Synthesis Via Organoborates of (2E, 4Z)-1-Oxy-functionalized Dienes, Useful Intermediates of Natural and Bioactive Compounds

P. Bovicelli, P. Lupattelli, and E. Mincione

J. Nat. Prod., **1993**, 56 (5), 676-681• DOI:
10.1021/np50095a003 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 56, No. 5, pp. 676-681, May 1993

SYNTHESIS VIA ORGANOBORATES OF (2*E*,4*Z*)-1-OXY-FUNCTIONALIZED DIENES, USEFUL INTERMEDIATES OF NATURAL AND BIOACTIVE COMPOUNDS

P. BOVICELLI,* P. LUPATTELLI,

Centro C.N.R. di Studio per la Chimica Delle Sostanze Organiche Naturali, Dipartimento di Chimica, Università "La Sapienza," P.le A. Moro, 5-00185 Roma, Italy

and E. MINCIONE

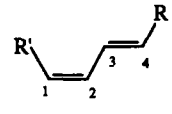
D.A.B.A.C., Università della Tuscia, V.S. Camillo De Lellis, 01100 Viterbo, Italy

ABSTRACT.—We report the synthesis, via iodine-induced migration reactions of organoborates, of (2*E*,4*Z*)-1-oxy-functionalized dienes. These latter are intermediates used to obtain certain flavors and odoriferous components of fruits and vegetables, together with bioactive compounds such as pheromones and prostanoids.

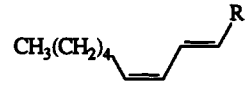
Stereodefined 2*E*,4*Z* dienyl moieties **A** (Scheme 1), which bear a functionalized C_1 vinylic carbon, are recognized in different classes of natural substrates, such as the flavor and odoriferous components **1** and **2** of fruits and vegetables (1), and bioactive compounds **3** and **4** like pheromones and prostanoids (2,3). Highly stereoselective methods are required to synthesize these compounds because their biological activity is significantly dependent on the stereoisomeric purity of the diene unit.

We considered that a useful approach to the synthesis of diene **A** was the utilization of organoborate-migration reactions that enable us to build these dienic units with high stereoselectivity (4–6). We were particularly interested in this method since hitherto no reports have been received of synthesis of diene units with functionalized vinylic carbons via iodine-induced migration reactions of organoborates.

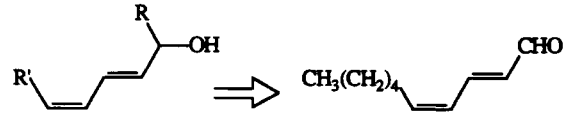
As a first approach to the synthesis of the *E,Z* diene system we utilized propargyl acetal **5** as starting material (Scheme 2). This was hydroborated by Sia_2BH at the most substituted carbon to give mainly the allenyl ether **6b** via the non-isolable intermediate **6a** and coordination of boron with an acetal oxygen. To prevent this we utilized the propargyl acetate **7** as starting material, which in this case furnished the expected trans vinylic borane **8** in good yield after hydroboration. Compound **8** was converted by reaction with heptynyllithium into the corresponding quaternary borate **9**; this, via an



A R=CH_2OH, CHO, COOH
R'=Alkyl or alkenyl group



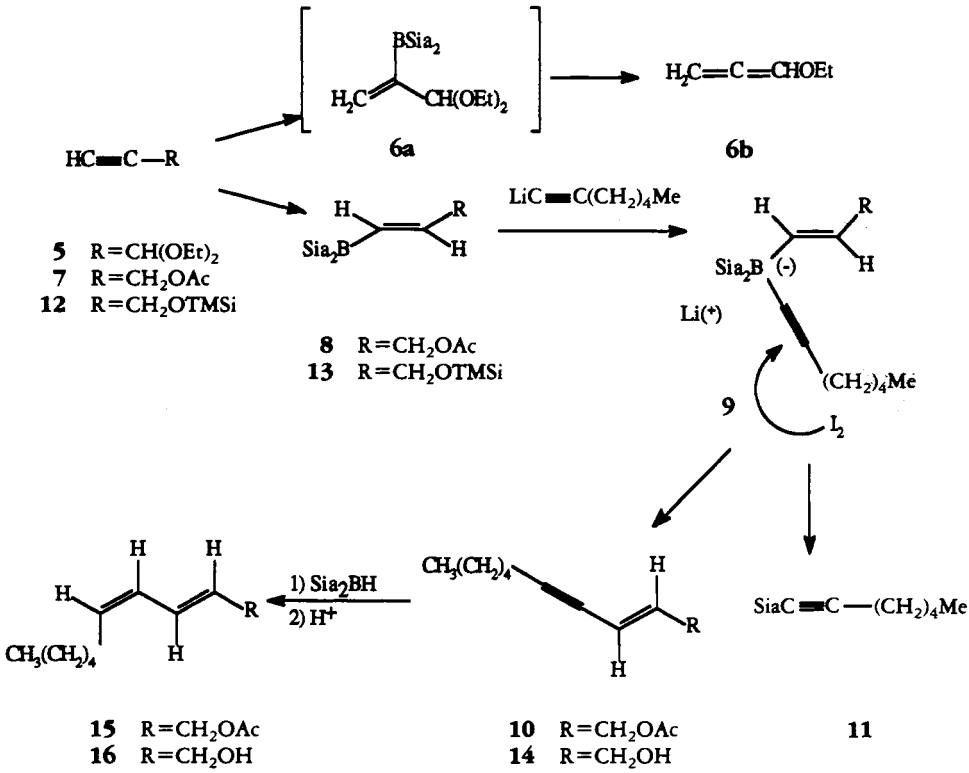
1 R=COOEt
2 R=CHO
3 R=COOMe



4 R=$(CH_2)_7COOH$, R'=$(CH_2)_4Me$ **2**

SCHEME 1

iodine-induced migration reaction, yielded the enyne **10**. We observed that control of the addition time of iodine and of the temperature of the reaction were important to ensure satisfactory yields of **10**. Therefore, the formation of only a moderate yield of **10** (35%) could be ascribed to the poor migratory aptitude of the propenyl group which bears an electron-withdrawing acetoxyl. With such a substituent, the alternative migration of the siamyl group to give the alkyne **11** is preferred (Scheme 2).

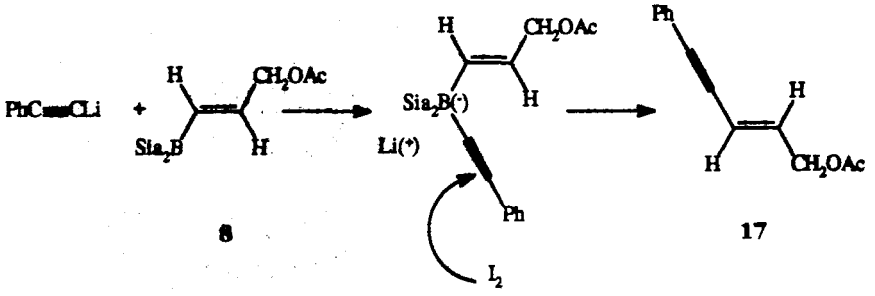


SCHEME 2

The migration reaction was therefore repeated by utilizing the borane **13**, which bears the better migrating propenyl trimethyl silyloxy group. Here we observed the formation of the desilylated enyne alcohol **14**, together with an increased yield (46%). Compound **14** was acetylated to **10**, and then converted into the dienyl acetate **15**. This was done by the selective hydroboration of the alkynyl function with disiamyl borane followed by the acid protonolysis of the carbon-boron vinylic bond. Acetate **15** was hydrolyzed to **16** and then oxidized with barium permanganate to afford the aldehyde **2**, a flavor component of groundnuts and carrot roots (1). Aldehyde **2** is also an intermediate in the synthesis of prostanoid **4** (Scheme 1) (3).

Alcohol **16** was further oxidized by $NaMnO_4$ to give the corresponding acid, which was then esterified to **1** (1), the odoriferous principle of Bartlett pears. By transesterification with NaOMe, **1** gave **3**, a highly active pheromone of the forest pest *Chalcographus pityogenes* (2).

The organoborate method was also utilized to prepare the antimycotic enyne **17** (7) (Scheme 3), starting from phenylethynyllithium and **8**.



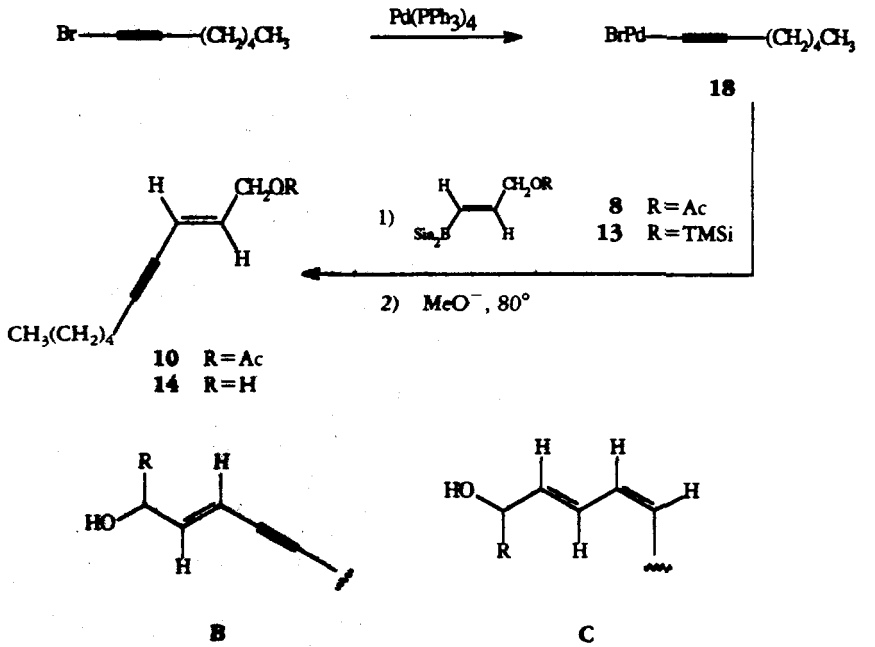
SCHEME 3

We also employed a different approach to these enynic structures, that is, the cross-coupling reactions of vinylboranes with haloalkynes catalyzed by $Pd(PPh_3)_4$ (Scheme 4). As reported by Suzuki and others (8,9), the formation of carbon-carbon bonds in these reactions proceeds with high retention of configuration of the olefinic double bond.

Addition of catalytic $Pd(PPh_3)_4$ to a C_6H_6 solution of 1-bromoheptyne formed the organopalladate **18** (Scheme 4). Coupling of **18** with the acetoxypropenyldisiamylborane **8** in the presence of NaOMe at 80° afforded **10** in 25% yield.

We alternatively utilized the trimethylsiloxypropenyldisiamylborane **13** to prevent a possible reaction of palladium with the acetoxy group and obtained the corresponding desilylated enyne **14** (Scheme 2) in 34% yield.

Further synthetic elaborations of the diene structure A for natural products could produce compounds of general structures **B** and **C** related to immunoactive enynes and phytotoxic dienes, (Scheme 4) (10). More work is in progress in this area.



SCHEME 4

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were recorded in $CHCl_3$ with a Perkin-Elmer 257 Infracord. ^{1}H-nmr and ^{13}C-nmr spectra were recorded with a Varian Gemini 200 MHz; the mass spectra of the reaction products were recorded with an AEI MS12 apparatus at 70 eV. Kieselgel from Merck was used for tlc. Glc capillary analysis were performed with an HP 5890 apparatus (HP-1 Capillar column, 25 m long).

HYDROBORATION OF **5**; FORMATION OF ALLENYLETHER **6b**.—2-Methyl-2-butene (18 mmol) was added to a borane/dimethylsulfide solution (9 mmol) in anhydrous THF (1.47 ml) at −14°, stirring under N_2 atmosphere. After 2 h, **5** (9 mmol) in anhydrous THF (1.0 ml) was added over 10 min. After 2 h, H_2O was added under stirring, and the mixture was extracted with Et_2O; the Et_2O extracts were washed until neutral, dried (anhydrous Na_2SO_4), and evaporated. The crude product thus formed was chromatographed on Si gel, eluting with C_6H_6-Et_2O (95:5). In the ir spectrum, **6b** showed a strong signal at 1950 cm^{-1} (C=C=C); ms *m/z* 84 $[M]^+$.

Acetoxypropenyldisiamylborane **8**.—Acetate **7** (9 mmol) in THF (1 ml) was added to a solution of disiamylborane in THF (9 mmol), prepared as above at 0° in 10 min. This solution was left to react for a further 5 min at 0° and for 2 h at room temperature. Ir ($CHCl_3$) band at 1640 cm^{-1} (C=C); the band at 2120 cm^{-1} (C≡C bond) disappeared.

Acetoxyenyne **10**.—A solution of butyllithium (2.5 M) in hexane (4.2 ml) was slowly added to a solution of 1-heptyne (10 mmol) in anhydrous THF (8 ml) at −78° under an N_2 atmosphere. After 25 min, this solution was added slowly to the previously obtained solution of **8** at −78° to form the borate **9**. After 1 h of stirring, the temperature was raised to −50°, and the reaction was left to proceed for a further 1 h. A solution of I_2 (10 mmol) in anhydrous THF (13 ml) was added to this solution under vigorous stirring for 15 min at −78°; after 1 h, the temperature was raised to 0° and the reaction mixture left under stirring for 14 h. A 5 M NaOAc solution (2.2 ml) was then added, and stirring was continued for a further 30 min. The reaction mixture was then extracted with Et_2O; the Et_2O extracts were washed with a 0.1 M solution of NaS_2O_3 followed by H_2O, and finally evaporated. The residue was treated with a 3 M NaOH solution (10 ml), and 40% H_2O_2 (2.9 ml) was added under stirring at room temperature to destroy the organoboranes present in the solution. After 1 h, the reaction mixture was extracted with Et_2O, washed until neutral, dried (anhydrous Na_2SO_4), and evaporated. The crude reaction mixture was chromatographed on Si gel, eluting with hexane-Et_2O (95:5) to give **10** as the main product (35% yield): ms *m/z* $[M]^+$ 194. Found C 74.30, H 9.41; calcd for $C_{12}H_{18}O_2$, C 74.19 , H 9.34. ^{1}H nmr ($CDCl_3$) δ 0.85 (3H, t, J = 7 Hz, Me), 1.2–1.6 (6H, m, CH_2), 2.05 (3H, s, OAc), 2.27 (2H, t, J = 7 Hz, CH_2-alkyne), 4.55 (2H, pseudo d, J = 6.6 Hz, CH_2OAc), 5.70 (1H, d, J = 15.6 Hz, HC=C), 6.05 (1H, dt, J_1 = 15.6 Hz, J_2 = 6.6 Hz, HC=C). Compound **11** was isolated in the form of a byproduct (25% yield): ms *m/z* $[M]^+$ 166. Found C 86.72, H 13.25; calcd for $C_{12}H_{22}$, C 86.67, H 13.33. ^{1}H nmr δ 0.85 (3H, t, MeCH), 0.95 (6H, pd, Me_2CH), 1.2 (3H, d, MeCH), 2.30 (2H, t, J = 7 Hz, CH_2-alkyne). The residue yield was a mixture of compounds formed by H_2O_2 oxidation of the unrearranged organoborate **9**.

(2E)-Enyne alcohol **14**.—The previous procedure was repeated utilizing silylated propargyl alcohol **12** (11) as starting material (Scheme 2). Compound **13** was formed by reaction with heptynyllithium, then I_2 was added to give enyne alcohol **14** (46% yield): ms *m/z* $[M]^+$ 152. Found C 78.85, H 10.53; calcd for $C_{10}H_{16}O$, C 78.90, H 10.59. ^{1}H nmr ($CDCl_3$) δ 0.85 (3H, t, Me), 1.2–1.6 (6H, m, CH_2), 2.27 (2H, t, J = 7. Hz, CH_2-alkyne), 3.55 (2H, pd, J = 5.8 Hz, CH_2OH), 5.68 (1H, d, J = 15.5 Hz, HC=C), 6.0 (1H, dt, J_1 = 15.5 Hz, J_2 = 5.8 Hz, HC=C). The observed coupling constants (15 Hz) for the olefinic protons of enynes **10** and **14** are in accordance with the *E* configuration (8,12). Glc capillary analysis confirmed the stereoisomeric purity of **10** and **14**. The ^{1}H-nmr spectrum evidenced the presence (4%) of some *Z* isomer as well.

(2E,4Z)Acetoxydiene **15** *and (2E,4Z)hydroxymethyldiene* **16**.—A THF solution of disiamylborane (1 mmol) was added to the enyne **10** (1 mmol) dissolved in anhydrous THF (0.2 ml) at room temperature under stirring. After 2 h, glacial HOAc (5 ml) was added, and the temperature of the resulting solution was raised to 50°. After 5 h, the solvent excess was evaporated in vacuum, a 30% H_2O_2 solution (0.5 ml) and 5M NaOAc (1 ml) were added, and the stirring was continued for 1 h. After usual workup, the crude mixture was chromatographed on Si gel. Eluting with C_6H_6-Et_2O (90:10), starting enyne **10** (26%) and **15** (60% yield) were isolated. Compound **15**: ms *m/z* $[M]^+$ 196. Found C 73.33, H 10.20; calcd for $C_{12}H_{20}O_2$, C 73.43, H 10.27. ^{1}H nmr ($CDCl_3$) δ 0.92 (3H, t, J = 6 Hz, Me), 2.03 (3H, s, OAc), 2.15 (2H, m, CH_2C=C), 4.52 (2H, pt, J = 6 Hz, CH_2OAc), 5.50 (1H, pt, J = 7 Hz, H-5), 5.67 (1H, dt, J_1 = 6 Hz, J_2 = 15.5 Hz, H-2), 5.94 (1H, dd, J_1 = J_2 = 9.5 Hz, H-4), 6.51 (1H, dd, J_1 = 9.5 Hz, J_2 = 15.5 Hz, H-3). The ^{1}H-nmr olefinic signals of **15** are in agreement with the literature reports for the analogous (*E,Z*)-decadienyl isopentanoate (13).

A solution of **15** (2 mmol) in dry Et_2O (1.5 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (2 mmol) in dry Et_2O (1 ml) at −30°. The mixture was stirred for 1 h at −30°, then quenched with a diluted solution of HCl. The organic layer was extracted with Et_2O, and the combined Et_2O layers were washed with H_2O and dried on $MgSO_4$. Removal of the solvent gave 1.5 mmol of **16**: ms *m/z* $[M]^+$ 154. Found C 77.82, H 11.72; calcd for $C_{10}H_{18}O$, C 77.87, H 11.76. ^1H nmr (CCl_4) δ 0.90 (3H, t, J = 6 Hz, Me), 2.13 (2H, m, CH_2C=C), 3.22 (1H, broad, OH), 4.10 (2H, pd, J = 5.5 Hz, CH_2OH), 5.04–6.78 (4H, m, olefinic protons); ^{13}C nmr ($CDCl_3$) δ 14.4, 21.3, 63.4, 126.6, 127.4, 131.6, 134.1.

(2E,4Z)-Diene aldehyde **2**.—Alcohol **16** (0.24 mmol) dissolved in anhydrous CH_2Cl_2 (0.2 ml) was treated with $Ba(MnO_4)_2$ (3.6 mmol). After 4 h, the reaction solution was diluted first with CH_2Cl_2 and then with H_2O; the organic layer was dried and evaporated and the residue chromatographed on Si gel, eluting with hexane-Et_2O (80:20) to give **2** (65% yield): ms *m/z* $[M]^+$ 152; ir ($CHCl_3$) 1675 cm^{-1} (CHO), 1628 cm^{-1} (C=C); ^1H nmr (CCl_4) δ 0.91 (3H, t, J = 5 Hz, Me), 2.30 (2H, m, CH_2C=C), 6.05 (3H, m, olefinic protons), 7.40 (1H, m, HC=C), 9.52 (1H, d, J = 8 Hz, CHO) (1).

(2E,4Z)-Dienyl ethyl ester **1**.—Alcohol **16** (3 mmol) dissolved in hexane (15 ml) was magnetically stirred with $NaMnO_4 \cdot 4H_2O$ (12 mmol) at reflux until the complete disappearance of the starting alcohol (20 h) by glc monitoring. Filtration of the reaction mixture and removal of solvent yielded the crude acid (60% yield). This acid was esterified with acidic EtOH according to the literature procedure (14), to give **1** (65% yield): ms *m/z* $[M]^+$ 196; ir ($CHCl_3$) 1710, 1635, 1610 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.90 (3H, t, J = 5 Hz, Me), 1.30 (3H, t, J = 7 Hz, Me), 2.28 (2H, m, CH_2C=C), 4.13 (2H, q, J = 7 Hz, COOEt), 5.53–6.45 (2H, m, olefinic protons), 5.74 (1H, d, J = 15 Hz), 7.47 (1H, dd, J_1 = 10, J_2 = 15 Hz).

(2E,4Z)-Dienyl methyl ester **3**.—Ester **1** (2.4 mmol) was dissolved in MeOH (20 ml), and NaOMe in MeOH (2.4 ml, 0.5 M) was added at 0°. The reaction mixture was stirred overnight at room temperature and neutralized with saturated NH_4Cl solution. The product was extracted with several portions of Et_2O, and the extracts were dried on anhydrous Na_2SO_4 and evaporated. After chromatographic purification on Si gel, eluting with hexane-Et_2O (70:30), **3** was obtained (70% yield): ms *m/z* $[M]^+$ 182, ^1H nmr ($CDCl_3$) δ 0.89 (3H, t, J = 5 Hz, Me), 2.30 (2H, m, CH_2C=C), 3.72 (3H, s, Me), 5.84 (2H, m, olefinic protons), 6.10 (1H, dd, $J_{4\text{-}3}$ = 12 Hz, $J_{4\text{-}5}$ = 11 Hz, olefinic protons), 7.65–7.52 (1H, dd, $J_{3\text{-}4}$ = 12 Hz, $J_{3\text{-}2}$ = 15.5 Hz, olefinic protons) (2).

(E)-Enyne **17**.—A 2.5 M solution of butyllithium (0.8 ml) was added to a solution of phenylacetylene (2 mmol) in anhydrous THF (1.5 ml) at −78° under argon atmosphere, stirring slowly. The mixture was left to react for 25 min, and then a THF solution of disiamylpropenylacetoxyborane **8** (2 mmol) was added dropwise. The resulting solution was left for an additional 2 h at −78° under stirring; a THF solution of I_2 (2 mmol in 2.5 ml) was then added in 15 min. After 1 h, the temperature was raised to 0°, and the reaction solution was left under stirring overnight. Then a 5 M solution of NaOAc (0.4 ml) was added, and the reaction solution was left under stirring at 30°. After the usual workup, the crude reaction mixture was chromatographed by silica flash chromatography. Acetate **17** was isolated (46% yield) as a liquid by eluting with C_6H_6-Et_2O (95:5): ms *m/z* $[M]^+$ 200. Found C 77.86, H 6.10; calcd for $C_{13}H_{12}O$, C 77.97, H 6.04. Ir ($CHCl_3$), 3020, 2120, 950 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.05 (3H, s, OAc), 4.15 (2H, m, CH_2OAc), 5.12 (1H, d, J = 16 Hz, olefinic proton), 5.96 (1H, m, olefinic proton), 7.25 (5H, s, aromatic protons). A mixture of products (34% yield) formed by the alternative migration of the siamyl group as well as by oxidation of the borate was also obtained.

PREPARATION OF COMPOUNDS **15** AND **16** VIA CROSS-COUPLING REACTION.—1-Bromoheptyne (5 mmol) was added to a solution of $Pd(PPh_3)_4$ (0.05 mmol) in anhydrous C_6H_6 (10 ml), stirring under argon atmosphere at room temperature. After 30 min, compound **8** (5.5 mmol) and a 2 M MeOH solution of NaOMe (10 mmol) were added. The resulting solution was left under reflux until the disappearance of bromoheptyne (as determined by gc monitoring of the reaction). The reaction mixture was then treated under stirring (1 h) with a 3 N solution of NaOH (0.3 ml), and a 30% solution of H_2O_2 (0.3 ml) was added to destroy the residue organoborane. The reaction mixture was extracted with Et_2O; the Et_2O extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was chromatographed on Si gel, eluting with hexane-Et_2O (90:10) to give 25% of **15**; compound **11** (15% yield) was also eluted.

The same cross-coupling procedure was repeated utilizing trimethylsilyloxypropenyldisiamylborane [**13**] as a starting compound. The (2*E*,4*Z*)-desilylated dienyl alcohol **16** was obtained in a 34% yield.

LITERATURE CITED

1. S. Tsuboi, T. Masuda, and A. Takeda, *J. Org. Chem.*, **47**, 4478 (1982).
2. P. Baeckstrom, U. Jacobsson, T. Norin, and R. Unelius, *Tetrahedron*, **44**, 2541 (1988).
3. A.V. Rama Rao, E. Rajarathnam Reddy, G.V.M. Sharma, P. Yadagiri, and J.S. Yadav, *Tetrahedron Lett.*, **26**, 465 (1985).

4. E. Negishi and A. Abramovitch, *Tetrahedron Lett.*, **5**, 414 (1977).
5. E. Negishi, T. Yoshida, A. Abramovitch, G. Lew, and R. Williams, *Tetrahedron*, **47**, 343 (1991).
6. E. Negishi, G. Lew, and T. Yoshida, *J. Chem. Soc., Chem. Commun.*, 874 (1973).
7. O.G. Yashina and L.I. Vereshchagin, *Russ. Chem. Rev. (Engl. Transl.)*, **47**, 557 (1978).
8. N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985).
9. T. Nakashima, T. Ueno, and H. Fukami, *Tetrahedron Lett.*, **23**, 4469 (1992).
10. R. Bauer, T.A. Khan, V. Wrang, and H. Wagner, *Planta Med.*, 424 (1986).
11. S. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958).
12. N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, pp. 85–88.
13. R. Tabacchi, J. Garnero, and P. Buil, *Helv. Chem. Acta*, **58**, 1186 (1975).
14. E.L. Eliel, M.T. Fisk, T. Prosser, *Org. Syn.*, Coll. vol. **4**, 169 (1963).

Received 15 June 1992