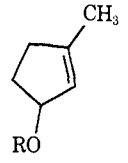
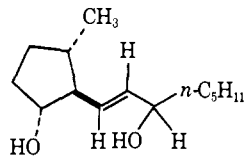
red max 980 cm^{-1}; nmr signals for olefinic protons δ 5.625 and 5.40 (2 H, as four doublets with $J_{CH=CH}$ = 16 Hz)) as a colorless liquid, identical in all respects with the product obtained in 80% yield by the reaction of cyclohexanecarboxaldehyde with the β-oxido phosphonium ylide **9**.[10] The alcohol **8** was homogeneous both by vpc and tlc analysis; none of the analog of **8** having *tert*-hexyl instead of cyclohexyl groups could be detected. From these results it is clear that (1) thexylborane can be used in the coupling process without complications arising from thexyl migration, (2) boron to carbon migration occurs from **5** in the presence of methoxide to form **6** without loss of tetrahydropyranyl, and (3) the vinylborane, which is very resistant to acidic protolysis, is readily cleaved under mildly basic conditions using silver catalysis.

We next attempted the application of the coupling process detailed above for **8** to the more complex cyclopentene derivative **10** only to find that at best only



10, R = CH_3OCH_2
11, R = $(CH_3)_2Si$-*t*-Bu



12

traces of the desired product could be detected. It became clear that elimination of the oxygen substituent was occurring subsequent to the initial hydroboration step. In order to circumvent this undesirable reaction course, the dimethyl-*tert*-butylsilyl derivative **11**[6,11] was used as substrate.[11] Happily, when **11** was subjected to the process as detailed above and the resulting silylated THP derivative cleaved with acetic acid–water (65:35) at 45° for 3 hr, the desired coupling product **12**[6] was obtained as a colorless liquid which was revealed by tlc analysis to be a mixture of two diastereomers (R_f 0.38 and 0.23 on silica gel thin layer using ethyl acetate), as expected for the use of racemic reagents in the coupling reaction. The diastereomers of **12**[6] were separated by chromatography on silica gel (ether–ethyl acetate 1:1 for elution). The trans geometry about the olefinic bond in each was indicated by infrared absorption at 975 cm^{-1} and the presence of hydroxyl by a band centered at 3400 cm^{-1}.

The successful synthesis of **12** by the mixed hydroboration–rearrangement sequence provides the basis for pursuing the application of this method to prostanoid synthesis. We are currently studying the synthesis and coupling of the optically active forms of **2** and **3** which should produce the desired coupling product stereospecifically.[12]

(10) The preparation of **8** *via* the ylide **9** was carried out by Dr. A. Venkateswarlu in these laboratories. See ref 3 and also E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 226, 3523 (1970).

(11) The preparation of **11** was accomplished by silylation of the corresponding alcohol which in turn was made by the reduction of 3-methyl-2-cyclopentenone (Aldrich Chemical Co.) with diisobutylaluminum hydride in pentane [see K. E. Wilson, R. T. Seidner, and S. Masamune, *Chem. Commun.*, 213 (1970)].

(12) This study was assisted by financial aid from the National Institutes of Health and the Agency for International Development.

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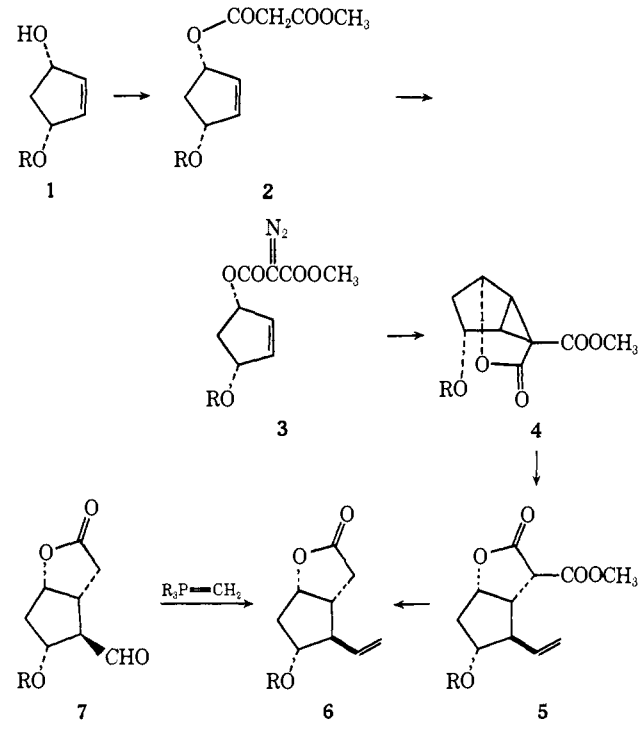
Homoconjugate Addition of Organocopper Reagents to Cyclopropanes and Its Application to the Synthesis of Prostanoids

Sir:

A variety of approaches to the synthesis of prostaglandins which allow stereochemical control have been devised.[1-4] This communication describes a new and highly promising attack on the problem which is based on a novel process for cyclopropane ring cleavage by an organocopper reagent. Chart I outlines a

Chart I



R = 2-tetrahydropyranyl

sequence of reactions which has been carried out to test the validity of the new synthetic scheme.

cis-2-Cyclopentene-1,4-diol monotetrahydropyranol ether (mono-THP) (**1**)[5,6] was treated with methyl malonyl chloride (1.1 equiv) and pyridine (1.2 equiv) in ether (30 ml/g of **1**) at 0–5° for 1.5 hr to give the malonate ester **2**[6] as a colorless oil (99% yield), ir max (neat) 5.68, 5.76 μ. Reaction of **2** with *p*-toluenesulfonyl azide (1.0 equiv) and triethylamine (2.5 equiv) in acetonitrile (15 ml/g of **2**) at 45° for 36 hr resulted in formation of the diazo ester **3**[6,7] (a pale yellow liquid, ir max (neat) 4.69, 5.68, 5.76, 5.91 μ; nmr peaks (in

(1) See E. J. Corey and T. Ravindranathan, *J. Amer. Chem. Soc.*, **94**, 4013 (1972).

(2) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971).

(3) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7319 (1971).

(4) (a) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971); (b) E. J. Corey, *Ann. N. Y. Acad. Sci.*, **180**, 24 (1970).

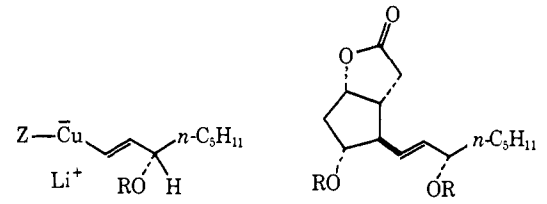
(5) Prepared in 80% yield according to a convenient procedure developed by Dr. David J. Beames in these laboratories from *cis*-2-cyclopentene-1,4-diol [H. Z. Sable and T. Pasternak, *Helv. Chim. Acta*, **45**, 370 (1962)] and dihydropyran in methylene chloride at 23° with *p*-toluenesulfonic acid as catalyst.

(6) Satisfactory (a) infrared and nuclear magnetic resonance spectra and (b) high-resolution mass spectral data were obtained for a purified sample (homogeneous by tlc) of this intermediate. Unless otherwise indicated, products were isolated by chromatography on silica gel.

(7) See M. Regitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 733 (1967).

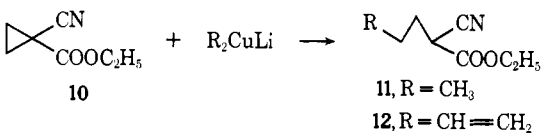
$CDCl_3$) due to $COOCH_3$ at δ 3.84 and 2 olefin H as a quartet centered at 6.08) in 95% yield. Thermolysis of **3** in the presence of copper powder (Fisher, electrolytic, 10 g/g of **3**) in xylene (20 ml/g of **3**) at reflux under nitrogen for 6 hr afforded in *ca.* 50% yield[8] the tricyclic lactone ester **4**[6] (infrared max (neat) at 5.62 and 5.77 μ, no olefinic proton peaks in the nmr spectrum). Reaction of **4** with divinylcopperlithium[9] in ether (2.0 equiv) at $-12°$ for 19 hr followed by addition of aqueous ammonium chloride solution and extraction gave the vinylcyclopentane lactone ester **5**, which was treated directly with dry lithium iodide (5 equiv) in pyridine[10] (2 ml/g of **5**) at reflux for 3 hr to produce the desired lactone **6**[6] in *ca.* 37% yield[8] as a colorless oil, ir max ($CHCl_3$) 5.65 μ (γ-lactone), 6.09, 10.10, 10.85 ($-CH{=}CH_2$). The structure and stereochemistry of this product were established by comparison with an authentic sample obtained by the reaction of the previously prepared lactone aldehyde **7**[4a] with methylenetriphenylphosphorane.[11]

Having established the feasibility of the conversion **4** → **5** by homoconjugate addition of vinyl, we are now studying the synthesis and combination of the optically active **4** with the (*S*)-vinylcopper reagent **8** which should afford an intermediate **9** that has previously been converted to prostaglandins.[4b] A report of this work will be made in due course.



8 **9**

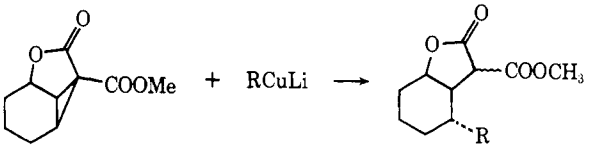
Some evidence of generality for the homoconjugate addition process involving organocopperlithium reagents has also been obtained. Reaction of ethyl α-cyanocyclopropanecarboxylate (**10**)[12] with dimethylcopperlithium (2 equiv) in ether (70 ml/g of **10**) at $-20°$ for 45 min yielded 75% of ethyl α-cyanovalerate (**11**).[6,8] Similarly, the reaction of **10** with 2 equiv



10 **11**, R = CH_3; **12**, R = $CH{=}CH_2$

of divinylcopperlithium in ether–tetrahydrofuran (10:1, 27 ml/g of **10**) at $-10°$ for 5 hr and 3° for 18 hr gave ethyl 2-cyano-5-pentenoate[6,8] (**12**) in 70% yield.

Further, the tricyclic lactone **13** with dimethylcopperlithium (1.5 equiv) in ether ($-10°$, 40 min, and 0°, 5 min) yielded **14**[6,8] (60%), and reaction of **13** with divinylcopperlithium (1.5 equiv) in ether ($-3°$, 13 hr) afforded **15**[6,8] (60% yield). The starting lactone **13**,[6] mp 93–94°, was obtained by a synthesis, starting with the methyl malonyl ester of 2-cyclohexen-1-ol, which parallels that outlined for the cyclopentyl analog **4** in Chart I.



13 **14**, R = CH_3; **15**, R = $CH{=}CH_2$

The synthetic approach to prostanoids by the scheme disclosed above has a number of potential advantages, not the least of which is brevity.[13,14]

(13) This work was assisted financially by grants from the National Institutes of Health and the Agency for International Development.
(14) We are grateful to our colleagues Drs. Ronald Ruden and David Beames for helpful suggestions.

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(8) This yield has not been optimized.
(9) E. J. Corey and R. L. Carney, *J. Amer. Chem. Soc.*, **93**, 7318 (1971).
(10) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 43, 113 (1960).
(11) This reaction was conducted by Dr. A. Venkateswarlu of these laboratories.
(12) H. C. H. Carpenter and W. H. Perkin, *J. Chem. Soc.*, 921 (1899).

Negative Nuclear Overhauser Effects as Probes of Macromolecular Structure

Sir:

The investigation of the structure of biomacromolecules is a matter of intense current interest in molecular biology and biochemistry. Of diverse methods employed, X-ray diffraction[1] and nmr[2] have proven extremely powerful in recent years. We wish to report an extension of the nmr method which appears to have great potential in such investigations.

The nuclear Overhauser effect (NOE) is defined as the change in integrated intensity of a nuclear resonance signal arising from one nucleus caused by saturation of the signal from a second nucleus. The change occurs as a result of nuclear polarization from one nucleus to another *via* relaxation mechanisms which contribute to the spin lattice relaxation time (T_1). Detailed discussion of the chemical applications of this phenomenon have been published.[3] While intramolecular effects have been extensively studied, intermolecular effects have been relatively neglected. Two reports of intermolecular NOE's have appeared. Kaiser[4] observed an increase in the intensity of the chloroform signal when the cyclohexane signal in a chloroform–cyclohexane–TMS mixture was saturated. Chan and Kreishman[5] observed selective increases in the intensities of purine protons 2 and 8, in a solution of purine and polyuridilic acid, when specific sugar resonances on the polymer were saturated. The polymer was in a random coil form and rapid segmental motion leading to long relaxation times yielded sharp lines.[6] In both cases an increase in the intensity of the signal was observed as predicted by theory.[3]

(1) D. Eisenberg in "The Enzymes," Vol. 1, P. D. Boyer, Ed., Academic Press, New York and London, 1970, p 1.
(2) O. Jardetsky and N. G. Wade-Jardetsky, *Annu. Rev. Biochem.*, **40**, 605 (1971).
(3) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect," Academic Press, New York, N. Y., 1971.
(4) R. Kaiser, *J. Chem. Phys.*, **42**, 1838 (1965).
(5) S. I. Chan and G. P. Kreishman, *J. Amer. Chem. Soc.*, **92**, 1102 (1970).
(6) B. W. Bangerter and S. I. Chan, *Biopolymers*, **6**, 983 (1968).