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SYNTHESIS OF dl-VERMICULINE *VIA* CONTROL OF OLEFIN FORMATION

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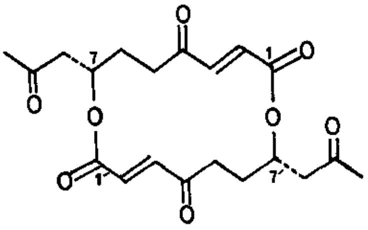
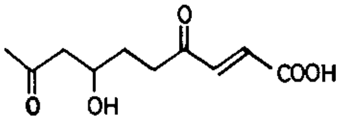
Abstract - The Synthesis of the macrodiolide antibiotic vermiculine 1 has been achieved starting from the enediol(trimethylsilyl) enol ether via the macrocyclization of hydroxycarboxylic acids followed by the formation of the requisite trans double bonds.

A great deal of effort has been devoted[1] toward the synthesis of vermiculine 1, a macrocyclic dilactone antibiotic isolated from *penicillum 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 neccessarily 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.



1 Vermiculine



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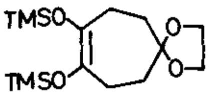
The silyl enol ether 3[5] was hydrolyzed (aqueous THF, reflux) to the hydroxyketone 4 and this was transformed to the vicinal glycol 5 ($CH_2=CHCH_2MgBr$, THF, 84% from 3). Oxidative cleavage of 5 ($Pb(OAc)_4$, C_6H_6, rt) followed by Jones oxidation gave the keto acid 6 which was subjected to reduction ($NaBH_4$, CH_3OH, -10°C) to afford the hydroxycarboxylic acis 7 (90% from 5).

Lactonization [6,7] of 7 ($ClPO(OEt)_2$, Et_3N, CH_3CN, -20°C, then DMAP, CH_3CN, reflux, 3.5 mmol/L) smoothly occurred to give diolide 8 in 75% yield. Selenenylation[8] 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, oxidation[10] 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%).



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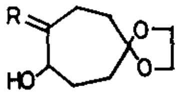
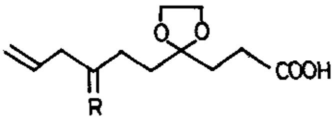


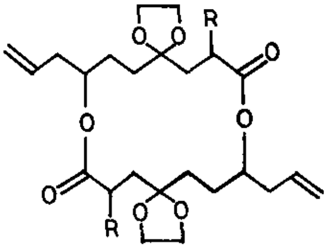
4 R=O

5 R=OH, $CH_2CH=CH_2$



6 R=O

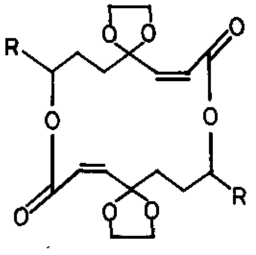
7 R=H,OH



8 R=H

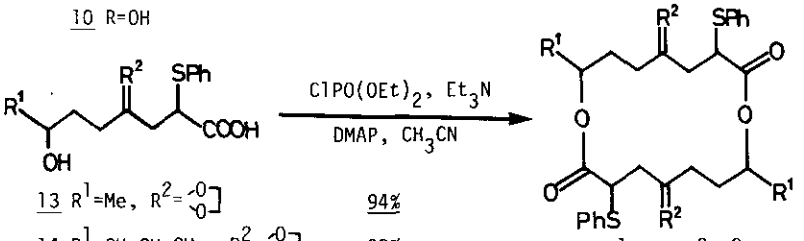
9 R=SePh

10 R=OH



11 R=$CH_2CH=CH_2$

12 R=Me



13 R^1=Me, $R^2=\begin{smallmatrix}\text{-O}\\\text{-O}\end{smallmatrix}]$ 94%

14 $R^1=CH_2CH=CH_2$, $R^2=\begin{smallmatrix}\text{-O}\\\text{-O}\end{smallmatrix}]$ 93%

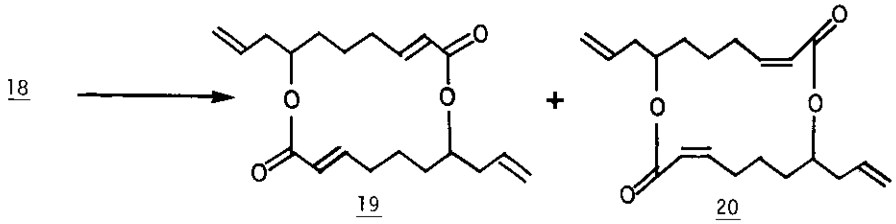
15 $R^1=CH_2CH=CH_2$, $R^2=H_2$ 80%

16 R^1=Me, $R^2=\begin{smallmatrix}\text{-O}\\\text{-O}\end{smallmatrix}]$

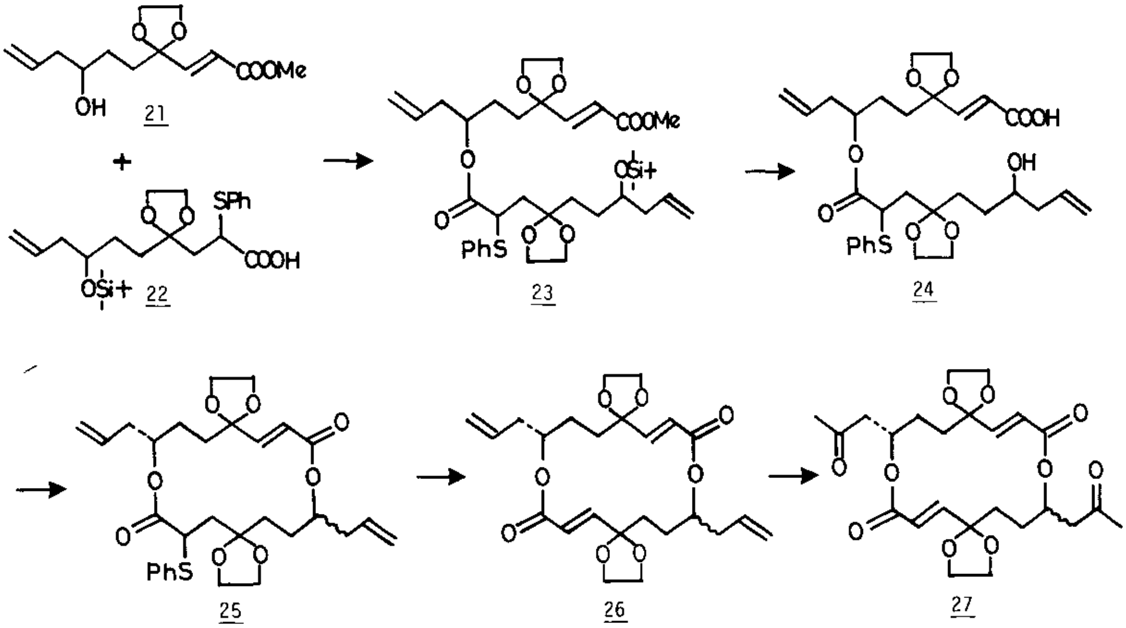
17 $R^1=CH_2CH=CH_2$, $R^2=\begin{smallmatrix}\text{-O}\\\text{-O}\end{smallmatrix}]$

18 $R^1=CH_2CH=CH_2$, $R^2=H_2$

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. $PdCl_2/CuCl$, O_2, DMF,[11] 62%. ii. CrO_3, $HOAc/Ac_2O$, 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 benezene gave ester 23 in 97% yield. This was deprotected (n-Bu_4NF, THF, 91%) and a derived alcohol was selectively hydrolyzed to the hydroxycarboxylic acid 24 (LiOH, aqueous t-BuOH, 100%). Lactonization[13] 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. $PdCl_2/CuCl$, 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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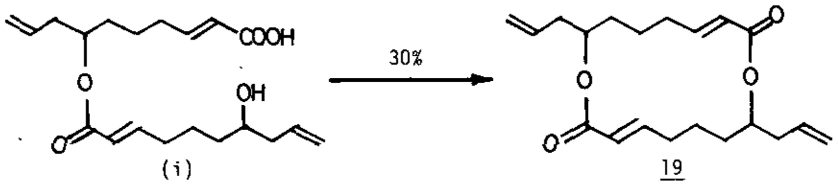
REFERENCES AND NOTES

1. (a) E. J. Corey, K. C. Nicolaou, and T. Toru, J. Am. Chem. Soc., 97, 2287 (1975). (b) Y. Fukuyama, C. L. Kirkemo, and J. D. White, J. Am. Chem. Soc., 99, 646 (1977). (c) D. Seebach, B. Seuring, H. O. Kalinowski, W. Lubosch, and B. Renger, Angew. Chem. Int. Ed., 16, 264 (1977). (d) K. F. Burri, R. A. Cardone, W. Y. Chen, and P. Rosen, J. Am. Chem. Soc., 100, 7069 (1978). (e) T. A. Hase, A. Ourila, and C. Holmberg, J. Org. Chem., 46, 3137 (1981). (f) K. Steliou and M.-A. Poupart, J. Am. Chem. Soc., 105, 7130 (1983) (g) P. G. Baraldi, A. Barco, S. Benetti, F. Moroder, G. P. Pollini, and D. Simoni, J. Org. Chem., 48, 1297 (1983).
2. R. K. Boeckmann, Jr., J. Fayos, and J. Clardy, J. Am. Chem. Soc., 96, 5954 (1974).
3. (a) H. Gerlach, K. Oertle, and A. Thalmann, Helv. Chim. Acta, 60, 2860 (1977). (b) P. Schnurrenbergur, E. Hungerbuhler, and D. Seebach, Tetrahedron Lett., 2209 (1984). (c) see ref. 1(e).
4. T. Wakamatsu, S. Yamada, Y. Ozaki, and Y. Ban, Tetrahedron Lett., 1989 (1985).
5. J. J. Bloomfield, Tetrahedron Lett., 591 (1968).
6. T. Kaiho, S. Masamune, and T. Toyoda, J. Org. Chem., 47, 1612 (1982).
7. For our previous results of lactonization or esterification, see ref. 4.
8. (a) H. J. Reich, I. L. Reich, and J.M. Rehga, J. Am. Chem. Soc., 95, 5813 (1973). (b) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, ibid., 6137 (1973).
9. Hydroxycarboxylic acid 14 was obtained from 6 (1) esterification of 6 ($ClPO(OEt)_2$, 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°C → -40°C) followed by hydrolysis (2N-KOH, CH_3OH, rt), 85%.
10. N. J. Leonard and C. R. Johnson, J. Org. Chem., 27, 282 (1962).
11. J. Tsuji, I. Shimizu, and K. Yamamoto, Tetrahedron Lett., 2975 (1976).
12. R. S. Mali, M. Pohmakotr, B. Weidmann, and D. Seebach, Liebigs Ann. Chem., 2272 (1981).
13. Lactonization of compound (i) under the same conditions gave 19 in 30% yield.



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