First Total Synthesis of *ent*-Gelsedine via a Novel Iodide-Promoted Allene *N*-Acyliminium Ion Cyclization

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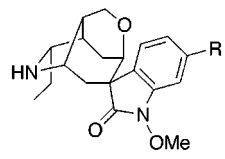
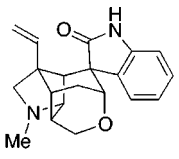
The first total synthesis of the oxindole alkaloid gelsedine (**1**) starting from (*S*)-malic acid is described. The key step is a novel iodide-promoted intramolecular reaction of an allene with an *N*-acyliminium ion intermediate which provided in a single step the bicyclic vinyl iodide **11**. Other important steps are the highly stereoselective Pd-catalyzed Heck cyclization of *N*-methylanilide **23a** which led to the desired spiro-oxindole **24a**, the fully regioselective intramolecular oxymercuration of **25a** to the desired cyclic ether, and the remarkable oxindole *N*-demethylation of **29** via a radical mechanism by using dibenzoyl peroxide. The total synthesis was concluded by the stereoselective introduction of the ethyl group from the bis-Boc compound **41** followed by methoxylation of the oxindole nitrogen. This total synthesis leads to the unnatural (+)-enantiomer of gelsedine in 21 steps and 0.10% overall yield.

Introduction

The plant genus *Gelsemium* (Loganiaceae) consists of three species *Gelsemium elegans* Benth., *G. sempervirens* Ait., and *G. rankinii* Small, all of which contain a number of indole and oxindole alkaloids with remarkably diverse and complex structures.[1] The *Gelsemium* alkaloids can be classified in six groups based on their skeletal types, of which gelsedine (**1**), gelsemine (**2**), koumidine (**3**), koumine (**4**), humentenine (**5**), and gelselegine (**6**) are representative members. Although specific biological activity of most of these alkaloids is poorly documented, extracts from *Gelsemium* species have a rich medicinal history, particularly in China.[1] Despite extensive synthetic research efforts for many years, successful de novo syntheses of Gelsemium alkaloids are only of relatively recent date. In 1989, Magnus et al. reported the total synthesis of (+)-koumine (**4**).[2] Well into the 1990s, we[3] and others[4] have published total syntheses of racemic gelsemine (**2**). Very recently, we completed the synthesis of gelsemine in enantiopure form.[5] In this article, we present full details of the first total synthesis of enantiopure *ent*-gelsedine.[6]



1: gelsedine, R = H
7: gelsemicine, R = OMe



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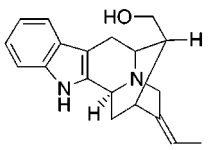
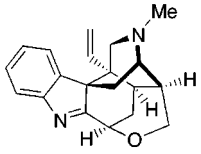
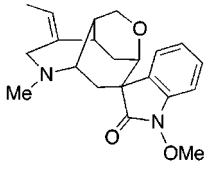


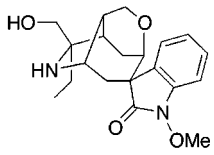
3: koumidine



4: koumine



5: humentenine



6: gelselegine

Gelsedine was first isolated from Carolina jasmine (*Gelsemium sempervirens*) in 1953 by Schwarz and Marion,[7] but also occurs in *G. elegans*.[8] One year after Przybylska and Marion elucidated the structure of gelsemicine (**7**) on the basis of its X-ray structure in 1961,[9] Wenkert proposed the structure for gelsedine

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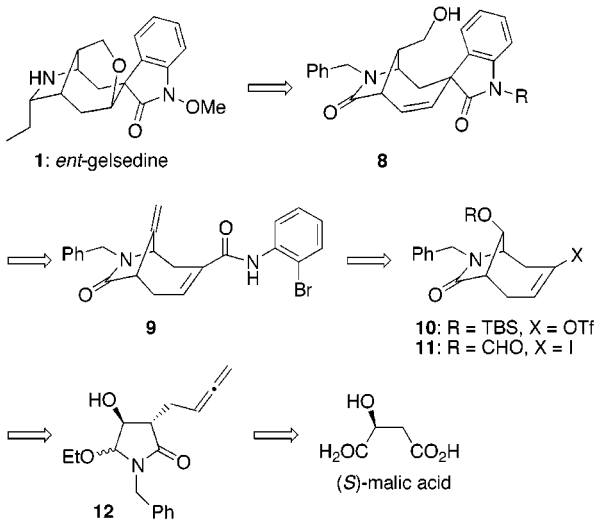
Scheme 1



based on NMR analogy with gelsemicine.[10] Although the biological activity of gelsedine has not been determined, gelsemicine was shown to be the most toxic component in *G. sempervirens*.[1b]

As a minor constituent of Carolina jasmine, the synthesis of gelsedine has not received as much attention as the parent alkaloid gelsemine. Until sofar, three groups have reported studies toward a total synthesis of gelsedine.[11,12,13] In 1979, a synthesis of the skeleton of gelsedine lacking the ethyl and oxindole moieties was published by Baldwin and Doll,[11] and a synthesis of a comparable structure using a different approach was reported by Hamer in 1990.[12] That same year, Kende et al. synthesized a more advanced compound, which had the oxindole moiety in place, albeit in the wrong stereochemical sense.[13] In 1994, Takayama et al. reported a semisynthesis of gelsedine starting from the natural product koumidine (**3**), the latter also being an intermediate in Magnus's synthesis of koumine (**4**).[14] This synthesis was based on the biogenetic pathway proposed for gelsedine and other *Gelsemium* alkaloids.[1b,c,15]

Synthetic Plan

Our retrosynthetic approach is depicted in Scheme 1. We envisioned that the introduction of the ethyl substituent into **8** should be possible via methodology developed earlier by our group on a model system.[16] The tetrahydropyran ring was expected to arise via mercuric ion-induced ring closure of the hydroxyl group onto the double bond for which we had collected precedence in our gelsemine synthesis.[3] Suitable protection of anilide **9** and subsequent Pd-catalyzed Heck spirocyclization should lead to the oxindole **8** after hydroboration of the bridge methylene group. The stereochemical outcome of the spirocyclization was an open question, but Overman has shown that this outcome can be drastically influenced by varying the conditions.[24b] The anilide **9** was thought to arise from a Pd-catalyzed aminocarbonylation of a suitably functionalized vinyl triflate or vinyl iodide (viz. **10** and **11**, respectively) after introduction of a one-carbon fragment onto the bridge. These two Pd-catalyzed steps have also served extremely well in our gelsemine synthesis.[3] The bicyclic lactams **10** and **11** have suitable skeletons to be accessed via *N*-acyliminium ion cyclization chemisty.[17] In a previous paper, we showed that **12** is the ideal cyclization precursor.[16] Inexpensive (*S*)-malic acid was chosen as the starting material, despite the fact that this will eventually lead to the unnatural isomer of gelsedine. The early stages of the synthesis bear resemblance to our total synthesis of the indole alkaloid peduncularine.[18]

Results

In the previous paper, we reported an efficient five-step synthesis of ethoxylactam **12** from (*S*)-malic acid and its *N*-acyliminium ion cyclization in neat formic acid to bicyclic ketone **14** in 79% yield (Scheme 2).[16] In nine steps, ketone **14** was further transformed into the ethyl-substituted ketone **15**.[16] We regarded **15** a suitable model system for the parent skeleton to study the introduction of the oxindole moiety (Scheme 2).

To perform the Heck cyclization in the appropriate way, vinyl triflate **17** had to be prepared regioselectively. Therefore, ketone **15** was subjected to kinetic deprotonation conditions (LiHMDS, −78 °C) and then treated with *N*-phenyltriflimide.[19] The ^{1}H NMR spectrum of the crude product showed two signals in the double bond region in a ratio of 4:1. The major component was isolated in 15% yield and was identified by a COSY experiment as being the undesired regioisomer **16**. The minor component could not be isolated and characterized due to

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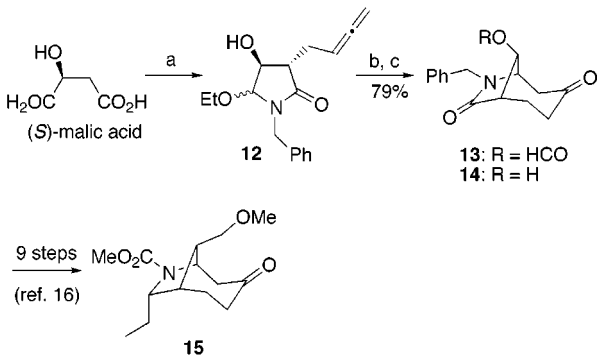
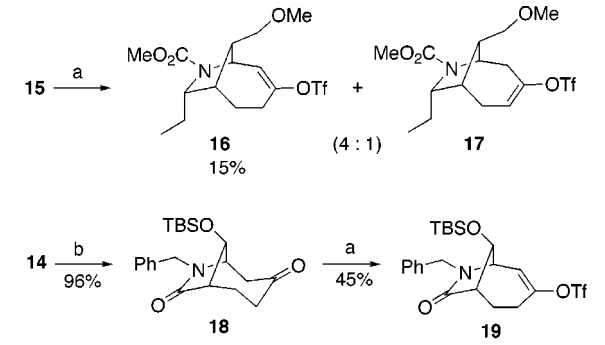
Scheme 2



Conditions: (a) ref. 16. (b) HCO_2H, 85 °C. (c) satd NH_3 in MeOH.

Scheme 3



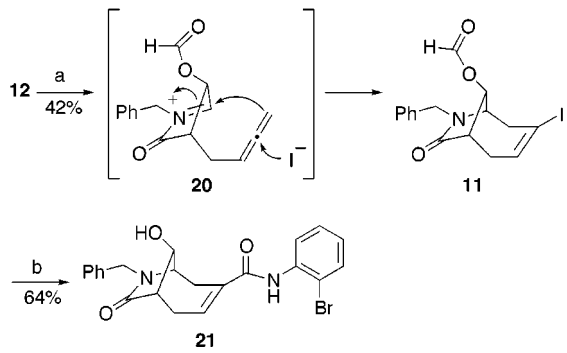
Conditions: (a) LiHMDS, THF, –78 °C, then $PhNTf_2$. (b) TBSCl, imid., DMAP, CH_2Cl_2.

purification problems. Thermodynamic conditions (KH, rt, and treatment with *N*-phenyltriflimide or treatment with sterically hindered 2,6-di-*tert*-butyl-4-methylpyridine and Tf_2O, rt) did not effectively yield any vinyl triflate.

As it appeared difficult to create the desired regioisomer at this stage of the synthesis, the formation of the vinyl triflate at an earlier stage of the synthesis was studied. Ketone **14** (which does not yet contain the ethyl group) was protected as its *tert*-butyldimethylsilyl ether **18** and subjected to kinetic deprotonation conditions as well. The ^1H NMR spectrum of the crude product showed only one product, which after isolation was identified by a COSY experiment to be the undesired regioisomer **19**. In addition, with similar but differently functionalized bicyclic ketones we were also unable to form the desired regioisomeric vinyl triflate in acceptable yield.

Because regioselective functionalization of the seven-membered ring after *N*-acyliminium cyclization appeared unpractical, we considered methods to regioselectively introduce a vinyl triflate (or its synthetic equivalent) in the cyclization step. However, few methods exist to introduce such functionality via an *N*-acyliminium ion reaction. There is one example by Overman where an iodide-terminated iminium ion cyclization of an alkyne leads to an *exo*cyclic vinyl iodide.[20] Because a similar reaction in our case would lead to the undesired regioisomer, we decided to investigate a similar cyclization of the allene **12**. *N*-Acyliminium ion cyclizations of allenes are scarce in the literature,[21] and iodide-promoted variants are unknown to the best of our knowledge. Unfortunately, subjection of **12** to the conditions used by Overman, i.e. CSA, NaI, H_2O, 100 °C or TfOH, *n*-Bu_4NI, $CHCl_3$, produced no vinyl iodide or ketone.[20,22] Alternatively, when allene **12** was dissolved in formic acid in the presence of a large excess of sodium iodide and heated to 85 °C for 18 h we were delighted to find vinyl iodide **11** as the main product in 42% yield (Scheme 4). We were unable to prevent competitive attack of formic acid providing ketone **13** as a byproduct in 34% yield. Lowering the temperature to as low as 40 °C or temperatures between 40 °C and 80 °C resulted in longer reaction times without improvement of the ratio. In fact, at these temperatures the reaction did not go to completion within 18 h. Varying the concentration and nature of the iodide source had no beneficial effect either. Probably formic acid-mediated formation and solvolysis of the intermediate *N*-acyliminium ion **20** is crucial for the cyclization to occur. We were nevertheless pleased with this unique reaction, which produced vinyl iodide **11** in only one step, suitably functionalized for elaboration to the oxindole moiety. Vinyl iodide **11** was readily separated from **13** by flash chromatography so that sufficient quantities of **11** could be assembled for the further study of the total synthesis of gelsedine.

Scheme 4

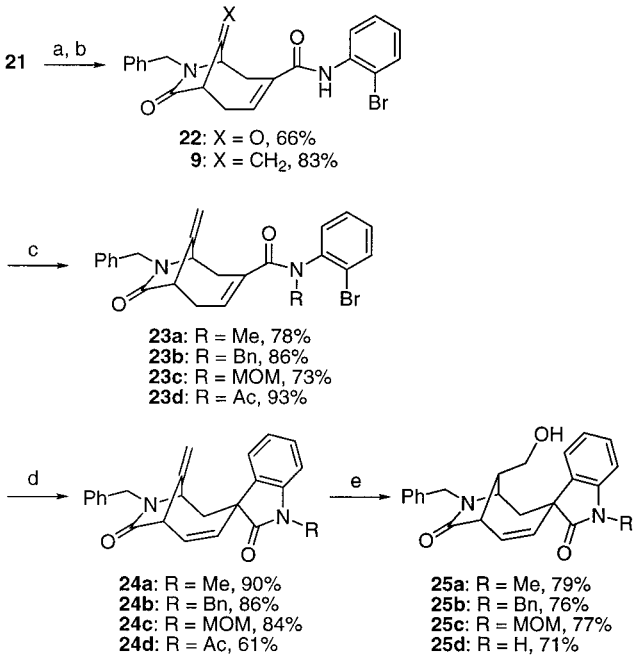


Conditions: (a) NaI, HCO_2H, 85 °C, (0.2 M of **12**). (b) *i.* *o*-bromoaniline, $Pd(OAc)_2$, PPh_3, Et_3N, CO; *ii.* satd NH_3 in MeOH.

The construction of the spiro-oxindole moiety onto **11** commenced by applying a Pd-catalyzed aminocarbonylation process[23] to give anilide **21** after subsequent deformylation. Because it is known that the stereochemical course of the Heck spiro-cyclization is dependent upon steric influences, we envisioned that a sterically nondemanding sp^2-hybridized bridge carbon would be ideal. The approach of the arylpalladium complex from the *exo* direction would then be sterically the least encumbered. Furthermore, by using an inert methylene substituent at the bridge, the use of protecting groups in this region of the molecule was avoided. Therefore, alcohol **21** was first oxidized with PCC to ketone **22** in 66% yield (Scheme 5). A Swern oxidation, which was successfully applied on our model system,[16] did not proceed satisfactorily in this case. The exocyclic double bond was then introduced by a Wittig reaction to provide **9** in 83% yield.

Overman discovered that Heck cyclizations of *N*-unsubstituted anilides are ineffective suggesting *N*-substitution of the anilide **9** is necessary.[24a] Initially, anilide **9** was *N*-functionalized with several groups, i.e. methyl, benzyl, methoxymethyl, and acetyl in good yields. Heck cyclizations were carried out ($Pd(PPh_3)_4$, Et_3N, MeCN, 100−120 °C, sealed tube) with each of these precursors to give products **23a**−**d**, respectively.[24] The yields in the case of the methyl, benzyl, and methoxymethyl substituents were high, while with the acetyl

Scheme 5



Conditions: (a) PCC, CH_2Cl_2, 40 °C. (b) Ph_3PMeBr, *n*-BuLi, THF, 0 °C, then **22**, reflux. (c) NaH, MeI or BnBr or MOMCl, THF; Ac_2O, Et_3N, DMAP, DMF. (d) $Pd(PPh_3)_4$, Et_3N, MeCN, 100-120 °C, sealed tube. (e) $(Chx)_2BH$, THF, 0 °C, then $NaOH/H_2O_2$.

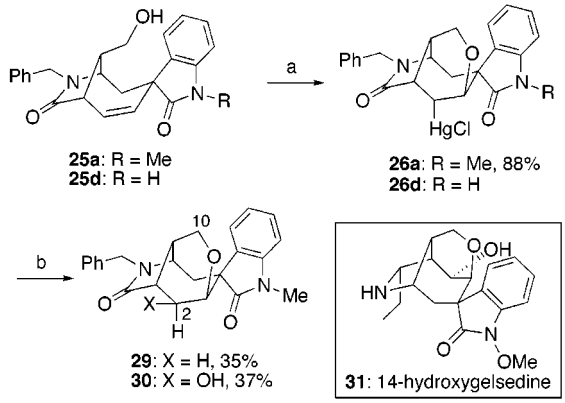
group it was somewhat lower, potentially due to in situ deacetylation.

Clearly, the nature of the *N*-substituent does not influence the outcome of the reaction. In principle all of these groups can be used. The stereochemistry in the case of R = Me was unambiguously proven in a later stage of the synthesis. By comparison of the ^1H NMR and ^{13}C NMR spectra, we concluded that **24b**−**d** possess the same stereochemistry. In all cases less than 5% of the spiro-isomer was observed in the ^1H NMR spectrum of the crude product.

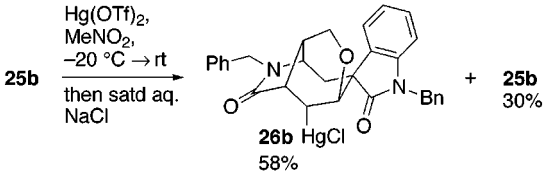
The bridge carbon was now further elaborated by hydroboration with sterically hindered dicyclohexylborane[25] to discriminate between the exo- and endocyclic double bond. In the case of **24a**−**c**, hydroxymethylene products **25a**−**c** were obtained in comparably high yields. Initially, commercially available 9-BBN was used for hydroboration of **24a**, but the resulting byproduct after workup (1,5-cyclooctanediol) could not be separated by column chromatography from product **25a** due to comparable R_f-values. In all cases, the desired stereoisomer was formed exclusively, as a result of attack of the borane from the less sterically encumbered *exo* face. Hydroboration of **24d** with dicyclohexylborane afforded deacetylated alcohol **25d**, which was probably formed by attack of hydroxide on the acetyl carbonyl during workup. The synthesis was eventually continued with the methyl as *N*-substituent, because in the course of our work we found out that it can be selectively removed, as will be detailed later.

To close the tetrahydropyran ring we initially tried to activate the double bond with iodine, but no reaction was observed. We then relied upon a procedure from our total synthesis of gelsemine.[3,26] For example, treatment of **25b** with $Hg(OTf)_2$ in $MeNO_2$ for 2 days followed by addition of saturated aqueous NaCl gave chloromercurial **26b** in 58% yield together with 30% of the starting material.

Scheme 6



Conditions: (a) $Hg(O_2CCF_3)_2$, THF, then satd aq. NaCl. (b) $NaBH_4$, Et_3BnNCl, 10% aq. NaOH, CH_2Cl_2.



The low yield, long reaction time, and the in situ preparation of $Hg(OTf)_2$ led us to adopt the procedure employing commercially available $Hg(O_2CCF_3)_2$. Treatment of **25a** with $Hg(O_2CCF_3)_2$ in THF followed by addition of saturated aqueous NaCl gave the chloromercurial **26a** (Scheme 6).[27] In the case of **25d**, application of an identical procedure provided the required product **26d**. However, the yield could not be determined, because **26d** was too polar to be purified by column chromatography. In all cases the six-membered ring ether was produced as a single product. MM2 force field calculations (CSChem3D Pro version 4.0) on model systems **27** and **28** showed that the steric energy of the six-membered ring ether is significantly lower (41.85 kcal/mol) than the undesired five-membered ring ether (45.48 kcal/mol, Figure 1). This difference is probably reflected in the transition states of the cyclic ether formation.

Reduction of the chloromercurial proved to be problematic. For the reduction of **26a** we first examined a procedure utilizing a two-phase system of aqueous NaOH and CH_2Cl_2.[3,28] After addition of the phase-transfer catalyst benzyltriethylammonium chloride and an excess of $NaBH_4$, metallic mercury precipitated, and the desired product **29** along with alcohol **30** was obtained in 35% and 37% yield, respectively. The stereochemistry of alcohol **30** was tentatively assigned based on the absence of a NOE effect between H-2 and H-10. This product probably arose from reaction of the intermediate alkyl radical with molecular oxygen present in the solution.[29] A similar problem was encountered in our total synthesis

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(26) Nishisawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806−813.

(27) Sutherlin, D. P.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5267−5283.

(28) Benhamou, M. C.; Etemad-Moghadam, G.; Speziale, V.; Lattes, A. *Synthesis* **1979**, 891−892.

(29) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870−876.

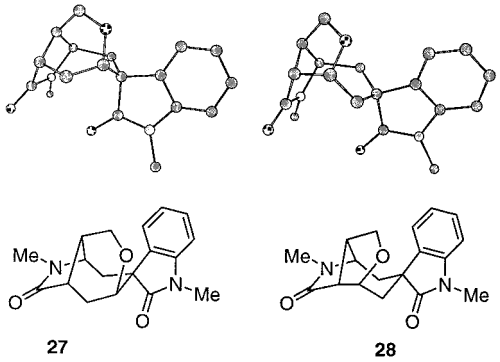
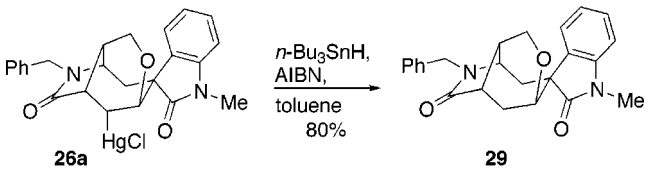


Figure 1. Optimized geometries (CSChem3D Pro) of the theoretical six- and five-membered ring ethers **27** and **28**, indicating that the former is more stable than the latter by ca. 3.5 kcal/mol (see text).

of gelsemine when the substrate concentration in the organic phase of the reaction mixture was too low. However, at a concentration of 0.4 M the desired product was selectively obtained in 88% yield.[3] Unfortunately, the use of higher concentration was not successful in the present case. Product **30** could in principle be elaborated toward 14-hydroxygelsedine (**31**), another *Gelsemium* alkaloid.[30]

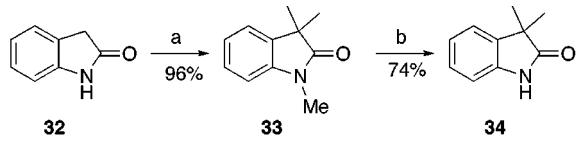
Finally, we relied upon a procedure initially developed by Whitesides and optimized by Evans for reduction of a tetrahydropyran chloromercurial in the total synthesis of the polyether antibiotic X-206.[31] Thus, treatment of **26a** with *n*-Bu_3SnH and AIBN at 55 °C in toluene provided exclusively the desired product **29** in 80% yield. The concentration of chloromercurial **26a** is crucial and should not be lower than 0.5 M. In this way, the concentration of *n*-Bu_3SnH remains sufficiently high to react directly with the intermediate alkyl radical.



Having installed the ether bridge, the next stage consisted of introduction of the ethyl moiety. This requires reductive removal of the benzyl group from the saturated lactam nitrogen. However, to achieve this using a dissolving metal reduction, the oxindole ring needs protection as the anion. Therefore, the oxindole methyl group should be removed first. We hoped that this might be accomplished by using a procedure which is known for removal of an *N*-methyl group from an indole.[32] Initially, we attempted this reaction on model system **33**, which was synthesized via exhaustive methylation of oxindole **32** (Scheme 7).[33] Treatment of **33** with dibenzoyl peroxide (CH_2Cl_2, 80 °C, sealed tube) followed by NaOH in methanol and subsequently NH_3 in methanol provided **34** in a remarkable 74% yield.

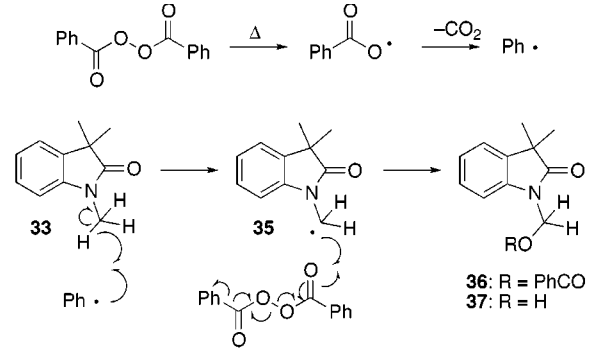
This reaction presumably starts with the formation of a phenyl radical,[34] which abstracts a hydrogen from the

Scheme 7

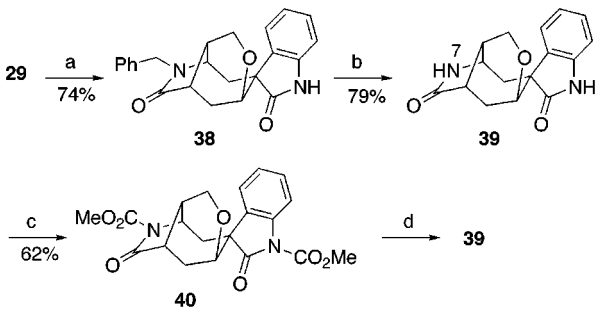


Conditions: (a) NaH, MeI, THF. (b) *i.* $(PhCO_2)_2$, CH_2Cl_2, 80 °C, sealed tube; *ii.* 1 M NaOH in MeOH; *iii.* satd NH_3 in MeOH.

Scheme 8



Scheme 9



Conditions: (a) *i*. $(PhCO_2)_2$, CH_2Cl_2, 80 °C, sealed tube; *ii*. satd I MeOH. (b) Li, NH_3, THF, –78 °C. (c) NaH, MeO_2CCl, THF. (d) EtMgBr, THF, –78 °C.

methyl group in **33** (Scheme 8). The resulting intermediate radical can then react with benzoyl peroxide to form **36**. This extraordinary reaction is probably viable due to the stability of the intermediate radical **35**.[35] Subsequent treatment with NH_3 in methanol was necessary, because after 18 h still a certain amount of intermediate **37** was present. In the presence of ammonia, **37** reacted smoothly to provide the deprotected oxindole **34**.

Application of these conditions to the more complex system **29** proceeded remarkably well providing the deprotected oxindole **38** in 74% yield after treatment with ammonia to cleave the intermediate benzoate (Scheme 9). It is a remarkable observation that the methylene hydrogens of the benzyl group do not react at all, although the benzyl radical might be even better stabilized. The benzyl group was then removed by treatment with lithium in liquid ammonia. The reaction was best

(30) Schun, Y.; Cordell, G. A. *J. Nat. Prod.* **1985**, *48*, 788−791.

(31) (a) Whitesides, G. M.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611−6624. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526.

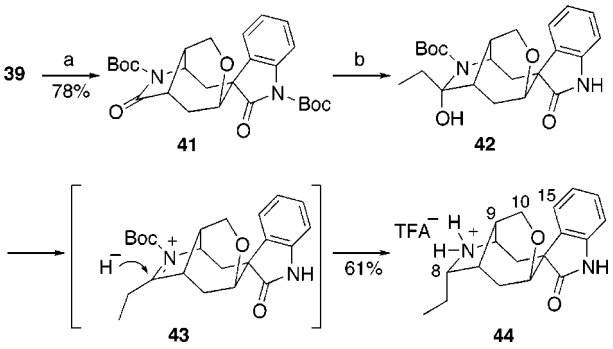
(32) Nakatsuka, S.; Asano, O.; Goto, T. *Heterocycles* **1986**, *24*, 2791−2792.

(33) Other syntheses of compound **34**: (a) Julian, P. L.; Pikl, J.; Boggess, D. *J. Am. Chem. Soc.* **1934**, *56*, 1797−1801. (b) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435−443. (c) Clark, A. J.; Davies, D. I.; Jones, K.; Millbanks, C. *J. Chem. Soc., Chem. Commun.* **1994**, 41−42. (d) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977−978.

(34) Ghosez, A.; Giese, B.; Zipse, H. In *Methoden Der Organischen Chemie* (Houben-Weyl); Regitz, M.; Giese, B., Eds.; Thieme: Stuttgart/New York, 1989; Vol. E19a, 533−716.

(35) For α-acylamino radicals, see: Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430−1432 and ref 4d.

Scheme 10



Conditions: (a) Boc_2O, DMAP, THF. (b) *i.* EtMgBr, THF, –78 °C, then satd aq. NH_4Cl; *ii.* TFA, Et_3SiH, CH_2Cl_2, then extra TFA.

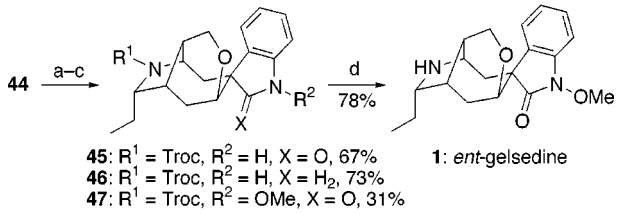
quenched with isoprene, and in this fashion bis-amide **39** was obtained in 79% yield.

With **39** in hand, the introduction of the ethyl moiety was studied (Scheme 9). In initial model studies, a methyl carbamate was successfully used to activate the lactam carbonyl for attack of EtMgBr leading to the desired stereoisomer.[16] Therefore, we anticipated that a similar sequence of reactions could also be applied to lactam **39**. Although we were aware that it would be impossible to selectively react the N-7 lactam NH with methyl chloroformate, we felt confident that in the Grignard step we would be able to discriminate between the carbamate and the oxindole carbonyl for steric reasons. Thus, by deprotonation with NaH, followed by addition of methyl chloroformate, the polar bis-amide **39** was converted to the less polar bis-methyl carbamate **40**. Subsequent treatment with excess of EtMgBr, however, gave exclusively the bis-amide **39** resulting from attack of EtMgBr onto the carbonyls of both carbamates. Variation of the temperature did not change the outcome of this reaction.

The sterically more hindered Boc protecting group was then used to suppress this undesired reaction (Scheme 10). Thus, treatment of **39** with Boc_2O and DMAP in THF gave bis-Boc carbamate **41** in 78% yield. On reaction with excess of EtMgBr the *N*,*O*-hemiacetal **42** was produced as a single product. The Boc group was removed from the oxindole in this process, presumably due to attack of EtMgBr on the Boc carbonyl as the oxindole carbonyl was too sterically hindered. As expected, the ethyl group was introduced selectively from the top face. Although **42** was stable at room temperature, it was treated in crude form with TFA (trifluoroacetic acid) generating the *N*-acyliminium ion **43**, which was reduced in situ with triethylsilane. Again, reduction took place selectively from the least hindered side to form a single product. Additional TFA removed the remaining Boc group, and the TFA salt of desmethoxygelsedine **44** was obtained in 61% yield over two steps. At this stage the stereochemistry of the ethyl and oxindole moieties was unambiguously proven by NOE measurements (a NOE of 5.0% was observed between H-8 and H-9 and a NOE of 3.9% between H-10 and H-15). The presence of the trifluoroacetate counterion was indicated with ^{19}F NMR and ^{13}C NMR. The ^{19}F NMR spectrum of **44** in CD_3OD showed one peak at δ −77.4 (^{19}F NMR spectrum of trifluoroacetic acid in CD_3OD, one peak at δ −78.2). In the ^{13}C NMR spectrum two quartets were observed at δ 163.4 (J_{CF} = 35.4 Hz) and δ 118.3 (J_{CF} = 290.6 Hz), respectively.

For the final stage introduction of the *N*-methoxy group, a procedure precedented to work on similar

Scheme 11



Conditions: (a) TrocCl, pyr., CH_2Cl_2. (b) $BH_3{\cdot}SMe_2$, THF, reflux, then Me_3NO, MeOH, reflux. (c) *i*. urea·H_2O_2, $Na_2WO_4\cdot 2H_2O$, MeOH; *ii.* CH_2N_2, Et_2O, MeOH. (d) Zn, AcOH.

molecules was followed.[14,36] This involves protection of the amine in **44** with 2,2,2-trichloroethyl chloroformate to give **45** and subsequent reduction of the oxindole carbonyl with borane to afford spiro-indoline **46** (Scheme 11). The oxidation of this indoline (urea·H_2O_2, $Na_2WO_4\cdot 2H_2O$, 10% aq MeOH) proceeded rather slowly, but did produce **47** after subsequent treatment with diazomethane.

The last step was the deprotection of the Troc group with zinc in acetic acid. After workup, the ^1H NMR spectrum of the crude product showed less than 5% of a byproduct, which was only different in the aromatic region. Presumably the N−O bond was partially reduced during the deprotection. After purification with preparative TLC, pure (+)-gelsedine was obtained in 84% yield, which was identical to natural (−)-gelsedine[14] (400 MHz ^1H NMR, 100 MHz ^{13}C NMR spectra and HRMS (FAB)), except for the optical rotation (synthetic (+)-gelsedine: $[\alpha]^{22}_D = +120$ ($c = 0.25$, $CHCl_3$); natural (−)-gelsedine: $[\alpha]^{25}_D = -159$ ($c = 1.35$, $CHCl_3$)).[7] The spectral comparisons were made by using NMR spectra and a sample of (−)-gelsedine kindly made available to us by Professor H. Takayama of Chiba University in Japan.

Conclusion

We have successfully completed the first de novo total synthesis of enantiopure *ent*-gelsedine in 21 steps from (*S*)-malic acid in an overall yield of 0.10%. The unique combination of iodide-promoted cationic allene cyclization producing a vinyl iodide and palladium-catalyzed elaboration of the latter in carbonylation and subsequent Heck chemistry has been the key to success. The Heck cyclization and the introduction of the ethyl moiety via *N*-acyliminium ion chemistry both proceeded with complete stereoselectivity. In addition, a methyl group has been shown to be a useful oxindole *N*-protective group. We anticipate that the novel transformations developed in this project will find further application in synthesis.

Experimental Section

General. All reactions involving oxygen or moisture sensitive compounds were carried out under a dry nitrogen atmosphere. Unless otherwise noted, reagents were added by syringe. IR spectra were measured as thin films on NaCl plates unless otherwise noted and wavelengths (ν) are reported in cm^{-1}. NMR spectra were measured as solutions in $CDCl_3$ (unless otherwise noted). Chemical shifts (δ) are expressed in ppm relative to an internal standard of $CHCl_3$ (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). Mass spectra and accurate mass determinations were performed using electron

(36) (a) Murahashi, S.-I.; Oda, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.* **1990**, *55*, 1744−1749. (b) Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1573−1578.

impact (EI) mass spectrometry, unless otherwise noted. R_f values were obtained using thin-layer chromatography (TLC) on Merck F-254 silica gel plastic sheets with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography using the solvent (mixture) mentioned above (unless otherwise noted) and Acros silica gel (0.030−0.075 mm).[37] Melting and boiling points are uncorrected. All starting materials were obtained from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone prior to use. DMF, CH_2Cl_2, and MeCN were distilled from CaH_2 and stored over 4 Å molecular sieves under dry nitrogen atmosphere. Triethylamine and diisopropylamine were distilled from and stored over KOH pellets.

(1*S*,6*R*,9*S*)-Formic Acid 7-Benzyl-4-iodo-8-oxo-7-azabicyclo[4.2.1]non-3-en-9-yl Ester (11). To a solution of **12**[16] (10.62 g, 0.0369 mol) in formic acid (185 mL) was added anhydrous sodium iodide (110.77 g, 0.739 mol). After stirring the reaction mixture at 85 °C for 18 h, the formic acid was evaporated, and the residue was taken up in CH_2Cl_2 (250 mL) and water (250 mL). The water layer was extracted with CH_2Cl_2 (2 × 75 mL), and the combined organic layers were washed with water (75 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed (first with EtOAc/petroleum ether 1:1, then with EtOAc/petroleum ether 4:1) to give **11** (6.16 g, 42%) and **13** (3.60 g, 34%) both as colorless oils; **11**: R_f 0.31 (EtOAc/petroleum ether 1:1); $[\alpha]^{22}_D$ +10.3 (c = 1.0, $CHCl_3$); IR 2920, 1735, 1682, 1495, 1446, 1165; ^{1}H NMR (400 MHz) δ 7.97 (s, 1H), 7.37−7.23 (m, 5H), 6.34 (s, 1H), 5.02 (s, 1H), 4.86 (d, J = 15.3 Hz, 1H), 4.12 (d, J = 15.3 Hz, 1H), 3.44 (t, J = 3.3 Hz, 1H), 2.99 (d, J = 18.7 Hz, 1H), 2.83 (d, J = 18.9 Hz, 1H), 2.77 (s, 1H), 2.70 (d, J = 18.5 Hz, 1H), 2.57 (d, J = 18.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 173.0, 159.8, 137.3, 135.4, 128.7, 127.6, 127.5, 93.1, 75.4, 61.9, 45.8, 45.2, 44.2, 32.5; HRMS calculated for $C_{16}H_{16}INO_3$ 397.0174, found 397.0146. **13**: R_f 0.40 (EtOAc/petroleum ether 4:1); $[\alpha]^{22}_D$ +6.4 (c = 0.5, $CHCl_3$); IR 2932, 1721, 1698, 1694, 1451, 1337, 1224, 1164; ^{1}H NMR (400 MHz) δ 7.94 (s, 1H), 7.37−7.27 (m, 5H), 5.00 (d, J = 15.1 Hz, 1H), 4.76 (s, 1H), 4.20 (d, J = 15.1 Hz, 1H), 3.70 (dd, J = 2.6, 4.3 Hz, 1H), 2.75 (t, J = 4.4 Hz, 1H), 2.60 (dd, J = 2.6, 16.2 Hz, 1H), 2.55 (dd, J = 4.4, 16.3 Hz, 1H), 2.48−2.38 (m, 2H), 2.30−2.23 (m, 1H), 1.93−1.84 (m, 1H); ^{13}C NMR (100 MHz) δ 207.9, 172.9, 159.7, 135.3, 129.0, 128.1, 128.0, 75.8, 57.5, 47.7, 44.3, 43.6, 39.9, 24.4; HRMS (FAB+) calculated for $C_{15}H_{18}NO_3$ (M + H − CO) 260.1287, found 260.1294.

(1*S*,6*R*,9*S*)-7-Benzyl-9-hydroxy-8-oxo-7-azabicyclo[4.2.1]non-3-ene-4-carboxylic Acid (2-Bromophenyl)amide (21). A solution of **11** (1.67 g, 4.20 mmol), $Pd(OAc)_2$ (0.141 g, 0.630 mmol), triphenylphospine (0.330 g, 1.26 mmol), *o*-bromoaniline (2.16 g, 12.6 mmol), and triethylamine (2.93 mL, 21.0 mmol) in DMF (14 mL) was stirred under carbon monoxide atmosphere (balloon) for 20 h at 40 °C. Then the solvents were evaporated under reduced pressure using a vacuum pump (<50 mbar, heat slightly with a heat gun to evaporate DMF), and the residue was chromatographed (EtOAc/petroleum ether 4:1) to give a reddish oil, which was dissolved in a saturated methanolic NH_3 solution (12 mL) and stirred for 15 min at room temperature. The solvent was evaporated and the residue chromatographed to give **21** (1.19 g, 64%) as a colorless oil; R_f 0.45 (CH_2Cl_2/acetone 1:1); $[\alpha]^{22}_D$ −16.3 (c = 1.0, $CHCl_3$); IR 3405, 2918, 1685, 1676, 1590, 1518, 1433, 1298, 1249; ^{1}H NMR (400 MHz) δ 8.23 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H, NH), 7.54 (d, J = 8.0 Hz, 1H), 7.34−7.25 (m, 5H), 7.20−7.16 (m, 1H), 6.99 (t, J = 7.8 Hz, 1H), 6.47 (s, 1H), 4.78 (d, J = 15.2 Hz, 1H), 4.20 (d, J = 15.2 Hz, 1H), 4.04 (s, 1H), 3.76 (s, 1H), 2.96 (d, J = 19.4 Hz, 1H), 2.87 (d, J = 18.5 Hz), 2.74−2.63 (m, 2H), 2.52 (d, J = 18.4 Hz, 1H), 2.35 (s, 1H, OH); ^{13}C NMR (100 MHz) δ 175.2, 167.8, 136.0, 135.4, 133.0, 132.2, 131.3, 128.6, 128.4, 128.2, 127.8, 127.5, 125.5, 122.4, 114.4, 75.0, 63.2, 48.7, 44.5, 30.6, 30.1; HRMS (FAB+) calculated for $C_{22}H_{22}{}^{79}BrN_2O_3$ (M + H) 441.0813, found 441.0815.

(1*S*,6*R*)-7-Benzyl-8,9-dioxo-7-azabicyclo[4.2.1]non-3-ene-4-carboxylic Acid (2-Bromophenyl)amide (22). To a solution of **21** (2.50 g, 5.66 mmol) in CH_2Cl_2 (28 mL) was added PCC (4.88 g, 22.64 mmol), and the reaction mixture was heated at 40 °C for 17 h. Then extra PCC (1.22 g, 5.66 mmol) was added, and the mixture was stirred at 40 °C for another 5 h, cooled to room temperature, and poured onto a short column of silica (4.0 × 6.0 cm). This was eluted with acetone. The top layer of the short column was removed and thoroughly stirred with acetone, and then poured back onto the column and eluted further with acetone until no more product came off. The acetone was evaporated and the residue was chromatographed (CH_2Cl_2/acetone 8:1) to give **22** (1.64 g, 66%) as a colorless oil; R_f 0.39 (CH_2Cl_2/acetone 8:1); $[\alpha]^{22}_D$ −30.8 (c = 1.0, $CHCl_3$); IR 3279, 2921, 1723, 1696, 1679, 1577, 1517, 1434, 1299; ^{1}H NMR (400 MHz) δ 8.21 (d, J = 8.2 Hz, 1H), 7.80 (s, 1H, NH), 7.53 (d, J = 8.0 Hz, 1H), 7.33−7.24 (m, 5H), 7.22−7.19 (m, 1H), 6.99 (t, J = 7.9 Hz, 1H), 6.54 (s, 1H), 4.91 (d, J = 14.7 Hz, 1H), 4.27 (d, J = 14.7 Hz, 1H), 3.99 (s, 1H), 3.10−3.06 (m, 3H), 2.68 (d, J = 16.9 Hz, 1H), 2.46 (d, J = 17.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 207.8, 170.7, 167.0, 135.2, 135.0, 133.7, 132.2, 129.7, 128.9, 128.4, 128.3, 128.1, 125.6, 121.9, 113.9, 62.9, 49.4, 43.9, 30.9, 29.6; HRMS calculated for $C_{22}H_{19}{}^{79}BrN_2O_3$ 438.0579, found 438.0605.

(1*S*,6*R*)-7-Benzyl-9-methylene-8-oxo-7-azabicyclo[4.2.1]non-3-ene-4-carboxylic Acid (2-Bromophenyl)amide (9). To a solution of methyltriphenylphosphonium bromide (3.33 g, 9.33 mmol) in THF (40 mL) was added at 0 °C a 1.6 M solution of n-BuLi in hexane (5.72 mL, 9.14 mmol). After stirring for 25 min a solution of **22** (1.64 g, 3.73 mmol) in THF (10 mL) was added. The reaction mixture was stirred at 70 °C for 18 h and then poured onto saturated aqueous NH_4Cl (100 mL). The water layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed to give **9** (1.37 g, 83%) as a colorless oil; R_f 0.34 (EtOAc/petroleum ether 2:1); $[\alpha]^{22}_D$ −31.0 (c = 1.0, $CHCl_3$); IR 3279, 2907, 1699, 1673, 1564, 1513, 1434, 1298; ^{1}H NMR (400 MHz) δ 8.28 (d, J = 8.2 Hz, 1H), 7.81 (s, 1H, NH), 7.54 (d, J = 7.9 Hz, 1H), 7.34−7.19 (m, 6H), 6.99 (t, J = 7.6 Hz, 1H), 6.52 (s, 1H), 5.05 (d, J = 7.9 Hz, 2H), 4.88 (d, J = 15.1 Hz, 1H), 4.20 (s, 1H), 4.10 (d, J = 15.2 Hz, 1H), 3.22 (s, 1H), 3.11 (d, J = 17.9 Hz, 2H), 2.63 (d, J = 19.2 Hz, 1H), 2.49 (d, J = 18.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 174.4, 168.1, 147.1, 136.0, 135.2, 133.4, 132.2, 131.2, 128.7, 128.3, 128.1, 127.6, 125.3, 121.9, 113.8, 106.8, 59.4, 46.1, 43.9, 35.5, 34.7; HRMS calculated for $C_{23}H_{21}{}^{79}BrN_2O_2$ 436.0786, found 436.0767.

(1*S*,6*R*)-7-Benzyl-9-methylene-8-oxo-7-azabicyclo[4.2.1]non-3-ene-4-carboxylic Acid Methyl-(2-bromophenyl)-amide (23a). To a solution of **9** (1.36 g, 3.11 mmol) in THF (15 mL) was added 60% sodium hydride in mineral oil (0.373 g, 9.33 mmol). Methyl iodide (0.484 mL, 7.78 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 4.5 h (not longer) and then poured onto saturated aqueous NH_4Cl (25 mL). The water layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed to give **23a** (1.10 g, 78%) as a colorless oil; R_f 0.36 (EtOAc/petroleum ether 10:1); $[\alpha]^{22}_D$ +56.6 (c = 0.5, $CHCl_3$); IR 3059, 2919, 1697, 1673, 1584, 1478, 1444, 1420, 1364; ^{1}H NMR (400 MHz, benzene-d_6, T = 340 K) δ 7.25 (d, J = 7.5 Hz, 1H), 7.19−7.03 (m, 5H), 6.82 (t, J = 7.4 Hz, 1H), 6.72 (d, J = 6.6 Hz, 1H), 6.61 (t, J = 6.6 Hz, 1H), 5.65 (s, 1H), 5.08 (d, J = 15.1 Hz, 1H), 4.45 (s, 2H), 3.79 (s, 1H), 3.68 (d, J = 14.1 Hz, 1H), 3.10 (s, 3H), 3.04 (d, J = 19.2 Hz, 1H), 2.76 (s, 1H), 2.60 (d, J = 17.9 Hz, 1H), 2.23 (d, J = 11.8 Hz, 1H), 1.87 (d, J = 18.1 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6, T = 340 K) δ 173.9, 172.7, 149.2, 145.0, 137.9, 134.4, 132.7, 130.9, 129.3, 128.9, 128.7, 128.5, 128.2, 127.9, 123.5, 105.8, 59.8, 47.0, 44.1, 37.1, 36.5, 35.9; HRMS (FAB+) calculated for $C_{24}H_{24}{}^{79}BrN_2O_2$ (M + H) 451.1021, found 451.0993.

***N*-Methyl Spiro-oxindole 24a.** A solution of **23a** (0.365 g, 0.809 mmol), $Pd(PPh_3)_4$ (0.187 g, 0.162 mmol) and triethylamine (1.12 mL, 8.08 mmol) in MeCN (8 mL) in a sealed tube was heated slowly to 120 °C. After stirring for 40 h, the reaction mixture was cooled to room temperature, and the solvent was evaporated. The residue was chromatographed

(37) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(load with CH_2Cl_2) to give **24a** (0.270 g, 90%) as a colorless oil; R_f 0.42 (EtOAc/petroleum ether 10:1); $[\alpha]^{22}_D$ +14.9 (c = 1.0, $CHCl_3$); IR 3027, 2930, 1712, 1673, 1608, 1492, 1343, 1248; ^{1}H NMR (400 MHz) δ 7.33−7.21 (m, 6H), 7.07 (dd, J = 7.3, 16.4 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 6.30 (dd, J = 8.7, 11.4 Hz, 1H), 5.32 (d, J = 15.7 Hz, 1H), 5.04 (s, 1H), 4.95 (s, 1H), 4.93 (d, J = 11.1 Hz, 1H), 4.17 (s, 1H), 3.98 (d, J = 15.7 Hz, 1H), 3.62 (d, J = 8.7 Hz, 1H), 3.17 (s, 3H), 2.56 (dd, J = 3.5, 15.5 Hz, 1H), 2.06 (dd, J = 2.8, 15.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 177.4, 172.9, 147.8, 142.2, 136.5, 132.2, 131.6, 128.8, 128.4, 128.2, 127.7, 127.1, 123.7, 122.9, 107.9, 105.9, 61.0, 54.7, 49.9, 44.4, 38.2, 26.4; HRMS calculated for $C_{24}H_{22}N_2O_2$ 370.1681, found 370.1692.

***N*-Methyl Spiro-oxindole 25a.** To a solution of **24a** (0.803 g, 2.16 mmol) in THF (7 mL) was added at 0 °C a freshly prepared 0.5 M solution of dicyclohexylborane in THF (8.67 mL, 4.33 mmol).[25] After stirring the reaction mixture for 2 h at 0 °C, a 3 M solution of NaOH in water (4.33 mL, 13.0 mmol) and a 35% solution of H_2O_2 in water (1.68 mL, 17.3 mmol) were added slowly. The mixture was stirred for 1 h at room temperature and then poored onto saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed to give **25a** (0.665 g, 79%) as a white solid; R_f 0.37 (CH_2Cl_2/acetone 1:1); mp 87−89 °C; $[\alpha]^{22}_D$ −13.4 (c = 1.0, $CHCl_3$); IR 3394, 2932, 1699, 1682, 1610, 1495, 1471, 1450, 1342, 1252. ^{1}H NMR (400 MHz) δ 7.31−7.24 (m, 7H), 7.07 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.00 (dd, J = 9.1, 11.6 Hz, 1H), 5.33 (d, J = 15.7 Hz, 1H), 5.20 (d, J = 11.7 Hz, 1H), 4.12−4.02 (m, 2H), 3.86 (d, J = 15.7 Hz, 1H), 3.78 (t, J = 4.5 Hz, 1H), 3.26 (dd, J = 6.8, 8.7 Hz, 1H), 3.19 (s, 3H), 2.79−2.75 (m, 1H), 2.30 (dd, J = 4.3, 16.3 Hz, 1H), 2.21 (dd, J = 1.6, 16.1 Hz, 1H); ^{13}C NMR (100 MHz) δ 176.6, 174.9, 142.2, 137.2, 135.1, 132.4, 128.5, 128.4, 128.2, 127.7, 127.2, 123.2, 123.0, 107.9, 59.3, 56.9, 55.3, 45.3, 45.1, 45.0, 32.7, 26.5; HRMS calculated for $C_{24}H_{24}N_2O_3$ 370.1787, found 370.1787.

Chloromercurial 26a. To a solution of **25a** (0.540 g, 1.39 mmol) in THF (14 mL) was added mercury(II) trifluoroacetate (1.19 g, 2.78 mmol). After stirring the reaction mixture for 5 h at room temperature, saturated aqueous NaCl (7 mL) was added, and the mixture was stirred vigorously for an additional 18 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (load with CH_2Cl_2) to give **26a** (0.762 g, 88%) as a white solid; R_f 0.33 (EtOAc/petroleum ether 4:1); mp 158−160 °C; $[\alpha]^{22}_D$ +14.5 (c = 1.0, $CHCl_3$); IR 2919, 1687, 1680, 1608, 1494, 1470, 1449, 1349, 1258; ^{1}H NMR (400 MHz) δ 7.49 (d, J = 7.5 Hz, 1H), 7.33−7.22 (m, 6H), 7.10 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 5.29 (d, J = 15.4 Hz, 1H), 4.28 (dd, J = 3.1, 11.4 Hz, 1H), 4.19 (dd, J = 1.1, 11.3 Hz, 1H), 3.92−3.89 (m, 2H), 3.74 (d, J = 15.4 Hz, 1H), 3.27 (s, 3H), 3.22 (dd, J = 3.9, 9.8 Hz, 1H), 2.97 (t, J = 9.4 Hz, 1H), 2.75 (t, J = 7.4 Hz, 1H), 2.26 (dd, J = 3.4, 15.4 Hz, 1H), 2.17 (dd, J = 1.7, 15.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 179.6, 177.1, 141.4, 136.1, 134.9, 128.5, 128.2, 127.9, 127.4, 124.2, 123.1, 108.0, 79.5, 61.2, 59.1, 57.8, 45.1, 44.4, 43.3, 36.7, 32.6, 26.7; HRMS (FAB+) calculated for $C_{24}H_{24}ClHgN_2O_3$ (M + H) 625.1182, found 625.1215.

Tetrahydropyran 29. To a solution of **26a** (0.600 g, 0.962 mmol) in toluene (1.9 mL, 0.5 M!), which was stirred vigorously, were added AIBN (0.0158 g, 0.0962 mmol) and n-Bu_3SnH (0.647 mL, 2.40 mmol) at one time. The reaction mixture was stirred at room temperature for 1 h and then at 55 °C for 1 h. After cooling to room temperature, CCl_4 (0.5 mL) was added, and the mixture was stirred for an additional 1 h and then poured onto a 5% aqueous solution of KF (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (first load and eluate with CH_2Cl_2, then with CH_2Cl_2/acetone 2:1) to give **29** (0.299 g, 80%) as a white solid; R_f 0.34 (CH_2Cl_2/acetone 2:1); mp 68−70 °C; $[\alpha]^{22}_D$ +139.0 (c = 1.0, $CHCl_3$); IR 2917, 1698, 1693, 1609, 1493, 1470, 1447, 1345, 1256; ^{1}H NMR (400 MHz) δ 7.45 (d, J = 7.4 Hz, 1H), 7.31−7.21 (m, 6H), 7.05 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 5.29 (d, J = 15.4 Hz, 1H), 4.23 (dd, J = 3.0, 11.3 Hz, 1H), 4.18 (d, J = 1.5, 11.2 Hz, 1H), 3.81−3.77 (m, 1H), 3.74−3.72 (m, 1H), 3.70 (d, J = 15.4 Hz, 1H), 3.19 (s, 3H), 2.80 (dd, J = 8.6, 9.9 Hz, 1H), 2.66 (t, J = 8.0 Hz, 1H), 2.57 (d, J = 15.0 Hz, 1H), 2.29−2.23 (m, 1H), 2.15−2.14 (m, 2H); ^{13}C NMR (100 MHz) δ 176.4, 175.5, 141.9, 136.8, 134.9, 128.7, 128.5, 128.0, 127.3, 123.9, 122.6, 107.5, 75.2, 61.8, 58.6, 56.9, 43.1, 36.5, 35.0, 31.7, 26.8, 26.2; HRMS (FAB+) calculated for $C_{24}H_{25}N_2O_3$ (M + H) 389.1865, found 389.1871.

Spiro-oxindole 38. A solution of **29** (0.646 g, 1.66 mmol) and benzoyl peroxide (0.806 g, 3.32 mmol) in CH_2Cl_2 (3.5 mL) in a sealed tube was heated slowly to 80 °C. After stirring for 18 h, the reaction mixture was cooled to room temperature, and the solvent was evaporated. The residue was dissolved in a saturated methanolic NH_3 solution (15 mL) and stirred at room temperature for 20 h. The solvent was evaporated and the residue chromatographed (pulverize the residue and load on column with the eluens) to give **38** (0.463, 74%) as a colorless oil; R_f 0.33 (CH_2Cl_2/acetone 1:3); $[\alpha]^{22}_D$ +141.8 (c = 1.0, $CHCl_3$); IR 3169, 2923, 1713, 1677, 1619, 1472, 1451, 1113; ^{1}H NMR (400 MHz) δ 8.67 (s, 1H, NH), 7.42 (d, J = 7.4 Hz, 1H), 7.31−7.17 (m, 6H), 7.01 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 5.27 (d, J = 15.4 Hz, 1H), 4.21 (dd, J = 2.8, 11.4 Hz, 1H), 4.18 (dd, J = 1.1, 11.4 Hz, 1H), 3.82−3.80 (m, 2H), 3.74 (d, J = 15.4 Hz, 1H), 2.84 (t, J = 8.8 Hz, 1H), 2.67 (t, J = 8.2 Hz, 1H), 2.61 (d, J = 16.9 Hz, 1H), 2.32−2.24 (m, 1H), 2.26 (d, J = 16.9 Hz, 1H). 2.16 (dd, J = 3.5, 15.9 Hz, 1H); ^{13}C NMR (100 MHz) δ 178.6, 176.7, 139.4, 136.7, 135.6, 132.9, 130.0, 128.7, 128.3, 128.1, 127.4, 124.3, 122.6, 109.6, 75.1, 61.9, 58.7, 57.6, 44.0, 36.7, 35.1, 31.9, 26.8; HRMS calculated for $C_{23}H_{22}N_2O_3$ 374.1631, found 374.1641.

Spiro-oxindole 39. To condensed NH_3 (10 mL) was added lithium (0.036 g, 5.18 mmol) at −78 °C. After stirring the deep blue solution for 5 min, **38** (0.200 g, 0.531 mmol) in THF (4 mL) was added slowly. The reaction mixture was stirred for 30 min at −78 °C, and then isoprene (1.32 mL, 13.3 mmol) was added carefully. The ammonia was allowed to evaporate slowly at room temperature by passing a stream of nitrogen over the solution, and the THF was evaporated. The residue was chromatographed (pulverize the residue and load on column with the eluens) to give **39** (0.119 g, 79%) as a white solid; R_f 0.40 (CH_2Cl_2/methanol 4:1); mp 191−193 °C; $[\alpha]^{22}_D$ +143.4 (c = 1.1, $CHCl_3$); IR 3407, 1698, 1682, 1621, 1472, 1109. ^{1}H NMR (400 MHz) δ 9.65 (s, 1H, NH), 7.37 (d, J = 7.1 Hz, 1H), 7.08 (t, J = 6.6 Hz, 1H), 7.06 (s, 1H, NH), 6.95 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 4.19−4.16 (m, 2H), 4.00 (d, J = 7.6 Hz, 1H), 3.77 (d, J = 3.3 Hz, 1H), 2.76 (t, J = 7.9 Hz, 1H), 2.57 (t, J = 8.6 Hz, 1H), 2.46 (d, J = 14.7 Hz, 1H), 2.26−2.17 (m, 2H), 1.92 (d, J = 14.7 Hz, 1H); ^{13}C NMR (100 MHz) δ 180.8, 179.0, 139.7, 135.9, 127.9, 124.2, 122.4, 109.7, 74.7, 61.9, 57.5, 56.9, 36.7, 36.6, 36.2, 26.7; HRMS calculated for $C_{16}H_{16}N_2O_3$ 284.1161, found 284.1167.

Bis-*tert*-butyl Carbamate 41. To a solution of **39** (0.285 g, 1.00 mmol) in THF (8 mL) were added *N*,*N*-(dimethylamino)pyridine (0.735 g, 6.02 mmol) and Boc_2O (1.75 g, 8.03 mmol). The reaction mixture was stirred for 5 h and then poured onto saturated aqueous NH_4Cl (15 mL). The waterlayer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed to give **41** (0.379 g, 78%) as a colorless oil; R_f 0.41 (EtOAc/petroleum ether 6:1); $[\alpha]^{22}_D$ +60.4 (c = 1.0, $CHCl_3$); IR 2979, 1789, 1759, 1730, 1711, 1605, 1369, 1306, 1251; ^{1}H NMR (400 MHz) δ 7.74 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 4.57−4.52 (m, 1H), 4.25 (dd, J = 1.3, 11.4 Hz, 1H), 4.20 (dd, J = 2.9, 14.4 Hz, 1H), 3.88 (d, J = 3.6 Hz, 1H), 2.81 (t, J = 8.7 Hz, 1H), 2.72 (t, J = 8.2 Hz, 1H), 2.66 (d, J = 15.8 Hz, 1H), 2.53 (d, J = 15.3 Hz, 1H), 2.35−2.27 (m, 1H), 2.22 (dd, J = 3.8, 15.9 Hz, 1H), 1.58 (s, 9H), 1.52 (s, 9H); ^{13}C NMR (100 MHz) δ 175.2, 173.8, 150.2, 149.3, 138.0, 133.7, 128.4, 124.6, 124.1, 114.2, 84.2, 82.7, 74.8, 61.6, 60.3, 56.7, 38.2, 34.2, 33.3, 28.1, 28.0, 26.6; HRMS calculated for $C_{26}H_{32}N_2O_7$ 484.2210, found 484.2197.

TFA Salt of Desmethoxygelsedine (44). To a solution of **41** (0.168 g, 0.346 mmol) in THF (2 mL) at −78 °C was added

a 1 M solution of ethylmagnesium bromide in THF (2.08 mL, 2.08 mmol). The reaction mixture was stirred at −78 °C for 15 min at room temperature for 15 min and then quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL, water (a few mL) was added to get a clear separation). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was not purified, but directly used in the following reaction. To a solution of the residue in CH_2Cl_2 (1.5 mL) was added trifluoroacetic acid (0.320 mL, 4.15 mmol) at 0 °C, and the mixture was stirred at 0 °C for 10 min. Then triethylsilane (0.416 mL, 2.77 mmol) was added. After stirring the solution for 1.5 h at 0 °C and 2.5 h at room temperature, additional trifluoroacetic acid (0.4 mL) was added, and the reaction mixture was stirred for an additional 18 h. The solvents were evaporated, and the residue was chromatographed to give **44** (0.087 g, 61%) as a white solid; R_f 0.42 (CH_2Cl_2/methanol 4:1); mp 118−120 °C; $[\alpha]^{22}_D$ +83.0 (c = 1.0, MeOH); IR 2971, 1679, 1620, 1472, 1435, 1201, 1124; ^{1}H NMR (400 MHz) δ 11.5 (s, 1H, NH), 11.3 (s, 1H, NH), 9.32 (s, 1H, NH), 7.33 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 4.51 (s, 1H), 4.28−4.24 (m, 2H), 3.80 (s, 1H), 3.72 (d, J = 6.5 Hz, 1H), 2.88 (s, 1H), 2.56 (s, 1H), 2.35 (dd, J = 3.4, 16.4 Hz, 1H), 2.26 (d, J = 15.5 Hz, 1H), 2.21−2.06 (m, 2H), 2.03−1.95 (m, 2H), 1.08 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 184.2, 163.4 (q, J_{CF} = 35.4 Hz), 141.5, 136.5, 129.9, 126.0, 124.4, 118.3 (q, J_{CF} = 290.6 Hz), 111.5, 76.6, 66.4, 63.7, 61.3, 60.9, 40.9, 35.2, 32.0, 22.1, 20.6, 11.4; ^{19}F NMR (282 MHz, CD_3OD) δ = −77.4; HRMS calculated for $C_{18}H_{22}N_2O_2$ 298.1682, found 298.1679.

Troc-Protected Desmethoxygelsedine (45). To a solution of **44** (0.144 g, 0.349 mmol) in CH_2Cl_2 (0.50 mL) and dry pyridine (1.00 mL) was added TrocCl (2,2,2-trichloroethyl chloroformate) (0.057 mL, 0.419 mmol). After stirring for 4.5 h at room temperature, extra TrocCl (0.048 mL, 0.349 mmol) was added, and the reaction mixture was stirred for another 18 h. Then the solvents were evaporated, and the residue was chromatographed (EtOAc/petroleum ether 2:3, load with CH_2Cl_2) to give **45** (0.111 g, 67%) as a colorless oil; R_f 0.31 (EtOAc/petroleum ether 2:3); $[\alpha]^{22}_D$ +126.5 (c = 1.0, $CHCl_3$); IR 2934, 2874, 1715, 1699, 1618, 1472, 1404, 1290, 1118; ^{1}H NMR (400 MHz, benzene-d_6, T = 340 K) δ 7.37 (d, J = 7.4 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.35 (d, J = 7.3 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.60 (s, 1H), 4.21 (s, 1H), 3.86−3.82 (m, 2H), 3.56−3.50 (m, 2H), 3.08−3.00 (m, 1H), 2.74 (d, J = 16.0 Hz, 1H), 2.62 (d, J = 15.3 Hz, 1H), 2.52−2.48 (m, 1H), 2.00−1.87 (m, 2H), 1.66−1.58 (m, 1H), 0.82 (t, J = 7.6 Hz, 3H); HRMS (FAB+) calculated for $C_{21}H_{24}Cl_3N_2O_4$ (M + H) 473.0801, found 473.0794. A useful ^{13}C NMR spectrum could not be obtained due to rotamers.

Indoline 46. To a solution of **45** (0.110 g, 0.232 mmol) in THF (2 mL) was added at 0 °C BH_3·SMe_2 (0.440 mL, 4.64 mmol) and the reaction mixture was heated at 70 °C for 18 h. Then it was poured onto cold 10% aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH (2 mL), and trimethylamine *N*-oxide dihydrate (0.128 g, 1.16 mmol) was added. The reaction mixture was heated at reflux for 2 h and then poured onto water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried ($MgSO_4$) and concentrated, and the residue was chromatographed to give **46** (0.078 g, 73%) as a colorless oil; R_f 0.29 (EtOAc/petroleum ether 2:3); $[\alpha]^{22}_D$ +110.9 (c = 1.0, benzene); IR 3363, 2933, 2861, 1713, 1604, 1398, 1292, 1121; ^{1}H NMR (400 MHz, benzene-d_6, T = 340 K) δ 7.63 (d, J = 7.4 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 7.4 Hz, 1H), 6.43 (d, J = 7.7 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.12 (s, 1H), 3.89 (d, J = 5.3 Hz, 1H), 3.83 (s, 2H), 3.41 (d, J = 8.9 Hz, 1H), 3.41 (s, 1H), 2.96 (br s, 1H), 2.83 (d, J = 8.7 Hz, 1H), 2.84−2.76 (m, 1H), 2.68 (d, J = 15.2 Hz, 1H), 1.94−1.92 (m, 1H), 1.81−1.76 (m, 2H), 1.69−1.57 (m, 2H), 1.45−1.37 (m, 1H), 0.74 (t, J = 7.5 Hz, 3H); HRMS (FAB+) calculated for $C_{21}H_{26}Cl_3N_2O_3$ (M + H) 459.1009, found 459.1005. A useful ^{13}C NMR spectrum could not be obtained due to rotamers.

Troc-Protected Gelsedine (47). To a solution of **46** (0.0147 g, 0.0319 mmol) in 10% aqueous MeOH (0.6 mL) were added Na_2WO_4·$2H_2O$ (6.3 mg, 0.019 mmol) and urea·H_2O_2 (0.030 g, 0.32 mmol). After stirring the reaction mixture for 2 h at room temperature, more urea·H_2O_2 (0.030 g, 0.32 mmol) was added, and the mixture was stirred for an additional 2 h. Then it was poured onto saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH (4 mL), and a freshly prepared solution of diazomethane in ether (0.5 mL) was added at 0 °C. After stirring the reaction mixture for 1 h at room temperature, the solvent was evaporated and the residue chromatographed to give **47** (5.0 mg, 31%) as a colorless oil; R_f 0.23 (EtOAc/petroleum ether 1:2); $[\alpha]^{22}_D$ +95.5 (c = 0.26, $CHCl_3$); IR 2925, 1716, 1621, 1463, 1402, 1291, 1119; ^{1}H NMR (400 MHz, benzene-d_6, T = 340 K) δ 7.38 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 4.66 (s, 2H), 4.18 (s, 1H), 3.83 (dd, J = 3.4, 10.9 Hz, 1H), 3.81 (d, J = 11.0 Hz, 1H), 3.60 (s, 3H), 3.54−3.51 (m, 1H), 3.43 (d, J = 6.7 Hz, 1H), 3.04−2.98 (m, 1H), 2.72 (d, J = 15.9 Hz, 1H), 2.55 (d, J = 15.2 Hz, 1H), 2.52−2.46 (m, 1H), 2.03−1.85 (m, 3H), 1.67−1.58 (m, 1H), 0.83 (t, J = 7.6 Hz, 3H); HRMS (FAB+) calculated for $C_{22}H_{26}Cl_3N_2O_5$ (M + H) 503.0908, found 503.0904. A useful ^{13}C NMR spectrum could not be obtained due to rotamers.

***ent*-Gelsedine (1).** To a solution of **47** (4.7 mg, 0.093 mmol) in acetic acid (0.6 mL) was added zinc dust (0.012 g, 0.18 mmol). After stirring the reaction mixture at room temperature for 2 h, more zinc dust (0.012 g, 0.18 mmol) was added, and the mixture was stirred for an additional 18 h. The suspension was filtered and diluted with ice−water (2 mL). The mixture was basified with a 25% aqueous solution of NH_4OH (pH > 10) and was extracted with MeOH/$CHCl_3$ (1:9, 3 × 10 mL). The organic layers were washed with brine (4 mL), dried ($MgSO_4$), and concentrated, and the residue was purified by preparative TLC (plate 10 × 10 cm, after eluting with MeOH/$CHCl_3$ (1:3), the plate was turned around (180°) and eluted with EtOAc) to give **1** (2.6 mg, 84%) as a colorless oil; R_f 0.81 (MeOH/$CHCl_3$ 1:3), $[\alpha]^{22}_D$ +120.4 (c = 0.25, $CHCl_3$); IR 3246, 2926, 1707, 1616, 1465, 1435, 1327, 1221, 1044; ^{1}H NMR (400 MHz) δ 7.39 (d, J = 7.4 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 4.33 (dd, J = 4.1, 10.9 Hz, 1H), 4.24 (d, J = 10.8 Hz, 1H), 4.00 (s, 3H), 3.74 (s, 1H, NH), 3.70 (s, 1H), 3.50 (d, J = 6.9 Hz, 1H), 2.97 (s, 1H), 2.49−2.47 (m, 1H), 2.19 (d, J = 6.9 Hz, 1H), 2.13−2.09 (m, 1H), 2.12 (d, J = 3.6, 16.0 Hz, 1H), 2.02 (d, J = 16.0 Hz, 1H), 1.96−1.87 (m, 1H), 1.85−1.78 (m, 1H), 1.76−1.69 (m, 1H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz) δ 174.5, 137.9, 131.7, 128.2, 125.3, 123.7, 107.1, 74.6, 65.4, 63.8, 63.4, 59.6, 57.3, 41.6, 34.6, 33.8, 21.4, 21.2, 11.9; HRMS (FAB+) calculated for $C_{19}H_{25}N_2O_3$ (M + H) 329.1865, found 329.1867.

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Supporting Information Available: Experimental procedures and spectral data for compounds **18**, **19**, **23b**−**d**, **24b**−**d**, **25b**−**d**, **26b**, **30**, **33**, **34**, and **40** and ^{1}H NMR and ^{13}C NMR spectra of many compounds including *ent*-gelsedine. This material is available free of charge via the Internet at http://pubs.acs.org.

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