Table I. Synthesis of Homopropargylic Alcohols and Ethers

entry	ketone, aldehyde, or acetal	allene	reaction conditions	method[a]	product (% yield[b])
1	$PhCH_2CH_2CHO$	5	−78 °C, 1 h	B	10 (84)
2	cyclohexanone	5	−78 → 25 °C, 2 h	B	11[c] (89)
3	$PhCH_2COCH_3$	5	−78 °C, 2 h	B	12 (72)
4	$PhCH_2CH_2CH(OCH_3)_2$	5	−78 °C, 1 h	B	13 (75)
5	CH_3COCH_3	6	−78 → 25 °C, 2 h	B	14 (38[d])
6	cyclohexanone	6	−78 → 25 °C, 2 h	B	15 (49)
7	*i*-$PrCOCH_3$	7	−78 → 25 °C, 1.5 h	A	16 (86)
8	$PhCH_2CH_2CHO$	7	−78 °C, 1 h	A	17 (85)
9	*i*-$PrCOCH_3$	8	−78 → 0 °C, 2.5 h	A	18 (51)
10	$PhCH_2CH_2CHO$	8	−78 °C, 1 h	A	19 (89)
11	cyclohexanone	8	−78 → 25 °C, 2 h	A	20 (84)

[a] For explanation, see text. [b] Isolated yields[12] based on carbonyl compound. [c] Ziele, K.; Meyer, H. *Chem. Ber.* **1942**, *75*, 356. [d] Yield based on allene.

(1.01 g, 7.5 mmol) and distilled $TiCl_4$ (1.57 g, 8.25 mmol) in 30 mL of CH_2Cl_2 (distilled from CaH_2) was stirred at −78 °C for 5 min and then treated with the allene **5** (1.01 g, 9.0 mmol). The resulting mixture was stirred at −78 °C for 1 h, diluted with aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 2.08 g of a yellow oil.[18] A solution of this material and KF (1.10 g, 18.4 mmol) in 25 mL of Me_2SO (distilled from CaH_2) was stirred at 25 °C for 4 h, then diluted with H_2O, and extracted with ether. The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (elution with ethyl acetate–hexane) to afford 1.10 g of the homopropargylic alcohol **10** as a colorless oil.[19]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this research.

(18) IR (film) 3580, 3445, 3025, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.16 (s, 9 H), 1.8 (m, 2 H), 2.1 (s, 1 H), 2.34–2.95 (m, 4 H), 3.9 (m, 1 H), 5.84 (s, 1 H), 7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −0.9, 32.0, 38.2, 46.8, 68.6, 125.8, 128.2, 128.3, 130.6, 141.7, 143.4.

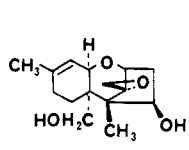
(19) IR (film) 3545, 3400, 3025, 2118, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 2 H, $PhCH_2CH_2$), 2.02 (t, 1 H, *J* = 3 Hz), 2.34 (m, 2 H, $CH_2C{\equiv}C$), 2.62 (s, 1 H, OH), 2.75 (m, 2 H, $PhCH_2$), 3.72 (m, 1 H, CHOH), 7.21 (m, 5 H).

Rick L. Danheiser,* David J. Carini
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received May 5, 1980

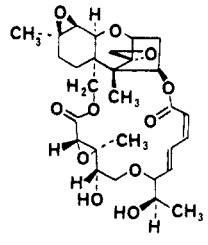
Studies on the Total Synthesis of Verrucarol: A Stereoselective Synthesis of 13,14-Dinor-15-hydroxytrichothec-9-ene

Summary: A stereoselective synthesis of 13,14-dinor-15-hydroxytrichothec-9-ene (**3**) is described.

Sir: Verrucarol (**1**) possesses the 12,13-epoxytrichothecene skeleton common to the trichothecene family of terpene antibiotics.[1] The remarkable biological activities of certain macrocyclic di- and triester derivatives of **1** (one example being baccharin (**2**)[2]) has stimulated considerable interest in the synthesis of verrucarol.[3,4] We describe herein a synthetic approach to the trichothecene ring system, exemplified by stereospecific syntheses of **3** and the derived deoxy compound **4**, by a route involving annelation of ring



1



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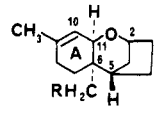

3 R = OH
4 R = H

A onto a preformed bicyclic precursor. A crucial element of this approach is that stereochemical control of C-6 relative to C-5 is achieved as a consequence of the sterically biased nature of bicyclic intermediate **7**. The remaining stereocenter at C-11 is introduced in a reaction (**14** → **3**) patterned after the last step in the biosynthesis of trichodermin.[5] Compound **3** is the first trichothecene derivative bearing a C-15 hydroxymethyl group to be synthesized.

The synthesis of **3** is outlined in Scheme I. Baeyer–Villiger oxidation of commercially available norcamphor (**5**) afforded **6**[6] (90%), formylation of which gave the highly crystalline **7**,[7a,b] mp 122–123 °C, in 85% yield. It is necessary to use *tert*-butyl formate[8] in the latter reaction, since with ethyl formate and KO-*t*-Bu **7** is obtained in lower yield (50%) together with a hydroxy ethyl ester (38%)

(1) (a) Bamburg, J. R.; Strong, F. M. "Microbial Toxins"; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. 3, pp 207–292. (b) Bamburg, J. R. *Adv. Chem. Ser., No. 149*, **1976**, 144. (c) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 74.

(2) Kupchan, S. M.; Streetman, D. R.; Jarvis, B. B.; Daily, R. G., Jr.; Sneden, A. T. *J. Org. Chem.* **1977**, *42*, 4221.

(3) Synthetic studies on verrucarol: (a) Colvin, E. W.; Malchenko, S.; Raphel, R. A; Roberts *J. Chem. Soc., Perkin Trans. 1* **1978**, 658; (b) Snider, B. B.; Amin, S. G. *Synth. Commun.* **1978**, *8* 117; (c) Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1978**, *43*, 2938.

(4) Synthetic studies on other trichothecenes: (a) Still, W. C.; Tsai, M.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 3655; (b) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989; (c) Welch, S. C.; Wong, R. Y. *Tetrahedron Lett.* **1972**, 1583; *Synth. Commun.* **1972**, *2*, 291; (d) Goldsmith, D. J.; Lewis, A. J.; Still, W. C. *Tetrahedron Lett.* **1973**, 4807; (e) Fugimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T. *Ibid.* **1974**, 2523; (f) Masuoka, E.; Kamikawa, T. *Ibid.* **1976**, 1691; (g) Pearson, A. J.; Rathby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 395.

(5) (a) Machoda, Y.; Nozoe, S. *Tetrahedron* **1972**, *28*, 5113. (b) Archilladelis, B. A.; Adams, P. M.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1425. Masuoka and Kamikawa (ref 4f) have applied this biomimetic cyclization in a synthesis of vominotoxin.

(6) Meinwald, J.; Frauenglass, E. *J. Am. Chem. Soc.* **1960**, *82*, 5235.

(7) (a) All new compounds were fully characterized by NMR, IR, and mass spectroscopy. (b) This compound gave a satisfactory combustion analysis. (c) The elemental composition of this compound has been verified by high-resolution mass spectroscopy.

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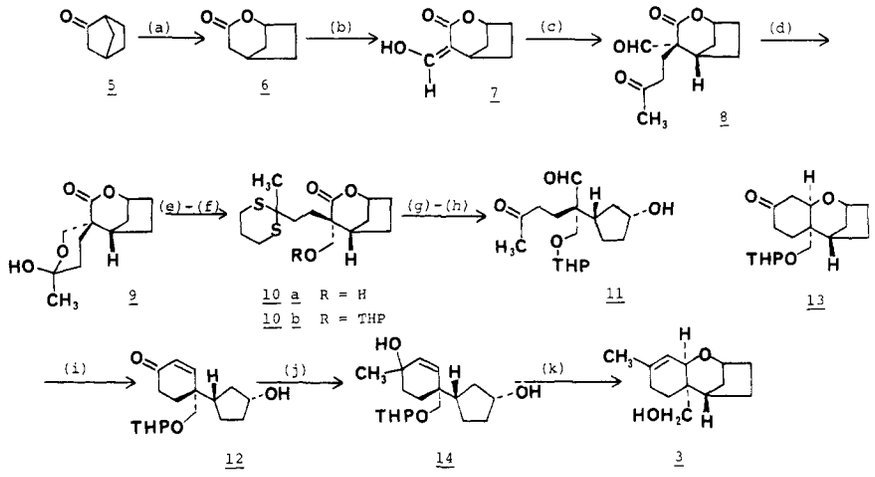
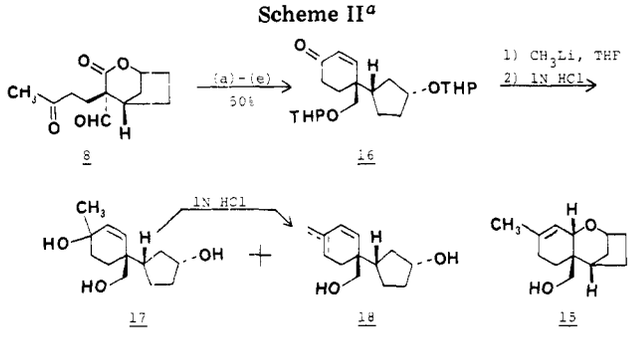
Scheme I[a]



[a] (a) MCPBA, $NaHCO_3$, CH_2Cl_2, 2 h (90%); (b) *tert*-butyl formate, KO-*t*-Bu, THF, 23 °C, 90 min (85%); (c) methyl vinyl ketone, THF, *t*-BuOH, KO-*t*-Bu (catalytic), 2 h (90%); (d) 0.25 equiv of $NaBH_4$, EtOH, −10 °C, 2 h (96%); (e) 1,3-propanedithiol, BF_3-Et_2O, 20 min (96%); (f) dihydropyran, *p*-TsOH (catalytic), CH_2Cl_2, 1 h (95%); (g) DIBAL, toluene, −78 °C, 3 h (80–85%); (h) NBS, collidine, CH_3CN-H_2O (4:1), 0 °C, 20 min (74%); (i) KOH, CH_3OH, H_2O, 3 h (80–89%); (j) CH_3Li (excess), THF, −78 °C; (k) 1 N HCl, THF, 6–18 h (65–75% from **12**).

Scheme II[a]



[a] (a) $HS(CH_2)_3SH$, BF_3·Et_2O; (b) DIBAL (xs), THF; (c) dihydropyran, CH_2Cl_2, *p*-TsOH (cat.); (d) NBS, collidine, H_2O-CH_3CN (1:4); (e) KOH, H_2O, CH_3OH.

deriving from **6** by lactone ethanolysis. Michael reaction of **7** with methyl vinyl ketone (KO-*t*-Bu, *t*-BuOH, THF) afforded adduct **8**[7a,c] in 90–98% yield. The 270-MHz ^1H NMR spectrum of **8** so obtained failed to reveal the presence of any isomeric impurities. The stereochemistry depicted for **8** was assigned by assuming that MVK approaches the enolate of **7** from the less hindered exo face of the bicyclic nucleus; the exo mode of reagent approach to bicyclo[3.2.1] systems is well-known.[9]

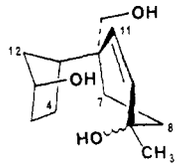
Reduction of **8** with 0.25 equiv of $NaBH_4$ (exactly 1 hydride equiv) afforded **9**[7a,b] (96%), mp 133–134 °C, which exists in solution largely as a hemiketal. Considerable difficulty was encountered in differentiating the functionality of this intermediate. However, treatment of **9** with 1,3-propanedithiol and BF_3·Et_2O afforded a highly crystalline alcohol **10a**[7a,b] (96%, mp 120–124 °C) which was tetrahydropyranylated to give **10b**[7a,c] (95%). DIBAL reduction (1.2 equiv, toluene, −78 °C, 3 h, 80–85%) of **10b** afforded a hydroxyaldehyde,[7a,c] the dithiane group of which was removed under standard conditions (NBS, collidine, H_2O–CH_3CN, 1:4) to give keto aldehyde **11**[7a,c] (74%). Internal aldol condensation (KOH, H_2O, CH_3OH) then afforded **12**[7a,c] (80%) together with a small amount of Michael adduct **13** (10%). Control experiments established that this mixture is, in fact, the equilibrium mixture.

The stage was now set for ring closure of **12** to **3**. This was accomplished by treating a THF solution of **12** with excess CH_3Li followed by treatment with 1 N HCl for 6–18 h at 23 °C. This one-pot sequence afforded **3** directly in 65–75% yield. A detailed examination of this cyclization sequence revealed that two isomeric alcohols **14**[7a] (3:1, high-performance LC analysis) are produced by CH_3Li treatment of **12**; these can be isolated if the reaction is worked up under nonacidic conditions. However, both isomers of **14** cyclize to **3** when treated with acid and thus need not be separated.

The spectroscopic properties of **3**[10] are consistent with the assigned structure and compare favorably with those of known trichothecene derivatives.[1,11] In particular, it is clear from ^1H NMR data that the A–B ring fusion is cis ($J_{10,11}$ = 4.9 Hz; if the ring fusion is trans, $\theta_{10,11}$ = 90° and $J_{10,11} \simeq 0$ Hz). Attempts were made to synthesize the endo A–B cis-fused isomer **15** for comparative purposes (Scheme II). However, treatment of **16** with CH_3Li and then 1 N HCl under the conditions used for the transformation **12** → **3** afforded none of **15**. Rather, mixtures of **17** and **18** (57%, a 2:1 mixture of endo- and exocyclic olefins) as well as small amounts of the corresponding mono THP ethers were obtained. Prolonged acid treatment of **17** afforded only **18** (68%). Molecular model analysis reveals that if the attempted cyclization **17** → **15** were to occur, the developing tetrahydropyranyl ring would be forced to adopt a boat-like conformation in the transition state. This conformation contains a flagpole interaction between C11-H and C12-H and eclipsing interactions between C-4 and either C-7 or C-8, depending on the half-chair cyclo-

(8) Stevens, W.; Van Es, A. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1287.
(9) (a) Zirkle, C. L.; Geissman, T. A.; Bloom, M.; Craig, P. M.; Gerns, F. R.; Indek, Z. K.; Povloff, A. M. *J. Org. Chem.* **1962**, *27*, 1269. (b) Sauers, R. R.; How, H. M.; Feilich, H. *Tetrahedron* **1965**, *21*, 983. (c) Acharya, S. P.; Brown, H. C. *J. Org. Chem.* **1970**, *35*, 196. (d) Ikoto, B.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 351. (e) Stork, G.; Logusch, E. W. *Tetrahedron Lett.* **1979**, 3361; (f) Logusch, E. W. *Ibid.* **1979**, 3365. (g) Takaishi, N.; Inamoto, Y.; Aigami, K. *Chem. Lett.* **1979**, 803.

(10) Spectral data for **3**: ^1H NMR (250 MHz, $CDCl_3$) δ 5.37 (br d, *J* = 4.9 Hz, H_{10}), 4.31 (br s, H_2), 3.46–3.30 (m, 3 H, CH_2OH and H_{11}) 1.69 (s, 3 H, CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 139.0 (s, C-9), 120.2 (d, C-10), 66.6 (d, C-11), 62.0 (q, C-15), 76.0 (d, C-2); IR (CH_2Cl_2) 3620, 1678 cm^{-1}; high-resolution mass spectrum, calcd for $C_{13}H_{20}O_2$ 208.147 15, found 208.146 33.
(11) ^{13}C data: (a) Wehrli, F. W.; Nishida, T. *Prog. Chem. Org. Prod.* **1979**, *36*, 37; (b) Riisom, T.; Jakobsen, H. J.; Rastrup-Andersen, N.; Lorch, H. *Acta Chem. Scand. Ser. B* **1978**, *32*, 499; (c) Breitenstein, W.; Tamm, Ch. *Helv. Chim. Acta* **1975**, *58*, 1172; (d) Hanson, J. R.; Marten, T.; Siverns, M. *J. Chem. Soc., Perkins Trans. 1* **1974**, 1033.



17

hexene conformation under consideration.[12] These interactions, which are absent in the cyclization **14** → **3**, are presumably responsible for the failure of the reaction **17** → **15**. Since Masuoka and Kamikawa have previously employed a biomimetic cyclization analogous to **14** → **3** in a total synthesis of (±)-vominotoxin,[4f,5] the stereochemical assignments for **3** are therefore well-founded.

This sequence is also useful for the synthesis of C15-deoxy derivatives. Thus, tosylation of **3** (*p*-TsCl, pyridine) followed by reduction with lithium triethylborohydride[13] gave **4**[14] in 41% overall yield.

This study demonstrates that the trichothecene ring system can be prepared with exceptional stereochemical control by a route involving annelation of the A ring onto a preformed bicyclic precursor. Application of this strategy to a total synthesis of verrucarol is in progress.

Acknowledgment. This research was supported by grants from the Whitaker Health Sciences Fund and NCI (Grant No. CA 26830). We are grateful to Dr. Catherine Costello for high-resolution spectra.

(12) The cyclization of **17** to the trans-fused isomer of **15** is precluded on steric grounds, since the hydroxyl group of **17** cannot easily interact with the p lobe cis to the adjacent hydroxymethyl group.

(13) Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 171.

(14) Spectral data for **4**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.33 (br d, J = 4.8 Hz, H_{10}), 4.27 (br s, H_2), 3.51 (d, J = 4.8 Hz, H_{11}), 1.67 (3 H, s, allylic CH_3), 0.74 (s, 3 H, CH_3); IR (neat) 1675 cm^{-1}; high-resolution mass spectrum, calcd for $C_{13}H_2O$ 192.151 41, found 192.150 29.

William R. Roush,* Thomas E. D'Ambra
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received April 17, 1980

Stereochemistry of Photochemical Cycloaddition: 4-*tert*-Butylcyclohex-2-enone and Ethylene[1]

Summary: The photochemical cycloaddition of ethylene and 4-*tert*-butylcyclohex-2-enone is inconsistent with a model that implies overlap of orbitals at the α and β carbons of the enones.

Sir: The effective application of the photochemical cycloaddition reaction to the syntheses of complex molecules is limited by lack of knowledge of the reaction mechanism. Although some aspects of the mechanism are generally agreed upon, e.g., the intermediacy of an exiplex[2] and a reversibly formed biradical,[3] other features remain in dispute. Are trans-fused adducts (e.g., from cyclohexenone and olefins) formed via the same path as cis-fused adducts? Does cyclobutane formation always start with bonding of the olefin to the β carbon of the enone? To which face of an enone does cycloaddition occur if there is a preference? Wiesner has proposed two models by which this last question may be answered.[4] In the first (A), similar to that proposed by Stork for metal–amine reductions of enones,[5] the excited cyclohexenone adopts a half-chair conformation with a pyramidal β carbon capable of assuming the more stable configuration. Orbital overlap in the reactive excited enone is an important feature of model A; however, the required axial orientation of the orbital at C-β may be the result of a conformational preference of substituents at C-β.[6] The second model (B) assumes a planar excited state[8] in which "the β-carbon is pyramidalized in the process of reacting with the olefin".[5] Now the more stable biradical (new bond at C-β) leads to product. We report here the photoaddition of ethylene and 4-*tert*-butylcyclohex-2-enone (**1**)[9] and its bearing on the validity of Wiesner's models.

Irradiation of **1** in methylene chloride saturated with ethylene at −78 °C through Pyrex with a 1000-W mercury lamp[10] gave three isomeric cycloadducts, I, II, and III, in a ratio of 61:15:24, respectively. The product composition was monitored throughout the irradiation and after workup, including short-path distillation, by capillary GC and by ^{13}C NMR spectroscopy and was constant throughout; thus the observed ratios represent the relative rates at which the cycloadducts were formed. Treatment of the crude mixture of cycloadducts, in the presence of eicosane as a standard for quantitative GC, with potassium hydroxide or triethylamine gave a new mixture containing only I and II (82:18, respectively) without loss of material. Thus, III undergoes isomerization to I and must be a trans-fused C-2 epimer of the cis-fused I; II is the other cis-fused cycloadduct. Reirradiation of the equilibrated mixture (with internal standard) produced no change. Reduction of the equilibrated mixture of adducts with lithium trisiamylborohydride[11] gave two alcohols (82:18) in 83% yield. The major alcohol was isolated by preparative gas chromatography and converted into its *p*-bromobenzoate. Single crystal X-ray diffraction analysis established structure **5** for the ester and thereby the anti stereochemistry **2** for the major cycloadduct I. Structures **3** and **4** follow for cycloadducts II and III.

In a related study, Wiesner has found that cycloaddition of allene and 4-isopropylcyclohexenone gave equal amounts of the syn and anti (cis-fused) cycloadducts.[12] Our results coupled with those of Wiesner clearly rule out model A, which would require **3** to be the major (or sole) cycloadduct; on the other hand, they are consistent with, but do not prove, model B (the less well-known of Wiesner's proposals). On the other hand, since cleavage of the bi-

(1) Grateful acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

(2) R. A. Caldwell, D. Creed, *Acc. Chem. Res.*, **13**, 45 (1980).

(3) R. O. Loutfy and P. deMayo, *J. Am. Chem. Soc.*, **99**, 3559 (1977). See also P. B. Dervan and T. Uyehara, *ibid.*, **98**, 1262, 2003 (1976).

(4) K. Wiesner, *Tetrahedron*, **31**, 1655 (1975).

(5) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960). See also D. F. Caine, *Org. React.*, **23**, 1 (1976).

(6) In all cases cited in support for this model, there is a bulky substituent at C-β.[5-7]

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(8) C. R. Jones and D. R. Kearns, *J. Am. Chem. Soc.*, **99**, 344 (1977).

(9) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).

(10) The apparatus, which is useful for large-scale irradiations is described in a procedure submitted to *Organic Syntheses*.

(11) S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **99**, 344 (1977).

(12) We thank Professor Wiesner for many useful discussions, for informing us of his recent unpublished work, and for permission to quote these results here.

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