weak base catalyzed elimination in β-phenylethyl derivatives is corroborated. Below this critical level of nucleofugal activity, the minimum energy pathway for H transfer to base is linear and consistent with the prescribed E2 geometry.[5]

These results indicate as well that the earlier proposal of Winstein[27] that all β-elimination processes proceed through a spectrum of transition states between extreme E2H and E2C cannot be correct.

The size of A_H/A_D in the E2C can be correlated with nucleofugal activity by the results of model calculations,[28] which show that at a single (constant) temperature, (i.e., $[\Delta E_a]^H_D = 0$), the angle of H transfer is a direct function of A_H/A_D. The value of $A_H/A_D = 6.6$ for $^+S(CH_3)_2$ is the largest found thus far. On the basis of such model calculations for a C–H bond, this corresponds to a ~160° angle of H transfer. Tosylate, the best leaving group tested thus far, also has the lowest value of $A_H/A_D = 3.6$, corresponding to an angle of ~110°.

Thus the larger angles of H transfer are to be reconciled with the smaller extents of bond making and breaking at C_α during rearward approach of the nucleophilic base and the departure of the leaving group. Consequently, large angles of H transfer denote a tighter TS with respect to the degree of double-bond development. Figure 1 summarizes the features of the extreme types 1 and 2 of transition states to be encountered with variation of nucleofugal, nucleophilic, and base properties of the reagents engaged in an E2C mechanism, as revealed by application of the TDKIE criteria.

Finally, the data in Table I indicate that in the E2C a tighter TS is associated with larger values of a temperature-independent k_H/k_D. Apparently, previous interpretations holding that increasing size of k_H/k_D generally bears a direct relationship to the looseness of the TS in β-elimination reactions can be incorrect when founded on a single temperature measurement.[5,11,13]

Moreover, the same β-phenylethyl derivatives, when subjected to HX elimination in a single-step reaction[29] with strong bases like NaOEt in EtOH, show strongly temperature-dependent isotope effects[30] with A_H/A_D values of less than $2^{1/2}$. In such cases, too, measurement of a single-temperature k_H/k_D, as is common practise, is to be recognized as an approach of dubious value in interpreting the tightness or looseness of the E2 TS.

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Registry No. $C_6H_5CHDCH_2X$ (X = p-$CH_3C_6H_4SO_3$), 84649-05-8; $C_6H_5CHDCH_2X$ (X = Br), 84649-06-9; $C_6H_5CHDCH_2X$ (X = $(CH_3)_2S^+$), 84649-07-0; $C_6H_5CHDCH_2X$ (X = $(CH_3)_3N^+$), 84649-08-1; deuterium, 7782-39-0.

(27) Winstein, S. "Abstracts of Papers", 144th National Meeting of the American Chemical Society, Los Angeles, CA, April 1, 1963; American Chemical Society: Washington, D.C., 1963; p 8M. *Academia Nazionale dei Lincei (Roma), VIII Corso* Estivo Di Chimica, Chimica Teoretica, **1965**, 327.

(28) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 785.

(29) For considerations of the isotope effect when the HX elimination involves more than one step, see: Kwart, H.; Horgan, A. G. *J. Org. Chem.* **1982**, *47*, 159.

(30) Unpublished results from these laboratories.

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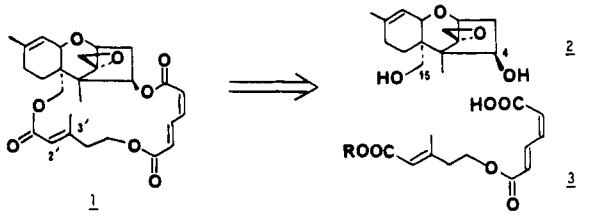
Synthesis of Verrucarin J

Summary: A synthesis of verrucarin J from verrucarol, 3-butyn-1-ol, and malealdehydic acid is described.

Sir: The trichoverroids, roridins, and verrucarins are important classes of biosynthetically related trichothecene metabolites produced by various *Myrothecium* species.[3,4] Many of these compounds possess a range of biological properties including antibacterial, antifugal, and cytostatic activity which is associated with the intact macrocycle present in the roridins and verrucarins. These factors have prompted a number of groups to initiate syntheses of some of these mycotoxins.[5] Our attention has focused recently on verrucarin J (1) which was first isolated in 1965 from the mycotoxin complex produced by *M. verrucaria*.[6] The natural product was originally assigned a *Z* configuration for the C(2′)–C(3′) double bond on the basis of chemical evidence. This assignment was later reversed to that of 1 by using spectroscopic methods;[5d,f,g] this correct structure was confirmed by the recent synthesis of verrucarin J from trichoverrin B.[5b] We report herein an alternative synthesis of 1 starting from verrucarol, 3-butyn-1-ol, and malealdehydic acid.

Our initial approach to 1 concentrated on a convergent strategy by which a differentiated version of diacid 3 would be coupled in a regiochemically controlled fashion to verrucarol (2).[5g,7] This approach has not yet proven



successful, however, in large measure as a consequence of our inability to esterify appropriately functionalized (*Z*,*E*)-muconate half esters to C(4)–OH of the verrucarol nucleus without substantial (up to 50% even with DCC[5a]) isomerization to (*E*,*E*)-muconate diesters.[8] The successful synthesis described herein features an alternative strategy

(1) Roger and Georges Firmenich Assistant Professor of Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982–1984.

(2) National Science Foundation Predoctoral Fellow, 1979–1982. Fellow of the Whitaker Health Sciences Fund, 1982–83.

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(6) Fetz, E.; Böhner, B.; Tamm, C. *Helv. Chim. Acta* **1965**, *48*, 1669.

(7) (a) Verrucarol was prepared from anguidine by a method developed by Fraser-Reid (described in detail in footnote 8 of ref 5b). We thank Professor Fraser-Reid for providing us with this procedure prior to publication. (b) Three total syntheses of racemic verrucarol have now been recorded: Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. Trost, B. M.; McDougal, P. G. *Ibid.* **1982**, *104*, 6110. Roush, W. R.; D'Ambra, T. E. *Ibid.*, in press.

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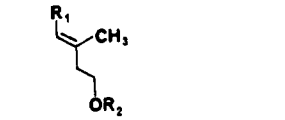
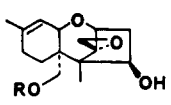
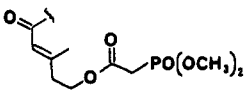
in which the growing macrocyclic chain is first attached to C(15)–OH and the macrocycle closed by a lactonization reaction involving C(4)–OH.

Treatment of 3-butyn-1-ol with Me_3Al (3.0 equiv) and Cl_2ZrCp_2 (0.25 equiv) followed by trichloroethyl chloroformate (1.1 equiv) according to Negishi's procedure[9] afforded ester **4**[10] in 20–25% yield. Treatment of **4** with 1.2



4 $R_1 = CO_2CH_2CCl_3$, $R_2 = H$
5 $R_1 = CO_2CH_2CCl_3$, $R_2 = COCH_2PO(OCH_3)_2$
6 $R_1 = CO_2H$, $R_2 = COCH_2PO(OCH_3)_2$
10 $R_1 = CO_2H$, $R_2 = TBDMS$
11 $R_1 = I$, $R_2 = H$





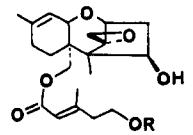
7, R =

8, R =

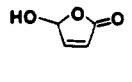
9, R =

equiv of the mixed anhydride prepared from trifluoroacetic anhydride and dimethylphosphonoacetic acid[11] (CH_2Cl_2, pyridine, 94% yield) yielded **5**, deprotection of which (Zn, THF, KH_2PO_4) gave acid **6** in 76% yield. Esterification of verrucarol (**2**) with **6** (1.5 equiv), DCC, and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 according to Hassner's method[12] afforded trichothecene monoester **7** in 34–55% yield as a 3:1 mixture of *E*/*Z* olefin isomers together with up to 19% of diene **8** (ca. 3:1 olefin mixture) and 19% of phosphonoacetate **9**. Although a number of coupling methods (DCC, mixed anhydrides, etc.) proved to be highly selective[5a] for the primary hydroxyl group of **2**, we were not able to eliminate the formation of **8**, **9**, or (*Z*)-**7**. Moreover, we were unable to separate (*E*)-**7** from its olefin isomer.

A parallel series of coupling experiments was performed by using acid **10**. This intermediate was prepared initially from **4** [(i) TBDMS-Cl, imidazole, DMF; (ii) Zn, THF, KH_2PO_4; 59% for both steps], but a higher yielding sequence proceeded from 3-butyn-1-ol via vinyl iodide **11**[9] [(i) TBDMS-Cl, imidazole, DMF; (ii) *n*-BuLi, Et_2O, –60 °C; (iii) CO_2, –78 °C; 67% yield of **10** from **11**; 43% overall yield from 3-butynol]. Thus, treatment of verrucarol with **10** (1.5 equiv), DCC, and DMAP in CH_2Cl_2 (6 h, 23 °C) afforded ester **12** as a 4:1 mixture of *E* and *Z* olefin isomers in 82–85% yield; careful separation of such mixtures by silica gel chromatography afforded pure (*E*)-**12** in 56–60% overall yield along with 14–16% of (*Z*)-**12**.[13] Deprotection



12, R = TBDMS
13, R = H
7, R = $COCH_2PO(OCH_3)_2$



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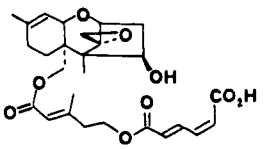

15

of (*E*)-**12** by treatment with HOAc and H_2O in THF (3:1:1, 4 h, 23 °C) smoothly provided **13** (96%), a known degradation product of verrucarin J,[14] acylation of which [$(MeO)_2POCH_2CO_2H$ (1.1 equiv), DCC, DMAP, CH_2Cl_2], gave pure (*E*)-phosphonate **7** in 53% yield (33% of **13** was recovered).[15] Condensation of **7** with malealdehydic acid (**14**)[16] by using the procedure outlined previously[5g] afforded verrucarin J seco acid **15** reproducibly in 57–58% yield. Finally, **15** was treated with pivaloyl chloride (2 equiv) and triethylamine (3 equiv) in CH_2Cl_2 (0.01 M) to form the mixed anhydride which was treated in situ with 4-pyrrolidinopyridine to effect ring closure (23 °C, 2 h). In this manner verrucarin J was isolated by chromatography in 55–60% yield which, following recrystallization from $CHCl_3$–ether, was identical in all the usual respects with an authentic sample generously provided by Professor B. B. Jarvis.[17]

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Supplementary Material Available: ^1H NMR data for compounds **10**, (*E*)-**12**, (*Z*)-**12**, (*E*)-**13**, (*Z*)-**13**, (*E*)-**7**, **15**, and synthetic verrucarin J (3 pages). Ordering information is given on any current masthead page.

(8) Compound **3** (R = $CH_2CH_2SiMe_3$) has been synthesized by a combination of the methods reported in our preliminary studies[5g] and those described herein. A C(15)-monoprotected derivative of verrucarol was prepared by treating **2** with $HO_2C(CH_2)_3OTBDMS$, DCC, and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 (70% yield).

(9) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.

(10) The spectroscopic properties (250- or 270-MHz ^1H NMR, IR, mass spectrum) of all new compounds were in accord with the assigned structures.

(11) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, 3287.

(12) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

(13) Condensation of **2** and **10** with Mukaiyama's salt afforded *E* esters exclusively but in low yield and with poor regioselectivity [60:40 C(15) vs. C(4)]: Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045. Other procedures (mixed anhydride, 2-pyridylthiol ester, CDI[5d]) led to mixtures of olefin isomers, and the Mitsunobu procedure failed altogether.

(14) Tamm originally reported that **13** possessed a *Z* double bond.[6] The spectroscopic properties of (*E*)-**13**, however, are identical with those previously reported for the naturally derived compound. Moreover, we have prepared authentic (*Z*)-**13** by deprotection of (*Z*)-**12** with CH_3CO_2H in aqueous THF (3:1:1; 86% yield), which leaves little doubt that the natural material possesses an *E* double bond.

(15) The yield of **7** is not improved substantially when larger excesses of dimethylphosphonacetic are employed; diacylation [C(4) and C(5′)] is a serious problem under such conditions.

(16) Doerr, I. L.; Willette, R. E. *J. Org. Chem.* **1973**, *38*, 3878.

(17) (a) Synthetic verrucarin J isolated by chromatography was contaminated with ~10% of an isomer which was removed during the crystallization step. (b) Also isolated from the ring closure step was 30% of an isomer tentatively assigned the *E,E*-configuration for the muconate diester linkage. This compound (R_f 0.5) is easily separated from **1** (R_f 0.7 in 1:1 ether–CH_2Cl_2) by silica gel chromatography. A report on the synthesis of other isomers of **1** will be published in due course.

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Observation of the Cyclohexadienone Intermediate in the Aqueous Bromination of Phenol

Summary: The unstable 4-bromo-2,5-cyclohexadienone intermediate involved in the aqueous bromination of phenol has been observed for the first time by stopped-flow UV spectrophotometry (λ_{max} ~240 nm, ϵ ~10 000). In the pH range 0–6 its rearrangement to *p*-bromophenol occurs by acid-catalyzed and uncatalyzed pathways. The intermediate derived from 2,6-dimethylphenol behaves similarly but rearranges more slowly and so is more easily studied.

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