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TRIPLY-CONVERGENT TOTAL SYNTHESIS OF A HOMOCHIRAL BENZOINDANE-FUSED PROSTACYCLIN ANALOG[1]

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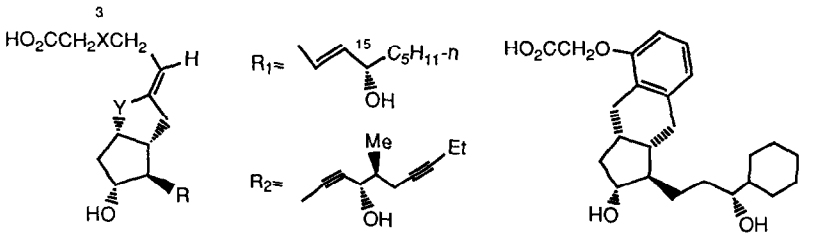
Summary: Benzoindane-fused prostacyclin analog 14 was prepared from homochiral ammonium salt 5 in 7 steps and 35% overall yield. Key steps include addition of "soft" aryllithium reagent 6b to 5 to afford 7; and addition of homochiral acetylide 9 to the vinyl sulfone moiety of chloride 8 (with subsequent in situ cyclization) to afford 10, thereby rapidly assembling the tricyclic framework of 14. Compound 14 was a weak inhibitor of collagen-induced platelet aggregation having an IC_{50} = 2.5μM.

The finding that prostacyclin 1 is the most potent endogenous inhibitor of platelet aggregation has spurred an enormous effort to develop analogs which retain this property but avoid the hydrolytic instability engendered by the enol ether moiety.[2] A major step in this direction was the synthesis of carbacyclin 2 which is approximately 10% as potent as prostacyclin.[2]



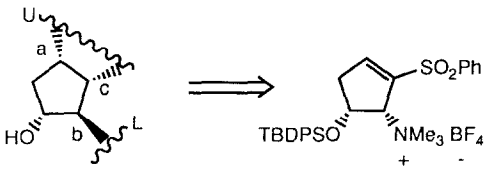
1 (X=CH_2, Y=O, R=R_1)
2 (X=CH_2, Y=CH_2, R=R_1)
3 (X=CH_2, Y=O, R=R_2)

4

Unfortunately, although hydrolytically stable, carbacyclin is subject to enzymatic deactivation by C-15 dehydrogenase at a rate equal to that seen with prostacyclin.[3] An important second locus for metabolic inactivation involves enzymatic oxidation at C-3.[4,5] In

response to these findings, a series of "third generation" analogs, bearing groups designed to provide steric or electronic inhibition of the enzymatic oxidation, have appeared and are currently undergoing clinical evaluation. Among the most promising of these are the 3-oxo carbacyclin analog Schering 96,480 3[4] (treatment of vascular disease) and the arene-fused Upjohn 68,215 4 (a cytoprotective agent for treatment of peptic ulcer disease).[5]

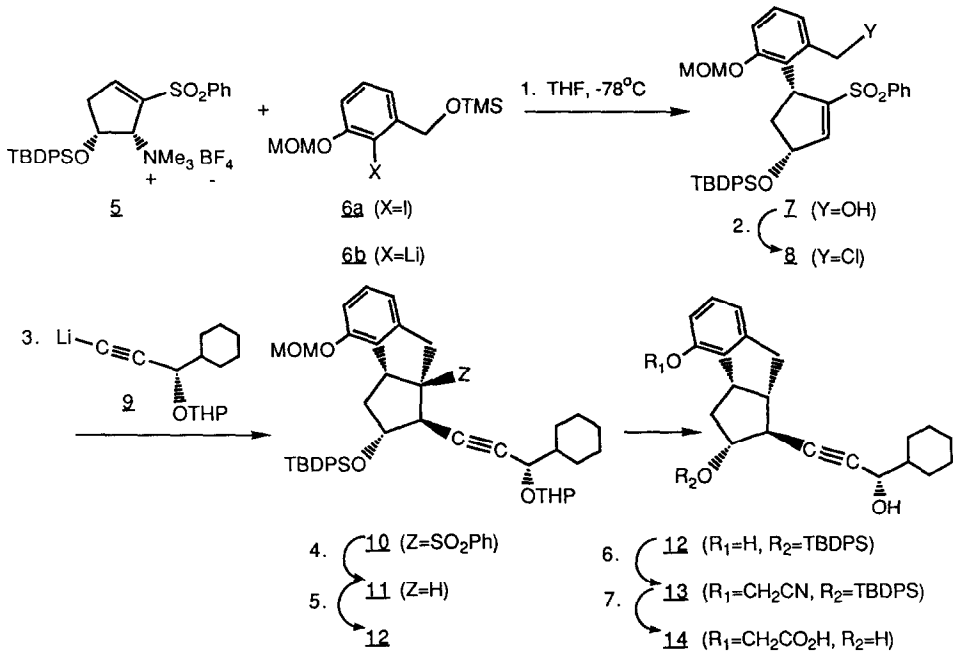
Synthesis of such analogs should be possible from a triply-convergent strategy that utilizes homochiral ammonium salt 5 as a progenitor for the cyclopentane nucleus. Sequential formation of bonds a,b,c would then rapidly affix the necessary "upper" and "lower" appendages, thereby providing a "smorgasbord" approach for the rapid construction of selected targets.[6] Genesis of this concept is found in our efficient total synthesis of d-(+)-carbacyclin 2,[7] a study which provided the impetus for further extension of this strategy



5

Addition of homochiral ammonium salt 5[8] to aryllithium 6b (prepared via transmetalation of the readily available iodide 6a[9]) stereospecifically affords alcohol 7 after mild acidic workup to cleave the benzylic silyl ether. It is worth noting that this (presumably chelated) aryllithium reagent is the first "basic" nucleophile that has been successfully added to homochiral ammonium salt 5.[8] Conversion to chloride 8 required several days using triphenylphosphine and CCl_4 at reflux[10] but was complete within *2 min* simply by substituting p-dimethylaminophenyldiphenylphosphine,[11] providing 8 in 85% overall yield from 5. Following our general protocol for acetylene additions to vinyl sulfones,[12] 8 was added to a THF/HMPA solution of the homochiral acetylenic anion 9[13] which effected addition/cyclization to produce tricyclic sulfone 10 in 77% yield. Desulfonylation of 10 with sodium amalgam[14] in Na_2HPO_4 buffered ethanol at reflux smoothly provides tricyclic 11, which is reacted with isopropanol/p-TsOH·H_2O to effect deprotection of both acetal groups (the THP can easily be removed in the presence of the MOM ether, if desired) affording phenol 12 in 67% yield for the two-step process. Reaction of 12 with chloroacetonitrile under the conditions (acetone, reflux, K_2CO_3) employed in the Upjohn synthesis of 4[5] is slow and low yielding. Phenol 12 is more susceptible to oxygen alkylation in neat chloroacetonitrile using two equivalents of cesium carbonate[15] (the potassium phenolate

appears insoluble in this medium) providing the aryloxy nitrile 13 in 86% yield. Culmination of the synthesis is accomplished by reaction of 13 with NaOH (MeOH/H_2O), conditions which also effect concurrent deprotection of the TBDPS ether (92% yield). The *overall yield* from homochiral ammonium salt 5 for synthesis of "indynaprost[16]" 14 is 35%. Compound 14 was a weak inhibitor of collagen-induced platelet aggregation having an IC_{50} of 2.5± 0.4 μM.[17]



2. p-$Me_2NC_6H_4PPh_2$, CCl_4; 3. THF-1%HMPA, 1.5h 25°C; 4. Na (Hg), Na_2HPO_4, EtOH, Δ 3h
5. i-C_3H_7OH, p-TsOH•H_2O, Δ 17h; 6. $ClCH_2CN$, Cs_2CO_3, 24h 25°C; 7 i. NaOH, MeOH, Δ 24h, ii. 5% HCl.

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[17] 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.