Bioorganic & Medicinal Chemistry Letters, Vol.1, No.11, pp. 649-652, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

TRIPLY-CONVERGENT SYNTHESIS OF A HOMOCHIRAL 3,3-DIMETHYL, 15-CYCLOHEXYL PROSTACYCLIN ANALOG[1]

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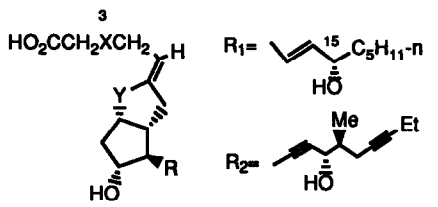
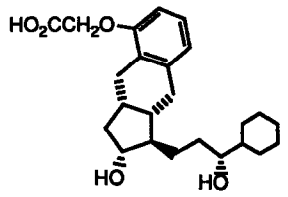
(*Received* 9 *September* 1991)

Abstract: Allylic bromocuprate reagent 13b undergoes synfacial SN2' addition to homochiral allyl ammonium salt 14 to provide vinyl sulfone 15 as a single stereoisomer. Addition of homochiral acetylenic anion 18 to vinyl sulfone 17 smoothly provides the bicyclic sulfone 19 which is further transformed to prostacyclin analog 22. Analog 22 was only a weak inhibitor of platelet aggregation having an IC_{50} of 0.48 μM.

The observation that prostacyclin (PGI_2 1) is the most potent endogenous inhibitor of platelet aggregation has stimulated an intense effort at synthesis of more stable analogs with similar pharmacological properties. Although carbacyclin 2 does not suffer from the hydrolytic instability imparted by the enol ether moiety of 1, its serum half-life is almost exactly that of PGI_2 because of oxidation at C-15 by the enzyme C-15 dehydrogenase, resulting in biologically inactive enones.[2] Second-generation analogs bearing steric encumbrance near C-15 prevent this problem. A second locus of metabolic deactivation is at C-3. Third-generation clinical trial candidates including cicaprost 3[3] and U68,215 4[4] feature replacement of the C-3 carbon with an oxygen atom to avoid this difficulty.





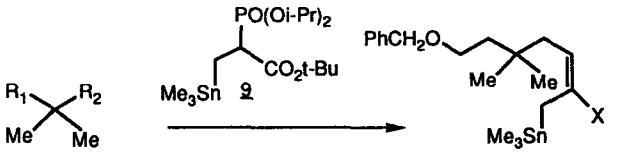
4

1 (X=CH_2, Y=O, R=R_1)

2 (X=Y=CH_2, R=R_1)

3 (X=O, Y=CH_2, R=R_2)

In connection with our own program to synthesize, model, and test a series of third-generation analogs[5], we elected to undertake the synthesis of 22, a 3,3-dimethyl carbacyclin derivative bearing a lower sidechain with probable C-15 dehydrogenase stability. The synthetic approach is an extension of the "trimethylene methane" strategy which we recently used to advantage in our synthesis of *d*-(+)-carbacyclin 2.[6] In this instance, the top sidechain reagent 12Z is prepared from 3,3-dimethyl glutaric acid 5. Reduction of 5 with diborane in THF[7] provides a 95% yield of diol 6 which is monobenzylated to 7 using 1.0 eq of benzyl bromide in THF containing KH and 18-crown-6 (70%). Oxidation of 7 to aldehyde 8 was accomplished in 66% yield using pyridinium chlorochromate and molecular sieves in methylene chloride.[8] Wadsworth-Emmons reaction of 8 with reagent 9[5] provides an inseparable 5:1 mixture of 10Z and its E isomer in 94% yield. This represents a considerable loss of stereospecificity relative to the C-3 unsubstituted aldehyde which yielded a 96:4 mixture of vinyl esters.[5] DIBAL-H reduction of the 10Z/10E mixture yielded an identical mixture of allylic alcohols 11Z/11E (90%) which could be separated at this stage. Protection of the primary alcohol with methoxymethyl chloride[9] proceeds in very high yield to produce the desired allyl stannane 12Z.



5 (R_1=R_2=CH_2CO_2H)

6 (R_1=R_2=CH_2CH_2OH)

7 (R_1=$PhCH_2OCH_2CH_2$, R_2=CH_2CH_2OH)

8 (R_1=$PhCH_2OCH_2CH_2$, R_2=CH_2CHO)

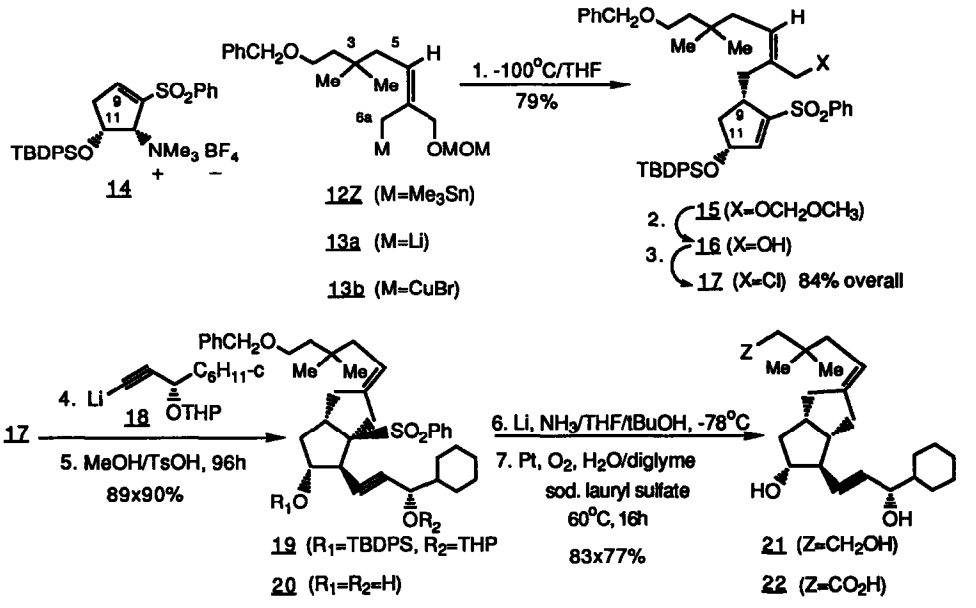
10Z (X=CO_2t-Bu)

11Z (X=CH_2OH)

12Z (X=CH_2OMOM)

The key coupling reaction was conducted as follows: Copper bromide-dimethylsulfide complex (1.45 eq)[10] is added to a mixture of lithium bromide (4.6 eq) and copper powder (0.05 eq) in THF. The mixture is stirred until all traces of yellow (Copper [II]) disappear (several minutes), and the mixture is cooled to -100°C. This cold reagent is added via cannula to a preformed solution of allyl lithium 13a (1.4 eq) which was prepared by reaction of n-butyllithium with 12Z in THF at -100°C. The resultant bromocuprate reagent 13b was maintained at this temperature and a methylene chloride solution of homochiral allyl

ammonium salt 14[11] was added and stirring continued at -100°C for 1h. This procedure stereo- and regiospecifically afforded 71-79% yields of 15 on a 1-4g scale. Exclusion of the copper metal from this procedure results in substantial lowering of the yield. Cleavage of the MOM ether is accomplished smoothly using p-toluenesulfonic acid in isopropanol at reflux producing allyl alcohol 16 which is directly treated with NCS and triphenylphosphine to afford chloride 17 in 84% overall yield for the two steps. Reaction of 17 with the chiral acetylenic lithium reagent 18[5] in THF containing 0.1 eq HMPA at 0°C to room temperature gives bicyclic sulfone 19 in 89% yield. Deprotection of both secondary alcohols was accomplished using p-toluenesulfonic acid and methanol at reflux for 96h (90%). Reductive cleavage of both the sulfone and benzyl ether moiety resulted from exposure of diol 20 to the Birch conditions at -78°C for 0.5h to produce triol 21 in 83% yield. The oxidation of triol 21 to "carbynaprost" 22 proved troublesome. Despite the use of several different samples of platinum oxide and varied solvent systems (water-acetone, aqueous acetic acid, water-dioxane) the oxidation was inconsistent.[6,12] However, the use of water:diglyme (2:1) and Engelhard platinum oxide (lot no. 2510) along with trace amounts of sodium lauryl sulfate[13] enabled carbynaprost 22 to be obtained in 77% yield.



Biological testing of carbynaprost 22 along with its Z-dihydro and tetrahydro derivatives (obtained by catalytic hydrogenation) revealed that 22 was only a weak inhibitor of platelet aggregation, having an IC_{50} of 0.48 ± 0.07 μM (Mean ±SE, n=3) and the di and tetrahydro derivatives were essentially inactive (IC_{50} >10μM).[14]

Acknowledgment: We thank the National Institute of Health (GM 32693) for support of this work. We also thank Arlene Rothwell for providing mass spectral data.

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[14]This experiment was performed by preincubation of the compounds 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.