Tetrahedron Letters,Vol.28,No.22,pp 2455-2458,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

TOTAL SYNTHESIS OF CITREOMONTANIN AND ITS $C_{18}Z$ POLYENE ISOMER

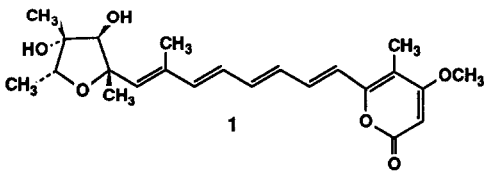
Hemalatha Venkataraman and Jin K. Cha*
Department of Chemistry
Vanderbilt University
Nashville, TN 37235

Abstract: A total synthesis of citreomontanin **5**, a biologically active mycotoxin isolated from *P. pedemontanum*, and its $C_{18}Z$ isomer **6**, is described.

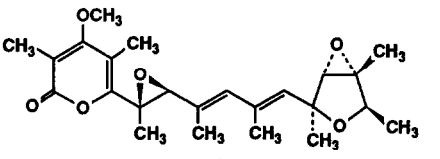
Citreoviridin **1** belongs to a group of mycotoxins which act as inhibitors of ATP-synthesis and ATP-hydrolysis catalyzed by mitochondrial enzyme systems.[1,2] This toxic metabolite has been responsible for the occurrence of acute cardiac beriberi in E. Asia. Citreoviridin is structurally related to aurovertins **2**,[3] asteltoxin **3**,[4] and verrucosidin **4**,[5] and also to citreomontanin **5**, a polyene α-pyrone isolated from *Penicillium pedemontanum*[6] (Scheme I).

Biosynthetic studies of citreoviridin by Nagel et al.[7] indicated that it is formed from a C_{18}-polyketide and five C_1 units derived from methionine. Based on elegant ^{13}C- and ^{18}O- isotope incorporation studies Vleggaar

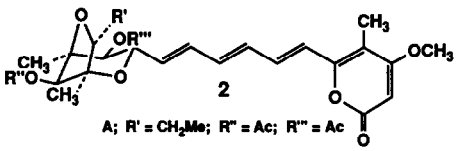
Scheme I



1

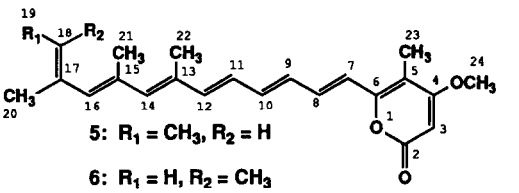


4

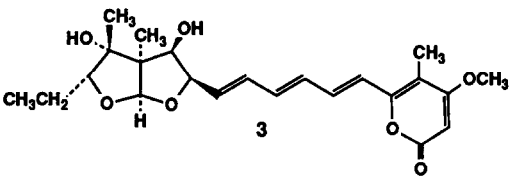


2

A; R' = CH_2Me; R'' = Ac; R''' = Ac
B: R' = CH_2Me; R'' = Ac; R''' = H
C: R' = Me; R'' = Ac; R''' = H
D: R' = CH(OH)Me; R'' = Ac; R''' = H
E: R' = CH_2Me; R'' = H; R''' = H

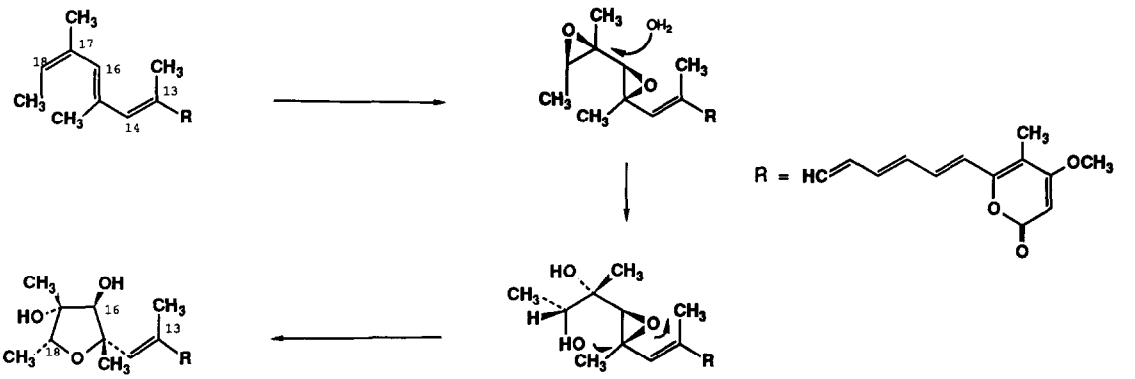


5: $R_1 = CH_3$, $R_2 = H$
6: $R_1 = H$, $R_2 = CH_3$
7: $R_1 = Br$, $R_2 = CH_3$



3

Scheme II. Vleggaar's postulated mechanism for the formation of the tetrahydrofuran moiety of citreoviridin (ref. 8).

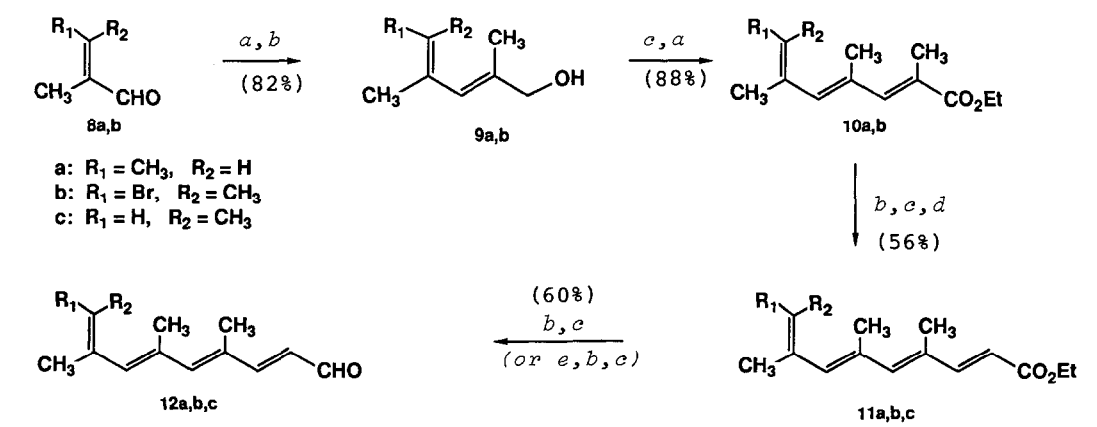


has further delineated the biosynthetic pathway for citreoviridin; the proposed mechanism includes the formation of C_{18} polyketide-derived **6**, followed by bis-epoxide formation by a mono-oxygenase, attack by water at C-17 and subsequent tetrahydrofuran formation (Scheme II).[8] It is noteworthy that the putative polyene intermediate **6** differs from citreomontanin in that it has the $C_{18}Z$ configuration. Herein we report a total synthesis of polyenes **5** and **6**,[9] along with their ^{13}C-labelled compounds.

The all-E-tetraenal **12a** was prepared from tiglic aldehyde **8a** by successive Wittig-Horner olefinations (Scheme III); two iterative applications of (carbethoxyethylidene)triphenylphosphorane followed by a third homologation with diisopropyl carbethoxymethyl phosphonate afforded the all-E-polyene ester **11a** in overall 40% yield. Reduction of ester **11a** (LAH, ether, 0°) followed by MnO_2 oxidation then gave the all-E-tetraenal **12a**.[10]

The preparation of 6-formyl pyrone **14** was achieved according to known literature methods (Scheme IV).[11] Carboxylation of 3-methyl-2,4-pentanedione was carried out *via* the dianion. Cyclization through aegis of TFAA, and subsequent methylation with dimethyl sulfate afforded α-pyrone **13**. 6-Formyl-α-pyrone **14**(mp 137~138°C) was then obtained smoothly by selective oxidation wtih SeO_2[11], and converted into phosphonium salt **18** in a straightforward manner.

Scheme III



a. $Ph_3PC(CH_3)CO_2Et$, PhH, reflux; *b*. LAH, ether, 0°C;
c. MnO_2, CH_2Cl_2, RT; *d*. $(iPrO)_2P(O)CH_2CO_2Et$, tBuOK, THF, -23°C;
e. Zn-Ag, EtOH, reflux.

Final condensation of tetraenal **12a** with the ylide derived from phosphonium salt **18** (nBuLi, THF, -78°→ RT) resulted in an efficient construction of the desired polyene (60~85% yield), but the newly formed (C_9-C_{10}) olefinic bond was a 3:2 mixture of E and Z.[10,12] Chromatographic separation (SiO_2, 1:3 EtOAc-hexane) gave the pure all-E-isomer **5**, citreomontanin, the spectroscopic data of which was identical with that of the natural product from *P. pedemontanum*, mp 159~161°C(lit.[6] mp 165~166°C); exact mass calcd for $C_{23}H_{28}O_3$ 352.2038513, Found 352.2036285. Alternative approach of the final Wittig reaction, i.e., between aldehyde **15** and phosphonium salt derived from **12a**, failed due to the extreme instability of corresponding alcohol and bromide intermediates.

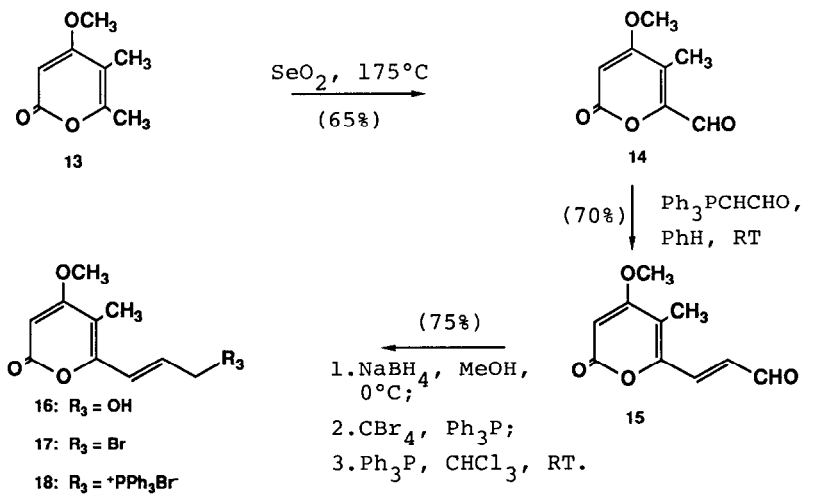
In order to reduce the number of iterative olefinations the Wollenberg vinylstannane methodology was also investigated.[13] Condensation between 6-formyl pyrone **14** and the vinyllithium reagent derived from transmetalation, followed by treatment of pTsOH, gave the vinylogous E,E-diene aldehyde in a disappointingly low (≤10%) yield.[14]

Identical application of the olefination sequences as described above to angelic aldehyde would lead to polyene **6**. Well cognizant of the configurational instability of angelic aldehyde, however, we chose 3-bromoangelic aldehyde **8b** as the starting material.[15] Bromopolyene **7** was prepared in good overall yield but, unfortunately, numerous attempts to effect the required debromination of **7** failed, resulting in intractable product mixtures. We then chose to first achieve the debromination of ester **11b** prior to the final condensation with **18**. Thus, treatment of **11b** with freshly prepared zinc-silver couple in refluxing ethanol[16] (3hr) cleanly provided the debrominated ester **11c** (77% yield), which was subsequently converted as described above into polyene **6**, mp 112~114°C; exact mass found 352.2028503. Interestingly, in marked contrast to **11c**, the debromination product from **10b** suffered isomerization during the SiO_2 chromatographic purification to give a 1:2 mixture of E and Z.

Similarly C_8-^{13}C-labelled **6** [including δ 7.22 ppm (ddd, C_8-H, J= 156.1, 14.9 & 11.4Hz)] was prepared by employing formyl-^{13}C-methylidenetriphenylphosphorane.[17] Further biosynthetic studies utilizing the ^{13}C-labelled **6** will be reported in due course.

Acknowledgment Financial support from the National Institutes of Health (GM 35956 and ES 00267) is gratefully acknowledged. We are indebted to Dr. S. Rebuffat for an authentic sample of citreomontanin. We also thank Dr. Brian Sweetman (NIH RR 01688) for obtaining the mass spectral data.

Scheme IV



References and Footnotes

1. N. Sakabe, T. Goto, and Y. Hirata, Tetrahedron **33**, 3077 (1977); **Tetrahedron Lett.**, 1825 (1964); N. Niwa, T. Endo, S. Ogiso, H. Furukawa, and S. Yamamura, **Chem. Lett.**, 1285 (1981); B. Franck and H. P. Gehrken, **Angew. Chem. Int. Ed., Engl., 19**, 461 (1980).
2. P. E. Linnett, A. D. Mitchell, M. D. Osselton, L. J. Mulheirn, and R. B. Beechey, **Biochem. J., 170,** 503 (1978).
3. L. J. Mulheirn, R. B. Beechey, D. P. Leworthy, and M. D. Osselton, **J. Chem. Soc., Chem. Commun.,** 874 (1974).
4. G. J. Kruger, P. S. Steyn, R. Vleggaar, and C. J. Rabie, **J. Chem. Soc., Chem. Commun.,** 441 (1974).
5. L. T. Burka, M. Ganguli, and B. J. Wilson, **J. Chem. Soc., Chem. Commun.,** 544 (1983).
6. S. Rebuffat, D. Davoust, L. Molho, and D. Molho, **Phytochemistry, 19,** 427 (1980); S. Rebuffat, D. Davoust, and D. Molho, **ibid., 20,** 1279 (1981); C. Brassy, B. Bachet, C. Guidi-Morosini, S. Rebuffat, and D. Molho, **Acta Crystallogr., Section B, 38,** 1624 (1982).
7. D. N. Nagel, P. S. Steyn, and N. P. Ferreira, **Phytochemistry, 11**, 3215 (1972).
8. (a) P. S. Steyn and R. Vleggaar, **J. Chem. Soc., Chem. Commun.**, 1531 (1985).
   (b) Within the proposed biosynthetic pathway there are some variations possible. For example, attack by water at C-15 of a diastereomeric bis-epoxide would also lead to the identical tetrahydrofuran. Alternatively, it could also be formed by mono-epoxide formation, followed by cyclization, epoxidation and subsequent ring opening.
9. Recently appeared a somewhat similar total synthesis of citreomontanin; P. Patel and G. Pattenden, **Tetrahedron Lett., 26,** 4789 (1985).
10. Satisfactory spectroscopic data were obtained for all new compounds. Listed below are some selected IR, UV, ^1H and ^{13}C spectroscopic data:
    10a. ν_{max}(neat) 1708 cm^{-1}; λ_{max}(EtOH) 298(4.22); d 1.29(t, J=7.1Hz, 3H), 1.71(d, J=6.9Hz, 3H), 1.77(s, 3H), 1.98(s, 3H), 2.01(s, 3H), 4.19(q, J=7.1Hz, 2H), 5.49(q, J=6.9Hz, 1H), 6.01(s, 1H), 7.14(s, 1H); ^{13}C 169.2, 144.0, 139.1, 133.2, 131.0, 126.9, 125.5, 60.5, 18.2, 16.5, 14.3, 14.1, 13.8;
    10b. ν_{max}(neat) 1710 cm^{-1}; λ_{max}(EtOH) 278(4.16); d 1.26(t, J=7.1Hz, 3H), 1.76(s, 3H), 1.89(s, 3H), 2.01(s, 3H), 2.22(s, 3H), 4.19(q, J=7.1Hz, 2H), 5.94(s, 1H), 7.10(s, 1H); ^{13}C 169.1, 141.6, 134.7, 133.7, 131.8, 127.6, 120.5, 61.0, 27.0, 23.6, 18.3, 14.6, 14.3;
    11a. ν_{max}(neat) 1713 cm^{-1}; λ_{max}(EtOH) 324(4.44); d 1.28(t, J=7.1Hz, 3H), 1.71(d, J=6.9Hz), 1.77(s, 3H), 1.94(s, 3H), 1.97(s, 3H), 4.19(q, J=7.1Hz, 2H), 5.50(q, J=6.9 Hz, 1H), 5.82(d, J=15.6Hz, 1H), 5.94(s, 1H), 6.29(s, 1H), 7.34(d, J=15.6Hz, 1H);
    11b. ν_{max}(neat) 1715 cm^{-1}; λ_{max}(EtOH) 309(4.43); d 1.29(t, J=7.1Hz, 3H), 1.76(s, 3H), 1.90(s, 3H), 1.95(s, 3H), 2.24(s, 3H), 4.2(q, J=7.1Hz, 2H), 5.86(s, 1H), 5.87(d, J=15.6Hz, 1H), 6.26(s, 1H), 7.33(d, J=15.6Hz, 1H);
    11c. ν_{max}(neat) 1713 cm^{-1}; λ_{max}(EtOH) 313(4.42); d 1.28(t, J=7.1Hz, 3H), 1.52(d, J=6.9Hz, 3H), 1.77(s, 3H), 1.78(s, 3H), 1.96(s, 3H), 4.2(q, J=7.1Hz, 2H), 5.39(q, J=6.9Hz, 1H), 5.84(d, J=15.6Hz, 1H), 5.91(s, 1H), 6.31(s, 1H), 7.35(d, J=15.6Hz, 1H);
    12a. 1.72(d, J=6.9Hz, 3H), 1.81(s, 3H), 2.01(s, 3H), 2.05(s, 3H), 5.55(q, J=6.9Hz, 1H), 6.02(s, 1H), 6.14(dd, J=7.8&15.7Hz, 1H), 6.4(s, 1H), 7.15(d, J=15.7Hz, 1H), 9.56(d, J=7.8Hz, 1H);
    12b. 1.82(s, 3H), 1.94(s, 3H), 2.03(s, 3H), 2.27(s, 3H), 5.98(s, 1H), 6.19(dd, J=7.8&15.7Hz, 1H), 6.38(s, 1H), 7.14(d, J=15.7Hz, 1H), 9.57(d, J=7.8Hz, 1H);
    12c. 1.54(d, J=6.9Hz, 3H), 1.78(s, 3H), 1.83(s, 3H), 2.02(s, 3H), 5.42(q, J=6.9Hz, 1H), 6.01(s, 1H), 6.16(dd, J=7.8&15.4Hz, 1H), 6.43(s, 1H), 7.15(d, J=15.4Hz, 1H), 9.57(d, J=7.8Hz, 1H);
    14. ν_{max}(KBr) 1740, 1710, 1635 cm^{-1}; λ_{max}($CHCl_3$) 316(3.81); d 2.27(s, 3H), 3.87(s, 3H), 5.73(s, 1H), 9.78(s, 1H);
    15. ν_{max}($CHCl_3$) 2850, 1712, 1689, 1605 cm^{-1}; λ_{max}($CHCl_3$) 341(4.12); d 2.09(s, 3H), 3.85(s, 3H), 5.63(s, 1H), 6.89(dd, J=7.3&15.4Hz, 1H), 7.28(d, J=15.4Hz, 1H); 9.72(d, J=7.3Hz, 1H).
    5. ν_{max}(nujol) 1705, 1538 cm^{-1}; λ_{max}(EtOH) 414(4.72); δ ^{13}C 170.6, 163.5, 154.7, 142.3, 139.7, 139.1, 136.5, 136.3, 133.6, 133.4, 132.1, 130.6, 127.1, 125.9, 118.2, 107.5, 88.5, 56.1, 18.9, 16.7, 14.1, 13.9, 8.9;
    6. ν_{max}(nujol) 1698, 1625, 1531 cm^{-1}; λ_{max}(EtOH) 408(4.75); δ ^{13}C 170.6, 163.7, 154.7, 142.1, 139.0, 138.5, 136.2, 134.1, 133.8, 133.5, 131.6, 130.7, 127.3, 123.0, 118.3, 107.5, 88.5, 56.1, 23.7, 18.7, 15.1, 14.1, 8.9.
11. E. Suzuki, B. Katsuragawa, and S. Inoue, **J. Chem. Research (S)**, 224 (1982).
12. Attempts to improve the E:Z ratio through use of the corresponding phosphonate is currently in progress.
13. R. H. Wollenberg, **Tetrahedron Lett.**, 717 (1978); See also J. M. Williams and G. J. McGarvey, **ibid., 26,** 4891 (1985).
14. A Wittig-Horner reaction between pyrone **14** and (formylmethylene)triphenylphosphorane (2 equiv) produced a mixture of the E,E-diene aldehyde and the E-aldehyde **15** in 80% yield. However, their separation was problematic and accordingly, this approach was not pursued.
15. For example, angelic aldehyde is known to slowly isomerize at room temperature to tiglic aldehyde; U. Vogeli and W. von Philipsborn, **Org. Magn. Reson., 7**, 617 (1975).
16. R. D. Clark and C. H. Heathcock, **J. Org. Chem., 41**, 636 (1976).
17. The requisite ^{13}C-labelled phosphorane was prepared efficiently from ^{13}C-methyltriphenylphosphonium iodide and ethyl formate through the action of potassium bis(trimethylsilyl)amide. This preparation represents considerable improvement over the original Trippett's procedure. cf. See also the recent modification of Schlessinger's [**Tetrahedron Lett., 26,** 2391 (1985)].

(Received in USA 24 February 1987)