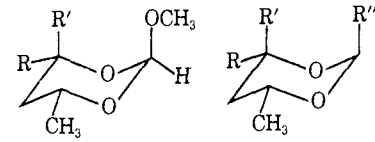
The results reported here demonstrate the first total synthesis of the natural form of prostaglandin E_1 (**5**); further, together with previously accomplished transformations of prostaglandin E_1 to other prostaglandins of the first family,[7] they constitute a formal total synthesis of the natural forms of prostaglandins $F_{1\alpha}$, $F_{1\beta}$, A_1, and B_1. An especially important element in this synthesis is the great ease and high efficiency of the resolution of the intermediate amine **4**. It is also worthy of note that the synthesis becomes effectively stereoselective with the choice of the appropriate conditions for the cyclization of **1** and the use of recycling to convert the C-15 epimer of **3** to **2**.

We are currently studying further improvements in the synthetic route here outlined as well as a number of other, quite different synthetic approaches to prostaglandins.[8]

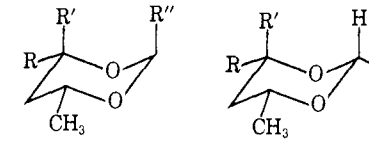
(7) See S. Bergstrom, *Science*, **157**, 382 (1967).

(8) This work was supported in part by the National Institutes of Health.

E. J. Corey, Isidoros Vlattas, Kenn Harding
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received December 2, 1968

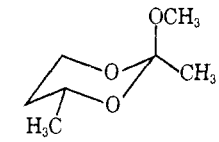


trans-I, R = R′ = H
trans-III, R = CH_3; R′ = H
trans-V, R = R′ = CH_3



trans-II, R = R′ = H; R″ = CH_3
trans-IV: R = CH_3; R′ = H; R″ = CH_3, C_2H_5, *i*-C_3H_7, C_6H_5
trans-VI, R = R′ = R″ = CH_3

cis-I, R = R′ = H
cis-III, R = CH_3; R′ = H
cis-V, R = R′ = CH_3



VII

Stereochemistry of the Reaction of Grignard Reagents with Ortho Esters. A Case of Orbital Overlap Control Synthesis of Unstable Polyalkyl-1,3-dioxanes

Sir:

Little is known about the mechanism of the reaction of orthoformates with Grignard reagents to give acetals.[1] Our recent synthesis of stereoisomeric 2-alkoxy-4-methyl-1,3-dioxanes[2] (I, *cis* and *trans*) and the recently achieved assignment of configuration to a number of 2,4-dialkyl-1,3-dioxanes and other polysubstituted dioxanes[3] provided a handle for studying the stereochemistry of the Grignard orthoformate reaction. We now report that acetals with axial 2-alkoxy groups (*trans*-I, *trans*-III, *trans*-V) react rapidly with a variety of Grignard reagents with high retention of configuration to give the (very unstable) products with axial 2-alkyl groups (*trans*-II,[4] *trans*-IV, *trans*-VI). In contrast, the diastereoisomers with equatorial 2-alkoxy groups (*cis*-I, *cis*-III, *cis*-V) appear to be unreactive and, under forcing conditions, give mixtures of several products.

Methoxydioxanes I, III, and V were obtained from trimethyl orthoformate and the appropriate diols as previously described.[2] Stereoisomers were separated by distillation through a 2-ft spinning-band column at reduced pressure.[5] Configurational assignments, previously made[2] tentatively on the basis of the chemical shift of the orthoformate proton (H-2), were confirmed by measurement of the shift of the ether proton (H-4a; the axial 2-methoxy group shifts this proton downfield) and by measurement of dipole moments (the moments for the equatorial 2-methoxyl compounds are calculated to be about 1 D greater than those of the axial isomers). As shown in Table I, the three sets of measurements plus the boiling points and refractive indices plus the chemical shifts of the methoxyl and equatorial 4-methyl groups provide an unassailable configurational correlation of the three series of orthoesters (I, III, and V). A convincing absolute assignment was obtained in series V by a measurement of nuclear Overhauser effects.[6] In the case of the compound assigned the *cis* configuration on the basis of the chemical shift and dipole data (*cis*-V) saturation of one of the two singlet methyl groups led to a 12% enhancement in the signal area of H-2 whereas the stereoisomer (*trans*-V) showed no significant change in signal area of H-2 upon saturation of either singlet methyl. These findings prove unequivocally that H-2 is close to R′ (CH_3) in *cis*-V, but remote from R′ in *trans*-V.[7] The correlation of the thermodynamically more stable orthoacetate VII (almost certainly[2,3] axial OCH_3, equatorial CH_3) with *trans*-I, -III, and -V (Table I) is in agreement with the assigned configurations.

Treatment of *trans*-I, *trans*-III, and *trans*-V (axial OCH_3) with methylmagnesium iodide or bromide and, in the case of *trans*-III, ethylmagnesium iodide, isopropylmagnesium bromide, and phenylmagnesium bromide (Table II) in ether at room temperature under nitrogen for 1.5–2 hr followed by work-up with ice-cold concentrated aqueous ammonium chloride gave very largely the axial 2-alkyl-1,3-dioxanes *trans*-II, *trans*-IV, and *trans*-VI, as shown in Table II.[8]

(1) *Cf.* M. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp 586–591; H. W. Post, "The Chemistry of the Aliphatic Orthoesters," Reinhold Publishing Corp., New York, N. Y., 1943, pp 96–105.

(2) E. L. Eliel and C. Giza, *J. Org. Chem.*, **33**, 3754 (1968).

(3) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(4) *trans*-II is conformationally heterogeneous; the conformer with axial Me-4, equatorial Me-2 no doubt predominates.[3]

(5) Final purification of analytical samples was by gas chromatography. All analyses of new compounds were within 0.5% of the calculated C and H.

(6) *Cf.* F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).

(7) A 9.7% increase in the H-2 area was found in *trans*-V upon saturation of CH_3O; no such enhancement occurred with *cis*-V. In *trans*-V, the OCH_3 group largely points outside the ring and is thus *gauche* to H-2, whereas *cis*-V evidently exists in the "OMe-down" conformation, which is the one of lowest dipole moment and having the fewest "rabbit-ear effects"; *cf.* R. O. Hutchins, L. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968).

(8) Reaction of *cis,trans*-I with *t*-butylmagnesium chloride led only to reduction, the products being 4-methyl-1,3-dioxane and starting material.

Table I. 2-Alkoxy-1,3-dioxanes

Compd	Chemical shifts, cps[a] H-2	H-4a	MeO	Me-4e	μ, D	Bp, °C (mm)	n^{25}D
trans-I	308	*c*	194	66.2	1.96	55–56 (18)	1.4158
trans-III	311	245.5	195.5	66.2	1.97	57–58 (18)	1.4133
trans-V	313	251	194	69.5, 67.5	1.93	58–59 (15)	1.4189
VII		240.5	192	66.0	1.79	47–48 (15)	1.4182
cis-I	301	*c*	199	71.7	2.88	69–70 (18)	1.4230
cis-III	302	221.5	200	72	2.93	72–73 (18)	*d*
cis-V	315[b]	234	197	71, 74	2.92	72–73 (15)	1.4231

[a] At 60 Mcps, CCl_4 solution. [b] Shift affected by *syn*-axial methyl group. [c] Complex signal. [d] Mp 38–39°, n^{40}D 1.4140.

Table II. Reaction of 2-Alkoxy-1,3-diocanes with Grignard Reagents

Starting material	Compn,[a] %	Grignard reagent	Product % yield	Product Nature
trans-I	100 *trans*	CH_3MgI	67	86% *trans*-II, 14% *cis*
trans-III	100 *trans*	CH_3MgI	70	90% *trans*-IV,[b] 10% *cis*; 20% starting material recovered
trans-III	100 *trans*	C_2H_5MgI	70	95% *trans*-IV,[c] 5% *cis*; 5% starting material recovered
trans-III	89 *trans*	$(CH_3)_2CHMgBr$	63	90% *trans*-IV,[d] 10% *cis*
trans-III	94 *trans*	C_6H_5MgBr	95	95% *trans*-IV,[e] 5% *cis*
trans-V	100 *trans*	CH_3MgI	62	88% *trans*-VI, 12% *cis*
Mixed I	69 *trans*, 31 *cis*	CH_3MgI	51	88% *trans*-II, 12% *cis*
cis-III	100 *cis*	CH_3MgI	0	See text
cis-V	96 *cis*	CH_3MgI		See text

[a] Composition of starting material. [b] R'' = CH_3. [c] R'' = C_2H_5. [d] R'' = $(CH_3)_2CH$. [e] R'' = C_6H_5, analysis by nmr.

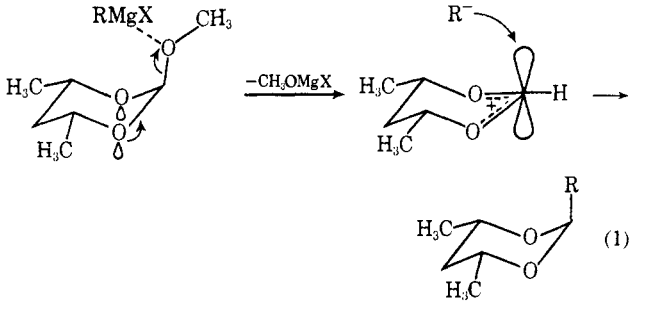
Diastereoisomeric purity (*i.e.*, per cent *trans* isomer) was 86–95%; the small amount of *cis* (equatorial) isomer may well have formed through equilibration during reaction or work-up, since it is known[3] that equilibration under acidic conditions (both MgX_2 and NH_4Cl are acidic!) leads to a mixture containing over 99% of the 2-equatorial (*cis*) isomer.

Treatment of *cis*-III with methylmagnesium iodide (3 hr), in contrast, yielded no 2,4,6-trimethyl-1,3-dioxane. There was obtained *ca.* 40% of a mixture of compounds boiling over a 70° range and 53% of recovered starting material III (partially epimerized, probably in the work-up). *cis*-V yielded a mixture of *cis*-VI and 4-methylpent-4-en-2-ol formate, $CH_2{=}C(CH_3)CH_2CH(OCHO)CH_3$ which is also obtained by treatment of *cis*-V with acid. The reaction of *cis*-I with methylmagnesium iodide yielded little II and much recovered starting material; a mixture of 69% *trans*-I and 31% *cis*-I yielded a mixture of 88% *trans*-II and 12% *cis*-II in 51 % yield (along with partially isomerized starting material), suggesting that reaction involved mainly the *trans* isomer of I.

Assignment of structure, including configuration, to compounds *trans*-IV (R'' = C_2H_5, *i*-C_3H_7, C_6H_5) and *trans*-VI is based on elemental analysis, nmr spectra, and acid-catalyzed epimerization to the more stable *cis* isomers which are readily synthesized from *meso*-2,4-pentanediol or 2-methyl-2,4-pentanediol and the appropriate aldehyde.[3] Compounds *trans*-II and *trans*-IV (R'' = Me) were identical with previously prepared samples.[3]

The results show that orthoformates with axial 2-alkoxy groups react smoothly with Grignard reagents with a high degree of retention of configuration (probably over 90%) to give dioxanes with axial 2-alkyl substituents, even though the resulting compounds are over 3.5 kcal/mol less stable than their equatorial stereoisomers;[3] the stereospecificity of the reaction thus corresponds to an advantage of the transition state involving retention of configuration of at least 5 kcal/mol. It is worthy of note that little ring cleavage occurs. In contrast, equatorial 2-alkoxy-1,3-dioxanes react sluggishly with Grignard reagents; what reaction does occur may be due to conformational inversion, epimerization of starting material prior to reaction, attack on the ring oxygens, side reactions, etc.

The results are most readily interpreted in terms of stereoelectronic factors, as shown in eq 1. Participation of unshared (axial) pairs on oxygen in the



(1)

departure of alkoxide (presumably catalyzed by RMgX or MgX_2 acting as an acid) is possible only when the alkoxyl group is axial. The resulting bisoxocarbonium ion is again axially attacked by the alkyl group (R^-) from the top to give the product directly in the chair form; bottom-side attack would give the highly unstable boat form[9] of the dioxane.

Acknowledgment. We are greatly indebted to Professor F. A. L. Anet and Mr. G. O. Schenck (University of California at Los Angeles) for performing the Overhauser effect experiment. We thank Sr. M. C. Knoeber for preliminary experiments and encouragement of this work which was supported by Air Force Grant AF-AFOSR-779. We also acknowledge helpful discussions with Dr. R. O. Hutchins.

(9) K. Pihlaja, *Acta Chem. Scand.*, 22, 716 (1968).

Ernest L. Eliel, Franz Nader
Department of Chemistry, University of Notre Dame
Notre Dame, Indiana 46556
Received November 20, 1968

Book Reviews

The Chemistry of the Rarer Platinum Metals (Os, Ru, Ir and Rh). By W. P. GRIFFITH, Imperial College, London. Interscience Publishers, John Wiley and Sons, Inc., 605 Third Ave., New York, N. Y. 1967. ix + 491 pp. 16 × 23.5 cm. $16.00.

As pointed out by the author in the preface, the past decade has seen a growing interest in the coordination chemistry of these four heavy members of group VIII of the periodic table. This book has been written in an attempt to provide a summary of the current state of knowledge concerning these metals with special reference to the synthesis, structure, properties, and catalytic importance of the complexes which they form.

So much information is provided that in reviewing the book one is tempted to try to answer two questions only. First, is such an effort necessary at present? And if so how far has the author succeeded in achieving his stated objective?

But first we summarize the facts. Following a brief (13 pp) discussion of the metals themselves, including an interesting summary of the history of their discovery, a general comparative survey of chemical behavior is provided; this covers some 30 pages. Then about 100 pages are devoted to each element in turn. The book concludes with an appendix giving natural and artificial isotopes and a very extensive list of references covering authors, subjects, and formulas. It is in praise and not disrespect that one notes that these references should be recorded in pages (39) or feet (20) rather than by number since each heading is a multiple one and the work involved in obtaining these must have been enormous. The author has done his best to be as up-to-date as possible; this is evidenced by the frequency with which 1966 references occur. Much of the data throughout the book are summarized in tables which are provided with adequate references.

The printing is clear and the diagrams are satisfactory, emphasizing essential features rather than extraneous detail.

To return to the two queries. There is no doubt that this book fills a real need in industrial and university research laboratories. The reviewer also believes that within the compass available the author has done a good job of work. For anybody working in this field Griffith's book will be the first place to look for a particular compound.

It is perhaps churlish to mention one or two reservations. Chemists are very interested in the reasons for changes in properties in vertical and horizontal sequences in the periodic table; *e.g.*, why is $Ni(CO)_4$ stable at 25° whereas the corresponding palladium and platinum compounds are not? Questions such as this one are little discussed; perhaps the author considers that speculation on many of these matters is idle at present, but for the industrial chemist designing new catalysts they are valuable, especially if they stimulate investigation in new areas, even if the theory upon which they are based is ultimately shown to be wrong.

Also, the treatment of kinetics and mechanism of complex formation and reaction will disappoint some readers. But this subject is still groping toward real understanding with several elements, and undoubtedly structural facts are more important than speculative mechanistic uncertainty at this stage in the development of the subject.

Finally the price—$16.00. For the effort involved by the author this is justified, but it is a pity that such a book will fall into the luxury class for all but the dedicated and the librarian.

To sum up, the author has achieved his objectives and is to be complimented on a scholarly effort. It is a pity that the price will preclude most chemists (outside U. S. A. at least) from possessing their own copy.

Ronald Nyholm
Department of Chemistry, University College
London, W.C.1. England

X-Ray Structure Determination, A Practical Guide. By GEORGE H. STOUT, Department of Chemistry, University of Washington, and LYLE H. JENSEN, Department of Biological Structure, University of Washington. The Macmillan Co., 866 Third Ave., New York, N. Y. 1968. xi + 467 pp. 16 × 24.5 cm. $16.95.

"It is the thesis of this book that the average chemist who is willing to devote some time to study, and who can obtain a suitable set of programs, can learn without great difficulty to perform crystallographic structural analyses for himself." This is the contention of the authors and their book goes a long way to making such a proposition feasible. The need for access to a reasonably sized computer and for some understanding of the programming languages is obvious but ought not to deter the chemist.

This is perhaps the first comprehensive treatment of the techniques of structure analysis by X-rays to fully acknowledge the impact of the computer on the subject and to try to make the method comprehensible to the chemist. It is certainly the most successful coverage within a single volume to date.

The plan of the book follows the development of a "typical" crystal structure analysis, being in three parts. Part I deals with X-rays, diffraction, crystal symmetry, the selection of a crystal, and photographic and counter methods of measuring intensity as well as Fourier syntheses and structure factors. Part II concentrates on the phase problem—nowadays almost always soluble—and the location of approximate atomic positions, while Part III discusses methods of refining parameters and, usually a major pitfall for the inexperienced, the assessment of the reliability of the answers obtained.

In keeping with the title the emphasis throughout the book is placed on practical considerations. Necessary theory is presented though derivations are not often provided and most literature references are to secondary sources (an unhappy blemish here is that several crystallographers have their names misspelled in references and text). Within these limitations, which are after all self-imposed, the authors have produced a good book. It contains a quite remarkable store of sound conventional wisdom, most of the likely traps for the unwary are recognized, and errors of fact are few (summation limits and signs are wrong, however, in the equations on p 254). The book may be recommended to chemists (to those less adventurous than Professor Stout it will serve as a guide to how the structural crystallographer goes about his business) and also to beginning graduate students in crystallography where it may usefully supplement the now somewhat dated Volume III of "The Crystalline State."

Robert F. Bryan
Department of Chemistry, The University of Virginia
Charlottesville, Virginia