

THE ABSOLUTE CONFIGURATION OF CYCLONERODIOL

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The cyclopentanoid sesquiterpene, cyclonerodiol (1), was first isolated by Nozoe from extracts of Trichothecium roseum.¹ Subsequently this substance was also found in Gibberella fujikuroi^{2,3} and most recently in cultures of Fusarium culmorum.⁴ In the latter case cyclonerodiol was accompanied by a related metabolite, cyclonerotriol (2).

Nozoe has synthesized cyclonerodiol⁵ by a sequence based primarily on the known Alder ene reaction of linalool.^{6,7} The synthesis established the relative configuration of the three ring substituents but gave an epimeric mixture of alcohols at C-6, leaving the relative stereochemistry at this position undetermined. Very recently Hanson has reported a single crystal X-ray analysis of a derivative of cyclonerotriol.⁴ Since this latter substance could be correlated with 1,⁸ the study settled the question of the relative stereochemistry at C-6 while confirming Nozoe's earlier conclusions with regard to the ring stereochemistry. We have been studying this problem independently and our results are reported below.

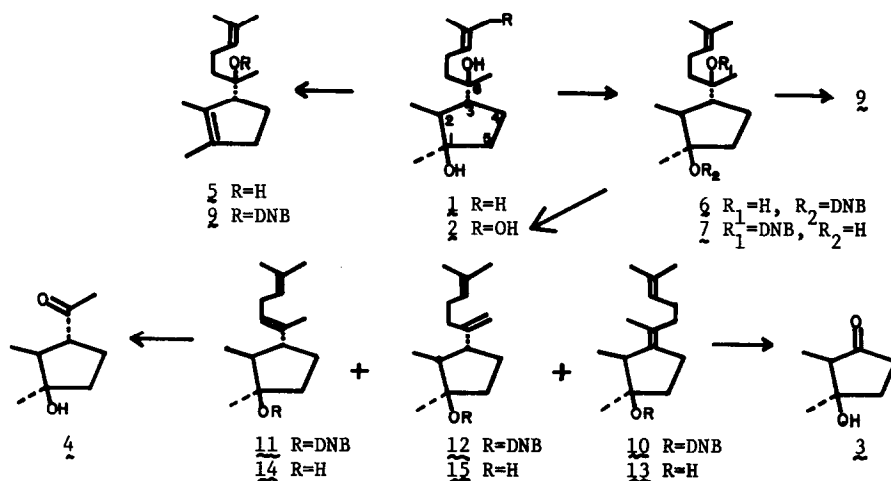
To determine the absolute configuration of cyclonerodiol, we chose to degrade 1 to a pair of known compounds, (-)(2R,3R)-2,3-dimethyl-3-hydroxy cyclopentanone (3) and (-)(1R,2S,3R)-1,2-dimethyl-3-acetyl-cyclopentan-1-ol (4) or their respective enantiomers. Both 3 and 4 have been previously prepared by synthesis from (-)(3R)-linalool.^{7b,c} Initial attempts to effect selective dehydration of the side chain of 1 (3 equiv POC₁₃, pyridine, 0°, 110 min) gave the known cyclopentene alcohol 5 (45%)¹ as the predominant product, accompanied by no more than 10% of isomeric alcohols. While this result precluded direct introduction of a double bond on the side chain, it did suggest that the ring hydroxyl might be preferentially esterified. Indeed, treatment of 1, with 3,5-dinitrobenzoyl chloride (1.5 equiv,

pyridine, 25°, 22 hr) gave 1-dinitrobenzoate 6 (47%)¹⁰ and 6-dinitrobenzoate 7 (6%)¹⁰ as well as the 1,6-bis-dinitrobenzoate 8 (2.5%).^{3,10} In confirmation of the above structural assignments, dehydration of the minor dinitrobenzoate ester 7 with POCl₃ gave a product 9 (mp 78.5-80.5°)¹⁰ identical in all respects with the ester obtained by treatment of the alcohol 5 with 3,5-dinitrobenzoyl chloride.

With the cyclopentanol suitably protected, treatment of 6 with POCl₃ (pyridine, 25°, 20 hr) gave a mixture which was separated by repeated PLC into the tetra-substituted olefin 10, m.p. 119.5-121.5° (56%)^{10,11} and a 1:1 mixture of the double bond isomers 11¹⁰ and 12¹⁰ (44%). Subsequent reductive cleavage of 10 with lithium aluminum hydride (10 equiv, THF, 25°, 3.5 hr) yielded the olefinic alcohol 13,^{10,12} [α]_D + 24.1°. Ozonolysis of 13 (MeOH, -78°) and mild, neutral reduction of the ozonide (dimethylsulfide, 0°, 18 hr) followed by repeated PLC purification gave the desired cyclopentanone 3 as a single compound (33%):¹³ mp 60-62°, nmr (CDCl₃) δ 1.05 (d, J = 7Hz, 2-CH₃, 3H), 1.44 (s, 1-CH₃, 3H), 1.2-2.6 (m, 6H); ir $\lambda_{\max}^{\text{CCl}_4}$ 3620, 3480 (OH), 1750 cm⁻¹ (C=O); [α]_D - 179° (c 0.12, CCl₄),¹⁴ ORD (CHCl₃)¹⁴ ϕ_{311} - 4720°, ϕ_{291} 0°, ϕ_{274} + 4470°; CD (CHCl₃) θ_{296} - 820°.

In a similar sequence of reactions, the mixture of olefinic alcohols 14 and 15, obtained by LAH cleavage of 11 and 12, was oxidized using Schooley's modification of the catalytic ruthenium tetroxide cleavage^{15,16} (RuO₂/NaIO₄/H₃IO₅ 1.2:60:1, 0.8 mole% RuO₂; tBuOH/H₂O 1:3; 25°, 18 hr). Extraction of the neutral products and PLC gave 4 (68%) which was recrystallized 3 times from hexane:¹³ nmr (CDCl₃) δ 0.96 (d, J = 7 Hz, 2-CH₃, 3H), 1.28 (s, 1-CH₃, 3H), 2.18 (s, CH₃CO, 3H) 1.4-2.8 (m, 7H); ir $\lambda_{\max}^{\text{CCl}_4}$ 3620, 3500 (OH), 1710 cm⁻¹ (C=O); [α]_D - 73° (c 0.070, CCl₄);¹⁷ CD (CHCl₃) θ_{285} + 71.3°.

The above sequence of reactions thus correlates C-1 of cyclonerodiol with (-) (3R)-linalool via 3 and 4. Based on the known relative stereochemistry of 1 the absolute configuration is established as 1R, 2S, 3R, 6R.¹⁸ Further work on the stereochemical details of cyclonerodiol biosynthesis will be reported in due course.^{19,20}



References and Notes

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 8. The stereochemical correlation of **1** and **2** is based on the biosynthetic conversion of the former to the latter⁹ as well as on the ozonolytic cleavage of each to a common norlactone **16**.⁴
- 1** \longrightarrow **16**
9. R. E. Evans, J. R. Hanson, and R. Nyfeler, *J. C. S. Perkin I*, 1214 (1976).
 10. Satisfactory nmr and ir spectra were obtained on chromatographically pure material.
 11. Anal., Calcd for $C_{22}H_{28}N_2O_6$: C 63.45, H 6.78, N 6.73; found: C 63.63, H 7.04 N 6.63.

12. In a control experiment, the bis-dinitrobenzoate 8 was treated with LAH to give cyclonerodiol of unchanged optical purity, $[\alpha]_D - 20.8^\circ$ (CHCl_3).
13. The nmr and ir spectra were in agreement with those reported.^{7b,c}
14. $[\alpha]_D^{7b}$ ca- 93° , ORD^{7b,c} ϕ_{307} - 2750° , ϕ_{290} 0° , ϕ_{269} + 2625° . The sample prepared by Strickler et al. in their thorough study of the stereochemistry of the plinols was stated to be 95% pure. The three unidentified impurities were assumed to be optically inactive in calculating the rotations. Although the values reported are certainly too low, this does not affect the validity of the conclusions drawn above regarding absolute configuration.
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17. $[\alpha]_D^{7b}$ -80° ; $[\alpha]_D^{7c}$ -71.4° .
18. The absolute configuration is that arbitrarily depicted by Hanson⁴, although it should be noted that the configuration at C-6 is incorrectly named in the latter reference.
19. D. E. Cane and M. S. Shiao, submitted for publication.
20. This work was supported by NSF Grant PCM 74-07924. We would like to thank Mr. Walter Cullen of Chas. Pfizer, Inc., Groton, Ct. for a generous gift of G. fujikuroi extract, and Dr. H. Strickler for a copy of ref. 7c.