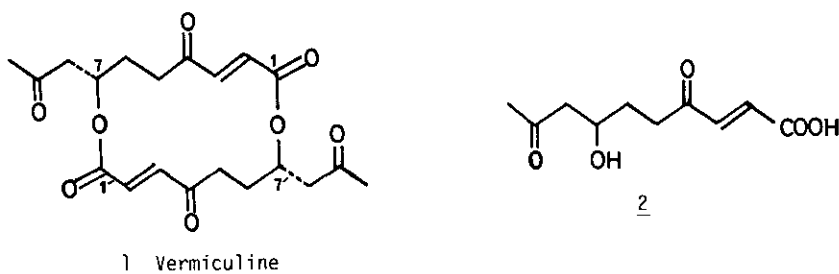


SYNTHESIS OF dl-VERMICULINE VIA CONTROL OF OLEFIN FORMATION

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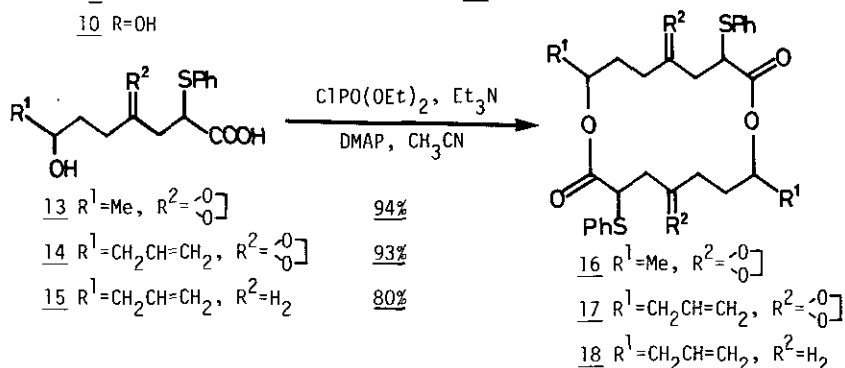
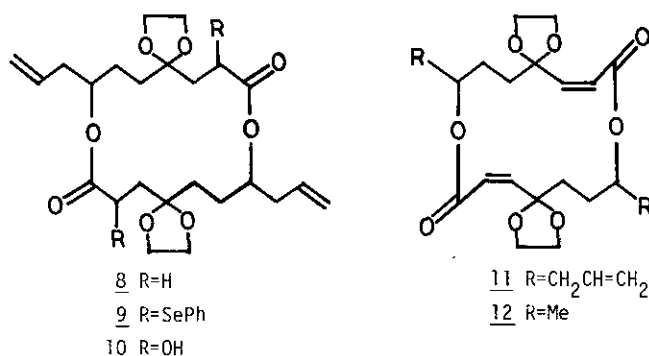
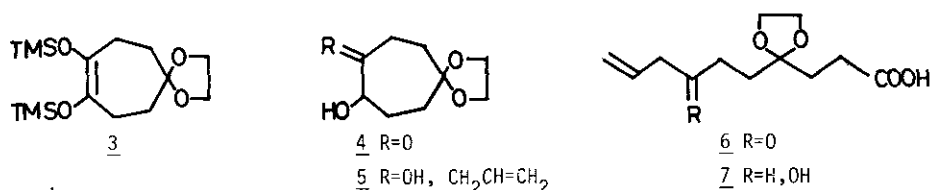
Abstract - The Synthesis of the macrodiolide antibiotic vermiculine 1 has been achieved starting from the enediol(trimethylsilyl) enol ether via the macrocyclization of hydroxycarboxylic acids followed by the formation of the requisite trans double bonds.

A great deal of effort has been devoted¹ toward the synthesis of vermiculine 1, a macrocyclic dilactone antibiotic isolated from *penicillium vermiculatum* Dangeard.² This compound was characterized by a 16-membered ring derived by head to tail lactonization of two identical C-10 α,β -unsaturated hydroxycarboxylic acid subunit 2. The preparation of 2 in a suitably protected form followed by lactonization was most of the synthetic approaches to the target macrodiolide 1. But lactonization process with the activation of carboxyl group was not necessarily efficient.³ Recently, we communicated a new method for the construction of macrodiolides.⁴ We herein describe the further application of this process to the synthesis of dl-vermiculine 1.

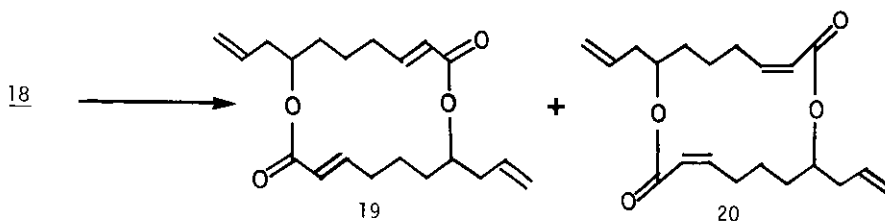


The silyl enol ether 3⁵ was hydrolyzed (aqueous THF, reflux) to the hydroxyketone 4 and this was transformed to the vicinal glycol 5 ($\text{CH}_2=\text{CHCH}_2\text{MgBr}$, THF, 84% from 3). Oxidative cleavage of 5 ($\text{Pb}(\text{OAc})_4$, C_6H_6 , rt) followed by Jones oxidation gave the keto acid 6 which was subjected to reduction (NaBH_4 , CH_3OH , -10°C) to afford the hydroxycarboxylic acid 7 (90% from 5).

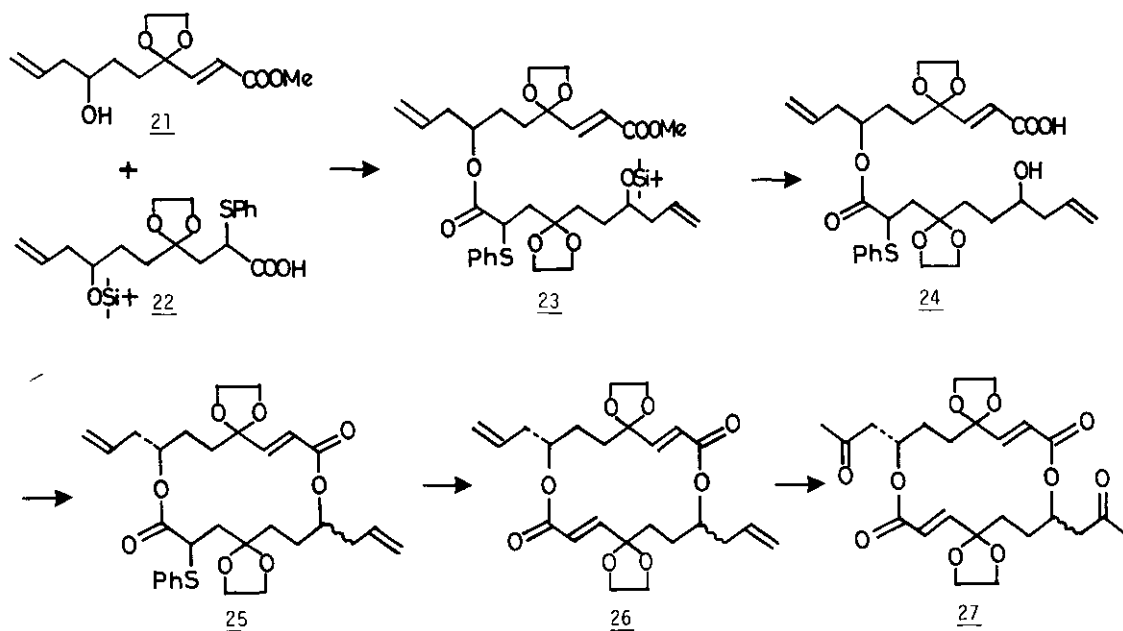
Lactonization^{6,7} of 7 ($\text{ClPO}(\text{OEt})_2$, Et_3N , CH_3CN , -20°C , then DMAP, CH_3CN , reflux, 3.5 mmol/L) smoothly occurred to give diolide 8 in 75% yield. Selenenylation⁸ of enolate anion (LDA, THF, PhSeBr , -78°C) derived from 8 produced a mixture of selenide 9 (14%) and alcohol 10 (46%), respectively. Oxidation of selenide 9 (30% H_2O_2 , pyridine, CH_2Cl_2 , 0°C) furnished the cis diolide 11 as the only observed product in 86% yield. These results were completely different from those of trans stereoselection observed in the case of pyrenophorin synthesis.⁴ These facts also demonstrated that the selectivity of double bond formation depends on the bulkiness of the substituents at C-7 or C-7' (methyl or allyl group). Many attempts for the isomerization of cis double bond of 11 to the trans olefin 26 resulted in failure. Subsequently, attention was turned to the α -phenylthiocarboxylic acid derivatives as a potential intermediate to introduce double bond. Compounds 13, 14,⁹ and 15 were subjected to lactonization in a similar manner as described above to give rise to the respective diolides 16 (94%), 17 (93%), and 18 (80%) in excellent yields. However, oxidation¹⁰ of 16 or 17 (NaIO_4 , CH_3OH , rt) followed by reflux in toluene resulted in the formation of the cis diolides 12 (75%) and 11 (91%).



On the other hand, oxidative elimination of compound 18 not having ethylene acetal moiety under the same conditions afforded a mixture of the desired trans diolide 19 (17%) and the cis diolide 20 (78%), respectively. Diolide 19 obtained in this way was converted to dl-vermiculine 1 and meso-vermiculine in two steps (i. $\text{PdCl}_2/\text{CuCl}$, O_2 , DMF,¹¹ 62%. ii. CrO_3 , $\text{HOAc}/\text{Ac}_2\text{O}$, C_6H_6 ,¹² 32%).



A more efficient route to the synthesis of vermiculine 1 has been explored. Treatment of alcohol 21 and carboxylic acid 22 with diethyl phosphorochloridate containing triethylamine in the presence of DMAP in benzene gave ester 23 in 97% yield. This was deprotected ($n\text{-Bu}_4\text{NF}$, THF, 91%) and a derived alcohol was selectively hydrolyzed to the hydroxycarboxylic acid 24 (LiOH , aqueous $t\text{-BuOH}$, 100%). Lactonization¹³ of 24 gave cleanly diolide 25 in 68% yield after purification by chromatography. A crucial oxidative elimination of 25 (i. NaIO_4 , CH_3OH . ii. toluene, reflux) afforded the desired trans diolide 26 in 85% yield. Finally, 26 was converted into dl-vermiculine 1 and meso-vermiculine (i. $\text{PdCl}_2/\text{CuCl}$, O_2 , DMF, 97%. ii. excess CF_3COOH , wet CH_2Cl_2 , 0°C , then rt, 1h, 98%). Spectral properties of the synthetic vermiculine 1 were identical with those of reported data.^{1a}

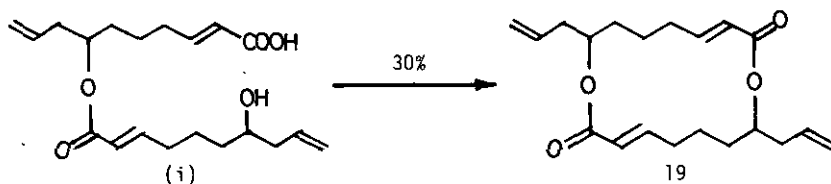


ACKNOWLEDGMENTS

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- Hydroxycarboxylic acid **14** was obtained from **6** (1) esterification of **6** ($\text{ClPO}(\text{OEt})_2$, Et_3N , CH_3OH , DMAP in benzene, rt) followed by reduction (NaBH_4 , CH_3OH , 0°C), 78%. (2) treatment of hydroxyester (LDA, PhSSPh , THF, $-78^\circ\text{C} \rightarrow -40^\circ\text{C}$) followed by hydrolysis (2N-KOH , CH_3OH , rt), 85%.
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- Lactonization of compound (i) under the same conditions gave **19** in 30% yield.



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