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# A SHORT, ENANTIOSPECIFIC SYNTHESIS OF A PROTECTED SECO ACID PRECURSOR TO (R,R)-(-) PYRENOPHORIN

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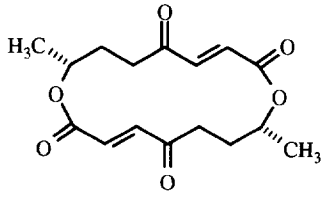
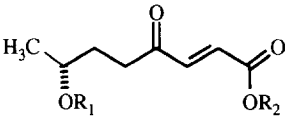
Summary: Described herein is a four-step enantiospecific synthesis of a protected seco acid precursor of (R,R)-(-)-pyrenophorin in 23% yield from a chiral β-ketoester **3**, which can be prepared in one step from ethyl acetoacetate by a standard procedure. 

(R,R)-(-)-Pyrenophorin **1** is one member of a small group of 16-membered macrocyclic dilactones having $C_2$ symmetry. These macrodiolides are of interest because of their potent antibacterial and antifungal properties.[1] Moreover their interesting γ-keto-α,β-unsaturated ester functionality has made them continuing targets for synthetic efforts in which one of two general strategies is utilized. One uses carbon-carbon bond formation as the means to close the macrocyclic ring,[2] and the other uses dimerization of derivatives of the seco acid **2a** ($R_1$,$R_2$ = H) to produce the dilactone in both racemic[3] and enantioselective versions.[4] Crucial to the biological activity is the γ-keto-α,β-unsaturated ester.[4a]



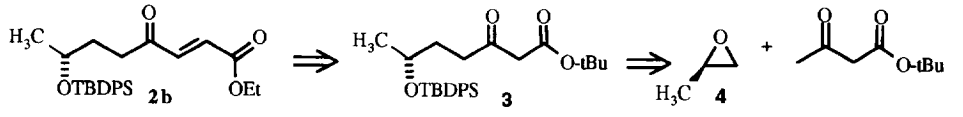
**1**



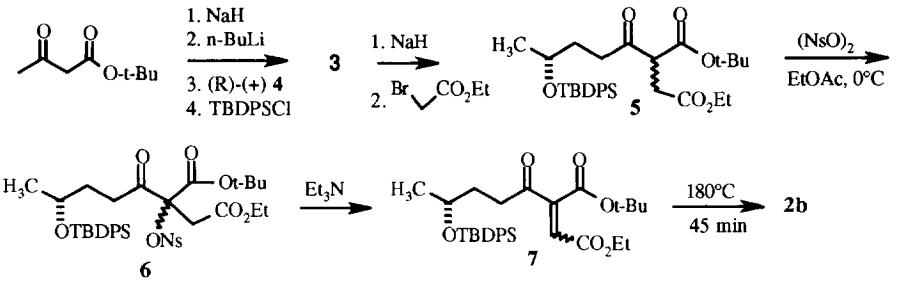
**2**

We reported earlier that the γ-keto-α,β-unsaturated ester functional grouping can be introduced efficiently by a simple four step protocol from β-keto tert-butyl esters,[5] and we sought to incorporate this methodology into an enantioselective synthesis of seco acid derivative (R)-**2b** ($R_1$ = tert-BuPh$_2$Si, $R_2$ = Et) which can be transformed into (R,R)-(-)-pyrenophorin.[4b] Thus a projected synthesis of **2b** required the β-ketoester **3**. There is ample precedent to expect that the chiral center at C-6 of **3** could be installed enantiospecifically by reaction of the dianion of ethyl acetoacetate with (R)-(+)-propylene oxide **4** [6] (Scheme 1).

Scheme 1

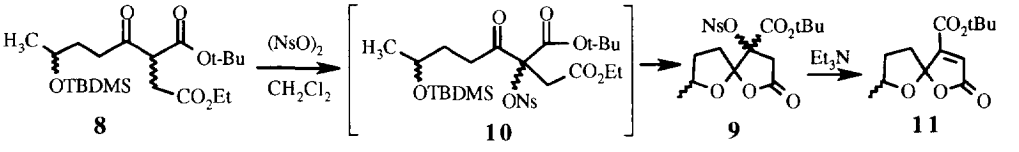


By a standard procedure tert-butyl acetoacetate was converted to its dianion (NaH followed by n-BuLi) and reacted with (R)-(+)- **4**.[6c] The resulting alkoxide was quenched with tert-butyldiphenylsilyl chloride at 0°C to give tert-butyldiphenylsilyl ether **3**.[7,8] Alkylation of **3** with ethyl bromoacetate gave keto diester **5**[7,8] as a mixture of diastereomers.[9] Diester **5** was converted to nosylate **6**[7,8] by reaction with p-nitrobenzenesulfonyl peroxide $(NsO)_2$.[10] The unsaturated keto diester **7**[7,8] from base promoted elimination of **6**[5] did not undergo acid catalyzed decarboxylation with TFA but could be decarboxylated thermally at 180°C to give **2b.** The spectral characteristics of **2b** are in full accord with the assigned spectrum.




The stereochemical integrity of the synthetic sequence anticipated from the literature[6] was verified by a chiral LIS study of **2b** using $Eu(hfc)_3$. By comparison with a racemic sample, it was determined that **2b** was enantiomerically pure within the limits of measurement (>95%).

The use of the tert-butyldiphenylsilyl protecting group is essential for the success of the process. Upon reaction with $(NsO)_2$ the tert-butyldimethylsilyl protected analog **8** gave the unique spirolactone **9**[7,8] as a 3:2 mixture of diastereomers, rather than expected tricarbonyl analog **10**. Interestingly the tricarbonyl precursor **8** did not show any propensity towards lactonization. As observed previously the attachment of nosyloxy group increases the electrophilicity of the ketone group markedly,[11] and in this instance the ketone is rendered sufficiently electrophilic to initiate the cyclization and the TBDMS group is insufficiently bulky to prevent it. Use of the bulkier and more acid stable TBDPS group prevents such lactonization.




The use of an oxidative trigger to initiate spirolactonization is a novel approach to this class of molecules.[12] Treatment of **9** with triethylamine gives the unsaturated spirolactone **11**[8] which is well suited for further elaboration. The ramifications of this chemistry in the synthesis of spiroketal natural products is under investigation.

The conversion of tricarbonyl compound **6** to **2b** reported here utilized elimination to **7** followed by thermolysis to effect decarboxylation. We had previously used the reverse sequence, namely, acid catalyzed

decarboxylation followed by base promoted elimination to prepare γ-keto-α,β-unsaturated esters in related tricarbonyl precursors.[6] While both these procedures are effective, the latter gives somewhat higher overall yields and is preferred.

In summary we have described a short, four step sequence for the enantiospecific synthesis of a protected seco acid precursor of (R,R)-(-)-pyrenophorin in 23% yield from the chiral β-ketoester **3**, which is prepared in one step from ethyl acetoacetate by a standard procedure.

**References and Notes**

1. Omura, S., "Macrolide Antibiotics: Chemistry, Biology, and Practice", Academic Press, New York, NY, 1984, pp 538-541.

2. a. Asaoka, M.; Mukuta, T.; Takei, H., *Tetrahedron Lett.* **1981**, *22*, 735. b. Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S., *Tetrahedron Lett.* **1987**, *28*, 2717. c. Yoshida, M.; Harada, N.; Nakamura, H.; Kanematsu, K., *Tetrahedron Lett.* **1988**, *29*, 6129. d. Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H., *Synlett* **1992**, 875. e. Nokami, J.; Taniguchi, T.; Gomyô, S.; Kakihara, T., *Chem. Lett.* **1994**, 1103. f. Le Floc'h, Y.; Dumartin, H.; Grée, R., *Bull. Soc. Chim. Fr.* **1995**, *132*, 114.

3. a. See for example: a. Gerlach, H.; Oertle, K.; Thalmann, A., *Helv. Chim. Acta.* **1977**, *60*, 2860. b. Seuring B.; Seebach, D., *Liebigs Ann. Chem.* **1978**, 2044. c.Trost, B. M.; Gowland, F. W., *J. Org. Chem.* **1979**, *44*, 3448. d. Hase, T. A.; Ourila, A.; Homberg, C., *J. Org. Chem.* **1981**, *46*, 3137. e. Baraldi, P. G.; Barco, A.; Benetti, S.; Moroder, F.; Pollini, G. P.; Simoni, D., *J. Org. Chem.* **1983**, *48*, 1297. f. Bates, G. S.; Ramaswany, S., *Can. J. Chem.* **1983**, *61*, 2466. g. Labadie, J. W.; Stille, J. K., *Tetrahedron Lett.* **1983**, *24*, 4283. h. Dumont, W.; Vermeyen, C.; Krief, A.,*Tetrahedron Lett.* **1984**, *25*, 2883. i. Breuilles, P.; Uguen, D., *Tetrahedron Lett.* **1984**, *25*, 5759. j. Derguini, F.; Linstrumelle, G., *Tetrahedron Lett.* **1984**, *25*, 576. k. Petrini, M.; Ballini, R.; Rosini, G.; Marotta, E., *Tetrahedron* **1986**, *42*, 151. l. Zschiesche, R.; Hafner, T.; Reissig, H. U., *Liebigs Ann. Chem.* **1988**, 1169. m. Breuilles, P.; Uguen, D., *Bull. Soc. Chim. Fr.* **1988**, 705. n. Nagooi, T. K.; Scilimati, A.; Guo, Z.; Sih, C. J., *J. Org. Chem.* **1989**, *54*, 911. o.Barre, V.; Massias, F.; Uguen, D., *Tetrahedron Lett.* **1989**, *30*, 7389. p. Solladié, G.; Gerber, C., *Synlett* **1992**, 449.

4. a. Mali, R. S.; Pohmakotr, M.; Weidmann, B.; Seebach, D., *Liebigs. Ann. Chem.* **1981**, 2272. b. Machinaga, N.; Kibayashi, C., *Tetrahedron Lett.* **1993**, *34*, 841. c. Matsushita, Y.; Furusawa, H.; Matsui, T.; Nakayama, M., *Chem. Lett.* **1994**, 1083

5. Hoffman, R. V.; Kim, H.-O.; Lee, J. C., *J. Org. Chem.* **1994**, *59*, 1933.

6. a. (R)-(+) propylene is available from Fluka. b. Mori, K.; Sasaki, M.; Tamada, S.; Suguro, T.; Masuda, S., *Tetrahedron* **1979**, *35*, 1601. c. Yamaguchi, M.; Hirao, I., *Chem. Lett.* **1985**, 337. d. Lygo, B.; O'Connor, N., *Tetrahedron Lett.* **1987**, *28*, 3597.

7. Satisfactory elemental analysis (±0.3%) was obtained for this compound.

8. **3:** (39%); $[\alpha]_D^{25}$ = + 8.6 (c 0.89, $CHCl_3$); $^1H$ nmr δ 7.66 (dd, J= 6 Hz, 4H), 7.44-7.35 ( m, 6H), 3.90 (m, 1H), 3.26 ( AB q, J = 15.6 Hz), 2.56 (m, 2H), 1.73 ( m, 2H), 1.45 (s, 9H), 1.05 ( s, 9H), 1.04 (d, 3H, J=not available from spectrum); IR 1737, 1716, 1645 (enol) $cm^{-1}$.

**5** (77%); $[\alpha]_D^{25}$ = + 7.6 (c 1.85, $CHCl_3$), $^1H$ nmr δ 7.67 (dd, 4H), 7.39 ( m, 6H), 4.11 (q, J = 7 Hz, 2H), 3.81-3.93 (m, 2H), 2.58-2.88 (m, 4H), 1.77 (m, 2H), 1.43 (s, 9H), 1.24 (t, J = 7 Hz), 1.05 (s, 9H), 1.04 (d, 3H, J=not available from spectrum); IR 1735, 1715 $cm^{-1}$.

**6:** oil, (59%, mixture of disatereomers); mp 123-128°C; $^1H$ nmr δ 8.33 (d, 2H), 8.15 (d, 2H, *major* ), 8.10 (d, 2H, *minor*), 7.64 (dd, 4H), 7.43-7.33 ( m, 6H), 4.02-3.86 ( m, 3H), 3.75 and 3.43 (*major*), 3.42(*minor*) (ABq, J=18 Hz, 2H), 3.11-2.66 (m, 2H), 1.75, (m, 2H), 1.48 (s, 9H), 1.17, 1.15 (two t, 3H), 1.00 (*minor* )and 0.99 (*major*) ( s, 9H), 0.98 (d, 3H).

**7**: (94%, mixture E/Z diastereomers), $^1H$ nmr δ 7.66 (m, 4H), 7.43-7.33 (m, 6H), 6.66 and 6,49 (s, $1H_{tot}$), 4.27 and 4.17 (q, J = 7 Hz, $2H_{tot}$), 3.95 (m, 1H), 2.79 and 2.66 (m, $1H_{tot}$), 1.87 (m, 2H), 1.56 and 1.47 (s, $9H_{tot}$), 1.33 and 1.26 (t, J = 6.8 Hz, $3H_{tot}$), 1.04 (d and s, $12H_{tot}$).

**2b**: oil, (39%), $[\alpha]_D^{25}$ +28.41 (c 3.6, MeOH); $^1H$ NMR δ 7.63-7.69 (m, 4H), 7.25-7.42 (m, 6H), 6.97 (d, J= 16.0 Hz, 1H), 6.56 (d, J= 16.0 Hz, 1H), 4.30 (q, J= 7.1 Hz, 2H), 3.92 (m, 1H), 2.59-2.70 (m, 2H), 1.69-1.78 (m, 2H), 1.33 (t, J= 7.1 Hz, 3H), 1.08 (d, J= 6.2 Hz, 3H), 1.05 (s, 9H); IR(neat) 1726, 1730, 1640 $cm^{-1}$.

**9**: solid (28%), mp 106-107°C, IR 1802, 1735 $cm^{-1}$; $^1H$ nmr major diastereomer: δ 8.42 ( d, 2H), 8.13 ( d, 2H), 4.47 ( m, 1H), 3.75, 3.24 ( ABq, J = 18.7 Hz, 2H), 2.4-2.56 ( m, 2H), 2.02-2.25 ( m, 2H), 1.57 ( s, 9H), 1.18 ( d, J = 6.2 Hz, 3H); $^1H$ nmr minor diastereomer: δ 8.42 ( d, 2H), 8.13 ( d, 2H), 4.13 ( m, 1H), 3.77, 3.23 ( ABq, J = 18.7 Hz, 2H), 2.4-2.56 ( m, 2H), 2.02-2.25 ( m, 2H), 1.55 ( s, 9H), 1.30 ( d, J = 5.9 Hz, 3H).

**11**: oil (90%); $^1H$ nmr δ ( major diastereomer) 6.59 (s, 1H), 4.55 ( m, 1H), 2.75 ( m, 1H), 2.25 ( m, 2H), 1.87 ( m, 1H), 1.54 ( s, 9H), 1.40 ( d, J = 5.6 Hz); (minor diastereomer) 6.59 (s, 1H), 4.49 ( m, 1H), 2.75 ( m, 1H), 2.25 ( m, 2H), 1.87 ( m, 1H), 1.55 ( s, 9H), 1.33 ( d, J = 5.6 Hz); IR 1775, 1723, 1644 $cm^{-1}$.

9. Hoffman, R. V.; Kim, H.-O., *Tetrahedron Lett.* **1992**, *33*, 3579.

10. Hoffman, R. V.; Wilson, A. L.; Kim, H.-O., *J. Org. Chem.* **1990**, *55*, 1267.

11. a. Hoffman, R. V., *Tetrahedron* **1991**, *47*, 1109. b. Hoffman, R. V.; Jankowski, B. C.; Carr, S. C.; Duesler, E. N., *J. Org. Chem.* **1986**, *51*, 130.

12. Perron, F.; Albizati, K. F., *Chem. Rev.* **1989**, *89*, 1617.

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