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TOTAL SYNTHESIS OF A HOMOCHIRAL ARENE-FUSED PROSTACYCLIN ANALOG[1]

C.R. Nevill, Jr.†, T.F. Braish†, J. A. Jakubowski§, P.L. Fuchs*,†
†Department of Chemistry, Purdue University, West Lafayette, IN 47907
§Department of Cardiovascular Pharmacology, Eli Lilly, Indianapolis, IN 46285

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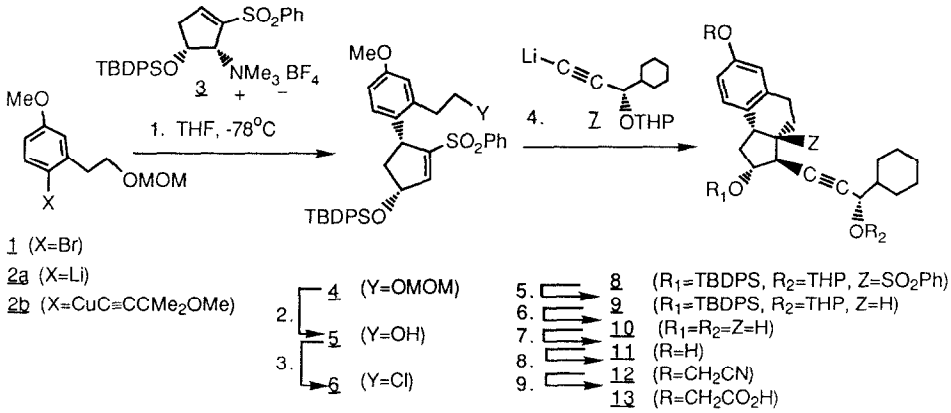
ABSTRACT: Reaction of aryl cuprate reagent 2b with homochiral allyl ammonium salt 3 stereospecificially affords arene 4. Conversion of this intermediate to chloride 6 followed by a conjugate-addition/cyclization protocol generates tricyclic sulfone 8. Refunctionalization of this material provides homochiral prostacyclin analog 13. Compound 13 was inactive as an inhibitor of collagen-induced platelet aggregation having an IC_{50} > 10μM.

In conjunction with our program, we sought to synthesize prostacyclin analog 13 for the purpose of biological evaluation.[1] The arene portion (1) of this target is simply prepared in 74% overall yield from m-methoxyphenylacetic acid.[2] Transmetalation[3] of 1 with two eq. of t-butyllithium in THF at -78°C affords aryllithium 2a which is treated with one eq. of the Corey cuprous acetylide reagent[4] to afford mixed cuprate 2b. Addition of a CH_2Cl_2 solution of homochiral vinyl sulfone 3[5,6] to 2b at -78°C provides the adduct 4[8] in 79% yield as a single stereo- and regioisomer. Deprotection of the MOM ether is accomplished in 99% yield by treatment with p-TsOH in isopropanol at reflux for 10 h. Alcohol 5 is reacted with a preformed reagent prepared from NCS and triphenylphosphine[7] to give chloride 6[8] in 87% yield.

Addition of the lower side chain reagent 7[1] required carefully defined conditions. The optimal conditions involved treatment of 6 with 2.0 eq of 7 in 3% HMPA/ether at 15°C for 3-5 min. Use of more HMPA, longer reaction times, higher temperatures, or THF as co-solvent resulted in base-catalyzed elimination of the homobenzylic sulfone moiety of the tricyclic product 8. Anunulation occurs via intramolecular alkylation of the phenethyl chloride by the initially-formed α-sulfonyl anion. Reductive cleavage[9] of the sulfone provided tricyclic 9 which was reacted without prior purification with p-toluenesulfonic acid and methanol at reflux for 48 h to provide the diol 10[13] in 66% overall yield from 8. Demethylation of the aryl ether of 10 was smoothly accomplished with lithium diphenylphosphide[10] in THF at reflux for 48 h

affording a 95% yield of phenolic diol 11. Treatment of 11 with cesium carbonate[2] in neat chloroacetonitrile[4] at 25°C for 2 h provided nitrile 12[13] in 75% yield. Completion of the synthesis of tetralynaprost 13,[8] was accomplished by hydrolysis of 12 in methanolic sodium hydroxide at reflux for 24 h (78% yield; 25% overall from homochiral ammonium salt 3). Compound 13 was inactive as an inhibitor of platelet aggregation having an IC_{50} >10 μM.[11]



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REFERENCES

[1]Syntheses via vinyl sulfones 31. For an expanded discussion of the synthetic strategy and resulting biological activity, see Hardinger, S. A.; Fuchs, P. L , previous and subsequent papers, this journal For a review of vinyl sulfone chemistry, see Braish, T. F.; Fuchs, P. L. Chem. Rev. **1986**, 86, 903.

[2] Ponton, J.; Helquist, P , Conrad, P C ; Fuchs, P L. J. Org. Chem., **1981**, 46, 118

[3] a) Corey, E J ; Beames, D J. J. Amer Chem Soc **1978**, 94, 7210, b) Seebach, D.; Neumann, H Chem. Ber **1978**, 111, 2755.

[4] Corey, E. J.; Floyd. D.; Lipschutz, B. H. J. Org. Chem. **1978**, 43, 3418.

[5] Hutchinson, D K.; Fuchs, P L. J. Amer. Chem. Soc., **1985**, 107, 6137.

[6] Hutchinson, D K.; Fuchs, P.L. J. Amer. Chem. Soc. **1987**, 109, 4755

[7] Meyers, A. I ; Flisak, J. R ; Aitken, R. A. J. Amer. Chem. Soc. **1987**, 109, 5446.

[8] 6 mp 98-100°C, $[\alpha]^{25}_D$=+51 9° (c 0.310, $CHCl_3$), 10: mp 136-137°C, $[\alpha]^{25}_D$=+99.3 (c 0.281,$CHCl_3$), 12 mp 112-113°C, $[\alpha]^{25}_D$=+50 8° (c 0.386, CH_3OH); 13 mp 87-89°C, dec, $[\alpha]^{25}_D$=+91 5° (c 0 180, CH_3OH)

[9] Trost B M , Arndt, H C ; Strege, P. E., Verhoven, T. R Tet. Lett. **1976**, 3477.

[10] a) Ref 4a; b) Lin, C.-H., Aristoff, P A., Johnson, P D.; McGrath, J P , Timco, J P ; Robert, A J Org Chem **1987**, 52, 5594

[11]This experiment was performed by preincubation of compound 13 with human platelets for 1 min followed by addition of 2μg/ml collagen. Activity was assessed as the concentration required to inhibit collagen-induced platelet aggregation by 50% relative to the vehicle (phosphate-buffered saline) alone