followed by back-extraction with 5 mL of ethyl acetate. Organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude oil, which solidified on standing at room temperature. Further purification by preparative TLC using one (10 cm × 20 cm × 0.5 mm) plate with two elutions of 30% ethyl acetate in hexanes yielded 18.3 mg (91.6%) of pure epoxide **22**: mp 104 °C (sealed capillary); $[\alpha]^{26}_D$ +143.9° (*c* 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.44 (q, 1 H, *J* = 3.61 Hz), 3.81 (dq, 1 H, *J* = 2.53, 10.1 Hz), 3.73 (t, 1 H, *J* = 11.6 Hz), 3.69 (s, 3 H), 3.38 (dd, 1 H, *J* = 4.69, 11.6 Hz), 3.16 (d, 1 H, *J* = 10.1 Hz, D_2O exchange), 2.93 (s, 2 H), 2.63 (tt, 1 H, *J* = 3.61, 11.9 Hz), 2.30 (ddd, 1 H, *J* = 2.53, 4.33, 14.8 Hz), 1.96–2.06 (m, 2 H), 1.854 (dd, 1 H, *J* = 2.89, 14.4 Hz), 1.60 (dd, 1 H, *J* = 3.25, 14.4 Hz), 1.6–1.4 (m, 3 H), 1.24–1.50 (m, 2 H), 0.89 (d, 3 H, *J* = 6.86 Hz); IR (KBr pellet) 3510, 2950, 1734, 1440, 1165, 1110, 1055, 950, 855 cm^{-1}; MS (70 eV), *m/e* (no M^+), 71.10 (100), 191.10 (9.3), 182.20 (71.1), 164.20 (33), 140.10 (38), 131.10 (86), 113.10 (49), 81.1 (47); ^{13}C NMR ($CDCl_3$) δ 175.95, 103.52, 73.81, 70.43, 68.01, 62.35, 51.68, 49.83, 38.14, 37.13, 36.69, 34.48, 29.60, 26.31, 22.03, 13.02.

(+)-Synthetic Phyllanthocin (1). To a solution of epoxide **22** (17.7 mg, 0.058 mmol) in 2.0 mL of dry methylene chloride under argon in a 10-mL round-bottom flask fitted with a condenser was added excess anhydrous 4-(dimethylamino)pyridine (25 mg) followed by 20 mg of freshly distilled cinnamoyl chloride. This yellow solution was stirred at room temperature for 10 min then warmed to reflux under argon. A white precipitate was formed with refluxing for 8 h. TLC analysis showed a new product at R_f 0.41. After it was quenched with aqueous saturated NH_4Cl solution (2 mL) and ethyl acetate (10 mL), the aqueous phase was separated and back-extracted twice with 5.0 mL of ethyl acetate. Organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude brown product, which was further purified on two (20 cm × 20 cm × 0.25 mm) TLC plates eluted 3 times with 30% ethyl acetate in hexanes. Recovery from silica gel followed by evaporation furnished a crystalline (+)-phyllanthocin **1**, 18.6 mg (72.6%): mp 118–120 °C uncorrected (pentane); $[\alpha]^{24}_D$ +24.9° (*c* 1.86, $CHCl_3$); ^1H NMR 360 MHz ($CDCl_3$) δ 7.76 (d, 1 H, J = 15.9 Hz), 7.53 (m, 2 H), 7.38 (m, 3 H), 6.48 (d, 1 H, *J* = 15.9 Hz), 5.09 (br q, 1 H, *J* = 2.89 Hz), 4.39 (q, 1 H, *J* = 3.43 Hz), 4.02 (t, 1 H, *J* = 11.2 Hz), 3.45 (dd, 1 H, *J* = 4.33, 10.8 Hz), 3.28 (s, 3 H), 2.97 (d, 1 H, *J* = 5.42 Hz), 2.92 (d, 1 H, *J* = 5.42 Hz), 2.42 (tt, 1 H, *J* = 3.61, 11.9 Hz), 2.23 (br d, 1 H, *J* = 14.4 Hz), 2.04 (dd, 1 H, *J* = 2.89, 15.2 Hz), 1.84–2.00 (m, 3 H), 1.72 (ddd, 1 H, *J* = 3.61, 12.3, 14.8 Hz), 1.63 (dd, 1 H, *J* = 3.25, 15.2 Hz), 1.60 (m, 1 H), 1.35 (dq, 1 H, *J* = 3.61, 13.7 Hz), 1.22 (dq, 1 H, *J* = 3.25, 14.8 Hz), 0.88 (d, 3 H, *J* = 6.86 Hz); IR (KBr pellet) 2950, 1720, 1700, 1635, 1625, 1445, 1434, 1357, 1292, 1287, 1248, 1200, 1167, 1120, 1050, 1020, 988, 978, 945, 898, 763, 705, 678, 618; UV λ_{max} (ϵ) 202 (15 100), 214 (15 400), 220 (13 000), 274 (20 100); ^{13}C NMR 90 mHz ($CDCl_3$) δ 176.08, 166.64, 144.43, 134.64, 129.97, 128.73, 127.98, 118.91, 101.98, 72.65, 71.12, 69.83, 63.00, 51.21, 50.23, 38.63, 36.86, 34.37, 33.11, 29.94, 26.54, 22.22, 12.79.

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Supplementary Material Available: A complete listing of experimental procedures, proton and carbon NMR, infrared, mass spectral data, rotations, and combustion analyses for remaining compounds of Schemes I and II (5 pages). Ordering information is given on any current masthead page.

Total Synthesis of a Macrocyclic Pyrrolizidine Alkaloid, (±)-Integerrimine, Utilizing an Activable Protecting Group

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Abstract: A new esterification reaction has been developed utilizing a (methylthio)methyl (MTM) group as an activable protecting group of carboxylic acid. A total synthesis of a 12-membered pyrrolizidine alkaloid, (±)-integerrimine (**1**), has been achieved by applying the above method to formation of the macrocyclic bislactone skeleton. The acid anhydride (**16b**) of the integerrinecic acid derivative was coupled with lithium alkoxide of retronecine silyl ether (**5b**) in the presence of DMAP to afford the α,β-unsaturated ester. Oxidation of the MTM group afforded an active (methylsulfonyl)methyl ester (**28b**), which cyclized to give the macrocyclic bislactone **29**.

Large-ring bislactonic pyrrolizidine alkaloids, which display diverse biological activities, have attracted much interest as synthetic targets due to their characteristic tricyclic bislactonic structures.[1,2] These macrocyclic pyrrolizidine alkaloids generally consist of necine base (pyrrolizidine diol) and necic acid (long-chain diacid) components, combined through ester linkages. Although syntheses of the pyrrolizidine moiety of these alkaloids have been widely studied, a successful total synthesis of a macrocyclic pyrrolizidine alkaloid had not been reported when we first commenced this work in spite of the recent rapid progress made in macrolide synthesis. We therefore sought to develop a strategy for the synthesis of macrocyclic pyrrolizidine alkaloids.

During the course of our studies, a few examples have been reported concerning the formation of 11-membered bislactonic skeletons.[3] As a model study, Robins demonstrated that the formation of a large-ring bislactone proceeds efficiently utilizing the Corey–Mukaiyama method.[3a] And they successfully applied

(1) (a) Warren, F. L. *Fortschr. Chem. Org. Naturst.* **1955**, *12*, 198; **1966**, *24*, 329: (b) Robins, D. J. *Ibid.* **1981**, *41*, 8: (c) Gelbaum, L. T.; Gordon, M. M.; Miles, M.; Zalkow, L. H. *J. Org. Chem.* **1982**, *47*, 2501 and references cited therein.

(2) For recent synthesis of pyrrolizidine bases, see: (a) Hart, D. J.; Yang, T. K. *Tetrahedron Lett.* **1982**, *23*, 2761. (b) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (c) Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *Heterocycles* **1982**, *19*, 1605. (d) Rüeger, H.; Benn, M. *Ibid.* **1982**, *19*, 23: (e) Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096 and references cited therein.

(3) (a) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Chem. Commun.* **1980**, 282. (b) Devlin, J. A.; Robins, D. J. *Ibid.* **1981**, 1272. Brown K.; Devlin, J. A.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1819. (c) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861. (d) After submission of this paper we learned that the total synthesis of 11-membered pyrrolizidine alkaloids, (±)-fulvine and (±)-crispatine, has been accomplished by E. Vedejs and S. D. Larsen on the basis of the lactonization of ω-mesyloxy carboxylates. We thank Professor Vedejs for communicating his results to us prior to publication.

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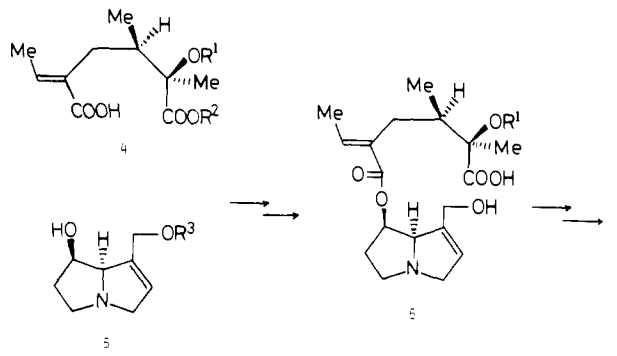
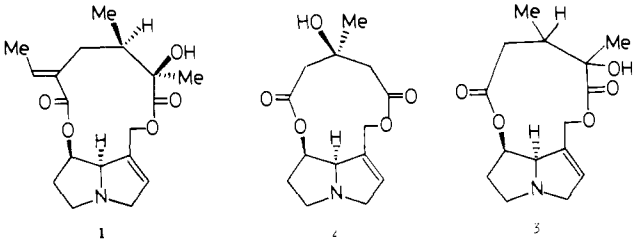
Scheme I



this method to the synthesis of a naturally occurring simple 11-membered alkaloid, dicrotaline (**2**).[3b] Meinwald directed efforts toward the synthesis of crobarbatine (**3**), an 11-membered pyrrolizidine alkaloid. They prepared the acetate derivative; however, attempts to deprotect the acetyl group were unsuccessful due to the instability of the alkaloid under both acidic and basic conditions.[3c]

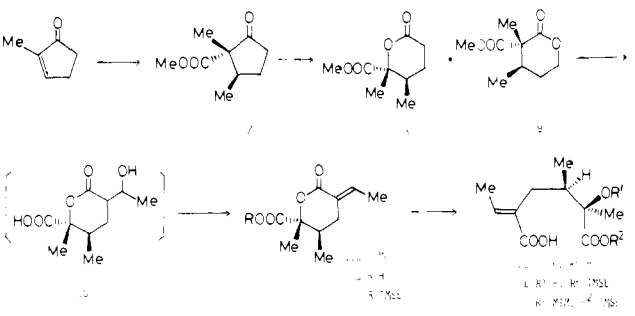


In this paper we wish to report the total synthesis of a 12-membered pyrrolizidine alkaloid, (±)-integerrimine (**1**), utilizing a (methylthio)methyl group as an activable protecting group in the key step for construction of the macrocyclic bislactone system.[4] Integerrimine was first noted by Manske as a minor alkaloid after separation of senecionine from *S. integerrinus*,[5] and Adams isolated it as a sole alkaloid from *Crotalaria incana*.[6] The structure of this alkaloid has been determined as the isomer of senecionine, differing only in the configuration of ethylidene group.[6,7] We thus chose integerrimine (**1**) as a challenging synthetic target since it is a typical 12-membered pyrrolizidine alkaloid bearing a rather complicated unsymmetrical necic acid moiety. Furthermore the preparation of this alkaloid should afford a general pathway for synthesis of other macrocyclic pyrrolizidine alkaloids.

The general synthetic approach is presented in Scheme I. First, integerrinecic acid (**4**) and retronecine (**5**), the two hydrolysis products of **1**, were to be synthesized in a stereoselective manner. We then proposed to couple these two components to form an unsaturated acid ester, the target molecule, (±)-integerrimine, being envisaged to arise by lactonization of the corresponding hydroxy acid (**6**) using pyridinium salt methodology.[8]

A synthesis of integerrinecic acid (**4**) has been reported by Geissman in 1961,[9] however, this route is inappropriate on a large preparative scale in stereoselectivity. Therefore it was desirable to establish a convenient route for the stereoselective synthesis of integerrinecic acid (**4**). This was achieved starting from 2-methyl-2-cyclopentenone, the relative stereochemistry between C-2 and C-3 being controlled by carboxylation of the lithium

Scheme II



enolate of cyclopentanone system. Thus, 2-methyl-2-cyclopentenone was treated with (dimethylcopper)lithium at 0 °C in ether and the resulting enolate was quenched with carbon dioxide at −78 °C. The reaction mixture was acidified to pH 2 by addition of hydrochloric acid, and the etheral extract was treated with diazomethane to afford methyl 2,3-dimethyl-1-oxocyclopentane-2-carboxylate in 80% yield. Gas chromatography and NMR analysis of the product showed that reaction proceeds stereoselectively and the desired *cis*-dimethyl isomer (**7**) was contaminated with less than 6% of the *trans*-dimethyl isomer (Scheme II).

Next, the product (**7**) was submitted to Baeyer–Villiger oxidation. The Baeyer–Villiger oxidation of 1,3-diketones and β-keto esters bearing an active hydrogen generally does not follow the normal pattern of the Baeyer–Villiger reaction.[10] On the other hand, it has been demonstrated that an α,α-disubstituted β-diketone (no α-hydrogen available) presumably undergoes the normal Baeyer–Villiger reaction.[11] In fact, when **7** was treated with *m*-chloroperbenzoic acid in the presence of lithium carbonate, the oxidation proceeded smoothly to give the 4,5-dimethyl lactone **8** (76% yield) and the 2,3-dimethyl isomer **9** (13% yield) as major and minor products, respectively.

Usually the more electron-releasing group migrates in the Baeyer–Villiger oxidation, however, the predominant migration of the electronically unfavorable C(Me)COOMe group was observed in the above reaction. This phenomenon might be explained considering steric and dipole–dipole interactions in the cyclic transition state[12] of the oxidation. That is, a transition state in which the leaving acyloxy group orients toward the methylene group of the cyclopentanone ring should be more favorable than a transition state with the acyloxy group oriented in the opposite direction due to steric interactions[13] and dipole–dipole repulsion between the two carbonyl groups. Hence, the electronically disfavored C(Me)COOMe group migrates predominantly from the anti direction to the leaving acyloxy group.

Next, the ethylidene group was introduced by treatment of the lithium enolate of **8** with freshly distilled acetaldehyde to give the adduct **10**, which was used directly in the next reaction. Dehydration of the β-hydroxy lactone **10** was examined by conventional methods such as *p*-toluenesulfonic acid catalysis or by methanesulfonyl chloride–triethylamine, but satisfactory results were not obtained. On the other hand, when crude **10** was treated with 2-fluoro-1-methylpyridinium *p*-toluenesulfonate[14] and triethylamine, 2(*E*)-ethylidenepentanolide **11a** and the 2-*Z* isomer were isolated in 60% and 9% yields, respectively. Successive hydrolysis of the methyl ester with lithium hydroxide at 0 °C afforded integerrinecic acid lactone (**11b**) quantitatively. The hydrolysis of **11b** under strong alkali conditions gave (±)-integerrinecic acid (**12a**), the melting point of which was identical with that reported in the literature.[9]

(4) Preliminary work of the synthesis of (±)-integerrimine has been briefly reported as communications: (a) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Morimoto, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 455. Narasaka, K.; Uchimaru, T. *Ibid.* **1982**, 57.

(5) Manske, R. H. F. *Can. J. Res., Sect. B* **1939**, *17B*, 1; *Chem. Abstr.* **1939**, *33*, 6321.

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(10) Hassal, C. H. "*Organic Reactions*"; Wiley: New York, 1957; Vol. 9, pp 73.

(11) Mannich, C. *Chem. Ber.* **1941**, *74*, 1007.

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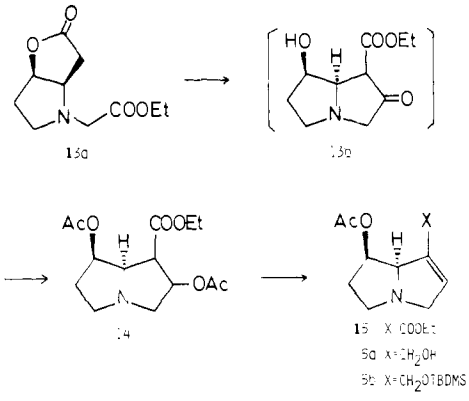
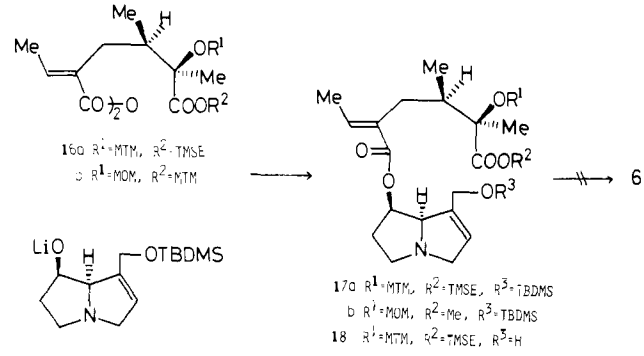
(13) Stereochemical effect on the selectivity of the Baeyer–Villiger oxidation was also reported: Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611.

(14) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

Scheme III



Scheme IV



For the preparation of integerrinecic acid monoester **12c**, the acid lactone **11b** was converted to its (trimethylsilyl)ethyl (TMSE) ester (**11c**). Selective ring opening of lactonic ester **11c** was carried out utilizing 1.1 equiv of lithium hydroxide in the presence of excess hydrogen peroxide.[15] In accordance with this procedure, hydrolysis of the lactone moiety proceeded selectively to afford **12b** in 71% yield. The resulting tertiary hydroxyl group was protected as a (methylthio)methyl (MTM) ether (Me_2SO–acetic anhydride).[16] Having now in hand the desired integerrinecic acid monoester (**12c**), preparation of necic base **5** was next investigated.

Although the necic base, retronecine, has been synthesized by several research groups,[17a] we chose to modify a procedure developed by Geissman.[17a] Thus, the Dieckmann condensation of bicyclic lactone **13a**, which was prepared according to the Geissman's route, afforded β-keto ester **13b**. We found it best to reduce this product without isolation. Therefore, the reaction mixture was quenched with acetic acid, and the concentrated mixture was reduced immediately with excess sodium borohydride in ethanol. Successive acetylation of the resultant crude mixture yielded the diester **14**, which was converted to the unsaturated ester **15** on treatment with potassium *tert*-butoxide. The reduction of **15** to retronecine was first attempted using lithium aluminum hydride, however, reduction of the olefin also occurred and a saturated diol was obtained as main product. The reduction using a slight excess of diisobutylaluminum hydride (DIBAl) was also tried, but an undesired product incorporating the isobutyl group was produced in addition to retronecine (**5a**). Selective reduction was only observed when the unsaturated ester **15** was added at −78 °C to a methylene chloride solution of a large excess of DIBAl yielding (±)-retronecine (**5a**) in 80% yield.[18]

Prior to attachment of retronecine to the necic acid moiety, the allylic hydroxyl function of **5a** needed to be suitably protected. It had been reported that the allylic alcohol of **5a** could be selectively esterified with simple acids by *N,N'*-dicyclohexylcarbodiimide;[19] however, acyl protection was considered not to be suitable in this synthetic pathway. Therefore, the *tert*-butyldimethylsilyl (*t*-$BuMe_2Si$) group was investigated as a protecting group for the allylic hydroxyl group. When silylation was carried out using methylene chloride as solvent with *t*-$BuMe_2SiCl$, triethylamine, and a catalytic amount of 4-(dimethylamino)pyridine (DMAP),[20] the yield of silyl ether (**5b**) was very low. On the other hand, **5b** was obtained in 89% yield only when dimethylformamide (DMF) was employed as a solvent (Scheme III).

As the suitably protected necic acid **12c** and base **5b** components were now in hand, various attempts were made to esterify these two components. Trials using 2-chloro-1-methylpyridinium iodide[14] and triethylamine gave none of the corresponding ester but the acid anhydride **16a**. Use of *N,N'*-dicyclohexylcarbodiimide or acid chloride methods (oxalyl chloride,[21] thionyl chloride,[22] and triphenylphosphine–carbon tetrachloride[23]) gave no ester product. Further, some mixed anhydride methods such as *p*-toluenesulfonyl chloride–pyridine, ethyl chloroformate–triethylamine, and trifluoroacetic anhydride–pyridine were applied, but the desired ester could not be obtained.

On the other hand, when 2,4,6-trichlorobenzoyl chloride–catalytic DMAP[24] or *N,N'*-carbonyldiimidazole–catalytic sodium hydride[25] was employed, the corresponding ester (**17a**) was isolated albeit in very low yields (25% and 15% yields, respectively). Finally it was noted that the acid anhydride **16a**, prepared by the reaction of **4c** with 2-chloro-1-methylpyridinium iodide and triethylamine in high yield, reacted smoothly with the lithium alkoxide of retronecine silyl ether (**5b**) in the presence of a catalytic amount of DMAP in tetrahydrofuran (THF) to afford the desired ester **17a** in 76% yield. The resulting **17a** was found to be so unstable under acidic conditions that it completely decomposed when subjected to preparative TLC on silica gel. Therefore, isolation of **17a** was performed on basic alumina. Having essentially solved the problem of the ester (**17a**) formation, the transformation of **17a** to the key hydroxy acid intermediate **6** was examined next. Attempted deprotection of TMSE and *t*-$BuMe_2Si$ groups utilizing tetrabutylammonium fluoride resulted in a complex mixture and no hydroxy acid (**6**) could be detected. Furthermore, attempts to hydrolyze the corresponding methyl ester (**17b**) with alkali were nonselective, retronecine being regenerated as the major isolable product presumably by cleavage of the unsaturated acid ester part of **17b**. At this point, we considered that the desired hydroxy acid (**6**) may be sufficiently acidic to render it too unstable to be isolated. Accordingly we were obliged to design an alternative synthetic route that does not pass through the hydroxy acid **6** (Scheme IV).

Fortunately, it became apparent that treatment of **17a** with ammonium fluoride in aqueous methanol at 60 °C resulted in clean deprotection of *t*-$BuMe_2Si$ group of the allylic hydroxyl group to give hydroxy ester **18**. This discovery prompted us to consider the introduction of "an activable protecting group" for protection of the tertiary carboxylic acid. That is, if an appropriate protecting

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(18) Retronecine can be kept without decomposition after purification. However, retronecine and these synthetic intermediates are rather unstable without isolation. Therefore, these synthetic steps should be carried out successively.

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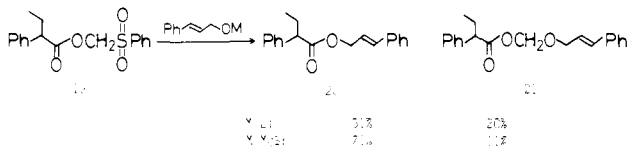
Scheme V



group that could be transformed to an activated acyl intermediate was employed for protection of acid in the hydroxy ester **18**, it was anticipated that macrocyclic bislactonic skeleton might be formed directly, bypassing the unstable hydroxy acid **6**.

Our attention was consequently turned to the development of an effective activable protecting group. The (methylthio)methyl (MTM) group is well-known as a protecting group of alcohols and carboxylic acids, and deprotection is generally carried out by heavy metal salts or oxidizing agents.[26] For example, (methylsulfonyl)methyl esters, which are derived from the MTM esters by oxidation with hydrogen peroxide–Mo(VI),[26b,27] are readily hydrolyzed by aqueous alkali. It was therefore expected that (phenylsulfonyl)methyl ester, when treated with a metal alkoxide instead of aqueous alkali, would produce the corresponding ester by elimination of metal benzenesulfinate and formaldehyde. According to this assumption, we undertook a model study using (phenylsulfonyl)methyl ester **19**. When **19** was added to a THF solution of lithium cinnamyl oxide at 0 °C, the corresponding cinnamyl ester (**20**) was obtained in 51% yield along with the acylal **21** (20% yield). Among various metal alkoxides examined, magnesium alkoxides exhibited moderate selectivity (**20**, 70%; **21**, 11%) (Scheme V).

Formation of the acylal (**21**) was not diminished reasonably when (phenylsulfonyl)methyl esters were employed. Therefore esterification via the (methylsulfinyl)methyl ester **22** was investigated. Conversion of MTM esters to **22** was achieved by oxidation with sodium periodate in aqueous ethanol in high yield. The reactions of **22b** with various metal cinnamyl oxides such as sodium, potassium, lithium, and aluminum afforded cinnamyl ester **20** in good yield. Finally it was demonstrated that (methylsulfinyl)methyl esters **22** smoothly reacted with magnesium alkoxides in THF–HMPA to yield the corresponding esters in high yields as shown in Table I. An attempt at selective esterification of **22b** under neutral conditions using cesium fluoride as an activator of cinnamyl alcohol[28] failed, with predominant formation of the acylal **21** being observed (Scheme VI).

As mentioned above, the MTM group was found to be effective as an activable protecting group of a carboxylic acid. Since this MTM methodology seemed to be promising for furnishing the macrocyclic bislactonic structure, the synthesis of (±)-integerrimine was undertaken using the MTM group as an activable protecting group. The key intermediate (**27**) was derived from **12b** according to the following pathway.

The carboxylic acid group of **12b** was converted to the MTM ester **23a** by treatment with MTM chloride, diisopropylethylamine, and sodium iodide. Then the sterically hindered tertiary hydroxyl group of **23a** was protected as a (methoxy)methyl (MOM) ether upon treatment with MOMCl, diisopropylethylamine, and sodium iodide in refluxing 1,2-dimethoxyethane (DME), in 81% yield from **12b**. Then, removal of the TMSE group with tetrabutylammonium fluoride and oxidation of the MTM group with hydrogen peroxide catalyzed by ammonium molybdate[27] afforded monoacid **24b** in an 85% yield. The free acid was protected as its MTM ester (**25a**)[29] and the (methylsulfonyl)methyl group was selectively hydrolyzed using lithium hydroxide. Treatment of the resulting monoacid **25b** (86% from **24b**) with 2-chloro-1-methylpyridinium iodide and triethylamine gave the corresponding

Scheme VI

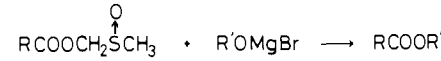
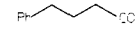
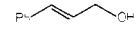
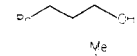
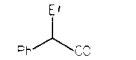
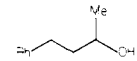
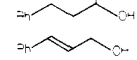
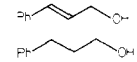
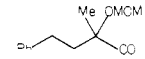
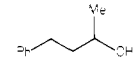
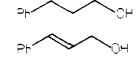
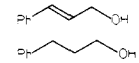
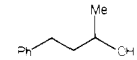
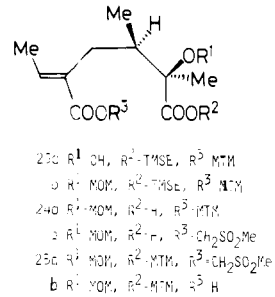


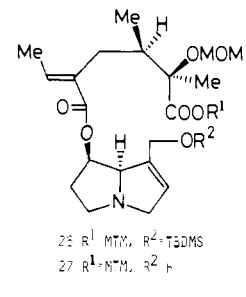
Table I. Ester Formation via (Methylsulfinyl)methyl Esters 22

22	RCO	R'OH	yield of ester, %
22a			91
			89
22b			89
			89
			93
22c			85
			92
			87
			49[a]

[a] Acylal was isolated in 30% yield.

acid anhydride (**16b**) in 91% yield. Coupling of the anhydride **16b** and retronecine silyl ether (**5b**), was achieved according to the above procedure to form the ester in 81% yield. As the present coupling was carried out starting from the racemic necic acid and the racemic necic base, the resulting ester should consist of two diastereomeric isomers (**26** and its diastereomer), which were inseparable by chromatography at this stage.[30] The *t*-BuMe$_2$Si group was then removed by treatment with ammonium fluoride in aqueous methanol to yield the key intermediate **27** (82%).

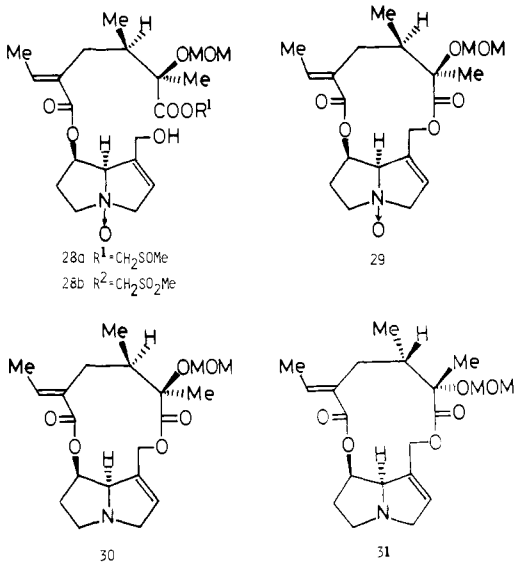




Our attention was then turned to formation of the macrocyclic bislactonic structure employing the activable protecting group methodology. The hydroxy MTM ester **27** was converted to the (methylsulfinyl)methyl ester **28a** (65%) by using hydrogen peroxide, accompanied by oxidation of necine base to the corresponding *N*-oxide. Cyclization was first attempted using the sulfinyl ester **28a**. Thus, **28a** was treated with an equimolar amount of butylmagnesium bromide in THF–HMPA at −78 °C, and the temperature was gradually elevated to 0 °C. However, the sulfinyl ester **28a** failed to cyclize, and no **29** was detected. Further attempts to cyclize **28a** via lithium alkoxide or by treatment with tetrabutylammonium fluoride[28] also did not afford bislactone **29**. Since decomposition of **28a** was expected to take place prior to cyclization, the more reactive (methylsulfonyl)methyl ester **28b**, which was derived from **27** in 73% yield by treatment with hydrogen peroxide–Mo(VI) catalysis, was employed for the cyclization. Lactonization did not occur via the magnesium alkoxide of **28b** but proceeded when the lithium alkoxide was employed as an intermediate. Treatment of **28b** with an equimolar amount of butyllithium or (triphenylmethyl)lithium in THF

(26) (a) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269. (b) Wade, L. G., Jr.; Gerdes, J. M. *Ibid.* **1979**, 689.
(27) Hardy, P. M.; Rydon, H. N.; Thompson, R. C. *Tetrahedron Lett.* **1968**, 2525.
(28) Clark, J. H.; Miller, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 498.
(29) By use of **25a**, direct esterification with the sodium alkoxide of **5b** was also examined, and the desired ester **26** was obtained in 33% yield.
(30) All subsequent reactions were carried out as a diastereomer mixture. Separation was successfully achieved at a latter stage of the synthesis (**30** and **31**).

Scheme VII



yielded the desired bislactonic product **29** in 40% yield (Scheme VII).

Having formed the integerrimine skeleton, reduction of the *N*-oxide and deprotection of the MOM group should afford (±)-integerrimine. Thus the reduction of the *N*-oxide **29** with zinc powder[31] in 1 N sulfuric acid–DME afforded diastereomeric isomers **30** and **31**, which were easily separated by preparative TLC. The less polar component was the MOM ether of integerrimine **30** (27%), and the more polar one was the corresponding diastereomer **31** (59%). Acid-catalyzed deprotection of **30** in DME–1 N sulfuric acid at 40 °C furnished (±)-integerrimine (**1**), which was spectrally and chromatographically identical with a natural authentic sample.

Thus, the total synthesis of (±)-integerrimine, a 12-membered pyrrolizidine alkaloid was successfully achieved. The present route to (±)-integerrimine affords an effective method for the synthesis of various large-ring pyrrolizidine alkaloids.

Experimental Section

Preparation of MTM Esters. As an example, preparation of (methylthio)methyl 2-phenylbutanoate is described. Under an argon atmosphere a mixture of sodium iodide (4.50 g, 30.0 mmol) and MTMCl (2.70 g, 28.0 mmol) in DME (15 mL) was stirred for 20 min. Then a DME (20 mL) solution of 2-phenylbutanoic acid (3.28 g, 20 mmol) and diisopropylethylamine (3.90 g, 30 mmol) was added. The mixture was stirred for 5 h at room temperature and for 1 h under reflux. The mixture was quenched by the addition of water (40 mL) and was extracted 4 times with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to leave an oily residue. The residue was chromatographed over silica gel with hexane–ether (10:1) as the eluting solvent to yield (methylthio)methyl 2-phenylbutanoate (4.42 g, 99%). Spectral data of MTM esters: [(Methylthio)methyl 4-phenylbutanoate] IR (neat) 1730 cm^{-1}; NMR (CCl_4) δ 1.4–2.9 (m, 6 H), 2.15 (s, 3 H), 5.00 (s, 3 H), 7.10 (br s, 5 H). [(Methylthio)methyl 2-phenylbutanoate] IR (neat) 1735 cm^{-1}; NMR (CCl_4) δ 0.92 (t, J = 7 Hz, 3 H), 1.5–2.5 (m, 2 H), 2.03 (s, 3 H), 3.45 (t, J = 7 Hz, 1 H), 5.05 (s, 2 H), 7.27 (br s, 5 H). [(Methylthio)methyl 2-(methoxymethoxy-2-methyl-4-phenylbutanoate] IR (neat) 1740 cm^{-1}; NMR (CCl_4) δ 1.45 (s, 3 H), 1.6–2.9 (m, 2 H), 2.17 (s, 3 H), 3.30 (s, 3 H), 4.63 (s, 2 H), 4.98 (s, 2 H), 6.98 (br s, 5 H).

(Phenylthio)methyl 2-phenylbutanoate was also prepared according to this procedure using chloromethyl phenyl sulfide: IR (neat) 1735 cm^{-1}; NMR (CCl_4) δ 0.85 (t, J = 7 Hz, 3 H), 1.4–2.4 (m, 2 H), 3.33 (t, J = 7 Hz, 1 H), 5.23 (s, 2 H), 7.10 (br s, 5 H), 7.17 (br s, 5 H).

Preparation of (Phenylsulfonyl)methyl Ester 19. Ester **19** was prepared by a modification of the procedure reported by Hardy.[29] A mixture of the (phenylthio)methyl ester of 2-phenylbutanoic acid (855 mg, 2.99 mmol), 28% hydrogen peroxide (8 mL), 0.1 M aqueous ammonium molybdate (2 mL), and ethanol (23 mL) was stirred overnight. After usual workup and chromatography on silica gel eluting with hexane–ether (3:1), **19** was obtained in 88% yield (841 mg): IR (neat) 1760, 1335 cm^{-1}; NMR (CCl_4) δ 0.77 (t, J = 7 Hz, 3 H), 1.3–2.3 (m, 2 H), 3.37 (t, J = 7 Hz, 1 H), 4.88 and 5.06 (AB q, J = 12 Hz, 2 H), 6.9–7.7 (m, 5 H), 7.17 (br s, 5 H). Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70; S 10.07. Found: C, 64.08; H, 5.73; S, 9.56.

Preparation of (Methylsulfinyl)methyl Esters (22). To a methanol (163 mL) solution of (methylthio)methyl 2-phenylbutanoate (4.42 g, 19.7 mmol) was added sodium periodate (6.33 g, 29.6 mmol) in water (30 mL), and the mixture was stirred for 15 h at room temperature. After addition of water (50 mL), most of methanol was evaporated, and the residue was extracted 5 times with methylene chloride. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel with methylene chloride–ethanol (50:1) as the eluting solvent to afford (methylsulfinyl)methyl 2-phenylbutanoate (**22b**, 4.42 g, 93%): IR (neat) 1740, 1140, 1060 cm^{-1}; NMR (CCl_4) δ 0.88 (t, J = 7 Hz, 3 H), 1.4–2.4 (m, 2 H), 2.22 (br s, 3 H), 3.48 (t, J = 7 Hz, 1 H), 4.5–5.1 (m, 2 H), 7.17 (br s, 5 H). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; S, 13.34. Found: C, 59.71; H, 6.90; S, 13.11. (Methylsulfinyl)methyl 4-phenylbutanoate (**22a**): 88% yield; IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.6–3.1 (m, 6 H), 2.43 (s, 3 H), 4.74 and 5.00 (ABq, J = 11 Hz, 2 H), 7.10 (br s, 5 H). (Methylsulfinyl)-methyl 2-(methoxymethoxy)-2-methyl-4-phenylbutanoate (**22c**): 95% yield; IR (neat) 1750 cm^{-1}; NMR (CCl_4) δ 1.50 (s, 3 H), 1.8–2.9 (m, 4 H), 3.27 (s, 3 H), 4.67 (s, 2 H), 4.70 and 4.97 (AB q, J = 10 Hz, 2 H), 7.03 (br s, 5 H).

Esterification Utilizing (Methylsulfinyl)methyl Esters (22). To a THF (4 mL) solution of 3-phenylpropanol (144 mg, 1.06 mmol) was added a THF solution of butylmagnesium bromide (1.54 mL, 1.06 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 30 min; then HMPA (1 mL) and a THF (4 mL) solution of **22b** (243 mg, 1.01 mmol) were added. After stirring for 5 h at 0 °C, the mixture was quenched with 0.1 N HCl (10 mL) and extracted 4 times with ether. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. A liquid residue was chromatographed over silica gel using hexane–ether (6:1) to give 3-phenylpropyl 2-phenylbutanoate (264 mg, 93%): IR (neat) 1730 cm^{-1}; NMR (CCl_4) δ 0.83 (t, J = 6 Hz, 3 H), 1.4–2.7 (m, 6 H), 3.32 (t, J = 7 Hz, 1 H), 3.93 (t, J = 6 Hz, 2 H), 6.7–7.4 (m, 5 H), 7.17 (br s, 5 H). The esters in the table were also prepared according to the same procedure and their NMR and IR spectra agreed well with the assigned structures.

2,7-Diacetoxy-1-(ethoxycarbonyl)pyrrolizidine (14). To a suspension of sodium hydride (573 mmol) in benzene (350 mL) were added ethanol (26.4 g, 574 mmol) and a benzene (200 mL) solution of *N*-[(ethoxycarbonyl)methyl] lactone (**13a**, 30.5 g, 143 mmol), which was prepared according to Geissman's procedure.[17a] The mixture was refluxed for 9 h, quenched with acetic acid (41.7 g, 695 mmol), and concentrated in vacuo. The residue was dissolved in ethanol (315 mL)–water (135 mL), and small portions of sodium borohydride (25 g, 658 mmol) were added under ice cooling. The mixture was then stirred for 30 min, and acetic acid was added dropwise until the evolution of gas stopped. the mixture was concentrated under reduced pressure, the resulting precipitate was removed by filtration and washed with methylene chloride, the filtrate was concentrated, and the precipitate was filtered and washed with methylene chloride (the procedure was repeated 2 or 3 times if needed). To the concentrated residue were added pyridine (360 mL), acetic anhydride (240 mL), and a catalytic amount of DMAP. After stirring overnight, the mixture was concentrated in vacuo and a cold solution of sodium hydroxide was added. The aqueous solution was extracted 5 times with methylene chloride and the extracts were washed with brine and dried over Na_2SO_4. The methylene chloride extract was concentrated, and the residue was purified by column chromatography over silica gel with methylene chloride–ethanol (50:1) to yield **14** (10.44 g, 24%): IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 1.8–2.3 (m, 2 H), 2.5–4.4 (m, 8 H), 5.1–5.7 (m, 2 H). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N 4.68. Found: C, 55.98; H, 7.28; N, 4.66.

7-Acetoxy-1,2-didehydro-1-(ethoxycarbonyl)pyrrolizidine (15). A mixture of the diacetate **14** (5.2 g, 17.4 mmol) and potassium *tert*-butoxide (3.9 g, 34.8 mmol) in ether (80 mL) was stirred at room temperature for 30 min under an argon atmosphere. The mixture was poured into ice–water and extracted 5 times with methylene chloride. The combined extracts were washed with brine and dried over Na_2SO_4. After concentration, the oily redisue was chromatographed over silice gel by using methylene chloride–ethanol (20:1) to give **15** (2.95 g, 71%): IR (neat) 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H), 1.90 (s, 3 H), 2.0–4.7 (m, 7 H), 4.10 (q, J = 7 Hz, 2 H), 5.35 (m, 1 H), 6.68 (m, 1 H). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24, H, 7.16, N, 5.85. Found: C, 59.65; H, 7.47; N, 5.77.

(±)-Retronecine (5a). To a methylene chloride (0.8 mL) solution of diisobutylaluminum hydride (0.16 mL, 1.14 mmol) was added a meth-

(31) Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1966**, *19*, 2127.

ylene chloride (1.4 mL) solution of the unsaturated ester **15** (54 mg, 0.226 mmol) at −78 °C under an argon atmosphere. With stirring of the solution, the temperature was slowly elevated to −10 °C during 3 h, and methanol was added. The resulting precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by preparative TLC (alumina) with methylene chloride–methanol (10:1) to give (±)-retronecine (**5a**, 28 mg, 80%). Recrystallization from ethyl acetate afforded the pure sample: mp 129–130.5 °C (lit. 130–131 °C);[17a] IR (KBr) 3350 cm^{-1}; NMR (D_2O) spectrum of the synthetic (±)-retronecine agreed well with the natural one,[32] δ 1.67–1.97 (m, 2 H), 2.36–2.73 (m, 1 H), 2.93–3.43 (m, 2 H), 3.53–3.87 (m, 1 H), 5.63 (s, 1 H), 3.9–4.3 (m, 4 H). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.79; H, 8.73; N, 8.78.

(±)-9-*O*-(*tert*-Butyldimethylsilyl)retronecine (5b). To a DMF (1.5 mL) solution of retronecine (**5a**, 81 mg, 0.523 mmol) was added triethylamine (0.4 mL), *tert*-butyldimethylsilyl chloride (91 mg, 0.607 mmol), and a catalytic amount of DMAP. The mixture was stirred for 2.5 h, quenched with 0.1 N NaOH, and extracted 5 times with methylene chloride. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by preparative TLC (alumina, ether–hexane–methanol (135:15:1) gave **5b** (125 mg, 89%): IR (neat) 3450, 1100, 1080 cm^{-1}; NMR ($CDCl_3$, Me_4Si external standard) δ 0.06 (s, 6 H), 0.80 (s, 9 H), 1.7–2.0 (m, 2 H), 2.4–2.8 (m, 1 H), 2.9–3.9 (m, 4 H), 3.9–4.4 (m, 4 H), 5.60 (s, 1 H); high-resolution MS, *m/e* 269.1786, calcd for $C_{14}H_{27}O_2NSi$ 269.1811.

2-(Methoxycarbonyl)-*cis*-2,3-dimethylcyclopentanone (7). To a suspension of cuprous iodide (34.4 g, 181 mmol) in ether (100 mL) was added an ether (346 mL) solution of methyllithium (360 mmol) dropwise, while being cooled with ice–NaCl under an argon atmosphere. After this mixture was stirred for 15 min, an ether (30 mL) solution of 2-methyl-2-cyclopentenone[33] (14.41 g, 151 mmol) was added, and the mixture was stirred for 3 h. Then a large excess of powdered dry ice was added. After it was stirred for 1.5 h, the mixture was quenched and acidified carefully with 3 N HCl to pH 2. The resulting precipitate was removed by filtration, and the filtrate was extracted 4 times with ether. The combined ether extracts were treated with an ether solution of diazomethane (ca. 245 mmol). Concentration of the dried ($MgSO_4$) extract and distillation afforded 28.82 g (80%) of **7**: bp 65–70 °C (0.5 mmHg); IR (neat) 1745, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, *J* = 8 Hz, 3 H), 1.13 (s, 3 H), 1.43–3.13 (m, 5 H), 3.63 (s, 3 H). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.22; H, 8.41. The GLPC analysis and NMR spectrum showed that less than 6% of the *trans*-dimethyl isomer was contaminated in the distilled product.

5-(Methoxycarbonyl)-4,5-dimethyl-5-pentanolide (8). To a suspension of *m*-chloroperbenzoic acid (80% purity, 8.55 g, 39.7 mmol) and lithium carbonate (125 mg, 1.70 mmol) in methylene chloride (80 mL) was added a methylene chloride (20 mL) solution of the keto ester **7** (5.25 g, 30.9 mmol). The mixture was refluxed with stirring for 13.5 h under an argon atmosphere. The excess peracid was reduced by addition of aqueous sodium sulfite. The mixture was diluted with methylene chloride, washed with aqueous K_2CO_3 and brine, and dried over Na_2SO_4. Concentration in vacuo and column chromatography over silica gel using hexane–ether (1:1) as the eluting solvent gave 5-(methoxycarbonyl)-4,5-dimethyl-5-pentanolide (**8**, 4.37 g, 76%) and 2-(methoxycarbonyl)-2,3-dimethyl-5-pentanolide (**9**, 0.72 g, 13%). 5-(Methoxycarbonyl)-4,5-dimethyl-5-pentanolide (**8**): IR (neat) 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, *J* = 7 Hz, 3 H), 1.48 (s, 3 H), 1.43–2.76 (m, 5 H), 3.73 (s, 3 H). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.80; H, 7.82. 2-(Methoxycarbonyl)-2,3-dimethyl-5-pentanolide (**9**): NMR ($CDCl_3$) δ 0.97 (d, *J* = 7 Hz, 3 H), 1.38 (s, 3 H), 1.67–2.00 (m, 2 H), 2.27–2.90 (m, 1 H), 3.67 (s, 3 H), 4.03–4.53 (m, 2 H).

2(*E*)-Ethylidene-5-(methoxycarbonyl)-4,5-dimethyl-5-pentanolide (11a). A hexane solution (18.8 mL) of butyllithium (29 mmol) was added to a THF (50 mL) solution of diisopropylamine (3.23 g, 32 mmol) at −30 °C under an argon atmosphere. The solution was cooled to −70 °C, and a THF (30 mL) solution of **8** (4.98 g, 26.7 mmol) was added dropwise within 15 min. The temperature of cooling bath was elevated to −40 °C, then freshly distilled acetaldehyde (ca. 40 mmol) was added, and the mixture was stirred for 1 h between −40 and −30 °C. The reaction mixture was poured into 1 N HCl (100 mL) and extracted with four portions of ethyl acetate and five portions of methylene chloride. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residual oil was dried azeotropically with benzene and used in the next reaction without purification. To a methylene chloride (50 mL) solution of 2-fluoro-1-methylpyridinium *p*-toluenesulfonate (9.60 g, 34 mmol) was added a methylene chloride (30 mL) solution of the crude residue and triethylamine (4.04 g, 40 mmol) with ice cooling. After it was stirred overnight, the mixture was quenched with brine and extracted 4 times with methylene chloride. The extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel with hexane–acetone (5:1) to yield 60% of 2(*E*)-ethylidene lactone **11a** (3.41 g) and 9% of its 2-*Z* isomer (0.51 g). 2(*E*)-Ethylidene-5-(methoxycarbonyl)-4,5-dimethylpentanolide (**11a**): mp 56–59 °C; IR (neat) 1745, 1720, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (d, *J* = 7 Hz, 3 H), 1.50 (s, 3 H), 1.77 (d, *J* = 7 Hz, 3 H), 2.0–2.7 (m, 3 H), 3.73 (s, 3 H), 7.13 (q, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.95; H, 7.60. 2-*Z* isomer: IR (neat) 1740, 1720, 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, *J* = 7 Hz, 3 H), 1.48 (s, 3 H), 2.0–3.0 (m, 3 H), 2.12 (d, *J* = 7 Hz, 3 H), 3.68 (s, 3 H), 6.10 (q, *J* = 7 Hz, 1 H).

(±)-Integerrinecic Acid Lactone (11b). A mixture of *E* lactone **11a** (2.28 g, 10.8 mmol) and $LiOH·H_2O$ (521 mg, 12.4 mmol) in THF (20 mL) and water (20 mL) was stirred overnight at 0 °C. The mixture was washed 2 times with ether, and the water layer was acidified to pH 2 with 2 N HCl and then extracted with ether. Evaporation of dried extracts (Na_2SO_4) afforded white crystals of (±)-**11b** (2.06 g, 96%): mp 141.8–142 °C (recrystallized from benzene) (lit. 142–143 °C[9]); IR (KBr) 1750, 1680, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, *J* = 5 Hz, 3 H), 1.47 (s, 3 H), 1.73 (d, *J* = 7 Hz, 3 H), 2.0–3.0 (m, 3 H), 7.10 (q, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.39; H, 7.30.

2-(Trimethylsilyl)ethyl Ester of Integerrinecic Acid Lactone (11c). To a methylene chloride (2 mL) suspension of 2-chloro-1-methylpyridinium iodide (1.57 g, 5.96 mmol) was added a mixture of the acid lactone **11b** (787 mg, 3.97 mmol), 2-(trimethylsilyl)ethanol (709 mg, 6.01 mmol), and triethylamine (1.24 g, 12.3 mmol) in methylene chloride (10 mL). After it was stirred overnight, the mixture was quenched with water, and the organic layer was separated. The aqueous layer was extracted 3 times with ether, and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel by using hexane–ether (1:1) as the eluting solvent. The silylethyl ester **11c** (1.16 g) was obtained in 98% yield and purified by bulb-to-bulb distillation (bath temp 152 °C (2 mmHg): IR (neat) 1730, 1640 cm^{-1}; NMR ($CDCl_3$, Me_4Si external standard) δ 0.03 (s, 9 H), 0.7–1.2 (m, 5 H), 1.47 (s, 3 H), 1.67 (d, *J* = 7 Hz, 3 H), 1.9–2.5 (m, 3 H), 3.9–4.3 (m, 2 H), 7.07 (q, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78. Found: C, 60.18, H, 8.50.

2(*E*)-Ethylidene-5-hydroxy-4-methyl-5-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoic Acid (12b). A mixture of the lactone **11c** (838 mg, 2.81 mmol), $LiOH·H_2O$ (130 mg, 3.10 mmol), 28% hydrogen peroxide (7.5 mL), water (1.5 mL), and THF (10 mL) was stirred for 3 h. The mixture was acidified to pH 1 by additon of 1 N HCl and extracted 5 times with methylene chloride. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The oily residue was chromatographed over silica gel (hexane–ether; 1:1) to afford the acid **12b** (632 mg, 71%): mp 111.0–111.5 °C (recrystallized from hexane); IR (KBr) 3460, 1715, 1675, 1635 cm^{-1}; NMR ($CDCl_3$, Me_4Si external standard) δ 0.03 (s, 9 H), 0.65–1.20 (m, 5 H), 1.31 (s, 3 H), 1.77 (d, *J* = 7 Hz, 3 H), 1.95–2.50 (m, 3 H), 4.00–4.35 (m, 2 H), 6.90 (q, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{15}H_{28}O_5Si$: C, 56.93; H, 8.92. Found: C, 56.93; H, 9.14.

MTM Ester of 2(*E*)-Ethylidene-5-hydroxy-4-methyl-5-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoic Acid (23a). A mixture of sodium iodide (6.05 g, 40.3 mmol) and chloromethyl methyl sulfide (3.45 g, 35.7 mmol) in DME (60 mL) was stirred for 20 min at room temperature. To this mixture was added a DME (100 mL) solution of the carboxylic acid **12b** (8.50 g, 26.9 mmol) and diisopropylethylamine (5.20 g, 38.9 mmol). The mixture was stirred at room temperature overnight followed by refluxing for 1 h. The reaction mixture was quenched by addition of water (100 mL) and extracted 4 times with methylene chloride. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography on silica gel using hexane–ether (5:1) as the eluting solvent afforded the (methylthio)methyl ester **23a** (9.30 g, 92%): bulb-to-bulb distillation, bath temp 165 °C (1.5 mmHg); IR (neat) 1718, 1640 cm^{-1}; NMR (CCl_4, Me_4Si external standard) δ 0.03 (s, 9 H), 0.78 (d, *J* = 7 Hz, 3 H), 1.22 (s, 3 H), 0.6–1.3 (m, 2 H), 1.73 (d, *J* = 7 Hz, 3 H), 2.08 (br s, 3 H), 2.13 (s, 3 H), 2.97 (s, 1 H), 3.8–4.4 (m, 2 H), 5.02 (s, 2 H), 6.73 (q, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{17}H_{32}O_5SSi$: C, 54.22; H, 8.56; S, 8.51. Found: C, 53.97; H, 8.67; S, 8.55.

MTM Ester of 2(*E*)-Ethylidene-5-(methoxymethoxy)-4-methyl-5-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoic Acid (23b). A mixture of sodium iodide (4.31 g, 28.7 mmol) and chloromethyl methyl ether (2.99 g, 37.1 mmol) in DME (10 mL) was stirred for 10 min at room temperature. Then a solution of the alcohol **23a** (2.71 g, 7.21 mmol) and diisopropylethylamine (5.11 g, 39.6 mmol) in DME (30 mL) was stirred for 1 h at room temperature and for an additional 12 h under reflux. The

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reaction mixture was quenched with saturated Na_2CO_3 (40 mL) and water (30 mL) and extracted 4 times with methylene chloride. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over silica gel with hexane–ether (7:1) as the eluting solvent to give the methoxymethyl ether **23b** (2.65 g, 88%): bulb-to-bulb distillation, bath temp 160 °C (1.5 mmHg); IR (neat) 1725, 1645 cm^{-1}; NMR ($CDCl_3$, Me_4Si external standard) δ 0.06 (s, 9 H), 0.78 (d, J = 7 Hz, 3 H), 1.43 (s, 3 H), 2.20 (s, 3 H), 3.30 (s, 3 H), 4.67 (s, 2 H), 5.08 (s, 2 H), 4.0–4.7 (m, 2 H), 6.83 (q, J = 7 Hz, 1 H). Anal. Calcd for $C_{19}H_{36}O_6SSi$: C, 54.25; H, 8.63; S, 7.62. Found: C, 53.70; H, 8.61; S, 7.26.

5(*E*)-Ethylidene-2-(methoxymethoxy)-2,3-dimethyl-5-(((methylthio)methoxy)carbonyl)hexanoic Acid (24a). To a THF (100 mL) solution of tetrabutylammonium fluoride (8.70 g, 33.3 mmol) was added a THF solution of the 2-(trimethylsilyl)ethyl ester **23b** (6.92 g, 16.5 mmol), and the mixture was stirred for 3.5 h at room temperature. Then an aqueous solution of oxalic acid (2.97 g, 33.0 mmol) was added. The solution was extracted 4 times with methylene chloride. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The remaining oil was chromatographed over silica gel with methylene chloride–methanol (30:1) to give **24a** (4.89 g, 93%): IR (neat) 1715, 1645 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (br s, 3 H), 1.45 (s, 3 H), 1.80 (d, J = 7 Hz, 3 H), 2.20 (s, 3 H), 2.0–2.6 (m, 3 H), 3.35 (s, 3 H), 4.75 (s, 2 H), 5.12 (s, 2 H), 6.90 (q, J = 7 Hz, 1 H).

5(*E*)-Ethylidene-2-(methoxymethoxy)-2,3-dimethyl-5-(((methylsulfonyl)methoxy)carbonyl)hexanoic Acid (24b). A mixture of the MTM ester **24a** (6.00 g, 18.7 mmol), 28% hydrogen peroxide (14 mL), 0.1 M aqueous ammonium molybdate (19 mL), acetone (80 mL), and water (32 mL) was stirred for 3 h at room temperature. Water was added, and most of the acetone was evaporated in vacuo. The aqueous solution was extracted 4 times with methylene chloride, and the combined extracts were washed with brine. After drying over $MgSO_4$, the mixture was concentrated and chromatographed over silica gel with methylene chloride–methanol (50:1) as the eluting solvent. The methylsulfonyl ester **24b** (5.87 g) was obtained in 89% yield: IR (neat) 1725, 1645, 1325 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (d, J = 5 Hz, 3 H), 1.43 (s, 3 H), 1.82 (d, J = 7 Hz, 3 H), 2.0–2.6 (m, 3 H), 2.90 (s, 3 H), 3.33 (s, 3 H), 4.70 (s, 2 H), 5.03 (s, 2 H), 6.98 (q, J = 7 Hz, 1 H).

(Methylsulfonyl)methyl 2(*E*)-Ethylidene-5-(methoxymethoxy)-4-methyl-5-(((methylthio)methoxy)carbonyl)hexanoate (25a). Under an argon atmosphere, a mixture of sodium iodide (875 mg, 5.85 mmol) and chloromethyl methyl sulfide (488 mg, 5.06 mmol) in DME (25 mL) was stirred for 20 min at room temperature. Then a DME solution of the acid **24b** (1.37 g, 3.89 mmol) and diisopropylethylamine (753 mg, 5.83 mmol) was added, and stirring was continued for 6 h at room temperature. The reaction mixture was quenched with water (40 mL) and extracted 4 times with methylene chloride. The combined extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The oily residue was chromatographed on silica gel by using hexane–ether (2:1) to give the (methylthio)methyl ester **25a** (1.38 g, 86%): IR (neat) 1740, 1725, 1645, 1330 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (d, J = 6 Hz, 3 H), 1.43 (s, 3 H), 1.83 (d, J = 7 Hz, 3 H), 2.18 (s, 3 H), 2.0–2.6 (m, 3 H), 2.83 (s, 3 H), 3.32 (s, 3 H), 4.68 (s, 2 H), 5.02 (s, 2 H), 5.10 (d, J = 1.6 Hz, 2 H), 7.02 (q, J = 7 Hz, 1 H). Anal. Calcd for $C_{16}H_{28}O_8S_2$: C, 46.59; H, 6.84; S, 15.55. Found: C, 46.39; H, 6.88; S, 15.66.

2(*E*)-Ethylidene-5-(methoxymethoxy)-4-methyl-5-(((methylthio)methoxy)carbonyl)hexanoic Acid (25b). To a solution of the (methylsulfonyl)methyl ester **25a** (5.20 g, 12.6 mmol) in DME (60 mL) and water (10 mL) was added dropwise 1 N NaOH (25.2 mL) within 20 min. After the mixture was stirred for 5 h at room temperature, an aqueous solution of oxalic acid (2.50 g, 27.8 mmol) was added, and most of the DME was removed in vacuo. The mixture was extracted 4 times with methylene chloride. The combined extracts dried over $MgSO_4$ were concentrated and chromatographed over silica gel with methylene chloride–methanol (30:1) as the eluting solvent. The carboxylic acid **25b** (4.10 g) was isolated quantitatively: IR (neat) 1740, 1685, 1645 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (d, J = 5 Hz, 3 H), 1.47 (s, 3 H), 1.83 (d, J = 7 Hz, 3 H), 2.0–2.7 (m, 3 H), 2.22 (s, 3 H), 3.37 (s, 3 H), 4.75 (s, 2 H), 5.07 and 5.20 (AB q, J = 12 Hz, 2 H), 7.00 (q, J = 7 Hz, 1 H); high-resolution MS, m/e 320.1262, calcd for $C_{14}H_{24}O_6S$ 320.1292.

Acid Anhydride 16b. To a suspension of 2-chloro-1-methylpyridinium iodide (1.93 g, 7.59 mmol) in methylene chloride (15 mL) was added a methylene chloride (30 mL) solution of the carboxylic acid (**25b**, 4.03 g, 12.6 mmol) and triethylamine (1.78 g, 17.6 mmol), and the mixture was stirred for 1 day at room temperature. The reaction mixture was concentrated and purified by column chromatography on silica gel using hexane–ether (3:2) to afford the acid anhydride **16b** (3.56 g, 91%): IR (neat) 1765, 1735, 1710, 1640 cm^{-1}; NMR (CCl_4) δ 0.83 (d, J = 5 Hz, 6 H), 1.40 (s, 6 H), 1.85 (d, J = 7 Hz, 6 H), 2.0–2.7 (m, 6 H), 2.17 (s, 6 H), 3.27 (s, 6 H), 4.65 (s, 4 H), 4.98 and 5.12 (AB q, J = 12 Hz, 4 H), 6.88 (q, J = 7 Hz, 2 H); high-resolution MS, m/e 622.2455, calcd for $C_{28}H_{46}O_{11}S_2$ 622.2480.

Esterification of 5b with 16b. To a THF (20 mL) solution of the retronecine silyl ether **5b** (553 mg, 2.06 mmol) and a catalytic amount of DMAP was added a hexane solution (1.32 mL) of *n*-butyllithium (2.06 mmol) at 0 °C. After the mixture was stirred 10 min, a THF solution of the acid anhydride **16b** (1.394 g, 2.24 mmol) was added, and the mixture was stirred for 4.5 h at room temperature. The solvent was removed in vacuo and column chromatography on alumina using a hexane–ethyl acetate increasing polarity gradient (2:1–1:1) afforded the retronecine monoester **26** (954 mg, 81%): IR (neat) 1740, 1710, 1645 cm^{-1}; NMR ($CDCl_3$, Me_4Si external standard) δ 0.06 (s, 6 H), 0.84 (s, 12 H), 1.41 (s, 3 H), 1.77 (d, J = 7 Hz, 3 H), 2.18 (s, 3 H), 3.33 (s, 3 H), 4.72 (s, 2 H), 5.13 and 5.17 (AB q, J = 12 Hz, 2 H), 5.32 (m, 1 H), 5.61 (br s, 1 H), 6.81 (q, J = 7 Hz, 1 H), 1.8–4.2 (m signals); high-resolution MS, m/e 571.3005, calcd for $C_{28}H_{49}O_7NSSi$ 571.2999.

Preparation of 27 by Desilylation. A solution of retronecine monoester **26** (185 mg, 0.324 mmol) and ammonium fluoride (130 mg, 3.51 mmol) in methanol (6.6 mL)–water (3.0 mL) was heated to 60 °C for 6 h. Water (5 mL) was added and most of methanol was removed in vacuo. The mixture was extracted 5 times with methylene chloride, and the combined extracts were dried over Na_2SO_4. Concentration in vacuo and purification by preparative layer chromatography (alumina plate, eluted with methylene chloride–methanol, 20:1) gave the hydroxy ester **27** (121 mg, 82%): IR (neat) 3350, 1735, 1705, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (d, J = 5 Hz, 3 H), 1.43 (s, 3 H), 1.77 (d, J = 7 Hz, 3 H), 2.22 (s, 3 H), 3.33 (s, 3 H), 4.68 (s, 2 H), 5.12 (s, 2 H), 5.32 (br s, 1 H), 5.55 (br s, 1 H), 6.73 (q, J = 7 Hz, 1 H), 1.7–4.4 (m signals); high-resolution MS, m/e 457.2138, calcd for $C_{22}H_{35}O_7NS$ 457.2133.

Preparation of (Methylsulfonyl)methyl Ester 28b. To an ethanol (10 mL)–water (2.3 mL) solution of the hydroxy (methylthio)methyl ester **27** (433 mg, 0.95 mmol) was added 28% hydrogen peroxide (1.1 mL) and 0.1 M aqueous ammonium molybdate (1 mL), and the mixture was stirred for 1.5 h. Most of the ethanol was removed in vacuo and excess hydrogen peroxide was decomposed with manganese dioxide. The mixture was concentrated in vacuo and chloroform was added to the residue. The solid mass was removed by filtration (washed with chloroform) and the chloroform extract was concentrated in vacuo. The oily residue was purified by preparative layer chromatography (alumina plate, eluted with methylene chloride–methanol, 10:1) to give the (methylsulfonyl)methyl ester **28b** (349 mg, 73%): IR (neat) 3300, 1750, 1705, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.81 (d, J = 5 Hz, 3 H), 1.47 (s, 3 H), 1.73 (d, J = 7 Hz, 3 H), 2.93 (s, 3 H), 3.31 (s, 3 H), 4.71 (s, 2 H), 5.00 and 5.12 (AB q, J = 12 Hz, 2 H), 5.64 (br s, 1 H), 6.26 (br s, 1 H), 6.68 (m, 1 H), 1.8–4.9 (m signals).

Methoxymethyl Ether of Integerrimine *N*-Oxide (29). A THF solution of (triphenylmethyl)lithium was prepared by treatment of triphenylmethane (46.6 mg, 0.191 mmol) with a hexane solution (0.125 mL) of *n*-butyllithium (0.19 mmol) in THF (10 mL). To a THF (30 mL) solution of the active ester **28b** (92.0 mg, 0.182 mmol) was added dropwise the THF solution of (triphenylmethyl)lithium at −78 °C. The mixture was stirred for 2 h and the temperature was gradually raised to −60 °C, then concentrated in vacuo. The residue was purified by preparative layer chromatography (alumina plate, eluted with methylene chloride–methanol, 15:1) to give the cyclized product **29** (30 mg, 41%): IR (CH_2Cl_2 solution) 1735, 1720, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (m, 3 H), 1.43 (s, 3 H), 1.73 (d, J = 7 Hz, 3 H), 3.33 and 3.38 (s + s, 3:2, total 3 H), 5.17 (d, J = 12 Hz, 1 H), 5.40 (br s, 1 H), 6.00 and 6.20 (s + s, 3:2, total 1 H), 2.0–5.0 (m signals); MS base peak 379 ($M^+ - 16$).

MOM Ether of (±)-Integerrimine (30). To a mixture of the *N*-oxide **29** (22 mg, 0.056 mmol), 1 N H_2SO_4 (2 mL), and DME (1 mL) was added zinc dust (150 mg, 2.29 mmol), and the mixture was stirred for 1 h at room temperature. Excess Na_2CO_3 and acetonitrile were added and the mixture was concentrated in vacuo. Methylene chloride was added and the solid residue was removed by filtration. The methylene chloride solution was concentrated and the oily residue was purified by preparative layer chromatography (alumina plate, eluted with chloroform–methanol, 70:1) to afford the MOM ether of (±)-integerrimine (**30**, 5.6 mg, 27%) and the corresponding diastereoisomer (**31**, 12.5 mg, 59%).

MOM ether of (±)-integerrimine (**30**); less polar, R_f = 0.55 ($CHCl_3$–MeOH, 50:1); IR (CH_2Cl_2 solution) 1730, 1705, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (d, J = 7 Hz, 3 H), 1.47 (s, 3 H), 1.74 (d, J = 7 Hz, 3 H), 3.47 (s, 3 H), 4.78 and 5.03 (AB q, J = 7 Hz, 2 H), 4.97 (br s, 1 H), 4.00 and 5.73 (AB q, J = 12 Hz, 2 H), 6.18 (br s, 1 H), 6.50 (q, J = 7 Hz, 1 H), 1.2–4.4 (m signals); high-resolution MS, m/e 379.1977, calcd for $C_{20}H_{29}NO_6$ 379.1993. The diastereoisomer **31**; more polar, R_f = 0.48; IR (CH_2Cl_2 solution) 1710 having a shoulder at 1730, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (d, J = 7 Hz, 3 H), 1.46 (s, 3 H), 1.75 (d, J = 7 Hz, 3 H), 3.38 (s, 3 H), 4.54 and 4.92 (AB q, J = 8 Hz, 2 H),

5.24 (d, J = 12 Hz, 1 H), 6.03 (br s, 1 H), 6.68 (q, J = 7 Hz, 1 H), 1.2-5.2 (m signals); high-resolution MS, m/e 379.1961, calcd for $C_{20}H_{29}NO_6$ 379.1993.

(±)-Integerrimine (1). A solution of the MOM ether of integerrimine (**30**, 5.6 mg) in DME (1 mL) and 1 N H_2SO_4 (2 mL) was stirred at 40 °C for 2.5 h. Excess Na_2CO_3 and then acetonitrile were added, and the mixture was concentrated in vacuo. Methylene chloride was added and the solid residue was filtered off. Concentration of the filtrate and purification by preparative layer chromatography (alumina plate, eluted with chloroform–methanol, 60:1) afforded **(±)-integerrimine** (**1**, 4.2 mg, 86%); mp 162 °C (recrystallized from ethanol). IR (CH_2Cl_2 solution) 3540, 1710, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, 3 H), 1.33 (s, 3 H), 1.77 (d, J = 7 Hz, 3 H), 4.13 and 5.42 (AB q, J = 12 Hz, 2 H), 4.33 (br s, 1 H), 5.03 (br s, 1 H), 6.23 (br s, 1 H), 6.55 (q, J = 7 Hz, 1 H), 2.0-4.0 (m signals); ^{13}C NMR ($CDCl_3$, ppm, relative intensity %) 178.3 (7.7), 169.2 (7.3), 136.9 (15.7), 135.3 (15.6), 134.0 (10.3), 131.8 (9.2), 77.2 (28.6), 76.6 (15.3), 75.6 (15.3), 62.8 (17.3), 61.0 (16.6), 53.2 (18.9), 39.5 (16.1), 33.9 (17.3), 29.6 (15.2), 25.2 (11.6), 14.2 (12.2), 11.9 (11.6); high-resolution MS, m/e 335.1773, calcd for $C_{18}H_{25}O_5N$ 335.1743.

NMR (^1H), mass spectra, and also chromatographic mobility were completely identical with those of natural integerrimine.

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Stereochemistry of the Ethanolamine Ammonia Lyase Reaction with Stereospecifically Labeled [1-$^2H_1$]-2-Aminoethanol[1]

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Abstract: The antipodes of [1-$^2H_1$]-2-aminoethanol (**10**) have been synthesized from (*S*)-[α-$^2H_1$]benzyl alcohol and separately subjected to the action of ethanolamine ammonia lyase in the presence of alcohol dehydrogenase, in order to determine whether the migration of a hydrogen atom from C-1 to C-2 during acetaldehyde formation is stereospecific. (*R*)-**10** reacts 4 times as fast as (*S*)-**10**, the isotope effect showing that the *pro-S* hydrogen migrates preferentially in each case. ^1H and ^{13}C NMR spectra of the ethanol formed show that (*R*)-**10** leads to CH_3CHDOH while (*S*)-**10** affords DCH_2CH_2OH, confirming the stereoselectivity of hydrogen transfer.

Ethanolamine ammonia lyase (ethanolamine deaminase, E. C.4.3.1.7), first described by Bradbeer[4] and purified and characterized by Kaplan and Stadtman,[5] is a clostridial cobamide dependent enzyme which catalyzes the conversion of ethanolamine to acetaldehyde and ammonia (eq 1). The reaction is directly

$$H_2NCH_2CH_2OH \rightarrow CH_3CHO + NH_3 \quad (1)$$

analogous to the enzymatic reactions catalyzed by diol dehydrase, such as the dehydration of ethylene glycol or 1,2-propanediol (eq 2), and is related to other alkyl arrangements catalyzed by vitamin B_{12} coenzymes.

$$RCHOHCH_2OH \rightarrow RCH_2CHO + H_2O \qquad R = H \text{ or } CH_3 \quad (2)$$

The extensive studies of Babior[6,7] have revealed that a hydrogen atom from C-1 of ethanolamine migrates to C-2 without exchanging with solvent protons but that it becomes transiently attached to C-5′ of the adenosine unit of the coenzyme en route to product. A deuterium kinetic isotope effect of 6.8 shows that this hydrogen transfer is part of the rate-determining step.[6] The oxygen atom of acetaldehyde was shown to originate from the substrate, not water.[6] Current understanding of the mechanism of this and related adenosylcobalamin-dependent rearrangements is summarized in recent reviews.[8]

Stereochemistry. Although neither substrate nor product in this enzymatic reaction is chiral, two "cryptic" stereochemical questions[9] originate in the prochiral methylene groups of ethanolamine. The first is the following: does the replacement of the amino group by hydrogen occur with retention, inversion, or racemization of configuration at C-2? This question has been answered by the elegant labeling experiments of Rétey et al.:[10] chirality is lost at C-2 in the rearrangement of (*R*)- or (*S*)-[2-$^2H_1$, $^3H_1$]-2-aminoethanol (eq 3), a rare example of racemization during

$$(R)\text{- or } (S)\text{-}H_2NCDTCH_2OH \rightarrow (R,S)\text{-}CHDTCHO \quad (3)$$

biological formation of a chiral methyl group. This result has been interpreted[10] as implicating a freely rotating methylene radical intermediate at C-2. Remarkably, the related substrate

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