Dehydration of 4 (P_2O_5–CH_3SO_3H, 25 °C, 1 h, N_2)[13] gave rise to enone 7 [NMR ($CDCl_3$, 270 MHz) δ 0.99 (3 H, s), 1.26 (3 H, d, J = 7.1 Hz), 6.01 (1 H, dd, J = 13.0, 2.7 Hz, C_8-H), 6.26 (1 H, ddd, J = 13.0, 5.6, 3.3 Hz, C_7 H); IR (CCl_4, FT) 1745, 1665 cm^{-1}], containing 10% of its β,γ isomer. Reduction ($LiAlH_4$, Et_2O, 25 °C) of the mixture proceeded stereoselectively (α attack) to provide diol 8 [mp 163–165 °C; NMR ($CDCl_3$, 270 MHz) δ 0.72 (3 H, s), 0.97 (3 H, d, J = 6.6 Hz), 1.70–1.51 (1 H, m, C_{10} H), 3.85 (1 H, ddd, J = 9.7, 3.0, 2.8 Hz, C_9 H), 5.77–5.57 (2 H, m, vinyl)] in 49% yield (from 4). Irradiation of the C_{10} CH_3 group (δ 0.97) revealed the C_{10} H multiplet as a triplet (J = 10.0 Hz), requiring the relative stereochemistry present at C_1, C_9, and C_{10}.

Introduction of the C_7 β-acetic acid residue was achieved by employing the Eschenmoser[14] variant of the Claisen rearrangement. Thus, diol 8 was converted [$(CH_3)_2NCCH_3(OCH_3)_2$, xylene, 138 °C, 7.5 h; 10% K_2CO_3 (1:1 aqueous CH_3OH), reflux, 2 h] to 9 [NMR ($CDCl_3$, 270 MHz) δ 2.95 (3 H, s, $N(CH_3)_2$), 3.00 (3 H, s, $N(CH_3)_2$), 5.27 (2 H, br s); IR ($CHCl_3$, FT) 3003, 1632 cm^{-1}] in 72% yield. The potassium carbonate treatment was necessary to expose the partially acetylated hydroxyl function. Direct iodolactonization of amide 9 (I_2, 50% aqueous THF, 25 °C, 10 h) yielded the iodo lactone **10a** [89% yield; NMR ($CDCl_3$, 270 MHz) δ 3.64 (1 H, m, HCR_2OH), 4.67 (1 H, dd, J = 8.1, 3.1 Hz, C_9 H), 4.92 (1 H, dd, J = 8.1, 6.7 Hz, C_8 H); IR ($CHCl_3$, FT) 3607, 1787, 1771 cm^{-1}][15] as a pale yellow solid, which was directly submitted to reductive dehalogenation [$(n\text{-}Bu)_3SnH$, AIBN (catalyst), C_6H_6, 50 °C, 1 h, N_2], affording hydroxy lactone **10b** [NMR ($CDCl_3$, 270 MHz) δ 0.84 (3 H, s), 0.98 (3 H, d, J = 7.3 Hz), 4.77 (1 H, ddd, J = 11.8, 8.0, 3.0 Hz, C_8H); IR ($CHCl_3$, FT) 3607, 3487, 1765 cm^{-1}].

Incorporation of the methylene group was accomplished by a new procedure. Treatment of lactone **10b** with Bredereck's reagent[16] [$[(CH_3)_2N]_2CHOCH_3$, 25–83 °C, 1.5 h; 83 °C, 8 h] yielded the crystalline vinylogous carbamate **11a** [mp 178–180 °C dec; NMR ($CDCl_3$, 270 MHz) δ 3.03 (6 H, s, $N(CH_3)_2$), 4.58 (1 H, ddd, J = 11.8, 8.0, 2.9 Hz), 7.09 (1 H, s, vinyl H); IR ($CHCl_3$, FT) 3606, 3417, 1714, 1624 cm^{-1}] in nearly quantitative yield. Reduction[17] of **11a** [DIBAL, THF (hexane), −78 to +25 °C, 2 h; saturated NH_4Cl, 25 °C, 8 h] provided methylene lactone **11b** (97%) upon workup [NMR ($CDCl_3$, 270 MHz) δ 5.59 (1 H, d, J = 2.6 Hz, =CH_2), 6.26 (1 H, d, J = 2.6 Hz, =CH_2); IR ($CHCl_3$, FT) 3604, 3386, 1758, 1600 cm^{-1}]. Oxidation of **11b** with pyridinium chlorochromate afforded quantitatively (±)-2,3-dihydroaromatin [**12a**, mp 118.5–120.5 °C (lit.[1] mp 113–114 °C)] whose 270-MHz NMR spectra and infrared spectrum were identical with those of an authentic sample. Finally, introduction of the 2,3 double bond was effected via selenylation–selenoxide elimination[1,18] to provide (±)-aromatin (52%), whose NMR spectral properties[19] were in accord with those of (−)-aromatin.

Entry into the ambrosanolide series was accomplished in the following way. Dehydrohalogenation of iodide **10a** [DBN (30 equiv), THF, 53 °C, 10 h] provided olefin **13** as an oil in 94% yield. Crystallization afforded pure material [mp 120.5–121.5 °C; NMR ($CDCl_3$, 270 MHz) δ 1.74 (3 H, br s, C_{10} CH_3), 5.32 (1 H, br s, $W_{1/2}$ = 13 Hz, C_8 H), 5.41 (1 H, br s, $W_{1/2}$ = 6 Hz, C_9 H); IR ($CHCl_3$, FT) 3020, 1765, 1665 cm^{-1}]. Hydrogenation of **13** (PtO_2/H_2, EtOH, atmospheric press) occurred from the α face,[20] giving rise to **14a** [NMR ($CDCl_3$) δ 0.91 (3 H, s), 1.02 (3 H, d, J = 7.0 Hz)] in 73% yield after chromatography. Acetylation of **14a** (Ac_2O/pyr, 2 h) quantitatively provided acetoxy lactone **14b** [mp 108.5–109.5 °C (lit.[2d] mp 110 °C), mmp 108.5–109.5 °C] identical (270-MHz NMR and IR) with a sample of **14b** previously converted to (±)-confertin by Schlessinger.

The utility of sulfur-stabilized anions, as adumbrated in this communication, holds promise as an important technique for the synthesis of more highly oxygenated pseudoguaianolides and as a general method for the generation of enolate equivalents.

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(13) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

(14) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.

(15) The 1787-cm^{-1} band presumably arises from Fermi resonance. Removal of the iodine atom (**10b**) affords a single carbonyl absorption in the infrared spectrum.

(16) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.

(17) We are indebted to Professor R. H. Mueller and Mr. M. Thompson for making this method available to us prior to publication.

(18) Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 7393.

(19) The 60-MHz NMR spectrum of (−)-aromatin was supplied by Dr. A. Romo de Vivar.

(20) Examination of the crude reaction mixture (270-MHz NMR) indicated the absence of isomer **10b**. Cf. ref 2d.

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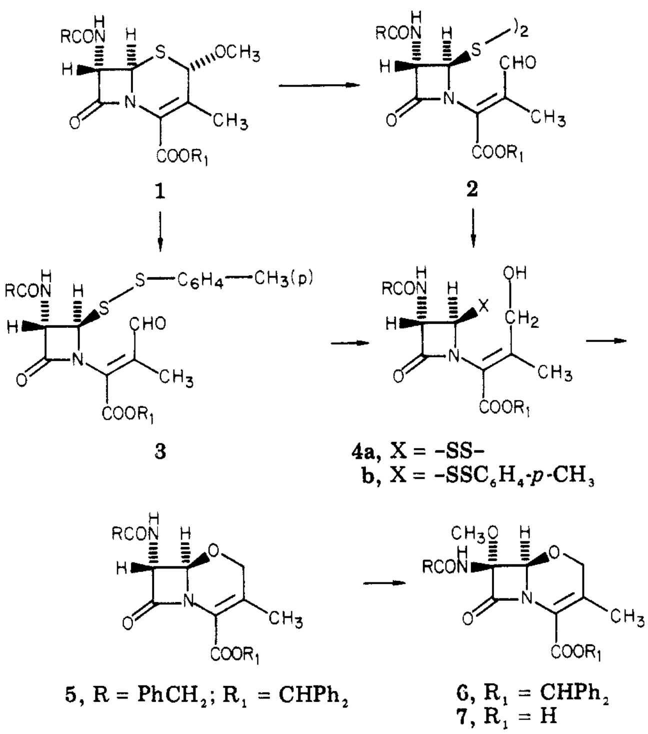
Synthesis of 7β-Amido-7α-methoxy-3-methyl-1-oxacephalosporin[1]

Summary: The aldehyde disulfides 2 and 3 were prepared from 2α-methoxy-3-cephem 1 and subsequently reduced to the corresponding alcohols 4. Treatment of these alcohols with mercuric trifluoroacetate resulted in cyclization to 1-oxacepham 5. The epimerization of the 7α-amide and incorporation of the 7α-methoxy group in 5 were achieved with lithium methoxide and *tert*-butyl hypochlorite. The ester group was removed from the obtained compound 6 with trifluoroacetic acid, providing the biologically active 1-oxacepham acid 7.

Sir: The recent discovery that 1-oxacephalosporins are potent antibiotics prompted us to explore their synthesis.

(1) Azetidinone Antibiotics. 20. Paper 19: S. R. Lammert, A. I. Ellis, R. R. Chauvette, and S. Kukolja, *J. Org. Chem.*, **43**, 1243 (1978).

Scheme I



1, 2, 3, 4a, X = -SS-; b, X = $-SSC_6H_4$-p-CH_3

5, R = $PhCH_2$; R_1 = $CHPh_2$ 6, R_1 = $CHPh_2$; 7, R_1 = H

The first preparation of cephalosporin analogues in which the sulfur atom is replaced by an oxygen atom was reported by Christensen and co-workers.[2] By total synthesis they prepared racemic but biologically active 1-oxacephalothin[2a] and 1-oxacefamandole.[2b] Brain et al.[3] reported a synthesis of 1-oxacephalexin via an intramolecular Wittig reaction. Similarly, Narisada et al.[4] were able to prepare several 1-oxacephalosporins which exhibited antibacterial activity 4–8 times greater than that of the corresponding cephalosporins. Recently, Kim and McGregor[5] published the preparation of biologically inactive 3-methyl-6-epi-1-oxacephem by chemical transformation of the dihydrothiazine ring of a deacetoxycephalosporin. We report here the development of new methodology for replacing S in the cephalosporin nucleus by O with retention of C_6 configuration and illustrate its promise by a short synthesis of the biologically active title compound 7 which contains the valued 7α-methoxy group.[6]

The 2α-methoxy sulfide 1 (Scheme I) served as a particularly useful starting material for two reasons. Specifically, the methoxyl group at the C-2 position was seen to facilitate the dihydrothiazine ring opening,[7] while the 7α-amido group subsequently directed the oxygen-centered cyclization (4 $\rightarrow$ 5) cleanly from the β face of the azetidinone ring. Steric factors are believed responsible for the latter phenomenon.

The starting 2α-methoxy compound 1 was prepared, together with the corresponding 4-methoxy isomer, by treatment of benzhydryl 7α-(phenylacetamido)-3-methyl-3-cephem-4-carboxylate[8] with N-chlorosuccinimide in methanol/methylene chloride solution.[9]

Treatment of 1 with N-chlorosuccinimide (CH_2Cl_2, 0 °C, 15 min) followed by mercuric chloride with cadmium carbonate in water at room temperature for 30 min according to the method described by Paquette et al.[10] provided the monocyclic aldehyde disulfide 2: 90% yield; NMR ($CDCl_3$) δ 2.02 (s, 3, CH_3), 3.48 (s, 2, CH_2Ph), 4.88 (dd, J = 2, 9 Hz, 1, azetidinone H), 5.25 (d, J = 2 Hz, 1, azetidinone H), 6.92 (s, 1, $CHPh_2$), 7.25 (br s, 15, aromatic H), 9.77 (s, 1, CHO).[11] The *unsym*-azetidinone disulfide 3 was prepared in 59% yield by treatment of 1 with p-toluenesulfenyl chloride (CH_2Cl_2, 0 °C, 30 min).[12]

Reduction of aldehyde 2 with sodium cyanoborohydride in acidic, aqueous THF (pH 3.2, 25 °C, 30 min)[13] furnished alcohol 4a (X = disulfide group) in 70% yield as colorless foam: NMR ($CDCl_3$) δ 2.18 (s, 3, CH_3), 3.48 (s, 2, CH_2Ph), 3.93 and 4.20 (AB q, J = 13 Hz, 2, CH_2OH), 4.78 (dd, J = 2, 9 Hz, 1 azetidinone H), 5.04 (d, J = 2 Hz, 1, azetidinone H), 6.86 (s, 1, $CHPh_2$), 7.28 (br s, 15, aromatic H). Similarly, reduction of 3 provided alcohol 4b (X = SSC_6H_4-p-CH_3).[14] The allylic alcohol intermediates 4a and 4b contained all functional groups[15] and stereochemistry necessary for cyclization to the desired oxacephem.

To achieve ring closure, the sulfur atom in 4a (X = –SS–) was abstracted from the azetidinone ring by treatment with mercuric trifluoroacetate[16] in CH_3CN at 25 °C for 30 min. The desired 1-oxacephem 5 was isolated as a crystalline compound: mp 190–191 °C (acetone); 30% yield; NMR (acetone-d_6) δ 1.93 (s, 3, CH_3), 3.65 (s, 2, CH_2Ph), 4.35 (br s, 2, C_2H), 4.73 (dd, J = 1.5, 9 Hz, 1, C_7H), 4.99 (d, J = 1.5 Hz, 1, C_6H), 6.89 (s, 1, $CHPh_2$), 7.33 (m, 15, aromatic H); IR ($CHCl_3$) 1780 cm^{-1}; mass spectrum, *m/e* 482. Similar cyclization of 4b resulted in isolation of 5 in 49% yield.

As mentioned earlier, the purpose underlying attachment of the amide group to the α face of the azetidinone ring was to force the oxygen atom to attack exclusively from the β face. Once this goal had been satisfactorily met and with compound 5 in hand, the ensuing task was to endow the amide group with β stereochemistry. This manipulation is necessary because in biologically active

(2) (a) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974); (b) R. A. Firestone, J. L. Fahey, N. C. Maciejewica, G. S. Patel, and B. G. Christensen, *J. Med. Chem.*, **20**, 551 (1977).

(3) E. G. Brain, C. L. Branch, A. J. Elington, J. H. C. Nayler, N. F. Osborn, M. J. Pearson, J. C. Smale, R. Suthgate, and P. Tolliday In "Recent Advances in the Chemistry of β-Lactam Antibiotics", J. Elks, Ed., The Chemical Society, London, 1977, p 204.

(4) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, *J. Med. Chem.*, **22**, 757 (1979), and references cited therein.

(5) C. U. Kim and D. N. McGregor, *Tetrahedron Lett.*, 409 (1978).

(6) The 7α-methoxy group is a characteristic feature of the cephamycin family of azetidinone antibiotics. It provides the molecule with a remarkable degree of resistance to all β-lactamases.

(7) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* **24**, 362 (1976); **25**, 2082 (1977).

(8) This compound was prepared by B. J. Foster and D. C. Hunden from the corresponding penicillin sulfoxide (epimeric at carbon atom 6) according to the procedure described in U.S. Patent 4003894 (1977). Dioxane was used as the solvent and α-picoline hydrobromide as the catalyst. See also: P. G. Claes, G. Decoster, L. A. Kerremans, and H. Vanderhaeghe, *J. Antibiot.*, **32**, 820 (1979).

(9) D. O. Spry, *Tetrahedron Lett.*, 3717 (1972); A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **23**, 2507, 2518 (1975); **24**, 362 (1976); **25**, 2082 (1977).

(10) L. A. Paquette, W. D. Klobucar, and R. A. Snow, *Synth. Commun.*, **6**, 575 (1976).

(11) Electrochemical reduction and osmotic molecular weight determination proved the disulfide dimer structure of 2. We thank D. A. Hall and G. M. Maciak of the Lilly Research Laboratories for these results. Correct elemental analyses were obtained for all new compounds.

(12) NMR ($CDCl_3$) spectrum of amorphous 3: δ 1.73 (s, 3, CH_3), 2.20, (s, 3, CH_3), 3.48 (s, 2, CH_2Ph), 4.68 (dd, J = 3, 8 Hz, 1, H-3), 5.35 (d, J = 3 Hz, 1, H-2), 6.38 (d, J = 8 Hz, 1, NH), 7.02 (s, 1, $CHPh_2$), 6.8–7.6 (m, 19, arom), 9.32 (s, 1, CHO).

(13) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

(14) NMR spectrum of alcohol 4b: δ 2.00 (s, 3, CH_3), 2.30 (s, 3, toluyl CH_3), 2.88 (br s, 1, OH), 3.41, 3.90 (AB q, J = 13 Hz, 2, CH_2OH), 3.47 (s, 3, CH_2Ph), 4.62 (dd, J = 3, 8 Hz, 1, H-3), 5.17 (d, J = 3 Hz, 1, H-2), 6.32 (d, J = 8 Hz, 1, NH), 6.97 (s, 1, $CHPh_2$), 7.25 (m, 19, aromatic protons).

(15) In our studies X was the disulfide group (symmetric or unsymmetric), but in general X could be also other leaving groups capable of generating a carbocation on the azetidinone ring.

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cephalosporins the amide group is always located on the β face. The epimerization of the 7α-amide function in **5** was achieved according to the elegant method of Baldwin and co-workers[17] and Koppel and Koehler.[18] They demonstrated that methanol adds to acylimines derived from 7β-amidocephems stereoselectively from the α face, and, consequently, the amide group assumes the biologically active β configuration.

In order to isomerize the α-amide side chain to the β orientation, compound **5** was methoxylated with lithium methoxide and *tert*-butyl hypochlorite in THF at –70 °C for 30 min,[18] and 7β-(phenylacetamido)-7α-methoxy-1-oxacephem ester **6**[19] was obtained as crystals: mp 187–187.5 °C (acetone); 88% yield; NMR (acetone-d_6) δ 1.99 (s, 3, CH_3), 3.46 (s, 3, OCH_3), 3.68 (s, 2, CH_2Ph), 4.34 (br s, 2, C_2H), 5.05 (s, 1, C_6H), 6.91 (s, 1, $CHPh_2$), 7.3 (m, 15, aromatic H); IR ($CHCl_3$) 1780 cm^{-1}; mass spectrum, *m/e* 512.

The ester group in **6** was removed with trifluoroacetic acid in anisole at 0 °C for 10–12 min, and the free acid **7** was isolated in 84% yield: mp 169–170 °C (acetone); NMR δ (acetone-d_6) 2.00 (s, 3, CH_3), 3.43 (s, 3, OCH_3), 4.39 (br s, 2, C_2H), 5.08 (s, 1, C_6H), 7.35 (s, 5, aromatic H); IR (KBr) 1782 cm^{-1}.

The 7β-(phenylacetamido)-7α-methoxy-3-methyl-1-oxacephem acid **7** proved in in vitro tests to be biologically active against gram-negative bacteria.

Registry No. 1, 76172-98-0; 2, 76190-18-6; 3, 76172-99-1; 4a, 76173-00-7; 4b, 76173-01-8; 5, 76231-32-8; 6, 76173-02-9; 7, 76173-03-0; benzhydryl 7α-(phenylacetamido)-3-methyl-3-cephem-4-carboxylate, 76173-04-1; toluenesulfenyl chloride, 933-00-6.

(17) J. E. Baldwin, F. Urban, R. D. G. Cooper, and F. L. Jose, *J. Am. Chem. Soc.*, **95**, 2401 (1973).
(18) G. A. Koppel and R. E. Koehler, *J. Am. Chem. Soc.*, **95**, 2403 (1973).
(19) The β configuration of the amide group in compounds **6** and **7** is also substantiated by antibacterial activity of the acid **7** as discussed below.

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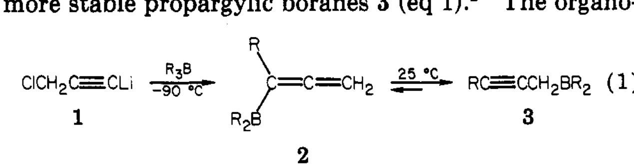
Synthesis of 1,3-Enynols and 1,2,4-Trienols via Allenic and Propargylic Borane Intermediates

Summary: Sequential treatment of lithium chloropropargylide **1** with thexylalkenylchloroboranes and aldehydes affords, depending on the reaction conditions, 1,3-enynols or 1,2,4-trienols.

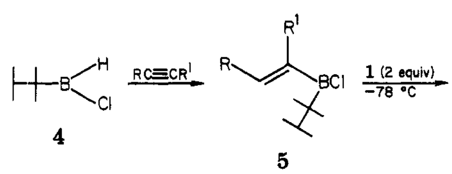
Sir: Treatment of lithium chloropropargylide **1** with trialkylboranes at low temperature results in the transfer of one alkyl group from boron to the propargylic moiety to furnish allenic boranes **2**.[1] On being warmed to room temperature, these rearrange to the thermodynamically more stable propargylic boranes **3** (eq 1).[2] The organo-

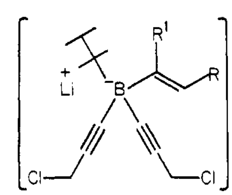


boranes **2** and **3** have proven to be versatile intermediates which react with protic reagents and with aldehydes to afford alkylallenes[1,3] or alkynes[3] and homopropargylic[2] or α-allenic alcohols,[2] respectively.

It is apparent that the synthetic utilities of the allenic and propargylic boranes would be greatly enhanced if the conversion **1** → **2** could be extended to the transfer of alkenyl groups. This would provide access to 1-alkenylallenic boranes **7** and via rearrangement of these to 3-alkenylpropargylic boranes **8**. Thus, we report here that these transformations have now actually been achieved and that the organoboranes **7** and **8** react with aldehydes to produce stereochemically defined 1,3-enynols **9** and 1,2,4-trienols **10** not readily accessible via previously available methodologies.

In our initial studies, we probed the possibility of selectively transferring the alkenyl groups of dialkylalkenylboranes onto lithium chloropropargylide **1**. Unfortunately, treatment of dicyclohexyl- or disiamyl(*trans*-1-octenyl)borane[4] with **1** in both cases resulted in nearly exclusive migration of the saturated moieties. It occurred to us that the use of thexylalkenylchloroborane **5** might provide a solution to the problem, since the thexyl group exhibits a low migratory tendency in many organoboron-mediated carbon–carbon bond-forming reactions.[5] We have recently shown that thexylchloroborane **4** is readily accessible through the reaction of thexylborane with ethereal hydrogen chloride.[6] The reagent cleanly monohydroborates 1-alkynes and disubstituted alkynes to produce the thexylalkenylchloroboranes **5**.





6

We were gratified to observe that addition of the thexylalkenylchloroboranes **5** to 2 equiv of lithium chloropropargylide **1** at –78 °C furnished, via the intermediacy of the ate complexes **6**, the alkenylallenic boranes **7**. Treatment of the reaction mixture containing **7** with an aldehyde afforded the 1,3-enynol **9**. However, if the initially formed organoborane **7** was brought to room tem-

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(2) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc.* **1978**, *100*, 5561.
(3) Midland, M. M. *J. Org. Chem.* **1977**, *42*, 2650.
(4) The organobroanes were obtained by hydroboration of 1-octyne with dicyclohexylborane and disiamylborane, respectively.
(5) Brown, H. C. "Boranes in Organic Chemistry"; Cornell University Press: Ithaca, New York, 1972. Pelter, A.; Smith, K. In "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. III. Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77.
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