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TRIPLY-CONVERGENT SYNTHESES OF TWO HOMOCHIRAL ARENE-FUSED PROSTACYCLIN ANALOGS RELATED TO U68,215[1]

S. A. Hardingert, 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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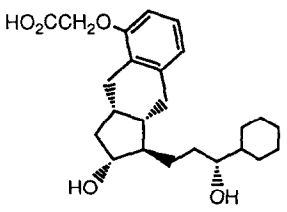
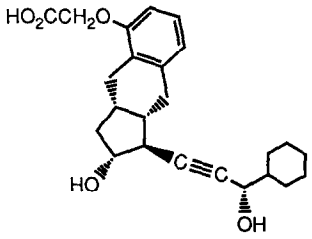
ABSTRACT: The syntheses of arene-fused prostacyclin analogs 2 and 3 are described. Rapid assembly of the tricyclic skeleton is achieved in a triply-convergent manner from oxazoline-bearing homocuprate 6b, homochiral ammonium salt 7 and homochiral propargyl acetylide 12. Compound 2 was a potent inhibitor of collagen-induced platelet aggregation having an IC_{50} = 2.9nM; while 3 exhibited an IC_{50} = 52nM.

In connection with our program to model, synthesize, and test a series of alkyne-bearing "third generation" prostacyclin analogs,[2] we wished to prepare targets 2 and 3 which are closely related to 1, an Upjohn compound that is currently undergoing clinical trials as a cytoprotective agent in human peptic ulcer disease.[3]



1 U68,215



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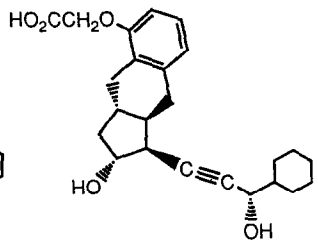
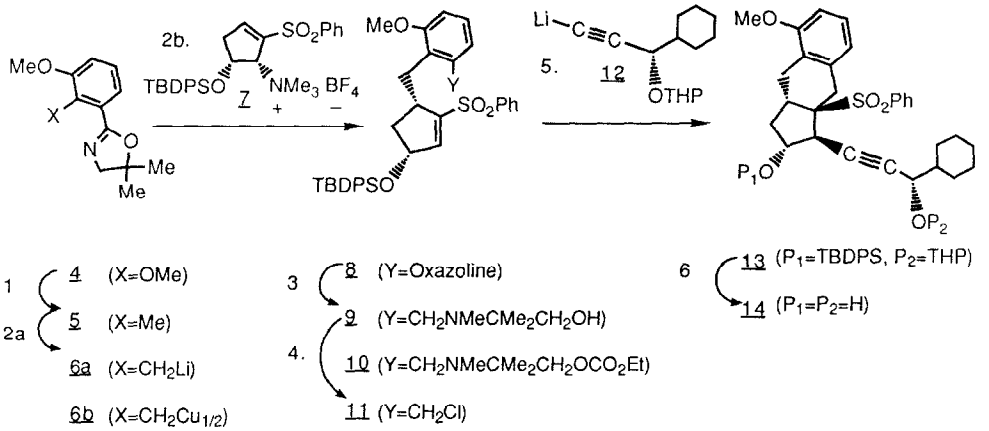


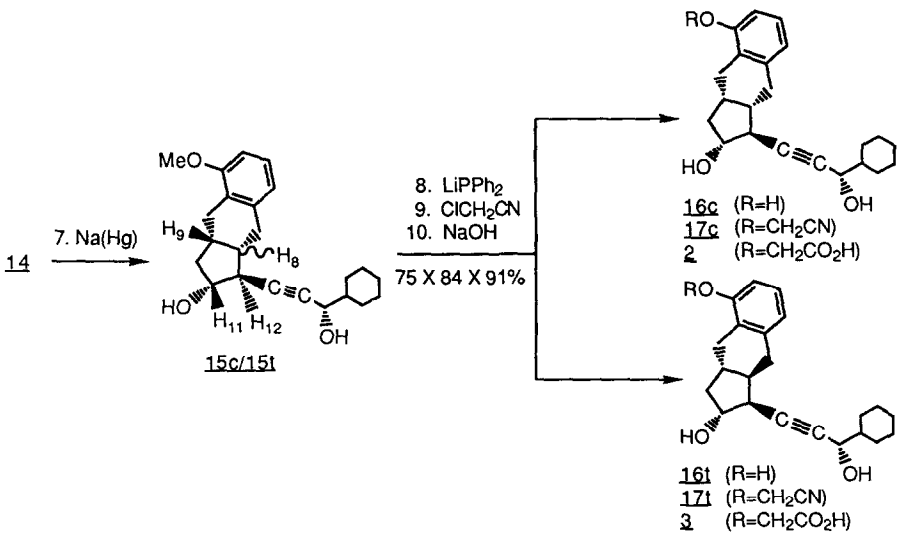
3

The arene reagent 6b for synthesis of 2 and 3 is prepared in two steps from 2,3-dimethoxyphenyl oxazoline 4 (94% overall from 2,3-dimethoxy benzoic acid). Reaction of 4 with methyl Grignard reagent according to the method of Meyers[4] provides 5 in 96% yield. Directed metalation of this material with n-butyllithium affords benzyllithium 6a which is treated in THF at -78°C with 0.5 eq of copper iodide[5] to produce blood-red homocuprate reagent 6b. Cannula transfer of this solution to a THF suspension of homochiral ammonium salt 7[6] gives a 92% yield of adduct 8[7] in addition to 77% recovery of oxazoline 5 (from quenching of the monoaryl copper reagent produced after transfer of the reactive ligand from cuprate 6b).[8] HPLC comparison of 8 with an authentic sample of its trans isomer[9] reveals

that this reaction proceeds with >99% stereospecificity. Treatment of 8 with methyl triflate in methylene chloride followed by sodium cyanoborohydride in acetic acid affords benzylic aminoalcohol 9[7] in 99% yield. This material is directly reacted with 80 equiv. of ethyl chloroformate and 10 equiv. of triethylamine at -78°C followed by warming to room temperature to yield the benzylic chloride 11[7] (88% overall from 8). Control studies show that this reaction proceeds by initial formation of the aminocarbonate 10.[10] Treatment of 11 in THF at 0°C with the homochiral lithium acetylide reagent 12[2] in the presence of 5% HMPA yields tricyclic sulfone 13 as a mixture of THP diastereomers (85%). Heating this material in a 2:1 mixture of methanol and chloroform at reflux for 72 h with 0.2 equiv. of p-toluenesulfonic acid monohydrate effects cleavage of both secondary ether moieties and provides diol 14[7] in 88% yield.



Reductive cleavage of 14 with 6% sodium amalgam[11] produces a 1.9:1 mixture of tricyclic acetylenes 15c/15t in 75% yield which are separated by chromatography on silica. Assignment of the stereochemistry of 15c/15t follows from NMR[12] as well as direct comparison of a derivative of 15c with an authentic sample.[13] Each of the two diols are processed separately to the final products; the sequence involves lithium diphenyl phosphide cleavage of the aryl methyl ether,[1,3] alkylation of the phenolic oxygen with neat chloroacetonitrile[3] in the presence of cesium carbonate,[1] followed by hydrolysis of the α-alkoxy nitrile to the homochiral carboxylic acids 2 and 3.[7] Yields for these steps are given in the scheme. Compound 2 was a potent inhibitor of collagen-induced platelet aggregation having an IC_{50} of 2.9± 0.2 nM; while trans-isomer 3 had an IC_{50} of 52± 11 nM.[14,15]



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[1] Synthesis Via Vinyl Sulfones # 32. For papers 30 and 31 in this series see two previous papers, this journal

[2] See also: following paper, this journal.

[3] a) Aristoff, P.; Johnson, P.; Harrison, A. J. Amer. Chem. Soc., **1985**, 107, 7967; b) Lin, C-H.; Aristoff, P ; Johnson, P.; McGrath, J.; Timko, J.; Robert, A J. Org. Chem., **1987**, 52, 5594.

[4] Meyers, A.I.; Gabel, R., Mihelich, E.D. J. Org. Chem., **1978**, 43, 1372.

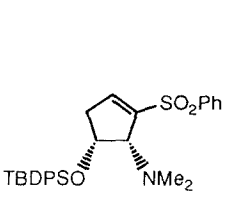
[5] Alpha Ultrapure, used without further purification.

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

[7] 8: mp 172-173°C, $[\alpha]^{25}_D$ = +21.8° (c 1.1, $CHCl_3$); 9: foam; $[\alpha]^{25}_D$ = +6 3° (c 3.1, $CHCl_3$); 11: mp 45.5-47°C $[\alpha]^{25}_D$ = +10.2° (c 4.0, $CHCl_3$); 14: mp 176°C, $[\alpha]^{25}_D$ + 140.7° (c 1.0, $CHCl_3$); 2: mp 173-174°C $[\alpha]^{25}_D$ + 121.9° (c 1.0, MeOH); 3: mp 169-170°C $[\alpha]^{25}_D$ = 18.6° (c 0.67, MeOH).

[8] Homocuprate 6b proved superior to all mixed cuprates examined. That quenched 5 could be recovered and recycled in good yield made the superiority of 6b especially fortuitous.

[9] Authentic trans-8 was prepared by addition of 6a to amine i[6] which afforded amino sulfone ii (74%) Reaction of this material with mCPBA in THF for 24h affords trans-8 (79%), presumably by way of amine oxide iii (For a reference on the synthesis of vinyl sulfones from β-sulfonyl amine oxides see: Drozd, V.N., Sergeichuk, V V Zh. Org. Khim., **1979**, 15, 730; and Donaldson, R E, Ph D. Thesis, Purdue University 1981)



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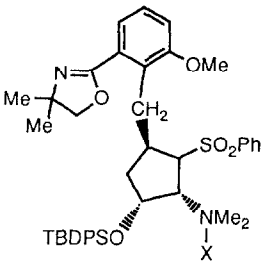
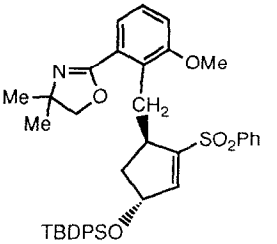


ii (X = :)
iii (X = O)



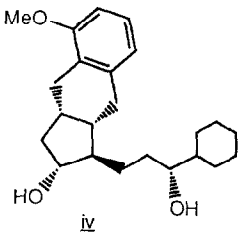
trans-8

[10] For related syntheses of benzyl halides from benzyl amines see: a) Dean, R.T., Rapoport, H. J. Org. Chem., **1978**, 43, 2115, b) Kashdan, D S., Schwartz, J.A ; Rapoport, H. J. Org.Chem., **1982**, 47, 2638

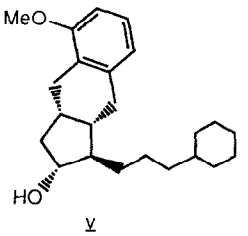
[11] Trost, B.M ; Arndt, H.C.; Strege, P E.; Verhoeven, T.R Tetrahedron Lett., **1976**, 3477.

[12] Compound 15t exhibited $J_{11,12}$=1.6Hz; $J_{8,12}$=6.4Hz; and $J_{8,9}$=12.3Hz. Coupling constants for 15c were not directly observable, but the stereochemistry of 15c was demonstrated on derivative v [13]

[13] Hydrogenation of 15c over 10% Pd/C in ethanol at 40 psi for 24h at 25°C does not produce the tetrahydro compound iv, but rather v, which has undergone hydrogenolysis of the propargylic alcohol as well as reduction of the acetylene [14] Hydrogenation of 2 1 atm, 10% Pd/C in methanol quantitatively affords 1 which is shown to be identical to U68-215.[14]



iv



v

[14] We wish to thank Dr. Paul Aristoff of the Upjohn Company for providing authentic samples of 1, iv, and v

[15] This experiment was performed by preincubation of compound 14 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.