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ENANTIO- AND STEREOSELECTIVE SYNTHESES OF THE DIHYDROXYOCTADIENOIC ACID FRAGMENTS OF THE RORIDINS AND TRICHOVERRINS

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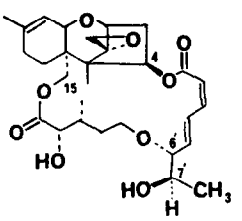
Summary: Syntheses of protected versions of the dihydroxyoctadienoic acid fragments corresponding to roridin A and trichoverrin B are described.

A characteristic structural feature of the roridins and trichoverrins, a group of biosynthetically related fungal metabolites, is the dihydroxyoctadienoic acid fragment esterified to the C.4 hydroxyl group of the epoxytrichothecene nucleus.[2] The configuration of C.6' in the roridins (cf, roridin A, 1) is R, whereas the configuration of C.6' of the trichoverrins (cf, trichoverrin B, 2) is S. The configuration of C.7' in either series



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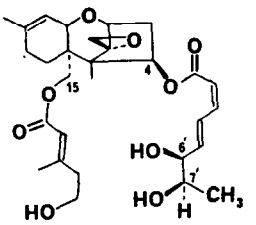

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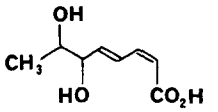
may be R or S; that is, derivatives of all four isomers of dihydroxyoctadienoic acid (3) are found in nature.[2a,3] Fraser-Reid has reported syntheses of the methyl esters of the 6(S),7(R) and 6(R),7(R) isomers of 3 (from D-glucose and D-galactose, respectively) by sequences which, unfortunately, failed to control the stereochemistry of the C.2-C.3 (Z)-olefinic linkage.[4,5]



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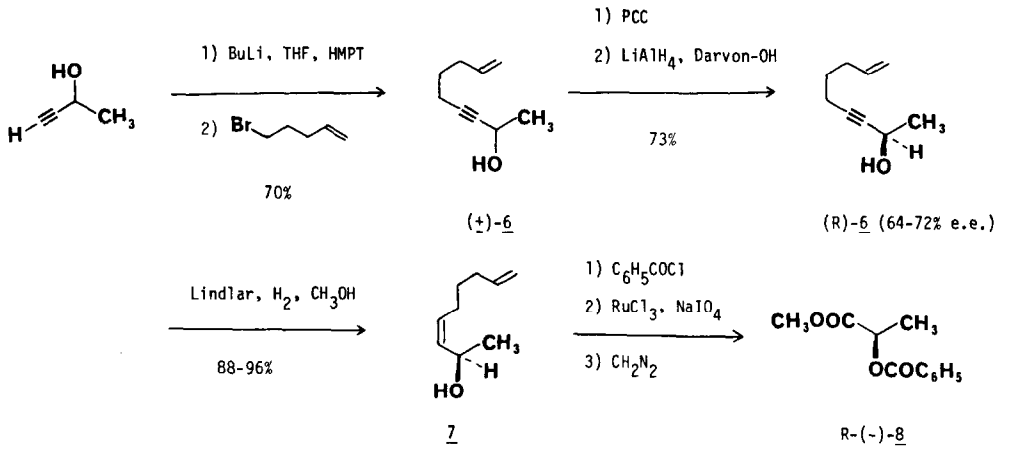
We report herein stereo- and enantioselective syntheses of diene acids 4 (6(R),7(R), roridin series; see 1) and 5 (6(S),7(R), trichoverrin series; see 2) by sequences which are ideally suited for the synthesis of the 6(R),7(S) and 6(S),7(S) isomers as well.

Syntheses of dienes 4 and 5 originate from the readily available propargyl alcohol 6 (Scheme I). Thus, alkylation of the dianion of butyn-3-ol (2.0 equiv. n-BuLi, 3 equiv. HMPT, THF, 23°C) with 5-bromopentene afforded racemic 6[6a,b] in 70% yield.[7] Oxidation of 6 with PCC (CH_2Cl_2, 3 h, 95% yield) followed by reduction of the intermediate ketone[6a,b] with the $LiAlH_4$-Darvon alcohol complex[8] afforded (+)-6 in 77% yield after distillation.[9] The optical purity of (+)-6 so obtained ranged from 64-72% e.e. from run to run (Mosher analysis).[10] The absolute

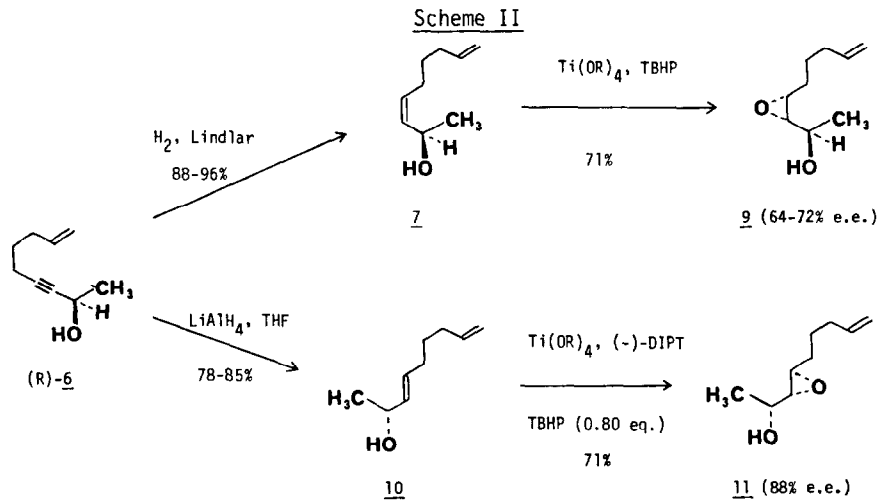
Scheme I



configuration of this intermediate was shown to be R by degradation of the derived Z-allylic alcohol 7[6a,b] to the R-(-)-enantiomer of benzoyl lactic acid methyl ester, 8.[11]

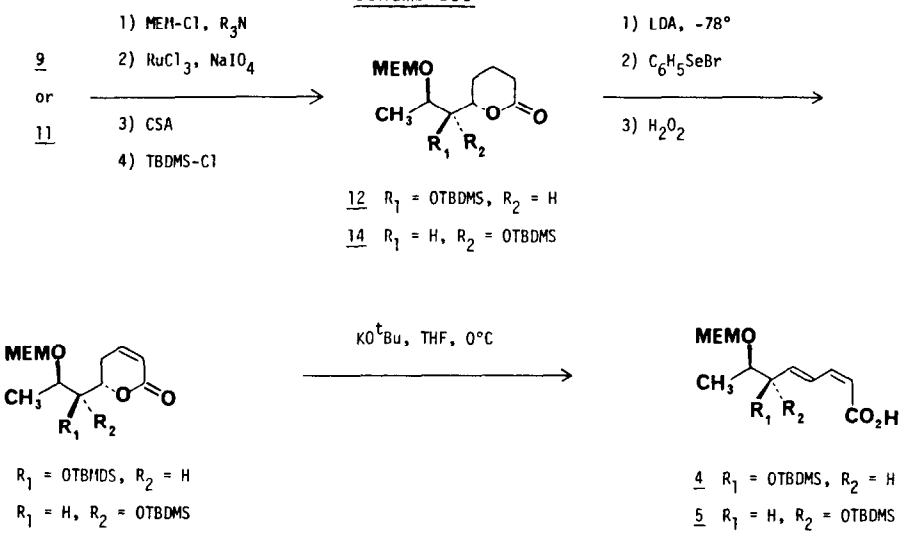
Epoxidation of 7 with $Ti(O^iPr)_4$ and t-butylhydroperoxide (TBHP; CH_2Cl_2, -20°C)[12] afforded threo epoxyalcohol 9[6a,b] in 71% yield (Scheme II). This intermediate is a useful precursor of 6(R),7(R)-acid 4 (roridin series; Scheme III). Although a synthesis of the 6(S),7(R)-acid 5 (trichoverrin series) might also, in principle, be accomplished via 9 by performing an alpha opening of the oxirane function of this intermediate, such a route would probably not provide a convenient means for differentiation of the hydroxyl functionality of 5.[13,14] Accordingly, trichoverrin ester 5 was synthesized via erythro epoxyalcohol 11,[6a,b] which was prepared by reduction of 6 to 10[6a,b] ($LiAlH_4$, THF, reflux, 78-82% yield) and epoxidation of the latter using $Ti(O^iPr)_4$, TBHP (0.8 equiv.) and (-)-DIPT (1.2 equiv.) in CH_2Cl_2 at -20°C (71% yield; 88% e.e. by Mosher analysis).[12]

Scheme II



Epoxyalcohol 9 was elaborated to diene 4 by the sequence outlined in Scheme III. First, protection of the hydroxyl group as a MEM ether followed by oxidative cleavage of the vinyl group to a carboxylic acid (cat. $RuCl_3$, $NaIO_4$, CH_3CN-H_2O-CCl_4),[15] intramolecular epoxide opening (cat. camphorsulfonic acid (CSA), CH_2Cl_2) and protection of the free C.6 hydroxyl group (TBDMS-Cl, imidazole, DMF) afforded lactone 12[6a,b] in 61% overall yield. This intermediate was

Scheme III



then oxidized to unsaturated lactone 13[6a] using a standard selenenylation-selenoxide elimination sequence (82% yield).[16] Finally, the (Z,E)-diene unit was unmasked by treating 13 with KO^tBu in THF at 0°C,[17] which afforded 4[6a] in 59% yield. An analogous sequence was used to convert 11 to 5[6a] via intermediates 14[6a,b] and 15.[6a]

Since verrucarol and synthetic equivalents of the carboxylic acid fragments attached to C.15 of 1 and 2 are now readily available,[18] the stage is set for completion of partial syntheses of a variety of trichoverrins and roridins.[19]

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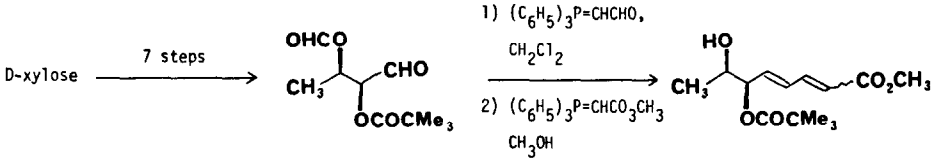
References

1. Roger and Georges Firmenich Career Development Assistant Professor of Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982-84.
2. (a) Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Midiwo, J.O.; DeSilva, T.; Holmlund, C.E.; Mazzola, E.P.; Geoghegan, R.F., Jr. J. Org. Chem. 1982, 47, 1117; (b) Jarvis, B.B.; Pavanasasivam, G.; Holmlund, C.E.; DeSilva, T.; Stahly, G.P.; Mazzola, E.P. J. Am. Chem. Soc. 1981, 103, 472.
3. Doyle, T.W.; Bradner, W.T. in "Anticancer Agents Based on Natural Product Models," Cassidy, J.M.; Douros, J., eds,; Academic Press: New York, 1980, Chapter 2, and references cited therein.

4. Tulshian, D.B.; Fraser-Reid, B. J. Am. Chem. Soc. 1981, 103, 474.

5. We, too, experienced considerable difficulty in initial approaches to derivatives of 3 by routes in which the diene unit was constructed by an olefination sequence. For example:



(E,E) : (Z,E) = ~6 : 4

6. (a) The spectroscopic properties (NMR, IR, mass spectrum) of all new compounds were fully consistent with the assigned structures. (b) A satisfactory combustion analysis (±0.3% for C and H) was obtained for this compound.

7. Smith, L.M.; Smith, R.G.; Loehr, T.M.; Daves, G.D., Jr.; Daterman, G.E.; Wohleb, R.H. J. Org. Chem. 1978, 43, 2361.

8. (a) Brinkmeyer, R.J.; Kapoor, V.M. J. Am. Chem. Soc. 1977, 99, 8339; (b) Cohen, N.; Lopresti, R.J.; Neukom, C.; Saucey, G. J. Org. Chem. 1980, 45, 582.

9. Optical rotation data ($[\alpha]_D$) for all optically active intermediates are reported below; unless indicated otherwise, all measurements were performed at 23°C in methylene chloride: 6, +17.9° (c=0.88; 72% e.e. sample); 7, +3.6° (c=0.72; prepared from 72% e.e. sample of 6); 8, -8.0° (c=0.9, $CHCl_3$; the optical rotation for (S)-8 is given in ref. 11); 9, +8.1° (c=1.2; prepared from 64% e.e. sample of 6); 10, +3.1° (c=0.90; prepared from 64% e.e. sample of 6); 11, +9.5° (c=0.84; 88% e.e.); 12, +11.6° (c=0.80); 13, -26.3° (c=4.2); 4, +39.7° (c = 2.52; 25°C); 14, -16.2° (c=0.71); 15, -114.7° (c=2.21); 5, +1.5 (c=0.60).

10. Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. 1969, 34, 2543.

11. (a) Aasen, A.J.; Kimland, B.; Engell, C.R. Acta Chem. Scand. 1973, 27, 2107; (b) A rotation of $[\alpha]_D$ +13.9° (c = 4.5, $CHCl_3$, 20°C) was reported for (S)-8.

12. Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yameda, Y.; Ikeda, M.; Sharpless, K.B. J. Am. Chem. Soc. 1981, 103, 6237.

13. Roush, W.R.; Brown, R.J. J. Org. Chem. 1982, 47, 1371.

14. It is necessary that the hydroxyl groups of 5 be differentiated if biomimetic approaches to 1 are pursued.

15. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. J. Org. Chem. 1981, 46, 3936.

16. (a) Reich, H.J.; Renga, J.M.; Reich, I.L. J. Am. Chem. Soc. 1975, 97, 5434; (b) Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. Ibid. 1973, 95, 6137.

17. (a) Eisner, U.; Elvidge. J.A.; Linstead, R.P. J. Chem. Soc. 1953, 1372; (v) Cardillo, G.; Orena, M.; Sandri, S. Tetrahedron 1976, 32, 1078; (c) Corey, E.J.; Schmidt, G. Tetrahedron Lett. 1979, 2317.

18. (a) Roush, W.R.; Blizzard, T.A.; Basha, F.Z. Tetrahedron Lett. 1982, in press; (b) White, J.D.; Carter, J.P.; Kezar, H.S., III J. Org. Chem. 1982, 47, 929; (c) Still, W.C.; Ohimizu, H. Ibid. 1981, 46, 5242; (d) Tulshian, D.B.; Fraser-Reid, B. Tetrahedron Lett. 1980, 4549.

19. We thank Professor Fraser-Reid for providing us with ^1H NMR spectra for the methyl esters of the 6(S),7(R) and 6(R),7(R) isomers of 3.

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