Studies Directed toward the Synthesis of Prostaglandins. Useful Boron-Mediated Olefin Syntheses

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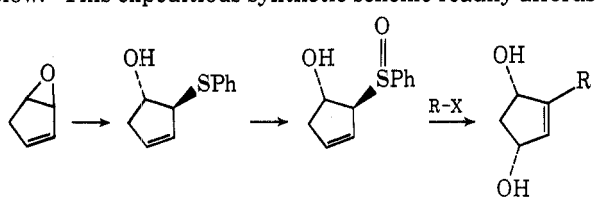
The reactions of bis(2-ethylcyclopentyl)borane, dicyclopentylborane, with 3-(*tert*-butydimethylsiloxy)-1-octyne and subsequent iodine-promoted rearrangement to *Z* olefins or unsymmetrical acetylenes are reported. Mixed dialkylboranes are also examined in this olefin–acetylene cross process. Significant amounts of thexyl-migrated acetylenic by-products are observed in several instances. The synthesis of either *E*- or *Z*-1,2-disubstituted olefins by reaction of boronic esters with both (*E*)- and (*Z*)-alkenyllithium reagents is examined. This study demonstrates that 50–70% yields of either *E*- or *Z*-1,2-disubstituted olefins are obtainable from the aforementioned reagents. The overall objectives in this investigation are to assess the potential of employing organoborane intermediates in the coupling of the C_{13}–C_{20} prostaglandin olefinic side chain to cyclopentenoid precursors.

As part of our program directed toward the total synthesis of prostaglandin hormones we recently reported a general stereospecific approach to the synthesis of *cis*-2-alkyl-2-cyclopentene-1,4-diols (1) via the three-step sequence illustrated below.[2] This expeditious synthetic scheme readily affords a



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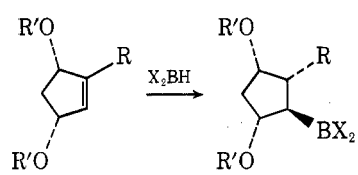
variety of functionalized cyclopentene derivatives which should be amenable to further elaboration to various prostanoids and known intermediates in published prostaglandin syntheses.[3] Based upon the multitude of cross-coupling reactions that have been developed in recent years which have employed organoboranes,[4] we have initiated studies aimed at transforming olefins such as 1 to organoborane intermediates (cf. 2). These intermediates could serve as versatile precursors to elaborated prostanoid intermediates such as 3–5.



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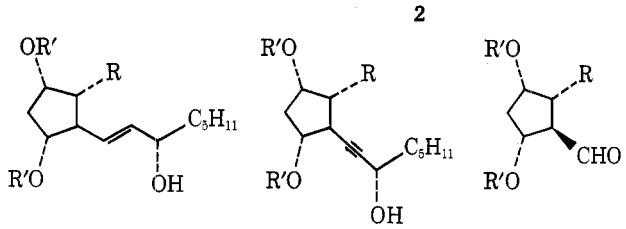

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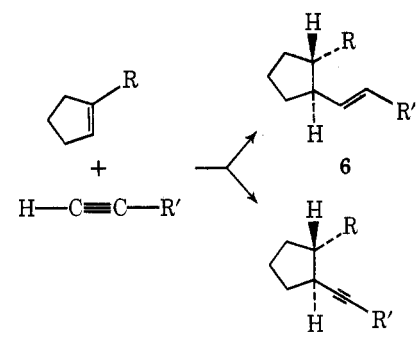
At the present time it is a rare occurrence when boron-mediated carbon–carbon bond constructions are employed in a multistage organic synthesis. This underutilization of a potentially powerful class of reactions generally is due to the relative inefficiency with which a single carbon ligand on a given boron atom can be coupled to other carbon substrates. Partial solutions to this shortcoming have been provided via the design of boron-bound carbon ligands such as 9-BBN[5] and thexyl[6] which generally exhibit low migratory aptitudes in organoborane transformations; however, in specific cases even these ligands lead to unwanted side reactions (vide infra). The purpose of this study has been to survey those organoborane cross-coupling processes which could be ultimately applicable to coupling the C_{13}–C_{20} prostaglandin side chain (cf. 3, 4) to cyclopentene precursors in high efficiency with respect to the cyclopentene moiety.

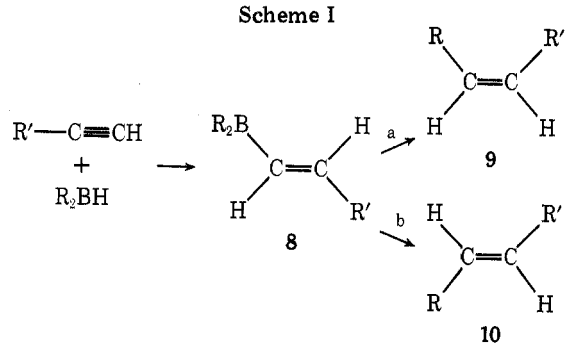
Boron-Mediated Olefin Synthesis. The application of organoboranes to carbon–carbon bond construction has been extensively studied, and a wide variety of processes are becoming available for carbon skeletal assemblage.[4] Of particular interest in the present study were those processes which assemble cyclic olefinic and acetylenic moieties to *E* olefins and internal acetylenes as schematically represented below (cf. 6 and 7).



6 7

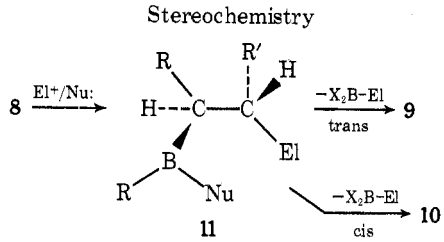
Recently, an elegant approach to the synthesis of both *E*- and *Z*-1,2-disubstituted olefins from common intermediates has been reported by Zweifel (Scheme I).[7] Dialkylborane–

Scheme I



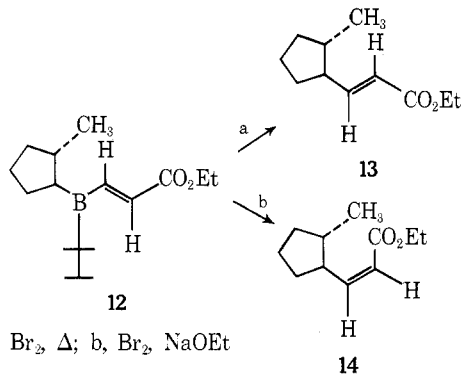
a, I_2, ^-OH; b, BrCN

Stereochemistry



11

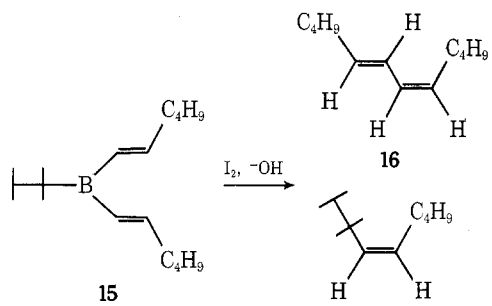
acetylene hydroboration has been shown to readily produce vinylborane intermediates **8**. In situ electrophile-induced (El^+) rearrangements of these species has been postulated to proceed via **11** to either the *Z* olefin **9** by base-induced trans fragmentation or to the *E* olefin **10** by thermal cis elimination of the boron and electrophile functions.[7] Both processes have been shown to be highly stereoselective and afford olefins of high (92–99%) stereochemical purity. Recently Negishi has employed this olefination sequence in the synthesis of the α,β-unsaturated esters **13** and **14** in 91–95% isomeric purity.[8]



12 **13** **14**

a, Br_2, Δ; b, Br_2, NaOEt

It is noteworthy that less than 3% of competitive thexyl migration was observed in the rearrangement of **12**. In various related olefination processes it has been reported that competitive thexyl ligand migration has not posed serious problems.[9-11] One notable exception is the diene synthesis shown below where the alkenyl and thexyl ligands in **15** exhibit

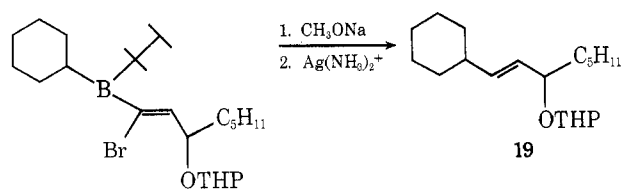


15 **16** **17**

ratio **16**:**17** 52:48

comparable migratory aptitudes.[7b] With respect to results which are to be presented (vide infra) we have observed a similar competition between thexyl and secondary alkyl ligands in analogous vinylborane rearrangements.

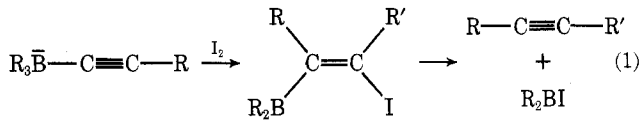
In a preliminary communication closely related to the present study, Corey[11] has reported that the base-catalyzed rearrangement of vinylborane **18** and subsequent deborona-



18 **19**

tion afforded the *E* olefin **19** in 65% yield with no mention of the thexyl-migrated olefin.

Mechanistically related olefin–acetylene coupling reactions have recently been reported by several investigators.[12,13] Lithium alkynyltrialkylboronates have been shown to rearrange and undergo subsequent cis elimination upon treatment with either iodine[12] or methanesulfinyl chloride to afford good yields of internal acetylenes (eq 1). Superficially, such acetylene syntheses appear to be attractive candidates for appending alkenyl side chains to cyclic olefinic substrates. This mode of bond construction, however, loses much of its appeal



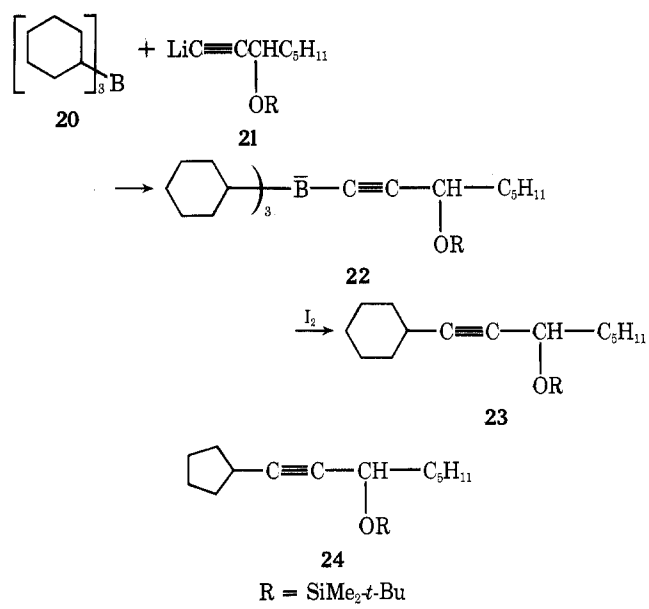
(1)

with the realization that only one of the three carbon ligands on boron can be effectively utilized in the cross-coupling process. Studies directed toward defining practical "nonmigrating" carbon ligands have met with mixed success in the above process.[13b,14]

In an effort to ascertain whether any or all of the above olefination sequences could be efficiently applied to the elaboration of the C_{13}–C_{20} olefinic prostanoid side chain onto cycloalkene derivatives (cf. **1** → **3**), the following general studies were undertaken.

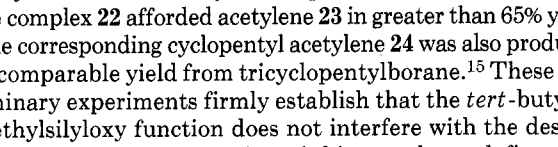
Synthesis of Internal Acetylenes. The reaction sequence chosen for initial study was the acetylene synthesis illustrated in eq 1.[12,13] Following the procedure of Brown and co-workers,[12] reaction of tricyclohexylborane (**20**) with the lithium acetylide **21** followed by iodine-promoted decomposition of ate complex **22** afforded acetylene **23** in greater than 65% yield. The corresponding cyclopentyl acetylene **24** was also produced in comparable yield from tricyclopentylborane.[15] These preliminary experiments firmly establish that the *tert*-butyldimethylsilyloxy function does not interfere with the desired coupling reaction. Extension of this acetylene–olefin cross-coupling to trisubstituted olefins was next examined. Reaction of ethylcyclopentene (3 equiv) with BH_3–THF (1 equiv)[16] followed by successive addition of lithium acetylide **21** (R = $SiMe_2$-*t*-Bu) and iodine afforded the desired acetylene **25** in

Scheme II



20 **21** **22** **23** **24**

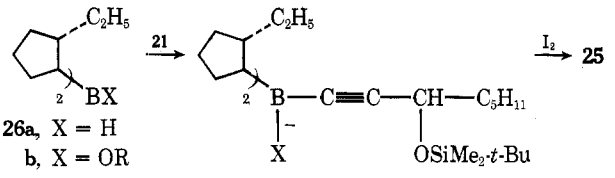
R = $SiMe_2$-*t*-Bu



25

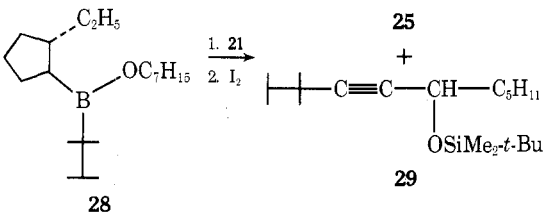
only 31% yield. The lower yields encountered in this instance could have been associated with difficulties in the formation of the trialkylborane with this olefin,[17] or due to possible steric factors associated with either formation or rearrangement of the intermediate ate complex.[18] Since the penultimate intermediate in the acetylene coupling reaction is the presumed ate complex **27** (X = C_7H_{13}) (Scheme III), various alternate approaches to **27** from the dialkylborane **26a**[17] were investi-

Scheme III

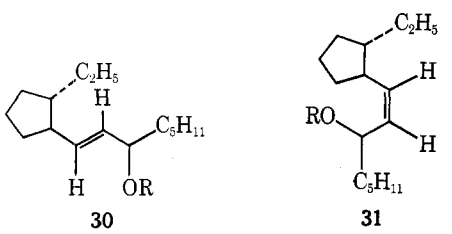


Procedure	Yield of **25**, %
A: 1, n-C_4H_9OH; 2, **21**; 3, I_2	20
B: 1, **21**; 2, n-$C_6H_{13}CHO$; 3, I_2	25
C: 1, n-$C_6H_{13}CHO$; 2, **21**; 3, I_2	72

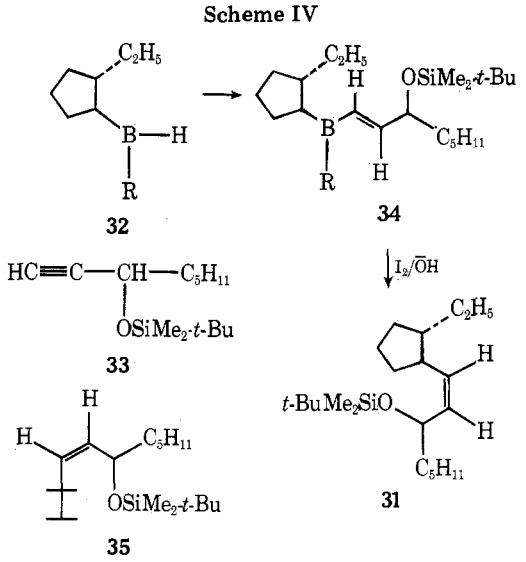
gated. In order to avoid competitive ligand migration in the rearrangement of **27**, an alkoxyl group was chosen as the nonmigrating ligand in the ate complex.[19] In situ generation of dialkylborane **26a** followed by the successive addition of 1-butanol (1 equiv) and lithium acetylide **21** afforded the presumed complex **27b** (X = OC_4H_9). Subsequent rearrangement afforded acetylene **25** in only 20% yield (procedure A). An alternate procedure was examined within **27a**, produced via the addition of **21** to **26a**, was transformed into the alkoxy ate complex **27b** (X = OC_7H_{15}) by reaction with heptanal. However, after stirring the borohydride complex in the presence of 1-heptanal (1 equiv, 0 °C, 1 h), the addition of iodine gave only a 25% yield of acetylene **25** (procedure B). A successful variant of this latter procedure involving initial generation of a borinate ester **26b** via reduction of heptanal with **26a** followed by the successive addition of **21** and iodine was found to afford the desired coupled acetylene in 72% yield (procedure C). This latter experiment demonstrates that dialkyl borinic esters (cf. **26b**) *can* serve as valuable substrates in such acetylene coupling reactions. In addition, the olefin: acetylene stoichiometry has been improved by this modification from 3:1 (Scheme II) to 2:1 (Scheme III) while comparable yields have been maintained. In an effort to achieve cross-coupling stoichiometry of unity for olefinic and acetylenic moieties, the mixed dialkylborinic ester **28** was prepared in analogous fashion (cf. Scheme III, procedure C). Reaction of **28** with acetylide **21** and subsequent iodine-induced rearrangement afforded acetylene **25** (34%) and **29** (6%), the latter having been formed as a result of thexyl ligand migration.



Stereoselective Olefin Synthesis. Attention was next turned to the application of the Zweifel olefin synthesis (Scheme I)[7] to the construction of the prostanoid olefin models **30** and **31** (R = H). Hydroboration of acetylene **33** with the dialkylborane derived from 1-ethylcyclopentene (**32**, R = C_7H_{13}) afforded the presumed vinyl borane **34** which was rearranged to the *Z* olefin **31** in 73% yield (Scheme IV). However, the use of thexyl-2-ethylcyclopentylborane (**32**, R = C_6H_{13}) in the *same* reaction sequence resulted in only a 30% yield of olefin **31** which was accompanied by 14% of the olefin

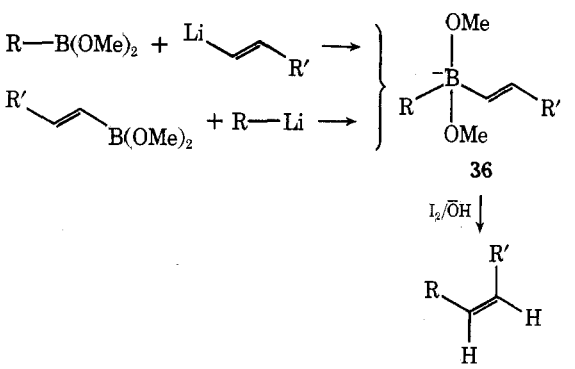


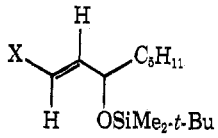
Scheme IV



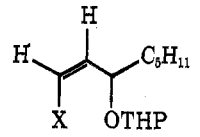
35. These results demonstrate excellent internal consistency with our acetylene cross-coupling study (Scheme III). Iodine-promoted rearrangement of dicyclopentylvinylborane **34** (R = C_7H_{13}) and acetylene ate complex **27** afforded good yields of *Z* olefin **31** and acetylene **25**, respectively. However, attempts to execute analogous reactions on the "mixed" thexylcyclopentylboranes (cf. **28** and **32**, R = C_6H_{13}) resulted in lower yields of both the desired acetylene **25** and olefin **31** and, in addition, products derived from competitive thexyl migration **35** and **29** were formed. Further complications were encountered in attempts to rearrange the dicyclopentylvinylborane **34** (R = C_7H_{13}) to the silyl-protected *E* olefin **30** with cyanogen bromide according to literature precedent.[14d] The major product from this reaction, although not fully characterized, was consistent with the expected olefinic product which had incorporated a nitrile function with concomitant loss of the silyloxy moiety.

As a result of the problems encountered in applying precedented borane cross-coupling reactions to the specific types of olefin syntheses under discussion, we turned to a study of the potential olefin synthesis illustrated below.[20] Based upon analogy, the boronic ester-derived ate complex **36**, readily obtained via alkyl or alkenylboronic ester precursors, might be expected to undergo stereospecific rearrangement to olefinic products in the presence of iodine–base. In this overall olefin construction the final olefin geometry may be defined by the stereochemistry of either the alkenyllithium or vinylboronic boronic ester moieties chosen for the synthesis of the ate complex **36**. An important feature of this process is the *absence* of ligands in the ate complex which can compete with the illustrated boron extrusion process.[19] To test the viability of the illustrated olefin synthesis, vinyllithium reagents **37b** and **38b** were prepared from the corresponding iodides **37a**[21] and **38a**[22] by metal–halogen exchange, and boronic ester **39**





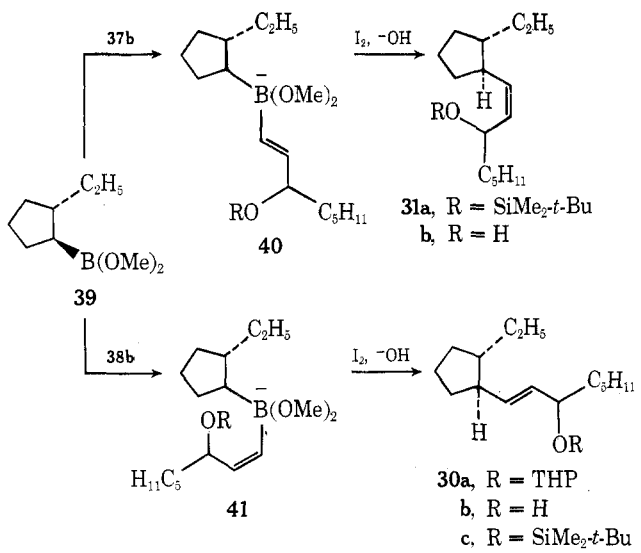
37a, X = I
b, X = Li
c, X = H



38a, X = I
b, X = Li
c, X = H

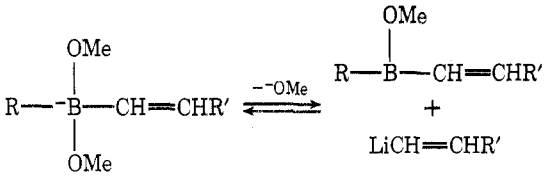
was prepared by analogy to the procedure of Brown (Scheme V).[5d] Addition of 1 equiv of boronic ester **39** to a tetrahydrofuran (THF) solution of *E* vinyllithium reagent **37b** (0 °C) followed by the addition of iodine (1 equiv) and subsequent stirring at 25 °C (3 h) afforded the *Z* olefin **31a** (22%) as well

Scheme V



as vinyl iodide **37a** (22%) and olefin **37c** (11%). Although these results were encouraging, the presence of vinyl iodide suggested that, under the reaction conditions, either the formation of ate complex **40** was not complete or "direct iodination" of the alkenyl–boron bond was competing *directly* with the desired rearrangement. Control experiments implicated the latter explanation. Brown and co-workers have reported a related process in the reaction of vinylboronic acids with iodine and base.[23] It is noteworthy that "direct iodination" of vinylborane **34** or its ate complex was *not* observed to be a significant side reaction, although we have observed **37a** as a minor by-product in this reaction. Minor improvements in the olefination reaction were made when the ate complex **40** was treated with iodine in the presence of sodium hydroxide. After a careful study of the iodine-promoted rearrangement of both **40** and **41**, we have found the overall process to be dramatically solvent dependent. Rearrangement of **40** with iodine in a methoxide–methanol medium afforded a 75% yield of desired olefin **31a**, accompanied by only 15% of the "direct iodination" product **37a**. GLC analysis of the *Z* olefin **31a** indicated that the *Z*:*E* isomer ratio was greater than 96:4, indicating that olefins of high geometric purity are accessible via this route.[24]

Mechanistically, it was predicted that the *E* olefin would result from the iodine-promoted rearrangement of ate complex **41**. Indeed, the addition of 1 equiv of boronic ester **39** to *Z* vinyllithium reagent **38b** generated in ether,[25] followed by iodine-promoted rearrangement in methanol–methoxide solution, afforded the desired *E* olefin **30a** in 58% yield. The *E*:*Z* olefinic isomer ratio was greater than 99:1 in this instance. The successful synthesis of **30a** via this route, as contrasted by the failure to obtain the same compound via the cyanogen bromide rearrangement of vinylborane **34** (Scheme IV), is noteworthy. Other mechanistic points in the olefination sequence illustrated in Scheme V are worthy of discussion. Heteroatom-substituted boronate complexes are known to be labile intermediates.[26] The potentially serious ligand exchange reaction shown below (eq 2) could complicate these and related boronic ester cross-coupling reactions. Ligand exchange on **36** which can occur via tricoordinate borane in-



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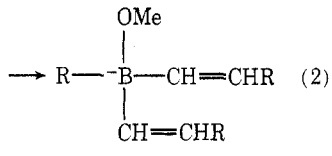

(2)

42

termediates could lead to alternate ate complex **42**. Based upon the known migratory aptitudes of alkyl and alkenyl ligands,[7b] the presence of **42** would be implicated by the observation of dienes subsequent to iodine-promoted rearrangement. Careful examination of the products of the boronic ester mediated olefination sequence (Scheme V) revealed that diene by-products are not significant contaminants. Hence, the ate complexes **40** and **41** do not undergo ligand exchange under the stated reaction conditions. With simple procedures now available for the synthesis of both alkyl and alkenylboronic esters,[27] the results of this study indicate that such organoboranes will be useful substrates for olefin synthesis.

Conclusion

Over the last several years boron-mediated cross-coupling reactions which result in the stereospecific synthesis of olefins and acetylenes have been developed by numerous investigators. The major limitations of these synthetic methods relate to the overall cross-coupling stoichiometry. The present study has sought to solve some of the inherent problems associated with these highly useful bond construction reactions. In particular, the use of boronic esters in hydrocarbon coupling reactions shows considerable promise. The application of the chemistry detailed herein to the synthesis of prostaglandin hormones will be detailed elsewhere.

Experimental Section

Materials. THF and ether were dried by distillation under nitrogen from lithium aluminum hydride or benzophenone ketyl. Dry methanol was anhydrous reagent or spectral grade and was stored over 3 Å molecular sieves. Alkyllithium reagents were purchased from Ventron as solutions in *n*-hexane or cyclohexane, and were standardized by the procedure of Gilman.[28]

Procedure. GLC analyses were run on a Varian Aerograph Model 1400 gas chromatograph equipped with a flame ionization detector using a 6 ft by 0.125 in. stainless steel column of 6% SE-52 or Carbowax 20M on 60–80 mesh acid-washed dimethyldichlorosilanized Chromosorb W. Preparative GLC was carried out using a Varian Aerograph Model 90-P gas chromatograph. Detector response calibrations were determined by comparison of the peak areas (measured by triangulation) of the compound and standard at a variety of weight ratios. Infrared spectra were recorded using a Perkin-Elmer Model 700 or a Beckman IR 4210 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian Associates Model T-60, A-60, or A-60D spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard or chloroform internal standard for silicon-containing compounds. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants, and interpretation.

3-(*tert*-Butyldimethylsiloxy)-1-octyne (33). To a dry 100-ml flask containing 15 ml of dry DMF was added 6.99 g (55.5 mmol) of 1-octyn-3-ol, 9.2 g (61 mmol) of *tert*-butyldimethylchlorosilane, and 9.4 g (139 mmol) of imidazole (freshly sublimed). The reaction mixture was stirred under nitrogen for 36 h. Hexane (150 ml) was added, and the solution was washed five times with water and dried (brine, Na_2SO_4). Removal of the solvent and molecular distillation of the remaining liquid at 45 °C (12 mmHg) afforded 12.34 g (51.4 mmol, 92%) of acetylene **33.** Analytically pure material was obtained by a second molecular distillation of the above liquid: ir (neat) 3320 cm^{-1}; NMR ($CDCl_3$) δ 0.13 (d, 6, CH_3Si–), 0.93 (s, 12, $-CH_3$), 1.12–1.92 (m, 8), 2.35 (d, 1, $-C{\equiv}CH$), 4.34 (m, 1, –CHO–).

Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.92; H, 11.74. Found: C, 70.20; H, 11.58.

1-Cyclohexyl-3-(*tert*-butyldimethylsiloxy)-1-octyne (23). Tricyclohexylborane was prepared by adding 0.67 ml (6.6 mmol) of cyclohexene to 1.8 ml of 1.1 M solution of borane (2.0 mmol) in THF at −20 °C. After 5 min, the heterogeneous solution was warmed to room temperature and was stirred for 12 h. The resulting homogeneous solution was cooled to 0 °C. In another flask containing 4 ml of dry THF and 0.483 g (2.0 mmol) of acetylene **33** under nitrogen was added at −20 °C 2.0 mmol of *n*-butyllithium in hexane. The solution was warmed to room temperature and after 10 min was added to the solution containing the tricyclohexylborane. After 5 min this solution was cooled to −60 °C and 0.513 g (2.02 mmol) of iodine in 3 ml of dry THF was added. After stirring at −60 °C for 70 min and room temperature for 20 min, 80 ml of ether was added, and the organic phase was extracted with 15 ml of 5% sodium hydroxide. The basic layer was extracted with 30 ml of ether, and the combined ether layers were extracted with 13 ml of base, 5 ml of base and 2 ml of 30% hydrogen peroxide, and brine. Benzene (50 ml) was added, and the organic layer was dried ($MgSO_4$). Removal of the solvent and chromatography of the remaining liquid on 15 g of alumina (hexane) afforded 0.574 g (1.78 mmol, 89%) of acetylene **23** as a clear liquid (greater than 75% pure by GLC). Analytically pure material was obtained by preparative gas chromatography: ir (neat) 2245 cm^{-1}; NMR (CCl_4) δ 0.12 (s, 6, CH_3Si), 0.93 (s, 12, $-CH_3$), 1.02–2.00 (m, 18), 2.36 (m, 1, $-C{\equiv}CCH$–), 4.36 (m, 1, –CHO–); MS *m/e* 322 (less than 1), 266 (25), 265 (100), 165 (29), 75 (39), 73 (22).

Anal. Calcd for $C_{20}H_{38}OSi$: C, 74.46; H, 11.87. Found: C, 74.42; H, 11.92.

1-Cyclopentyl-3-(*tert*-butyldimethylsiloxy)-1-octyne (24). Acetylene **24** was prepared using the same precedure that was used to prepare acetylene **23.** Tricyclopentylborane (2.2 mmol) and the lithium salt of acetylene **33** were combined and iodine was added. After workup, 0.623 g (2.02 mmol, 92%) of crude liquid was obtained. A portion of this crude material (0.238 g, 0.765 mmol) was molecularly distilled at 39 °C (0.001 mmHg) to afford 0.210 g (0.68 mmol) of octyne **24** which was greater than 92% pure by GLC (75% isolated yield). An analytical sample was prepared by preparative GLC: ir (neat) 2240 cm^{-1}; NMR ($CDCl_3$) δ 0.12 (s, 6, CH_3Si–), 0.93 (s, 12, $-CH_3$), 1.03–2.02 (m, 16), 2.68 (m, 1, $-CHC{\equiv}C$–), 4.36 (m, 1, –CHO–).

Anal. Calcd for $C_{19}H_{36}OSi$: C, 73.95; H, 11.76. Found: C, 73.86; H, 11.72.

1-(*trans*-2-Ethylcyclopentyl)-3-(*tert*-butyldimethylsiloxy)-1-octyne (25). Procedure A. From Tris(*trans*-2-ethylcyclopentyl)borane. To a solution of 288 mg (3.0 mmol) of 1-ethylcyclopentene in 1.5 ml of THF stirred at 0 °C under nitrogen was added 0.91 ml (1.0 mmol) of 1.1 M borane in THF solution. The reaction mixture was stirred for 15 h (25 °C). In a separate flask, a solution of 240 mg (1.0 mmol) of acetylene **33** in 1.5 ml of THF at 0 °C was treated with 0.46 ml (1.0 mmol) of a 2.2 M solution of *n*-BuLi in hexane. The resulting acetylide **21** was transferred to the borane mixture at 0 °C, stirred for 5 min, and cooled to −65 °C. The reaction mixture was treated with a solution of 260 mg (1.0 mmol) of iodine in 2 ml of THF for 1 h at −65 °C and 2 h at room temperature. The solution was poured into 50 ml of ether washed with aqueous sodium thiosulfate, water, basic hydrogen peroxide solution, water, and brine. The ether layer was dried ($MgSO_4$) and filtered and solvent removed in vacuo to yield 580 mg of colorless oil. Analysis by GLC with eicosane as an internal standard showed a 31% yield of acetylene **25** and a large amount of acetylene **33.** Preparative GLC (6 ft, 15% SE-52, 240 °C) gave an analytical sample: ir (neat) 2960, 2940, 2870, 1470, 1355, 1260, 1090, 845, 785 cm^{-1}; NMR ($COCL_3$) δ 4.33 (t, 1), 0.8–2.4 (m, 24), 0.92 (s, 9), 0.13 (s, 6).

Anal. Calcd for $C_{21}H_{40}OSi$: C, 74.93; H, 11.98. Found: C, 74.67; H, 12.03.

Procedure B. From Borane 26a. To a three-necked 25-ml pear-shaped flask under N_2 was added 194 mg (2.0 mmol) of ethylcyclopentene and 1 ml of dry THF. The solution was cooled to 0–5 °C and 0.92 ml (1 mmol) of 1.1 M borane in THF solution was added dropwise. After 1 h stirring, a solution of acetylide **21** [prepared from 240 mg (1.0 mmol) of acetylene (**33**) and 0.46 ml (1.0 mmol) of 2.2 M *n*-BuLi in hexane solution in 1.5 ml of THF at <0 °C] was added dropwise with stirring. After 5 min at 0–5 °C, 0.135 ml (1.0 mmol) of heptanal was introduced dropwise and the solution was stirred for an additional 1 h. The reaction was then cooled to <−60 °C and a solution of 255 mg (1.0 mmol) of iodine in 2 ml of THF was added. After 2 h at 25 °C the mixture was poured into 50 ml of Et_2O and 25 ml of aqueous thiosulfate solution. Workup as previously described gave 700 mg of colorless oil which darkened on standing. By GLC internal standard (eicosane) the yield of **25** was 27%.

Procedure C. From Borinate 26b. To 196 mg (2.0 mmol) of ethylcyclopentene and 1 ml of dry THF in a 25-ml pear-shaped flask stirred under nitrogen at 0–5 °C was added 0.92 ml (1.0 mmol) of a 1.1 M borane in THF solution. After 2 h, 0.135 ml (1.0 mmol) of heptanal was added dropwise and the solution was stirred for 1.75 h. A solution of acetylide **21** [prepared from 242 mg (1.0 mmol) of acetylene **33** and 0.46 ml (1.0 mmol) of a 2.2 M *n*-BuLi in hexane solution, in 1.5 ml of THF] was then added. After 10 min the mixture was cooled to <−70 °C and a solution of 258 mg (1.0 mmol) of iodine in 2 ml of dry THF was added dropwise. The mixture was stirred for 1 h and then brought to room temperature for 2 h. The product was isolated as previously described to give 680 mg of colorless oil which darkened on standing. By GLC internal standard (eicosane) the yield of **25** was 72%.

Procedure D. From Ethylcyclopentylthexylborane (28). To 89 mg (1.07 mmol) of 2,3-dimethyl-2-butene stirred under N_2 at 0–5 °C was added 0.92 ml (1.0 mmol) of a 1.1 M borane in THF solution. After 1.5 h, 0.12 ml (1.0 mmol) of ethylcyclopentene was added and stirring was continued for 1.25 h. Heptanal (0.13 ml, 1.0 mmol) was then added and the solution was stirred for 1.5 h at 0–5 °C. To the resulting solution was added a solution of 1.0 mmol of acetylide **21** in 2 ml of THF. After 5 min, the reaction was cooled to <−65 °C and a solution of 260 mg (1.0 mmol) of iodine in 2 ml of THF was added. The mixture was brought to room temperature after 1 h and was stirred for another 2 h. Workup as previously gave 640 mg of colorless oil which darkened on standing. By GLC internal standard (eicosane) the yield of **25** was 34%.

In addition, the thexyl-migrated acetylene **29** (ca. 6%) was identified by GLC–MS: *m/e* 323, 309, 267, 253, 167, 157.

1-(*trans*-2-Ethylcyclopentyl)-3-(*tert*-butyldimethylsiloxy)-1-(*Z*)-octene (31). Procedure A. From Bis(*trans*-2-ethylcyclopentyl)borane. To 194 mg (2.0 mmol) of 1-ethylcyclopentene stirred under nitrogen in a 25-ml pear-shaped flask was added 1 ml of THF. The reaction mixture was stirred at −30 °C and 0.46 ml (1.0 mmol) of a 2.2 M solution of borane in THF was added. The solution was brought to 0 °C and stirred for 1.5 h. Acetylene **33** (250 mg, 1.1 mmol) was added and the reaction mixture was stirred for 1 h at 25 °C. The solution was cooled to −40 °C and 0.4 ml (2.4 mmol) of 6 N aqueous sodium hydroxide was added followed by a solution of 260 mg (1.0 mmol) of iodine in 2 ml of THF. The solution was stirred for 2 h at room temperature. Ether (50 ml) was added and the solution was washed with 5% sodium hydroxide, 5% sodium bisulfite with ~10% hydrogen peroxide, and brine. The ether layer was dried ($MgSO_4$) and filtered, and solvent removed in vacuo to yield 530 mg of colorless oil. Analysis by GLC with eicosane as an internal standard showed a 73% yield of **31.** Preparative GLC afforded an analytical sample: ir (neat) 1650, 1452, 1250, 1075, 835, 770, 670 cm^{-1}; NMR ($CDCl_3$) δ 5.33 (m, 2, vinyl) 4.50 (m, t, –CHO–), 1.20–2.30 (m, 18), 0.85 (s, 15, $-CH_3$), 0.12 (s, $-SiCH_3$).

Anal. Calcd for $C_{21}H_{42}OSi$: C, 74.48; H, 12.50. Found: C, 74.26; H, 12.20

Procedure B. From (*trans*-2-Ethylcyclopentyl)thexylborane. To 91.4 mg (1.09 mmol) of 2,3-dimethyl-2-butene stirred under nitrogen at 0 °C in a 25-ml three-necked pear-shaped flask was added 0.48 ml (1.05 mmol) of a 2.19 M solution of borane in THF. The reaction mixture was stirred for 2.5 h and cooled to −20 °C, and 0.12 ml (1.0 mmol) of 1-ethylcyclopentene was added dropwise. The solution was stirred for 1.75 h, 250 mg (1.1 mmol) of acetylene **33** was added, and stirring was continued for 2 h at −20 °C and 1.5 h at 0 °C. The solution was cooled to −50 °C and 1 ml of THF was added followed by 0.4 ml (2.4 mmol) of 6 N aqueous sodium hydroxide and a solution of 270 mg (1.1 mmol) of iodine in 2 ml of THF. The mixture was brought to room temperature over 30 min and stirred for 2.5 h. Workup as previously described gave 600 mg of colorless oil. Analysis by GLC with eicosane as an internal standard showed a 30% yield of olefin **31** and ~15% of a second product, identified as **35,** the product of competitive thexyl migration, by GLC–MS: *m/e* 326, 325, 311, 283, 269, 255.

1-(*trans*-2-Ethylcyclopentyl)-3-(*tert*-butyldimethylsiloxy)-(*Z*)-1-octene (31) from Boronic Ester 39. To a solution of 388 mg (1.05 mmol) of (*E*)-1-iodo-3-(*tert*-butyldimethylsiloxy)-1-octene[21] (**37a**) in 6 ml of dry THF, cooled to −78 °C under argon in a 25-ml pear-shaped flask, was added 3.18 ml (2.10 mmol) of a 0.66 *M* solution of *sec*-butyllithium in *n*-hexane. The reaction mixture was stirred for 1 h at −78 °C and then brought to 0 °C. Boronic ester **39** (0.204 ml, 1.05 mmol) was added to **37b** and the solution stirred for 10 min at 0 °C. To the reaction mixture was added a solution of 3.15 mmol of sodium methoxide in 1 ml of methanol, and a solution of 1.33 g (5.25 mmol) of iodine in 8 ml of methanol. The reaction mixture was stirred for 3 h at room temperature and diluted with 200 ml of ether. The solution was washed with 5% sodium thiosulfate solution, H_2O, 5% sodium hydroxide solution with ~10% hydrogen peroxide, 5% sodium thiosulfate solution, and brine. The ether layer was dried ($MgSO_4$) and filtered and solvent removed in vacuo to yield 549 mg of a pale yellow oil. Eicosane (40.9 mg) was added as an internal standard. Analysis by GLC (5% SE-52, 80–250 °C at 6 °C/min) showed a 75% yield of olefin **31** along with vinyl iodide **37a** (~15%) and olefin **37c** (~15%). The product was chromatographed on 100 g of silica gel with petroleum ether to give 373 mg of colorless oil. A portion of this material was purified by medium-pressure liquid chromatography on 100 g of preparative TLC grade silica gel, eluting with petroleum ether, to give pure olefin **31.**

1-(*trans*-2-Ethylcyclopentyl)-3-(tetrahydropyran-2-yloxy)-(*E*)-1-octene (30a). To a solution of 168 mg (0.497 mmol) of (*Z*)-1-iodo-3-(tetrahydropyran-2-yloxy)-1-octene (**38a**)[22] in 5 ml of ether cooled to −78 °C under argon in a 25-ml pear-shaped flask was added 0.89 ml (0.994 mmol) of a 1.12 M solution of *sec*-butyllithium in cyclohexane. The solution was stirred for 1 h at −78 °C and 0.096 ml (0.497 mmol) of boronic ester **39** was added. The reaction mixture was stirred for 10 min at −78 °C and 10 min at 0 °C. To the reaction mixture was added a solution of 1.49 mmol of sodium methoxide in 1 ml of methanol and a solution of 630 mg (2.48 mmol) of iodine in 15 ml of methanol. The reaction mixture was stirred for 3 h at room temperature and the bulk of the methanol was removed in vacuo. Ether (150 ml) was added and the solution was washed with 5% sodium thiosulfate, 5% sodium hydroxide solution, 5% sodium hydroxide solution containing ~10% hydrogen peroxide, 5% sodium thiosulfate, and brine. The ether layer was dried (Na_2SO_4) and filtered, and solvent removed in vacuo to yield 235 mg of product. Tetracosane (55.3 mg) was added, and analysis by GLC (5% SE-52, 100–250 °C at 6 °C/min) showed the presence of olefin **30a** (51%) and vinyl iodide **38a** (21%). Fractional molecular distillation at 120 °C (0.001 mm) gave an analytical sample: ir (neat) 1660, 1020, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.1–5.6 (m, 2, vinyl), 4.65 (m, 1, –OCHO–), 3.30–4.20 (m, 3, –CHO–), 0.60–2.20 (m, 30).

Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76. Found: C, 77.77; H, 11.82.

1-(*trans*-2-Ethylcyclopentyl)-(*Z*)-1-octen-3-ol (31b). To a solution of 100 mg (0.296 mmol) of silyl ether **31a** in 2 ml of dry THF stirred under nitrogen in a 25-ml round-bottomed flask was added a solution of 235 mg (0.90 mmol) of tetra-*n*-butylammonium fluoride in 8 ml of THF. The reaction mixture was stirred for 6 h at room temperature and diluted with 100 ml of hexane. The solution was washed with aqueous sodium bicarbonate and brine. The solution was dried ($MgSO_4$) and filtered and solvent removed in vacuo to yield 100 mg of yellow oil. Chromatography on 20 g of activity III neutral alumina (hexane/$CHCl_3$) followed by molecular distillation at 50 °C (0.1 mm) gave 50 mg (75%) of alcohol **31b:** ir (neat) 3350, 1650, 1450, 1370, 1015 cm^{-1}; NMR ($CDCl_3$) δ 5.28 (m, 2, vinyl), 4.35 (m, 1, –CHOH–), 0.5–2.8 (m, 25).

Analysis by GLC (6 ft of 5% Carbowax 20M, 160 °C) showed the product to be a mixture of diastereomers containing ~5% of the isomeric alcohol **30b.**

Anal. Calcd for $C_{15}H_{28}$: C, 80.29; H, 12.58. Found: C, 80.15; H, 12.66.

1-(*trans*-2-Ethylcyclopentyl)-(*E*)-1-octen-3-ol (30b). Tetrahydropyranyl ether **30a** was prepared exactly as described on a 0.762-mmol scale. The crude product (282 mg of brown oil) was dissolved in a mixture of 8 ml of 66% acetic acid and 4 ml of THF. The reaction mixture was heated at 55 °C for 3.5 h. The cooled reaction mixture was neutralized with cold 5% sodium hydroxide solution and extracted twice with ether. The combined ether layers were washed with water and brine and dried (Na_2SO_4) and solvent removed in vacuo to yield 198 mg of yellow oil. The material was chromatographed on 30 g of activity III neutral alumina (hexane/chloroform) to give 76 mg (0.34 mmol, 45%) of alcohol **30b.** Molecular distillation at 100 °C (0.001 mm) gave an analytical sample: ir (neat) 3340, 2960, 2930, 1660, 1275, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.35–5.60 (m, 2, vinyl), 4.00 (m, 1, –CHOH–), 0.70–2.20 (m, 25).

Analysis by GLC indicated the product to be a diastereoisomeric mixture containing less than 1% of the isomeric alcohol **31b.**

Anal. Calcd for $C_{15}H_{28}O$: C, 80.15; H, 12.66. Found: C, 80.24; H, 12.66.

Dimethyl *trans*-2-Ethylcyclopentylboronate (39). In a 250-ml, round-bottomed flask under nitrogen atmosphere was placed 67 ml (75 mmol) of 1.2 M borane in THF solution. The reaction mixture was cooled to 0 °C and 8.9 ml (75 mmol) of 2,3-dimethyl-2-butene was added slowly. After stirring for 1.5 h, the resulting solution of thexylborane was cooled to −30 °C and 9.1 ml (75 mmol) of 1-ethylcyclopentene was added dropwise over 10 min. The reaction mixture was stirred for 1.5 h at −30 °C and 41.7 ml (300 mmol) of dry triethylamine was added over 20 min. The reaction mixture was brought to room temperature and stirred for 2.5 h. Dry methanol (12.1 ml, 300 mmol) was slowly added (vigorous gas evolution) and the reaction mixture was stirred for 1 h at room temperature. The flask was fitted with a distillation head and the solvents were removed in vacuo (<45 °C at 70–110 mm) to ~20 ml volume. The material was transferred to a 50-ml flask and distilled (60 °C at ~2 mm) to give 9.4 g (55 mmol, 74%) of product. The product was redistilled at 40 °C (~1 mm) to give 6 g of boronic ester **39** as a colorless liquid: ir ($CHCl_3$) 2950, 2862, 1470, 1320, 1013 cm^{-1}; NMR ($CDCl_3$) δ 3.57 (s, 6, $-OCH_3$), 0.65–2.0 (m, 13).

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Registry No.—**20,** 1088-01-3; **21,** 60134-82-9; **23,** 60134-83-0; **24,** 60134-84-1; **25,** 60134-85-2; **26a,** 60134-86-3; **26b,** 60134-87-4; **28,** 60134-88-5; **29,** 60134-89-6; **30** (R = tetrahydropyran-2-yl), 60134-90-9; **30** (R = H), 60134-91-0; **31** (R = SiMe, Bu-*t*), 60134-92-1; **33,** 60134-93-2; **35,** 60134-94-3; **37b,** 39178-67-1; **38a,** 39647-92-2; **39,** 60134-95-4; 1-octyn-3-al, 818-72-4; *tert*-butyldimethylchlorosilane, 18162-48-6; tricyclopentylborane, 23985-40-2; tris(*trans*-2-ethylcyclopentyl)borane, 60134-96-5; (*trans*-2-ethylcyclopentyl)thexylborane, 60134-97-6; thexylborane, 3688-24-2; 1-ethylcyclopentene, 933-06-2.

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Total Synthesis of (±)-*cis*-Sativenediol

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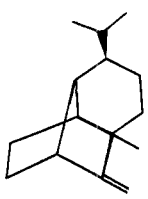
A total synthesis of the plant growth promoter *cis*-sativenediol (**2**) is reported. The key step involves internal alkylation to cyclopropane **7** followed by thermal rearrangement to tricyclic enone **6**. Cis hydroxylation of the double bond, followed by transformation of the carbonyl into a methylene group, completes the synthesis.

Some years ago we reported[1] a stereospecific total synthesis of the tricyclic sesquiterpene hydrocarbon sativene (**1**). More recently, our continuing interest in this skeletal class has also led to syntheses of copacamphene[2] and of longifolene.[3] When, therefore, Marumo[4] and Arigoni[5] independently assigned the *cis*-sativenediol structure (**2**) to a metabolite isolated from the fungus *Helminthosporium sativum*, we were drawn to attempt a synthesis of the molecule.[6] The Marumo report is particularly interesting because it appears that *cis*-sativenediol posesses gibberellin-like plant growth promoter activity.



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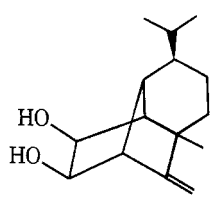
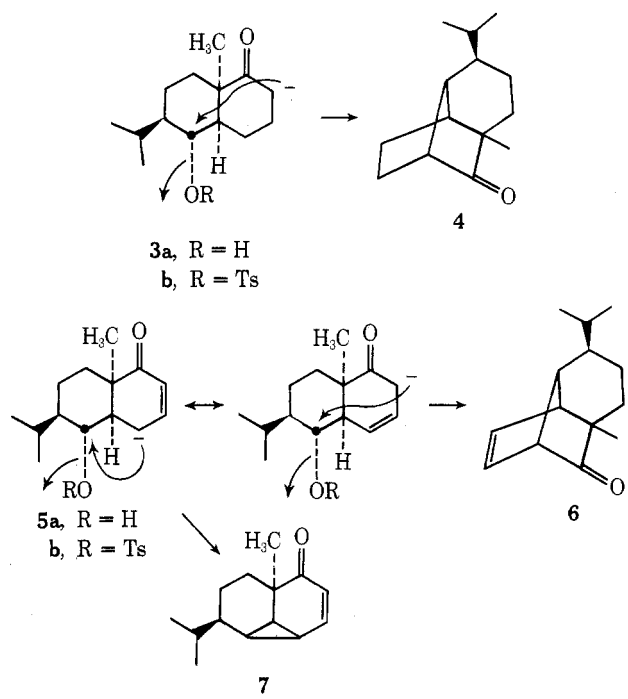


2

The key step in our sativene synthesis was the intramolecular alkylation of bicyclic keto tosylate **3b** to tricyclic ketone **4**. If one imagines that the cis diol functionality in the target **2** arises by less hindered exo hydroxylation of the proper olefinic ketone **6**, then this requires that we synthesize and cyclize the enone tosylate **5b**. One conceivable difficulty with this route is that **5b** might choose an alternate mode of cyclization leading to cyclopropane **7**, but only experiment can show which cyclization path is more favorable.

Enone **5b** was therefore synthesized in straightforward manner from **3a** whose synthesis we have previously reported[1] (Scheme I). One modification made in the present work, however, is the use of aqueous titanous ion[7] to cleave 2,4-DNP **14** to the corresponding ketone **3a**. The transformation occurred in 97% yield vs. the 70% reported earlier when ozonolytic cleavage was used. Ketone **3a** was readily transformed into enone **5a** in 82% yield by the Reich–Sharpless procedure,[8] and, after tosylation, we were ready to attempt intramolecular alkylation.

Treatment of keto tosylate **5b** with 1.2 equiv of dimsyl sodium in Me_2SO for 5 min at room temperature led to a 96% yield of pure cyclization product. Ir and NMR spectroscopy clearly showed, however, that the product was exclusively the undesired cyclopropane, **7** (ir 1670 cm^{-1}).



We had hoped, from inspection of molecular models, that geometric constraints imposed by the decalin system would hinder the development of orbital overlap necessary for three-membered ring formation, but this was clearly not the case.

Since the cause of the problem is the extended enolate system in **5b** one can devise potential solutions based on carrying out the cyclization with enone equivalents to **5** in which the double bond is somehow masked. The actual resolution of the problem turns out to be much simpler, however, when one realizes that the undesired product **7** and the desired product **6** are formally interconvertible by a vinylcyclopropane → cyclopentene rearrangement. Thus they should be in a thermal equilibrium, and one would expect the relatively unstrained **6** to predominate rather than cyclopropane **7**. When, in fact, **7** was heated to 450 °C in a nitrogen swept quartz pyrolysis system, **6** was isolated as the sole product in nearly quantitative yield.

With this key rearrangement completed, **6** was then