## On the Absence of Lithium-6–Lithium-7 Spin–Spin Coupling in Alkyllithium Compounds[1]

*Sir:*

The results of the preceding communication by McKeever, Waack, Doran, and Baker[2] prompt us to report results relating to the absence of observable $^6$Li–$^7$Li scalar coupling in alkyllithium compounds.

Methyllithium was prepared as previously described[3] from normal abundance lithium metal and from 96% $^6$Li metal. An ether solution containing methyllithium with about 50% abundance $^6$Li was prepared by mixing appropriate quantities of the two methyllithium solutions. The $^7$Li spectrum of the resulting solution was examined in the temperature region corresponding to slow intermolecular exchange, below −60°. The $^7$Li appeared as a single line with essentially the same width as reported previously[3] for a normal abundance $^7$Li sample. This result indicates that scalar coupling between $^6$Li and $^7$Li must be on the order of perhaps 0.3 Hz or less.

A similar experiment involving about 38% abundance $^6$Li was performed on *t*-butyllithium in cyclopentane solvent. Again, no evidence of $^7$Li–$^6$Li scalar coupling was observed; the line width observed is essentially the same as for a sample containing 99.2% abundance $^7$Li.

It should be emphasized that, since $^7$Li, which has the larger quadrupole moment of the two nuclei, appears as a relatively sharp resonance, decoupling of the spins through a rapid relaxation of the Li spin states is not involved. The results indicate that the scalar coupling between lithium spins in the alkyllithium tetramers is very small.

It is difficult to estimate what the $^6$Li–$^7$Li coupling might be for a pair of singly bonded lithium atoms, but a crude indication can be obtained[4,5] from a comparison of the quantity $J = \tau\gamma_N\gamma_{N'}[\phi_N(0)]^4/\Delta E$ for $^6$Li–$^7$Li, as compared with $H_2$. The coupling in $H_2$ is evaluated as 278 Hz from the value observed in HD. Assuming that $\Delta E$ for the $Li_2$ system is about 0.25 that for $H_2$, and inserting the appropriate $\gamma$'s, $J(^6\text{Li}-^7\text{Li})/J(H_2) \approx 0.25 \times [\phi_{Li}(0)]^4/[\phi_H(0)]^4$. The contact charge densities cannot be estimated with any reliability for the molecular case, even when reliable atomic wave-function data are available. Mixing of core (1s) orbitals of Li in the valence-shell molecular orbitals, in particular, would greatly increase $[\phi_{Li}(0)]^2$. Accordingly the ratio of coupling constants could be as small as 0.01, or as large as perhaps 0.25. An estimate of about 10 Hz for $J(^6\text{Li}-^7\text{Li})$ seems reasonable.[6] *The results indicate that the effective metal–metal bond order may be near zero, despite a close Li–Li distance[7,8] of 2.5–2.6 Å, as compared with 2.67 Å in $Li_2$.*[9] Presumably most of the bonding charge distribution in the alkyllithium tetramer lies in the region about the bridging alkyl carbon. There is apparently sufficient covalency, however, to give rise to a scalar $^7$Li–$^{13}$C interaction, as reported in the previous communication.[2]

(1) This research is sponsored by the National Science Foundation.
(2) L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *J. Am. Chem. Soc.*, 90, 3244 (1968).
(3) L. M. Seitz and T. L. Brown, *ibid.*, 88, 2174 (1966).
(4) H. M. McConnell, *J. Chem. Phys.*, 24, 460 (1956).
(5) M. Barfield and D. M. Grant, *Advan. Magnetic Resonance*, 2, 149 (1965).
(6) The appreciable value seen for the $^7$Li–$^{13}$C coupling,[2] in a bond which is no doubt highly polar, is consistent with the magnitude of contact charge density from the valence orbitals which is implied in this estimate.
(7) H. Dietrich, *Acta Cryst.*, 16, 681 (1963).
(8) E. Weiss and E. A. C. Lucken, *J. Organometal. Chem.* (Amsterdam), 2, 197 (1964).
(9) Although the Li–Li distance observed in the solid may be different in the tetrameric solution species, a slight increase in this quantity would not seriously alter the coupling constant.
(10) National Defense Education Act Fellow.

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## Total Synthesis of Prostaglandins. Synthesis of the Pure *dl*-$E_1$, -$F_{1\alpha}$, -$F_{1\beta}$, -$A_1$, and -$B_1$ Hormones

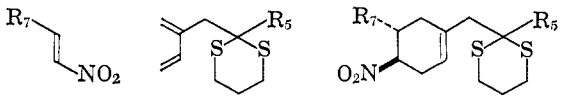
*Sir:*

The isolation and structural characterization of the naturally occurring $C_{20}$ carboxylic acids of the prostaglandin family coupled with the discovery of their profound and diverse biological effects has opened a new chapter of hormone research,[1] the fundamental and practical significance of which already seems assured. Even at nanomolar concentrations the prostaglandins elicit widespread physiological responses, for example, in the cardiovascular, nervous, reproductive, renal, and gastric systems. Further, the individual prostaglandins often manifest qualitatively different activities despite the commonality of carbon skeleton. The lack of a satisfactory natural source of any of the prostaglandins and their biological importance have prompted the investigations of chemical synthesis which are reported in this and the following note.[2] Pure, crystalline synthetic prostaglandins have been obtained for the first time, and as a result of this work, the chemical synthesis of prostaglandins on a substantial scale becomes feasible.

The diene **1** was synthesized from 2-bromomethyl-1,3-butadiene[3] and 2-lithio-2-*n*-amyl-1,3-dithiane[4] in tetrahydrofuran–pentane at −25° (65–70%);[5,6,7b] [molecular ion found at *m/e* 256.1346 (theory 256.1320), $\lambda_{max}^{CH_3CN}$ 225 nm (ε 10,200), sh 256 nm (ε 1670)]. The dienophile **2**[6,7a,b] (*Anal.* Found: C, 59.52; H, 8.01; N, 15.02) was obtained from 7-cyanoheptanal[8] in ~60% yield

(1) For recent reviews of the field including the pioneering work of the Bergström school, see (a) S. Bergström, *Science*, 157, 382 (1967); (b) "Prostaglandins," Nobel Symposium 2, S. Bergström and B. Samuelsson, Ed., Interscience Publishers Inc., New York, N. Y., 1967.
(2) For other approaches to the synthesis of $E_1$ and $F_1$ hormones, see (a) G. Just and C. Simonovitch, *Tetrahedron Letters*, 2093 (1967); (b) D. Nugteren, H. Vonkeman, and D. A. van Dorp, *Rec. Trav. Chim.*, 86, 1237 (1967); also (c) the conflicting report of K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock, M. Harman, and J. A. Weisbach, *Tetrahedron Letters*, 1569 (1968), relative to the results reported in ref 2a.
(3) R. C. Krug and T. F. Yen, *J. Org. Chem.*, 21, 1082 (1956). An improved procedure used in this work involved bromination of 3-methyl-2,5-dihydrothiophene 1,1-dioxide using N-bromosuccinimide in methylene chloride to give the corresponding bromomethyl sulfone (66%) followed by thermolysis at low pressure (~1 mm and 170–190°) to form the bromomethyldiene (60–75%).
(4) E. J. Corey and D. Seebach, *Angew. Chem. Intern. Ed. Engl.*, 4, 1075, 1077 (1965).
(5) High-resolution mass spectral determinations were performed with an AEI-MS-9 double focusing spectrometer.
(6) The infrared and nuclear magnetic resonance spectra of this substance were in excellent agreement with the assigned structure.
(7) (a) Purified by adsorption chromatography using silica gel; (b) purified by vacuum distillation; (c) unless otherwise indicated, purified reaction products were obtained as colorless liquids; in several cases these could not be distilled without appreciable decomposition.
(8) (a) M. Ohno, N. Naruse, S. Torimitsu, and M. Okamoto, *Bull. Chem. Soc. Japan*, 39, 1119 (1966); (b) M. Ohno, N. Naruse, S. Tori-

by a standard sequence: (1) addition of nitromethane (0.03 equiv of KOH in methanol), (2) acetylation ($Ac_2O$, $H_2SO_4$ as catalyst) of the resulting nitro alcohol to form the corresponding nitro acetate, and (3) elimination of HOAc ($NaHCO_3$ in EtOAc). The Diels–Alder addition of **1** to **2** proceeded readily and in high yield to give the adduct **3** as the major product[6,7a] [molecular ion at *m/e* 438.2363 (theory 438.2375)] along with the position-isomeric adduct as a minor product. The mixture, which was used in the synthesis (purification could be more readily carried out at the stage of **4**), was subjected to the sequence of functional group modifications: (1)

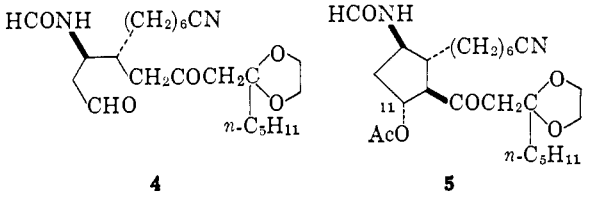


**2** **1** **3**

$R_7=(CH_2)_6CN$

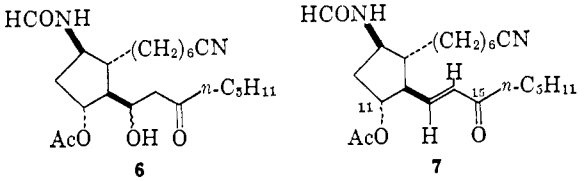
$R_5=n\text{-}C_5H_{11}$

reduction of $NO_2$ to $NH_2$ [(Al–Hg)–$Et_2O$–$H_2O$–$CH_3OH$, 25°], yield[6,7a,b] 90% (*Anal.* Found: C, 67.47; H, 10.04; N, 6.78); (2) formylation of $NH_2$ to NHCHO (formic acetic anhydride), yield[6,7a,b] 85% [molecular ion at *m/e* 436.2576 (theory 436.2581)]; (3) dithiane–dioxolane ketal exchange (dry ethylene glycol–tetrahydrofuran–mercuric chloride, 3 hr, 25°), yield[6,7a,b] 80% [*Anal.* Found: C, 70.41; H, 9.88; N, 7.04; molecular ion at *m/e* 390.2882 (theory 390.2882)]; (4) hydroxylation of C=C ($OsO_4$–pyridine) followed by lead tetraacetate oxidation (dry acetone at −50°) to give the pure keto aldehyde[6,7a] **4** in 43% yield. Treatment of **4** with 0.1



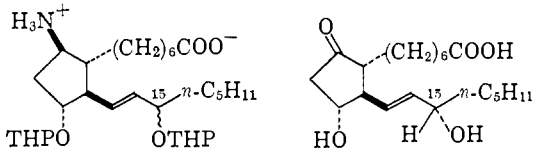
**4** **5**

equiv of 1,5-diazabicyclo[4.3.0]-5-nonene[9] in methylene chloride at 0° for 24 hr followed by acetylation ($Ac_2O$, pyridine) and chromatography furnished the crystalline cyclopentanol derivative **5**,[6] mp 56° (45% yield) [*Anal.* Found: C, 65.18; H, 8.64; N, 6.03; molecular ion at *m/e* 464.2884 (theory 464.2886)] and lesser amounts of an epimeric by-product,[6] mp 78° (*Anal.* Found: C, 64.75; H, 8.57; N, 6.15) probably differing in configuration only at $C_{11}$. Reduction of the ketone function of **5** (excess $NaBH_4$ in ethanol at −20°) followed by ketal hydrolysis (0.25 *N* sulfuric acid in 1:1 THF–$H_2O$ at 25° for 5 hr) afforded **6** which was dehydrated cleanly to the enone **7** using dicyclohexylcarbodiimide and cupric chloride as catalyst in ether.[10,11] The enone **7**,[6] mp 56.5°, $\lambda_{max}^{CH_3OH}$ 226.5 nm (ε 15,000) (*Anal.* Found: C, 68.28; H, 9.02; N, 6.95), was formed in 60–80% over-all yield for the three steps from **5**.[12] Selective



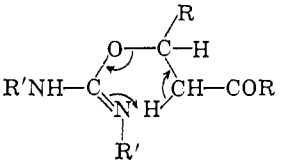
**6** **7**

reduction of the carbonyl group in **7** using zinc borohydride in diglyme at 25° for 8 hr produced a mixture of $C_{15}$ epimers which was converted to a mixture of $C_{15}$ epimers of the amino acid **8**[6] by the sequence: (1) deacetylation (1 *N* KOH in MeOH, 15 min at 30°), (2) reaction with excess dihydropyran in dioxane at 25° with anhydrous *p*-toluenesulfonic acid catalyst, and (3) hydrolysis of cyano to carboxyl and deformylation (KOH in MeOH–$H_2O$ at 110–125°). Conversion of **8** to the N-bromo derivative (N-bromosuccinimide)



**8** **9**

followed by base-catalyzed dehydrobromination and hydrolysis of the resulting imine at pH 2[13] afforded after chromatography on silica gel using ethyl acetate–cyclohexane for elution 25% (over-all yield from **7**) pure *dl*-prostaglandin $E_1$ (**9**), mp 112.8–113.1° (*Anal.* Found: C, 67.77; H, 9.74), having infrared, nmr, and mass spectra identical with those of natural prostaglandin $E_1$, and 20–25% (over-all from **7**) of *dl*-15-epiprostaglandin $E_1$, obtained as an oil, but spectroscopically and chromatographically identical with authentic 15-epiprostaglandin $E_1$ (also an oil) prepared from natural prostaglandin $E_1$.[14] The synthetic prostaglandin $E_1$ was further characterized by (1) biological activity identical with that exhibited by natural prostaglandin at one-half the concentration of synthetic prostaglandin $E_1$ solutions in tests with isolated rat uterus and with guinea pig ileum and in tests of vasodepression in rats;[15] (2) rate susceptible to cycloelimination of the form



mitsu, and I. Terasawa, *J. Am. Chem. Soc.*, **88**, 3168 (1966). The specific procedure used is one which is to appear in *Org. Syn.* and which was kindly provided to us by Dr. Ohno.

(9) H. Oediger, H-J. Kabbe, F. Möller, and K. Eiter., *Ber.*, **99**, 2012 (1966), and previous papers therein cited.

(10) This represents a new and useful method for the dehydration of β-hydroxy carbonyl compounds under mild nonacidic, nonbasic conditions which we have shown to be of broad generality. The method was devised on the expectation that reaction of the β-hydroxyl function with carbodiimide would lead to a carbamidate derivative which should be

(11) For copper ion activation of carbodiimides, see E. Schmidt and F. Moosmüller, *Ann.*, **597**, 235 (1955).

(12) By a similar sequence from the adduct **3** but involving N acetylation, the N-acetyl analogs of **5** and **7** were obtained as crystalline compounds; for the analog of **5**,[6] mp 64–65° (*Anal.* Found: C, 65.29; H, 9.04; N, 6.01), and for the analog of **7**,[6] mp 90–91° (*Anal.* Found: C, 68.80; H, 9.21; N, 6.79).

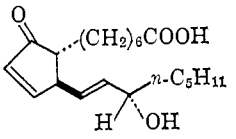
(13) For previous applications of this type of reaction see (a) W. E. Bachmann, M. P. Cava, and A. S. Dreiding, *J. Am. Chem. Soc.*, **76**, 5554 (1954); (b) L. Labler and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 2975 (1959); (c) H. Ruschig, W. Fritsch, J. Schmidt-Thome, and W. Haede, *Ber.*, **88**, 883 (1955).

(14) We are grateful to Dr. W. P. Schneider of the Upjohn Co. for a sample of 15-epi-$E_1$ and to Dr. John Pike of the Upjohn Co. and Professor Bengt Samuelsson of the Karolinska Institutet, Stockholm, for generous samples of natural prostaglandin $E_1$, $A_1$, $F_{1\alpha}$, and $F_{1\beta}$.

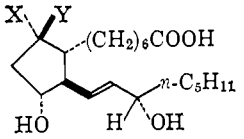
(15) We are indebted to Drs. Peter Ramwell and Jane Shaw of the Worcester Foundation for Experimental Biology for performing with great skill the quantitative biological measurements.

of conversion to prostaglandin $B_1$[1] [$\lambda_{max}$ 278 nm ($\epsilon$ 28,600)] in 0.11 *N* methanolic potassium hydroxide identical with that for natural prostaglandin $E_1$; and (3) thin-layer chromatographic behavior on silica gel using several solvent systems identical with that of authentic $E_1$. The same comparative studies were also made with synthetic and natural samples of 15-epi-prostaglandin $E_1$, confirming the nature of this synthetic product.

Synthetic *dl*-prostaglandin $E_1$ was converted to *dl*-prostaglandin $A_1$ (**10**) using 0.5 *N* hydrochloric acid in 1:1 water–tetrahydrofuran (60 hr, 25°) and isolated by chromatography as a colorless oil, spectroscopically identical with natural prostaglandin $A_1$ and possessing one-half its biological activity. Reduction of synthetic **9** using sodium borohydride in methanol at 0° followed



**10**



**11**, X = OH; Y = H
**12**, X = H; Y = OH

by chromatographic isolation afforded *dl*-prostaglandin $F_{1\alpha}$ (**11**), mp 81°, and *dl*-prostaglandin $F_{1\beta}$ (**12**), mp 116.4–116.8°, spectroscopically and chromatographically identical, respectively, with natural[14] prostaglandin $F_{1\alpha}$ and $F_{1\beta}$.

Further studies on the synthesis of prostaglandins by this and other routes are under way. We shall report on the control of stereochemistry at $C_{15}$ and on the resolution of our synthetic prostaglandins in due course.

**Acknowledgment.** This work was generously supported by the National Institutes of Health. We are grateful to Professor Sune Bergström for first arousing our interest in the prostaglandins during a visit by one of us to his laboratory at Lund in 1957. Finally, we are pleased to acknowledge help in various aspects of the problem from Drs. Tse Lok Ho, Manning Cooke, Jr., and Kenn Harding.

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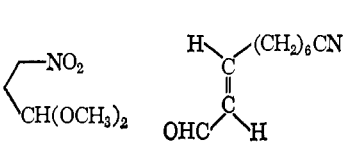
## A New Total Synthesis of Prostaglandins of the $E_1$ and $F_1$ Series Including 11-Epiprostaglandins

*Sir:*

A previous communication[1] describes the total synthesis of *dl*-prostaglandins $E_1$, $F_{1\alpha}$, $F_{1\beta}$, $A_1$, and $B_1$. We report herein a second and different synthetic route to these substances which can be adapted to provide the $C_{11}$ epimers of the natural $E_1$ and $F_1$ hormones as well as either of the corresponding $C_{15}$ epimers.[1] Of special note in this connection is the discovery that certain of these synthetic stereoisomers of prostaglandin $E_1$ manifest interesting, potent, and possibly useful biological activity.

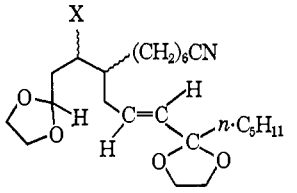
(1) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).

Reaction of 3-nitropropanal dimethyl acetal (**1**)[2,3] with 9-cyano-2-nonenal (**2**)[3,4] in the presence of base led to the Michael adduct **3**,[3,5] which was converted to the conjugated enone **4**[3,5] (80%) by reaction[6] with the sodio derivative of dimethyl 2-oxoheptylphosphonate;[7] molecular ion of **4** at *m/e* 410.2781 (theory 410.2773).[8] Reaction of **4** with ethylene glycol–*p*-toluenesulfonic

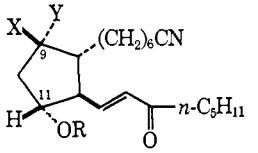


**1** **2** **3**, X = O
**4**, X = CHCO–*n*-$C_5H_{11}$

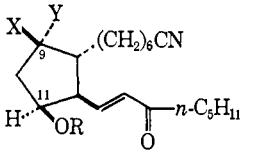
acid in benzene produced the nitro bisdioxolane **5**[3,5] (89%), molecular ion at *m/e* 452.2880 (theory 452.2886), which gave after reduction [(Al–Hg)–$Et_2O$–$H_2O$–$CH_3OH$][1] and formylation (formic acetic anhydride) the corresponding formylamino bisdioxolane **6**,[3] molecular ion at *m/e* 450.3089 (theory 450.3094) (*Anal.* Found: C, 66.52; H, 9.61; N, 6.22). Treatment of the bis-



**5**, X = $NO_2$
**6**, X = NHCHO



**7a**, X = HCONH; Y = H
**b**, X = H; Y = HCONH



**8a**, X = HCONH; Y = H
**b**, X = H; Y = HCONH

dioxolane **6** with *p*-toluenesulfonic acid in acetone at 25° for 40 hr led to four stereoisomeric cyclization products in 85% total yield; these were cleanly separated by chromatography (silica gel; $CHCl_3$–$Et_2O$–$CH_3OH$, 5:4.5:0.5) into the pairs of alcohols **7a** + **8b** (R = H), $R_f$ 0.12 and **7b** + **8a** (R = H), $R_f$ 0.20. The latter pair was separated cleanly by chromatography on neutral alumina using the same solvent system to give pure **7b** (R = H), $R_f$ 0.45,[3,5] and **8a** (R = H), $R_f$

(2) Prepared from 3-bromopropanal dimethyl acetal and sodium nitrite in dimethyl sulfoxide; bp 96° (15 mm) (*Anal.* Found: C, 40.33; H, 7.54; N, 9.19); see N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *ibid.*, 78, 1497 (1956).

(3) The infrared and nuclear magnetic resonance spectra of this substance were in excellent agreement with the assigned structure.

(4) Prepared from 7-cyanoheptanal[1] and formylmethylenetriphenylphosphorane and purified by evaporative distillation *in vacuo* (*Anal.* Found: C, 72.52; H, 9.08; N, 8.37).

(5) This liquid substance was not sufficiently stable to allow distillation at 1 $\mu$; however, isolation in sufficiently pure form (>95%) for further transformations was readily effected chromatographically.

(6) (a) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961); (b) L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. G. Toscano, *Ber.*, **95**, 581 (1962), and earlier papers.

(7) Prepared from ethyl hexanoate and dimethyl $\alpha$-lithiomethanephosphonate: E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5654 (1966).

(8) High-resolution mass spectral determinations were performed with an AEI-MS-9 double-focusing spectrometer.