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Total Synthesis of Optically Active Integerrimine, a Twelve-membered Dilactonic Pyrrolizidine Alkaloid of Retronecine Type

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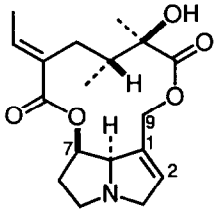
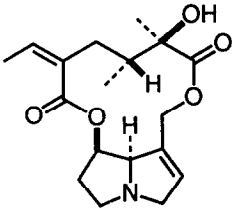
Abstract - A total synthesis of the natural enantiomer of integerrimine (**1**), a twelve-membered dilactonic pyrrolizidine alkaloid of retronecine type has been achieved through the enantioselective synthesis and regioselective coupling of (+)-retronecine (**4**) and (+)-integerrinecic acid (methylthio)methyl ether (**6**).

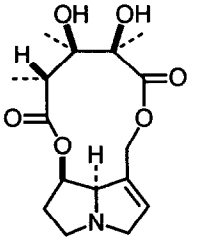
A number of pyrrolizidine alkaloids are found in various plant species belonging to Compositae, Leguminosae, and Boraginaceae families.[1] Most of the pyrrolizidine alkaloids are esters of hydroxylated 1-methylpyrrolizidines: the amino alcohol portions are called necines, and the acid moieties necic acids. Of those, the pyrrolizidine alkaloids having retronecine (**4**) or otonecine as the necine portion exhibit marked hepatotoxicicty and, in certain cases, antitumor activity and carcinogenicity.[2] The unsaturation between C-1 and C-2 and esterification of C-7 and C-9 hydroxyl groups in the necine portion (*e.g.*, **4**) are believed to be the most important structural features necessary for toxicity.[2] The greatest toxicity is shown by the macrocyclic



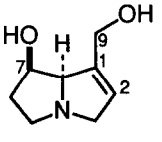
1 integerrimine



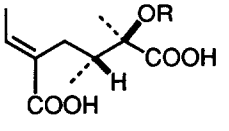
2 senecionine



3 monocrotaline



4 retronecine

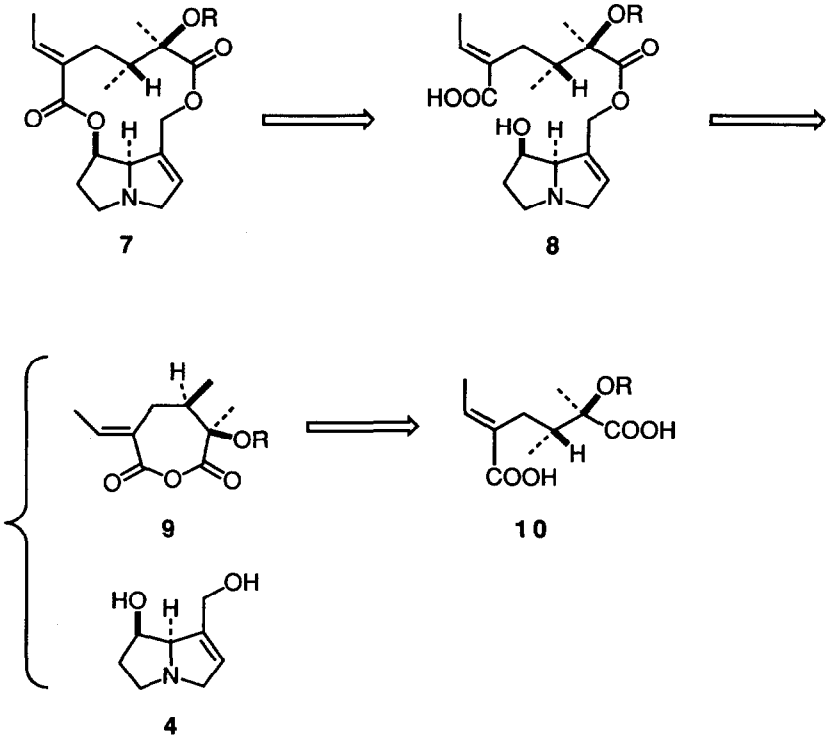


5 R = H
6 R = CH_2SCH_3

dilactonic alkaloids such as integerrimine (**1**) and monocrotaline (**3**), which are representatives of 12-membered and 11-membered alkaloids, respectively.[2] The highly reactive pyrrolic metabolites acting as bifunctional alkylating agents are supposed to be responsible for the acute (liver lesion) and the chronic (carcinogenicity) toxicity.[2] The interesting chemical structures and the unique biological activities have made the macrocyclic pyrrolizidine alkaloids attractive synthetic targets. Although a numerous synthetic work in pyrrolizidine alkaloids has been published, most of that has been directed towards the necine base portions such as retronecine (**4**),[1b,c] and only a few 11-membered[3] and 12-membered[4] dilactonic alkaloids have so far been synthesized. Herein we disclose a full account of the total synthesis of the natural enantiomer of integerrimine (**1**) through the enantioselective synthesis and regioselective coupling of (+)-retronecine (**4**) and (+)-integerrinecic acid (methylthio)methyl ether (**6**).[5]

Integerrimine (**1**) was initially isolated from *Senecio integerrimus* Nutt. (Compositae) as the minor constituent along with senecionine (**2**), and later as the only alkaloidal component from *Crotalaria incana* L. (Leguminosae).[6] The structure of integerrimine (**1**) including the absolute stereochemistry was determined as the geometrical isomer of senecionine (**2**) on the basis of extensive chemical and spectral studies coupled with the X-ray crystallographic analysis of the related compound.[7] The first synthesis of integerrimine (**1**) in racemic form was achieved by Narasaka and coworkers in 1982.[4a] White and Ohira also reported a synthesis of optically active integerrimine (**1**) in a different approach.[4b]

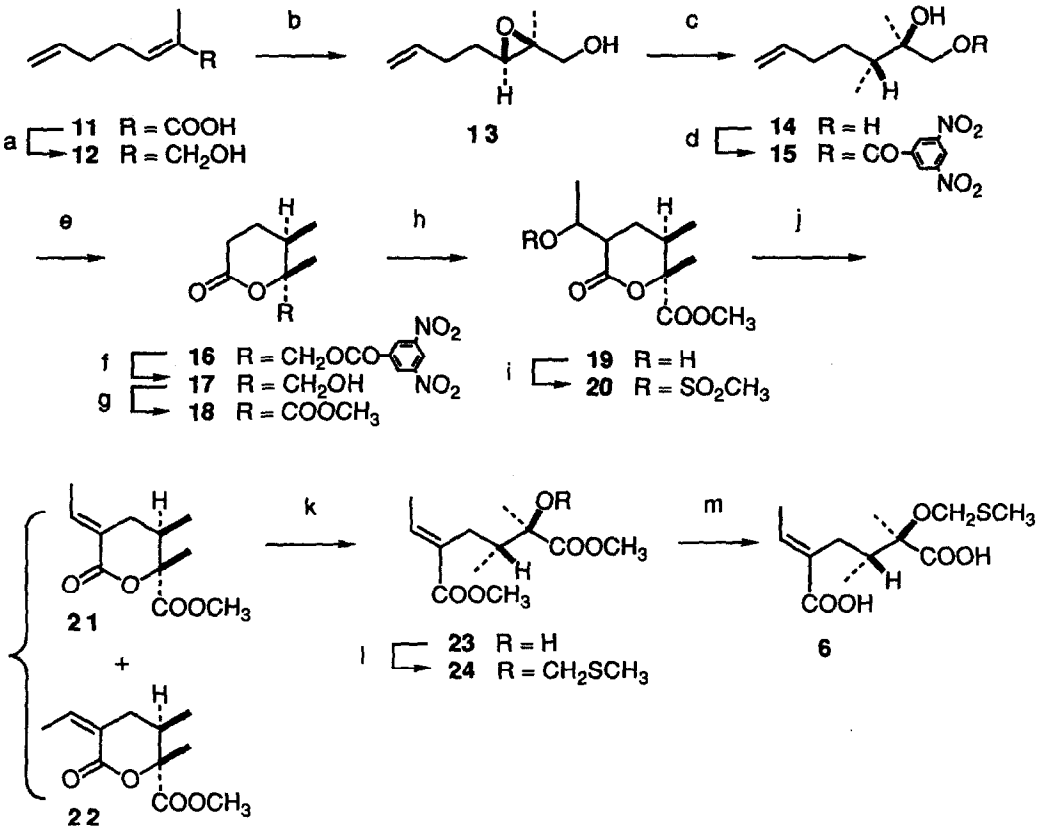
Scheme I



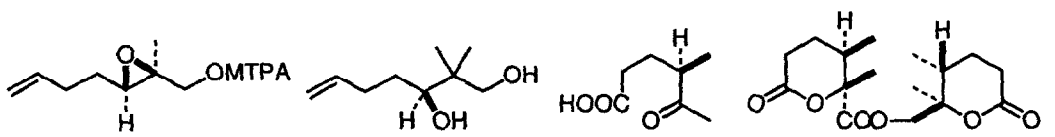
For the enantioselective total synthesis of (-)-integerrimine (**1**), three synthetic problems should be solved: (i) the enantioselective synthesis of (+)-retronecine (**4**); (ii) the enantioselective synthesis of (+)-integerrinecic acid (**5**); (iii) regioselective coupling of the unsymmetrical diol **4** and the unsymmetrical dicarboxylic acid **5** to elaborate the unsymmetrical 12-membered dilactone moiety in **1**. The crucial step in the synthesis was considered to be regioselective construction of the characteristic 12-membered dilactone moiety. As the penultimate step in the total synthesis of integerrimine (**1**), we envisaged lactonization of a seco acid **8** leading to a protected integerrimine **7**, from which integerrimine (**1**) could be synthesized on deprotection (Scheme I). We anticipated that the reaction of retronecine (**4**) with a cyclic anhydride **9**, which could be obtained from an appropriately protected integerrinecic acid **10**, would proceed regioselectively to give the desired seco acid **8** because the carbonyl group conjugated with a double bond in the cyclic anhydride **9** was expected to be less reactive than the other one with an α-alkoxy substituent by electronic effects. The nucleophilic approach trajectory analysis[8] of the cyclic anhydride **9** also predicted that the carbonyl group adjacent to the fully substituted carbon atom would be more reactive than the other one. As the protecting group of the hydroxyl function in integerrinecic acid (**5**), we selected the (methylthio)methyl (MTM) group owing to the stability and the ease of formation and removal. Thus, the initial phase of the total synthesis of optically active integerrimine (**1**) involved the synthesis of optically active integerrinecic acid MTM ether (**6**).

Although many synthetic routes to racemic integerrinecic acid (**5**) have been developed,[4a,9] there had been no report on the enantioselective synthesis of (+)-integerrinecic acid (**5**) when our project started. White and coworkers reported the enantioselective synthesis of (+)-integerrinecic acid (**5**) as part of their total synthesis of (–)-integerrimine (**1**).[4b,10] Our synthesis of (+)-integerrinecic acid MTM ether (**6**) started with readily available (*E*)-2-methylhepta-2,6-dienoic acid (**11**)[11] (Scheme II). Reduction of **11** with $LiAlH_4$ provided the allylic alcohol **12** in 69% yield, which was subjected to Sharpless asymmetric epoxidation[12] to give the optically active epoxide **13** in 71% yield. The enantiomeric excess of this material was determined to be 96% by the ^1H NMR spectral analysis of the derived (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA] ester **25**.[13] Stereospecific and regioselective ring opening of the epoxy group in **13** with trimethylaluminum[14] proceeded smoothly to furnish the 1,2-diol **14** in 72% yield along with a small amount of the isomeric 1,3-diol **26** (9%). Direct conversion of the 1,2-diol **14** into the lactone alcohol **17** by utilizing ozonolysis turned out to be less than satisfactory in practice (ca. 30% yield) and the alternative route to **17** was devised. After protection of the 1,2-diol **14** as its 3,5-dinitrobenzoate **15** (88%), the terminal olefinic bond of **15** was oxidatively cleaved with $RuCl_3$–$NaIO_4$.[15] Subsequent treatment of the resulting crude product with acid (*p*-toluenesulfonic acid, benzene, reflux)[16] afforded the lactone **16** in 99% yield. Methanolysis of **16** with NaOMe in MeOH followed by acid treatment[16] of the resulting crude product afforded the lactone alcohol **17** in 76% yield. Oxidation of **17** with $RuCl_3$–$NaIO_4$[15] proceeded smoothly to give the desired carboxylic acid, which upon treatment with CH_2N_2 afforded the lactone ester **18** in 79% overall yield. In contrast, oxidation of **17** with the Jones reagent or pyridinium dichromate (PDC) resulted in the preferential formation of the undesired **27** and **28**, respectively. Conversion of **18** into integerrinecic acid lactone methyl ester (**21**) was effected by the Narasaka route with slight procedural modifications.[4a,9f] Thus, aldol condensation of **18** with acetaldehyde gave the hydroxy lactone **19** as a mixture of diastereomers, which was converted to the corresponding mesylate **20**. Elimination of methanesulfonic acid from **20** was effected with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give **21** in 34% unoptimized yield, together with a small amount of the geometrical isomer, senecic acid lactone methyl ester (**22**) (3%). The spectral (^1H NMR, IR, and mass) and physical (mp and $[\alpha]_D$) properties of synthetic **21**

Scheme II



(a) $LiAlH_4$, THF, 69%; (b) *t*-BuOOH, (+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, –25 °C, 71%; (c) Me_3Al, hexane, 0 °C, 72%; (d) 3,5-dinitrobezoyl chloride, pyridine, 0 °C, 88%; (e) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4–CH_3CN–pH 7 phosphate buffer, then *p*-TsOH, benzene, reflux, 99%; (f) NaOMe, MeOH, then *p*-TsOH, benzene, reflux, 76%; (g) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4–CH_3CN–pH 7 phosphate buffer, then CH_2N_2, 79%; (h) LDA, THF, –78 to –30 °C, then CH_3CHO, –78 to –30 °C; (i) MsCl, pyridine; (j) DBU, benzene, reflux, 34% **21** and 3% **22** from **18**; (k) NaOMe, MeOH; (l) DMSO, Ac_2O, 40 °C, 61% from **21**; (m) KOH, MeOH–H_2O, reflux, 88%.

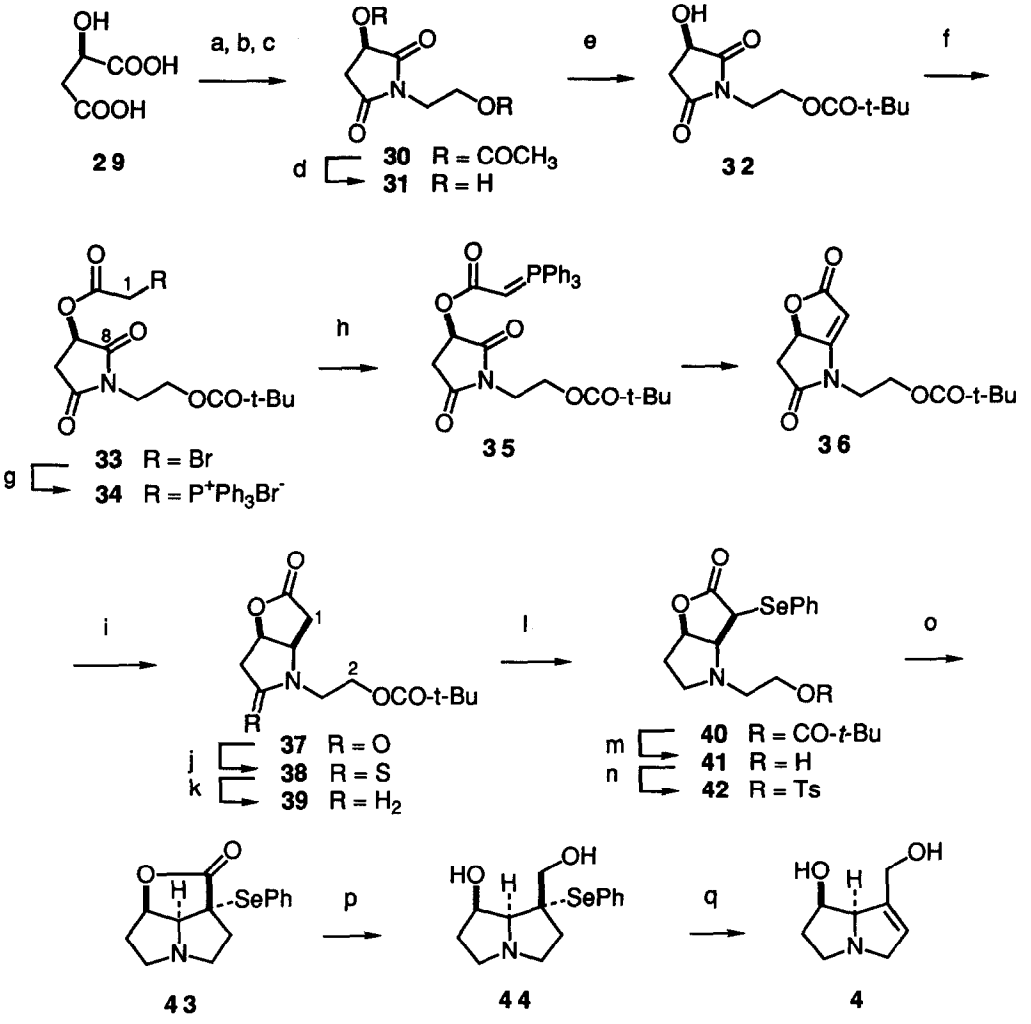


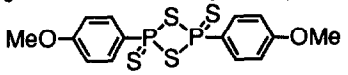
25 **26** **27** **28**

[mp 92.5–93.5 °C (benzene–hexane), $[\alpha]_D^{12}$ +48.0° (*c* 0.63, $CHCl_3$)] were identical with those of an authentic sample [mp 92.5-94 °C (benzene–hexane), $[\alpha]_D^{21}$ +47.3° (*c* 0.68, $CHCl_3$)] obtained from natural senkirkine.[17] Since transformation of **21** into integerrinecic acid (**5**) was the known procedure,[4a,9f] the enantioselective synthesis of **5** was formally achieved. For the synthesis of integerrimine (**1**), integerrinecic acid lactone methyl ester (**21**) should be converted into integerrinecic acid MTM ether (**6**), which was achieved by a three-step sequence. First, methanolysis of **21** with NaOMe in MeOH provided integerrinecic acid dimethyl ester (**23**), which was then treated with dimethyl sulfoxide and acetic anhydride[18] to furnish integerrinecic acid dimethyl ester MTM ether (**24**) in 61% overall yield. Finally, saponification of **24** gave **6** in 88% yield, thereby securing the necic acid portion required for the synthesis of (-)-integerrimine (**1**).

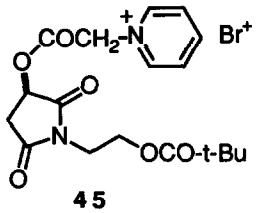
The next phase involved the enantioselective synthesis of (+)-retronecine (**4**). Since the first synthesis of retronecine (**4**) was achieved by Geissman and Waiss,[19a] many routes to racemic retronecine (**4**) including our synthesis[19f] have been developed.[4a,19] However, the enantioselective synthesis of (+)-retronecine (**4**) has been rather recent development.[20] Previously, we developed a convenient route to racemic retronecine (**4**).[19f] In this route, the tricyclic lactone **43** was employed as a key intermediate. For the synthesis of optically active retronecine (**4**), our efforts were therefore concentrated on the construction of optically active **43**, from which (+)-retronecine (**4**) could be synthesized in two steps.[19f] As the starting material for the construction of **43** in optically active form, we selected (*R*)-(+)-malic acid (**29**), the secondary hydroxyl group of which corresponds to that of (+)-retronecine (**4**) (Scheme III). (*R*)-(+)-Malic acid (**29**) was converted into the cyclic imide **30** by a three-step sequence [(1) acetyl chloride; (2) ethanolamine; (3) acetyl chloride] in 62% overall yield. Acidic ethanolysis of **30** provided the diol **31**, which was selectively acylated with pivaloyl chloride and pyridine to give the monopivalate **32** in 55% overall yield. Bromoacetylation of **32** with 1.2 equiv of bromoacetyl bromide and 1.5 equiv of pyridine in ether afforded the desired bromoacetate **33** in 94% yield. In this reaction, the use of an excess of pyridine should be avoided, otherwise the yield of **33** decreased owing to the formation of the unpleasant pyridinium salt **45**. A carbon-carbon bond formation between C-1 and C-8 (pyrrolizidine numbering) in **33** was effected by utilizing a novel intramolecular Wittig reaction involving the imide carbonyl group in a one-pot procedure.[21] Thus, the bromoacetate **33** was first converted into the corresponding phosphonium salt **34** by reaction with triphenylphosphine in acetonitrile at 50 °C. The phosphonium salt **34** was then treated with 1.1 equiv of triethylamine in acetonitrile at 50 °C to generate the ylide **35**. The intramolecular Wittig reaction involving the imide carbonyl group in **35** proceeded smoothly to furnish the desired, unsaturated lactone **36** in 85% overall yield from **33**. Catalytic hydrogenation of **36** over 5% Rh/alumina in EtOAc at room temperature afforded the saturated lactone **37** in almost quantitative yield. The next problem was conversion of **37** into the compound **39** having a pyrrolidine skeleton through selective reduction of the lactam carbonyl group. Preliminary experiments using the Borch procedure [(i) $Et_3O{\cdot}BF_4$; (ii) $NaBH_4$][22a] suffered from the problem of low conversion (ca. 40%). Fortunately, selective reduction of the lactam carbonyl group in **37** was effected by using a modified procedure of Raucher.[22b] Thus, the saturated lactone **37** was converted into the thiolactam **38** with the Lawesson reagent.[23] Treatment of **38** with triethyloxonium tetrafluoroborate in CH_2Cl_2 at room temperature, and subsequent reduction of the generated iminium salt with sodium cyanoborohydride in CH_2Cl_2-MeOH at 0 °C furnished the desired pyrrolidine lactone **39** in 82% overall yield from **37**. In contrast, reduction of the intermediary iminium salt with $NaBH_4$ [22b] in various solvents (MeOH, DME, or *i*-PrOH) or with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF proved to be unsatisfactory (40–60%). At this point, the remaining operations for the construction of the key intermediate **43** involved the

Scheme III

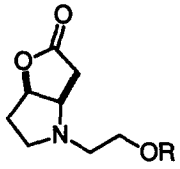


(a) AcCl, reflux; (b) ethanolamine, CH_2Cl_2, reflux; (c) AcCl, reflux, 62% from **29**; (d) HCl, EtOH, 50 °C, 84%; (e) pivaloyl chloride, pyridine, ether, –30 °C, 66%; (f) $BrCH_2COBr$, pyridine, ether, 94%; (g) Ph_3P, CH_3CN, 50 °C; (h) Et_3N, CH_3CN, 50 °C, 85% from **33**; (i) H_2, Rh/alumina, EtOAc, 99%; (j) 

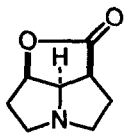
, toluene, 105 °C; (k) $Et_3O{\cdot}BF_4$, CH_2Cl_2, then $NaBH_3CN$, MeOH–CH_2Cl_2, 0 °C, 82% from **37**; (l) LDA, THF, –78 °C, then PhSeCl, –78 °C, 71%; (m) 6 M HCl, MeOH, 50 °C, 84%; (n) *n*-BuLi, THF, –78 °C, then TsCl, –78 °C; (o) LDA, HMPA, THF, –78 to –30 °C, 53% from **41**; (p) $LiAlH_4$, THF, –10 °C, 84%; (q) 30% H_2O_2, AcOH, 78%.



45



46 (R = Cl or Ts)



47

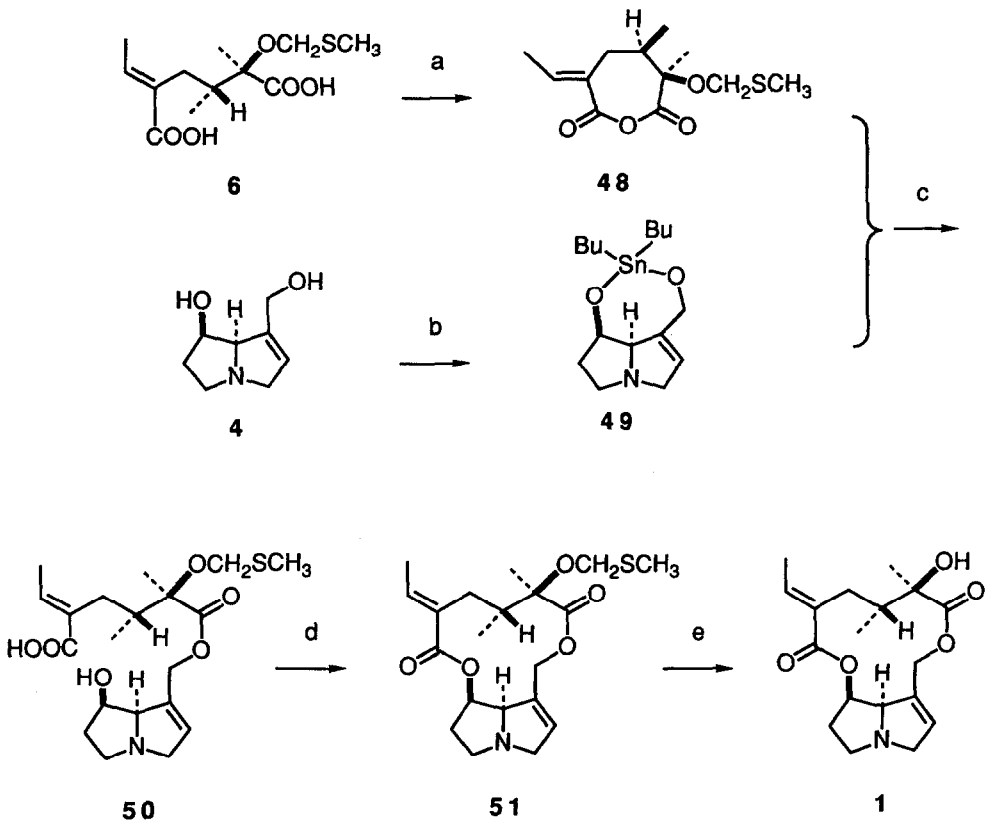
carbon-carbon bond formation between C-1 and C-2 and introduction of a phenylselenenyl group into C-1. For obtaining **43**, two routes were examined. In our initial efforts, cyclization of the compound **46** derived from **39** could never be induced to provide none of the tricyclic lactone **47**, from which **43** could be obtained according to our procedure.[19f] We therefore intended to introduce the phenylselenenyl group into **39** prior to the bond formation between C-1 and C-2. Introduction of the phenylselenenyl group into **39** was effected with lithium diisopropylamide (LDA) and PhSeCl to yield the selenide ester **40**,[24] which in turn was hydrolyzed under acidic conditions to give the selenide alcohol **41**[24] in 60% overall yield. The pivotal cyclization of **41** into the key intermediate **43** was achieved by a three-step sequence in a one-pot procedure. Thus, treatment of **41** with 1.5 equiv of *n*-BuLi in THF (–78 °C, 10 min) followed by reaction with *p*-toluenesulfonyl chloride (–78 °C, 1 h) afforded the tosylate **42** in situ, which without isolation was treated with 2.0 equiv of LDA in the presence of hexamethylphosphoric triamide (–78 °C, 30 min and then –30 °C, 5 h) to give the desired cyclization product **43** in 53% overall yield from **41**. Synthetic **43** was spectrally (^{1}H NMR, IR, and mass) identical with racemic **43**.[19f] The optical rotation [$[\alpha]_D^{12}$ +50.9° (*c* 1.14, $CHCl_3$)] of **43** was comparable to that of an authentic sample [$[\alpha]_D^{19}$ +45.9° (*c* 0.54, $CHCl_3$)], which was prepared by phenylseleneylation[19f] of the optically active tricyclic lactone **47**[25] derived from natural retronecine (**4**). Finally, the key intermediate **43** was converted into (+)-retronecine (**4**) by the two-step sequence reported by us[19f] in 66% overall yield: (i) $LiAlH_4$ reduction of **43** into **44**; (ii) H_2O_2 oxidation of **44** followed by in situ elimination of the selenoxide group. Spectral (^{1}H NMR, IR, and mass) and physical (mp, $[\alpha]_D$) properties of synthetic **4** [mp 118–119 °C (acetone), $[\alpha]_D^{14}$ +50.5° (*c* 0.20, EtOH)] were completely identical with those of natural retronecine (**4**) [lit.[26] mp 121–122 °C (acetone), $[\alpha]_D$ +50.2° (*c* 1.83, EtOH)].

Both acid and base components required for the synthesis of (–)-integerrimine (**1**) were now secured. At this point all that remained for completion of the synthesis of (–)-integerrimine (**1**) was regioselective construction of the unsymmetrical dilactone moiety by coupling the unsymmetrical diol **4** with the unsymmetrical dicarboxylic acid **6**. For the solution of this synthetic problem, we decided to utilize the reaction of the cyclic anhydride **48** with the cyclic stannoxane **49** (Scheme IV). Thus, treatment of (+)-**6** with 1 equiv of dicyclohexylcarbodiimide in CH_2Cl_2 at room temperature provided the desired cyclic anhydride **48**. On the other hand, treatment of (+)-retronecine (**4**) with 1.1 equiv of dibutyltin oxide[27] in benzene at reflux temperature provided the benzene solution of the cyclic stannoxane **49**.[3b,28] As expected, reaction of **48** with **49** in benzene at 5 °C proceeded regioselectively to give the desired the seco acid **50** in 98% yield from **6**. In contrast, direct reaction of (+)-retronecine (**4**) and **48** proved to be inferior to the tin-mediated esterification both in yield and in regioselectivity.[29] Lactonization of **50** was achieved by the Yamaguchi method.[30] Thus, the seco acid **50** was allowed to react with trichlorobenzoyl chloride (1.1 equiv) and Et_3N (4 equiv) in THF at room temperature for 2 h and the reaction mixture was diluted with toluene. The resulting solution was added slowly

over 1.5 h to a refluxing toluene solution containing 4-(dimethyamino)pyridine (4 equiv) and refluxing was continued for an additional 2 h. After chromatography, the desired integerrimine MTM ether (**51**) was obtained in 75% yield. Finally, deprotection of **51** with triphenylcarbenium tetrafluoroborate[31] provided (–)-integerrimine (**1**) in 81% yield. Spectral (^{1}H NMR, IR, and mass), chromatographic, and physical (mp, $[\alpha]_D$) properties of synthetic (–)-integerrimine (**1**) [mp 169–170.5 °C (acetone), $[\alpha]_D^{17}$ –19.5° (*c* 0.15, $CHCl_3$)] were identical with those of natural integerrimine [lit.[32] mp 168–169 °C (acetone), $[\alpha]_D$ –21.4° (*c* 9.00, $CHCl_3$)] in all respects. Now we completed the enantio- and regioselective, total synthesis of (–)-integerrimine (**1**).

It is noteworthy that the present approach for regioselective construction of the unsymmetrical dilactone requires no protecting groups to distinguish each of two reacting sites present in each of components **4** and **6**, and may be applicable to the synthesis of other members of the macrocyclic pyrrolizidine alkaloids.

Scheme IV



(a) DCC, CH_2Cl_2; (b) Bu_2SnO, benzene, reflux; (c) benzene, 5 ° C to room temp., 98% from **6**; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, reflux, 75%; (e) $Ph_3C{\cdot}BF_4$, CH_2Cl_2, 81%.

Experimental

Melting points are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on either JEOL FX-90QE (90 MHz) or JEOL JNM-C675 (270 MHz) spectrometer: Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane and coupling constants in Hz. Low-resolution (EIMS and CIMS) and high-resolution mass spectra (HREIMS and HRCIMS) were measured on a JEOL JMS-LG-2000 instrument. Fuji-Davison silica gel BW-820 MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness were used for analytical thin layer chromatography (TLC) and Merck silica gel PF_{254} for preparative TLC. Ether and tetrahydrofuran (THF) were distilled from sodium–benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2), pyridine, and triethylamine (Et_3N) were distilled from calcium hydride under nitrogen. Dimethyl sulfoxide and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride under reduced pressure. Hexane, toluene, and benzene were distilled from sodium under nitrogen. Ethanol (EtOH) and methanol (MeOH) were distilled from $Mg(OEt)_2$ and $Mg(OMe)_2$ under nitrogen, respectively. Acetaldehyde was distilled just prior to use under nitrogen. Unless otherwise stated, the organic solutions obtained by extractive workup were washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure by a rotary evaporator.

(*E*)-2-Methyl-2,6-heptadien-1-ol (12). To a cooled (0 °C), stirred solution of (*E*)-2-methyl-2,6-heptadienoic acid (**11**)[11] (970 mg, 7.0 mmol) in THF (40 ml) under nitrogen was added a 1.0 M solution of $LiAlH_4$ in THF (14 ml, 14 mmol). The reaction mixture was stirred at room temperature for 3 h and NaF (6 g) was added. The mixture was stirred for a while and H_2O (3 ml) was added dropwise. The resulting mixture was vigorously stirred at room temperature for an additional 30 min and filtered through a pad of Celite. The filter cake was washed thoroughly with ether. The filtrate and washings were combined and concentrated. The resulting oily residue was purified by column chromatography on silica gel (6 g) with 10:1→ 5:1 hexane–ether, providing **12** (600 mg, 69%) as a colorless oil. The ^{1}H NMR spectral analysis indicated that this material contained a small amount (ca. 7%) of 2-methylhept-6-en-1-ol resulting from overreduction. This material was used for the next reaction without further purification. **12**: IR ($CHCl_3$) 3630, 3440, 3080, 1640, and 1380 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.61 (1 H, br, OH), 1.67 (3 H, s), 2.13 (4 H, m), 4.01 (2 H, s), 5.05 (2 H, m), 5.42 (1 H, m), and 5.83 (1 H, m); EIMS *m/z* (relative intensity) 126 (M^+, 3), 108 (100), 95 (50), and 93 (60) [HREIMS. Found: 108.0923. C_8H_{12} [$(M–H_2O)^+$] requires: 108.0938].

(2*S*,3*S*)-2,3-Epoxy-2-methyl-6-hepten-1-ol (13). To a cooled (–25 °C), stirred solution of Ti(O-*i*-Pr)$_4$ (293 mg, 1.03 mmol) in CH_2Cl_2 (5 ml) under nitrogen was added a solution of diethyl (+)-tartrate (210 mg, 1.05 mmol) in CH_2Cl_2 (2 ml). To the solution was added a solution of **12** (118 mg, 0.94 mmol) in CH_2Cl_2 (5 ml) followed by a 3 M solution of *t*-butylhydroperoxide in toluene (0.69 ml, 2.07 mmol). After the reaction mixture was stirred at –25 °C for 3 h, 10% tartaric acid solution (2.5 ml) was added. The mixture was stirred at –25 °C for 30 min and then at room temperature for 1 h and extracted with CH_2Cl_2 (3 x 10 ml). The extracts were combined, washed, dried, and concentrated to give an oily residue, which was dissolved in ether (8 ml). To the ice-cooled, ethereal solution was added 1 M NaOH (3 ml). The mixture was vigorously stirred at 0 °C for 30 min and extracted with ether (3 x 10 ml). The extracts were combined, washed, dried, and

concentrated. The oily residue was purified by column chromatography on silica gel (4 g) with 3:1 hexane–ether, affording **13** (94 mg, 71%) as a colorless oil, together with the recovered **12** (5 mg). The optical purity of **13** was determined by the ^{1}H NMR analysis of the derived (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA] ester **25** to be 96% ee. **13**: $[\alpha]_D^{11}$ –18.1° (*c* 1.92, $CHCl_3$); IR ($CHCl_3$) 3580, 3450, 3080, 1640, 1385, and 1055 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.27 (3 H, s), 1.71 (2 H, m), 2.00 (1 H, dd, *J* = 10.8, 9.4 Hz, OH), 2.22 (2 H, m), 3.04 (1 H, dd, *J* = 6.3, 6.3 Hz), 3.61 (2 H, m), 5.15 (2 H, m), and 5.85 (1 H, ddt, *J* = 17.4, 9.9, 6.4 Hz); CIMS *m/z* (relative intensity) 143 [$(M+H)^+$, 19], 125 (47), 107 (34), 87 (42), 85 (79), and 67 (100) [HREIMS. Found: 111.0780. $C_7H_{11}O$ [$(M-CH_2OH)^+$] requires: 111.0809].

(+)-MTPA Ester 25. Epoxide **13** (8.2 mg, 0.058 mmol) was converted into (+)-MTPA ester **25** by the reported procedure[13] in 80% yield. The diastereomeric excess of this material was determined by ^{1}H NMR spectral analysis to be 96% de. **25**: a colorless oil; $[\alpha]_D^{12}$ +31.5° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 3080, 1750, 1640, 1270, 1245, 1185, and 1170 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (3 H, s), 1.29 (2 H, m), 1.93 (2 H, m), 2.52 (1 H, dd, *J* = 6.6, 5.6 Hz), 3.43 (3 H, q, *J* = 1.3 Hz), 3.85 (1 H, d, *J* = 11.5 Hz), 4.06 (1 H, d, *J* = 11.5 Hz), 4.93 (2 H, m), 5.61 (1 H, ddt, *J* = 16.8, 10.6, 6.6 Hz), 7.09 (3 H, m), and 7.68 (2 H, m); EIMS *m/z* (relative intensity) 358 (M^+, 53), 317 (2), 303 (7), 291 (3), 259 (11), and 190 (92) [HREIMS. Found: 358.1366. $C_{18}H_{21}O_4F_3$ (M^+) requires: 358.1392].

(2*R*,3*R*)-2,3-Dimethyl-6-heptene-1,2-diol (14). To an ice-cooled, stirred solution of **13** (62.5 mg, 0.44 mmol) in hexane (4 ml) under nitrogen was added a 1.74 M solution of Me_3Al in hexane (1.3 ml, 2.3 mmol). The reaction mixture was stirred at 0 °C for 2 h and diluted with CH_2Cl_2 (4 ml). To the mixture was added NaF (0.95 g, 23 mmol) followed by dropwise addition of H_2O (0.4 ml). The mixture was vigorously stirred at room temperature for 1 h and filtered through a pad of Celite. The filter cake was washed thoroughly with ether. The filtrate and washings were combined and concentrated to leave an oil. Purification by preparative TLC on silica gel (1:1 CH_2Cl_2–ether) gave the desired **14** (50.0 mg, 72%) and the isomer **26** (6.1 mg, 9%) as a colorless oil, respectively. **14**: $[\alpha]_D^{16}$ +34.2° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 3620, 3460, 3080, 1640, 1385, and 1040 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.86 (3 H, d, *J* = 6.8 Hz), 1.06 (3 H, s), 1.1–2.3 (5 H, m), 2.35 (2 H, br s, OH), 3.40 (1 H, d, *J* = 11.0 Hz), 3.57 (1 H, d, *J* = 11.0 Hz), 5.01 (2 H, m), and 5.83 (1 H, ddt, *J* = 17.1, 9.9, 6.4 Hz); CIMS *m/z* (relative intensity) 159 [$(M+H)^+$, 22], 142 (100), 127 (56), and 123 (99) [HRCIMS. Found: 159.1361. $C_9H_{19}O_2$ [$(M+H)^+$] requires: 159.1385]. **26**: $[\alpha]_D^{28}$ –27.3° (*c* 0.245, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 3080, and 1640 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.89 (3 H, s), 0.90 (3 H, s), 1.57 (2 H, m), 2.14 (2 H, m), 2.40 (2 H, br s, OH), 3.44 (1 H, d, *J* = 10.8 Hz), 3.51 (1 H, dd, *J* = 6.2, 6.2 Hz), 3.60 (1 H, d, *J* = 10.8 Hz), 5.06 (2 H, m), and 5.87 (1 H, ddt, *J* = 17.3, 9.9, 6.5 Hz); CIMS *m/z* (relative intensity) 159 [$(M+H)^+$, 100], 141 (79), 124 (23), 103 (21), and 99 (34) [HRCIMS. Found: 159.1413. $C_9H_{19}O_2$ [$(M+H)^+$] requires: 159.1385].

Dinitrobenzoate 15. To an ice-cooled, stirred solution of **14** (47.3 mg, 0.30 mmol) in pyridine (2 ml) under nitrogen was added 3,5-dinitrobenzoyl chloride (276 mg, 1.2 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h, and ice (ca. 0.5 g) was added. The mixture was stirred for a while, diluted with saturated $NaHCO_3$ solution (2 ml), and extracted with ether (4 x 7 ml). The extracts were combined, washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried, and concentrated to

leave an oily residue. Purification by preparative TLC on silica gel (4:1 benzene–EtOAc) provided **15** (93 mg, 88%) as colorless crystals: mp 88–89.5 °C (hexane-ether); $[\alpha]_D^{19}$ +16.0° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 3590, 3450, 3100, 1730, 1625, 1595, 1545, 1340, 1275, 1160, 990, and 920 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.99 (3 H, d, *J* = 6.6 Hz), 1.25 (3 H, s), 1.72 (1 H, br s, OH), 1.5–2.4 (5 H, m), 4.34 (1 H, d, *J* = 11.4 Hz), 4.49 (1 H, d, *J* = 11.4 Hz), 5.04 (2 H, m), 5.83 (1 H, ddt, *J* = 16.9, 9.9, 6.6 Hz), 9.15 (2 H, m), and 9.24 (1 H, m); CIMS *m/z* (relative intensity) 353 [$(M+H)^+$, 11], 335 (31), 269 (16), 141 (30), and 127 (100). Anal. Calcd for $C_{16}H_{20}N_2O_7$: C, 54.54; H, 5.72; N, 7.95. Found: C, 54.42; H, 5.70; N, 7.82.

(4*R*,5*R*)-4-Methyl-5-[(3,5-dinitrobenzoyloxy)methyl]-5-hexanolide (16). To a solution of **15** (36.5 mg, 0.104 mmol) in a mixture of CCl_4 (1 ml) and CH_3CN (1 ml) was added pH 7 (0.25 M) phosphate buffer (1.5 ml). To the vigorously stirred, two-phase mixture was added $NaIO_4$ (112 mg, 0.524 mmol) followed by $RuCl_3 \cdot 3H_2O$ (3 mg, 0.013 mmol). The reaction mixture was vigorously stirred at room temperature for 1 h, acidified to pH 1 by the addition of 1 M HCl (2 ml), and extracted with ether (4 x 10 ml). The extracts were combined, dried, and concentrated. The resulting oily residue was dissolved in benzene (5 ml), and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) (2 mg) was added. The mixture was heated under reflux for 1 h, cooled to room temperature, poured into saturated $NaHCO_3$ solution (2 ml), and extracted with ether (4 x 10 ml). The extracts were combined, washed, dried, and concentrated to give an oily residue. Purification by column chromatography on silica gel (2 g) with 4:1 benzene–EtOAc gave **16** (36.1 mg, 99%) as a colorless oil: $[\alpha]_D^{20}$ +19.0° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 3120, 1735, 1625, 1550, 1350, 1280, and 1165 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.12 (3 H, d, *J* = 6.6 Hz), 1.42 (3 H, s), 1.6–2.4 (3 H, m), 2.64 (2 H, m), 4.51 (2 H, s), 9.13 (2 H, m), and 9.25 (1 H, m); CIMS *m/z* (relative intensity) 353 [$(M+H)^+$, 100] and 141 (43) [HRCIMS. Found: 353.0961. $C_{15}H_{17}N_2O_8$ [$(M+H)^+$] requires: 353.0984].

(4*R*,5*R*)-4-Methyl-5-(hydroxymethyl)-5-hexanolide (17). To a solution of **16** (34.8 mg, 0.0989 mmol) in MeOH (2 ml) under nitrogen was added a 2.0 M solution of NaOMe in MeOH (0.05 ml, 0.01 mmol). The mixture was stirred at room temperature for 30 min. The reaction was quenched by the addition of ion-exchange resin Amberlite IRC-50 (acid form, 20 mg). The mixture was filtered through a cotton plug. The resin was washed thoroughly with MeOH. The filtrate and washings were combined and concentrated. The resulting oily residue was dissolved in benzene (3 ml), and *p*-TsOH·H_2O (2.3 mg, 0.012 mmol) was added. The mixture was heated under reflux for 1 h, cooled to room temperature, poured into saturated $NaHCO_3$ solution (3 ml), and extracted with EtOAc (4 x 7 ml). The extracts were combined, washed, dried, and concentrated to leave an oily residue, which was purified by column chromatography on silica gel (2 g) with 2:1 → 1:1 benzene–EtOAc, yielding **17** (11.8 mg, 76%) as colorless crystals: mp 85–86 °C (benzene–hexane); $[\alpha]_D^{13}$ +49.1° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 3600, 3420, 1715, and 1285 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.99 (3 H, d, *J* = 6.6 Hz), 1.22 (3 H, s), 1.95 (1 H, br s, OH), 1.6–2.4 (3 H, m), 2.55 (2 H, m), and 3.60 (2 H, s); CIMS *m/z* (relative intensity) 159 [$(M+H)^+$, 100], 142 (46), 129 (38), 127 (35), 123 (20), and 113 (50). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.60; H, 8.99.

(4*R*,5*R*)-4-Methyl-5-(methoxycarbonyl)-5-hexanolide (18). To a solution of **17** (14.9 mg, 0.0943 mmol) in a mixture of CCl_4 (0.4 ml) and CH_3CN (0.4 ml) was added pH 7 (0.25 M) phosphate buffer (0.6 ml). To the vigorously stirred, two-phase mixture cooled to 0 °C was added $NaIO_4$ (140 mg, 0.65 mmol)

followed by $RuCl_3 \cdot 3H_2O$ (7.8 mg, 0.035 mmol). The reaction mixture was vigorously stirred at 0 °C for 1.5 h and then at room temperature for 1 h, diluted with 1 M HCl (1 ml), and extracted with EtOAc (4 x 7 ml). The organic layers were combined, dried, and concentrated. The oily residue was dissolved in a small amount of ether. To the ethereal solution was added ethereal CH_2N_2 until the yellow color persisted. Excess CH_2N_2 was decomposed with AcOH and the mixture was concentrated. The oily residue was purified by column chromatography on silica gel (1 g) with 1:1 hexane–ether, affording **18** (13.8 mg, 79%) as a colorless oil: $[\alpha]_D^{19}$ +6.5° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 1745, 1735, 1270, 1135, 1120, and 1080 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.09 (3 H, d, *J* = 7.0 Hz), 1.53 (3 H, s), 1.6–1.9 (2 H, m), 2.30 (1 H, m), 2.55 (2 H, m), and 3.79 (3 H, s); CIMS *m/z* (relative intensity) 187 [$(M+H)^+$, 100], 169 (40), 155 (38), 141 (10), and 127 (27) [HREIMS. Found: 127.0763. $C_7H_{11}O_2$ [$(M-CO_2CH_3)^+$] requires: 127.0759].

Integerrinecic Acid Lactone Methyl Ester (21). To a cooled (–78 °C), stirred solution of **18** (24.4 mg, 0.131 mmol) in THF (1 ml) under nitrogen was added a 0.5 M solution of lithium diisopropylamide (LDA) in THF (0.8 ml, 0.4 mmol). The reaction mixture was stirred at –78 °C for 1 h and then at –30 °C for 10 min. After the mixture was recooled to –78 °C, freshly distilled acetaldehyde (0.1 ml) was added. The reaction mixture was gradually warmed to –30 °C over a period of 2 h. The reaction was quenched with saturated NH_4Cl solution (1 ml), and the mixture was extracted with ether (3 x 10 ml). The extracts were combined, washed, dried, and concentrated to give an oily residue, which was purified by column chromatography on silica gel (3 g) with 5:1 → 2:1 benzene–EtOAc to give hydroxy lactone **19** as a mixture of diastereomers. To a solution of **19** in pyridine (3 ml) under nitrogen was added methanesulfonyl chloride (0.1 ml, ca. 1.3 mmol). The reaction mixture was stirred at room temperature for 2 h and ice (1 g) was added. The mixture was stirred for a while and extracted with ether (4 x 20 ml). The combined extracts were washed with saturated NaCl solution, dried, and concentrated to give the crude mesylate **20** as a mixture of diastereomers. To a solution of crude **20** in benzene (1.5 ml) under nitrogen was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 ml). The reaction mixture was heated under reflux for 2 h. After the reaction mixture was cooled to room temperature, 1 M HCl (2 ml) was added and the mixture was extracted with ether (4 x 10 ml). The extracts were combined, washed, dried, and concentrated to give an oily residue. Purification by preparative TLC on silica gel (5:1 benzene–EtOAc) yielded **21** (9.4 mg, 34% from **18**) and the geometrical isomer **22** (0.7 mg, 3% from **18**) as colorless crystals and a colorless oil, respectively. **21**: mp 92.5–93.5 °C (benzene–hexane) [authentic sample,[17] mp 92.5–94 °C (benzene–hexane)]; $[\alpha]_D^{12}$ +48.0° (*c* 0.63, $CHCl_3$) [authentic sample,[17] $[\alpha]_D^{21}$ +47.3° (*c* 0.68, $CHCl_3$)]; IR ($CHCl_3$) 1750, 1715, 1640, 1260, and 1140 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.05 (3 H, d, *J* = 7.0 Hz), 1.56 (3 H, s), 1.79 (3 H, d, *J* = 7.3 Hz), 2.1–2.6 (3 H, m), 3.78 (3 H, s), and 7.24 (1 H, tq, *J* = 2.0, 7.3 Hz); EIMS *m/z* (relative intensity) 212 (M^+, 29), 153 (100), and 125 (20) [HREIMS. Found: 212.1047. $C_{11}H_{16}O_4$ (M^+) requires: 212.1048]. **22**: IR ($CHCl_3$) 1750, 1725, 1640, 1260, and 1140 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.03 (3 H, d, *J* = 7.0 Hz), 1.52 (3 H, s), 2.0–2.8 (3 H, m), 3.77 (3 H, s), and 6.15 (1 H, q, *J* = 7.2 Hz); EIMS *m/z* (relative intensity) 212 (M^+, 33) and 153 (100) [HREIMS. Found: 212.1028. $C_{11}H_{16}O_4$ (M^+) requires: 212.1048].

Integerrinecic Acid Dimethyl Ester MTM Ether (24). To a solution of **21** (17.2 mg, 0.0811 mmol) in MeOH (2 ml) under nitrogen was added a 0.43 M solution of NaOMe in MeOH (0.2 ml, 0.086 mmol), and the reaction mixture was stirred at room temperature for 2.5 h. The reaction was quenched by the addition of

ion-exchange resin Amberlite IRC-50 (acid form, 0.2 g). The mixture was filtered through a cotton plug, and the resin was thoroughly washed with MeOH. The filtrate and washings were combined and concentrated to give crude integerrinecic acid dimethyl ester (**23**) as a colorless oil. To a solution of the crude **23** in dimethyl sulfoxide (1 ml) under nitrogen was added acetic anhydride (1 ml). The mixture was stirred at 40 °C for 24 h and concentrated to leave an oily residue, which was purified by preparative TLC on silica gel (5:1 benzene–EtOAc), providing **24** (15.0 mg, 61% from **21**) as a colorless oil, together with unreacted **21** (2.3 mg, 13%). **24**: $[\alpha]_D^{16}$ +33.2° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 1730, 1710, 1645, 1440, and 1280 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.80 (3 H, d, *J* = 6.4 Hz), 1.44 (3 H, s), 1.82 (3 H, d, *J* = 7.0 Hz), 2.24 (3 H, s), 1.95–2.5 (3 H, m), 3.72 (3 H, s), 3.73 (3 H, s), 4.54 (1 H, d, *J* = 10.5 Hz), 4.72 (1 H, d, *J* = 10.5 Hz), and 6.92 (1 H, tq, *J* = 0.7, 7.0 Hz); EIMS *m/z* (relative intensity) 304 (M^+, 6), 286 (15), 257 (15), 245 (28), 227 (59), and 195 (100) [HREIMS. Found: 304.1323. $C_{14}H_{24}O_5S$ (M^+) requires: 304.1343].

Integerrinecic Acid MTM Ether (6). A mixture of **24** (98 mg, 0.32 mmol), a 1 M solution of KOH in MeOH (3.2 ml), and H_2O (10 ml) under nitrogen was heated under reflux for 1 h, cooled to room temperature, and acidified (pH 2) by the addition of 1 M HCl. The mixture was saturated with NaCl and extracted with EtOAc (4 x 20 ml). The extracts were combined, dried, and concentrated to leave an oily residue, which was purified by column chromatography on silica gel (4 g) with 2:1 benzene–EtOAc to give **6** (78 mg, 88%) as colorless crystals: mp 125–128 °C (benzene–hexane); $[\alpha]_D^{11}$ +52.2° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 3600–2400, 1700, 1645, and 1285 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.90 (3 H, d, *J* = 6.6 Hz), 1.50 (3 H, s), 1.86 (3 H, d, *J* = 7.3 Hz), 2.24 (3 H, s), 2.2–2.4 (2 H, m), 2.52 (1 H, m), 4.59 (1 H, d, *J* = 10.9 Hz), 4.74 (1 H, d, *J* = 10.9 Hz), 7.07 (1 H, q, *J* = 7.3 Hz), and 7.2 (2 H, br, COOH); CIMS *m/z* (relative intensity) 277 [$(M+H)^+$, 3], 259 (9), 239 (6), 229 (43), 211 (65), 199 (30), 181 (50), and 171 (100). Anal. Calcd for $C_{12}H_{20}O_5S$: C, 52.16; H, 7.30. Found: C, 52.19; H, 7.34.

(3*R*)-3-Acetoxy-1-(2-acetoxyethyl)pyrrolidine-2,5-dione (30). A mixture of (*R*)-(+)-malic acid (**29**) (5.0 g, 37 mmol) and acetyl chloride (75 ml) was heated under reflux for 3 h, cooled to room temperature, and concentrated to leave an oily residue, which was dissolved in CH_2Cl_2 (40 ml). To the solution was added a solution of ethanolamine (6 ml, 100 mmol) in CH_2Cl_2 (10 ml). The mixture was heated under reflux for 3 h, cooled to room temperature, and concentrated. The residue was dissolved in acetyl chloride (100 ml), and the mixture was heated under reflux for 4 h. After being cooled to room temperature, the reaction mixture was concentrated to leave an oily residue, which was diluted with H_2O (100 ml) and extracted with $CHCl_3$ (4 x 100 ml). The extracts were combined, dried, and concentrated. The oily residue was purified by column chromatography on silica gel (250 g) with 2:1 hexane–EtOAc, affording **30** (5.58 g, 62% from **29**) as a colorless oil: $[\alpha]_D^{22}$ +16.5 ° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 1790, 1740, 1720, and 1230 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.02 (3 H, s), 2.17 (3 H, s), 2.67 (1 H, dd, *J* = 18.5, 5.1 Hz), 3.20 (1 H, dd, *J* = 18.5, 8.6 Hz), 3.82 (2 H, m), 4.26 (2 H, m), and 5.45 (1 H, dd, *J* = 8.6, 5.1 Hz); EIMS *m/z* (relative intensity) 243 (M^+, 9), 200 (100), 183 (92), 171 (35), 158 (94), 123 (87), and 111 (92) [HREIMS. Found: 200.0585. $C_8H_{10}NO_5$ [$(M–COCH_3)^+$] requires: 200.0559].

(3*R*)-3-Hydroxy-1-(2-hydroxyethyl)pyrrolidine-2,5-dione (31). To a stirred solution of **30** (2.3 g, 5.06 mmol) in EtOH (30 ml) was added acetyl chloride (1.1 ml, 15 mmol), and the mixture was stirred at 50

°C for 3 h, cooled to room temperature, and concentrated. The resulting oily residue was azeotroped with benzene (3 x 10 ml), and purified by column chromatography on silica gel (20 g) with 5:1 EtOAc–acetone, providing **31** (676 mg, 84%) as colorless crystals: mp 77-78 °C (EtOAc); $[\alpha]_D^{25}$ +71.2 ° (*c* 1.08, acetone); IR ($CHCl_3$) 3350, 1780, 1700, 1400, and 1180 cm^{-1}; ^1H NMR (90 MHz, CD_3COCD_3) δ 2.48 (1 H, dd, *J* = 16.9, 5.4 Hz), 3.06 (1 H, dd, *J* = 16.9, 8.3 Hz), 3.60 (4 H, m), 3.96 (2 H, br s, OH), and 4.64 (1 H, dd, *J* = 8.3, 5.4 Hz); CIMS *m/z* (relative intensity) 160 [$(M+H)^+$, 36], 142 (15), 130 (19), 116 (18), 88 (35), and 59 (100). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.01; H, 5.80; N, 8.75.

(3*R*)-3-Hydroxy-1-(2-pivaloyloxyethyl)pyrrolidine-2,5-dione (32). To a cooled (–30 °C), stirred solution of **31** (1.50 g, 9.43 mmol) in pyridine (10 ml) under nitrogen was added a solution of pivaloyl chloride (1.28 ml, 10.4 mmol) in ether (10 ml) over a period of 1 h. The reaction mixture was stirred at –30 °C for 1 h, and then the reaction was quenched by the addition of MeOH (5 ml). The mixture was warmed to room temperature with stirring, diluted with water (10 ml), and extracted with EtOAc (4 x 50 ml). The combined extracts were dried and concentrated to give an oily residue. Purification by column chromatography on silica gel (45 g) with 5:1 benzene–EtOAc gave **32** (1.52 g, 66%) as a colorless oil; $[\alpha]_D^{23}$ +56.1° (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 3570, 3450, 1785, 1715, 1400, and 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.16 (9 H, s), 2.66 (1 H, dd, *J* = 18.1, 5.1 Hz), 3.01 (1 H, dd, *J* = 18.1, 8.1 Hz), 3.79 (2 H, m), 3.62 (1 H, br s, OH), 4.26 (2 H, m), and 4.64 (1 H, dd, *J* = 8.1, 5.1 Hz); EIMS *m/z* (relative intensity) 243 (M^+, 3), 200 (36), 188 (23), 158 (92), 143 (60), 142 (95), 141 (88), 116 (80), 85 (90), and 69 (100) [HREIMS. Found: 243.1122. $C_{11}H_{17}NO_5$ (M^+) requires: 243.1107].

(3*R*)-3-(Bromoacetoxy)-1-(2-pivaloyloxyethyl)pyrrolidine-2,5-dione (33). To a cooled (0 °C), stirred solution of **32** (1.08 g, 4.44 mmol) in ether (15 ml) under nitrogen was added pyridine (0.54 ml, 6.66 mmol) followed by bromoacetyl bromide (0.46 ml, 5.33 mmol). The reaction mixture was stirred at room temperature for 0.5 h, diluted with cold water (10 ml), and extracted with CH_2Cl_2 (3 x 50 ml). The combined extracts were successively washed with saturated $CuSO_4$ solution (2 x 10 ml), water (10 ml), and saturated NaCl solution (100 ml), dried, and concentrated to leave an oily residue. Purification by column chromatography on silica gel (5 g) with 5:1 benzene–EtOAc yielded **33** (1.52 g, 94%) as a colorless oil: $[\alpha]_D^{14}$ +9.4° (*c* 2.02, $CHCl_3$); IR ($CHCl_3$) 1795 (weak), 1760, 1725, 1405, 1280, and 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.16 (9 H, s), 2.69 (1 H, dd, *J* = 18.5, 5.1 Hz), 3.22 (1 H, dd, *J* = 18.5, 8.6 Hz), 3.84 (2 H, m), 3.91 (2 H, s), 4.28 (2 H, m), and 5.52 (1 H, dd, *J* = 8.6, 5.1 Hz); CIMS *m/z* (relative intensity) 366 [$(M+H+2)^+$, 8], 364 [$(M+H)^+$, 8], 280 (7), 264 (10), 262 (9), 226 (7), 85 (43), and 55 (100) [HRCIMS. Found: 364.0367. $C_{13}H_{19}{}^{79}BrNO_4$ [$(M+H)^+$] requires: 364.0395].

(1*R*)-6-(2-Pivaloyloxyethyl)-2-oxa-6-azabicyclo[3.3.0]oct-4-ene-3,7-dione (36). To a solution of **33** (653 mg, 1.79 mmol) in CH_3CN (15 ml) under nitrogen was added Ph_3P (706 mg, 2.69 mmol). The mixture was stirred at 50 °C for 4 h and then Et_3N (0.27 ml, 1.97 mmol) was added. The reaction mixture was stirred at 50 °C for an additional 16 h, cooled to room temperature, and concentrated. The resulting residue was purified by column chromatography on silica gel (40 g) with 9:1 benzene–EtOAc, providing **36** (407 mg, 85%) as colorless crystals: mp 79.5–81 °C (benzene–hexane); $[\alpha]_D^{19}$ +62.5° (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 3150, 1770, 1725, 1655, 1395, and 1145 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.17 (9 H, s), 2.67 (1 H, dd, *J*

= 16.0, 7.7 Hz), 3.12 (1 H, dd, *J* = 16.0, 7.7 Hz), 3.5–4.4 (4 H, m), 5.17 (1 H, ddd, *J* = 8.8, 7.7, 1.8 Hz), and 5.31 (1 H, d, *J* = 1.8 Hz); EIMS *m/z* (relative intensity) 267 (M^+, 4), 165 (50), 137 (25), and 108 (26). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.23; H, 6.39; N, 5.25.

(1*R*,5*R*)-6-(2-Pivaloyloxyethyl)-2-oxa-6-azabicyclo[3.3.0]octane-3,7-dione (37). A mixture of **36** (610 mg, 2.28 mmol) and 5% rhodium on alumina (122 mg) in EtOAc (10 ml) was vigorously stirred at room temperature under hydrogen for 3 h. The mixture was filtered through a pad of Celite. The filter cake was thoroughly washed with EtOAc. The filtrate and washings were combined and concentrated to leave an oily residue. Purification by column chromatography on silica gel (2 g) with 1:1 ether–EtOAc gave **37** (606 mg, 99%) as colorless crystals: mp 111–112 °C (benzene–hexane); $[\alpha]_D^{17}$ +48.8° (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 1790, 1720, 1710, 1400, and 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.19 (9 H, s), 2.77 (4 H, m), 2.9–3.3 (1 H, m), 3.6–4.5 (3 H, m), 4.54 (1 H, ddd, *J* = 5.5, 4.0, 4.0 Hz), and 5.13 (1 H, ddd, *J* = 5.5, 3.7, 3.7 Hz); CIMS *m/z* (relative intensity) 270 [$(M+H)^+$, 28], 226 (5), 196 (5), 186 (16), 168 (100), 167 (60), 103 (15), and 85 (20). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.10; H, 7.10; N, 5.12.

(1*R*,5*R*)-7-Thioxo-6-(2-pivaloyloxyethyl)-2-oxa-6-azabicyclo[3.3.0]octan-3-one (38). A mixture of **37** (505 mg, 1.88 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (610 mg, 1.51 mmol) in toluene was heated at 105 °C for 1 h under nitrogen, cooled to room temperature, and concentrated. The resulting solid was purified by column chromatography on silica gel (20 g) with 3:2 hexane–EtOAc, yielding **38** (602 mg) as colorless crystals: mp 105-106 °C (EtOAc-hexane); IR ($CHCl_3$) 1790, 1730, 1465, and 1145 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (9 H, s), 2.90 (2 H, m), 3.30 (1 H, dd, *J* = 19.7, 6.1 Hz), 3.44 (1 H, d, *J* = 19.7 Hz), 3.46 (1 H, m), 4.28 (1 H, ddd, *J* = 11.9, 6.8, 4.1 Hz), 4.45 (1 H, ddd, *J* = 11.9, 6.6, 3.7 Hz), 4.64 (1 H, ddd, *J* = 14.5, 6.6, 4.1 Hz), 4.85 (1 H, ddd, *J* = 5.6, 5.6, 2.3 Hz), and 5.16 (1 H, m); EIMS *m/z* (relative intensity) 285 (M^+, 47), 200 (25), 184 (50), 183 (100), 182 (77), and 158 (55). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.66; H, 6.72; N, 4.84.

(1*R*,5*R*)-6-(2-Pivaloyloxyethyl)-2-oxa-6-azabicyclo[3.3.0]octan-3-one (39). To a cooled (0 °C), stirred solution of **38** (602 mg, 2.11 mmol) in CH_2Cl_2 (6 ml) under nitrogen was added a solution of triethyloxonium tetrafluoroborate (497 mg, 2.62 mmol) in CH_2Cl_2 (4 ml). The mixture was stirred at 0 °C for 5 min and then at room temperature for 1 h. After the mixture was cooled to 0 °C, a solution of $NaBH_3CN$ (658 mg, 10.5 mmol) in MeOH (4 ml) was added. The mixture was stirred at 0 °C for 2 h and concentrated. The resulting oily residue was purified by column chromatography on silica gel (20 g) with 4:1 benzene–EtOAc, affording **39** (82% from **37**) as a pale yellow oil: $[\alpha]_D^{11}$ –8.6° (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) 1770, 1720, 1280, and 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (9 H, s), 2.0–2.7 (7 H, m), 2.92 (1 H, ddd, *J* = 13.3, 7.3, 5.0 Hz), 3.24 (1 H, m), 4.10 (1 H, ddd, *J* = 11.6, 5.6, 5.0 Hz), 4.25 (1 H, ddd, *J* = 11.6, 7.3, 4.6 Hz), and 4.94 (1 H, ddd, *J* = 7.3, 5.9, 3.0 Hz); CIMS *m/z* (relative intensity) 256 [$(M+H)^+$, 7], 153 (20), 140 (23), 103 (28), 85 (65), and 58 (100) [HRCIMS. Found: 256.1606. $C_{13}H_{22}NO_4$ [$(M+H)^+$] requires: 256.1549].

(1*R*,4*R*,*S*,5*S*)-4-(Phenylseleno)-6-(2-pivaloyloxyethyl)-2-oxa-6-azabicyclo[3.3.0]octan-3-one (40). To a cooled (–78 °C), stirred solution of **39** (164 mg, 0.643 mmol) in THF (4.0 ml) under nitrogen was added a 0.2 M solution of LDA in THF (4.8 ml, 0.97 mmol). After 15 min, a solution of PhSeCl (194 mmol, 1.02 mmol) in THF (2.0 ml) was added, and the mixture was stirred at –78 °C for 1 h. The reaction was quenched by the addition of saturated NH_4Cl solution (2 ml). The mixture was warmed to room temperature, diluted with saturated $NaHCO_3$ solution (2 ml), and extracted with EtOAc (4 x 10 ml). The extracts were combined, washed with saturated NaCl solution, dried, and concentrated. The resulting oily residue was purified by column chromatography on silica gel (20 g) with 7:1→2:1 hexane–EtOAc to give **40** (186 mg, 71%; a 9:1 mixture of diastereomers as to the PhSe group) as a pale yellow oil: IR ($CHCl_3$) 1770, 1720, 1475, 1285, and 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$; signals for the major diastereomer) δ 1.18 (9 H, s), 2.03 (1 H, m), 2.14 (1 H, m), 2.31 (1 H, ddd, J = 9.1, 7.6, 7.6 Hz), 2.50 (1 H, ddd, J = 12.9, 4.6, 4.6 Hz), 2.84 (1 H, m), 3.23 (1 H, d, J = 5.7 Hz), 3.24 (1 H, m), 3.71 (1 H, s), 4.02 (1 H, m), 4.19 (1 H, m), 4.46 (1 H, ddd, J = 7.3, 5.7, 2.9 Hz), 7.3–7.4 (3 H, m), and 7.71 (2 H, m); EIMS *m/e* (relative intensity) 411 (M^+, ^{80}Se; 24), 409 (12), 309 (27), 307 (14), 296 (75), 294 (39), 213 (40), 129 (60), 82 (55), and 56 (100) [HREIMS. Found: 411.0923. $C_{19}H_{25}NO_4{}^{80}Se$ (M^+) requires: 411.0949].

(1*R*,4*R*,*S*,5*S*)-4-(Phenylseleno)-6-(2-hydroxyethyl)-2-oxa-6-azabicyclo[3.3.0]octan-3-one (41). To a solution of **40** (46.1 mg, 0.112 mmol) in MeOH (0.5 ml) under nitrogen was added 6 M HCl (1.5 ml). The mixture was stirred at 50 °C for 17 h, cooled to room temperature, made basic (pH 9) with saturated $NaHCO_3$ solution, and extracted with EtOAc (4 x 6 ml). The extracts were combined, washed, dried, and concentrated. The resulting oily residue was purified by column chromatography on silica gel (1 g) with 2:1 hexane–EtOAc and EtOAc to give **41** (30.8 mg, 84%; a 9:1 mixture of diastereomers as to the PhSe group) as a pale yellow oil: IR ($CHCl_3$) 3670, 3500, 1765, 1580, and 1170 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$; signals for the major diastereomer) δ 2.08 (1 H, m), 2.21 (1 H, m), 2.33 (1 H, ddd, J = 9.0, 7.8, 7.8 Hz), 2.46 (1 H, ddd, J = 12.8, 3.7, 3.7 Hz), 2.78 (1 H, ddd, J = 12.8, 4.5, 4.5 Hz), 3.21 (1 H, ddd, J = 7.8, 3.1, 3.1 Hz), 3.29 (1 H, d, J = 5.6 Hz), 3.5–3.8 (2 H, m), 3.78 (1 H, s), 4.51 (1 H, ddd, J = 7.3, 5.6, 2.7 Hz), 7.3–7.4 (3 H, m), and 7.71 (2 H, m); EIMS *m/z* (relative intensity) 327 (M^+, ^{80}Se; 24), 325 (12), 296 (88), 294 (40), 157 (18), 129 (37), 113 (37), 98 (33), and 82 (100) [HREIMS. Found: 327.0399. $C_{14}H_{17}NO_3{}^{80}Se$ (M^+) requires: 327.0374].

(1*R*,4*R*,10*S*)-1-(Phenylseleno)-3-oxa-7-azatricyclo[5.2.1.0^{4,10}]decan-2-one (43). To a cooled (–78 °C), stirred solution of **41** (39.9 mg, 0.122 mmol) in THF (0.5 ml) under nitrogen was added a 1.64 M solution of *n*-BuLi in hexane (0.11 ml, 0.180 mmol), and the mixture was stirred at this temperature for 5 min. To the resulting solution was added a solution of *p*-toluenesulfonyl chloride (25.8 mg, 0.135 mmol) in THF (0.5 ml). After the mixture was stirred at –78 °C for 1 h, hexamethylphophoric triamide (HMPA) (0.045 ml, 0.256 mmol) followed by a 0.2 M solution of LDA in THF (1.21 ml, 0.244 mmol) was introduced. The reaction mixture was stirred at –78 °C for 30 min and then at –30 °C for 5 h. The reaction was quenched by the addition of saturated NH_4Cl solution (2 ml). The mixture was made basic (pH 9) with saturated $NaHCO_3$ solution (2 ml) and extracted with EtOAc (4 x 8 ml). The extracts were combined, washed, dried, and concentrated to leave an oil. Purification by column chromatography on silica gel (2 g) with 1:1 benzene–EtOAc and EtOAc provided **43** (20.0 mg, 53%) as a colorless oil, together with the recovered **41** (1.7 mg,

4%). **43**: $[\alpha]_D^{12}$ +50.9° (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 1765, 1580, and 1165 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.95 (1 H, m), 2.13 (1 H, ddd, *J* = 13.9, 5.9, 1.7 Hz), 2.31 (1 H, ddd, *J* = 11.9, 10.6, 6.6 Hz), 2.52 (1 H, ddd, *J* = 9.9, 9.9, 5.5 Hz), 2.74 (2 H, m), 3.10 (1 H, ddd, *J* = 9.9, 7.6, 1.7 Hz), 3.23 (1 H, m), 4.12 (2 H, m), 7.3–7.5 (3 H, m), and 7.72 (2 H, m); EIMS *m/z* (relative intensity) 309 (M^+, ^{80}Se; 12), 307 (6), and 156 (100) [HREIMS. Found: 309.0264. $C_{14}H_{15}NO_2{}^{80}Se$ (M^+) requires: 309.0269].

(4*R*,5*S*,6*R*)-6-Hydroxy-4-(hydroxymethyl)-4-(phenylseleno)-1-azabicyclo[3.3.0]octane (44). To a cooled (–78 °C), stirred solution of **43** (20.0 mg, 0.0647 mmol) in THF (1.0 ml) under nitrogen was added a 1.0 M solution of $LiAlH_4$ in THF (0.325 ml, 0.325 mmol), and the mixture was stirred at –10 °C for 30 min. After the reaction was quenched by the addition of 5% H_2O in THF (6 ml), the mixture was filtered through a pad of Celite. The filter cake was washed thoroughly with 5% H_2O in THF. The filtrate and washings were combined and concentrated. The resulting oily residue was purified by preparative TLC on silica gel (MeOH) to give **44** (17.0 mg, 84%) as colorless crystals: mp 169.5–171 °C ($CHCl_3$); $[\alpha]_D^{17}$ –94° (*c* 0.21, MeOH); IR (KBr) 3420, 1625, 1430, and 1115 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (1 H, dd, *J* = 13.2, 5.3 Hz), 1.8–1.9 (2 H, m), 2.27 (1 H, ddd, *J* = 14.2, 9.6, 9.6 Hz), 2.80 (1 H, dd, *J* = 9.2, 9.2 Hz), 2.93 (1 H, m), 3.15 (1 H, d, *J* = 3.0 Hz), 3.30 (1 H, m), 3.63 (1 H, ddd, *J* = 10.4, 10.4, 6.6 Hz), 3.96 (1 H, d, *J* = 14.5 Hz), 4.00 (1 H, d, *J* = 14.5 Hz), 4.20 (1 H, m), 7.3–7.5 (3 H, m), and 7.68 (2 H, m); EIMS *m/z* (relative intensity) 313 (M^+, 3), 311 (2), 155 (14), 138 (11), and 112 (100). Anal. Calcd for $C_{14}H_{19}NO_2Se$: C, 53.85; H, 6.13; N, 4.49. Found: C, 53.81; H, 6.03; N, 4.47.

(+)-Retronecine (4). To a solution of **44** (14.9 mg, 0.0487 mmol) in AcOH (0.2 ml) was added 30% H_2O_2 (0.015 mmol), and the mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of Me_2S (0.4 ml), and the mixture was concentrated. The resulting oily residue was azeotroped with benzene (3 x 1 ml) and purified by column chromatography on silica gel (1 g) with 20:1 EtOH–Et_2NH to give (+)-**4** (5.8 mg, 78%) as colorless crystals: mp 118–119 °C (acetone) [lit.[26] mp 121–122 °C (acetone)]; $[\alpha]_D^{14}$ +50.5° (*c* 0.20, EtOH) [lit.[26] $[\alpha]_D$ +50.2° (*c* 1.83, EtOH)]; IR ($CHCl_3$) 3660, 3600, 3300, 990, and 835 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 1.9–2.0 (2 H, m), 2.74 (1 H, m), 3.24 (1 H, m), 3.39 (1 H, dd, *J* = 15.2, 1.7 Hz), 3.83 (1 H, br d, *J* = 15.2 Hz), 4.1–4.2 (3 H, m), 4.30 (1 H, m), and 5.69 (1 H, d, *J* = 1.7 Hz); EIMS *m/z* (relative intensity) 155 (M^+, 100), 138 (8), 124 (7), 111 (84), 94 (57), 80 (60), and 68 (47) [HREIMS. Found: 155.0975. $C_8H_{13}NO_2$ (M^+) requires: 155.0946].

Cyclic Anhydride 48. To a solution of **6** (43 mg, 0.16 mmol) in CH_2Cl_2 (3 ml) under nitrogen was added dicyclohexylcarbodiimide (32 mg), and the mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was taken up in benzene (ca. 2 ml), and the insoluble materials were removed by filtration through a cotton plug. The filtrate and washings were combined and concentrated to leave crude **48** (41 mg) as a colorless oil, which was sufficiently pure and used for the next reaction without further purification. **48**: IR ($CHCl_3$) 1785, 1745, 1645, 1055, and 965 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.02 (3 H, d, *J* = 6.8 Hz), 1.58 (3 H, s), 1.88 (3 H, d, *J* = 7.3 Hz), 2.18 (3 H, s), 2.19 (1 H, m), 2.44 (2 H, m), 4.40 (1 H, d, *J* = 11.4 Hz), 4.56 (1 H, d, *J* = 11.4 Hz), and 7.20 (1 H, q, *J* = 7.3 Hz); EIMS *m/z* (relative intensity) 258 (M^+, 4), 240 (2), 230 (1), 212 (2), 210 (1), 200 (1), 183 (7), 164 (7), and 153 (100).

Seco Acid 50. A mixture of (+)-retronecine (**4**) (39 mg, 0.25 mmol) and Bu_2SnO (69 mg, 0.28 mmol) in benzene (20 ml) under nitrogen was heated under reflux for 19 h with continuous removal of water by using Molecular Sieves 4A. After being cooled to room temperature, the reaction mixture was concentrated to a volume of ca. 10 ml, yielding the benzene solution of the retronecine stannoxane **49**. To the cooled (5 °C), stirred benzene solution containing **49** under nitrogen was added a solution of **48** (41 mg, 0.16 mmol) in benzene (3.5 ml). The reaction mixture was stirred at 5 °C for 10 min and then at room temperature for 3 h, and concentrated to leave an oily residue, which was purified by column chromatography on silica gel (3 g) with 10:8:1 $CHCl_3$–MeOH–H_2O to give **50** (63 mg, 98% from **6**) as a colorless oil: $[\alpha]_D^{15}$ +51.4° (*c* 0.66, $CHCl_3$); IR ($CHCl_3$) 3600–2400, 1730, 1635, 1555, 1400, 1135, and 1115 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (3 H, d, *J* = 6.6 Hz), 1.48 (3 H, s), 1.75 (3 H, d, *J* = 6.9 Hz), 2.24 (3 H, s), 2.29 (1 H, s, OH), 1.9–2.4 (5 H, m), 2.92 (1 H, m), 3.53 (1 H, br d, *J* = 16.0 Hz), 3.76 (1 H, m), 4.27 (1 H, br d, *J* = 16.0 Hz), 4.56 (1 H, d, *J* = 10.7 Hz), 4.78 (1 H, d, *J* = 10.7 Hz), 4.5–4.9 (4 H, m), 5.73 (1 H, br s), 6.79 (1 H, q, *J* = 6.9 Hz), and 8.0 (1 H, br, COOH); EIMS *m/z* (relative intensity) 413 (M^+, 5), 366 (2), 308 (3), 238 (5), 210 (6), 199 (10), 138 (100), 136 (99), and 93 (99) [HREIMS. Found: 413.1930. $C_{20}H_{31}NO_6S$ (M^+) requires: 413.1872].

Integerrimine MTM Ether (51). To a stirred solution of **50** (63 mg, 0.15 mmol) in THF (3.5 ml) under nitrogen was added Et_3N (0.09 ml, 0.65 mmol) followed by a solution of 2,4,6-trichlorobenzoyl chloride (41 mg, 0.17 mmol) in THF (1 ml). The reaction mixture was stirred at room temperature for 2 h and diluted with toluene (18 ml). The diluted mixture was added dropwise over a 1.5-h period to a refluxing toluene (30 ml) solution containing 4-(dimethylamino)pyridine (112 mg, 0.92 mmol) under nitrogen, and the mixture was heated under reflux for an additional 2 h. After being cooled to room temperature, the reaction mixture was concentrated to leave an oily residue, which was purified by preparative TLC on silica gel (70:10:1 $CHCl_3$–MeOH–conc. NH_3), affording **51** (45 mg, 75%) as a colorless oil: $[\alpha]_D^{24}$ +51.2° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 1735, 1720, 1655, 1455, 1270, and 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (3 H, d, *J* = 6.6 Hz), 1.46 (3 H, s), 1.76 (3 H, d, *J* = 6.9 Hz), 2.26 (3 H, s), 2.1–2.4 (3 H, m), 2.4–2.6 (3 H, m), 3.39 (2 H, m), 3.98 (1 H, m), 4.02 (1 H, d, *J* = 11.9 Hz), 4.40 (1 H, m), 4.64 (1 H, d, *J* = 10.9 Hz), 4.99 (1 H, d, *J* = 10.9 Hz), 5.02 (1 H, m), 5.35 (1 H, d, *J* = 11.9 Hz), 6.22 (1 H, m), and 6.52 (1 H, q, *J* = 6.9 Hz); EIMS *m/z* (relative intensity) 395 (M^+, 10), 348 (16), 334 (4), 319 (8), 290 (99), and 136 (100) [HREIMS. Found: 395.1767. $C_{20}H_{29}NO_5S$ (M^+) requires: 395.1766].

(–)-Integerrimine (1). To a solution of **51** (10.8 mg, 0.027 mmol) in CH_2Cl_2 (1 ml) under nitrogen was added triphenylcarbenium tetrafluoroborate ($Ph_3C{\cdot}BF_4$) (10.8 mg, 0.33 mmol), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution (5 ml), and the mixture was extracted with $CHCl_3$ (4 x 7 ml). The combined extracts were washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried, and concentrated. The residual oil was purified by column chromatography on silica gel (1 g) with 70:10:1 $CHCl_3$–MeOH–conc. NH_3, providing (–)-**1** (7.4 mg, 81%) as colorless crystals: mp 169–170.5 °C (acetone) [lit.[32] mp 168–169 °C (acetone)]; $[\alpha]_D^{17}$ –19.5° (*c* 0.15, $CHCl_3$) [lit.[32] $[\alpha]_D$ –21.4° (*c* 9.00, $CHCl_3$)]; IR ($CHCl_3$) 3660, 3520, 1715, 1655, 1450, 1275, and 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (3 H, d, *J* = 6.9 Hz), 1.33 (3 H, s), 1.75 (3 H, d, *J* = 6.9 Hz), 1.8–2.3 (4 H, m), 2.50 (2 H, m), 3.20 (1 H, br s, OH), 3.25 (1 H, dd, *J* = 7.8, 7.8 Hz), 3.40 (1

H, ddd, J = 15.2, 5.9, 1.7 Hz), 3.95 (1 H, d, J = 15.2 Hz), 4.11 (1 H, d, J = 11.9 Hz), 4.32 (1 H, m), 5.01 (1 H, ddd, J = 4.0, 4.0, 2.0 Hz), 5.42 (1 H, d, J = 11.9 Hz), 6.22 (1 H, m), and 6.52 (1 H, q, J = 6.9 Hz); EIMS *m/z* (relative intensity) 335 (M^+, 11), 291 (13), 248 (8), 220 (19), 138 (43), 136 (60), 119 (100), 95 (65), 93 (78), and 80 (39) [HREIMS. Found: 335.1712. $C_{18}H_{25}NO_5$ (M^+) requires: 335.1732].

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