

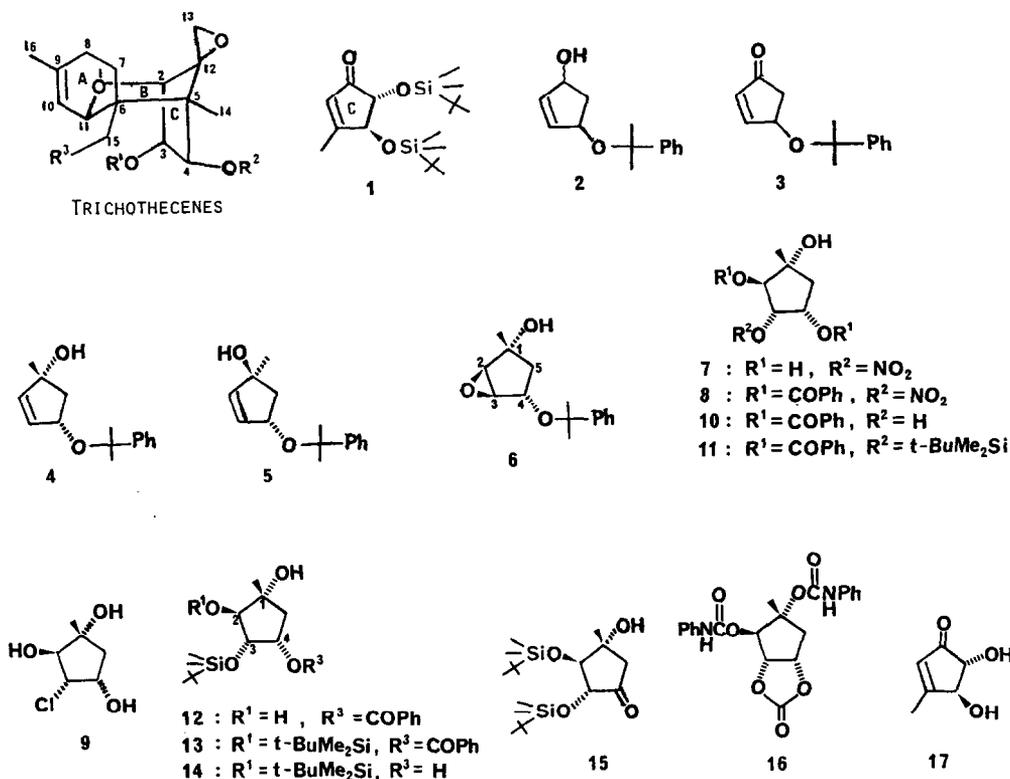
STUDIES ON THE ASYMMETRIC TOTAL SYNTHESIS OF
TRICHOHECENES. STEREOSELECTIVE CONSTRUCTION OF
THE C-RING FRAGMENT

Duy H. Hua* and S. Venkataraman
Department of Chemistry, Kansas State University
Manhattan, Kansas 66506

Summary: A stereoselective construction of the C-ring fragment of trichothecenes from readily available 4-cumyloxy-2-cyclopentenol in 12 steps (24% overall yield) is described.

We have recently described an asymmetric synthesis based on the reaction of enones with chiral sulfynylallyl anions.¹ The utilization of this Michael-type addition reaction in the asymmetric synthesis of trichothecene mycotoxins² is being developed. In this communication we describe a stereoselective construction of the C-ring fragment (1)^{3,4} of trichothecenes from the readily available 4-cumyloxy-2-cyclopenten-1-ol (2).⁵

Oxidation of alcohol 2 with 1.5 equiv. of pyridinium chlorochromate⁶ and 3A molecular sieves in CH₂Cl₂ at r.t. for 1 h provided enone 3 in 95% yield. Treatment of enone 3 with 1.1 equiv. of CH₃Li in THF (40 mL/g of 3) at -30°C for 1 h gave alcohol 4⁷ in 86% yield and isomer 5⁸ in 6% yield. In this 1,2-addition reaction, methyllithium attacks the carbonyl group predominantly from the side trans to the cumyloxyl group. Epoxidation of 4 with 1.1 equiv. of *m*-chloroperbenzoic acid (MCPBA) in CH₂Cl₂ at r.t. for 20 h produced epoxide 6,⁹ isolated in 85% yield after column chromatographic separation. The peracid apparently approaches the double bond from the side trans to the cumyloxyl group despite the proximity of the allylic hydroxyl. The stereochemistry of 6 is supported by the selective hydrolysis of the C-2 benzoate group of 11 to alcohol 12 and the formation of 16 from 12 (*vide infra*). Hydrolysis of the cumyloxyl group and regioselective epoxide opening with 1.5 equiv. of Tl(ONO₂)₃·3H₂O¹⁰ in CH₂Cl₂ (20 mL/g) at r.t. for 2.5 h provided the nitrate triol (7).¹¹ Benzoylation of 7 with 2.5 equiv. of benzoyl cyanide and 5 equiv. of Et₃N in CH₃CN at r.t. for 2 h furnished dibenzoate 8 in 60% overall yield from epoxide 6. During the study of this oxirane-ring



cleavage reaction, we found that **6** could be treated with 2 equiv. of TiCl₄ in AcOH - H₂O (50:1; 50 mL/g) at r.t. for 20 min to give chloride **9**¹² in 85% yield.¹³ The regioselective attack at C-3 of **5** by chloride ion was proven by using the ¹H NMR decoupling experiments on **9** and its C-2, C-4 diacetate derivative. Similarly, the stereochemistry of **7** was established by the decoupling experiment on it and its derivatives (i.e., **8**, **10** - **14**). It is assumed that hydrolysis of the cumyl group was followed by oxirane-ring cleavage. Silylether **11**¹⁴ was obtained from **8** by the two-step sequence: (i) reduction with Zn-AcOH at r.t. for 1 h; 92% yield and (ii) silylation with 1.2 equiv. of *t*-BuMe₂SiCl, 2 equiv. of imidazole and 0.2 equiv. of *p*-dimethylaminopyridine (DMAP) in CH₂Cl₂ at r.t. for 6 h; 98% yield. Selective debenzoylation of **11** (i.e., C-2 benzoate) with 0.15 equiv. of K₂CO₃ in MeOH (10 mL/g) at 0°C for 12 h provided 85% yield of **12**. Transformation of diol **12** to enone **1**¹⁵ was accomplished by the sequence: (i) silylation with 1.5 equiv. of *t*-BuMe₂SiCl, 2.0 equiv. of imidazole and 0.3 equiv. of DMAP in CH₂Cl₂ at r.t. for 15 h; 90% yield, (ii) debenzoylation with 1 equiv. of K₂CO₃ in MeOH at r.t.; 98% yield, (iii) oxidation of C-4 hydroxy group with pyridinium chlorochromate in CH₂Cl₂ at r.t. for 4 h; 90% yield and (iv) dehydration with 1.5 equiv. of methanesulfonyl chloride and 3.0 equiv. of Et₃N in ether at 0°C; 95% yield.

The stereochemistry at C-3 and C-4 of nitrate **7** was proven by converting intermediate **12** to cyclic carbonate **16** by the sequence: (i) carbamoylation of **12** with PhN=C=O and DMAP in

pyridine at 60°C for 10 h; (ii) debenzoylation with K_2CO_3 in MeOH at r.t. and (iii) desilylation with HF in $CH_3CN : H_2O$ at r.t. followed by methyl chloroformate - Et_3N .

Finally disilylether **1** was deprotected to trans-4,5-dihydroxy-3-methyl-2-cyclopentenone (**17**), the acid hydrolyzed cleavage product Zi of moenomycin,¹⁶ by treatment with $n-Bu_4NF$ in THF at r.t. in 90% yield. The above synthesis provides a general route for the stereoselective construction of highly oxygenated cyclopentanes.

Acknowledgement. We thank the NSF and Kansas State University for a grant for the purchase of the Bruker WM-400 NMR spectrometer. Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society and Research Corporation for generous financial support.

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- The history, structure, biological significance and anticancer activity of naturally occurring trichothecenes have been reviewed: a) Doyle, T. W.; Bradner, W. T. "Anticancer Agents based on Natural Product Models," a series of monographs of medicinal chemistry, vol. 16, edited by Cassady, J. M.; Douros, J. D.; Academic Press: New York, 1980, p. 43-72. b) Jarvis, B. B.; Mazzola, E. P. Acc. Chem. Res. **1982**, 15, 388-395. c) Tamm, Ch. "Chemistry and Biotechnology of Biologically Active Natural Products"; Szantay, Cs. Ed.: Elsevier Science Pub., New York, 1984; pp. 59-77 and references therein.
- A general scheme for assembling the trichothecene skeleton involving the addition of an A-ring unit to a C-ring unit followed by an intramolecular cyclization providing the B-ring has been described: a) Brooks, D. W.; Grothaus, P. G.; Palmer, J. T. Tetrahedron Lett. **1982**, 4187-4190. b) Brooks, D. W.; Grothaus, P. G.; Mazdiyasi, H. J. Am. Chem. Soc. **1983**, 105, 4473-4474 and references therein.
- The asymmetric total synthesis of trichothecenes will be discussed at a later date.
- Alcohol **2** was prepared from cyclopentadiene and cumyl hydroperoxide: Stork, G.; Isobe, M. J. Am. Chem. Soc. **1975**, 97, 6260-6261.
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- All new compounds displayed satisfactory 1H NMR (400 MHz), ^{13}C NMR (100 MHz), UV, IR and low-resolution mass spectra and satisfactory elemental analysis or chemical ionization MS. **4**: 1H NMR ($CDCl_3$) δ 7.5 ~ 7.2 (m, 5H, Ph), 5.81 [dd, $J = 5.5$, $J = 1.2$, 1H, =CHC(OH)CH₃], 5.71 (dd, $J = 6$, $J = 2$, 1H, =CH), 4.15 (m, 1H, CHO), 2.25 (dd, $J = 14$, $J = 7$, 1H, CH₂), 1.92 (s, 1H, OH), 1.88 (dd, $J = 14$, $J = 4$, 1H, CH₂), 1.57 (s, 3H, CMePh), 1.55 (s, 3H, CMePh), 1.24 [s, 3H, C(OH)Me]. ^{13}C NMR ($CDCl_3$) δ 146.8 (s, Ph), 140.5 (d, =CHCOH), 134 (d, =CH), 128.2 (d, o-Ph), 127 (d, p-Ph), 126 (d, m-Ph), 80.9 (s, C-Ph), 77.7 (s, CMeOH), 76.5 (d, C-O), 50.4 (t, CH₂), 29.8 (q, CMePh), 28.6 (q, CMePh), 27 (q, Me).
- Isomer **5**: 1H NMR 7.5 ~ 7.2 (m, 5H, Ph), 5.78 (s, 2H, HC=CH), 4.50 (dd, $J = 6.5$, $J = 5.2$, 1H, CH-O), 2.20 (dd, $J = 14$, $J = 7$, 1H, CH₂), 1.87 (dd, $J = 14$, $J = 5$, 1H, CH₂), 1.60 (s,

- 1H, OH), 1.55 (s, 6H, CMe_2Ph), 1.46 (s, 3H, CH_3). ^{13}C NMR 146.8 (s, Ph), 139.3 (d, =CHCOH), 136.2 (d, =CH), 128.2 (d, o- Ph), 127.0 (d, p- Ph), 126.0 (d, m- Ph), 81.8 (s, C-Ph), 77.8 (d, C-O- CMe_2Ph), 77.6 (s, COHMe), 49.5 (t, CH_2), 29.6, 28.7 (q, CMe_2), 28.5 (q, Me).
9. Epoxide 6: ^1H NMR 7.5 - 7.2 (m, 5H, Ph), 3.55 (t, d, $J = 8$, $J = 1.3$, 1H, CHOCMe_2Ph), 3.32 (dd, $J = 2.2$, $J = 1.3$, 1H, C-3 H), 3.16 (d, $J = 2.2$, 1H, C-2 H), 2.5 (broad s, 1H, OH), 1.80 (dd, $J = 13$, $J = 7.5$, 1H, CH_2), 1.55 (1H, CH_2 , overlap with CH_3), 1.61 (s, 3H, CMePh), 1.55 (s, 3H, CMePh), 1.10 (s, 3H, CH_3). ^{13}C NMR 146.3 (s, Ph), 128.2 (d, o- Ph), 127.2 (d, p- Ph), 125.9 (d, m- Ph), 77.6 (s, CMe_2Ph), 75.0 (s, CMeOH), 71.7 (d, C-OCMe $_2$ Ph), 60.8 (d, C-2), 58.3 (d, C-3), 41.6 (t, CH_2), 29.5 (q, CMePh), 28.6 (q, CMePh), 23.7 (q, CH_3).
10. Mincione, E.; Lanciano, F. Tetrahedron Lett. **1980**, 21, 1149-1150.
11. Nitrate 7: ^1H NMR 5.12 (dd, $J = 5.4$, $J = 3$, 1H, CHONO_2), 4.13 [m, 1H, CH(OH)CH_2], 3.81 [d, $J = 5.4$, 1H, CH(OH)], 2.70 (broad s, 3H, OH), 2.08 (dd, $J = 15$, $J = 1.5$, 1H, CH_2), 2.01 (dd, $J = 15$, $J = 6$, 1H, CH_2), 1.35 (s, 3H, CH_3). ^{13}C NMR 96.7 (d, C- ONO_2), 80.3 [d, CH(OH)CMeOH], 78.8 (s, CMeOH), 73.6 (d, C-OH), 43.1 (t, CH_2), 24.2 (q, CH_3).
12. Chloride 9: ^1H NMR 4.17 [m, 1H, CH(OH)-CH_2], 4.04 (dd, $J = 7$, $J = 4$, 1H, CHCl), 3.76 [d, $J = 7$, 1H, CH(OH)CMe], 3.03 (s, 2H, OH), 2.88 (s, 1H, OH), 2.21 (dd, $J = 15$, $J = 7$, 1H, CH_2), 1.98 (dd, $J = 15$, $J = 3$, 1H, CH_2), 1.34 (s, 3H, CH_3). ^{13}C NMR 84.5 [d, CH(OH)CMeOH], 77.50 (s, CMeOH), 77.13 (d, C-OH), 70.61 (d, C-Cl), 43.9 (t, CH_2), 25.6 (q, CH_3).
13. As far as we are aware, this is the first example of an oxirane ring-opening reaction with TiCl_4 . A full study with various epoxides will be reported in due course.
14. Silylether 11: ^1H NMR 8.1 (m, 4H, o-Ph), 7.6 (m, 2H, p-Ph), 7.45 (m, 4H, m-Ph), 5.21 (d, $J = 7.4$, 1H, C-2 H), 5.17 (ddd, $J = 8$, $J = 5.3$, $J = 4$, 1H, C-4 H), 4.79 (dd, $J = 7.4$, $J = 5.3$, 1H, CHOSi), 2.56 (dd, $J = 15$, $J = 8$, 1H, CH_2), 2.02 (dd, $J = 15$, $J = 4$, 1H, CH_2), 1.61 (s, 1H, OH), 1.38 (s, 3H, CH_3), 0.78 (s, 9H, t-Bu), 0.03 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3). ^{13}C NMR 166.1 (s, C=O), 165.8 (s, C=O), 133.4, 133.1 (ss, quaternary C of Ph), 130.0, 129.9 (d, p-Ph), 129.8, 129.7 (d, o-Ph), 128.5, 128.4 (d, m-Ph), 82.7 (d, C-4), 79.4 (d, C-2), 77.8 (s, C-OH), 75.9 (d, C-OSi), 42.5 (t, CH_2), 26.8 (q, CMeOH), 25.5 (q, 3C, CMe_3), 18.5 (s, SiCMe_3), -4.7, -4.8 (qq, SiMe_2).
15. Enone 1: ^1H NMR 5.9 (s, 1H, =CH), 4.52 (m, 1H, C=C- CHOSi), 4.15 (d, $J = 2.7$, 1H, O=C- CHOSi), 2.06 (dd, $J = 1.1$, C=C-Me), 0.94 (s, 9H, CMe_3), 0.93 (s, 9H, CMe_3), 0.19, 0.18, 0.17, 0.15 (s, 3H, SiMe_2). ^{13}C NMR 201.7 (s, C=O), 172.8 (s, =C-Me), 128.4 (d, =CH), 82.9 (d, C=C-COSi), 80.3 (d, C-OSi), 26.0, 25.8 (q, CMe_3), 18.4, 18.0 (s, CMe_3), 16.5 (q, CH_3), -3.7, -4.0, -4.5, -4.6 (q, SiMe_2).
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(Received in USA 13 May 1985)