Synthesis of 7,7,8-Trideuteriated Trichothecenes

George A. Kraus* and P. J. Thomas

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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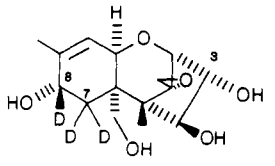
Trideuteriated trichothecenes can be generated from diacetoxyscirpenol by a reaction sequence involving acetylation, epoxide deoxygenation, allylic oxidation, deuterium exchange, epoxidation, and reduction.

The total synthesis of trichothecene mycotoxins has been an extremely active area of research in the past decade.[1] These compounds became attractive synthetic objectives due to both the potent biological activity exhibited by some members of this class and their challenging topology. For example, McLaughlin has reported that T-2 toxin is one of the most potent inhibitors of eukaryotic protein synthesis known.[2] The past decade of research has resulted in total syntheses of diacetoxyscirpenol (DAS), verrucarol, calonectrin, and trichodiene.[1] Mycotoxins such as T-2 toxin and vomitoxin have not yet been synthesized.

More recently, the need for labeled analogues of some of the trichothecene mycotoxins has arisen. While total synthesis could, in principle, supply this need, a more efficient protocol might be to modify a readily available trichothecene such as diacetoxyscirpenol. Indeed, Roush has employed this tactic for the synthesis of radiolabeled trichothecenes.[3] Our efforts have focused on the synthesis of 7,7,8-trideuterio T-2 tetrol **1a** and its tetraacetate. T-2 tetrol is a significant metabolite of T-2 toxin as demonstrated by the elegant studies of Pace and Yoshizawa.[4] The tetraacetate **1b** is also found.[5]

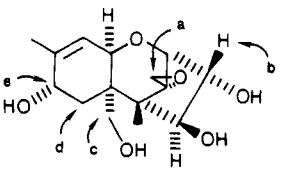


1a
b = tetraacetate

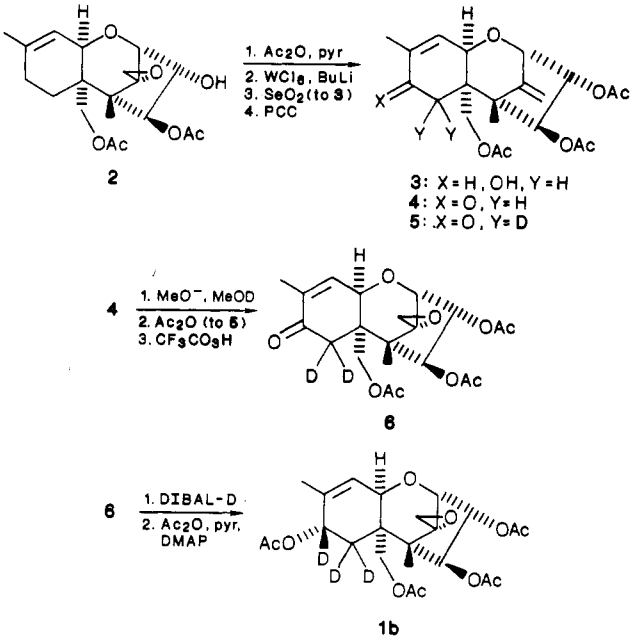
One of the problems that complicates the introduction of a label when devising the synthesis of labeled analogues is the loss of the label by exchange reactions (e.g., OD → OH) or by rapid metabolic oxidation reactions when the analogue is introduced in vivo or in vitro. Additionally, chemical modification at certain sites in a complex natural product poses a real challenge. Therefore, the number of sites at which a label may be directly introduced is limited. Scheme I shows sites for the possible introduction of deuterium atoms into scirpenetetraol.

One of the difficulties that hindered the structure elucidation of the trichothecenes was the propensity of the skeleton to rearrange. The spiro epoxide moiety was involved in several rearrangement reactions. The removal and later reintroduction of this potentially troublesome

Scheme I



Scheme II



unit was a key element of our synthetic strategy. An epoxide deoxygenation reaction using WCl_6 and *n*-butyllithium discovered by Sharpless[6] and developed by Colvin[7] for the trichothecenes enabled us to solve this facet of the synthetic plan.

The synthetic route began with the acetylation[3] of **2** (Scheme II). The Colvin reaction[3] had already been used for the deoxygenation of this molecule and in our hands afforded a 94% yield of the desepoxy compound. On a millimole scale, we found that the THF had to be precooled to −78 °C before the WCl_6 was added in order to obtain a high yield. The selenium dioxide reaction produced a mixture of diastereomeric allylic alcohols **3** in 74% yield after 1 day in hot aqueous dioxane.[8] That these alcohols were indeed diastereomers was confirmed when oxidation of the crude mixture with PCC provided a single enone (**4**) in 74% yield. The structure of this enone was supported by NMR singlets at 4.98 and 5.36 and a broad doublet at 6.55 (1 H each) and by infrared absorptions at 1740 and 1678 cm^{-1}. The stage was now set for the in-

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troduction of two of the three deuterium atoms by deuterium exchange. The exchange was initiated by using CD_3ONa in CD_3OD. This combination not only effected complete deuteriation of **4** but also permitted the reaction to be monitored directly by NMR. Another consideration was that these conditions readily cleaved the acetate groups, preventing any intramolecular reaction of the acetate at C-15 with the enolate of the enone. Interestingly, while monodeuteriation was quite rapid (as evidenced by NMR), the complete formation of the dideuterio compound required almost 1 day. In order to facilitate isolation and purification, the reaction was first neutralized with DCl and then acetylated by using acetic anhydride, pyridine, and DMAP. The triacetate **5** was dideuteriated to at least 98% according to the high resolution mass spectrum. Triacetate **5** reacted with MCPBA very slowly. Fortunately, freshly prepared trifluoroperacetic acid afforded a single monoepoxide (**6**) in 32% yield. From the NMR spectrum, it was clear that the exo methylene group had been selectively epoxidized. The stereochemistry of epoxidation had been anticipated by the earlier work of Roush[9] and Colvin.[10] It was confirmed by comparison with NMR spectra of known 8-oxotrichothecenes.[11] With the epoxide now in place, the enone was chemoselectively reduced to *one* allylic alcohol with DIBAL-D (prepared from i-Bu_2AlCl and LiD).[12] Based on literature precedent,[11] we had expected to obtain two allylic alcohols in which the desired isomer predominated. The literature reduction (with DIBAL-H) was on an enone bearing a free alcohol at C-3. Reduction of the nondeuteriated enone **4** with DIBAL-H also afforded one allylic alcohol, the stereochemistry of which was confirmed to be α by NMR decoupling studies. The product from the DIBAL-D reduction of the epoxy enone is the trideuteriated analogue of the naturally occurring trichothecene neosolaniol.[13] The NMR of the trideuteriated neosolaniol was in close agreement with that of the published NMR spectrum.[11] The crude reduction product was treated with acetic anhydride, pyridine, and DMAP to isolate tetraacetate **1b** that could be hydrolyzed to provide **1a**. The NMR spectrum of **1b** matched closely with the NMR of the nondeuteriated compound.[5]

This direct preparation provides a base from which trideuteriated T-2 toxin and other metabolites of T-2 toxin can be produced. The starting material, diacetoxyscirpenol, is one of the most readily available trichothecenes, making this preparation an economical one. This route could also be adapted for the preparation of tritium-labeled trichothecenes.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Perkin-Elmer 1320 spectrometer. Nuclear magnetic resonance spectra were determined on a Nicolet 300-MHz instrument. High resolution mass spectra were determined on a Kratos mass spectrometer.

Trichotheca-9,12-diene-3α,4β,8α,15-tetrol 3,4,15-Triacetate and Trichotheca-9,12-diene-3α,4β,8β,15-tetrol 3,4,15-Triacetate. A mixture of pure triacetate[3] from the WCl_6 reaction (0.210 g, 0.51 mmol) and selenium dioxide (0.175 g, 1.59 mmol) in dioxane (24 mL) and water (1 mL) was heated for 20 h at 110 °C. The mixture was then cooled, filtered through Celite, washed with brine, and dried over magnesium sulfate. Purification via flash chromatography using 30% ethyl acetate in hexanes afforded 0.162 g (74% yield) of alcohol **3**, as a mixture of epimers. The mixture of alcohols was a viscous liquid.

3: 300-MHz ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.2–1.65 (m, 2 H), 1.82 (br s, 3 H), 2.06 (s, 3 H), 2.08 (s, 3 H), 2.15 (s, 3 H), 3.85–4.05 (m, 2 H), 4.25–4.30 (m, 1 H), 4.48 (d, J = 6 Hz, 1 H), 4.83–4.87 (m, 1 H), 4.91 (s, 1 H), 5.27 (s, 1 H), 5.48–5.55 (m, 1 H), 5.68 (d, J = 4 Hz, 1 H).

3α,4β,15-Triacetoxytrichotheca-9,12-dien-8-one (4). To a suspension of PCC (0.140 g, 0.65 mmol) and NaOAc (0.040 g, 0.48 mmol) in methylene chloride (10 mL) was added alcohol **3** (0.162 g, 0.40 mmol). The reaction was stirred at ambient temperature for 2.5 h, diluted with ether (50 mL), filtered through Celite, and concentrated in vacuo. Purification via flash chromatography using 20% ethyl acetate in hexanes afforded 0.120 g (74% yield) of **4**. The product was an oil.

4: 300-MHz ^1H NMR ($CDCl_3$) δ 0.97 (s, 3 H), 1.82 (br s, 3 H), 2.02 (s, 3 H), 2.09 (s, 3 H), 2.18 (s, 3 H), 2.37 (br d, J = 16 Hz, 1 H), 2.78 (d, J = 16 Hz, 1 H), 4.15 (d, J = 12 Hz), 4.32 (d, J = 12 Hz, 1 H), 4.37–4.42 (m, 1 H), 4.57 (d, J = 5 Hz, 1 H), 4.92–4.96 (m, 1 H), 4.98 (s, 1 H), 5.36 (s, 1 H), 5.72 (d, J = 3 Hz, 1 H), 6.55 (br d, J = 4 Hz); IR ($CDCl_3$ solution) 1740, 1678, 1366, 1230, 1150 cm^{-1}; MS, m/e 108, 180, 244, 287, 304, 406; HRMS, m/e for $C_{21}H_{26}O_8$ calcd 406.16278, found 406.16435.

3α,4β,15-Triacetoxy-7,7-dideuteriotrichotheca-9,12-dien-8-one (5). To a solution of enone **4** (0.060 g, 0.15 mmol) in 0.2 mL of CD_3OD at 0 °C was added 0.5 mL of a solution of CD_3ONa in CD_3OD (prepared by dissolving 21 mg of Na in 1 mL of CD_3OD). The reaction was stirred at 0 °C for 30 min and then allowed to warm to ambient temperature and stir for 20 h. The solution was acidified with DCl (prepared by adding 1 mL of acetyl chloride to 2 mL of CD_3OD) and the solvent was removed in vacuo. Methylene chloride was added to the residue, the solution was cooled to 0 °C, and pyridine (1 mL), acetic anhydride (0.3 mL), and DMAP (3 mg) were added. The solution was stirred at ambient temperature for 10 h. The solvent was then removed and replaced with ethyl acetate, which was washed with dilute HCl, sodium bicarbonate, and then brine. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to afford 0.050 g (83% yield) of **5**.

5: 300-MHz ^1H NMR ($CDCl_3$) δ 0.94 (s, 3 H), 1.82 (br s, 3 H), 2.02 (s, 3 H), 2.09 (s, 3 H), 2.19 (s, 3 H), 4.17 (d, J = 12 Hz, 1 H), 4.31 (d, J = 12 Hz, 1 H), 4.39 (d, J = 6 Hz, 1 H), 4.56 (d, J = 5 Hz, 1 H), 4.92–4.96 (m, 1 H), 4.98 (s, 1 H), 5.36 (s, 1 H), 5.72 (d, J = 3 Hz, 1 H), 6.55 (br d, J = 6 Hz, 1 H); IR ($CHCl_3$ solution) 1740, 1676, 1370, 1230, 1153 cm^{-1}; MS, m/e 108, 140, 246, 288, 306, 408; HRmS, m/e for $C_{21}H_{24}D_2O_8$ calcd 408.17843, found 408.17895.

3α,4β,15-Triacetoxy-7,7-dideuterio-12,13-epoxytrichothec-9-en-8-one (6). To a solution of **5** (0.045 g, 0.11 mmol) in 1 mL of methylene chloride at 0 °C was added 0.2 mL of a solution of trifluoroperacetic acid in methylene chloride (prepared by adding 0.14 mL of 90% hydrogen peroxide to 0.86 mL of trifluoroacetic anhydride in 5 mL of methylene chloride). The solution was stirred at 0 °C for 30 min and then stirred at ambient temperature for 8 h. The solution was diluted with ethyl acetate and washed with $NaHSO_3$ solution, sodium bicarbonate, and then brine. The organic layer was dried and concentrated. The crude product was purified by flash chromatography using 25% ethyl acetate in hexanes. The yield of purified product was 32%.

6: 300-MHz ^1H NMR ($CDCl_3$) δ 0.74 (s, 3 H), 1.85 (br s, 3 H), 2.01 (s, 3 H), 2.13 (s, 3 H), 2.19 (s, 3 H), 2.84 (d, J = 4 Hz, 1 H), 3.10 (d, J = 4 Hz, 1 H), 3.96 (d, J = 5 Hz, 1 H), 4.15 (d, J = 12 Hz), 4.33 (d, J = 12 Hz), 4.39 (d, J = 6 Hz, 1 H), 5.23–5.29 (m, 1 H), 5.73 (d, J = 3 Hz, 1 H), 6.57 (br d, J = 6 Hz, 1 H); IR ($CDCl_3$ solution) 1741, 1679, 1370, 1225 cm^{-1}; MS, m/e 124, 191, 218, 290, 320, 424; HRMS, m/e for $C_{21}H_{24}D_2O_9$ calcd 424.1702, found 424.1688.

7,7-Dideuterio-12,13-epoxytrichothec-9-ene-3α,4β,8α,15-tetrol Tetraacetate (1b). To a solution of enone (0.015 g, 0.035 mmol) in 5 mL of ether at −78 °C under nitrogen was added DIBAL-D (0.15 mL of 0.85 M solution in ether, 0.127 mmol). The

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solution was stirred at −78 °C for 4 h, quenched with 0.3 mL of saturated sodium bicarbonate solution, diluted with ethyl acetate, dried, and concentrated in vacuo. Benzene was added and the solution was again concentrated in vacuo. The residue was dissolved in methylene chloride (10 mL) and cooled to 0 °C. Pyridine (0.5 mL), acetic anhydride (0.15 mL), and DMAP (1 mg) were then added and the solution was allowed to slowly warm to room temperature overnight. The solution was concentrated in vacuo, ether (30 mL) was added, and the organic layer was extracted with copper sulfate solution. The organic layer was dried, concentrated in vacuo, and purified by chromatography using hexanes/ethyl acetate. The purification afforded 9 mg (55% yield).

1b: 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3 H), 1.75 (br s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.11 (s, 3 H), 2.16 (s, 3 H), 2.82 (d, J = 4 Hz, 1 H), 3.07 (d, J = 4 Hz, 1 H), 3.85 (d, J = 5 Hz, 1 H), 4.08–4.18 (m, 2 H), 4.35 (d, J = 12 Hz, 1 H), 5.18–5.22 (m, 1 H), 5.72–5.80 (m, 1 H), 5.82 (d, J = 3 Hz, 1 H); IR ($CDCl_3$ solution) 1740, 1438, 1220 cm^{-1}; MS, m/e 107, 122, 164, 181, 218, 229, 248, 275, 320, 367, 409, 427, 469, 470; HRMS, m/e for $C_{21}H_{23}D_3O_8$ (M^+ − HOAc) calcd 409.18161, found 409.18165.

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Registry No. **1a**, 112841-34-6; **1b**, 112818-29-8; **1b** (3,4,15-triacetate), 112818-32-3; **2**, 2270-40-8; **2** (triacetate), 4297-61-4; **8a-3**, 112818-25-4; **8β-3**, 112818-30-1; **3** (X = H, H; Y = H), 105669-62-3; **4**, 112818-26-5; **5**, 112818-27-6; **5** (triol), 112818-31-2; **6**, 112818-28-7.

Cycloaddition Reactions of Bridgehead Enones

George A. Kraus,* Yung-Son Hon, James Sy, and Jeff Raggon

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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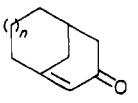
The cycloaddition reactions of bridgehead enones derived in situ from ketones **8**, **9**, and **10** with various dienes at 0 °C afford good yields of adducts. Even 1,1,3-trisubstituted dienes work well. The exclusive exo stereochemistry can be rationalized in terms of a stepwise mechanism involving ionic intermediates.

The synthesis of molecules containing a combination of fused and bridged rings has been a longstanding problem in organic synthesis. Most strategies for a compound such as **1** are linear and involve the construction of a fused tricyclic intermediate such as **2** followed by the appendage of the two-carbon bridge. One advantage of this strategy is that many routes to compounds such as **2** have already been worked out.[1] A clear disadvantage is the linear approach. A quite different strategy would involve the connection of **3** and **4** to produce **1** (Scheme I). This strategy is both convergent and flexible. It requires, however, bond formation to a bridgehead carbon atom, a process that has been relatively little studied.[2]

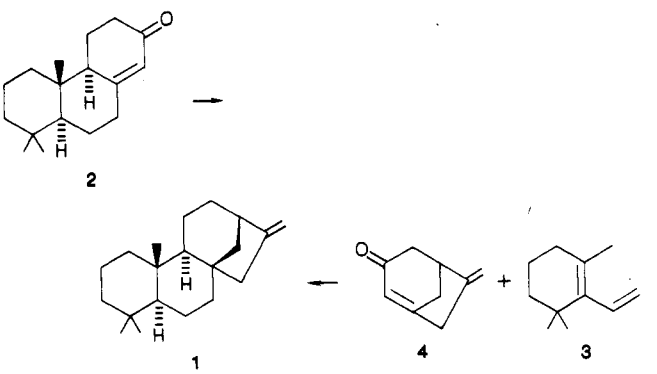
Bridgehead carbon–carbon bond formation is complicated by the high reactivity of bridgehead intermediates. Bridgehead anions, carbocations, and radicals are all more reactive than their acyclic counterparts. Double bonds at a bridgehead are also reactive, but not as reactive as bridgehead enones such as **5**. These bridgehead enones



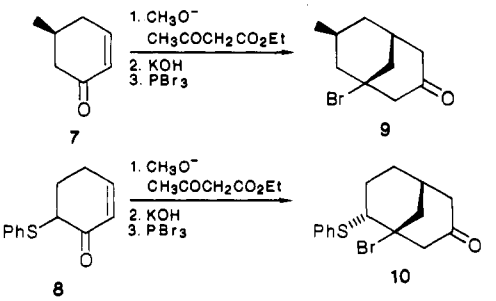
5 (n = 1, 2)

are extremely unstable. Calculations using Allinger's MM2 program indicate that the bridgehead alkene is twisted from planarity by approximately 25°.[3] This twist greatly enhances the inherent electrophilicity of the enone subunit. Alcohols and amines add readily at ambient temperature.[4]

Scheme I



Scheme II



In the absence of nucleophiles, the bridgehead enone dimerizes. Recently, House and Trahanovsky have demonstrated that enone **5** (n = 1) when produced by flash vacuum pyrolysis is stable in solution at −78 °C.[5]

In addition to our own work, the trapping of bridgehead enones with dienes has been accomplished by Magnus and by House.[6] We were the first to demonstrate the regio-

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