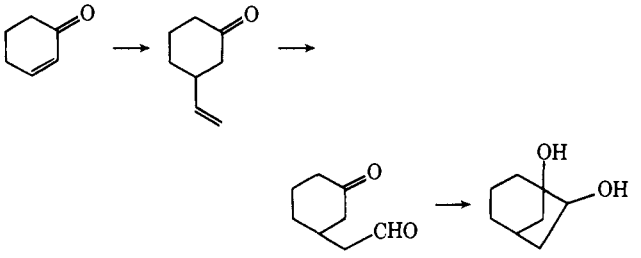
New Methods for Carbocyclic Synthesis Applicable to the Gibberellic Acids. Stereoselective Introduction of the Angular Vinyl Grouping and Pinacolic Cyclization of Keto Aldehydes

Sir:

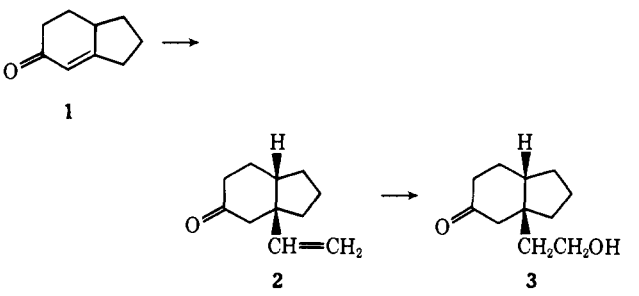
As part of a project aimed at finding a stereospecific synthetic route to gibberellic acids, a new approach has been developed for the synthesis of the requisite bicyclo[3.2.1]octane system analogously functionalized by bridgehead hydroxyl and two-carbon bridge unsaturation.[1] It has been observed that the conjugate addition of divinylcopperlithium to 2-cyclohexenones is an outstandingly useful process for the introduction of a β or even angular β vinyl substituent. This reaction is depicted in Scheme I along with subsequent steps for

Scheme I

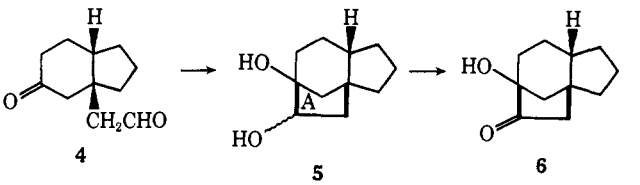


the development of the functionalized bicyclo[3.2.1]-octane unit.

Birch reduction (4.5 atom equiv of lithium in 3:1:1.5 ammonia–tetrahydrofuran–*tert*-butyl alcohol at reflux for 0.5 hr) of 5-methoxyindan[2] produced the expected 4,7-dihydro derivative cleanly, and this was converted to the conjugated indenone **1**[3] by sequential treatment with 0.5 *N* hydrochloric acid in 1:3 water–THF (tetrahydrofuran) for 10 hr at 25° (to effect enol ether hydrolysis) and with a 1% solution of diazabicycloundecene in methanol for 0.5 hr at 25° (to effect C=C, C=O conjugation) (overall yield 83%). Addition of the enone **1** in a little ether (dropwise) to a solution of 1.3 mol equiv of divinylcopperlithium[4] in THF at −72° under argon[5] led to an *exothermic* reaction (temperature held below −65° by external cooling). After 10 min at −70° the reaction mixture was allowed to warm over 20 min to −40° and then poured directly into ice-cold aqueous ammonium chloride buffered to pH 8 with ammonia. Extractive work-up followed by distillation gave stereospecifically (vpc analysis) a single β vinylated ketone, bp 62–64° (35 mm), in >90% yield, shown to be the cis fused isomer **2**[6] by the structural correlation outlined in a later section.



Ketalization of **2** using ethylene glycol–toluenesulfonic acid–benzene at reflux for 6 hr gave the ethylene ketal[6a] which was hydroborated with 1.15 equiv of diborane in THF (15 min, 0°) and oxidized with alkaline peroxide. The hydroxy ketone **3**[6a] was then obtained by deketalization (THF–0.1 *N* HCl, 2:7, at 25° for 15 hr) in 80% overall yield from **2**. Oxidation of **3** using Collins reagent[7] produced the keto aldehyde **4**,[6a] homogeneous by thin-layer chromatographic (tlc) analysis. Gradual addition of **4** to a mixture of magnesium amalgam (7.5 equiv, prepared from magnesium turnings) and dimethyldichlorosilane (2 equiv) in dry THF at 25° with stirring produced after an additional 1 hr stirring and subsequent alkaline desilylation a mixture of the *cis*- and *trans*-diols **5** (*cis*- and *trans*-



hydroxyl designation relative to the five-membered ring A in **5**) in a ratio of 80:20 and a yield of 75%. Chromatographic separation on silica gel using ether as eluent afforded the crystalline diols *cis*-**5**,[6] mp 88–89°, and *trans*-**5**,[6] mp 109–111°.[8] Oxidation of the mixture of stereoisomeric diols **5** using *tert*-butyl hypochlorite (1.1 equiv) and pyridine (2 equiv) in methylene chloride at 0° for 7 hr afforded the α-ketol **6**.[6] Reduction of **6** using sodium borohydride in ethanol at 20° for 8 hr yielded *trans*-**5**, with high stereoselectivity.

The use of the chlorosilane[9,10] in the pinacol cyclization of **4** to **5** is crucial to the success of this process,

(1) For other studies on the construction of this unit, see (a) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, 87, 1148 (1965); (b) S. J. Etheredge, *Tetrahedron Lett.*, 4527 (1965); (c) K. Mori, M. Matsui, and Y. Sumiki, *ibid.*, 429 (1970); (d) F. E. Ziegler and J. A. Kloek, *ibid.*, 2201 (1971); (e) E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Amer. Chem. Soc.*, **92**, 396 (1970); (f) H. O. House and J. K. Larson, *J. Org. Chem.*, 33, 61 (1968).

(2) S. L. Shapiro, T. Bazga, K. Weinberg, and L. Freedman, *J. Amer. Chem. Soc.*, 80, 3726 (1958).

(3) The ketone **1** has previously been prepared by other routes; see (a) V. Prelog and M. Zimmermann, *Helv. Chim. Acta*, 32, 2360 (1949), and (b) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 85, 207 (1963).

(4) The organometallic reagent was prepared from a solution of dry, recrystallized cuprous iodide in dry isopropyl sulfide (3.1 mol equiv) by reaction at −25 to −15° (−50° for mixing) with a 2.2 *M* solution of vinyllithium (1.92 equiv) in THF. The dark colored solution of the reagent was cooled to −72° after 15 min at −15° to allow complete formation.

(5) All reactions involving organometallic reagents or strong bases were carried out under an argon atmosphere.

(6) Satisfactory (a) nuclear magnetic resonance and infrared spectra and (b) elemental analysis and/or high-resolution (AEI MS-9) mass spectral data were obtained for this intermediate.

(7) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(8) The assignments of *cis*- and *trans*-hydroxyl orientations to the glycols **5** were made on the basis of their relative behavior toward Jones chromic acid reagent. The diol mp 109–111° gave mainly hydroxy ketone **6**, whereas the diol mp 88–89° produced mainly keto aldehyde 4. See, for example, J. Rocek and F. H. Westheimer, *J. Amer. Chem. Soc.*, **84**, 2241 (1962).

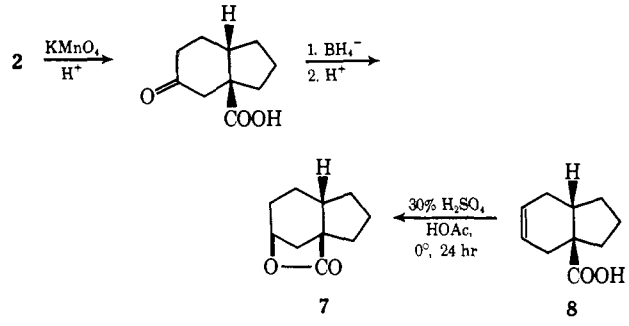
(9) See K. Rühlmann, *Synthesis*, 236 (1971).

(10) To our knowledge the conversion of 4 to **5** is the first successful pinacol cyclization of a cycloaliphatic keto aldehyde.

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



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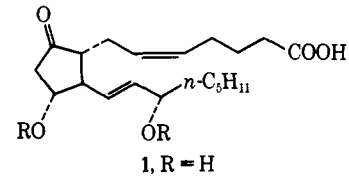
Specific Reduction of E Prostaglandins to F_α Prostaglandins and Prostaglandin E_2 to Prostaglandin E_1

Sir:

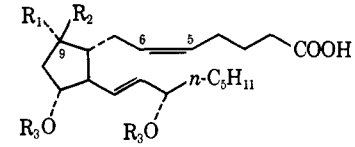
Reported here are two highly specific reductive processes for the interconversion of primary[1] prostaglandins. These transformations have important implications both for the design of synthetic approaches to primary prostaglandins and with regard to the development of new chemical manipulations of these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



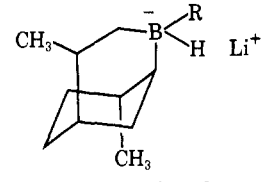
1, R = H



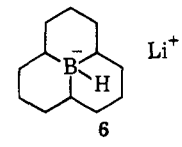
2, R_1 = OH; R_2 = H; R_3 = H
3, R_1 = H; R_2 = OH; R_3 = H
4, R_1 = OH; R_2 = H; R_3 = THP

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



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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).