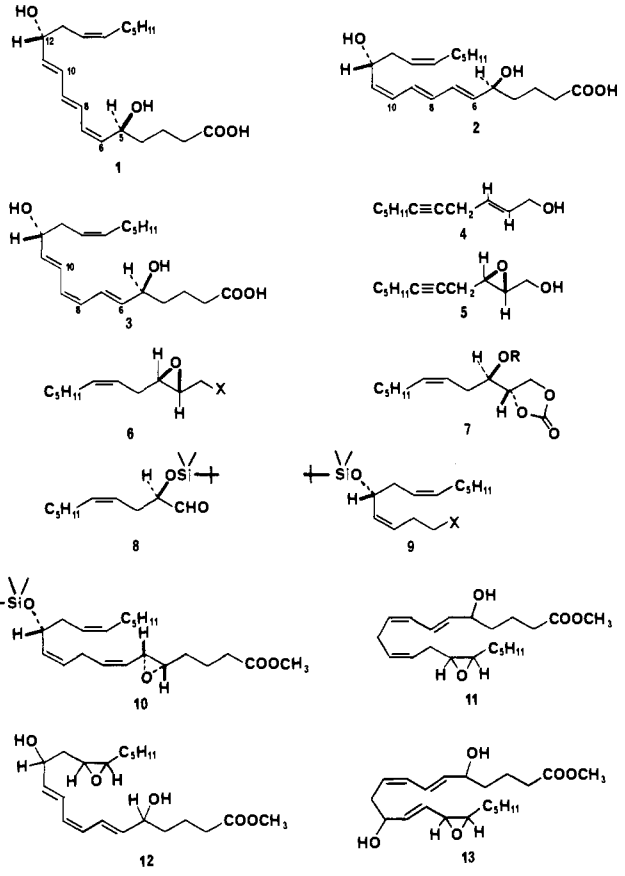
Total Synthesis of 6-Trans,10-cis and (±)-6-Trans,8-cis Isomers of Leukotriene B

Sir:

In the foregoing communication the total synthesis of 5-(*S*), 12-(*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid (**1**) and its identity with native leukotriene B (LTB) are reported.[1]



The limited supply of native LTB (microgram amounts), the paucity of physical or chemical data on this substance, the possibility that the "LTB" so far obtained might in fact be a mixture of stereoisomers, and the appreciation of the role of LTB in various inflammatory diseases[2] all dictated that the synthesis of the 6-trans,10-cis isomer of LTB (**2**) and the 6-trans,8-cis isomer of LTB (**3**) be undertaken along with a careful physical and biological comparison of these substances with native LTB. Such a study is obviously a prerequisite to a definitive assignment of detailed structure of LTB. We describe here the processes used for the synthesis of **2** and **3**, which proved, in the event, to be different from naturally derived LTB.

The synthesis of **2** was accomplished in an unambiguous and stereospecific way via intermediates **4**–**10** without need for optical resolution. Reduction of 2,5-undecadiyn-1-ol[3] by lithium aluminum hydride in ether at 23 °C as elsewhere reported afforded cleanly the trans allylic alcohol **4**.[4] Oxidation of **4** admixed with 1.05 equiv of titanium tetraisopropoxide and 1.10 equiv of the dimethyl ester of (*S*,*S*)-(−)-tartaric acid in methylene chloride (0.15 M concentration of **4**) at −20 °C followed by 3.3 equiv of anhydrous *tert*-butyl hydroperoxide (5 M solution in 1,2-dichloroethane) for 24 h at −20 °C[5] afforded after isolation the acetylenic epoxy alcohol **5**, $[\alpha]^{20}_D$ +10.7° (*c* 0.6, $CHCl_3$), which could be reduced by hydrogen (1 atm) over Lindlar catalyst (deactivated by triethylamine) in tetrahydrofuran (THF) at 25 °C to the corresponding *cis*-olefin **6**, X = OH, $[\alpha]_D^{20}$ +17.9° (*c* 2.0, $CHCl_3$) (75% overall from **4**),[6] and thence converted to the phenyl urethane **6**, X = $OCONHC_6H_5$ (1.1 equiv of phenylisocyanate in methylene chloride containing 10% triethylamine at 25 °C for 12 h, 95% yield). Exposure of this phenyl urethane to 1:3 5% aqueous perchloric acid/acetonitrile at 25 °C for 1.5 h provided the hydroxy carbonate **7**, R = H (75% yield after chromatographic purification on silica gel column), IR_{max} ($CHCl_3$), 1800 cm^{-1} which was treated with 2 equiv of *tert*-butyldimethylsilyl chloride and 5 equiv of imidazole in dimethylformamide at 60 °C for 20 h to give cleanly the silylated carbonate **7**, R = Si-$(CH_3)_2$-*t*-C_4H_9. Reductive cleavage of the carbonate function (1.0 equiv of lithium aluminum hydride in ether at −25 °C for 10 min) and chromatographic purification gave a 1,2-glycol (80% from **7**, R = H) which upon oxidative glycol cleavage by using lead tetraacetate and powdered potassium carbonate in methylene chloride at −20 °C for 1 h produced the aldehyde **8** in 95% yield.[7] Wittig reaction of **8** with 1.5 equiv of the ylide prepared from the 2-methoxy-2-propyl ether of (3-hydroxypropyl)triphenylphosphonium bromide[8] (using *n*-butyllithium in THF at −20 °C under argon) in a 10:1 mixture of THF–hexamethylphosphoric triamide (HMPA) at −78 °C for 30 min and from −78 to 0 °C for over 60 min afforded, after addition of pH 4 buffer and stirring at 25 °C for 24 h (to cleave the protecting group) and extractive isolation and chromatography on a silica gel column, 84% of the cis olefinic alcohol **9**, X = OH (none of the trans isomer could be detected in the crude reaction product). This cis alcohol was converted via the corresponding tosylate and iodide into the phosphonium salt **9**, X = $PPh_3^+I^-$ (2 equiv of triphenylphosphine in acetonitrile at 60 °C for 21 h, 83% overall), mp 124–126 °C.[9]

Conversion of the phosphonium salt **9**, X = $PPh_3^+I^-$, to the corresponding ylide (1 equiv of *n*-butyllithium in THF at −78 °C for 1 h under argon), followed by reaction with 1 equiv of methyl 5-(*S*),6-(*S*)-oxido-7-oxoheptanoate[5b,10] at −78 °C for 1 h and from −78 to 0 °C for 1 h, afforded after chromatographic purification on silica gel 60% of the epoxy triene **10** which was converted to **2** in 70% overall yield by a three-step sequence: (1) saponification using excess lithium hydroxide in 4:1 dimethoxyethane/water at 23 °C for 3.5 h, (2) epoxide → allylic alcohol isomerization using 5 equiv of the bromomagnesium derivative of isopropylcyclohexylamine[11] in THF under argon at −20 °C for 30 min, 0 °C for 3 h, and 25 °C for 30 min, and (3) desilylation using excess tetra-*n*-butylammonium fluoride in THF at 25 °C for 4.5 h. Only a single isomeric product could be detected by careful reversed phase high preformance liquid chromatography (RP-HPLC) using a very high selectivity column (dimethyloctadecylsilyl bonded to Waters Associates μ-Porasil) with 3:1 methanol/water containing 0.01% acetic acid as the mobile phase. The known tendency of the epoxide allylic alcohol isomerization to afforded trans double bonds (cf. ref 11 and literature cited therein) and the stereospecificity observed in the isomerization of **10** clearly indicate the stereochemistry expressed in **2**. Synthetic **2** showed ultraviolet absorption essentially identical with synthetic LTB (**1**) (or native LTB), i.e., UV_{max} (CH_3OH) at 260, 269.5 and 280.5 nm. However, LTB (**1**) and **2** were clearly distinguished by RP-HPLC

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(4) Corey, E. J.; Marfat, A.; Goto, G. *J. Am. Chem. Soc.* **1980**, *102*, 6607.
(5) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. See also: (b) Corey, E. J.; Hashimoto, S.; Barton, A. E. *Ibid.*, submitted for publication.
(6) Satisfactory spectroscopic data were obtained for each intermediate by using purified chromatographically homogeneous samples.
(7) Reaction of **7**, X = $Si(CH_3)_2$-*t*-C_4H_9, with aqueous base caused not only carbonate cleavage but silyl migration as well to give a mixture of products.
(8) This phosphonium salt (mp 154–157 °C dec) was prepared by dropwise addition of a solution of (3-hydroxypropyl)triphenylphosphonium bromide in chloroform (0.07 M) for over 10 min to a 25% solution of 4 equiv of 2-methoxypropene in chloroform at −20 °C, stirring at −20 °C for an additional 5 min, addition of excess triethylamine (stabilizer), removal of solvent in vacuo, and washing with dry ether.
(9) Previous experience[5] indicates that this salt contains at least 97% of the enantiomer required for the synthesis of **2**.
(10) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436, 3663.
(11) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.

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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.
(13) Corey, E. J.; Niwa, H.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 1586.
(14) Corey, E. J.; Albright, J. O.; Barton, A. E.; Hasimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 1435.
(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.

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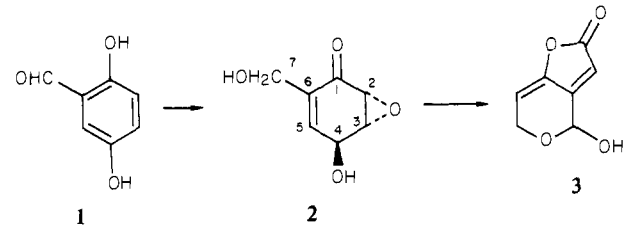
Stereospecific Synthesis of *dl*-Isoepoxydon, a New Metabolite of Importance to the Patulin Pathway

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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(3) Swain, T. *Annu. Rev. Plant Physiol.* **1977**, *28*, 479.
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(6) Sekiguchi, J.; Gaucher, G. M. *Biochem. J.* **1979**, *182*, 445.
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(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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