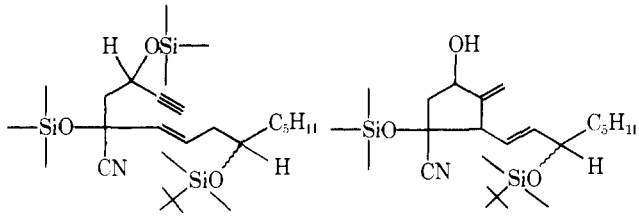
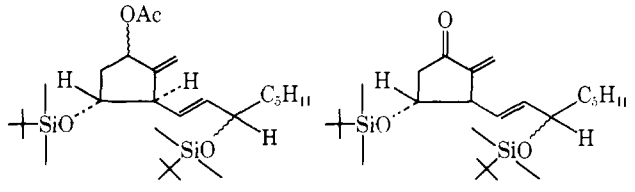
kinetic aldol process is well illustrated by this example which, in spite of the acidity of the acetylene hydrogen, gives acceptable (60–70%) yields of **5**.[7]

Simultaneous cyanohydrin formation and protection of the two free hydroxyls as their trimethylsilyl ethers was achieved conveniently by reaction of **5** with trimethyl silyl cyanide[8] (catalytic amount of potassium cyanide and dicyclohexyl-18-crown-6 in carbon tetrachloride at 75 °C) to yield, in quantitative yield, **6** (mixture of diastereoisomers: δ 5.4–6.5 (m; trans HC=CH), 4.4–4.9 (m; $Me_3SiOCHC{\equiv}C$), 3.65–3.9 (m; $HCOSi\text{-}t\text{-}BuMe_2$) 2.1–2.45 (m; $CH_2C{=}C$, $C{\equiv}CH$), 0.9–1.6 (m; C_5H_{11}, $Me_3SiOC(CN)CH_2$) 0.9 (s; $Si\text{-}C(CH_3)_3$), 0.15 (s; $OSi(CH_3)_3$, $O\,Si\text{-}t\text{-}Bu(CH_3)_2$), 0.05 (s, $OSi\,(CH_3)_3$). Thermal cyclization of **6** was effected remarkably easily (10% in deoxygenated toluene 250 °C, 27 min)[9] to produce, after selective desilylation of the ring secondary hydroxyl[10] (10^{-4} N HCl in tetrahydrofuran, 50 min at room temperature), the methylenecyclopentanol **7**, in 60% yield (*m/e:* (P + 1) − HCN 425).



6 7

Acetylation of the newly liberated hydroxyl (acetic anhydride-pyridine) was followed by treatment with sodium borohydride in methanol and protection of the new hydroxyl as its *tert*-butyl dimethylsilyl ether which gave **8** in 50% yield from **7**. In this molecule, the important trans relationship between the vinyl carbinol chain and the adjacent cyclopentanol hydroxyl (C_{11} and C_{12} of the eventual prostaglandins) has been established stereoselectively by taking advantage of the expected[11] formation of a *trans* 2-alkylcyclopentanol in the reduction of a 2-alkylcyclopentanone with sodium borohydride. The cyclopentanone function required for this operation was generated in situ, under the conditions of the borohydride reduction, from the silylated cyanohydrin which thus allowed the survival of a latent carbonyl function in what would otherwise have been an incompatible environment.

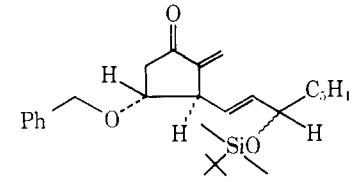


8 9

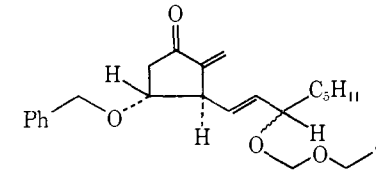
Transformation to the desirable 2-methylenecyclopentanone system and confirmation of the stereoselectivity of the borohydride reduction were carried out by deacetylation (potassium carbonate–aqueous methanol, room temperature) followed by Jones oxidation (−20 → −10 °C). The expected isomer **9** was isolated in 75–80% yield after purification by silica gel chromatography (1:10 ether–pentane) (*m/e:* (P + 1) 467); NMR δ 6.0–6.15 (dd, 1 H, $H_2C{=}C{-}C{=}O$), 5.75 (m, 2 H), 5.1–5.25 (m, 1 H), 3.9–4.35 (m, 2 H), 3.1–3.4 (m, 1 H, $C{=}C{-}CH{-}C{=}C$), 1.95–2.8 (m, 2 H, $O{=}C\text{-}CH_2CHO$-); ir ν 1740, 1642.

The structure and stereochemistry of **9** were corroborated by correlation with the previously synthesized methylene cyclopentanone **11**.[1] This was achieved by protection of the alcohol function of **7** (ethyl vinyl ether), borohydride reduction and benzylation (benzyl iodide on lithium salt) to **10** followed, after desilylation, by introduction of the requisite benzyloxymethyl group on the side chain hydroxyl and, finally, by Jones oxidation (−20 °C). Chromatography on silica gel (1:3 ether–pentane) easily separated the desired **11** from its cis isomer (ratio ~3.5:1). The more rapidly eluted methylene cyclopentanone **11** had an identical NMR spectrum as that of the substance prepared previously.[12]

The ene reaction would seem to be an excellent route to 2,3-disubstituted-4-hydroxycyclopentanones in general, and prostaglandins in particular.



10



11

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

References and Notes

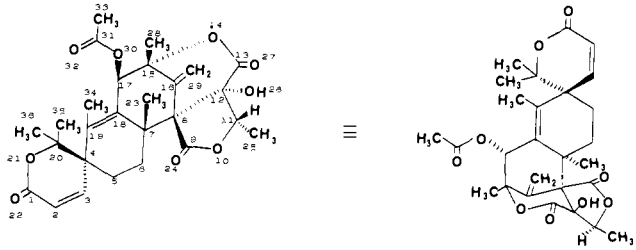
(1) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 4745 (1975).
(2) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 6260 (1975).
(3) The formation of a methylenecyclopentane system by the thermal cyclization of 6-octen-1-yne has been described by W. D. Huntsman and R. P. Hall, *J. Org. Chem.*, **27**, 1988 (1962).
(4) G. Stork and G. A. Kraus, *J. Am. Chem. Soc.*, **98**, 2351 (1976).
(5) Cf. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(6) G. Stork, G. A. Kraus, and G. Garcia, *J. Org. Chem.*, **39**, 3459 (1974).
(7) The spectral properties (NMR, ir) of the compounds reported here were in agreement with the postulated structures. The various compounds were purified by chromatography on silica gel (ratio 10–20:1) with ether–pentane (ratios 1:3, 1:4, 1:7, 1:10, 1:7, and 1:3 for compounds **5**, **7**, **9**, **10**, and **11**, respectively). The mass spectra referred to are chemical ionization spectra.
(8) D. Evans, L. K. Truesdale, and G. L. Carroll, *J. Chem. Soc., Chem. Commun.* 55 (1973).
(9) The sealed tube was previously washed with pyridine.
(10) The slower hydrolysis of the silylated cyanohydrin may reflect either steric hindrance to hydrolysis or a rate-determining oxygen protonation step in this case, or both.
(11) J. B. Umland and B. W. Williams, *J. Org. Chem.*, **21**, 1302 (1956).
(12) This compound is actually a mixture of "C_{15}" epimers (prostaglandin numbering), as are all the other "15"-hydroxy compounds.

Gilbert Stork,* George Kraus
Department of Chemistry, Columbia University
New York, New York 10027
Received June 10, 1976

Austin, a Novel Polyisoprenoid Mycotoxin from *Aspergillus ustus*

Sir:

The discovery of the highly toxic and carcinogenic aflatoxins[1] has generated considerable interest in other toxins produced by fungi contaminating stored foodstuffs. Steyn has reported austamide[2] and substances biogenetically related to it as toxic metabolites from a strain of *Aspergillus ustus*. Vleggaar, Steyn, and Nagel have described austdiol as the major toxin from the same source.[3] We now report the highly unusual structure **1** for the major toxin elaborated by a strain of *A. ustus* found on stored black-eyed peas (*Vigna sinensis*).[4] We propose the trivial name austin for this metabolite.



1

A. ustus was grown in Fernbach flasks (2.8 l.) each containing shredded wheat (100 g) supplemented with Difco mycological broth (pH 4.8) (200 ml), yeast extract (2% by weight), and sucrose (15%). The toxic metabolite was extracted into chloroform and purified by extensive chromatography on silica gel and neutral alumina. The toxicity was monitored by oral dosing of day-old cockerels. Vegetable oil was used as the inert carrier.[5]

The purified toxin was crystallized from chloroform–methanol mixtures (mp 298–300 °C). The molecular formula, deduced from x-ray diffraction, ^{1}H NMR and ^{13}C NMR,[6] was $C_{27}H_{32}O_9$. The largest ion observable in the mass spectrum (electron impact, 16 eV) was 442.163 (calcd for $C_{24}H_{26}O_8$, 442.1627) and indicated loss of C_3H_6O from the parent ion. The ir, uv, ^{1}H NMR, and ^{13}C NMR spectra of austin (**1**) (vide infra) suggested that austin was a novel substance, but no substantial structural features could be deduced. Recourse was provided by a single-crystal, x-ray diffraction experiment.

Austin (**1**), crystallized from methanol–chloroform mixtures as stout needles suitable for x-ray analysis. The crystal symmetry was consistent with the space group $P2_12_12_1$ with a = 7.774 (1), b = 15.092 (2), and c = 21.243 (2) for a calculated density of 1.33 g/cm^3 with Z = 4. One unique octant of data was collected within a 2θ sphere of 114° by use of graphite monochromated Cu radiation (λ 1.5418 Å). Of the 1953 reflections measured, 1864 (95%) were considered to be observed ($I \geq 3\sigma(I)$) after correction for polarization, background, and Lorentz effects. A multiple solution weighted tangent formula approach was used to obtain an initial set of phases.[7] Subsequent electron density syntheses revealed all non-hydrogen atoms.[8] Atom types were assigned on the basis of bond distances and thermal parameters. Full-matrix least-squares refinements of positional and anisotropic thermal parameters for non-hydrogen atoms and positional and isotropic thermal parameters for hydrogen atoms reduced the unweighted R factor to its present value of 0.033. All bond distances and angles are consistent with the formulation given in **1** (esd's of 0.004 Å and 0.2°). There were no abnormally short intermolecular contacts in the crystal or high residual peaks in a final difference synthesis. Figure 1 is a computer generated perspective drawing of austin (**1**).[9] See the paragraph at the end of the paper on supplemental material for additional crystallographic details.

The spectral properties of austin agree with formulation **1**. The infrared spectrum (KBr) displayed prominent bands at 3490 (hydroxyl), 1780 (γ-lactone), 1747, 1740 (acetate and δ-lactone), and 1710 cm^{-1} (α,β-unsaturated δ-lactone). The uv spectrum showed λ_{max}^{EtOH} 243 nm with a molar extinction coefficient of 11 900.

The ^{1}H NMR spectrum ($CDCl_3$) is deceptively simple in appearance because all of the protons are so highly insulated. Six of the methyl groups appear as singlets at δ 1.24 (C(23)H_3), 1.42 (C(28)H_3), 1.58 and 1.66 (C(35)H_3 and C(36)H_3), 1.92 (C(34)H_3), and 2.06 (C(33)H_3). These assignments, based only on chemical shift, are tentative. The remaining methyl, C(25)H_3, appears as a doublet at δ 1.34 (J = 6.8 Hz). It is coupled to the lone proton on C(11) which appeared at δ 4.46 (q, J = 6.8 Hz). A signal for an exchangeable proton at

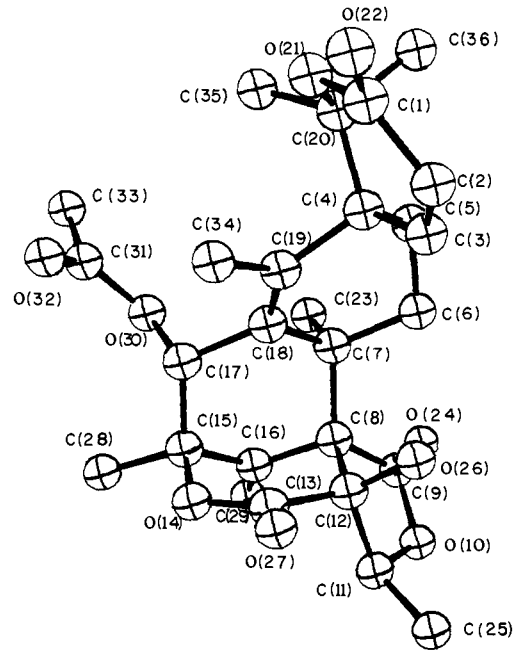
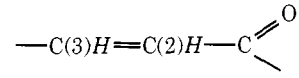


Figure 1. A computer generated perspective drawing of austin (**1**). Hydrogens have been omitted for clarity, and no absolute configuration is implied.

δ 3.64 is attributed to –O(26)H. Downfield there are signals for the exocyclic methylene group, =C(29)H_2, at δ 5.52 and 5.74 (both doublets, J = 1.5 Hz), a singlet at δ 6.05 for >C(17)HOAc, and doublets at δ 6.65 and 6.10 (J = 10 Hz) for



There remain four methylene protons which are not accounted for. Between δ 1.5 and 1.9 there is a 3 H multiplet and at δ 3.24 a 1 H multiplet. The chemical shift of the δ 3.24 signal requires comment. The α hydrogen (pro-R) on C(6) is only 2.12 Å from the hydroxyl oxygen O(26)H so that its signal is shifted downfield.[10]

The proton decoupled ^{13}C NMR spectrum shows all 27 carbons, which could be divided into four groups: (a) carbonyl carbons at 171.0, 170.1, 168.5, 163.8 for C(1), C(9), C(13), and C(31); (b) sp^2 hybridized carbons at 146.6, 143.8, 137.6, 132.7, 120.2, 118.2 for C(2), C(3), C(16), C(18), C(19), C(29); (c) sp^3 hybridized carbons attached to a heteroatom 85.6, 84.2, 80.7, 78.8, 74.8 for C(11), C(12), C(15), C(17), and C(20); and (d) sp^3 hybridized carbons at 62.9, 46.7 42.2, 27.1, 26.7, 26.0, 23.7, 22.5, 20.7, 20.4, 15.5, and 11.5 for C(4), C(5), C(6), C(7), C(8), C(23), C(25), C(28), C(33), C(34), C(35), and C(36). The shifts are relative to Me_4Si and the order of the atoms in each group has no significance.

The largest ion in the mass spectrum indicates the facile loss of CH_3COCH_3 from austin. This could arise from loss of acetone from the α,β-unsaturated δ-lactone moiety.

Austin (**1**) is a novel metabolite with no resemblance to the previously reported austamides or austdiol. The austamides[2] are diketopiperazines of tryptophan and proline with one mevalonate derived unit. Austdiol is an azaphilone,[3,11] presumably derived from a dialkylated pentaketide precursor. Austin (**1**) is most plausibly derived from a polyisoprenoid precursor and may be a sesterterpene or degraded triterpene. The oxidation of the A ring and its rearrangement into a spirofused system has precedence in the fungal metabolite andibenin.[12] We are currently attempting to elucidate the biosynthesis of austin.

The lack of austin (**1**) has hampered complete biological

testing. The only distinctive, gross signs of toxicity in cockerels were a general listlessness followed either by eventual improvement (250 mg/kg, oral) or ataxia and death (375 mg/kg, oral). Austin elicited no effects in etiolated *Triticum* coleoptiles.

Acknowledgments. We thank Dr. Dorothy I. Fennell, NRRL for accession and identification of the fungus. Mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

Supplementary Material Available: Fractional coordinates (Table I), bond distances (Table II), bond angles (Table III), observed and calculated structure factors (Table IV) and ir, ^{1}H NMR, and ^{13}C NMR spectra (17 pages). Ordering information is given on any current masthead page.

References and Notes

(1) G. Büchi and I. D. Rae in "Aflatoxin", L. A. Goldhlatt, Ed., Academic Press, New York, N.Y., 1969, pp 55–75.
(2) P. S. Steyn, *Tetrahedron Lett.*, 3331 (1971).
(3) R. Vleggaar, P. S. Steyn, and D. W. Nagel, *J. Chem. Soc., Perkin Trans. 1*, 45 (1974); P. S. Steyn and R. Vleggaar, *ibid.*, 204 (1976).
(4) The fungus has been accessioned by the NRRL culture collection as NRRL 6017.
(5) J. W. Kirksey and R. J. Cole, *Mycopath. Mycolog. Appl.*, **54**, 291 (1974).
(6) The ^{1}H NMR spectrum revealed 32 protons and the ^{13}C NMR spectrum showed 27 carbons. The preliminary unit cell and density calculations suggested mol wt ~ 500.
(7) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971). We had to rescale all special normalized structure factors (*h0l*, *0kl*, and *hk0*) to ~90% of their observed value to obtain a sensible solution.
(8) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFLS, A Fortran Crystallographic Least Squares Program", U.S. Atomic Energy Commission Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1962.
(9) C. A. Johnson, "ORTEP-II: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations", U.S. Atomic Energy Commission Report ORNL-3794. (2d Revision with Supplemental Instructions), Oak Ridge National Laboratory, Oak Ridge, Tenn., 1970.
(10) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5247 (1965).
(11) G. Büchi, J. D. White, and G. N. Wogan, *J. Am. Chem. Soc.*, **87**, 3484 (1965).
(12) A. W. Dunn, R. A. W. Johnstone, B. Sklarz, and T. J. King, *J. Chem. Soc., Chem. Commun.*, 270 (1976).
(13) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee 1972–1977.

K. K. Chexal, James P. Springer, Jon Clardy* [13]
Ames Laboratory-USERDA and Department of Chemistry
Iowa State University
Ames, Iowa 50011

Richard J. Cole, Jerry W. Kirksey, Joe W. Dorner
National Peanut Research Laboratory-USDA-ARS
Dawson, Georgia 31742

Horace G. Cutler, Billy J. Strawter
USDA-ARS Coastal Plain Experiment Station
Tifton, Georgia 31794
Received June 14, 1976

Thallium in Organic Synthesis. 44. Oxidative Rearrangements via Oxythallation with Thallium(III) Nitrate Supported on Clay[1,2]

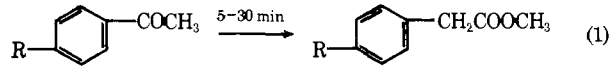
Sir:

Considerable recent use has been made of the concept of utilizing reagents or reactants adsorbed on insoluble inorganic supports for organic synthesis. Silver carbonate deposited on Celite is a highly selective and very effective reagent for the oxidation of alcohols to carbonyl compounds;[3] alcohols, thiols, and acetic acid adsorbed on dehydrated alumina effect various SN2 displacement reactions and epoxide ring openings under very mild conditions;[4] isopropyl alcohol adsorbed on dehydrated alumina can be used for the selective reduction of an aldehyde in the presence of a ketone;[5] and both Collins' reagent supported on Celite,[6] and chromic acid intercalated in graphite,[7] possess distinct advantages (greater selectivity, manipulative convenience) over solutions of the same reagents. Moreover, simple addition of certain supports to a reaction mixture can have a dramatic effect on reaction rate.[8] The effectiveness of the inorganic support in these reactions appears to be due to a combination of factors—an increase in the effective surface area for reaction; the presence of pores which constrain both substrate and reactant and thus lower the entropy of activation of reaction; and a synergism (for displacement reactions) resulting from bringing electrophile and nucleophile into proximity, while at the same time enhancing the nucleophilicity (and basicity) of the latter.[4]

We now report that thallium(III) nitrate (TTN) adsorbed on K-10, a readily available and inexpensive acidic montmorillonite clay,[9] is a remarkably effective reagent for the rapid, selective, high yield, room temperature oxidation of a variety of unsaturated organic substrates.

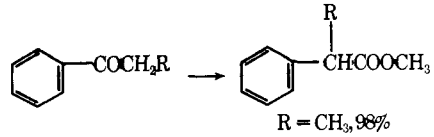
The TTN/K-10 reagent is readily prepared by stirring K-10 with a solution of TTN in a mixture of methanol and trimethyl orthoformate followed by evaporation to dryness.[10] The resulting colorless, free-flowing powder can be stored in well-capped bottles for months without any appreciable loss in activity. All of the oxidations described below were carried out by stirring a suspension of the TTN/K-10 reagent with a solution of the substrate in an inert solvent (heptane, methylene chloride, carbon tetrachloride, toluene, dioxane) until a starch iodide test for thallium(III) was negative. Products were isolated by removal of the spent reagent system by filtration, washing of the filtrate with aqueous sodium bicarbonate, then water, drying, evaporation of the solvent, and recrystallization or distillation of the crude product.

Oxidative rearrangement of alkyl aryl ketones is a particularly smooth reaction. Acetophenones, for instance, are rapidly converted into methyl arylacetates, and yields are excellent (eq 1).[11] Propiophenone and butyrophenone are converted into methyl α-methyl- and α-ethyl phenylacetate, respectively, under the same reaction conditions (eq 2). These results contrast sharply with those obtained using TTN in refluxing acidic methanol; under the latter conditions, for example, propiophenone gives a mixture of methyl α-methylphenylacetate (45%) and α-methoxypropiophenone (32%).[12] Oxidations of benzo-fused cycloalkanones with TTN/K-10 also proceed more cleanly than with TTN in methanol. 1-Tetralone is converted to a mixture of more than ten products by TTN in methanol, but with TTN/K-10 a 1:1 mixture of methyl indane-1-carboxylate and 2-methoxy-1-tetralone is formed (eq 3).



(1)

R = H, 86%
R = CH_3, 84%
R = CH_3O, 92%
R = F, 88% (cf. 44% in CH_3OH)[12]
R = Br, 89% (cf. 35% in CH_3OH)[12]



(2)

R = CH_3, 98%
R = C_2H_5, 98%