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TOTAL SYNTHESIS OF PROSTAGLANDINS. CONTROL OF REGIOSPECIFICITY IN THE ALANE-EPOXIDE REACTION AND SELECTIVE CATALYTIC OXIDATION OF ALKYNYLATION PRODUCTS

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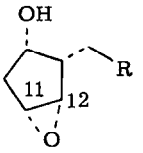
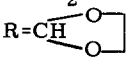
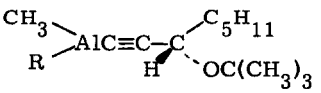
One of the key reactions in the synthesis of the prostaglandins[1,2] and 13-dehydroprostaglandins[3] reported from this laboratory is the alkynylation of the diol epoxide Ia in both its racemic and optically active forms with (S)-3-t-butyloxy-1-octynyldimethylalane (IIa) to yield exclusively the triol IIIa.[2] We wish to report recently discovered facts concerning the composition of the alane reagent essential for achieving complete regiospecificity in this reaction, which we consider of sufficient importance to communicate at this time. In all previous work IIa[4] and related reagents were prepared using a 1.5 M solution of dimethylchloroalane (DMCA) in toluene, furnished in rubber septum-sealed glass bottles (Texas Alkyls). When our supply of bottled DMCA was exhausted it was decided to use henceforth dimethylchloroalane supplied in cylinders, since such material was more securely protected from atmospheric contamination. When this change was instituted two differences were immediately noted. 1) The reaction was very much faster being 80% complete within 5 min at 25° and 2) the regiospecificity was lost, ratios of alkynylation products at C-12 versus C-11 ranging from 4·1 to 1:1. It was at once suspected that the difference in the results associated with the two types of containers was due to air oxidation of the bottled material via the repeatedly pierced septum resulting in the formation of varying amounts of methoxymethylchloroalane (MMCA). That this was indeed a possible explanation became clear when after contaminating pure DMCA with MMCA by either air oxidation or addition of methanol the rate decreased and complete regiospecificity was again observed. Extensive experimentation indicated that a fixed ratio of DMCA:MMCA was not essential, and that the arbitrary decision of converting DMCA into MMCA by addition of one mole equivalent of methanol achieved the desirable standardization of reaction conditions. The fact that regiospecificity is achieved under these conditions may be ascribed to the slower rate of alkynylation as compared to the rate of bond formation between the



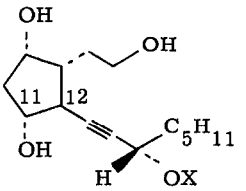
Ia R=CH_2OH

Ib R= 



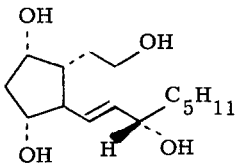
IIa R=CH_3

IIb R=OCH_3

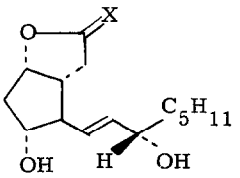


IIIa X=$C(CH_3)_3$

IIIb X=H

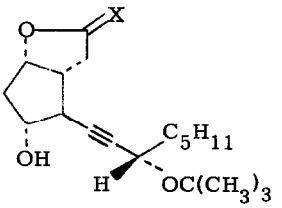


IV



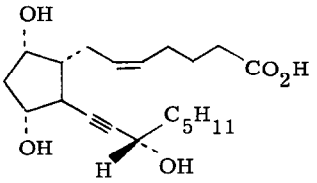
V X=O

VI X= 



VII X=O

VIII X= 



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primary hydroxyl group of Ia and the alane IIb so as to assure the transition state favoring intramolecular alkynylation at C-12 (Cf. structure V of ref. 2).

We have also examined the reaction of the acetal epoxide Ib, $[\alpha]_D^{25}$ -6.9° (c, 2.4 in $CHCl_3$) with (S)-IIa, which afforded a mixture (64% yield) consisting of 84% of the desired and 16% of the 11-alkynylated product. Interestingly, reaction of the enantiomer of Ib, $[\alpha]_D^{25}$ +6.4° (c, 2.62 in $CHCl_3$) gave (67% yield) 35% of the 12-substituted and 65% of the isomeric product.[5]

A stock solution of MMCA was prepared as follows. DMCA (1.4 M in toluene, 30 ml, 42 mmoles), was transferred from the cylinder to a 100 ml three-neck flask under dry nitrogen.

Dry methanol (40 mmoles) in dry toluene (8.0 ml) was then added dropwise to the stirred solution at 0° over a 5 minute period. The temperature was allowed to rise to 25° and the contents stirred for an additional 25 minutes. The MMCA solution[6] was transferred under dry nitrogen to a septum-fitted bottle for storage. The alkynylation reaction was carried out as follows: To a stirred solution of (S)-3-t-butyloxy-1-octyne (6.38 g, 35 mmoles) in 8.4 ml of dry toluene was added (5 min) under nitrogen at 0-5° n-butyllithium in hexane (1.5 M, 23.4 ml, 35 mmoles),followed after 15 minutes by addition of MMCA in toluene (1.2 M, 19 ml, 23 mmoles).[7] After stirring for 50 minutes at 0°, a solution of the epoxide Ia, $[\alpha]_D^{25}$ +1.8° (c, 2.0 in $CHCl_3$) (387 mg, 2.70 mmoles) in 7 ml of dry toluene was added slowly, and the mixture allowed to warm to 25°. It was then heated at 60° and the progress of the reaction followed by glc of the TMS ethers. When reaction was complete (ca. 2 hours) the mixture was cooled to 0°, decomposed with saturated sodium sulfate, extracted with ether and dried over sodium sulfate. t-Butyloxy-1-octyne was recovered by distillation and the product purified by chromatography on silica gel (75 g). Total yield 620 mg (62%) $[\alpha]_D^{25}$ -39.2° (c, 3.24 in $CHCl_3$). Anal. Calcd for $C_{19}H_{34}O_4$. C, 69.91, H, 10.50. Found C, 69.98; H, 10.59. This product was free from the isomer of reverse epoxide opening, as shown by the absence of the characteristic nmr signal at δ3.05[1] as well as by the absence on tlc analysis of the corresponding isomeric products from IIIb and IV, and from the monotrityl ether of IIIa, all of which are readily separable from their position isomers.

Previous reports dealing with the sequence leading from the triol IIIa to both $PGF_{2\alpha}$[2] and the biologically highly active 13-dehydro-$PGF_{2\alpha}$[3] have described the conversion of IIIb and IV to the corresponding hemiacetals VIII ($C(CH_3)_3$=H) and VI in four steps involving selective protection and deprotection of the primary and secondary hydroxyl groups. We have now achieved the direct selective dehydrogenation of IIIa and IV with Pt and O_2[8] to the lactones VII and V, respectively.[9] The oxidation of IIIa was carried out with an equal weight of PtO_2[10] (prereduced in H_2O), the substrate being added in acetone-water to make a final concentration of 0.0115 M in 12% acetone. Oxygen was bubbled through the suspension at 57° for 3-4 hours, the reaction being followed by glc of the TMS-ether. Yield: 80-85%, $[\alpha]_D^{25}$ -40° (c, 1.86 in $CHCl_3$), mass spectrum (TMS-ether): 379 (M-15), 337 (M-57). The oxidation of the tetraol IV was more critical requiring the presence of excess bicarbonate to achieve reproducible results. In a typical experiment[11] 21 mg of IV and 67 mg of sodium bicarbonate in 2.0 ml water-acetone 4:1 was added to prereduced PtO_2 (42 mg)[10] in 5 ml water after replacing the hydrogen atmosphere by oxygen. After oxygenating for 7-10 hours at 58°, the reaction was 50-60% complete and proceeded no further. Separation of starting material and acidification to achieve lactonization afforded 9.5 mg of IV and 10 mg of lactone V, identical with an authentic sample.[12] Reduction of the lactone VII with diisobutyl aluminum hydride in toluene at -60°[12] furnished in 95% yield the hemiacetal VIII, $[\alpha]_D^{26}$ -49.5° (c, 1.83 in $CHCl_3$), mass spectrum

(bis-TMS ether): M^+ 468. Wittig reaction of VIII as previously described[3] followed by debutylation with trifluoroacetic acid at 0-5° for 5 hours afforded after high pressure chromatography pure 13-dehydro-$PGF_{2\alpha}$[3] (55% yield from VII), mp 50-52°, $[\alpha]_D^{26}$ +35° (c, 2.02 in EtOH).

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5. Reaction of (±)-Ib with (±)-IIa gave in 80% yield 2 pairs of diastereomeric racemates, which on tlc furnished 61% of the 12-alkynylated-15-epimeric products and 39% of the corresponding 11-substituted products. Calcd from the results obtained with chiral reactants: 59 and 41%. From these data it appears possible that the reaction of (-)-Ia with IIa might produce some of the isomeric product. However, the reaction of (±)-Ia with (±)-IIa has been examined and none of the isomeric products were detected.
6. The nmr spectrum of this material at 30° (Varian A-60) showed signals of equal intensity at 69 Hz downfield ($AlOCH_3$) and 163 Hz upfield ($AlCH_3$) from $C_6H_5CH_3$.
7. The deficiency in MMCA was found desirable to exclude chlorohydrin formation.
8. K. Heyns and H. Paulsen in Newer Methods of Preparative Organic Chemistry Vol. II, Editor, Wilhelm Foerst, Academic Press, 1963.
9. In no case were the hemiacetals VI and VIII observed.
10. Commercial Adams catalyst was employed. Three different lots were successfully tried, two purchased from Engelhard and one from Bishop and Co.
11. These reaction conditions could also be employed for the selective oxidation at C-1. Thus, 15-epi-$PGF_{1\alpha}$ alcohol gave 15-epi-$PGF_{1\alpha}$ in 90% yield, mp 60.5-62°(ref. 13).
12. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Am. Chem. Soc., 91, 5675 (1969).
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