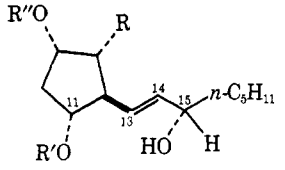
Communications to the Editor

A New Synthetic Approach to Prostanoids *via* Cyclopentene Vinylation

Sir:

The development of new synthetic routes to chiral prostaglandins which are stereospecific, simple, and efficient depends in part on the availability of good methods for the stereoselective elaboration of the characteristic (*S*)-3-hydroxy-*trans*-1-octenyl side chain (as in **1**). At present two such stereoselective methods are



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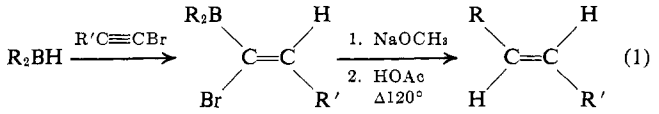
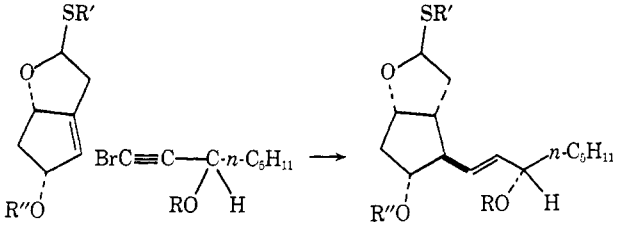
available. The first of these involves the selective formation of the (15*S*)-alcohol unit of **1** (prostanoid[1a] numbering) by reduction of a 15-keto precursor possessing a suitable control group at C-11 (*e.g.*, *p*-phenylbenzoate) by a selective hydride donor.[1b] This technique, even in its present (unoptimized) form, permits the transformation of 15-ketone to (15*S*)-alcohol in 88% yield. The second method utilizes optically active β-oxidophosphonium ylide reagents (available, *e.g.*, from (*S*)-(−)-malic acid without resolution) to construct **1** by a coupling in which the $\Delta^{13(14)}$ bond is formed.[2,3] This communication presents still another approach to this problem which has been developed by appropriate modification of a recently reported process for the synthesis of trans olefinic hydrocarbons (eq 1).[4]



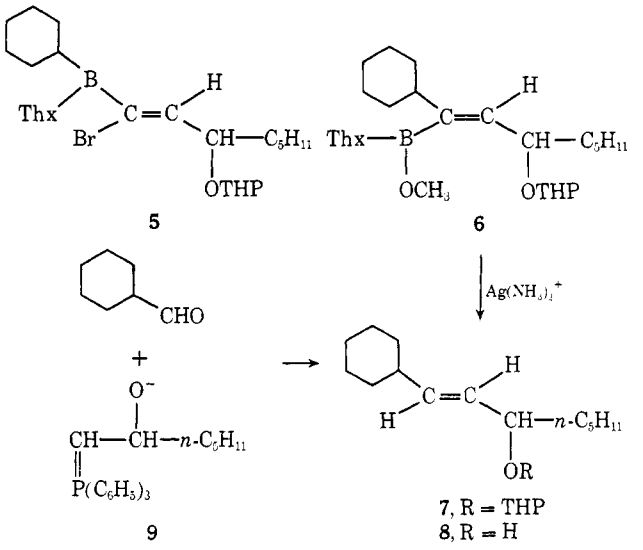
(1)

Specifically our objective has been to effect the joining of components **2** and **3** (each in optically active form) starting with a monoalkylborane as boron source so that **2** could be utilized without sacrifice in a 1:1 mole ratio with **3**. It seemed probable at the outset that the previously reported procedure[4] would not be applicable, since (among other difficulties) the conditions for vinyl deboronation (acetic acid, reflux) would destroy the sensitive allylic alcohol and acetal functions of the desired product **4**. Initial studies were therefore carried out with model systems to establish a feasible process. These have confirmed the inoperability of the previously reported[4] procedure as applied to **3**, while leading to a successful method.



2 **3**, R = THP **4**

A solution of diborane in tetrahydrofuran (THF) (1 *M*) was treated sequentially under nitrogen with tetramethylethylene (1 equiv, −10°, 15 min) and cyclohexene (1 equiv, 0°, 1 hr) to generate cyclohexylthexylborane, and to this solution was then added (0°) 1 equiv of the bromoacetylene **3**.[5,6a] After 2.5 hr at 25° the desired bromovinylborane (**5**) had formed, judging from the consumption of the acetylene **3** (tlc analysis), and methanolic sodium methoxide (1.5 equiv) was added to effect rearrangement[4,7,8] (0°, 5 min; 25°, 3 hr) to the vinylborane **6**. The resulting solution was neutralized using acetic acid dissolved in ethanol (5 mg/ml), and then stirred with 5 equiv of 2 *M* aqueous silver ammonium nitrate complex, $Ag(NH_3)_2NO_3$,[9] at 75–80° for 8 hr. Evaporation of solvents, addition of water, and extraction with pentane afforded after vacuum distillation or chromatography the desired coupling product **7**[6] as a colorless oil in 65% yield from **3**. The trans olefinic geometry for this product was indicated by the occurrence of characteristic infrared absorption at 980 cm^{-1}. Hydrolysis of **7** with aqueous acetic acid at 40° yielded the corresponding alcohol **8**[6] (infra-



5 **6** **9**

7, R = THP
8, R = H

(1) (a) E. J. Corey, T. Ravindranathan, and S. Terashima, *J. Amer. Chem. Soc.*, **93**, 4326 (1971); (b) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971).

(2) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971).

(3) E. J. Corey, *Ann. N. Y. Acad. Sci.*, **180**, 24 (1971).

(4) G. Zweifel, R. P. Fisher, J. T. Snow, and C. C. Whitney, *J. Amer. Chem. Soc.*, **93**, 6309 (1971).

(5) This intermediate, bp 90° (0.05 mm), was prepared from the tetrahydropyranyl derivative of 1-octyn-3-ol (Farchan Research Laboratory) by treatment in THF with 1 equiv of *n*-butyllithium (solution in pentane) at −70° for 10 min and −20° for 20 min followed by reaction with *N*-bromosuccinimide (2 equiv) at −70° for 5 min and 0° for 16 hr.

(6) Satisfactory (a) infrared and nuclear magnetic resonance spectra and (b) mass spectral data were obtained for this compound.

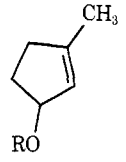
(7) P. Binger and R. Koester, *Tetrahedron Lett.*, 1901 (1965).

(8) G. Zweifel and H. Arzoumanian, *J. Amer. Chem. Soc.*, **89**, 5086 (1967).

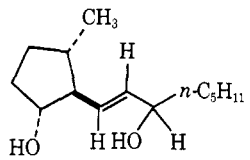
(9) The use of this nonacidic reagent was suggested by the reaction, *e.g.*, with trivinylborane to form ethylene. See (a) T. D. Parsons, M. B. Silverman, and D. M. Ritter, *ibid.*, **79**, 5091 (1957), and (b) F. E. Brinckman and F. G. A. Stone, *ibid.*, **82**, 6218 (1960).

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 = $(CH_3)_2$Si-*t*-Bu



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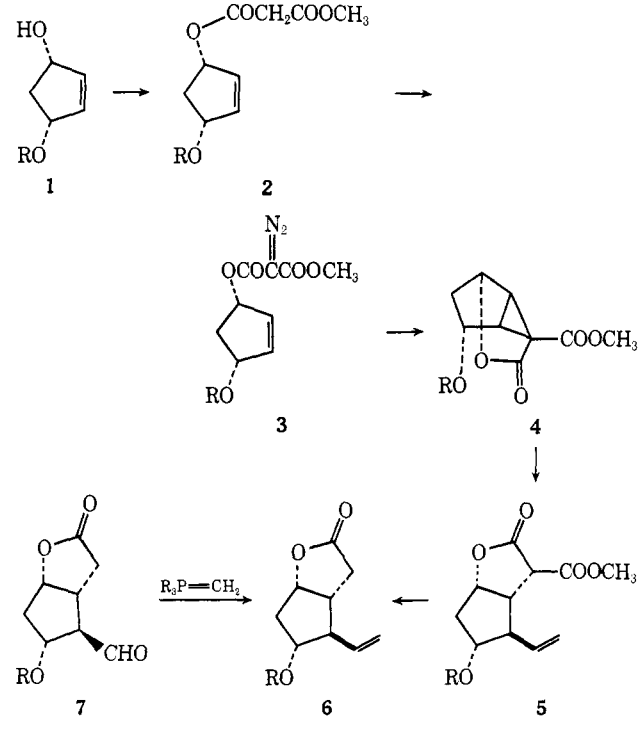
Homoconjugate Addition of Organocopper Reagents to Cyclopropanes and Its Application to the Synthesis of Prostanoids

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).