittig reaction yielded α,β-unsaturated nitrile **64**. Hydrogenation of **64** led to saturated nitrile **65**, and after removal of the silyl protecting group, the resulting alcohol was oxidized to give keto nitrile **66**. A key step in the strategy was investigated next. We were pleased to find that exposure of keto nitrile **66** to samarium diiodide afforded a good yield of

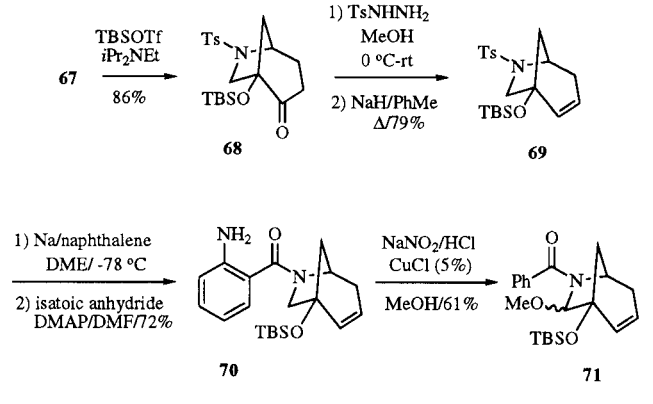
bridged α-hydroxy ketone **67** [20]. This compound incorporates the requisite B/C-ring system of the alkaloids (*cf.* **60**, Scheme 12).

Scheme 13



To continue with the synthesis, the hydroxyl group of **67** was cleanly silylated to give α-siloxy ketone **68** (Scheme 14). This compound could be converted to the olefin **69** using a Shapiro reaction [21]. We were now prepared to investigate the application of the amide oxidation procedure to construction of the A-ring.

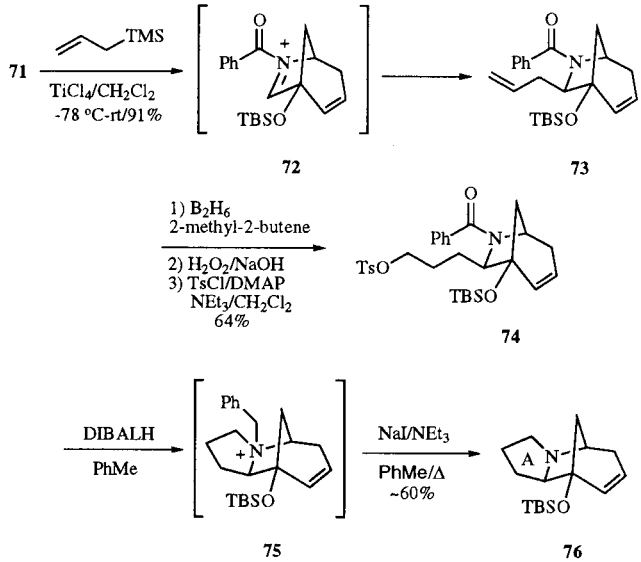
Scheme 14



The *N*-tosyl protecting group could be removed under dissolving metal conditions and the resulting amine was *N*-acylated with isatoic anhydride to produce *o*-aminobenzamide **70.** Using the standard oxidation conditions, compound **70** was converted regioselectively to α-methoxy benzamide **71**. None of the other possible regioisomer was detected.

With this important bicyclic intermediate in hand, we have begun to explore procedures for A-ring annulation. In order to access (-)-norsecurinine (**57**), allyltrimethylsilane was added to **71** in the presence of titanium tetrachloride to produce an excellent yield of a single stereoisomeric alkylation product **73** (Scheme 15). We have tentatively assigned **73** as being the C-2 exo isomer shown, assuming that the silane addition occurs from the least encumbered face of *N*-acyl iminium ion **72**. In order to complete the construction of the five-membered A-ring, terminal alkene **73** could be regioselectively hydroborated, and the resulting primary alcohol was converted to the corresponding tosylate. At this point, hydrolytic removal of the *N*-benzoyl group proved unsuccessful and therefore an alternative annulation strategy was adopted. It was found that amide reduction with DIBALH proceeds to give the *N*-benzyl quaternary ammonium salt **75**, which can be debenzylated *in situ* with sodium iodide/triethylamine to yield the desired (-)-norsecurinine A/B/C ring synthon **76** in 60% unoptimized yield from amide tosylate **74**.

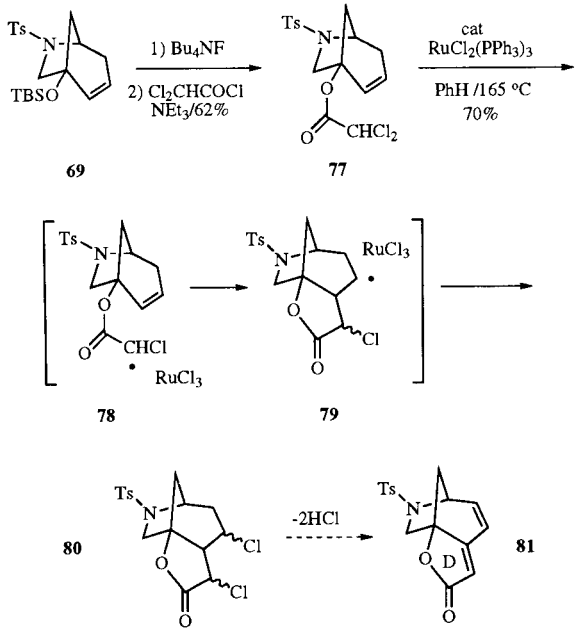
Scheme 15



We have also begun to investigate methodology for introduction of the unsaturated lactone D-ring of these alkaloids. Using bicyclic system **69** as a model, *O*-silyl group removal and acylation of the resulting tertiary alcohol with dichloroacetyl chloride afforded dichloroacetate **77** (Scheme 16). Exposure of this ester to a catalytic amount of Ru^{+2} afforded a tricyclic dichloro γ-lactone **80** as a single stereoisomer whose configu-

ration is not known at present. This transformation presumably occurs *via* radical intermediates **78** and **79** [22]. It is intended to next effect double HCl elimination of **80** to produce **81** having the B/C/D-ring system of the *Securinega* alkaloids, and then to apply the chemistry to (-)-norsecurinine intermediate **76**.

Scheme 16



In conclusion, we have developed experimental conditions for converting readily prepared *o*-amino benzamides into α-methoxy benzamides in a variety of systems. This free radical-based methodology shows good regiochemical control in a number of cases, but additional work is required to more fully understand the process. Application of this chemistry as a key step in a general strategy for construction of the *Securinega* alkaloids has been achieved. Work is in progress on completion of a total synthesis of (-)-norsecurinine (**57**), along with some of the other members of this class of fascinating natural products.

Acknowledgments.

I am grateful to my coworkers Matthias C. McIntosh, James J. Folmer, Gyoonhee Han and Matthew LaPorte for their important contributions to this program. The National Institutes of Health is thanked for financial support on grant GM-32299.

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