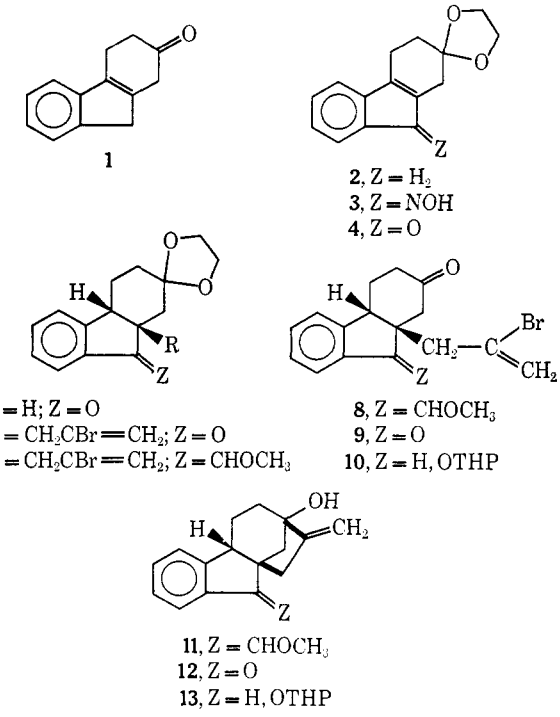
acetate led to formation of the saturated keto ketal **5**,[5,7] mp 80–82°. Alkylation of **5** by 2,3-dibromopropene (2 equiv) and potassium *t*-butoxide (1.5 equiv) in *t*-butyl alcohol at 25° for 6 hr[4] produced the tricarbocyclic bromide **6**,[5] mp 100–102°, stereospecifically in 90% yield.[8] Reaction of **6** with methoxymethylenetriphenylphosphorane in tetrahydrofuran at 25° for 15 hr[4] afforded the enol ether **7**[5] (>98% yield) as an oily mixture (3:1 by nmr analysis) of geometrical isomers about the newly created double bond. Exposure of **7** to 80% acetic acid–20% water at 25° for 2 hr resulted in formation of the bromo ketone **8**.

Reaction of **8** with 6 equiv of di-*n*-butylcopperlithium[1] in ether (0.15 *M*) at −50° for 2.5 hr[4] gave the desired cyclization product, 7-hydroxy-10-methoxymethylene-8-methylenegibba-1,3,4a(10a)-triene (**11**) (as a mixture of geometric isomers about C=CHOCH$_3$), in 73% yield.[9] The structural assignment follows (a) from the infrared spectrum which indicates hydroxyl (2.65, 2.83 μ), enol ether C=C (5.99 μ), and C=CH$_2$ (11.21 μ) as well as the absence of carbonyl; (b) from the nmr spectrum which exhibits C=CH$_2$ proton peaks at 4.89 and 5.22 ppm (downfield from internal tetramethylsilane); and (c) from the mass spectrum (molecular ion at *m/e* 268).[10] In addition, **11** undergoes the allogibberic acid rearrangement[2] upon refluxing in concentrated hydrochloric acid–ethanol (1:3) for 1 hr to form a keto aldehyde having infrared maximum (CCl_4) at 5.80 and 5.73 μ. The simplicity and success of the cyclization of the bromo ketone **8** to the gibbane derivative **11** illustrate the utility of the new process outlined in the foregoing communication. It seems quite possible that the efficiency of the cyclization might be made even greater by experimental modifications designed to reduce the occurrence of competing cross coupling, and, therefore, such studies are being carried out.

It is noteworthy that the same cyclization process can even be applied effectively to the diketone **9** (using *ca.* 6 equiv of the copper reagent[4] in ether at −20 to −35°) to afford the tetracyclic hydroxy ketone **12**,[5] mp 137°, in 60% yield.[11] It is clear from this fact that there is considerable selectivity between different carbonyl groups, so that in favorable circumstances the use of conventional carbonyl protection may not be necessary.[12] The bromo ketone **10**, in which a benzylic secondary alcohol group is protected as the tetrahydropyranyl ether, also undergoes smooth cyclization with di-*n*-butylcopperlithium[4] (conditions as for the cyclization of **8**) to form **13** in 70% yield.



1

2, Z = H_2
3, Z = NOH
4, Z = O

5, R = H; Z = O
6, R = $CH_2CBr{=}CH_2$; Z = O
7, R = $CH_2CBr{=}CH_2$; Z = $CHOCH_3$

8, Z = $CHOCH_3$
9, Z = O
10, Z = H, OTHP

11, Z = $CHOCH_3$
12, Z = O
13, Z = H, OTHP

The availability of an effective method for the synthesis of the bicyclo[3.2.1]octane part of the gibberellic acid structure should simplify substantially the task of synthesis of the gibberellins. Further studies along these lines will be published at a later time.[13]

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Total Synthesis of Prostaglandins $F_{2\alpha}$ and E_2 as the Naturally Occurring Forms

Sir:

An effective stereocontrolled synthesis of the racemic forms of prostaglandins $F_{2\alpha}$ and E_2 has recently been described.[1] In this communication we outline the adaptation of this approach to allow the first synthesis of these hormones in the naturally occurring, optically active forms.[2,3]

The oily (±)-hydroxy acid **2**, obtained by hydrolysis of the readily available lactone **1**[1] followed by acidification and extraction (>90% yield), afforded a crystalline salt when treated with (+)-ephedrine[4] in hot benzene as fine colorless needles, $[\alpha]^{23}D$ +35.8° (*c* 0.86, CH_3OH).[5] One recrystallization of this salt from benzene afforded in 67% of the theoretical yield the fully

(7) For a recent synthesis of the corresponding diketone by a different route, see F. E. Ziegler and M. E. Condon, *Tetrahedron Lett.*, 2315 (1969).

(8) Formation of the *cis*-fused alkylation product, as anticipated on steric grounds, finds analogy in similar systems; see, for example, H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964), and references cited therein.

(9) The tetracyclic alcohol **11** was readily separated chromatographically from the major by-product (23% yield) which resulted from the replacement of bromine in **8** by *n*-butyl.

(10) The formation of a similar tetracyclic structure by cyclization of an acetylenic hydrofluorenone derivative using sodium in liquid ammonia (apparently in low yield) has been reported by G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, **87**, 1148 (1965).

(11) This result was obtained by Dr. Thomas M. Brennan in these laboratories. The yield is probably not optimal, since only a single experiment has been performed.

(12) For other examples of the use of dialkylcopperlithium reagents with substrates having unprotected and unreactive carbonyl compounds, see E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **90**, 5615 (1968).

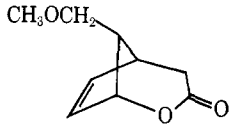
(1) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(2) We have previously reported the first total synthesis of the naturally occurring forms of prostaglandins $F_{1\alpha}$ and E_1; see E. J. Corey, I. Vlattas, and K. Harding, *ibid.*, **91**, 535 (1969).

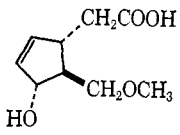
(3) For other syntheses of the racemic forms of prostaglandins $F_{2\alpha}$ and E_2, see (a) W. P. Schneider, *Chem. Commun.*, 304 (1969); (b) E. J. Corey, Z. Arnold, and J. A. Hutton, *Tetrahedron Lett.*, in press; and (c) E. J. Corey and R. Noyori, *ibid.*, in press.

(4) The hydrochloride of (+)-ephedrine was obtained from Fluka, A.G.

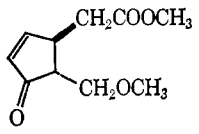
(5) The rotation of the 1:1 mixture of diastereomeric salts from (±)-**2** and (+)-ephedrine was found to be $[\alpha]^{23}D$ +21.5° (*c* 1.14, CH_3OH).



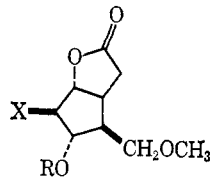
1



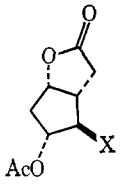
2



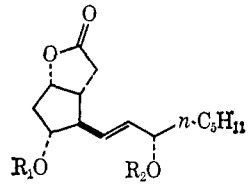
3



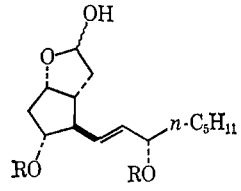
4, X = I; R = H
5, X = I; R = Ac
6, X = H; R = Ac



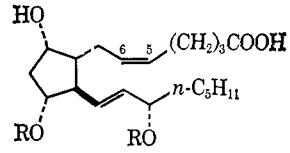
7, X = CH_2OH
8, X = CHO
9, X = $CH{=}CHCOn\text{-}C_5H_{11}$



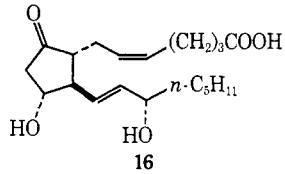
10, R_1 = OAc; R_2 = H
11, R_1 = R_2 = H
12, R_1 = R_2 = THP



13, R_1 = R_2 = THP



14, R = THP
15, R = H



16

resolved salt of (+)-ephedrine with **2**, $[\alpha]^{23}D$ +37.2° (*c* 1.0, CH_3OH), mp 133.5–134°.[6] *Anal.* Found: C, 64.58; H, 8.32; N, 3.88. The resolution could also be performed (though less efficiently) using methanol–ether for recrystallization of the (+)-ephedrine salt, in which case three recrystallizations produced salt of the same properties as recorded above in 60% yield.

The resolution of (±)-**2** with (−)-ephedrine[7] as described above afforded the diastereomeric crystalline (−)-ephedrine salt, mp 132.5–133.5°, $[\alpha]^{29}D$ −37.0°. Recovery of the free hydroxy acid from this salt gave an oily product, $[\alpha]^{29}D$ −11.7° (*c* 1.35, CH_3OH). This was shown to be the antipode of the desired hydroxy acid (**2**) by treatment with diazomethane followed by oxidation with activated manganese dioxide to form a keto ester which was indicated to be of absolute configuration **3** by optical rotatory dispersion data. The keto ester **3** from the (−)-hydroxy acid showed a negative Cotton effect with a trough in the ORD curve at 238 nm (ϕ −14,000°), in contrast to the positive Cotton effect shown by the ORD curve of natural prostaglandin A_1,[8] which implied the absolute configuration represented by **3**. This tentative assignment allowed the selection (shown below to be correct) of the (+)-hydroxy acid **2**, obtained using (+)-ephedrine for resolution, for use in the synthesis of prostaglandins of natural configuration.

Treatment of the sodium salt of the dextrorotatory acid **2** in water at 0–5° with potassium triiodide (2.5 equiv) for 20 hr produced (97% yield) the iodo lactone **4**, mp 99.5–100°, $[\alpha]^{26}D$ −45.8° (*c* 1.0).[9] From this point the synthesis was carried out using essentially the same experimental conditions as described earlier[1] to give successively the following optically active intermediates: **5** (mp 76.5–77°, $[\alpha]^{28}D$ −9.15° (*c* 2.25)); **6** (oil, $[\alpha]^{29}D$ −70.3° (*c* 2.90); **7** (oil, $[\alpha]^{26}D$ −40.3° (*c* 2.68)); **8** (oil used directly without purification); **9** (oil, $[\alpha]^{28}D$ −9.96° (*c* 2.88)); **10** (oil, $[\alpha]^{27}D$ −20.0° (*c* 1.67)); **11** (oil, $[\alpha]^{27}D$ −7.00° (*c* 1.43)); **12** (oil, $[\alpha]^{25}D$ −20.8° (*c* 2.55)); **13** (oil, $[\alpha]^{26}D$ −23.6° (*c* 1.90)); and **14** (oil, $[\alpha]^{24}D$ +13.3° (*c* 1.02)).

Hydrolysis of **14** in acetic acid–water (2:1) containing a small amount of tetrahydrofuran (to achieve homogeneity) at 47° for 4 hr afforded prostaglandin $F_{2\alpha}$ (**15**) in 82% yield after chromatographic purification. The synthetic **15** had $[\alpha]^{25}D$ +23.8° (*c* 1.00, tetrahydrofuran) as compared with $[\alpha]^{25}D$ +23.5° (*c* 1.00, tetrahydrofuran) found for an authentic sample of naturally derived prostaglandin $F_{2\alpha}$. Further, the infrared and nmr spectra and chromatographic behavior of natural and synthetic **15** were completely identical. Oxidation of **14** using Jones reagent at −10° for 30 min and subsequent work-up and hydrolysis in 2:1 acetic acid–water to remove the tetrahydropyranyl groups afforded, after chromatography, pure synthetic prostaglandin E_2 (**16**, 70%). Recrystallization from ethyl acetate–hexane gave colorless crystals of **16**, mp 65–66°, and mmp 64.5–66° when admixed with a sample of naturally derived prostaglandin E_2 of mp 64.5–65.5°. The optical rotations of samples of synthetic and natural prostaglandin E_2 were the same within experimental error, $[\alpha]^{26}D$ −61° (*c* 1.0, tetrahydrofuran). The biological activities of synthetic and natural samples of prostaglandin $F_{2\alpha}$ (**15**) and of prostaglandin E_2 (**16**) were identical.[10]

The synthesis of the naturally occurring forms of prostaglandins $F_{2\alpha}$ and E_2 which is described herein can probably be improved by further studies which are now under way. However, the efficiency of the process is quite good as it now stands, since the conversion of the optically active hydroxy acid **2** to the immediate precursor **14** of prostaglandins $F_{2\alpha}$ and E_2 can be effected under presently known optimal conditions in *ca.* 50% yield.[11] A route is thus available for the synthesis of these hormones in sufficient quantities for physiological and medical studies.[12]

(6) Further recrystallization of this salt from benzene did not increase the rotation.
(7) Aldrich Chemical Co.
(8) N. H. Andersen, *J. Lipid Res.*, **10**, 320 (1969).
(9) The infrared and nmr spectra of this and all other optically active intermediates in the synthesis agreed with those obtained earlier for the corresponding racemic compounds. All rotations were measured in chloroform unless otherwise indicated.
(10) We are indebted to Dr. Peter Ramwell and Dr. Jane Shaw of The Worcester Foundation for Experimental Biology for the biological assays.
(11) Based on separation of the epimeric carbonyl reduction products of **9** and the conversion of both epimeric alcohols (ref 1) to **11**.
(12) This work was assisted by a grant from the National Institutes of Health.

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