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TRIPLY-CONVERGENT SYNTHESIS OF TWO SETS OF HOMOCHIRAL CYCLOPENT[a]INDENE CARBACYCLIN ANALOGS[1]

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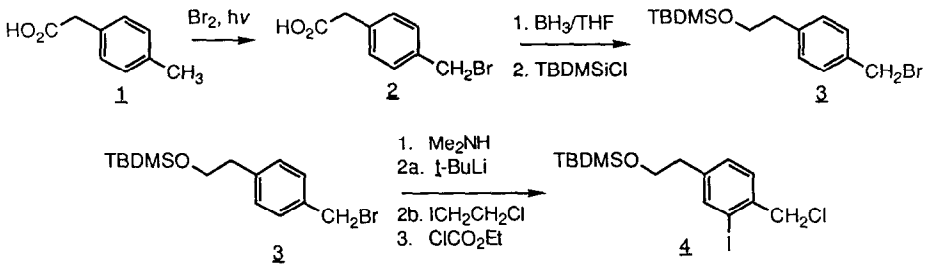
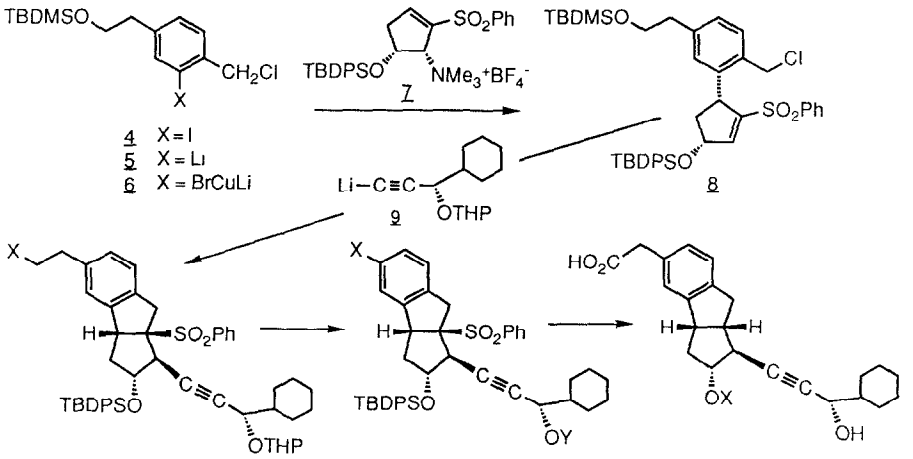
ABSTRACT: Reaction of o-chloromethyl aryl cuprate 6 with optically active ammonium salt 7 regio- and stereospecifically affords vinyl sulfone 8. Conjugate-addition of acetylenic anion 9 followed by *in situ* cyclization provides sulfone 10 which is refunctionalized to provide two sets of carbacyclin analogs, 15-17 and 25-27. IC_{50} values of these six compounds for inhibition of collagen-induced platelet aggregation were 0.18, >100, 0.33, 0.33, >100, and 2.2μM, respectively.

As part of our program to evaluate metabolically-stable prostacyclin analogs,[2] we have synthesized two sets of computationally-designed cyclopent[a]indenes 15-17 and 25-27. The aryl portion of these targets was prepared from p-tolylacetic acid 1 in 31% overall yield using the following sequence. Bromination of 1 in carbon tetrachloride[3] at reflux gave p-bromomethylphenylacetic acid 2 in 57% yield. Reduction of the acid 2 with borane/THF over 16 h followed by protection of the alcohol as the silyl ether afforded 3 in 84% yield. The benzyl bromide was converted to the corresponding N,N-dimethylbenzylamine in 96% yield by bubbling dimethylamine in a THF solution of 3 at -15°C followed by warming to 25°C and stirring for 22 h. Amine-directed metalation[4] of the aromatic ring with t-butyllithium in a 1:1 solution of pentane/ether for 2 h followed by quenching the reaction with 1-chloro-2-iodoethane[5] afforded the aryl iodide in 75% yield. The synthesis of 4 was completed by conversion of the N,N-dimethylbenzylamine moiety to a benzyl chloride with ethyl chloroformate and triethylamine[4] in methylene chloride starting at -78°C and allowing to warm to room temperature over 10 h providing 4 in 90% yield.



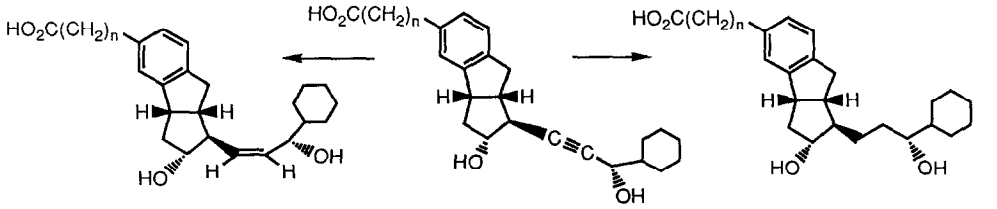
Halogen-metal exchange of aryl iodide 4 with n-butyllithium at -100°C in THF generated aryllithium 5.[6] To the solution of 5 (1.75 eq) was added a preformed solution of copper[I] bromide- dimethylsulfide complex (1.50 eq), excess lithium bromide (6 eq) and copper metal (0.05 eq) in THF cooled to -100°C to generate aryl "bromocuprate" 6.[7] Addition of a methylene chloride solution of homochiral ammonium salt 7 (1.0 eq) to the solution of 6 at -100°C afforded adduct 8[8] in 89% yield as a single regio- and stereoisomer.[9] Treatment of a solution of 8 in ether at 25°C with 1.9 equiv. of lithium acetylide 9[2] and 3.0 equiv. of HMPA for 9 min. gave 10 in 97% yield as a mixture of THP diastereomers. Selective deprotection of the TBDMS ether of 10 with TBAF at -10°C for 2 h afforded alcohol 11 in 75% yield.

Oxidation of the phenethyl alcohol of 11 either directly to the acid or via the aldehyde and then to the acid in a two-step sequence proved to be extremely difficult. A variety of reagents and conditions were tried with the best sequence being Swern oxidation with TFAA[10] which afforded the aldehyde 12 in 43% yield; 58% based upon recovered starting material. Oxidation of the aldehyde was then accomplished with a solution of sodium chlorite and hydrogen peroxide in acetonitrile/THF/water for 30 min.[11] Crude THP-aldehyde 12 was deprotected using catalytic TsOH in t-butyl alcohol at 50°C for 16 h to provide carboxylic acid 13 (66% overall from aldehyde 12).



Desulfonylation[12] of 13 was achieved with lithium in ammonia/THF/t-butyl alcohol followed sequential addition of isoprene and ammonium chloride, affording 14 in 83% yield. Completion of the synthesis involved removing the t-butyldiphenylsilyl ether with excess

TBAF at room temperature for 16 h providing pseudoindynaprost 15[8] in 69% yield (14% overall from homochiral ammonium salt 7). Partial hydrogenation of the acetylene moiety in 15 to the Z-olefin was accomplished using a 5% palladium on calcium carbonate catalyst, poisoned with lead (Aldrich 20,573-7) in ethyl acetate at ambient temperature under one atmosphere of hydrogen in a Brown hydrogenator for 2.5 h. This procedure afforded a 92% yield of Z-pseudoindenaprost 16.[8] The final analog in this set, pseudoindanaprost 17, was obtained by hydrogenation of 15 in a Brown hydrogenator with 5% palladium on alumina catalyst in ethyl acetate at room temperature for 4.5 h affording 17[8] in 68% yield. IC_{50} values of these compounds for inhibition of collagen-induced platelet aggregation[13] are given in the scheme below.

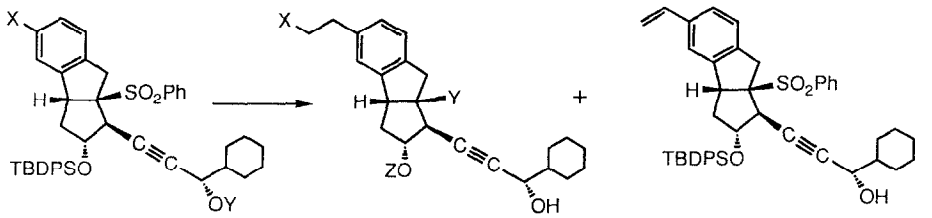


16 (n=1); IC_{50} > 100 μM 15 (n=1); IC_{50} =0.18±0.07μM 17 (n=1); IC_{50} =0.33±0 07μM

26 (n=2); IC_{50} > 100 μM 25 (n=2); IC_{50} =0.33±0.02μM 27 (n=2); IC_{50} =2.2±0.2μM

Synthesis of the second set of analogs 25-27 began with alcohol 11. The alcohol was converted to mesylate 18 with mesyl chloride and diisopropyl ethyl amine in methylene chloride at ambient temperature. Attempts to displace the mesylate with cyanide were unsuccessful, so the mesylate was converted to iodide 19 with a large excess of sodium iodide in acetone at room temperature for 16 h. This procedure partially removed the THP protecting group giving some 20, so the mixture obtained from the Finkelstein reaction was stirred in a 1:1 methanol/methylene chloride solution with p-TsOH for 2 h at room temperature affording the completely deprotected alcohol 20. Reaction of the crude iodide with sodium cyanide in DMSO at 50°C for 20 min gave nitrile 21[8,14] in 94% from alcohol 11 along with a 6% yield of styrene 22 obtained from cyanide-induced elimination of the iodide. With 21 in hand, attempts were made to hydrolyze the nitrile to the acid giving an intermediate which would parallel the synthetic sequence described above; however, no hydrolysis conditions were found, possibly due to the elimination of the homobenzylic sulfone moiety under the basic conditions. Desulfonylation of 21 was accomplished with 6% sodium amalgam affording 23 in 57% yield.[15] Removal of the silyl ether of 23 with excess TBAF at 40°C for 16 h gave 24 in 77% yield. Hydrolysis of 24 was easily achieved with

methanolic sodium hydroxide heated to reflux for 5 h providing homopseudoindynaprost 25[8] in 86% yield (23% overall from homochiral ammonium salt 7).



11 X = $(CH_2)_2OH$, Y = THP
18 X = $(CH_2)_2OMs$, Y = THP
19 X = $(CH_2)_2I$, Y = THP
20 X = $(CH_2)_2I$, Y = H

21 X = CN, Y = SO_2Ph, Z = TBDPS
23 X = CN, Y = H, Z = TBDPS
24 X = CN, Y = H, Z = H
25 X = CO_2H, Y = H, Z = H

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Conversion of 25 to Z-homopseudoindynaprost 26 and homopseudoindanprost 27 was accomplished as described for 16 and 17, affording a 73% yield of 26[8] and a 75% yield of 27,[8] respectively.[16,17]

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8 This compound exhibited satisfactory spectral and analytical properties. Yields refer to material of >95% purity $[\alpha]^{25}_D$ values were recorded at ambient temperature in the following form - (compound number, mp if a solid, rotation, concentration, solvent): 8, +41.7°, c = 1 950, $CHCl_3$; 15, +162°, c = 0 436, MeOH; 16, 138-9°C, +128°, c = 0 123, MeOH, 17, 135-6°C, +63.8°,c =0 207, MeOH; 21, +8 7°, c = 0.355, $CHCl_3$, 25, 114-6°C, +143°, c = 1.120, MeOH, 26, 173-4°C, +101°, c = 0.180, MeOH; 27, 171-2°C, +113°, c = 0 320, MeOH
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13 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. These numbers can be compared to PGI_2 which has an IC_{50} of 0 84 ±0 24 nM
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