Stereogenic Propargylic Centers *via* Base-Mediated Terminal Allene Isomerization

John D. Spence, Justin K. Wyatt, Daniel M. Bender, David K. Moss, and Michael H. Nantz*

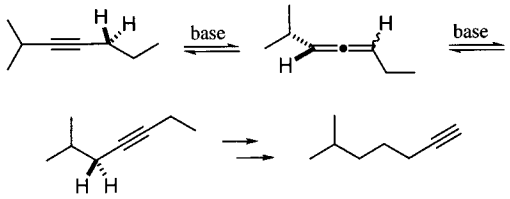
Department of Chemistry, University of California−Davis, Davis, California 95616

Received February 9, 1996[⊗]

A study of alkali metal amide-mediated isomerizations of terminal allenes is described. The isomerizations of substituted ethenylidenecyclohexanes to form diastereomeric mixtures of terminal alkynes have been conducted to determine factors which may influence the stereochemistry at the newly formed propargylic centers. An initial base screen revealed that potassium *N*-methylbutylamide (KMBA) exhibits the highest level of equatorial to axial alkyne diastereoselectivity. With the severely hindered terminal allene **26**, the use of potassium 3-aminopropylamide is required to effect isomerization. A general synthesis of deuterated terminal allenes has also been achieved, and a mechanistic study using d_2-allenes **18a**,**b** has revealed the involvement of a propargylic anion in the course of the KMBA-mediated isomerizations.

Introduction

The base-mediated isomerization of alkynes has found numerous applications in organic synthesis, particularly in connection with transposition of an internal alkyne along an unbranched, unsubstituted carbon chain to the terminus.[1,2] The synthesis of terminal alkynes in this manner has been the subject of several mechanistic investigations,[3−5] and these studies have indicated that the alkyne migration proceeds via a random and reversible sequence of 1,3-proton transfers between alkyne and allene intermediates (eq 1).[6] The use of lithium and sodium metal amides, particularly those of diamines, was



(1)

shown by Wotiz[3] to effect the rapid rearrangement of an internal alkyne and result in the accumulation of a terminal acetylide anion. Further studies by Brown[7] indicated that potassium amides, specifically potassium 3-aminopropylamide (KAPA), are well suited to facilitate the formation of terminal acetylide anions from internal alkynes.[8,9] The rapid reaction times[10] and the high isolated yields of terminal alkyne products obtained by protonation of the isomerization mixture have made the KAPA protocol the current method of choice for the "acetylene zipper" reaction. Few studies,[5,11] however, have employed the KAPA or other amine base conditions for the isomerization of allenic starting materials to their corresponding terminal alkynes.

We have undertaken an investigation of alkali metal amide-mediated isomerization reactions of terminal allenes with the objective being synthesis of stereogenic propargylic centers in conjunction with formation of the terminal alkyne moiety (eq 2).[12] Although this specific transformation has not been reported previously,[13,14] it

* Author to whom correspondence should be addressed.

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1996.

(1) (a) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 5746. (b) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120. (c) Balova, I. A.; Zakharova, I. V.; Remizova, L. A. *Zh. Org. Khim.* **1993**, *29*, 1732. (d) Brown, H. C.; Iyer, R. R.; Bhat, N. G.; Racherla, U. S.; Brown, C. A. *Tetrahedron* **1992**, *48*, 9187. (e) Swenton, J. S.; Bradin, D.; Gates, B. D. *J. Org. Chem.* **1991**, *56*, 6156. (f) Nantz, M. H.; Fuchs, P. L. *J. Org. Chem.* **1987**, 52, 5298. (g) Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139. (h) Igner, E.; Paynter, O. I.; Simmonds, D. J.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2447. (i) Baudler, M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480. (j) Midland, M. M.; Halterman, R. L.; Brown, C. A.; Yamaichi, A. *Tetrahedron Lett.* **1981**, *22*, 4171.

(2) In the synthesis of ω-acetylenic alkan-1-ols: (a) Okada, S.; Matsuda, H.; Otsuka, M.; Kikuchi, N.; Hayamizu, K.; Nakanishi, H.; Kato, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 455. (b) Menger, F. M.; Yamasaki, Y. *J. Am. Chem. Soc.* **1993**, *115*, 3840. (c) Tellier, F.; Hammoud, A.; Ratovelomanana, V.; Linstrumelle, G.; Descoins, C. *Bull. Soc. Chim. Fr.* **1993**, *130*, 281. (d) Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779. (e) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1992**, *48*, 4465. (f) Negishi, E.; Yoshida, T.; Abramovitch, A. *Tetrahedron* **1991**, *47*, 343. (g) Augustin, K. E.; Schäfer, H. J. *Liebigs Ann. Chem.* **1991**, 1037. (h) Ma, D.; Lu, X. *Tetrahedron* **1990**, *46*, 6319. (i) Almansa, C.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *Synthesis* **1988**, 707. (j) Blade, R. J.; Robinson, J. E.; Peek, R. J.; Weston, J. B. *Tetrahedron Lett.* **1987**, *28*, 3857. (k) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138. (l) Remizova, L. A.; Kryukov, A. V. *Zh. Org. Khim.* **1985**, *21*, 1001. (m) Schwarz, M.; Klun, J. A.; Leonhardt, B. A.; Johnson, D. T. *Tetrahedron Lett.* **1983**, *24*, 1007. (n) Gensler, W. J.; Prasad, R. S.; Chaudhuri, A. P.; Alam, I. *J. Org. Chem.* **1979**, *44*, 3643. (o) Utimoto, K.; Tanaka, M.; Kitami, M.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2301. (p) Henrick, C. A. *Tetrahedron* **1977**, *33*, 1845. (q) Lindhoudt, J. C.; van Mourik, G. L.; Pabon, H. J. J. *Tetrahedron Lett.* **1976**, 2565.

(3) Wotiz, J. H.; Barelski, P. M.; Koster, D. R. *J. Org. Chem.* **1973**, *38*, 489.

(4) Théron, F.; Verny, M.; Vessiére, R. In *The Chemistry of the Carbon-Carbon Triple Bond*; John Wiley and Sons: New York, 1978; Part I, Chapter 10, pp 381−345.

(5) Abrams, S. R.; Shaw, A. C. *J. Org. Chem.* **1987**, *52*, 1835.

(6) (a) Bushby, R. J. *Quart. Rev., Chem. Soc.* **1970**, *24*, 585. (b) Hass, E. C.; Mezey, P. G.; Abrams, S. R. *J. Comput. Chem.* **1982**, *3*, 185.

(7) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Brown, C. A.; Yamashita, A. *J. Chem. Soc., Chem. Commun.* **1976**, 959.

(8) Experimental modifications of the Brown procedure (ref 7a) for KAPA formation have been reported; see: (a) Kimmel, T.; Becker, D. *J. Org. Chem.* **1984**, *49*, 2494. (b) Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333.

(9) For the preparation of sodium 3-aminopropylamide, see: (a) Hommes, H.; Brandsma, L. *Recl. Trav. Chim. Pays. Bas.* **1977**, *96*, 160. (b) Macaulay, S. R. *J. Org. Chem.* **1980**, *45*, 734.

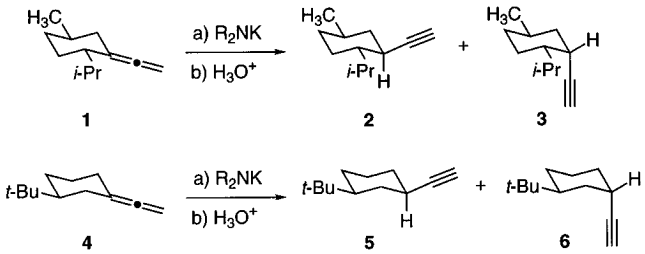
(10) A *minimum* of 13 allenyl rearrangements catalyzed by KAPA were shown to occur within seconds at 0 °C; see ref 7a.

(11) (a) Grattan, T. J.; Whitehurst, J. S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 11. (b) Djerassi, C.; Giner, J.-L. *J. Am. Chem. Soc.* **1991**, *113*, 1386.

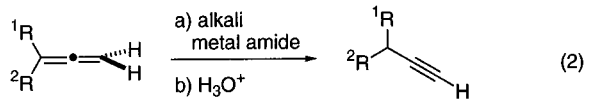
(12) Enzyme-mediated propargylic rearrangements to afford alkynes with stereogenic propargylic centers have been reported; see: (a) Gil, G.; Ferre, E.; Barre, M.; Le Petit, J. *Tetrahedron Lett.* **1988**, *29*, 3797. (b) Schwab, J. M.; Lin, D. C. T. *J. Am. Chem. Soc.* **1985**, *107*, 6046.

S0022-3263(96)00276-9 CCC: $12.00

Scheme 1



was anticipated to occur using the KAPA conditions as a consequence of its involvement within the mechanistic sequence reported for the "acetylene zipper" reaction. The



(2)

isomerization of a dissymmetrically disubstituted terminal allene (eq 2, $^1R \neq {}^2R$) would constitute a direct method for the introduction of terminal alkyne functionality onto a secondary position in a stereogenic fashion. Since the nucleophilic displacement of a secondary leaving group by an acetylide anion generally proceeds with very low conversion to the substitution product,[15] the allene isomerization reaction may serve as a useful alternative to nucleophilic substitution and other[16,17] approaches that are available for the synthesis of terminal alkynes. We report the generality of this synthetic transformation and the selection of amine bases suited for mediating a diastereoselective terminal allene isomerization.

Results and Discussion

Initial Base Screen. The terminal allenes **1** and **4** (Scheme 1) were prepared using our previously reported method.[18] The treatment of allenes **1** or **4** with alkali metal amides induced the 1,3-proton transfer to give a diastereomeric mixture of axial and equatorial terminal alkynes in varying ratios. The product distributions were determined by gas chromatographic analysis on the crude reaction mixtures and are given in Table 1. The assignment of stereochemistry for the alkyne diastereomers was made on the basis of the ^{1}H NMR chemical shifts for their respective propargylic protons. In the absence of complicating factors, equatorial protons in the cyclohexane ring have been shown to give rise to resonances downfield from their axial counterparts.[19] Additional support for the structure assignments is found on comparison of the propargylic ^{1}H NMR signal widths at half-height. The alkyne diastereomers **2** and **5** exhibit their axial propargylic resonances at δ 2.28 ($w_{1/2}$ = 22.8 Hz) and δ 2.21 ($w_{1/2}$ = 24.3 Hz), respectively. The large signal width at half-height in these signals confirms the presence of a diaxial H−H coupling to the propargylic proton. In contrast, the alkynes **3** and **6** exhibit equatorial propargylic resonances that are downfield and markedly narrower than their axial counterparts at δ 2.90 ($w_{1/2}$ = 8.4 Hz) and δ 2.77 ($w_{1/2}$ = 7.0 Hz), respectively.

Treatment of allene **1** with KAPA in propane-1,3-diamine as solvent (entry 1, Table 1) resulted in rapid allene isomerization to give a mixture of alkynes **2** and **3** in a 1.2:1 ratio. The potassium amide of ethane-1,2-diamine (entry 2) mediated the isomerization of **1** with similar selectivity. No starting allene was observed by GC after workup of the reactions in which the acetylene zipper conditions were used (e.g., entries 1, 2). In contrast, the metalation of allene **1** using *n*-BuLi (THF, −78 to 0 °C)[20] and quenching the reaction at 0 °C with aqueous ammonium chloride gave a 1:1 mixture of starting allene to terminal alkynes.[21] The **2**:**3** selectivity in this reaction was measured at 4:1, an increase in selectivity that prompted us to examine the allene isomerization in THF. The isomerization of **1** in THF was conducted using the primary potassium amides KAPA and *n*-BuNHK, a monoamide structural mimic of KAPA. Essentially no change in the product selectivity was noted on using KAPA in THF (entry 3); however, *n*-BuNHK mediated the isomerization of **1** with greater selectivity, although with low overall conversion. A similar mono- vs diamine comparison of potassium amides derived from secondary amines was performed (entries 5, 6). The increased basicity that is attained in going from a primary amide to a secondary amide, a principal difference on substitution of potassium butylamide with potassium *N*-methylbutylamide (KMBA), resulted in a dramatic improvement of allene isomerization reactivity. The isomerization of **1** mediated by KMBA proved to be facile and gave a higher selectivity for the equatorial alkyne **2** than that exhibited by the diamine-derived potassium *N*,*N*′-dimethyl-3-aminopropylamide. Interestingly, treatment of **1** with a sterically encumbered secondary potassium amide, potassium diisopropylamide (KDA,[22] entry 7), resulted in a reversal of selectivity to favor the axial alkyne **3**. A further increase in the steric bulk of the potassium amide was found to precipitously slow the allene isomerization. Thus, treatment of allene **1** with potassium tetramethylpiperidide (KTMP) did not effect isomerization at 0 °C, and was incomplete after 48 h at room temperature.

(13) The base-mediated isomerization of a monosubstituted allene has been reported; see: Thompson, H. W. *J. Org. Chem.* **1967**, *32*, 3712.

(14) The distinction should be noted between a method that delivers the chiral terminal alkyne *via* a 1,3-proton transfer, and methods wherein the propargylic chirality is established by alkylation of an allenyl anion; see, for example: (a) Baudouy, R.; Delbecq, F.; Gore, J. *Tetrahedron Lett.* **1979**, 937. (b) Pyo, S.; Skowron, J. F., III; Cha, J. K. *Tetrahedron Lett.* **1992**, *33*, 4703.

(15) Ben-Efraim, D. A. In *The Chemistry of the Carbon-Carbon Triple Bond*; John Wiley and Sons: New York, 1978; Part II, Chapter 18, pp 790−800.

(16) Pattenden, G. In *Comprehensive Organic Chemistry*; Stoddart, J. F., Ed.; Pergamon Press: New York, 1979; Vol. 1, pp 193−197.

(17) For terminal alkyne syntheses *via* functional group interconversion, see: (a) Aitken, R. A.; Atherton, J. I. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1281. (b) Van Hijfte, L.; Kolb, M.; Witz, P. *Tetrahedron Lett.* **1989**, *30*, 3655. (c) Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1986**, 64, 44. (d) Bryant, M. W.; Smith, R. A. J.; Wong, L. *Aust. J. Chem.* **1982**, *35*, 2529. (e) Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Tetrahedron Lett.* **1982**, *23*, 4607. (f) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. (g) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869. (h) Midland, M. M.; Sinclair, J. A.; Brown, H. C. *J. Org. Chem.* **1974**, *39*, 731. (i) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(18) Nantz, M. H.; Bender, D. M.; Janaki, S. *Synthesis* **1993**, 577.

(19) Jackman, L. M.; Sternhell, S. *Nuclear Magnetic Resonance Spectroscopy In Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969; pp 238−241.

(20) (a) Linstrumelle, G.; Michelot, D. *J. Chem. Soc., Chem. Commun.* **1975**, 561. (b) Michelot, D.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, 275.

(21) Previous literature reports on the reaction of (3,3-dialkylallenyl)lithium species with electrophiles have shown diverse ambident reactivity; see: (a) van Kruchten, E. M. G. A.; Haces, A.; Okamura, W. H. *Tetrahedron Lett.* **1983**, *24*, 3939. (b) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6259. (c) Pasto, D. J.; Chou, S.-K.; Fritzen, E.; Shults, R. H.; Waterhouse, A.; Hennion, G. F. *J. Org. Chem.* **1978**, *43*, 1389. (d) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632.

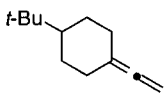
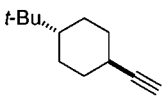
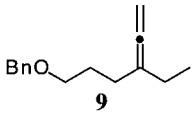
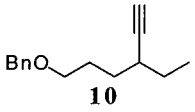
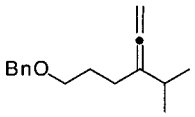
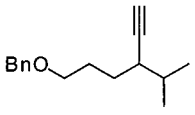
(22) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1978**, *43*, 3794.

Table 1. Diastereoselectivity as a Function of the Base Employed in the Isomerization of Allenes 1 and 4 (Scheme 1)

				selectivity[b]	
entry	allene	base[a]	reaction conditions	**2**:**3**	**5**:**6**
1	**1**	KAPA	$H_2N(CH_2)_3NH_2$, rt, 15 min	1.2:1	
2		$H_2N(CH_2)_2N(Me)K$	$H_2N(CH_2)_2NH_2$, rt, 15 min	1.1:1	
3		KAPA	THF, 0 °C, 1 h	1.3:1	
4		*n*-BuNHK	THF, 0 °C, >12 h	3:1[c]	
5		$(Me)HN(CH_2)_3N(Me)K$	THF, 0 °C, 1 h	1.8:1	
6		KMBA	THF, 0 °C, 15 min	6.8:1	
7		KDA	THF, −30 to 0 °C, 1 h	1:1.7	
8	**4**	KAPA	$H_2N(CH_2)_3NH_2$, rt, 15 min		1:1.1
9		KMBA	THF, 0 °C, 15 min		4.7:1
10		KDA	THF, −30 to 0 °C, 1 h		1.9:1

[a] Reactions were carried out using 3.5 equiv of potassium amide, and quenched with saturated aqueous NH_4Cl. [b] Ratio determined by capillary GC analysis. [c] Incomplete isomerization with ≥40% unreacted starting allene present.

Table 2. KMBA-Mediated Allene Isomerization

entry	allene[a]	alkyne[b]	yield,[c] %	ratio[d]
1	**1**	**2**	77	7 : 1
2	**4**	**5**	75	5 : 1
3	 **7**	 **8**	81	6 : 1
4	 **9**	 **10**	81	-
5	 **11**	 **12**	75	-

[a] all reactions were conducted on ≥ 1 mmol scale using 3.5 equivalents of KMBA in THF. [b] the major diastereomer is indicated where applicable. [c] isolated yield by chromatography. [d] equatorial:axial alkyne, determined by GC analysis on the crude reaction mixture.

The isomerization of allene **4** followed a similar trend in product diastereoselectivity for the bases screened. The formation of equatorial alkyne **5** was greatest when using KMBA (Table 1, entry 9), whereas the KAPA-mediated isomerization again showed little diastereoselectivity. The proportion of axial alkyne product, alkyne **6**, was increased on using the more bulky base KDA. These results suggest that the secondary amide KMBA may be a useful alternative base for 1,3-prototropic rearrangements that result in the formation of stereogenic propargylic centers, especially in cases involving exocyclic allenes. We have found that the KMBA-mediated allene isomerization may be employed to isomerize terminal allenes in good yield (Table 2). The reaction avoids the use of noxious propane-1,3-diamine as solvent and is amenable to synthesis of terminal alkynes on preparative scale.

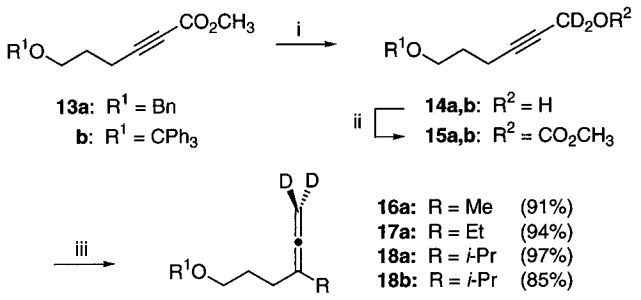
Deuterium Isotope Studies. One of the questions that arose during the course of these studies was whether the KMBA diastereoselectivity could be attributed to the intermediacy of a discrete propargylic anion. An axial quench[23] of such an intermediate anion by reaction with *N*-methylbutylamine would result in the formation of an equatorial alkyne. It was hypothesized that the placement of a deuterium label on the terminal allenic carbon would differentiate the principal mechanisms previously invoked to account for base-induced 1,3-proton transfers. Cram *et al.*[24] have demonstrated that the base-mediated isomerization of 1,3,3-triphenylprop-1-yne proceeds with intramolecularity, the 1,3-proton transfers occurring via a "conducted tour" mechanism that does not involve a discrete propargylic anion.[25] Wotiz *et al.*[3] proposed a mechanism for the base-induced isomerization of 3-hexyne which also does not involve the intermediacy of a propargylic anion. In this instance, the extremely rapid reaction rates observed when using amides of diamines such as ethylenediamine were attributed to facile, concerted 1,3-proton transfers; however, it was noted that a

(23) For studies on diastereoselective protonation and electrophilic reactions of cyclohexyllithium derivatives, see: (a) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, Y. *Chem. Ber.* **1993**, *126*, 1205. (b) Reich, H. J.; Medina, M. A.; Bowe, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 11003. (c) Keys, B. A.; Eliel, E. L.; Juaristi, E. *Isr. J. Chem.* **1989**, *29*, 171.

(24) (a) Cram, D. J.; Willey, F.; Fischer, H. P.; Scott, D. A. *J. Am. Chem. Soc.* **1964**, *86*, 5370. (b) Cram, D. J.; Willey, F.; Fischer, H. P.; Relles, H. M.; Scott, D. A. *J. Am. Chem. Soc.* **1966**, *88*, 2759.

(25) The isomerization of vinyl acetylenes to vinyl allenes has also been postulated to occur *via* a conducted tour mechanism; see: Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435.

Scheme 2[a]



[a] Reaction conditions: (i) $LiAlD_4 \cdot AlCl_3$, Et_2O, 0 °C, 75−84%; (ii) $ClCO_2CH_3$, Et_3N, DMAP, CH_2Cl_2, −78 °C to rt, 90%; (iii) RMgX (6 equiv), LiBr (6 equiv), CuI (6 equiv), THF, −50 °C to −5 °C.

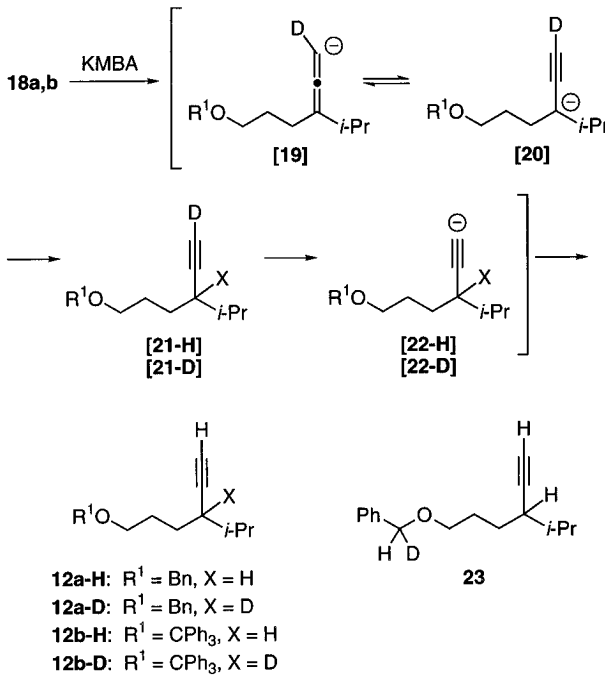
concerted mechanism with a monoamine anion was unlikely. Work by Abrams[5] has since shown that alkali metal amides of diamines effect, to some extent, 1,3-proton transfers through nonconcerted processes that may involve discrete propargylic anions. In the present study, a series of deuterated terminal allenes was prepared to examine the mechanism of the terminal allene isomerization and to determine the intermediacy of a distinct propargylic anion.

The reaction sequence shown in Scheme 2 constitutes an efficient route to deuterated terminal allenes and represents a general synthesis of geminally labeled terminal allenes.[26] Reduction of the acetylenic ester **13a**[27] using the reagent combination $LiAlD_4 \cdot AlCl_3$ afforded the deuterated propargylic alcohol **14a** in good yield.[28] Activation of the hydroxyl group in **14a** as a methyl carbonate derivative was followed by a LiBr−CuI-promoted S_N2' displacement of the carbonate moiety using a Grignard reagent according to the method of Macdonald.[29] In this manner, the deuterated terminal allenes **16a**−**18a** were obtained in excellent yields.

The isomerization of d_2-allene **18a** to the corresponding terminal alkyne by a "conducted tour" mechanism would be expected to transfer deuterium to the propargylic position. Under this mechanism, the addition of excess amine (R_2NH) to the reaction solution would not be expected to diminish the extent of propargylic deuterium incorporation since no distinct propargylic anion would be available for reaction with the added amine. However, if a propargylic anion were involved (e.g., [**20**], Scheme 3), an intermolecular reaction with added amine (R_2NH) may occur to incorporate hydrogen in the propargylic position to give **12a-H**. The recapture of deuterium by reaction of the propargylic anion with deuterated amine (R_2ND), formed on initial allenic deuterium abstraction, would compete with the added amine and would occur to give **12a-D**. Thus, the extent of propargylic deuterium incorporation would be influenced by the presence of added amine, and the percent deuterium incorporation would be expected to decrease relative to the equivalents of added R_2NH.

As a control experiment, the isomerization of allene **18a** was conducted in the absence of excess amine by

Scheme 3



using 3.5 equiv of KMBA, formed by the combination of *equimolar* amounts of *n*-BuLi, *N*-methylbutylamine, and KO*t*-Bu. Under these conditions, the expected product for both the conducted tour and the discrete propargylic anion mechanisms would be alkyne **12a-D** (Scheme 3). However, ^1H NMR analysis revealed that the product was terminal alkyne **23**, and the extent of deuterium incorporation in the benzylic position was measured at >95%. Only trace deuterium incorporation was detected in the propargylic position of alkyne **23**. For this reaction, the workup had involved the addition of water. To test whether the propargylic hydrogen was introduced by a water quench of propargylic anion [**20**], the identical reaction was quenched by the addition of D_2O. The results of this reaction showed no increase in propargylic deuterium incorporation and suggest that the proton source may be the pendant benzylic protons or *N*-methylbutylamine, formed as a consequence of benzylic deprotonation.

To circumvent the problems associated with benzylic deprotonation, the trityl protected terminal allene **18b** (Scheme 2) was prepared and isomerized under identical conditions. Analysis of the isomerization product showed that only 32% deuterium incorporation[30] had occurred in the propargylic position, an observation that is inconsistent with a conducted tour mechanism. In this reaction, the extent of hydrogen incorporation in the propargylic position under rigorous anhydrous conditions suggests that the propargylic anion [**20**] ($R^1 = C(Ph)_3$) is quenched by reaction with a proton source, presumably *N*-methylbutylamine formed from partial reaction of KMBA with THF.[31] The lack of significant deuterium transfer to the propargylic position in these examples suggests that the allene isomerization reaction is a nonconcerted process

(26) For previous syntheses of 1,1-dialkyl-3,3-dideuterioallenes see: (a) Pasto, D. J.; Warren, S. E.; Morrison, M. A. *J. Org. Chem.* **1981**, *46*, 2838. (b) Stang, P. J.; Hargrove, R. J. *J. Org. Chem.* **1975**, *40*, 657.

(27) Schlessinger, R. H.; Poss, M. A.; Richardson, S. *J. Am. Chem. Soc.* **1986**, *108*, 3112.

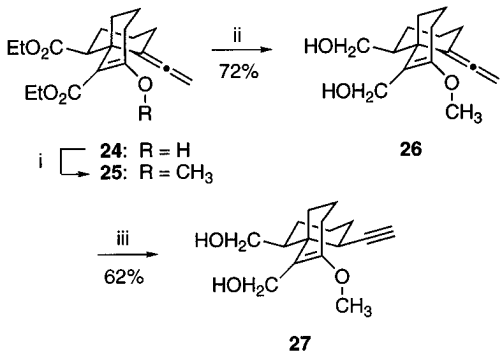
(28) The putative reducing agent on using a 1:1 ratio of $LiAlD_4$:$AlCl_3$ is AlD_2Cl; see: Kruglikova, R. I.; Babaeva, L. G.; Polteva, N. A.; Unkovskii, B. B. *Zh. Org. Khim.* **1974**, *10*, 956.

(29) Macdonald, T. L.; Reagan, D. R. *J. Org. Chem.* **1980**, *45*, 4740.

(30) Deuterium incorporation was measured using mass spectrometry according to the method described in: Biemann, K. *Mass Spectrometry: Organic Chemical Applications*; McGraw-Hill: New York, 1962.

(31) KMBA reacts slowly with THF under the isomerization conditions as evidenced by a control experiment in which a solution of KMBA in THF at 0 °C was quenched by addition of acetic anhydride and resulted in the detection of vinyl acetate (GC).

Scheme 4[a]

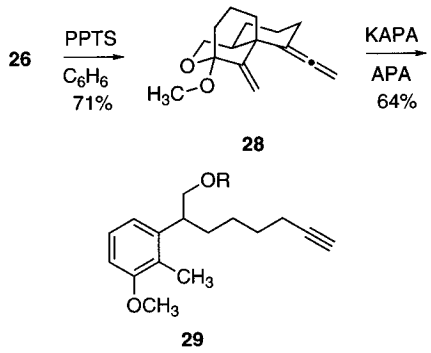


[a] Reaction conditions: (i) KOH (4.0 equiv), CH_3I (4.0 equiv), DMSO, rt; (ii) $LiAlH_4$, Et_2O, 0 °C to 10 °C; (iii) KAPA (9 equiv) in APA, rt, 20 h.

and is likely to involve an intermolecular quench of a discrete propargylic anion.

Isomerization of a Sterically Hindered Terminal Allene. In conjunction with our studies on functionalized spirocyclic allenes,[32] we have used the isomerization reaction to incorporate a terminal alkyne group onto a secondary neopentyl position in a diastereoselective fashion (Scheme 4). Spirocyclic allene **24**,[32] readily available using the Schinzer approach[33] to polycyclic systems, was converted to allene **26** via *O*-methylation[34] followed by $LiAlH_4$ reduction in 67% yield. Treatment of allene **26** with excess KMBA (7.0 equiv) in THF at 0 °C for 3 h failed to induce any detectable allene to alkyne isomerization. The severe crowding of the incipient propargylic anion by the spirocyclic construct likely interferes with efficient 1,3-proton transfer, and this steric problem represents a limitation in the use of secondary amide bases to effect allene isomerization. We were gratified to find, however, that application of Brown's KAPA conditions[7] resulted in the isomerization of allene **26** to afford equatorial alkyne **27** as the only detectable isomer. Presumably the lower steric requirement of the primary amine in this instance enabled proton transfer to the congested neopentyl center. The assignment of alkyne stereochemistry is based on the presence of a characteristic ^1H NMR diaxial coupling constant for the propargylic hydrogen at δ 2.41 (ddd, J = 12.0, 3.2, 2.4 Hz). As this example illustrates, the ready availability of exocyclic allenes from the reactions of propargylic silanes[32,33] (e.g., **24**) coupled with base-induced allene isomerization constitutes an efficient two-step protocol for the diastereoselective delivery of terminal alkynes.

We have also noted that the hyperbasicity of the potassium amide bases used to mediate the allene isomerization may result in undesired elimination reactions. For example, treatment of allene **28**, available from **26** via acid-catalyzed dehydration and concomitant acetal formation, resulted in extensive elimination and isomerization to produce terminal alkyne **29**, isolated as the corresponding acetate. Cycloaromatization products have been previously observed in base-mediated isomerizations of exocyclic allenes.[5]



Conclusion

These studies have led to a new and straightforward approach for the preparation of stereogenically positioned terminal alkynes. The axial vs equatorial selectivity in the isomerization of cyclohexyl terminal allenes was found to be influenced by the selection of potassium amide base. The secondary monoamide base KMBA exhibited excellent conversion and good selectivity in the formation of the equatorial alkyne product. In the case of a severely hindered terminal allene, the use of KAPA under standard acetylene zipper conditions was most effective. Our study on the KMBA-mediated isomerization of deuterated allenes clearly demonstrates the involvement of a propargylic anion. Extension of this methodology by using chiral amide bases for the isomerization of prochiral terminal allenes potentially may lead to a new asymmetric synthesis.

Experimental Section

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as a solvent. Infrared (IR) spectra were obtained using neat films unless otherwise noted. Melting points are uncorrected. High-resolution mass spectra determinations were conducted at the University of California, Davis, Facility for Advanced Instrumentation. Elemental analyses were performed by Midwest Microlab of Indianapolis, IN. GC analyses were performed on a gas chromatograph fitted with a capillary column (30 m × 0.25 mm, DB-5).

THF and Et_2O were distilled from sodium benzophenone ketyl immediately prior to use. All amine reagents were distilled from CaH_2 prior to use. A solution of KO*t*-Bu in THF was prepared by adding a small quantity of freshly cut potassium metal to freshly distilled THF containing excess KO*t*-Bu(s). The KO*t*-Bu/K mixture was heated to 60 °C for 15 h and then stored at room temperature under argon. The titer of KO*t*-Bu in the stock THF solution was determined according to a literature procedure.[35]

All reactions were carried out under an atmosphere of nitrogen. The potassium amides were prepared by a modification of the Raucher procedure[22] for synthesis of KDA. Allenes **1**, **4**, and **7** have been prepared previously.[18] Allenes **9** and **11** were prepared according to the method of Alexakis.[36] Column chromatography was carried out on 230−400 mesh silica gel, slurry packed in glass columns, eluting with the solvents indicated. Yields were calculated for material judged to be homogeneous by TLC and NMR. TLC was performed on Merck kieselgel 60 F_{254} plates, staining with an ethanolic solution of *p*-anisaldehyde and sulfuric acid.

Standard Procedure for Allene Isomerization. (1*R*,2*S*,5*R*)-1-Ethynyl-2-(methylethyl)-5-methylcyclohexane (2). To a stirred solution of *N*-methylbutylamine (0.57 mL, 4.8 mmol) in THF (1.0 mL) at −20 °C was added dropwise

(32) Spence, J. D.; Lowrie, L. E.; Nantz, M. H. *Tetrahedron Lett.* **1995**, *36*, 5499.
(33) (a) Schinzer, D; Sólyom, S.; Becker, M. *Tetrahedron Lett.* **1985**, *26*, 1831. (b) Schinzer, D.; Steffen, J.; Sólyom, S. *J. Chem. Soc., Chem. Commun.* **1986**, 829.
(34) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.
(35) Ehrlich-Rogozinski, S.; Bosshard, H. R. *Anal. Chem.* **1973**, *45*, 2436.
(36) Alexakis, A.; Commercon, A.; Villieras, J.; Normant, J. F. *Tetrahedron Lett.* **1976**, 2313.

n-BuLi (1.7 mL of a 2.5 M solution in hexanes, 4.2 mmol). After stirring for 10 min, a solution of KO*t*-Bu in THF (2.6 mL of a 1.6 M solution, 4.2 mmol) was added and the solution was warmed to 0 °C and stirred for an additional 20 min. A solution of allene **1** (194 mg, 1.20 mmol) in THF (1.0 mL) at 0 °C was then added dropwise *via* cannula. The reaction was quenched after 15 min by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was separated, washed with saturated aqueous NH_4Cl and brine and then dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (hexane) to afford a mixture of **2** and **3** as a colorless oil (150 mg, 77%). A subsequent chromatographic step on the product mixture eluting with *n*-pentane afforded an analytical sample of **2**: IR 3312, 2113 cm^{-1}; ^1H NMR δ 2.28 (m, 1H), 2.19−2.11 (m, 1H), 2.05 (d, J = 2.3 Hz, 1H), 2.01−1.96 (m, 1H), 1.73−1.69 (m, 2H), 1.65−1.62 (m, 1H), 1.36−1.09 (m, 4H), 0.92 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 88.0, 68.8, 47.1, 42.4, 34.8, 33.2, 32.4, 28.5, 24.0, 22.2, 21.3, 15.6. Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 88.00; H, 12.17.

***cis*-1-Ethynyl-3-(1,1-dimethylethyl)cyclohexane (5):** prepared as described above, IR 3314, 2119 cm^{-1}; ^1H NMR δ 2.21 (m, 1H), 2.05 (d, J = 2.2 Hz, 1H), 2.01−1.93 (m, 1H), 1.81−1.71 (m, 2H), 1.27−1.17 (m, 2H), 1.09−0.95 (m, 4H), 0.84 (s, 9H); ^{13}C NMR δ 89.5, 67.3, 47.6, 34.3, 33.0, 32.5, 30.0, 27.4, 26.5, 26.1; exact mass calcd for $C_{12}H_{20}$ 164.1565, found 164.1560.

***trans*-1-Ethynyl-4-(1,1-dimethylethyl)cyclohexane (8):** prepared as described above, IR 3312, 2119 cm^{-1}; ^1H NMR δ 2.14 (m, 1H), 2.08−2.05 (m, 2H), 2.02 (d, J = 2.2 Hz, 1H), 1.79−1.74 (m, 2H), 1.36−1.27 (m, 2H), 1.03−0.92 (m, 3H), 0.82 (s, 9H); ^{13}C NMR δ 89.2, 67.3, 47.3, 33.5, 32.4, 29.5, 27.4, 26.8. Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 88.22; H, 12.44.

6-(Benzyloxy)-3-ethyl-1-hexyne (10): prepared as described above, IR 3305, 3031, 2933, 2112, 1455, 1102 cm^{-1}; ^1H NMR δ 7.33−7.25 (m, 5H), 4.52 (s, 2H), 3.51 (t, J = 6.3 Hz, 2H), 2.31−2.25 (m, 1H), 2.06 (d, J = 2.4 Hz, 1H), 1.90−1.42 (m, 6H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 138.6, 128.3, 127.6, 127.4, 87.5, 72.8, 70.1, 69.4, 33.0, 31.1, 27.9, 27.5, 11.6. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.16; H, 9.20.

6-(Benzyloxy)-3-(methylethyl)-1-hexyne (12): prepared as described above, IR 3307, 3031, 2962, 2110, 1454, 1103 cm^{-1}; ^1H NMR δ 7.41−7.39 (m, 5H), 4.56 (s, 2H), 3.56 (t, J = 6.4 Hz, 2H), 2.31−2.25 (m, 1H), 2.1 (d, J = 2.4 Hz, 1H), 1.95−1.90 (m, 1H), 1.81−1.53 (m, 4H), 1.05 (d, J = 5.7 Hz, 3H), 1.03 (d, J = 5.7 Hz, 3H); ^{13}C NMR δ 138.6, 128.3, 127.6, 127.5, 86.0, 72.8, 70.3, 70.0, 38.5, 31.4, 29.2, 27.9, 21.0, 18.3. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.23; H, 9.57.

Methyl 6-(Benzyloxy)-2-hexynoate (13a). To a solution of 5-(benzyloxy)-1-pentyne[27] (8.00 g, 46.2 mmol) in THF (230.0 mL) at −50 °C was added dropwise *n*-BuLi (31.8 mL of a 1.6 M solution in hexanes, 50.8 mmol). After stirring for 1 h, methyl chloroformate (5.35 mL, 69.3 mmol) was added dropwise. The reaction mixture was warmed to room temperature after 5 min and stirred for 15 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (20 mL) and diluted with diethyl ether (250 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), water (50 mL), and brine (50 mL) and then dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the crude product was purified by flash chromatography (3% EtOAc/hexane to 12% EtOAc/hexane gradient) to give 7.06 g (66%) of ester **13a** as a light yellow oil: IR 2237, 1715, 1258 cm^{-1}; ^1H NMR δ 7.35−7.28 (m, 5H), 4.51 (s, 2H), 3.75 (s, 2H), 3.56 (t, J = 6.0 Hz, 2H), 2.48 (t, J = 7.1 Hz, 2H), 1.87 (quintet, J = 6.5 Hz, 2H); ^{13}C NMR δ 153.9, 138.1, 128.2, 127.4 (2), 88.9, 72.9, 72.8, 68.1, 52.3, 27.7, 15.4. HRMS calcd for $C_{14}H_{15}O_3$ 231.1021, found 231.1018.

6-(Benzyloxy)-1,1-dideuterio-2-hexyn-1-ol (14a). To a suspension of $LiAlD_4$ (173 mg, 4.34 mmol) in diethyl ether (5.0 mL) at 0 °C was added via syringe a solution of freshly sublimed $AlCl_3$ (579 mg, 4.34 mmol) in diethyl ether (6.0 mL). The reaction was stirred for 5 min before addition via cannula of a solution of ester **13a** (1.01 g, 4.34 mmol) in diethyl ether (6.0 mL). The reaction was stirred for 2 h at 0 °C and quenched by addition of 10% NaOH (5 mL) followed by warming to room temperature. The quenched reaction was diluted with diethyl ether (10 mL), and the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl (10 mL), water (10 mL), and brine (10 mL) and then dried (Na_2SO_4). The solvent was removed by rotary evaporation and the crude product was purified by flash chromatography (5% EtOAc/hexane to 10% EtOAc/hexane gradient) to give 758 mg (85%) of alcohol **14a** as a colorless oil: IR 3402, 2250 cm^{-1}; ^1H NMR δ 7.35−7.27 (m, 5H), 4.51 (s, 2H), 3.55 (t, J = 6.2 Hz, 2H), 2.34 (t, J = 7.1 Hz, 2H), 1.81 (m, 2H); ^{13}C NMR δ 138.5, 128.4, 127.7, 127.6, 85.8, 78.6, 72.9, 68.7, 28.7, 15.6. HRMS calcd for $C_{13}H_{13}D_2O_2$ 205.1197, found 205.1186.

Methyl 6-(Benzyloxy)-1,1-dideuterio-2-hexynyl Carbonate (15a). To a solution of alcohol **14a** (660 mg, 3.20 mmol) in CH_2Cl_2 (15 mL) at room temperature were added DMAP (79 mg, 0.64 mmol) and Et_3N (0.89 mL, 6.4 mmol). The reaction mixture was cooled to 0 °C, and methyl chloroformate (0.50 mL, 6.4 mmol) was added dropwise. After stirring for 1 h, the reaction mixture was warmed to room temperature and quenched by addition of saturated aqueous NH_4Cl (5 mL) and diluted with diethyl ether (15 mL). The layers were separated, and the organic layer was washed with saturated aqueous NH_4Cl (10 mL), water (10 mL), brine (10 mL), and then dried (Na_2SO_4). The solvent was removed by rotary evaporation and the residue was purified by flash chromatography (5% EtOAc/hexane) to afford 761 mg (90%) of carbonate **15a** as a colorless oil: IR (neat) 2253, 2240, 1753, 1718, 1286 cm^{-1}; ^1H NMR δ 7.35−7.27 (m, 5H), 4.50 (s, 2H), 3.79 (s, 3H), 3.55 (t, J = 6.1 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H), 1.81 (quintet, J = 6.6 Hz, 2H); ^{13}C NMR δ 155.2, 138.4, 128.3, 127.6, 127.5, 87.7, 73.6, 72.9, 68.6, 54.9, 28.4, 15.6; HRMS calcd for $C_{15}H_{15}D_2O_4$ ($M^+ - H_{benzylic}$) 263.1252, found 263.1269.

6-(Benzyloxy)-1,1-dideuterio-3-methyl-1,2-hexadiene (16a). A solution of LiBr (99 mg, 1.14 mmol) and CuI (216 mg, 1.14 mmol) in THF (4 mL) was prepared at room temperature and cooled to 0 °C. To the reaction mixture was added dropwise MeMgBr (0.38 mL of a 3.0 M solution in diethyl ether, 1.14 mmol). After stirring for 5 min, the reaction mixture was cooled to −5 °C and a solution of carbonate **15a** (50 mg, 0.19 mmol) in THF (1 mL) was added dropwise via cannula. The reaction was quenched after stirring 0.5 h by addition of saturated aqueous NH_4Cl (3 mL) and diluted with diethyl ether (15 mL). The organic layer was separated, washed with saturated aqueous NH_4Cl (5 mL), water (10 mL), and brine (10 mL), and then dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the crude product was purified by chromatography (100% hexane to 2% EtOAc/hexane gradient) to afford 35 mg (91%) of allene **16a** as a colorless oil: IR 1941 cm^{-1}; ^1H NMR δ 7.35−7.27 (m, 5H), 4.50 (s, 2H), 3.50 (t, J = 6.5 Hz, 2H), 2.02 (t, J = 7.1 Hz, 2H), 1.76 (m, 2H), 1.68 (s, 3H); ^{13}C NMR δ 206.0, 138.6, 128.3, 127.6, 127.5, 98.2, 72.9, 69.9, 29.9, 27.6, 18.8; HRMS calcd for $C_{14}H_{15}D_2O$ ($M^+ - H_{benzylic}$) 203.1404, found 203.1391.

6-(Benzyloxy)-1,1-dideuterio-3-ethyl-1,2-hexadiene (17a). Carbonate **15a** (50 mg, 0.19 mmol) was reacted at −35 °C according to the procedure described for the preparation of **16a** using ethylmagnesium chloride (0.57 mL of a 2.0 M solution in THF, 1.14 mmol) to afford 39 mg (94%) of allene **17a** as a colorless oil: IR 1936 cm^{-1}; ^1H NMR δ 7.35−7.27 (m, 5H), 4.50 (s, 2H), 3.50 (t, J = 6.5 Hz, 2H), 2.03 (t, J = 7.2 Hz, 2H), 1.94 (q, J = 7.4 Hz, 2H), 1.76 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 205.3, 138.7, 128.3, 127.6, 127.4, 104.8, 72.9, 69.9, 28.5, 27.7, 25.2, 12.1; HRMS calcd for $C_{15}H_{17}D_2O$ ($M^+ - H_{benzylic}$) 217.1561, found 217.1569.

6-(Benzyloxy)-1,1-dideuterio-3-isopropyl-1,2-hexadiene (18a). Carbonate **15a** (50 mg, 0.19 mmol) was reacted at −50 °C according to the procedure described for the preparation of **16a** using isopropylmagnesium chloride (0.57 mL of a 2.0 M solution in diethyl ether, 1.14 mmol) to give 43 mg (97%) of allene **18a** as a colorless oil: IR 1933 cm^{-1}; ^1H NMR δ 7.35−7.30 (m, 5H), 4.50 (s, 2H), 3.50 (t, J = 6.5 Hz, 2H), 2.10 (m, 1H), 2.03 (t, J = 7.4 Hz, 2H), 1.75 (m, 2H), 1.01

(d, J = 6.7 Hz, 6H); ^{13}C NMR δ 204.5, 138.7, 128.3, 127.5, 127.4, 109.4, 72.8, 69.9, 30.5, 27.8, 26.6, 21.5; HRMS calcd for $C_{16}H_{19}D_2O$ ($M^+ - H_{benzylic}$) 231.1717, found 231.1725.

Methyl 6-[(Triphenylmethyl)oxy]-2-hexynoate (13b). To a solution of 5-[(triphenylmethyl)oxy]-1-pentyne (1.82 g, 5.57 mmol) in THF (55 mL) at −78 °C was added *n*-BuLi (2.53 mL of a 2.4 M solution in hexanes, 6.13 mmol) dropwise. The reaction mixture was stirred for 1 h before the dropwise addition of methyl chloroformate (0.82 mL, 8.36 mmol) and followed by warming to room temperature over 15 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL) and diluted with diethyl ether (100 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$, water, and brine, and then dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the solid residue was purified by chromatography (3% EtOAc/hexane to 10% EtOAc/hexane gradient) to give 2.00 g (93%) of ester **13b** as a white solid: mp = 103.0−103.9 °C; IR 2236, 1715, 1259 cm^{-1}; ^{1}H NMR δ 7.47−7.23 (m, 15H), 3.78 (s, 3H), 3.20 (t, *J* = 5.9 Hz, 2H), 2.54 (t, *J* = 7.3 Hz, 2H), 1.88 (quintet, *J* = 6.5 Hz, 2H); ^{13}C NMR δ 154.0, 144.0, 128.6, 127.7, 126.9, 89.3, 86.5, 73.0, 61.6, 52.4, 28.1, 15.8; HRMS calcd for $C_{26}H_{24}O_3$ 384.1725, found 384.1742.

6-[(Triphenylmethyl)oxy]-1,1-dideuterio-2-hexyn-1-ol (14b). To a suspension of $LiAlD_4$ (167 mg, 4.21 mmol) in a 5:1 mixture of Et_2O:THF (14 mL) at 0 °C was added dropwise via syringe a solution of freshly sublimed $AlCl_3$ (561 mg, 4.21 mmol) in a 5:1 mixture of Et_2O:THF (14 mL). After stirring 5 min, a solution of ester **13b** (1.62 g, 4.21 mmol) in a 5:1 mixture of Et_2O:THF (14 mL) was added dropwise via cannula and the reaction was stirred for 30 min. The reaction was quenched by addition of 10% NaOH (5 mL) and warmed to room temperature. The reaction was diluted with diethyl ether (200 mL), and the layers were separated. The organic layer was washed with 10% NaOH, water, and brine and then dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the crude product was purified by chromatography (10% EtOAc/hexane to 20% EtOAc/hexane gradient) to give 1.16 g (77%) of alcohol **14b** as a white solid: mp = 87.1−90.0 °C; IR 3314, 2214 cm^{-1}; ^{1}H NMR δ 7.47−7.23 (m, 15H), 3.23 (t, *J* = 6.0 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 1.93 (s, 1H), 1.85 (quintet, *J* = 6.5 Hz, 2H); ^{13}C NMR δ 144.1, 128.6, 127.6, 126.8, 86.3, 85.6, 78.6, 61.8, 29.0, 15.7; HRMS calcd for $C_{25}H_{22}D_2O_2$ 358.1901, found 358.1913.

Methyl 6-[(Triphenylmethyl)oxy]-1,1-dideuterio-2-hexynyl Carbonate (15b). To a solution of alcohol **14b** (1.36 g, 3.79 mmol) in CH_2Cl_2 (38 mL) at room temperature were added Et_3N (1.06 mL, 7.58 mmol) and DMAP (93 mg, 0.758 mmol). The reaction was cooled to −78 °C and methyl chloroformate (0.59 mL, 7.58 mmol) was added dropwise via syringe. The reaction mixture was stirred and warmed to room temperature over 15 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and diluted with CH_2Cl_2 (200 mL). The organic layer was separated, washed with saturated aqueous NH_4Cl, water, and brine, and then dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the crude oil was purified by chromatography (3% EtOAc/hexane to 10% EtOAc/hexane gradient) to afford 1.46 g (92%) of carbonate **15b** as a colorless oil: IR 2254, 1754, 1285 cm^{-1}; ^{1}H NMR δ 7.47−7.23 (m, 15H), 3.82 (s, 3H), 3.19 (t, *J* = 6.0 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.84 (quintet, *J* = 6.4 Hz, 2H); ^{13}C NMR δ 155.3, 144.2, 128.6, 127.7, 126.8, 87.9, 86.4, 73.5, 61.8, 54.9, 28.9, 15.9; HRMS calcd for $C_{27}H_{24}D_2O_4$ 416.1957, found 416.1921.

6-[(Triphenylmethyl)oxy]-1,1-dideuterio-3-isopropyl-1,2-hexadiene (18b). A solution of LiBr (1.67 g, 19.3 mmol) and CuI (3.67 g, 19.3 mmol) in THF (65 mL) was prepared at room temperature and cooled to −50 °C. To the reaction mixture was added *i*-PrMgCl (9.63 mL of a 2.0 M solution in diethyl ether, 19.3 mmol) dropwise. After stirring 10 min, a solution of carbonate **15b** (1.34 g, 3.21 mmol) in THF (15 mL) was added dropwise via cannula. The reaction mixture after stirring for 0.5 h was quenched by addition of saturated aqueous NH_4Cl (10 mL) and diluted with diethyl ether (200 mL). The organic layer was separated and washed with saturated aqueous NH_4Cl (2 × 30 mL), water (30 mL), and brine (35 mL) and then dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the crude product was purified by chromatography (0.2% EtOAc/hexane to 1% EtOAc/hexane gradient) to yield 1.04 g (85%) of allene **18b** as a colorless oil: IR 1933 cm^{-1}; ^{1}H NMR δ 7.50−7.23 (m, 15H), 3.12 (t, *J* = 6.5 Hz, 2H), 2.10 (m, 1H), 2.07 (t, *J* = 7.6 Hz, 2H), 1.80 (quintet, *J* = 6.9 Hz, 2H), 1.03 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR δ 204.5, 144.5, 128.7, 127.6, 126.8, 109.6, 86.3, 63.2, 30.5, 28.2, 26.8, 21.6; HRMS calcd for $C_{28}H_{28}D_2O$ 384.2422, found 384.2440.

7-Ethenylidene-1,11-bis(hydroxymethyl)-2-methoxyspiro[5.5]undec-1-ene (26). To a suspension of finely powdered KOH (230 mg, 4.08 mmol) in DMSO (1.5 mL) at room temperature were added successively a solution of enol **24**[32] (340 mg, 1.02 mmol) in DMSO (1.5 mL) *via* cannula and methyl iodide (0.26 mL, 4.08 mmol). The heterogeneous solution was stirred for 1 h. The mixture was then diluted with water and extracted with Et_2O. The combined organic extract was washed with water, saturated aqueous $NaHCO_3$, and brine and then dried (Na_2SO_4). Removal of the solvent by rotary evaporation afforded 330 mg (93%) of the corresponding vinylogous carbonate **25** as a white solid that did not require further purification: mp 69−72 °C; IR 3041, 1957, 1721, 1681, 1627, 1294, 1156 cm^{-1}; ^{1}H NMR δ 4.64−4.47 (m, 2H), 4.23−4.11 (m, 2H), 4.07−4.00 (m, 2H), 3.54 (s, 3H), 3.23−3.18 (m, 1H), 2.20−2.13 (m, 4H), 2.02−1.97 (m, 1H), 1.80−1.64 (m, 7H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 206.7, 173.4, 167.0, 161.3, 115.7, 104.6, 74.4, 59.4, 59.1, 55.8, 47.3, 43.0, 27.0, 26.6, 25.2, 24.5, 24.4, 17.2, 13.9, 13.8; exact mass calcd for $C_{20}H_{28}O_5$ 348.1937, found 348.1958.

To a solution of **25** (330 mg, 0.95 mmol) in THF (6 mL) at 0 °C was added $LiAlH_4$ (3.3 mL of a 1.0 M solution in THF, 3.32 mmol). After stirring for 3 h, the solution was warmed to 10 °C and stirred an additional 1 h. The solution was then recooled to 0 °C and quenched by slow dropwise addition of MeOH. The quenched reaction mixture was diluted with Et_2O and poured into an equal volume of saturated aqueous Rochelle's Salt (sodium potassium tartrate), and the resultant mixture was stirred vigorously until the organic layer was clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic extract was washed with brine and dried (Na_2SO_4). Rotary evaporation of the solvent gave a yellow oil that was purified using flash column chromatography (ethyl acetate) to give 180 mg (72%) of **26** as a white solid: mp 89−91 °C; IR 3356, 3045, 1952, 1664, 1214, 1141 cm^{-1}; ^{1}H NMR δ 4.50−4.41 (m, 3H), 3.74−3.63 (m, 2H), 3.57 (s, 3H), 3.24 (dd, *J* = 11.0, 5.4 Hz, 1H), 2.96 (s, 1H, OH), 2.38 (s, 1H, OH), 2.26−2.00 (m, 4H), 1.95−1.80 (m, 4H), 1.70 −1.11 (m, 5H); ^{13}C NMR δ 205.9, 155.8, 120.1, 106.0, 73.5, 65.6, 57.9, 55.2, 46.7, 45.6, 30.7, 27.5, 26.2, 25.7, 24.2, 18.3; exact mass calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1719.

7-Ethynyl-1,11-bis(hydroxymethyl)-2-methoxyspiro-[5.5]undec-1-ene (27). To propane-1,3-diamine (3.0 mL) at 0 °C was added *n*-BuLi (2.2 mL of a 2.5 M solution in hexanes, 5.5 mmol). After stirring for 10 min, a solution of KO*t*-Bu in THF (3.4 mL of a 1.6 M solution, 5.5 mmol) was added dropwise, and the reaction was warmed to room temperature and stirred for 25 min. A solution of allene **26** (160 mg, 0.606 mmol) in propane-1,3-diamine (3.0 mL) was then added dropwise *via* cannula. After stirring overnight, the reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ and brine and then dried (Na_2SO_4). The solvents were removed by rotary evaporation and the residue was purified by flash column chromatography (ethyl acetate) to give 95 mg (62%) of **27** as a white solid: mp 92−95 °C; IR 3376, 3306, 2109, 1660, 1210 cm^{-1}; ^{1}H NMR δ 4.43 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 3.71 (dd, *J* = 10.8, 5.1 Hz, 2H), 3.60 (s, 3H), 3.24 (dd, *J* = 10.8, 6.1 Hz., 2H), 2.54 (br s, 2H, OH), 2.41 (ddd, *J* = 12.0, 3.2, 2.4 Hz., 1H), 2.22−2.15 (m, 2H), 2.01−1.95 (overlapping m, 1H), 1.98 (d, *J* = 2.4 Hz, 1H), 1.82−1.51 (m, 6H), 1.31−1.24 (m, 2H); ^{13}C NMR δ 157.0, 119.6, 86.8, 77.2, 70.2, 65.7, 56.4, 55.3, 46.4, 42.2, 39.1, 28.2, 25.4, 25.2, 24.1, 20.7; exact mass calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1738.

2-Methoxy-2,6-(methylenemethano)-7-ethenylidene-3-oxabicyclo[6.4.0]dodecane (28). A solution of alcohol **26** (17 mg, 0.063 mmol) in benzene (1.5 mL) was stirred over powdered 4 Å molecular sieves at room temperature for 1 h. Pyridinium *p*-toluenesulfonate (16 mg, 0.063 mmol) was added, and the reaction mixture was stirred at room temperature for 20 min. The mixture was then diluted with benzene and filtered through a short column of silica gel. The benzene was removed by rotary evaporation, and the crude product was purified by flash chromatography (ethyl acetate) to give 11 mg (71%) of **28** as a clear oil: IR 3048, 1951, 1739, 1649, 1112 cm^{-1}; ^1H NMR δ 5.59 (d, $J = 1.3$ Hz, 1H), 5.27 (d, $J = 1.3$ Hz, 1H), 4.69 (dd, $J = 2.3$, 2.4 Hz, 2H), 3.90 (m, 2H), 3.39 (s, 3H), 2.38−2.20 (m, 4H), 2.18−1.91 (m, 2H), 1.84−1.55 (m, 4H), 1.43−1.22 (m, 2H), 0.88 (m, 1H); ^{13}C NMR δ 205.3, 149.4, 106.2, 105.2, 99.2, 75.7, 68.4, 49.6, 44.1, 37.3, 33.6, 29.1, 28.9, 23.5, 22.6, 21.5; exact mass calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1620.

3-[1-(Acetoxymethyl)-6-heptynyl]-1-methoxy-2-methylbenzene (29). To a solution of allene **28** (98.0 mg, 0.400 mmol) in propane-1,3-diamine (1.2 mL) was added potassium aminopropylamide[7a] (2.8 mL of a 1 M solution in propane-1,3-diamine, 2.8 mmol). The resultant dark brown mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of EtOAc/Et_2O and followed by addition of saturated aqueous $NaHCO_3$. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ and brine. The aqueous fractions were extracted with Et_2O, and the combined organic extract was dried (Na_2SO_4). The solvents were removed by rotary evaporation to give a crude product that was purified by flash chromatography (10% ethyl acetate/hexane) to afford 73.9 mg (64%) of **29** as a light yellow oil: IR 3294, 3072, 2117, 1741, 1583, 1464, 1256 cm^{-1}; ^1H NMR δ 7.14 (t, $J = 8.0$ Hz, 1H); 6.80 (d, $J = 7.9$ Hz, 1H); 6.74 (d, $J = 8.1$ Hz, 1H), 4.14 (m, 2H), 3.86 (s, 3H), 3.3 (m, 1H), 2.12 (s, 3H), 2.04 (m, 2H), 1.91 (s, 3H), 1.81 (t, $J = 2.6$ Hz, 1H), 1.82−1.47 (overlapping m, 2H), 1.23 (m, 2H), 0.88 (m, 2H); ^{13}C NMR δ 171.0, 157.6, 141.2, 126.2, 125.4, 118.2, 108.2, 84.4, 68.4, 68.2, 55.5, 39.4, 31.9, 28.6, 26.3, 20.9, 18.2, 11.1; exact mass calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1708.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Sincere thanks are given to Dr. A. Daniel Jones for the mass spectral measurements and helpful discussions.

Supporting Information Available: 75 MHz ^{13}C NMR spectra of new compounds lacking combustion data (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960276I