NEW SYNTHESES OF PROSTAGLANDINS[+,1,2]

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A detailed account of the total synthesis of prostaglandins by the tropolone approach is given. The preparation of novel modified prostaglandins, including 11-substituted and 11-nor-prostaglandins, is also mentioned.

In the past, we have reported the preparation of a number of modified prostaglandins (PG) by two different approaches[3]. The first pathway used a known synthetic scheme, which was appropriately modified in order to obtain new PG analogs. The second route used PGA_2, isolated from the marine corals Plexaura homomalla, which was submitted to a number of chemical and photochemical processes, thus affording structurally interesting, novel entities.

In recent years, we have been engaged in a research program having as its main objective the design of a synthesis that would allow the preparation of both natural and modified PG through an

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+ Dedicated to Dr. Ken'ichi Takeda on occasion of his seventieth birthday.

intermediate possessing the cyclopentenone moiety characteristic of PGA_2.

This paper presents a detailed account of our new synthetic approach.

Our synthesis is based on work by Dauben *et al.*[4] who reported that irradiation of α-tropolone methyl ether (3b) in methanol afforded in 55% yield 7-methoxy-3,6-bicyclo[3.2.0]heptadiene-2-one (5) *via* the 1-methoxy isomer (4). Tropolone (3a) is commercially available[5] and is prepared in two steps from cyclopentadiene (1).

Cyclopentadiene (1) constitutes an ideal starting material, since it is a cheap compound and available in large quantity. It reacts with dichloroketene to give the bicyclic intermediate (2)[6], which readily rearranges upon treatment[6d] with aqueous acetic acid in the presence of triethylamine, to afford α-tropolone (3a) in yields higher than 50% from (1). Methylation of (3a) with diazomethane in ether solution gives nearly quantitatively tropolone methyl ether (3b).

We investigated the photochemical reaction further because we felt that the bicyclic photo-product (5) constituted an ideal starting material for PG synthesis. Indeed, compound (5), obtained in one step from (3b), contains the cyclopentenone unit of PGA_2 as well as fragments of both alkyl chains at C-8 and C-12.

We found that quartz-filtered irradiation of tropolone methyl ether (3b) in relatively concentrated anhydrous methanol solution at room temperature for 6 hr, using a Hanau TQ-150 high pressure mercury arc lamp, afforded the bicyclic enone (5), in 80% yield.

The photochemical rearrangement of (3b) to (5) is of fundamental interest. Mechanistic explanation of this deep-seated change must account not only for the problematic methoxyl shift but also for the observation that a methyl group in the 4-position shifts simultaneously, while a methyl group in the 6-position is unaffected.

The rearrangement has been accounted for by two distinct steps, as follows[4,7,8]. The first step is an electrocyclic reaction, *in extenso* a light-induced valence tautomerization of the tropolone ring (3b), which yields the isolable bicyclic valence tautomer (4). This is analogous to the photoisomerization of colchicine[7]. An examination of the geometry of compound (4) with molecular models indicates that the intermediate (4) exists as a bent bicyclic system in which the stereochemistry (A) is such that the π-orbital of the nonconjugated double bond can interact with the π-orbital of the conjugated double bond during quantum absorption of (4). This is evidenced by an ultraviolet absorption band at λ_{max} 224 nm, whereas PGA_2, for example, exhibits an absorption at λ_{max} 217 nm. The excited state that is directly responsible for the second rearrangement step is schematically represented as a dipolar state (B), because the ensuing rearrangement is characteristically a polar process. Migration of the acyl group, as shown in (B), leads to a new excited state (C), which collapses to a ground state — the rearranged bicyclic photoisomer (5) (λ_{max} 225 nm, ε 6,800). The driving force of the acyl migration in (B) is presumed to be the stabilization of the positive charge by the methoxyl in the rearranged excited state (C). The sequence of events leading to

a dipolar state such as (C) is reasonable and has some precedents in photochemistry[9].

In addition, to the shift of the methoxyl group from position 1 to 7, this mechanism also accounts for the results obtained from the series of labelling experiments in which alkyl groups were used as labels[4,7,8].

An alternative interpretation has been proposed for this photochemical reaction[8]. Irradiation of the bicyclic compound (4) at liquid nitrogen temperature (-196°) showed the presence of an intermediate exhibiting a ketene carbonyl band in the infra-red spectrum. This ketene (D), also formed on irradiation of the 7-methoxy-compound (5), isomerizes thermally at -70° to the bicyclic ketones. The authors[8] assigned the structure cis, cis-2-methoxy-bicyclo[2.1.0]pent-2-en-5-yl ketene (D) to this int rmediate, presumably formed photochemically from the bicyclic ketones (4) and (5) by a Norrish type I process, which probably occurs in a $^1(n,\pi^*)$ excited state. The thermal isomerization of the ketene to the bicyclic ketones is a Cope rearrangement[8].

In our hands, the only product isolated at the end of the reaction was the photo-product (5). Its isomer (4) was not present. Additionally, in spite of the known reactivity of ketenes toward methanol, the solvent in which the irradiation is performed, we have never isolated reaction products resulting from the addition of methanol to the presumed ketene intermediate (D).

The mechanistic pathway of the α-tropolone methyl ether (3a) to 7-methoxy-3,6-bicyclo[3.2.0]heptadiene-2-one (5) is quite complex,

in either interpretation, yet it gives the photo-product (5) in high yield[10].

Specific examples of the methodology used to build PG intermediates and products from the bicyclic intermediate (5) are illustrated in sequence.

An important chemical property of the bicyclic intermediate (5) is the selective reactivity displayed by the double bonds. Indeed, on the one hand ozonolysis of compound (5) in pyridine-methanol-methylene chloride solution at -78° took place selectively at the enol ether double bond to provide the ozonide, which was cleaved with distilled sulfur dioxide at -20°, thus affording the dimethyl acetal (6). This substituted cyclopentenone in principle can be transformed to natural PG by the methodology known in PG chemistry[11], such as epoxidation, Michael addition of a proper group at position 11[12], or other appropriate chemical transformations[13].

On the other hand, catalytic reduction of the substituted cyclopentenone (5) over prehydrogenated platinum in ethyl acetate solution took place selectively at the conjugated double bond yielding almost quantitatively the corresponding cyclopentanone (7). Ozonolysis of the enol ether bond of the bicyclic intermediate (7) at -78° in 5:1-methylene chloride-methanol solution was followed by treatment of the ozonide with liquid sulfur dioxide[14], thus providing the relatively stable dimethyl acetal (8). Alkylation of this keto-ester at position 8[12] was performed by reaction with potassium hydride in dimethyl sulfoxide[15] under an atmosphere of argon, followed by treatment with ethyl 7-iodoheptanoate[16], producing

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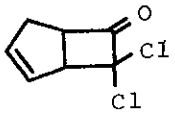

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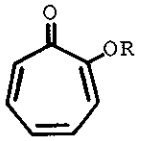
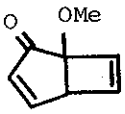


3 a, R=H

b, R=Me



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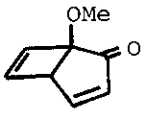
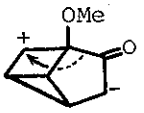


A



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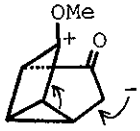

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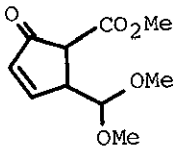

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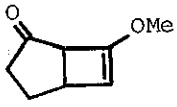

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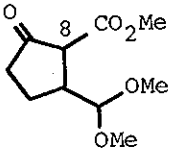

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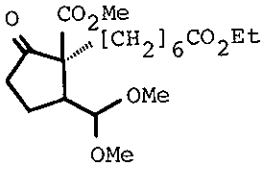

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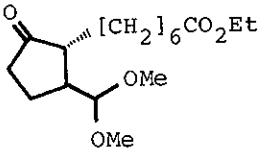


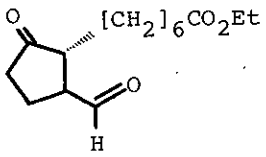
10

the diester (9) in good yield.

Decarboxylation of compound (9), a key-step in the synthesis, was smoothly effected with sodium cyanide in hexamethylphosphoric triamide for one hour at 70°[17], affording in 90% yield the keto-ester (10). The acetal group is not affected by these mild reaction conditions. Treatment of ketone (10) with ethanolic potassium acetate, known equilibration conditions[18], led to unchanged material thus confirming the trans relationship between the substituents on the cyclopentanone. Cleavage of the acetal protecting group in the intermediate (10) with p-toluenesulfonic acid in acetone liberated the aldehyde (11) in quantitative yield.

The concluding steps of the synthesis have been worked out previously[19,20]. Reaction of intermediate (11) with the sodium salt of dimethyl 2-oxoheptylphosphonate provided the expected enedione (12), characterized by the tipical spectral properties of its enone chromophore[20].

In our initial approach, the dione (12) was converted to the diketal (13) by treatment with ethyleneglycol in the presence of a trace amount of p-toluenesulfonic acid in benzene solution. Selective hydrolysis of the 15-ketal was performed by reaction with p-toluenesulfonic acid in acetone at -20°, thus regenerating the enone chromophore (14). Zinc borohydride reduction in dimethoxyethane[21] gave a mixture of epimeric 15-alcohols (15), which were treated with aqueous acetic acid to remove the 9-ketal protecting group. Separation by thin layer chromatography (TLC) of the resulting 11-deoxy PG ethyl esters (16a) and (17) afforded



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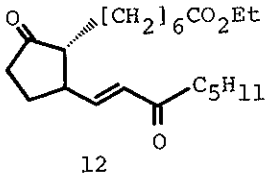

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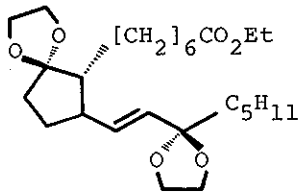

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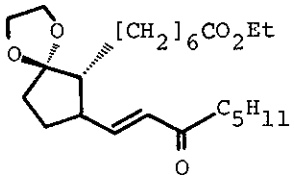

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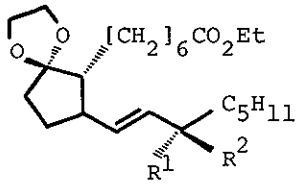
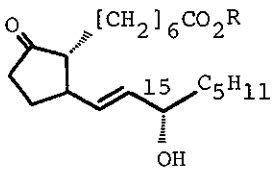


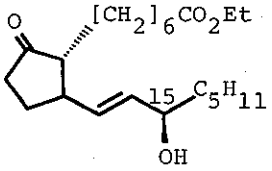
15 a, R_1=OH; R_2=H

b, R_1=H; R_2=OH



16 a, R=Et

b, R=H

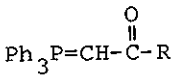


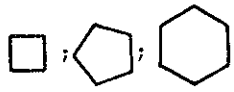
17

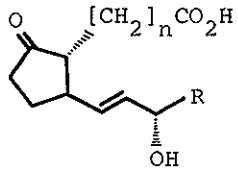
I-$[CH_2]_n$-CO_2Et

18 a, n=6

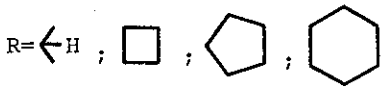
b, n=5



19, R= 



20, n=5,6

R= 

the desired keto-ester (16a), which was hydrolyzed using aqueous methanol potassium carbonate to give 11-deoxy PGE_1 (16b).

This was a long sequence, which has now been shortened. We investigated a number of borohydride reducing agents on the ene-dione (12), in the hope that a selective reagent could be found. Borohydride reagents, in some similar cases had been shown to be extremely sensitive to the environment of the carbonyl group.

First, we found that both zinc borohydride and sodium borohydride gave very substantial reduction at C-9. We then turned our attention to thexyllimonylborohydride (TLBH)[22], a highly selective reducing agent, which had been used successfully for the conversion of the enone to the allylic alcohol in the E_1 series[23], although the yield was only of the order of 40%.

Unfortunately, in the case of the 11-deoxy series the 15α:15β-alcohol ratio obtained on reduction with TLBH was less useful than that of the 11-hydroxy-series, i.e. a ca. 2:1 mixture of 15β-OH (17) : 15α-OH (16a), respectively, was isolated.

Other borohydride reducing agents[24], such as lithium perhydro-9b-boraphenalylhydride (PBPH)[25] and lithium tri-sec-butylborohydride (L-Selectide)[26] also gave mainly the wrong 15β-isomer (15R) (17) and a substantial amount of diols.

Fortunately, reduction of dione (12) with sodium cyano-borohydride in acidic medium[23,27] gave satisfactory results. Indeed, direct treatment of the enedione (12) with this reagent led to a reasonably regioselective reduction, affording a nearly equal mixture of 15-alcohols. The 15(R)-isomer (17), together

with any diols could be reoxidized in high yield to the enone (12), by the Brown and Garg procedure[28], thus giving a good yield of the desired alcohol (16a) after recycling. The ester group at C-1 was hydrolyzed with aqueous methanolic potassium carbonate to provide the crystalline dl-11-deoxy-PGE_1 (16b), identical with an authentic sample, thus confirming the correct stereochemistry at the three asymmetric centers, as well as the trans-geometry of the double bond. This improved reduction process substantially simplified the synthesis, since it shortened the whole route by three steps.

The approach just described leading to PG of the 1 series (saturated upper chain) is so simple, easy to perform and high yielding that it was given to undergraduate students for laboratory practice in organic chemistry[29]. The students prepared the appropriate intermediate compounds, e.g. the keto-esters (8), different iodo-esters (18) for alkylation at position 8, as well as phosphoranes (19) for the Wittig reaction or the corresponding phosphonates for the Horner-Emmons reaction[30] on the aldehyde at position 12 in intermediates such as compound (11). This allowed the preparation of a large array of novel prostaglandins of the type (20).

11-Desoxy-PG are of interest not only because of their intrinsic biological properties, such as antagonists of the PG belonging to the E and F-series[31], but also since they can be transformed chemically[32] to PGA and hence to 11-hydroxylated entities[11].

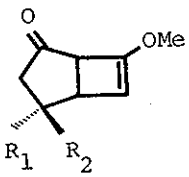
The difference in the chemical reactivity of the double

bonds in 7-methoxy-3,6-bicyclo[3.2.0]heptadiene-2-one (5) (vide supra) is further illustrated by the conjugate addition of lithium dimethylcopper[33] to the cyclopentenone (5), which proceeded regioselectively in ca. 70% yield to afford only 11-methylated derivatives[12]. In addition, a reasonably good stereoselectivity was observed, affording 80% of 11α-methyl cyclopentanone (21a) viz. 20% of the 11β-methyl isomer (21b). An exo-attack of alkyl group was anticipated in this 1,4-addition because of the bent geometry of the bicyclic system in (5).

Ozonolysis of the enol ether group of the 11α-methyl isomer (21a), followed by decomposition of the ozonide with sulfur dioxide in methanol solution, afforded the keto-ester-acetal (22).

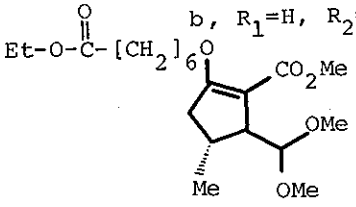
Various attempts to alkylate the substituted β-keto-ester (22) with ethyl 7-iodoheptanoate (18a)[16] gave mainly (ca. 60%) the O-alkylation product (23) and little (ca. 15%) of the desired C-alkylated material (24). An examination of keto-ester (22) with molecular models indicates that both sides are sterically hindered, thus blocking C-alkylation at position 8. Fortunately, this steric problem could be circumvented by making use of a more "linear" alkylating chain, namely ethyl 7-iodo-5-heptynoate (25)[34]. Reaction of keto-ester (22) with potassium hydride in dimethyl sulfoxide, followed by treatment with ethyl 7-iodo-5-heptynoate (25) at room temperature for 16 hr, gave exclusively the desired diester (26) in 73% yield.

The decarboxylation of the diester (26) was performed with sodium cyanide[17] to afford the acetylenic mono-ester (27) in 95% yield. Hydrogenation of the triple bond in the presence of



21 a, R_1=Me, R_2=H

b, R_1=H, R_2=Me



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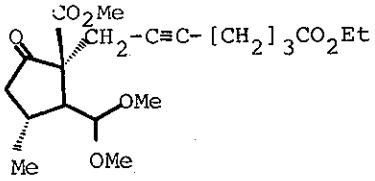

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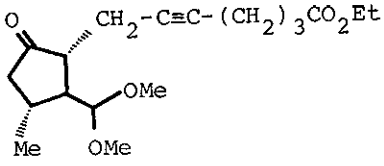

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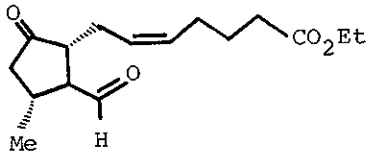

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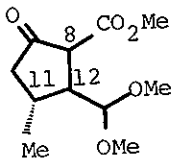

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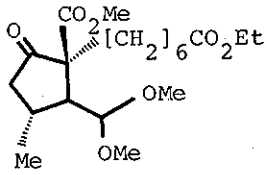

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$I-CH_2-C\equiv C-(CH_2)_3CO_2Et$

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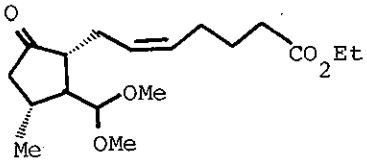

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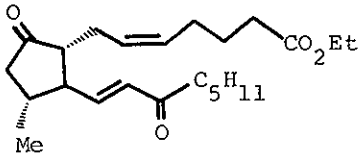


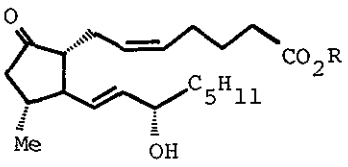
30

Lindlar catalyst[35] gave quantitatively the corresponding cis-olefin intermediate (28). Cleavage of the acetal group was achieved with Amberlite IR-120 in anhydrous acetone solution for 16 hr at room temperature, thus affording quantitatively the aldehyde (29). Treatment of aldehyde (29) by the usual procedure[20,29] gave the diene-dione (30) in ca. 60% yield.

After again surveying several known selective reducing agents for the reduction of the diketone (30), sodium cyanoborohydride in acidic medium[23,27] was still found to be the reagent of choice, furnishing the 15(S)-hydroxy compound (31a). The ester group was hydrolyzed with aqueous methanolic potassium carbonate to afford dl-11α-methyl-11-deoxy PGE_2 (31b), identical in all respects (but for the optical properties) with a sample obtained by lithium dimethylcopper addition to PGA_2[36,37]. This completed the total synthesis of a PG belonging to 11-alkyl PG 2-series ($\Delta^{5,13}$).

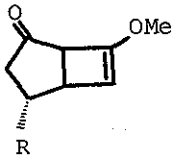
Some other modifications of the ring have also been performed. In particular, conjugate addition of lithium diphenylcopper and lithium di-n-butylcopper to the enone (5) provided the 11α-phenyl (32a) and 11α-n-butyl (32b) substituted cyclopentanones, respectively, which can be transformed to the corresponding PG of the 2-series (33) and the 1-series (34) by the above described sequence of reactions.

Additionally, cyanide addition to the cyclopentenone (5) has also been performed. Reaction of enone (5) with acetone cyanohydrin in ethanol containing a catalytic amount of aqueous potassium carbonate[38] furnished exclusively the 11α-cyano-intermediate



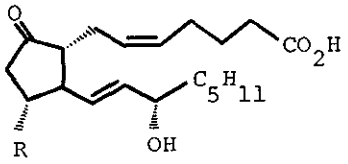
31 a, R=Et

b, R=H



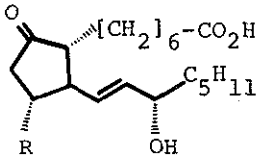
32 a, R=C_6H_5

b, R=n-Bu



33 a, R=C_6H_5

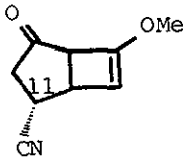
b, R=n-Bu



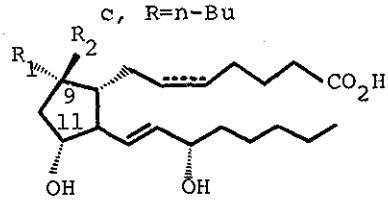
34 a, R=Me

b, R=C_6H_5

c, R=n-Bu



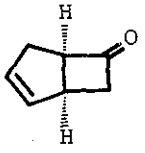
35



36 a, R_1=R_2=ketone

b, R_1=OH, R_2=H

c, R_1=H, R_2=OH



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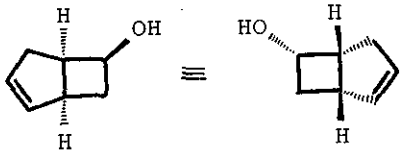


38

(35) in about 70% yield. This result is significant since it gives potential access to 11-oxygenated PG of type (36) by known methodology[11].

So far, we have mentioned the use of our new synthetic approach for the preparation of natural PG, as well as PG modified on the five-membered ring, and in the chains. The last part of this report is concerned with the preparation of four membered ring PG.

Reduction of the dichloro-cyclobutanone intermediate (2) with zinc in acetic acid produced the bicyclic ketone (37) in over 90% yield[6c,39]. Treatment of this ketone (37) with lithium aluminum hydride in tetrahydrofuran at -78° gave selectively (90%) the endo-alcohol (38) by hydride attack from the exo-side of the bicyclic ketone (37).

Ozonolysis of the olefinic bond of compound (38), followed by treatment of the ozonide with hydrogen peroxide and formic acid afforded the crystalline acid lactone (39a) in over 88% yield. The acid was then converted to its methyl ester (39b) for further identification and characterization.

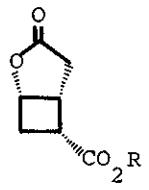
The acid (39a) could be reduced to the primary alcohol (40) by conversion to the mixed methyl carbonic anhydride by reaction with methyl chloroformate in tetrahydrofuran solution in the presence of triethylamine[40], followed by treatment with zinc borohydride in tetrahydrofuran solution. The γ-lactone group was not affected under these conditions but the alcohol (40) was only obtained in ca. 25% yield. Sodium borohydride in methanol also did not give a satisfactory result.

The yield in the conversion of acid (39a) to the corresponding alcohol (40) was substantially increased, however when this reduction was performed with borane in tetrahydrofuran[41], thus affording the desired compound (40) in ca. 75% yield.

Oxidation of the primary alcohol (40) to the corresponding aldehyde (41) was carried out in 70% yield by usual procedure[42].

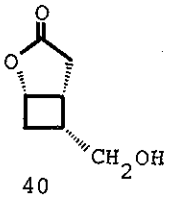
The concluding steps of the synthesis for the most part have been worked out previously[20]. Reaction of intermediate (41) with the sodium salt of dimethyl 2-oxoheptylphosphonate, followed by equilibration, furnished the expected enone (42), characterized by the typical spectral properties of the conjugated keto-chromophore. Reduction of the keto-group with sodium borohydride gave a mixture of isomers at C-15 (43a). The hydroxyl was converted to the tetrahydropyranyl ether (43b) by treatment with dihydropyran in the presence of acid. The lactone group was then reduced with diisobutylaluminum hydride in toluene solution[43], thus providing the hemi-acetal (44). Reaction with the Wittig reagent, generated from (4-carboxybutyl)triphenylphosphonium bromide using potassium hydride in dimethylsulfoxide, afforded the dl-11-nor $PGE_{2\alpha}$ as its tetrahydropyranyl ether derivative (45a). Acid hydrolysis then liberated the novel four-membered PGF analog (45b), as a separable mixture of isomers at C-15[44].

This part of the synthetic work benefited greatly from two features, which are worth emphasizing. One is the stereoselectivity observed during the reduction of ketone (37) to the endo-alcohol (38). The other is the efficient methodology employed in the conversion of the bicyclic alcohol (38) to the lactone-aldehyde (41), thus giving ready access to this novel series of 11-nor-prostaglandins.

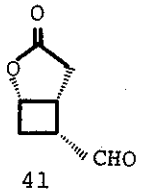


39 a, R=H

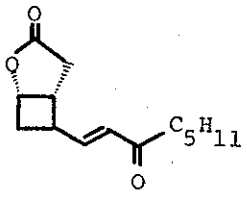
b, R=Me



40



41



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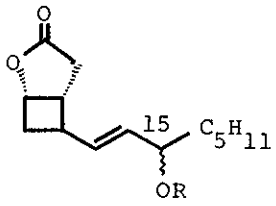
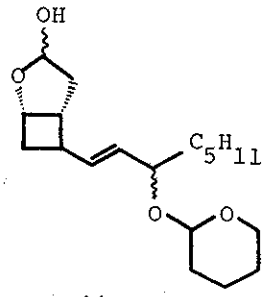
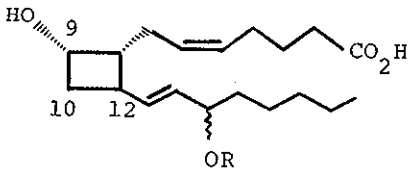


43 a, R=H

b, R=THP



44



45 a, R=THP

b, R=H

The noteworthy features of these syntheses are their simplicity and flexibility. Substituted tropolones are known[45], hence allowing the preparation of a large array of new prostanoids not easily secured by other routes. The key intermediates (5), (6), (7), (35), and (37) provide an ideal entry to a number of novel modified PG not readily available by other routes. This work also illustrates that photochemical reactions present an attractive potential in the synthesis of biologically important substances.

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REFERENCES

1. First presented on the occasion of the Centennial American Society Meeting, New York City, April 6, 1976.
2. Contribution n°12 from the Laboratoire de Chimie Organique, C.E.R.M.O., Université Scientifique et Médicale, Grenoble. For contribution n°11, see : A. Greene, A. Cruz and P. Crabbé, Tetrahedron Letters, 1976, 2707.
3. a) P. Crabbé, H. Carpio and A. Guzman, Intra-Science Chem. Rept., 1972, 6, 55 ; b) P. Crabbé, Arch. Invest. Med. (Mexico), 1972, 3, 151 ; c) P. Crabbé, An. Acad. Brasileira de Ciencias, 1973, 45, 63 ; d) P. Crabbé, Chem. in Britain, 1975, 11, 132.
4. W.G. Dauben, K. Koch, S.L. Smith, and O.L. Chapman, J. Amer. Chem. Soc., 1963, 85, 2616.
5. Aldrich Chemical Co., Milwaukee (Wisconsin), U.S.A.
6. a) H.C. Stevens, D.A. Reich, D.R. Brandt, K.R. Fountain, and E.J. Gaughan, J. Amer. Chem. Soc., 1965, 87, 5257 ; b) L. Ghosez, R. Montaigne and P. Mollet, Tetrahedron Letters, 1966, 135 ; c) L. Ghosez, R. Montaigne, A. Roussel, H. Van Liere and P. Mollet, Tetrahedron, 1971, 27, 615 ; d) W.T. Brady and J.P. Hieble, J. Amer. Chem. Soc., 1972, 94, 4278.
7. O.L. Chapman and D.J. Pasto, J. Amer. Chem. Soc., 1960, 82, 3642 ; O.L. Chapman and P. Fitton, ibid., 1963, 85, 41 ; O.L. Chapman, H.G. Smith and R.W. King, ibid., 1963, 85, 803.
8. Ch.H. DePuy and O.L. Chapman, Molecular Reactions and Photo-

chemistry, Chapter 5, Prentice-Hall, Inc., Englewood Cliffs, New Jersey (USA), 1972.

9. H.E. Zimmerman and D.I. Schuster, J. Amer. Chem. Soc., 1961, 83, 4486 ; 1962, 84, 4527.

10. For a preliminary communication see : A. Greene and P. Crabbé, Tetrahedron Letters, 1975, 2215.

11. See : P. Crabbé, (Edit.), Prostaglandin Research, Academic Press, New York (U.S.A.), in press.

12. Prostanoic acid numbering.

13. A. Greene, E. Barreiro and P. Crabbé, work in progress.

14. R.D. DeMaster, Ph.D. Dissertation, University of Minnesota, Diss. Abstr. Int. B., 1971, 31, 5871 ; see also : W.E. Noland and R.D. DeMaster, Org. Synth., 1972, 52, 135.

15. a) D.M. Pond and R.L. Cargill, J. Org. Chem., 1967, 32, 4064 ; b) C.A. Brown, ibid., 1974, 39, 3913.

16. a) M.E. Synerholm, J. Amer. Chem. Soc., 1947, 69, 2581 ; b) D.E. Ames, R.E. Bowman and R.G. Mason, J. Chem. Soc., 1950, 174 ; c) E.J. Corey and H.S. Sachdev, J. Amer. Chem. Soc., 1973, 95, 8483.

17. P. Müller and B. Siegfried, Tetrahedron Letters, 1973, 3565.

18. J.E. Pike, F.H. Lincoln, and W.P. Schneider, J. Org. Chem., 1969, 34, 3552.

19. J. Bagli and T. Bogri, Tetrahedron Letters, 1972, 3815 ; id., J. Org. Chem., 1972, 37, 2132 ; F.S. Alvarez, D. Wren and A. Prince, J. Amer. Chem. Soc., 1972, 94, 7823.

20. E.J. Corey, N.M. Weinshenker, T.K. Schaaf and W. Huber, J. Amer. Chem. Soc., 1969, 91, 5675 ; E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker and N.M. Weinshenker, ibid., 1970, 92, 397 ; E.J. Corey, K.B. Becker and R.K. Varma, ibid., 1972, 94, 8616, and references cited.

21. See : P. Crabbé, G.A. Garcia and C. Rius, J. Chem. Soc. Perkin Trans. I, 1973, 810.

22. a) E.J. Corey and R.K. Varma, J. Amer. Chem. Soc., 1971, 93, 7319 ; b) R.E. Schaub and M.J. Weiss, Tetrahedron Letters, 1973, 129.

23. M. Miyano and M.A. Stealey, Chem. Comm., 1973, 180 ; id., J. Org. Chem., 1975, 40, 1748.

24. See : E.J. Corey, K.B. Becker and R.K. Varma, J. Amer. Chem. Soc., 1972, 94, 8616.

25. H.C. Brown and W.C. Dickason, J. Amer. Chem. Soc., 1970, 92, 709.

26. H.C. Brown and S. Krishnamurthy, J. Amer. Chem. Soc., 1972, 94, 7159.

27. See : R.O. Hutchins and D. Kandasamy, J. Org. Chem., 1975, 40, 2530.

28. a) H.C. Brown and C.P. Garg, J. Amer. Chem. Soc., 1961, 83, 2952 ; b) H.C. Brown, C.P. Garg and K.T. Liu, J. Org. Chem., 1971, 36, 387.

29. A. Krief, W. Dumont, J.P. Deprés, A. Greene, and P. Crabbé, manuscript in preparation.

30. a) W.S. Wadsworth and W.D. Emmons, J. Amer. Chem. Soc., 1961, 83, 1733 ; b) L. Horner, H. Hoffmann, W. Klink, H. Ertel and V.G. Toscano, Chem. Ber., 1962, 95, 581, and references cited therein.

31. J.F. Bagli, T. Bogri, and R. Deghengli, Tetrahedron Letters, 1966, 465 ; J.F. Bagli and T. Bogri, ibid., 1967, 5.

32. G. Stork and S. Raucher, J. Amer. Chem. Soc., 1976, 98, 1583.

33. See : H.O House, Acc. Chem. Res., 1976, 9, 59, and references therein.

34. E.J. Corey and H.S. Sachdev, J. Amer. Chem. Soc., 1973, 95, 8483.

35. H. Lindlar, Helv. Chim. Acta, 1952, 35, 446.

36. a) A. Guzman and P. Crabbé, Chem. and Ind., 1973, 635 ; b) C.V. Grudzinskas and M.J. Weiss, Tetrahedron Letters, 1973, 141.

37. P. Crabbé and G. Gagnaire, manuscript in preparation.

38. A. Ercoli and P. De Ruggieri, J. Amer. Chem. Soc., 1953, 75, 650.

39. a) E.J. Corey, Z. Arnold and J. Hutton, Tetrahedron Letters, 1970, 307 ; b) P. Grieco, J. Org. Chem., 1972, 37, 2363.

40. K. Ishizumi, K. Koga and S. Yamada, Chem. Pharm. Bull. (Japan), 1968, 16, 492.

41. R. Peel and J.K. Sutherland, Chem. Comm., 1974, 151.

42. a) J.C. Collins, W.W. Hess, and F.J. Frank, Tetrahedron Letters, 1968, 3363 ; b) E.J. Corey and J.W. Suggs, ibid., 1975, 2647.

43. L.I. Zakharkin and I.M. Khorlina, Tetrahedron Letters, 1962, 619.

44. For further information see : A.E. Greene, J.P. Deprès, M.C. Meana and P. Crabbé, Tetrahedron Letters, submitted for publication.

45. a) R. Noyori, S. Makino, T. Okita and Y. Hayakawa, J. Org. Chem., 1975, 40, 806 ; b) D.M.G. Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds", Elsevier Publ. Co., Amsterdam (Holland),1966.

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