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A FORMAL TOTAL SYNTHESIS OF SECURININE *VIA* AN INTRAMOLECULAR [4+2] CYCLOADDITION REACTION†

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Abstract – An intramolecular Diels-Alder reaction of the enol ester derived from 2-acetylpyridine and sorbic anhydride gave the cycloaddition product, stereoselectively, which was further converted into the key intermediate for the synthesis of securinine.

Securinine,[1] a member of the Securinega family of alkaloids having a tetracyclic indolizidine skeleton with an α,β-unsaturated γ-lactone, was originally isolated from *Securinega suffruticasa*,[2] and its structure was determined by chemical and spectroscopic studies,[3,4] and also by X-Ray crystallographic analysis[5] as shown in Figure 1.

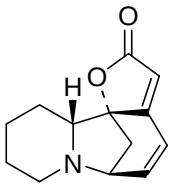


Figure 1. The structure of securinine.

Since this alkaloid has been shown to exhibit a stereospecific GABAA receptor antagonist activity, a number of syntheses and synthetic approaches were developed with the hope of understanding the shape

of the GABAA receptor site.[6] To date, only two total syntheses of securinine have been reported.[7] The first total synthesis of securinine was published by Horii and co-workers in 1967,[7a] where cyclohexane-1,2-dione was employed as the A-ring precursor and 2-lithiopyridine was introduced as the C-ring moiety. Although a number of synthetic approaches to this alkaloid were developed after Horii's synthesis, most of them could not reach to its total synthesis. Very recently, a concise total synthesis of securinine was achieved by using a ring closing metathesis leading to the construction of the A-ring, as a key reaction by Liras and co-workers.[7b] Due to the attractive biological activity and also its unique structural feature, we are also interested in developing a novel strategy for the synthesis of securinine, in which we planned to utilize an intramolecular Diels-Alder reaction of an enol ester to construct the A and D rings in one-step.[8] Our retrosynthetic strategy was depicted in Figure 2.[9]

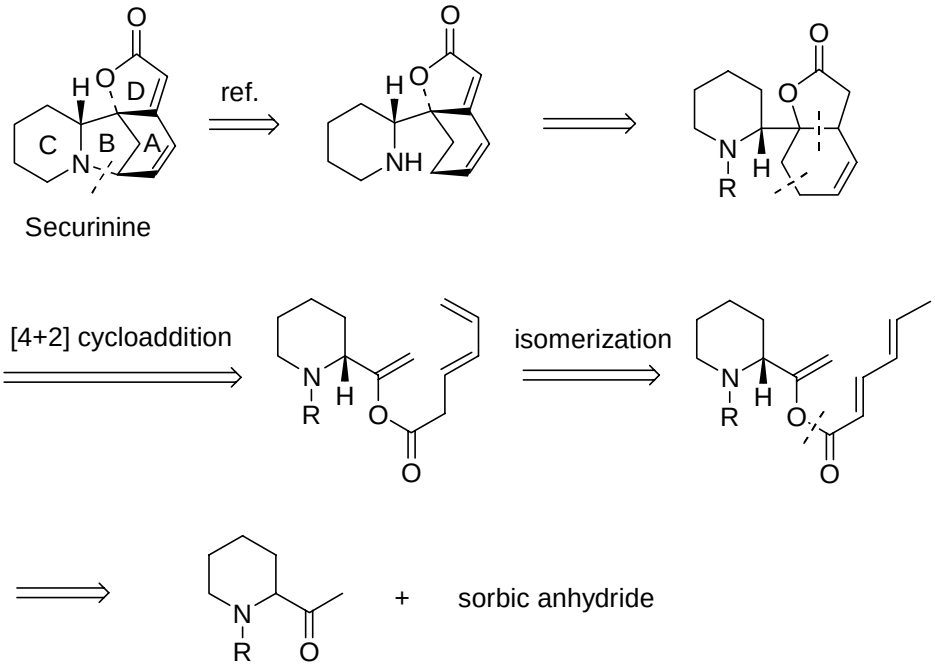
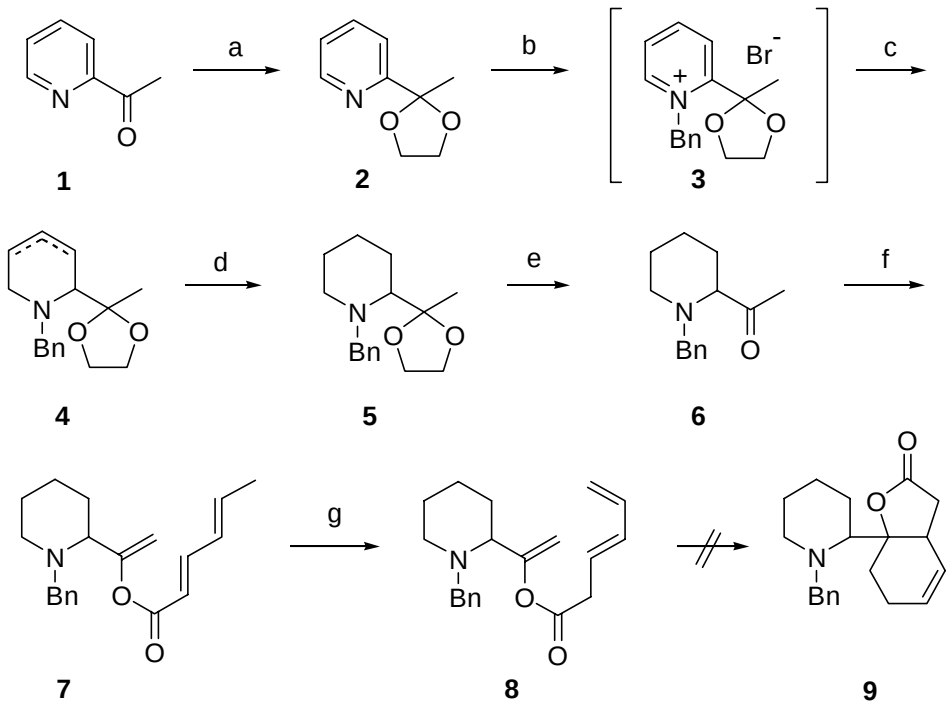


Figure 2. Retrosynthesis for securinine.

Thus, we investigated the preparation of the enol ester (**8**), a precursor for Diels-Alder reaction, as follows.

The ketal (**2**), derived from 2-acetylpyridine (**1**) and ethylene glycol, was alkylated with benzyl bromide in

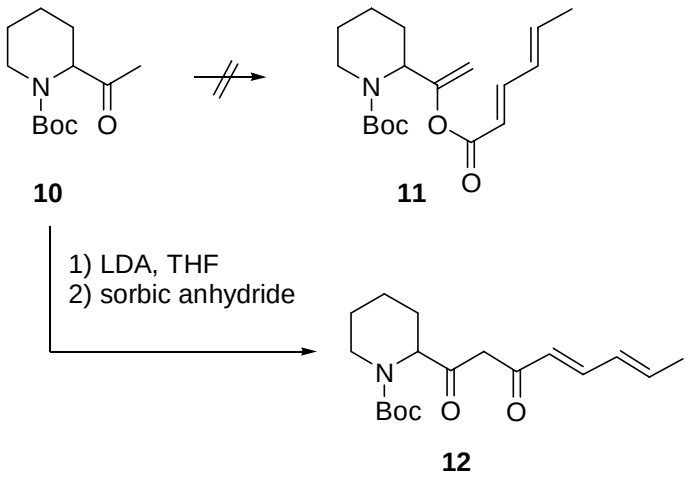
acetonitrile to afford the quaternary salt, which on successive reduction with sodium borohydride, then over platinum oxide under an atmospheric pressure of hydrogen gave the piperidine derivative (**5**). After removal of the ketal group of **5** by acid treatment, the resulting acetyl compound (**6**) was treated with sorbic anhydride in the presence of lithium hexamethyldisilazide in THF to give the conjugated enol ester (**7**). Deconjugation reaction of **7** was achieved by treatment with lithium hexamethyldisilazide, followed by protonation with acetic acid[10] to provide the enol ester (**8**) (Scheme 1).



Scheme 1. a) $HO(CH_2)_2OH$, *p*-TsOH, benzene; b) BnBr, MeCN; c) $NaBH_4$, MeOH; d) H_2, PtO_2, EtOAc; e) aq. TFA; f) LDA, then sorbic anhydride, THF; g) LiHMDS, then AcOH, THF-HMPA.

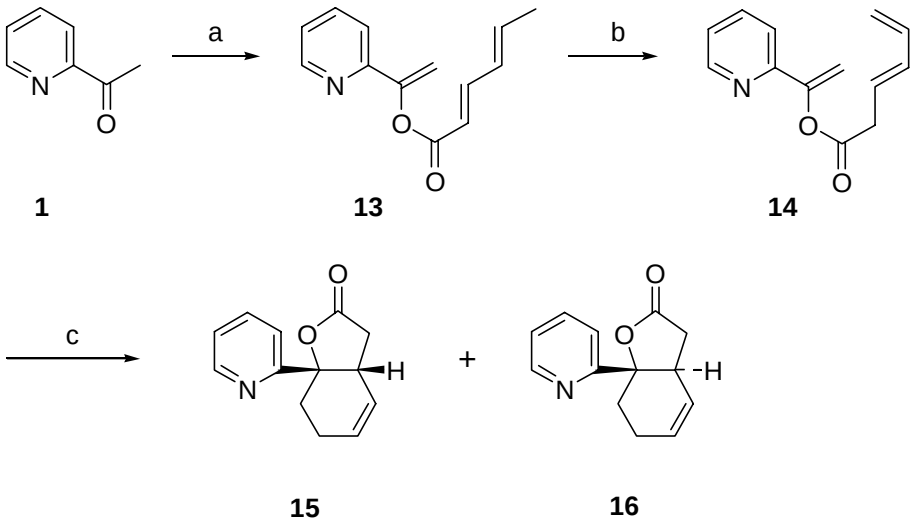
Attempted Diels-Alder reaction of **8**, however, afforded none of the desired product under the various reaction conditions, unfortunately. Although the similar synthetic approach was applied to 1-*tert*-butoxycarbonyl-2-acetylpiperidine[11] to synthesize an enol ester, the *C*-acylated product (**12**) was only isolated (Scheme 2).

We therefore decided to use a pyridine derivative (**14**) instead of a piperidine derivative for an intramolecular cycloaddition reaction, although a stereoselective reduction of the pyridine ring would be required to synthesize the target molecule, at a later stage of this synthesis.



Scheme 2.

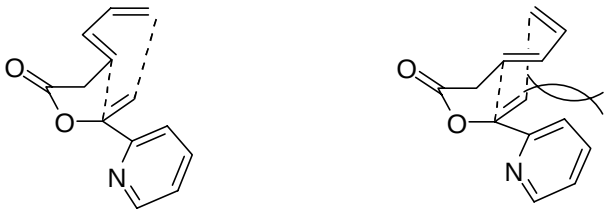
Again, treatment of 2-acetylpyridine with sorbic anhydride in the presence of lithium hexamethyldisilazide in THF gave the conjugated enol ester (**13**), whose deconjugation was achieved by adopting the procedure as described above[10] to afford the precursor for Diels-Alder reaction. Heating of **14** in toluene at 180 °C in a sealed tube for 12 h gave the cycloaddition products (**15** and **16**) in 70 and 8% yields, respectively (Scheme 3).



Scheme 3. a) LDA, then sorbic anhydride, THF; b) LiHMDS, then AcOH, THF-HMPA; c) toluene, 180ºC in a sealed tube.

Although the stereochemistry of the products could not be determined at this stage, the major product was

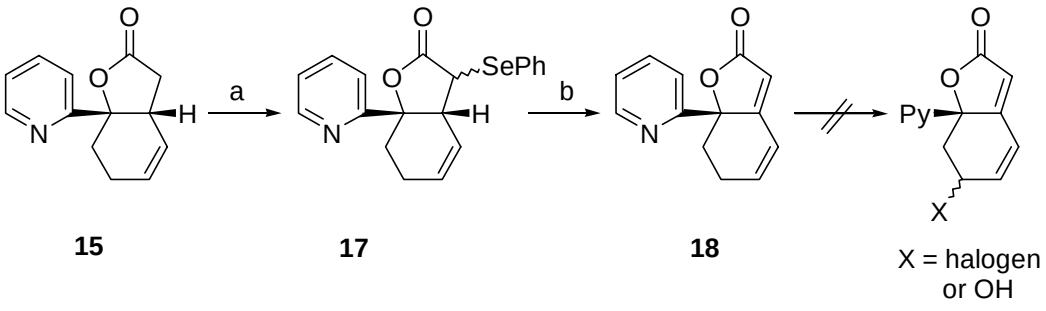
assumed to have *cis* configuration based on the examination of the transition states as shown in Figure 3. In the *endo*-transition, the steric repulsion between the pyridine ring and the diene moiety was observed. On the contrary, none of such steric repulsion could be observed in the *exo*-transition state, which leads to the *cis*-fused compound.



exo-TS *endo*-TS

Figure 3. Transition states for the cycloaddition.

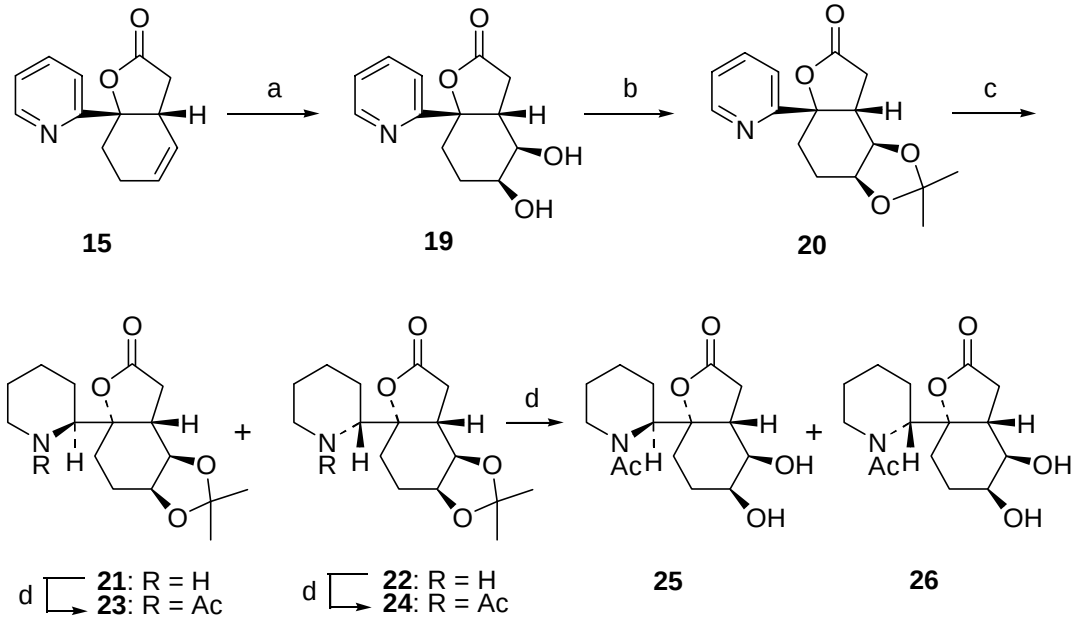
Since we could succeed in the synthesis of the rings A and D unit in one-step by an intramolecular cycloaddition reaction, our attention was focused on the construction of the basic skeleton for securinine according to the synthetic path as shown in Figure 2. Treatment of the major cycloadduct (**15**) with phenylselenenyl chloride in the presence of LDA afforded the selenide (**17**), which on oxidation with 30% hydrogen peroxide in the presence of sodium hydrogen carbonate in ethyl acetate-THF (1:1) gave the conjugated olefin (**18**) (Scheme 4).



Scheme 4. a) LDA, then PhSeCl, THF; b) 30% H_2O_2, EtOAc-THF, $NaHCO_3$.

Attempted allylic oxidation with selenium dioxide or allylic bromination with *N*-bromosuccinamide,

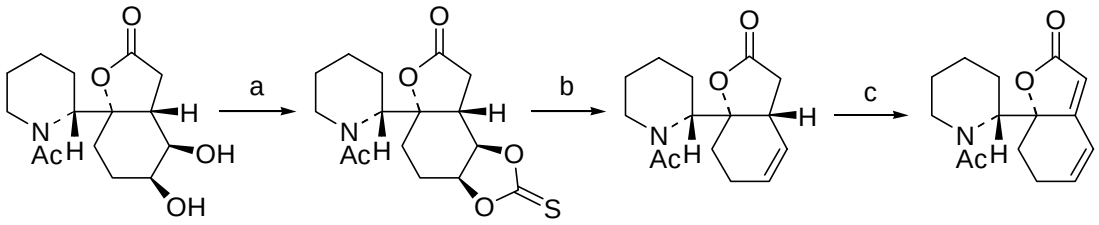
however, gave none of the desired product, unfortunately. In order to accomplish the synthesis of securinine, a stereoselective reduction of the pyridine ring was, therefore, investigated prior to the introduction of the diene system. The olefin moiety of **15** was protected as the acetonide (**20**) prior to the reduction of the pyridine ring by dihydroxylation, followed by acetonization of the diol (**19**). Catalytic hydrogenation of **20** over platinum oxide under an atmospheric pressure of hydrogen furnished the piperidine derivatives (**21** and **22**), which on acetylation with acetic anhydride, gave the inseparable acetonides (**23** and **24**) in a ratio of *ca.* 2:3, respectively, in 91% yield from **20**. Acid hydrolysis of the mixture gave the diols, which were separated by column chromatography on silica gel to provide **25** and **26** in 55 and 36% yields, respectively. The structure of the later compound (**26**) was determined by X-Ray analysis unambiguously confirming the stereochemistry of the cycloadduct to be *cis* as proposed (Figure 4). Although the expected high stereoselectivity for the catalytic reduction of the pyridine ring in **20** could not be obtained, unfortunately, we used the major compound in further conversion into the key intermediate for the synthesis of securinine (Scheme 5).



Scheme 5. a) OsO_4, NMO, *tert*-BuOH; b) 2,2-dimethoxypropane, CSA, DMF; c) H_2, PtO_2, AcOH; d) Ac_2O, Py, DMAP; d) 1N HCl, THF.

Treatment of the diol (**26**) with thiocarbonyldiimidazole afforded the thionocarbonate (**27**) in 85% yield.

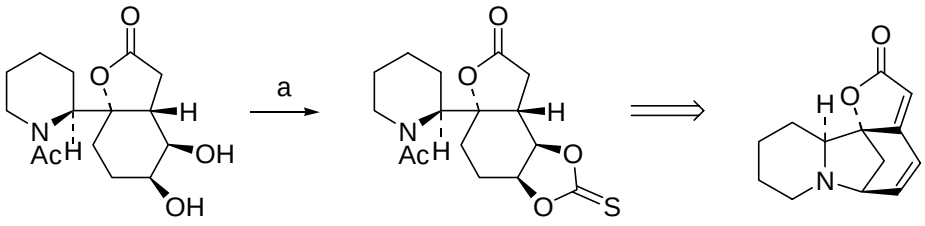
Reductive deoxygenation of **27** with bis(1,5-cyclooctadiene)nickel(0) [$Ni(COD)_2$],[12] provided the olefin (**28**), mp 138°C, in 90% yield. Finally, the diene system was introduced by phenylselenylation of **28** in the presence of lithium diisopropylamide, followed by oxidative elimination of the selenide (Scheme 6). Since the compound (**29**) was already converted into securinine by Horii and co-workers,[7a] this synthesis constitutes its formal synthesis.



26 **27** **28** **29**

Scheme 6. a) 1,1'-thiocarbonyldiimidazole, toluene; b) $Ni(COD)_2$, DMF; c) LDA, PhSeCl, THF, then 30% H_2O_2, EtOAc-THF, $NaHCO_3$.

As means to confirm the stereochemistry of the minor reduction product (**25**), it was also converted into thionocarbonate (**30**) by employing the same procedure as for the synthesis of **27** (Scheme 7).



25 **30**

Scheme 7. a) 1,1'-thiocarbonyldiimidazole, toluene.

Again, X-Ray crystallographic analysis of **30** showed this compound to be a diastereoisomer of **27**, which might be a potential intermediate for the synthesis of allosecurinine (Figure 5).

In summary, we could achieve a formal total synthesis of securinine by using an intramolecular [4+2] cycloaddition reaction of the enol ester as a key step. Although the conversion of **29** to securinine

proceeded in quite low yield in the literature, the intramolecular cycloaddition reaction of enol ester developed here would be a useful synthetic strategy for the synthesis of polycyclic natural products having a lactone ring in their molecules in relatively short steps.

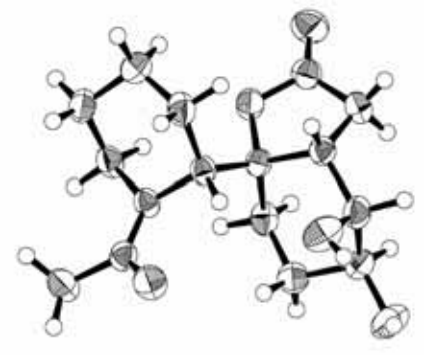


Figure 4. ORTEP drawing for **26**.

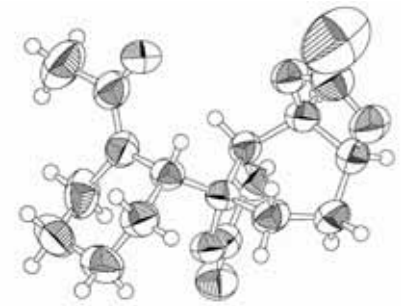


Figure 5. ORTEP drawing for **30**.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in $CDCl_3$, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

2,4-Hexadienoic Acid Anhydride (Sorbic Anhydride): A solution of sorbic acid (8.4 g, 75 mmol) and Et_3N (10.5 mL, 75 mmol) in CH_2Cl_2 (500 mL) was stirred for 30 min at 0 °C. To this solution was added diphenyl phosphorochloride (7.9 mL, 37.5 mmol) at the same temperature, and the resulting mixture was stirred for further 10 h at rt. After treatment with saturated aq. NH_4Cl solution, the mixture was extracted with CH_2Cl_2, and the extract was washed with brine and dried (Na_2SO_4), and concentrated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (20:1) gave sorbic anhydride (5.7 g, 73%) as a colorless oil; IR: νmax 1780 and 1660 cm^{-1}; ^{1}H-NMR: δ 1.82 (6H,

m, 2×Me), 5.74 (2H, d, *J*=15.3 Hz, 2×2-CH), 6.27 (4H, m, 2×4-CH and 2×5-CH), 7.30 (2H, m, 2×3-CH).

2-(1',1'-Ethylenedioxy)ethylpyridine (2): A stirred solution of 2-acetylpyridine (**1**) (20 g, 165 mmol) and ethylene glycol (27.6 mL, 495 mmol) in benzene (150 mL) was heated at reflux in the presence of *p*-TsOH (6.28 g, 33 mmol) for 10 h. After cooling to rt, the mixture was diluted with EtOAc, and washed with saturated aq. $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (10:1) gave the ketal (**2**) (25 g, 92%) as a colorless oil; bp 85-87 °C/2 mmHg; IR: νmax 1020 cm^{-1}; ^{1}H-NMR: δ 1.74 (3H, s, Me), 3.85-3.95 and 4.08-4.13 (each 2H, each m, OCH_2CH_2O), 7.21 (1H, ddd, *J*=1.2, 4.9 and 7.3 Hz, 5-CH), 7.55 (1H, dt, *J*=1.2 and 7.9 Hz, 3-CH), 7.69 (1H, ddd, *J*=1.8, 7.3 and 7.9 Hz, 4-CH), 8.64 (1H, dd, *J*=1.8 and 4.9 Hz, 6-CH); HRMS *m/z* calcd for $C_9H_{12}NO_2$ (M^++1): 166.0868. Found: 166.0863.

1-Benzyl-2-(1',1'-ethylenedioxy)ethylpyridine (5): A stirred solution of **2** (25 g, 151.5 mmol) and benzyl bromide (180 mL, 1.52 mol) in MeCN (250 mL) was heated at 100 °C for 4 days. After evaporation of the solvent, the residue was dissolved into MeOH (250 mL), and $NaBH_4$ (22.9 g, 606 mmol) was added portionwise to this solution at 0 °C. The resulting mixture was stirred at rt for 4 days, and then treated with saturated aq. NH_4Cl solution. After removal of the solvent, the residue was extracted with EtOAc, and the extract was washed with brine, and dried (Na_2SO_4). Evaporation of the solvent gave the residue, which was again dissolved into EtOAc. The organic layer was treated with 10% $KHSO_4$ solution, and the aqueous layer was basified with 10% NaOH solution, and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane gave the ketal (16.9 g, 51%) as a mixture of olefinic isomers, which was used in next step without further separation. A solution of the mixture obtained above in EtOAc was hydrogenated over PtO_2 (542 mg) under an atmospheric pressure of hydrogen for 1 h. After removal of the insoluble material by filtration, the filtrate was concentrated to give the residue, which was purified by column chromatography on silica gel to provide the piperidine derivative (**5**) (14.9 g, 87%) as a colorless oil; bp 137 °C/2 mmHg; IR: νmax 1162 cm^{-1}; ^{1}H-NMR: δ 1.42 (3H, s, Me), 1.33-1.50 (4H, m, 4- and 5-CH_2), 1.77-2.05 (3H, m, 3-CH_2 and 6-C*H*H), 2.41 (1H, dd, *J*=3.1 and 10.4 Hz, 6-CH*H*), 2.86 (1H, m, 2-CH), 3.23 and 4.46 (each 1H, each d, *J*=14.7 Hz, CH_2Ph), 3.85-3.98 (4H, m, OCH_2CH_2O), 7.16-7.36

(5H, m, aromatic protons); HRMS *m/z* calcd for $C_{16}H_{23}NO_2$ (M^+): 261.1729. Found: 261.1729. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.82; N, 5.37. Found: C, 73.43; H, 8.86; N, 5.36.

2-Acetyl-1-benzylpiperidine (6): A solution of the ketal (**5**) (13.68 g, 52.4 mmol) in CF_3CO_2H-H_2O (100 mL; 9:1, v/v) was stirred at ambient temperature for 2 days. After evaporation of the solvent, the residue was treated with 25% NH_4OH at 0 °C, and extracted with $CHCl_3$. The extract was washed with brine and dried (Na_2SO_4), and concentrated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (20:1) gave **6** (9.73 g, 91%) as a colorless oil; bp 140 °C/2 mmHg; IR: νmax 1712 cm^{-1}; ^{1}H-NMR: δ 1.21-1.80 (6H, m, 3-, 4- and 5-CH_2), 1.91 (1H, ddd, *J*=3.7, 11.0 and 11.6 Hz, 6-C*H*H), 2.25 (3H, s, Me), 2.85-2.94 (2H, m, 2-CH and 6-CH*H*), 3.18 and 3.65 (each 1H, each d, *J*=14.0 Hz, CH_2Ph), 7.21-7.33 (5H, m, aromatic protons); HRMS *m/z* calcd for $C_{14}H_{19}NO$ (M^+): 217.1467. Found: 217.1461.

1'-[2"-(*N*-Benzylpiperidyl)]ethenyl 2,4-Hexadienoate (7): To a stirred solution of LDA [prepared from diisopropylamine (0.34 mL, 2.4 mmol) and *n*-BuLi (1.45 mL of 1.65M hexane solution, 2.4 mmol)] in THF (7.5 mL) was added HMPA (0.43 mL, 2.46 mmol) at –78 °C. To this solution was added a solution of **6** (300 mg, 1.33 mmol) in THF (5 mL), and the resulting mixture was stirred for further 2 h at the same temperature. A solution of sorbic anhydride (495 mg, 2.4 mmol) in THF (10 mL) was added slowly to the solution and the whole mixture was stirred for 1 h at the same temperature. After treatment with saturated aq. NH_4Cl solution, the mixture was extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (20:1) gave the enol ester (**7**) (312 mg, 75%) as a colorless oil; bp 190 °C/2 mmHg; IR: νmax 1732, 1645, 1261, 1125, and 999 cm^{-1}; ^{1}H-NMR: δ 1.22-1.92 (7H, m, 3"-, 4"-, 5"-CH_2 and 6"-C*H*H), 1.88 (3H, d, *J*=5.5 Hz, Me), 2.75 (1H, dd, *J*=3.1 and 10.4 Hz, 2"-CH), 2.87 (1H, m, 6"-CH*H*), 2.98 and 4.35 (each 1H, each d, *J*=14.0 Hz, CH_2Ph), 4.96 and 5.14 (each 1H, each d, *J*=1.5 Hz, 2'-CH_2), 5.89 (1H, d, *J*=15.3 Hz, 2-CH), 6.11-6.31 (2H, m, 4- and 5-CH), 7.18-7.39 (6H, m, 3-CH and aromatic protons); HRMS *m/z* calcd for $C_{20}H_{25}NO_2$ (M^+): 311.185. Found: 311.1885.

1'-[2"-(*N*-Benzylpiperidyl)]ethenyl 3,5-Hexadienoate (8): To a stirred solution of LiHMDS (1.05 mL of 1.0M hexane solution, 1.05 mmol) and HMPA (0.27 mL, 1.54 mmol) in THF (7.5 mL) was added a

solution of the conjugated enol ester (**7**) (280 mg, 0.90 mmol) in THF (1.75 mL) at –78 °C, and the resulting mixture was stirred for further 2 h at the same temperature. The reaction was quenched by addition of AcOH-H_2O (1:2, v/v)(3 mL), and the mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$ gave the deconjugated enol ester (**8**) (280 mg, 100%) as a colorless oil; IR: νmax 1768 and 1125 cm^{-1}; ^{1}H-NMR: δ 1.18-1.90 (7H, m, 3”-, 4”-, 5”-CH_2 and 6”-C*H*H), 2.72 (1H, dd, *J*=3.1 and 10.4 Hz, 2”-CH), 2.82-2.89 (1H, m, 6”-CH*H*), 2.94 and 4.31 (each 1H, each d, *J*=13.4 Hz, CH_2Ph), 3.27 (2H, br d, *J*=7.0 Hz, 2-CH_2), 4.94 and 5.13 (each 1H, each d, *J*=1.8 Hz, 2’-CH_2), 5.09 (1H, d, *J*=10.4 Hz, 6-C*H*H), 5.19 (1H, d, *J*=15.9 Hz, 6-CH*H*), 5.84 (1H, dt, *J*=7.0 and 14.7 Hz, 3-CH), 6.17-6.40 (2H, m, 4- and 5-CH), 7.22-7.29 (5H, m, aromatic protons).

1’-(2”-Pyridyl)ethenyl 2,4-Hexadienoate (13): The enol ester was prepared from 2-acetylpyridine (**1**) (1.1 mL, 10 mmol), sorbic anhydride (3.7 g, 18 mmol), and LDA (18 mmol) by using the same procedure as for the preparation of **7** to give the product (**13**) (1.01 g, 47%) as a pale yellowish oil; IR: νmax 1725 and 1705 cm^{-1}; ^{1}H-NMR: δ 1.90 (3H, d, *J*=5.5 Hz, 6-Me), 5.25 (1H, d, *J*=1.8 Hz, 2’-C*H*H), 6.00 (1H, d, *J*=15.3 Hz, 2-CH), 6.11 (1H, d, *J*=1.8 Hz, 2’-CH*H*), 6.18-6.34 (2H, m, 4- and 5-CH), 7.20 (1H, m, 5”-CH), 7.37-7.48 (2H, m, 3-CH and 3”-CH), 7.66 (1H, dt, *J*=1.8 and 7.9 Hz, 4”-CH), 8.59 (1H, dd, *J*=1.8 and 4.9 Hz, 6”-CH); HRMS *m/z* calcd for $C_{13}H_{13}NO_2$ (M^+): 215.0933. Found: 215.0939.

1’-(2”-Pyridyl)ethenyl 3,5-Hexadienoate (14): Deconjugation of **13** (1.72 g, 8 mmol) was carried out by using the same procedure as for the preparation of **8** to give the ester (**14**) (1.4 g, 81%) as a pale yellowish oil; IR: νmax 1770 and 1745 cm^{-1}; ^{1}H-NMR: δ 3.40 (2H, d, *J*=7.3 Hz, 2-CH_2), 5.11 (1H, ddd, *J*=0.8, 1.8 and 9.9 Hz, 6-C*H*H), 5.22 (1H, dt, *J*=0.8 and 16.2 Hz, 6-CH*H*), 5.24 (1H, d, *J*=1.8 Hz, 2’-C*H*H), 5.90 (1H, dt, *J*=7.3 and 14.7 Hz, 3-CH), 6.04 (1H, d, *J*=1.8 Hz, 2’-CH*H*), 6.21-6.46 (2H, m, 4- and 5-CH), 7.20 (1H, ddd, *J*=1.2, 4.8 and 7.6 Hz, 5”-CH), 7.38 (1H, ddd, *J*=1.0, 1.2 and 7.9 Hz, 3”-CH), 7.66 (1H, ddd, *J*=1.8, 7.6 and 7.9 Hz, 4”-CH), 8.57 (1H, ddd, *J*=1.0, 1.8 and 4.8 Hz, 6”-CH); HRMS *m/z* calcd for $C_{13}H_{13}NO_2$ (M^+): 215.0930. Found: 215.0937.

7-Oxa-6-(2’-pyridyl)bicyclo[4.3.0]non-2-en-8-ones (15 and 16): A solution of the enol ester (**14**) (860 mg, 4 mmol) in toluene (50 mL) in a sealed tube was heated at 180 °C for 12 h. After evaporation of the

solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (10:1) gave the *cis* isomer (**15**) (593 mg, 69%) as colorless prisms; mp 66-67.5 °C (EtOAc-Et_2O-hexane=1:2:4); IR: νmax 1770 cm^{-1}; ^{1}H-NMR: δ 2.07-2.41 (5H, m, 4-, 5-CH_2 and 9-C*H*H), 2.57 (1H, dd, *J*=8.4 and 17.3 Hz, 9-CH*H*), 3.69 (1H, m, 1-CH), 5.61 (1H, m, 3-CH), 5.94 (1H, m, 2-CH), 7.24 (1H, ddd, *J*=1.2, 4.8 and 7.9 Hz, 5'-CH), 7.59 (1H, dt, *J*=1.8 and 7.9 Hz, 3'-CH), 7.74 (1H, dt, *J*=1.8 and 7.9 Hz, 4'-CH), 8.60 (1H, ddd, *J*=1.0, 1.8 and 4.8 Hz, 6'-CH); HRMS *m/z* calcd for $C_{13}H_{13}NO_2$ (M^+): 215.0931. Found: 215.0938. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.37; H, 6.11; N, 6.45.

Further elution with the same solvent gave the trans isomer (**16**) (59 mg, 8%) as a colorless oil; IR: νmax 1770 cm^{-1}; ^{1}H-NMR: δ 2.07-2.62 (6H, m, 4-, 5- and 9-CH_2), 3.40 (1H, m, 1-CH), 5.46 (1H, m, 2-CH), 6.02 (1H, m, 3-CH), 7.22 (1H, m, 5'-CH), 7.49 (1H, d, *J*=7.9 Hz, 3'-CH), 7.69 (1H, dt, *J*=1.8 and 7.9 Hz, 4'-CH), 8.52 (1H, dd, *J*=1.8 and 4.9 Hz, 6'-CH).

7-Oxa-9-phenylselenenyl-6-(2'-pyridyl)bicyclo[4.3.0]non-2-en-8-one (17): To a stirred solution of LDA [prepared from diisopropylamine (1.4 mL, 10 mmol) and 1.62 M hexane solution of *n*-butyllithium (6.2 mL, 10 mmol)] in THF (20 mL) in the presence of HMPA (1 mL) was added a solution of the lactone (**15**) (860 mg, 4 mmol) in THF (10 mL) at –78 °C, and the resulting solution was stirred for further 1 h at the same temperature. To this mixture was added a solution of phenylselenenyl chloride (1.5 g, 8 mmol) in THF (15 mL) at –78 °C and the whole mixture was stirred for further 1 h. After treatment with brine, the mixture was extracted with EtOAc, and the extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (10:1) gave the selenide (**17**) (1.26 g, 85%) as white solid; mp 143-144 °C; IR: νmax 1765 cm^{-1}; ^{1}H-NMR: δ 2.03-2.53 (5H, m, 4-, 5-CH_2 and 9-CH), 3.61-3.93 (1H, m, 1-CH), 5.60-5.79 (1H, m, 2-CH), 5.94-6.06 (1H, m, 3-CH), 7.09-7.81 (8H, m, aromatic protons), 8.36-8.61 (1H, m, 6'-CH); Anal. Calcd for $C_{19}H_{17}NO_2Se$: C, 61.63; H, 4.63; N, 3.78. Found: C, 61.67; H, 4.70; N, 3.77.

7-Oxa-6-(2'-pyridyl)bicyclo[4.3.0]nona-2,9-dien-8-one (18): To a stirred solution of the selenide (**17**) (370 mg, 1 mmol) in EtOAc-THF (1:1, 10 mL) in the presence of $NaHCO_3$ (840 mg, 10 mmol) was added 30% H_2O_2 (5.7 mL, 50 mmol) at 0 °C, and the mixture was stirred for further 30 min at the same

temperature. After treatment with saturated aq. $Na_2S_2O_3$ solution, the mixture was extracted with ether and the ethereal layer was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (5:1) gave the olefin (**18**) (202 mg, 95%) as white needles; mp 110-110.5 °C (hexane-EtOAc); IR: νmax 1740 and 1640 cm^{-1}; ^{1}H-NMR: δ 2.15-2.25 (2H, m, 4-*H*H and 5-C*H*H), 2.44 (1H, m, 4-CH*H*), 5.61 (1H, m, 5-CH*H*), 5.89 (1H, s, 9-CH), 6.21 (1H, m, 2-CH), 6.66 (1H, m, 3-CH), 7.31 (2H, m, 3'- and 5'-CH), 7.69 (1H, m, 4'-CH), 8.58 (1H, m, 6'-CH); HRMS *m/z* calcd for $C_{13}H_{11}NO_2$ (M^+): 213.0792. Found: 213.0791. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.33; H, 5.36; N, 6.49.

2,3-Dihydroxy-7-oxa-6-(2'-pyridyl)bicyclo[4.3.0]nonan-8-one (19): To a stirred solution of **15** (540 mg, 2.51 mmol) in *tert*-BuOH-H_2O (1:2, 15 mL) were added NMO (883 mg, 7.53 mmol) and a solution of OsO_4 in *tert*-BuOH (5 mg/mL; 3.8 mL, 0.75 mmol) at ambient temperature, and the resulting solution was stirred for further 6 h. To this solution was added $NaHSO_3$ (1.31 g, 12.6 mmol) and the mixture was stirred for 30 min. After treatment with brine, the mixture was extracted with EtOAc, and the extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with EtOAc gave the diol (**19**) (625 mg, 100%) as a colorless oil; IR: νmax 3440 and 1778 cm^{-1}; ^{1}H-NMR: δ 1.57 (1H, m, 5-C*H*H), 1.73 (1H, m, 5-CH*H*), 2.01 (1H, m, 4-C*H*H), 2.14 (1H, m, 4-CH*H*), 2.68 (1H, dd, *J*=12.2 and 17.6 Hz, 9-C*H*H), 2.78 (1H, dd, *J*=9.1 and 17.6 Hz, 9-CH*H*), 2.84 (1H, d, *J*=9.9 Hz, OH), 3.20 (1H, m, 1-CH), 3.87 (1H, m, 3-CH), 3.98 (1H, m, 2-CH), 7.15 (1H, d, *J*=9.4 Hz, OH), 7.36 (1H, ddd, *J*=1.2, 5.0 and 7.6 Hz, 5'-CH), 7.69 (1H, ddd, *J*=1.0, 1.2 and 7.9 Hz, 3'-CH), 7.86 (1H, ddd, *J*=1.6, 7.6 and 7.9 Hz, 4'-CH), 8.54 (1H, ddd, *J*=1.0, 1.6 and 5.0 Hz, 6'-CH); ^{13}C-NMR: δ 24.7, 31.6, 33.1, 43.4, 67.4, 70.1, 88.0, 120.1, 122.9, 137.7, 147.5, 160.5, 175.8; HRMS *m/z* calcd for $C_{13}H_{15}NO_4$ (M^+): 249.1001. Found: 249.0975.

2,3-Isopropylidenedioxy-7-oxa-6-(2'-pyridyl)bicyclo[4.3.0]nonan-8-one (20): A solution of the diol (**19**) (109 mg, 0.44 mmol) and 2,2-dimethoxypropane (0.08 mL, 0.66 mmol) in DMF (1.5 mL) in the presence of CSA (0.51 mg, 0.22 mmol) was stirred at rt for 12 h. The reaction was quenched by addition of saturated aq. $NaHCO_3$ solution and the mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column

chromatography on silica gel. Elution with hexane-EtOAc (3:1) gave the acetonide (**20**) (122 mg, 96%) as colorless prisms; mp 95-95.5 °C ($CHCl_3$-hexane); IR: νmax 1778 cm^{-1}; ^{1}H-NMR: δ 1.38 and 1.53 (each 3H, each s, Me), 1.88-2.02 (3H, m, 4-C*H*H and 5-CH_2), 2.05-2.33 (1H, m, 4-CH*H*), 2.46 (1H, dd, *J*=4.0 and 18.1 Hz, 9-C*H*H), 2.73 (1H, dd, *J*=9.6 and 18.1 Hz, 9-CH*H*), 3.47 (1H, ddd, *J*=4.0, 5.9 and 9.6 Hz, 1-CH), 4.21 (1H, dd, *J*=5.9 and 6.3 Hz, 2-CH), 4.49 (1H, m, 3-CH), 7.23 (1H, ddd, *J*=1.0, 4.6 and 7.3 Hz, 5'-CH), 7.52 (1H, dd, *J*=1.0 and 7.6 Hz, 3'-CH), 7.72 (1H, ddd, *J*=1.6, 7.3 and 7.6 Hz, 4'-CH), 8.61 (1H, dd, *J*=1.6 and 4.6 Hz, 6'-CH); ^{13}C-NMR: δ 22.9, 24.5, 26.8, 28.7, 33.3, 39.7, 71.5, 75.5, 88.0, 108.3, 119.2, 122.5, 136.6, 149.0, 161.5, 175.4; HRMS *m/z* calcd for $C_{16}H_{19}NO_4$ (M^+): 289.1314. Found: 289.1336. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.15; H, 6.48; N, 4.74.

2,3-Isopropylidenedioxy-7-oxa-6-(2'-piperidyl)bicyclo[4.3.0]nonan-8-ones (21 and 22): A suspension of **20** (476 mg, 1.65 mmol) and PtO_2 (10 mg) in AcOH (5 mL) was stirred at rt for 2 h under an atmospheric pressure of hydrogen. After filtration of the catalyst, the filtrate was concentrated to leave the residue, which was basified with saturated aq. $NaHCO_3$ solution, and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$-MeOH (19:1) gave the inseparable piperidine derivatives (**21** and **22**) (474 mg, 98%) as colorless oil; IR: νmax 1770 and 1260 cm^{-1}; ^{1}H-NMR: δ 1.22-1.87 (10H, m, 4-, 5-, 3'-, 4'-CH_2, 5'-C*H*H and NH), 1.32 and 1.47 (each 3H, each s, Me), 2.06 (1H, m, 5'-CH*H*), 2.23 (1H, dd, *J*=8.1 and 18.7 Hz, 9-C*H*H), 2.62 (2H, m, 6'-CH_2), 2.89 (1H, dd, *J*=12.3 and 18.7 Hz, 9-CH*H*), 3.08 (1H, m, 2'-CH), 3.15 (1H, ddd, *J*=2.1, 8.1 and 12.3 Hz, 1-CH), 4.32 (1H, dd, *J*=2.1 and 7.3 Hz, 2-CH), 4.43 (1H, m, 3-CH); ^{13}C-NMR: δ 23.0, 23.3, 23.7, 24.4, 25.7, 25.9, 33.7, 33.8, 47.8, 63.2, 70.8, 73.7, 90.3, 107.4, 175.0; HRMS *m/z* calcd for $C_{16}H_{25}NO_4$ (M^+): 295.1783. Found: 295.1791.

2,3-Isopropylidenedioxy-7-oxa-6-[2'-(*N*-acetyl)piperidyl]bicyclo[4.3.0]nonan-8-ones (23 and 24): A solution of the amines (**21** and **22**) (440 mg, 1.49 mmol), 4-dimethylaminopyridine (18 mg) and Ac_2O (6 mL) in pyridine (3 mL) was stirred at ambient temperature for 1 h. After treatment with brine, the mixture was extracted with EtOAc, and the extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$-MeOH (19:1) gave the acetate (**23** and **24**) (467 mg, 93%) as colorless needles; mp 152-152.5 °C

($CHCl_3$-hexane); IR: νmax 1770 and 1634 cm^{-1}; ^{1}H-NMR: δ 1.26-2.28 (10.4H, m, 4-, 5-, 3'-, 4'- and 5'-CH_2 for the mixture, and 9-C*H*H for **23**), 1.32 and 1.59 (3H, s, Me for the mixture), 2.14 (1.8H, s, Ac for **24**), 2.18 (1.2H, s, Ac for **23**), 2.25 (0.6H, dd, *J*=9.2 and 18.5 Hz, 9-C*H*H for **24**), 2.69 (0.4H, dd, *J*=11.9 and 18.5 Hz, 9-CH*H* for **23**), 2.80 (0.6H, dd, *J*=11.9 and 18.7 Hz, 9-CH*H* for **24**), 2.95 (0.6H, m, 1-CH for **24**), 3.16 (0.4H, m, 1-CH for **23**), 3.34-3.49 (1H, m, 6'-C*H*H for the mixture), 3.62-3.73 (1H, m, 6'-CH*H* for the mixture), 4.37-4.70 (2H, m, 2- and 3-CH for the mixture), 4.79 (0.4H, dd, *J*=5.6 and 5.9 Hz, 2'-CH for **23**), 4.86 (0.6H, m, 2'-CH for **24**); ^{13}C-NMR: δ 20.4, 21.8, 22.8, 23.2, 24.0, 24.7, 25.4, 25.9, 32.1, 36.8, 43.4, 54.5, 70.6, 73.7, 91.0, 108.3, 169.8, 174.7; HRMS *m/z* calcd for $C_{17}H_{24}NO_5$ (M^+-15): 322.1653. Found: 322.1655.

2,3-Dihydroxy-7-oxa-6-[2'-(*N*-acetyl)piperidyl]bicyclo[4.3.0]nonan-8-ones (25 and 26): To a stirred solution of the acetates (**23** and **24**) (123 mg, 0.42 mmol) in THF (3 mL) was added 1N HCl (1 mL) at rt and the resulting solution was stirred for further 2 days at the same temperature. The solution was basified with saturated aq. $NaHCO_3$ solution, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$-MeOH (19:1) gave the diol (**26**) (59.4 mg, 55%) as colorless prisms; mp 190 °C ($CHCl_3$-EtOAc); IR: νmax 3404, 1772 and 1618 cm^{-1}; ^{1}H-NMR: δ 1.41-2.21 (10H, m, 4-, 5-, 3'-, 4'- and 5'-CH_2), 2.16 (3H, s, Ac), 2.47 (1H, dd, *J*=2.2 and 17.6 Hz, 9-C*H*H), 2.68 (1H, dd, *J*=8.9 and 17.6 Hz, 9-CH*H*), 2.93 (1H, m, 1-CH), 3.34-3.47 (3H, m, 6'-CH_2 and OH), 3.61 (1H, m, 2-CH), 3.87 (1H, m, 3-CH), 3.99 (1H, d, *J*=2.5 Hz, OH), 5.25 (1H, dd, *J*=2.5 and 4.2 Hz, 2'-CH); ^{13}C-NMR: δ 19.8, 21.8, 23.1, 24.4, 24.9, 29.0, 31.6, 42.6, 43.3, 51.2, 67.7, 70.0, 89.9, 171.0, 175.0; HRMS *m/z* calcd for $C_{15}H_{23}NO_5$ (M^+): 297.1576. Found: 297.1585. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.59; H, 7.61; N, 4.83.

Further elution with the same solvent system gave the diol (**25**) (39.2 mg, 36%) as colorless prisms; mp 178-181 °C ($CHCl_3$-EtOAc); IR: νmax 3380, 1772, 1615, 1429, 1426, 1252, and 1196 cm^{-1}; ^{1}H-NMR: δ 1.23-2.05 (9H, m, 5-, 3'-, 4'-, 5'-CH_2 and 4-C*H*H), 2.21 (3H, s, Ac), 2.26 (1H, m, 4-CH*H*), 2.49 (1H, dd, *J*=12.4 and 17.3 Hz, 9-C*H*H), 2.61 (1H, dd, *J*=8.4 and 17.3 Hz, 9-CH*H*), 2.72 (1H, m, 1-CH), 3.07 (1H, d, *J*=9.7 Hz, OH), 3.47 (1H, ddd, *J*=7.1, 10.2 and 14.5 Hz, 6'-C*H*H), 3.63 (1H, m, 6'-CH*H*), 3.78 (1H, m,

3-CH), 3.92 (1H, m, 2-CH), 4.81 (1H, dd, *J*=6.3 and 6.9 Hz, 2'-CH), 5.49 (1H, d, *J*=3.1 Hz, OH); ^{13}C-NMR: δ 18.4, 22.0, 23.3, 23.4, 24.5, 29.0, 32.1, 42.2, 43.2, 53.4, 68.0, 68.8, 88.8, 173.0, 174.1. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.56; H, 7.86; N, 4.65.

Crystal Data of 26: $C_{15}H_{23}NO_5$, *M*=297.35, monoclinic, space group *P* 2_1/n, *a*=7.406(2), *b*=20.818(2), *c*=9.688(2) Å, β=107.94(1)°, *V*=1431.21(1) Å^3, *Z*=4, *D*c=1.390 g cm^{-3}; 2111 reflections with 4.24<2*θ*<120.02° were recorded on a four-circle diffractometer using graphite-monochromated Cu-Kα radiation. Of those, 1911 with *I*>3σ(*I*) were judged as observed. The structure was solved using MALTAN88. *R*=0.0385, *R*w=0.0328.

6-[2'-(*N*-Acetyl)piperidyl]-7-oxa-2,3-thionocarbonyldioxybicyclo[4.3.0]nonan-8-one (27): A stirred solution of the diol (**26**) (443 mg, 1.49 mmol) and 1,1'-thiocarbonyldiimidazole (161 mg, 1.49 mmol) in toluene (2 mL) was heated at 110 °C for 24 h. The solution was treated with water and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$-MeOH (19:1) gave the thionocarbonate (**27**) (448 mg, 89%) as colorless prisms; mp 218-218.5 °C ($CHCl_3$); IR: νmax 1772, 1630, 1288, 1271 and 1196 cm^{-1}; ^{1}H-NMR: δ 1.51-2.17 (10H, m, 4-, 5-, 3'-, 4'- and 5'-CH_2), 2.17 (3H, s, Ac), 2.27 (1H, dd, *J*=8.6 and 19.0 Hz, 9-C*H*H), 2.98 (1H, dd, *J*=12.1 and 19.0 Hz, 9-CH*H)* 3.28-3.42 (2H, m, 1-CH and 6'-C*H*H), 3.70 (1H, m, 6'-CH*H*), 4.82 (1H, m, 2'-CH), 5.12 (1H, dd, *J*=2.5 and 8.3 Hz, 2-CH), 5.24 (1H, m, 3-CH); ^{13}C-NMR: δ 20.2, 22.1, 22.2, 22.7, 24.4, 24.9, 31.7, 35.6, 43.4, 54.4, 77.7, 79.4, 89.1, 170.9, 173.1, 190.2; HRMS *m/z* calcd for $C_{16}H_{21}NO_5S$ (M^+): 339.1140. Found: 339.1167.

6-[2'-(*N*-Acetyl)piperidyl]-7-oxabicyclo[4.3.0]non-2-en-8-one (28): A stirred solution of the thionocarbonate (**27**) (20 mg, 0.06 mmol) and $Ni(COD)_2$ (34 mg, 0.12 mmol) in DMF (1 mL) was heated at 60 °C for 3 h under argon. After the insoluble material was filtered off by filtration through the pad of Celite, the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$-MeOH (49:1) gave the olefin (**28**) (14 mg, 90%) as colorless needles; mp 138 °C (hexane-EtOAc); IR: νmax 1778, 1635, 1425 and 1205 cm^{-1}; ^{1}H-NMR: δ 1.44-2.25 (10H, m, 4-, 5-, 3'-, 4'- and 5'-CH_2), 2.25 (3H, s, Ac), 2.27 (1H, dd, *J*=8.1 and 17.6 Hz, 9-C*H*H), 2.71 (1H, dd, *J*=9.4 and 17.6 Hz, 9-CH*H*), 2.96 (1H, m, 1-CH), 3.42 (1H, ddd, *J*=4.9, 12.1 and 14.3 Hz, 6'-CH*H*), 3.62 (1H, m,

6'-CH*H*), 4.80 (1H, dd, *J*=6.1 and 6.3 Hz, 2'-CH), 5.60 (1H, m, 3-CH), 5.84 (1H, m, 2-CH); ^{13}C-NMR: δ 20.2, 21.7, 21.9, 23.4, 25.4, 28.1, 36.1, 37.6, 43.4, 50.8, 89.9, 125.4, 128.3, 175.9, 179.5; HRMS *m/z* calcd for $C_{15}H_{21}NO_3$ (M^+): 263.1521. Found: 263.1513. Anal. Calcd for $C_{15}H_{21}NO_3 \cdot 1/4H_2O$: C, 67.27; H, 8.09; N, 5.23. Found: C, 67.33; H, 8.08; N, 5.27.

6-[2'-(*N*-Acetyl)piperidyl]-7-oxabicyclo[4.3.0]nona-2,9-dien-8-one (29): To a stirred solution of LiHMDS [prepared from hexamethyldisilazane (0.35 mL, 1.65 mmol) and *n*-BuLi (1.6M solution in hexane, 0.99 mL, 1.59 mmol)] in THF (3.3 mL) were added HMPA (0.14 mL, 0.79 mmol) and a solution of the lactone (**28**) (174 mg, 0.66 mmol) in THF (1 mL) at –78 °C, and the resulting solution was stirred at the same temperature for further 1 h. To this mixture was added a solution of PhSeCl (253 mg, 1.32 mmol) in THF (1 mL) and the whole mixture was stirred at –78 °C for 1 h. The mixture was treated with brine and extracted with EtOAc. The extract was dried (Na_2SO_4), and evaporated to leave the crude selenide, which, without further purification, was used to the next step.

To a stirred solution of the selenide in CH_2Cl_2 (2.4 mL) were added pyridine (0.11 mL, 1.38 mmmol) and 30% H_2O_2 (0.09 mL, 0.76 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for further 30 min. The mixture was treated with 10% sodium thiosulfate solution, and extracted with ether. The ethereal solution was dried (Na_2SO_4), and evaporated to leave the residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (1:1) gave the unsaturated lactone (**29**) (69.1 mg, 40% from **27**) as colorless prisms; mp 162-163 °C (EtOAc-hexane); IR: νmax 1747, 1637, 1423, 1272 and 1209 cm^{-1}; ^{1}H-NMR: δ 1.41-1.85 (7H, m, 3'-, 4'-, 5'-CH_2 and 5-C*H*H), 2.20 (3H, s, Ac), 2.26-2.38 (2H, m, 4-C*H*H and 5-CH*H*), 2.95 (1H, m, 4-CH*H*), 3.63-3.77 (2H, m, 6'-CH_2), 5.01 (1H, dd, *J*=3.6 and 5.4 Hz, 2'-CH), 5.76 (1H, s, 9-CH), 6.32 (1H, m, 3-CH), 6.49 (1H, ddd, *J*= 0.5, 2.5 and 11.9 Hz, 2-CH); ^{13}C-NMR: δ 20.2, 22.1, 23.2, 25.1, 25.5, 30.9, 43.4, 90.0, 110.0, 119.2, 141.0, 166.9, 171.0, 172.8; HRMS *m/z* calcd for $C_{15}H_{20}NO_3$ (M^++1): 262.1443. Found: 262.1465. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.79; H, 7.54; N, 5.23.

Thionocarbonate (30): The thionocarbonate was synthesized from **25** (560 mg, 1.89 mmol) by the same procedure as for the preparation of **27** to give **30** (494 mg, 77%); mp 235-236 °C (CH_2Cl_2-acetone); IR:

νmax 1772, 1734, 1636, 1456, 1261 and 1196 cm^{-1}; ^{1}H-NMR: δ 1.44-2.17 (10H, m, 4-, 5-, 3'-, 4'- and 5'-CH_2), 2.17 (3H, s, Ac), 2.18 (1H, dd, *J*=12.0 and 19.0 Hz, 9-C*H*H), 2.97 (1H, dd, *J*=12.2 and 19.0 Hz, 9-CH*H*), 3.38 (1H, ddd, *J*=5.1, 11.9 and 14.3 Hz, 6'-C*H*H), 3.53 (1H, ddd, *J*=2.7, 12.0 and 12.2 Hz, 1-CH), 3.64 (1H, ddd, *J*=0.2, 4.9 and 14.3 Hz, 6'-CH*H*), 4.70 (1H, t, *J*=6.1 Hz, 2'-CH), 5.20 (1H, m, 3-CH), 5.29 (1H, dd, *J*=2.7 and 8.3 Hz, 2-CH); ^{13}C-NMR: δ 18.7, 21.5, 22.1, 22.8, 24.0, 25.0, 30.8, 33.3, 42.6, 54.7, 78.2, 80.3, 88.5, 171.5, 174.1, 191.2; HRMS *m/z* calcd for $C_{16}H_{21}NO_5S$ (M^+): 339.1140. Found: 339.1158. Anal. Calcd for $C_{16}H_{21}NO_5S$: C, 56.52; H, 6.24; N, 4.13. Found: C, 56.56; H, 6.34; N, 4.05.

Crystal Data of 30: $C_{16}H_{20}NO_5S$, *M*=338.40, monoclinic, space group *P* 2_1/a, *a*=11.878(2), *b*=11.178(2), *c*=12.950(1) Å, β=113.21(7)°, *V*=1580.4(3) $Å^3$, *Z*=4, *D*c=1.422 g cm^{-3}; 2360 reflections with 4.24<2*θ*<120.02° were recorded on a four-circle diffractometer using graphite-monochromated Cu-Kα radiation. Of those, 1571 with $I>3\sigma(I)$ were judged as observed. The structure was solved using MALTAN88. *R*=0.0889, *R*w=0.1333.

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REFERENCES AND NOTE

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1. V. Snieckus, "*The Alkaloids*", Vol. 14, ed. by R. H. F. Manske, Academic Press, New York, 1973, pp. 425-503 and references cited therein.
2. V. I. Murav'eva and A. I. Ban'kovskii, *Dokl. Akad. Nauk SSSR*, 1956, **110**, 998.
3. S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki, and Y. Tamura, *Tetrahedron*, 1963, **19**, 2085; Z. Horii, M. Ikeda, N. Sugimoto, Y. Tamura, S. Saito, and K. Kotera, *Tetrahedron*, 1963, **19**, 2101; I. Sakoda, M. Maruyama, J. Tsuji, and E. Yoshii, *Tetrahedron Lett.*, 1962, 1199; J. Parello, A. Melera, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1963, 898; S. –F. Chen,

C. –H. Hsieh, and H. –T. Liang, *Scientia Sinica*, 1963, **12**, 1525.

4. T. Nakano, T. H. Yang, and S. Terao, *Tetrahedron*, 1963, **19**, 609; T. Nakano, T. H. Yang, and S. Terao, *J. Org. Chem*., 1963, **28**, 2619.
5. S. Imado, M. Shiro, and Z. Horii, *Chem. Pharm. Bull*., 1965, **13**, 643.
6. J. A. Beutler, E. W. Karbon, A. N. Brubaker, R. Malik, D. R. Curtis, and S. J. Enna, *Brain Res*., 1985, **330**, 135.
7. (a) Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Kotera, H. Yoshikawa, Y. Sato, H. Nakai, and N. Sugimoto, *Tetrahedron*, 1967, **23**, 1165; (b) S. Liras, J. E.Davoren, and J. Bordner, *Org. Lett*., 2001, **3**, 703.
8. Some examples of intramolecular Diels-Alder reactions of enol esters in natural product synthesis: S. J. Baily and E. J. Thomas, *J. Chem. Soc., Chem. Commun*., 1978, 474; K. Takeda, M. Sato, and E. Yoshii, *Tetrahedron Lett*., 1986, **27**, 3903.
9. A part of this work was published as a preliminary communication: T. Honda, H. Namiki, M. Kudoh, N. Watanabe, H. Nagase, and H. Mizutani, *Tetrahedron Lett*., 2000, **41**, 5927. The references for total synthesis or synthetic approaches of Securinega alkaloids are cited therein.
10. R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, and R. Lapalme, *J. Am. Chem. Soc*., 1976, **98**, 6317.
11. S. Aoyagi, T. C. Wang, and C. Kibayashi, *J. Am. Chem. Soc*., 1993, **115**, 11393.
12. M. F. Semmelhack and R. D. Stauffer, *Tetrahedron Lett*., 1973, 2667.