produces ion pairs similar to **5** and **6** except that the counterion is $CH_3COO^-\cdots HOH$.[4,5,7a,12] In the case of the axial amine **1d** the decreased stereoselectivity might indicate that, although over one-half of the proton removal is executed by the counterion,[19,20] a substantial proportion of the axial protons are removed by solvent either in E2 fashion or, more likely, after the C–N bond cleavage.[21]

Acknowledgment. We wish to thank the National Institutes of Health for providing the LKB 9000 combined gas chromatograph–mass spectrometer which was used for the deuterium analysis. We also thank Mr. John Naworal for recording the mass spectra.

(19) Cram and Sahyun suggested that nitrous acid deamination in acetic acid could be included in their over-all elimination scheme in which the leaving group removes the proton provided that the leaving group is considered to be NH_2NO.[14b]

(20) White and Woodcock[3] mentioned the possibility that the elimination in this type of reaction is executed by the counterion, but the stereochemical consequences were not discussed.

(21) The explanation of the greater elimination/substitution ratio from **5** must await further experiments, but it may be that the ease of substitution is greater in **6** than in **5** due to steric repulsions that come into play in the latter as the anion approaches the covalent bonding distance.

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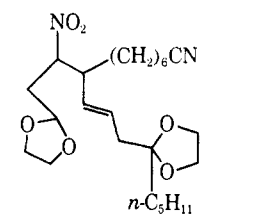
Total Synthesis of Natural (Levo) and Enantiomeric (Dextro) Forms of Prostaglandin E_1

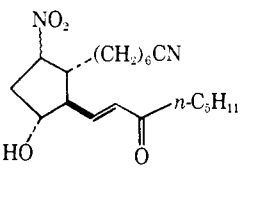
Sir:

In recent communications the total synthesis of racemic prostaglandin E_1 by a number of different routes has been described.[1,2] The readily available nitro ketal **1**, an intermediate in one of the previously described approaches,[1b,3] has recently been found to undergo cyclization using stannic chloride in acetone to give the oily prostanoic acid derivative **2**, essentially free of the undesired 11β-hydroxy epimer[4] and readily purified by column chromatography using silica gel with chloroform as eluent. The intermediate **2** was obtained earlier along with the C-11 epimer using a different cyclization procedure.[1b] Reduction of the enone **2** with zinc borohydride in dimethoxyethane followed by mild base treatment to place the 9-nitro substituent in the more stable β orientation gave a mixture of two nitro diols epimeric at C_{15} (**3** and its C-15 epimer).[1b] These are easily separated chromatographically on silica gel (using CH_2Cl_2–Et_2O–THF, 5:4:1, as solvent), and further, the undesired 15β-hydroxy epimer is reconverted to the intermediate 15-ketone **2** in high yield by selective oxidation with 2,3-dicyano-5,6-dichloro-*p*-benzoquinone, as indicated earlier.[1b] This recycling procedure allows stereoselective channeling of the synthesis to the desired nitro diol **3**, reduction of which with aluminum amalgam affords the corresponding amine **4**. The racemic amine **4** is readily purified *via* the nicely crystalline salt with *p*-nitrobenzenesulfonic acid, mp 134.5–136°.

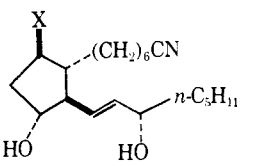
Treatment of the racemic amine **4** with (−)-α-bromocamphor-π-sulfonic acid[5] in ethyl acetate produced a crystalline salt, $[\alpha]_{578}$ −54° (*c* 1, methanol) in *ca.* 115% of the theoretical amount calculated for a single diastereomer. One recrystallization from methanol (a very small amount) and ethyl acetate afforded in high yield a single diastereomeric salt, mp 157–159°, $[\alpha]_{578}$ −59.6° (*c* 1, methanol). Further recrystallization led to only a slight change in the rotation of this salt (maximum observed, $[\alpha]_{578}$ −59.65°). The free resolved amine **4**, generated from this levo salt using potassium carbonate in aqueous methanol as base, was obtained after extraction as a solid, $[\alpha]_{578}$ −21° (*c* 1.7, methanol). This levo amine **4** was converted to prostaglandin E_1 by the reaction sequence previously described.[1] Recrystallization of



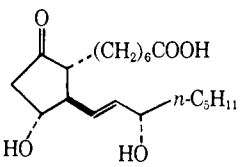
1



2 (racemic)



3, X = NO_2 (racemic)
4, X = NH_2



5

the synthetic product afforded material identical in all respects with natural prostaglandin E_1 (**5**) (including nmr and ir spectra); found: mp 114–116.5°, $[\alpha]_{578}$ −61.6° (*c* 0.56, tetrahydrofuran).

By a similar process the racemic amine **4** was resolved *via* the salt with (+)-α-bromocamphor-π-sulfonic acid[5] to give dextro **4**, $[\alpha]_{578}$ +21° (*c* 1, methanol). The procedure for the conversion of *dl*-**4** to *dl*-prostaglandin E_1[1] when applied to dextro **4** yielded the enantiomer of natural prostaglandin E_1, mp 114–117°, $[\alpha]_{578}$ *ca.* +57° (*c* 0.5, tetrahydrofuran), showing the same infrared spectrum and chromatographic R_f values as racemic and natural forms of prostaglandin E_1. The biological activity of the synthetic preparation of the enantiomer of prostaglandin E_1 was found to be 0.1% of that of the natural hormone in the stimulation of smooth muscle contraction.[6]

(1) For a description of three synthetic routes developed at Harvard, see (a) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968), and (b) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968).

(2) The most recent synthesis of racemic prostaglandin E_1 has been described by a group at the Upjohn Co.; see W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *ibid.*, **90**, 5895 (1968).

(3) See also E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 5947 (1968).

(4) The orientations of hydroxyl in prostaglandin $F_{1\alpha}$ at carbons 9, 11, and 15 are taken as α in this nomenclature. See B. Samuelsson, *Angew. Chem. Intern. Ed. Engl.*, **4**, 410 (1965).

(5) Obtained from the Aldrich Chemical Co.

(6) We are indebted to Drs. Peter Ramwell and Jane Shaw of the Worcester Foundation for Experimental Biology for the biological measurements. The measured activity may be explained by assuming that this sample contained *ca.* 0.1% of natural (levo) prostaglandin E_1. The slope of the log (dose)–response plot was found to be the same as for natural prostaglandin E_1, which argues against the alternative explanation based on slight bioactivity for the enantiomer of prostaglandin E_1.

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.

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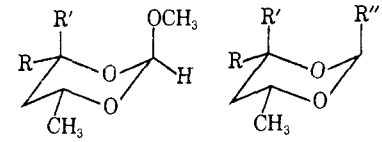
Stereochemistry of the Reaction of Grignard Reagents with Ortho Esters. A Case of Orbital Overlap Control Synthesis of Unstable Polyalkyl-1,3-dioxanes

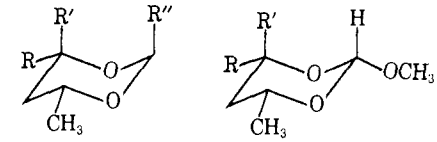
Sir:

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

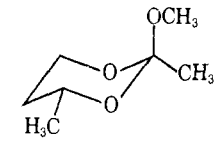


trans-I, R = R′ = H
trans-III, R = CH_3; R′ = H
trans-V, R = R′ = CH_3



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

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.