EtOAc as eluant to afford 60 mg of crude **8a**. This material was dissolved in a solvent mixture containing 0.46 mL of HOAc, 0.23 mL of THF, and 0.23 mL of H_2O and was stirred at 40 °C for 6 days. This mixture was coevaporated from heptane (2 × 50 mL) and the crude product was purified by preparative TLC (1:1 hexane–EtOAc) to afford 19 mg (0.052 mmol) of pure, semisynthetic anguidine. The overall yield for the four-step sequence from **11a** was 94%. The physical properties of semisynthetic **1** were indistinguishable from those of authentic, naturally derived material:[12] mp 160–162°; $[\alpha]^{21}_D$ -30.9° (*c* 1.11, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 5.51 (d, 1 H, J = 4.9 Hz, H_{10}), 5.10 (d, 1 H, J = 2.9 Hz, H_4), 4.15 (m, 2 H, H_{15a} and H_3), 3.93 (d, 1 H, J = 12.4 Hz, H_{15b}), 3.68 (d, 1 H, J = 4.9 Hz, H_2), 3.18 (d, 1 H, J = 2.6 Hz, OH), 3.05 (d, 1 H, J = 3.9 Hz, H_{13a}), 2.76 (d, J = 3.9 Hz, H_{13b}), 2.12 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 1.69 (s, 3 H, H_{16}), 0.80 (s, 3 H, H_{14}).

[^{14}C]Methyltriphenylphosphonium Iodide. To a -78 °C solution of PPh_3 (56.3 mg, 0.22 mmol) in 0.15 mL of dry THF was added via syringe a solution of $^{14}CH_3I$ (13.7 mg, 0.1 mmol, 5 mCi, 52 mCi/mmol, New England Nuclear) in 1.5 mL of THF that had been precooled to -78 °C. The sealed reaction mixture was stirred at ambient temperature for 2 h before addition of cold CH_3I (7.3 μL, 0.11 mmol). This mixture was then stirred for 43 h. The solvent was removed by syringe and the crystals of $Ph_3P^{14}CH_3I$ were carefully rinsed under N_2 with dry toluene (3 × 1 mL). This sample of phosphonium salt was dried in vacuo for 1.5 h (25 °C) and was used immediately in the next reaction.

Synthesis of [^{14}C]-12b. To a stirred suspension of $PPh_3{}^{14}CH_3{}^+I^-$ (from the previous experiment, theoretically 0.22 mmol) in 0.54 mL of dry THF at -78 °C was added PhLi (0.13 mL of 1.7 M solution in 7:3 cyclohexane–Et_2O, 0.22 mmol). The suspension turned bright yellow and was stirred at -78 °C for 20 min and then warmed to 0 °C and stirred at this temperature for 10 min. The clear, red-orange ylid solution was cooled to 0 °C and then a solution of ketone **4b** (117 mg, 0.22 mmol) in 1.1 mL of THF was added dropwise. The mixture was heated to 50 °C for 6 h and stored at -78 °C overnight. The solution was diluted with Et_2O (30 mL) and washed with H_2O (10 mL) and 1:1 saturated Na_2SO_3–1 M K_2CO_3 (10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were dried (Na_2SO_4), filtered, and concentrated to afford 147 mg of an orange oil. The product mixture was separated by flash chromatography (25 mm × 15 cm column, hexane–EtOAc 20:1; mixed fractions were rechromatographed on a 15 mm × 12 cm column), giving 44.9 mg (38%) of [^{14}C]-**12b** and 56 mg (47%) of recovered **4b**. The yield of **12b** based on unrecovered **4b** was 72%. Compound **12b** was identical with authentic samples by TLC and 300-MHz ^{1}H NMR analysis and had a specific activity of 26 mCi/mmol.

In a second experiment, $[^{14}C]CH_3PPh_3{}^+I^-$ was prepared from Ph_3P (0.36 mmol), $[^{14}C]CH_3I$ (0.09 mmol, 5 mCi, 58 mCi/mmol), and unlabeled CH_3I (0.27 mmol). The salt was dried in vacuo for 6 h before use and then was converted to the ylide by using the procedure described above. The ylide was treated with **4b** (195 mg, 0.36 mmol) in THF at reflux for 1 h. The reaction was worked up and the product purified as described above, giving 113 mg (58% yield) of **12b** (specific activity 9.5 ± 0.5 mCi/mmol).

Synthesis of [^{14}C]Anguidine. [^{14}C]-**12b** (44.9 mg, 0.08 mmol, 26 mCi/mmol) was converted into 25 mg of [^{14}C]-**1** (19.2 mCi/mmol) by using the procedures described previously for unlabeled materials. The overall yield was 80%. Only two purifications were performed—the first at the stage of [^{14}C]-**11** and the second at the end of the sequence. The [^{14}C]anguidine so obtained was identical with authentic samples by TLC, HPLC (radiochemical detection used in both cases), and 300-MHz ^{1}H NMR.

Acknowledgment. This research was supported by the U.S. Army Medical Research and Development Command (Contract No. DMAD 17-82-C-2235). We also gratefully acknowledge the use of Professor S. Masamune's radiolabeling laboratory during the synthesis of [^{14}C]-**1**.

Trichothecene Degradation Studies. 3. Synthesis of 12,13-Deoxy-12,13-methanoanguidine and 12-Epianguidine, Two Optically Active Analogues of the Epoxytrichothecene Mycotoxin Anguidine

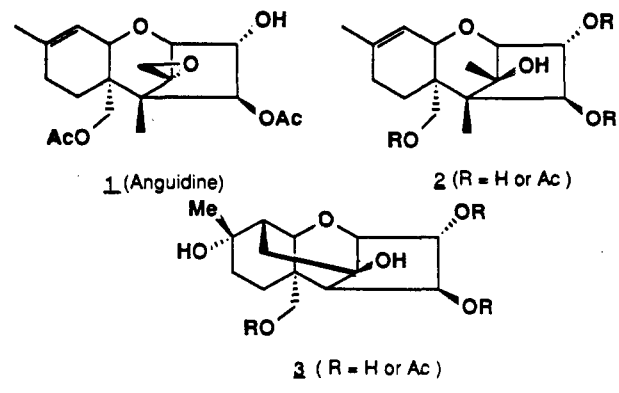
William R. Roush*[1] and Sandra Russo-Rodriguez

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received August 13, 1986

The title compounds were synthesized in order to further explore the apparent requirement of the trichothecene 12,13-epoxide unit for biological activity. Cyclopropane analogue **4** was prepared via a sequence involving a Simmons–Smith cyclopropanation of the anguidine degradation intermediate **6**, whereas the key step in the synthesis of 12-epianguidine (**5**) was the dimethylsulfonium methylide mediated cyclopropanation of norketone **9**. These compounds are among the first skeletally modified, semisynthetic trichothecene analogues to be prepared for biological evaluation.

A characteristic structural feature of the trichothecene mycotoxins is the 12,13-epoxide that occurs with high frequency in the naturally occurring members of this family.[2] This unit appears to be essential for the manifestation of cytotoxicity and other deleterious biological effects (e.g., feed refusal by animals) since chemically modified trichothecenes such as **2** (prepared via $LiAlH_4$ reduction of **1**) and **3** (product of epoxide substitution via

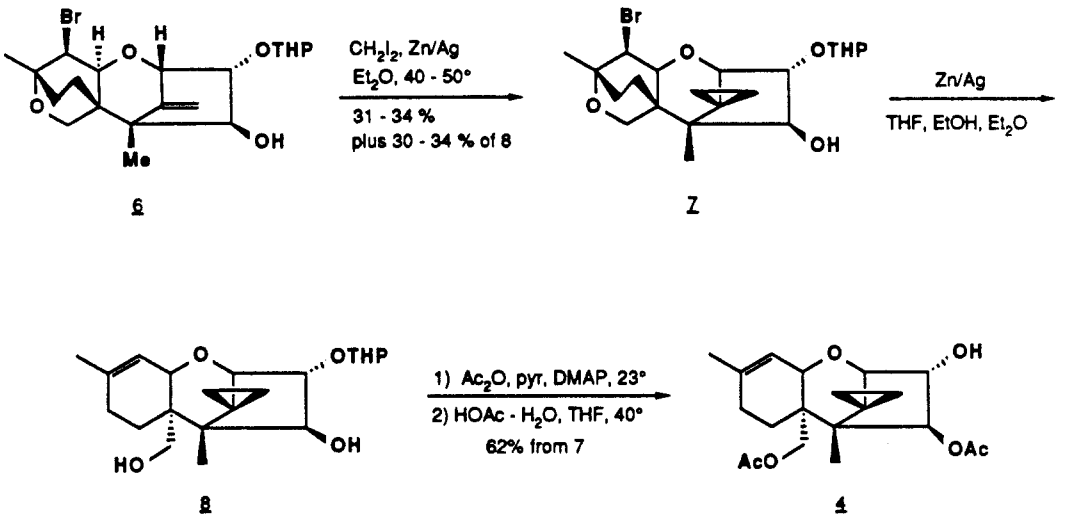


(1) (a) Fellow of the Alfred P. Sloan Foundation, 1982–1986. (b) Address correspondence to this author at the Department of Chemistry, Indiana University, Bloomington, IN 47405.

(2) (a) *Developments in Food Science: Trichothecenes: Chemical, Biological and Toxicological Aspects*; Ueno, Y., Ed.; Elsevier: New York, 1983; Vol. 4. (b) Doyle, T. W.; Bradner, W. T. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Chapter 2. (c) Ueno, Y. *Adv. Nutr. Res.* **1980**, *3*, 301. (d) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. (e) Bamburg, J. R.; Strong, F. M. In *Microbial Toxins*; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. 7, p 207.

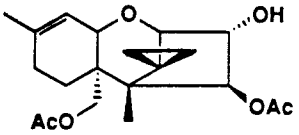
0022-3263/87/1952-0603$01.50/0

Scheme I

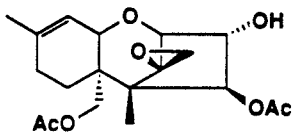


participation by the C(9)–C(10) double bond) are devoid of any significant activity.[3] These data have prompted speculation that the mode of action involves nucleophilic additions to the epoxide group.[2b,4] This is difficult to reconcile, however, with the well-established low reactivity of the 12,13-epoxide unit under nonacidic S_N2 conditions.[5,6] Moreover, the simple trichothecenes such as **1** appear to be *reversible* inhibitors of eucaryotic protein synthesis;[7] at present, the ribosome is the only known site of action of these mycotoxins.[1b]

In order to probe further the apparent structural requirement for the 12,13-epoxide unit, we have synthesized two analogues of anguidine in which the epoxide has been replaced by essentially isosteric groups: 12,13-deoxy-12,13-methanoanguidine (**4**) and 12-epianguidine (**5**).



4



5

These compounds more closely resemble **1** than **2** or **3**, especially in terms of the geometry and polarity in the vicinity of C(12). To the best of our knowledge, these are among the first skeletally modified, semisynthetic trichothecene analogues to be prepared for biological evaluation.[8-10]

In the preceding paper we described an efficient four-step synthesis of the fully differential trichothecene derivative **6** using natural anguidine as starting material.[11] This intermediate served as the point of departure for the synthesis of **4** described here. Thus, treatment of **6** with CH_2I_2 and zinc–silver couple[12] in Et_2O at reflux provided 31–34% of cyclopropane **7** plus 30–34% of trichothecene **8** in which the C(9)–C(10) double bond had been unmasked (Scheme I). Attempts to improve the efficiency of this step by using the CH_2I_2–$ZnEt_2$ procedure[13] provided **7** in only 30% yield. Completion of the synthesis of anguidine analogue **4** proceeded uneventfully by using the now well-established deprotection and acylation steps indicated in the scheme.[11,14]

The synthesis of 12-epianguidine (**5**), the unnatural epoxide diastereomer of **1**, originated from norketone **9**, an intermediate also previously used in our synthesis of [^{14}C]anguidine.[11] Treatment of **9** with excess dimethylsulfonium methylide[15] in THF at 0 °C provided a 3:1 mixture of epoxide **10** and methylthio adduct **11** (Scheme II). Separation of these materials was accomplished only after removal of the triethylsilyl ether protecting group. Comparison of the ^{1}H NMR spectra of **12** and the corresponding epoxide prepared either from anguidine or by MCPBA epoxidation of **6**[11] clearly shows that **12** is a diastereomer of the natural system. This result confirms, therefore, the earlier observations by the Cambridge group that use of the $Me_2S{=}CH_2$ epoxidation procedure leads to the unnatural trichothecene epoxide configuration.[16] Completion of the synthesis of 12-epianguidine (**5**) from **12** was easily accomplished as summarized in Scheme II.

(3) (a) Grove, J. F.; Mortimer, P. H. *Biochem. Pharmacol.* **1969**, 1473. (b) Grove, M. D.; Burmeister, H. R.; Taylor, S. L.; Weisleder, D.; Plattner, R. D. *J. Agric. Food Chem.* **1984**, *32*, 541.

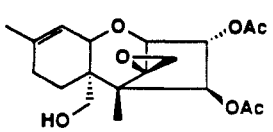
(4) Ueno, Y. *Pure Appl. Chem.* **1977**, *49*, 1737.

(5) Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.* **1985**, *50*, 5465 and literature cited therein.

(6) Although Ueno has presented evidence that epoxytrichothecenes react with thiol residues in thiol-containing enzymes (ref 4), other work has noted the lack of reactivity with thiols such as glutathione, cysteine, and dithiothreitol: (a) Nakamura, K.; Ohta, M.; Ueno, Y. *Chem. Pharm. Bull.* **1977**, *25*, 3410. (b) Ueno, Y.; Matsumoto, H. *Ibid.* **1975**, *23*, 2439.

(7) Hernandez, F.; Cannon, M. *J. Antibiot.* **1982**, *35*, 875 and references therein.

(8) While this manuscript was in preparation, Dr. E. W. Colvin informed us of his independent trichothecene degradation studies resulting in the synthesis of trichothecene analogue **i**, a second system possessing unnatural stereochemistry at C(12).



i

(9) For previous efforts directed toward the total synthesis of trichothecene analogues, see: (a) Pearson, A. J.; Chen, Y.-S. *J. Org. Chem.* **1986**, *51*, 1939. (b) Pearson, A. J.; Ong. C. W. *J. Am. Chem. Soc.* **1981**, *103*, 6686. See also: (c) Anderson, W. K.; Lee, G. E. *J. Org. Chem.* **1980**, *45*, 501. (d) Anderson, W. K.; LaVoie, E. J.; Lee, G. E. *Ibid.* **1977**, *42*, 1045. (e) Anderson, W. K.; Lee, G. E. *J. Med. Chem.* **1980**, *23*, 96. (f) Fullerton, D. S.; Chen, C. M.; Hall, I. H. *Ibid.* **1976**, *19*, 1391.

(10) For a summary of substituent effects and changes in oxidation state around the periphery of **1**, see: Kaneko, T.; Schmitz, H.; Essery, J. M.; Rose, W.; Howell, H. G.; O'Herron, F. A.; Nachfolgen, S.; Huflalen, J.; Bradner, W. T.; Partyka, R. A.; Doyle, T. W.; Davies, J.; Cundliffe, E. *J. Med. Chem.* **1982**, *25*, 579.

(11) Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.*, preceding paper in this issue.

(12) Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549.

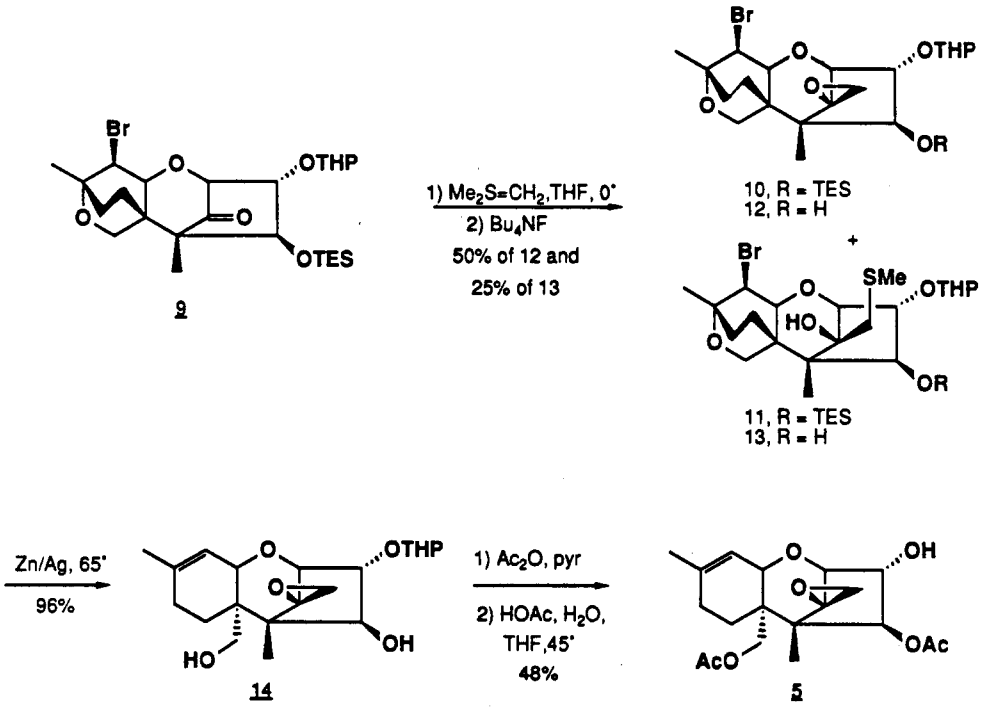
(13) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647.

(14) Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.* **1985**, *50*, 3224.

(15) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(16) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989.

Scheme II



In summary, this work demonstrates for the first time that skeletally modified trichothecene analogues designed to probe questions of structure and biological activity can be prepared by using the natural, optically active trichothecenes as starting materials. Results of biochemical and biological investigations of 4 and 5 will be reported in due course.

Experimental Section

For general experimental details, the reader should refer to the Experimental Section of the preceding paper.[11]

Isomerically pure THP diastereomers of the **a** series[5,11,14] were used throughout this work in order to facilitate analysis of reaction mixtures.

10β-Bromo-3α-[(tetrahydropyranyl)oxy]-9α,15-epoxy-12,13-methanotrichothecan-4β-ol (7a). To a solution of **6a** (30 mg, 0.070 mmol) in 4.0 mL of dry Et_2O were added Zn/Ag couple (freshly prepared from 11 mg of AgOAc and 1.7 g of Zn in 10 mL of HOAc) and 1.0 mL of CH_2I_2 (12.4 mmol).[12] The mixture was heated to 40 °C for 12 h and then 10 mL of Et_2O and 1.5 mL of pyridine were added. The resulting solids were removed by filtration through a pad of Celite. The filtrate was concentrated and the crude product was purified by preparative TLC (2 × 0.25-mm plates, 1:1 EtOAc–hexane), giving 10 mg (32%) of **7a** and 8.6 mg (34%) of **8a**.

Data for 7a: R_f 0.37 (1:1 hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (m, 1 H, THP), 4.25 (dd, 1 H, J = 2.0, 8.5 Hz, H_{10}), 4.19 (br s, 1 H), 4.14 (dd, 1 H, J = 2.3, 8.7 Hz, H_{11}), 3.95 (dd, 1 H, J = 3.0, 4.6 Hz, H_3; overlapping with m, 1 H, THP), 3.73 (AB, 2 H, J = 11 Hz, H_{15}), 3.55 (m, 1 H, THP), 3.51 (d, 1 H, J = 4.6 Hz, H_2), 2.4–2.2 (m, 2 H), 1.9–1.4 (m, 8 H), 1.25 (s, 3 H, H_{16}), 0.89 (m, 1 H, cyclopropane), 0.52 (s overlapping m, 5 H, H_{14} and cyclopropane), 0.00 (m, 1 H, cyclopropane); IR ($CHCl_3$) 3600–3400 (br), 2920, 2870, 1453, 1382, 1347, 1320, 1263, 1158, 1120, 1070, 1050, 1030, 970, 900 cm^{-1}; mass spectrum, m/e 363 (M^+–Br), 359, 357 ($M^+ - C_5H_9O$).

3α-[(Tetrahydropyranyl)oxy]-12,13-methanotrichothec-9-ene-4β,15-diol (8a). To a solution of **7a** (10 mg, 0.022 mmol) in 2 mL of dry THF, 1 mL of dry Et_2O and 0.4 mL of dry EtOH were added seven spatula scoops of freshly prepared Zn/Ag couple.[12] The mixture was heated to 60 °C for 5 h, and then all solvents were removed in vacuo. The residue was suspended in acetone and solids were removed by filtering through a 0.25-in. pad of silica gel overlayered with Celite. The filtrate was evaporated to give 8 mg (100%) of crude **8a**, which was used directly in the next reaction without purification: R_f 0.15 (1:1 hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (br d, 1 H, J = 2.8 Hz), 4.66 (dd, 1 H, J = 2.1 Hz, THP), 4.32 (d, 1 H, J = 3.0 Hz, H_4), 3.97 (dd, 1 H, J = 2.9, 5.2 Hz, H_3, overlapping over m, 1 H, THP), 3.85 (d, 1 H, J = 5.4 Hz, H_{11}), 3.76 (d, 1 H, J = 11.7 Hz, H_{15a}), 3.58 (m, 1 H, THP), 3.50 (d, 1 H, J = 11.6 Hz, H_{15b}), 3.36 (d, 1 H, J = 5.2 Hz, H_2), 2.40 (m, 1 H), 2.1–1.6 (m, 9 H), 1.71 (br s, 3 H, H_{16}), 0.90 (m, 1 H, cyclopropane), 0.80 (s, 3 H, H_{14}), 0.63 (m, 1 H, cyclopropane), 0.52 (m, 1 H, cyclopropane), 0.0 (m, 1 H, cyclopropane).

12,13-Deoxy-12,13-methanoanguidine (4). To a solution of **8a** (8.6 mg, 0.024 mmol) in 1.0 mL of dry pyridine were added 4-DMAP (4 mg, 0.03 mmol) and Ac_2O (0.04 mL, 0.42 mmol.). The mixture was stirred for 12 h at ambient temperature. The solution was then coevaporated with heptane (2 × 50 mL) and the crude product purified by preparative TLC (0.25-mm plate, 1:1 hexane–EtOAc), two elutions) to afford 9 mg (84%) of pure diacetate: R_f 0.78 (1:1 hexane–EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 5.57 (d, 1 H, J = 2.9 Hz, H_4), 5.40 (br d, 1 H, J = 5.3 Hz, H_{10}), 4.72 (br t 1 H, J = 3.1 Hz, THP), 4.29 (d, 1 H, J = 12.2 Hz, H_{15a}), 4.22 (dd, 1 H, J = 3.0, 4.7 Hz, H_3), 4.09 (br d, 1 H, J = 5.4 Hz, H_{11}), 3.79 (m, 1 H, THP), 3.50 (m, 1 H, THP), 3.42 (d, 1 H, J = 4.6 Hz, H_2), 2.40 (m, 2 H), 2.06 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.0–1.5 (m, 8 H), 1.68 (s, 3 H, H_{16}), 0.93 (m, 1 H, cyclopropane), 0.58 (s, 3 H, H_{14}), 0.57 (m, 2 H, cyclopropane), 0.04 (m, 1 H, cyclopropane).

A solution of the above diacetate (9 mg, 0.02 mmol) in 0.4 mL of THF, 0.4 mL of HOAc, and 0.2 mL of H_2O was stirred at 60 °C for 7 days. The mixture was coevaporated with heptane and purified by preparative TLC (two elutions, 1:1 hexane–EtOAc, 1 × 25 mm) to give 5.3 mg (73%) of **4**: mp 150–151 °C; $[\alpha]^{21}_D$ –53° (c 0.35, $CHCl_3$); R_f 0.23 (1:1 hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 (br d, 1 H, J = 5.8 Hz, H_{10}), 5.04 (d, 1 H, J = 3.0 Hz, H_4), 4.12 (d, 1 H, J = 12.5 Hz, H_{15a}), 4.07 (br m, 2 H, H_{11} and H_3), 3.92 (d, 1 H, J = 12.5 Hz, H_{15b}), 3.38 (d, 1 H, J = 5.1 Hz, H_2), 3.04 (br s, OH), 2.45 (ddd, 1 H, J = 6.2, 12.6, 12.6 Hz), 2.12 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.70 (s, 3 H, H_{16}), 0.97 (m, 1 H, cyclopropane), 0.70 (s, 3 H, H_{14}), 0.60 (m, 2 H, cyclopropane), 0.08 (m, 1 H, cyclopropane); IR 3550 (br), 3000, 2958, 2910, 1725, (br), 1435, 1378, 1250–1200 (br), 1140, 1073, 1050, 1030, 973, 962 cm^{-1}; FAB mass spectrum (glycerol-CH_2Cl_2), m/e 365 ($M + H^+$).

12-Epi-3α-[(tetrahydropyranyl)oxy]-10β-bromo-9α,15:12,13-diepoxytrichothecan-4β-ol (12a). To a solution of **9a** (47 mg, 0.089 mmol, dried before use by coevaporation with toluene) in 2 mL of dry THF at –10 °C was added a solution of $Me_2S{=}CH_2$ in THF (0.1 M, 3.62 mmol, prepared from 0.62 mmol

of freshly recrystallized and dried $Me_3S^+I^-$, and 0.62 mmol of *n*-BuLi in 6.2 mL of THF at −78 °C). The reaction was stirred at 0–5 °C for 3 h and then the THF was evaporated and the residue partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was extracted with EtOAc (1 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to give 63 mg of crude product. This material was purified by preparative TLC (0.5-mm silica gel plate, 9:1 hexane–EtOAc, two elutions), giving 54 mg of an inseparable 3:1 mixture (^1H NMR analysis) of epoxide **10a** and the methylthio adduct **11a** (R_f 0.29, 9:1 hexane–EtOAc). A portion of the above mixture (38 mg, 70% of total) was dissolved in 2 mL of dry THF and treated with Bu_4NF (0.08 mL, 0.08 mmol, 1 M in THF) at 0 °C. After 2 h, the reaction was diluted with Et_2O (30 mL) and was washed with brine (1 × 10 mL). The organic phase was dried (Na_2SO_4) and evaporated; the crude mixture (71 mg) was separated by preparative TLC (0.5-mm silica gel plate, three developments with 1:1 hexane-EtOAc) to give 8 mg (25%) of **13a** and 14.1 mg (52%) of **12a**: mp 177–179 °C; $[\alpha]^{22}_D$ − 22.7° (*c* 1.04, $CHCl_3$); R_f 0.16 (1:1 hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3/D_2O$ washed) δ 4.64 (m, 1 H, THP), 4.26 (dd, 1 H, *J* = 1.7, 8.6 Hz, H_{10}), 4.18 (m, 2 H, H_4 and H_{11}), 3.95 (m, 1 H, THP), 1.90 (br m, 1 H, H_3), 3.77 (d, 1 H, *J* = 9 Hz, H_{15a}), 3.69 (dd, 1 H, *J* = 3.1, 9.3 Hz, H_{15b}), 3.58 (m, 1 H, THP), 2.74 (d, 1 H, *J* = 4.2 Hz, H_{13a}), 2.44 (d, 1 H, *J* = 5 H, H_{13b}), 2.38 (m, 1 H), 2.27 (m, 1 H), 1.90–1.5 (m, 8 H), 1.28 (s, 3 H, H_{16}), 0.66 (s, 3 H, H_{14}); IR ($CHCl_3$) 3600 (br), 2950, 2880, 1450, 1380, 1170, 1120, 1050, 1025, 965, 700 (br) cm^{-1}; mass spectrum, *m/e* 359, 361 ($M^+-C_5H_9O$).

Data for **13a**: $[\alpha]^{23}_D$ − 29.8° (*c* 0.67, $CHCl_3$); R_f 0.38 (1:1 hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (m, 1 H, THP), 4.3–4.2 (m, 3 H, H_4, H_{10} and H_{11}), 3.95 (m, 1 H, THP), 3.82 (dd, 1 H, *J* = 3, 5.5 Hz, H_3), 3.73 (br s, 3 H, H_{15} and H_2), 3.60 (m, 1 H, THP), 2.93 (d, 1 H, *J* = 14 Hz, H_{13a}), 2.87 (s, 1 H, OH), 2.79 (d, 1 H, *J* = 14 Hz, H_{13b}), 2.17 (s, 3 H, SMe), 1.9–1.5 (m, 10 H), 1.28 (s, 3 H, H_{16}), 0.86 (s, 3 H, H_{14}); IR ($CHCl_3$) 3550 (br), 2960, 2880, 1450, 1380, 1350, 1200, 1150, 1120, 1060, 1050, 1025 cm^{-1}.

12-Epi-3α-[(tetrahydropyranyl)oxy]-12,13-epoxytrichothec-9-ene-4β,15-diol (14a). To a solution of **12a** (11.0 mg, 0.025 mmol) in 2 mL of dry THF and 0.4 mL of dry EtOH were added six spatula scoops of freshly prepared Zn/Ag couple and 1 mL of dry Et_2O. This mixture was heated to 45 °C for 12 h. Solvents were then evaporated, and the residue was suspended in acetone and filtered through a 0.25-in. pad of silica gel overlayered with Celite. The filtrate was evaporated to give 11 mg of crude product that was purified by TLC (0.25-mm plate, two elutions with 2:1 EtOAc–hexane), giving 8.8 mg (96%) of **14a**: mp 74–75 °C; R_f 0.20 (1:2 hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (br dd, 1 H, *J* = 1.4, 3.4 Hz, H_{10}), 4.71 (m, 1 H, THP), 4.51 (br s, 1 H, H_4), 4.03 (d, 1 H, *J* = 5 Hz, H_{11}), 3.93 (m, 1 H, H_3), 3.76 (d, 1 H, *J* = 12.2 Hz, H_{15a}), 3.70 (d, 1 H, *J* = 4.7 Hz, H_2), 3.58 (d, 1 H, *J* = 12.2 Hz, H_{15b}), 3.5 (s, 1 H, OH), 2.80 (d, 1 H, *J* = 4.6 Hz, H_{13a}), 2.70 (br s, 1 H, OH), 2.39 (d, 1 H, *J* = 4.6 Hz, H_{13b}, overlapping with m, 1 H), 2.1–1.5 (m, 10 H), 1.70 (s, 1 H, H_{16}), 0.95 (s, 3 H, H_{14}); IR ($CHCl_3$) 3600–3400 (br), 2940, 2860, 1450, 1375, 1345, 1200, 1165, 1125, 1070, 1020, 955, 899 cm^{-1}; FAB mass spectrum (glycerol-CH_2Cl_2), *m/e* 367 ($M + H^+$).

12-Epianguidine (5). To a solution of **14a** (12.6 mg, 0.025 mmol) in 1.0 mL of dry pyridine were added 4-DMAP (4 mg, 0033 mmol) and acetic anhydride (0.04 mL, 0.42 mmol). The mixture was stirred for 2.5 h, and then the pyridine was removed by coevaporation with heptane (2 × 50 mL). The residue was dried in vacuo to afford the crude diacetate THP ether (R_f 0.45, 1:1 hexane–EtOAc). This material was dissolved in 0.4 mL of THF, 0.2 mL of H_2O, and 0.4 mL of glacial HOAc and then heated at 50 °C for 7 days. All volatile reaction components were then removed by coevaporation with heptane (3 × 25 mL). The crude product was purified by preparative TLC (0.25-mm silica gel plate, 1:1 hexane–EtOAc, two elutions) to give 4.4 mg of pure 12-epianguidine (**5**, 48% from **14a**): $[\alpha]^{21}_D$−45° (*c*, 0.17, $CHCl_3$); R_f 0.16 (1:1 hexane–EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (m, 1 H, H_{10}), 5.16 (d, 1 H, *J* = 3.0 Hz, H_4), 4.17 (br d, 1 H, *J* = 5.0 Hz, H_{11}), 4.10 (d, 1 H, *J* = 12.0 Hz, H_{15a}), 4.00 (m, 2 H, H_3, H_{15b}), 3.70 (d, 1 H, *J* = 4.9 Hz, H_2), 3.02 (d, 1 H, *J* = 2 Hz, OH), 2.79 (d, 1 H, *J* = 4.7 Hz, H_{13a}), 2.40 (d, 1 H, *J* = 4.7 Hz, H_{13b}), 2.13 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 1.70 (s, 3 H, H_{16}), 0.83 (s, 3 H, H_{14}); IR ($CHCl_3$) 3580 (br), 2960, 2920, 1735 (br), 1445, 1435, 1400, 1370, 1240-1200 (br), 1070, 1030, 960 cm^{-1}; mass spectrum, *m/e* 366 (M^+); high resolution mass spectrum for $C_{19}H_{26}O_7$, calcd 366.1679, found 366.1679 ± 0.0004.

Acknowledgment. This research was supported by the National Institute of Allergy and Infectious Diseases (AI 20779) and the U.S. Army Medical Research and Development Command (Contract DAMD 17-82-C-2235).

Ruthenium-Catalyzed Rearrangements of 15,16-Epoxybeyerane Diterpenes Functionalized at C-14

Andres Garcia-Granados,* Antonio Martinez, and M. Esther Onorato

Departamento de Quimica Organica, Facultad de Ciencias, Universidad de Granada, Spain

Received March 19, 1986

Several rearrangements, catalyzed by ruthenium acetylacetonate, of *ent*-18-acetoxy-15α,16α-epoxybeyeranes with exo- or endo-hydroxyl or exo- or endo-acetoxy groups at C-14 were carried out. In the case of the 14-endo-hydroxy compound, only *ent*-18-acetoxy-14α-hydroxy-(16*R*)-kauran-15-one was isolated. However, the rearrangement of the exo-hydroxy compound gave *ent*-18-acetoxy-14β,15α,16β-trihydroxybeyerane, *ent*-18-acetoxy-14α-hydroxy-(16*S*)-kauran-15-one, *ent*-18-acetoxy-14α,15β-dihydroxykaur-16-ene, and *ent*-18-acetoxy-14α-hydroxy-(16*S*)-atisan-15-one. Under the same conditions the exo-acetoxy compound yielded *ent*-15β,18-diacetoxy-14α-hydroxykaur-16-ene, *ent*-14β,18-diacetoxy-15α,16β-dihydroxybeyerane, and *ent*-15β,18-diacetoxy-14α-hydroxy-(16*S*)-kaur-11-ene. On the other hand, the endo-acetoxy derivative yielded *ent*-18-acetoxy-14α-hydroxy-(16*R*)-kauran-15-one, *ent*-15α,18-diacetoxy-14α-hydroxykaur-16-ene, *ent*-14α,18-diacetoxy-15α,16β-dihydroxybeyerane, *ent*-15α,18-diacetoxy-14α-hydroxy-(16*S*)-kaur-11-ene, and *ent*-14α,18-diacetoxybeyer-9(11),15-diene. The stereochemistry of the rearrangement processes is discussed.

Introduction

A considerable number of papers devoted to the study of rearrangements of the tetracyclic diterpenoids have been published. On some occasions, rearrangements of epoxy compounds were carried out.[1-7] Solvolytic reactions in protic media[8-12] and rearrangements of thiocarbonates[13] have also been reported.

(1) Kapadi, A. H.; Dev, S. *Tetrahedron Lett.* **1965**, *18*, 1255.
(2) Hanson, J. R. *Tetrahedron* **1967**, *23*, 793.

0022-3263/87/1952-0606$01.50/0