Pure Appl. Chem., Vol. 82, No. 9, pp. 1773–1783, 2010.
doi:10.1351/PAC-CON-09-08-06

Development of an efficient synthetic strategy for bioactive alkaloids possessing a spirocyclic ring system*

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Abstract: Efficient synthetic strategies for several bioactive alkaloids bearing a spirocyclic ring system have been developed. By application of an intramolecular aromatic oxidation of a phenolic intermediate, derived from L-tyrosine and glycine, with hypervalent iodine reagents, TAN1251A, isolated from *Penicillium thomii* RA-89, was synthesized in an optically pure form. Similarly, a novel synthetic path to TAN1251C and TAN1251D was established by employing an L-tyrosine dimer as a common starting material. Moreover, an enamide-phenol oxidative coupling reaction was applied to the synthesis of spirocyclic isoquinoline alkaloids, stepharine and annosqualine. Finally, stereoselective syntheses of securinine and viroallosecurinine in optically active forms were established by using a tandem ring-closing metathesis (RCM) of the enyne as a key reaction.

Keywords: bioactive alkaloids; isoquinoline; securinine; spirocyclic compounds; synthetic strategy.

INTRODUCTION

Spirocyclic ring systems are often observed in various types of bioactive natural products as core structural fragments. Some of those natural products exhibit various interesting biological activities, although a spirocyclic ring system does not seem to be essential to elicit the activities. The well-known spirocyclic bioactive natural products are [5,5]-, [5,6]-, and [6,6]-spiroacetals, which have a wide range of structural features and biological activities. Spirocyclic frameworks have also been found in bioactive alkaloids. For example, halichlorine, isolated from the marine sponge *Halichondria okadai*, inhibits the induction of VCAM-1. Drugs that block VCAM-1 may be useful for treating coronary artery diseases, angina, and noncardiovascular inflammatory diseases. Pinnaic acids, isolated from *Pinna muricata*, are recognized to be potent cPLA2 inhibitors, although their structures are closely related to that of halichlorine.

Moreover, pinnatoxin A is one of the major toxic principles responsible for outbreaks of Pinna shellfish intoxication. This alkaloid is also known to be a calcium ion channel activator. Interestingly, norzoanthamine, another characteristic spirocyclic alkaloid, suppresses decreases in bone weight and strength in ovariectomized mice and could be a good candidate for an osteoporotic drug. Due to the attractive biological activities and also unique structural features, development of a synthetic strategy for spirocyclic natural products has received considerable attention. In relation to our synthesis of bioactive

*Paper based on a presentation at the 22nd International Congress on Heterocyclic Chemistry (ICHC-22), 2–7 August 2009, St. John's, Newfoundland and Labrador, Canada. Other presentations are published in this issue, pp. 1735–1853.

natural products, we are interested in developing an efficient synthetic strategy for spirocyclic alkaloids, and we have succeeded in the synthesis of several types of structurally simple but different alkaloids, which are depicted in Fig. 1.

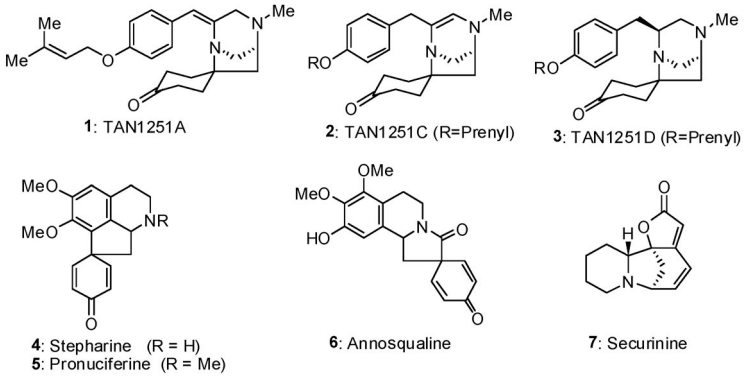


Fig. 1 Structures of target spirocyclic alkaloids.

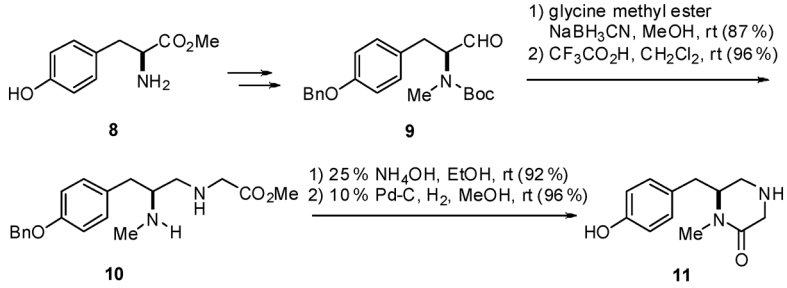
RESULTS AND DISCUSSION

Synthesis of TAN1251A, TAN1251C, and TAN1251D

In general, the crucial step for the synthesis of spirocyclic alkaloids obviously lies in the construction of a spirocyclic ring system. Although different routes to the spirocyclic framework have been developed, an aromatic oxidation of phenolic compounds with hypervalent iodine reagents [1] would provide one of the most promising approaches for constructing the desired ring systems.

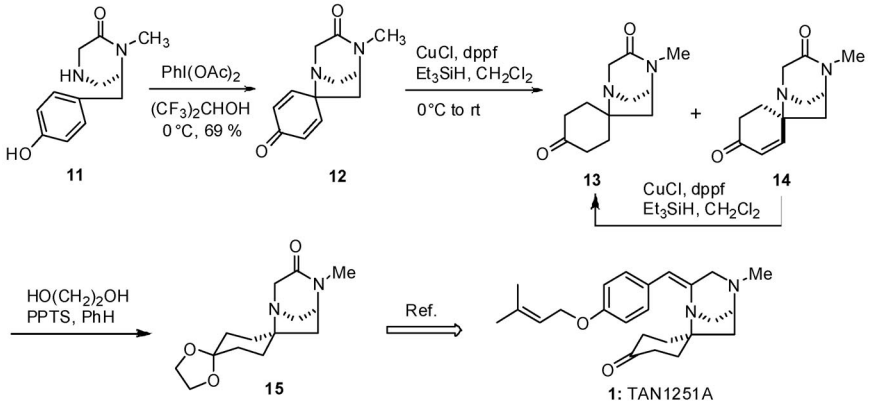
By employing an aromatic oxidation strategy, TAN1251A (**1**), TAN1251C (**2**), and TAN1251D (**3**), isolated from a *Penicillium thomii* RA-89 by researchers at Takeda Chemical Industries Ltd. [2], have been synthesized as follows [3,4]. The TAN1251 series of compounds have unique structural features with a 1,4-diazabicyclo[3.2.1]octane ring system and a spirocyclic cyclohexanone. TAN1251A exhibits cholinergic activity and inhibits acetylcholine-induced contraction of the guinea-pig ileum. TAN1251A is also known as a selective muscarinic M_1 subtype receptor antagonist [5]. Due to its intriguing structural features and attractive biological activity, several total syntheses have appeared in the past few years. In previous enantioselective syntheses, the problematic spirocyclic carbon–nitrogen bond was constructed by various strategies, including; (1) a 1,3-dipolar cycloaddition reaction of a chiral nitrone [6], (2) an *N*-methoxy-*N*-acylnitrenium ion-induced spirocyclization [7], (3) an insertion reaction of an alkylidene carbene [8], (4) an aromatic oxidation of a chiral oxazoline [9], and (5) a diastereoselective alkylation of a chiral *trans*-4-hydroxy-proline [10] as the key reactions. We thought that carbon–nitrogen bond formation to generate a spirocyclic ring would provide the most straightforward synthesis to TAN1251A and that this bond formation could be achieved by intramolecular aromatic oxidation of a secondary amine using a hypervalent iodine reagent.

Thus, we started the synthesis of TAN1251A by preparing the requisite secondary amine, as a key intermediate, from L-tyrosine methyl ester (**8**), which was converted into aldehyde (**9**) in several steps. Treatment of **9** with glycine methyl ester in the presence of sodium cyanoborohydride, followed by deprotection of the Boc group under acidic conditions, provided diamine (**10**). Treatment of **10** with 25 % ammonium hydroxide in ethanol gave an optically pure piperazinone derivative (**11**) as the key precursor for the aromatic oxidation (Scheme 1).



Scheme 1 Preparation of the precursor for an aromatic oxidation.

First, we attempted carbon–nitrogen bond formation at this stage via an aminylium ion intermediate prepared from **11** by halogenation with *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS), followed by treatment with silver(I) oxide or other conditions. However, the desired product could unfortunately not be isolated. On the other hand, aromatic oxidation of **11** with iodobenzene diacetate (PIDA) in 2,2,2-trifluoroethanol provided the desired spirocyclic compound (**12**) in 43 % yield. By changing the solvent to hexafluoroisopropanol (HFIP), the yield of this oxidation reaction was increased to 69 % (Scheme 2). The use of iodobenzene ditrifluoroacetate as an oxidizing agent under the same reaction conditions produced a desired product (**12**) in less than 10 % yield.



Scheme 2 Formal synthesis of TAN1251A.

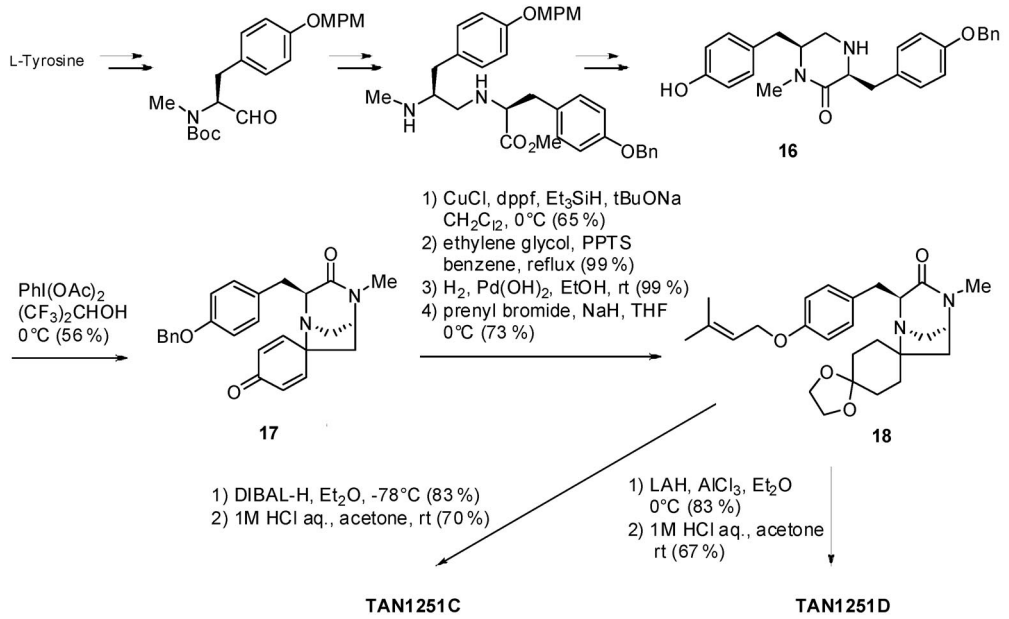
Thus, the desired carbon–nitrogen bond formation providing a spirocyclic framework was successfully achieved by exploitation of an aromatic oxidation of a phenolic secondary amine with a hypervalent iodine reagent in reasonable yield. In order to complete the synthesis of TAN1251A, reduction of the carbon–carbon double bond of the dienone (**12**) was carried out with 2 equiv of triethylsilane [11] in the presence of 20 mol % of copper(I) chloride and 20 mol % of dppf in dichloromethane to provide ketone (**13**) in 60 % yield, together with enone (**14**). The enone (**14**) was able to convert to ketone (**13**) by further reduction under the same reaction conditions in 87 % yield. When the reduction of **12** was carried out with 3 equiv of triethylsilane, **13** was isolated in 60 % yield.

Finally, a ketalization of the ketone (**13**) with ethylene glycol and a catalytic amount of pyridinium *p*-toluenesulfonate in refluxing benzene gave ketal (**15**), a known key intermediate for the synthesis of (–)-TAN1251A. Since the compound (**15**) has already been converted to (–)-TAN1251A by Wardrop and co-workers, this synthesis constitutes its formal total synthesis (Scheme 2). Thus, we have

succeeded in a novel synthesis of optically pure (–)-TAN1251A, in which the aromatic oxidation reaction of the secondary amine with PIDA was involved as the key reaction.

As can be seen in Fig. 1, the TAN1251 series of compounds have closely related structural features; however, little attention has been given to the enantioselective synthesis of TAN1251C and TAN1251D as compared to the synthesis of TAN1251A. In our synthesis of TAN1251A, the benzylidene side chain at the α-position of the piperazinone ring was introduced at a later stage of the synthesis. However, it does not seem to be sufficiently efficient from a synthetic point of view. Therefore, we tried to develop a more effective synthetic path to those alkaloids, especially to TAN1251C and TAN1251D. In searching the structures of TAN1251C and TAN1251D for retrosynthetic disconnections, we focused on the formation of the spirocyclic carbon–nitrogen bond by an aromatic oxidation of the dimeric L-tyrosine derivative having a desired benzyl side chain in its molecule.

Thus, the requisite starting material was prepared as follows. Tyrosine was successfully transformed to a tyrosine dimer (**16**) by the same procedure as that used for the preparation of **11** (Scheme 3).



Scheme 3 Synthesis of TAN1251C and D.

An aromatic oxidation of the mono-phenolic compound **16** with $PhI(OAc)_2$ in HFIP as the solvent afforded the desired dienone **17** in the best yield (56 %). Reduction of the dienone with copper hydride generated in situ was carried out by using the same reaction conditions as those used for the synthesis of TAN1251A to furnish the corresponding cyclohexanone in 65 % yield. After ketalization of the carbonyl group, removal of the benzyl group of the resulting amide with palladium hydroxide under hydrogenolysis conditions gave a phenolic compound. O-alkylation of the phenolic compound with prenyl bromide in the presence of sodium hydride in tetrahydrofuran (THF) gave the prenyl ether **18**, which, on reduction with lithium aluminum hydride followed by deprotection of the ketal group under acidic conditions furnished TAN1251D.

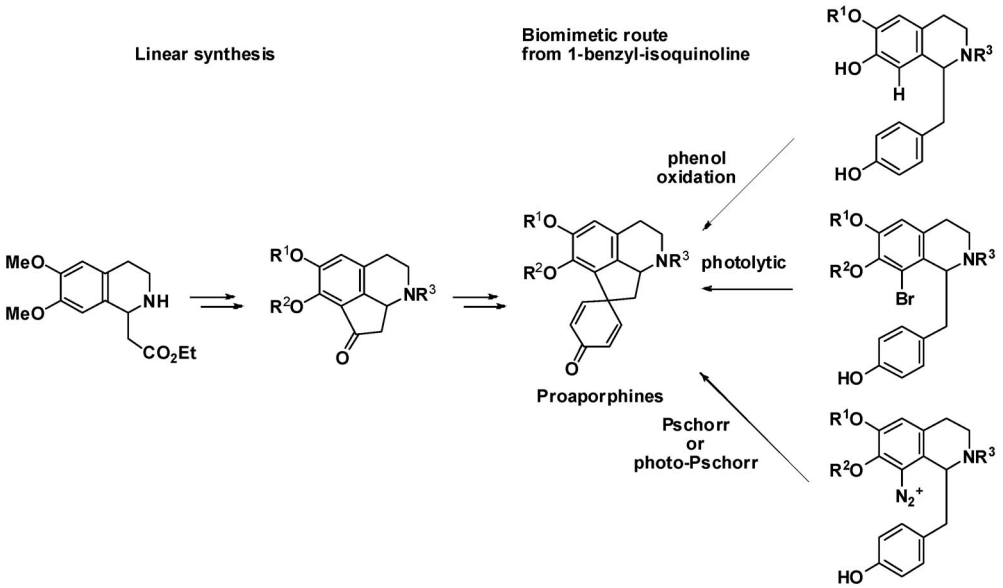
To accomplish the synthesis of TAN1251C, introduction of the double bond in the piperazine ring would be required. Fortunately, we found that diisobutylaluminum hydride (DIBAL-H) reduction of the

amide **18** in Et_2O provided the desired enamine, in 83 % yield, in one step. Again, deprotection of the ketal group under acidic conditions afforded TAN1251C.

We were able to establish efficient syntheses of TAN1251 series of compounds in optically pure forms starting from tyrosine derivatives. These syntheses demonstrated that an aromatic oxidation with a hypervalent iodine reagent was applicable to secondary amines for constructing a problematic carbon–nitrogen bond.

Synthesis of proaporphine alkaloids

Proaporphine alkaloids, which are one of the minor groups of isoquinoline alkaloids, occur in a variety of oxidation states. They have been recognized as the biosynthetic precursors of aporphine alkaloids bearing a wide range of oxygenated substitution patterns with mainly a spiro-cyclohexadienone ring system. Some of these alkaloids have been shown to exhibit interesting biological activities. Stepharine (**4**) has antihypertensive activity without side effects, such as α- or β-adrenergic blockade, sedative or depressant effects, or ganglion blockade, and also inhibits cholinesterase and pseudocholinesterase in vitro [12]. Although a number of routes to the proaporphine skeleton involving phenol oxidation [13], photolysis [14], and Pschorr cyclization [15] of 1-benzylisoquinoline derivatives have been developed, formation of the C8'–C1 bond served as the key step in many of the previous syntheses [16]. Our own interest in proaporphine chemistry grew out of a desire to develop an entirely new, perhaps practical and general, route for the total synthesis of this class of alkaloids (Scheme 4).



Scheme 4 Previous synthetic methodologies for aporphine alkaloids.

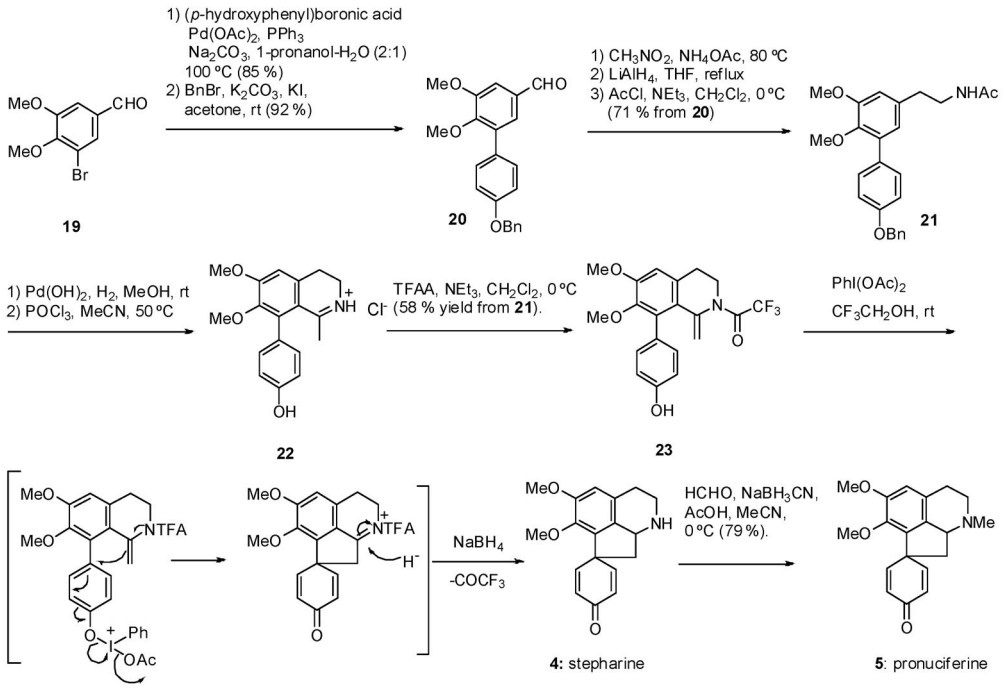
Thus, we decided to investigate the synthesis of a typical proaporphine alkaloid, stepharine (**4**), since it seemed to be more difficult to synthesize a proaporphine alkaloid having a secondary amino group (NH group) rather than its *N*-methyl derivative. Furthermore, N-methylation of **4** leading to pronuciferine (**5**) would be achieved without any problems at the final stage of the synthesis. Indeed, to date, there is only one reported synthesis of **4**, although several syntheses of **5** have appeared.

In the synthesis of TAN1251 series of compounds as described above, we developed a general carbon–nitrogen bond-forming reaction to construct a spirocyclic ring system by using an aromatic

oxidation of secondary amines as the key step. For the synthesis of proaporphine alkaloids, we focused on direct formation of the spirocyclohexadienone framework by an unprecedented carbon–carbon bond formation between the *para*-position of a phenolic hydroxy group and an enamide-carbon. We thought that the desired bond formation would be achieved by employing an intramolecular aromatic oxidation of a phenolic enamide with a hypervalent iodine reagent as the key reaction.

The coupling reaction of 3-bromo-4,5-dimethoxybenzaldehyde (**19**) with (*p*-hydroxyphenyl)boronic acid (1.1 equiv) in the presence of a catalytic amount of palladium acetate (1 mol %), triphenylphosphine (2.5 mol %), and sodium carbonate (1.2 equiv) was carried out in 1-propanol-H_2O (2:1) [17] at 100 °C to afford the biaryl compound in 85 % yield. After protection of the phenolic hydroxy group as its benzyl ether, the aldehyde (**20**) was condensed with nitromethane to give nitrostyrene, which, on reduction with lithium aluminum hydride followed by acetylation of the corresponding phenethylamine with acetyl chloride, provided amide (**21**) in 71 % yield from **20**. Since a phenolic function would be desirable for the aromatic oxidation, debenzylation of **20** was carried out under catalytic hydrogenation conditions to give the phenolic compound, before the Bischler–Napieralski cyclization. Treatment of **9** with phosphoryl chloride in acetonitrile followed by acylation of the 3,4-dihydroisoquinoline (**22**) with trifluoroacetic anhydride gave the desired key precursor, enamide (**23**), for aromatic oxidation in 58 % yield from **21**.

With the requisite enamide in hand, a study was carried out to determine the best conditions for the aromatic oxidation. By testing a variety of reaction conditions, we were able to find the appropriate reaction conditions for obtaining the desired cyclization product in reasonable yield, as follows. Aromatic oxidation of **23** with PIDA (1.1 equiv) in trifluoroethanol at 0 °C, followed by sodium borohydride reduction of the resulting mixture, proceeded smoothly to give the desired spiro-dienone, stepharine (**4**), in 90 % yield as the sole product [17]. The labile N-protecting trifluoroacetyl group was removed during this conversion. Thus, the facile synthesis of a proaporphine alkaloid, stepharine, involving an unprecedented carbon–carbon bond-forming reaction (*enamide-phenol oxidative coupling*



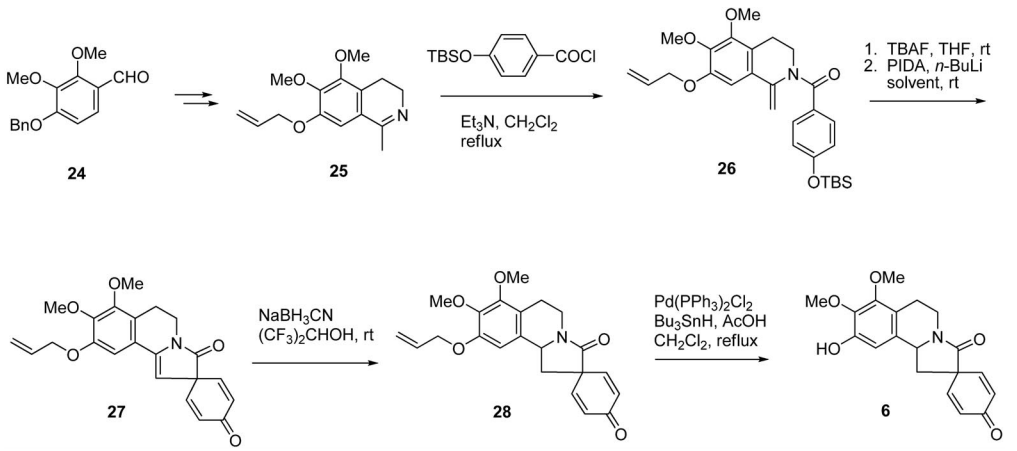
Scheme 5 Synthesis of stepharine and pronuciferine.

reaction) between the *para*-position of a phenolic hydroxy group and an enamide-carbon, has been established in very short steps with remarkably high yield. Stepharine (**4**) was further converted into pronuciferine (**5**) by N-methylation with formalin under reductive reaction conditions in 79 % yield (Scheme 5).

Synthesis of annosqualine

Annosqualine (**6**), isolated from the stems of *Annona squamosa* by Wu and co-workers in 2004 [18], is a novel isoquinoline alkaloid composed of a tetracyclic core including a tetrahydroisoquinoline, a 5-membered lactam, and a spirocyclohexadienone moiety. Wu and co-workers also suggested a hypothetic biogenesis of **6** together with a possibility of its biogenetic precursor for oxoprotoberberine and protoberberine alkaloids in the plant by focusing on its structural motif, although it is generally accepted that protoberberine alkaloids are biosynthetically derived from the corresponding *N*-methyl-1-benzylisoquinolines via the *N*-methyl *N*-oxides. Although the structure of **6** was elucidated spectroscopically, its synthesis has not been reported yet. Therefore, we decided to apply the synthetic strategy for proaporphine alkaloids to the synthesis of annosqualine by employing an aromatic oxidation of a phenolic enamide with a hypervalent iodine reagent leading to the formation of a spirocyclohexadienone moiety as the key step.

The starting enamide (**26**) was prepared from 3,4-dihydroisoquinoline (**25**), derived from the known aldehyde (**24**) in the usual manner, by benzoylation with (4-*tert*-butyldimethylsilyloxy)benzoyl chloride. After removal of the silyl group of **26** with tetrabutylammonium fluoride (TBAF) at room temperature, the resulting crude product was oxidized with PIDA in HFIP at 0 ºC to afford the spiro-enamide (**27**) in 73 % yield. Sodium cyanoborohydride reduction of **27** in HFIP gave the reduction product (**28**) in 86 % yield. Finally, deprotection of the allyl group of **28** with a catalytic amount of bis(triphenylphosphine)dichloride and tributyltin hydride afforded the natural product annosqualine (**6**) in 98 % yield (Scheme 6) [19].



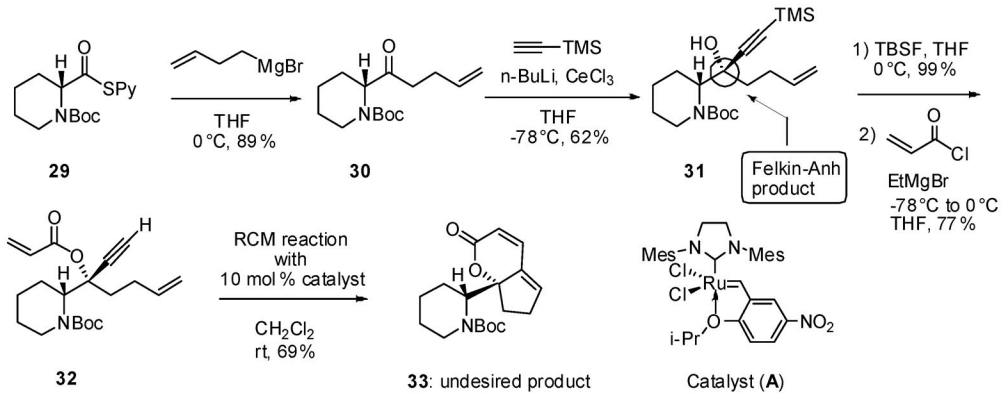
Scheme 6 Synthesis of annosqualine.

By exploiting an enamide-phenol oxidative coupling of the enamide derivative (**26**), a facile synthesis of a unique spiroisoquinoline alkaloid, annosqualine (**6**), has been achieved. Again, this strategy was proven to be useful for constructing a spirocyclic ring system.

Synthesis of *Securinega* alkaloids

Naturally occurring *Securinega* alkaloids continue to provide challenging synthetic targets, since these alkaloids exhibit attractive biological activities. Securinine (**7**), embodying the basic structural features of this class of alkaloids, was first isolated from *Securinega suffruticasa* in 1956. It contains an indolizidine skeleton that forms part of an azabicyclo[3.2.1]octane system fused onto an α,β-unsaturated γ-lactone ring. This alkaloid has been clinically used in Russia as a central nervous system (CNS)-stimulating drug [20], acting as a stereospecific antagonist at the GABA binding site of the GABAA-receptor complex [21]. As part of our continuing efforts to synthesize and study the biological activities of compounds related to important CNS-stimulating drugs, we aimed at developing a new and general strategy for obtaining securinine and its relatives in optically active form. In order to synthesize (–)-securinine, (+)-pipecolinic acid was chosen as the starting material since its chirality would be transferred to the quaternary carbon center of the target compound. For forming the conjugated diene system, we intended to exploit a tandem ring-closing metathesis (RCM) of a dienyne system as a key reaction.

The optically active thioester (**29**), derived from (+)-pipecolinic acid, was treated with 3-butenylmagnesium bromide to give the ketone (**30**), which on treatment with lithium trimethylsilylacetylide in the presence of cerium(III) chloride gave the tertiary alcohol (**31**) as the sole product. The observed stereoselectivity was rationalized by assuming that the addition of the lithium reagent to **30** would proceed via the Felkin–Anh model. After deprotection of the silyl group with TBAF, the resulting alkyne was further transformed into the ester (**32**) by acylation with acryloyl chloride. Attempted RCM of the ester (**32**) with the highly active ruthenium catalyst (**A**), however, afforded the δ-lactonic compound (**33**) instead of the desired compound, where a ruthenium carbene complex generated from the terminal alkene in the butenyl group reacted with alkyne prior to the olefin in the α,β-unsaturated ester (Scheme 7).

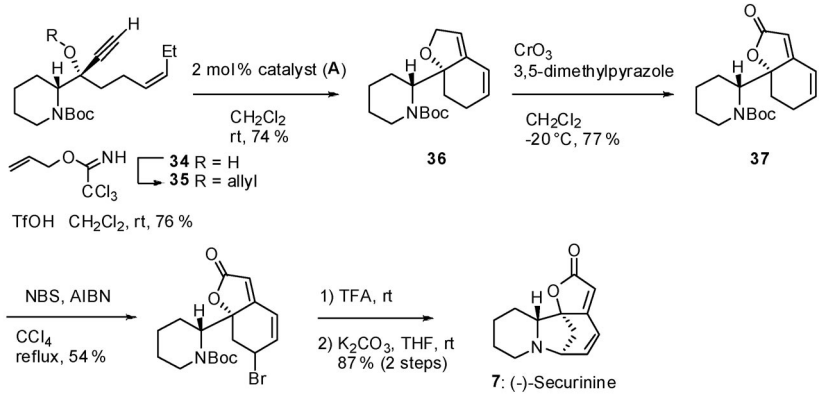


Scheme 7 Attempted RCM for the enyne.

Thus, we focused on the introduction of a less-reactive alkene moiety and also a more reactive allyl ether instead of the ester group into **29**. The key precursor for a tandem RCM was prepared from **29** by introduction of (3*Z*)-hexenylmagnesium bromide affording the corresponding ketone followed by alkynylation with lithium trimethylsilylacetylide in the presence of a stoichiometric amount of cerium(III) chloride to provide the tertiary alcohol (**34**) as the sole product. Although difficulties were initially encountered in the O-allylation of **34**, we eventually found that the reaction of **34** with allyl trichloroacetimidate afforded the desired allyl ether **35** in fairly good yield. The tandem RCM of **35**

with the highly active ruthenium catalyst (**A**) in dichloromethane at room temperature gave the cyclized compound (**36**) in 74 % yield.

Thus, the stereoselective construction of the A, C, and D rings of securinine was achieved in a relatively short sequence. To accomplish the total synthesis of securinine, the diene (**36**) was oxidized at the allylic position with chromium trioxide and 3,5-dimethylpyrazole to provide the lactone (**37**). Finally, allylic bromination of **37** with NBS and azobisisobutyronitrile (AIBN) followed by removal of the protecting group with trifluoroacetic acid (TFA) and subsequent cyclization of the resulting amino bromide with potassium carbonate furnished (–)-securinine (**7**). This is the first synthesis of optically pure securinine (Scheme 8) [22].

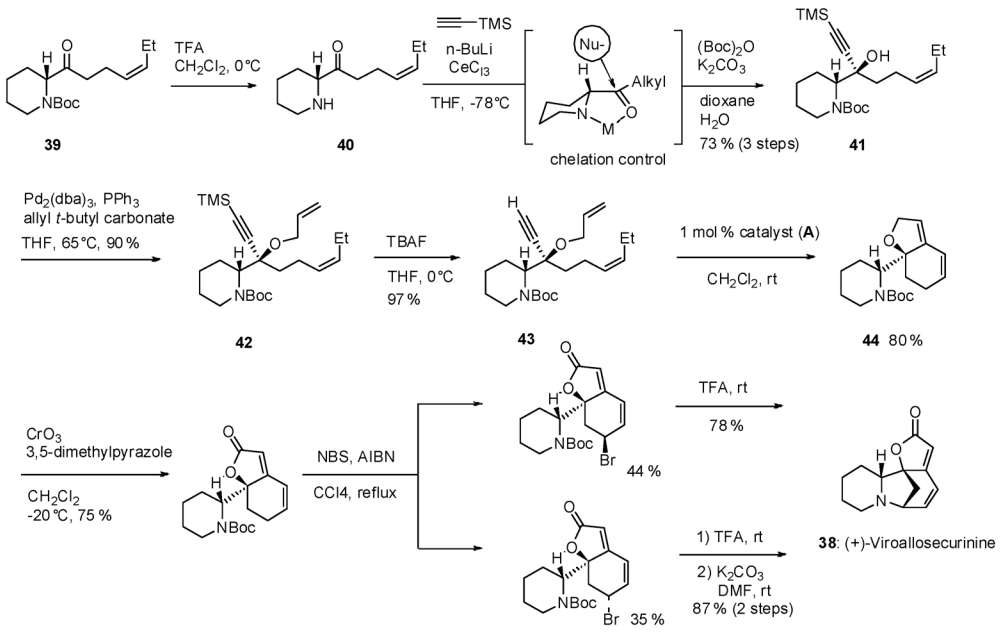


Scheme 8 Stereoselective synthesis of (–)-securinine.

(+)-Viroallosecurinine (**38**), a diastereoisomer of securinine (**7**), exhibited an MIC of 0.48 μg/ml for *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This alkaloid also showed significant cytotoxicity with an ED_{50} value of 0.9 μg/ml in vitro P-338 tissue culture cells [23]. For the synthesis of viroallosecurinine, the diastereoselective construction of the tertiary alcohol with the opposite stereoselectivity to the case of the synthesis of securinine would be required. Since such stereoselective introduction would be achieved via a chelation transition state by employing the corresponding NH compound as the starting material, we started to prepare the key starting material as follows. Deprotection of the *N*-Boc group of the optically active ketone (**39**) gave the amino-ketone (**40**), which, on treatment with lithium trimethylsilylacetylide in the presence of cerium(III) chloride in THF followed by protection with $(Boc)_2O$, gave the desired *tert*-alcohol (**41**).

Treatment of the alcohol (**41**) with allyl *tert*-butylcarbonate and triphenylphosphine in the presence of a palladium catalyst afforded the O-allylation product (**42**) in satisfactory yield. After deprotection of the trimethylsilyl group, the resulting dienyne (**43**) was subjected to a tandem RCM reaction using 1 mol % loading of the catalyst (**A**) in methylene chloride to give the cyclization product (**44**) having a 7-oxabicyclo[4.3.0]nona-2,9-diene system corresponding to the C and D rings of the target compound. B-ring formation was achieved by using the same procedure as that used for the synthesis of securinine to give viroallosecurinine (**38**) (Scheme 9) [24].

We were able to establish the first diastereoselective chiral synthesis of viroallosecurinine by employing a tandem RCM of the dienyne system as a key reaction. It is noteworthy that construction of the desired stereochemistry at the quaternary carbon center for both securine and viroallosecurinine can be easily achieved from the same starting material depending on the substituents on the piperidine nitrogen.



Scheme 9 Stereoselective synthesis of (+)-viroallosecurinine.

CONCLUSIONS

Over the past two decades, there has been a rapid development in the use of hypervalent iodine compounds in synthetic organic chemistry due to their mild, safe, and environmentally friendly characteristics. The catalytic utilization of hypervalent iodine reagents is a most attractive strategy due to their unique features as extremely useful oxidants with selective oxidizing properties. Organic iodine(III) and iodine(V) derivatives are now routinely used in organic synthesis as reagents for various selective oxidative transformations of complex organic molecules such as the oxidation of alcohols, α-oxidation of ketones, and oxidative coupling of aromatic compounds. We thought that an oxidative dearomatization of phenolic derivatives with a hypervalent iodine reagent would provide a powerful synthetic method for construction of a spirocyclic ring system. Efficient synthetic strategies for several bioactive alkaloids possessing a spirocyclic framework have been developed by application of an intramolecular aromatic oxidation of a phenolic derivative with hypervalent iodine reagents as the key step. By starting from L-tyrosine and glycine, TAN1251A was synthesized in an optically pure form. Similarly, TAN1251C and TAN1251D were synthesized by employing an L-tyrosine dimer as a common starting material. Moreover, aromatic oxidation with a hypervalent iodine reagent was applied to the synthesis of spirocyclic isoquinoline alkaloids, stepharine and annosqualine.

Securinine and viroallosecurinine, tetracyclic securinega alkaloids, were also synthesized diastereoselectively by exploitation of a tandem RCM strategy. The syntheses described herein are the first enantioselective total syntheses of these particular alkaloids.

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