Tetrahedron Letters No. 29, pp 2523 - 2526, 1974. Pergamon Press. Printed in Great Britain.

TOTAL SYNTHESIS OF (±)-12,13-EPOXYTRICHOTHEC-9-ENE.[*1]

Yasuo Fujimoto,[*] Susumu Yokura, Tadaharu Nakamura,[*2] Tamio Morikawa[*3] and Takashi Tatsuno.

RIKAGAKU KENKYUSHO (The Institute of Physical and Chemical Research) Wako-Shi, Saitama 351, Japan.

(Received in Japan 27 May 1974; received in UK for publication 11 June 1974)

A number of trichothecene-type sesquiterpenoids have been isolated from the metabolites of various species of Trichothecium, Trichoderma, Myrothecium and Fusarium.[1] These sesquiterpenoids have been noted by their pronounced cytotoxic[2] and phytotoxic activities.[3] The total synthesis of (±)-trichodermin (I; R=OAc) was achieved by Colvin et al.[4]

In this communication, we wish to report the stereoselective total synthesis of (±)-12,13-epoxytrichothec-9-ene (I; R=H), isolated from the metabolite of Trichothecium roseum by Nozoe et al.[5]

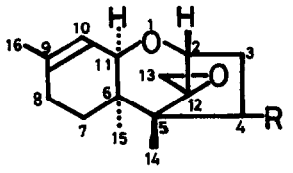
The keto-ester[6] (II) was reacted with crotonaldehyde (NaOMe, room temp., overnight) to give a keto-aldehyde, which without purification was converted into the acetal (III) [75% yield from II; bp 147-149°/0.003 Torr; IR: 1720, 1670, 1630]. The Meerwein-Ponndorf reduction of III (toluene, reflux, 48 hr) gave the cis-fused pyrane derivative (IV) [40% yield; bp 84-85°/0.1 Torr; IR: 1725, 1655; NMR: 0.96 (d, 3H, J=7 Hz; C_{11}-H), 1.70 (bs, 3H; C_{13}-H), 4.42 (bd, 1H, J=5 Hz; C_{10}-H), 4.70 (dd, 1H, J=5, 6 Hz; C_3-H), 5.78 (bd, 1H, J=5 Hz; C_9-H),

---

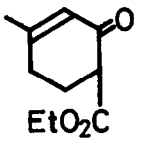
*1. All racemic structures are illustrated by one enantiomer. The IR spectra (cm^{-1}) were taken in KBr for crystallized compounds and in film for oily compounds unless otherwise stated. The NMR spectra (δ, 100 MHz) were measured in $CDCl_3$.

*2. Present address: Research Laboratory, Nippon Chemiphar Co., Ltd., Misato, Saitama 341, Japan.

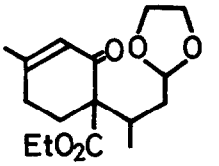
*3. Present address: Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda, Saitama, Japan.



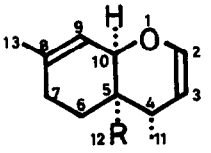
I R=H or OAc



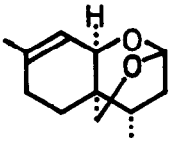
II



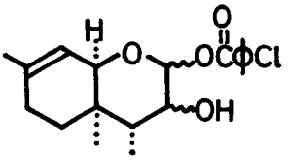
III



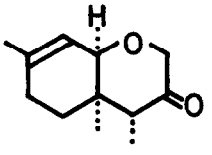
IV R=CO_2Et
V R=CH_2OH
VI R=CH_2OTs
VII R=CH_3



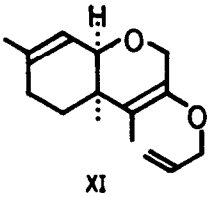
VIII



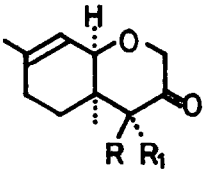
IX



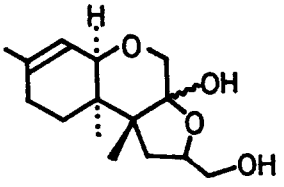
X



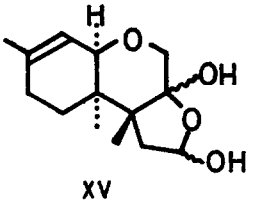
XI



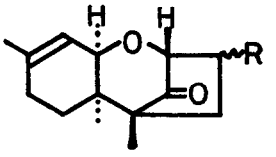
XII R=CH_3, R_1=$CH_2CH{=}CH_2$
XIII R=$CH_2CH{=}CH_2$, R_1=CH_3



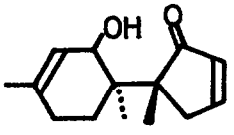
XIV



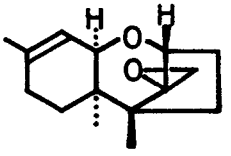
XV



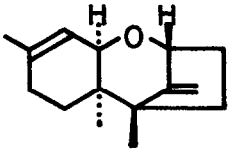
XVI R=OH
XVII R=I
XVIII R=H



XIX



XX



XXI

6.24 (dd, 1H, J=1, 6 Hz; C_2-H)]. The cis-relationship of the A/B ring juncture of IV was proved by agreement between the coupling constant of C_9-H ($J_{9,10}$ =5 Hz) of IV and that of C_{10}-H ($J_{10,11}$=5 Hz) of I (R=H). Reduction of IV with $LiAlH_4$ (ether, reflux, overnight) afforded an alcohol (V)[IR: 3350, 1650; NMR: 3.29, 3.60 (AB_q, 2H, J=10 Hz; CH_2OH)] which without purification was submitted to the next reaction because the alcohol (V) was easily transformed to the compound (VIII)[IR: no OH and O-C=C bands; NMR: 3.37 (dd, 1H, J=2, 9 Hz; C_{12}-H), 4.00 (d, 1H, J=9 Hz; C_{12}-H), 4.90 (d, 1H, J=2 Hz; C_2-H)] by silica gel chromatography. Tosylation of V with p-TsCl-pyridine (0°, overnight), followed by treatment of the resulting tosylate (VI)[NMR: 3.87, 4.01 (AB_q, 2H, J=10 Hz; C_{12}-H)]with $LiAlH_4$ (ether, reflux, 48 hr) gave the methyl derivative (VII)[30% yield from IV, 30% recovery of V; bp 95-96°/5 Torr; IR: 1650; NMR; 0.88 (s, 3H; C_{12}-H), 0.88 (d, 3H, J=8 Hz; C_{11}-H), 4.38 (dd, 1H, J=2, 6 Hz; C_3-H) 6.20 (dd, 1H, J=2, 6 Hz; C_2-H)]. Selective attack of VII by m-chloroperbenzoic acid (AcOEt, -20°) produced a diastereomeric mixture of the hydroxyester (IX) which was pyrolized (triglyme, 1 eq. of pyridine, refluxed 2 min) to the ketone (X)[63% yield from VII ; bp 65-70°/0.1 Torr; IR: 1715; NMR: 1.02 (d, 3H, J=7 Hz; C_{11}-H), 2.68 (q, 1H, J=7 Hz; C_4-H), 3.86, 4.15 (AB_q, 2H, J=16 Hz; C_2-H)]. Allylation of X with allyl bromide (NaH, glyme, room temp., 5 hr) did not give the C-alkylated product, but gave an unexpected O-alkylated compound (XI)[IR: 1640, no C=O band; NMR: 1.63 (m, 3H; C_{11}-H)]. Rearrangement of XI was accomplished by heating (toluene, reflux, 3 hr) to give a mixture of XII and XIII in a 2:1 ratio (90% yield from X; bp 94-96°/0.002 Torr) which was separated by silica gel chromatography (benzene)[XII; IR: 1720, 1640; NMR: 4.98, 5.12 (bs, 1H, and bd, 1H, J=6 Hz; -CH=CH_2), 5.60 (m, 1H; -CH=CH_2), 3.88, 4.06 (AB_q, 2H, J= 16 Hz; C_2-H), XIII; IR: 1720, 1640; NMR: 4.07 (s, 2H; C_2-H), 5.97, 5.12 (bs, 1H, and bd, 1H, J=6 Hz; -CH=CH_2), 5.80 (m, 1H; -CH=CH_2)]. Treatment of XII with OsO_4-$KClO_3$ (THF-H_2O, room temp., 60 hr) afforded the diol (XIV)[50-60% yield, mp 163-169°, IR: 3350, no C=O band] which was cleaved by $NaIO_4$ (THF-H_2O, room temp., 3 hr) to yield the keto-aldehyde monohydrate (XV)[quantitative yield; mp 129-130°; IR: 3250, no C=O band; NMR (60°): 2.50, 3.10 (dd, 1H, J=3.5, 16 Hz and bd, 1H, J=16 Hz; -CH_2CHO), 9.69 (dd, 1H, J=2, 3.5 Hz; -CHO)]. XV was cyclized

with NaOMe (MeOH, reflux, 30 min) to give a diastereomeric mixture of the tricyclic ketol (XVI)[90% yield; mp 118-122°; IR: 3420, 3300, 1755] which was converted into the keto-iodide (XVII) by the action of triphenylphosphite methiodide (HMPA, 70°, 2 hr, 85% yield)[α-iodide; IR: 1750; NMR: 3.62 (d, 1H, J=4 Hz; C_2-H), 4.28 (m, 1H; C_3-H), β-iodide; IR: 1760; NMR: 4.12 (s, 1H; C_2-H), 4.46 (dd, 1H, J= 3, 9 Hz; C_3-H)]. Reduction of XVII with Raney-Ni (W-2)(50% AcOH, 0°, 5 min), gave the ketone (XVIII)[quantitative yield, mp 90-93°; IR: 1750; NMR: 0.84, 0.98 (s, 3H each; C_{14}- and C_{13}-H), 3.82 (d, 1H, J=4 Hz; C_2-H)], while treatment of XVII with Zn-EtOH (reflux, 30 min) gave an undesired ketol (XIX)[IR: 3380, 1690; λ_{max}^{EtOH} 220 mμ]. Reaction of XVIII with dimethyloxosulfonium methylide produced an epimer (XX) of I (R=H)[XX; 70% yield; NMR: 0.73, 0.75 (s, 3H each; C_{14}- and C_{15}-H), 2.22, 2.55 (AB_q, 2H, J=5 Hz; C_{13}-H)]. The Wittig reaction of XVIII with methylene triphenylphosphorane (DMSO, 50-60°, overnight) gave the corresponding methylene compound (XXI)[85% yield; IR ($CHCl_3$): 1670, 900; NMR: 4.60, 4.95 (s, 1H each; C_{13}-H)] which was treated with m-chloroperbenzoic acid (CH_2Cl_2-Na_2HPO_4, room temp., 2 hr) to afford (±)-12,13-epoxytrichothec-9-ene (I; R=H) [30% yield, 40% recovery of XXI] after purification by preparative thin-layer chromatography (benzene-AcOEt=10:2). The IR and NMR spectra of the final product was superimposable on that of the authentic sample kindly provided by Dr. S. Nozoe.[7] Further investigation for the extension of this method is now in progress.

References

1. W. B. Turner, Fungal Metabolite, Academic Press, London, 1971, P. 219
2. T. Tatsuno, Cancer Res., 28, 2393 (1968); Y. Ueno, M. Hosoya, Y. Morita, I. Ueno and T. Tatsuno, J. Biochem. (Tokyo), 64 479 (1968).
3. P. W. Brian, A. W. Dawkins, J. F. Grove, H. G. Hemming, D. Lowe and G. L. F. Norris J. Exp. Bot., 12, 1, (1961).
4. E. W. Colvin S. Malchenko, R. A. Raphael and J. S. Roberts, J. C. S. Perkin I, 1989 (1973).
5. Y. Machida and S. Nozoe, Tetrahedron, 28, 5105, 5113 (1972).
6. H. Henecka, Ber., 81, 179, (1948).
7. We are grateful to Dr. S. Nozoe, Institute of Applied Microbiology, University of Tokyo, Bunkyo-ku, Tokyo, Japan, for generously providing us with the IR and NMR charts of 12,13-epoxytrichothec-9-ene.