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Total Synthesis of (–)-Vermiculine

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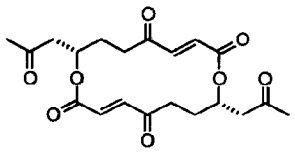
Abstract: Macrodiolide (–)-vermiculine has been synthesized via intramolecular Mitsunobu reaction utilizing a C_2 symmetrical diepoxide chiral synthon.

(–)-Vermiculine (**1**) is a dimeric sixteen-membered macrolide (diolide) antibiotic isolated from the culture of *Penicillium vermiculatum*[1,2] and exhibits inhibitory effects on the growth of Gram-positive bacteria and of some protozoa;[1] moreover it has a strong cytotoxic effect against Ehrlich ascites carcinoma, lymphoadenoma, sarcoma, and leukemia cells.[3] Extensive synthetic efforts in the preparation of **1** and the hydroxy acid derivatives as monomeric precursors to **1** have been reported during the past two decades. Most of the reported approaches, however, have been based on the racemates, which lead to the formation of 1:1 mixture of the racemic and meso forms of **1**.[4] As for the chiral synthesis of **1**, only a few successful syntheses for the unnatural and natural enantiomers have been published by Seebach's group[5] and Burri et al.,[6] respectively, which have enabled the relative and absolute configuration of **1** to be established.



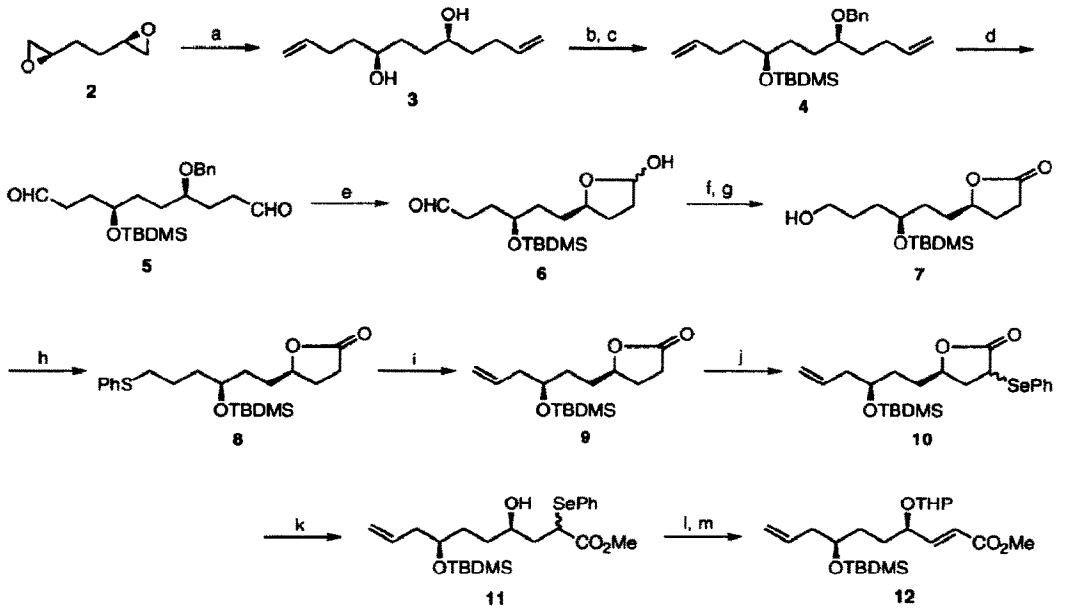
(–)-Vermiculine (1)

Recent investigations from this laboratory have revealed the synthetic versatility of C_2 symmetrical 1,2:5,6-diepoxyhexane (**2**), economically accessible in both enantiomeric forms from D-mannitol,[7] as a multi-purpose chiral synthon for the enantioselective preparation of various natural products.[8] In this communication we report a chiral synthesis of the natural (–)-enantiomer of **1** based on this chiron protocol utilizing the enantiopure (*R,R*)-diepoxide **2**.

The (*R,R*)-diepoxide **2**[7] underwent nucleophilic ring opening with two equivalents of allylmagnesium bromide in the presence of CuI to give the diol **3**, which was converted to **4** by selective benzylation (1 equiv BnBr, NaH, Bu_4NBr) followed by further protection by the silyl group (Scheme 1). Oxidative cleavage of the terminal olefins of **4** with periodate catalyzed by OsO_4 furnished the dialdehyde **5** in 85% yield.

Differentiation of the two formyl groups of **5** was conveniently achieved by hydrogenolytic removal of the benzyl protecting group to form the lactol **6** in 87% yield. Oxidation (PDC) of the lactol to the lactone followed by $NaBH_4$ reduction of the aldehyde provided the hydroxy lactone **7**. Olefination of **7** was achieved via the sulfide **8**, which underwent oxidative pyrolytic elimination (*m*-CPBA, then reflux in xylene in the presence of pyridine) to produce **9** in 80% overall yield from **7**. Introduction of the (*E*)-olefinic function was then effected via a selenylation–oxidation sequence. Accordingly, the lithium enolate of the γ-lactone **9** was treated with phenylselenenyl bromide to give the α-phenylselenolactone **10** (42% yield with 51% of the starting material recovered), which was subjected to hydrolysis followed by diazomethane esterification to give the α-phenylselenohydroxy ester **11** (97%). Oxidation with *m*-CPBA generated the intermediate phenylselenoxide which collapsed at room temperature to furnish the (*E*)-α,β-unsaturated hydroxy ester (76% from **11**), which was protected as its THP ether to give **12**.

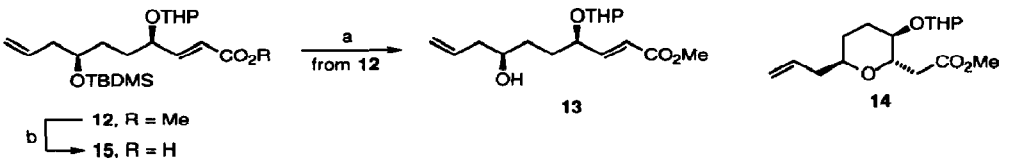
Scheme 1



(a) CH_2=$CHCH_2MgCl$, CuI, THF, –40 °C (87%); (b) BnBr, NaH, Bu_4NBr, THF, r.t. (86%); (c) *t*-$BuMe_2SiCl$, imidazole, DMF, r.t. (100%); (d) OsO_4, $NaIO_4$, MeCN–10% $KHCO_3$, r.t. (85%); (e) H_2, 10% Pd–C, MeOH (87%); (f) PDC, CH_2Cl_2, r.t. (67%); (g) $NaBH_4$, EtOH, –30 °C (88%); (h) $(PhS)_2$, Bu_3P, Py, r.t. (97%); (i) i, *m*-CPBA, CH_2Cl_2, –78 °C; ii, xylene, Py, reflux (82%); (j) $(Me_3Si)_2NLi$, THF, –78 °C, then PhSeBr, THF, –78 °C (42% or 85% based on recovered **9**); (k) i, 3.5 N KOH, THF–MeOH (2:1), 0 °C; ii, CH_2N_2, Et_2O, 0 °C (97%); (l) i, *m*-CPBA, CH_2Cl_2, –78 °C; ii, toluene, Py, r.t. (76%); (m) 2,3-dihydropyran, PPTS, CH_2Cl_2, r.t. (96%).

The two monomeric units **13** and **15** for the construction of the diolide could be prepared utilizing **12** as a common intermediate. When desilylation of **12** was carried out using Bu_4NF in THF at 60 °C, this

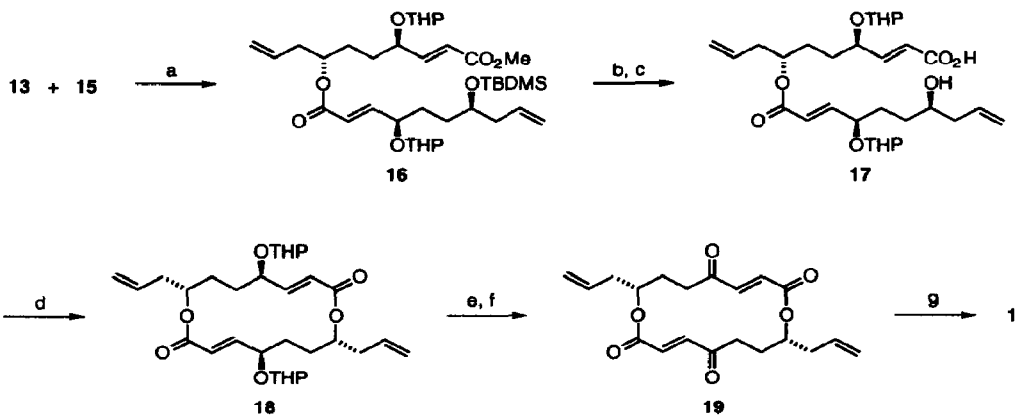
proceeded with concomitant intramolecular 1,4-conjugate addition catalyzed by fluoride ion on the resulting hydroxy ester **13** to produce the tetrahydropyran derivative **14**.[9] To avoid the formation of **14**, the desilylation was then performed under acidic conditions (10 equiv Bu_4NF, 4 equiv benzoic acid)[10] to provide **13** (65%). The alternative monomeric fragment **15** was readily available by basic hydrolysis of the ester function of **12**.



(a) Bu_4NF (10 equiv), $PhCO_2H$ (4 equiv), THF, 50 °C (65%); (b) 3.5 N KOH, THF–MeOH (2:1), r.t. (97%).

Coupling of the two fragments **13** and **15** under Mitsunobu conditions (1.5 equiv DEAD, 3.0 equiv Ph_3P) led to **16** (80%), which was converted to the hydroxy acid **17** in 78% yield by acidic desilylation (Bu_4NF, $PhCO_2H$) followed by basic hydrolysis (Scheme 2). Intramolecular lactonization, again under Mitsunobu conditions, resulted in the construction of the diolide **18** as a single isomer in 62% yield.[11] Deprotection of the THP ether (TsOH, MeOH) followed by oxidation of the alcohol with PDC produced the diketo diolide **19** (66%), which was now subjected to Wacker oxidation ($PdCl_2$, CuCl, O_2) to furnish (–)-vermiculine (**1**), mp 158–161 °C (lit.[1] 175–177 °C dec, lit.[2] 160–162 °C); $[\alpha]^{24}_D$ –10.0° (*c* 0.02, $CHCl_3$) (lit.[1] $[\alpha]^{20}_D$ –12.5° (*c* 0.2, $CHCl_3$), lit.[6] $[\alpha]_D$ –10.6° (*c* 0.2, $CHCl_3$)). The synthetic sample of **1** exhibited ^1H NMR spectrum identical with that reported[2] for natural **1**.

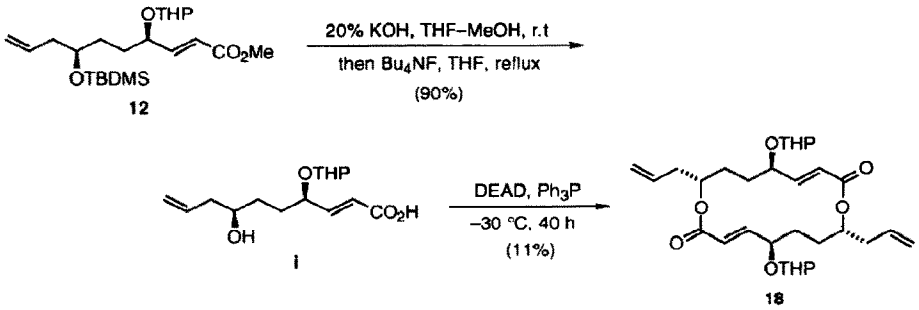
Scheme 2



(a) DEAD (1.5 equiv), Ph_3P (3 equiv), toluene, –40 °C to 0 °C (24 h), then r.t. (24 h) (80%); (b) Bu_4NF (10 equiv), $PhCO_2H$ (4 equiv), THF, 50 °C (78%); (c) 0.4 N LiOH, THF, r.t. (100%); (d) DEAD (3 equiv), Bu_3P (3 equiv), toluene, –40 °C to 0 °C (24 h), then r.t. (24 h) (62%); (e) TsOH, MeOH, r.t. (70%); (f) PDC, DMF, r.t. (94%); (g) $PdCl_2$, CuCl, O_2, DMF–H_2O (7:1), r.t. (46%).

References and Notes

1. Fuska, J.; Nemec, P.; Kuhr, I. *J. Antibiot.* **1972**, *25*, 208.
2. Massias, M.; Molho, L.; Rebuffat, S.; Cesario, M.; Guilhen, J.; Pascard, C.; Bodo, B. *Phytochemistry* **1989**, *28*, 1491.
3. Fuska, J.; Ivanitskaya, L. P.; Horakova, K.; Kuhr, I. *J. Antibiot.* **1974**, *27*, 141. Horakova, K.; Kernacova, B.; Nemec, P.; Fuska, J. *J. Antibiot.* **1976**, *29*, 1109.
4. For syntheses of (±)-vermiculine, see: (a) Corey, E. J.; Nicolaou, K. C.; Toru, T. *J. Am. Chem. Soc.* **1975**, *97*, 2287. (b) Fukuyama, Y.; Kirkemo, C. L.; White, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 646. (c) Wakamatsu, T.; Yamada, S. Ban, Y. *Heterocycles* **1986**, *24*, 309. For syntheses of racemic hydroxy seco acid, see: (a) Hase, T. A.; Ourila, A.; Holmberg, C. *J. Org. Chem.* **1981**, *46*, 3137. (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Moroder, F.; Pollini, G. P.; Simoni, D. *J. Org. Chem.* **1983**, *48*, 1297. (c) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130.
5. Seebach, D.; Seuring, B.; Kalinowski, H. O.; Lubosch, W.; Renger, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 264. Seuring, B.; Seebach, D. *Liebigs Ann. Chem.* **1978**, 2044.
6. Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.
7. Machinaga, N.; Kibayashi, C. *Synthesis* **1992**, 989.
8. (a) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *31*, 3637. (b) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 1386. (c) Machinaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405. (d) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 51. (e) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1992**, *34*, 841. (f) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 5739.
9. We have recently observed a similar construction of the tetrahydropyranyl nucleus in the synthesis of (+)-decarestrictine L (see ref 8f).
10. Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2860.
11. Dimerization of the hydroxy seco acid **i**, obtained from **12**, by Mitsunobu coupling resulted in only 11% yield of the diolide **18** owing to the concomitant formation of the trimer and tetramer.



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