Table II. Comparison of Interproton Distances (Å) Calculated Using MARDIGRAS without and with Incorporation of Upper Limits to Exchange Rates for an Experimental 2D NOE Data Set for d(C1-A2-T3-T4-T5-G6-C7-A8-T9-C10)·d(G11-A12-T13-G14-C15-A16-A17-A18-T19-G20)

	calculated distance[a]			calculated distance[a]	
proton interaction	lower bound[b]	upper bound[c]	proton interaction	lower bound[b]	upper bound[c]
T5-H3–G6-H1	2.98	3.88	T4-H3–A18-H2	2.97	3.60
A2-H2–T3-H3	3.18	3.82	C7-NHA–G14-H1	2.58	2.85
A8-H2–T13-H3	2.27	2.76	C7-NHB–G14-H1	2.84	3.13
T5-H3–A16-H2	2.29	2.77	G6-H1–C15-NHA	2.62	2.90
T4-H3–A17-H2	2.37	2.86	G6-H1–C15-NHB	2.80	3.09
T3-H3–A18-H2	2.34	2.84			

[a] Distances were analyzed using experimental 2D NOE spectral intensities (25 °C, 500 MHz, 140-ms mixing time, corrected for nonlinear radio frequency excitation)[22] via MARDIGRAS using an overall tumbling correlation time of 1.8 ns and fast three-state methyl jumps. Interactions listed are only those which differed by more than 0.2 Å when exchange effects were considered and are ordered by decreasing size of the difference. Hundreds of distances were affected negligibly by exchange. Two pairs of amino protons were resolved and included in the calculations. [b] Distance calculated from MARDIGRAS including exchange. For solution conditions employed, an upper limit to the exchange rate of 20 s^{-1} for exchangeable AT protons and 4 s^{-1} for exchangeable GC protons was estimated. [c] Distance calculated from MARDIGRAS ignoring exchange.

bulk water and thus yield observable resonances only in H_2O. Depending on the method of dealing with the potentially huge water proton signal, possible effects from nonlinear radio frequency excitation and accuracy of peak integrals for such spectra provoke concern, but the problems are tractable. The imino proton exchange rate with water can also affect the signal intensity; that rate depends on identity (T or G), temperature, pH, buffer type and concentration, inner or terminal base, and secondary structural features and slightly on sequence.[12-16] Generally, T imino protons exchange about 3–4 times faster than G imino protons. Unfortunately, amino proton exchange rates in nucleic acids are not well characterized. Relative pK_a values suggest that they should exchange more slowly than imino protons, but, to a first approximation, we will assume that they exchange at the same rate.[17]

Although the exchange rate with water has many variables, if ignored, typical rates can introduce significant error into distance determinations. This is shown by Table I. With exchange rates of 1 s^{-1} for exchangeable GC protons and 10 s^{-1} for exchangeable AT protons (on the high side of average) for a data set simulated assuming that the structure determined for d(GTATAATG)·d(CATTATAC) is the "true" structure,[18] overestimation of distances by nearly 20% occurs for some cases. It is not coincidental that the distances with greater error entail exchangeable protons with the largest exchange rate; indeed, the distances with greatest error entail two exchangeable protons. Distances involving nonexchangeable protons were affected negligibly by exchange. Although values are not shown, distance errors are even larger if multispin effects are ignored and the two-spin approximation is used to estimate distances.

As an adjutant to structural studies, it is possible to determine the imino proton exchange rate.[14,16,19] Our iterative complete relaxation rate matrix program, MARDIGRAS,[5,20,21] has been modified such that exchange rates can be accommodated in calculating interproton distances when exchange data is available. Alternatively, on the basis of exchange studies described in the literature, it is possible to estimate upper limits to exchange rates. Using these with MARDIGRAS will provide lower limits to distances involving exchangeable protons. Upper limits to distances can be obtained by ignoring the exchange rates. These limits can thus establish upper and lower distance bounds to be used for structure determination with subsequent distance geometry or restrained molecular dynamics calculations. Table II illustrates the approach using experimental 2D NOE data for d(CATTTGCATC)·d(GATGCAAATG).[22]

In general, imino protons can be included in practical calculations for DNA, but, if data are available, MARDIGRAS is set up to accommodate exchange rate information from other exchangeable protons, such as amino protons in nucleic acids or amide protons in proteins. We set distance bounds on the basis of (i) the minimum error dictated by the experimental noise level, (ii) the error calculated between an observed 2D NOE cross-peak intensity and the corresponding MARDIGRAS-converged matrix element intensity, (iii) distances calculated from spectra at different mixing times, and (iv) in the case of motional or overlap averaging, extreme distances calculated using worst-case geometries.[5,20,21,23] The majority of distances have upper and lower bounds differing by less than 10%. The results presented here, however, show that the range of bounds involving some exchangeable protons needs to be made somewhat larger and that a logical means of establishing those bounds exists.

Acknowledgment. This work was supported by National Institutes of Health grants GM41639, GM39247, and RR01695.

---

(12) Chou, S.-H.; Wemmer, D. E.; Hare, D. R.; Reid, B. R. *Biochemistry* **1984**, *23*, 2257–62.

(13) Mirau, P. A.; Kearns, D. R. *Biopolymers* **1985**, *24*, 711–24.

(14) Leroy, J. L.; Kochoyan, M.; Huynh-Dinh, T.; Gueron, M. *J. Mol. Biol.* **1988**, *200*, 223–38.

(15) Kochoyan, M.; Leroy, J. L.; Gueron, M. *Biochemistry* **1990**, *29*, 4799–805.

(16) Bendel, P. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 352–9.

(17) There is also exchange of the two amino protons with one another via rotation about the C–N bond.

(18) Schmitz, U.; Sethson, I.; Egan, W.; James, T. L. *J. Mol. Biol.* **1992**, *227*, 510–31.

(19) Adams, B.; Lerner, L. *J. Magn. Reson.* **1992**, *96*, 604–7.

(20) Borgias, B. A.; James, T. L. *J. Magn. Reson.* **1990**, *87*, 475–87.

(21) Liu, H.; Thomas, P. D.; James, T. L. *J. Magn. Reson.* **1992**, *98*, 163–75.

(22) Weisz, K.; Shafer, R. H.; Egan, W.; James, T. L. *Biochemistry* **1992**, *31*, 7477–87.

(23) Schmitz, U.; Pearlman, D. A.; James, T. L. *J. Mol. Biol.* **1991**, *221*, 271–92.

(24) Borgias, B. A.; James, T. L. *J. Magn. Reson.* **1988**, *79*, 493–512.

Synthesis and Structure of an Octasila[4.4]betweenallene

Scott A. Petrich, Yi Pang, Victor G. Young, Jr., and Thomas J. Barton*

Ames Laboratory (U.S. Department of Energy) and Department of Chemistry
Iowa State University, Ames, Iowa 50011

Received November 9, 1992

To date there are very few examples of the bicyclic, doubly-bridged allenes[1] known as "betweenallenes".[2] Although examination of models suggests that the smallest all-carbon betweenallene capable of isolation should be a [5.5]betweenallene, the smallest yet reported[5] is [8.10]betweenallene, consisting of fused 11- and 13-membered rings. Highly strained, symmetrical betweenallenes would be of considerable interest owing to the fact that the theoretically predicted[6] relief of strain in small cyclic allenes by concomitant bending and twisting is rendered impossible. Thus strained symmetrical betweenallenes can gain no strain relief by bending, since what is gained in one ring is lost in the other, and therefore only twisting, as defined as a reduction in the normal

---

(1) For an excellent review of cyclic allenes, see: Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111.

(2) The term "betweenallene" was coined by Jim Marshall,[3] and the [*a*,*b*]betweenallene nomenclature is an extrapolation from the nomenclature of "betweenanenes".[4]

(3) Marshall, J. A.; Rothenberger, S. D. *Tetrahedron Lett.* **1986**, *27*, 4845.

(4) Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213.

(5) Nakazaki, M.; Yamamoto, K.; Maeda, M.; Satu, O.; Tsutsui, T. *J. Org. Chem.* **1982**, *47*, 1435.

(6) Angus, R. O., Jr. Ph.D. Dissertation, Iowa State University, 1985. Ruedenberg, K.; Valtazanos, P. Unpublished results, cited in ref 1.

0002-7863/93/1515-1591$04.00/0 © 1993 American Chemical Society

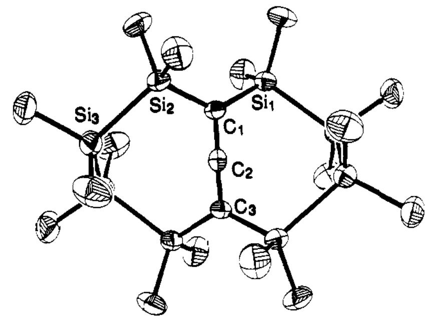
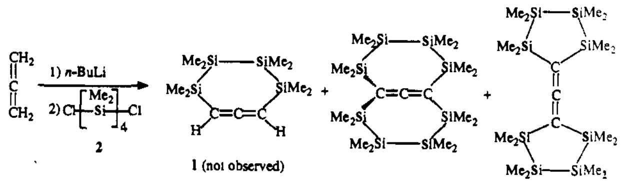


Figure 1. ORTEP "bird's eye" view of 3 with hydrogens omitted. Selected bond distances (Å) and angles (deg) are as follows: Si_2–C_1 = 1.877(3), C_1–C_2 = 1.313(4), Si_2–Si_3 = 2.348(2), C_1–C_2–C_3 = 179.7(4), C_1–Si_2–Si_3 = 107.2(1), Si_1–C_1–Si_2 = 130.2(2), C_2–C_1–Si_1 = 114.9(2).

allene dihedral angle of 90°, is available for relief of strain. We report here the synthesis, structure, and thermal behavior of the first highly strained betweenallene.

In a continuance of our program of synthesis and study of strained silacycles,[7] it was found that attempted synthesis of cyclohepta-1,2-diene **1** by reaction of "dilithioallene"[8] and 1,4-dichlorooctamethyltetrasilane (**2**) afforded instead an ca. 1:1 mixture of endo- and exocyclic allenes **3**[10] and **4**[11] in 26% yield.



3 26%, ca. 1:1 4

Octasila[4.4]betweenallene **3** and its exocyclic isomer 1,1:3,3-bis(octamethyltetrasilane-1,4-diyl)propadiene (**4**), may be envisioned as arising from sequential condensations and metalations, or from condensation with tetralithioallene[9] to produce either both isomers or only one followed by equilibration to both. A modicum of light was shed on these questions by direct generation of one of the potential intermediates, dilithioallene **6**. This was accomplished by the sequential metalation of propargyl bromide with magnesium and *n*-BuLi (a procedure which we have found to cleanly produce products expected from 1,3-dilithiopropyne) followed by quenching with dichlorotetrasilane **2** to afford tetrasilacycloheptyne **5**[12] in 81% yield. Reaction of **5** with 2 equiv of *n*-BuLi followed by quenching with **2** produced betweenallene **3** in 20% yield. Most importantly, none of isomer **4** was found in the product mixture. Thus, while **3** can be formed either from $Li_2C_3H_2$ via **6** or directly from Li_4C_3, **4** must arise from reaction of Li_4C_3.

Table I. Spectral Comparison of Linear and Cyclic Allenes

allene	infrared ($\nu_{C=C=}$)	^{13}C NMR ($\delta_{C=C=}$)
$(Me_3Si)_2C=C=C(SiMe_3)_2$	1870 cm^{-1}	64.03, 203.6
betweenallene 3	1852 cm^{-1}	62.1, 206.7

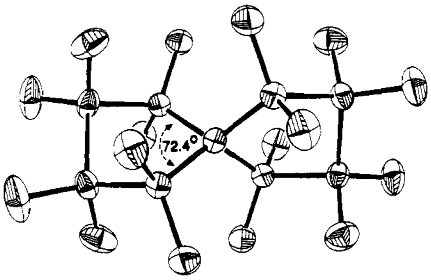
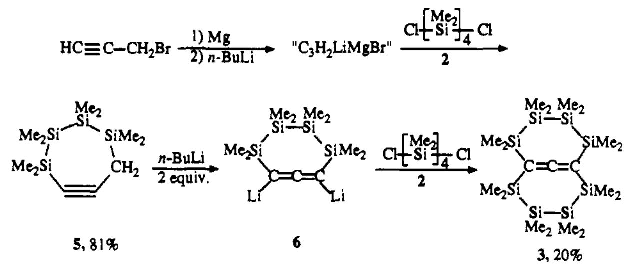


Figure 2. ORTEP view of 3 sighting down the linear allene unit.

Scheme I



The strained nature of **3** is suggested, but by no means demanded, by comparison (Table I) of its spectral features with those of tetrakis(trimethylsilyl)allene. In the infrared spectrum the asymmetric stretching frequency of the allenic unit is found to be reduced by 18 cm^{-1}, and the ^{13}C NMR spectrum reveals the allenic carbons to be shifted downfield by only 2–3 ppm.

The molecular structure of **3** was determined by X-ray diffraction[13] and is shown in Figures 1 and 2. As anticipated the allenic unit is linear, but is twisted to a remarkable dihedral angle of 72.4°. The 17.6° deviation from normal orthogonality may be compared with the dihedral angle of 79.8° found in the smallest cyclic allene for which structural information is available, a cyclonona-1,2-diene,[14] for which the allenic unit is also bent to 168°. The ring strain of **3** is also partially accommodated by opening of the external allenic bond angles ($\angle Si_1$–C_1–Si_2 = 130.2°) while the bond angles inside the ring are decreased ($\angle C_2$–C_1–Si_1 = 114.9°).

Although we have seen no evidence of interconversion of allenic isomers **3** and **4** under the experimental conditions of synthesis, gas-phase pyrolysis of **3** (N_2 flow, 520 °C) afforded remarkably clean conversion to **4** in 83% yield. While the thermal isomerization of **3** to **4** can be rationalized by either a series of sequential 1,3- or 1,2-silyl migrations, the most economical route is a 1,3-dyatropic isomerization. Isomerization by silyl migration on an allenic framework has been examined in detail by Kwart[15] and found to proceed by a concerted 1,3-shift with inversion on silicon. Future work in our laboratory will attempt to obtain Arrhenius parameters for the isomerization of **3** and to calculate the preferred pathway for the isomerization. Attempted ring contraction of **3** by photochemical extrusion of dimethylsilylene, Me_2Si:, produced no volatile cyclic products, although Me_2Si: was produced, as

---

(7) Pang, Y.; Schneider, A.; Barton, T.; Gordon, M.; Carroll, M. *J. Am. Chem. Soc.* **1992**, *114*, 4921.

(8) The attempted (and obviously unsuccessful) synthesis of dilithioallene consisted of bubbling allene into a solution of *n*-BuLi in THF at –30 °C. Perlithiation of allene and quenching of the resulting anions with trimethylsilyl chloride has been studied by Jaffe,[9] who reported varying degrees of silylation from a variety of experimental conditions. These problems are to some degree obviated by the procedure developed in Scheme I, and we will soon report the use of this technique in the preparation of other strained, cyclic allenes.

(9) Jaffe, F. *J. Organomet. Chem.* **1970**, *23*, 53.

(10) **3**: mp 195–200 °C; ^1H NMR δ 0.224 (s, 12 H), 0.171 (s, 12 H), 0.161 (s, 12 H), 0.095 (s, 12 H); ^{13}C NMR δ 206.7, 62.1, 0.55, –1.21, –5.20, –7.16; ^{29}Si NMR δ –17.05, –40.33; IR (GC–FTIR) 2955, 2896, 1852, 1402, 1253, 890, 841, 809 cm^{-1}; mass spectrum *m/z* 500 (M^+, 12), 428 (10), 427 (21), 155 (11), 73 (100); *m/z* calcd for $C_{14}H_{48}Si_8$ 500.19103, found 500.19046.

(11) **4**: ^1H NMR δ 0.153 (s, 24 H), 0.128 (s, 24 H); ^{13}C NMR δ 198, 62.7, –1.89, –7.28; IR (GC–FTIR) 2956, 1860, 1860, 1404, 1251, 853, 805 cm^{-1}; mass spectrum *m/z* 500 (M^+, 19), 427 (16), 155 (12), 73 (100).

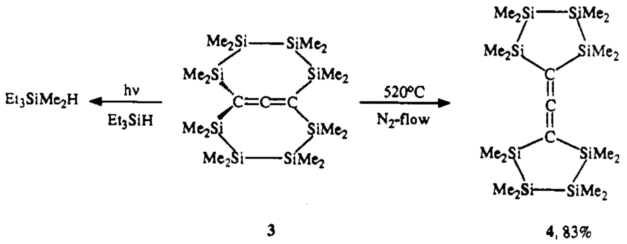
(12) **5**: ^1H NMR δ 1.63 (s, 2 H), 0.197 (s, 6 H), 0.176 (s, 12 H), 0.146 (s, 6 H); ^{13}C NMR δ 117.45, 88.34, 7.93, –2.687, –2.72, –6.00, –7.01; ^{29}Si NMR δ –3.86, –29.13, –31.34, –42.27; IR (GC–FTIR) 2957 (s), 2900 (s), 2126 (m), 1405 (w), 1254 (s), 821 (s), 777 (s) cm^{-1}; mass spectrum *m/z* calcd for $C_{11}H_{26}Si_4$ 270.11117, found 270.11043.

(13) Crystal data for **3** at –80 °C: a = 17.570(5) Å, b = 12.627(3) Å, c = 17.261(6) Å, β = 120.67(2)°, V = 3291(2) $Å^3$, monoclinic system, space group $C2/c$, Z = 4, ρ = 1.012 g cm^{-3}. Of the 2424 independent reflections (Siemens P4/RA diffractometer, λ = 1.54178 Å, θ–2θ technique with $2\theta_{max}$ = 115°, Lp correction applied, no absorption correction), 2042 reflections with $F_o^2 > 2.0\sigma(F_o^2)$ were used and gave a final R = 0.042 and R_w = 0.057.

(14) Luche, J. L.; Damiano, J. C.; Crabbé, P.; Cohen-Addad, C.; Lajzerowicz, J. *Tetrahedron* **1977**, *33*, 961.

(15) Kwart, H.; Slutsky, J. *J. Am. Chem. Soc.* **1973**, *95*, 8678.

evidenced by trapping with Et_3SiH.



Acknowledgment. Ames Laboratory is operated for the U.S. Department of Energy by Iowa State University under Contract No. W-7405-ENG-82. This work was supported by the Director for Energy Research, Office of Basic Energy Sciences.

Synthesis of (*R*)-(−)-Muscone by an Asymmetrically Catalyzed Macrocyclization of an ω-Alkynal

Wolfgang Oppolzer* and Rumen N. Radinov

Département de Chimie Organique, Université de Genève
CH-1211 Genève 4, Switzerland

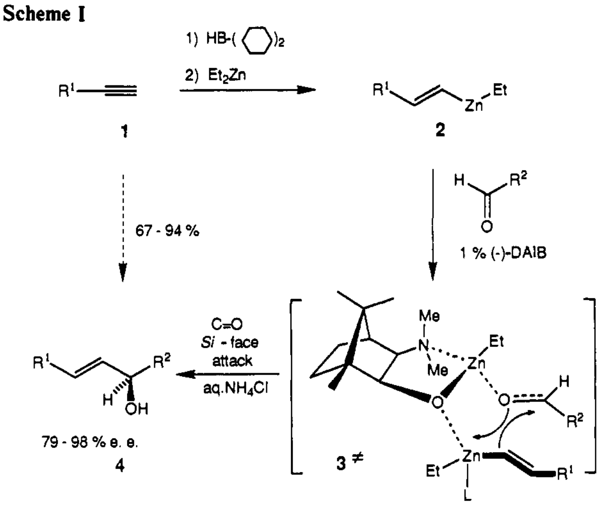
Received December 7, 1992

Recently, we reported a catalytic enantio-controlled approach to secondary (*E*)-allyl alcohols **4** (Scheme I).[1] Monohydroboration of alkynes **1** and "transmetalation" of the resulting (*E*)-(1-alkenyl)dicyclohexylboranes with diethylzinc conveniently provides (1-alkenyl)ethylzinc reagents **2**. Nonisolated reagents **2** undergo exclusively π-face selective 1-alkenyl transfer to various aldehydes in the presence of 1 mol % of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB).[2] This catalyst-directed 1-alkenyl/aldehyde addition is consistent with transition state $\mathbf{3}^{\ddagger}$, where the zinc–aminoalkoxide chelate coordinates with both the aldehyde and the alkenylzinc reagent.[2] Were these two reactive units to be linked by a chain, one could expect a smooth macrocyclization to occur.

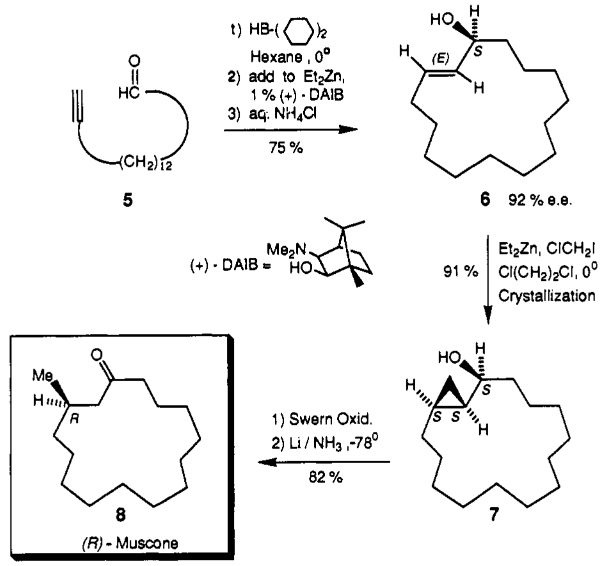
Hence, optically pure, macrocyclic (*E*)-allyl alcohols should be readily available from ω-alkynals in a single operation. This, however, requires that the dicyclohexylborane and the diethylzinc should react faster with the acetylene and alkenylborane functionalities, respectively, relative to their reaction with the aldehyde group.

We report here that this idea is feasible and applicable to the synthesis of enantiomerically pure (*R*)-muscone (**8**, Scheme II). This rare and valuable perfumery ingredient has been isolated from the male musk deer *Moschus moschiferus*,[3] and many syntheses of the racemate as well as of the natural antipode have appeared in the literature.[4]

Scheme I



Scheme II



ω-Alkynal **5**,[5] easily prepared by Swern oxidation[6] of 14-pentadecyn-1-ol[7] (95%), was added to a solution of freshly prepared dicyclohexylborane in hexane at 0 °C. After the reaction mixture was stirred at 0 °C for 2 h and diluted with hexane, the resulting 0.05 M solution of alkenylborane was added over 4 h to a 0.05 M solution of diethylzinc (1.5 mol equiv) in hexane containing (1*S*)-(+)-DAIB (0.01 mol equiv). Aqueous workup furnished the cyclic (*S*)-C_{15}-allyl alcohol **6**[5] in 75% yield and in 92% ee.[8] To transfer the chirality from C(1) to C(3) we envisaged a hydroxy-directed cyclopropananation[9] using the Denmark protocol.[10] Indeed, slow addition of alcohol **6** to a mixture of Et_2Zn (2 mol equiv) and $ClCH_2I$ (4 mol equiv) in 1,2-dichloroethane at 0 °C,

---

(1) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170.

(2) Reviews on asymmetric additions of organozinc reagents to aldehydes: Noyori, R.; Kitamura, M. *Angew. Chem.* **1991**, *103*, 34; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

(3) Isolation: Walbaum, H. *J. Prakt. Chem. II* **1906**, *73*, 488. Structure: Ruzicka, L. *Helv. Chim. Acta* **1926**, *9*, 715, 1008. Ställberg-Stenhagen, S. *Ark. Kemi* **1951**, *3*, 517. Olfactive comparison of (*R*)- and (*S*)-muscone: Pickenhagen, W. *Flavor Chemistry; Trends and Developments*; ACS Symposium Series 388; American Chemical Society: Washington, DC, 1989; p 151.

(4) Syntheses of (*R*)-muscone: (a) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *60*, 925. (b) Abad, A.; Arno, M.; Pardo, A.; Pedro, J. R.; Seoane, E. *Chem. Ind.* **1985**, *29*. (c) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721. (d) Terunuma, D.; Motegi, M.; Tsuda, M.; Sawada, T.; Nozawa, H.; Nohira, H. *J. Org. Chem.* **1987**, *52*, 1630. (e) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309. (f) Xie, Z.-F.; Sakai, K. *J. Org. Chem.* **1990**, *55*, 820. (g) Tanaka, K.; Ushio, H.; Kawabata, Y.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1445. (h) Ogawa, T.; Fang, C.-L.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1991**, 1438. (i) Dowd, P.; Choi, S.-C. *Tetrahedron* **1992**, *48*, 4773.

(5) All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR, and mass spectra.

(6) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(7) Prepared by alkylation of bilithiated propargyl alcohol with 1-bromododecane (98%) and base-induced alkyne isomerization of resulting 2-pentadecyn-1-ol (93%): Utimoto, K.; Tanaka, M.; Kitai, M.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2301. Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333.

(8) Enantiomeric excess (ee) determined by ^{19}F NMR of the (1*S*)-α-methoxy-α-(trifluoromethyl) phenylacetate: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Absolute configuration of **6** assigned in analogy to the topicity of bimolecular 1-alkenylzinc/aldehyde additions[1] and confirmed by the conversion of **6** into (*R*)-muscone.

(9) Simmons–Smith reaction of (*E*)-cycloocten-3-ol: DePuy, C. H.; Marshall, J. L. *J. Org. Chem.* **1968**, *33*, 3326. Diastereoselective cyclopropanations of cyclic (*Z*)-allyl alcohols: Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892; **1970**, *92*, 4274. NOESY correlation indicates a conformation of **6** with a synperiplanar C(1)H/C(3)H orientation.

(10) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

0002-7863/93/1515-1593$04.00/0