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A SIMPLE ENANTIOCOMPLEMENTARY ROUTE TO PROSTANOIDS; INVERSION OF CHIRALITY OF 2,5-DIHYDROXY-CYCLOPENT--3-ENYL-ACETIC ACID LACTONE DERIVATIVES

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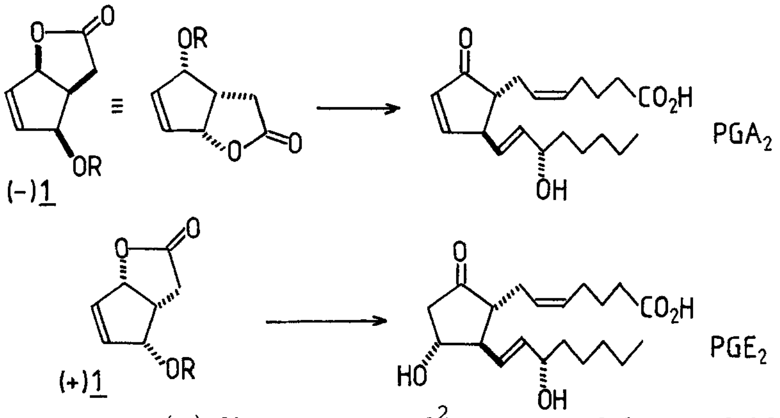
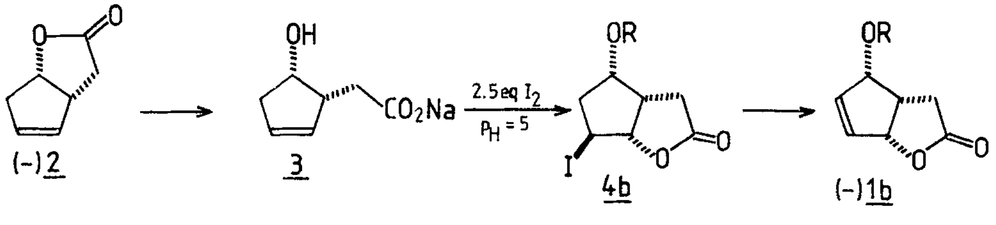
Abstract: An enantiocomplementary route to PGA_2 *and* PGE_2 *synthons is presented.*

The enantiomers of unsaturated bicyclic lactone[1] 1 are valuable chiral intermediates in the Corey[2] and Stork[3] synthesis of PGA_2 and PGE_2, respectively.

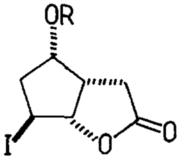


The precursor (-) 1b was reported[2] to be readily available from (-) 2 without formation of appreciable by-products by a sequence outlined below:



a, R=H; b, R=t-BuMe$_2$Si-

We examined the effect of pH upon the products of iodolactonisation, anticipating the interference of OH group in 4a with the favorably oriented lactone moiety, that might induce facile O-O acyl migration[4], which leads to the formation of 5a. Iodolactonisation[5] conducted at various pH values ($5 \leq pH \leq 9$) with 1.1-1.2 eq iodine actually reveals striking dependence of product distribution on the pH value as reflected by ^1H NMR spectra of the crude products. With TLC, however, only one new spot could be detected in various eluent mixtures. Further intervention of acyl migration (trans-lactonisation) could be excluded by blocking the pertinent OH group. Both acetylation (1.2 eq Ac_2O, 1.2 eq pyridine, 0.2 eq 4-dimethyl-aminopyridine in CH_2Cl_2, 20 °C, 1 h) and tetrahydropyranylation (2 eq DHP, cat. pyridinium tosylate in CH_2Cl_2, 20 °C, 4 h) yielded a chromatographically inseparable product mixture, however, t-butyldimethylsilyl (4b and 5b)[6,8] or 2-methoxy-2-propyl (4c and 5c)[7,8] derivatives were easily detected on TLC [R_f 4b: 0.38, 5b: 0.27 (hexane-ethyl acetate 3:1), 4c: 0.50, 5c: 0.33 (hexane-ethyl acetate 2:1 + 1% NEt_3)] and could be readily separated by column chromatography.



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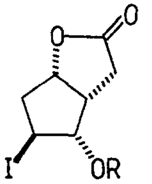
a, R = H
b, R = $t\text{-}BuMe_2Si\text{-}$
c, R = $Me_2(MeO)C\text{-}$
d, R = Ac
e, R = THP



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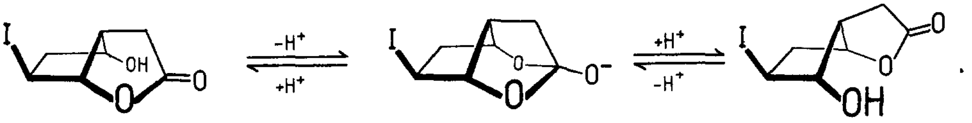


In iodolactonisations, performed at pH=5-6 followed by protection and separation of isomers, 4b or 4c was formed in an amount four times as high as 5b or 5c whereas in experiments conducted at pH=8 the inverse isomeric ratio (4 : 5 = 1 : 4) was obtained. It has been assumed that the ratio 4 : 5 formed in aqueous solution by trans-lactonisation remains essentially unchanged during protection, as the same 4b : 5b and 4c : 5c ratios were obtained irrespective of the character of the catalysts applied (imidazole or pyridinium tosylate).

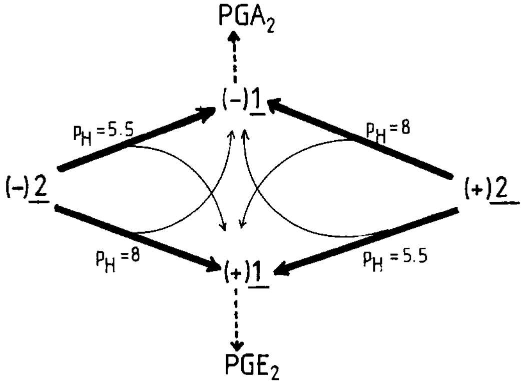
Dehydroiodination of 4b or 4c with 1.5 eq DBU in dry THF (20 °C, 4-8 h) gave optically pure (-) 1b or 1c in contrast to 5b or 5c, which, upon the same treatment yielded (+) 1b or 1c in identical magnitude but opposite sign of rotation in 90-95 % yield.

Details of several experiments performed at pH=5.5 and 8 are summarized in the Table.

start.mat^1.		4		1		5		1	
2 $[\alpha]_D$	pH	$\%_p^h$	$[\alpha]_D$	%y	$[\alpha]_D$	$\%_p^h$	$[\alpha]_D$	%y	$[\alpha]_D$
				(R=t-BuMe$_2$Si-)^c					
-106	5.5	81.6 84.0	+28.2	54.0	-27.4	18.4 16.0	+51.2	10.0	+26.8
+106	8.0	23.7 -	-28.9	10.3	+26.9	76.3 -	-50.8	52.5	-27.2
				(R=Me$_2$(MeO)C-)^m					
-106	5.5	- 76.0	-17.1	52.0	-100.3	- 24.0	+82.3	9.7	+99.6
+106	8.0	19.0 17.5	+17.9	10.9	+100.4	81.0 82.5	-81.9	53.5	-99.5

h: determined by HPLC (upper value); p: determined by prep. column chrom; y: isolated overall yield; $[\alpha]_D$ values refer to $CHCl_3$(c) or to MeOH(m), (conc=1 %).

Graphic illustration of the enantiocomplementarity is given below.



Heavy and light arrows represent respective processes of 52-54 % and 10-12 % overall yields, including separation during the process; pH data refer to conditions used in iodolactonisation.

Undesirable isomers can be deprotected and recycled after separation instead of being converted to 1 (light arrows), thus allowing further increase in effectivity.

References and notes

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3. G. Stork, C. Kowalski, G. Garcia, *J. Amer. Chem. Soc.*, **97**, 3258 (1975); L. Gruber, I. Tömösközi, E. Major, and G. Kovács, *Tetrahedron Letters*, 3729 (1974)
4. I. Tömösközi, L. Gruber, G. Kovács, I. Székely, V. Simonidesz, *Tetrahedron Letters*, 4639 (1976)
5. In a typical procedure 10.0 g **2** was dissolved in 95 ml 1n NaOH and after stirring for 3 hrs the pH was adjusted to 8 or 5.5 by adding solid CO_2 or 1n $NaHSO_4$, respectively, 22.8 g I_2 was then added in one portion and the reaction mixture was stirred overnight. After extraction with ethyl acetate the excess iodine was destroyed with $Na_2S_2O_3$, the organic phase was dried and evaporated to give **4a** + **5a**, 19 g (94%). This mixture was treated either with 1.5 eq t-butyl-dimethylsilyl chloride[9] and 2 eq imidazole in DMF (rt, 20 hrs) to give **4b** + **5b** or with 2 eq 2-methoxy-1-propene and cat. amount of pyridinium tosylate in CH_2Cl_2 (rt, 6 hrs) to give **4c** + **5c** after quenching with triethylamine and evaporation of the solvent. Purification and separation of the isomers were performed by chromatography on silica gel using hexane-ethyl acetate 3:1 (**4b** + **5b**) or hexane-ethyl acetate 2:1 containing 0.5% NEt_3 (**4c** + **5c**) as eluent.
6. ^{1}H NMR δ in ppm ($CDCl_3$) **5b**: 4.95(1H,m), 4.33(1H,dd), 4.05(1H,m), 3.2(1H,m), 2.7-2.3(4H,m), 0.90(9H,s), 0.14(6H,d)
   4b: 5.15(1H,dd), 4.60(1H,m), 4.35(1H,m), 3.2-2.1(5H,m), 0.90(9H,s), 0.08(6H,s)
   1b: 6.0(2H,s), 5.26(1H,d), 4.87(1H,d), 3.45-2.25(3H,m), 0.92(9H,s), 0.10(6H,s)
7. ^{1}H NMR δ in ppm ($CDCl_3$)**5c**: 4.98(1H,m), 4.39(1H,dd), 4.14(1H,m), 3.29(3H,s), 1.33, 1.39(3H,s)
   4c: 5.13(1H,d), 4.77(1H,m), 4.36(1H,dd), 3.18(3H,s), 1.34, 1.31(3H,s)
8. Satisfaytory combustion data, IR and ^{1}H NMR[6,7] spectra were obtained for all the new compounds.
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