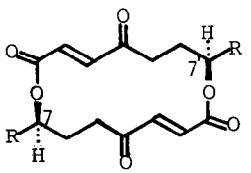
Tetrahedron Letters,Vol.28,No.24,pp 2717-2720,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A SYNTHESIS OF (-)-PYRENOPHORIN USING 4-DMAP-CATALYZED ESTER EXCHANGE REACTION OF PHOSPHONOACETATES WITH LACTOLS

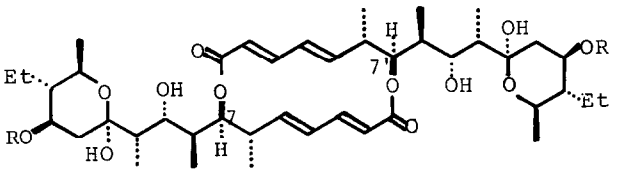
Susumi Hatakeyama, Kumiko Satoh, Kuniya Sakurai, and Seiichi Takano*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Summary: A C_2-symmetrical 16-membered macrodiolide, (-)-pyrenophorin has been synthesized enantioselectively using newly developed 4-DMAP-catalyzed ester exchange reaction of phosphonoacetates with lactols.

A great deal of effort[1] has been devoted toward the synthesis of 16-membered macrodiolides with C_2-symmetry such as pyrenophorin (1), vermiculine (2), and elaiophylin (3) because of their unique structural features and biological activities. One of the most crucial problems in the synthesis of these

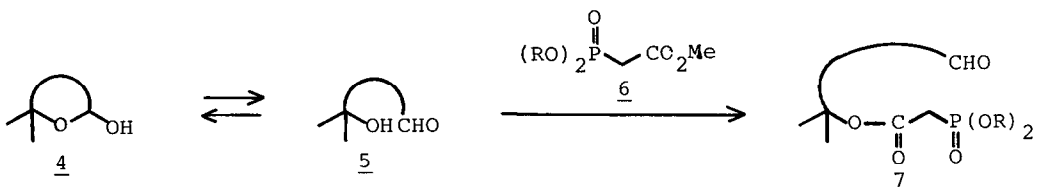


1 : R=Me, pyrenophorin
2 : R=CH_2COMe, vermiculine



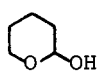
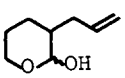
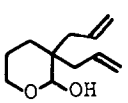
3 : R=2-deoxy-(L)-fucos-1-yl, elaiophylin

molecules is the construction of their characteristic 7,7'-disubstituted dienolide systems. Most of the reported synthetic routes rely on dimerization of a suitably functionalized hydroxy acid except Hoffmann-La Roche's synthesis[2] of vermiculine (2) in which the Wadsworth-Emmons olefination reaction served to achieve the critical closure of the macrodiolide ring. The synthetic route based on the Wadsworth-Emmons olefination seems to be attractive one,[3] however, the requisite aldehydophosphonoacetates are often difficult to prepare. We have recently developed a new synthetic method of phosphonoacetates from alcohols by 4-DMAP-catalyzed ester exchange reaction of easily available phosphonoacetates as reported in the preceding paper. We assumed that reaction of a lactol 4 with a phosphonoacetate 6 would directly lead to formation of an aldehydophosphonoacetate 7 without any protection-deprotection sequence if an aldehydoalcohol 5 can undergo ester exchange reaction much faster than a lactol 4.



The potential of this type of ester exchange reaction for the preparation of aldehydophosphonoacetates was initially tested in a model study. Thus, the lactols 8, 9, and 10 were allowed to react with threefold excess of diisopropyl methoxycarbonylmethylphosphonate (11) in the presence of a catalytic amount of 4-DMAP (30 mol %) in boiling toluene. The results are summarized in the Table. It shows that lactols reacted with 11 selectively as their open form rather than their closed form presumably by steric reasons. It is interesting to add that none of the Wadsworth-Emmons olefination products were formed under these conditions.

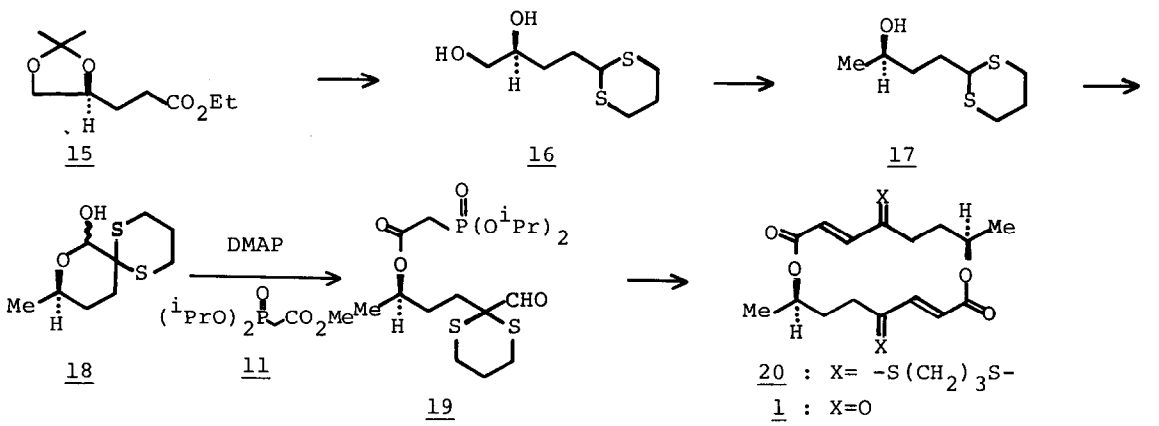
Table

lactol	reaction time (h)	product[a] $(^{i}PrO)_2\overset{\overset{O}{\|}}{P}CH_2CO_2(CH_2)_3CRR'CHO$	yield[b] (%)
 8	60	12: R=R'=H	43
 9	100	13: R= $CH_2CH=CH_2$, R'=H	40
 10	100	14: R=R'= $CH_2CH=CH_2$	56

a) purified by silica gel column chromatography, b) isolated yield

Having thus developed a new method for the preparation of aldehydophosphonoacetates, the synthesis of (-)-pyrenophorin (1) was then investigated. Ethyl O-isopropylidene-(S)-4,5-dihydroxypentanoate (15),[5] easily prepared from D-mannitol, was successively subjected to reduction (LAH, THF, 25°C), oxidation (PCC, CH_2Cl_2, 25°C), and thioacetalization ($HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 25°C) to give the diol 16, $[\alpha]_D^{28}$ -4.1° (c 0.690, $CHCl_3$), in 76% yield. Tosylation (p-TsCl, pyridine, 25°C) followed by reduction (LAH, THF, 0°C) gave the alcohol 17, $bp_{0.05}$ 120°C (Kugelrohr), $[\alpha]_D^{24}$ -10.6° (c 1.018, $CHCl_3$) (lit.[6] +8.0° for its antipode), in 66% yield. According to the Seebach's procedure,[6] the alcohol 17 was then converted to the lactol 18 via the dianion ($^{n}BuLi$, THF, -30°C, then DMF) in 58% yield (quantitative yield based on consumed 17). Reaction of the lactol 18 with 11 (30 mol % 4-DMAP, toluene, reflux, 3 days) afforded the key aldehydophosphonoacetate 19, $[\alpha]_D^{28}$ +5.4° (c 0.558, $CHCl_3$), in 75% yield. Upon

treatment 19 with 1.1 equiv of sodium hydride in THF according to the procedure developed by Hoffmann-La Roche's group,[2] cyclization took place at ambient temperature to give the desired diolide 20, mp 196-197°C (Et_2O) (lit.[6] 182-185°C (Et_2O/pentane)), $[\alpha]_D^{26}$ -125° (c 0.400, $CHCl_3$) (lit.[6] -109°) in 52% yield together with the trimer (18% yield) and the tetramer (4% yield). Finally, the total synthesis of (-)-pyrenophorin (1) was achieved by hydrolysis[7] of the dithiane groups of 20 ($NCS\text{-}AgNO_3$, aq. MeCN, 25°C) in 57% yield. The synthetic material, mp 174-175°C (EtOH) (lit.[6] 175°C), $[\alpha]_D^{26}$ -72.9° (c 0.650, acetone) (lit.[6] -54.5°) exhibited spectral properties (^{1}H-NMR, IR, MS) in accord with those reported.[7,8]



References and Notes

1. For pyrenophorin: T. Wakamatsu, S. Yamada, Y. Ozaki, and Y. Ban, Tetrahedron Lett., 26, 1989 (1985) and references therein; For vermiculine: T. Wakamatsu, S. Yamada, and Y. Ban, Heterocycles, 24, 309 (1986) and references therein; For elaiophylin: K. Toshima, K. Tatsuta, and M. Kinoshita, Tetrahedron Lett., 27, 4741 (1986); D. Seebach, H. -K. Chow, R. F. W. Jockson, M. A. Sutter, S. Thaisrivongs, and J. Zimmermann, Liebigs Ann. Chem., 1986, 1281; T. Wakamatsu, H. Nakamura, E. Naka, and Y. Ban, Tetrahedron Lett., 27, 3895 (1986).
2. K. F. Burri, R. A. Cardone, W. Y. Chen, and P. Rosen, J. Am. Chem. Soc., 100, 7069 (1978).
3. The synthetic application of the Wadsworth-Emmons olefination to the ring-closure of macrolides: G. Stork and E. Nakamura, J. Org. chem., 44, 4010 (1979); K. C. Nicolaou, S. P. Seitz, and M. R. Pavia, and N. A. Petasis, ibid., 44, 4011 (1979); K. C. Nicolaou, S. P. Seitz, and M. R. Pavia, J. Am. Chem. Soc., 104, 2030 (1982); W. C. Still and V. J. Novack, J. Am. Chem. Soc., 106, 1148 (1984); N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa, and O. Yonemitsu, J. Am. Chem. Soc., 108, 4645 (1986).

4. ^{1}H-NMR data ($CDCl_3$) for the following compounds: 12: δ 1.34 (12H, d, 7.0 Hz), 1.70 (4H, m), 2.50 (2H, m), 2.92 (2H, d, 22 Hz), 4.15 (2H, brt, 7.0 Hz), 4.75 (2H, d hept, 1.7 Hz and 7.0 Hz), 9.77 (1H, t, 1.7 Hz). 13: δ 1.35 (12H, d, 7.0 Hz), 1.69 (4H, m), 2.40 (2H, m), 2.92 (2H, d, 22 Hz), 4.12 (2H, t, 6.9 Hz), 4.75 (2H, br hept, 7.0 Hz), 4.90-6.05 (3H, m), 9.61 (1H, brs). 14: δ 1.33 (12H, d, 7.0 Hz), 1.57 (4H, m). 2.28 (4H, d, 7.5 Hz), 2.91 (2H, d, 22 Hz), 4.09 (2H, brt), 4.75 (2H, d hept, 1.7 Hz and 7.0 Hz), 4.90-5.94 (6H, m), 9.48 (1H, s). 18 (ca 7:3 mixture of the isomeric lactols): δ 1.19 (0.9H, d, 7.0 Hz), 1.27 (2.1 H, d, 7.0 Hz), 1.30-3.50 (11H, m, 1H disappeared upon treatment with D_2O), 3.61 (0.7H, m), 4.14 (0.3H, m), 4.78 (0.7H, d, 7.5 Hz, s upon treatment with D_2O), 5.39 (0.3H, brs). 19: δ 1.24 (3H, d, 6.9 Hz), 1.33 (12H, d, 7.0 Hz), 1.50-2.30 (6H, m), 2.40-3.25 (4H, m), 2.90 (2H, d, 21 Hz), 4.80 (2H, d hept, 1.7 Hz and 7.0 Hz), 4.85 (1H, m), 9.05 (1H, s).

5. S. Takano, A. Kurotaki, M. Takahashi, and K. Ogasawara, Synthesis, 1986, 403.

6. B. Seuring and D. Seebach, Liebigs Ann. Chem., 1978, 2044.

7. E. W. Colvin, T. A. Purcell, and R. A. Raphael, J. Chem. Soc. Perkin I, 1976, 1718.

8. R. S. Mali, M. Pohmakotr, B. Weidmann, and D. Seebach, Liebigs Ann. Chem., 1981, 2272.

(Received in Japan 26 February 1987)