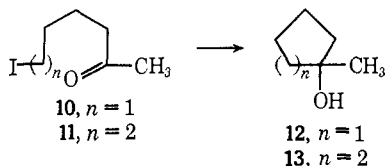


not promoted efficiently by a number of reagents of type R_2CuLi including $R = n-C_4H_9$, $i-C_4H_9$, and CH_3 under a variety of conditions. For example, the reaction of the butyl reagent with **10** in pentane-ether (5.5:1) at 0° for 9 hr produced the cyclic product **12** in only 18% yield. The reagent prepared from cuprous iodide and 1,5-dilithiopentane (1:1) converted **10** to the 1-methylcyclopentanol (**12**) in ca. 35% yield (tetrahydrofuran, -20° , 6 hr). In all these instances noncyclic products predominated.

In view of the inefficiency of cyclization of the iodo ketones **10** and **11** by reagents of type R_2CuLi and the occurrence of side reactions such as cross coupling, the behavior of certain anionic transition metal complexes having "fixed" ligands was studied, for example, the anion derived by two-electron transfer to copper



phthalocyanine¹² and the ions similarly derived from copper and nickel tetraphenylporphine.¹³ Of these reagents the anion prepared by reaction of nickel tetraphenylporphine¹⁴ with 2 equiv of lithium naphthalene in tetrahydrofuran (at 0° under argon) was clearly the most effective; this anion is designated herein as $NiTPP^{2-}$. The reaction of 6-iodo-2-hexanone (**10**) with 3 mol equiv of $NiTPP^{2-}$ in tetrahydrofuran at -50° for 7 hr produced 1-methylcyclopentanol (**12**) in 61% yield.¹⁵ Similarly, 7-iodo-2-heptanone was converted to 1-methylcyclohexanol by reaction with 3 mol equiv of $NiTPP^{2-}$ in tetrahydrofuran at 0° for 20 hr in 88% yield. Surprisingly, the vinylic iodo ketone **5** was unaffected by exposure to excess $NiTPP^{2-}$ at 0° for 20 hr, indicating the inertness of vinylic halides and carbonyl groups toward this reagent. In contrast to the good yields of cyclization products obtained from **10** and **11** using the reagent $NiTPP^{2-}$ are previous findings that the reaction of these halo ketones with lithium-liquid ammonia, sodium, naphthalene, or sodium phenanthrene affords cyclic alcohols in only low yields (7–33%).¹⁶

On the basis of the studies described above, it would seem that the reagents di-*n*-butylcopperlithium and $NiTPP^{2-}$ can effectively bring about the cyclization of iodo or bromo ketones to cyclopentanol or cyclohexanol derivatives, the former reagent being applicable to C_{sp^2} halides and the latter to C_{sp^3} halides. The investigation is currently being extended to ascertain in more detail the scope of these reactions relative to a range of halo carbonyl substrates and anionic organometallic reagents. There is at present no basis for mechanistic conclusions, especially with regard to the question of whether the primary process consists of nucleophilic replacement of halogen by metal or electron transfer from

metal to halide. An application of the new cyclization process to the synthesis of tetracyclic compounds in the gibberellic acid series is presented in the following communication.^{17, 18}

(17) E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Amer. Chem. Soc.*, **92**, 396 (1970).

(18) This study was aided by a grant from the National Science Foundation.

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Studies on the Total Synthesis of Gibberellic Acids. A Simple Route to the Tetracyclic Network

Sir:

The preceding communication describes a method for the construction of carbon rings by intramolecular reductive addition of a δ - or ϵ -halo ketone.¹ We outline herein the application of this process as a key step in a synthesis of the carbon network and bridged-ring functionality which characterize the gibberellin family of plant hormones.²

The crystalline tricyclic ketal **2** was synthesized from the corresponding ketone **1** which in turn was obtained by a Robinson annelation sequence. Reaction of 2-(*N*-pyrrolidyl)indene³ with methyl vinyl ketone (1 equiv) in tetrahydrofuran at 0° for 47 hr⁴ produced after isolation in the usual way an oily 1:1 Michael (keto-enamine) adduct which was subjected to cyclization in dioxane-glacial acetic acid-water-sodium acetate trihydrate (10:1:1:1) at 97° for 11 hr⁴ to form tricyclic ketone **1**,⁵ mp $94-95^\circ$, after distillation and recrystallization from ether. In practice crude semisolid **1** was treated without purification with ethylene glycol and *p*-toluenesulfonic acid in benzene at reflux to afford after distillation at $130-132^\circ$ (0.1 mm) the ketal **2**,⁵ mp $43-47^\circ$ (mp $49-50^\circ$ after recrystallization), in 58% overall yield from 2-(*N*-pyrrolidyl)indene.

Reaction of the ketal **2** with 3.8 equiv of *t*-butyl nitrite and 3 equiv of potassium *t*-butoxide in dry *t*-butyl alcohol at 35° for 15 hr⁴ resulted in formation of the oxime **3**,⁵ mp $182-183^\circ$, which could be obtained in 91% yield by acidification at 0° with 2 *N* hydrochloric acid, extraction, and recrystallization. However, treatment of the reaction mixture with 2 *N* sodium hydroxide prior to acidification with 2 *N* hydrochloric acid at 40° afforded the keto ketal **4**,⁵ mp $91-92^\circ$ (64% yield), in addition to the oxime **3** in 35% yield. The ketone **4** and oxime **3** were readily separated on silica gel, and the oxime could be converted to ketone by sequential treatment with *t*-butyl nitrite-*t*-butoxide solution,⁴ aqueous base, and aqueous acid at 40° .⁶ Hydrogenation of the enone **4** using palladium-on-carbon catalyst and ethyl

(1) E. J. Corey and I. Kuwajima, *J. Amer. Chem. Soc.*, **92**, 395 (1970).

(2) See N. Ya. Grigor'eva and V. F. Kucherov, *Russ. Chem. Rev.*, **35**, 850 (1966).

(3) From 2-indanone and pyrrolidine according to the procedure of A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).

(4) Under an atmosphere of argon.

(5) Satisfactory (a) analytical and (b) infrared and nmr data were obtained for this intermediate.

(6) Further discussion of this interesting method for converting oxime to ketone in the presence of a ketal grouping will be presented in due course.

(12) R. Taube and H. Arfert, *Z. Naturforsch.*, **22b**, 219 (1967).

(13) F. H. Felton and H. Linschitz, *J. Amer. Chem. Soc.*, **88**, 1113 (1966), and references cited therein. See also L. D. Rollmann and R. T. Iwamoto, *ibid.*, **90**, 1455 (1968).

(14) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, and L. Korsakoff, *J. Org. Chem.*, **32**, 476 (1967).

(15) Lower yields of **12** were obtained at lower or higher temperatures.

(16) H. O. House, J.-J. Riehl, and C. G. Pitt, *J. Org. Chem.*, **30**, 650 (1965).

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 hr⁴ produced the tricyclic bromide **6**,⁵ mp 100–102°, stereospecifically in 90% yield.⁸ Reaction of **6** with methoxymethylenetriphenylphosphorane in tetrahydrofuran at 25° for 15 hr⁴ 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*-butylcopperlithium¹ in ether (0.15 *M*) at –50° for 2.5 hr⁴ 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=CHOCH₃), 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=CH₂ (11.21 μ) as well as the absence of carbonyl; (b) from the nmr spectrum which exhibits C=CH₂ 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 alligibberic acid rearrangement² upon refluxing in concentrated hydrochloric acid–ethanol (1:3) for 1 hr to form a keto aldehyde having infrared maximum (CCl₄) 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 reagent⁴ 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*-butylcopperlithium⁴ (conditions as for the cyclization of **8**) to form **13** in 70% yield.

(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).

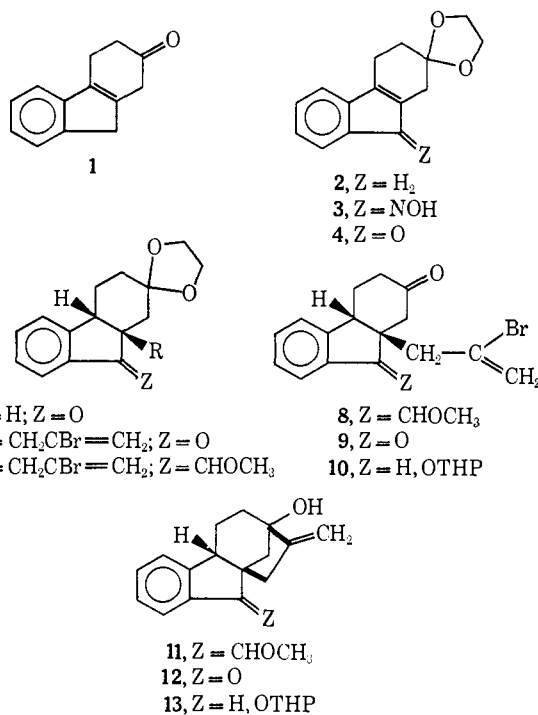
(8) Formation of the *cis*-fused alkylation product, as anticipated on steric grounds, finds analogy in similar systems; see, for example, H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964), and references cited therein.

(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).



The availability of an effective method for the synthesis of the bicyclo[3.2.1]octane part of the gibberelic 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

(13) This work was supported by the National Science Foundation.

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Total Synthesis of Prostaglandins F_{2α} and E₂ as the Naturally Occurring Forms

Sir:

An effective stereocontrolled synthesis of the racemic forms of prostaglandins F_{2α} and E₂ 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 (+)-ephedrine⁴ in hot benzene as fine colorless needles, [α]_D²⁵ +35.8° (*c* 0.86, CH₃OH).⁵ One recrystallization of this salt from benzene afforded in 67% of the theoretical yield the fully

(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_{1α} and E₁; see E. J. Corey, I. Vlattas, and K. Harding, *ibid.*, **91**, 535 (1969).

(3) For other syntheses of the racemic forms of prostaglandins F_{2α} and E₂, 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 [α]_D²⁵ +21.5° (*c* 1.14, CH₃OH).