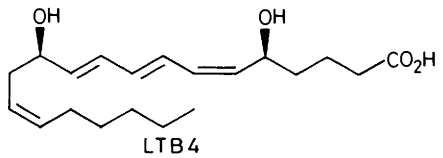
Synthesis of (±)-Benzoleukotriene B_3: a Novel Leukotriene B_4 Analogue

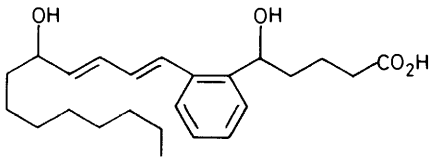
Stevan W. Djurić,* Richard A. Haack, and Stella S. Yu
Gastrointestinal Diseases Research, G. D. Searle and Co., Skokie, IL 60077

As part of a program to identify therapeutically effective leukotriene B_4-antagonists, we have synthesized benzoleukotriene B_3 in which the *Z*-6,7 double bond of LTB_4 has been replaced by a phenyl group. The synthesis relies heavily on palladium(0)-mediated vinylstannane/vinyl halide coupling reactions.

Leukotriene B_4, 5(*S*),12(*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid (LTB_4),[1] is believed to be a significant mediator of a number of inflammatory diseases,[2] a stimulant of aggregation and degranulation of human neutrophils, a promotor of chemotaxis and chemokinesis of leukocytes,[3] and a mediator of lysosomal enzyme release and superoxide generation.[4] As part of our program directed towards the synthesis of potential new therapeutic agents for the treatment of inflammatory bowel diseases, we have examined the possibility that a receptor level antagonist of LTB_4[5] might be a useful therapeutic agent for the treatment of ulcerative colitis.



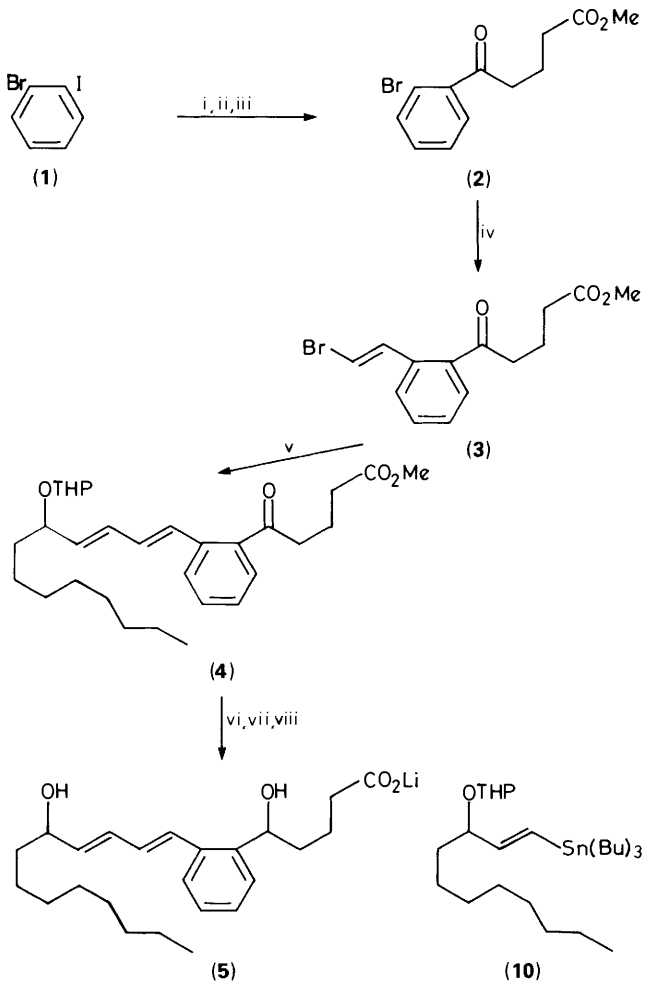
LTB4



BenzoLTB3

Our initial efforts at designing an antagonist based on the structure of the natural ligand focussed upon the introduction of bulky substituents adjacent to potential key binding sites on the LTB_4 framework. To this end, the benzoleukotriene B_3 (BenzoLTB$_3$)† [6] analogue was selected as a primary target. The molecule was efficiently constructed in racemic form as shown in Scheme 1 with a heavy bias towards C–C bond construction *via* organopalladium(0) coupling reactions being adopted throughout the sequence.[7]

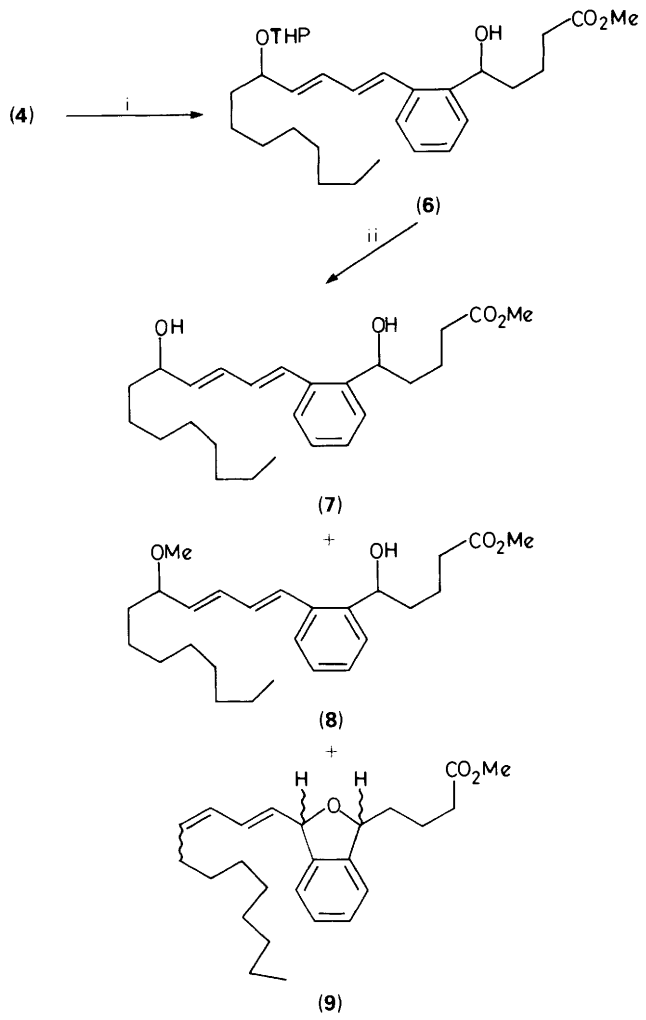
1-Bromo-2-iodobenzene (**1**) was exposed to pent-4-ynoic acid under the conditions of Sonogashira *et al.*[8] and the resultant crude disubstituted alkyne dissolved in concentrated sulphuric acid at 0 °C. Quenching of the reaction mixture with water and work-up of the crude keto acid with ethereal diazomethane afforded the keto ester (**2**) in 96% overall yield after chromatography on silica gel. Coupling of (**2**) with *trans*-1,2-bis(tributylstannyl)ethylene under palladium(0) catalysis followed by treatment with molecular bromine[9] provided the vinyl bromide (**3**) (57%). Compound (**3**) underwent further facile Pd^0 catalysed coupling with the vinylstannane (**10**)‡ under similar conditions [$Pd(PPh_3)_4$, toluene, heat] to give the intermediate (**4**) (54%). Compound (**4**) requires only a minimum of functional group manipulation in order to afford benzoleukotriene B_3. Of note is the extremely efficient construction of



Scheme 1. *Reagents and Conditions:* i, pent-4-ynoic acid Et_2NH, CuI, $Pd(PPh_3)_4$; ii, conc. H_2SO_4, then H_2O; iii, CH_2N_2, Et_2O; iv, *trans*-1,2-bis(tributylstannyl)ethylene, $Pd(PPh_3)_4$, $PhCH_3$, 100 °C, then Br_2 in CCl_4, 0 °C; v, (**10**), $Pd(PPh_3)_4$, PhMe, 100 °C; vi, HOAc, THF, H_2O; vii, $NaBH_4$, EtOH; viii, LiOH, MeOH, H_2O

† Leukotriene B_4 and B_3 have similar biological properties (see Ref. 6). We chose to examine LTB_3 analogues because of potential synthetic simplification.

‡ Prepared in racemic form by addition of Bu_3SnH to the corresponding tetrahydropyranylated acetylenic alcohol *cf.* K. C. Nicolaou, T. Ladduwahetty, I. M. Taffer, and R. E. Zipkin, *Synthesis*, 1986, 344.



Scheme 2. *Reagents:* i, $NaBH_4$, EtOH; ii, PPTS, MeOH

the entire BenzoLTB$_3$ framework in only 5 steps in excellent overall yield (30%). In our initial efforts to complete the synthetic scheme, (**4**) was converted into the mixture of alcohols (**6**) under standard conditions ($NaBH_4$, MeOH, 0 °C, 95%) and then exposed to a solution of pyridinium toluene-*p*-sulphonate (PPTS) in methanol (Scheme 2). Surprisingly, little BenzoLTB$_3$ methyl ester was formed (12%) with the 12-methoxy derivative (**8**) (leukotriene numbering) and the isobenzofurans (*cis*/*trans*, ~1:1) (**9**) being major side products. The synthesis was completed successfully by sequential unmasking of the 12-hydroxy group (HOAc–THF–H_2O, 3:1:1, 25 °C), borohydride reduction of the resultant keto ester ($NaBH_4$, EtOH, 0 °C, 85%), and lithium hydroxide induced saponification of benzo-leukotriene B_3 methyl ester. The racemic mixture (**5**) was obtained in 20% overall yield from 1-bromo-2-iodobenzene.*

Our current efforts are focused on the asymmetric synthesis of the four individual components of benzo LTB$_3$ in order to determine the relative agonist/antagonist profile of each isomer. The initial pharmacological profile of (**5**) proved to be quite interesting, however, as (**5**) was able to inhibit LTB_4 induced neutrophil degranulation (IC_{50} 0.3 μM) but was unable to inhibit LTB_4 induced neutrophil migration in a modified Boyden Chamber at concentrations up to 10^{-5} M.†

In summary, we have completed a concise, stereocontrolled synthesis of a pharmacologically unique leukotriene B_4 receptor antagonist using a route which should prove to be eminently adaptable to the synthesis of other novel leukotriene B_4 analogues.

* All new compounds exhibited analytical data (^1H and ^{13}C n.m.r, i.r. and m.s.) consistent with their assigned structures. The yields reported are for chromatographically pure samples.

† Biological assays are provided by Dr. B. S. Tsai, R. Keith, and D. Villani-Price of the GIDR biochemistry group at Searle.

References

1 R. M. McMillan and S. J. Foster, *Agents Actions*, 1988, **24**, 114.
2 A. W. Ford-Hutchinson, *J. Allergy Clin. Immunol.*, 1984, **74**, 437.
3 A. W. Ford-Hutchinson, M. A. Bray, M. V. Doig, M. E. Shipley, and M. J. H. Smith, *Nature* (*London*), 1980, **286**, 264.
4 J. T. O'Flaherty, M. J. Hammett, T. B. Shewmake, R. L. Wykle, S. H. Love, C. E. McCall, and M. J. Thomas, *Biochem. Biophys. Res. Commun.*, 1981, **103**, 552; E. J. Goetzl and W. Pickett, *J. Immunol.*, 1980, **125**, 1789.
5 Few examples of receptor level antagonists of leukotriene B_4 have been reported in the literature, M. Namiki, Y. Igarashi, K. Sakamoto, T. Nakamura, and Y. Koga, *Biochem. Biophys. Res. Commun.*, 1986, **138**, 540; J. Morris and D. G. Wishka, *Tetrahedron Lett.*, 1988, 143.
6 S. Charleson, J. F. Evans, R. J. Zamboni, Y. Leblanc, B. J. Fitzsimmons, C. Leveille, P. Dupuis, and A. W. Ford-Hutchinson, *Prostaglandins*, 1986, **32**, 503; T. H. Lee, T. Sethi, A. E. G. Crea, W. Peters, J. P. Arm, C. E. Horton, M. J. Walport, and B. W. Spur, *Clin. Science*, 1988, **74**, 467; S. W. Djunć, P. W. Collins, P. H. Jones, R. L. Shone, B. S. Tsai, D. J. Fretland, G. M. Butchko, D. V. Price, R. H. Keith, J. M. Zemaitis, L. Metcalf, and R. F. Bauer, *J. Med. Chem.*, 1989, **32**, 1145.
7 R. F. Heck, 'Palladium Reagents in Organic Synthesis.' Academic Press, 1985, London and New York; J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **28**, 508.
8 K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.
9 R. A. Haack, T. D. Penning, S. W. Djurić, and J. A. Dziuba, *Tetrahedron Lett.*, 1988, 2783.

Received 4*th July* 1989; *Paper* 9/02826I