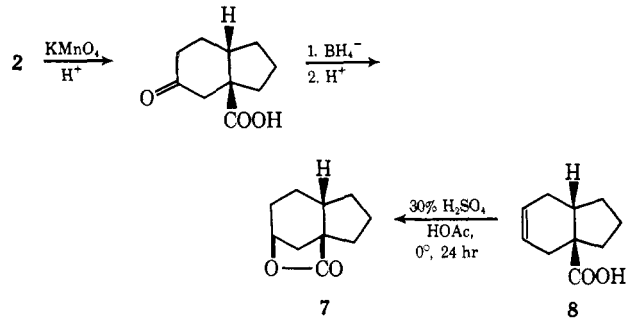
since in its absence a complex mixture of compounds, including the expected isomeric aldol cyclization products, results. The highly effective β vinylation and pinacol cyclization processes illustrated in the present synthesis of the tricyclic ketol **6** from **1** are currently being applied to a synthesis of gibberellic acid (gibberellin A_3).[11]

The cis ring junction of **2** was established by its conversion to the lactone **7**[6] by the sequence outlined in Scheme II together with the synthesis of identically

Scheme II



the same substance[6] from the unsaturated acid **8** which results from addition of 1,3-butadiene to 1-cyclopentenecarboxylic acid.[12]

Additionally, the synthetic sequence outlined in Scheme I has also been carried out in good overall yield starting with 2-cyclohexenone by procedures similar to those outlined above for the conversion **1** → **5**. We expect that both the β vinylation and pinacol cyclization processes described herein will prove to be highly useful general methods.

Acknowledgment. This work was assisted financially by the National Institutes of Health and the National Science Foundation.

(11) Previous work in this laboratory by Dr. M. Narisada (1967) demonstrated that diallylcopperlithium could be used for effective β addition of a CH_2CHO group to conjugated enones; see also, H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969). However, the use of the vinylation reagent is clearly superior, especially when an angular appendage is being introduced.

(12) (a) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934); (b) H. O. House, S. G. Boots, and V. K. Jones, *J. Org. Chem.*, **30**, 2519 (1965); (c) R. L. Kronenthal and E. I. Becker, *J. Amer. Chem. Soc.*, **79**, 1095 (1957).

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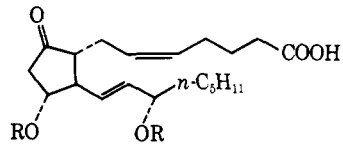
Specific Reduction of E Prostaglandins to F_α Prostaglandins and Prostaglandin E_2 to Prostaglandin E_1

Sir:

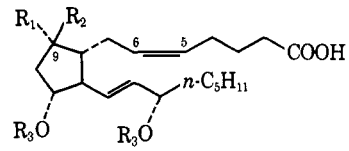
Reported here are two highly specific reductive processes for the interconversion of primary[1] prostaglandins. These transformations have important implications both for the design of synthetic approaches to primary prostaglandins and with regard to the development of new chemical manipulations of these substances.

(1) S. Bergström, *Science*, **157**, 382 (1967).

It has previously been reported that the reduction of prostaglandin E_2 (**1**) by means of sodium borohydride proceeds nonstereoselectively to form prostaglandins $F_{2\alpha}$ (**2**) and $F_{2\beta}$ (**3**) with the latter (which is biologically far less potent) predominating slightly, and parallel results have been obtained for prostaglandin E_1.[2-4] The lack of stereochemical control in the conversion



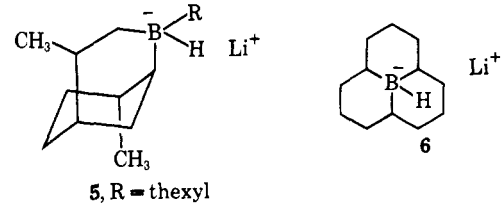
1, R = H



2, R_1 = OH; R_2 = H; R_3 = H
3, R_1 = H; R_2 = OH; R_3 = H
4, R_1 = OH; R_2 = H; R_3 = THP

of the E to the F_α prostaglandins suggested that chemical syntheses of these substances should be designed to allow the synthesis of a protected F_α derivative (*e.g.*, **4**) and its use as a precursor of *both* F_α and E prostaglandins rather than a sequence in which an E derivative is synthesized first.[5] The development of a stereospecific reduction of E to F_α prostaglandins as is described herein now validates the use of the second approach and hence opens a wider range of reasonable synthetic schemes.

It has been found that the reduction of prostaglandin E_2 with the bulky trialkyl borohydride reagent **5**[6] or **6**[7] in tetrahydrofuran (THF) at −78° produces stereospecifically prostaglandin $F_{2\alpha}$ (**2**); no appreciable for-



5, R = thexyl

mation of prostaglandin $F_{2\beta}$ (**3**) could be found by thin-layer chromatographic (tlc) analysis which allows easy detection of small amounts of **3** in the presence of **2**. The effectiveness and simplicity of this process can be seen from the following procedure. A solution of 30 mg of prostaglandin E_2 (synthetic,[6] natural form) in 0.5 ml of dry THF was stirred in a bath at −78° under an inert atmosphere. A solution of 0.36 mmol of reagent **6** in 0.9 ml of THF was added dropwise

(2) S. Bergström, L. Krabisch, B. Samuelsson, and J. Sjöval, *Acta Chem. Scand.*, **16**, 969 (1962).

(3) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(4) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968).

(5) A general synthesis of prostaglandins which received guidance from these considerations has been realized; see E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971), and preceding papers noted therein.

(6) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971).

(7) H. C. Brown and W. C. Dickason, *ibid.*, **92**, 709 (1970).

over 3 min and after 20 min water was added and the mixture was allowed to warm to room temperature. Acidification of the aqueous phase to pH 3.5, after extraction with ethyl acetate to remove nonacidic materials, and extraction with ethyl acetate yielded, after drying ($MgSO_4$) and concentration under reduced pressure, 29.6 mg (98.7%) of prostaglandin $F_{2\alpha}$ (**3**) as a colorless oil, $[\alpha]^{25}D$ +23.9° (*c* 0.955, THF), exhibiting infrared and nmr (100 MHz) spectra and tlc behavior (in six solvent systems with silica gel and silica gel–$AgNO_3$ as adsorbants) identical with that of a sample of pure prostaglandin $F_{2\alpha}$.

The conversion of prostaglandin E_2 to E_1, which in conjunction with the $E \rightarrow F_\alpha$ reduction described above would make possible the selective synthesis from prostaglandin E_2 of the three prostaglandins E_1, $F_{2\alpha}$, and $F_{1\alpha}$, has also been accomplished in a straightforward way. We have reported previously that the 11,15-bistetrahydropyranyl derivative of prostaglandin $F_{2\alpha}$ (**4**) can be selectively hydrogenated over Pd/C at the Δ^5 olefinic bond to give the corresponding $F_{1\alpha}$ derivative.[8] The success of this reduction depends to a considerable extent on the steric screening of the Δ^{13} linkage by the 11- and 15-tetrahydropyranyl groups. It now appears that the dimethylisopropylsilyl (DMIS) grouping is even more effective than is tetrahydropyranyl in promoting selective reduction of the Δ^6 over the Δ^{13} olefinic linkage. In addition, this silyl group is readily introduced and removed, even in the sensitive E series, which enhances still further its utility.

Reaction of prostaglandin E_2 (63 mg) in a little dry tetrahydrofuran with an excess of a 1:1 mixture of dimethylisopropylchlorosilane[9] and 1,1,3,3-tetramethyl-1,3-diisopropyldisilazane[10] at 25° for 48 hr produced the 11,15-bis-DMIS ether of prostaglandin E_2 DMIS ester in 97.4% yield as a colorless liquid which was homogeneous by tlc analysis. A solution of this substance (54 mg) in methanol at −23° was stirred with 5% palladium/charcoal catalyst (Engelhard Industries) under 1 atm of hydrogen until no starting material could be detected by tlc analysis (using silica gel impregnated with silver nitrate) (*ca.* 4 hr). Removal of catalyst and methanol and treatment with 3:1 acetic acid–water at 35° for 10 min gave after dilution with water, extraction, and evaporation almost pure prostaglandin E_1 (by tlc analysis) in an analytical yield (by conversion to prostaglandin B_1 and spectroscopic analysis[11]) of 102 ± 10%. Three recrystallizations of this material from ethyl acetate–cyclohexane gave very pure prostaglandin E_1 (22 mg, 77% yield), mp 115–115.5° (undepressed upon admixture with an authentic sample), $[\alpha]^{25}D$ −58.3°, $[\alpha]^{25}_{578}$ −61.7° (*c* 0.47, THF), which was spectroscopically (nmr, infrared) identical with pure prostaglandin E_1. Additional prostaglandin E_1 could be obtained from the mother liquors after chromatography.[12] It should be noted that the acid-catalyzed cleavage of the DMIS ethers occurs under markedly milder conditions (generally 3:1 acetic acid–water, 35°, 10 min) than are required for tetrahydropyranyl ethers. We have found this property to be useful in other studies in the prostaglandin area.[13] It has also been observed[13] that DMIS ethers are frequently nicely crystalline substances whereas the corresponding THP ethers are usually oils (additional chiral center!). We have not studied other bulky silyl derivatives extensively, but it is obvious that there are probably several besides the DMIS series which will prove useful because of the range of properties which can be obtained.

As a result of the present study any stereoselective synthesis of prostaglandin E_2 can also be considered as a stereoselective route to prostaglandins E_1, $F_{1\alpha}$, and $F_{2\alpha}$.

Acknowledgment. This research was assisted financially by grants from the U. S. Agency for International Development and the National Institutes of Health.

(8) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970).

(9) Prepared from dimethyldichlorosilane (small excess) and isopropyllithium.

(10) Prepared from dimethylisopropylchlorosilane and dry ammonia in ether. See C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(11) N. H. Andersen, *J. Lipid Res.*, **10**, 320 (1969).

(12) The reduction at Δ^5 of the 11,15-bistetrahydropyranyl ether of prostaglandin E_2 is considerably less selective than that of the dimethylisopropylsilyl (DMIS) derivative reported above and also less selective than that observed[8] with the 11,15-bistetrahydropyranyl ether of prostaglandin $F_{2\alpha}$ (**4**).

(13) Unpublished work with Dr. A. Venkateswarlu.

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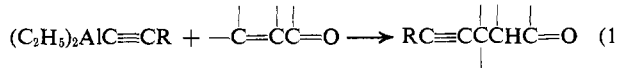
The Reaction of Diethylalkynylalane Reagents with Conjugated Enones. A Method for 1,4 Addition of Acetylene Units to Simple α,β-Unsaturated Ketones

Sir:

γ,δ-Acetylenic ketones are valued synthetic intermediates since they are easily converted to a variety of important structural classes (*inter alia*, 1,4-diketones,[1] 1,5-dienes[2]). Although the conceptually most direct approach for their synthesis involves a Michael-type reaction between an acetylenic unit and a conjugated enone, in practice, all attempts to carry out this transformation have been unsuccessful.[3,4] This communication describes a new reaction which fills this gap in methodology (eq 1): diethylalkynylalanes react with a range



(1)

of simple conjugated enones to give fair–excellent yields of 1,4-addition products.[5]

(1) G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964).

(2) W. S. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *ibid.*, **90**, 5872 (1968).

(3) (a) A review of this problem appears in the Ph.D. Thesis of J. H. Rea, University of Missouri, 1965; *Diss. Abstr.*, **26**, 5043 (1966). (b) Dilithium trialkynylcuprate complexes also fail to effect the conjugate addition of an alkynyl group to a conjugated enone: H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969).

(4) In contrast, the conjugate addition reactions of alkyl, vinyl, and aryl Grignard reagents or organocopper species are part of standard synthetic repertoire: (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, New York, N. Y., 1954, Chapter 6; (b) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968); (c) E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969); (d) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970).

(5) A model for the development of this method was the Nagata hydrocyanation reaction (W. Nagata and M. Yoshioka, *Tetrahedron Lett.*, 1913 (1966)), in which the sp-hybridized carbon of a cyano function is delivered to the β carbon of a conjugated enone. This reaction prompted the expectation that an alkynyl group might behave similarly.