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SYNTHESIS OF (+)-5,6,7-TRINOR-4,8-INTER-m-PHENYLENE PGI_2[1)]

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Abstract: The titled compound, which is a stable and potent analog of prostacyclin, was synthesized from readily available 1,4-dibromocyclopentene via cyclopenta[b]benzofuran carboxylic acid **5**.

Our discovery that (±)-5,6,7-trinor-4,8-inter-m-phenylene PGI_2 is a stable and potent inhibitor of platelet aggregation[2)] has prompted us to develop a synthesis of an optically active form **1**. In this communication we wish to report a regio- and stereo-controlled synthesis of **1**, which involves resolution of a bromo acid **5**.

Readily available cis-1,4-dibromocyclopent-2-ene (**2**)[3)] was utilized as a starting material for our synthesis. The dibromide **2** was treated with potassium 2,4,6-tribromophenoxide in the presence of 18- crown-6 in DME to afford cis-1,4-bis(2,4,6-tribromophenoxy)cyclopent-2-ene (**3**) (80%). The cyclopentene **3** was metalated with cyclohexylmagnesium chloride and the resulting Grignard reagent cyclized by an addition of CuI to give dibromocyclopenta[b]benzofuran **4**, m.p.110-112 ℃(70%). The dibromide **5** was metalated with cyclohexylmagnesium chloride and treated with carbon dioxide to afford a bromo acid **5** (86%, m.p. 205-205 ℃ sublimed).

Resolution of the bromo acid **5** with (+)-cis-N-benzyl-2-(hydroxymethyl)cyclohexylamine[4)] afforded an optically active bromo acid **5** (m.p. 207-209 ℃ sublimed, $[\alpha]_D^{22}$-181° [c=0.3,MeOH]), which was converted to an ester **5a** so as to determine the absolute configulation (3aS, 8bS) by X-ray analysis.

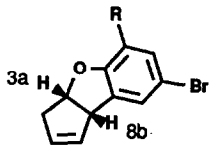
The bromo acid **5** was subjected to Prins reaction to give diacetate **6a** concomitant with small amount of monoacetates, **6b** and **6c**, and diol **6d**[5)].

Hydrolysis with NaOHaq (1N), followed by the treatment with diazomethane yielded a single compound **7** (60% from **5**) whose stereochemistry was determined by 2D NMR spectra (normal, COSY, and NOE deference spectra)[6)]. The dihydroxy ester **7** was protected with 1,1-dimethoxyethane in the presence of p-TsOH in THF to give an acetal **8** (80%). Conversion of the acetal ester **8** into three carbon elongated acid **10** (46% from **8**) was effected by following sequence. (1) $LiAlH_4$-THF (2) $SOCl_2$-Py (3) Mg and (4) β-propiolactone-CuI[7)].

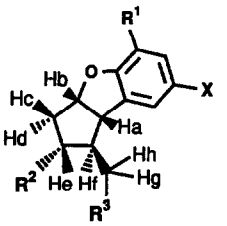
Methylation of the acid **10** with diazomethane, followed by hydrolysis with HCl (1.0 N) provided a dihydroxy ester **11** (70%). Conversion of **11** into a monoacetate **12** was effected by the following sequence, (1) TrCl-Et_3N (2) Ac_2O-Py (3) HCl-MeOH in 75% overall yield. The monoacetate **12** was oxidized with DCC-DMSO[8)] in THF to give an aldehyde, which was immediately condensed with dimethyl 2-oxo-heptylphosphonate and sodium hydride in THF[9)] to afford a conjugated ketone **13** (80%). The ketone **13** was reduced with $NaBH_4$-$CeCl_3$ in MeOH[10)] to yield a mixture of two isomeric alcohols (ratio 1:1).

Methanolysis of the mixture led to corresponding diols (**14a** and **14b**) which were separated by column chromatography (silica gel) to give pure **14a** (43% from **13**). Hydrolysis of **14a** with NaOHaq in MeOH afforded a dihydroxy acid **1** (90%, m.p. 96.0-97.5 ℃, $[\alpha]_D^{22}$+105° , [c=0.48, MeOH]) [11)12)].

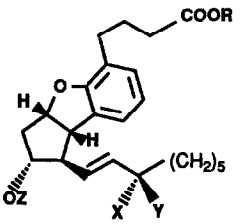
Activity of 1 on the inhibition of human platelet aggregation induced by ADP was nearly four times as strong as PGE_1[13].



4: R=Br
5: R=COOH
5a: R=COOMe



6a: X=Br, R^1=COOH, R^2=R^3=OAc
6b: X=Br, R^1=COOH, R^2=OAc, R^3=OH
6c: X=Br, R^1=COOH, R^2=OH, R^3=OAc
6d: X=Br, R^1=COOH, R^2=R^3= OH
7: X=Br, R^1=COOMe, R^2=R^3=OH
8: X=Br, R^1=COOMe, R^2=R^3= -OCH(CH_3)O-
9: X=H, R^1=CH_2Cl, R^2=R^3= -OCH(CH_3)O-
10: X=H, R^1=$(CH_2)_3COOH$, R^2=R^3= -OCH(CH_3)O-
11: X=H, R^1=$(CH_2)_3COOMe$, R^2=R^3=OH
12: X=H, R^1=$(CH_2)_3COOMe$, R^2=OAc, R^3=OH



13: R=Me, X=Y=O, Z=Ac
14a: R=Me, X=OH, Y=H, Z=H
14b: R=Me, X=H, Y=OH, Z=H
1: R=H, X=OH, Y=H, Z=H

References and Notes

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6) On irradiation of protn a, a NOE was observed for proton b. Moreover irradiation of the methine proton b afforded a NOE on protons a and c. On the other hand irradiation of the methine proton f gave a NOE on protons g and h, but not on proton a, b, and c.
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11) Spectra of **2**: IR(KBr): 3600-2400, 1705, 1405, 1275, 1195, 1090, 1015, 965, 865, 775, 765, 740 cm^{-1}. ^{1}H-NMR(400MHz, $CDCl_3$)δ: 0.90(3H,t,J=7.0Hz), 1.32(6H,brs.), 1.48(1H,m), 1.60(1H,m), 1.95(4H,m), 2.35(3H,m), 2.65(4H,m), 3.40(1H,t,J=8.4Hz), 3.88(1H,m), 4.10(1H,m), 5.08(1H,m), 5.58(2H,m), 6.75(1H,t,J=7.4Hz), 6.85(2H,m). MS(m/e): 388(M^+), 370, 352.
12) The stereochemistry of 15-hydroxyl group of the diols (14a and 14b) was temporarily determined as follows. The more poler one on silica gel TLC (Rf = 0.37, EtOAc) was regarded as 15S hydroxy compound (**14a**). The hydorolysis product of **14a**, 1, was more potent than that of **14b** on the inhibition of human platelet aggregation induced by ADP. The absolute configulation of 15-hydroxyl group of 1 is now examining by X-ray analysis. The result of the analysis will be published in Tetrahedron near future.

13) The authors thank Dr. Shintaro Nishio at BRL for pharmacological assays of the compound.

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