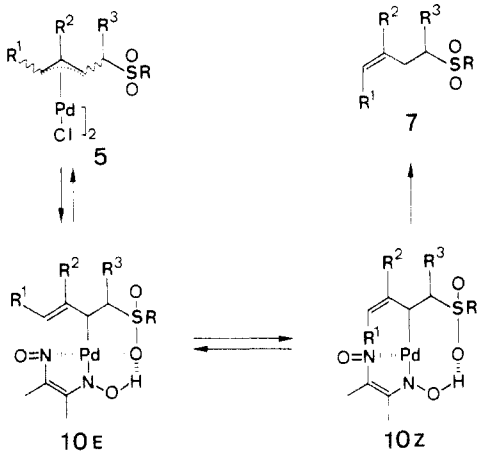
Scheme II



complexes **5** and **6** are produced in comparable amounts (entries 1, 3, and 8). But formation of **6** could be minimized by conducting the sulfonylpalladation in CH_3CO_2H–H_2O (4–5:1 v/v, entries 2, 4, 9, and 10). Furthermore, complex **6** could be eliminated partially by passing a mixture of **5** and **6** through a silica gel column, probably due to decomposition of the latter as observed in the change of ratio of **7b** and **8b** (96:4; cf. entry 3).

The regio- and stereoselectivity of degradation of **5** with DMG is as high as 95%, and the structures of **7** are ascertained unequivocally by comparison of their spectral data (^1H NMR, IR) and VPC and/or HPLC retention times with those of authentic samples prepared by a relevant method.[13]

Although we have previously failed in the sulfonylpalladation of 2,4-hexadiene,[10] addition of water (CH_3CO_2H–H_2O, 5:1 v/v) effected the reaction (**5e**, R^1 = R^3 = CH_3, R^2 = H; 34% isolated yield), and **7e** was obtained as a single product in 64% overall yield.[14] Among the cases in Table I, especially rewarding is the formation of trisubstituted *Z* olefin **7f**. The *E* isomer was not detectable.[15] The structures of **7f** and its *E* isomer were determined on the basis of the nuclear Overhauser effect.[16] Irradiation of the allylic methylene protons of *E* isomer, prepared by alkylation of neophylsulfonyl methyllithium with (*E*)-2-methyl-2-butenyl bromide, enhanced the area intensity of the olefinic proton by 15%, whereas in **7f** irradiation of the analogous protons showed no effect on the intensity of the olefinic proton signal.

As expected, partial hydrogenation of **5b** (1 atm of H_2 for 10 min at ambient temperature in CH_3OH in the presence of 3 equiv of pyridine)[17] furnished a 1:1 mixture of (*E*)-2- and (*E*)-3-hexenyl neophyl sulfones in 63% yield. An attempted reduction of **5b** with $NaBH_4$ (0.33 molar equiv at 0 °C in CH_3OH) failed and gave 1,3-hexadienyl neophyl sulfone in 64% yield.

It seems worthwhile to consider some mechanistic aspects of the somewhat unusual regio- and stereoselectivities of the present reaction. The stereocontrol might be rationalized in terms of protonation of the *Z*-allylic anion generated kinetically through intermediate (*Z*)-**10**[18] (due to either steric repulsion between R^1 and Pd or inherent stability of the *Z*-allylic anion as compared with the *E* counterpart;[19] Scheme II). In partial support of an intermediacy of allylic anion, it was observed that upon treatment of [1-[(neophylsulfonyl)methyl]-1,2-dimethyl-π-allyl]palladium chloride with DMG in CH_3OD selective monodeuteration took place at the 2-position of 2,3-dimethyl-3-butenyl neophyl sulfone. Taking into consideration the lack of regiocontrols in eq 2 and for other π-allylpalladium complexes,[20] the high regiocontrol in Scheme I might be a result of some kind of participation of the sulfonyl group, which involves a coordination of the sulfonyl oxygen to palladium(II) and also might involve a hydrogen bonding between the sulfonyl oxygen and the hydroxyl group of DMG to form a tricyclic intermediate as depicted in (*E*)-**10** and (*Z*)-**10**. Studies are in progress which are focussed on an elucidation of mechanism, an extension to reactions with electrophiles other than proton, and the stereoselective synthesis of trisubstituted olefins functionalized by groups other than a sulfonyl group.

Acknowledgment. Partial support from the Ministry of Education, the Japanese Government (Grant-in-Aid for Scientific Research No. 575559 and 443020 (A)), is gratefully acknowledged.

Registry No. 3, 77944-68-4; (*E*)-**4a**, 2004-70-8; (*Z*)-**4a**, 1574-41-0; (*E*)-**4b**, 20237-34-7; (*Z*)-**4b**, 14596-92-0; (*E*)-**4c**, 32763-70-5; (*Z*)-**4c**, 66597-11-3; (*E*)-**4d**, 64234-49-7; (*Z*)-**4d**, 77983-47-2; (*E,E*)-**4e**, 5194-51-4; (*Z,Z*)-**4e**, 6108-61-8; (*E*)-**4f**, 2787-43-1; (*Z*)-**4f**, 2787-45-3; **5a**, 77944-69-5; **5b**, 77944-70-8; **5c**, 77944-71-9; **5d**, 77944-72-0; **5e**, 77944-73-1; **5f**, 77944-74-2; **6a**, 77944-75-3; **6b**, 77944-76-4; **7a**, 77944-24-2; **7b**, 77944-25-3; **7c**, 77944-26-4; **7d**, 77944-27-5; **7e**, 77944-28-6; **7f**, 77944-29-7; **8a**, 77944-30-0; **8b**, 77944-31-1; **9**, 77944-32-2; (*Z*)-1-*p*-tolyl-5-phenylhex-3-ene, 77944-33-3; (*Z*)-1-*p*-tolyl-5-phenylhex-2-ene, 77944-34-4; (*E*)-2-hexenyl neophyl sulfone, 77944-35-5; (*E*)-3-hexenyl neophyl sulfone, 77944-36-6.

(13) All new compounds have been fully characterized by spectral means and elemental compositions.
(14) The large discrepancy between the yields of **5e** and **7e** may be due to decomposition of **5e** during column purification.
(15) The retention times of **9** and **7f** and its *E* isomer on VPC (SiDC550, 240 °C, He gas) are 6.5, 8.2, and 9.0 min, respectively.
(16) Gaudemer, A. In "Stereochemistry"; Kagan, H. B., Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. 1.
(17) (a) Tamaru, Y.; Yoshida, Z. *Tetrahedron Lett.* **1978**, 4527. (b) Tamaru, Y.; Yoshida, Z. *J. Org. Chem.* **1979**, *44*, 1188.
(18) (a) Verdone, J. A.; Mangravite, J. A.; Scarpa, N. M.; Kuivila, H. G. *J. Am. Chem. Soc.* **1975**, *97*, 843. (b) Yatagai, H.; Yamamoto, Y.; Maruyama, K. *Ibid.* **1980**, *102*, 4578.
(19) (a) Hoffmann, R.; Olofson, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 943. (b) Schlosser, J.; Hartmann, J. *Ibid.* **1976**, *98*, 4674. (c) Bartmess, J. E.; Hehre, W. J.; McIver, R. T., Jr.; Overman, L. E. *Ibid.* **1977**, *99*, 1976. (d) Schleyer, P. v. R.; Dill, J. D.; Pople, J. A.; Hehre, W. J. *Tetrahedron* **1977**, *33*, 2497.
(20) Lawrence, R. V.; Ruff, J. K. *J. Chem. Soc., Chem. Commun.* **1976**, 9.

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Received April 24, 1981

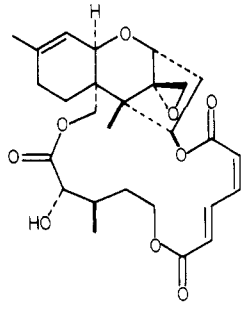
A Novel Synthesis of the Tricyclic Nucleus of Verrucarol

Summary: A substance possessing the ABC rings of verrucarol has been prepared, using a photochemical cycloaddition of acetylene and a cyclobutenyl carbinol → cyclopentenol rearrangement as key constructions for the C ring.

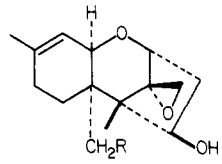
Sir: The biologically potent verrucarins and roridins, exemplified by verrucarin A (**1**), are macrocycles based on verrucarol (**2**) or a closely related nucleus of the trichothecane group.[1] A number of approaches to the synthesis

(1) Tamm, Ch.; *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63.

0022-3263/81/1946-3376$01.25/0



1

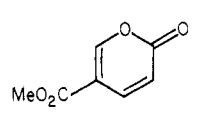


2, R = OH
3, R = H

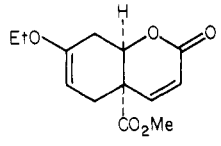
of trichothecane sesquiterpenes have been described,[2] including two successful routes to trichodermol (3);[3] however, it has become clear that many of these strategies cannot be readily extended to a synthesis of 2, bearing an angular hydroxymethyl group.[4]

We describe a synthesis of 17, containing the (ABC) ring system of the trichothecanes in a stereocontrolled fashion. This substance, which bears all of the functionality required for its eventual transformation to verrucarol (2), is expected to play a key role in our quest for the verrucarins.[5]

The first stage of our route parallels an approach recently reported by Kraus,[6] in which a Diels–Alder reaction of isoprene with methyl coumalate (4)[7] was employed for the elaboration of an AB synthon for 2. In practice, it was found that the Diels–Alder reaction of 4 with 2-ethoxybutadiene[8] (C_6H_6, 100 °C, 20 h) was much more satisfactory and gave a single regioisomer 5 in 79% yield. This



4



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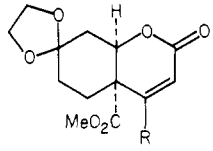
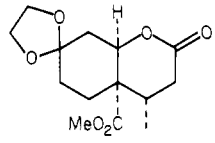


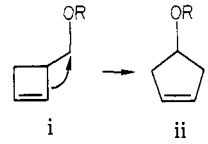
6, R = H
8, R = Me



7

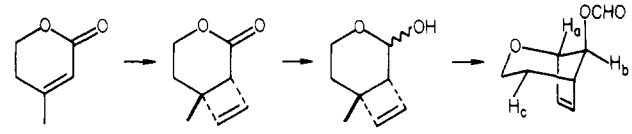
enol ether was transformed directly ($(CH_2OH)_2$, C_6H_6, *p*-TsOH, reflux, 3 h) to the crystalline ketal 6 (mp 131–132 °C). The C-14 methyl substituent was introduced into 6 by conjugate addition with lithium dimethylcuprate (THF, 20 min at −10 °C, then 0.5 h at 0 °C), which afforded 7 as a single epimer in 74% yield. Regeneration of the α,β-unsaturated lactone was accomplished by α-phenylselenation (LiN(*i*-Pr)$_2$, PhSeCl, THF, −70 °C for 2 h, then −5 °C for 20 min), followed by oxidation (30% H_2O_2, AcOH, 25 °C, 1 h),[9] to provide a key intermediate 8 (49%; mp 95–98 °C) for elaboration of the trichothecanoid C ring.

The plan for annelation of 8 called for solvolytic rearrangement of a cyclobutenylcarbinol to a cyclopenten-4-ol, represented schematically as i → ii. Although the corresponding ring enlargement of cyclobutyl systems is well documented,[10] no example involving a cyclobutene appears to have been described. Since it was crucial to determine whether the expected migration of the cyclobutene sp^2 carbon would prevail in this rearrangement, the ring homologation was first examined in the model system 11.



i ii

Irradiation (450-W mercury arc, Pyrex, 30 h) of anhydromevalonolactone (9)[11] in acetonitrile[12] saturated with a stream of acetylene gave the cyclobutene 10 in 73% yield.



9 10 11 12

Reduction of 10 with diisobutylaluminum hydride (toluene, −70 °C, 0.5 h) furnished a pair of epimeric hemiacetals 11 which, upon solvolysis in formic acid (25 °C, 0.5 h), produced a formate ester in good yield. The proton NMR spectrum of this product, particularly signals at δ 4.38 (H_a, br t, J = 7 Hz) and 4.57 (H_b, doublet of doublets, J = 3, 7 Hz, W-type coupling to H_c), is clearly consistent with the oxabicyclo[3.2.1]octene framework of 12[13] rather than the alternative fused ring system derived from migration of the internal cyclobutene bond.

On the basis of this result, a parallel sequence was undertaken with 8. It was expected from steric considerations that addition to the α,β-unsaturated carbonyl system of 8 should occur from the exo (α) direction, and, in fact, irradiation of this lactone in the presence of acetylene afforded 13 stereospecifically in 62% yield. Selective reduction of the lactone carbonyl of 13 was effected with diisobutylaluminum hydride (1 equiv, toluene, −70 °C, 0.5 h) and gave a pair of unstable, epimeric hemiacetals 14 (84%).[14] These were converted to the corresponding acetates 15 (80%, Ac_2O, pyridine).

Attempts to bring about solvolytic ring enlargement of either 14 or 15 with formic acid were complicated by ketal hydrolysis and subsequent β elimination. However, when

(2) Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1978**, *43*, 2938, and references cited. See also: Anderson, W. K.; Lee, G. E. *Ibid.* **1980**, *45*, 501; Roush, W. R.; D'Ambra, T. E. *Ibid.* **1980**, *45*, 3927.

(3) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkins Trans. 1* **1973**, 1989; Still, W. C.; Tsai, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654.

(4) For example, see: Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkins Trans. 1* **1978**, 658.

(5) White, J. D.; Carter, J. P., manuscript to be published.

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(9) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120.

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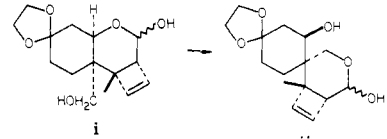
(11) Cornforth, J. W.; Cornforth, R. H.; Popjak, G.; Gore, I. *Biochem. J.* **1958**, 146.

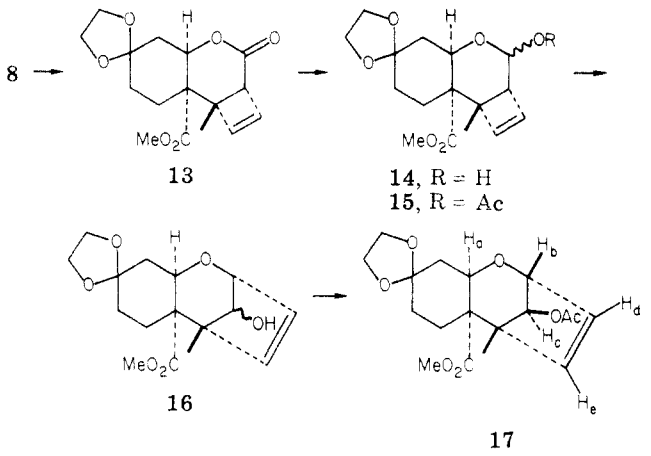
(12) Gueldner, R. C.; Thompson, A. C.; Hedin, P. A. *J. Org. Chem.* **1972**, *37*, 1854. The use of acetonitrile as solvent is crucial for the success of this reaction. Other solvents favored the formation of a 2-vinylvalerolactone via an ene reaction.

(13) The configuration shown for the formate residue of 12 is that expected on the basis of π bond participation and is consistent with the results presented in ref 10. A minor product (ca. 15%), believed to be the formate epimer of 12, was also present.

(14) Reduction of 13 with an excess of diisobutylaluminum hydride gave a 73% yield of diol i. Upon chromatography (silica gel), this substance underwent clean rearrangement to ii.



i ii



15 was exposed to *p*-toluenesulfonic acid in wet benzene containing acetic acid at 50 °C, it underwent rapid rearrangement to **16**, as a mixture of endo and exo hydroxy epimers (ca. 2.5:1, respectively), in 46% yield. This conversion was accompanied by disappearance of the characteristic acetal proton (δ 6.32, singlet) of **15** and its replacement by signals at δ 4.89 (s),[15] 4.43 (br t), and 3.94 (m) anticipated for stereoisomeric alcohols with the bridged, tricyclic nucleus of **16**. Acetylation of **16** (Ac_2O, pyridine, 25 °C, 24 h) followed by chromatographic purification on silica gave the oily, endo acetate **17** [δ 1.24 (3 H, s), 2.07 (3 H, s), 3.78 (3 H, s), 3.90 (H_a, m), 4.25 (H_b, 3 d, J = 5, 2, 1 Hz), 4.92 (H_c, br s), 6.08 (H_e, 2 d, J = 4, 2 Hz), and 6.15 (H_d, m)] in 65% yield.

(15) The methine proton of the minor (exo) alcohol is deshielded due to its proximity to one of the ketal oxygens.

The preparation of **16** in a relatively direct, stereocontrolled manner from methyl coumalate (**4**) makes available a potentially useful intermediate for the synthesis of certain functionalized trichothecanoid systems. These include not only verrucarol (**2**), but also scirpenol derivatives and the tumor inhibitory substance anguidin.[16]

Acknowledgment. We are indebted to the National Institutes of Health for support of this work through Grant AI-10964. Funds for purchase of a Varian FT-80A NMR spectrometer were provided by the National Science Foundation (CHE 77-06753).

Registry No. **4**, 6018-41-3; **5**, 78217-50-2; **6**, 78217-51-3; **7**, 78217-52-4; **8**, 78217-53-5; **9**, 2381-87-5; **10**, 78217-54-6; **11** (isomer 1), 78217-55-7; **11** (isomer 2), 78247-43-5; **11** formate (isomer 1), 78217-56-8; **11** formate (isomer 2), 78247-44-6; **13**, 78217-57-9; **13** (diol i) (isomer 1), 78217-58-0; **13** (diol i) (isomer 2), 78247-45-7; **13** (diol ii) (isomer 1), 78217-59-1; **13** (diol ii) (isomer 2), 78217-60-4; **14** (isomer 1), 78217-61-5; **14** (isomer 2), 78247-46-8; **15** (isomer 1), 78217-62-6; **15** (isomer 2), 78247-47-9; **16** (isomer 1), 78217-63-7; **16** (isomer 2), 78247-48-0; **17**, 78217-64-8; 2-ethoxybutadiene, 4747-05-1; acetylene, 74-86-2.

(16) Tamm, Ch. "Mycotoxins in Human and Animal Health"; Pathotox Publishers: Park Forest South, IL, 1977; pp 209–228.

(17) National Institutes of Health Research Career Development Awardee, 1976–1981.

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Received February 2, 1981