interpretation of the "aromatic stability" of benzene.

A detailed treatment of electronic delocalization in conjugated π-systems and their isoelectronic species will follow in a future publication.

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† The laboratory is associated with the CNRS, UA 506.

Philippe C. Hiberty,* Sason S. Shaik*[1]
Jean-Michel Lefour, Gilles Ohanessian
Laboratorie de Chimie Théorique
Bat. 490, Université de Paris-Sud
91405 Orsay Cedex, France†

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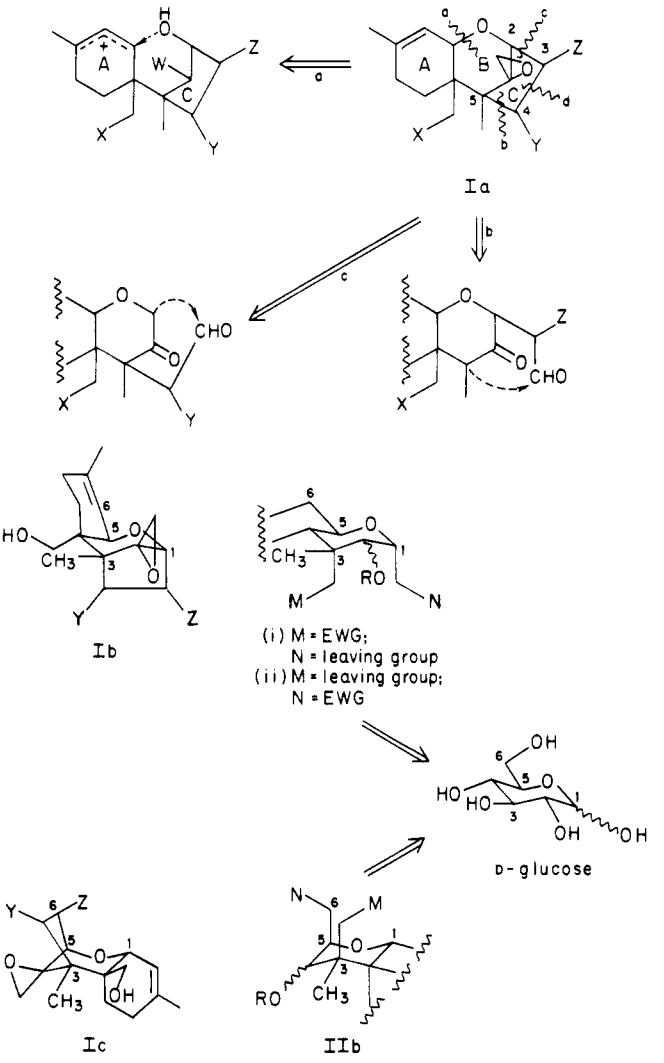
A Route to Optically Active Trichothecane Skeleton by Bisannulation of a Pyranose Derivative[1,2]

Summary: A process has been developed for bisannulation of a pyranose ring to produce the trichothecene skeleton in which (a) the cyclohexeno (A) ring is connected at C1/C2 of the sugar, (b) an Eschenmoser–Claisen rearrangement is applied at C3 to generate an equatorially oriented acetamido unit, and (c) the activated methylene group is used to displace a sulfonate at C6 of the original sugar in a process that forms the C ring.

Sir: Most recent syntheses[4,5b-f] of the trichothecane system Ia have relied upon variations of the biogenetic process[6] (path a, Scheme I) in which the pyran ring is formed by the intramolecular addition of a hydroxyl group on ring C to a ring A electrophilic center.[7] In connection with our longstanding interest in these substances,[8,9] we have been concerned with the development of routes to the optically active sesquiterpene core, and we describe herein some pertinent results.

We were mindful of the seminal studies of the Raphael group which culminated in the first synthesis of a trichothecene, trichodermol.[5a] This achievement, which employed a bond b disconnection (Scheme I) was difficult, and could not be extended to a synthesis of verrucarol.[10] Goldsmith[7d] and Kraus[5g] have utilized a bond c disconnection via an intramolecular aldol condensation, this being particularly convenient since their target molecules were hydroxylated at C3 (Z = OH).

Scheme I



Formation of bond d remained an unexplored possibility, and the conformational representations depicted in Ib and Ic revealed two independent approaches, via the counterparts IIa and IIb, both of which emanate from D-glucose. Theoretically, IIa offered two options, i and ii, (Scheme I), depending on how the activated and leaving groups are positioned. Option ii was rejected since such activated *C*-glycopyranosides undergo ready based-catalyzed $\alpha \rightarrow \beta$ "anomerization" initiated by a retro-Michael reaction.[11] The other possibility, option i, would require the preparation of a precursor bearing a one-carbon, electrophilic substituent at C1 of the pyranose ring in an α-D orientation. The equivalent precursor, IIb, seemed considerably more attractive, since the one-carbon electrophile would already be present in the guise of C6 of glucose.

The ring closure arising from IIb is reminiscent of the formation of a 3,6-anhydro sugar[12] in which the pyranoside ring is also required to adopt the unfavorable $^1C_4$ confor-

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(2) Portions of this work were presented at the 14th International Symposium on the Chemistry of National Products, Poznan, Poland, July, 1984.

(3) Taken from the Ph.D. Thesis of R.T., Duke University, 1985.

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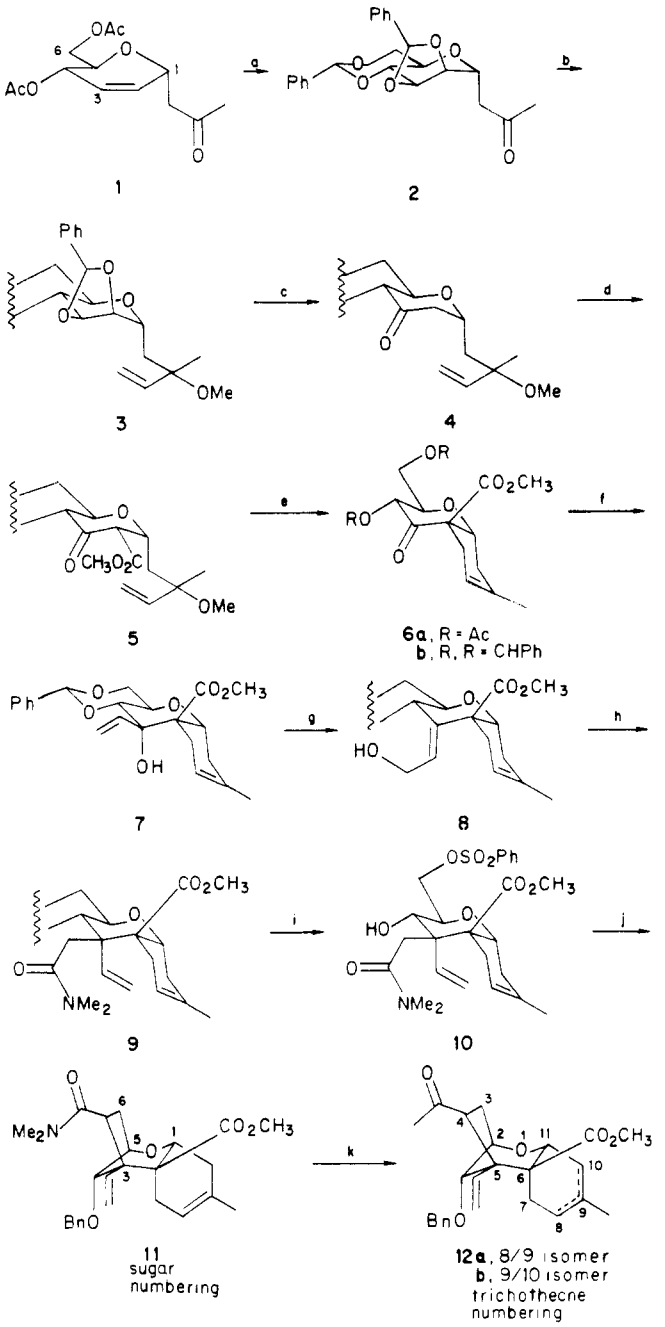
Scheme II[a]



1 2 3 4 5 6a, R = Ac b, R, R = CHPh 7 8 9 10 11 12a, 8/9 isomer b, 9/10 isomer

[a] [a] (i) $KMnO_4$, aqueous EtOH, (ii) $MeOH/H_2O/Et_3N$, (iii) $PhCH(OMe)_2$, CSA (55%); [b] (i) $CH_2CHMgBr$, (ii) NaH, MeI (80%); [c] *n*-BuLi, THF, −40 °C (85%); [d] (i) ref 15, (ii) HCl, (iii) CH_2N_2 (65%); [e] (i) $SnCl_2$, Ac_2O, CH_2Cl_2, (ii) NaOMe, MeOH, (ii) $PhCH(OMe)_2$, CSA (55%); [f] $CH_2CHMgBr$, THF (95%); [g] (i) $SOCl_2$, py, THF, (ii) KOAc, DMF, (iii) NaOMe, MeOH (90%). [h] $CH_3C(OMe)_2NMe_2$, $PhCH_3$, reflux (88%); [i] (i) CSA, MeOH; (ii) $PhSO_2Cl$, py (83%); [j] (i) KN $(Me_3Si)_2$, THF, −78 °C → 25 °C, (ii) $PhCH_2Br$ (75%); [k] CH_3Li, Et_2O, −40 °C (78%).

mation. However, for the case at hand, we reckoned that the ring closure process would be facilitated if the precursor did not have to overcome a substantial anomeric effect.[13] This could be ensured by the presence of a carbon (rather than oxygen) substituent at the anomeric center. This reasoning dictated that the carbocyclic ring A (at the "front" of the sugar) should be developed first and that the sequence for assembling the rings should therefore be B → B–A → C–B–A.

The readily obtained[14] *C*-glycopyranoside **1** underwent hydroxylation exclusively from the β-face, and the product was deesterified. The resulting tetrol was converted directly into the bis(benzylidene) ketone **2**, from which the allyl methyl ether **3** was obtained by routine operations (Scheme II). Chemo- and regiospecific cleavage of the dioxolane ring was effected by treatment with *n*-butyllithium, as prescribed by Rodemeyer.[15] Attempts to carboxylate the intermediate enolate generated in this process led to O-acylation;[16] however, isolation of ketone **4** and subsequent carboxylation by application of Stiles' reagent[17] afforded a carboxylic acid, from which ester **5** was obtained in 65% overall yield.

Attempts to effect ring closure of **5** via Pd(0) catalysis[18] were unavailing. Lewis acids were investigated as alternative reagents, but the expected concomitant debenzylidination seemed to encourage decomposition. It transpired that specific combination of stannic chloride and acetic anhydride led smoothly to the bicyclic diacetate **6a**.

In order to provide the conformational rigidity necessary to ensure stereoselectivity[19] in the upcoming Claisen rearrangement, the benzylidene ring was reinstalled in **6b**. In a modification of our previous protocol,[19] **6b** was reacted with vinylmagnesium bromide, and the resulting alcohol **7** was rearranged and solvolyzed to give the allylic alcohol **8**. Application of the Eschenmoser modification[20] of the Claisen rearrangement afforded amide **9** in 88% yield. After routine preparation of the sulfonate **10** the key step for the bond d disconnection (Scheme I) was readily achieved. Thus treatment of **10** with $KN(SiMe_3)_2$ led to the cyclized material, isolated as a single diastereomer.

Systematic procedures for manipulating the richly functionalized intermediate **12** are currently being examined and some encouraging results have already been obtained.[3] Thus reaction with methyllithium occurred chemoselectively at the amide to give the methyl ketone **12a**. Confirmation of the exo orientation at C4 was gratifying[21]

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(21) (a) For **12a**: $[\alpha]_D$ −177°; ^1H NMR (250 MHz, $CDCl_3$, Me_4Si) δ 1.59 (br s, 3, 9-CH_3), 1.98 (s, 3, $COCH_3$), 1.97–2.07 (m, 2, $H3_{en}$, H10), 2.16 (dt, 1, $J_{3ex,3en}$ = 15 Hz, $J_{2,3ex}$ = $J_{3ex,4}$ = 5.0 Hz, $H3_{ex}$), 2.30 (dd, 1, $J_{7,7'}$ = 18 Hz, $J_{7,8}$ = 6.0 Hz, H7), 2.46 (br d, 1, $J_{10,10'}$ = 18 Hz, H10′), 3.46 (br d, 1, H7′), 3.72 (s, 3, CO_2CH_3), 3.70–3.78 (m, 2, H12, H4), 4.41 (d, 1, *J* = 12 Hz, OC*H*H′Ph), 4.47–4.54 (m, 2, H11, H2), 4.75 (d, 1, OCH*H*′Ph), 5.06 (d, 1, *J* = 17 Hz, CH=C*H*H′), 5.21 (d, 1, *J* = 12 Hz, CH=CH*H*′), 5.32 (br s, 1, H8), 5.91 (dd, 1, C*H*=CH_2), 7.20–7.33 (m, 5, Ph). (b) For **12b**: $[\alpha]_D$ −218°; ^1H NMR (250 MHz, $CDCl_3$, Me_4Si), δ 1.65 (s, 3, 9 CH_3), 1.80–2.10 (m, 4, $H3_{en}$, H7, H8, H8′), 1.96 (s, 3, $COCH_3$), 2.17 (dt, 1, $J_{3en,3ex}$ = 15 Hz, $J_{2,3ex}$ = $J_{3ex,4}$ = 5 Hz, $H3_{ex}$), 2.77 (m, 1, H7), 3.51 (dd, 1, $J_{3en,4}$ = 10 Hz, H4), 3.75 (s, 3, CO_2CH_3), 3.76 (d, 1, $J_{2,12}$ = 3.0 Hz, H12), 4.40 (d, 1, *J* = 12 Hz, OC*H*H′Ph), 4.50 (dd, 1, H2), 4.57 (d, 1, $J_{10,11}$ = 5.0 Hz, H11), 4.77 (d, 1, OCH*H*′Ph), 5.09 (dd, 1, *J* = 18 Hz, 1.5 Hz, CH=C*H*H′), 5.24 (dd, 1, *J* = 11 Hz, 1.5 Hz, CH=CH*H*′), 5.49 (d, 1, H10), 6.02 (dd, 1, C*H*=CH_2), 7.20–7.33 (m, 5, Ph). For trichodermol:[7] H2, δ 3.81 (d, $J_{2,3en}$ = 0.2 Hz, $J_{2,3ex}$ = 5.0 Hz); $H3_{en}$ δ 2.60 (dd, $J_{3en,3ex}$ = 15.5 Hz, $J_{3en,4}$ = 8 Hz); $H3_{ex}$ δ 1.9 (dd, $J_{3ex,4}$ = 3.5 Hz); H4, δ 4.32 (dd)).

since a Baeyer–Villiger reaction can now be used to install the C4 oxygen. A serendipitous result provides a mechanism for the isomerization **12a** → **12b**. Thus treatment of **12a** with ethylene glycol and camphorsulfonic acid led not to a ketal but to a 3:2 mixture of the readily separated isomers **12b** and **12a**, respectively.

The work described herein outlines the second route[5f] to provide the trichothecane system in optically active form. The dense functionalization of **12a** and **12b** should permit the preparation of a wide array of trichothecanoid analogues.

Raymond Tsang,[3] Bert Fraser-Reid*
Paul M. Gross Chemical Laboratories
Duke University
Durham, North Carolina 27706
Received June 14, 1985

Arylation of Diethyl Phosphate by *N*-(Sulfonatooxy)acetanilides: A Model for a Possible in Vivo Reaction of Carcinogenic Metabolites of Aromatic Amides

Summary: *N*-(Sulfonatooxy)acetanilides, which serve as models for the carcinogenic metabolites of aromatic amides, arylate diethyl phosphate in aqueous solution.

Sir: Sulfuric acid esters of *N*-hydroxy-*N*-arylacetamides have been implicated as important carcinogenic metabolites of polycyclic *N*-arylacetamides.[1,2] Almost all the investigations concerned with the in vivo activity of these species have concentrated on their reactions with the purine and pyrimidine bases of DNA and RNA.[1,3] Although a number of alkylating and arylating agents have been shown to react with the phosphate backbone of DNA to form stable triesters or cause chain cleavage,[4] the possibility that the *N*-(sulfonatooxy)-*N*-arylacetamides may undergo a similar reaction has been given scant consideration.[5] Since such a reaction may be important to the in vivo activity of these reagents, we have investigated the reactions of the model compound *N*-(sulfonatooxy)-*p*-chloroacetanilide (**1**)[6] with diethyl phosphate in aqueous solution. Two ring-phosphorylated products, **2** and **3**, have been isolated from these reactions and characterized.

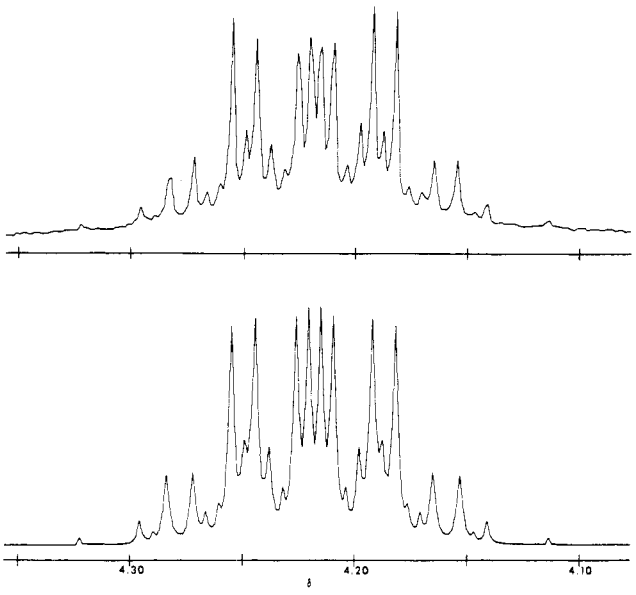

Figure 1. Observed (upper) and calculated (lower) ^{1}H NMR spectra for **2** in the methylene resonance region. Parameters used to generate the calculated spectrum are shown in Table I.

The decomposition of **1** (5×10^{-5} M) at 40 °C in 5% CH_3CN–H_2O containing 0.5 M diethyl phosphate at pH 3.1 follows a first-order pattern when monitored by UV spectroscopic methods.[7] The rate constant for the decomposition of **1** under these conditions is $(8.4 \pm 0.1) \times 10^{-2}$ h^{-1}, which is comparable to the rate constant for its decomposition under similar conditions in the absence of diethyl phosphate.[6] When the decomposition of **1** [$(1.25–2.50) \times 10^{-3}$ M] in the presence of diethyl phosphate is monitored by HPLC (μ-Bondapak C-18 reverse-phase column, 1/1 MeOH/H_2O solvent) two products, which are not observed in the absence of diethyl phosphate, can be detected. These materials can be separated from the other solvolysis products[6] by extraction into CH_2Cl_2, followed by preparative layer chromatography on silical gel (4/1 CH_2Cl_2/EtOAc eluent). The two compounds, which elute as a single band under these conditions, can then be separated from each other by preparative HPLC (Altex Ultrasphere-ODS 10 mm × 25 cm, 1/1 MeOH/H_2O solvent).

All spectral data obtained for these compounds indicate that they are ring-phosphorylated isomers.[8,9] The major

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(5) We are aware of only one report that indicates that *N*-acetoxy-4-acetamidostilbene reacts with the phosphate backbone of RNA, although no triester derivatives were isolated: Scribner, N. K.; Scribner, J. D. *Chem.-Biol. Interact.* **1979**, *26*, 47–55. It is not clear whether strand breaks induced in RNA and DNA by derivatives of *N*-hydroxy-*N*-arylacetamides are caused by triester formation, depurination, or some other mechanism: Vaught, J. B.; Lee, M.-S.; Shayman, M. A.; Thissen, M. R., King, C. M. *Chem.-Biol. Interact.* **1981**, *34*, 109–124. Drinkwater, N. R.; Miller, E. C.; Miller, J. A. *Biochemistry* **1980**, *19*, 5087–5092; Kadlubar, F. F.; Melchior, W. B.; Flammang, T. J.; Springgate, C.; Moss, A. J.; Nagle, W. A. *J. Supramol. Struct. Cell. Biochem., Suppl.* **1981**, *5*, 457.

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(7) The diethyl phosphate was titrated with 1.0 N KOH to achieve a base/acid ratio of ca. 20/1.

(8) **2** was isolated as a white, waxy solid: mp 69.0–70.5 °C; IR (KBr) 3300, 3260, 2950, 1695, 1600, 1530, 1265, 1050 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.4 (1 H, s, br), 8.17 (1 H, d, J = 8.8 Hz), 7.23 (1 H, dd, J_{PH} = 1.35 Hz, J_{HH} = 2.25 Hz), 7.17 (1 H, m, J_{PH} = 1.0 Hz, J_{HH} = 2.25, 8.8 Hz), 4.23 (2 H, m, $^3J_{PH}$ = 8.55 Hz, $^3J_{HH}$ = 7.11 Hz, $^2J_{HH}$ = 10.09 Hz), 4.20 (2 H, m, $^3J_{PH}$ = 8.55 Hz, $^3J_{HH}$ = 7.11 Hz, $^2J_{HH}$ = 10.09 Hz), 2.15 (3 H, s), 1.34 (6 H, td, $^4J_{PH}$ = 1.10 Hz, $^3J_{HH}$ = 7.11 Hz); MS, *m/e* (relative intensity) 321 (M^+, 42.3), 323 ($M + 2^+$, 13.8), 281 (35.0), 279 (100), 253 (13.6), 251 (39.8), 225 (17.4), 223 (51.2); high-resolution MS, *m/e* 321.0532 ($C_{12}H_{17}NO_5P^{35}Cl$ requires 321.0534), 323.0484 ($C_{12}H_{17}NO_5P^{37}Cl$ requires 323.0504).

(9) **3** was isolated as a clear oil: IR (neat) 3270, 3000, 1690, 1600, 1530, 1270, 1030 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.28 (1 H, d, J_{HH} = 9.4 Hz), 7.5 (1 H, s, br), 7.30 (1 H, dd, J_{PH} = 1.1 Hz, J_{HH} = 2.8 Hz), 7.12 (1 H, m, J_{PH} = 0.9 Hz, J_{HH} = 2.8, 9.1 Hz), 4.19 (4 H, quintet, $J_{PH} \simeq J_{HH}$ = 7.1 Hz), 2.19 (3 H, s), 1.34 (6 H, td, J_{PH} = 1.0 Hz, J_{HH} = 7.1 Hz); MS, *m/e* (relative intensity) 321 (M^+, 51.2), 323 ($M + 2^+$, 18.5), 286 (76.3), 281 (34.6), 279 (100), 253 (12.9), 251 (45.4), 225 (19.5), 223 (56.9); high-resolution MS, *m/e* 321.0541 ($C_{12}H_{17}NO_5P^{35}Cl$ requires 321.0534), 323.0504 ($C_{12}H_{17}NO_5P^{37}Cl$ requires 323.0504).

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