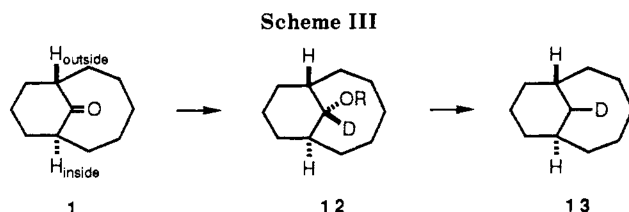
Scheme III



The location of the deuterium in the monodeuterated *trans*-bicyclo[5.3.1]undecane obtained via n-Bu_3SnD reduction of 4 could permit the distinction between a sequence of transannular hydrogen atom abstractions and the 1,2-shift as the pathway for the conversion of 7 to 8. While the presence of deuterium at C-11 in the trans-monodeuterated product would be consistent with both mechanistic possibilities, the absence of deuterium at C-11, i.e., deuteration at any other position, would be consistent only with the series of transannular hydrogen abstractions for the conversion of 7 to 8, thereby excluding the possibility of a 1,2-shift. To establish whether the deuterium in the trans-monodeuterated product was indeed at C-11, an authentic sample of **13**, the C-11 deuterated trans-bridged hydrocarbon, was prepared as outlined in Scheme III.

Reduction of **1** with lithium aluminum deuteride, followed by treatment of the derived xanthate with 10 equiv of n-Bu_3SnH, led, after preparative gas chromatography, to the isolation of the 11-deuterio-*trans*-bicyclo[5.3.1]undecane, **13**. The ^{13}C NMR spectrum of this monodeuterated *trans*-bicyclo[5.3.1]undecane **13** showed a different resonance (33.52 ppm) coupled to deuterium than had been observed in the monodeuterated trans product obtained by reduction of **4** with n-Bu_3SnD (29.14 ppm). These preliminary experiments clearly indicate that the rearrangement of **7** to **8** is not a consequence of a 1,2-shift of hydrogen, but instead the result of a sequence of transannular hydrogen atom abstractions which lead to the formation of **8**, and ultimately to the cis product **5**. Further studies directed toward the determination of the precise location of the radical center in the initial rearrangement product, and the establishment of the scope of this unusual rearrangement, are currently under way in our laboratory.

Acknowledgment. We would like to thank Professor Thomas Hoye for stimulating discussions, Professor Stephen Martin for providing an authentic sample of *cis*-bicyclo[5.3.1]undecane, **6**, and Professor David Lynn and Mr. Timothy Logan for invaluable assistance in obtaining the NMR spectral data. Support from the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (Grants CA40250 and CA45686), the Alfred P. Sloan Foundation, American Cyanamid, Merck, Sharp and Dohme, and Glaxo is gratefully acknowledged. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (Grant CA 14599).

Structure of the Fatty Acid Component of an Antibiotic Cyclodepsipeptide Complex from the Genus *Fusarium*

Lee A. Flippin,* Keyvan Jalali-Araghi, and Peter A. Brown

Department of Chemistry and Biochemistry, San Francisco State University, San Francisco, California 94132

Harland R. Burmeister and R. F. Vesonder

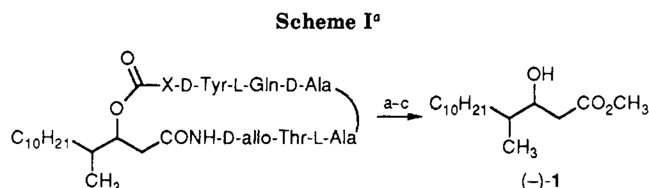
Northern Regional Research Laboratory, U.S. Department of Agriculture, Peoria, Illinois 61604

Received November 22, 1988

Summary: The fatty acid component of the *Fusarium* cyclodepsipeptide complex CDPC 3510 is (−)-*anti*-3-hydroxy-4-methyltetradecanoic acid. A diastereoselective synthesis of the racemic methyl ester of CDPC 3510 fatty acid is described.

Sir: A recent report by Carr et al.[1] concerning the structure of a novel cyclodepsipeptide complex isolated from several species of the genus *Fusarium* intrigued us in part because a β-hydroxy carboxylic acid obtained by hydrolytic degradation of the complex was postulated to be 3-hydroxy-4-methyltetradecanoic acid. Murai and co-workers[2] have recently shown that the fatty acid unit common to the *Bacillus circulans* cyclodepsipeptide metabolites polypeptin A, permetin A, and BMY-28160 is (−)-*syn*-3-hydroxy-4-methylhexanoic acid; therefore characterization of a structurally similar 3-hydroxy-4-methylalkanoic acid[3] from depsipeptide metabolites of the deuteromycete *Fusarium* could provide a unique opportunity to compare the lipid biosynthesis steps of cyclodepsipeptide anabolism in a prokaryotic organism (*B. circulans*) with that of a eukaryote (*Fusarium sporotrichiodes*). However, the structural characterization of the *Fusarium* depsipeptidic fatty acid was based solely on a mass spectrometric analysis of its methyl ester derivative without the benefit of authentic samples of the syn and anti diastereomers[4] of methyl 3-hydroxy-4-methyltetradecanoate, thus nothing could be deduced concerning the C(3)–C(4) relative stereochemistry of the degradation product.

Scheme I[a]



[a] (a) 5 M HCl, 100 °C, 2 h. (b) Diazomethane in ether. (c) Column chromatography (silica gel; 19:1 hexane–ether).

We isolated the three-component cyclodepsipeptide complex, CDPC 3510, from methanol extracts of *F. sporotrichiodes* NRRL 3510 grown on white corn grit medium;

(1) Carr, S. A.; Block, E.; Costello, C. E.; Vesonder, R. F.; Burmeister, H. R. *J. Org. Chem.* **1985**, *50*, 2854.

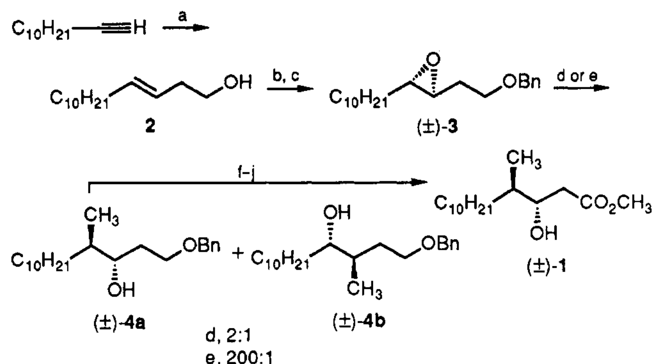
(2) Murai, A.; Amino, Y.; Ando, T. *J. Antibiot.* **1985**, *38*, 1610.

(3) For additional examples of fungal cyclodepsipeptide metabolites that contain the 3-hydroxy-4-methylalkanoic acid unit, see: (a) Elsworth, J. F.; Grove, J. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1795. (b) Grove, J. F. *J. Chem. Soc, Perkin Trans. 1* **1980**, 2878. It should be noted that the fatty acid residues described in these two papers were characterized by mass spectrometric methods and currently remain unassigned with respect to their C(3)–C(4) stereochemistry.

(4) The descriptors "syn" and "anti" are employed here in the sense described in the following: Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557.

0022-3263/89/1954-3006$01.50/0 © 1989 American Chemical Society

Scheme II[a]



[a] (a) DIBAL; then n-BuLi, ethylene oxide (69% yield). (b) NaH, benzyl chloride in DMSO (68% yield). (c) m-CPBA (79% yield). (d) $LiMe_2Cu$, ether, 0 °C (60% yield; **4a**:**4b** = 2:1) or (e) 2 equiv of Me_3Al–n-BuLi, hexane, 0 °C (80% yield; **4a**:**4b** > 200:1). (f) TBDMSCl, imidazole (91% yield). (g) H_2/Pd–C (97% yield). (h) PDC in DMF. (i) CH_2N_2 (g, h: 62% yield). (j) Tetrabutylammonium fluoride in THF (77% yield).

the crude CDPC 3510 was further purified by methods that have been previously described.[5] Hydrolysis of 1.237 g of CDPC 3510 with 5 M HCl (100 °C; 2 h) and ether extraction of the hydrolysate afforded 0.252 g of a crude hydroxyalkanoic acid. These conditions are considerably milder than a previously described hydrolytic degradation[1] and afforded in the present case a saturated hydroxyalkanoic acid with only slight (<5 mol %) contamination by a dehydration product.[6] The crude product mixture was methylated with excess diazomethane, and 0.247 g of a homogeneous β-hydroxy ether, (−)-**1**, was isolated by column chromatography on silica gel using 19:1 hexane–ether as the eluent (Scheme I).

Although the methylated fatty acid obtained from CDPC 3510 is diastereomerically homogeneous and its ^1H NMR and ^{13}C NMR spectral characteristics[7] are compatible with the gross structure suggested by Carr et al. (vide supra), there is no evidence within our spectroscopic data that would allow us to make a firm assignment of the C(3)–C(4) relative stereochemistry of (−)-**1**.[8]

A syn-selective aldol method[9] provided us with a mixture of racemic methyl 3-hydroxy-4-methyltetradecanoate diastereomers (syn:anti = 1.5:1), however, spectroscopic comparison of the homogeneous natural material with the synthetic mixture indicated that the CDPC 3510 degradation product was identical with our minor synthetic product. Therefore, we abandoned the aldol strategy and turned to an approach that required the stereospecific anti addition of a methyl group to C(4) of racemic *trans*-1-(benzyloxy)-3,4-epoxytetradecane, (±)-**3**, in order to establish the correct C(3)–C(4) stereochemistry in an intermediate to be carried on to (±)-**1**. Compound (±)-**3**, prepared in three steps from 1-dodecyne (Scheme II), was allowed to react with lithium dimethylcuprate (ether, 0 °C) to give a disappointing 2:1 mixture of regioisomers (±)-**4a** and (±)-**4b**, which, however, were easily separated and characterized. On the other hand, treatment of compound (±)-**3** with a reagent formed in hexane from 3 equiv of Me_3Al and 1.5 equiv of n-BuLi[10,11] proved to be stereospecific and highly C(4) selective to give the desired product (**4a**:**4b** > 200:1). Compound (±)-**4a** was then carried on in five steps to (±)-**1** (16% overall), which proved identical (^1H and ^{13}C NMR, TLC) with authentic CDPC 3510 β-hydroxy ester.

Acknowledgment. This work was supported in part by a Cottrell grant from Research Corporation and in part by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Supplementary Material Available: Detailed conditions for the isolation and hydrolytic degradation of CDPC 3510, a scheme describing the syn-selective aldol preparation of methyl (±)-3-hydroxy-4-methyltetradecanoate, experimental procedures for the steps of Scheme II, and complete spectral and analytical data for compounds (±)-**3** (±)-**4a**, (±)-**4b**, and (±)-**1** (4 pages). Ordering information is given on any current masthead page.

(5) Burmeister, H. R.; Vesonder, R. F.; Peterson, R. E.; Costello, C. E. *Mycopathologia* **1985**, *91*, 53.

(6) More vigorous hydrolysis conditions have been reported to give a β,γ-unsaturated carboxylic acid side product presumed to be 4-methyl-3-decenoic acid (ref 1). The α,β-unsaturated ester isolated after methylation of our CDPC 3510 hydrolysate exhibited the following characteristics: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (dd, J = 17, 7 Hz, 1 H), 5.77 (d, J = 17 Hz, 1 H), 3.75 (s, 3 H), 2.32 (m, 1 H), 1.35–1.10 (m, 18 H), 1.05 (d, J = 7 Hz, 3 H), 0.83 (t, J = 7 Hz, 3 H).

(7) (−)-1: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.87 (ddd, J = 9.4, 5.5, 3.2 Hz, 1 H), 3.71 (s, 3 H), 2.86 (br s, 1 H), 2.49 (dd, J = 16.5, 3.2 Hz, 1 H), 2.40 (dd, J = 16.5, 9.4 Hz, 1 H), 1.60 (m, 1 H), 1.28–1.22 (m, 18 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.87 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 71.9, 51.7, 38.2, 37.7, 32.3, 31.9, 29.9, 29.6, 29.3, 27.1, 22.7, 14.9, 14.1; $[\alpha]^{24}_D$ = −8.5° (CH_2Cl_2; c = 2.7). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.32; H, 11.80.

(8) The main difficulty in assigning the relative stereochemistry of 3-hydroxy-4-methylalkanoic acid derivatives arises from the fact that C(4) lies outside of the six-member ring defined by hydrogen bonding between the carbonyl group and the C(3) hydroxyl substituent in these compounds thus, the typical H(3)–H(4) coupling constants (J = 5.5 Hz in (−)-1) cannot be relied on in the absence of authentic standards. For example, $J_{H(3),H(4)}$ = 4.5 Hz in methyl (±)-*syn*-3-hydroxy-4-methylhexanoate (cf. ref 10).

(9) For a related example, see: Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

(10) Flippin, L. A.; Brown, P. A.; Jalali-Araghi, K. Manuscript submitted to *J. Org. Chem.*

(11) For related examples of previous work in this area, see: (a) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459. (b) Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 744. (c) Pfaltz, A.; Mattenberger, A. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 71.

Oxidative Coupling Reactions of Phenols with $FeCl_3$ in the Solid State

Fumio Toda,* Koichi Tanaka, and Shinji Iwata

Department of Industrial Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan

Received February 14, 1989

Summary: Some oxidative coupling reactions of phenols with $FeCl_3$ are faster and more efficient in the solid state than in solution. Some coupling reactions in the solid state are accelerated by irradiation with ultrasound. Some coupling reactions are achieved by using a catalytic amount of $FeCl_3$.

Sir: Oxidative couplings of phenols are usually carried out by treatment of phenols in solution with more than equimolar amount of metal salts such as $FeCl_3$ or manganese tris(acetylacetonate), although the latter one is too expensive to use in a large quantity. The coupling reactions of phenols with $FeCl_3$, however, sometimes give

0022-3263/89/1954-3007$01.50/0 © 1989 American Chemical Society