Tin-Mediated Esterification in Macrolide Synthesis[1]

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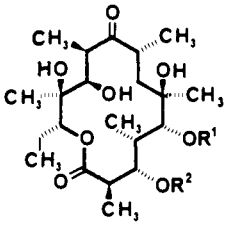
Abstract: A neutral and relatively simple new method for effecting internal macrocyclic esterification of ω-hydroxycarboxylic acids, based on a tin "template-driven" extrusion process, is discussed and its application to the synthesis (macrocyclization step) of the macrolide antibiotics zearalenone, ingramycin, and nodusmicin detailed. An efficient, formal total synthesis of pyrenophorin using this technique is also presented. Attemps to extend the methodology to include the macrocyclization of ω-bromo carboxylic acids or ω-mercapto carboxylic acids were unsuccessful. However, although β- and ω-amino carboxylic acids preferentially gave way to polymer formation, 4-, 5-, and 6-amino carboxylic acids readily condensed to give the corresponding five-, six-, and seven-membered lactams in excellent yields. For example, in this way, the bridged lactam 1-azabicyclo-[3.3.1]nonan-2-one was prepared in 77% yield as compared to the previously reported yield of less than 2%.

Recent progress in the total synthesis of natural products, particularly of the macrolide type,[2] has brought forth an advent of new and powerful synthetic methods.[3] Macrolides characteristically have elaborately complex structures that are frequently adorned by a plethora of multifunctional groups and asymmetric centers. Since many of these compounds possess potent antibiotic, antitumoral, and other types of interesting biochemical activity,[2b,3] their syntheses have currently captured the imagination of many synthetic natural products chemists. Inevitably, the penultimate synthetic hurdle in the construction of these molecules is usually associated with the closure of a seco precursor into the cyclic skeleton. This at times can be as formidable a task to effect as might be the synthetic assembly of the seco precursor itself. The recently reported total synthesis of the macrolide erythromycin (**1**) by Woodward and co-workers[4] exemplifies some of the difficulties associated with this type of synthetic transformation.



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R^1 = desosaminyl
R^2 = cladinosyl

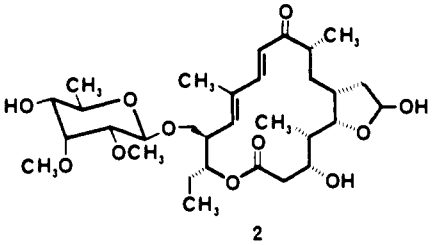

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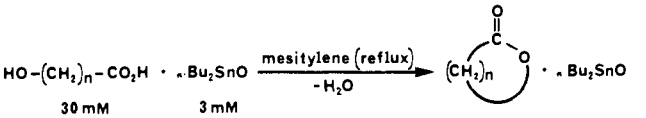
Table I



lactone	n	reaction time, h	isolated yield (diolide), % this work	isolated yield (diolide), % from ref 5n
octanolide	7	3.5	0 (20)	8 (41)
8-methylnonanolide	8	7.5	0 (36)	
undecanolide	10	19.0	5	47 (30)
dodecanolide	11	21.0	22	66 (7)
pentadecanolide	14	23.0	43	80 (5)
hexadecanolide	15	19.0	60	85 (15)[5k]

Thus, a considerable amount of effort continues to be expended in search of new, milder and more efficient methods for accomplishing ring closure in macrolide synthesis.[2b-6] Although macrocyclization can be initiated by a carbon–carbon bond forming reaction, as was opted for by Nicolaou[5b] in his elegant synthesis of *O*-mycinosyltylonolide (**2**), methodology that directly effects lactonization of the corresponding hydroxy seco acid, or some activated derivative thereof, has drawn most of the attention.[4,5] We recently communicated a novel approach for macrocyclization using a tin-mediated "template-driven" esterification process.[6] We herein report the results of our detailed study in applying this new methodology to the partial synthesis of the recently characterized new macrolide antibiotics nodusmicin[7a] and ingramycin,[7b] as well

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(2) (a) Orchin, M.; Kaplan, F.; Macomber, R. S.; Wilson, R. M.; Zimmer, H. "The Vocabulary of Organic Chemistry"; Wiley: New York, 1980; Chapter 13, p 472. (b) For some recent reviews see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. Back, T. G. *Ibid.* **1977**, *33*, 3041.

(3) Symposium on "New Synthetic Methods in Macrolide Synthesis"; 65th Canadian Chemical Conference, Toronto, Ontario, May/June 1982. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981 and references cited therein. Wang, C. C. *Trends Biochem Sci., (Pers. Ed.)* **1982**, *7*, 354. Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds.; Elsevier: New York, 1981; Vol. I, Chapter 4, and references cited therein.

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(7) (a) Whaley, H. A.; Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659. (b) Thomas, R. C.; Chidester C. G. *J. Antibiot.* **1982**, *35*, 1658. See also: Nagahama, N.; Takamori, I.; Suzuki, M. *Chem. Pharm. Bull.* **1971**, *19*, 660.

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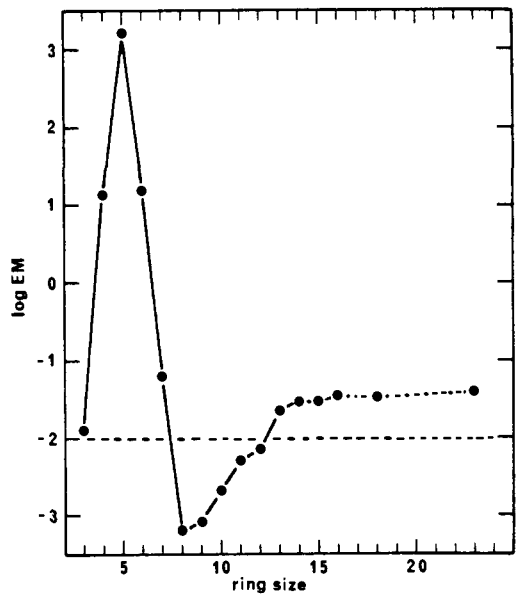


Figure 1. EM profile for lactonization of ω-bromoalkanoates in Me_2SO.[8]

as to the formal total synthesis of (±)-pyrenophorin, (±)-vermiculine, and other macrocyclic lactones.

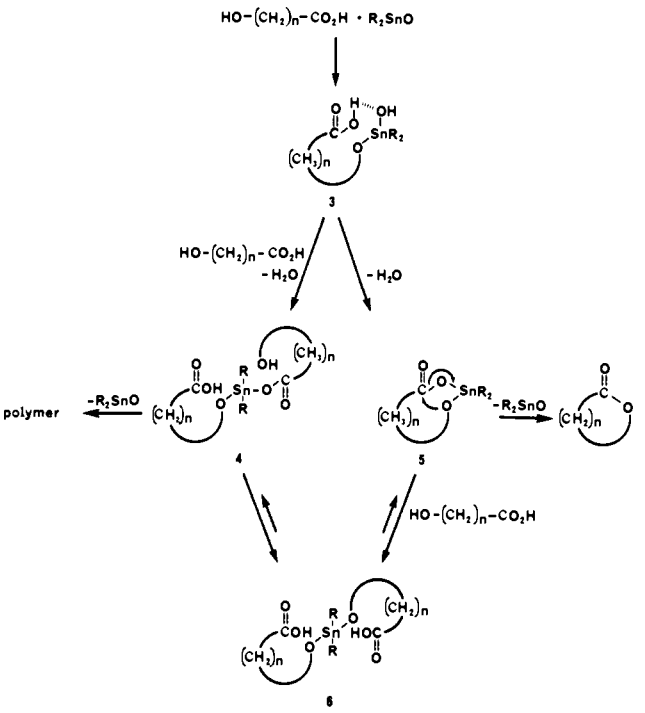
Results and Discussion

Macrolide forming methodology (in particular Kellogg's,[5j] Rastetter's,[5k] and possibly our own[6]) invoking the concept of a "template-held", doubly activated intermediate for favoring intramolecular over intermolecular esterification has been seriously brought into question by Mandolini and co-workers.[8] These authors suggest that from their studies of the kinetics of ring forming reactions employed in some macrolide syntheses the yield for intramolecular cyclization is more likely to be a consequence of the "effective-molarity"[8] of the reaction and not due to any implied "template" effect that could be rigorously defended. Thus, for example, they report in accordance to Figure 1[8] that concentrations of more than 10^{-2} M of ω-bromoalkanoate ions in Me_2SO at 50 °C did not yield any significant amounts of 8- to 12-membered ring lactones, whereas, however, concentrations of 10^{-3} M preferentially gave all but the eight- and nine-membered lactones in excellent yields.[8]

Our experimental results (See Table I) for the macrocyclization of some ω-hydroxy carboxylic acids using di-*n*-butyltin oxide as the catalytic agent for macrolide formation are generally consistent with Mandolini's[8] conclusions. For example, treating 3×10^{-2} M solutions of a series of ω-hydroxy carboxylic acids in refluxing mesitylene (bp 165 °C) with 10% (mol equiv) di-*n*-butyltin oxide with use of a Dean–Stark apparatus for the continuous removal of water gave respectable yields (22–63%) of the corresponding 13- to 17-membered lactones. However under these same conditions, we were not able to isolate any monomeric eight- to ten-membered lactones. Their dimeric and polymeric forms prevailed.

Our strategy in employing di-*n*-butyltin oxide as an effective mediator for the macrocyclization of ω-hydroxy carboxylic acids was based on the premise that stannylation of an ω-hydroxy carboxylic acid with di-*n*-butyltin oxide would give way, due to initial preferential stannylation of the hydroxy functional group,[9a] to the formation of an ω-hydroxystannylenealkoxy carboxylic acid intermediate, **3** (see Scheme I). The fate of this intermediate, in essence, predetermines the extent to which macrolide formation will occur. Thus, in a reasonably dilute solution[8] (which we experimentally found to be 10^{-2} M; see Table I) "double activation"

Scheme I



through internal hydrogen bonding favors the formation of cyclic alkoxystannylene carboxylate **5**. The formation of undesirable intermediates **4** or **6** by intermolecular stannylation or by transstannylation accordingly leads to polymeric condensation. (A similar mechanism based on kinetic studies[10a] for the dimethyltin oxide catalyzed polyesterification of aromatic carboxylic acids with ethylene glycol has been recently put forth by Parshall[10b].)

Cyclic alkoxystannylene carboxylate **5** inherently possesses the characteristic virtues ("doubly activated" and "template-held") required for macrolide formation. The nucleophilicity of the alkoxy group is activated by being bonded to tin[11] while at the same time, activation of the carboxylate group is enhanced by the leaving ability of di-*n*-butyltin oxide.[5f,6] The "template" effect is a natural consequence of the *chemical binding* of tin oxide into the cyclic skeleton. Hence, thermal extrusion of di-*n*-butyltin oxide from this "template-held" cyclic intermediate concomitantly leads to macrolide formation (vide infra).

The use of tri-*n*-butyltin as a carboxylate substrate for directing the lactonization of ω-bromo carboxylic acids, on the other hand, gave disappointing results. For example, refluxing a 10^{-2} M mesitylene solution of tri-*n*-butyltin 16-bromohexadecanoate gave less than 15% hexadecanolide (eq 1; hexadecanolide is stable under

$$\mathrm{Br(CH_2)_{15}CO_2Sn}n\text{-}\mathrm{Bu_3} \xrightarrow{\Delta} \text{hexadecanolide (15\%)} + \text{polymers} + n\text{-}\mathrm{Bu_3SnBr} \quad (1)$$

these reaction conditions). Since Kellogg[5j] reports excellent yields for the analogous cesium-based reaction, employing cesium as the carboxylate counterion in these types of internal macrocyclizations must incorporate some positive contributory effect not present with tri-*n*-butyltin. Thus, dilution,[8] although probably the predominating factor, is also in itself insufficient cause for initiating intramolecular lactonization.[5j]

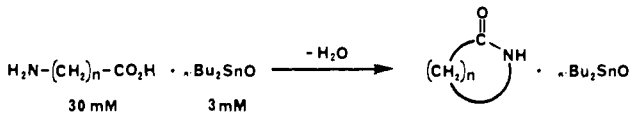
(8) (a) Galli, C.; Mandolini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 251. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. See also references to previous work cited therein.

(9) (a) Davies, A. G.; Kleinschmidt, D. C.; Palan, P. R.; Vasishtha, S. C. *J. Chem. Soc. C* **1971**, 3972. (b) Frankel, M.; Gertner, D.; Wagner, D.; Zilkha, A. *J. Org. Chem.* **1965**, *30*, 1596.

(10) (a) Nondek, L.; Málek, J. *Makromol. Chem.* **1977**, *178*, 2211. Habib, O. M. O.; Málek, J. *Collect. Czech. Chem. Commun.* **1976**, *41*, 2724. (b) Parshall, G. W. "Homogenious Catalysis"; Wiley-Interscience: New York, 1980; Chapter 11, p 213.

(11) (a) Davies, A. G.; Mitchell, T. N.; Symes, W. R. *J. Chem. Soc. C* **1966**, 1311. (b) Itoh, K.; Kato, Y.; Ishii, Y. *J. Org. Chem.* **1969**, *34*, 459. (c) *Adv. Chem. Ser.*, **1976**, *No. 157*. (d) Davies, A. G. in "Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds"; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon Press: New York, 1982; Vol. 2, Chapter 11.

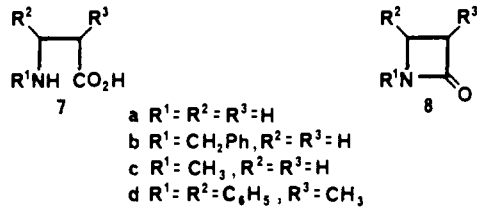
Table II



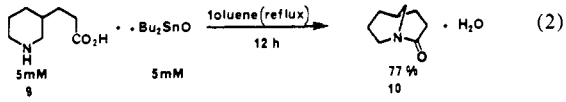
lactam	n	solvent[a]	reaction time, h	isolated yield, %
2-pyrrolidinone	3	X	12	95
δ-valerolactam	4	X	12	95
ε-caprolactam	5	X	12	95
2-azacyclooctanone	6	M	6	8
2-azacyclononanone	7	M	6	0

[a] M = mesitylene, X = xylene.

Tin mediated internal condensation of ω-amino carboxylic acids is of limited utility. Although several β-amino carboxylic acids (**7**) were treated with di-*n*-butyltin oxide under a variety of reaction conditions, no corresponding β-lactam (**8**) was formed. Similarly,



macrocyclization of ω-amino carboxylic acids using di-*n*-butyltin oxide predominantly led to polymer formation. However, five-, six-, and seven-membered lactams, on the other hand, are easily prepared in nearly quantitative yield (see Table II). For example, by this process, the bridged lactam **10** was prepared directly from **9** in 77% yield (eq 2). This is far greater than the 2% yield reported in the literature[12] for this compound.



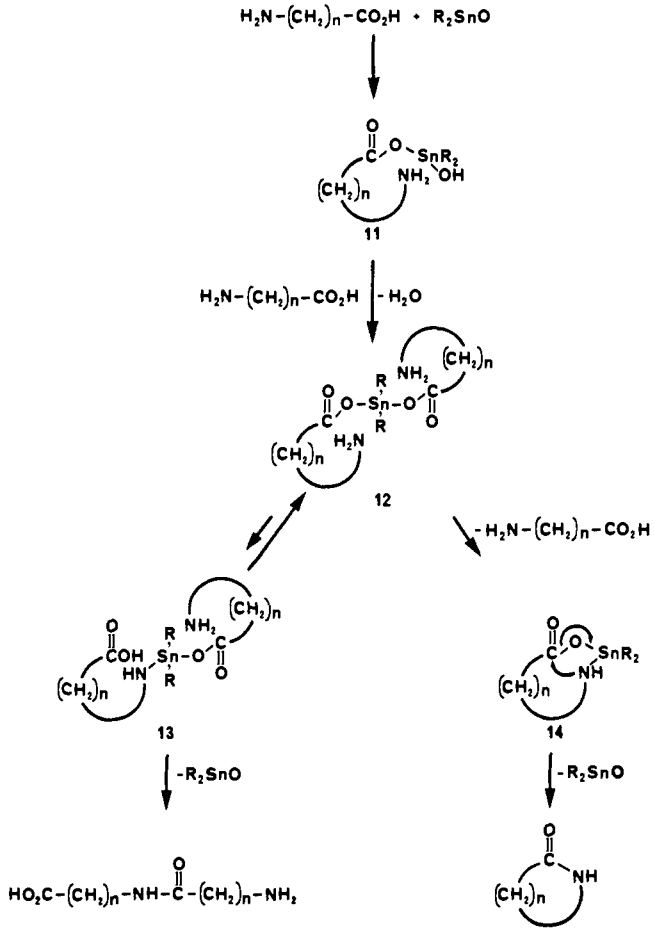
(2)

The inefficient macrocyclization of ω-amino carboxylic acids by this technique can be readily explained if different functional group stannylating preferences are taken into account. In contrast to the proposed pathway (Scheme I) for lactone formation, initial stannylation of an ω-amino carboxylic acid occurs primarily at the carboxylic acid group.[9b] This gives way to the formation of a hydroxystannylene amino carboxylate intermediate **11** (Scheme II). Unlike the corresponding hydroxystannylenealkoxy carboxylic acid **3**, **11** does not possess any incentive for internal stannylation of the amino functionality. Instead, even under the dilution concentrations successful for lactone formation, **11** intermolecularly stannylates to give **12**. This in turn, through a process of transstannylation, is converted into **13**. Extrusion of tin oxide from **13** leads to polymer formation. The preparation of cyclic aminostannylene carboxylate **14**, the required intermediate for lactam synthesis, from **12** or directly from **11** is a much less favorable process. On the other hand, for five-, six-, and seven-membered lactams formation of **14** is kinetically favored and accounts for the high yields obtained in these examples.

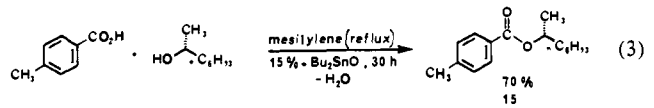
Application to Macrolide Synthesis

The lactone-forming hydroxy functional group in most natural macrocyclic lactones is usually found substituted on a chiral secondary carbon atom.[5j] Thus, retention or complete inversion of the sense of chirality at this carbon center during the lactonization process is an essential requirement for any useful synthetic macrolide forming methodology. Implicit in Scheme I is that tin-mediated esterification should proceed with complete retention

Scheme II



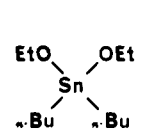
of the sense of chirality at this center. This was borne out in the tin-mediated esterification of *p*-toluic acid with *l*-2-octanol (eq 3). The resulting known optically active ester **15** was achieved in 70% chemical yield with 100% optical purity.



(3)

Although the macrolides discussed herein are stable in refluxing mesitylene (bp 165 °C) in the presence of catalytic amounts of di-*n*-butyltin oxide, their corresponding hydroxy seco acid derivatives undergo significant decomposition at this temperature. However, when stoichiometric amounts of di-*n*-butyltin oxide at 1–5 mM concentrations are used, loss due to decomposition is considerably reduced and macrolide formation somewhat enhanced. In addition, the reaction proceeds at a faster rate. For example, treating 16-hydroxyhexadecanoic acid (30 mM) with 10% (mol equiv) di-*n*-butyltin oxide in refluxing mesitylene for 19 h afforded 60% hexadecanolide. In contrast, the same reaction using stoichiometric amounts of the acid and di-*n*-butyltin oxide (3 mM) gave 64% hexadecanolide after only 12 h of reaction time. Further, since stannylation is a relatively mild process, stoichiometric amounts of di-*n*-butyltin oxide allow for this part of the reaction to be independently carried out at much lower temperature (refluxing benzene or toluene). In practice, we found it more convenient to carry out the stannylation in mesitylene under reduced pressure (bp 100 °C (100 mmHg)) and then subsequently allow the pressure to reach ambient pressure (760 mmHg) at which the reflux temperature (165 °C) permits the extrusion of di-*n*-butyltin oxide to take place. Alternatively, stannylation could be effected virtually at room temperature by using more reactive stannylating agents such as di-*n*-butyltin diethoxide (**16**) or di-*n*-butyltin diimidazole (**17**). Thus, for example, stoichiometric stannylation of 16-hydroxyhexadecanoic acid (5 mM) with **17** in

(12) Hall, H. K., Jr.; Shaw, R. G.; Deutschmann, A. *J. Org. Chem.* **1980**, *45*, 3722.



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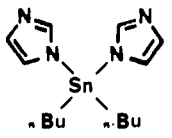

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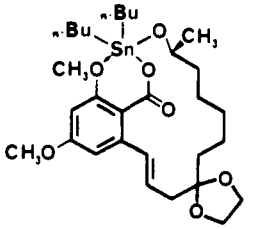
mesitylene at 50 °C followed by refluxing for 12 h gave a 75% yield of hexadecanolide.

Zearalenone

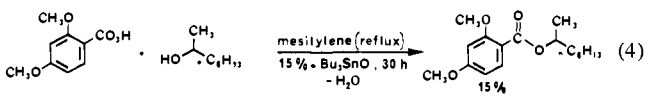
Traditionally, the 14-membered macrolide antibiotic zearalenone (**18**, Scheme III) is used as an example to test the efficacy of new macrolide forming methodology.[5j,m13a] Thus, protection of the phenolic hydroxy groups and the ketone at C-9 according to the literature procedure[13b] followed by hydrolysis (aqueous NaOH 5 M) in refluxing Me_2SO[13b] afforded the protected hydroxy seco acid derivative **20** in 49% overall yield. However, attempts to recyclize this hydroxy seco acid by using catalytic amounts of di-*n*-butyltin oxide led only to decomposition of the seco acid, with no detectable (TLC) amounts of **19** being formed. Similarly, stoichiometric stannylation with di-*n*-butyltin oxide in mesitylene (100 °C (100 mmHg)) followed by refluxing (165 °C/760 mmHg) for 48 h also did not lead to the formation of any detectable amounts of the desired lactone **19**. However, this latter procedure did net, after workup, 90% recovery of the starting hydroxy seco acid **20**.

We believe this to represent an isolated example of failure of the methodology to effect lactonization and can attribute this failure to the presence of the 4,6-dimethoxybenzoic acid substructure in **20**. The incompatibility of this substructure with tin-mediated macrocyclization is probably related to favorable strong intramolecular chelation of the *o*-methoxy substituent with the tin atom through a six-membered cyclic intermediate as shown in **21**. This chelation in effect acts to restrict, as molecular models



21

suggest, pseudorotational ability and conformational freedom about the tin atom, and thereby favorable geometrical orientation of the substituents on tin may not be possible for extrusion of tin oxide to take place. A similar chelating problem in the analogous silicon tetrachloride mediated coupling of amines to salicyclic acid derivatives has been reported by Chan and Wong.[14] The parent acid, 2,4-dimethoxybenzoic acid itself, however, can be esterified, albeit in low yield (15%, eq 4), with 2-octanol in the presence of



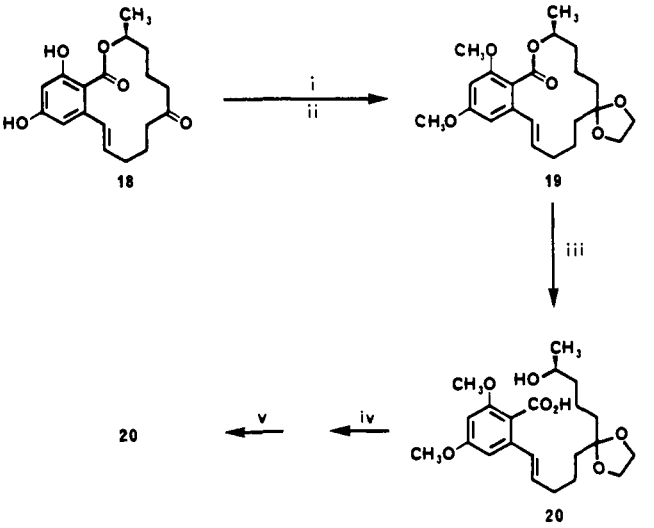
(4)

di-*n*-butyltin oxide. In this example, however, the absence of the macrocyclic skeleton in its corresponding alkoxystannylene carboxylate intermediate adds an extra degree of conformational mobility compared to the zearalenone analogue **21**.

Ricinelaidic Lactone

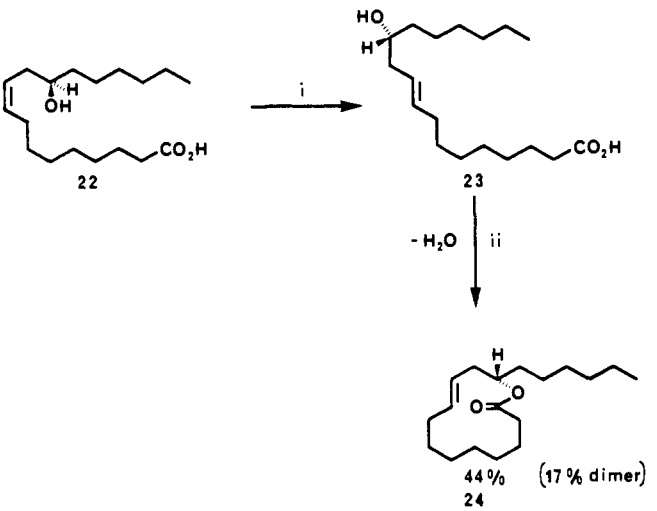
Naturally occuring ricinoleic acid (**22**, Scheme IV), was photochemically isomerized into ricinelaidic acid (**23**) according to the literature procedure.[15a] Treatment of this acid[15b] with

Scheme III



(i) $(MeO)_2SO_2$, aq NaOH 5 M
(ii) $(HOCH_2-)_2$, p-TsOH, toluene (reflux)
(iii) aq NaOH 5 M, DMSO (reflux)
(iv) 1 eq n-Bu_2SnO, mesitylene (reflux), 48 h
(v) "Work-up"

Scheme IV



(i) 0.1 eq Ph_2S_2, hv, benzene, 3 h
(ii) 1 eq n-Bu_2SnO, mesitylene (reflux), 77 h

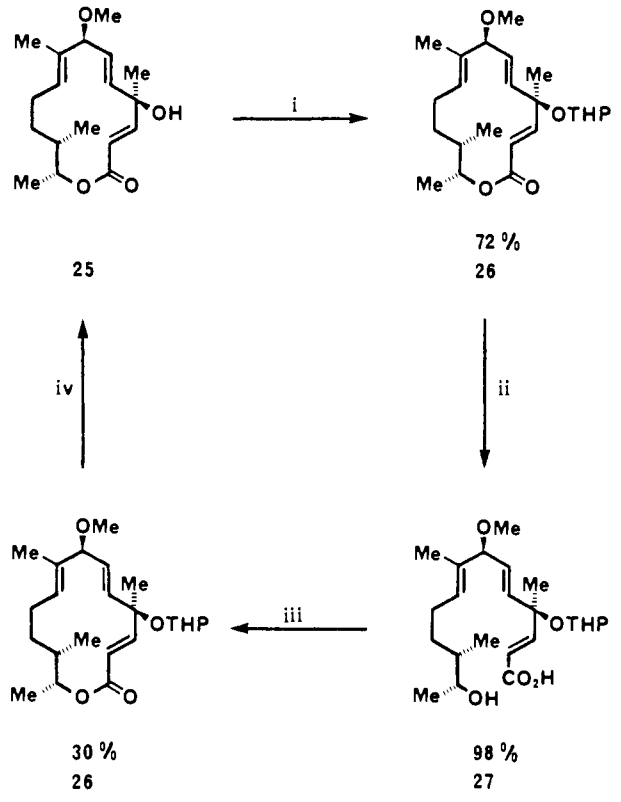
stoichiometric amounts of di-*n*-butyltin oxide (5 mM) in refluxing mesitylene for 77 h using a Dean–Stark apparatus afforded after workup 44% optically pure ricinelaidic lactone (**24**), 17% dimer, 19% ricinelaidic acid, and the rest polymeric material. Similar yields were obtained by stannylating at lower temperature (100 °C (100 mmHg)) by using reagent **16** or **17** followed by refluxing (165 °C) at ambient pressure for 77 h. On the other hand, only 3% of this 13-membered lactone and 90% polymeric material were obtained when catalytic (15%, mol equiv) amounts of di-*n*-butyltin oxide were used instead.

(13) (a) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612 and references cited therein. (b) Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443.

(14) Chan, T. H.; Wong, L. T. L. *J. Org. Chem.* **1969**, *34*, 2766.

(15) (a) Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* **1977**, *57*, procedure 2010. See also: Moussebois, C.; Dale, J. *J. Chem. Soc. C* **1966**, 260. (b) The *E* configuration of the double bond in this example is essential for macrocyclization. We were not able to cyclize ricinoleic acid or its saturated derivative, 12-hydroxystearic acid. This is probably related to conformational stability as predicted by the Celmer type models. See: Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413. Dale, J. *J. Chem. Soc.* **1963**, 93. Ogura, H.; Furuhata, K.; Kuwano, H.; Suzuki, M. *Tetrahedron* **1981**, *37*, 165 and references cited therein.

Scheme V



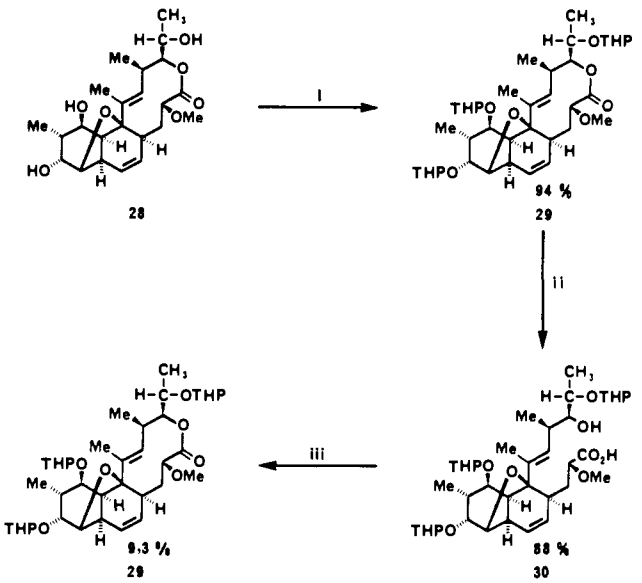
(i) 30 eq DHP, cat. H^+, CH_2Cl_2, 6 h

(ii) 1.1 eq LiOH, H_2O/THF 1:1, 8 h

(iii) 1.0 eq Bu_2SnO (1 mM), mesitylene (reflux), 24 h

(iv) MeOH, cat. H^+, 5 h

Scheme VI



(i) 10 eq DHP, cat. H^+, CH_2Cl_2, 5 h

(ii) 1.1 eq KOH, H_2O/MeOH 1:1 (reflux), 28 h

(iii) 1.0 eq Me_2SnO (1 mM), mesitylene (reflux), 24 h

Ingramycin

Ingramycin (**25**, Scheme V), a 14-membered macrolide, is a potent antimicrobial agent against several bacterial type of infections.[16] It possesses a highly labile doubly allylic activated tertiary hydroxy functional group[7b] that is extremely sensitive to nonneutral reaction conditions. Protected as the tetrahydropyranyl derivative **26** it can be readily hydrolyzed (LiOH) to give the hydroxy seco acid derivative **27** in 71% yield from **25**. (The corresponding methyl ether analogue of **26** does not survive the reaction conditions required for hydrolysis of the lactone.)

Treatment of **27** with stoichiometric amounts of di-*n*-butyltin oxide (1 mM) for 24 h afforded after workup **26** (identical in all respects with **26** derived directly from the natural product) in 30% yield (40% based on recovered **27**). Surprisingly however, ingramycin obtained from the deprotection of **26** (H^+/MeOH, 79% yield) prepared from **27** or directly from **25** results in a substantial loss in optical activity ($[\alpha]^{23}_D$ −77.2° vs. $[\alpha]^{25}_D$ −90°). Although we cannot fully account for this difference, it is obviously not related to the tin-mediated cyclization step. (The drop in optical activity is primarily due to epimerization of the tertiary hydroxy group through facile reversible solvolysis during the protection/deprotection steps. For example, 5-methoxyingramycin can be isolated from the treatment of ingramycin with catalytic amounts of anhydrous camphor sulfonic acid in methanol.)

Nodusmicin

Nodusmicin (**28**, Scheme VI), an elaborately adorned 10-membered macrocyclic lactone,[7a,17a] is a representative of a new group of natural products in the macrolide family of compounds that exhibit very strong antibiotic activity against a wide spectrum of microorganisms.[7a,17b,c] Although nodusmicin can be readily hydrolyzed in alkaline aqueous methanol (24 h, 25 °C),[7a] its 9,18-bis(*tert*-butylidimethylsilyl ether) derivative[17c] is completely resistant to ring opening even in THF/H_2O 1:1 at 50 °C for 57 h. The per(tetrahydropyranyl ether) **29**, on the other hand, smoothly undergoes hydrolysis (Scheme VI) to give protected hydroxy seco acid **30** in 88% yield.

Lactonization back into **29** was best effected by using stoichiometric amounts of dimethyltin oxide (1 mM) in 9.3% yield. This yield, although not "high", is quite respectable considering that 10-membered macrolides are among the most difficult to prepare through cyclization techniques[3,8] (see Figure 1). Further, the pro-lactone-forming hydroxy functional group in **30** is severely sterically hindered, and selective preferential stannylation of it over the acid functionality, as required by Scheme I, is not easily accomplished. Hence, dimethyltin oxide, a less bulky stannylating agent than di-*n*-butyltin oxide, in this case gave the best yield.

Pyrenophorin and Vermiculine

The 16-membered dilactone metabolites (−)-pyrenophorin (**31**, a fungicide[18a]) and (−)-vermiculine (**32**, an antibiotic[18b]) have been the subject of numerous total syntheses.[19] Our synthetic approach (Scheme VII) to these two diolides (based on a modification of the Hase[19d] synthesis) expeditiously leads to a common synthetic intermediate (epoxide **35**) for both syntheses. Thus, regioselective epoxidation (Scheme VII) of diolefinic ester **34** (26% overall yield in 4 steps from levulinic acid (**33**)[19d]) with MCPBA gave epoxide

(16) Nagahama, N.; Suzuki, M.; Awataguchi, S. *J. Antibiot., Ser. A.* **1967**, *20*, 261. U.S. Patent 3651219 March 21, 1972. See also: Slechta, L.; Ciadella, J.; Hoeksema, H. *Ibid.* **1978**, *31*, 319.

(17) (a) Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203. (b) Magerlein, B. J.; Reid, R. J. *J. Antibiot.* **1982**, *35*, 254 and references cited therein. (c) Magerlein, B. J. "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, NY, August 1981; American Chemical Society: Washington DC, 1981; MEDI72.

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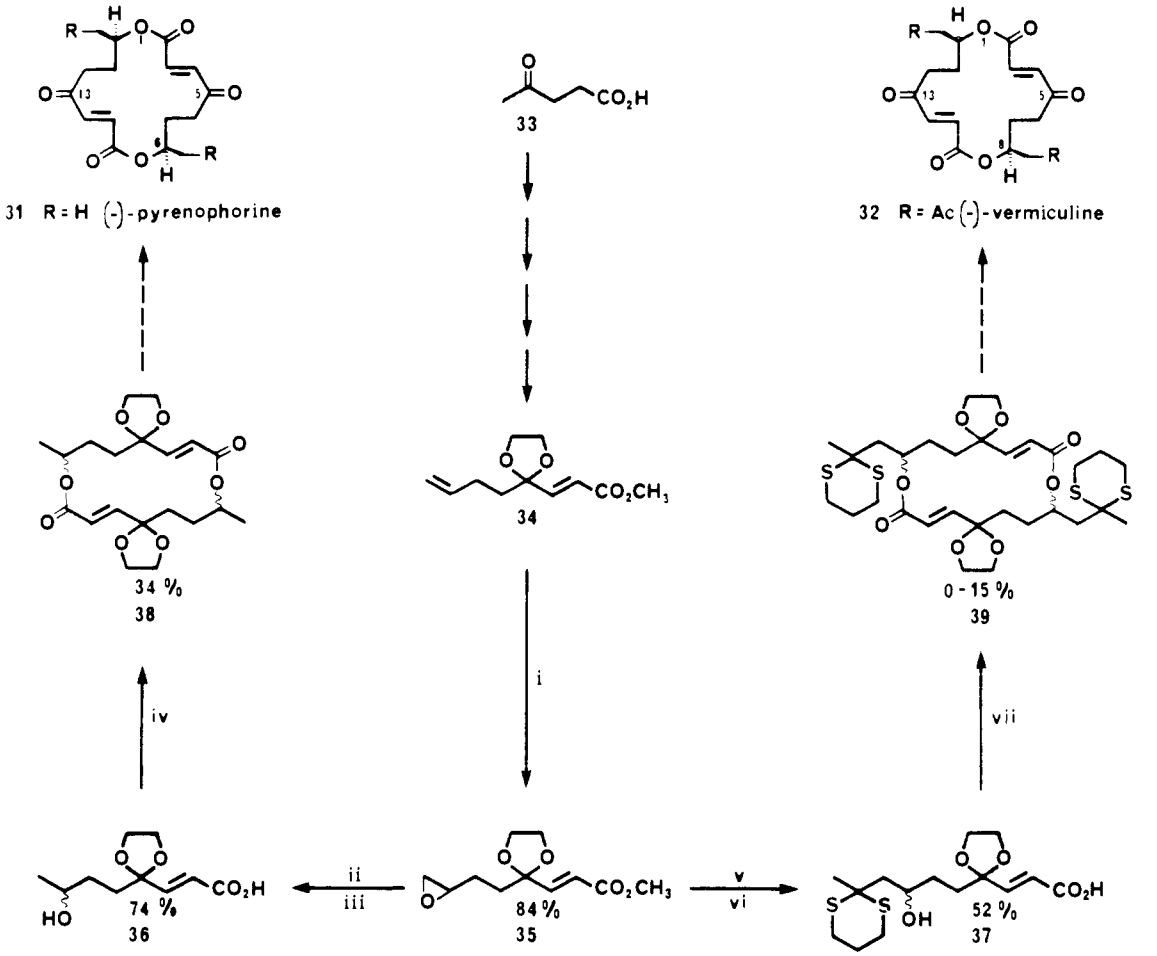
(19) (a) Corey, E. J.; Nicolaou, K. C.; Toru, T. *J. Am. Chem. Soc.* **1975**, *97*, 2287. (b) Asoaka, M.; Mukuta, T.; Takaei, H. *Tetrahedron Lett.* **1981**, *22*, 735, and references cited therein. (c) Mali, R. S.; Pohmakotr, M.; Weidmann, B.; Seebach, D. *Liebigs Ann. Chem.* **1981**, 2272. (d) Hase, T. A.; Ourila, A.; Holmberg, C. *J. Org. Chem.* **1981**, *46*, 3137. (e) Fujisawa, T.; Takeuchi, M.; Sato, T. *Chem. Lett.* **1982**, 1795, and references cited therein.

Scheme VII

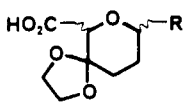


(i) 1.0 eq m-CPBA , CH_2Cl_2 (reflux) , 2h
(ii) 1,1 eq LiOH 1M , H_2O , 1,5h
(iii) 1.5 eq LiBr , 1,5 eq $NaBH_4$, H_2O , 24h
(iv) 1.0 eq Me_2SnO (5 mM) , mesitylene (reflux) , 50h
(v) 1,1 eq LiOH 1M , H_2O , 3h
(vi) 2,2 eq  , THF -78 → -23 °C , 48h
(vii) 1,0 eq Me_2SnO (5 mM) , mesitylene (reflux) , 17 h

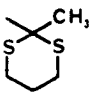
35 in 84% yield. Hydrolysis of the ester (LiOH) followed by regioselective opening of the epoxide with $LiBH_4$[20] (without prior isolation) afforded the protected (±)-pyrenophorin hydroxy seco acid derivative **36** in 74% isolated yield.

On the other hand, hydrolysis of **35** with 1.1 N LiOH and treatment of the epoxy acid thus produced with 2.2 equiv of 2-lithio-2-methyl-2,3-dithiane in THF (−78 → −23 °C) for 48 h afforded the corresponding protected (±)-vermiculine hydroxy seco acid derivative **37** in 52% overall yield from **35**. Treatment of **36** with stoichiometric amounts (5 mM) of dimethyltin oxide in refluxing mesitylene for 50 h gave a mixture of *dl*- and *meso*-5,5:13,13-bis(ethylenedioxy)pyrenophorine (**38**) in 34% yield. Similar treatment of **37** for 17 h correspondingly gave the protected vermiculin derivative **39** in 0–15% yield. Since removal of the protecting groups has been reported,[19,21] this represents a formal total synthesis of the *dl* and meso forms of these two diolides.

The yield for the "dimerization–cyclization" of hydroxy seco acid **36** and more particularly for **37** is highly discriminated against by a kinetically favored internal Michael type of addition of the hydroxy group across the conjugated double bond. This correspondingly gave way to the formation of adducts **40** and **41** in



40 R = H

41 R = 

21 and 40% yields, respectively. Regardless however, the tin-mediated "dimerization–cyclization" yield obtained for **38** is among the best to be reported.[19,21]

Conclusions

From our experimental results, we conclude that tin-mediated esterification is particularly well suited for the formation of 13- to 17-membered macrolides. Lactam formation, on the other hand, is useful only for five-, six-, and seven-membered rings. Although we tried various substituent modifications on tin,[6] our best results for macrocyclization were obtained with di-*n*-butyltin

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oxide and dimethyltin oxide. Diphenyltin oxide preferentially led to polymerization. Dicyclohexyltin oxide, on the other hand, reacts too slugishly to be of any value.

We also note that solvents which can stabilize the cyclic alkoxystannylene carboxylate intermediate **5** by coordination considerably retard the extrusion of tin oxide. For example, only trace amounts of hexadecanolide could be obtained by using anisole as the solvent in place of mesitylene. This further supports the incompatibility of 2,4-dimethoxybenzoic acid as a substructure with this methodology.

Although we tried to form thiolactones by treating ω-mercapto carboxylic acids with di-*n*-butyltin oxide in an analogous manner to the ω-hydroxy carboxylic acids, the tin–sulfur bond that is formed is too strong[22] to allow the reaction to proceed in the desired direction.

The simplicity of the methodology described, coupled with the good yields that can be obtained for the formation of 13- to 17-membered macrocyclic lactones, should make this approach to macrolide synthesis a competitive one.

Experimental Section

Unless stated otherwise, chemical reagents were obtained from commercial sources and were used directly. Solvents were purified and dried according to literature procedures.[23a,b] All reactions were carried out under an atmosphere of argon.[23c] Melting points were determined on a Gallenkamp block apparatus and are uncorrected. Routine proton nuclear magnetic resonance spectra were recorded on a Bruker Model WH-90 90-MHz instrument. Proton nuclear magnetic resonance spectra (400 MHz) were recorded on a Bruker Model WH-400 spectrometer. ^{13}C NMR spectra were measured at 20.15-MHz on a Bruker WH-80 instrument. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Significant ^1H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad), coupling constant(s) in hertz. Infrared spectra were recorded on a Perkin-Elmer Model 710B grating spectrophotometer, calibrated with the 1602-cm^{-1} band of a polystyrene film. Optical rotations were measured on a Perkin-Elmer Model 241 automatic polarimeter using the D band of sodium as the light source. Mass spectra were obtained with Micromass-1212 (chemical ionization (CI); low resolution) and Kratos MS-902 (electron impact; high resolution) mass spectrometers. Significant mass spectral data are tabulated as *m/z* (intensity expressed as percent total ion current). Analytical and preparative thin-layer chromatography (TLC) were carried out with E. Merck F-254 silica gel plates. "Flash chromatography"[23d] was performed according to the literature[23d] procedure using E. Merck silica gel 230–400 mesh size.

Di-*n*-butyltin diethoxide (**16**)[24a] and di-*n*-butyltin dimidazole (**17**)[24b] were prepared according to the general literature procedure.[24a] Similarly, dimethyltin oxide, diphenyltin oxide, and dicyclohexyltin oxide were prepared by the alkaline hydrolysis of the corresponding dihalides.[24c]

General Procedure for the Tin-Catalyzed Cyclization of the ω-Hydroxy Carboxylic Acids[25] Listed in Table I. Preparation of Hexadecanolide. A mixture of 16-hydroxyhexadecanoic acid (817.3 mg, 3.0 mmol) and di-*n*-butyltin oxide (74.7 mg, 0.3 mmol) was stirred in refluxing mesitylene (100 mL) for 19 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) yielded a yellow oily residue, which was Kugelrohr distilled (60 °C (0.2 mmHg)) to give 457.9 mg (60%) of hexadecanolide, identical with an authentic sample: IR ($CHCl_3$) 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.31 (26 H, b s), 2.33 (2 H, t), and 4.13 (2 H, t).

Preparation of Hexadecanolide from 16-Bromohexadecanoic Acid and Bis(tri-*n*-butyltin) Oxide. A mesitylene (100 mL) solution of 16-bromohexadecanoic acid (168 mg, 0.5 mmol) and bis(tri-*n*-butyltin) oxide (149 mg, 0.25 mmol) was refluxed for 31 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) and sublimation (60 °C (0.2 mmHg)) of the resulting residue gave 19.1 mg (15%) of hexadecanolide, identical with an authentic sample.

Preparation of Hexadecanolide by Di-*n*-butyltin Diimidazole. A mixture of 16-hydroxyhexadecanoic acid (136 mg, 0.5 mmol) and di-*n*-butyltin diimidazole (184 mg, 0.5 mmol) was stirred in mesitylene (100 mL) at 50 °C for 2 h and then at reflux temperature (165 °C) for 12 h. The reaction mixture was then concentrated in vacuo (40 °C (0.2 mmHg)) to 10 mL and filtered. The filtrate was further concentrated in vacuo (40 °C (0.2 mmHg)) and the resulting waxy residue sublimed (60 °C (0.2 mmHg)) to give 95 mg (75%) hexadecanolide, identical with an authentic sample.

Attempted Preparation of β-Lactam 8a (a Representative Example). β-Amino carboxylic acids **7b,d** were prepared by the hydrolysis[26a] of β-lactams 8b[26b] and 8d,[26b] respectively. A mixture of β-alanine (44.5 mg, 0.5 mmol) and di-*n*-butyltin oxide (124.5 mg, 0.5 mmol) was refluxed in xylene (100 mL) with use of a Dean–Stark appartus for the continuous removal of water. Water was rapidly collected and ammonia gas given off. Removal of the solvent in vacuo gave a white solid residue whose infrared spectrum was inconsistent with the presence of β-lactam **8a**. The solid was not characterized any further.

General Procedure for the Tin-Catalyzed Cyclization of the ω-Amino Carboxylic Acids Listed in Table II. Preparation of ε-Caprolactam. A mixture of 6-aminocaproic acid (393.5 mg, 3.0 mmol) and di-*n*-butyltin oxide (74.7 mg, 0.3 mmol) was stirred in refluxing xylene (100 mL) for 12 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo and sublimation of the resulting residue gave 322.5 mg (95%) ε-caprolactam, identical with an authentic sample.

Preparation of 1-Azabicyclo[3.3.1]nonan-2-one (10). A mixture of amino acid **9**[27] (98.6 mg, 0.63 mmol) and di-*n*-butyltin oxide (156.8 mg, 0.63 mmol) was stirred in refluxing toluene (125 mL) for 12 h with use of a Dean–Stark apparatus for the continuous removal of water. The solvent was removed in vacuo at room temperature and the residue taken up in $CHCl_3$ (20 mL) and filtered through a layer of Celite. The filtrate was concentrated by rotary evaporation and the resulting oily residue "flash chromatographed"[23d] (EtOAc) to give 63.2 mg (77%) of lactam **10**. Sublimation (25 °C (1 mmHg)) gave analytically pure material: mp 77–81 °C, (lit.[12] mp 77–79 °C); R_f (15% EtOAc/$CHCl_3$) 0.36; IR (film) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.27–1.88 (5 H, m), 2.17–2.86 (5 H, m), 3.20 (2 H, AB q, J = 13.6 Hz) and 4.11 (1 H, d); ^{13}C NMR ($CDCl_3$) δ 20.7, 25.1, 30.0, 33.5, 51.8, 53.1, and 185.7 (C=O).

Preparation of *l*-β-Octyl *p*-Toluate (15).[28a] A mixture of *p*-toluic acid (136.2 mg, 1.0 mmol), *l*-2-octanol (130.2 mg, 1.0 mmol), and di-*n*-butyltin oxide (37.5 mg, 0.15 mmol) was stirred in refluxing mesitylene (10 mL) for 30 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) left an oily residue, which when Kugelrohr distilled (100 °C (0.1 mmHg)) gave 173.9 mg (70%) of the optically active ester as a colorless oil: IR (film) 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.68–1.54 (16 H, m), 2.25 (3 H, s), 7.50 (4 H, AB q); $[\alpha]^{23}_D$ −40.2° (neat) [lit.[28b] $[\alpha]^{23}_D$ −39.4° (neat)].

Attempts To Prepare Zearalenone Derivative 19 from 20. A mixture of seco acid **20**[13b] (77.5 mg, 0.19 mmol) and di-*n*-butyltin oxide (47.3 mg, 0.19 mmol) was stirred in refluxing mesitylene (38 mL) for 48 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) and analysis of the residue (IR, TLC) showed only starting material to be present. Similar attempts to prepare **19** by using catalytic amounts of di-*n*-butyltin oxide led to considerable decomposition of **20** (TLC), with no trace of **19** (IR, TLC) being formed.

Preparation of β-Octyl 2,4-Dimethylbenzoate. A mixture of 2,4-dimethylbenzoic acid (182.2 mg, 1.0 mmol), 2-octanol (130.2 mg, 1.0 mmol), and di-*n*-butyltin oxide (37.5 mg, 0.15 mmol) was stirred in refluxing mesitylene (10 mL) for 30 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in

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(25) We thank Professor Clark Still for providing us with a sample of 9-hydroxy-8-methylnonanoic acid and the spectral properties of its corresponding monolide and diolide. 8-Hydroxyoctanoic acid was obtained by the hydrolysis of octanolide which was prepared by the Baeyer–Villiger oxidation of cycloheptanone (see: Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981). The remaining ω-hydroxy carboxylic acids and their corresponding lactones are commercially available.

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(27) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 1209.

(28) (a) Esterification by di-*n*-butyltin oxide in this example is reversible (see ref 6). (b) Rule, G.; Hay, W.; Numbers, A. H.; Paterson, T. R. *J. Chem. Soc.* **1928**, 178.

vacuo (40 °C (0.2 mmHg)) left an oily residue, which was chromatographed on silica gel (10 g) with CCl_4 to give 44.2 mg (15%) of the ester: IR (film) 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.80–1.58 (16 H, m), 3.79 (3 H, s), 3.85 (3 H, s), 5.11 (1 H, m), 6.46 (2 H, m), and 7.82 (1 H, d, J = 10 Hz); MS calcd for $C_{17}H_{26}O_4$, m/z 294.1831, found, m/z 294.1833.

Preparation of (−)-(*R*,*E*)-12-Hydroxy-9-octadecenoic Acid Lactone (24). A mixture of ricinelaidic acid[5j] (149.2 mg, 0.5 mmol) and di-*n*-butyltin oxide (124.5 mg, 0.5 mmol) was stirred in refluxing mesitylene (100 mL) for 77 h with use of a Dean–Stark apparatus for the continuous removal of water. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) left an oily residue (289 mg), which when "flash chromatographed"[23d] (1% AcOH/2% EtOAc/97% petroleum ether, bp 35–60 °C) gave 61.8 mg (44%) of ricinelaidic lactone as a colorless oil and 24.2 mg (17.3%) of its dimer as a white solid. Further elution of the column with EtOAc gave 64 mg of residual material, which was rechromatographed on preparative TLC (EtOAc) to give 28.8 mg (19%) of ricinelaidic acid.

Ricinelaidic Lactone (24): R_f (CH_2Cl_2) 0.59; IR (film) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.87–2.30 (29 H, m), 4.92 (1 H, m), and 5.45 (1 H, m), ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 23.7, 25.3, 26.9, 27.5, 29.1, 31.6, 32.1, 34.9, 34.9, 37.7, 73.0 (C—OR), 126.2 (C=C), 134.1 (C=C), and 173.5 (C=O); MS, m/z $M^{+\cdot}$ = 280 (15); $[\alpha]^{23}_D$ +40.4° (c 0.98, $CHCl_3$) [lit.[29] $[\alpha]^{23}_D$ +42° (c = 1, $CHCl_3$)].

Dimer: mp 38–40 °C; R_f (CH_2Cl_2) 0.43; IR (film) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.82–2.28 (29 H, m) and 5.29–5.54 (3 H, m); MS (CI), m/z M^+ + 1 = 561 (19); $[\alpha]^{23}_D$ + 1.2° (c 0.85, $CHCl_3$).

Similar yields were obtained by using di-*n*-butyltin diethoxide (**16**) or di-*n*-butyltin diimidazole (**17**) in place of di-*n*-butyltin oxide and carrying out the stannylation at (100 °C (100 mmHg)) for 10 h prior to refluxing (165 °C (760 mmHg)) for 77 h.

Preparation of (4-Tetrahydropyranyl)oxy)ingramycin Derivative 26. To a methylene chloride (50 mL) solution of ingramycin (324.6, 1.05 mmol) was added freshly distilled dihydropyran[23a] (2.9 mL, 31.6 mmol) and a catalytic amount (14.6 mg, 0.06 mmol) of anhydrous camphorsulfonic acid. The reaction mixture was stirred at room temperature for 6 h and then washed with a 20% aqueous solution of $NaHCO_3$ (3 × 30 mL). The organic layer was separated, dried (Na_2SO_4), and rotary evaporated to remove the solvent. The resulting residual oil (570 mg) was "flash chromatographed"[23d] (10% EtOAc/petroleum ether, bp 35–60 °C) to give 296.8 mg (72%) of **26** as a mixture of diastereomers: R_f (15% EtOAc/$CHCl_3$) 0.56; IR (film) 1710 cm^{-1} (C=O); ^1H NMR 400 MHz ($CDCl_3$) δ 0.88 (3 H, J = 6.8 Hz), 1.21 (5 H, dd, J = 6.4 Hz) 1.23–1.9 (15 H, m), 3.28 (3 H, s), 3.31 (3 H, s), 3.50 (1 H, m), 4.02 (2 H, m), 4.58 (1 H, m), 4.92 (1 H, m), 5.25 (1 H, m), 5.61–5.69 (1 H, m), 5.82–5.94 (1 H, m), and 6.78 (1 H, t, J = 16.3 Hz); ^{13}C NMR ($CDCl_3$) δ 15.4, 14.8, 16.0, 16.1, 18.2, 19.7, 23.3, 24.1, 24.9, 25.4, 31.9, 34.1, 34.2, 39.6, 39.6, 56.7, 57.2, 62.3, 75.1, 78.3, 83.9, 84.4, 94.6, 94.9, 115.3, 116.1, 129.3, 129.6, 132.6, 134.5, 135.3, 135.9, 153.8, and 166.3 (C=O).

Preparation of Hydroxy Seco Acid 27. To a solution of **26** (128.1 mg, 0.33 mmol) in H_2O/THF 1:1 (15 mL) was added dropwise 0.36 mL of 1 M LiOH (1.1 equiv) at room temperature. The reaction mixture was stirred for 8 h, cooled (ice bath) to 0 °C, and acidified to pH 3 with 10% aqueous HCl. The acidified mixture was then transferred to a separatory funnel and extracted with EtOAc (5 × 15 mL). The extracts were combined, dried (Na_2SO_4), and then rotary evaporated to afford 131.7 mg (98%) of hydroxy seco acid **27** as a mixture of diastereomers. The acid (a colorless oil), which was pure by TLC (R_f (EtOAc) 0.36), was used without further purification: IR (film) 3400 (b, OH), 1690 (C=O), and 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 6.2 Hz), 1.12 (3 H, d, J = 6.2 Hz), 1.25–2.26 (17 H, m), 3.21 (3 H, s), 3.50–4.00 (4 H, m), 4.74 (1 H, m), 5.41 (1 H, t, J = 7.1 Hz), 5.62–5.67 (1 H, m), 6.38 (2 H, b s, exchangeable with D_2O), 6.47 (1 H, AB q, J = 15.6 Hz), and 6.49 (1 H, AB q, J = 15.6 Hz); MS (CI), m/z M^+ + 1 = 361 (3), 309 (8), 277 (100), 259 (12), 153 (8), and 85 (44).

Preparation of 26 from 27. A mixture of hydroxy seco acid **27** (85.5 mg, 0.21 mmol) and di-*n*-butyltin oxide (51.9 mg, 0.21 mmol) was stirred in 200 mL of refluxing mesitylene (100 °C (100 mmHg)) for 14 h with use of a Dean–Stark apparatus for the continuous removal of water. The reaction mixture was then further refluxed at ambient pressure (165 °C (760 mmHg)) for an additional 24 h. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) left an oily residue, which was "flash chromatographed"[23d] (2% AcOH/10% EtOAc/88% petroleum ether, bp 35–60 °C) to give 24.7 mg (30%) lactone **27** (spectroscopically identical with **27** obtained from **26**), 32.8 mg (40%) of a mixture containing the dimer (R_f (2% AcOH/25% EtOAc/73% petroleum ether, bp 35–60 °C) 0.33 and 0.24, respectively), and 40 mg of residual material, which was "flash chromatographed"[23d] (1% AcOH/10% EtOAc/89% petroleum ether, bp 35–60 °C) a second time to recover 20.0 mg (24%) of hydroxy seco acid **27**. The IR and ^1H NMR spectra of the dimer/trimer mixture are almost identical with the corresponding spectra of the monomer.

Preparation of Ingramycin from 26 Obtained from 27. A solution of **26** (17.3 mg, 0.44 mmol) in 5 mL of anhydrous methanol containing a catalytic amount (1 mg) of anhydrous camphorsulfonic acid was stirred for 2.5 h. The reaction mixture was then diluted with EtOAc (30 mL), transferred to a separatory funnel, and washed (2 × 5 mL) with 20% aqueous $NaHCO_3$. The organic phase was separated, dried (Na_2SO_4), and rotary evaporated to give 14.9 mg of a colorless oil, which was chromatographed on preparative TLC plates (2 ×, 15% EtOAc/$CHCl_3$) to afford 10.8 mg (79%) of **25**: R_f (15% EtOAc/$CHCl_3$) 0.36; IR ($CHCl_3$) 3575 (OH, free), 3400 (b, OH), 1705 (C=O, conjugated), and 1640 cm^{-1} (C=C, conjugated); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6.5 Hz), 1.16–1.84 [16 H, m, 1.20 (d, J = 6.4 Hz), 1.52 (s), and 1.62 (s)], 3.28 (3 H, s), 4.04 (1 H, d, J = 3.8 Hz), 4.55 (1 H, t, J = 6.5 Hz), 5.38 (2 H, t), 5.65–572 (2 H, m), and 6.36 (2 H, AB q, J = 15.6 Hz); MS (CI), m/z M^+ + 1 = 309 (25); $[\alpha]^{23}_D$ −76.8° (c = 0.85, MeOH), −90.0° (c = 0.85, $CHCl_3$) (lit.[16a] $[\alpha]^{25}_D$ −90.0° (c 1, MeOH), −110° (c 1, $CHCl_3$)).

Preparation of Ingramycin from 26 Obtained from Natural Ingramycin. A procedure identical with the one cited above was followed. Spectroscopic properties (R_f, IR, ^1H NMR, MS, and $[\alpha]_D$) of the compound obtained are identical with those recorded for **25** obtained by the above procedure.

Preparation of 9,11,18-Per(tetrahydropyranyl ether) of Nodusmicin (29). To a methylene chloride (30 mL) solution of nodusmicin (100.0 mg, 0.24 mmol) was added freshly distilled dihydropyran[23a] (0.66 mL, 7.2 mmol) and a catalytic amount (5.6 mg, 0.02 mmol) of anhydrous camphorsulfonic acid. The reaction mixture was stirred at room temperature for 4.5 h, transferred to a separatory funnel, and washed with 10% aqueous $NaHCO_3$ (3 × 10 mL). The organic phase was separated, dried (Na_2SO_4), and rotary evaporated to remove the solvent. The resulting residual oil (196.2 mg) was "flash chromatographed"[23d] (2% AcOH/(EtOAc/petroleum ether, bp 35–60 °C, 1:3)) to afford 150.3 mg (94%) of **29** as a mixture of diastereomers: R_f (15% EtOAc/$CHCl_3$) 0.47; IR (KBr) 3400 (OH), 1715 (C=O), and 1600 cm^{-1} (C=C); MS (CI), m/z M^+ + 1 = 675 (20), 458 (23), 85 (100); ^1H NMR 400 MHz and ^{13}C NMR are given as supplementary material; MS calcd for $C_{38}H_{58}O_{10}$, m/z 674.4030, found, m/z 674.4023.

Preparation of Hydroxy Seco Acid 30. To a solution of **29** (152.3 mg, 0.23 mmol) in MeOH/H_2O 1:1 (30 mL) was added dropwise 0.27 mL of 1 M KOH (1.2 equiv) at room temperature. The reaction mixture was heated to 70 °C for 20 h, cooled (ice bath) to 0 °C, and acidified to pH 3 with 5% aqueous HCl. The acidified mixture was then transferred to a separatory funnel and extracted with EtOAc (5 × 5 mL). The extracts were combined, dried (Na_2SO_4), and then rotary evaporated to give 193.1 mg of a colorless oil that was "flash chromatographed"[23d] (0.5% AcOH/EtOAc) to afford 138.0 mg (88%) of **30** as a colorless oil: R_f (1% AcOH/EtOAc) 0.39; IR ($CHCl_3$) 3400 (OH) and 1730 cm^{-1} (C=O); MS (CI) m/z M^+ + 1 = 610 (6), 526 (10), 185 (6), 169 (21), 85 (100); ^1H NMR 400 MHz is given as supplementary material.

Preparation of 29 from 30. A mixture of hydroxy seco acid **30** (51.8 mg, 0.075 mmol) and dimethyltin oxide (12.3 mg, 0.075 mmol) was stirred in 75 mL of refluxing mesitylene (100 °C (100 mmHg)) for 12 h with use of a Dean–Stark apparatus for the continuous removal of water. The reaction mixture was then further refluxed at ambient pressure (165 °C (760 mmHg)) for an additional 24 h. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) left an oily residue, which was "flash chromatographed"[23d] (1% AcOH/(EtOAc/petroleum ether, bp 35–60 °C, 1:2)) to afford 4.7 mg (9.3%) of 9,11,18-per(tetrahydropyranyl ether) of nodusmicin (**29**), identical with an authentic sample prepared directly from nodusmicin.

Preparation of 7,8-Epoxy-4,4-(ethylenedioxy)-2-octenoic Acic, Methyl Ester (35). A mixture of diolefinic ester 34[19d] (5.30 mg, 25.0 mmol) and MCPBA (5.68 mg (76%)[30], 25.0 mmol) was stirred in refluxing methylene chloride (125 mL) for 2.5 h. The reaction mixture was allowed to reach ambient temperature and filtered. The filtrate was transferred to a separatory funnel and washed first with 10% aqueous $NaHSO_3$ (2 × 25 mL) and then with a saturated solution of $NaHCO_3$ (5 × 25 mL). The organic phase was separated, dried (Na_2SO_4), and rotary evaporated to leave 6.0 g of a colorless oil, which after Kugelrohr distillation (100 °C (0.2 mmHg)) afforded 4.76 g (84%) of epoxy ester **35** as a racemic mixture: R_f (2% EtOAc/$CHCl_3$) 0.40; IR (film) 1720 (C=O) and 1645

(29) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755.

(30) The peracid was titrated according to the procedure outlined in "Practical Organic Chemistry Including Organic Analysis", 3rd ed.; Vogel, A. I., Ed.; Longman: London, 1970; p 809.

cm^{-1} (C=C, conjugated); ^{1}H NMR 400 MHz ($CDCl_3$) δ 1.58–1.64 (2 H, m), 1.83–1.90 (2 H, m), 2.44 (1 H, m), 2.72 (1 H, t, J = 4.2 Hz), 2.91 (1 H, m), 3.72 (3 H, s), 3.73–3.96 (4 H, m), and 6.38 (2 H, AB q, J = 15.7 Hz); ^{13}C NMR ($CDCl_3$) δ 26.3, 33.8, 37.0, 47.0, 51.6, 51.8, 65.0, 107.8, 121.6 (C=C), 146.1 (C=C), and 166.3 (C=O); MS (CI), m/z $M^+ + 1$ = 299 (91).

Preparation of (±)-4,4-(Ethylenedioxy)-7-hydroxy-2-octenoic Acid (36). To a magnetically stirred aqueous (20 mL) suspension of epoxy ester **35** (1.00 g, 4.71 mmol) was added dropwise 5.18 mL of 1 M LiOH (1.5 equiv). After 1.5 h, 610 mg of LiBr (1.5 equiv) and 270 mg of $NaBH_4$ (1.5 equiv) were added. The reaction mixture was stirred for 24 h at room temperature, cooled to 0 °C (ice bath), and acidified to pH 3 with 5% HCl. The mixture was transferred to a separatory funnel and extracted with EtOAc (5 × 15 mL). The extracts were combined, dried (Na_2SO_4), and rotary evaporated to leave 0.95 g of a colorless oil that was "flash chromatographed"[23d] (0.5% AcOH/EtOAc) to afford 0.75 g (74%) of racemic hydroxy seco acid **36**[19d] as a colorless oil: R_f (1% AcOH/EtOAc) 0.36; IR (film) 2400–3600 (OH) and 1700 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.21 (3 H, d, J = 6.2 Hz), 1.60 (2 H, t, J = 5.9 Hz), 1.82–1.89 (2 H, m), 3.81–3.97 (5 H, m), 6.24 (2 H, b s, exchangeable with D_2O), and 6.45 (2 H, AB q, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$) δ 23.3, 29.7, 32.3, 33.8, 64.9, 67.8, 108.0, 121.3 (C=C), 148.0 (C=C), and 170.3 (C=O).

Preparation of *dl*- and *meso*-5,5:13,13-Bis(ethylenedioxy)pyrenophorine (38). A mixture of **36** (157.4 mg, 0.73 mmol) and dimethyltin oxide (120.3 mg, 0.73 mmol) was stirred in 146 mL of refluxing mesitylene (100 °C (100 mmHg)) for 12 h with use of a Dean–Stark apparatus for the continuous removal of water. The reaction mixture was then further refluxed at ambient pressure (165 °C (760 mmHg)) for an additional 50 h. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) left an oily residue (194.2 mg) which was "flash chromatographed"[23d] (150 mL of EtOAc/petroleum ether, bp 35–60 °C, 1:1, and 150 mL of 1% AcOH/(EtOAc/petroleum ether, bp 35–60 °C, 1:1)) to give 48.8 mg (34%) of a mixture of *dl*- and *meso*-**38** and 33.3 mg (21%) of adduct **40** in racemic form.

Diolide 38: R_f (15% EtOAc/$CHCl_3$) 0.50; IR ($CHCl_3$) 1710 (C=O, conjugated) and 1640 cm^{-1} (C=C, conjugated); ^{1}H NMR ($CDCl_3$) δ 1.23 (6 H, d, J = 6.2 Hz), 1.74–1.89 (8 H, b s), 4.94–5.25 (2 H, m), 6.34 (2 H, AB q, J = 15.6 Hz), and 6.36 (2 H, AB q, J = 15.6 Hz); MS calcd for $C_{20}H_{28}O_8$, m/z 396.1784, found, m/z 396.1774.

Adduct 40: R_f (1% AcOH/EtOAc) 0.41; IR ($CHCl_3$) 2400–3500 (OH) and 1705 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.23 (3 H, d, J = 6.2 Hz), 1.59–1.77 (4 H, m), 2.54–2.61 (2 H, m), 3.94–4.00 (6 H, b s), and 7.24 (1 H, b s, exchangeable with D_2O); MS calcd for $C_{10}H_{16}O_5$, m/z 216.0998, found m/z 216.1000.

Preparation of Protected (±)-Vermiculine Hydroxy Seco Acid Derivative 37. To a magnetically stirred aqueous (15 mL) suspension of epoxy ester **35** (456 mg, 2.0 mmol) was added dropwise 2.2 mL of 1 M LiOH (1.1 equiv). After 3 h, the reaction mixture was cooled to 0 °C (ice bath) and acidified to pH 3 with 5% aqueous HCl. The acidified mixture was transferred to a separatory funnel and extracted with EtOAc (5 × 20 mL). The extracts were combined, dried (Na_2SO_4), and rotary evaporated to give 420 mg (100%) of the epoxy acid for the subsequent reaction: R_f (1% AcOH/EtOAc) 0.41; IR ($CHCl_3$) 2450–3500 (OH), 1700 (C=O), and 1660 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 1.63–1.95 (4 H, m), 2.46–2.54 (1 H, m), 2.77 (1 H, t, J = 4.7 Hz), 2.97 (1 H, m), 3.92–3.95 (4 H, b d), 6.84 (2 H, AB q, J = 15.6 Hz), and 9.93 (1 H, b s, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 26.1, 33.5, 47.2, 41.9, 64.9, 107.6, 121.3 (C=C), 148.2 (C=C), and 170.8 (C=O).

A solution of 420 mg (2.0 mmol) of the above epoxy acid (freshly prepared) in 75 mL of anhydrous THF was cooled to −78 °C and then slowly transferred (with the aid of a stainless steel double-tip needle) over a period of 20 min to a magnetically stirred solution of 2-lithio-2-methyl-1,3-dithiane[31] (2.2 equiv) in 10 mL of anhydrous THF also kept at −78 °C. The resulting yellow reaction mixture was placed in the freezer (−23 °C) and left to stand there for a period of 48 h.

Removal of the solvent in vacuo gave a yellow solid residue, which was dissolved in 40 mL of water, cooled to 0 °C (ice bath), and acidified to pH 3 with 10% aqueous HCl. The acidified mixture was transferred to a separatory funnel and extracted with EtOAc (5 × 15 mL). The extracts were combined, dried (Na_2SO_4), and rotary evaporated to give 800 mg of a yellow oil. The crude product was "flash chromatographed"[23d] (2% AcOH/(EtOAc/petroleum ether, bp 35–60 °C, 4:1)) to afford 363 mg (52%) of hydroxy seco acid **37** as a colorless oil: R_f (1% AcOH/EtOAc) 0.41; IR ($CHCl_3$) 2400–3450 (OH), 1700 (C=O) and 1670 cm^{-1} (C=C); ^{1}H NMR 400 MHz ($CDCl_3$) δ 1.25–1.62 (3 H, m), 1.64 (3 H, s), 1.80–2.08 (6 H, m), 3.01 (2 H, m), 2.75–2.80 (2 H, m), 3.88–4.01 (5 H, m), and 6.47 (2 H, AB q, J = 15.9 Hz); ^{13}C NMR ($CDCl_3$) δ 24.7, 26.6, 28.5, 29.7, 31.2, 33.6, 47.4, 47.6, 65.0, 68.6, 108.2, 121.2 (C=C) and 170.6 (C=O); MS calcd for $C_{15}H_{24}O_5S_2$, m/z 348.1065, found, m/z 348.1061.

Preparation of *dl*- and *meso*-Vermiculine Derivative 39. A mixture of **37** (171.5 mg, 0.49 mmol) and dimethyltin oxide (80.7 mg, 0.54 mmol) was stirred in 100 mL of refluxing mesitylene (100 °C (100 mmHg)) for 10 h with use of a Dean–Stark apparatus for the continuous removal of water. The reaction mixture was then further refluxed at ambient pressure (165 °C (760 mmHg)) for an additional 17 h. Removal of the solvent in vacuo (40 °C (0.2 mmHg)) gave 309 mg of a yellow solid residue. The crude product was "flash chromatographed"[23d] (2% AcOH/(EtOAc/petroleum ether, bp 35–60 °C, 1:5)) to afford 24.3 mg (15%) of a mixture of *dl*- and *meso*-**39** and 68.6 mg (40%) of adduct **41** in racemic form.

Diolide 39: R_f (15% EtOAc/$CHCl_3$) 0.42; IR ($CHCl_3$) 1710 (C=O) and 1600 cm^{-1} (C=C); ^{1}H NMR 400 MHz is given as supplementary material; MS calcd for $C_{15}H_{22}O_4S_2$ (monomer), m/z 330.0959, found, m/z 330.0960.

Adduct 41: R_f (1% AcOH/EtOAc) 0.41; IR ($CHCl_3$) 2400–3500 (OH), 1720 (C=O) and 1640 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 1.60–2.16 (11 H, m), 2.49–2.85 (6 H, m), and 3.99 (7 H, b s); MS calcd for $C_{15}H_{24}O_5S_2$, m/z 348.1065, found, m/z 348.1061.

Acknowledgment. We are grateful to Dr. J. E. Grady and Dr. R. Keene of the Upjohn Co. for their generous gift of a sample of ingramycin and nodusmicin. We are also grateful to Dr. B. J. Magerlein of the Upjohn Co. for sharing with us some of his preliminary and unpublished results concerning the chemistry of nodusmicin. Similarly, we thank Dr. T. Y. Shen and Dr. D. Taub of Merck Sharp and Dohme for their gift of a sample of zearalenone. We also thank Professor Clark Still for his gift of a sample of 9-hydroxy-8-methylnonanoic acid and especially for his discussions and interest in this work. High-resolution NMR spectra were recorded by Dr. M. T. Phan Viet and mass spectra by M. Evans of his department and by G. Boulay of the Department of Chemistry, Université de Sherbrooke. Finally, we wish to thank the Upjohn Co., the Natural Sciences and Engineering Research Council of Canada, and le Ministère de l'Éducation du Québec for financial support.

Supplementary Material Available: ^{1}H NMR 400-MHz spectral data for compounds **26**, **29**, **30**, **35**, **37**, and **39** and ^{13}C NMR spectral data for compounds **29**, **35**, and **37** (6 pages). Ordering information is given on any current masthead page.

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