measurements (retention volumes 5.0 and 4.4, respectively) and by bioassay. Unlike LTB, synthetic **2** was inactive as a chemotactic agent for neutrophils and also had no effect on pulmonary smooth muscle. Therefore structure **2** is excluded for LTB.[12]

The synthesis of **3** as the racemate was carried out starting from arachidonic acid in a stereochemically controlled manner. The 14,15-epoxide of arachidonic acid, available in 98% yield by internal oxygen transfer from peroxyarachidonic acid,[13] was transformed (in 55% overall yield) into the methyl ester of the 14,15-epoxide of 5-HETE (**11**), UV_{max} (CH_3OH) 235 nm (29,000), essentially as described for the synthesis of 5-HETE methyl ester from arachidonic acid.[14,15]

Photosensitized oxygenation of **11** in methylene chloride using methylene blue as sensitizer at 0–6 °C for 7 h (Westinghouse 150-W sunlamp), followed by addition of triphenylphosphine to the resulting solution of hydroperoxides to effect reduction, afforded a mixture of diastereomers of **12** and of **13** (55% total yield).[16] This mixture was then converted to **3** and its diastereomer by the sequence (1) deoxygenation of the 14,15-epoxide unit to a cis 14,15 double bond by heating with potassium selenocyanate in methanol at 60 °C for 50 h,[11] (2) saponification using lithium hydroxide in aqueous methanol at 23 °C, and (3) acidification to pH 6 with acetic acid and purification by RP-HPLC. In the RP-HPLC separation (Waters Associates C_{18}-μ-Bondapak, 7:3:0.002 methanol/water/acetic acid) the four components were cleanly separated. The more rapidly eluted pair (59.4 and 65.7 min) had UV_{max} 233 nm (ϵ 50 000) (conjugated diene chromophore) and clearly originated from **13**; the last two peaks eluting at 71.4 and 76.8 min had UV_{max} 258, 268, and 278 nm and thus were diastereomers of **3**. Each purified diastereomer of **3** showed UV_{max} (CH_3OH) 258, 268, 278 nm (ϵ 36 800, 46 800, 34 400) and thus was clearly different from LTB which showed each peak of the triplet at 2-nm higher wavelength under carefully standardized conditions (Perkin-Elmer 559-A spectrometer, rigorously calibrated). The racemate eluting at 76.8 min was biologically inactive in both chemotactic and pulmonary smooth muscle assay and also clearly different from LTB by RP-HPLC comparison; it is considered to be the diastereomer of **3**. The compound eluting at 71.4 min is considered likely to be the racemate of **3**. It shows some chemotactic activity toward neutrophils but is biologically inactive in the more sensitive pulmonary muscle assay. Interestingly it shows the same RP-HPLC mobility as LTB. These data taken together indicate that **3** is not a tenable representation of LTB.

In conclusions, the studies reported herein rule out both **2** and **3** as possible structures for LTB and thus support the assignment of formula **1**.[1] Interestingly, **2**[17] and **3**[18] are the only structures for LTB to have appeared previously in the literature.[19]

Supplementary Material Available: Experimental details (25 pages). Ordering information is given on any current masthead page.

(12) We are indebted to Drs. E. J. Goetzl, R. A. Lewis, and K. F. Austen of the Harvard Medical School, I. Otterness of the Chas. Pfizer Co., and P. Sirois of the University of Sherbrooke for the biological measurements which will be described in detail elsewhere.
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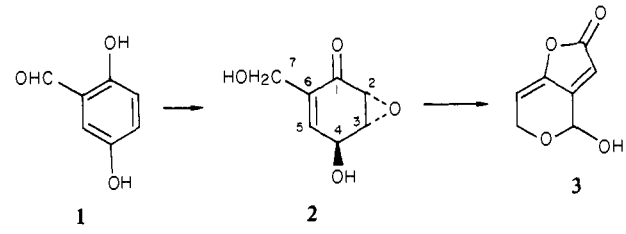
(15) The intermediate **11** was obtained as a mixture (~1:1) of two racemic diastereomers.
(16) The mixture showed UV_{max} (ether) at 233 nm due to **13** and 258, 268, and 278 nm due to **12**. Chromatographic separation was difficult at this stage and consequently was deferred until the last step.
(17) Samuelsson, B.; Hammarström, S. *Prostaglandins* **1980**, *19*, 645.
(18) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643.
(19) This work was assisted financially by the National Science Foundation and the National Institutes of Health.

E. J. Corey,* Paul B. Hopkins, John E. Munroe
Anthony Marfat, Shun-ichi Hashimoto
Department of Chemistry
Harvard University, Cambridge, Massachusetts 02138
Received November 3, 1980

Stereospecific Synthesis of *dl*-Isoepoxydon, a New Metabolite of Importance to the Patulin Pathway

Sir:

More than 30 years after its discovery,[1] the origin of the polyketide patulin **3** and its role in nature remain shrouded in controversy.[2-4] While the principal involvement of acetate-derived intermediates from 6-methyl salicylate to gentisaldehyde **1** has been firmly established,[5] details surrounding oxidative cleavage



1 2 3

of the aromatic ring late in the biogenesis of **3** are still obscure. During very recent studies with a patulin-negative mutant of *Penicillium urticai*, Sekiguchi and Gaucher identified an unstable new metabolite (UIII) arising from **1** which was named isoepoxydon and shown to possess structure **2**.[6] Surprisingly, isoepoxydon proved to be an efficient precursor of patulin in strains of *P. urticai* having full postgentisaldehyde biosynthetic capabilities. This remarkable observation thus implicated a complex, multistep transition from **1** to **3** rather than a simple, dioxygenase-mediated cleavage of gentisaldehyde as was long assumed.[5,6]

Amidst growing interest in the family of patulin-related antibiotics[7,8] and mycotoxins,[9] we wish to disclose the first stereocontrolled total synthesis of isoepoxydon in high overall yield. Using synthetic **2**, we have explored the chemistry of isoepoxydon in an effort to explain its perplexing role in the biosynthesis of patulin.

The synthesis of **2** began with 1,4-dihydrobenzoic acid, which was converted to hydroxy lactone **4**.[10] Although the corresponding bicyclic enone **5** underwent retro-Claisen ring fragmentation upon attempted epoxidation (NaOH, H_2O_2), alcohol **4** could be smoothly and stereospecifically oxidized by using *unbuffered* peroxytrifluoroacetic acid ($ClCH_2CH_2Cl$, reflux, 92%) to afford epoxide **6** (mp 130.5–131 °C) (Scheme I).[11] Silylation of the free hydroxyl in **6** gave ether **7** [91%, mp 74.5–76 °C; NMR ($CDCl_3$) δ 5.08 (d, 1 H, J = 3.8 Hz), 4.75 (s, 1 H), 4.11 (dd, 1 H, J = 4, 2.2 Hz), 3.48 (t, 1 H, J = 4 Hz), 3.18 (dd, 1 H, J = 3.8, 4 Hz), 2.80 (br s, 1 H), 0.10 (s, 9 H)].

When treated with excess lithium borohydride in THF (room temperature, 21 h), the lactone bridge in **7** was selectively reduced, notably without disturbing the epoxide, bromide, or *O*-trimethylsilyl group, and furnished bromo diol **8** in 97% yield [oil, R_f 0.45 in 3:2 ethyl acetate–hexane; mass spectrum (CI) m/e 311, 313 (M + 1)].[11] In acetic anhydride–pyridine, diol **8** formed diacetate **9** (88%), which was useful for characterization purposes,

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(6) Sekiguchi, J.; Gaucher, G. M. *Biochem. J.* **1979**, *182*, 445.
(7) Phyllostine: (a) Sakamura, S.; Ito, J.; Sadai, R. *Agric. Biol. Chem.* **1971**, *35*, 105. (b) Ichihara, A.; Oda, K.; Sakamura, S. *Ibid.* **1971**, *35*, 445.
(8) For a nonstereoselective synthesis of epoxydon, see: Ichihara, A.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1972**, 5105.
(9) These include ascladiol, terreic acid, and terrein; see: Scott, P. M. In "Mycotoxins"; Purchase, I. R. H., Ed.; Elsevier: Amsterdam, 1974; pp 383–403.
(10) Ikota, N.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 351.
(11) Satisfactory spectral data and elemental analysis were obtained for this and all other new compounds.

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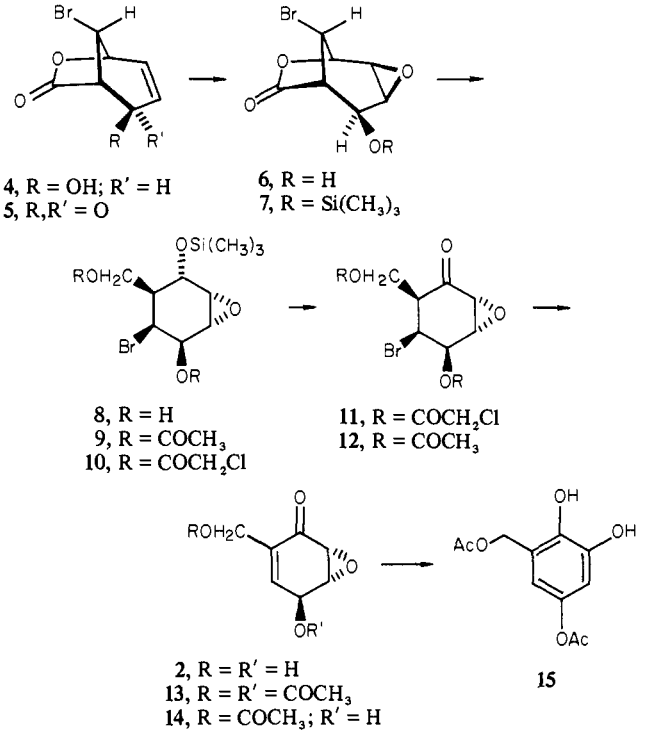
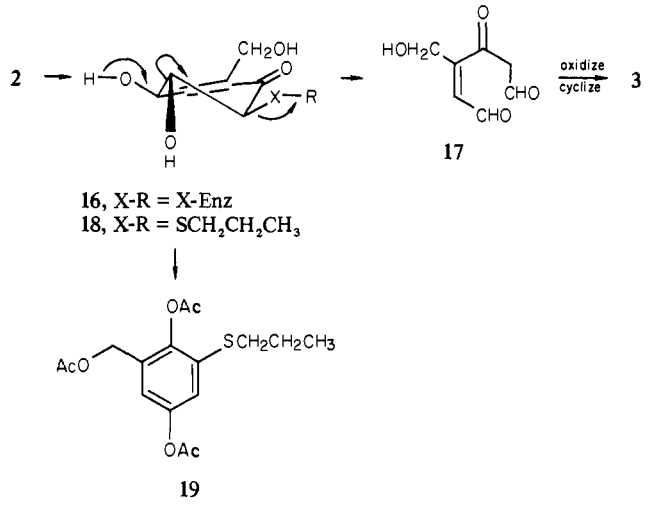
Scheme I





but bis(α-chloroacetyl) derivative **10**, prepared from **8** in 95% yield [$(ClCH_2CO)_2O$, pyr, CH_2Cl_2, -20°C], proved to be superior for the completion of the synthesis. Upon exposure to Jones reagent, ether-diester **10** was hydrolyzed and oxidized in one step to keto diester **11** [98%, NMR ($CDCl_3$) δ 5.43 (d, 1 H, J = 5Hz, CHBr), 4.28, 4.10 (2 s, 4 H, $ClCH_2$); IR λ_{max} (film) 5.68, 5.75 μm]. 5.75 μm]. Usually **11** was not isolated; rather the crude oxidation product was immediately dissolved in a mixture of methanol-powdered $NaHCO_3$ (15 equiv), whereupon alcoholysis of the two protecting groups and elimination of HBr rapidly generated racemic isoepoxydon **2**, mp 79.5-80 °C [(+)-**2** lit.[6] mp 53 °C], in 68% yield (six steps and 52% overall yield from **4**). Spectral comparison of synthetic **2** with the natural product showed them to be identical in every respect.[12]

Like its C-4 epimer epoxydon,[13] **2** proved unstable even to weak bases such as aqueous sodium acetate or pyridine. Since direct acetylation was difficult,[6] racemic isoepoxydon diacetate **13** could best be prepared from **9** by a similar oxidation-elimination sequence **9** → **12** → **13** (60% overall). When stirred with base (Et_3N, room temperature, 20 min, $CHCl_3$), **13** was transformed into diacetoxycatechol **15**, whose structure was unequivocably established by its AB pattern of meta aromatic hydrogens [($CDCl_3$) δ 6.57, 6.77, J = 3 Hz].[13] Synthetic isoepoxydon was reasonably acid stable, even in glacial HOAc at 70 °C. Added p-TsOH had no effect on the epoxide ring and merely catalyzed the formation of primary monoacetate **14** (60%).[11]

The biosynthesis of patulin from isoepoxydon requires an oxidative ring cleavage and is best rationalized by rupture of the C3-C4 bond in **2**. Among possible mechanisms, attack of an enzymic "X-group" nucleophile[14] (RNH_2, RSH) at the more electropositive oxirane carbon[15] would furnish the necessary antiperiplanar relationship in **16** for a 1,3-fragmentation leading to **17**. As a test of this model, isoepoxydon was warmed with propanethiol (4 equiv, HOAc, 70 °C, 1 h) and found to produce α-thioketone **18** in greater than 40% yield after preparative TLC. *No products arising from Michael addition to* **2** *could be detected.* The structure of **18** was strongly supported both by spectroscopic data [UV λ_{max} (EtOH) 235 nm (ϵ 11, 200); IR λ_{max} (film) 2.95, 6.0 μm; NMR (acetone-d_6) δ 6.83 (m, 1 H, vinyl), 3.88 (t, 1 H, J = 5 Hz, C3 H), 3.59 (d, 1 H, J = 5 Hz, CHSPr); m/e (CI) 233 (M + 1, 80%)] and by its conversion (Ac_2O, pyr, 3 h) to aromatic triacetoxy sulfide **19** [88%; NMR ($CDCl_3$) δ 7.10, 7.04 (AB quartet, 2 H, J = 3 Hz, meta aromatics), 5.06 (s, 2 H), 2.92 (t, 2 H, J = 7 Hz, CH_2S), 2.35, 2.30, 2.07 (3 s, 9 H), 1.67 (sextet, 2 H, J = 7 Hz), 1.01 (t, 3 H, J = 7 Hz); IR λ_{max} (film) 5.68, 5.73 μm; m/e (CI) 341 (M + 1, 28%)]. Additional experiments to probe this hypothesis further are planned.

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David Teh-Wei Chou, Bruce Ganem*[16]
Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, New York 14853

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(12) An authentic sample of (+)-isoepoxydon was not available for side-by-side TLC comparisons; however, TLC characteristics in two different solvent systems agreed well with the published data for **2**.
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(16) Fellow of the A. P. Sloan Foundation, 1978-1982; recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1978-1983.

Taft σ^* Values of Alkyl Groups: An Artifact

Sir:

The Taft equation provides a useful quantitative empirical summary of steric effects and polar effects on rates and equilibria of aliphatic compounds.[1-3] Equation 1 is the older form based on the obsolete $\sigma^*\rho^*$ constants and eq 2 is the more modern form.

$$\log k = a + \rho^*\sigma^* + \delta E_s \quad (1)$$

$$\log k = a + \rho_I\sigma_I + \rho_s E_s \quad (2)$$

The σ_I constants use σ_I = 0 for H and are now based on a wide range of reactions.[2,4-7] For strongly polar substituents such as

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