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APPROACHES TO THE CHEMICAL SYNTHESIS OF THE PROSTAGLANDINS

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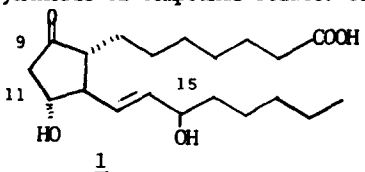
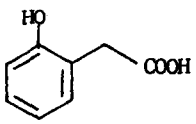
Since their discovery in 1933 (1) and the elegant work of Bergstrom and co-workers in the early 1960's on the isolation and determination of structure, the prostaglandins have attracted the intense interest of many laboratories. The continuing efforts (2) on the substances include studies related to the distribution and the identity of structural variants found in nature (3), the physiological function of these lipids (3), the biogenetic pathways for their formation (3), and the organic chemical synthesis (4) of members of the family. We would like to report in this communication a portion of our effort which has been directed toward the synthesis of compounds related to PGE_1 (1).



1

The basic idea of our approach has been to attach one or both of the side chains to an appropriately substituted benzene ring and to subsequently convert the aromatic nucleus to the cyclopentane system.

The starting material for our synthetic sequence, o-hydroxyphenylacetic acid (2), which was available to us as a by-product of penicillin G fermentation, can be converted conveniently and in good yield to compound 3, mp 59-60°, possessing the proper acid side chain. This was accomplished by treatment of the methyl ether acid chloride of 2 with the morpholine-enamine of cyclopentanone, followed by base hydrolysis and Wolff-Kishner reduction. (5)



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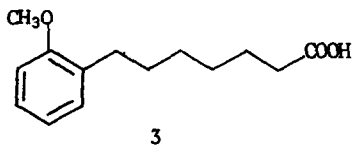
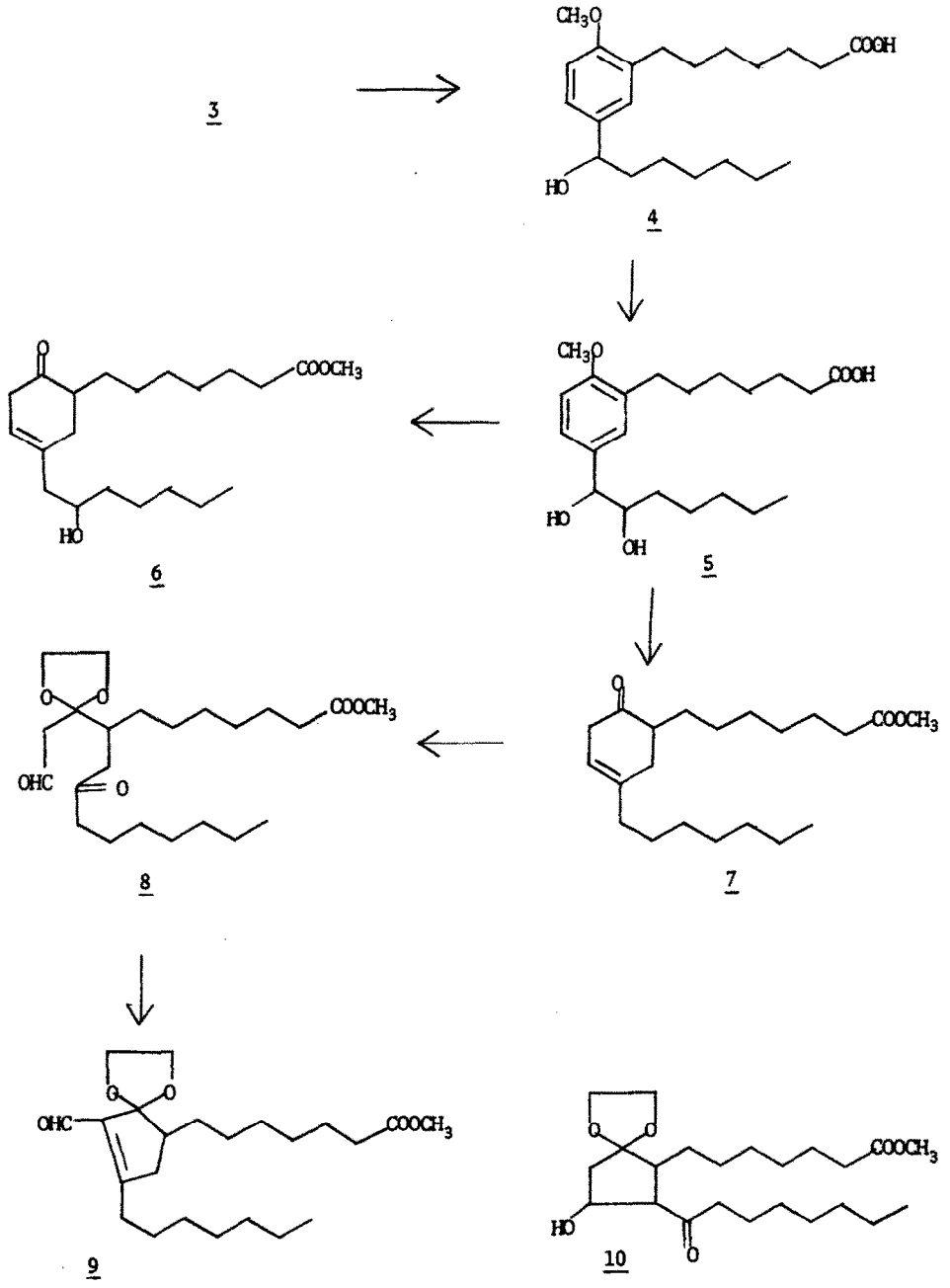


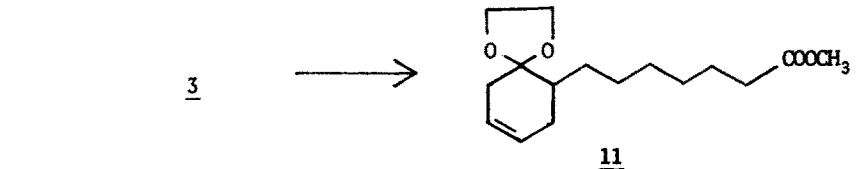
3

Concurrent with the work to be described, the second side chain was introduced by a Friedel-Crafts acylation. The resulting keto acid was reduced to the hydroxy acid 4, mp 75.5-76.5°, which was converted to the crystalline glycol (5), mp 90-92°, by dehydration,

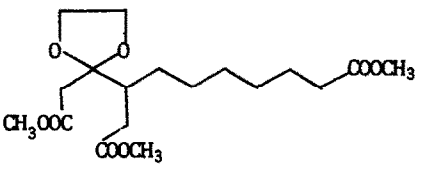


epoxidation, and hydrolysis. A Birch reduction of 5, followed by hydrolysis and esterification, gave a mixture from which could be isolated by chromatography on silica a substance in which the ring was deoxygenated; compound 7; and compound 6, the intermediate possessing a hydroxyl group in the correct position for the prostaglandins. The conversion of the 6-membered ring to a 5-membered ring was initially studied on compound 7, which can be obtained more directly from 4. After preparation of the ketal from the ketone, cleavage of the double bond in 7 by ozone provided the keto aldehyde 8. Treatment of 8 with alkali, pyrrolidine, or pyrrolidine acetate gave 9 in good yield instead of the desired 10 or its dehydration product. A preliminary investigation of a similar sequence applied to 6 has not led to a definitive result. In the recently reported synthesis of PGE_1, (4a) this formal sequence has been used, employing a compound related to structure 6.

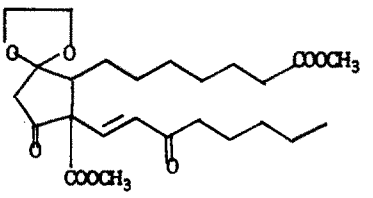
The alternate of the above approach was to convert the 6- to a 5-ring before attaching the second side chain. The key intermediate, 11, easily obtained from 3 by Birch reduction and subsequent esterification and ketalization, was initially ozonized, cleaved oxidatively, and esterified to give the unstable tri-ester, 12, in poor yield. Failure to obtain the Dieckmann cyclization product of 12 precluded using the chloroketone 13 as a procedure for introducing the hydroxyl-bearing side chain. Such an alkylation has been carried out in good yield on 2-carbomethoxy cyclopentanone. (6)

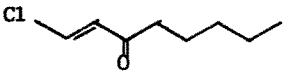


11



12





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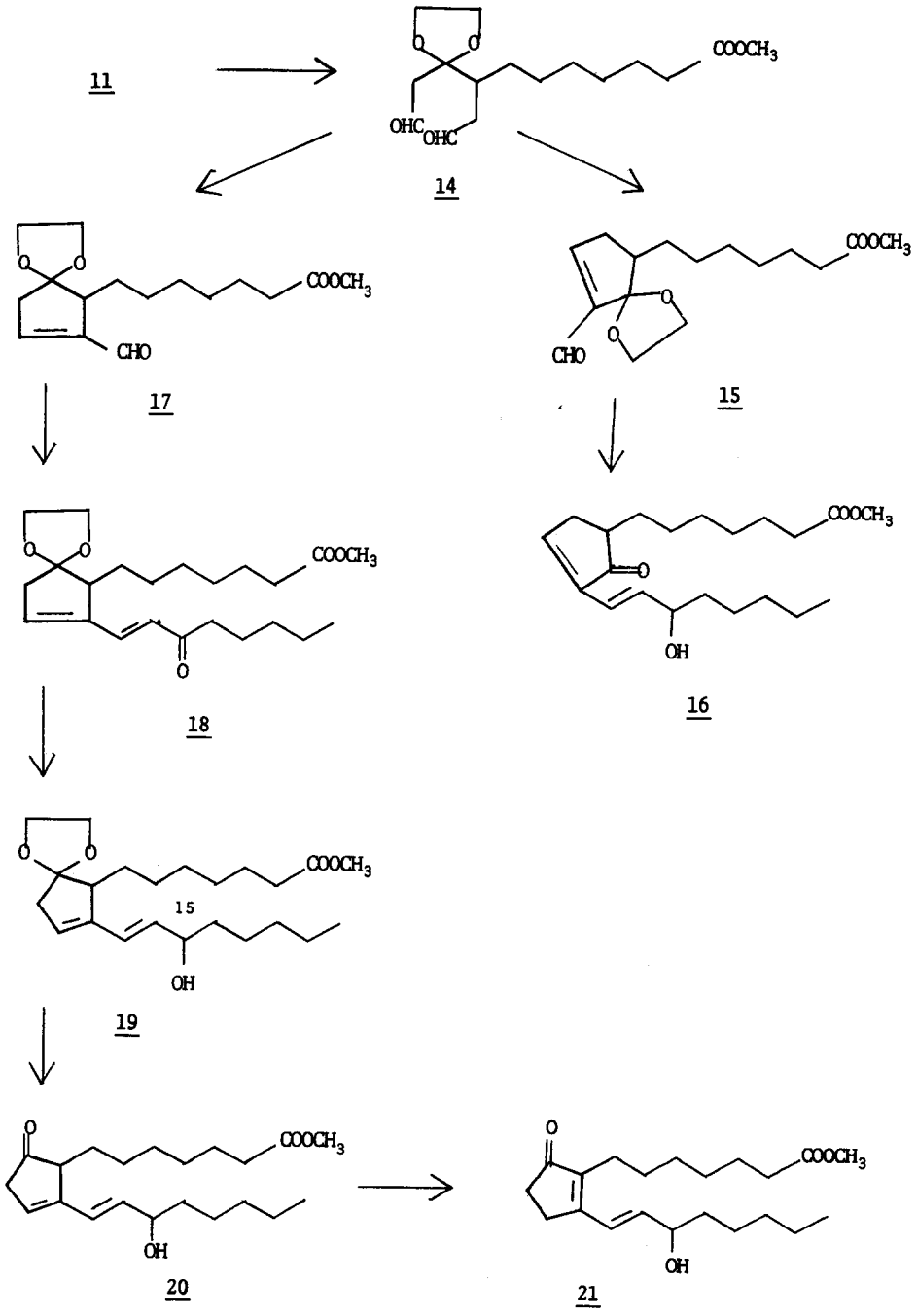
11
14
17
15
18
16
19
20
21
COOCH3
CHO
OHC
OH
O
15

Reductive cleavage of the ozonide of 11 gave the dialdehyde 14 which could be used directly in subsequent reactions without further purification. The reaction of 14 with pyrrolidine acetate gave the α,β-unsaturated aldehyde 15. Treatment of this aldehyde with n-hexanoylmethylenetriphenylphosphorane (7), followed by $NaBH_4$ reduction and deketalization, provided 16, a structural isomer of PGB_1. The physical data rule out consideration of structure 20 or 21, but are entirely consistent with 16, thus providing additional evidence for assigning structure 15 to the aldehyde. A large variety of conditions, acids, alkali, sec. and tert. amines, and chromatographic absorbents cyclize the dialdehyde with no indication of the alternate ring closure. However, the amine, 3-azabicyclo [3.2.2]nonane, (8), gave a mixture of 15 and a new aldehyde in nearly equal amounts. This aldehyde, which could be separated from 15 by chromatography on silica, is the isomeric compound 17. The Wittig reaction on 17 gave the dienone 18 (λ^{282}, ε 14,500), which could be reduced with $NaBH_4$ to 19, an equimolar mixture of the two epimers at C-15.

The ketal could not be removed from mixture 19 by acid catalyzed exchange to acetone without causing extensive dehydration of the C-15 hydroxyl group. However, a substance was isolated in low yield which must be a mixture of 20 and 21. The mass spectrum was very similar to that of PGB_1. In the uv spectrum two peaks were observed, 233 mμ and 278 mμ; on treatment of the compound with base, the former disappeared whereas the latter was intensified. Deketalization of 18 under similar conditions resulted in the diketone (9) (λ^{283}, ε 16,300, $\lambda^{500,283}_{OH^-}$; ε 16,000, 12,000), which on treatment at low temperature with $LiAl(OtBu)_3H$ gave reduction of the unconjugated C_9 ketone (λ^{282} ε 17,100, $\lambda^{282}_{OH^-}$, ε 17,100) instead of the desired C_{15}-center.

Although it has been possible to obtain the aldol product of adipyl dialdehyde and to subject this to the Wittig reaction without ring opening or dehydration (10), conditions to effect a similar sequence starting from 14 have not yet been found.

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5. We are indebted to Dr. E. C. Kornfeld of these laboratories for the development of this procedure.

6. Unpublished results of R. A. Mueller and R. B. Morin.

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8. We are indebted to Dr. N. J. Leonard, University of Illinois, for the suggestion of this amine.

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10. Unpublished results of D. O. Spry and R. B. Morin.