nuclei such as ^{15}N and ^{29}Si where the Overhauser enhanced the signal is inverted and where an incomplete Overhauser effect can result in signal cancellation. One solution to this problem has been to suppress the nuclear Overhauser effect in ^{15}N spectra; under such conditions the polarization transfer experiment would provide an enhancement factor K of ~ 10, in addition to the benefits of faster spin-lattice relaxation.

The proposed polarization transfer experiment bears a superficial resemblance to another technique for sensitivity enhancement which also employs spin echoes and restores the focussed magnetization to the Z axis.[15] This is the "driven equilibrium Fourier transform method" (DEFT). We have consequently adopted the code name INEPT (insensitive nuclei enhanced by polarization transfer).

Acknowledgments. This work was made possible by an equipment grant from the Science Research Council and a Research Studentship to G.A.M. Dr. Moniz kindly provided a copy of his manuscript[4] prior to publication.

References and Notes

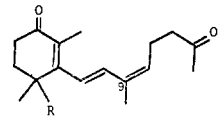
(1) Solomon, I. *Phys. Rev.* **1955**, *99*, 559.
(2) Hartmann, S. R.; Hahn, E. L. *Phys. Rev.* **1962**, *128*, 2042.
(3) Pines, A.; Gibby, M. G.; Waugh, J. S. *J. Chem. Phys.* **1973**, *59*, 569.
(4) Bertrand, R. D.; Moniz, W. B.; Garroway, A. N.; Chingas, G. C. *J. Am. Chem. Soc.* **1978**, *100*, 5227.
(5) Ernst, R. R. Eighteenth Experimental NMR Conference, Asilomar, Calif., 1977; Sixth International Symposium on Magnetic Resonance, Banff, Canada, 1977.
(6) Maudsley, A. A.; Ernst, R. R. *Chem. Phys. Lett.* **1977**, *50*, 368.
(7) Maudsley, A. A.; Müller, L.; Ernst, R. R. *J. Magn. Reson.* **1977**, *28*, 463.
(8) Bodenhausen, G.; Freeman, R. *J. Magn. Reson.* **1977**, *28*, 471.
(9) Hahn, E. L.; Maxwell, D. E. *Phys. Rev.* **1952**, *88*, 1070.
(10) Freeman, R.; Hill, H. D. W. *J. Chem. Phys.* **1971**, *54*, 301.
(11) Pachler, K. G. R.; Wessels, P. L. *J. Magn. Reson.* **1973**, *12*, 337; **1977**, *28*, 53.
(12) Sørensen, S.; Hansen, R. S.; Jakobsen, H. J. *J. Magn. Reson.* **1974**, *14*, 243. Jakobsen, H. J.; Linde, S. A.; Sørensen, S. *ibid.* **1974**, *15*, 385.
(13) Freeman, R.; Hill, H. D. W. *J. Magn. Reson.* **1971**, *5*, 278.
(14) The proton spin-lattice relaxation can be accelerated by the addition of relaxation reagents such as chromium acetylacetonate.
(15) Becker, E. D.; Ferretti, J. A., Farrar, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 7784.

Gareth A. Morris, Ray Freeman*
Physical Chemistry Laboratory, Oxford University
Oxford, England
Received October 10, 1978

Stereospecific Synthesis of (±)-Trisporol B, a Prohormone of *Blakeslea Trispora*, and a Facile Synthesis of (±)-Trisporic Acids

Sir:

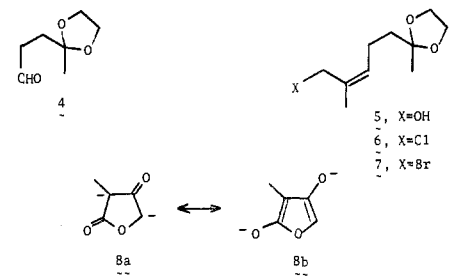
Sexual differentiation in Mucoraceous fungi is mediated by a system of C_{18} apocarotenoid hormones based on the trisporic acids (e.g., **1**) and congeners such as (9*Z*)-methyl trisporate B (**2**).[1] Extensive studies with plus and minus mating types of



1, R=CO_2H
2, R=CO_2Me
3, R=CH_2OH

B. trispora has led to the identification of certain prohormones[2] which are characteristic of the mating strain and are converted to a trisporic acid by the sexual partner. Trisporol B (**3**) is produced in very small amounts by minus cultures of this organism and has proven to be the most biologically active of the mating prohormones so far isolated.[3] The chemical synthesis of **3** and related members of the trisporic acid group is likely to be a key element in elucidating the reproductive process in fungi of the Mucorales, and we have therefore sought a practical, synthetic solution to the stereochemical and functional group problems posed by these regulatory substances.[4]

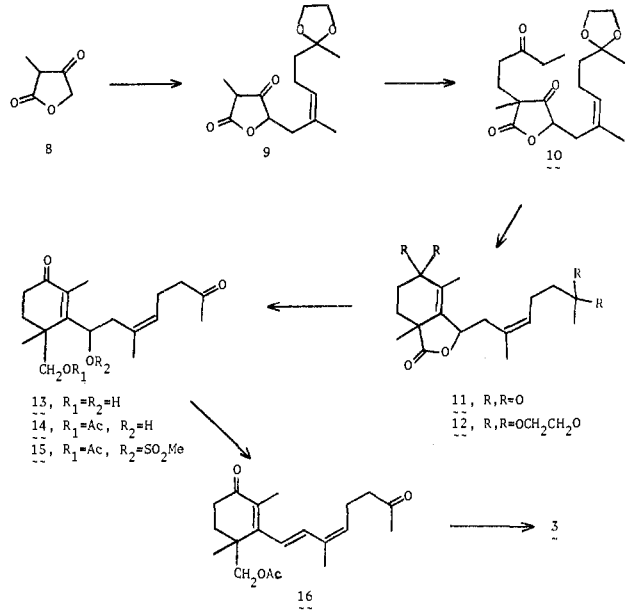
The requirement for 9*Z* stereochemistry in **3**, coupled with the desirability of fashioning the corresponding olefinic link in the trisporic acid and esters in a geometrically defined manner, dictated an approach strategically different from that adopted in previous syntheses of methyl trisporates.[5] First, a unit functionally equivalent to the C(8)–C(14) segment of **3** was prepared from ketal aldehyde **4**, readily obtainable from ethyl levulinate.[5a] Thus, **4** was treated with ethylidenetri-



4
5, X=OH
6, X=Cl
7, X=Br
8a ⟷ 8b

phenylphosphorane (THF, −78 °C, 5 min), and the derived oxido ylide (*n*-BuLi, THF, 0 °C) was allowed to react with paraformaldehyde (1 h at 0 °C and then 8 h at room temperature) to give the *Z* alcohol **5**: 69%; NMR δ 5.28 (1 H, t, J = 7 Hz), 4.10 (2 H, s), 3.92 (4 H, s), 2.66 (1 H, s, disappears in D_2O), 1.78 (3 H, s), 1.30 (3 H, s).[6] This alcohol was converted via its tosylate (MeLi, Et_2O–HMPA (3:1) and then $C_7H_7SO_2Cl$–Et_2O, 0 °C) to chloride **6** (82%; NMR δ 5.38 (1 H, t J = 7 Hz), 4.01 (2 H, s)) with LiCl (15 h, room temperature)[7] and then to bromide **7** (85%; NMR δ 5.41 (1 H, t, J = 7 Hz), 3.93 (2 H, s)) with NaBr (DMF, 3 h, room temperature).

The dianion **8a** of α-methyltetronic acid (**8**)[8] was generated using sodium hydride (1 equiv, THF–HMPA (1:1)), followed by butyllithium (1 equiv in hexane). A consideration of the resonance forms of this species, which logically include the furanoid structure **8b** as a major contributor, suggested that alkylation should occur with high selectivity at the γ position.[9] In fact, treatment of **8** with **7** (THF, −60 °C and then 24 h at room temperature) afforded the γ-substituted tetronic acid **9** (NMR δ 8.8 (1 H, br), 5.23 (1 H, t, J = 7 Hz), 4.67 (1 H, m),



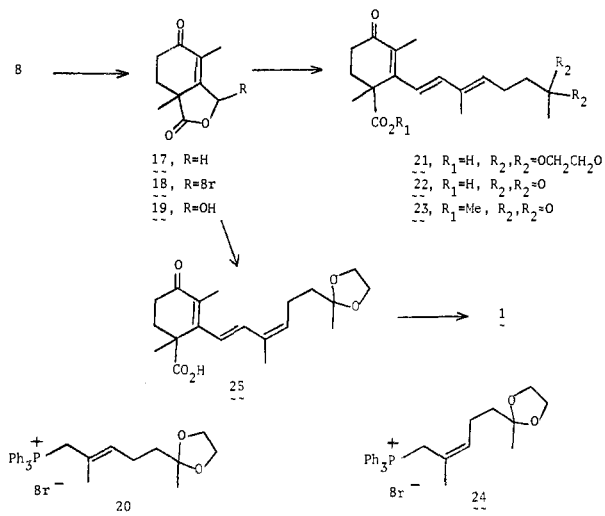
8 → 9 → 10
11, R,R=O
12, R,R=OCH_2CH_2O
13, R_1=R_2=H
14, R_1=Ac, R_2=H
15, R_1=Ac, R_2=SO_2Me
16 → 3

0002-7863/79/1501-0762$01.00/0 © 1979 American Chemical Society

3.86 (4 H, s), 2.06 (3 H, s), 1.73 (3 H, br s), 1.22 (3 H, s)) as the sole alkylation product in 63% yield after chromatography. Subsequent annelation of **9** was accomplished by condensation with ethyl vinyl ketone (97%, Et_3N, THF), to yield **10,** followed by acid-catalyzed dehydration (p-$C_7H_7SO_3H$, benzene, reflux) to give the cyclohexenone **11** as two epimers which were not separated: 59%; ν_{max} 1780, 1715, 1675 cm^{-1}; NMR δ 4.0–4.4 (2 H, m), 2.06 (3 H, s), 1.81 (3 H, s), 1.72 (3 H, s). 1.57 (3 H, s). After protection of **11** as its bis(ethylene ketal) **12** ($(CH_2OH)_2$, $HC(OEt)_3$, p-TsOH, Et_2O, 25 °C), reduction with lithium aluminum hydride (THF-Et_2O), followed by hydrolysis (AcOH, H_2O) of the ketal functions, afforded an epimeric mixture of diols **13:** 53% from **11;** ν_{max} 3380 (br), 1710, 1665 cm^{-1}; NMR δ 5.26 (1 H, br t), 4.95 (1 H, d of d, J = 2, 11 Hz), 3.86 (1 H, d, J = 11 Hz), 3.65 (1 H, d, J = 11 Hz), 2.18 (3 H, s), 1.91 (3 H, s), 1.80 (3 H, s), 1.39 (3 H, s).

The allylic, secondary hydroxyl function in **13** proved surprisingly resistant to dehydration under a variety of conditions and an indirect method for this transformation was therefore devised. The diol function in this system was found to undergo selective monoacetylation (Ac_2O, pyridine, room temperature) to **14** (56%), which was converted to mesylate **15** (90%) with methanesulfonyl chloride (pyridine, 12 h). This substance, like alcohol **13,** resisted elimination with acidic and basic reagents. However, when **15** was warmed at 80 °C in Me_2SO for 2 h,[10] the 7*E*,9*Z* triene **16** was produced isomerically pure in 34% yield. Saponification (K_2CO_3, H_2O–EtOH, 25 °C) then gave trisporol B (**3**) (98%; λ_{max}^{EtOH} 298 nm (log ϵ 4.0); ν_{max} 3460, 1710, 1665 cm^{-1}; NMR δ 6.63 (1 H, d, J = 16 Hz), 6.20 (1 H, d, J = 16 Hz), 5.40 (1 H, br t), 3.68 (1 H, d, J = 10 Hz), 3.37 (1 H, d, J = 10 Hz), 2.08 (3 H, s), 1.89 (3 H, s), 1.81 (3 H, s), 1.11 (3 H, s)), with the anticipated spectral properties.[3,11]

In principle, the bicyclic intermediate **11** affords entry to the 9-cis trisporic acid system (**1**), as well as the reduced trisporols, through hydrolysis of the γ-lactone and dehydration of the resulting allylic alcohol. In practice, this approach was thwarted by the extremely facile closure of the derived hydroxyl acid, and a modification of this scheme, utilizing lactol **19,** was therefore employed. The tetronic acid **8,**[8] after Michael



addition (98%) to ethyl vinyl ketone (Et_3N, THF) and condensation (catalytic p-TsOH, C_6H_6, 36 h) of the resulting diketone, afforded **17** (mp 58–60 °C; ν_{max} 1780, 1680 cm^{-1}; NMR δ 5.01 (2 H, s), 1.74 (3 H, s), 1.51 (3 H, s)) following chromatography in 95% yield. Treatment of **17** with *N*-bromosuccinimide (CCl_4, $(PhCO_2)_2$, 3 h) quantitatively gave bromide **18** as a single crystalline isomer, which was cleanly hydrolyzed in boiling water (5 min) to the crystalline lactol **19** (80%; dec >146 °C; ν_{max} 1740, 1670 cm^{-1}; NMR δ 6.43 (1 H, s), 1.78 (3 H, s), 1.50 (3 H, s)).

A Wittig reaction (−78 °C for 2 h and then 0 °C for 0.5 h) of **19** with the ylide prepared from *E* phosphonium salt **20**[5c] gave acid **21** (61%) containing, as expected, only *E* geometry at the newly generated olefin. This substance, upon hydrolysis (5% HCl, THF, 0 °C, 5 h), furnished (9*E*)-trisporic acid B (**22**) (95%; λ_{max}^{EtOH} 322 nm; ν_{max} 3150 (br), 1715, 1665, 1595 cm^{-1}; NMR δ 6.39 (1 H, d, J = 16 Hz), 6.19 (1 H, d, J = 16 Hz), 5.52 (1 H, t, J = 7 Hz), 2.09 (3 H, s), 1.89 (3 H, s), 1.82 (3 H, s), 1.48 (3 H, s)),[12] which was further characterized as its methyl ester **23** (CH_2N_2).[5a] The *Z* phosphonium bromide **24,** prepared from **7** (Ph_3P, Et_2O, 65 h), afforded an ylide (BuLi, −78 °C) which unfortunately underwent isomerization to the *E* form at a rate competitive with that of the Wittig reaction with **19.** Hence, a mixture of **25** and **21** (53%, ~1:1) was produced, although the proportion of **25** could be enhanced to >80% at the expense of yield with short reaction times (20 min at 0 °C). Hydrolysis of **25** (5% HCl, THF) gave (7*E*,9*Z*)-trisporic acid (**1**) (88%; NMR δ 6.82 (1 H, d, J = 16 Hz), 6.36 (1 H, d, J = 16 Hz), 5.47 (1 H, m), 2.08 (3 H, s), 1.88 (3 H, s), 1.80 (3 H, s), 1.46 (3 H, s)),[12] which was also characterized as its methyl ester **2.** Bioassays with plus and minus strains of *Mucor mucedo* revealed, as expected, that synthetic (±)-trisporol B (**3**) was effective on only the plus mating type.[13] However, zygophore induction was much more prominent in the minus strain with synthetic acids **1** and **22,** and their esters **2** and **23.**[14] Quantitatively similar activity (down to 3 μg per dose) was found for all four of these substances in minus *M. mucedo.*

Acknowledgment. We are indebted to the National Science Foundation for financial support through grants CHE77-04379 and CHE74-01286.

References and Notes

(1) J. D. Bu'Lock, B. E. Jones, and N. Winskill. *Pure Appl. Chem.*, **47,** 191 (1976), and references cited.
(2) R. P. Sutter, *Science*, **168,** 1590 (1970); B. A. Werkman and H. van den Ende, *Arch. Microbiol.*, **90,** 365 (1973).
(3) J. D. Bu'Lock, D. Drake, and D. J. Winstanley, *Phytochemistry*, 11, 2011 (1972).
(4) For a review of early structural work in this area, see L. Cagliotti G. Cainelli, B. Camerino, R. Mondelli, A. Prieto, A. Quilico, T. Salvatori, and A. Selva, *Tetrahedron Suppl.*, **7,** 175 (1966).
(5) (a) J. A. Edwards, V. Schwarz, J. Fajkos, M. L. Maddox, and J. H. Fried, *Chem. Commun.*, 292 (1971). (b) S. Isoe, Y. Hayase, and T. Sakan, *Tetrahedron Lett.*, 3691 (1971). (c) J. A. Secrist, C. H. Hickey, and R. E. Norris, *J. Org. Chem.*, **42,** 525 (1977); see also J. D. White and W. L. Sung, *J. Org. Chem.*, **39,** 2323 (1974). These esters are not convertible to the parent trisporic acis by saponification.
(6) E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92,** 226 (1970); U. T. Bhalerao and H. Rapoport, *ibid.*, **93,** 4835 (1971).
(7) G. Stork, P. Grieco, and M. Gregson, *Org. Synth.*, **54,** 68 (1974).
(8) D. W. Knight and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 635 (1975).
(9) Cf. S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96,** 1082 (1974); R. W. Skeean, G. L. Trammell, and J. D. White, *Tetrahedron Lett.*, 525 (1976).
(10) D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawski and N. L. Wendler, *Chem. Commun.*, 1258 (1970).
(11) J. D. Bu'Lock, B. E. Jones, and N. Winskill, *J. Chem. Soc., Chem. Commun.*, 708 (1974).
(12) We are indebted to Professor Richard P. Sutter, Department of Biology, West Virginia University, for samples and comparison UV, IR, and NMR spectra of trisporic acids.
(13) Bioassays were carried out in collaboration with Professor E. J. Trione, Department of Botany and Plant Pathology, Oregon State University. A detailed account of these studies will be published elsewhere.
(14) Both plus and minus mating cultures of *M. mucedo* have typically responded to naturally derived trisporic acids (see ref 1), although the methyl trisporates are more effective in zygophore induction with the minus strain.
(15) National Institutes of Health Research Career Development Awardee, 1976–81.

Michael P. Prisbylla, Kunihiko Takabe, James D. White*[15]
Department of Chemistry, Oregon State University
Corvallis, Oregon 97331
Received October 3, 1978