conjugated. Consequently, if the addition is stepwise, the intermediate carbanion is formed with charge localized on the α-carbon, and a proton must be transferred to it before any conformational change necessary for charge delocalization can occur.[18]

(18) Note Added in Proof. We have since obtained similar results with the photochemical addition of methanol to other seven- and eight-membered ring enones.

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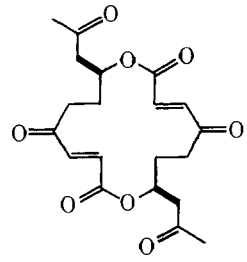
A Novel Synthesis of (±)-Vermiculine

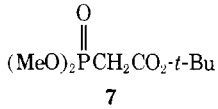
Sir:

The structure of the cytotoxic antibiotic vermiculine (**1**)[1] contains a 16-membered ring comprised of two identical C_{10} hydroxyacid units lactonized in head-to-tail fashion.[2] Recently, Corey has described a total synthesis of (±)-**1** via coupling of modified constituent halves as their pyridyl thioesters.[3] We now report a different synthesis of **1**, based on the alternative strategy of construction of a fully functionalized, acyclic hydroxyacid, which undergoes *intramolecular* lactonization to the completed macrolide.



1

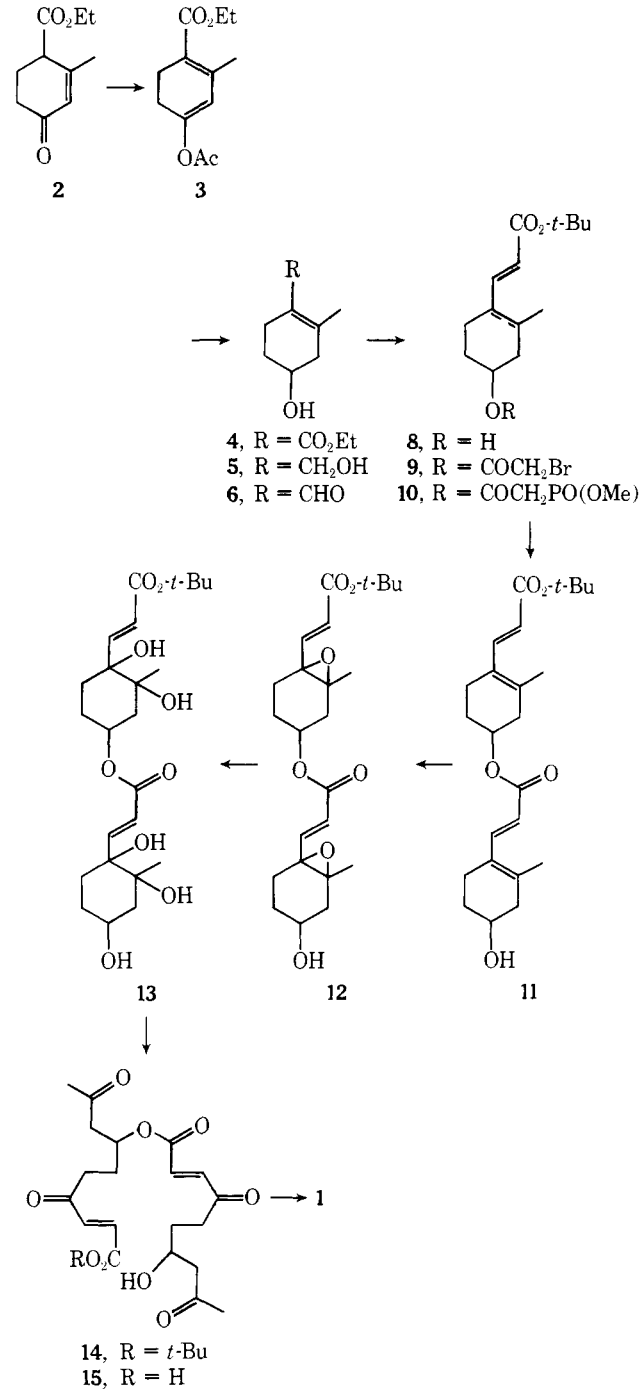
Dienol acetate **3**[4] (1760, 1706 cm^{-1}; δ 5.72 (1 H, s)), prepared from Hagemann's ester (**2**) by treatment with isopropenyl acetate containing *p*-toluenesulfonic acid (reflux),[5] was reduced with sodium borohydride in aqueous dioxane (95 °C, 2 h) to hydroxy ester **4** (68%, 3500, 1710 cm^{-1}; δ 3.98 (1 H, m)) and a minor quantity of the isomeric, allylic alcohol.[6] Further reduction of **4** with lithium aluminum hydride (ether, 0 °C, 6 h) afforded diol **5** (82%; δ 3.99 (1 H, m), 4.14 (2 H, d)), which was smoothly oxidized with manganese dioxide (CH_2Cl_2, 18 h) to aldehyde **6** (83%, 1675 cm^{-1}; δ 2.15 (3 H, s), 10.16 (1 H, s)). Condensation of **6** with the phosphonate **7**, derived from *tert*-butyl α-bromoacetate[7] and trimethyl phosphite, in the presence of sodium hydride (THF, 0 °C, 0.5 h) gave the diene ester **8** (82%; 3500, 1705, 1630 cm^{-1}; δ 1.52 (9 H, s), 2.88 (3 H, s), 3.92 (1 H, m), 5.70 (1 H, d, J = 16 Hz), 7.75 (1 H, d, J = 16 Hz)). The desired *E* configuration of the αβ-unsaturated linkage is clearly established by the coupling constant of vinyl protons in **8**.[8]



7

Compound **8** contains the structural elements of the monomeric unit (vermiculinic acid) from which the diolide system of **1** is derived, with the 1,6-diketo functions coveniently masked at this stage as a cyclohexenyl double bond. Attachment of the second C_{10} component to **8** began with acylation using bromoacetyl bromide (pyridine–ether, 0 °C, 1 h) to yield **9** (89%; 1740, 1710 cm^{-1}; δ 3.82 (2 H, s), 5.06 (1 H, p, J = 5 Hz)), followed by conversion with trimethyl phosphite (neat, 110 °C, 1 h) to phosphonate **10** (88%; δ 3.01 (2 H, d, J = 21 Hz)). The latter underwent condensation with aldehyde **6** in the presence of sodium hydride (THF, 0 °C, 0.5 h) to give a 95% yield of **11**, which was an approximately 1:1 mixture of diastereomers with respect to the pair of asymmetric centers in the two cyclohexane rings (δ 3.92 (1 H, m), 5.10 (1 H, m), 5.75 (2 H, d, J = 16 Hz), 7.76 (1 H, d, J = 16 Hz), 7.81 (1 H, d, J = 16 Hz)).

The remaining synthesis operation, an oxidative deannulation of **11** to a tetraketone, was effected via bisepoxide **12** (δ 1.26 (6 H, s)), prepared in 91% yield from **11** by oxidation with *m*-chloroperbenzoic acid (CH_2Cl_2, 24 h). Selective epoxidation of the γ,δ-double bonds in **11** was anticipated on the basis of the greater nucleophilicity of these tetrasubstituted linkages,[9] a supposition which had been previously verified by a selective epoxidation of the monomeric system **8**. Hydrolytic opening of the two epoxide functions, without damage to the *tert*-butyl ester, was accomplished using 8% perchloric acid (THF, 25 °C) and gave pentahydroxy diester **13** in good yield as a mix-



2 **3**

4, R = CO_2Et **8**, R = H
5, R = CH_2OH **9**, R = $COCH_2Br$
6, R = CHO **10**, R = $COCH_2PO(OMe)_2$

13 **12** **11**

14, R = *t*-Bu
15, R = H

ture of stereoisomers. This mixture was promptly subjected to oxidative cleavage with lead tetraacetate[10] (EtOAc/pyridine, 25 °C, 20 min) and, after purification by chromatography on silica (elution with 1:1 benzene-ethyl acetate), a 54% yield (based on **12**) of **14** (3500, 1728, 1708 cm^{-1}; δ 1.50 (9 H, s), 2.18 (6 H, s), 6.58 (1 H, d, J = 16 Hz), 6.64 (1 H, d, J = 16 Hz), 6.96 (1 H, d, J = 16 Hz), 7.06 (1 H, d, J = 16 Hz)) was obtained. Mild hydrolysis of **14** (TFA, 0 °C, 15 min) furnished the highly polar carboxylic acid **15,** which provided the substrate for subsequent lactonization studies.

Virtually all lactonization methods currently in vogue entail activation of the carboxyl group, followed by nucleophilic attack by hydroxyl.[11] Although this tactic has enjoyed noteworthy success in macrolide synthesis,[2,12] the sensitive enedicarbonyl functions in **14** frustrated all attempts to construct suitably activated ester derivatives. Consequently, we turned to an approach in which the roles of carboxyl and hydroxyl partners are reversed, adopting the principle of hydroxyl activation in the presence of a carboxyl group as nucleophile.[13] Thus, treatment of **14** in benzene with triphenylphosphine, followed by diethyl azodicarboxylate with vigorous stirring (25 °C, 2 days),[14] gave, after preparative thin-layer chromatography on silica, a 15% yield of (±)-vermiculine (**1**), identical by infrared, NMR, mass spectral, and chromatographic comparison with authentic material. A slightly more polar, chromatographic fraction corresponding to the unnatural, trans isomer of **1** was also isolated.

Although the yield of **1** from **14** is disappointingly low, the lactonization method demonstrated here provides a potentially useful alternative to the conventional carboxyl-activation methodologies.[15] Considerable refinement of this "reverse activation" technique may be anticipated.[16]

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(17) Recipient of a National Institutes of Health Research Career Development Award.

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A Comparison of the Heterolytic vs. Homolytic Cleavage of the Nitrogen–Chlorine Bond

Sir:

Over the last decade, we have carried out a detailed study of the reactions and properties of nitrenium ions (divalent positive nitrogen species).[1] As part of these investigations, we described the heterolytic cleavage of the N–Cl bond of *N*-chloramines in both silver ion promoted and purely solvolytic ionization reactions. However, recently it was stated that "Nitrenium ions *are not* generated from simple secondary chloramines in the presence of silver ions at room temperature."[2] Extrapolations of this statement[3] have prompted us to thoroughly establish the difference between the heterolytic and homolytic cleavage of the N–Cl bond of chloramines. We now wish to report the details of this study.

In our early work on the rearrangement of *N*-chloramines, we established that both the silver-ion promoted and noncatalyzed solvolysis of **1** in methanol gave a mixture of **2, 3,** and **4.**[4] It was proposed that the formation of **3** and **4,** which constituted greater than 90% of the product mixture arose via Wagner–Meerwein rearrangement of the initially generated nitrenium ion **5** to yield the carbonium ion **6.** Addition of solvent or internal return of chloride would then give **3** or **4,** respectively. In order to distinguish between a homolytic and a heterolytic cleavage of the N–Cl bond, it became necessary to generate the amino radical, **7,** and to compare the products derived from **7** with those arising from the solvolytic reactions previously studied. Three approaches were taken to the generation of **7.** These were (1) photolysis of the tetrazene **8,** (2) photolysis of **1,** and (3) benzoyl peroxide promoted decomposition of **1** in methanol.